FACTORS INFLUENCING THE DESIGN OF A PAEDIATRIC MULTIPARTICULATE DOSING DEVICE

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ABSTRACT

Paediatric specific medicines have become increasingly researched since the introduction of paediatric investigation plan requirements in 2007. Various dosage forms continue to be investigated for their appropriateness for children, including multiparticulates.

Multiparticulates are currently available as tablets, capsules, sachets and medicated spoons/straws/syringes. These presentations offer limited dose flexibility with some only providing a single fixed dose. A device capable of repeated flexible multiparticulate dosing is therefore required to exploit the inherent flexibility of the dosage form and allow for patient-specific personalised dosing.

This thesis takes a user-centered approach to conceptualise multiparticulate dosing devices through qualitative participatory design studies with user groups including children, caregivers and patients. Having explored User and Formulation requirements in terms of device design, a device specification has been generated with subsequent concept generation and mechanism prototyping.

The research with users provided further understanding of the different contributors to ease of use, and highlighted the importance of device simplicity, accuracy and speed of use.

Exploration of the concepts of self-administration and context of use with potential paediatric MP device users discovered that self-administration was more than a single step process. Caregivers also found it difficult to provide an age at which they would be happy for their child to self-administer and highlighted various influences upon their decision including child maturity, adult supervision and child familiarity with administration.

A knowledge gap surrounding the use of mass-based mechanisms to determine multiparticulate dose has also been addressed. With new knowledge surrounding MP measurement and the mechanical specifications required for a personalised dosing device presented.

A case study is presented, highlighting a possible application of multiparticulates and their dosing device in Cystic Fibrosis patients. This population was selected given their familiarity with a multiparticulate like

dosage form as part of their pancreatic enzyme replacement therapy. This study demonstrates how the global device requirements (presented in this work) can be refined on a case-specific basis allowing for a refined, user-centered device specification.

This work provides an industry road map for user engagement, acting as a platform for future multiparticulate dosing device design and development, guiding multiparticulate formulation design and ultimately advancing the field of personalised medicines and improving health outcomes (particularly of paediatric patients).

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ACRONYMS

API	Active Pharmaceutical Ingredient
BOS	Bristol Online Surveys
BSA	British Science Association
CAD	Computer Aided Design
CALF	Children's Acceptability of Oral Formulations
CDRH	Center for Devices and Radiological Health
CDT	Centre for Doctoral Training
CE	Conformité Européene
CF	Cystic Fibrosis
CG	Caregiver
D&D	Design and Development
DF	Dosage Form
DHF	Design History File
DIY	Design It Yourself
EC	Experienced Children

EMA	European Medicines Agency
EU	European Union
EuPFI	European Paediatric Formulation Inititative
GIT	Gastrointestinal Tract
GRAS	Generally Regarded As Safe
H&Ts	Hundreds and Thousands
HCP	Healthcare Professional
HF	Human Factors
IP	Intellectual Property
MCC	Micro-Crystalline Cellulose
MHRA	Medicines and Healthcare Products Regulatory Agency
MP	Multi-Particulate
mT	mini-Tablet
NC	Naïve Children
ODF	Oro-Dispersible Film
ODmT	Oro-Dispersible Mini Tablet
ODT	Oro-Dispersible Tablet
PERT	Pancreatic Enzyme Replacement Therapy
PIP	Paediatric Investigation Plan
PR	Paediatric Regulation
PSD	Particle Size Distribution
PUMA	Paediatric Use Marketing Authorisation
QMC	Queen's Medical Centre
QS	Quality System
RQ	Research Question
RSD	Relative Standard Deviation
SM	Self Medication
SODF	Solid Oral Dosage Form
STEM	Science Technology Engineering and Mathematics
UCD	User Centered Design
UK	United Kingdom
UoB	University of Birmingham
URS	User Requirement Specification
US	United States
WHO	World Health Organisation

CHAPTER 1 - INTRODUCTION

1.1 OVERVIEW

The majority of drugs used for children are either unapproved or off-label use (Schirm et al. 2002; 2003). Many medicines are used in unapproved indication, age group, dose or administration route (2000; T Jong et al. 2002). This poses a significant problem when the dosing of that medicine is critical. Dose manipulation or adaptation is often not an option, particularly when the drug's therapeutic index is small, and the presentation does not allow for the required flexibility in dosing (Richey et al. 2013). More paediatric specific Dosage Forms (DFs) and administration devices are therefore required (Batchelor and Mariott 2013).

In 2007 the Paediatric Regulation (PR) was established in Europe to guide high quality research into the development of appropriate paediatric medicines (EMA 2006b). This introduced a legal requirement whereby any medicine with a possible paediatric indication have this investigated. This legislation aimed to create a range of authorised paediatric DFs permitting safe and accurate dose administration to children. The PR was imposed with a view to enhance patients' medication adherence, whilst having minimal impact on lifestyle and well-being and reducing medication errors, all whilst not delaying drug authorisation in other age groups (EMA 2006b; 2013).

Many factors must be considered when developing a paediatric medicine, including the DF itself and the recipient. It is the interaction between the medicine/medical device and the user(s) that can become pivotal when ensuring adherence (Money et al. 2011; Sharples et al. 2012; EMA 2013; CDRH 2016).

Multiparticulates (MPs) are an increasingly researched DF for the paediatric population given their small pellet size and patient tolerability. Figure 1.1 shows a number of MP characteristics that lend themselves well to drug administration. An appropriate DF for both adults and paediatrics, large dose volumes when considering adult dose make them less feasible.

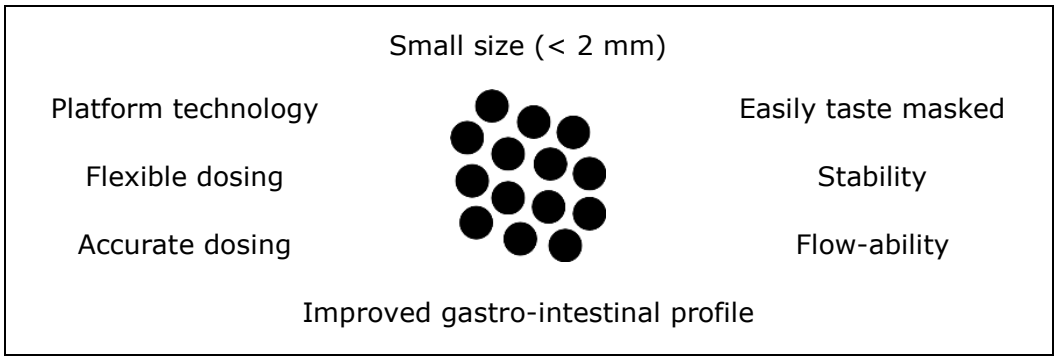


FIGURE 1.1 MP CHARACTERISTICS THAT LEND THEMSELVES TO DRUG ADMINISTRATION

Compaction of the MPs into tablets can pose a choking hazard, creating a DF that is too large for many young children to swallow (EMA 2013). MPs can be filled into sachets or capsules for opening and sprinkling onto food, this however, can make the food taste aversive, reducing the chance of successful, complete administration not to mention risks food-drug interactions. To this end, more sophisticated technology has been created including pulp spoons and dose-sipping technology. These however only offer a single fixed MP dose (Sternberger-Rutzel 2014).

Based upon the current technology, state of science and regulatory considerations what is required therefore is a cost-effective device capable of repeated flexible MP dosing. This will allow for paediatric, body-mass specific personalised dosing.

MP delivery is not well understood in terms of interaction with users, this is however, vitally important in ensuring adherence. The importance of undertaking Human Factors (HF) research during device development is well established and has been widely documented (Ernest et al. 2007; Money et al. 2011; Sharples et al. 2012; Lang et al. 2014b). Regulatory guidelines as well as case studies have demonstrated the significance of introducing user-based studies as soon as possible during the design process to ensure the creation of a successful user-centered device (FDA 2014a; ISO 2015; CDRH 2016; ISO 2016).

This research project came about through the meeting of industrial research interests and academic expertise, via the Centre for Doctoral Training (CDT). This project aligns the unmet need for a flexible paediatric MP dosing device with the University's and Pfizer's research goals.

This thesis investigates the design of a paediatric medical device capable of repeated flexible MP dosing through consideration of three key areas: Formulation, Device and User.

1.2 LITERATURE REVIEW

The six key areas underpinning this research, (summarised in Table 1.1) are now addressed through literature review.

TABLE 1.1 LITERATURE REVIEW STRUCTURE

	Topic	Regulation
1.2.1	Paediatric medicines	*
1.2.2	Oral administration	
1.2.3	Traditional oral DFs & devices	
1.2.4	Medical device Design and Development (D&D)	*
1.2.5	The importance of HF testing	*
1.2.6	Paediatrics as a user group	

1.2.1 PAEDIATRIC MEDICINES

In recent years there has been increased research into the development of paediatric specific formulations. With clear developmental differences between adults and children, it is unsurprising that their medication should also differ (Ivanovska et al. 2014). The majority of drugs however, do not have a paediatric specific DF, or dosing method (Standing and Tuleu 2005). Many drugs have no liquid formulation, and pharmacies often adapt formulations for paediatric use off-label (Schirm et al. 2002).

Clearly there is a need for paediatric specific research to enable development of formulations targeted to this population. In 2007 the PR was established to guide high quality research aiding the development of appropriate medicines for children (EMA 2006b). One of the roles of this agency is the assessment and agreement of Paediatric Investigatory Plans (PIPs). These are a legally required document detailing the timing and measures proposed to demonstrate the quality, safety and efficacy of a product in a paediatric indication. The introduction of PIPs into the legal framework shows integration of paediatric specific medicines into the general development process. Incentives are also offered to stimulate research, including free agency advice, Paediatric Use Marketing

Authorisation (PUMA), six month extension of supplementary protection certificates and ten year exclusivity is extended to twelve for orphan products.

Since the publication of the PR in 2007 there have been increased efforts in the development of paediatric-specific or paediatric appropriate formulations in terms of research and regulation.

A number of guidelines have been written by the World Health organization, WHO (2012) the European Medicines Agency, EMA (2006a; 2013) and the FDA, Pediatric Research Equity Act (PREA), detailing considerations when formulating paediatric medicines specifically. These guidelines are not legally binding, and their sole purpose is to set out principles/ instructions that should be followed. It is however, recommended to adhere to these guidelines as disregard for such documents will only make conforming to legal requirements more difficult.

Breitkreutz (2008) produced a commentary of these new European Union (EU) regulations and guidelines, with special attention paid to the impact on paediatric formulation science. He mentioned that since the PR came into force in 2007, a great emphasis has been placed on creating new organisations, scientific networks, and programs to deal with paediatric medicine development. He drew contrast between United States (US) and EU regulations and markets and mentioned the importance of having age-group specific formulations. He considered the appropriateness of: any excipients used and a delivery device, as well as emphasising the taste profile of formulations for children.

Zajicek et al (2013) produced a similar commentary on behalf of a US formed paediatric task force. They too, highlighted the importance of research into paediatric specific medicines.

Aside from this US led 'Paediatrics Formulation Task Force' there has been increased research into formulating better medicines for children in Europe, with a similar group set up; the EuPFI (European Paediatric Formulation Initiative). This EuPFI comprises of paediatric formulation experts from industry, academia and clinical pharmacy working to raise awareness of paediatric formulation issues and improve medicines for children.

1.2.2 ORAL ADMINISTRATION

The oral route is the most common method of administration for medicinal products (Walsh et al. 2011). Oral administration is the most convenient route for regular drug administration particularly in children, being simple, non-invasive and achieving higher patient compliance than other administration routes.

Barriers to non-oral medicine administration methods in children have been investigated (Venabales et al. 2016). This study suggested that any formulation should be child-friendly and age-appropriate in a bid to improve usability, acceptance and consequently adherence. Venebales et al. (2015) and Walsh et al. (2015) identified similar issues with usability and child-acceptance of non-oral formulations and their devices.

Formulators are tasked with creating appropriate DFs for this paediatric population. Given the diverse nature of the patient group they are divided into sub-groupings representing developmental change, Table 1.2.

TABLE 1.2 AGE CATEGORIES WITHIN THE PAEDIATRIC POPULATION (EMA 2006)

Preterm new born infants	< 0 days
Term new born infants	0-27 days
Infants and toddlers	1 month to 23 months
Children	2 – 11 years (2 – 5 years)(6 – 11 years)
Adolescents	12 – 16 or 18 years

It is important that the DF created is appropriate for the sub-population intended. Other important aspects such as the condition to be treated, the likely treatment duration (EMA 2013), and the formulation itself must also be considered. The DF's formulation is greatly important with many characteristics to consider. These include the properties of the Active Pharmaceutical Ingredient (API), the stability of the formulation and the excipients used for example. The use of colouring agents, preservatives and flavours in particular must be evaluated when formulating paediatric medicines.

Given the complex and variable nature of this patient population, dosing flexibility is often vital to ensure children receive the correct personalised dose. This is increasingly important with drugs of a narrow therapeutic window, where individualised dosing may be based on the patient's mass (Breitkreutz and Boos 2007).

Personalised medicines have become increasingly researched, with both UK and global agendas in this area (FDA 2013; EC 2016; NHS England 2016). Given that most common medicines are not effective in treating large numbers of patients, the increased costs associated with increased population ages and the fact that chronic diseases are more prevalent. Personalised medicine provides a means of tailor-making prevention, diagnosis and treatment strategies for individuals or groups of individuals based of their genes, lifestyle and environments (Budin-Ljøsne and Harris 2016; NHS England 2016).

The paediatric population is just one example of where personalised medicines are increasingly investigated, with the PR of 2007 only serving to further research in this area.

It terms of development and manufacturing costs, it is often preferable that a single DF is appropriate for use across multiple age ranges; however, this is not always easy given differences in physiology and patient preference. Different routes of administration and/or DFs may be needed for the same API in order to ensure adequate treatment of children in all target age group(s) (EMA 2013; Ivanovska et al. 2014).

Patient preferences heavily affect the acceptability of a product having significant impact on adherence and consequently, the safety and efficacy. Formulation acceptability is often user specific and is heavily influenced by the product characteristics. Areas of acceptability include; palatability, swallowability, appearance, required dose, dosing frequency and mode of administration (EMA 2013). Given the relative importance of formulation acceptability upon oral medication adherence, acceptability evaluations play an integral role in pharmaceutical and clinical development. Studies investigating acceptability include research into DF characteristics such as size, shape and colour as well as mouth feel and the influence of sensory systems (Overgaard et al. 2001; Mennella and Beauchamp 2008; Lopez et al. 2016). Ranmal et al. (2016) performed a Children's Acceptability of Oral Formulations (CALF) study to capture end-user perceptions and practices of

SODFs. They found that attitudes towards DFs primarily differed based on user age and prior use. Using this insight formulation development can be guided towards creating and selecting the most appropriate DFs for a particular age range.

Sam et al. (2012) developed a formulation ranking system whereby they considered three case studies, with an aim of selecting the most appropriate formulation in each case. They compared different formulations, the use of different colouring agents as well as looking at the appropriateness of liquid preparations across all paediatric age groups. In discussing the relative merits of each DF or approach, they made informed choices based on efficacy/ease of use, safety and patient access. By applying a weighting and scoring system to each case they could further refine the analysis and aid decision-making. They propose that a similar method would be useful for all formulation development in children.

Aside from the important considerations within formulation, it is also important to consider the dosing requirements. Is the dosing frequency reasonable? Will children have to medicate during school hours? Can this formulation have a modified release profile to reduce dosing frequency? Does this affect the ease of administration? What effect does this have on the user? (Claxton et al. 2001; EMA 2013)

The use of measuring or administration devices should also be considered including their relative dosing accuracy. As such there has been on-going research into the development of appropriate drug delivery devices for the paediatric population. Gauthier and Cardot (2011) provide a summary of developments in delivery devices from measuring bottles through to more sophisticated dosing straws, whilst Walsh et al. (2011) provide an overview of current practice, challenges and recent developments in paediatric administration devices.

Dose delivery devices often prove vital in the accurate administration of medicines to children. They should, therefore, always be designed for use in the target age group(s) to allow for appropriate use of the intended medicine. Carefully balancing the risk of inadequate patient acceptability with accidental intake is key (EMA 2013).

1.2.3 TRADITIONAL ORAL DFS

Traditional oral DFs can be broadly split in to liquids and solids, each have their merits when administering medicines to children.

1.2.3.1 LIQUIDS

Traditionally, liquid medications are the formulation of choice for paediatric patients and include solutions, syrups and suspensions (EMA 2006a). Generally considered acceptable from birth, liquids can provide greater dosing flexibility than traditional single-unit solid DFs and can be easily swallowed (EMA 2013). Liquid medications face challenges with taste however. Often difficult to taste mask, the bitter API can mean the formulation is aversive, hindering chances of successful administration (Walsh et al. 2014). Possible administration vehicles for use with ill-tasting liquids are being researched to improve palatability (Mishra et al. 2009). Liquids are typically less stable than their solid counterparts, meaning preservatives are often required (EMA 2013). This can be a problem when formulating medications for children as any excipients used must be carefully considered and acceptable in young people (EMA 2013). Aside from the use of stabilising agents within the formulation itself, an unstable DF may also require refrigeration. This will mean higher transport costs and can prove challenging in low resource settings (Lopez et al. 2015). Controlled release with liquid formulations can be challenging to achieve. This means liquid DFs often require more frequent dosing than their solid extended release counterparts. As such the dosing frequency can become a hindrance, with children having to medicate in school time. This can lead to further complications with regard to school policy and self-administration.

Liquid DFs have target dose recommendations of < 5 mL for children under five and < 10 mL for children five and older (EMA 2006a). This means a measuring device is often required for their accurate administration.

LIQUID DOSING DEVICES

An array of liquid dosing devices are available including measuring spoons, dosing cups, oral droppers and measuring syringes, with more recent innovations including sophisticated measuring spoons and dummys for example.

Walsh et al. (2011) provide a comprehensive review of measuring spoons, dosing cups, oral droppers and syringes with the relative advantages and disadvantages of each device discussed in the Table 1.3, taken from Walsh et al. (2011).

TABLE 1.3 ADVANTAGES AND DISADVANTAGES OF AVAILABLE DEVICES FOR ORAL LIQUID DFS

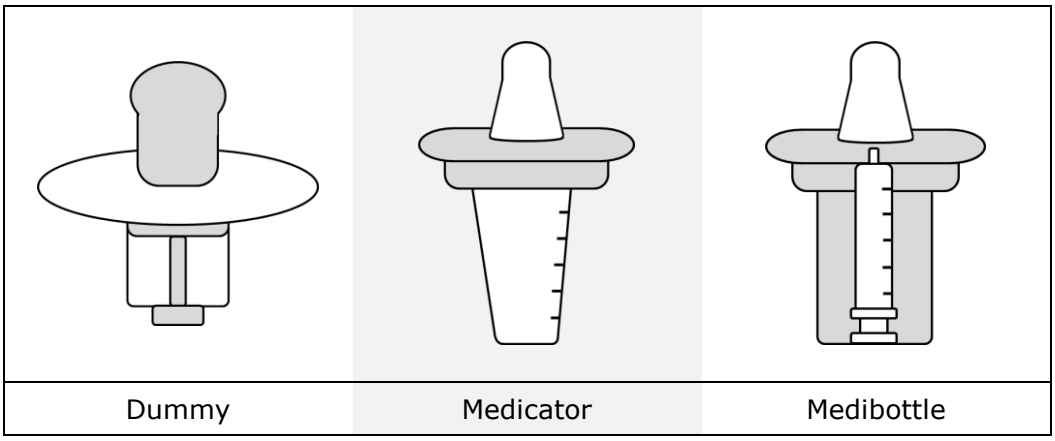
Device	Advantages	Disadvantages	Comments
 Measuring spoon	Widely available Generally easy to use	Fixed volume: usually 5 mL May get variability in volumes measured from same spoon Shape of spoon can affect dosing accuracy (Griessmann et al. 2007) Graduation can lead to inaccurate dosing Product can be spilled during dosing	Most commonly used delivery device: more accurate than household spoons (Aziz and Jameela 1990; Gauthier and Cardot 2011; Mehmood et al. 2014)
 Dosing cup	Widely available Multiple dosing operations may be avoided where larger volumes than 5 mL are required	Unacceptable doses more likely to be measured (Sobhani et al. 2008) Dosing errors highly prevalent (Yin et al. 2010a; Yin et al. 2010b; Ryu and Lee 2012) Multiple graduations may be confusing to carer May get residual volume remaining after dosing Product may be spilled during dosing Device may pose a choking hazard (Weiss et al. 1996)	

 Droppers	Widely available Useful for administering very small volumes (drops)	Dropper must be held vertically to ensure accuracy and consistency of dose (Brown et al. 2004) Drop size may be affected by physical properties of the liquid Inaccurate and inconsistent volume measurement (Hermanns-Clausen et al. 2009)	Tend to be used for babies and small children
 Oral syringe	Provide more accurate and less variable dosing than spoons and cups (Griessmann et al. 2007; Dockhorn et al. 2010) Allow dose flexibility in terms of volumes that can be measured Various sizes available Angle of delivery does not affect dose Spillage of dose unlikely	Measurement of dose may be confusing to some carers To make measuring liquids with a syringe less confusing and to limit the potential for dosing error: syringe clip (Spiegel et al. 2013) May cost more than spoons or dosing cups	Syringe with caps should not be used to avoid risk of choking Delivery device of choice for oral liquids for administration of oral liquids to children (Kairuz et al. 2007; Walsh et al. 2011; Walsh et al. 2015)

Given the limited dosing accuracy, issues of patient acceptance and the risk of dose spillage with traditional devices, a number of novel liquid devices have been created with many more patents filed.

'Pulp' spoons aim to reduce medicine spillage risk and improve dose measurement accuracy. The spoon provides a single fixed dose of solid medication which is subsequently submerged into liquid creating a pulp for direct oral consumption (Olenak 2006).

Devices resembling bottles and dummys (Figure 1.2) attempt to make pre-existing administration methods more 'child-friendly'. Their focus is in use with young children where the formulation or its mode of administration may create a barrier to successful ingestion.



Dummy	Medicator	Medibottle

FIGURE 1.2 EXAMPLE DUMMY AND BOTTLE DEVICES

The Medibottle (Figure 1.2) and dose sipping syringe go one step further Exploiting the dosing accuracy of the syringe and combining this with the 'child friendly' bottle or straw. Kraus et al. (2001) found the Medibottle to be more effective at administering liquid medicines to children than the oral syringe whilst also having a higher level of infant acceptance.

Whilst these advances begin to address issues surrounding dosing accuracy and patient adherence, one of the key factors influencing their success surrounds the increased cost of these devices.

1.2.3.2 SOLIDS

Solid DFs are arguably easier to formulate than liquids, having a well-established manufacturing process, less stability and solubility issues and being more easily taste masked (EMA 2006). Their dose flexibility however is often limited given that pre-defined dosages are common. Tablets and capsules are often difficult to swallow (depending upon their size) which is an important consideration in paediatric use (Overgaard et al. 2001; EMA 2006b)

Hansen et al. (2008) explored Danish adolescents' struggles with pill swallowing, finding over one-third had difficulties swallowing tablets. Given pill swallowing is often considered a challenge, various 'pill swallowing devices' have been patented to aid in this (Meltzer et al. 2006). Tablet splitting is also performed (provided the DF is not enterically coated for example) to provide smaller doses, reduce cost and facilitate swallowing (Quinzler et al. 2006). Despite tablet splitting devices having been developed, their use does not always lead to accurately divided doses (Cook et al. 2004). Rosenberg et al. (2002), Teng et al. (2002) and van Santen et al. (2002) investigated tablet splitting, finding it to be largely inaccurate.

Due to these inaccuracies, advances have been made to create SODFs more suited to being split. One method is the use of drug-free compartments whereby splitting does not affect the dose content of the resultant segment (Solomon and Kaplan, 2010; Green et al., 2009).

Wening et al. (2012) have developed a solid dosage pen capable of delivering variably sized doses of an extruded drug containing rod. The device works by having an exact feed rate, offering dose adjustment through a cutting mechanism.

Due to the limited dose flexibility offered by traditional DFs it can be preferable that a solid DF is converted into a liquid at the point of administration. This exploits SODF advantages for the majority of the product life cycle, including the ease of manufacture, reduced cost and improved stability whilst exploiting the liquids' dose flexibility at the point of administration.

Effervescent and dispersible tablets are one such example. These DFs are designed for dispersion, suspension or dissolution into a beverage prior to administration. Their use in paediatrics however is not recommended given the risk posed by excipients used and by premature ingestion (EMA 2006a). It is also recommended that multiple step procedures should generally be avoided to reduce the risk of dosing errors (EMA 2013).

A solid DF that provides inherent dosing flexibility whilst not requiring manipulation prior to administration is therefore required.

Novel SODFs

Formulators have worked to improve the flexibility of solid oral formulations with a focus on novel preparations such as Oro-Dispersible Tablets (ODTs), Oro-Dispersible films (ODFs), chewable tablets and multi-unit DFs for example. These novel DFs provide a greater level of dose flexibility whilst also being easier to administer and better accepted by children (in many cases).

ODTs and ODFs

These orodispersible DFs do not require administration devices and are simply placed in the mouth where they dissolve rapidly. Their rapid disintegration means they often do not require any water to aid swallowing circumventing swallowability issues and improving compliance over conventional formulations.

Despite these advantages, controlled release and taste masking can be particularly challenging with these DFs. They also likely require excipients with unknown safety profiles in children and their stability very much depends on their packaging and storage conditions. Bioavailability may be altered by the retention time in the mouth and the manufacturing technologies are subject to Intellectual Property (IP) licensing.

Whilst ODFs can provide excellent dose flexibility, the ODTs are only available in fixed doses, meaning various dose strengths are required. The ODTs also lack mechanical strength which may hinder the structural integrity of the DF during handling. ODTs can incorporate high API doses whilst ODFs cannot. Continuous manufacture may be achieved for ODFs

however dose uniformity can be challenging and solvents are often used during manufacture.

The suitability of ODTs in children has been investigated by Stoltenberg and Breitkreutz (2011) who successfully developed orally disintegrating mini-tablets (ODmTs) for paediatric patients. They had promising results indicating that ODmTs may serve as a novel platform technology for paediatrics in future.

Kimura et al. (2015) evaluated the palatability of ODTs containing core granules with different particle sizes, coatings, and types of formulations. They found that tableting the core granules into ODTs reduced rough mouth feel and improved overall palatability compared to the ingestion of core granules alone. Rough mouth feel was found to be significantly more intense when core granules had a particle size > 200 μm. The study found that the granules contained within the ODT must be 244 μm before a feeling of roughness was reported.

Despite offering some advantages for paediatric medicine administration, with a review of the literature and regulatory guidance suggesting they offer an innovative solution for paediatric drug delivery (Preis 2015). The increased development and production cost compared to traditional SODFs has meant that few orodispersible paediatric products have made it to market (Slavkova and Breitkreutz 2015).

CHEWABLE TABLETS

Like ODTs and ODFs, chewable tablets do not require water for administration. Given they do not need to be swallowed whole like traditional DFs they are often more accepted by young children.

Bioavailability may be improved by the quick disintegration and dissolution times, this is very much subject to the patient's chewing capability, how long the DF is chewed and whether it is ingested before complete drug release however.

The manufacturing and packaging technology are readily available to produce chewables; however, the use of excipients with unknown safety profiles in children may be required as well as solvents during manufacture. There is concern over the limited dose flexibility offered by

the DF as well as concern over possible overdose risk given their likeness to confectionery.

Michele et al. (2001) determined the safety of chewable tablets in children by means of a literature review. They found that over 60 chewable tablet formulations were approved for use in the US and that medical issues were extremely rare. They suggested that the advantages of chewable tablets included their palatability, stability, precise dosing, portability, and ease of delivery. Concluding that chewable tablets provide a safe, well-tolerated alternative to traditional paediatric drug formulations and offer significant advantages in children 2 years of age and older.

Den Uyl et al. (2010) performed a comparative study looking at patient acceptability and preference of the DF also. Their work compared chewable tablets with a sachet of the same drug formulation. They found that of the 102 patients indicating a preference for a trial medication, 67% preferred the chewable tablet. The two formulations were tolerated equally well, although a significantly greater number of patients considered the chewable tablet as preferable and acceptable to the sachet.

This suggests that chewable DFs have the potential for paediatric use. Despite this, few pharmaceutical chewables for children have made it to market, likely due to their added formulation complexity compared to widely available chewable vitamins.

MULTI-UNIT DFS

Multi-unit DFs include; granules, pellets, mini-Tablets (mTs) and MPs can provide precise dosing, modified release and taste masked medications for paediatric administration (Cram et al. 2013). Given their relative advantages over traditional DFs, it is unsurprising that the WHO has noted them, specifically MPs for particular consideration when formulating paediatric medicines (WHO 2012).

Unlike their single- unit counterparts multi-unit DFs have their total dose of API divided between individual subunits; each capable of having specific characteristics. Due to the multi-unit nature of the DF, versatile release profiles can be achieved through the combination of different subunits, or though the coating of individual units. This creates potential for great

flexibility and allows for personalised medication dosing (Dey et al. 2008; Patwekar and Baramade 2012).

The small size of the sub-units allows for easy ingestion, with less swallowability issues than the larger traditional DFs. Their small size means that they can travel through the Gastro- Intestinal Tract (GIT) easily; disintegrating within minutes sometimes seconds (FDA 2012). The small diameter also means that they are able to depart the stomach constantly (dependent on size), meaning absorption is less dependent upon nutritional state and gastric emptying. There is also less intra- and inter- patient variability in plasma levels and bioavailability (Dey et al. 2008; Patwekar and Baramade 2012; Gandhi and Baheti 2013).

Whilst single unit DFs have the disadvantage of releasing an all or nothing response during emptying, multi-unit systems release drug more uniformly. This uniform distribution along the GIT results in a lower risk of dose dumping, a reduced risk of local irritation, a decreased risk of systemic toxicity and ultimately more reproducible drug absorption. This improves patients' tolerability (Dey et al. 2008; Patel et al. 2011; Patwekar and Baramade 2012; Gandhi and Baheti 2013; Sharma and Chaurasia 2013).

Table 1.4 (taken from Lopez et al. (2015)) summarises the advantages and disadvantages of multi-unit DFs compared to traditional SODFs.

Whilst relatively few MP formulations are currently available on the market, a number of MP-like formulations, including granules and sprinkles are available. The majority of these formulations are prepared for reconstitution at the point of administration, or are available as an oral sprinkle with co-administration with food expected or encapsulated for direct ingestion.

Vantin and Voriconazole are both available for paediatrics for treatment of bacterial and fungal infections. These drug as available for reconstitution as an oral suspension at the point of use (Strickley et al. 2008). Montelukast sodium and Pancrealipase are available as free-flowing granules and as a capsule. Direct capsule ingestion is encouraged, whilst sprinkling of the granules on to food is also possible.

TABLE 1.4 ADVANTAGES AND DISADVANTAGES OF MULTI-UNIT DFS

Product characteristic		Advantages	Disadvantages
Efficacy/ acceptability	Dosage	Excellent flexibility in dose Small size: swallowing is aided	Grittiness/mouth feel may be an issue (Engelen et al. 2005; Lopez et al. 2016)
	Preparation	Flexibility of administration	Need for preparation or reconstitution
	Compliance	Ease of functionalisation Suitable for taste masking	
Safety profile	Bioavailability	Highly reproducible due to uniform GI transit Targeted release profiles can be achieved	Co-administration with food/drinks may alter bioavailability
	Excipients	Use of Generally Regarded As Safe (GRAS) excipients	
	Stability		Food-drug compatibility needs to be studied
	Medication error		Limited control over dose intake when mixed with food
Patient access	Manufacturability	Manufacturing technology readily available (Manivannan et al. 2010; Sharma and Chaurasia 2013; Lopez et al. 2015)	May need specialised equipment or accessories
	Affordability		Need to develop packaging/dosing technology platform

Thomson et al. (2009) assessed the acceptability and suitability of placebo mTs in preschool-aged children. They found that of the youngest children (2 years of age), almost half (46%) swallowed the mT and this proportion increased with age. This study demonstrated the potential for mT use in preschool-aged children.

Spomer et al. (2012) explored the acceptance and swallowability of 2 mm uncoated placebo mTs in children aged between 6 months and 6 years. They compared mT administration (with a beverage of choice) with the administration of 3 ml glucose syrup and found that the acceptance of the mTs was higher or at least equal to that of the syrup. Very young children (6–12 months) were fully capable of swallowing the mTs and may even accept them better than the sweet liquid formulation. They concluded that uncoated mTs seem to be a very promising alternative to liquid formulations and could be used at an earlier age in paediatric drug therapy than previously anticipated.

Klingmann et al. (2013), Riet-Nales et al. (2014) and Klingmann et al. (2015) found mTs to be acceptable in children aged 6 months to 6 years, in preschool aged children and in neonates.

Kluk et al. (2015) explored the acceptance of multiple mTs in 2 and 3 year old children. They found most children were fully capable of swallowing all units without chewing, and that neither the number nor size of the mT significantly influenced the child's ability to swallow them. They therefore suggested that mTs administered in several units mixed with jelly food are safe and could be accepted by a paediatric population.

Whilst these studies demonstrated mTs to be acceptable when taken directly, there may be need to administer with a vehicle should volumes prove large or the DF less acceptable. Co-administration of mTs with food or drink may alter bioavailability however. To this end, much research investigates food-drug effects with a list of acceptable food/drink vehicles desirable. Furthermore, research is being performed to create a specialised delivery vehicle for mT and pellet administration to children (Kluk and Sznitowska 2014).

MPs are currently available as tablets, sprinkles (in easy to open capsules (CAPSUGEL) and sachets) and medicated spoons, much like the pulp spoon (Olenak 2006).

Tablets and capsules are often too large for young children to swallow whilst sachets and medicated spoons offer only a single fixed dose.

In Japan, Nakamura and Ishikawa (2014) have found that powders for reconstitution are often dispensed in sachets, with Care-Givers (CGs) adding a small amount of water or syrup to make a paste. This compounding at the point of sale allows for personalised dosing superior to the fixed dosed sachets available in the UK.

Given the limited dosing flexibility of current MP presentations (despite their inherent flexibility) there is a need to develop MP packaging or a device amenable to repeated, flexible dosing.

MP ADMINISTRATION DEVICES

A device capable of handling these free-flowing MPs would overcome issues with the current presentations, allowing for a great deal of dosing flexibility and providing means of personalised dosing, Figure 1.3.

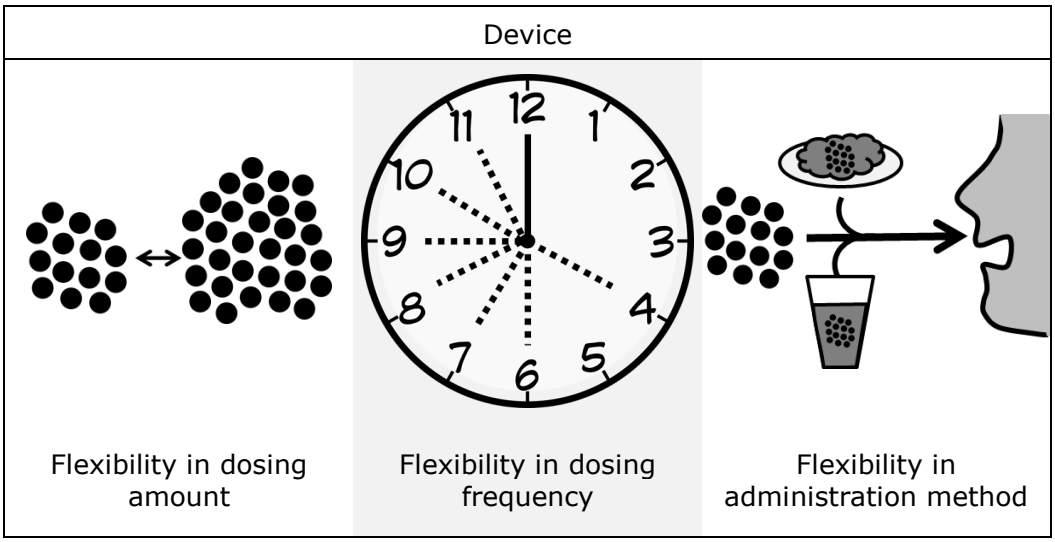


FIGURE 1.3 POTENTIAL FLEXIBILITY OFFERED BY AN MP DEVICE

Figure 1.3 demonstrates that a device can offer flexibility in the MP dosing amount, dosing frequency and administration method. These types of flexibility are important in dosing all of the paediatric population. Given the paediatric population ranges from preterm new-borns to adolescents (between 16 - 21 year olds depending on region) a range of physiological changes will occur throughout this time. Developing a drug delivery device amenable for this entire population therefore means that many factors

must be considered including differences in physiology, cognition and religion for example (EMA 2006a; EMA 2013).

FIXED DOSE DEVICES

A number of devices have been developed to provide a single fixed dose of MPs. One such device is the X Straw, which uses dose sipping technology to deliver an oral, fixed MP dose to paediatric and geriatric patients. Released to market in 2014 containing the antibiotic Erythromycin, the X Straw was later withdrawn due to the high manufacturing costs and a change in research portfolio of the vendor. The device is based on a simple drinking straw allowing for administration of a fixed MP dose along with the patient's favourite beverage. The patient places the straw in their chosen drink and ingests the 'liquefied' dose. The device is suitable for individuals over the age of two years and it is possible to combine different drugs and/or release profiles (Sternberger-Rutzel 2014).

Given pulp spoons, tablets, capsules, sachets and dose sipping technology only provide a single pre-defined dose however, a means of selecting or extracting a dose from a multi-dose container would aid flexibility and personalised medicine.

DOSE MEASURING/COUNTING DEVICES

A number of simple devices are available to extract defined volumes of MPs from a larger bulk container. These are commonly used in the therapy of pancreatic diseases, particularly in children. Devices include small, simple volumetric spoons (2) as well as more sophisticated 'dimpled' spoons (1), Figure 1.4 (Wening and Breitkreutz 2011).

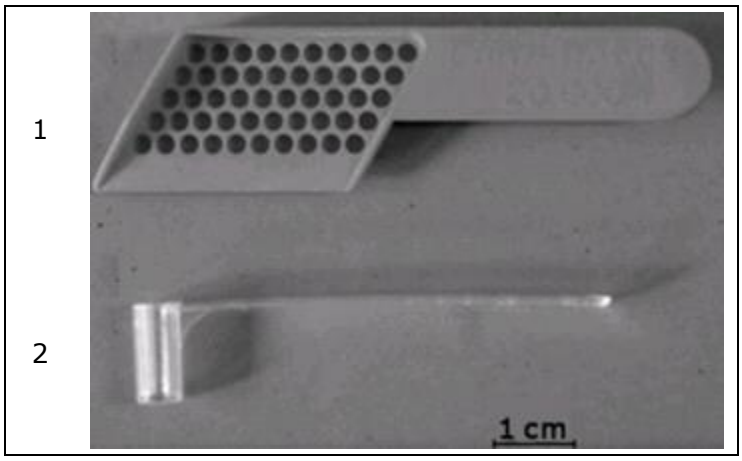


FIGURE 1.4 EXAMPLE MP MEASUREMENT SPOONS

(taken from Wening and Breitkreutz 2011)

To achieve different sized doses the spoons can be refilled multiple times or used to measure partial doses such as a half or a third of a scoop.

Given that multiple pellets are often required for paediatric dosing there is a risk that pellets may fall from the spoon or that children will refuse a meal covered in solid MPs. Given however drug-loading of most pellet formulations is relatively low, dosing errors are not particularly dangerous and these inaccuracies may well fall within pharmacopeia guidelines (Pharmacopoeia 2016). If however, the DF was to contain a more potent API, dosing with these devices would become less feasible.

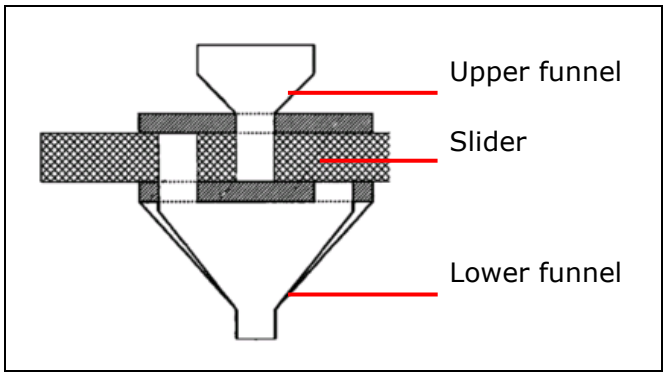


FIGURE 1.5 DEVICE MECHANISM PROPOSED BY BAURIEGEL, 2007

Figure 1.5 shows an improved device mechanism proposed by Bauriegel (2007) which connects two funnels with a slider. Movement of the slider allows for the extraction of a defined powder volume from the upper funnel and transfer to the lower funnel. This mechanism only provides a single predefined dose however. Flexibility in dose is achieved through multiple expulsions of that same fixed dose, requiring manual counting by the user.

Numerous patents have been filed exploiting similar mechanisms, such as that of Mishra et al. (2014).

A few devices have been developed whereby the final dose volume is measured within the device, through accumulation of multiple smaller doses before being expelled; this removes the onus on the user to count doses. One example is a German 1990s oral pellet delivery device from Boehringer Ingelheim for bronchial Asthma treatment. The device is filled with pellets and delivers one sub-dose per actuation. The accumulation of up to six sub-doses is possible before expulsion from the device. Graduation marks on the spoon (placed beneath device) allow for verification of dose.

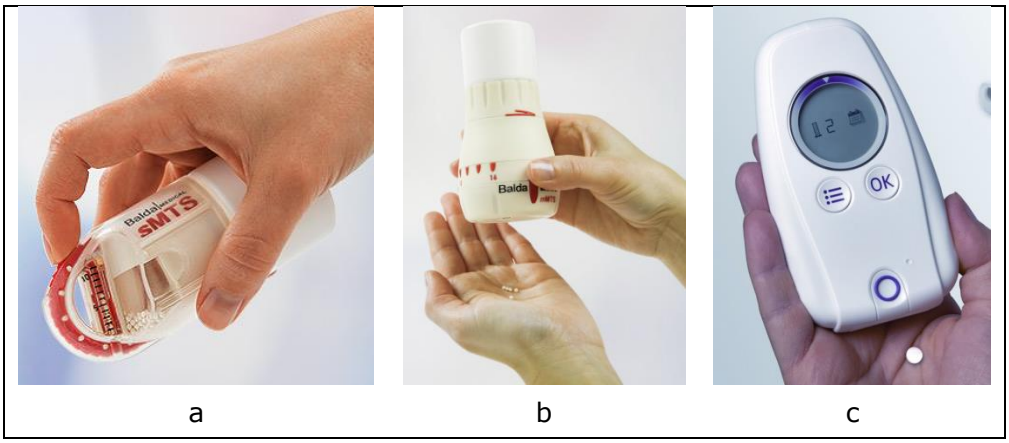
Whilst improving dose flexibility compared to the aforementioned devices and relying less on the user for dose counting, the relative dose flexibility is still limited.

A few patents have subsequently been filed, such as that from Desset-Brethes et al. (2013) who designed a MP dispensing device capable of dispensing variable dose volumes. These devices rely on volumetric dose measurement which can prove inaccurate. Dose accuracy is largely dependent on particle packing and Particle Size Distribution (PSD). This could be improved through individual counting of sub-units, something that would prove challenging with small MPs, but possible with larger mTs nonetheless.

To this end, numerous patents have been filed for mT counting devices, the most basic of which expels a single mT (Dobkin 1950; LeBlanc and Martin 1963; Neavin 1975)

Salamé (1991) proposed a more sophisticated dispenser allowing the counting of up to four pellets prior to expulsion. Whilst Breitkreutz and Wazlawik (2005) conceptualised devices capable of counting multiple mTs prior to expulsion.

Individual pellet counting is the method used by many mT devices created by Balda (Germany). Their portfolio (examples of which are shown in Figure 1.6) includes both manual (a & b) and electronic devices (c) capable of dispensing up to 21 individual mTs in a single expulsion.



a b c

FIGURE 1.6 BALDA MT COUNTING DEVICES

Bredenberg et al. (2003) developed an electronic mT counting device similar to Balda's device, Figure 1.6c. A predefined dose is counted and expelled in a single expulsion whilst dosing accuracy is determined and indicated on the electronic display. Claimed as being one of the safest devices for dispensing multiple-unit DFs, this device is costly and produces environmental burden with respect to its battery requirement (Wening and Breitkreutz 2011).

These devices keep the MPs in their free-flowing form throughout storage, dispensing and administration. This allows exploitation of their inherent flexibility, aiding personalised dosing.

Subsequent to dispensing, it is possible to package an MP dose into a tablet, sachet or into an ODT. These are yet to be offered at the point of vending however there is the possibility that devices capable of compacting MPs or even printing MP based tablets could one day be available in patients' homes.

1.2.4 Design and Development (D&D) process

There is no set approach to D&D with industries or research groups employing their own specific methodologies and approaches based on their own requirements.

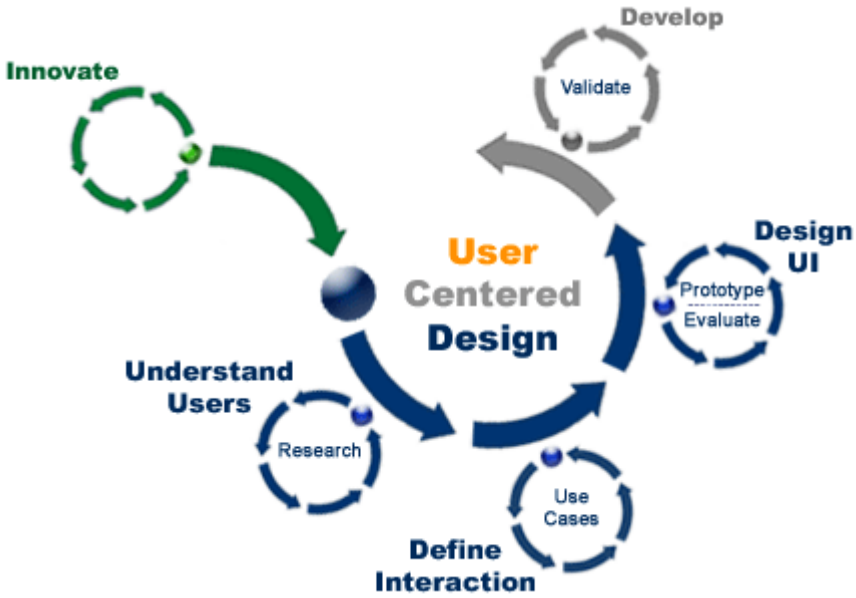


FIGURE 1.7 D&D PROCESS (DCN)

Figure 1.7 represents one example of how a design process may be approached. This often begins at the concept stage: 'innovate' where design inputs are created and compiled. This includes the capture of user requirements and the building of a specification. These design inputs such as stakeholder requirements and specifications, detail the needs of the project and manage the expectations of the project. The User Requirement Specification (URS) is usually developed during this initial concept stage to define the specific stakeholder needs and impose design constraints, 'Understand Users'. Once the project has gained approval the D&D plan will be created and the HF investigations can begin, UCD.

Performing user-centered studies with stakeholders and patients form a vitally important part of the D&D process in order to understand how users will interact with the device. HF studies are invaluable in understanding potential sources of use error and in aiding the direction of the development process. It is well documented that gaining user insight at every stage during development enhances the process and can save lengthy product recalls, improving the chances of product success (Shah

and Robinson 2008; Sharples et al. 2012; Lang et al. 2013; Lang et al. 2014b).

Throughout development, risk management activities are implemented to identify, review and mitigate risks associated with the device and materials used (CDRH 2016). Quality assurance activities are also performed to ensure product quality. As the concept develops, engineering tests are used to verify product specification. The Design History File (DHF) tracks all design control activities throughout the process and will commonly be initiated at this stage before being updated throughout the process, 'Develop and Validate'. After a number of review, planning and validation activities the design transfer/approval will occur allowing the manufacture of a commercial product. A technical file is then drawn up to ensure all regulatory requirements are met and to attain the required Conformité Européene (CE) marking. Post market surveillance is also performed.

1.2.4.1 REGULATIONS AND GUIDANCE

The regulations surrounding the D&D of medicines and their delivery devices for children are summarised briefly by Wachtel (2012).

Medical device development is regulated by directives such as; ISO 13485 (2003), 93/42/EEC (1993) (soon to be replaced with the European Medical Devices Regulation), 21 CFR 820 (2014a) and SI No 618 (2002).

These regulations define a devices as 'An instrument, apparatus, appliance, software, material or other article used alone or in combination for diagnosis, prevention, monitoring, treatment or alleviation of disease or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception'. They specify that the device must not compromise the clinical condition or safety of the patient/other persons. It must be designed and manufactured to reduce the associated risks and accompanied by instructions for safe and proper use. They also stipulate that measuring devices should be calibrated at specified intervals, or prior to use, against measurement standards, adjusted/ re-adjusted as necessary, identified to enable calibration status, safeguarded from adjustments that would invalidate measurement result.

Combination products are regulated by 21CFR part 4, with the Food and Drug Administration (FDA) providing various guidance documents. This document defines a combination product definition as, a drug and device, a device and biological, a biological and drug or a drug, device and biological. There are three types of combination product, single entity, whereby ≥ 2 regulated components are physically, chemically or otherwise combined/mixed, co-packaged where ≥ 2 separate products packaged together or cross-labelled where the components are packaged separately but intended for use with another product, with their intended use only achieved when used together, and the constituent parts retain regulatory status after they're combined.

HF in medical device design is regulated by ISO 62366 (2015; 2016) and HE 75 (2009). The Centre for Devices and Radiological Health, CDRH (2016) and the Medicines and Healthcare products Regulatory Agency MHRA (2016) also providing guidance documents.

ISO 62366 aims to help manufacturers of medical devices 'design in' usability and 'design out' use errors. It emphasises the importance of a UCD process and highlights the importance of usability testing throughout device D&D (ISO 2015; 2016).

The CDRH and MHRA guidance recommend that manufacturers follow HF or usability engineering processes during the development of new medical devices, focusing specifically on the user interface, where the user interface includes all points of interaction between the product and the user(s) including elements such as displays, controls, packaging, product labels, instructions for use, etc. While following these processes can be beneficial for optimizing user interfaces in other respects (e.g., maximizing ease of use, efficiency, and user satisfaction), FDA is primarily concerned that devices are safe and effective for the intended users, uses, and use environments. The goal is to ensure that the device user interface has been designed such that use errors that occur during use of the device that could cause harm or degrade medical treatment are either eliminated or reduced to the extent possible.

PR (2006b) forms the foundation for many guidelines surrounding the development of paediatric medicines. These include EMA (2006a; 2013), WHO (2012) and FDA (2014b) which all provide further insight into key

considerations when developing paediatric formulations and their means of administration.

In addition to these key regulations, there are also further regulations and guidance documents surrounding this evolving field of paediatric medical device D&D. These include regulations of medicinal products for human use (2001/83/EC) as well as more specific device regulations relating to device labelling (21CFR801), child-resistant packaging (BS ENO 14375) and guidance on appropriate materials for medical use.

It is clear device D&D is tightly regulated, with respect to the medical device itself, the Quality System (QS), the combination product and the specific target population.

1.2.5 THE IMPORTANCE OF HF TESTING

Engagement with users early in the D&D process is beneficial in ensuring acceptance, safety and reliability of the end product (CDRH 2016). Martin et al. (2006) substantiate this notion in their work capturing user requirements in medical device design. They explain that medical device users are a heterogeneous population and that for any one device there can be an array of users; including patients, CGs and Health Care Professional (HCPs) for example. They provide guidance to developers regarding issues to consider during the D&D process and provide recommendations for the full range of user requirements (Martin et al. 2008).

Access to these populations can prove difficult given the ethical, time and financial constraints. This means that the sample of users and the context in which the research is performed must be carefully considered, there may be the use of proxies in place of real-users for example.

A variety of HF methods are effective in identifying different types of data hence it is advised that various methods should be used at each point in development. As such, different techniques can be suitable at specific points in the device D&D. These include contextual inquiry and ethnography during initial user requirement capture, whilst others, like usability tests and focus groups may be used throughout the process.

1.2.5.1 INVOLVEMENT OF YOUNG PEOPLE IN HEALTHCARE RESEARCH

Lang et al. (2014b) investigated the engagement of adolescents as specific users, typically overlooked in the D&D of medical devices. They found that barriers to adolescent inclusion include; informed consent, assent, gatekeepers, confidentiality, appropriateness of topics and proxies.

It is therefore important that these challenges are overcome to gain access to these key user groups, understand their user requirements and ultimately improve device design.

Lang et al. (2013; 2014a) performed a series of interviews with adolescent users of a CF physiotherapy device to investigate their user requirements. They found that adolescents did not use the device correctly and often not as recommended by clinicians. The researchers identified a number of aspects of the current device that affected how and how often the device was used. These included engagement, information, confidence, aesthetics and compatibility with lifestyle. Adolescent users of medical technologies want their independence and capabilities to be respected. Adherence to use was associated with short and long-term motivations, with older users appearing to comprehend longer-term benefits of use against short-term inconvenience. It was suggested that medical devices could provide a tool for communication with families and clinicians and could support adolescents as they take responsibility for managing their condition. Themes such as "fitting into teenage life" and "use in the community" were associated with the user's needs to form their own identity and have autonomy.

Using this insight they then went forward in suggesting improvements to the device design, improving correct and frequent use of the device. This demonstrated how a more acceptable, safe and usable device could be created when developers engage with users.

Further UCD examples can be seen in the work of Fuchs et al. (2009) and Kappelgaard et al. (2012) who investigated the acceptability of growth hormone administration devices for paediatric patients. Pradel et al. (2001) and Howard et al. (2017) performed similar studies investigating asthma self-management in children and adolescents. Other examples of UCD can be seen in the design of health monitoring apps for example (Cafazzo et al. 2012). As well as in the design of user-friendly patient

information/instruction materials (Yin et al. 2008; Yin et al. 2011) (Montagne 2013) (Savage and Goodyer 2003).

All of these studies have provided insight into key user requirements with respect to medical device design. This provides a great amount of insight allowing for the creation of more acceptable and usable medical devices. Aside from the medical device, it is also important to use UCD during the development of the medicines themselves to ensure paediatric specific formulations are generated (Osuntokun 2006).

Notenboom et al. (2017) looks at how learning from patients can aid the identification of medicine design features that cause medication errors. This allows circumvention of these issues in future development, hopefully leading to the design of medicines for accurate administration.

Other UCD of formulations has included palatability testing; acceptance assessments and a CALF study to capture end-user perceptions and practices of SODFs (Overgaard et al. 2001; Den Uyl et al. 2010; Lopez et al. 2016; Ranmal et al. 2016; Drumond et al. 2017)

1.2.6 PAEDIATRICS AS A USER GROUP

Every child has a different rate of development dependent upon various influences. As such paediatric patient-specific dosing is often calculated by body mass. This mass-based dosing is particularly important for drugs with a narrow therapeutic index and in young children where dosing must be carefully considered (EMA 2006a).

Despite physical differences between adults and children often being obvious, these are key considerations during medical device D&D. Designers must ensure that they have considered the anthropometric and biomechanical profile of the child user to ensure a safe and effective medicines and administration device are created.

The minimum age for which a formulation is appropriate is a key consideration. It is likely that different formulations or administration routes are more or less appropriate for different aged children, for example, Riet-Nales et al. (2014) found that mTs were the most accepted DF in pre-school aged children in the Netherlands, whilst EMA (2006a)

highlights cultural differences in DF preference, such as liquorice flavourings being preferable in Scandinavia for example.

An individual's knowledge and perception of medicines will also alter with age. Bozoni et al. (2006) found that whilst children had a strong belief in the curative power of medicines, their limited knowledge on prevention and the easy accessibility to household medicines raises serious concerns. They found there to be socio-economic differences in knowledge of medicines, further supporting the need for school-based health education programmes.

The illness, treatment and condition must also be considered, along with condition-related characteristics such as physical or mental disabilities, poly-pharmacy and any elements of dysphagia. For example, Modi and Quittner (2006) identified barriers to treatment adherence for children with CF and Asthma. They found that barriers were quite similar by illness and informant (e.g. parent and child) for the same treatments, but unique barriers were identified for disease-specific treatments. Frequently mentioned barriers across diseases included forgetting, oppositional behaviours, and difficulties with time management. Trends were identified between adherence and barriers, suggesting that a greater number of barriers were related to poorer adherence.

School policy surrounding medication administration is somewhat varied and inconsistent. Further research into school-based medicines education would be beneficial (Costello et al. 2004).

The use environment should also be considered, whether this is school, home or a hospital for example. Bitterman (2011) looked specifically at the key considerations when designing medical devices for use in the home. He highlighted the importance of considering the device context of use during D&D in an effort to reduce use errors and improve patient outcomes.

Given that young children are likely to depend on their CG for medicine administration, it is important to consider the interaction of the CG with the medicine, the administration device (if required) and with the child. For example; What are the characteristics of the child and the CG? How do they each behave? Is the medicine acceptable? How easy is the medicine to administer? Is the device easy to operate? Can the child progress to using it alone? (EMA 2006a; 2013). These relationships can be described

by the 'onion model' which considers the users' relationship with others, to their surroundings and to the wider use environment (Wilson and Sharples 2015).

As they get older, children will likely progress to independent medicine use. Key considerations then include the practice of self-medication, medication management and the child's knowledge and perceptions of medicine use. Pfaffenbach et al. (2010) investigated Self- Medication (SM) amongst children and adolescents. They described a global pattern of SM in children and adolescents, as well as discussing public policies aiming to promote health interventions and strategies to prevent SM. Shehnaz et al. (2014) highlighted the need for responsible SM education to minimize the potential for adverse effects.

Understanding the links between various factors promoting SM can be helpful in deriving strategies aimed at reducing drug-related health risks among adolescents. These will aid in creating awareness among adolescents about the potential risks of using drugs without proper information and consultation.

Costello et al. (2004) found that treatment compliance and adherence is generally lower in children than in adults, particularly in adolescents as they approach independence.

An element of training, education and awareness appears key as children move towards managing their own medications. Young people need appropriate parental and professional support in taking control of their medication and treatment (Costello et al. 2004). An understanding of paediatric psychology as compared to adult is also important in ensuring effective and appropriate medicine administration.

Dean et al. (2010) found that education interventions alone are insufficient to promote adherence in children and adolescents, and that incorporating a behavioural component to adherence interventions may increase potential efficacy.

Hu et al. (2013) investigated the effectiveness of educational programs with oral antibiotic suspensions for paediatric use. They demonstrated that, when compared to reading a package insert or education sheet, a pharmacist's verbal education with photographic education materials was

significantly more effective and timesaving in providing CGs with the correct knowledge of oral antibiotic suspensions. This provided guidance as to the likely best practice when imparting similar knowledge on to children and adolescents.

1.3 SUMMARY AND IDENTIFICATION OF KNOWLEDGE GAPS

This literature review has highlighted a number of knowledge gaps, the main one being the lack of a marketed device capable of repeated, flexible MP dosing to children. Within this, there are more specific gaps in knowledge relating to Formulation, User and Device.

1.3.1 FORMULATION

Little is known about the appropriateness and acceptability of MP formulations in paediatrics. As such, ongoing research aims to address the palatability of MPs and the most appropriate means for their administration. Whilst the addressing of these acceptability issues is beyond the scope of this research, it is appreciated that the outcomes of other research will prove influential upon the design of an MP dosing device, in terms of dosing volumes and administration method for example. Here, Formulation characteristics are considered with respect to their likely influence upon the device design in the answering of RQ1: What are the requirements of the Formulation?

1.3.2 USER

As child involvement in research can prove difficult it is often limited. This means that there is little knowledge of child and CG perceptions of medicine administration and of oral medical devices. Including areas such as, medicine use in the home, ease of use perceptions and what factors influence device use. Here, a UCD approach has been taken to enable the design of a child-friendly, acceptable MP dosing device. By addressing RQ2: What are the requirements of the User(s)? These knowledge gaps begin to be addressed with user insight used to guide device D&D.

1.3.3 DEVICE

Whilst a few patents have been filed capable of repeated, flexible (to some degree) MP dosing, mass-based dose determination is fairly novel despite the relative advantages over volumetric methods in terms of accuracy. Here, the possibility of having a mass-based MP dosing device is explored alongside the development of device concepts that fulfill both the formulation and user needs (RQ1 and 2). This in turn, allows the answering of RQ2: What does this mean for Device design?

This thesis presents key factors important to consider during the D&D of an MP dosing device capable of repeated flexible dosing to the paediatric population. By addressing Formulation, Device and User in turn, knowledge gaps are addressed through the answering of each of the three RQs. A case study is used to highlight a potential use for an MP dosing device and allows for requirement refinement based on an example patient population.

1.4 RESEARCH QUESTIONS

In order to understand the key influential factors in the design of an MP device for children, the three Research Questions (RQs) shown in Figure 1.8 were considered.

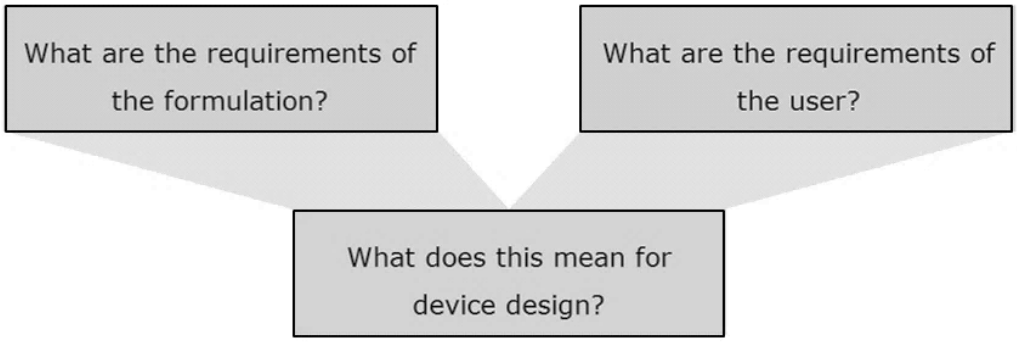


FIGURE 1.8 THE THREE RQS ADDRESSED BY THIS THESIS

1.4.1 WHAT ARE THE REQUIREMENTS OF THE FORMULATION?

The medication contained within a medical device (as part of a combination product) will influence the device design. Key features of the MP formulation were therefore considered and their influence on device design appreciated.

1.4.2 WHAT ARE THE REQUIREMENTS OF THE USER?

User-Centered Design (UCD) is vitally important in the generation of an acceptable product. Key users were approached and their opinions of currently available devices sought. These users also engaged in participatory design studies to allow for further comprehension of important user requirements. A case study was performed to allow for an understanding of specific user requirements in an example patient population.

1.4.3 WHAT DOES THIS MEAN FOR DEVICE DESIGN?

The User and Formulation requirements elicited in Chapters 3 and 4 provided insight into the MP dosing device specifications. Chapter 5 serves to conceptualise devices fulfilling these requirements through research into currently available devices and mechanisms.

These three RQs were addressed in various chapters, as shown in Table 1.5.

TABLE 1.5 WHERE ARE THE RQS ADDRESSED?

RQ	Chapter			
	3 Formulation	4 User(s)	5 Device	6 Case study
What are the requirements of the Formulation?	X		X	X
What are the requirements of the User?		X	X	X
What does this mean for Device design?			X	X

1.5 THESIS ORGANISATION

This Thesis considers the requirements of the Formulation and of the User, before bringing these together as a device specification, Figure 1.9.

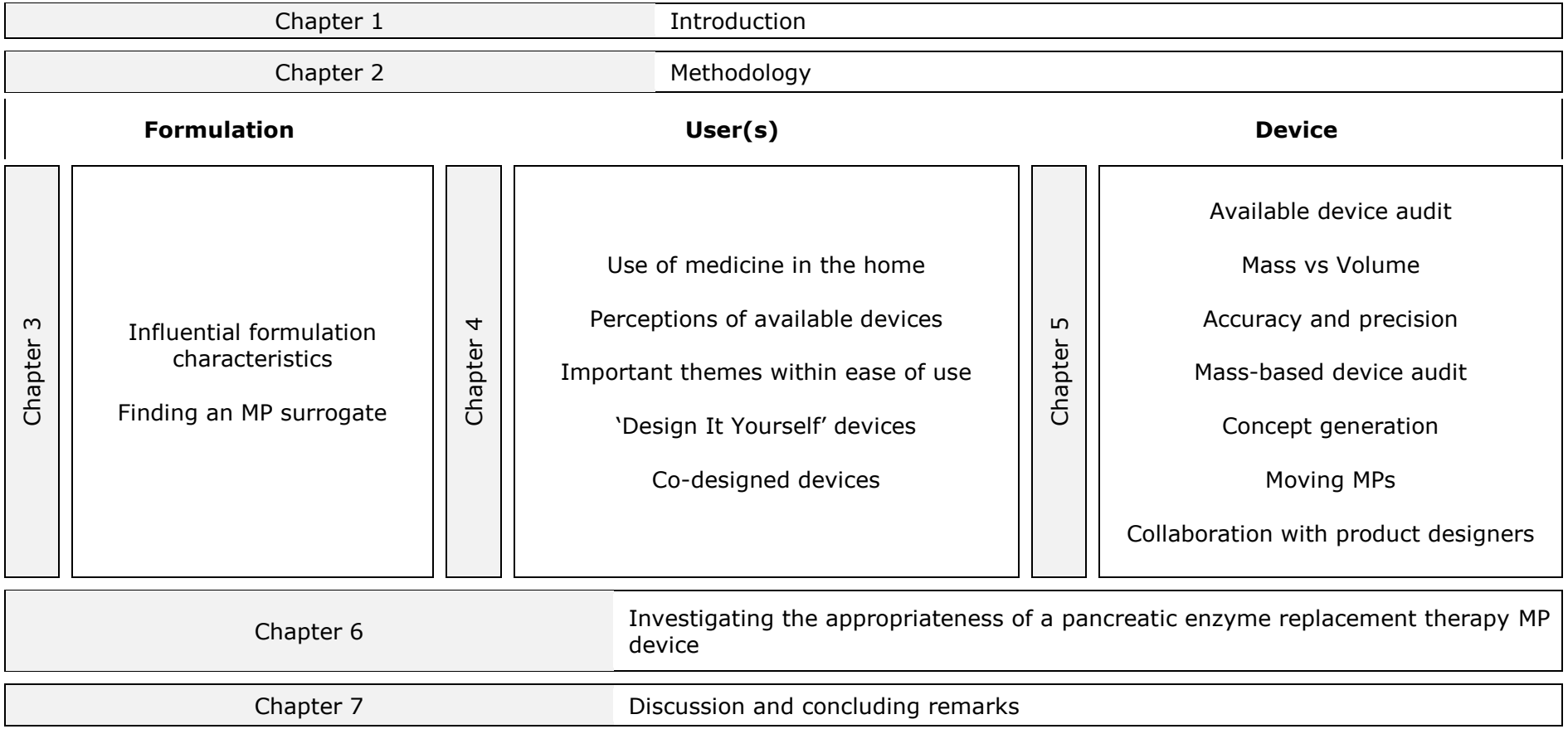


FIGURE 1.9 THESIS STRUCTURE

As per the structure shown in Figure 1.9, a summary of each of the chapters is detailed below.

1.5.1 Introduction

A broad overview is given of the research space and the rationale for this work is presented. Before, a literature review reviews and critically analyses previous and on-going work in the field is. Current state of the art is demonstrated and key knowledge gaps highlighted.

1.5.2 Methodology

The overall approach used in this research is presented with specific details of each method used.

1.5.3 Formulation

Key formulation characteristics important in device design are considered. A number of MP - like formulations are investigated for their appropriateness for use as an MP surrogate in lieu of the final Pfizer product.

1.5.4 User(s)

Four studies investigating experiences of paediatric medicines in the home, opinions of currently available devices, ease of use and child-centered device design are presented.

1.5.5 Device

A variety of currently available devices are investigated for their appropriateness of handling MP-like formulations. Mass-based methods are compared with volumetric, and a consensus of using mass-based means established. Devices capable of achieving the accuracy and precision required are dismantled and their mechanisms understood before device concepts are generated. The outcomes of a collaborative project with undergraduate product designers are presented before further consideration is made towards mechanisms for moving MPs.

1.5.6 Case study

Having considered the 'global' requirements of the formulation, the user(s) and the device in chapters 3 – 5, the final results chapter considers user-specific requirements of an MP dosing device in an example patient population. The Cystic Fibrosis (CF) patient population was selected given their familiarity with an MP-like formulation as part of their Pancreatic Enzyme Replacement Therapy (PERT).

This study is presented separately as an example case study of how the findings from the preceding three chapters can be applied to specific conditions and to particular patient populations.

1.5.7 Discussion and Conclusions

The findings of this research are summarised with respect to knowledge gaps. Limitations are addressed and considerations are made for future work.

CHAPTER 2 - METHODOLOGY

2.1 INTRODUCTION

To investigate factors influencing the design of a paediatric MP device, three key areas were examined and each of the RQs addressed, Figure 2.1.

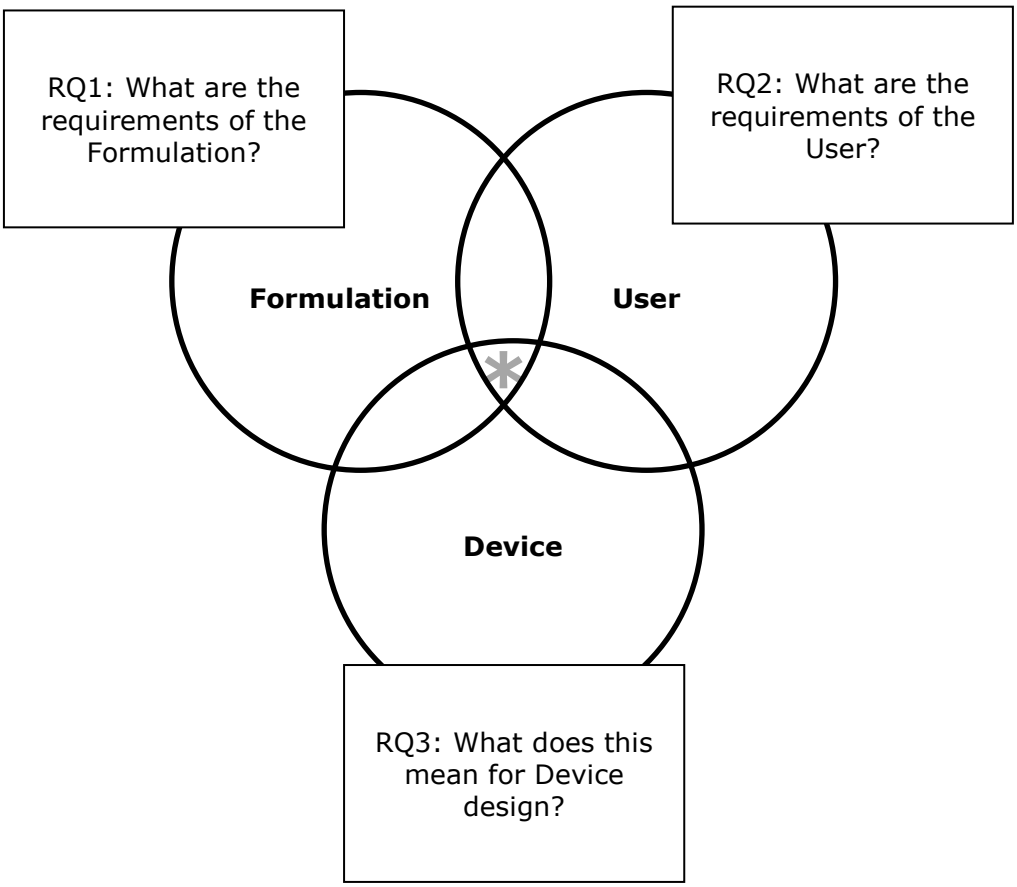


FIGURE 2.1 KEY CONTRIBUTORS IN THE DESIGN OF AN ACCEPTABLE MP DOSING DEVICE (*)

Considering Formulation, User and Device in turn allows for an appreciation of their influences on the design of a medical device. Whilst each of these three areas can have independent results, it is the compilation of these findings that underpin optimal device design.

Figure 2.2 summarises the 12 studies completed to understand the factors influencing the D&D of a platform MP technology. The methods used in each of these studies are discussed below with the results presented in the

three chapters that follow. A case study is presented in Chapter 6 investigating the potential use of an MP dosing device by the CF population, the survey method used is presented below.

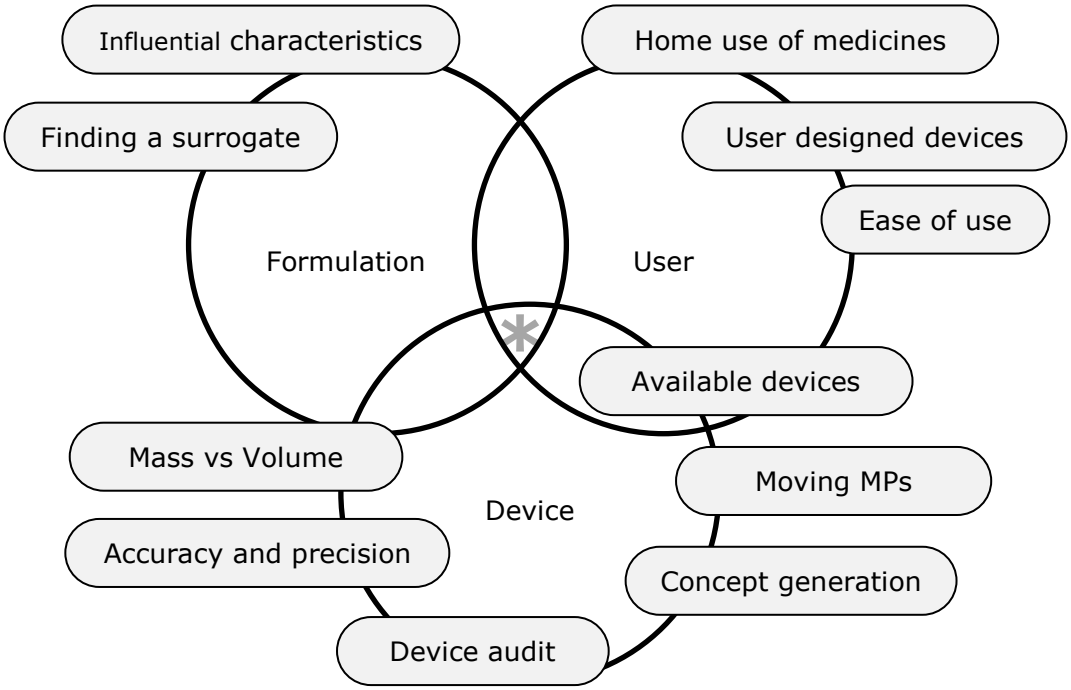


FIGURE 2.2 KEY STUDIES PRESENTED IN THIS THESIS

2.2 FORMULATION

MPs are currently investigated for their acceptability for use in paediatric patients across a range of indications and age groups. Like other pharmaceutical companies and research groups, Pfizer (the PhD's industrial partner) continue to refine and optimise the manufacture of their MP formulations. In lieu of a final marketed product, the formulation work (Chapter 3) focuses on the influences the MP formulation will have upon device design and the identification of a suitable MP-surrogate for D&D.

2.2.1 IDENTIFYING INFLUENTIAL FORMULATION CHARACTERISTICS

Early scoping work included discussions with Pfizer as a manufacturer of pharmaceutical products and combination devices. Discussion topics included the MP product specification, ranges of key parameters and their own stakeholder requirements. Following these discussions, considerations

were made as to how each of these formulation requirements will impact device design.

2.2.2 IDENTIFICATION OF AN MP SURROGATE

A surrogate MP-like formulation for use during device prototyping and testing was identified though characterisation of four different MP-like formulations: placebo MP sample; Glass beads; Hundreds and Thousands (H&Ts) and Cellets® (marketed Microcrystalline Cellulose, MCC spheres). These four samples were investigated given their likeness to the ideal MP, Table 2.1.

TABLE 2.1 SURROGATE MP FORMULATIONS INVESTIGATED

Reason for selection	 Placebo MPs	 Glass beads	 H & Ts	 Cellets®
Size	Similar to specification	Larger than specification		Different sizes available – similar to specification
Shape	Appear largely spherical upon first inspection			
Dose range	Given their multi-unit nature, all samples could be amenable to small dosing increments			
Density	Similar to specification given the likeness to the final MP product	Likely more dense than specification	Similarity to pharmaceutical (sugar content)	Similar to specification - Use in pharmaceutical development
Other	Improved safety profile over drug-loaded samples for use during device development		Readily available	
Supplier	Pfizer, Sandwich, UK	Creative expressions, Kettering, UK	Jane Asher's Kitchen, UK	Cellets®, Germany

Each sample was characterised by size, flow, morphology and mass given the importance of these features upon device design (as discussed in 2.2.1).

2.2.2.1 SIZE

LASER DIFFRACTION

A Helos KR or QicPic (Sympatec, Germany), gradis and vibri set-up were used. An 'M7' lens was chosen, capable of detecting particle size (diameter) between 10 and 3410 µm and a pressure of 1 bar set. Riffling was performed using a Retsch PT100 + DR100.

2.2.2.2 FLOW

BULK AND TAPPED DENSITY

Sample tapping was performed using a Copley SVM22. The sample was weighed and volume recorded pre and post tapping. If density change was not less than two percent, further taps were performed until it was. The compressibility index was calculated.

$$\text{Compressibility index (C)} = \frac{(\rho \text{ tapped} - \rho \text{ bulk})}{(\rho \text{ tapped})} \times 100$$

2.2.2.3 MORPHOLOGY

OPTICAL MICROSCOPY

Placebo samples were viewed naturally in silicone oil using a range of magnifications at Pfizer, Sandwich, UK. The remaining three samples were imaged dry in a glass petri dish (Leica MZ16 stereomicroscope with polarizer and Leica EC3 digital colour camera).

2.2.2.4 MASS

WEIGHING ON CALIBRATED REFERENCE BALANCE

Single pellets and batches of 100 glass beads and H&Ts were weighed using a Mettler Toledo AB265-S/FACT balance using a milligram setting to two decimal places.

In the case of the Cellet® sample, weighing of single pellets proved troublesome given their small size, and the difficulty in handling, batch data was therefore recorded. Batch mass was measured using a glass petri dish; weighed empty and when loaded with Cellets®. Subsequent imaging and counting of the number of Cellets® (by eye) allowed for an estimation of the individual Cellet® mass.

The mean pellet mass and standard deviation are presented to provide an indication of the average pellet mass, and the variation of mass within the weighed sample. Where batches of pellets have been weighed, the standard error is presented to demonstrate the variation of pellet mass within the total pellet sample, across all batches.

Placebo MP mass was not recorded given that the sample had already been excluded from consideration for device prototype development due to the infancy of its manufacturing process.

2.3 USER–CENTERED DESIGN

A mixed methods approach was chosen as an inclusive process, to ensure that the needs, wants and priorities of various stakeholders were explored, understood and incorporated into findings relevant for industry. Stakeholders included: Pfizer (as pharmaceutical manufacturer), children, CGs and patients. Specific methods were selected to suit the different user populations, aims of the study and the nature of the interaction with users.

Given the potentially vulnerable nature of the paediatric population it was important that any interaction with this group were appropriate in terms of the children's cognitive and emotional abilities (Kroemer 2005). For example, could the children read the questions? Would they understand the research area? How was it best to introduce the research to them? How would their interest be sparked and sustained throughout the activity? To address these areas, all study materials were submitted to an online Flesch-Kincaid test to ensure the reading age was below that of the sample population (Flesch 1948). Each study was also piloted with a young person to check comprehension and understanding of the research area and what was expected of them.

The researcher used their role as a Science Technology Engineering and Mathematics (STEM) ambassador and British Science Association (BSA)

volunteer to provide data collection and public engagement opportunities. Studies were often planned based on upcoming events, liaising/linking-in with a broader public engagement group.

All studies were approved by the School of Pharmacy's or the Faculty of Engineering's Research Ethics Committee. All data collected was anonymised and treated confidentially. Electronic data was encrypted and stored on a password protected computer whilst paper copies were stored in locked cabinets.

Table 2.2 summarises the user-based studies performed as part of this work, detailing the method used, the outputs of the studies, the analysis method employed and the context in which the study was performed.

While traditional HF studies require 15 participants of each distinct user group (ISO 2016), given the early nature of this research, a target sample size was not defined, with a view to gaining as much insight as possible. Where possible, greater than 15 users have been recruited.

TABLE 2.2 SUMMARY OF USER-BASED STUDIES

		Study context	Analysis method	Outcome(s)	Thesis location	
Method	Semi-structured interview	**Café Connect, Nottingham** Pop-up Research Café organised by a multidisciplinary, cross-faculty initiative at the University who's key focus is the interaction and engagement with public to initiate new ideas for future research.	Thematic analysis	Increased understanding of paediatric medicine use in the home, including common challenges during administration, storage and use environment as well as consideration of child self-administration.	Chapter 4	4.1 Experiences of medicines in the home (page 69)
	Picture-based questionnaire	**Think Tank, Birmingham** University of Birmingham (UoB) organised local clinical trial at Think Tank, Birmingham investigating paediatric palatability and acceptability of MP formulations. **School-based activities, Nottingham, UK** Two Nottinghamshire based schools interested in public engagement/ STEM outreach opportunities.	Frequency counts and Thematic analysis	Insight into user perceptions of currently available oral devices, including devices used for oral liquid medicines as well as devices for confectionary. Greater appreciation of the factors influencing device preferences, comfort with use, ease of use and interest in use.		4.2 Opinions of currently available devices (page 79)
	Pairwise comparison	**Big Bang Fair, Derby** The Big Bang UK Scientists & Engineers Fair is the largest celebration of STEM for young people in the UK. The event aims to show young people (primarily aged 7-19) the exciting and rewarding opportunities available.	Frequency counts	Greater understanding of the key themes within ease of use through interaction with both children and CGs.		4.3 Ease of use (page 89)
	Workshop and worksheet	**Fun Palace, Mansfield** Fun Palaces are a national movement promoting community at the heart of culture, with events of arts and science action created by, for and with local people. Their ethos being 'everyone an artist, everyone a scientist'.	Thematic analysis	Further insight gained into influential factors upon device design through the co-design of MP dosing devices with children.		4.4 Designing a medical device for Katy (page 94)
	Online survey	**Bristol Online Surveys** Co-designed online survey in collaboration with clinical CF staff at the Queen's Medical Centre (QMC) Nottingham to investigate Formulation, User and Device requirements in an example population. The survey was disseminated globally via social media.	Frequency counts and Thematic analysis	An appreciation of a possible MP dosing device application was achieved, with insight into the users likelihood of using such a device, the factors influencing that use and where a device may help the users.	Chapter 6	6.1 CF and PERT (page 149)

Using Table 2.2 as a base, each of the methods/approaches, analysis methods and study contexts shall be further described.

2.3.1 METHODS AND APPROACHES USED

2.3.1.1 SEMI-STRUCTURED INTERVIEWS

METHOD CHOICE RATIONALE

Given the rather fluid nature of likely interactions during a science café event (with many people coming and going eating snacks and drinking coffee) a semi-structured interview was deemed most appropriate (Wilson and Sharples 2015). To allow for a more 'natural discussion', improve eye-contact and limit potential barriers between the researcher and participant, the interviews were voice recorded with subsequent verbatim transcription allowing for detailed data analysis.

This interviewing technique allowed for a flexible approach to the enquiry topics whilst also complementing the participants other time commitments. Interviews also allowed for in depth probing of key areas dependent on the discussion content compared to questionnaires for example (Wilson and Sharples 2015).

RECRUITMENT AND CONSENT

Participants were approached at the public event and given a short introduction to the project prior to being invited to participate in the study. If a positive response was provided then participants were enrolled through the formal consent process. Example information sheet and consent form are contained within the Appendix 1, page 193.

DEFINITION OF RESEARCH AIMS

The interviews investigated two key areas affecting the administration of paediatric medicines in the home; medicine administration and medicine management (as determined by literature review and an understanding of UCD). The aim of this activity was to gain a greater understanding of device use, challenges in use, challenge resolution, environment of use and storage conditions so that a design specification which better meets the needs of the users in the home environment can be developed.

STUDY DESIGN

To investigate the administration of medicines to children in the home, participants were asked about any regular medications the child receives, and should they not be regularly medicating they were asked to think of the most recent medicine administration. CG and child behaviour was investigated along with context of use, associated enquiries were also explored, Table 3.3. CGs were also asked about any challenges they faced during the administration process, how these were overcome at the time and what could be done to improve this situation. Table 2.3 shows the interview plan based on investigation of medicine administration and management. These areas were identified for enquiry due to their role in the medicine administration process and management and their likely influences, as highlighted by literature review and an understanding of UCD.

TABLE 2.3 INTERVIEW SCHEDULE

High level interview topics		Interview questions
Personal information		Name Relationship to child(ren) Other children not present? Any regular medications?
Medicine administration	Most recent	Type of medicine? Thoughts? How did they administer it? Device use? Any manipulation?
	Administration method	How do they medicate usually? Who does the administering?
	Self-administration	Would you be happy with the child doing it all themselves? Why or why not? At what age?
Environment		Where are medicines administered? Why are they administered there?
Challenges		Any challenges or barriers? How did they overcome these? How could the situation be improved?
Management		Where are medicines stored? Why are they stored there?
Closing remarks		Thank you Prize draw

STUDY EXECUTION

Having read and understood the information sheet and having completed the consent form, the CG was notified that the recording would begin. Initial discussions began by the researcher asking "Do any of your children take medicines every day?" The discussions were then very much led by the participant's response to this question. The interview plan was referred to when ensuring key topics were covered or to probe further into particular topics.

2.3.1.2 PICTURE-BASED QUESTIONNAIRE

METHOD CHOICE RATIONALE

A simple tick box picture-based questionnaire was designed given their appropriateness for simple and timely completion (Wilson and Sharples 2015), particularly important for children participants (Bell 2007).

RECRUITMENT AND CONSENT

THINK TANK, BIRMINGHAM

Naïve CGs (having not ingested an MP-like formulation) and Experienced Children (EC) were recruited following their participation in a clinical trial (UoB) which looked at the acceptability and palatability of an MP-like formulation. Once the CG had expressed interest in the study they were provided with an information sheet and asked to complete a consent form (as during the interview work) before beginning the questionnaire.

SCHOOL-BASE ACTIVITIES, NOTTINGHAM

Naïve Children, NC (having not ingested the MP-like formulation) were recruited as part of a STEM outreach opportunity at two local Nottinghamshire (UK) primary schools. Both schools were suburban and had 'Outstanding' Ofsted rankings, this suggests the participant sample were from an above average socio-economic status and were well-educated (Ofsted 2017).

The school was supplied with copies of the information sheet and consent forms for circulation to the pupil's parents. These were completed and

returned to the teacher (and subsequently the researcher) prior to the activity taking place.

Definition of research aims

The aim of these studies was to investigate user preferences of widely available medical devices alongside 'other' devices which are capable of dispensing consumable items, and uncommonly used with medicines. By studying influential factors affecting users, a consensus on dispensing and administering this DF could be achieved.

Study design

Based on a literature search of paediatric and MP delivery devices both marketed and in development (included in part in Chapter 1), the 16 devices shown in Table 2.4 were selected for investigation. These include those typically used for liquid medicines, such as the Measuring cup and Single ended spoon, as well as those devices more commonly used for confectionary such as PEZ dispensers and Smint dispensers.

The 'medical' devices were selected for their common use in administering medicines as well as their potential appropriateness for administering the MP like DF. A range of devices were selected to cover an array of different device types, as well as a number of similar ones which differed only slightly, to elicit reasoning when distinguishing between them.

'Other' devices were selected based on their aesthetic, form or mechanistic similarity with MP devices in development and their likely appropriateness to handle MP-like formulation; again, different aesthetics were selected to detail specific choice reasoning.

Questionnaires were designed to address the key aims. They comprised of a series of picture-based tick box exercises with open-ended questions to elicit reasoning behind choices.

Questions were designed to explore familiarity and user perceptions (including asking participants to select the best and worst device). Familiarity was investigated given literature suggesting it can impact user decisions and experiences (Birch 1979; Park and Lessig 1981; Aldridge et al. 2009; Mustonen et al. 2012). User preferences were asked about to gain a broad appreciation of their perceptions of currently available

devices, with the qualitative reasoning providing further insight for device design.

A refined picture-based questionnaire was used created for school-based activities given an increased understanding of influential areas, and the limited opportunity to gain further detailed user insight using the initial lines of questioning. Table 2.5 shows an example of the refinements.

A copy of the questionnaire can be found in Appendix 2, page 196.

TABLE 2.4 THE 16 DEVICES INVESTIGATED

'Medical' devices		'Other' devices		
Measuring cup		PEZ dispensers	Elsa	
Single ended spoon			Storm-trooper	
Double ended spoon			Two eyed-minion	
Teaspoon			One-eye minion	
Measuring spoon		Smint		
Syringe		Bubble gum		
Medicator		Circle		
Dummy		Straw		

TABLE 2.5 QUESTION REFINEMENT

Questionnaire 1		Questionnaire 2
Thinking of the particles you just tried, which one would be the BEST/WORST way to take them? (✓)	→	Which of these would you be comfortable using on your own? (✓)
		Can you order these from easiest to use (1) to the hardest to use (8)?
		Thinking of the new medicine, which one would be the MOST/LEAST interesting way to take them? (✓)

The second questionnaire followed the same format as the first with further questioning based around ease of use, interest in use and comfort with independent use, Table 2.5. These three areas were selected for investigation given their importance in device use. The age at which children begin self-administering is somewhat subjective based on personal development, parental guidance and upbringing. Chambers et al. (1997) found that children began self-administering pain medication at the age of 11-12 years. However, this age will likely differ based on the medication type, dosing frequency and individual differences.

Both questionnaires closed with a 'design it yourself' (DIY) activity where the users were invited to conceptualise a device capable of handling the free-flowing MP 'medicine'. This activity was included to understand the user preferences further, and to gain further appreciation of influential factors aside from those enquired about during the questions.

The questionnaires' wording was deemed suitable for the 4-12 year age group through submission to online 'readability' software (Flesch 1948). The same wording was used for both children and adults to reduce the likelihood of the language causing any differences in response. The researcher was also on hand during all studies should any further explanation of the question or study in general be required.

STUDY EXECUTION

THINK TANK, BIRMINGHAM

Following an interest in the study, reading of the information sheet and completion of the consent form, CGs were asked to complete the

questionnaire whilst the child in their care completed the UoB clinical trial. Both studies were completed in the same room, with CGs having eye-sight of their child at all times.

Participants were provided with pens and pencils to complete the questionnaire and the exact devices asked about were displayed on a table, to limit confusion and allow for participant interaction, Figure 2.3.

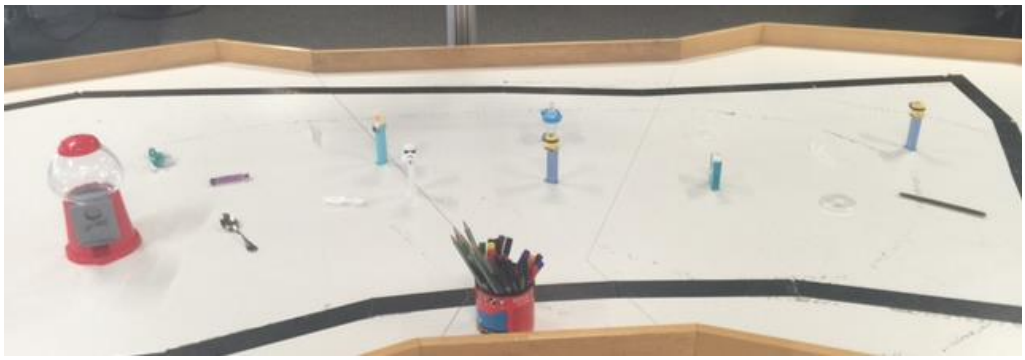


FIGURE 2.3 EXAMPLE STUDY SET-UP (THINK TANK, BIRMINGHAM)

The activity took approximately 20-30 minutes to complete, with children then completing the questionnaire following their involvement in the clinical trial. CGs were asked to sit on a table adjacent to their child so as to limit their influences upon the child's response. This request however, was not always followed, with some CGs aiding their child with the completion of some questions.

Upon completion of the activity participants were asked to explain their DIY device to the researcher if they wished. They were subsequently thanked for their time and contributions.

SCHOOL-BASED ACTIVITIES, NOTTINGHAM

Given the public-engagement/educational nature of this interaction and the greater time allowance of three hours, the researcher developed a presentation (Appendix 3, page 197) to introduce the children to the research area in more detail and to guide the whole class through the questionnaire one question at a time, with learning reflections at the end.

Table 2.6 shows the main themes introduced to the participants during the activity. Popular solid and liquid DFs were discussed and the concept of MPs introduced. Being naive users (having not experienced the MPs

before), the DF was introduced as miniature medicated cake sprinkles, something the children were familiar with. The potential benefits of the DF were discussed with respect to swallowability, taste masking and flexibility in dosing for example. The requirement of a device to handle and administer this DF was introduced with eight 'medical' and eight 'other' devices presented to the children. All devices were available on the table for interaction and were also demonstrated one at a time by the researcher to show their typical use. Classroom discussion was encouraged relating to children's experiences of medicines, familiarity with devices and their opinions. The session utilised Post-it® note activities to further engage the pupils, with their reasoning for device choices written on Post-it® notes before being stuck onto /an image of the device they wrote about. Different Post-it® notes were used to distinguish between the most (green) and least (pink) interesting device as shown in Figure 2.4.

TABLE 2.6 ACTIVITY THEMES

	Concept
1	Broad introduction and discussion of medicines, the children's experiences of these and the possible advantages and disadvantages of different DFs.
2	The MP-like formulations were introduced as 'miniature cake sprinkles' and the relative advantages over traditional DFs explained.
3	Dosing flexibility was introduced and its importance discussed.
4	The need for a device to handle the MP-like formulation was demonstrated to the class.
5	Each of the 16 devices was presented to the children with a brief explanation/discussion as to how they are traditionally used.
6	Questionnaires were completed, question-by-question as guided by the researcher.
7	Session closed with final remarks and a 'quiz' to check pupils understanding of the content covered.

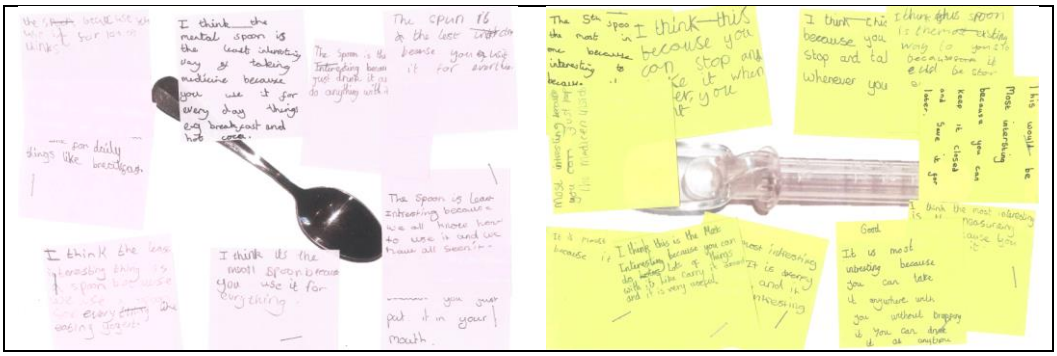


FIGURE 2.4 POST-IT® NOTE ACTIVITY

2.3.1.3 PAIRWISE COMPARISON SURVEY

METHOD CHOICE RATIONALE

A pairwise comparison grid was selected given that the interaction opportunity with participants would likely be brief. This was key in ensuring as much data as possible was collected in a short time period before participants lost interest or became fatigued (Wilson and Sharples 2015).

The pairwise comparison grid allowed for comparison of key areas with one another, with completion of the grid allowing ranking of the key areas compared (Wilson and Sharples 2015). This method provided an opportunity to collect data rich information in a relatively quick and easy manner.

RECRUITMENT AND CONSENT

Participants were recruited as they circulated the STEM, 'Big Bang Fair' event held in Derby (UK). Participants (pupils and CGs/teachers) were invited to complete the survey following an initial interaction at the event with the researcher or another STEM member from the University. Participants were asked if they wanted to be involved in 'real life research' or by engaging them in conversation about the devices displayed. Given that all data collected at this event was anonymous, assent/consent from participants was given through their completion of the survey.

DEFINITION OF RESEARCH AIMS

The aim of this study was to investigate eight key themes within 'ease of use' (as suggested by literature) using a pairwise comparison method. This

study provides insight into what are the key considerations when designing and developing a device, specifically ease of use.

STUDY DESIGN

The eight key themes of; Aesthetics, Familiarity, Little chance of error, Pre-measured dose, Simplicity, Size, Speed and Steps from bottle to mouth were investigated. These themes were selected based on previous work with participants where 'ease of use' was considered an important consideration. These factors were commonly cited in literature as being important within the broader usability theme (Quesenberg 2001; Rubin and Chisnell 2008).

Figure 2.5 shows the pairwise comparison grid completed by participants. This was preceded by an explanation of the wider research area, and what was expected of them in terms of survey completion (a copy of the full survey can be found in Appendix 7, page 207).

Participants were also asked about who administers medicines to them/the child in their care using a short multiple choice question. This was to begin to comprehend the likely age of self-administration and consequently the age of user for a medical device.

Theme		2 Little chance of error	3 Size of device	4 What the device looks like	5 How simple the device is to use	6 How quick the device is	7 If you are familiar with the device	8 Number of steps from bottle to mouth
1	Dose already measured	1 2	1 3	1 4	1 5	1 6	1 7	1 8
2	Little chance of error		2 3	2 4	2 5	2 6	2 7	2 8
3	Size of device			3 4	3 5	3 6	3 7	3 8
4	What the device looks like				4 5	4 6	4 7	4 8
5	How simple the device is to use					5 6	5 7	5 8
6	How quick the device is						6 7	6 8
7	If you are familiar with the device							7 8

FIGURE 2.5 PAIRWISE COMPARISON GRID

STUDY EXECUTION

A stall was set-up as part of the science event, Figure 2.6. Incentives for study participation were provided in the form of lolly-pops alongside a large poster explaining the study, an information sheet of sorts (Appendix 8, page 210). Figure 2.6 shows how the surveys were provided to participants on clip-boards to make their completion easier, and a box for completed surveys also provided.

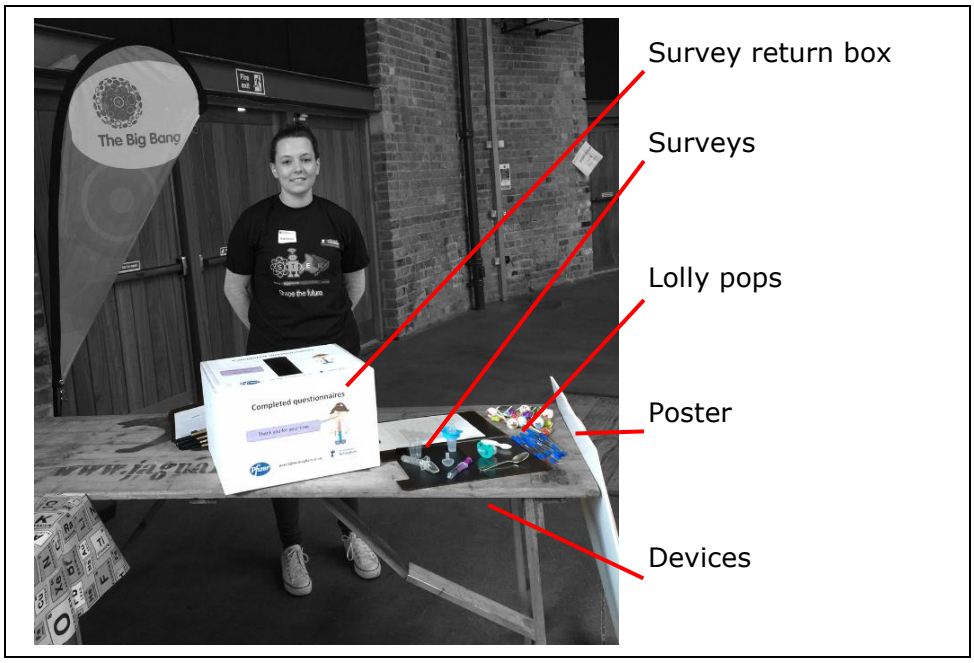


FIGURE 2.6 BIG BANG FAIR STUDY SET-UP

Participants had the research introduced to them through the devices on the stall, the poster and via discussion. Once they had agreed to partake in the study they were provided with a survey (on a clipboard) and pen. The grid was consequently explained to them by the researcher alongside instructions provided on the survey sheet.

Upon completion of the grid the researcher thanked the participant for their time, offered them a lolly and placed the completed form in the survey box.

Pooling of all complete responses allowed the researcher to rank the key areas in order of importance for both the child and caregiver groups.

2.3.1.4 STORYTELLING AND CO-DESIGN ACTIVITY

METHOD CHOICE RATIONALE

A persona and story were created to engage the children and to convey complex information in an appropriate way (Wilson and Sharples 2015). The creation of a story allowed for child engagement with a variety of detailed research areas, whilst providing an understanding of the work (Quesenberg and Brooks 2010).

The researcher created a persona 'Katy' and developed a story book (and video) for use in explaining the research topics to young people. This design method was chosen given it's suitability for use with children as demonstrated by Coulter et al. (2007) and its documented success at exploring and understanding user needs (Moggridge 1993; Joe 1997). The researcher told the story of Katy using a picture book they created (Appendix 9, page 248). Children were then invited to 'help Katy' though the design of a medical device.

This idea of getting children to design their own device builds upon the 'DIY task' used as an extension activity during the Think Tank and School-based events. The concept of co- or participatory design has been shown to aid public engagement with design helping to identify design options and direction as well as in creating and refining specific design solutions (Pedersen and Buur 2000). It was used here to gain further insight into the device requirements of paediatric users.

Recruitment and consent

Participants were self-selecting during their interaction with science engagement activities at a 'Fun Palace' event held at Mansfield Library, UK. The workshop was publicised through the event's front desk where participants were invited to partake in the workshop, natural footfall also supplied further participants. Workshops were run periodically throughout the day or when sufficient numbers were present.

The activity was briefly described, before the information sheet and consent forms were circulated to all CGs for completion during 'story time'.

Definition of research aims

The aim of this study was to comprehend factors influencing children's device design. The children were introduced to the research area in detail through story time.

Study design

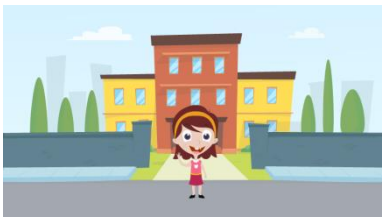
Creation of Katy's story

The researcher created the Katy persona based on their knowledge and experiences of young children and well as their understanding of the

research area. Having appreciated the child-friendly nature of this medium, the researcher created both a picture book and video of the story.

The storyline of Katy's story is presented in Figure 2.7.

a



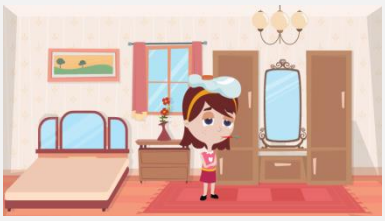
Katy's character introduced

b



Katy's hobbies described

c

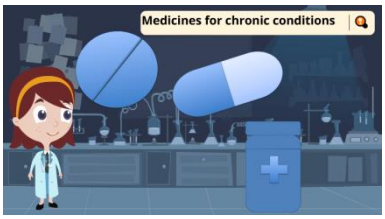


d



Katy's chronic condition explained as requiring regular medication everyday

e



Katy has tried many different DFs and faced struggles

f



MPs as a novel DF introduced

g



Requirement of an MP device explained

h



Flexibility of administration method

i



Example medical devices shown

j



Children invited to help Katy through design of a medical device

FIGURE 2.7 KATY'S STORY

SELECTION OF QUESTIONS

Worksheet questions were created based on outcomes of the three previous studies alongside the aim to further understand the children's design choices. Questions probed: why the device was designed the way it was; how it would work; who would use the device; where they would use it and what makes it appropriate for use in that environment and by them, Table 2.7.

A copy of the worksheet can be found in Appendix 10, page 212.

These enquiries provided a greater understanding of factors influencing child device design. This understanding aids the D&D of MP devices for children.

TABLE 2.7 WORKSHEET QUESTIONS

Topic	Questions
Device design	Why have you designed your device to look like this?
	Is your device based on something you have seen or used before?
Device mechanism	How does your device work?
	How does your device make sure it doesn't spill the medicine?
	How does your device measure the right amount of medicine?
Who is the user?	Who would use your device to administer the medicine?
Katy's use of the device	What about your device makes it good for Katy to use it?
	Where would Katy use your device?
	What about your device makes it good for Katy to use it there?
	How old would Katy have to be to use your device on her own?
	Why would she have to be this age to use your device alone?
Katy's mum's use of device	What about your device makes it good for Katy's mum to use?
	Where would Katy's mum use the device?
	What about your device makes it good for Katy's mum to use it there?

STUDY EXECUTION

The session began with story time, during which the researcher told 'Katy's story' using the picture book. The story ended with the children being invited to 'help' Katy, through designing a device for her. During story-time the children's CGs were given an information sheet along with a consent form to complete.

Children were allowed 10 – 15 minutes to design their device before being handed the worksheet to complete. The researcher was available for questions or queries throughout the activity.

Following completion of designs and worksheets the concepts were photographed and participants thanked for their time.

This session plan is summarised in Table 2.8.

TABLE 2.8 SESSION PLAN

	Concept
1	Introduction to research through reading of 'Katy's Story' to the children (and their CGs)
2	Children invited to design a device for Katy using play dough or colouring pencils and paper
3	Children allowed time to design their device for Katy
4	Worksheets handed out and children asked to complete these based on their device design
5	Periodic checking of participants and their progress
6	Collection of photographing of device designs along with completed worksheets
7	Closing remarks and thank you

Analysis of this worksheet alongside broad thematic analysis of factors influencing the designs allowed for greater insight into the user needs of an MP dosing devices.

2.3.1.5 Online survey

Method choice rationale

The CF population was identified given their familiarity with a MP-like medication: PERT. The chronic condition and patient group were researched to further understand their situation and medicine use. Colleagues from the CF clinic at the QMC, Nottingham provided further insight into the patient population and their medication requirements. Following discussions with nurses, dieticians and clinicians an online survey method was selected as most appropriate given CF patients rarely meet due to the risk of cross-infection. Consequently, any face-to-face contact with multiple patients in the same location on the same day would be challenging. An online survey would also allow for wider dissemination.

Recruitment and consent

Participants were recruited online through social media, most commonly using Twitter. The researcher used their contacts with CF awareness groups as well as their personal Twitter account to 'tweet' about the survey. Figure 2.8 shows an example Tweet circulated by the researcher's contact at @CFAware.



FIGURE 2.8 EXAMPLE TWEET SEEKING PARTICIPANTS

@CFAware is a Twitter account set-up by two mum's of children with CF who noticed the lack of information on Twitter about the condition. The page has over 12,000 global followers including CF patients, CGs and researchers.

The survey link was also circulated through the CFTrust's web forum, the CFAware's Facebook page, University email address books and via personal contacts outside of the University.

DEFINITION OF RESEARCH AIMS

The aim of this survey was to ascertain the appropriateness of an MP delivery device for this specific patient population. Given the familiarity of these patients to MP-like formulations, such as those used for PERT, this population was selected.

STUDY DESIGN

Survey questions were selected to ascertain whether an MP-handling device would be appropriate for this population and if so, what requirements these 'would-be users' had for such a device.

Following the welcome page containing the participant information and consent statements the survey opened with questions relating to the use of granules, CREON® micro, Table 2.9. Questions then enquired about capsule use, the transition between the DFs, posed several scenario based questions, before closing with a few demographic questions including age, location and the age and gender of the child in their care. Scenario based questions are useful in gaining insight into common practice and in understanding how an individual would likely react in real life (Campbell 1992; Carroll et al. 1997; Lang et al. 2013).

A copy of the survey can be found in Appendix 13, page 219.

TABLE 2.9 SURVEY PLAN

Area	Questioning		Example question	Rational for asking
Granules Capsules	Calculating dose Measuring dose Administering dose Challenges Device use	Home vs. Out and about	How do you work out the granule dose at home?	Appreciate the day-to-day use of an MP-like formulation as well as the capsule DF. Provide valuable insight for the design of an MP-handling device for use by the CF population, including whether and where a device may be appropriate.
Transition	Granules → Capsules Capsules → Granules		At what age did the child in your care transition from granules to capsules?	Understand the age of and reasons for transitioning from the MP-like formulation. Ascertain whether patient's would ever return to granules. Appreciate the likely target age group for an MP-device.
Scenario	What would you do? Happy with this? Device use Influences	Home vs. Out and about Snack vs Meal	You are at home when your child eats a snack. The snack's fat content does not equate to a full capsule. What do you do?	Ascertain whether diet manipulation was common place given the inflexible dosing presented by capsules. Understand whether patients are happy with the current situation. Gain an appreciation of the factors likely to influence device use. Appreciate any differences between snack and meal dosing.

Participants were asked about factors affecting whether they would use a device (capable of accurately measuring the MP-like formulation, or splitting capsules) in their current situation as well as in the scenario posed to them. Possible factors were suggested (based on previous study outcomes and discussions with CF experts) with participants asked 'how influential' each of these features would be. They were also provided with the option of 'other' whereby they could detail an alternative factor or action.

Where possible the survey utilised ranking questions/responses to understand in further detail the factors influencing decisions and device use, to appreciate their feelings towards the current state, and to ascertain their likeliness of using a device for example. Figure 2.9 shows an example ranking question.

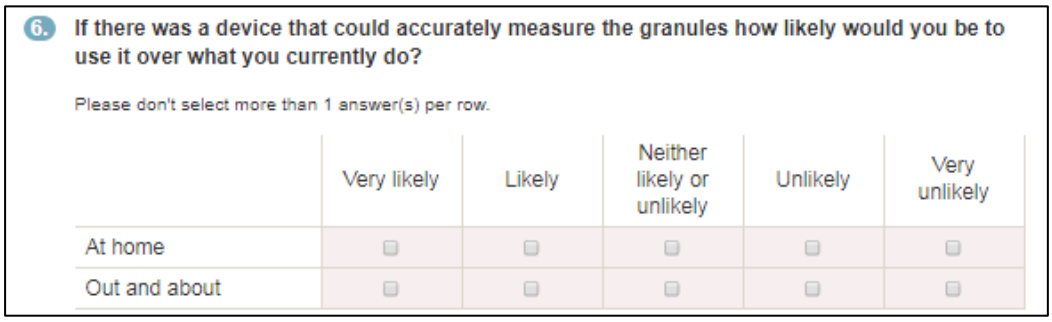


FIGURE 2.9 EXAMPLE RANKING QUESTION

STUDY EXECUTION

The 27 question online survey was developed using the BOS tool in collaboration with colleagues from the CF ward at the QMC, Nottingham, UK. Following several iterations the survey was disseminated via social media and was live for 7 weeks and 3 days.

The survey took approximately 20 minutes to complete. The fairly long completion time was due to the detailed nature of the survey, this did pose the risk of participant fatigue and incomplete responses however (Wilson and Sharples 2015). Nonetheless, questions were all deemed appropriate given their co-design with CF experts and were considered to provide rich information. These questions could have been further optimised to improve participant experience however, had greater time been available.

2.3.2 ANALYSIS METHODS

Data was analysed using simple frequency counts and thematic analysis, an example of which is shown in Figure 2.10.

When performing frequency counts, incomplete and inconsistent responses were excluded from these tallies. The researcher also considered the participant DIY devices and drew likely influential themes from these based on the participant's previous responses, annotations and any verbal comments made about the design. This allowed further comprehension of the themes influencing design decisions.

Given the qualitative nature of this work, no statistical analyses have been performed on the frequency counts or the number of times a themes has been cited. Given this research aims to provide HF-related insight and understanding, the power of statistical analyses is somewhat limited in this case.

2.3.2.1 THEMATIC ANALYSIS

The researcher considered each of the key areas (for each study) in turn, reading and highlighting prevalent themes within the transcripts/data as they occurred. Subsequent tabulating of the themes allowed for an appreciation of recurrent themes as discussed by participants before themes were grouped (Dey 1993; Sanderson and Fisher 1997).

Transcription of themes on to Post-it® notes allowed for grouping into broader sub-themes. Where relevant these sub-themes were further grouped into formulation, device and user (green Post-it® in Figure 2.10) if appropriate to align with the three RQs.

Examples of these three steps are represented in Figure 2.10 with the first image (a) showing the coding of the raw transcript (User, Study 1), different colours highlighting different medicines, devices and administration challenges for example. Subsequent tabulation (b) allowed for an appreciation of how prevalent particular medicines were and how often similar challenges were faced, before grouping of themes gave an overview of the responses (c).

Themes were validated (to limit the effect of researcher bias) by another individual with experience of qualitative research methods, specifically with young users of medical devices (Braun and Clarke 2008). Iterations of coding stopped when themes could not be grouped any further.

a

[CL]: Talk to people about, hopefully to and improve the situation because we appreciate how difficult it can be. So you mentioned Calpol

[P1f]: Yep

[CL]: How does that go?

[P1f]: Yeh, fine, just like with the syringes

[CL]: Syringe?

[P1f]: Or on a spoon now they're a bit older

[CL]: OK

[P1f]: But this one's always fine taking Calpol out of the syringe, when (eldest daughter) was a bit younger it was difficult to give, sometimes, occasionally it was difficult to give her some Calpol. But I wonder if that was just... me not being particularly confident (because) it was my first baby

b

Medicine	Administration device	Admin techniques	Challenges	Good things
Cream		Hold her down (two of us)	Running around Difficult to apply if she doesn't want it on Doesn't work Stains bed clothes	Fine
Eye drops			Waste of time, eye drops in 1 year old Pretty bad; stung	

c



FIGURE 2.10 EXAMPLES OF THE THEMATIC ANALYSIS STAGES

2.4 DEVICE D&D

2.4.1 COMPILATION OF FORMULATION AND USER REQUIREMENTS

Considering the Formulation and User requirements (Chapters 3 and 4), a number of influential factors, or specifications were defined. These formed the basis of subsequent design work guiding the development of a platform technology. The main six studies are outlined in Figure 2.11.

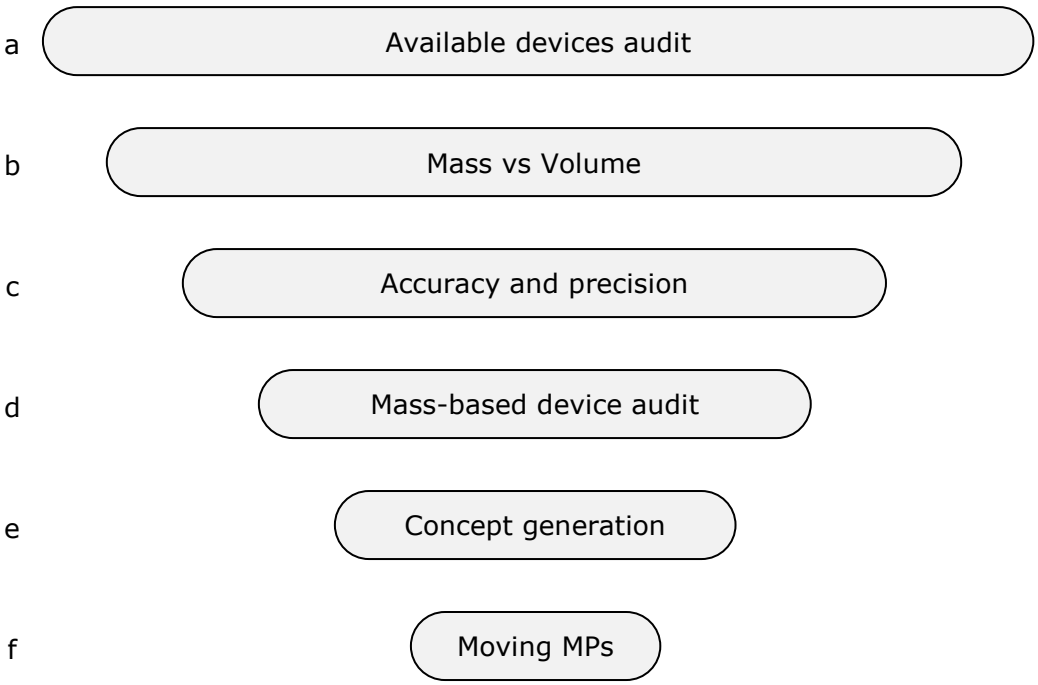


FIGURE 2.11 DEVICE-BASED STUDIES

Device work began by appreciating the current state through investigation of currently available devices and literature/patent searches, Figure 2.11 (a). Mass-based dose measurement was compared with volumetric (b), and a variety of readily available mass-based devices were assessed (c) including a full device audit (d). Design activities followed, with an array of devices conceptualised by both the researcher and design students (e), before looking more closely at how best to move the MPs within a device (f).

2.4.2 AVAILABLE DEVICES AUDIT

This first device-based study investigated currently available technologies to allow for an appreciation of potential MP-handling mechanisms. Subsequent ranking of these devices against requirements as determined by the Formulation, Users and Pfizer allowed for selection of preferred devices and mechanisms for MP handling.

2.4.2.1 DEFINITION OF RESEARCH AIMS

A series of assessments were performed to investigate the appropriateness of the devices shown in Figure 2.12 at handling MPs, either in their current form, conceptually or with some further modification.

Devices from a range of fields were chosen to ensure the study was not restricted to pharmaceutical products. Whilst not all devices were suitable at handling MPs in their current state, they were considered conceptually as being appropriate. By investigating a variety of devices a range of possible design concepts and mechanisms could be identified.

3.4.2.2 SELECTION OF DEVICES

The 21 devices shown in Figure 2.12 were selected given their current use handling free-flowing formulations such as liquid medicines (A – D and F – I), baking ingredients (E), Mini-tablets (J), nail art (K), pet food (L & M), sugar (N) and confectionery (O – U). Some devices were selected due to their similarity to MP devices in development (J and U), others due to slight differences in their appearance (P – S).

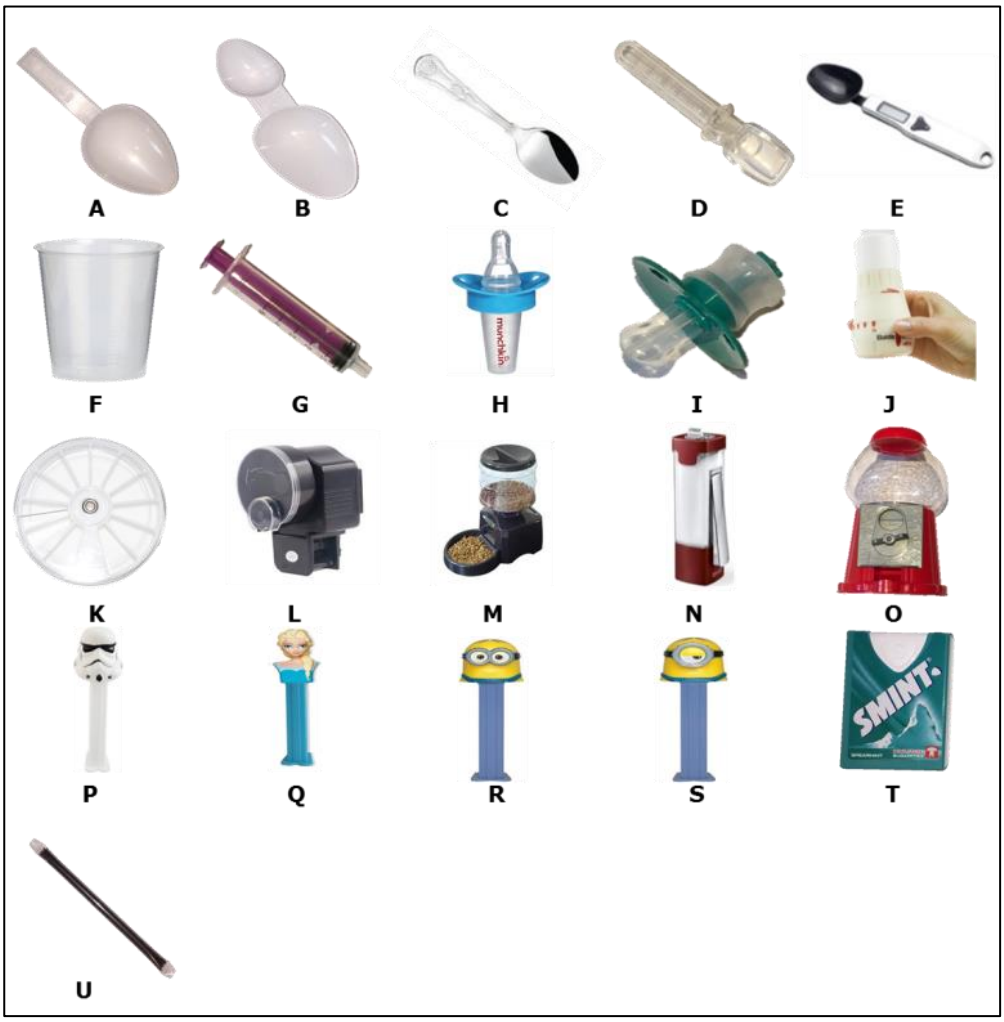


FIGURE 2.12 DEVICES CONCEPTUALLY CAPABLE OF DISPENSING FREE-FLOWING FORMULATIONS

2.4.2.3 ASSESSMENT METHOD

Where appropriate, MP-surrogates as defined in Chapter 3 were used to test the suitability of the devices at handling a free-flowing MP-like formulation. Where the device was not yet refined enough to handle this formulation, its dispensing mechanism was investigated, with devices often dismantled to appreciate how they work. Each device was then critically evaluated for its likely appropriateness for handling MPs (with or without modification) alongside key user based requirements.

2.4.3 Mass vs volume

2.4.3.1 Definition of research aims

A tapped density experiment was used to determine whether mass-based dispensing would offer improved accuracy over volumetric.

2.4.3.2 Method

A simple tapped density experiment was performed whereby a glass measuring cylinder containing an MP-like formulation is subjected to 500 and then 1250 (total) taps. Reading of the sample volume after each tapping stage and noting of any change in volume allows the calculation of bulk and tapped density.

2.4.4 Accuracy and precision

2.4.4.1 Definition of research aims

Six readily available balances were assessed for their accuracy and precision compared to the 'gold standard' of a calibrated reference balance. This was to ensure that the chosen mechanism was capable of repeatedly determining an accurate MP dose.

2.4.4.2 Method

A series of three experiments were performed to determine the accuracy and precision of the six weighing scales. The balances were used to measure both increasing and decreasing masses of calibration weights as well as being compared to the 'gold standard' balance.

Addition of mass

The range of masses detectable by each of the 6 scales was noted from the manufacturer's specification. The devices were then assessed in determining the mass of a set of calibration weights across the claimed range.

Each calibration weight (1, 10, 20, 50, 100, 200, 500 mg, 1, 2, 2, 5, 10, 20, 20, 50, 100, 500, 600 g) was weighed individually nine times with the mean mass recorded.

This allowed determination of the device's accuracy; how close to the known calibration mass the output was, and their precision; how often that same mass readout was achieved (standard deviation).

Comparison with gold standard

Following identification of accurate and precise balances across the mass range of interest, their accuracy compared to the gold standard was assessed using the addition of H&Ts up to 1 g. H&Ts were used to appreciate the device accuracy over smaller increments than the increments provided by the calibration weights.

Provided the devices appeared accurate up to 1 g, subsequent readings at 1.5, 2 and 3 g were performed using calibration weights to speed up the process.

Loss of mass

Provided the devices were as accurate as the gold standard, a loss of mass assessment was performed to ensure the devices were as accurate in detecting a decrease in mass.

2.4.5 Mass-based device audit

2.4.5.1 Definition of research aims

The top 3 mass-based devices (accurate and precise across the mass-range of interest) were selected and a detailed device audit performed, Figure 2.13. The audit highlighted that a strain gauge load cell was used in all 3 of the devices suggesting this was a feasible means for determining MP dose.



X	Y	Z

FIGURE 2.13 DEVICES SELECTED FOR AUDIT

2.4.5.2 METHOD

All three devices were disassembled part by part and a log kept of all components. Images were taken during the deconstruction stage to document the component parts and how the device was likely assembled. Given the apparent similarity of devices Y and Z during this audit, therefore only device Y is presented here.

2.4.6 CONCEPT GENERATION – RESEARCHER

2.4.6.1 DEFINITION OF RESEARCH AIMS

The aim of this work was to create device concepts amenable to handling free-flowing MPs in a safe, controlled and reproducible way. Whilst being user-friendly and appropriate for home use.

2.4.6.2 METHOD

The researcher conceptualised devices based on the three previous studies, whilst also considering the requirements of the Formulation (Chapter 3) and User (Chapter 4).

2.4.7 MOVING MPS

2.4.7.1 DEFINITION OF RESEARCH AIMS

Given the importance of the device's internal mechanism in handling MPs, the aim of this study was to investigate and prototype possible mechanisms.

2.4.7.2 METHOD

Different methods for moving free-flowing materials were identified via literature review and research into free-flowing material movement, including the movement of water and soil. Three possible mechanisms were highlighted for their potential use for this application.

Following basic prototyping, the mechanisms were assessed for their suitability in handling an MP surrogate formulation. Samples were imaged using optical microscopy before and after use as a visual inspection of friability.

Further prototype refinement was then performed and where appropriate, refined prototypes tested with Cellets®. Given the mechanism refinement, the smaller Cellets® could be more easily handled. The Cellets® also offered as a more refined MP surrogate being more aligned to the 'ideal MP' in terms of diameter.

2.4.8 FURTHER CONCEPT GENERATION – COLLABORATION WITH DESIGN STUDENTS

2.4.8.1 DEFINITION OF RESEARCH AIMS

The aim of this collaboration with undergraduate product design students was to generate a greater number and range of design concepts.

2.4.8.2 METHOD

Students were provided with a design brief (Appendix 14, page 235) and asked to conceptualise a device capable of repeated flexible dosing of MP formulation to children.

The researcher generated their own device concepts independently, alongside these activities.

2.5 SUMMARY

This research takes a holistic UCD approach to appreciate a versatile design space. Focussing on Formulation, User and Device in turn allows the identification of influential factors upon device D&D of a paediatric MP dosing device.

CHAPTER 3 - FORMULATION

Given the relative novelty of MP use in paediatric indications and therefore the infancy of MP device development, it was important to consider specific formulation characteristics likely to affect the device design.

Consideration of important formulation characteristics ensures that the most appropriate design is conceptualised, allowing for safe and accurate personalised dosing. Two studies were therefore performed to understand influential formulation factors and to identify a surrogate MP for device prototyping and testing, Table 3.1.

TABLE 3.1 FORMULATION–BASED STUDIES PRESENTED IN THIS CHAPTER

	Study
3.1	Identification of formulation characteristics influential upon device design
3.2	Identification of an MP surrogate

3.1 IDENTIFYING INFLUENTIAL FORMULATION CHARACTERISTICS

Various formulation characteristics were highlighted for their likely importance during device design through discussions with Pfizer (as the MP manufacturer). These included individual pellet characteristics and bulk material properties, Figure 3.1.

Many of these individual characteristics have an immediate effect on the properties of the bulk sample. For example, pellet size and morphology will impact the MPs flow-ability, including how well the sample moves through a dosing device. Pellet friability and sample bulk density can impact the dose accuracy, particularly if determined by volume. For example, the presence of fines and compaction of the sample will likely lead to a different dose dispensed. It is therefore important to consider these parameters when designing an MP dosing device.

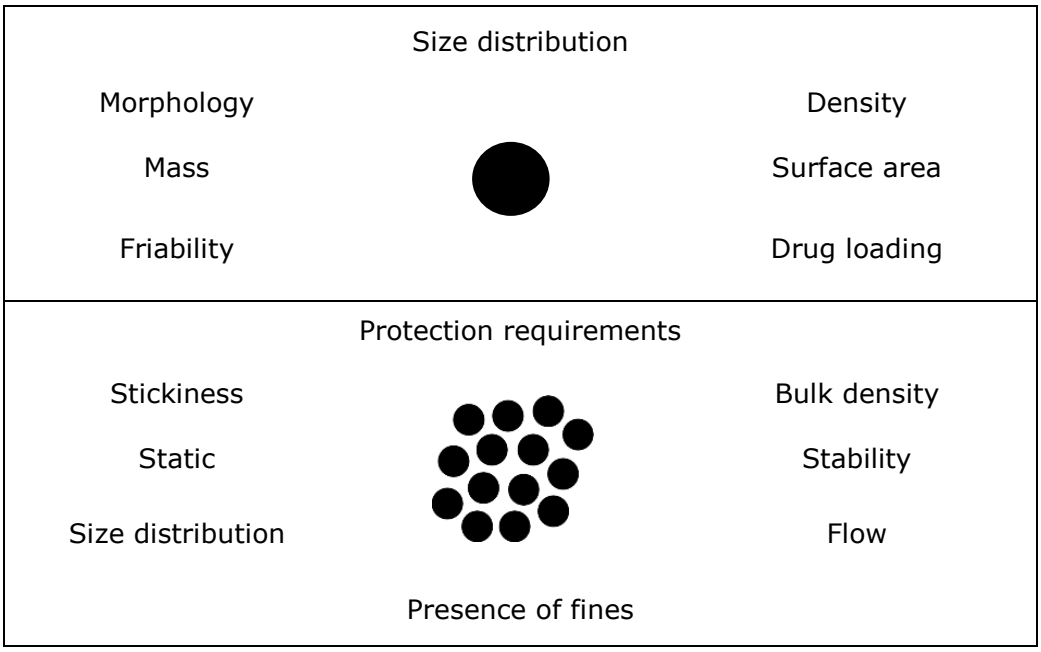


FIGURE 3.1 INDIVIDUAL PARTICLE AND BULK CHARACTERISTICS TO CONSIDER IN DEVICE D&D

For the purposes of this research, it is the Formulation factors affecting the device design that are key. It is also important however, to consider the influence of the Formulation on the User, Figure 3.2. This may prove crucial in ensuring compliance, influenced by both the Formulation and its Device.

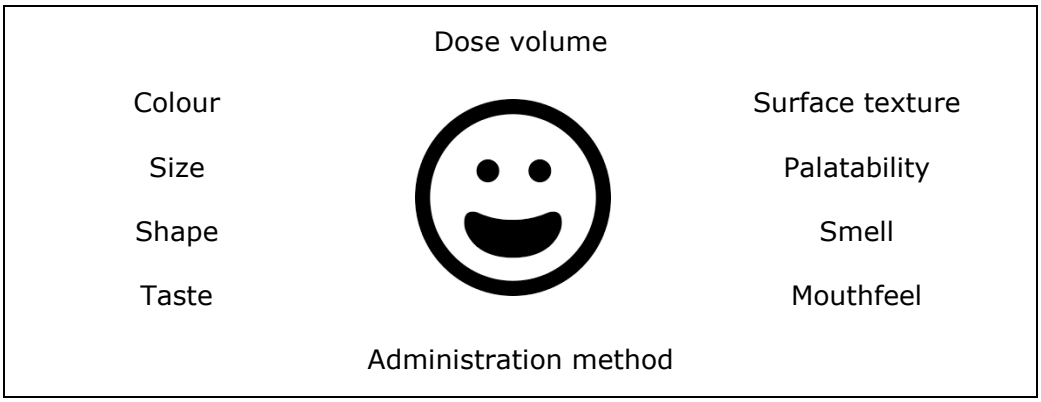


FIGURE 3.2 FORMULATION FACTORS LIKELY TO AFFECT USER ACCEPTANCE

Aside from the Formulation itself it is important to appreciate the full product life cycle of both formulation and device independently, as well as part of a combination product. The movements from manufacture, through to packaging, transport, distribution, sale and use are key. For example, it is important to protect the MPs inside the device including protection from; water, sunlight and extremes of temperature and pressure for example.

Having considered various formulation characteristics and their likely influence upon device design (and user acceptance), it was decided that a free-flowing MP sample with uniform size, mass and spherical morphology was desired for device concept generation, development and prototyping. This would provide a reliable means of testing prototypes given its similarity to the ideal MP, Table 4.2, as well as providing a readily available, safe sample for public-engagement.

3.2 IDENTIFICATION OF AN MP SURROGATE

3.2.1 INTRODUCTION

In lieu of a final marketed product from Pfizer, an ideal MP was discussed, Table 3.2.

TABLE 3.2 IDEAL MP CHARACTERISTICS

MP attribute		Target specification
Size	Target diameter	200-300 µm
	Particle Size	150-500 µm (Mono-dispersed with ≥ 85% yield at PSD range)
	Shape	Highly spherical and symmetrical
	Flow-ability	Excellent
	Dose Range	~50 – 1,500 mg (incremental steps)
Density	Bulk (g/cm^3)	0.65
	Tapped (g/cm^3)	0.743
	Known Sensitivities	Moisture, Static

A target particle diameter of 250 µm was specified based on the desire to have a non-gritty mouth feel (Engelen et al. 2005; Liu et al. 2014; 2015; Lopez et al. 2016). A narrow PSD improves content uniformity of the finished product better enabling accurate volumetric dispensing, if desired. A spherical/symmetrical core provides a better substrate for particle coating and also improves flow properties, particularly important when considering device design. A wide dose range with many increments was desired given the MP application in paediatric medicines and the

personalised dosing required. The MPs may be susceptible to clumping over long term storage when exposed to high temperature and humidity conditions they also exhibit static behaviour with some materials. These sensitivities are key to consider when designing an MP dosing device.

Having identified the characteristics of an ideal MP four potential surrogate formulations were investigated for their suitability for use during development.

3.2.2 METHOD

Placebo MPs, Glass beads, H&Ts and Cellets® were investigated given their likeness to the ideal MP. A Cellet® 200 sample was used given the manufacturer quoted PSD of 200- 355 µm being aligned to the target diameter of 250 µm.

Samples were characterised for their size, flow, morphology, and mass given the importance of these features upon device design. Further details can be found in Chapter 2 – Methodology, page 21.

3.2.3 RESULTS

3.2.3.1 SIZE

Special Thanks to Lourdes Contreras and Harry Dean of Pfizer for providing the majority of this size data.

Riffling was investigated to ascertain its importance in providing a representative sample. Figure 3.3 shows the size distribution of riffled and un-riffled placebo pellets (triplicate data shown).

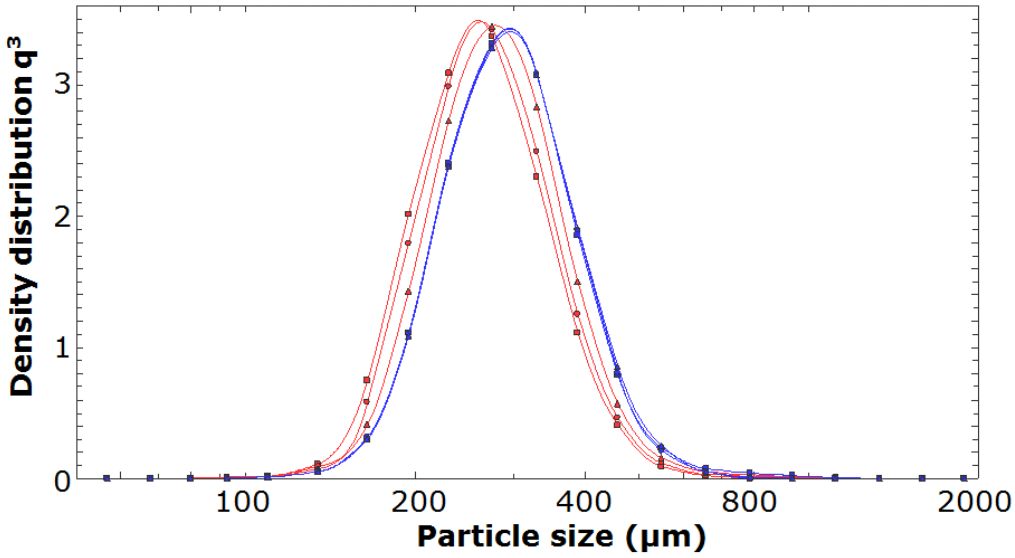


FIGURE 3.3 PLACEBO SIZE MEASUREMENT

The riffled sample provided a greater mean size of pellet, 291.4 µm compared to the un-riffled sample mean of 269.6 µm, Figure 3.3. The riffling also provides more reproducible pellet sampling compared to not riffling, % Relative Standard Deviation (RSD) of 0.22 compared to 3.29. This reproducibility is also demonstrated by the tight overlap of the size distributions in Figure 3.3. This result was expected given that spin riffling is known to provide a more representative sample of the pellet population (Montgomery 1968; Allen and Khan 1970; Hatton 1978).

All subsequent samples were therefore riffled given the improved sizing accuracy. Table 3.3 compares the diameters of each of the four riffled samples.

TABLE 3.3 SIZING SUMMARY

Sample	Mean particle size (µm)	% RSD
Placebo MPs	291.4	0.22
Glass beads	1341.7	0.80
H&Ts	1786.2	0.54
Cellets® 200	322.7	Single data set

The Placebo MP sample was the only surrogate with a mean diameter within the target range of 200 – 300 µm. The Cellet® 200 sample was near to this target. Despite the H&Ts being much larger than the ideal MP their

size was fairly consistent compared to the Glass beads with % RSDs of 0.54 and 0.80 respectively.

Despite the Glass beads and H&Ts having a larger average diameter, they were considered for use as an initial MP-like surrogate for use during basic prototyping. Their larger size provided the possibility of easily handling individual pellets for example. More refined prototyping was required for handling the smaller sized samples. All four samples were therefore considered for use as MP surrogates for device D&D and characterised in terms of their flow properties.

3.2.3.2 FLOW

Special Thanks to Lourdes Contreras and Harry Dean of Pfizer for providing the majority of this tapped density data.

Sample flow properties were measured by bulk and tapped density assessment. Density under tapped conditions indicates flow-ability.

All four samples had excellent flow-ability with a compressibility index, or Carr's index, C (1965) reading of less than or equal to 10, Table 3.4.

TABLE 3.4 TAPPED DENSITY

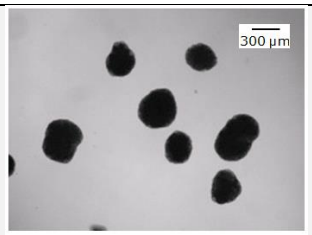
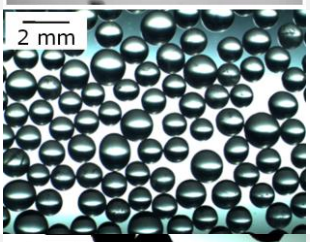
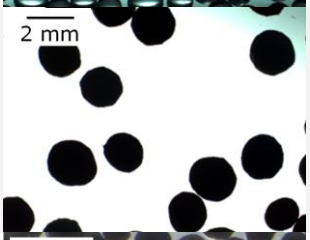
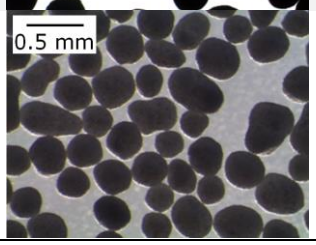
	Mass (g)	Volume (cm^3)			Density (g/cm^3)		C
		Initial	After 500 taps	After 1250 taps	Bulk	Tapped	
Placebo MPs	69.52	96.0	91.7	90.7	0.724	0.767	5.61
Glass beads	62.81	41.5	41.5	41.5	1.513	1.513	0.00
H & Ts	34.58	38.5	37.0	36.5	0.898	0.947	5.17
Cellets® 200	29.02	35.0	33.0	33.0	0.829	0.879	5.71

Mean data of at least 2 repeats shown

Given that all four samples demonstrated excellent flow properties none of them were ruled out as potential surrogates.

3.2.3.3 MORPHOLOGY

TABLE 3.5 COMPARISON OF SAMPLE MORPHOLOGY

	Image	Shape	Size
Placebo MPs		Not consistent	Not consistent
Glass beads		Consistently spherical	Not consistent
H&Ts		Consistently spherical	Consistent
Cellet® 200		Not consistent	Not consistent

H&Ts offer an MP-surrogate with consistent shape and size, Table 3.5. Glass beads had varied diameters, despite being consistently spherical. Both the Cellet® 200 sample and placebo MP sample had morphology that was not consistent in size or shape. PSD data suggests however that their size and consequently their shape were fairly consistent given the low RSDs.

H&Ts and Glass beads were therefore preferred as MP surrogates for initial device prototyping and testing given their excellent flow-ability, consistent spherical morphology and large size allowing for easy handling.

At this point, the placebo MP sample was excluded from further consideration based on the infancy of its development (Pfizer were continuing to optimise the manufacture).

3.2.3.4 MASS

Individual glass bead and H&T mass was determined by weighing individual pellets (n = 100). Batch mass (100 pellets) was also measured to compare consistency of measurement. The weighing of individual Cellets® proved difficult, given their small size and the unavailability of a suitable counting/dispensing device. Batches of Cellets® were therefore weighed and the average mass of an individual Cellet® estimated. The standard deviation (SD) and standard error (SE) were calculated to represent the variation within individual pellet mass and batch mass respectively.

Glass beads and H&Ts had similar average masses, approximately 4 mg, Table 3.6. This suggests they are a useful MP surrogate given the small increments in mass possible through individual pellet addition. Given that the average mass of an individual Cellet® 200 was estimated at 0.02 mg (0.0018) however, these were excluded from consideration as a primary surrogate. However, given their alignment to the ideal MP in terms of size and composition they were considered as a refined surrogate once suitable means of handling had been developed.

TABLE 3.6 AVERAGE PELLET MASS

		n	Mean pellet mass (mg)	Variation
Glass beads	Individual pellets	100	4.40	0.97 (SD)
	Batches of 100 pellets	12	4.33	0.11 (SE)
H & Ts	Individual pellets	100	4.39	0.88 (SD)
	Batches of 100 pellets	10	4.58	0.18 (SE)
Cellets® 200	Varying sized batches of pellets	10	0.02	0.0018 (SE)

3.2.4 SUMMARY: IDENTIFICATION OF AN MP SURROGATE

Table 3.7 summarises the characterisation data of the four samples, allowing comparison to the ideal MP.

TABLE 3.7 SUMMARY OF THE MP SURROGATES INVESTIGATED

	Size (µm) [% RSD]	Flow	Morphology	Mass (mg) [SD or SE]
Glass beads	1341.7 [0.80]	Excellent	Consistent	4.40 [0.88]
H & Ts	1486.2 [0.54]	Excellent	Consistent	4.39 [0.97]
Cellets® 200	322.7	Excellent	Inconsistent	0.02 [0.0018]

The Cellet® 200 sample had excellent flow properties and a pellet size most aligned to the ideal MP. Cellets® were therefore considered the 'best' MP-surrogate for use during device development, prototyping and testing. However, given the infancy of this development work and the requirement of a device to handle the small Cellets®, a larger, more easily handled MP sample was selected for initial prototyping and as a safe, readily available sample for interaction with user groups.

Despite Glass beads having a similar profile to the H&Ts, their unlikeness to pharmaceutical products (and their hardness meaning they damaged some devices during testing) meant they were discarded as a potential MP surrogate, leaving H&Ts as the surrogate of choice.

CHAPTER 3 – DISCUSSION

The work presented in this chapter has provided insight into Formulation features important to consider when designing a device for personalised MP dosing.

Given the unavailability of a final market MP product, H&Ts were found to be an appropriate surrogate for initial design work given their alignment to an ideal MP. They provide an easily handled, safe, readily available sample for explaining the research to the public also.

Cellets® provide a more refined MP surrogate for further, more developed prototype work. Their small size makes handling difficult, preventing their use during initial prototyping work.

Cellets® are available in various sizes meaning they can offer the flexibility to match in-house MP criteria based on different manufacturer specifications.

As well as the Formulation factors considerations highlighted in this chapter, drug-loaded MPs would require further specific considerations based on their composition, drug loading and the indication to be treated.

CHAPTER 3 – LIMITATIONS

The work is this chapter is limited by the fact that a final marketed MP product is not readily available; meaning the use of a surrogate was required.

Whilst it is appreciated that the H&Ts surrogate is not a perfect representation of the envisaged product, it does allow for an understanding of key influential characteristics in terms of device design and provides a readily available test material for prototyping and for use during public-engagement.

CHAPTER 3 - CONTRIBUTIONS TO THESIS

This work has identified an appropriate MP-like formulation for prototype testing and public-engagement.

This chapter addresses RQ1: What are the requirements of the Formulation? Through detailed consideration of Formulation factors influential for device D&D.

Using this insight, alongside the requirements of the User(s), Chapter 4, more considered device concepts can be generated (Chapter 5).

CHAPTER 4 - USER(S)

This chapter presents the findings of four studies performed with CGs and children as key stakeholder groups in the design of a paediatric medical device, Table 4.1. CGs are defined as providing direct care for an individual, in this case, a child. They include parents, guardians, grandparents and other family members for example.

TABLE 4.1 USER-BASED STUDIES PRESENTED IN THIS CHAPTER

Study		Participants
4.1	Experiences of medicines in the home	CGs (mostly)
4.2	Opinions of currently available devices	Children and CGs
4.3	What is ease of use?	Children and CGs
4.4	Designing a medical device for Katy	Children

4.1 EXPERIENCES OF MEDICINES IN THE HOME

4.1.1 INTRODUCTION

Whilst guidelines and policies shape medicine administration in schools and hospitals (Health 2007), there are no guidelines and limited literature relating to paediatric medicine administration in the home.

The aim of this study was to further understand the use of paediatric medicines in the domiciliary setting, to inform device D&D decisions.

4.1.2 METHOD

Exploratory semi-structured interviews were conducted using voice recording. Further details can be found in Chapter 2 – Methodology, page 21.

4.1.2.1 PARTICIPANTS

46 CGs (83 % female) including 34 mothers, 7 fathers, 3 grandmothers, 1 grandfather and a family friend were interviewed. 74 children were discussed (50 % female) aged between 6 months and 20 years, 15 of these (73 % female) contributed to the discussions (6 - 13 years).

4.1.3 RESULTS

Participants spoke of having used a variety of different DFs, including: oral liquids (56 refs); oral solids (22); inhalers (9); creams (6); eye drops (3) and injections (1). The majority of CGs were not administering regular medication to their child. The researcher therefore guided discussion towards the most recent oral medicine administration as an example.

The majority of medications administered were oral liquid formulations (57.7 %). This is consistent with most paediatric medicines being formulated as liquids (Nunn and Williams 2005). Eight different administration devices were discussed.

Questions were asked relating to CG and child experiences of medicine administration including challenges and administration method. The thematic analysis of their responses is discussed with key themes highlighted in **bold**.

The medicine's **formulation** (100) appeared to be the most commonly cited factor when CGs considered the challenges when administering medicines to children. In particular, the formulation's **physical characteristics** (64) such as **taste or flavour** (46) caused issues. These responses were not thought to have been influenced by the line of questioning, given the broad nature of the 'how did that go?' query.

> *"Some of them taste horrible" [P9C8f]*

CGs spoke about adding the medicine to food or drink (as a **vehicle**) to encourage administration (12). Some had tried a few different vehicles before having success.

> *"He doesn't really go for any kind of fruit drinks or anything so we've found that increasingly … difficult, so we've resorted to stirring it in to porridge and things like that" [P26m]*

The administration of medicines with food or drink vehicles is commonplace in CF patients using PERT, where the granular medication is added to applesauce for example (Fieker et al. 2011).

Other CGs used food as an **incentive** (10) either before or after medicine administration. They spoke of trying to convince the child to take the medicine, having had success using sweet food items.

> *"We've tried bribery with sweets or, you know you can have this after or a bit of chocolate" [P26f]*

The medicine's formulation also influenced the age of self-administration when CGs considered use of a 'real medicine' or 'just a vitamin'.

> *"I mean the actual drug I wouldn't be happy him giving it himself, but a multivitamin I would because … it's not a medicine is it" [P40f]*

The lack of **alternative DFs** (11) was also commented upon, including a desire to have medicines formulated as chewable tablets (3) for example.

> *"She has a vitamin … Every day and it's more like a chewy sweet isn't it? … she loves that, she asks for that … I don't know why they can't make antibiotics like that … Just teddy bears and pink" [P29f]*

The **DF's appropriateness** for children influenced CGs perception of administration ease (13). Many CGs and children spoke of difficulties swallowing solid tablet formulations (10).

> *"When he first started having the tablets he was struggling to swallow them" [P5f]*

To this end, two CGs encouraged their child to **practice** swallowing small pieces of fruit or sweets without chewing, in anticipation of using tablets.

> *"We just got him to try and sort of do it with a small bit of fruit actually … we just had a little bit of food cut up and drink something and swallow that" [P23m]*

These findings issue a challenge to formulators to create the most acceptable DF for children. Device D&D can do little to alter the formulation's taste, however, it is important that these issues are appreciated to best design an appropriate MP dosing device. For example, it may be that the device be amenable to co-administration with food to mask the medicine's flavour.

Aside from the formulation's ease of use, device **usability** was also highly cited (33) with most references relating to device **ease of use** (21).

> *"With syringes it's really quick and easy" [P39f]*

Familiarity of the user(s) with the medicine and its administration emerged as a factor influencing successful administration (14). Comments included the CG not being confident or familiar with the medicine and its administration (3) which caused challenges, whilst children being familiar with the medicine, aided administration (10).

> *"I wonder if that was just me not being particularly confident (because) it was my first baby" [P1f]*

> *"He's pretty used to it now" [P16f]*

This suggests that for a greater chance of successful dosing, both the CG and child should be familiar with the medicine and its administration.

Familiarity also influenced CG consideration of their child self-administering. Some described how their child would be unfamiliar with the process and that they had not had enough practice (2). Others stipulated that perhaps if their child took the medicine every day (2) then they would be happy with them self-administering.

> *"If you're taking it every day, maybe as a child you get used to that … And you can be quite responsible I don't know, but we don't (don't) do that … So I guess there's not enough, there isn't the opportunities if you like" [P35f]*

A common consideration for CGs was the dosing of the medicine (10), including **dose accuracy and spillage** risk (3).

> *"With the spoon some falls off, but in the dosing syringe if they accidently pop a bit you know how much is gone" [P20f]*

A concern over **potential mess** was highly cited with many CGs referencing occasions where medicine had been spat out (7) or dribbled (2).

> *"It just dribbled straight back out again" [P40m]*

Some CGs described how the exact dose is not always obvious on the device (3), and that sometimes the device is not appropriate for the dose (2).

"Difficulty was she had to have quite a precise amount" [P41f]

Dose accuracy was also referred to in terms of over/under dosing (10), a particular concern when CGs considered child self-administration.

"I think every child would just drink a bottle of Calpol" [P3f]

These references to dose accuracy and medicine spillage highlight that they are key features influencing user experience of medicine administration. A device for dosing MPs should therefore be accurate and pose as little spillage risk as possible.

Mess was also referenced when CGs explained the context or environment in which they administer medicine to their child. The relative ease with which an area could be cleaned (8) greatly influenced the CGs choice of administration location.

"That [steroid cream] stains all the bed clothes" [P29f]

The most common administration location (within the home) was the kitchen (16) with the main rationale for selecting the kitchen being that that was where the medicines were stored (17) and the ease of cleaning (8).

"In the kitchen because that's where I store their medicines" [P20f]

"Kitchen on the hard floor so we can wipe it up if it doesn't go in the mouth" [P26f]

The bedroom (9) and bathroom (7) were also suggested as administration locations, often for practical reasons such as the ease of cleaning (bathroom), administration timings (bedroom) and the availability of a drink to aid administration (bathroom).

"Bedroom it's more for the cream, cos that's where we keep it for bedtime and getting dressed" [P28f]

The room in which the medicines were stored appeared influential in determining the administration location. The controls upon specific storage spaces, particularly with regard to it being inaccessible to children were also important.

> *"They're kept in a high locked cupboard" [P5f]*

This provides an indication as to the likely use environment of an MP device. This allows for more informed D&D choices to be made with suitability to the context of use including the likely storage and use environments.

The CG and child's **state of mind** emerged as having influenced medicine administration (15). CGs spoke of how the tiredness of themselves and/or the child could affect the process (3), as well as the time of day (2) and the need to remember administration (2).

> *"You're tired, you're emotional, you've got a child in your arms" [P4f]*

The child's **reaction** was also important when attempting to administer medicine, including their physical reactions such as shouting or fighting back (n).

> *"If you could get her when she was mostly asleep (chuckles)… Then you could do it but if she was awake she would just fight you" [P21f]*

These reactions limited administration success, suggesting **affective response** related to perceived fear or pain impacted the child's relationship with medication.

A device should therefore consider the users relationship with the medicine and its administration, including any possibilities of eliciting fear or a negative relationship. Where possible, consideration should also be given to the use scenario, including the anticipated users' state of mind of the user.

CGs made reference to using **calming** methods to aid administration. These included comforting the child, singing to them and rocking them. Should these methods fail, **force** may have had to have been employed.

Force was used on a number of occasions when medicine administration was proving difficult (8).

> *"Rocking her, shushing her, singing to her I have to admit sometimes it doesn't work and I have to just hold her and dose her" [P20f]*

CGs also spoke of **encouraging** the child to take the medication, including words of encouragement, explanations of why medicine use is important, and having a particular technique for 'getting it down' (11).

> *"Well I just say oh we've nearly finished, we'll just do it one more time, just say that … so then he knows it's only once and then it's over with" [P3f]*

A number of comments highlighted the difficulty in trying to administer medicine to an unwilling young child (4). The child's level of **comprehension, knowledge and understanding** also proved influential, particularly when the medicine's importance cannot always be explained to children.

> *"I think the problem is with small children you can't explain to them what's happening" [P20f]*

This was a key theme when CGs considered the age of self-administration (10).

> *"They've got maturity to understand … measurements … and hopefully the understanding that it will make them feel better" [P29f]*

It is therefore important that user knowledge and understanding of both the medicine and its dosing device are considered during device D&D. An MP device should be designed for intuitive use and be accompanied by clear and appropriate instructions.

The age at which the child would be able to self-administer medicines proved a challenging question for many CGs. They often failed to suggest an exact age for self-administration, particularly if their child was young and yet to self-administer. Some CGs suggested a minimum age or an age

range for self-administration (13). One suggested that their child would never be able to self-administer in their care.

> *"Oh god I don't know if I'd ever do that…No, well, well, saying never, of course when she's like 20, 30, 40 (chuckles) … Of course she would, but as a child, whilst she's in my care at home I think I would always do it" [P39f]*

Those who did provide an exact age, often gave a stipulation such as referring to a particular DF or medication type such as inhalers or syrups (2).

Some CGs thought their child would be capable of self-administering now, it was something that was simply yet to occur or something that the CG liked to **supervise** (3).

> *"Well she could do it herself if I just watched her obviously it's easy enough" [P19f]*

These responses suggest a distinction between the CGs willingness and child's capability to self-administer. This influences device design, as exactly who the user is becomes unclear. The MP device should therefore be designed for as young of a user as possible, providing intuitive use for CGs as well as being appropriate for child use eventually.

CGs perceived self-administration as a big **responsibility** (8) and that the age of self-administration would be heavily influenced by the child's level of **independence** (5) and **maturity** (4).

> *"I think depends on the maturity of the child" [P12f]*

There was some distinction made with the regard to the degree of self-administration and that the age of self-administration would depend on the level of interaction the CG had with the administration process.

> *"Just thinking about having to pour herself the medicine and administer it herself … She could probably do it now …I would let her pour it out and uhhh let her drink it out of the spoon herself … but actually deciding on the medicine and the dosage… And having the self-control to decide it has been four hours now… Then, I would want her to be substantially older" [P20f]*

Some CGs were happy with the physical administration (putting in the mouth) being done by the child but insisted that selecting the medication and measuring the dose was an adults responsibility. This suggested that administration is more than a single step process, and that the age of self-administration may differ for different steps.

Figure 4.1 exemplifies the three main stages of self-administration as suggested by CGs.

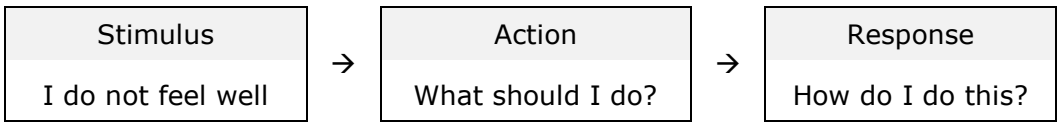


FIGURE 4.1 THE SUGGESTED 3-STAGE SELF-ADMINISTRATION PROCESS

The child's **knowledge and understanding** influenced all three stages of this administration process. Including, recognising the symptoms of feeling unwell and appreciating that medicine will make them better (3) as well as knowing 'what to do' (12) and 'how to do it' (65).

> *"Realising there's something wrong and you have to get something to sort it" [P6f]*

CGs described children as having a lack of medicine and dose **knowledge**, meaning they could not select an appropriate medicine (2), or know how to use it (7).

> *"Actually deciding on the medicine and the dosage … And having the self-control to decide it has been four hours now …Then, I would want her to be substantially older" [P20f]*

The third stage of the self-administration process, and the most reported (65 of 86 refs) was **knowing** how to 'do it', being able to measure the correct dose (11) and physically administer the medicine (23). The greater number of references to the medicines' administration may have been influenced by the line of questioning having related to administration specifically.

CGs highlighted **physical restrictions** (3), such as the child's arms not being long enough to handle the device, administration requiring dexterity,

or the opening and pouring from a bottle as being barriers to child self-administration (6).

> *"Her arms weren't quite long enough actually … So that was actually a physical issue really; spacer then inhaler and then holding it" [P37f]*

These findings highlight the importance of considering anthropometric and biometric data when considering the device user and the consequential device design. This is key in ensuing both the CG and child user are able to safely use the designed device.

4.1.4 Summary: Interviews exploring experiences of medicines in the home

A variety of medicines were discussed, with the majority being for ad hoc rather than for chronic use.

The most common challenges (100 of 217 refs) were related to the formulation itself, including problems with taste and added ingredients. Given these findings were unlikely a result of the questions wording, this finding issues a challenge to formulators to create acceptable formulations for young people.

Increased awareness of the challenges faced and tactics used when administering medicines to children allows for a greater appreciation of how this process can be improved, particularly through device D&D.

The age of self-administration was a concept many CGs were yet to consider given the young age of their child. The child's knowledge and understanding proved influential in their decision.

Knowledge and understanding also influenced the success of medicine administration. Along with physical user characteristics, familiarity and device accuracy these were key factors for consideration during device D&D.

Further in depth enquiry of self-administration is required to allow understanding of who the user is and what their capabilities and limitations are.

The majority of participants stored medicines in the kitchen, as well as administering them there. This provides insight into the likely use environment of paediatric medicines and devices, important to consider when designing a paediatric MP device.

4.2 OPINIONS OF CURRENTLY AVAILABLE DEVICES

4.2.1 INTRODUCTION

Little research has investigated user perceptions of oral medical devices. Here, user opinions of currently available liquid administration devices have been investigated alongside their thoughts of 'other' devices perhaps more suited to confectionery.

The aim of this work was to understand user preferences and influential themes to improve user acceptance and adherence to MPs through the D&D of a paediatric specific dosing device.

4.2.2 METHOD

An 8 question paper-based pictorial questionnaire was completed by naïve CGs and EC. A refined questionnaire was completed by NC. Further details can be found in Chapter 2 – Methodology, page 21.

4.2.2.1 PARTICIPANTS

Table 4.2 summarises the details of the 114 study participants. Only complete and consistent data sets were used for frequency counts. The full data set however was used during thematic analysis of participants' reasoning and of the DIY activity. The full data set was used to gain a broad appreciation of influential factors upon device preference and design.

TABLE 4.2 PARTICIPANT DETAILS

	Total participants			Complete and consistent responses		
Type	Number	Age (years)	Female (%)	Number	Age (years)	Female (%)
CGs	21	26 – 70	71	17	26 – 68	71
EC	24	4 – 12	67	8	5 – 12	75
NC	69	7 - 11	49	36	7 - 11	50

4.2.3 RESULTS

Areas investigated in this survey included, device: familiarity; preferences; comfort with independent use; ease of use and interest in use. Table 4.3 summarises the device choices made by children and CGs across each of these areas.

	Familiar	Preferred	Comfort with use	Easy to use	Interest in use	
CGs						Most
		 				Least
Children						Most
						Least

TABLE 4.3 DEVICE CHOICE SUMMARY

Child and CG device choices differ, with different devices chosen across all categories, Table 4.3. This is an important point to consider when designing a device, as a different target user (child or CG) will have difference device perceptions.

It is also worth noting the presence of the Measuring spoon across different categories. Children perceived this to be the most interesting device yet it was the least familiar, hardest to use and least comfortable device. It may be that children were least comfortable using this device because they were least familiar with it for example. Given the small sample size however, statistical analysis (Chi squared test) was not performed given the limited generalisability of the outcome.

Participants were asked to explain the reasoning behind their device choices. Alongside analysis of their DIY device designs (Appendices 4 -6, pages 199-206) the most common themes are discussed categorised as Formulation, Device and User.

4.2.3.1 FORMULATION

As in Study 4.1, the formulation's **taste** was influential for some children (7) and their CGs (1).

"You get the full impact of the taste and its boring" [NC-4: Straw]

Other children (3) commented on how the MPs **size** had influenced their device preferences.

"They're only small and it will be hard" [EC-E]

Compared to Device and User however, relatively few comments were made in relation to the Formulation itself, this was unlike Study 5.1 where Formulation greatly influenced the participants' responses. This was likely due to the device focus of Study 5.2 however.

4.2.3.2 DEVICE

CONTEXT OF USE

Within the Device theme, the device's **dosing capabilities** were by far the most referenced (143). This included reference to the device's accuracy and spillage risk (61), as well as its measurement capabilities (25) most commonly.

As in Study 4.1, device **accuracy** and the apparent risk of medicine **spillage** influenced CG and child device preferences (23+5) as well as children's perceptions of ease (8) and interest in use (25). There was a desire to have a device that was accurate and posed little spillage risk.

"Accurate. No spillage risk" [CG-C6: Syringe]

Twenty-five references were also made to dose measurement having influenced the children's perceptions of ease of use (19) and interest in use (6), both positively and negatively. Some children appeared to like the idea of measuring their medicine (6) with many selecting the Measuring spoon

for this reason. For others, dose measurement by the user brought mixed responses.

> *"This one would be most interesting because you would have to measure it" [NC-F: Measuring spoon]*

> *"You need to measure out the right amount of medicine and there is more chance to mess up" [NC-S3: Measuring cup]*

These comments along with Study 4.1 suggest that device dosing **accuracy** is an important consideration in device D&D including the potential inaccuracies during dose measurement by the user. It is suggested therefore that an MP dosing device should deliver pre-measured doses.

Many children suggested the device's **mechanism** was important, having influenced their device preferences (8), perceived ease of use (22) and interest in use (71). Children made reference to both the device administration mechanism (52) and/or the dispensing mechanism (50). They preferred basic, simple means of administering and dispensing medicines over more complex alternatives.

> *"I think the teaspoon is, because you can just tip it into your mouth" [EC-SA: Teaspoon]*

> *"I think the circle is the hardest because you have to twist it round to find to get the one you want" [NC-SE: Circle]*

Children enjoyed some level of gamification in getting the device to dispense medicine.

> *"The most interesting way to take medicine in my opinion is the Smints because I like how the medicine pops out" [NC-SG: Smint]*

> *"I think I'm right because its fun when you turn it and you will wait for it to come" [NC-S1: Bubblegum]*

These results suggest that an MP device should have a simple dispensing and administering mechanism which, where possible employs some level of gamification for child user interest.

The **commonality** (everyday nature) of devices greatly influenced the children's interest in use (53). Children were more interested in novel, less common devices such as the Bubblegum dispenser, compared to everyday, devices such as the Teaspoon.

> *"I think the gumball machine is the most interesting way because very few people have a medicine dispensing gumball machine" [NC-S9: Bubblegum]*

> *"It's something what you use in your everyday life" [NC-SF: Teaspoon]*

This suggests children would be more interested in a novel, uncommon MP device. This however, begins to contradict the importance of device familiarity, as suggested by Study 4.1. This poses a point of contention for device developers.

Children found **storage** (22) and **portability** (19) important as they considered their interest in device use. They preferred devices that were portable and allowed for medicine storage 'on the go'.

> *"Most interesting because if you put too much in you can save it for later and take it about" [NC-Measuring spoon]*

This suggests dose storage and device portability are key device D&D considerations for an MP device. This finding highlights the importance of considering device use environment. Despite Study 4.1 suggesting medicine administration takes place most in the kitchen, the study was limited to home use. Consequently device use outside of the home should also be considered.

Both children (26) and CGs (11) found the **appropriateness of a device** to be important when considering device preferences (4+11) and interest in use (22+0). Participants considered the appropriateness of a device for age (12); MPs (5) and co-administration with food/drink (7) in particular.

Many CGs and children disliked the dummy-like devices as they were childish and for younger children. However, this was one child's reasoning for their interest in the Bubblegum dispenser.

> *"My children are too old for dummys" [CG-12: Medicator]*

"The most interesting item is the gumball machine because it's childish because it normally has sweets in it" [NC-SB: Bubblegum]

Some children appeared to have difficulty conceptualising 'other' devices for their medical use, and considered some devices as inappropriate for MP use. Others appreciated the conceptual use of a device with MPs, but found the device to be inappropriate.

"It does not have any way to give medicine" [EC-L: Two-eyed minion]

"The sprinkles could get stuck in the end" [NC-Q: Dummy]

Two children and 2 CGs found the device suitability to co-administration (with a vehicle such as food or drink) influenced their preferences. A further 3 children found it influenced their interest in use. It may have been however that some children had difficult conceptualising the device's use for MPs in place of its current use with liquid for example.

"Less chance of spillage, easier to mix with fluids able to self-administer, less stress" [CG-10: Measuring cup]

"They can't carry liquid" [EC-R: PEZ and Smint]

This finding suggests that an MP device should be appropriately designed for the users age, its use for MP dosing and the possibility of co-administration with food or drink. These comments also highlight that there was some difficulty in participant's conceptualising all of the devices use with MPs. Every attempt was made to convey the device's current use to the children, without suggesting how a device would be used with MPs. Whilst this was done to limit the researcher's influence upon the children's' responses these results suggest further insight is required for some children to conceptualise device use with MPs independently.

FEATURES

The device **aesthetics** influenced both child and CG device preferences (1+10) as well as children's perceived ease (10) and interest (69) in use.

Sixty-seven references were made to the general device aesthetics with many relating to the child having a personal preference of PEZ dispenser's character for example.

"The hardest to use in my opinion is the Elsa PEZ because I hate frozen" [NC-SG: Elsa]

***"**I would be comfortable with using the Stormtrooper PEZ because I love star wars and it makes you look like eating sweets" [NC-SG: Stormtrooper]*

It is worth noting the difference in perceived ease of use across the four aesthetically distinct PEZ devices. Children selected the 2-eyed minion PEZ dispenser as the easiest to use, with the 1-eyed minion, Stormtrooper and Elsa PEZ dispenser more difficult. This suggests personal preference plays a role in children's perceptions of device aesthetics. This makes it difficult to suggest a universal aesthetic for an MP dosing device.

The majority of aesthetic-related comments (50) were made to the **device's likeness to other items** (24). These included their likeness to confectionery (18), to toys (4) and to medicines/medical products (2).

The likeness of devices to sweets was interesting for some children, whilst others, along with their CGs were concerned about this similarity.

"It's fun! And interesting and it's (like) you're eating sweets [NC-SF: Bubblegum]

"Medicine as sweets?! No!" [NC-SD: One-eyed minion]

There were four references made to the device aesthetics being **gender neutral** and how this had influenced the children's perceived interest in use.

"It's a good design; boys and girls will also like them" [NC-S6: Two-eyed minion]

These findings suggest that device aesthetics are an influential factor to consider during device D&D. The aesthetics of an MP dosing device should therefore be carefully considered, with attention paid to their likeness to confectionery or toys. This is aligned to regulatory guidelines which emphasise that paediatric medicines should not be similar to confectionery given the possible dangerous consequences (EMA 2006a).

Size also influenced the children's device preferences (8). It was less clear however, whether their preference was for a smaller or larger device.

"I think the spoon is the least interesting because it is too tiny and we always use spoons" [NC-SES]

"It's the biggest" [NC-L: Bubblegum]

This suggests that whilst size is an important factor to consider when designing an MP device, further research is required to understand whether a smaller of larger device would be preferred. Earlier device preferences however suggest that portability is key, implying that smaller devices would be preferential.

Given the suggested importance of device size it is key to consider the biomechanics and anthropometrics of child users when designing an MP dosing device. Consideration of child hand size and finger strength for example will allow for an appreciation of their capabilities in terms of device use. Equally, the device must be appropriate for adult use also, given that CGs are often the primary device user before the child.

USABILITY

Twenty-four references were made to **ease of use** (in general) by 5 CGs and 19 children. Ease of use influenced child and CG device preferences (5+5) as well as children's comfort with independent use (3) and their interest in use (11). There was a preference for easy to use devices.

"I would be most comfortable with a syringe because they are easy to use" [NC-S2: Syringe]

Both the ease of administration (21) and the ease of dispensing (7) were commented upon by the users. Again, a device which was easy to administer from was preferred, having influenced CG and child device preference (5+7), child comfort with independent use (1) and child interest in use (8). Participants were more comfortable and interested in devices they perceived as easy to administer/dispense from.

"*I would be comfortable using a teaspoon because you just put it in your mouth" [NC-S4: Teaspoon]*

"That one because you could just pour some out" [NC-C: Smint]

Device simplicity also influenced the children's choices in relation to comfort with use (2), ease of use (8) and interest in use (11) when

considering their comfort with use and ease of use, children preferred **simple** devices. When considering interest in use, they preferred more complex devices.

> *"I would be comfortable using a medicine spoon on my own because it is simple to use" [NC-S1: SES]*

> *"I think the most interesting one is the measuring spoon because it looks really confusing" [NC-SD: Measuring spoon]*

This suggests that participants prefer easy to use, simple devices, including devices which are easy to administer and dispense from. For a child to be interested in device use however, the device should be more complex. This offers a point of contention for device designers, whereby the simplicity of a device may aid ease of use, but will likely lessen a child's interest in use.

Device **speed** was also referenced by two CGs and three children. CGs preferred a quick administration, whilst children preferred being able to take their time.

> *"No spillage, quick and easy to administer" [CG-H: Syringe]*

> *"I think the pot because you can take your time and do it as fast as you like" [NC-B: Measuring cup]*

A further conflict is seen between CG preference of having a quick device and of children wanting a device with which they can take their time. This means that device designers will have to carefully consider their user group to ensure the most appropriate device specifications.

4.2.3.3 USER

Children's **affective response** (46) greatly influenced their interest in device use, with a preference for fun, cool devices over boring ones.

> *"I picked this one because it's fun" [NC-K: Straw]*

> *"It's just a boring old teaspoon it wouldn't look interesting" [NC-S2: Teaspoon]*

Participant's device choice (2 CG + 10 C) was influenced by their **familiarity**, with preferences for familiar devices that the users had used before.

> *"Children are familiar with spoons, so nothing overly alien or threatening. Provided the particles can be dissolved with minimal fluid it would allow very quick and no fuss administration" [CG-16: SES]*

Previous use (4) also influenced the children's perceptions of ease of use. Children perceived devices they had used before as easier to use, whilst novel devices were more difficult.

> *"The spoon, all you do is pour it in. You use it in everyday life so you have loads of practice" [NC-S8: Teaspoon]*

This is the opposite relationship to that found between commonality and interest in use where children perceived novel devices as more interesting. This suggests that device developers must consider their own/company requirements during design, would they prefer a device was interesting to children or that it was easy to use?

Along with familiarity and previous use, children's **knowledge** of devices affected their perceptions of ease of use, comfort with use and interest in use (8). Their knowledge of a device, or lack of, made children less comfortable using a device independently. This was the converse when considering knowledge and interest in use.

> *"I think this because I don't know how to use it" [NC-D: Straw]*

> *"The spoon is least interesting because we all know how to use it and we have all seen it" [NC-Teaspoon]*

This suggests that whilst knowledge is important for children to feel comfortable using a device alone, for them to feel interested in device use they should not have previous knowledge of the device. This links back to a preference for novel devices seen earlier.

4.2.4 Summary: Questionnaires exploring opinions of currently available devices

Through investigating device preferences, ease of use, interest in use and comfort with independent use, this study has provided insight into various key factors for consideration during device D&D and addresses RQ2: What are the requirements of the User?

This study highlights the importance of key themes within context of use, device features, usability and user when designing medical devices for children. This provides guidance for device designers and developers as to key device considerations.

Ease of use was considered to be an important element of device use and device D&D. It was therefore decided to further understand this theme a more in depth study solely focussing on ease of use was needed.

4.3 Ease of use

4.3.1 Introduction

Given the importance of **ease of use** suggested by the previous two studies and its common place as a specification for device design, what is meant by ease of use was investigated here.

There are many themes within ease of use that may or may not prove influential depending on the device, its use, its users and its use environment. Here the aim was to investigate ease of use more deeply.

4.3.2 Method

An exploratory survey was conducted using a paper-based pair-wise comparison grid. The survey was completed by NC and their CGs at a STEM event in Derby, UK. A question relating to medicine administration was also asked to further understand the likely age of self-administration when using an MP device. Further details can be found in Chapter 2 – Methodology, page 21.

4.3.2.1 PARTICIPANTS

Seventeen CGs were recruited (age and gender data not complete), 12 of these provided complete and consistent responses. 101 children were also recruited (aged 9 – 15 years, 59 % female), 84 (9 – 15 years, 57 % female) of which provided complete and consistent responses.

4.3.3 RESULTS

4.3.3.1 EASE OF USE

Figure 4.2 shows the total frequencies for each pairwise comparison completed by both CGs and children. Reading across each row, the values represent the number of times that the row theme was selected as more important than the column theme. Summing of these frequencies for each of the themes (row totals) allowed for their ranking in order of importance, Figure 4.3.

Theme			1 Dose pre-measured	2 Little chance of error	3 Size	4 Aesthetics	5 Simplicity	6 Speed	7 Familiarity	8 Bottle → mouth steps	**Total**
1	Dose pre-measured	CG		5	10	9	4	6	6	4	**44**
		NC		48	47	61	20	38	44	41	**299**
2	Chance of error	CG	7		11	11	5	6	9	8	**57**
		NC	35		60	60	34	49	56	51	**345**
3	Size	CG	2	1		10	2	3	5	5	**28**
		NC	36	23		61	10	28	40	27	**225**
4	Aesthetics	CG	3	1	2		5	3	3	4	**21**
		NC	22	23	22		18	21	28	18	**152**
5	Simplicity	CG	8	7	10	7		8	10	9	**59**
		NC	63	49	73	65		60	56	48	**414**
6	Speed	CG	6	6	9	9	4		10	7	**51**
		NC	45	34	55	62	23		58	46	**323**
7	Familiarity	CG	6	3	7	9	2	2		5	**34**
		NC	39	27	43	55	27	25		40	**256**
8	Bottle → mouth steps	CG	8	4	7	8	3	5	7		**42**
		NC	42	32	56	65	35	37	43		**310**

FIGURE 4.2 FREQUENCIES OF EACH PAIRWISE COMPARISON

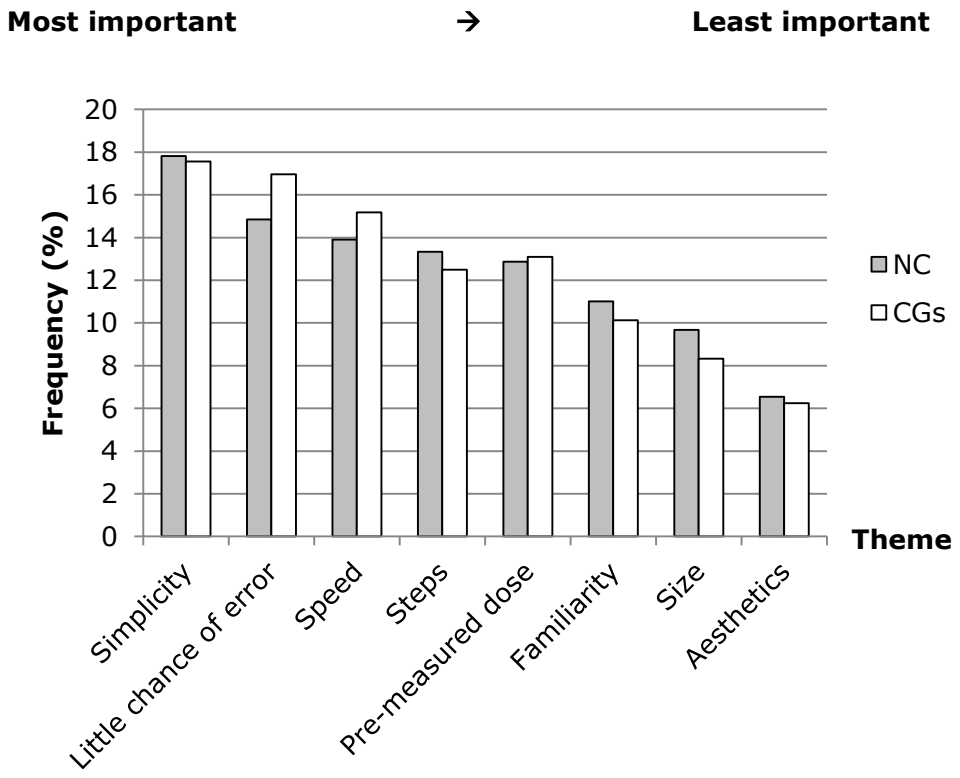


FIGURE 4.3 EASE OF USE THEMES RANKED BY IMPORTANCE

Figure 4.2 and 4.3 summarise the results of this study, showing that **simplicity** was the most important theme for both children and CGs. A**esthetics** was the least important. It is worth noting that children and CGs both ranked the 8 themes in the same order, aside from **steps** and **pre-measured dosing** (which switched order of importance in CGs as compared to children).

The finding that simplicity is a key requirement supports the findings of Study 4.2 where its importance in device preferences was highlighted.

Device familiarity and aesthetics however were found to be important considerations previously (Study 4.1 and 4.2) whilst being among the least important factors here. This may have been due to the fact that the children were presented with various devices upon which to make comment in Study 4.2, whilst here in Study 4.3, they were asked about device use more generally. This may have provided less chance that their responses were influenced by a particular device aesthetic for example.

4.3.3.2 MEDICINE ADMINISTRATION

Participants were asked who typically administers their (child's) medicine(s) to further understand the likely age of self-administration.

Of the six CG responses, all noted that they or the child's parent would administer the medicine. This was consistent with responses from the children, where the majority claimed their medicine was administered by their parent(s). Forty-five children stated that it was only their parents who administered their medicine with a further 12 referring to their parent(s) alongside other CGs. All 57 of these children were aged between 9 and 14.

The second most referenced administrator (by children) was themselves with 16 children aged 10-15 years stating only they administered their medicine. A further 11 children mentioned themselves alongside other CGs.

4.3.4 SUMMARY: PAIRWISE COMPARISON OF EASE OF USE THEMES

This study has shed light on the importance of key influential factors within **ease of use**. It suggests that a device's **simplicity**, **accuracy** and **speed** are most important, whilst the device **aesthetics** and **size** and less so.

Simplicity, accuracy and speed were all highlighted in Study 4.2. This further highlights their relative importance in device design.

This provides insight for device D&D with respect to an easy to use device specification and serves to guide D&D towards simple, accurate and quick devices.

This work also highlighted that the majority of children sampled (9 – 14 years) relied on their parents (to some degree) for medicine administration. This suggests who the likely user of an MP device would be.

4.4 DESIGNING A MEDICAL DEVICE FOR KATY

4.4.1 INTRODUCTION

Study 4.2 closed with a DIY activity where the participants were asked to conceptualise a device capable of handling the MP formulation. In this study 5.4, this device designing is further explored through a co-design activity with children. This detailed DIY activity asks the children to design an MP device before rationalising their design choices and considering their device's use. The aim of this study was to further understand user preferences and to appreciate further factors influencing children's device designs.

4.4.2 METHOD

Children were introduced to the research area through a storybook featuring character Katy. Having listened to the story the children were invited to create a device to help the character. After conceptualising a device the children completed a worksheet rationalising their design choices. Further details can be found in Chapter 2 – Methodology, page 21.

4.4.2.1 PARTICIPANTS

31 children (4 - 10 years, 87 % female) partook in the activity. Four children chose to work in pairs whilst the majority worked independently. In all cases, their CG was present in the room to supervise. On occasion CGs helped their child complete the worksheet questions if the child was struggling.

4.4.3 RESULTS

Children were asked as to why they had designed their device the way they had; whether it was based on something they had seen before, how the device worked, how it prevented medicine spillage and how it measured dose. They were also asked who would use their device and where, before rationalising these choices in terms of device design.

The majority of children (11) said that both Katy and her mum would use their device and that they could use it anywhere. They decided that Katy

would need to be at least 10 years of age to use the device independently (5).

Consideration of the 29 devices designed by the children (Appendix 11, page 213) and their written responses, allowed for an appreciation of the likely themes influencing their device designs. As before, the resultant themes were grouped as Formulation, Device and User.

4.4.3.1 FORMULATION

Very few references (8) were made to the MP formulation. This was likely a result of the activities' questions focusing on device design. Formulation references included the DF's likeness to sweets (2), the ease of swallowing (1) and their size preventing spillage (1) for example.

4.4.3.2 DEVICE

CONTEXT OF USE

The majority of children claimed their device was **novel** and not based on something they had previously seen (59 %). This is similar to the desire for non-common devices seen in Study 4.2, where common devices were perceived as less interesting.

Administration impacted the children's design choices particularly when they considered Katy's (4). Children explained that their device had variable modes of administration including inhalation, the use of a secondary device and co-administration with food. They also claimed that direct oral administration was something that prevented medicine spillage (2).

> *"Tip head back and tip them in" [P8]*

> *"The bottom can have several adapters like to inhale or stir. The adapter to inhale depends on how fast the medicine dissolves as to if it had to go directly under your tongue" [P2]*

The mode of administration was also found to be influential in Study 4.2, where basic means of administration were preferred. Studies 4.1 and 4.2 also suggested an MP device should be amenable to co-administration with food/drink to improve the acceptability of the poor tasting formulation.

This suggests that device designers should carefully consider the mode of MP administration when conceptualising dosing devices. This will be further aided by the investigation into the most appropriate means of MP administration by other research groups.

Seven references were made to the device's **dosing capabilities,** including four to age-based dosing and two suggesting the dispensing mechanism would determine dose.

"Press how old you are. It will give you right amount" [P10]

"It shoots out one at a time" [P25]

Means of **dose measurement** included: the use of a measurement marker (2); the device having programming (2); volumetric dose measurements (3), mass-based measurement (2); pre-determined dose portions (2); inserting the correct amount of medicine and the device only containing a single dose.

"Line on the side" [P5]

"Pre-determined portion control E.g. 4 tablets per turn" [P11]

The importance of dose measurement was highlighted in Study 4.1 as an important stage of self-administration. It also influenced device preferences in Study 4.2 whilst Study 4.3 suggested that a pre-measured dose was less important however. Despite this pre-measured dosing has the potential to overcome some accuracy and spillage concerns making it an attractive design feature for device developers.

Accuracy and **spillage** concerns also played a role in determining the age Katy would be able to **self-administer** using the children's devices (4). Particularly the risk associated with under/over dosing (2), as well as dose measurement (5).

"If she's young she may take too many or too less tablets" [P28]

The risk of **mess** (5) and device **safety** (3) were considered alongside **portability** (6) when the children decided on the use environment for their device. A preference for lower spillage risk, increased safety and elements of device portability was apparent.

"Easier for grown-ups and they wouldn't spill it" [KM-P13]

"A child lock could be place on the handle" [P11]

"It can be carried anywhere. It's small and discreet" [P6]

This element of portability was highlighted in Study 4.2, as a key consideration of use environments outside of the home. This suggests that portability is a key influential factor for consideration during MP dosing device D&D.

When the children considered the environment in which their device would be used, they commented upon how the device would be used in this environment (3), including it being somewhere Katy could be supervised (2), has easy access (1), facilities (1), enough space (1) and being somewhere Katy spent most of their time (1).

"There's a sink and hand wash facilities" [P4]

"Parent would be around for help. Also it is safe, sturdy environment to use it" [P4]

These specifications highlight user environment attributes for consideration during MP device D&D.

FEATURES

Children highlighted device **aesthetics** (8) when explaining their explanations of their device designs. Some desired devices that were attractive and appealing to children, whilst others preferred a medical aesthetic.

"A cat to make it appeal to younger kids" [P9]

"So it looks medically a bit" [P25]

This is similar to the suggested importance of device aesthetics in Study 4.2, but goes against Study 4.3 where much less importance was placed on them.

The device **size** was important when the children considered the use of their device by Katy and her mum (9). Children preferred small devices given the link to **portability.**

"Small enough to put in your bag" [P1]

Size was highlighted in Study 4.2 as an important feature. The findings of Study 5.4 further support the preference for small devices given the impact on portability.

Other features referred to by the children included buttons, sides and seals. Children wanted a device that was operated by the pressing of a button (7). **Buttons** (3) were also suggested as ways of ensuring correct dose measurement. Whilst device features such as sides (4) and seals (3) when considering important in their device preventing medicine spillage.

"You push the button and one dose comes out" [P6]

"It will have glass sides so it doesn't spill" [P4]

Previous studies did not provide this level of specific detail relating to device features. They did however, emphasise the importance of the device mechanism as well as highlighting the need for accurate dosing and a reduced spillage risk. This provides further insight to guide MP device design D&D highlighting possible device features for incorporation.

USABILITY

Ease of use was a key theme when children considered their device designs (7), the likely user and the use environment (23).There was a desire that the device be easy to use as well as being simple (8) and quick (2).

"So it's easy to use" [P23]

"It is simple and child friendly" [P26]

This echoes the findings of Studies 4.2 and 4.3 which conveyed the user's desire of easy and simple to use devices. Study 4.4 also highlights the importance of device speed which was found to be important in Study 4.3 also. Here, the desire is for a quick device, whilst in Study 4.2, the children's preference was to be able to take their time. This serves to inform device designers' decisions, particularly with reference to an MP dosing device.

4.4.3.3 USER

Knowledge was a key theme in the children's reasoning for their user and use environment choices (8). Knowledge included Katy being able to count (3), knowing how to use the device (3) and having knowledge of the correct dose.

"Learning to turn the handle the right amount of times and able to count" [P11]

Knowledge was also important in Study 4.1 when CGs considered medicine self-administration. It was also important in Study 4.2 where there were mixed results relating to knowledge, previous use and commonality and what this meant for device D&D. This suggests that user knowledge should be considered during the D&D of paediatric MP dosing devices.

Children said that Katy would need to be sensible, responsible and **trustworthy** (4) as well as being **supervised** (6) when using their device.

"She needs supervision and alongside her mum" [P3]

The user's **maturity** was also important, with Katy's mum being mature enough to use the device or Katy needing to be mature to use it (2).

The children also considered Katy's **independent use** (3) and the age-appropriateness (3) of their device. Physical restrictions influenced their choice of user, for example Katy/her mum needed to be tall enough for device use (2).

"She's tall and grown up enough" [P26]

Physical considerations were also important in Study 4.1 when CGs considered their children self-administering medicines. Study 4.4 further highlights the importance of anthropometric and biometric data when designing devices for specific user groups (Kroemer 2005).

Comments were also made relating to Katy's **health and wellbeing** (4) when children explained Katy's device use. They wanted their devices to be **fun** (4) for Katy to use.

"It will help Katy get better" [P27]

"So it doesn't seem like a boring task to keep having medicine, more fun" [P1]

The importance of the **affective response** was also apparent in Studies 4.1 and 4.2, being important in successful administration and in the child's interest in device use. Study 4.4 further demonstrates the importance of appreciating the user's interaction and relationship with a device during the D&D process.

4.4.4 Summary: Co-design activity exploring the design of medical devices by children

This study further highlights key factors for consideration during MP device D&D. These include the administration mechanism, dosing capabilities, dose accuracy, aesthetics, ease of use and user's knowledge and affective response having been elicited here through collaboration with child users.

This study provides further evidence of the importance of device aesthetics (as suggested by Study 4.2) and for accuracy and spillage risk (as suggested by all three of the previous studies), this study has provided a further level of detail, with specific features suggested by the children.

CHAPTER 4 - DISCUSSION

Little research has investigated the use of paediatric medicines in the home. Walsh et al. (2013) investigated medication errors of paediatric cancer patients in the home across various sites and Huang et al. (2009) looked at children's perceptions of using their assistive devices in the home. However, there is a lack of literature reporting the broad use of paediatric medicines in a domiciliary setting.

There is also limited literature related to child and CG perceptions of available liquid dosing devices. Whilst Pfützner et al. (2008) have investigated patient perceptions of prefilled insulin devices, and Walsh et al. (2015) the perceptions of HCP on oral and pulmonary devices, a knowledge gap existed surrounding paediatric perceptions of available oral medical devices.

Ease of use is commonplace as a device requirement, but how this is perceived by children is somewhat unclear. Studies are regularly performed by design companies in controlled laboratory based environments to ascertain how easy to use their prototype is. However, what exactly ease of use means to different users and in different, more 'real-life' scenarios is less clear.

Co- or participatory design is often used in device D&D, with many HF methods suitable for interactions with child users. Co-design activities allow the collaboration between designers and the experienced users to generate effective design concepts (Wilson and Sharples 2015). As a commonly used method in medical technology, its application in designing an MP dosing device is less well documented. Melonio (2013) and Vaajakallio et al. (2009) highlight the merits of co-design activities with children given their creativity and unconventional viewpoints. It is the involvement of children during device D&D that can prove fruitful, particularly in ensuring an acceptable end-product.

In this chapter, studies have addressed a number of these knowledge gaps relating to paediatric medicine use in the home, user perceptions of currently available devices, children's perceptions of ease of use and factors important in child device design. Through addressing these knowledge gaps a greater understanding of paediatric user requirements is achieved (RQ2).

The analysis of each of the four studies has elicited a number of key themes influential upon medical device D&D, specifically of an MP dosing device.

Whilst usability and ease of use have long been documented as important considerations during device design (Quesenberg 2001; Privitera 2015). Determining what ease of use really means to a child and how to assess this for a new device can be challenging. Its importance in the D&D of an MP dosing device for paediatrics was yet to be specifically considered before this work.

It is appreciated that usability considers the effectiveness; efficiency; engagement; error tolerance and ease of learning (Quesenberg 2001). This has been further evidenced in these studies through the participant views with the importance of device size, simplicity, accuracy, speed and ease of use. This suggests that an MP dosing device should be small (and portable), simple, accurate and quick in order to be easy to use.

The importance of device use context in the design of an MP dosing device has been demonstrated through the studies of this chapter. This includes careful consideration of the use environment and the likely state of mind of the user. These key considerations have been exemplified previously by where the importance of considering who the likely user would be and where they would likely use the device is documented (Shah and Robinson 2008; Money et al. 2011; Martin et al. 2012; Sharples et al. 2012). This is the first time user-centered HF studies have been used to elicit user requirements of an MP dosing device however.

The user themselves has been shown to be influential in these studies with their familiarity, knowledge and affective response playing key roles in determining device preferences. Whilst familiarity has been documented to affect user interactions with technology (Holzinger 2008; Pan et al. 2015) and children's perceptions of food (Birch 1979; Dovey et al. 2008; Salvy et al. 2008; Mustonen et al. 2012). Its role in medical device development is less well documented. Here, its role is exemplified in child and CG perceptions of devices, particularly in relation to the development of an MP dosing device.

A user's knowledge has also been documented to affect medicines use (Abraham et al. 2017), patient experience, their perceptions of medicines

and their adherence to medicine regimes (McQuaid et al. 2003). This work places further significance on the finding of these studies relating to the importance of user knowledge.

The users' affective response has also been shown to have been influential in the design of a paediatric MP dosing device. This is supported by the importance of the affective response by (Khalid 2006). They however, discussed the importance of diversity in understanding emotional needs as part of design requirements, without specific consideration of paediatric users. This work therefore adds evidence to support the importance of user affective response in device D&D.

All four studies have suggested device aesthetics are important to consider in the D&D of an MP dosing device. It is still unclear however as to what the preferred aesthetic profile would be. The importance of device aesthetics is not new; they have been shown to prove influential upon user perceptions of devices particularly in relation to ease of use previously. A Hitachi Design Centre found that more beautiful products were perceived to be easier to use than those that had less visual appeal despite users sometimes having more difficulty interacting with the more visually appealing design (McVey). The relationship between user pleasure and sensual gratification has also been shown (Hekkert 2006). As well as the importance of emotion upon our decision making which has been widely documented, though some would deny that they are influenced by emotion when choosing between one product and another, scientific studies have shown that emotion plays a large role in how everyone makes decisions. All things being equal, we would rather interact with an elegantly designed product than one to which little thought was given to aesthetic aspects of the design. Given a choice among products with similar functionality and usability, we often choose one product over another for purely aesthetic reasons. Exactly what a beautiful or elegant MP dosing device would look like remains to be seen, the importance of the aesthetics however have become further apparent through this Chapter.

The finding that formulation taste can affect successful medicine administration is not surprising. There has been increasing research into the poor taste of paediatric medicines, with much work aiming to overcome the bitter taste of APIs to improve adherence to children's medication (Mennella et al. 2013).

CHAPTER 4 - LIMITATIONS

The results of this chapter may be limited by the demographics of each sample populations as well as the location of the study and its specific context. The majority of participants were also self-selecting either on a direct personal level or through their schools. This will have impacted the population demographic, with more active recruitment required to engage with those users unlikely to engage of their own fruition.

Aside from Study 4.4, 3 studies had fairly small sample sizes, limiting the generalizability of the findings to the wider UK and global population.

It is also appreciated, that whilst measures were in place to reduce researcher bias, this will have inevitably affected the questions and participants responses. The researcher will have unknowingly influenced the children and their CGs during studies as well as influencing thematic analysis.

It is also important to consider the effect of other people upon the participants' when completing each of the studies, including the presence of teachers, parents and friends. This is particularly important when considering the group nature of all studies (to some degree) as peer pressure and conformity, are known to influence young people (Baumen and Ennett 1996; Salvy et al. 2012). It should also be noted that despite instructions not to, some CGs did aid their child's completion of questionnaires and worksheets. This will have introduced some bias to the results.

Despite various endeavours to limit the method bias, each study will have been limited by the method employed. For example, whilst picture-based tick box questionnaires provide simple, clear and quick means of data collection, they are limited in eliciting further in-depth qualitative responses relating to reasoning. Conversely, open-ended questions allow for breadth in responses, these however can often be difficult to categorise and are subject to thematic analysis which is inherently biased by the researcher.

CHAPTER 4 - CONTRIBUTIONS TO THESIS

These four studies have provided insight into factors influencing user perception and use of medical devices.

This work address RQ2: What are the requirements of the User? Through investigating paediatric medicine use in the home, user perceptions of currently available devices, ease of use and child-guided device design.

This research has highlighted key considerations for the D&D of a paediatric MP dosing device including the desire for an accurate, portable, quick, small, easy to use device. The device should also pose little risk of spillage and be appropriate for its anticipated environment of use; the kitchen, when at home (Study 4.1).

It is also key to appreciate the user's interaction with the device, including their familiarity, their knowledge and how common the device is. The user's state of mind and their affective response should also be considered.

Whilst it is highlighted how important device aesthetics are in user device interactions a preferred aesthetic profile for an MP dosing device is less clear.

The formulation's taste should also influence the device D&D in terms of the administration method (and mechanism). The device could be amenable to co-administration with a vehicle such as food or drink to limit the negative affective of taste on successful administration (Study 4.1). Further formulation research into MP acceptability will aid in this.

Consideration of these findings alongside the requirements of the Formulation (Chapter 3) serve to inform MP device designs in Chapter 5.

CHAPTER 5 - DEVICE

A device specification (Table 5.1) was created through consideration of Formulation and User requirements (Chapters 3 and 4), regulations and input from Pfizer. These considerations served as a starting point for device D&D.

TABLE 5.1 TEN KEY DESIGN CONSIDERATIONS

Device requirements	
Suitable for paediatric patients with chronic conditions	
Prevent foreseeable misuse and overdose	
Administration method flexibility (formulation taste issue?)	
Storage for a month's supply of MPs	
Formulation	User
Can handle free-flowing spherical particles between 150 and 500 µm diameter without damaging them	Ease of use, speed, simplicity, size and device aesthetics
Capable of accurately dosing 50 – 1500 mg doses in small increments (+/- 15 %)	Device portability and spillage risk
Protection of MPs from moisture and static forces	Environment of use and users state of mind, affective response and knowledge

A series of seven device-based studies narrowed the design brief, having further understood the broad design landscape, Table 5.2.

TABLE 5.2 DEVICE-BASED STUDIES

Study	
5.1	Available devices audit
5.2	Mass vs Volume
5.3	Accuracy and precision
5.4	Mass-based device audit
5.5	Concept generation - Researcher
5.6	Moving MPs
5.7	Further concept generation – Collaboration with design students

5.1 AVAILABLE DEVICES AUDIT

5.1.1 INTRODUCTION

To initiate the D&D process it is common for developers and designers to review the currently marketed devices to ascertain the current state of art and appreciate likely design improvements.

5.1.2 METHOD

A series of device audits were performed to investigate the appropriateness of 21 different devices for handling MP-like formulations, either in their current form, conceptually or with some modification. Further details can be found in Chapter 2 – Methodology, page 21.

5.1.3 RESULTS

All 21 devices work in slightly different ways (Table 5.3) allowing for appreciation of various methods for handling MPs. The majority of these devices use volumetric means of dose measurement (95%) whilst being fed manually (62%). Many of the mechanisms rely on the manual filling of a predetermined volumetric container, with some devices allowing for measurement verification. The majority of devices currently had the ability to dispense many entities (95%) often of their confectionery or would dispense many MPs in their current form. Modification of the internal mechanism could alter this however.

TABLE 5.3 MECHANISM FOR DISPENSING MPS

Device		Dispensing method			
		Feed	Measurement	Mechanism	Entities released
A - C	Spoons	Manual	Volumetric	Volume fill	Many
D	Measuring spoon	Manual	Volumetric	Volume fill & measurement verification	Many
E	Weighing spoon	Manual	Mass	Load cell	Many
F	Measuring cup	Manual	Volumetric	Volume fill & measurement verification	Many
G	Syringe	Manual	Volumetric	Volume fill & measurement verification	Many
H	Medicator	Manual	Volumetric	Volume fill & measurement verification	Many
I	Dummy	Manual	Volumetric	Volume fill	Many
J	Mini-tablet dispenser	Gravimetric	Volumetric/ number	Rotation	Single or many
K	Circle	Pre-filled	Volumetric	Volumetric	Many
L	Fish food dispenser	Rotation	Volumetric	Gravimetric	Many
M	Pet food dispenser	Gravimetric	Volumetric	Rotation	Many
N	Sugar dispenser	Gravimetric	Volumetric	Slide	Many
O	Bubblegum machine	Gravimetric	Volumetric	Rotation	Single
P - S	PEZ dispensers	Manual	Manual	Opening size	Single or many
T	Smint dispenser	Pre-filled	Volumetric	Push	Single
U	Milkshake straw	Pre-filled	Volumetrically filled and surface contact during use	Suck liquid over	N/A

Given the large number of devices assessed, one device (group) is presented in detail here as an example, with a summary table comparing all 16 devices found in Appendix 12, page 217.

5.1.3.1 BASIC SPOON DEVICES

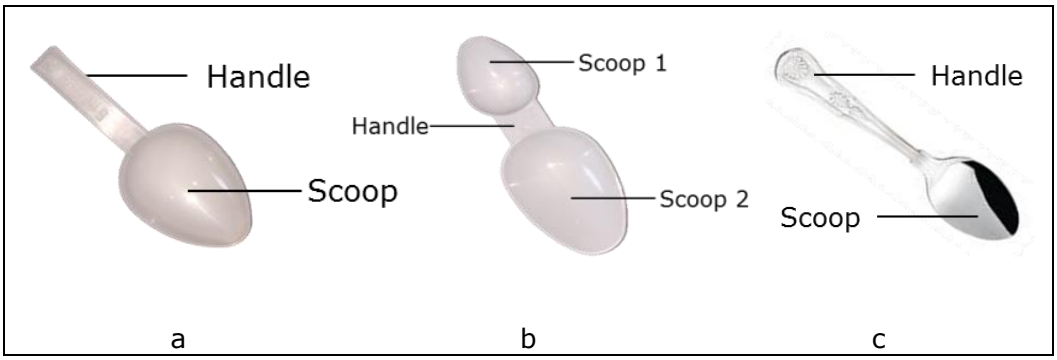


FIGURE 5.1 THE THREE BASIC SPOON DEVICES INVESTIGATED

The spoon devices (Figure 5.1) use volume to determine the liquid dose. The scoop has a pre-defined volume, usually a teaspoon or 2.5, 5 or 10 mL. These devices rely on the user to manually add the liquid until the scoop is full before ingestion, Figure 5.2.

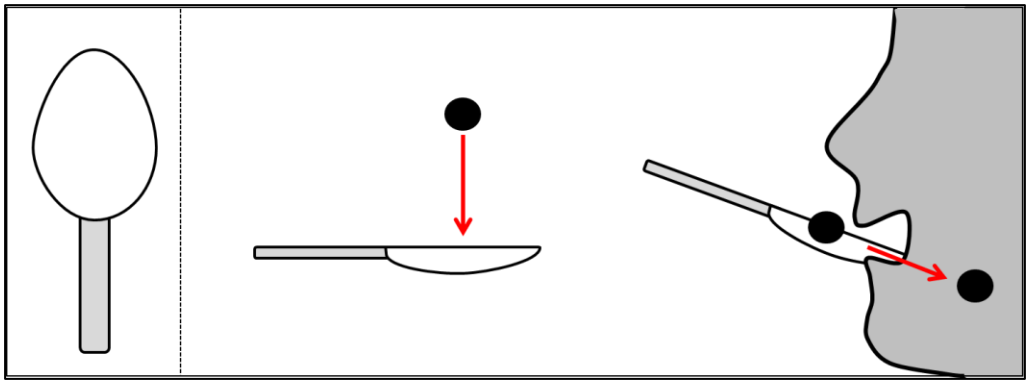


FIGURE 5.2 USE STEPS FOR THE SPOON BASED DEVICES

Use of these devices is simple, with only two key use steps, filling and emptying the spoon, Figure 5.2.

These devices provide great flexibility in terms of dosing frequency being amenable for use at any time of the day as well as repeated dosing following cleaning. They are also flexible in terms of administration method, allowing for direct oral administration (Figure 5.2), or co-administration with food or drink. These spoons do however offer limited dose flexibility, given their pre-set volumes and that they only offer one or two (Figure 5.1b) dose volumes.

These spoon-based devices are suitable for use in paediatric patients as well as being capable of handling free-flowing spherical MPs between 150 – 500 μm without damage. They are also of a handheld size, making them portable and easy to transport. They are also sufficiently large to prevent being too fiddly. They can be used suitably quickly given their simple form, there is however a reliance on the user to load the scoop, restricting the speed of use. They are also simple and easy to use and cheap to produce. Given that they are commonly used devices the user will likely be familiar with them and have knowledge of their use.

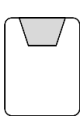
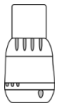
These spoon-based devices do not however prevent foreseeable misuse, cannot store a month's supply of medication and do not protect the MPs from moisture and static. Given that they also do not provide a pre-measured dose this allows room for dosing error, particularly given the great reliance on user for measurement.

The remaining 18 devices were critically assessed in the same way against the key device requirements. A summary can be found in Appendix 12 (page 217) which compares the requirements where ranking is possible or on a yes/no basis if not. Devices were ranked against each other with a score of 16 attributed to the best device(s) with subsequent rankings made from there; hence therefore equally ranked devices mean that not all ranks between 1 and 16 are always assigned.

The highest ranked device was the Smint dispenser (T) scoring 84 points, followed by the Straw (U) and the Balda mT dispenser (J) with 82. The lowest ranked devices were the Dummy (I), Pet food dispenser (M) and Fish food dispenser (L) with 73, 58 and 36 points respectively.

Table 5.4 demonstrates the fulfilment of 'non-rank-able' criteria of the top three devices. Whilst it is clear that (in its current form) the Balda mT dispenser fulfils most of the key criteria, the Smint dispenser and Milkshake straw could also achieve these with slight modification and refinement.

TABLE 5.4 HOW MANY OF THE OTHER KEY CRITERIA DO THE TOP 3 DEVICES FULFIL?

Key criteria	Device   		
Suitable for paediatric patients with chronic conditions	Likely		
Prevent foreseeable misuse and overdose	Possible with refinement	To some degree	Yes
Flexibility in administration method	Yes	No	Yes
Storage for a month's supply of MPs	Possible	No	Yes
Handle free-flowing spherical particles without damaging them	Not in current form but possibly with refinement	Possibile if open ended, or drug coating removed from internal beads	Likely, given the capability with mTs
Must determine dose accurately (+/- 15 %)	Possible with refinement		Yes
Flexibility in dosing amount	Yes, but relies on user to count expulsions	Not currently	Limited to between 1 and 21 mTs
Protection of MPs from moisture and statics	Possible with refinement		Likely, and possible through refinement
Some degree of portability	Yes		
Spillage risk	Minimal	None	Minimal
Aesthetics	Confectionary like		Medical
Users state of mind, affective response, familiarity and knowledge	Common, everyday items with which user is likely to be familiar		Less familiar

5.1.4 SUMMARY: INVESTIGATION OF CURRENTLY AVAILABLE DEVICES

This study provides insight into how the Formulation and User requirements can be satisfied by existing devices, in their current form or with slight modification.

This has provided a variety of devices and mechanisms upon which further concept refinements could be based. The three highly scored concepts provide guidance for subsequent work.

5.2 MASS VS VOLUME

5.2.1 INTRODUCTION

All (bar one) of the devices in Study 5.1 used a volumetric means of dose determination. Given the knowledge gap surrounding mass-based MP dosing and its likely improved accuracy over volumetric methods, mass-based mechanisms were investigated.

5.2.2 METHOD

A basic tapped density experiment was performed to investigate the likely effect that movement would have upon the packing on the MPs. Further details can be found in Chapter 2 – Methodology, page 21.

6.2.3 RESULTS

When the H&T sample was subjected to tapping, the volume occupied decreased, Table 5.5. This is represented by the increased tapped density of 0.947 g/cm^3 compared to the bulk density of 0.898 g/cm^3. The mass, however remained consistent a 34.58 g. This suggested volume-based dose measurement of H&Ts would be less accurate than mass-based.

TABLE 5.5 H&T'S TAPPED DENSITY (PAGE 100)

Mass (g)	Volume (cm^3)			Density (g/cm^3)	
	Initial	After 500 taps	After 1250 taps	Bulk	Tapped
34.58	38.5	37.0	36.5	0.898	0.947

5.2.4 Summary: Mass vs volume

This brief experiment has shown that the packed density of H&Ts changes when subjected to tapping. This suggests that a volumetric-based device mechanism could lead to inaccurate dose measurements having been subject to movement or vibration.

Mass-based dispensing was therefore investigated in order to achieve maximal dosing accuracy. This is of particular importance when the dose is small and a few MPs could prove crucial in achieving dose accuracy (+/- 15 %).

5.3 Accuracy and precision

5.3.1 Introduction

Given that mass-based dose measurement has been shown to be more accurate than volumetric, six ready available cost-effective balances were assessed across the mass range of interest. It was envisaged that should these devices prove accurate and precise between 50 and 1500 mg, their mechanism would be further investigated for potential incorporation in future device concepts.

5.3.2 Method

Three experiments were performed to determine the accuracy and precision of the six balances. The balances were used to measure both increasing and decreasing masses of calibration weights as well as being compared to the gold standard calibrated reference balance. Further details can be found in Chapter 2 – Methodology, page 21.

5.3.3 Results

5.3.3.1 Addition of mass

Figure 5.3 highlights how accurate and precise each of the six devices was. Considering the mass range of interest it is noted that the top three devices (A) were accurate and precise across this mass range. The remaining three devices, (B) were a less precise (larger standard

deviations) and less accurate (deviation from the known calibration weights) however. These three devices were also not capable at detecting all masses of interest therefore removing them from subsequent investigations.

5.3.3.2 Comparison with lab scales

Figure 5.5 plots calibration weight mass as determined by each of the three devices (X, Y and Z) against the mass as determined by the calibrated reference balance. This allowed for comparison of device accuracy with the 'gold standard'.

All three devices were as accurate as the calibrated balance when determining mass between 50 and 1500 mg.

5.3.3.3 Loss of mass

All three of the devices were also accurate at determining loss in mass between 50 mg and 1500 mg (+/- 15%) compared to the calibrated balance, Figure 5.5.

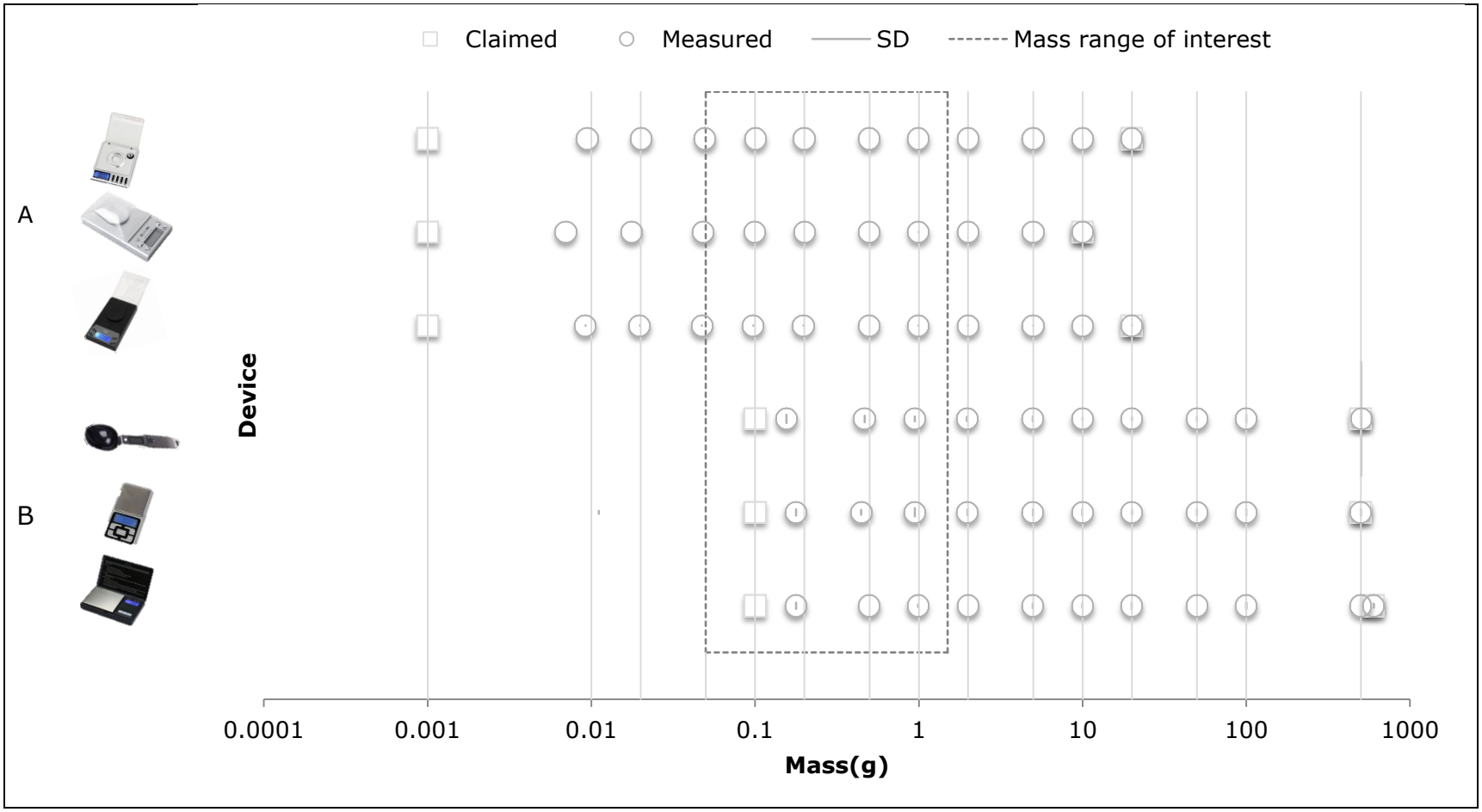


FIGURE 5.3 DEVICE ACCURACY AND PRECISION WITH CALIBRATION WEIGHTS

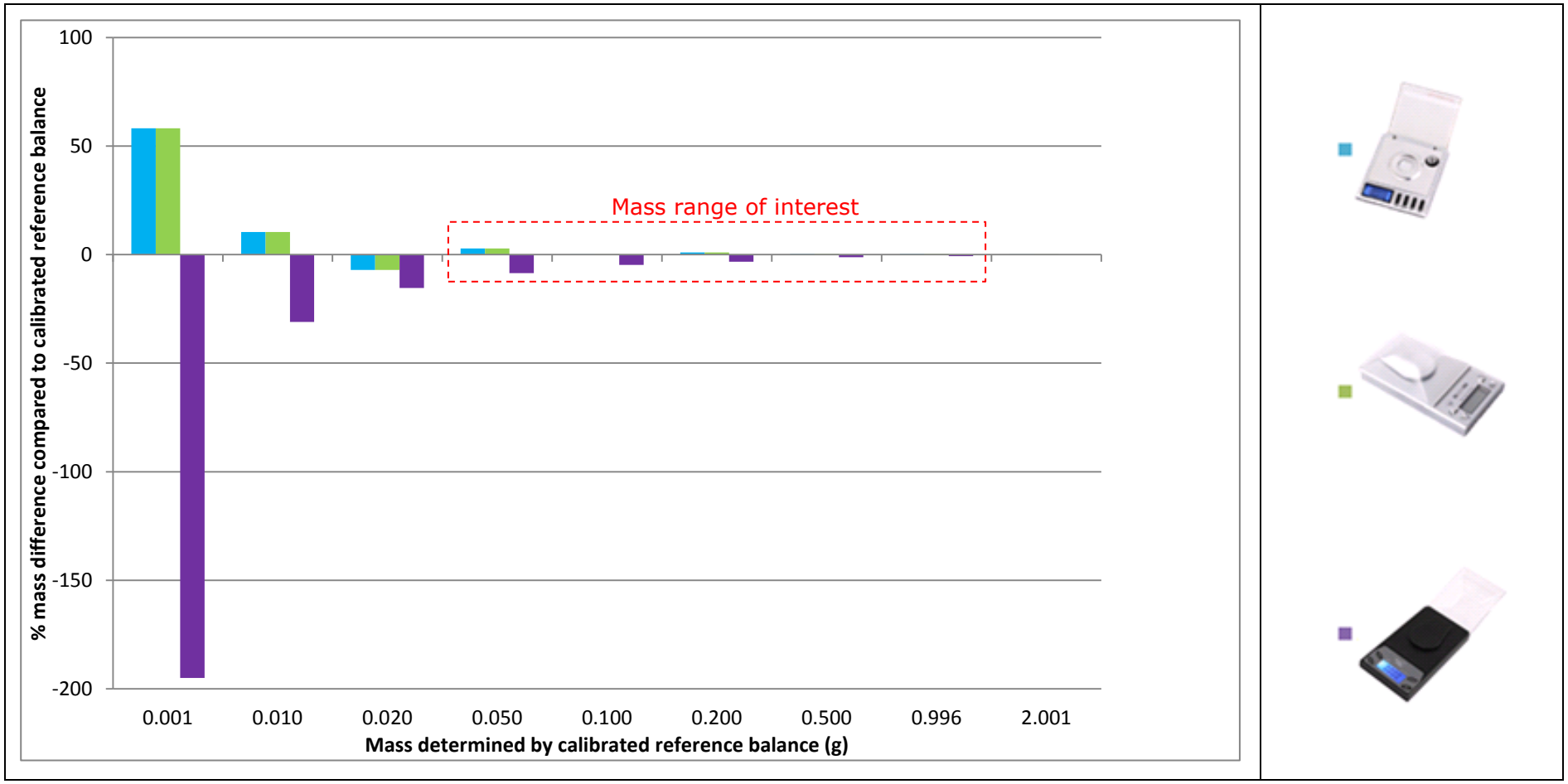


FIGURE 5.4 PERCENTAGE ERROR OF DEVICES COMPARED TO CALIBRATED BALANCE (ADDITION OF MASS)

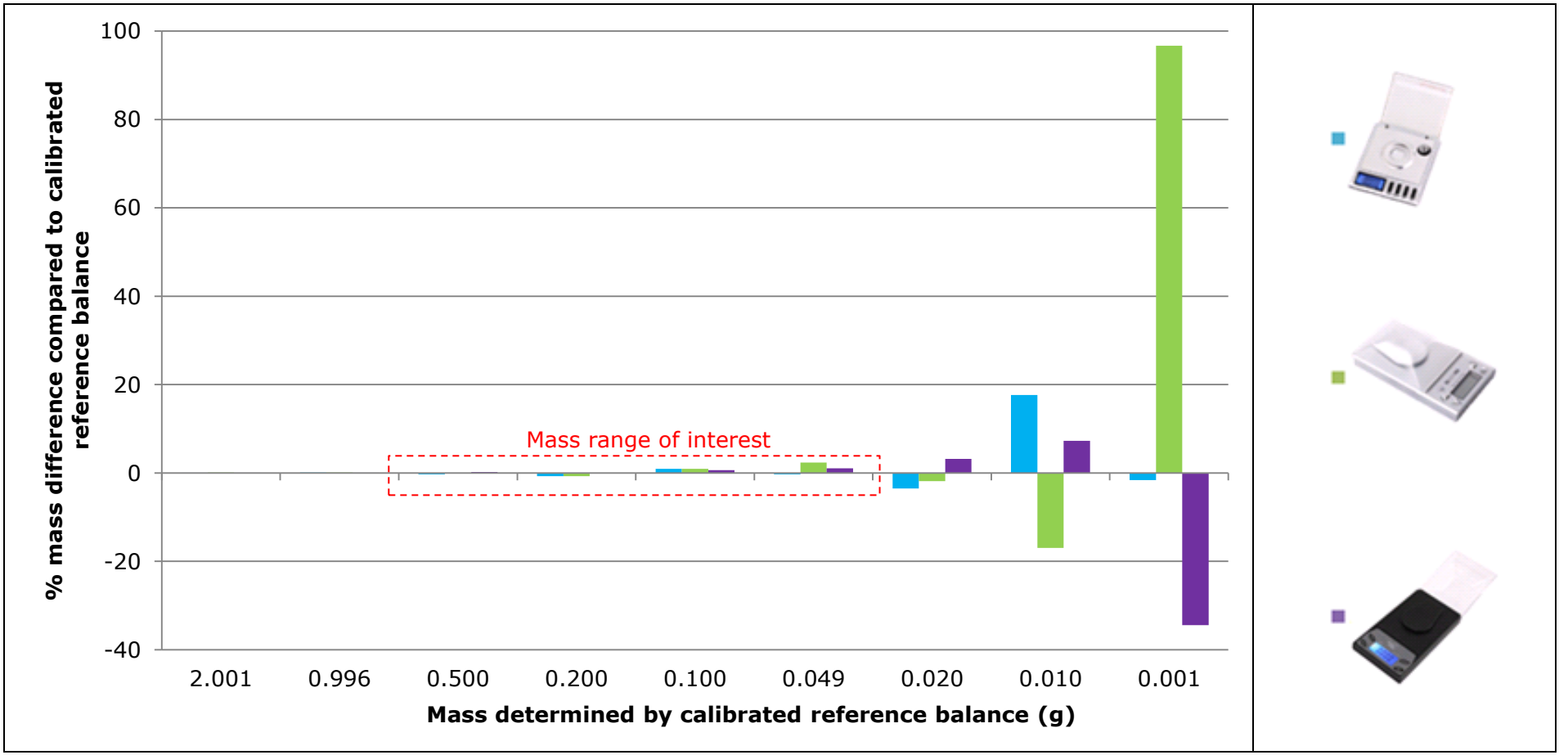


FIGURE 5.5 PERCENTAGE ERROR OF DEVICES COMPARED TO CALIBRATED BALANCE (LOSS OF MASS)

5.3.4 Summary: Accuracy and precision

Of the six readily available cost effective balances assessed, three fulfilled the requirement of detecting and measuring mass between 50 and 1500 mg. These three devices were sensitive enough to detect increments in mass of individual H&Ts (4.39 mg), but were less accurate in detecting small mass losses (≤ 10 mg for devices Y and Z, ≤ 1 mg for device X).

5.4 Measuring device audit

5.4.1 Introduction

Having identified three devices that satisfy the required dose accuracy criteria, a device audit was performed to understand device mechanisms.

5.4.2 Method

The devices were disassembled part by part with a log kept of all components. Photographs were taken during deconstruction to document component parts and likely device assembly. Further details can found in Chapter 2 – Methodology, page 21.

5.4.3 Results

Given the apparent similarity between devices Y and Z, only Y is presented here (Figure 5.7) alongside device X, Figure 5.6.

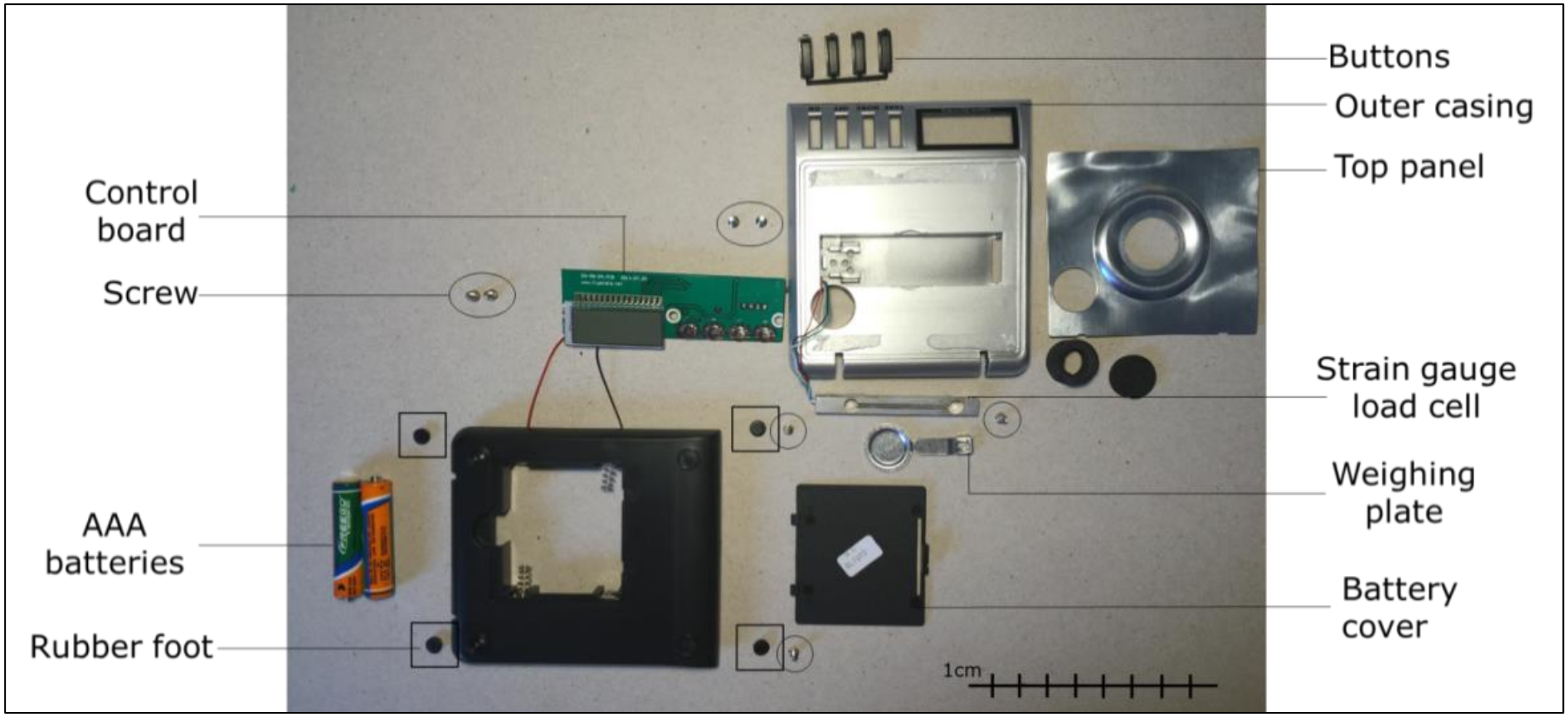


FIGURE 5.6 DEVICE X'S COMPOSITION

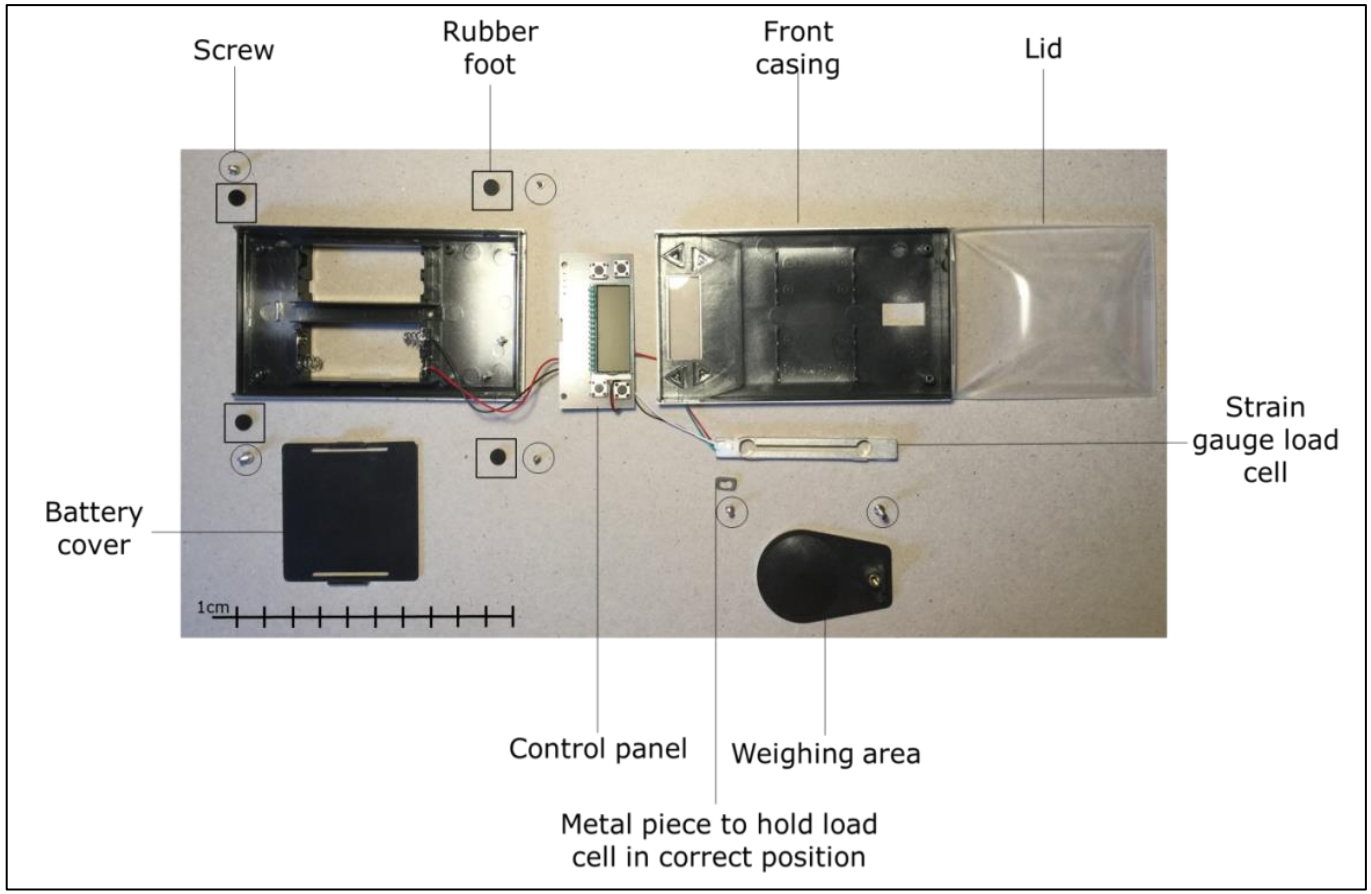


FIGURE 5.7 DEVICE Y'S COMPOSITION

Both devices were simple in terms of composition, having few parts and being relatively easy to dismantle, Figure 5.6 and 5.7. Both contained a basic circuit board, a display and a few buttons for operation, whilst also being battery powered (2 x AAA batteries in both cases). Both devices had small rubber feet to ensure stability during measurement, along with lids to reduce the interference of external motion. Device X had an additional weighing boat for placement upon the weighing pan, whilst device Y had this integrated into the device. Both devices used a strain gauge load cell to determine mass.

5.4.4 Summary: Measuring device audit

Of the three balances audited, two were almost identical in their composition (devices Y and Z). Despite some minor differences between the composition of devices Y and Z, the fundamental mechanism used to determine mass was the same; a strain gauge load cell. A strain gauge load cell therefore presents a means of cost effective, accurate and precise mass determination, suggesting a feasible means of determining MP dose.

5.5 Concept generation - Researcher

5.5.1 Introduction

Having investigated Formulation and User requirements (Chapters 3 and 4) and understood how a strain gauge load cell can achieve the dose accuracy and precision required, device concepts could be generated capable of repeated, flexible mass-determined dosing of MPs for paediatrics.

5.5.2 Method

Devices meeting the requirements in Table 5.1 were conceptualised with consideration given to the design space; based on literature, Formulation requirements, User requirements and the preceding four device-based studies. Further details can be found in Chapter 2 – Methodology, page 21.

5.5.3 RESULTS

Medication dosing can be split broadly into measurements or dispensing and administration. This may be completed by a single integrated device (3) or by two separate devices (1 and 2), Figure 5.8.

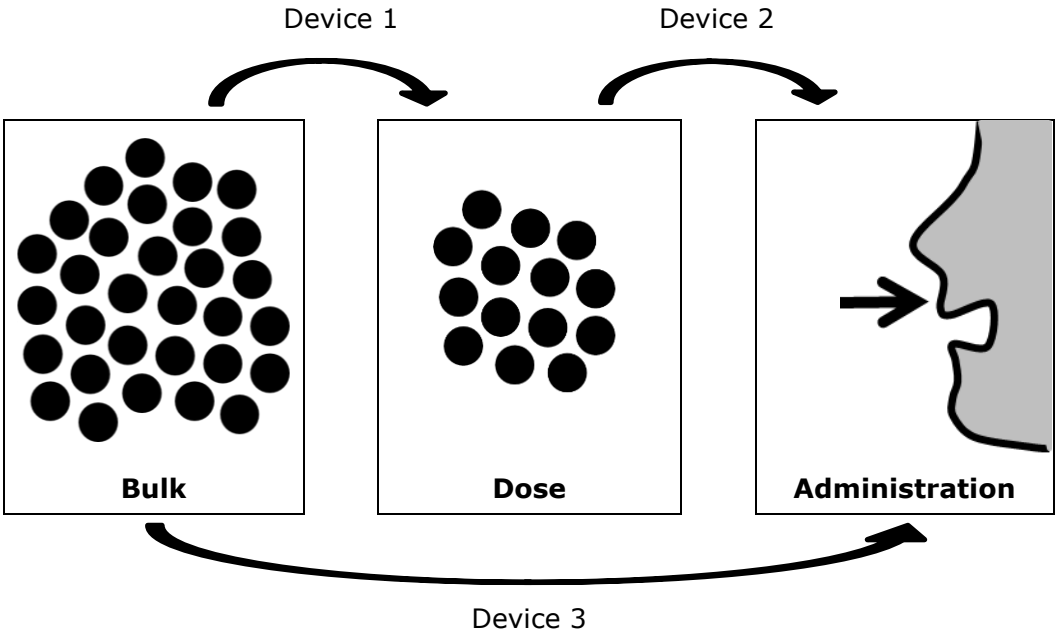


FIGURE 5.8 DOSING DEVICES

Concepts were generated for each of these scenarios with their attributes critically evaluated against device requirements.

5.5.3.1 TWO SEPARATE DEVICES

Initial concept generation investigated separate dispensing and administration devices. This was because mass-based dispensing requires a stable surface upon which to perform an accurate measurement, whilst an administration device required some degree of portability.

Dispensing devices for use alongside both existing administration and more sophisticated administration devices were conceptualised.

DISPENSING DEVICES

Concept A (Figure 5.9) is an addition of mass measurement device. The administration device is placed beneath the exit point but on top of a load cell to allow for addition of MPs to the administration device and

determination of dose. An internal feedback loop acts to halt dispensing once the correct mass had been ejected.

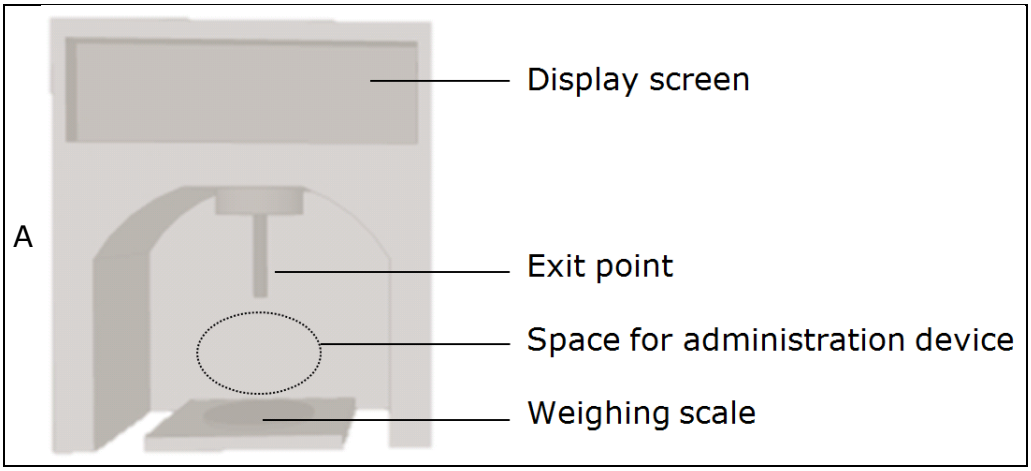


FIGURE 5.9 ADDITION OF MASS TABLE-TOP DISPENSER

Concepts B and C (Figure 5.10) are based on a loss of mass measurement. The administration device no longer has to be placed on a balance, reducing the chance of error. Instead, mass measurements are made of the hopper using a load cell contained within the hopper brace. Subsequent ejection of MPs can then be quantified in terms of a mass change in the hopper.

Concepts B and C vary slightly, with the addition of a riffling system to device B to ensure the sample ejected is representative of the bulk.

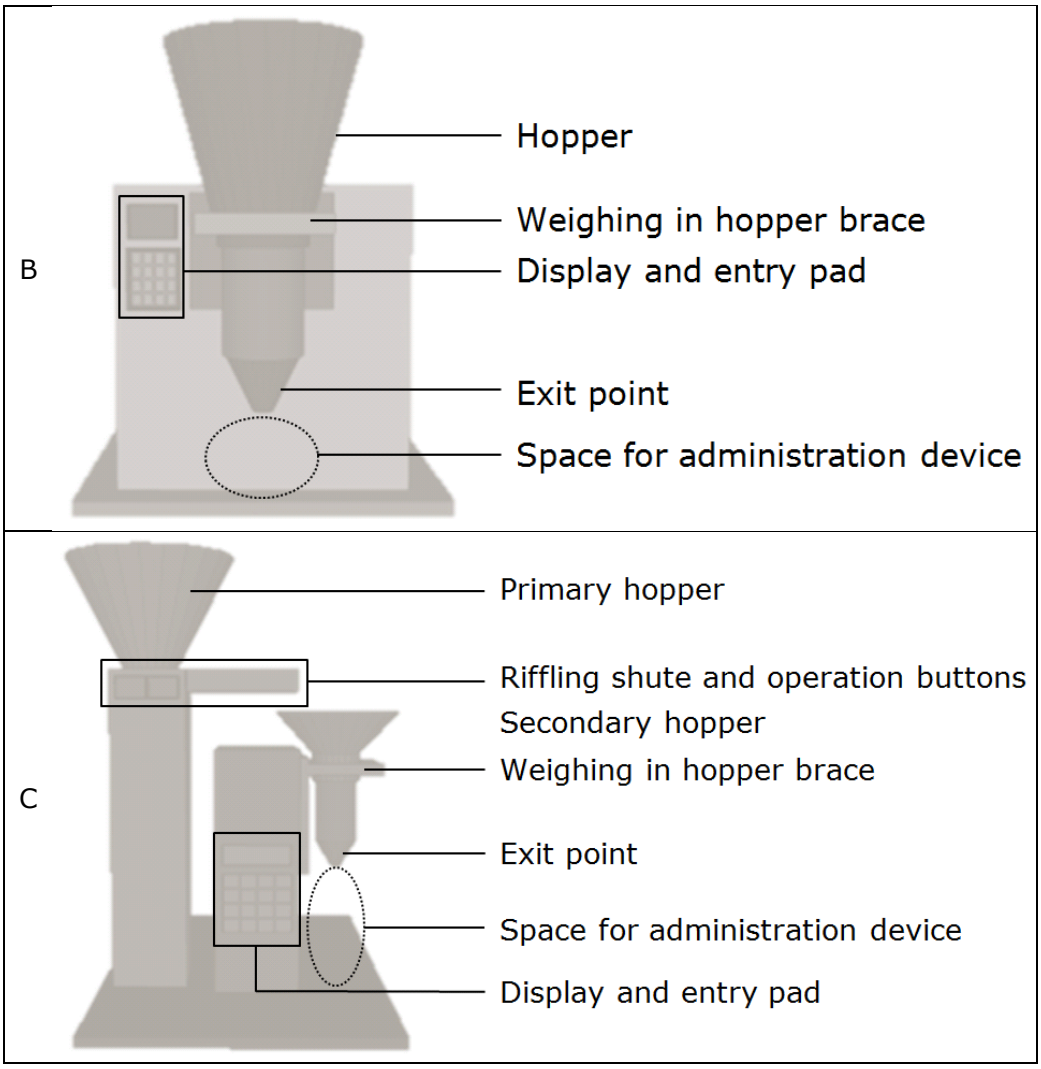


FIGURE 5.10 LOSS OF MASS DISPENSING DEVICES

All three of these dispensing devices consider the key device requirements. They are all designed as being suitable for paediatric patients (and their CGs) with chronic conditions. Given their suitability for use with existing administration devices, this further improves paediatric acceptability. Their use of existing administration devices such as measuring cups or spoons also improves flexibility in administration method. Each concept has considered the handling of free-flowing MPs and acts to prevent MP damage whilst protecting the sample from moisture. The devices have a month's capacity, and given their integrated strain gauge load cell system, are capable of accurately dosing 50 – 1500 mg in small increments. The concepts also consider misuse and overdose, with locks preventing access to the bulk MPs in the hopper. The concepts are designed not to be portable given the requirement of a mass-based system for a stable base. The administration device(s) offer portability however. All three devices are

designed as being easy to use, quick and have fairly non-descript aesthetics. The devices have simple interfaces requiring little user input and are designed for countertop use.

Figure 5.11demonstrates further concept refinement in terms of internal dispensing mechanism (a) and device aesthetics (b).

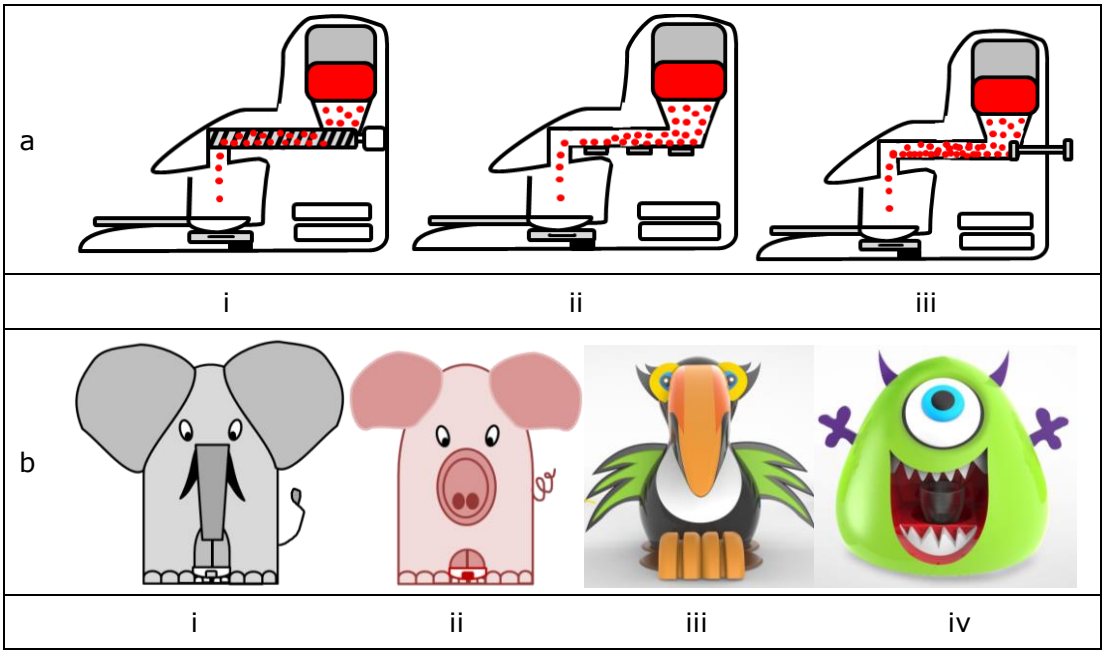


FIGURE 5.11 REFINEMENT OF CONCEPT MECHANISM (A) AND AESTHETICS (B)

Figure 5.11(a) shows how various dispensing mechanisms could be used to move the MPs within the same device, including screws (i), vibration (ii) and plungers (iii). Figure 5.11(b) demonstrates how these mechanisms could be encapsulated by a variety of device exteriors including an Elephant (i), Pig (ii), Monster (iii) or Toucan (iv).

Given traditional administration devices such as measuring cups and spoons only provide storage of a single dose for (near) immediate ingestion, more sophisticated administration devices were generated capable of storing a month's MP supply, Figures 5.12 - 5.14.

ADMINISTRATION DEVICES

The dispensing devices conceptualised in 5.5.3.1 would fill each of these administration devices having mass-measured individual doses. Unlike traditional administration devices however, these administration devices

serve to partition individual doses whilst allowing flexibility in administration method. This allows for storage of multiple predetermined doses (by mass) in a portable administration device.

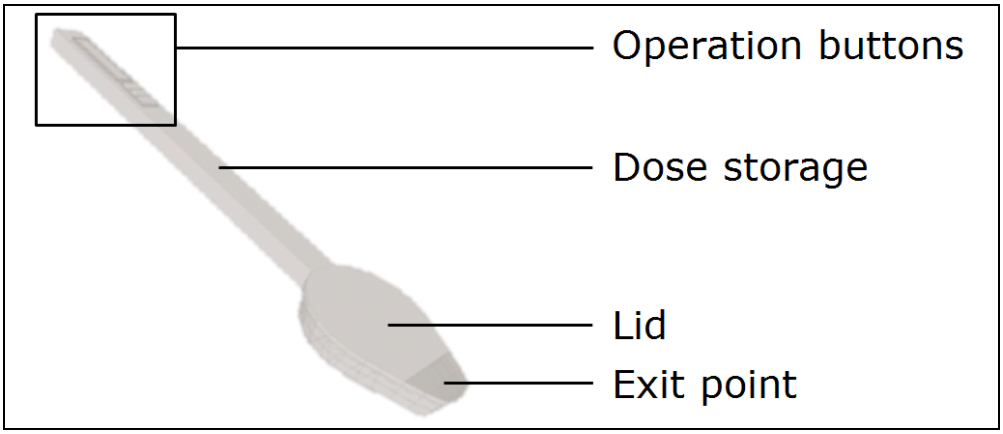


FIGURE 5.12 ADMINISTRATION DEVICE A

Administration device A is based on a spoon, Figure 5.12. The segregated doses are stored within the handle with button operation allowing for individual dose ejection into the spoon's scoop. This device is amenable to direct oral administration or for co-administration with food or drink. Direct oral administration would be cause to consider cleaning practises for the spoon. The end scoop could be removable and disposable, a thin sheath could be used to cover the scoop during administration, or the scoop could be cleaned between each use. Whilst scoop cleaning could be performed with it attached or unattached from the spoon, if attached, careful consideration should be made so as to prevent water ingress into the doses stored within the device handle.

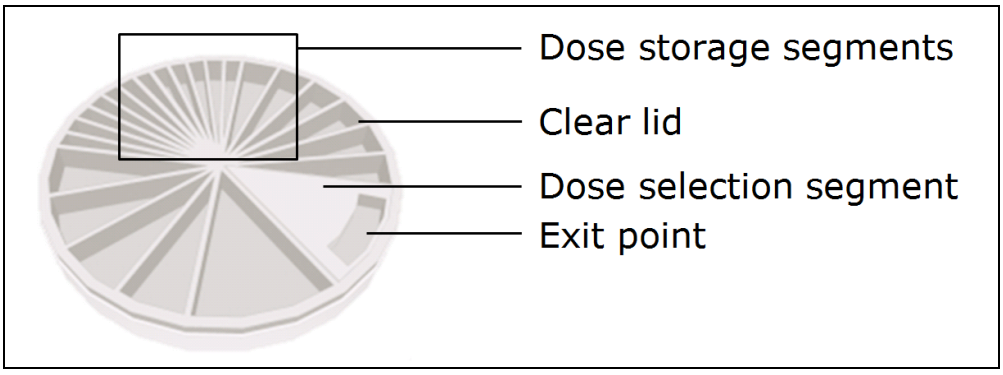


FIGURE 5.13 ADMINISTRATION DEVICE B

Administration device B (Figure 5.13) is similar to the 'Circle' device investigated in Chapter 4. This device works by partitioning individual

doses prior to administration (much like device A). Different sized dose segments allow for dosing flexibility and the personalisation of dosing. The device is manually operated with the user twisting the 'dose selection segment' and inverting the device allows for the ejection of the selected dose. Whilst amenable to direct administration in its current form, this device is more suited to MP administration with food or drink. A key consideration with this concept is the availability of all doses within the potential risk of misuse or overdose. The device would therefore require a locking system whereby only one dose can be ejected per time frame for example.

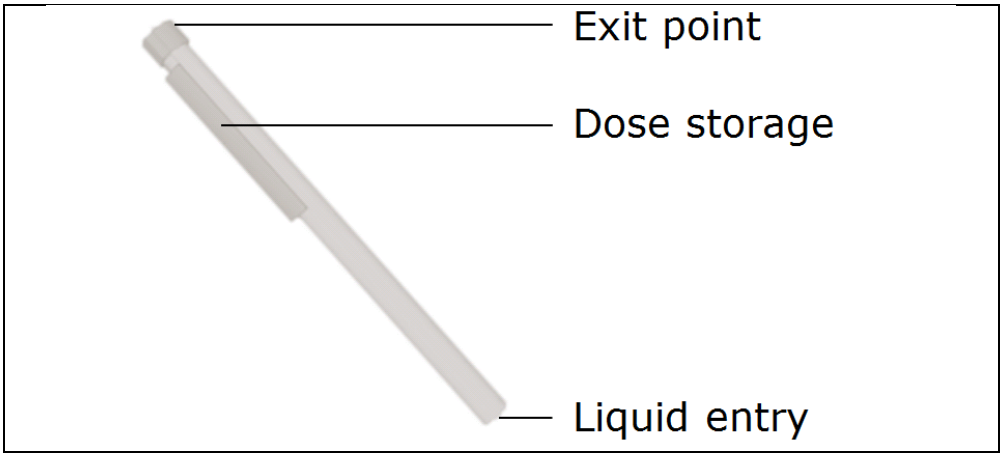


FIGURE 5.14 ADMINISTRATION DEVICE C

Administration device C (Figure 5.14) is based upon a drinking straw, much like dose sipping technology or the 'Milkshake straw' investigated in Chapter 4. Unlike these straws, this concept allows for repeated dosing given the storage compartment allows containment of multiple doses within a single device. Given these doses are pre-measured by the dispensing device; no measurement is required by this device. It simply serves to release a pre-defined dose from the storage compartment into the straw chamber. Subsequent submersion of the device into liquid allows for co-administration of MPs as the patient drinks. A filter at the base of the straw and removable lid at the top ensures the dose is contained within the device. Given this device would likely be reusable the dose storage compartment is removable for the main device body. Reattachment of the storage compartment to the same cleaned device, or to a new disposable device allows for repeated dosing.

Each of these three administration devices have been designed with the key device requirements in mind.

5.5.3.2 SINGLE DISPENSING AND ADMINISTERING DEVICE

Whilst section 5.5.3.1 designed separate dispensing and administration devices, these actions could be performed by a single device, Figure 5.15.

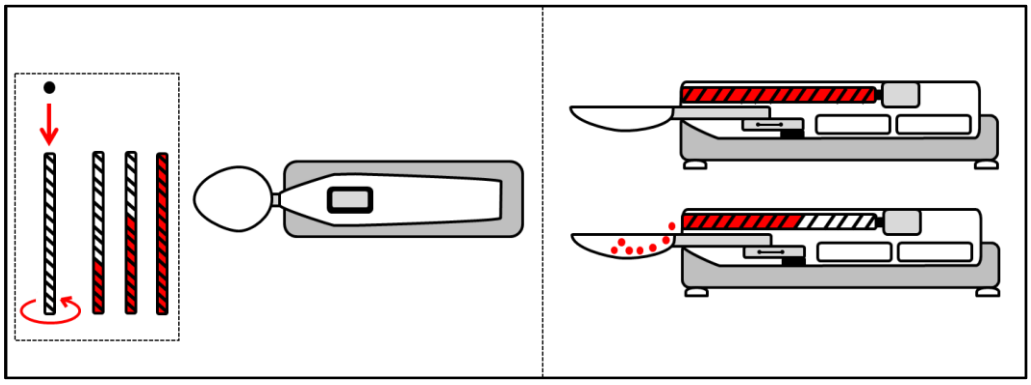


FIGURE 5.15 INTEGRATED DISPENSING AND ADMINISTRATION DEVICE

This concept is based on the 'weighing spoon' investigated in Study 4.1, whereby a load cell is used to determine the mass loaded into the spoon's scoop. Integration of a pre-filled MP stick pack/barrel/screw allows for controlled MP ejection from the spoon's body into the scoop. An internal feedback loop serves to halt dispensing once the scoop is loaded with the desired mass. As mass-based systems require a level surface, free-from vibration, the concept features a base unit to stabilise the spoon prior to dose measurement.

This concept fulfils the entire 10 device requirements, including the use of time delayed dispensing to prevent overdose and its suitability for direct and co-administration with food.

5.5.4 Summary: Concept generation

Concept generation has provided device designs for a single integrated dispensing and administration device as well as for separate dispensing and administration devices.

Each concept has been critically analysed in relation to the Device requirements including those based on the Formulation and User. This has allowed an appreciation of their suitability for use as a paediatric MP dosing device and serves to guide future device D&D.

Subsequent prototyping of device mechanisms will allow for concept refinement.

5.6 Moving MPs

5.6.1 Introduction

Following concept generation, attention focuses on the internal device mechanism. As alluded to in Study 5.3, a strain gauge load cell offers the accuracy and precision in dose measurement required. A further system is required to safely move the MPs within the device in a controlled reproducible manner without damage to sample. Three different mechanisms were investigated including screws, vibration and plungers, based on their common use in moving free-flowing materials.

5.6.2 Method

Following conceptualisation, the mechanisms were prototyped and tested for their suitability for handling H&Ts as an MP surrogate. More refined prototypes were tested with Cellets®. Further details can be found in Chapter 2 – Methodology, page 21.

5.6.3 Results

Each of the three mechanisms was investigated given their common use in moving free-flowing materials. Integration of these mechanisms within any of the concepts generated in Study 5.5 would allow fulfilment of the device requirements. Special attention was paid to the mechanisms capability of

handling the free-flowing MPs including safely moving the sample in a controlled and reproducible manner without damage to the MPs.

5.6.3.1 SCREW

An Archimedes screw was investigated given its common use for basic movement of water and soil.

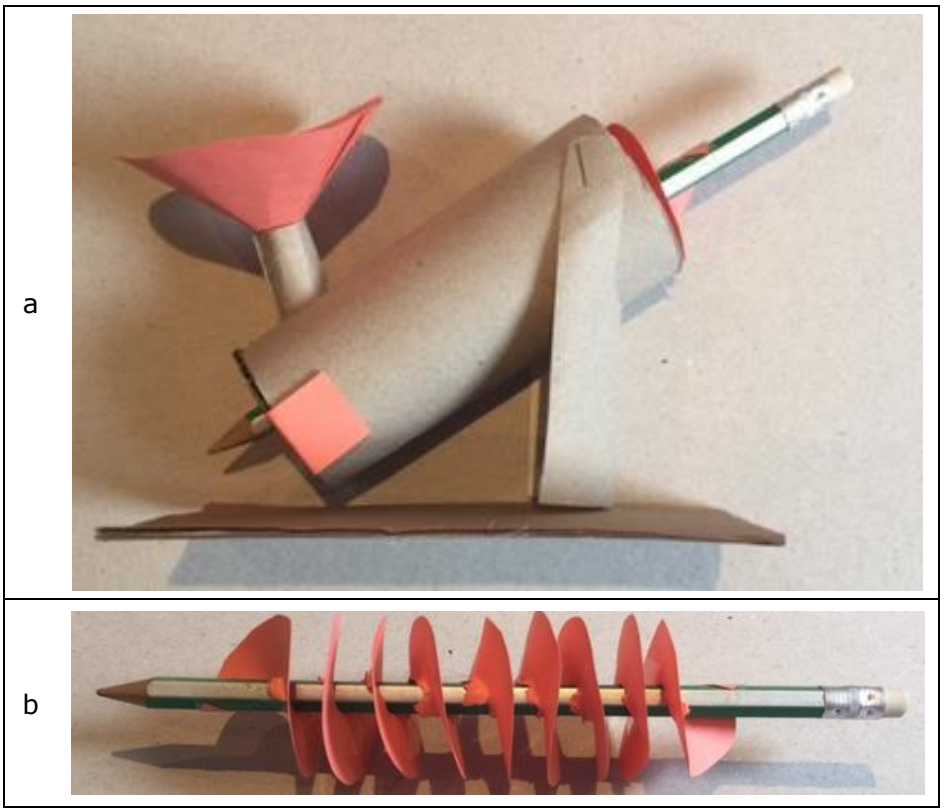


FIGURE 5.16 CARDBOARD SCREW PROTOTYPE

(pencil length: 150 mm)

To demonstrate the concept, a basic cardboard prototype was created to aid explanation, Figure 5.16. This allowed design parameters such as the screw's size and pitch to be considered, as well as hopper attachment.

Whilst the screw geometry was not optimised, its characteristics were specified based on the internal diameter of a readily available barrel and to become more aligned to the pharmaceutical application handling the small MPs. The designed screw was then 3D printed and inserted into a barrel, Figure 5.17.

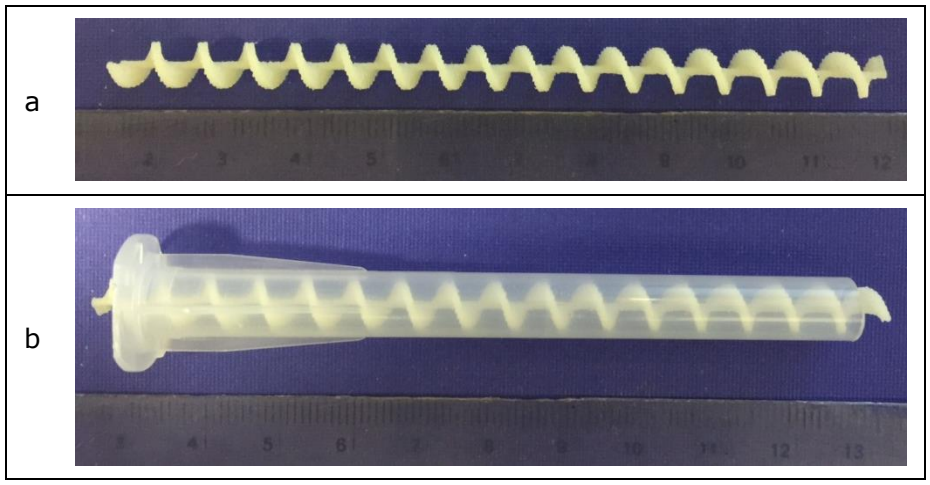


FIGURE 5.17 3D PRINTED SCREW PROTOTYPE

The screw and barrel were then attached to a geared motor to allow for movement of the MPs (Figure 5.18). Two different screw mechanisms were investigated, a one-piece screw whereby the screw and barrel are a single entity and move collectively, and a two-piece screw where the screw and barrel move independently of one another. Different screws were investigated to understand the chance of MP damage within the barrel and to compare the mechanisms suitability for handling the MPs in a safe, controlled and reproducible way.



FIGURE 5.18 ONE-PIECE SCREW PROTOTYPE FILLED WITH H&TS

Filling the one-piece screw prototype proved challenging given the slow motor speed and the barrel not being completely level. Nonetheless the prototype could be filled with relative ease when using gravity to move the formulation along.

The MPs were expelled through reversing the motor and the rotation of the screw in the opposite direction.

A representative sample was imaged before and after having travelled through this prototype to assess any damage to the formulation, Figure 5.19.

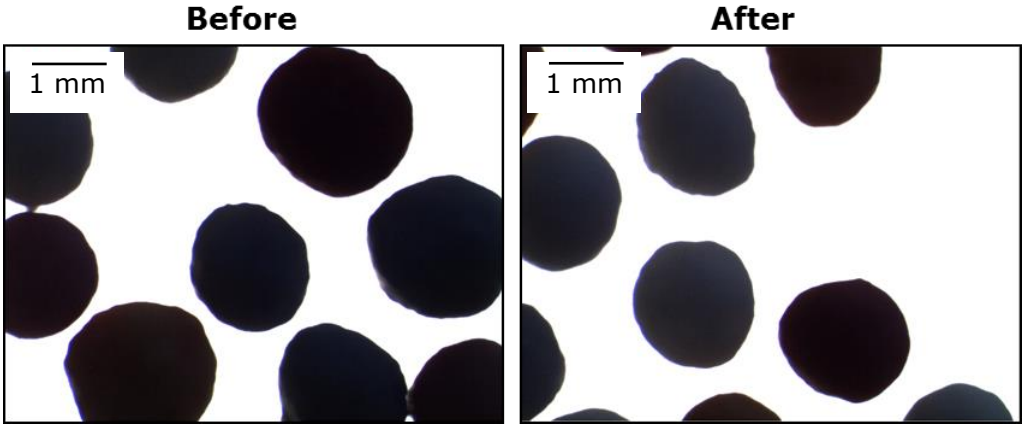


FIGURE 5.19 H&TS BEFORE AND AFTER ONE-PIECE SCREW TESTING

A visual inspection of friability using an optical microscope showed no damage to have been caused to the MPs by the screw. This suggested the one-piece screw is an appropriate mechanism for moving MPs.

It should be noted however that using a single piece screw requires the sample to be subjected to the mechanism twice; once for filling and once for ejecting. This has the potential to magnify any error or MP damage.

Further concept refinement would include an increased rotation speed and vertical screw docking to allow for more efficient filling.

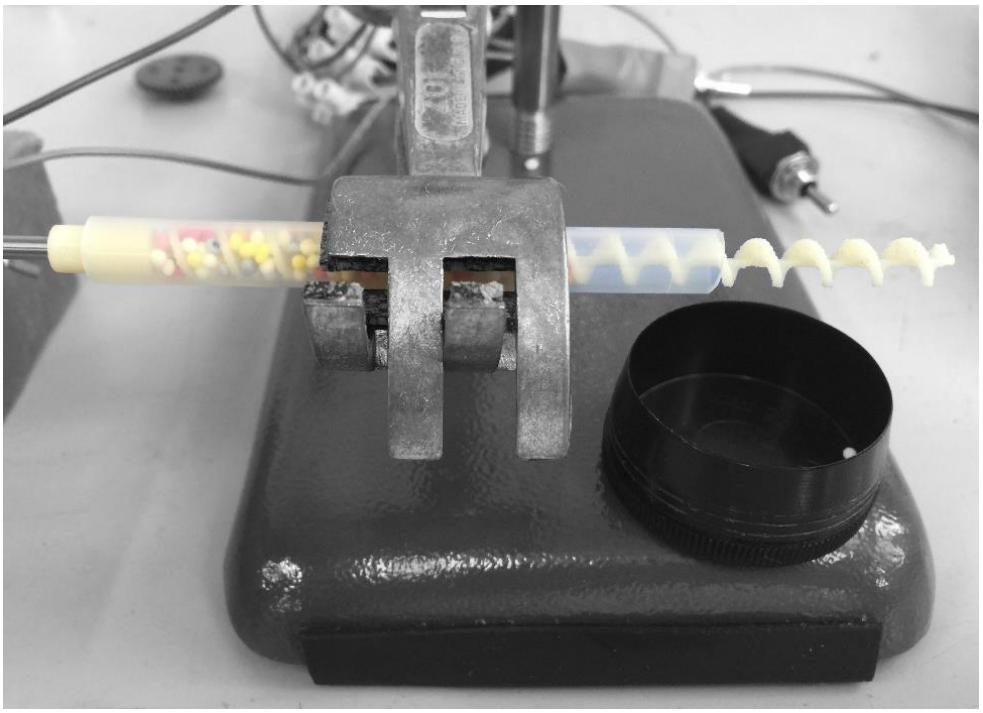


FIGURE 5.20 TWO-PIECE SCREW PROTOTYPE FILLED WITH H&TS

Figure 5.20 shows the two-piece screw prototype where the screw moves independently of the barrel. The barrel is held in place by a clamp whilst the screw rotates powered by a motor at one end. Here, one end of the barrel is blocked by the shaft attachment. In reality this attachment would be away from the barrel allowing entry of the sample from the hopper at one end of the screw and the subsequent ejection at the other end. Given there is no hopper attachment to feed the sample in to this screw, the H&Ts have been subjected to the screw twice, as with the one-piece screw.

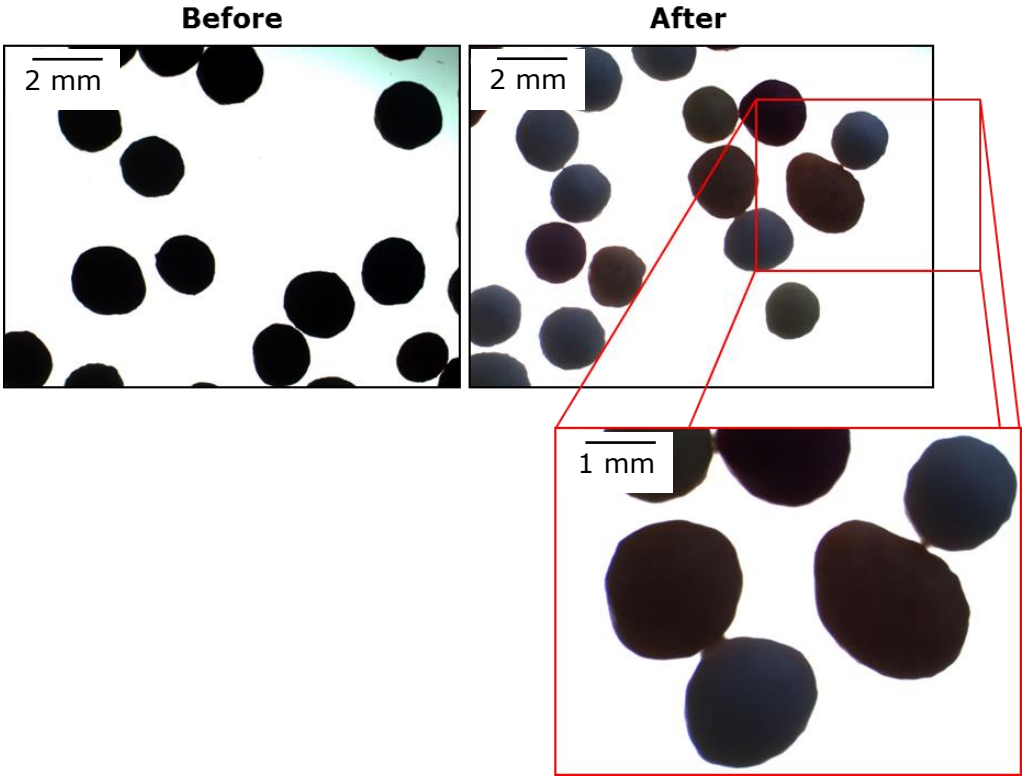


FIGURE 5.21 H&TS BEFORE AND AFTER TWO-PIECE SCREW TESTING

There was no observable damage to the sample, despite being subjected to the screw mechanism twice, Figure 5.21.

Given the apparent suitability of both the one- and two-piece screws for handling the MPs, further concept development was performed.

Figure 5.22 shows the development of a 'screw spoon' from initial concept (a) into a Computer Aided Design (CAD) model (b) and subsequent 3D printing (c). Given the lack of a motor and of electronic components, this prototype was non-working; it served to further demonstrate the 'screw spoon' concept however.

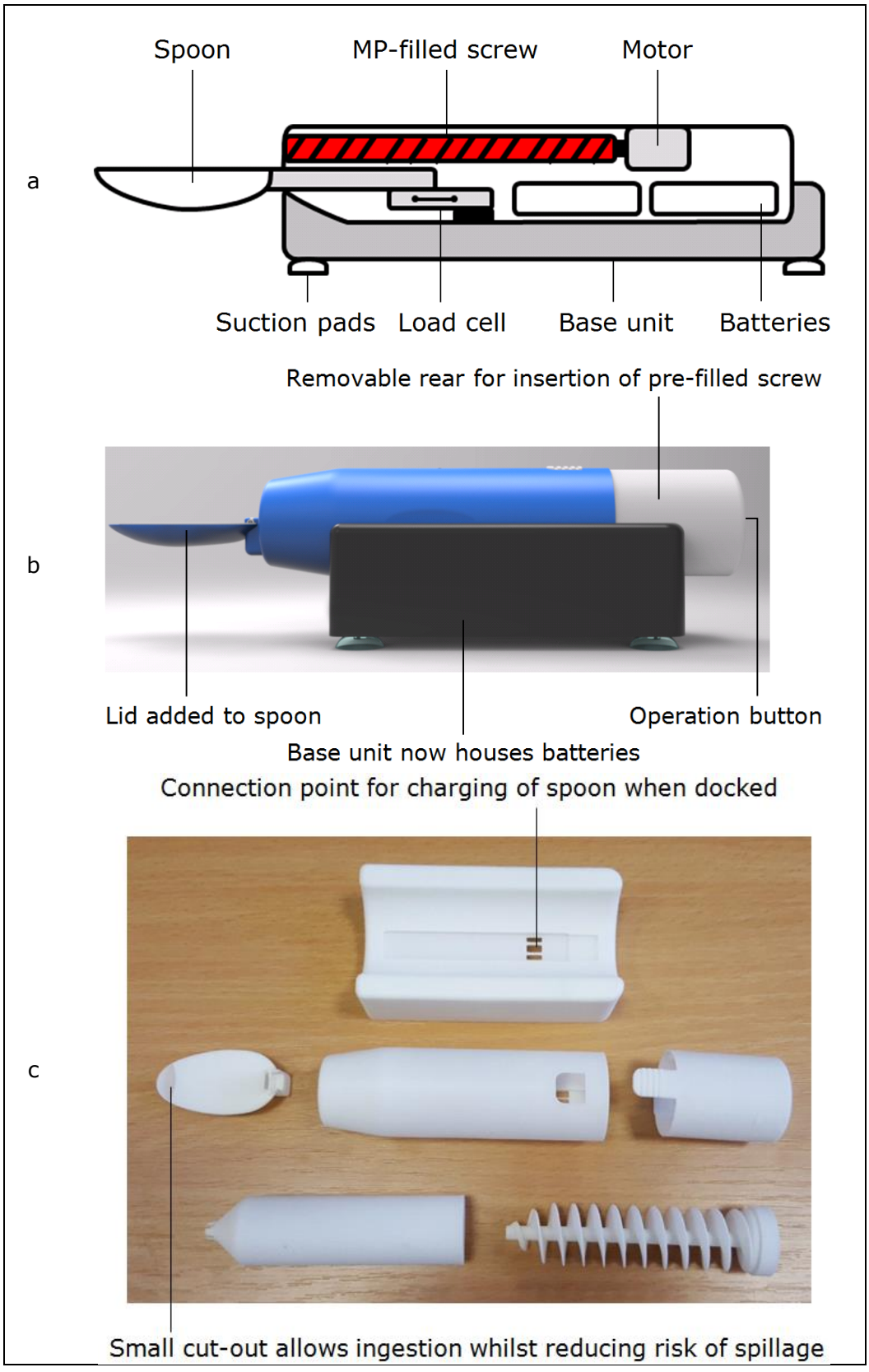


FIGURE 5.22 'SCREW SPOON' PROTOTYPE DEVELOPMENT (A) INITIAL CONCEPT, (B) CAD IMAGE, (C) 3D PRINT

5.6.3.2 VIBRATION

A basic, horizontal vibration prototype with a funnel hopper and vibrating tubing was created, Figure 5.23. The tubing was centrally secured by a clamp and a plastic bung used to prevent backflow.

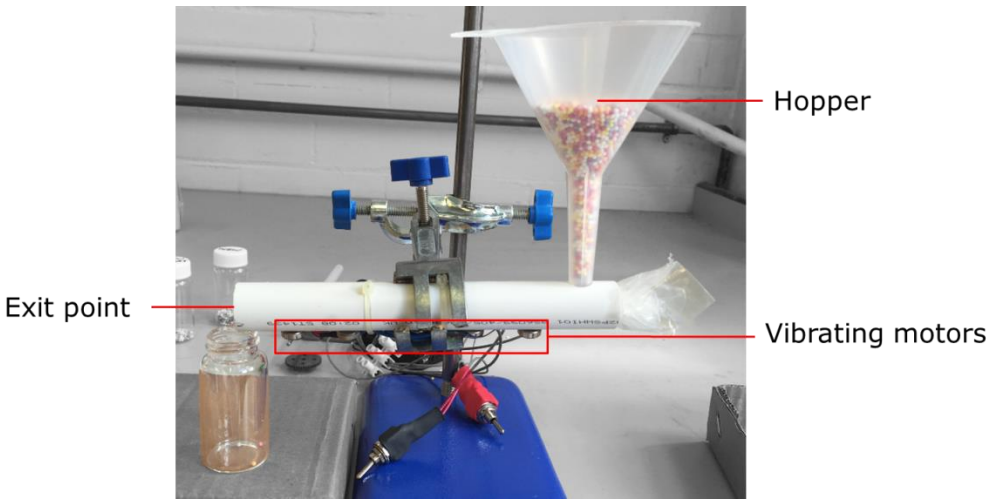


FIGURE 5.23 INITIAL VIBRATION PROTOTYPE

Prototype testing with H&Ts proved the mechanism to be effective in moving MPs from the hopper to a glass container (at the exit point). No noticeable damage to the sample was observed, Figure 5.24.

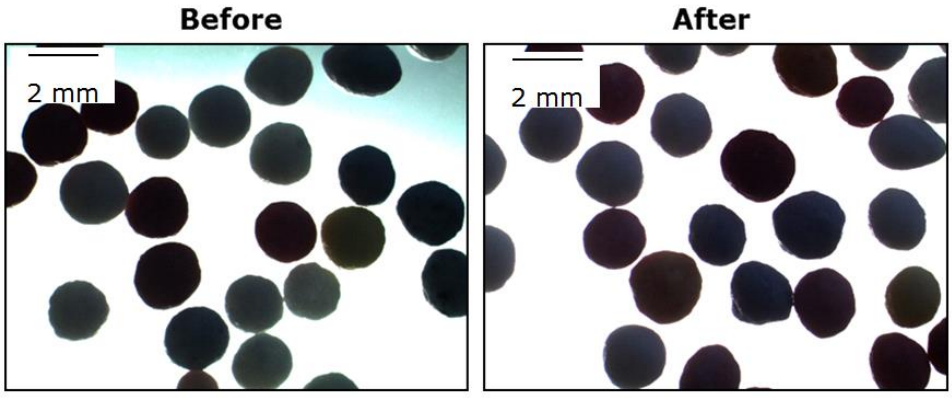


FIGURE 5.24 H&TS BEFORE AND AFTER VIBRATION PROTOTYPE TESTING

Given the suitability of vibration at moving the MPs, further concept refinement and prototyping was performed by colleagues from the Precision Manufacturing Group. Special thanks to Mark Strickland and George Sewell for their hard work developing and refining this vibration prototype.

Figures 5.25 – 5.29 show the stages of concept refinement, from an initial concept drawing (5.25) through three iterations (5.26 – 5.28) to a final prototype (5.29).

Figure 5.25 demonstrates the mechanistic concept and how this is integrated into a dispensing device. A hopper of MPs can be inverted and inserted the device. Vibration of an internal tube via vibrating pads allows for movement of the sample along and into an administration device placed on a balance.

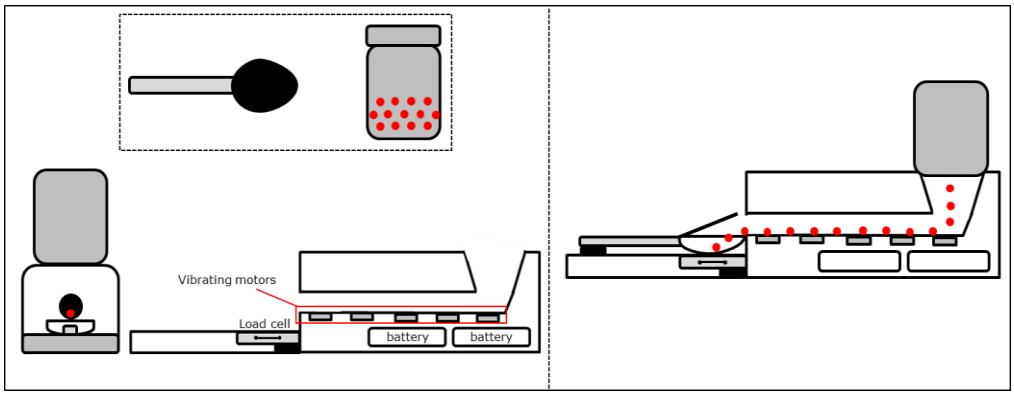


FIGURE 5.25 INITIAL VIBRATION CONCEPT

Figure 5.26 presents a refined CAD version of this concept with attention drawn to how the tube is secured in the base unit. Tube attachment was a key consideration given it must be secure yet still allow enough vibration to facilitate MP movement. The prototype secured the tube at two points; beneath the hopper and at the exit. This proved too secure however, and despite attachments designed to provide enough clearance for vibration, inaccuracies in the 3D printing of parts prevented sufficient vibration for sample movement.

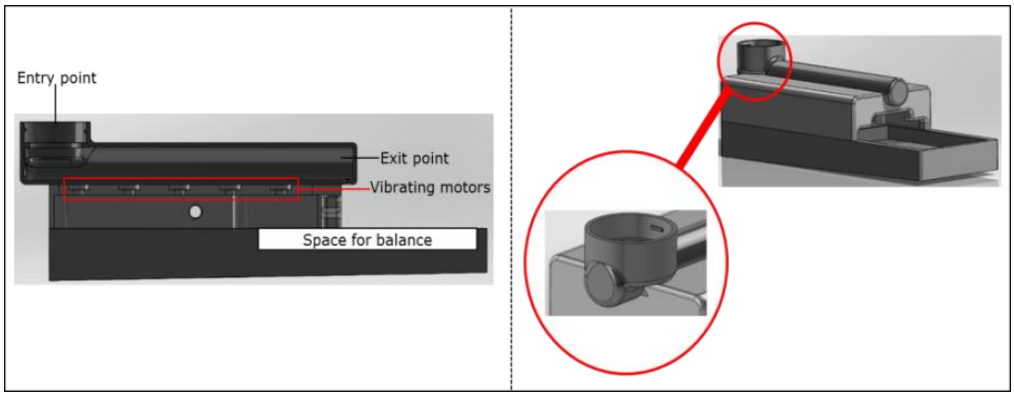


FIGURE 5.26 FIRST CAD VERSION OF CONCEPT

An alternative concept was subsequently developed with a greater amount of clearance to enable vibration, Figure 5.27. Special attention was paid to the geometries of the entrance point and the subsequent movement of the sample from the entry point into the tubing itself. Testing of this prototype showed that insufficient vibration was achieved to move the sample however.

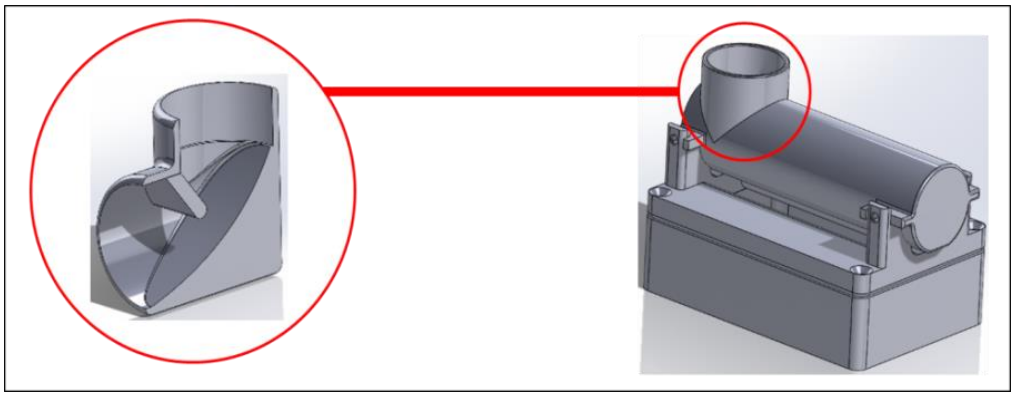


FIGURE 5.27 TUBE ENTRANCE GEOMETRY CONSIDERATIONS

The concept shown in Figure 5.28 was consequently proposed where the point of attachment was moved to the centre of the tube rather than either end. This however proved unsuccessful, with the clamping of the tube proving too tight to allow vibration.

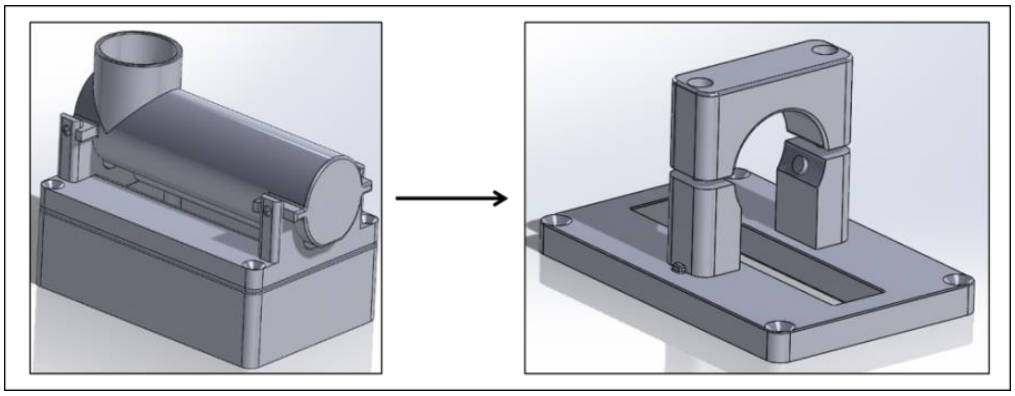


FIGURE 5.28 ALTERNATIVE POSITION OF ATTACHMENT

The final concept, Figure 5.29 employed a shorter tube which projected out from the device body and was only secured at one end (beneath the hopper entry). Special consideration was given to the geometry of the tube entrance. Given that the vibrating motors became unreliable, a motor with off-centre cog was used to allow for more controlled vibration.

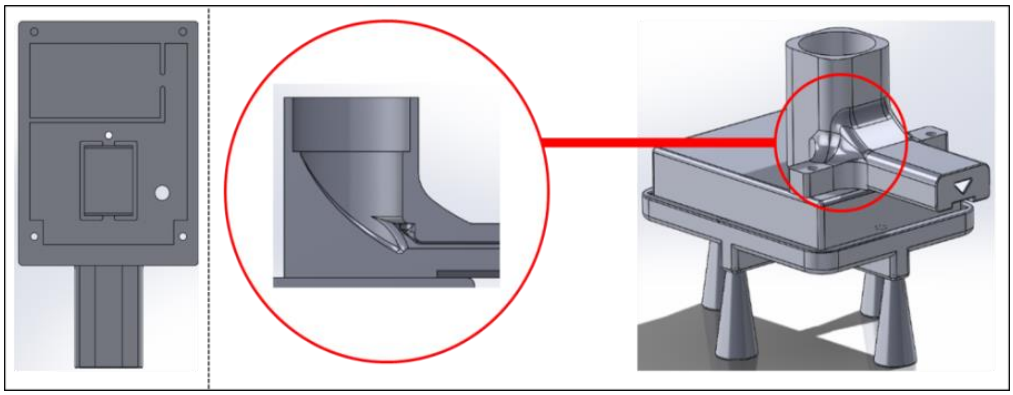
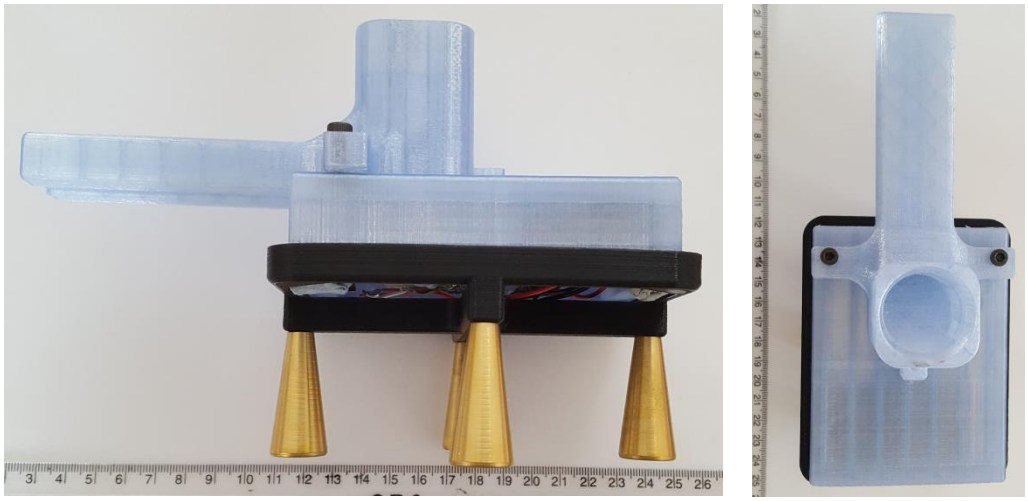


FIGURE 5.29 REFINEMENT OF FINAL PROTOTYPE

Despite initial testing of this prototype proving successful in moving Cellets®, the mechanism proved less reliable when performing a more thorough assessment that looked to quantify flow rate and dispensing reproducibility.

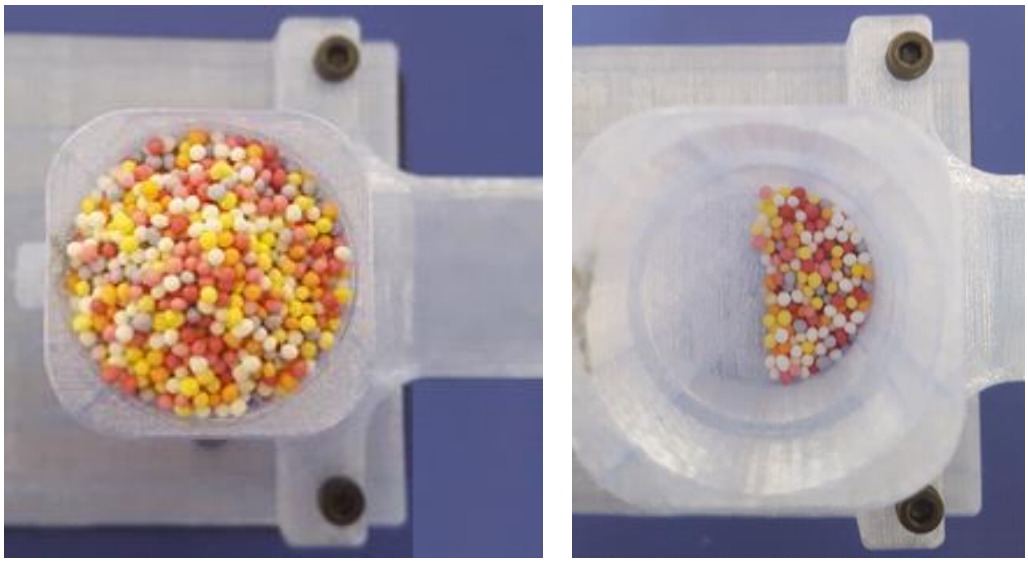


Side Top

FIGURE 5.30 REFINED VIBRATION PROTOTYPE

The prototype shown in Figure 5.30 was affixed to a work surface using 'sticky taq', to allow for adjustment of the devices positioning and levelling of the tube. Insertion of H&Ts and operation of the motor, lead to the sample becoming more compacted within the entrance chamber meaning little sample progressed to the tubing.

Testing of the prototype with different volumes of H&Ts saw little improvement in the prototype's effectiveness, Figure 5.31.



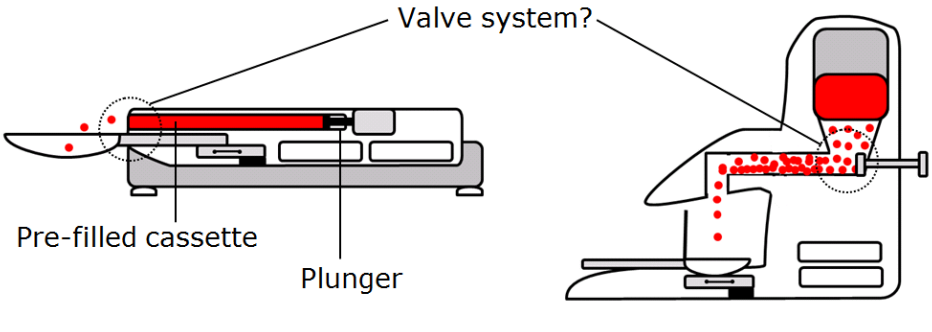
a b

FIGURE 5.31 TESTING OF VIBRATION PROTOTYPE WITH H&TS

There is therefore room for further refinement in order to create an effective and reliable means of MP movement using vibration. It is worth noting, that in its current form, this prototype would not be compatible with mass-based dose determination given that no attempt has been made to dampen the vibration from the strain gauge load cell. This is an important consideration for future work.

5.6.3.3 PLUNGER

A plunger was the third mechanism investigated with examples of where this mechanism could be employed, Figure 5.32.



a b

FIGURE 5.32 POSSIBLE PLUNGER BASED MECHANISMS (A) INTEGRATED DISPENSING AND ADMINISTRATION DEVICE, (B) SEPARATE DISPENSING DEVICE

The use of a plunger would circumvent issues related to vibration affecting mass-measurement however; a valve system is required to regulate flow within the device (b) and upon exit from the device (a). This valve system is crucial in concept (b) where pellets continue to fall behind the plunger from the hopper.

Widely available syringes were used to determine their suitability for moving the MPs including eccentric and concentric syringes, Figure 5.33.

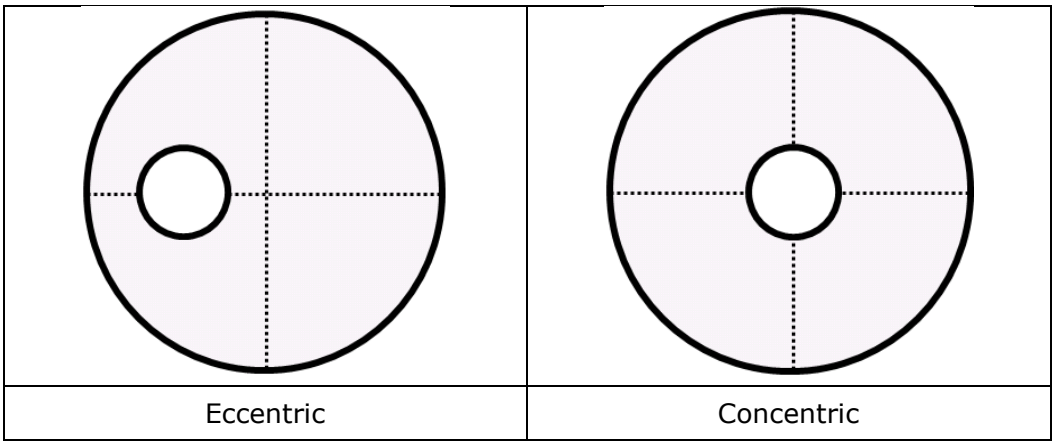


FIGURE 5.33 SYRINGE PROFILES

The eccentric syringe's geometry proved influential in determining the flow of sample from the syringe. Sample flow was disrupted due to the large size of the H&Ts (Figure 5.34a) and as a result of the nozzle geometry causing blockages of the smaller Cellets® (Figure 5.34b).

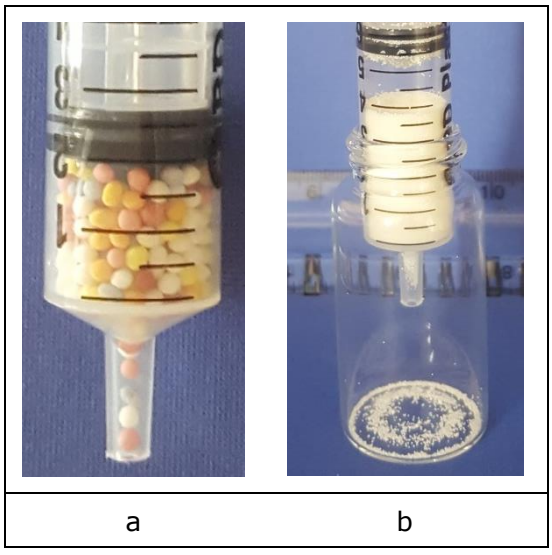
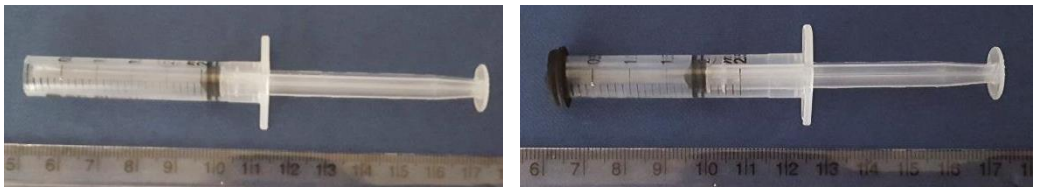


FIGURE 5.34 TESTING OF ECCENTRIC SYRINGE WITH H&TS (A) AND CELLETS® (B)

The concentric syringe had the same problems as seen with the eccentric syringe where, despite Cellet® flow being steadier and more controlled than with the eccentric syringe, the nozzle still became blocked and the flow was not constant.

Movement of the MPs along the syringe barrel (held horizontally) proved effective, with all pellets moved successfully and none left behind. The geometry of the nozzle however proved crucial in ensuring flow remained constant upon exit. Further optimisation of the exit and nozzle geometry is therefore be required.

Removal of the exit geometry all together circumvents this issue, with the MPs flowing freely from the tubing. There is however, little control over the rate at which the sample exits the syringe. The flow rate is controlled to some extent by the force applied to the plunger; this however does not always translate to a steady exit flow rate. Because of this, a valve is used to regulate flow. Figure 5.35 shows a crude prototype of a nozzle-less syringe (a) and the same device with a makeshift valve (b).

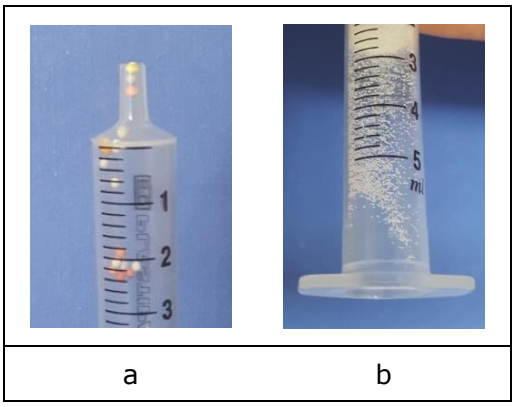


a b

FIGURE 5.35 'NOZZLE-LESS' SYRINGE WITH (B) AND WITHOUT VALVE (A)

As expected, the sample flowed steadily from the nozzle-less syringe (a), although the exit's geometry or employment of a valve would ensure exit flow rate is consistent. The pressure required to open the basic valve system (b) was too great to successfully pass MPs through. There is therefore room for further refinement of either the exit geometry or of the valve system to control sample exit.

It is worth noting that static between the sample (H&Ts (a) and Cellets® (b)) and the device wall was evident during testing, Figure 6.36. This highlights that static interactions are a key factor to consider when selecting the most appropriate device materials.



a b

FIGURE 5.36 STATIC SEEN WHEN HANDLING H&TS (A) AND CELLETS® (B)

5.6.4 SUMMARY: MOVING MPS

All three mechanisms successfully moved the MPs safely and with no visible damage. They all however require further refinement to handle the sample in a controlled and reproducible way.

The screw mechanism requires geometric refinement to determine the best screw profile for moving MPs. Consideration should also be given to the most appropriate motor and electronics system.

The vibration mechanism requires the most refinement, particularly in preventing vibration affecting mass measurement. Optimisation of the entry point geometry should also be considered.

The plunger prototype also requires refinement including the design of a valve system to control particle flow, exit geometry optimisation, as well as the selection of an appropriate motor should the device not be operated manually.

This study has provided insight into three possible means of MP movement. With refinement these mechanisms can be integrated into device concepts generated in Study 5.5.

5.7 Further concept generation – Collaboration with design students

5.7.1 Introduction

Alongside the researcher's concept generation activities a collaboration was formed with undergraduate product design students to identify a wide breadth of design concepts. The final year project was used to gain further insight into important design considerations from experienced design students.

5.7.2 Method

Students were introduced to the work through a design brief (Appendix 14, page 235) and set the task of conceptualising a mass-based MP dosing device for children.

5.7.3 Results

The three designs presented (Figure 5.37) were selected as the 'best' concepts having been critically evaluated for their fulfilment of the device requirements set out at the start of this chapter. The remaining 14 concepts can be found in Appendix 15, page 238.

Concept (a) is much like the dose sipping technology but with further personalisation of the straw device. A wall-mounted mass-based straw filling system also allows for dose flexibility. Unlike the X Straw, these straw devices are intended to be washable and consequently reusable.

Concept (b) uses a balance to determine dose before utilising air to propel the MPs from the device into the child's mouth. This device is customisable to align to the child's preferences. Unlike concepts (a) and (c) this device presents an integrated device capable of both dispensing and administering MP dose.

Concept (c) is based on a wall-mounted cuckoo clock. A mass-based addition of mass measurement is taken from beneath the sophisticated 'bird' administration device. The dispensing device ejects the cuckoo along

with the contained dose at pre-programmed times of the day, whilst locking between doses prevents misuse.

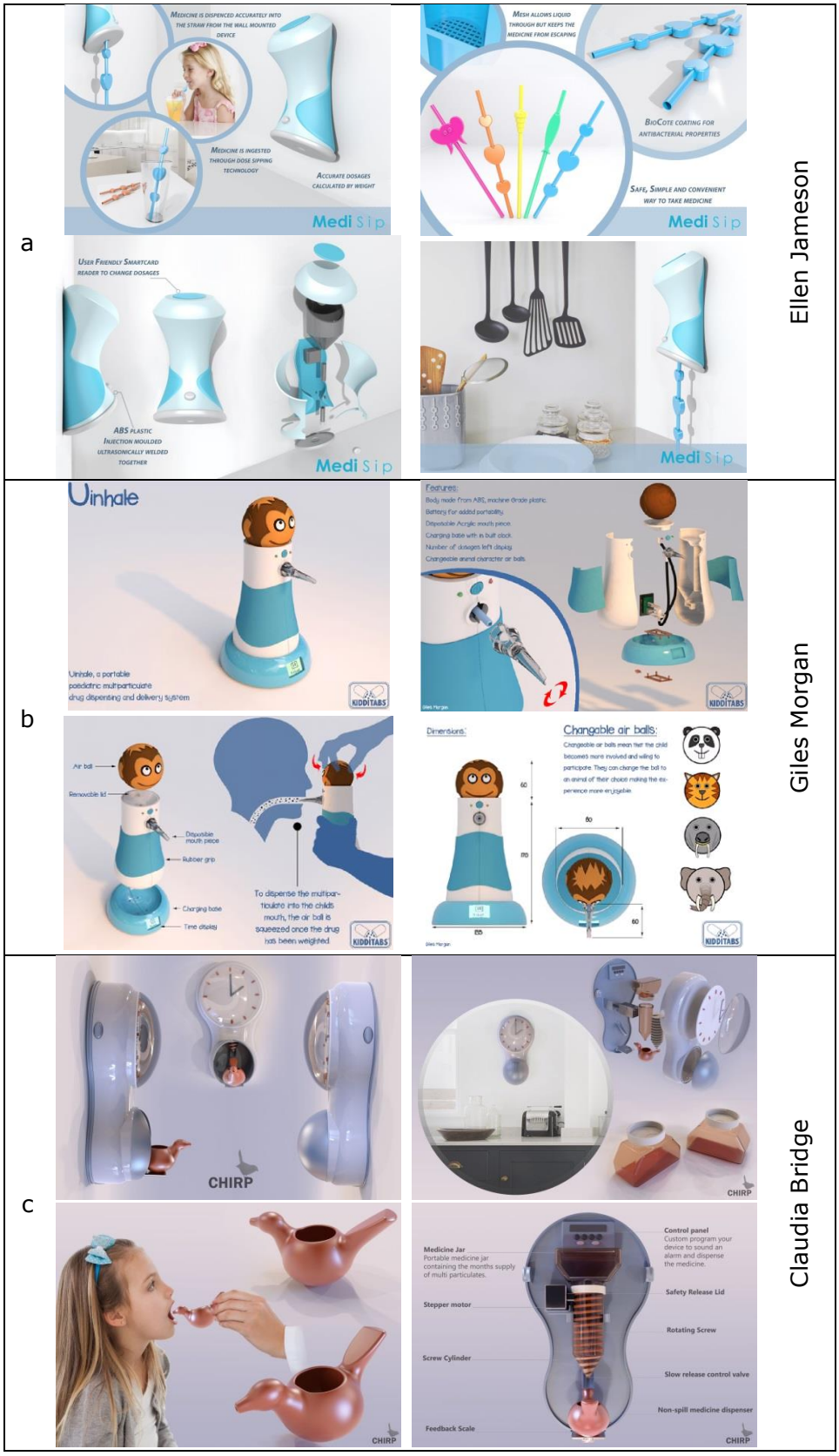


FIGURE 5.37 TOP 3 STUDENT-GENERATED DEVICE CONCEPTS

Each of these concepts carefully considered the 10 key device requirements. They have all given specific consideration of how a child user would interact with the device, with attention paid to designing a device suitable for paediatric patients with chronic conditions. They are all able to handle free-flowing MPs and are capable of accurately dosing 50 – 1500 mg in small increments. The students have also ensured the MPs are protected from moisture and have given special consideration to appropriate materials for use which prevent static. All three devices store a month's supply of medication, are easy to use, quick and simple.

Device (c) paid special attention to how overdose or misuse may be prevented with doses locked away and only available at set times throughout the day. (c) also considers flexibility in the administration method, being amenable to direct oral administration and co-administration with food or drink. Device (b) is the only portable device, whilst concepts (a) and (c) have stationary dispensing devices and a portable administration device. These devices have also given consideration to the likely environment of use in the home, being wall mounted in the kitchen. They are also devices with which the users are likely to be familiar given their similarity to straws and clocks. Device (b) is more novel, yet appeals to the child user through the customisable 'head piece'.

The remaining 14 student device designs varied widely including simplistic handheld devices using minimal electronics, through to sophisticated dispensing devices with finger print recognition for safety.

5.7.4 Summary: Further concept generation

This collaboration generated an array of design concepts. These included integrated dispensing and administration devices as well as separate dispensing and administration devices. Some devices utilised complex electronic systems whilst others were more simplistic. Devices were also created for different use environments including at home and in the pharmacy.

The breadth of concepts generated has provided insight into potential device designs as well as highlighting key considerations for further MP device development.

CHAPTER 5 - DISCUSSION

The seven studies presented in this chapter have provided insight into possible device concepts capable of dispensing personalised MP doses to children.

The work appreciates the requirements of the Formulation (Chapter 3) and the User(s) (Chapter 4) and addresses RQ3: What does this mean for Device design?

By highlighting the relative advantages of mass-based dosing over volumetric and conceptualising a variety of mass-based MP dosing device, this work addresses the knowledge gap surrounding mass-based medicine dosing.

The identification of three small, portable, cost effective balances demonstrated how feasible a mass-based system is. Along with consideration of mechanisms for MP movement, this provides insight into internal components of a device capable of repeated, flexible, mass-based MP dosing.

Concept generation provided insight into approved medical grade materials, the appropriateness of a portable mass-based system, and the potential for pharmacy and home based devices.

CHAPTER 5 - LIMITATIONS

Twenty-one devices with the potential to handle MPs were considered, it is appreciated however that there will have been devices outside of these which may be amenable to handling MPs.

There will also have been some researcher bias when ranking the 16 devices in Study 5.1. This was reduced by consideration of the opinions of the wider research team; however some bias may have remained.

Six balances were sourced due to their cost-effectiveness and ready availability. There may have been other more expensive means of determining mass that were not explored. The students' concepts have however investigated some of these including piezo-electrics and super-sensitive balances.

This work investigated three potential means of moving free-flowing material. There are other methods available which, whilst considered here, were not investigated in detail.

Concept generation activities highlighted key considerations such as the device being child friendly, secure and protective of the MPs. More refined concepts could have been generated however, should a clinical condition and target population have been defined. This would allow for more specific considerations to be made relating to the User, Formulation and Device.

CHAPTER 5 - CONTRIBUTIONS TO THESIS

This chapter considers the requirements of the User (RQ2), the requirements of the Formulation (RQ1) and addresses what this means for Device design (RQ3).

The work explores commonly used devices and mechanisms found in other areas to conceptualise device mechanisms and components for use in a paediatric MP dosing device.

Through combining research on available devices with an investigation of mass-based MP dosing, this chapter addresses the wider knowledge gap surrounding a device capable of repeated flexible MP dosing for paediatrics through concept generation and prototyping.

CHAPTER 6 - CASE STUDY

Given the CF populations' use of PERT, they are familiar with MP-like DFs. They have therefore been selected as a potential target population for an MP dosing device. Their experiences with the MP-like medication, their opinions of how it is delivered and how this could be improved will provide insight for MP device D&D. By understanding patient experiences, and narrowing the requirements of a platform technology, this study serves as an example application of a paediatric MP dosing device.

6.1 CF AND PERT

6.1.1 INTRODUCTION

CF is a genetic condition affecting more than 10,800 people in the UK (CFTrust 2017). It is caused by mutations to the CF trans-membrane conductance regulator (CFTR) protein which is involved in the production of sweat, digestive fluids and mucus (O'Sullivan and Freedman 2009). When this protein is not functional, these secretions become thick causing a build-up of mucus in the lungs, digestive system and other organs. This causes a range of challenging symptoms affecting the entire body, including reduced pancreatic enzyme activity.

Amongst various medications and therapies used to alleviate symptoms, 90% of CF sufferers will require PERT (Somaraju and Solis-Moya 2014). This involves taking digestive enzymes with every meal and snack to assist digestion of fat, carbohydrate and protein. The enzyme dose required varies based on the individual. It is influenced by lipase activity, bowel movements and food consumption. CREON® is the most commonly used PERT preparation used in the UK. It is available in a capsule and granule form, Figure 6.1 (Trang et al. 2014).



FIGURE 6.1 CREON® CAPSULES (A) AND CREON® MICRO (B AND C)

(Hashed area omits a capsule that is not CREON®)

At a young age, children are given CREON® micro (the granule DF) as it is easy to swallow and allows for some degree of dosing flexibility whilst clinicians determine personalised dosage. The specialised dosing scoop, Figure 6.2 (often supplied with the therapy) allows for flexibility in dosing (to some degree) with dose increments of a $\frac{1}{2}$,$\frac{1}{3}$ or even $\frac{1}{4}$ scoop possible. It is recommended that CREON® micro be co-administered with a vehicle such as apple sauce or puree to improve the formulation's palatability.



FIGURE 6.2 THE CREON® DOSING SCOOP

Children are encouraged to transition to capsules as young as possible, given the DFs ease of administration and portability.

The dosing flexibility requirement of this population and their use of an MP-like formulation is similar to the scope of this research. As such, an investigatory survey was designed to ascertain the appropriateness of an MP dosing device here.

6.1.2 METHOD

A 27 question online survey was developed in collaboration with CF specialists. The survey was disseminated via social media and was live for seven weeks and three days. Further details can be found in Chapter 2 – Methodology, page 21.

6.1.2.1 PARTICIPANTS

Twenty-six participants partook in this study (18 – 50 + years, 73 % female) with the majority (23) completing the survey on behalf of a child in their care (0 – 15 years, 30 % female). The remaining 3 participants were CF patients themselves (over 18 years old).

The majority of survey responses (21) were received from various UK locations. Four responses were completed internationally by participants in Australia (2), Ireland (1) and the USA (1).

Not all participants completed every survey question, for example, some children were yet to transition to capsules, or having transitioned to capsules did not complete the granule-based questions. As such, each question is treated independently with percentage responses recorded where appropriate.

6.1.3 RESULTS

6.1.3.1 GRANULES

CALCULATING DOSE

Of the 19 responses considering calculation of dose at home (aside from the 5 mentioning capsules instead of granules) the majority of people (47 %) calculated CREON® micro dose based on the food's fat content, or used the CREON® scoop (10).

> *"In scoops per grams of fat" [D]*

Participants also spoke of performing calculations (3), looking at food labels (3), using a medics/dieticians advice (2), guess work (2), the meal size, weighing food, rounding up, dose volume and using a phone application.

"Tiny scoop provided with the granules. Told how many scoops by medic/dietician. Had to guess how much fat was in the meal and try to correlate the number of scoops" [S]

The situation was similar when out and about (13 of 15 responses). Two people mentioned some differences however, including the use of a phone application or having already pre-calculated the dose at home.

Calculating the dose appeared to pose a challenge to the majority of participants (53.3 %) along with administering (50 %) and measuring the dose (44.4 %).

Of those who faced challenges calculating the dose, 75 % found this a challenge when out, with 25 % having a challenge both out and about and at home. The challenge when out and about is, not knowing the fat content of food prepared by someone else. This suggests that there is a gap for a novel device to aid in dose calculation (particularly when out) as well as a call for improved ingredient/fat content information in public restaurants.

"Sometimes it's hard to know how much fat is in meals out and about because you can't ask the person that has cooked them like you might be able to at home" [A]

Not only that, it is also important to consider the ease of administering and measuring CREON® micro dose given that (almost) half of the participants had a challenge with these actions.

MEASURING THE DOSE

The majority of participants (13 of 17) used a scoop to measure granule dose at home. Of these, 9 specified that the scoop used was provided with the medication.

"We used a small scoop that came with the packets of CREON®" [R]

16 of the 17 responses reported measuring the dose in the same way whilst out as at home. One participant reiterated the importance of ingredient and fat content information in public stating that there is more guesswork when out and about.

"Guess what the fat content is if eating out" [X]

50 % of the challenges with measuring CREON® micro were incurred out and about, 25 % of respondents had a problem at home, and the remaining 25 %; both at home and out.

Participants noted how measuring can be tricky if there is no scoop available, or if they are required to dose an incremental dosage less than a full scoop.

ADMINISTERING THE DOSE

The majority of participants used applesauce or puree as a delivery vehicle for the granules (9). 11 participants used a spoon for administration, including teaspoons (3) and a 'special spoon'.

> *"I mix the granules into a spoon of apple purée" [F]*

Other delivery vehicles mentioned included water, fruit sauce (3), Infacol liquid, yoghurt, ketchup and food stuffs in general (3).

> *"We used to get a teaspoon and put something like fruit puree on it and then tip the granules onto that. Sometimes when we didn't have fruit puree, we had to improvise with anything sticky that would sit on the spoon and that was edible (obviously). Sometimes we used ketchup for example (yuck)" [R]*

All of the 18 respondents stated they would administer CREON® granules in the same way out and about as they do at home.

One individual commented that on occasion, administration may differ based on the availability of a suitable vehicle.

> *"It was generally the same but sometimes when you are out, you literally have nothing to give the CREON® with so there were times when we had to give the granules to our sons with nothing, i.e. just the granules off a spoon. It must have been horrible for them, like chewing sand or grit" [R]*

The majority (50 %) of the challenges when administering CREON® micro were seen both at home and out. A further 37.5 % occurred when out, and 12.5 % at home.

Seven people spoke of granule administration challenges particularly with reference to administering them to young children (4). Administration proved difficult given the risk of mess or spillage as well as the potential to lose the scoop.

> *"The miniature scoops require a steady hand and inevitably the granules go everywhere! It's tricky always remembering to take apple puree everywhere, in addition to the medication. The scoops get easily lost - we ended up securing ours to the granule bottle with an elastic band!" [Y]*

A GRANULE DEVICE

Participants were asked how likely they would be to use a device capable of accurately measuring granule dose over what the currently do.

The majority of participants would be very likely to use such a device at home or out and about (55 %) if one were available.

Ease of use was found to be the most influential factor (ranked influential or very influential by participants) in determining whether participants would use a device at home (100 %). Out and about, **simplicity** was equally as important (95 %).

Other factors influencing participant willingness to use the device at home included whether there would be an improved clinical result for their child (2) if the device was pre-programmed with food to ease dose calculation (1), how easily the device could be cleaned (2), its size, its portability, its cost (2) and the required dexterity for use.

One participant stated that they were happy with the current state.

> *"I don't feel I needed anything, we were accurate enough. It would just be one more thing to clean and one more thing to remember when we went out" [D]*

When considering device use out and about, the participants had similar concerns relating to device cleaning and cost (2). Portability was also important, including comments relating to device size, weight, ease of carrying, hopper security, power source and remembering to take the device with you.

"Power source. Security of CREON® reservoir" [P]

Similarly to when considering device use at home, one participant was happy with current state, appearing concerned about the cost and burden of excess equipment.

This suggests that an MP dosing device for use by this population would need to be easy to use and simple. These factors were also found to be key during the general investigations of user requirements in Chapter 4.

6.1.3.2 CAPSULES

CALCULATING THE DOSE

Similarly to granule dose calculation at home, the majority of participants referred to the **fat content** of the food as determining the capsule dose (14). Of these, three also mentioned the food's protein content.

"1 to every 3 grams of fat, rounding up for protein" [C]

Eighteen participants stated that they used the same approach to calculating dose when out as they did at home. Three participants reported slight differences including there being more guesswork whilst out and about given there is often no packaging to refer to.

"Not possible to refer to packaging when out and about" [T]

42.9 % of participants had a challenge calculating granule dose. 66.7 % of these experienced challenges out and about and 33.3 % both out and at home.

These challenges are very similar to those faced when calculating CREON® granule dose. This further highlights the importance of aiding dose calculation, and the possible opportunity for a novel dose calculation device.

ADMINISTERING THE DOSE

The majority of participants (11) mentioned their child taking capsules at home with a drink. Eight participants specified that the child **swallowed** the capsules, with a further 2 mentioning oral administration.

"Swallowed whole with a drink" [B]

Four participants specified the timings of administration with respect to the meal, with capsules often being ingested before and during eating.

> *"He picks them up from the table and swallows them. He takes one at start of meal, and the rest through the meal" [D]*

All participants explained that the capsules would be administered in the same way out and about as they were at home.

Very few participants had a challenge administering the capsules (20 %), of these, 75 % had a challenge whilst out and 25 % both out and at home.

Two participants commented on the difficulty of swallowing capsules, whilst others referred to how the capsules can be dropped and break, that you need a suitable administration vehicle, that they offer limited dose flexibility and that they are not always acceptable to the child.

6.1.3.3 TRANSITIONING

GRANULES TO CAPSULES

Participants were asked at what age they/their child transitioned to capsules. The majority (52 %) transitioned between the ages of 2 and 3 years, Figure 6.3. Four children were yet to transition (aged 0 – 5 years).

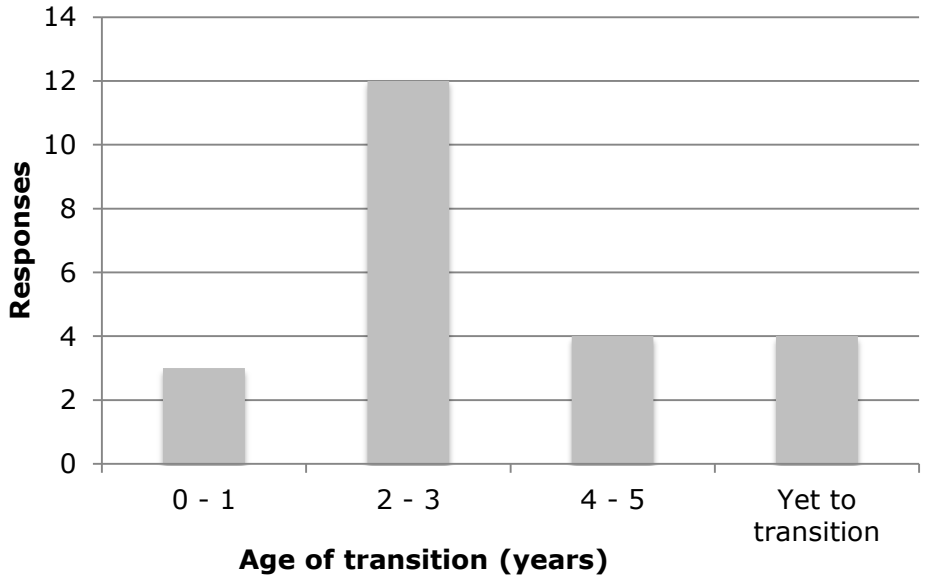


FIGURE 6.3 AGE OF TRANSITION FROM GRANULES TO CAPSULES

Participants were asked to rank how influential; the use of food, ease of transport, ease of administration, ease of self-administration and their child going to school, were upon determining the age of transition.

The most influential of these five factors was capsule **ease of administration** compared to granules (79 % voting this as influential or very influential).

This suggests that the ease of administration is a key factor to consider when designing a granule based dosing device. It is important to ensure that the ease of MP administration with the device is at least equal to that of capsules.

CAPSULES TO GRANULES

Participants were asked how likely they would be to return to granules having transitioned to capsules. The majority (71.4 %) of participants would be unlikely to return to granules with 85.7 % either unlikely or very unlikely.

In their reasoning, the majority of participants mentioned that the capsules were **easier** than granules (10), including being easier to administer and easier to swallow.

> *"Capsules are easier" [A]*

Four participants referred to the **mess** associated with granules as a reason they would be less likely to return to the DF. There were also concerns over the difficulty in **measuring** CREON® micro and the inaccurate dosing.

> *"Granules tend to be messy and harder to administer" [N]*

> *"Too tricky to measure" [J]*

One individual cited the **cost** of granules as affecting the likelihood of returning to the DF. Others commented upon the efficacy and inconvenience (2) of them.

> *"Capsules are easy to administer and CREON® micro is more expensive to provide" [B]*

"Too much to carry and transport. Apple sauce, spoon, CREON® scoop and an ice pack. Inconvenient when out and about" [L]

Some CGs explained how their child had a preference for capsules, and that they were happy taking them compared to 'unfriendly' and unpleasant granules (2).

"Capsules work better, are less messy, less work, easier to swallow, and he is happy with them. Texture of granules in his mouth is unpleasant" [D]

Participants were asked if they could envisage a scenario where they would return to using granules having transitioned to capsules. The majority (11) of participants could not.

Seven participants claimed they may return to granules should issues arise surrounding administration and swallowability of capsules.

"Only if my son started to refuse the capsules" [Y]

One parent mentioned that they would return to granules should capsules not be available, another considered times of illness where granules may prove easier, or should the dosing requirement be less than a full capsule.

"Sickness; may be easier with granules" [M]

"Yes for food portion that needs less granules than are in the capsule" [G]

6.1.3.4 SCENARIO BASED QUESTIONS

Participants were presented with the following scenario; you are at home when your child eats a snack, the snack's fat content does not equate to a full capsule. What do you do? An example of this scenario is shown in Figure 7.4.

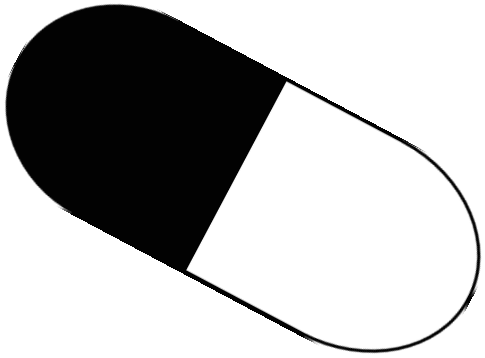
Snack eaten	Dosing requirements
	
5 grams of fat	***1 capsule = 3 grams of fat***

FIGURE 6.4 EXAMPLE OF FAT-BASED DOSING

The majority of participants would be likely (or very likely) to **round up the dose to the nearest capsule** (80 %). This suggests that there may be an issue with the dosing flexibility provided by the capsule DF. This issues a challenge for formulators and pharmaceutical companies to create a more appropriate DF in terms of dose sizes, increments and the consequential flexibility.

Nineteen participants claimed they would act in the same way when out and about as at home. Two highlighted some differences however; one CG would be more likely to round up the dose when out and about despite having said this was unlikely whilst at home. Conversely, another said they would be more cautious rounding the CREON® dose up when out despite this being the course of action at home.

> *"Probably round the amount up to a full capsule" [M]*

> *"Most likely to err on the side of upping the CREON® while out and about" [W]*

The majority of people were either happy or very happy with the current state both out (81.0 %) and at home (76.2 %).

45 % of participants claimed to be likely (or very likely) to use a granule measuring device at home over what they currently do. 40 % would use the device out and about. In both environments, more participants would be likely to use the device than unlikely (30 % at home and 40 % whilst out).

The participants' likeliness of using an MP dosing device was greater than that of using a capsule splitting device. This suggests an MP dosing device would be preferable in terms of the likely adoption by users. It is important to note however, that whilst many claim they would use an MP dosing device, the fact that they are not unhappy with the current situation would question this likelihood. It is therefore important to understand what about the device would make people use it despite not being unhappy with the current state. Further work is required to further comprehend this.

Participants were asked how influential 14 factors were in their likeliness in using a device in this scenario as before.

Device **simplicity** was voted as most influential, with 90 % of respondents likely (or very likely) to find this important at home and 80 % whilst out and about. The least important factor was the **interest in use** when both home and out (25 % and 20 % respectively).

Considering home and out and about use separately, **simplicity** was the most important feature in both situations but was joined by there being **little chance of error, speed** and device **size** (all 80 %) when considering out and about use only.

Noticeable differences between home and outside use were seen in terms of device **speed** and **size**. More people rated this as influential (or very influential) when out and about (both 80 %) compared to considering the same factors at home (65 % and 45 %).

The importance of simplicity is consistent with the themes that CGs noted as important when asked about a device initially. The relative importance placed on ease of use previously, was less documented here. This demonstrates the importance of understanding scenario-based device use in achieving a greater level of understanding into users likely actions. The

best course of action however would be to perform a device use activity with a prototype.

Participants also noted other factors that would influence their likeliness of using a device in this scenario. At home, participants appeared concerned of making administration more complicated and the possibility of more cleaning.

> *"Would it make taking CREON® more complicated for my son? Would it involve more cleaning for us?" [D]*

There were also concerns over device cost (2), simplicity and the applicability of the device to specific dosing regimens. There was also comment of support received from CF teams as influencing device use.

> *"Cost and availability. Ability to fill prescriptions relevant and usable in the device. Support from pharmacist and/or CF care team" [W]*

Out and about, the same concerns of complicating administration and extra cleaning were noted, as well as concern over the storage of the CREON® (2) and the device's portability.

> *"Whether it made taking CREON® more complicated. Carrying and storing it" [D]*

This suggests that an MP dosing device for this population should ease granule administration, be easily cleaned, be cost-effective and capable of securely storing the CREON® granules.

To understand the possibility of any differences in a meal-based scenario, participants were asked if they would do anything differently should a meal not correlate to a full capsule dose.

Six people referred to slight differences in how they would act had it have been a meal instead of a snack. These included subtle differences such as a different dose being used or the rounding of dose to the nearest capsule. One participant mentioned giving the same dose per meal, unless there was a big difference in meal content.

> *"I tend to give the same dose each meal unless it is obvious that there is more or less fat than an average meal" [S]*

Others said that they calculated CREON® dose for parts of the meal to ensure greater dose accuracy. Another commented that accuracy can be challenging during meal times, particularly if the child were to have a second helping.

> *"I will calculate the CREON® for parts of meal, and give CREON® throughout the meal rather than all at the end" [G]*

> *"With meals we often have problems getting accuracy particular if there are seconds" [N]*

Another participant found meal-based dosing easier, being able to pre-empt dosing as opposed to ad-hoc snacks.

> *"Typically we have more prep time for meals, which are on a more regular schedule than snacks. With snacks, you need to be able to act quickly to satisfy a hungry child and/or plan ahead for someone else to administer the snack/CREON® (such as at a camp)" [W]*

Participants were invited to add any further comments surrounding the survey, their experiences of CREON® and their thoughts on a device. Five participants took this opportunity referring to how helpful a granule device would be, but that their child would be less inclined to carry an extra device, and that they have concerns over being discrete.

> *"It may be good to have a device to help with taking granules, but my son wouldn't want to carry anything around to help him with capsules, he swallows them as quickly and discretely as possible. He doesn't want people to see him take them" [D]*

One participant raised concerns about the use of a device in schools, and how school policy can often impact medicine administration to young people.

> *"I hadn't considered the school impact. The schools here in our district in the USA are strict about medications and will not accept ranges or variances. We may be forced to follow traditional dosing instructions in school until such time the child is able to self-carry and administer" [W]*

Others mentioned how useful an online application would be to help calculate CREON® dose, or how much an improved formulation, with greater drug loading (and subsequently less dosing frequency) would help.

> *"We'd love to be able to give a 'super' CREON® i.e. just three tablets a day" [U]*

These comments suggest that participants would like to reduce the burden of the medication regime. Whilst formulation changes would be the responsibility of the manufacturer, a device could however be designed to help reduce the treatment burden including being simple, quick and as easy as possible in dosing the medication.

6.1.4 SUMMARY: CF AND PERT

This case study has acted as an exemplar for potential MP dosing device use by a paediatric population.

It has provided insight into how users currently calculate, measure and administer CREON® (granules and capsules) as well as highlighting key differences between use at home and whilst out and about.

By appreciating the current state and the challenges associated with this, a greater understanding of how or where an MP dosing device may help has been achieved.

The most common challenge related to dose calculation, particularly when the user (or their CG) had not prepared the food themselves. This suggests that a device aiding dose calculation would be beneficial, and that greater dietary/ingredient information should be available in restaurants, cafés and bakeries.

Whilst the majority of participants would likely use a device capable of accurately measuring granules the fact that they were not unhappy with current state poses question over the likelihood of device use. Further research is therefore required to more fully appreciate this area..

The average age of transitioning from granules to capsules was 2 -3 years. Given that the majority of participants were unlikely to ever return to granules having transitioned to capsules, this would suggest a target population of children under three for an MP dosing device.

The scenario based question provided further insight into a likely use situation. It demonstrated that the majority of people would likely (or very likely) round up the dose when capsule flexibility was insufficient to allow for exact dosing. Despite being happy doing this, this highlights a fundamental flaw in the current capsule DF and should issue formulators and pharmaceutical companies a challenge to develop a more suited DF for the users' needs.

Similarly to Chapter 4, device simplicity, speed, size and chance of error were found to be influential factors in participants likely device use. This further highlights their importance in device D&D particularly with reference to an MP dosing device.

CHAPTER 6 – DISCUSSION

This survey has provided insight into the appropriateness of an MP dosing device for the PERT using CF paediatric population through addressing the requirements of the Formulation and Device through consultation with Users.

Enquiries relating to granular and capsule forms of an existing MP-like formulation have allowed an understanding of the influential factors surrounding device use.

Given that many people would be unlikely to return to granules having progressed on to capsules, this device would be targeted towards younger children who are yet to swallow the capsule DF, less than 3 years old.

It was apparent that the main challenges faced with PERT related to the calculation of the correct fat-based dose. As such it is suggested that a device capable of aiding dose calculation and accurately measuring the granules is required.

The participants provided insight into features that would influence the likelihood of them using a device. However, given that participants were not unhappy with the current situation, it questions their apparent willingness to use a MP dosing device. Further work is therefore required to fully appreciate this design space.

CHAPTER 6 – LIMITATIONS

It is appreciated that the number of survey responses was fairly low, 26. This therefore limits the generalisability of these findings to the wider CF population.

The survey was also rather long, which may have deterred some potential participants from completing it, and may have led some participant fatigued during the later stages of completion.

Whilst every attempt was made to ensure the questions were not biased, the nature of closed questions will have meant some bias remained.

The survey was designed in collaboration with CF clinicians, whilst this improved the appropriateness of the questions it is appreciated however

that CF patients were not consulted. The questions therefore may have not been the most suitable in all cases.

Consideration has also been given to the fact that this case study represents only one sub-population of potential users of an MP dosing device. CF patients and their CGs were selected given their knowledge and experience of using an MP-like medication. It is appreciated however, that had an alternative population have been chosen such as HIV or asthma patients using MP-like medications, the results may have been different.

It should also be noted there will be differences in CREON® micro and any envisaged PERT MP, such as improved particle flow-ability and likely higher drug loading this therefore may influence device requirements.

CHAPTER 6 – CONTRIBUTIONS TO THESIS

This chapter has provided an example case study to examine challenges and opportunities for an MP device within a specific sub user population. Having used the findings from the preceding 5 chapters as a starting point, this chapter has begun to understand the CREON®/CF-specific user requirements.

This work has allowed for an appreciation of a particular condition and a specific user group, highlighting key influential factors to consider during MP device D&D. Other studies have been partially abstract in their nature asking participants to think about possible uses of MPs in practice.

This study has addressed all three RQs; relating to Formulation, Device and User requirements. It demonstrates their importance in a specific use scenario.

Whilst this work provides an example case study, it is appreciated that the study is limited to this specific population and that had an alternative condition or user group been selected, the resultant device and user requirements would likely differ.

CHAPTER 7 - DISCUSSION AND CONCLUSIONS

7.1 INTRODUCTION

At the beginning of this thesis the infancy of paediatric MP device development was highlighted. Whilst a number of MP presentations and delivery devices are available, none offer the capability of repeated, flexible and personalised MP dosing. Despite a number of patents having been filed relating to volumetric mechanisms, mass-based MP dosing has not previously been investigated.

This knowledge gap has been addressed through a holistic UCD approach. Investigating Formulation and User requirements in turn has allowed for the generation of a Device specification. Consideration of these requirements subsequently allowed for the generation of a number of specific design concepts and prototyping of internal mechanisms meant an appreciation of potential device components and methods for handling MPs was gained.

This work has led to an improved understanding of the requirements for paediatric medical device D&D, specifically for MP dosing. A case study refined these 'platform technology' requirements to a specific population; paediatric Cystic Fibrosis patients, as an example MP dosing device application.

This chapter presents the contributions made to addressing key knowledge gaps relating to the D&D of a flexible MP dosing device for children. The implications of these findings upon medical technology are presented, the design of a paediatric MP device specifically, as well as an appreciation of study limitations and suggestions for future work.

7.2 REFLECTION ON RESEARCH QUESTIONS

Figure 7.1 summarises how each of the RQs has been addressed.

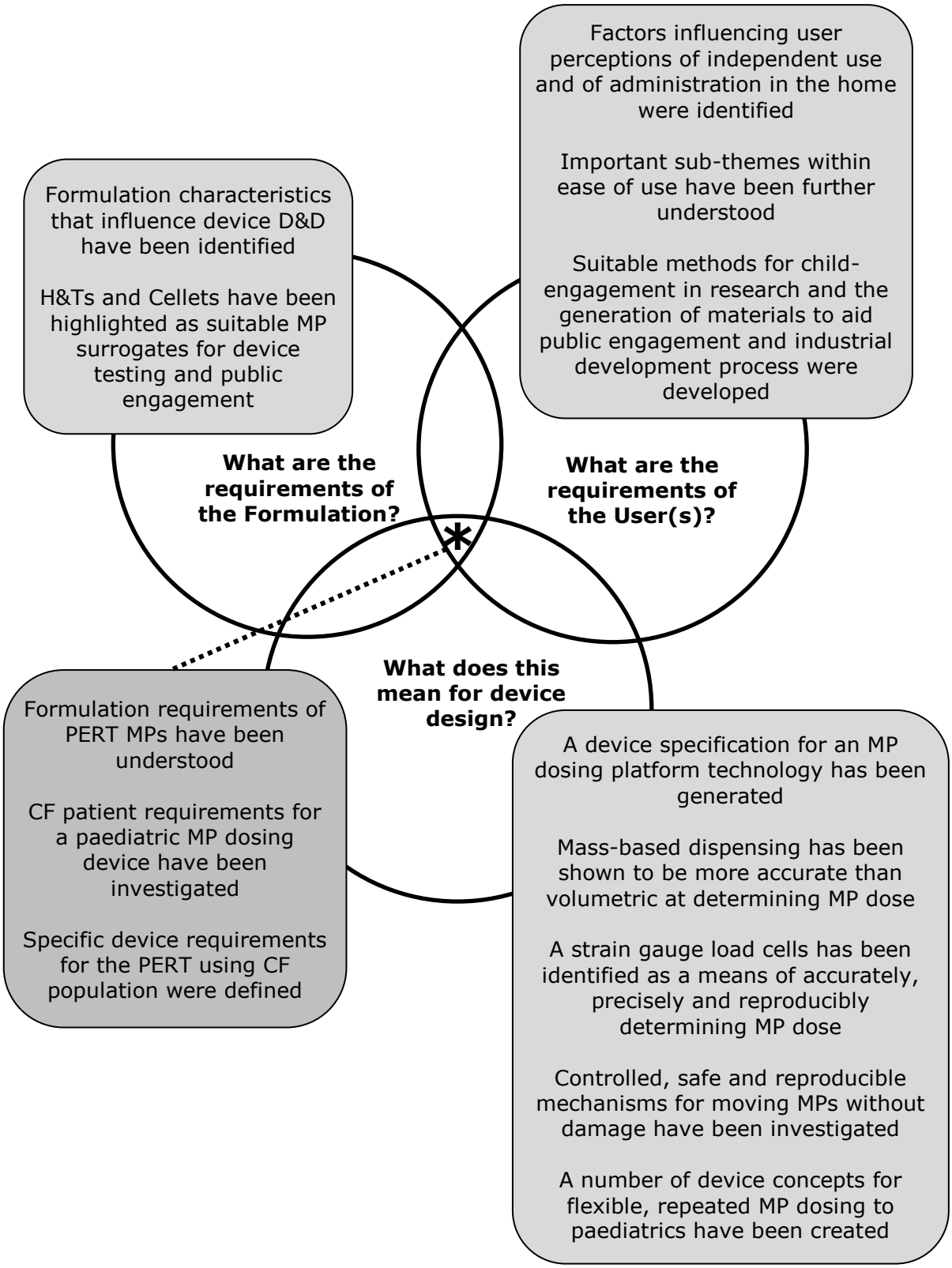


FIGURE 7.1 KEY CHAPTER OUTPUTS IN RELATION TO RESEARCH QUESTIONS

Combining outcomes of Formulation and User work (Chapters 3 and 4) in terms of a device specification (Chapter 5) has provided an understanding of the use and design factors influencing the development of a MP platform technology (Figure 7.1 *****).

This user-centered holistic approach has demonstrated the capability of a paediatric MP dosing device. Through addressing key knowledge gaps this work serves to guide the D&D of paediatric medical devices, specifically those used for dosing MPs.

7.3 CONTRIBUTIONS TO KNOWLEDGE

7.3.1 IMPROVED OPPORTUNITIES FOR PERSONALISED MEDICINE

Personalised medicines are of global interest (FDA 2013; EC 2016; NHS England 2016). Not only do they reduce the costs associated with trialling multiple medicines at different doses in different people, they serve to reduce this burden on patients, improve compliance, reduce the number of hospital administrations and decrease pharmaceutical waste.

The MP formulation itself is greatly amenable to personalised medicine. The free-flowing, multi-part nature allows for a great deal of dosing flexibility, meaning different patients can receive different personalised doses. Additionally, the flexibility of this DF goes beyond dosing amount. MPs can allow for the administration of multiple drugs with different doses and release profiles at the same time. The application of pellet coatings or co-administration of multiple different drug-loaded MPs at once provides a plethora of dosing flexibility. This flexibility is specifically useful for paediatric populations, who; because of their physical growth and development require relatively rapid changes in dosing. In time MP dosing could also be tailored to patient's genetic profiles, diet and culture serving to also reduce harmful side effects related to poly-pharmacy.

The D&D of an MP dosing device serves to facilitate this flexibility and the DFs suitability for personalised medicine further. By retaining the DF in its free-flowing form, the device imparts no restrictions on the dosing amount (unlike encapsulation, tableting or packaging). It also allows for flexible means of dose administration, being amenable to direct MP administration,

or co-administration with food or drink. This is important when considering paediatric MP use, as providing alternative methods of administration could ultimately improve adherence, through avoiding palatability issues of direct administration for example.

Having understood the requirements of the Formulation and User in this work, the development of an appropriate MP dosing platform technology has been facilitated by the generation of a device specification. Subsequent device design and prototyping has exemplified possible forms that an MP dosing device may take, and serves to guide device designers and developers in the future.

7.3.2 IMPROVED HEALTH OUTCOMES

The exploration of user requirements in Chapter 4 builds on work by Martin et al. (2006) and Sharples et al. (2012) that considered the importance of UCD, as well as the work of Lang et al. (2013) and Howard et al. (2017) who investigated medical device use by adolescents specifically. This work supports the importance of context of use and ease of use as key device requirements. Additionally it provides new insight into experiences of paediatric medicines in the home, paediatric self-administration and ease of use.

The findings demonstrate the importance of device simplicity, accuracy and speed in paediatric medical device design. Through understanding the age of paediatric self-administration a greater understanding of exactly who the device user will be is achieved. This work serves to guide the generation of subsequent paediatric medical device specifications, particularly for an MP dosing device.

By advancing the knowledge of user-centered paediatric medical device design through HF approaches, this work serves to improve patient health outcomes in the future. Children and their families benefit from safe, effective medical devices with timely access to these offering improvements in prognosis, better management of deterioration or relapse in chronic conditions and in some case improving life expectancies (Davis et al. 2007; NHS 2010; NHS England 2016). Systematic attention to children's needs and characteristics has been well documented as having great important in medical device design, use, and evaluation (Committee

of Postmarket Surveillance of Pediatric Medical Devices 2005; Martin et al. 2006; Shah and Robinson 2008; Sharples et al. 2012).

7.3.3 IMPROVED MP FORMULATION DESIGN

The identification of Formulation characteristics influential upon device D&D in Chapter 3 is new. Along with the enhanced understanding of paediatric user perceptions of independent use and medicine administration in the home, this work compliments knowledge of user perceptions of the MP formulation (Ranmal 2014; Lopez et al. 2016). This adds further understanding of the most appropriate method for administering this DF.

Identification of key challenges in paediatric medicine administration in Chapter 4 also highlights the importance of formulation taste upon successful administration. Whilst taste is known to affect palatability of medicines (Davies and Tuleu 2008; Mennella et al. 2015) and food (Birch 1979; Harrar and Spence 2013) this work further strengthens this argument. This poses a challenge to formulators to improve the taste profile of paediatric medicines.

Not only that, the exploration of mass-based dosing in Chapter 5 and patient requirements of an MP dosing device in Chapter 6 suggest that the added accuracy offered by mass-based dosing is not required. This is due to the fact that the maximum drug loading of MPs currently is around 60%, hence dosing accuracy within one or two MPs is not required. This was exemplified in Chapter 6 where it was commonplace that the CGs rounded up CREON® dose to the next full capsule, despite this dosing regimen suggesting an incremental capsule dose was required. This consequently serves two challenges to formulators: 1) to consider the limited dosing flexibility offered by the capsule DF (particularly in the case of PERT) and 2) to consider the optimal drug loading of MPs. Whilst high drug loading serves to reduce the overall dose volume, it may be preferable however that the drug loading remain around 50% to circumvent the requirement of highly accurate mass-based dosing, given the increased cost implications and allowing for accurate dose measurement by volume.

7.3.4 FOUNDATION FOR CASE SPECIFIC MP DEVICE D&D

Having highlighted H&Ts and Cellets as suitable MP surrogates in Chapter 3, the novel use of them in this process serves to improve MP device testing by providing an affordable, readily available material for use by device developers.

The generation of a device specification for an MP dosing platform technology in Chapter 5 is novel. This insight will provide device developers with a guide for subsequent concept refinement in the future.

The investigation of mass-based dispensing in Chapter 5 has demonstrated an accurate means of determining MP dose. Having identified a strain gauge load cell as a mechanism to accurately, precisely and reproducibly determine MP dose this provides a starting point for subsequent device development.

The identification of three different controlled, safe and reproducible mechanisms for moving MPs without damage will aid in this together with the generation of possible device concepts capable of flexible, repeated MP dosing to paediatrics.

The exploration of Formulation and Device requirements in a specific User group in Chapter 6 has allowed for an understanding of how the global requirements of a platform MP dosing device can be applied to specific indications and patient populations.

Whilst little research has considered user perceptions of PERT, it is widely appreciated that the medication regime required by CF patients is a great burden. Here, the possibility of reducing this burden through the design of a MP dosing device was investigated. Having considered the key requirement of dose flexibility based on food fat content, and the need for frequent medication a more appropriate device specification could be achieved.

Device design preferences and user requirements within the CF population have been explored previously by Lang et al. (2013); (2014a) with a focus on their use of Positive Expiratory Pressure (PEP) Therapy. This work serves to compliment the understanding of CF patient requirements for

medical devices in a broad sense, as well as adding new detail to the CF user requirements of a PERT dosing device.

This study discovered the importance of aiding dose calculation, dose measurement and dose administration of the granular PERT. It also exemplified the importance of selecting a specific population and condition for HF studies in order to allow for refinement of device specifications and ultimately to achieve a more appropriate end product.

The case study provides an example to industry of how the device requirements in Chapter 5 can be further refined on a case-by-case basis. This serves as a foundation upon which further specific MP dosing devices can be generated.

7.3.5 USER ENGAGEMENT TOOLS FOR INDUSTRY

The identification of H&Ts as an MP surrogate has the potential to improve public engagement interactions. The use of a tangible, relatable item allows for improved understanding by the user groups of MPs. It may also serve to improve user perceptions of the novel DF, given its familiarity and commonplace in the home. This is in contrast to and unlike, real medication or the Cellet® sample which will likely be foreign to most users, and may be intimidating.

The identification of suitable methods for child-engagement in research, and the generation of materials to aid knowledge transfer (Chapters 3 and 4) provide tools for industry-based user-centered research. Using established HF methods and building on their application in medical technology research, this work provides new insight for device developers and formulators into successful methods of engagement with young users and requirement capture. This serves to enhance the industrial development process by improving the chances that accurate information is disclosed during requirements elicitation and resulting in the creation of more acceptable medicines and devices.

7.3.6 CONSIDERATIONS FOR FUTURE REGULATORY AND GUIDANCE DOCUMENTS

The development of regulatory documents and guidelines is of upmost importance in ensuring the continued high standard of research and development into paediatric medicines and their administration devices. Alongside guidelines for HF in medical device D&D (ANSI/AAMI.HE75 2009; ISO 2015; ISO 2016), paediatric research (EMA 2006b) and device D&D (ISO 2003) this work presents possible areas for consideration in subsequent regulation iterations having provided an example of UCD in paediatric medical device development.

7.4 RECOMMENDATIONS FOR FUTURE WORK

Whilst this work has contributed to knowledge surrounding paediatric MP dosing devices, a number of important enquiries have been unearthed which were not examined within the scope of this research project. It is therefore suggested that future research be performed in these areas to further improve the theoretical and applied knowledge around MPs and their combination devices, including further understanding of the paediatric users.

Given this thesis has focussed on the development of an MP platform technology and has provided global device requirements, it is appreciated that further case specific work will aid in requirement refinement. Considerations of the medications dosing regimen, the MPs drug loading and the dose volumes will aid in the generation of more specific Formulation requirements. Through the identification of a specific indication, this would allow for interactions with real user groups, rather than proxies such as healthy children and CGs. This in turn allows for an appreciation of specific Formulation and User requirements, meaning more informed Device specifications can be created and concepts generated. An example of this is presented in Chapter 6, the CF patient case study.

7.4.1 FORMULATION

Whilst this research does not investigate MPs in terms of their formulation and acceptability, it is appreciated that further research is required to further comprehend the appropriateness of the DF in the paediatric population. This insight would allow further refinement of the target user age-range for example, which would in turn allow for a more appropriate device design to be generated.

Whilst some consideration has been given to the possible mode of MP administration here, this is a largely un-researched area. It is appreciated that MPs can be administered directly or via a vehicle such as food or drink. However, little is known about patient preferences towards each method of administration. Much work is therefore required to understand patient preferences of different modes of MP administration as well as considering any possible food effects should co-administration be used.

The dosing volume of MPs will also likely be a concern, with many patients likely to move towards capsule or tablet DFs once the volume becomes large and the relative disadvantages of handling MPs become too great (as exemplified in this case study). To this end, an appreciation of what this threshold volume is likely to be for young people, will allow refinement of the target population's age range.

7.4.2 USER(S)

There is also a largely unanswered question surrounding the age of self-administration. Whilst there are no guidelines relating to the age of paediatric self-administration, this is often a step dependent on the individual, their development, confidence and caregivers. As with many paediatric medicines there is no clear evidence as to the age a child would be capable of self-administering MP DFs. This will also likely differ depending on indication and patient group; hence focusing on a specific indication would aid refinement.

It would also be of interest to investigate the effects of age upon user's requirements of medical devices, including the MP dosing device specifically. Given that the cognitive and physical needs of children and young people alter over time this understanding would inform developers

of key developmental changes, allowing for further design refinement for the needs of specific sub-populations (EMA 2013; NHS 2016). This would ensure device designs are optimised for their target age group improving acceptance, adherence and health benefits. The importance of which was demonstrated in 7.3.2.

Investigation of device use in context as required by regulations (ISO 2015; ISO 2016) would provide further understanding of device use. Unlike the laboratory testing that is common during development, a wider appreciation of different use contexts and the subsequent impact these have of device requirements will provide valuable information to guide device D&D in a general sense, as well as in the case of paediatric MP dosing device specifically.

This research has focussed solely on the use of MPs in paediatric patients. It should also be considered however, that their applicability in geriatric patients has been demonstrated (Breitkreutz and Boos 2007). This presents a different user population to be explored by industry in order to understand what their needs of an MP dosing device might be. Whilst this is a line of enquiry outside the scope of this PhD, this work can be used as a foundation upon which to base subsequent geriatric studies however.

7.4.3 DEVICE

The selection of specific case studies will serve to further refine the platform technology requirements highlighted in this work (as demonstrated in Chapter 6). Whilst efforts have been made to demonstrate means of moving MPs in this work, these prototypes should be further refined with specific geometries based on a particular formulation, dosing regime and set of user requirements for example.

The device cost is also likely to be influential, whilst this was largely over-looked during this work in order to not constrain concept generation, in reality, as suggested by Chapter 6, the cost of a device will become a key influential feature. Because of this, case studies of specific conditions, indications and geographical location will allow for more appropriate device conceptualisation. For example the cost of mass-based MP dosing devices in the treatment of HIV in Sub-Saharan Africa is unfeasible.

7.5 CONCLUDING STATEMENTS

This research has employed a user-centered holistic approach to further comprehend the Formulation and User requirements of a paediatric MP dosing device. Through careful consideration of the Formulation's properties and their impact on device design, as well as using HF methods to interact with user groups, a number of user-centered device concepts have been generated and mechanisms prototyped.

This research provides guidance for MP formulation design and offers generic design detail for novel MP dosing devices. It also provides new resources for industry looking to engage paediatric users in device development processes.

Finally, this research investigation as a whole, offers academic contributions which advance the field of personalised medicines with a view to improving health outcomes for users of MPs generally and specifically paediatric patients.

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APPENDICES

APPENDIX 1 EXAMPLE INFORMATION SHEET AND CONSENT FORM

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

User Device Preferences_7

Participant Information Sheet

My name is Claire Lewis and I am a final year PhD student at The University of Nottingham.

As part of my research work, I would like to invite you and the child(ren) in your care to take part in a research exercise. Before I carry out this activity it is important for you to understand why the research is being done and what will be involved. Please take some time to read through this information sheet carefully and ask questions if anything is unclear or if you would like more information.

Purpose of the study

The purpose of this study is to understand the area of medicine administration to children. We would like to discuss how medicines are currently administered, how they are managed, how users communicate about medicines, whether any challenges are encountered and how these are or could be overcome. We aim to use this information to inform the design of a device capable of administering a new medicine to children. The new medicine is much like sprinkles and is hoped will allow improved administration of medicines to children.

What will happen if you/ the child(ren) in your care decide to take part?

You and the child(ren) in your care will be engaged in a discussion about medication administration. Areas such as current practices, challenges and challenge resolution, room for improvement, medication management and communication about medicines will be discussed.

The information shall be collected by recorded conversation.

If you agree that to take part, our research and the activity will be explained to you. You will be given the opportunity to ask any questions. You may also ask questions if you do not understand anything.

What will happen to my / the child(ren)'s in my care information?

All information provided will be captured electronically, encrypted, and stored on a password protected computer. It will be destroyed seven years after any publication arising from the work, in accordance with the university data storage policy. Your name (i.e. signature on consent form) will be kept separate from your responses. Consent forms will be stored in a locked filing cabinet for the duration mentioned above and kept seperate from the transcripts of our conversation(s) to ensure information is anonymous.

Your comments will be used to inform my device design and will only be accessible by myself and my supervision team. Your comments and the subsequent conclusions from this study may also be used for academic publications, for example as part of a journal article. Your/the child(ren) in your care gender and ages may be used to categorise findings, however your name will not be used in association with the data. All recordings will anonymised at the point of transcription.

What will happen if I/ the child(ren) in my care don't want to carry on with the activity?

You can withdraw from the activity at any time without having to provide a reason. If you do withdraw, the information collected will be destroyed and will not be included in the study. You also do not have to answer any particular question.

Will my/our taking part in this study be kept confidential?

Yes. You will also be asked to give some personal details of your child such as name, age, and gender. These details will be kept confidential and held according to the Data Protection Act, and will not be published. They will be held on a secured database and made anonymous before sharing any information.

Who is organising and funding the research?

This research is being conducted as a research project at The University of Nottingham. It is funded by the Engineering and Physical Sciences Research Council (EPSRC) and Pfizer.

Who has reviewed the study?

This study has been approved by the University of Nottingham's School of Pharmacy Research Ethics Committee.

In case of concern/complaint regarding this study, please contact:

Dr Franco H. Falcone

Chair, School of Pharmacy Research Ethics Committee

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Who do I contact if I have questions or require further information?

If you have any questions or concerns about the study, please contact:
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Nottingham
NG7 2RD

Alexandra.lang@nottingham.ac.uk

User Device Preferences_7

Consent Form

	Please Initial Box
I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that the participation of myself and the child(ren) in my care is voluntary and that they are free to withdraw at any time, without giving reason.	
I understand that our responses will be used by the researcher to support the development of their design. I understand that our data will be anonymised.	
I agree that the I/ the child(ren) in my care may take part in the above study.	

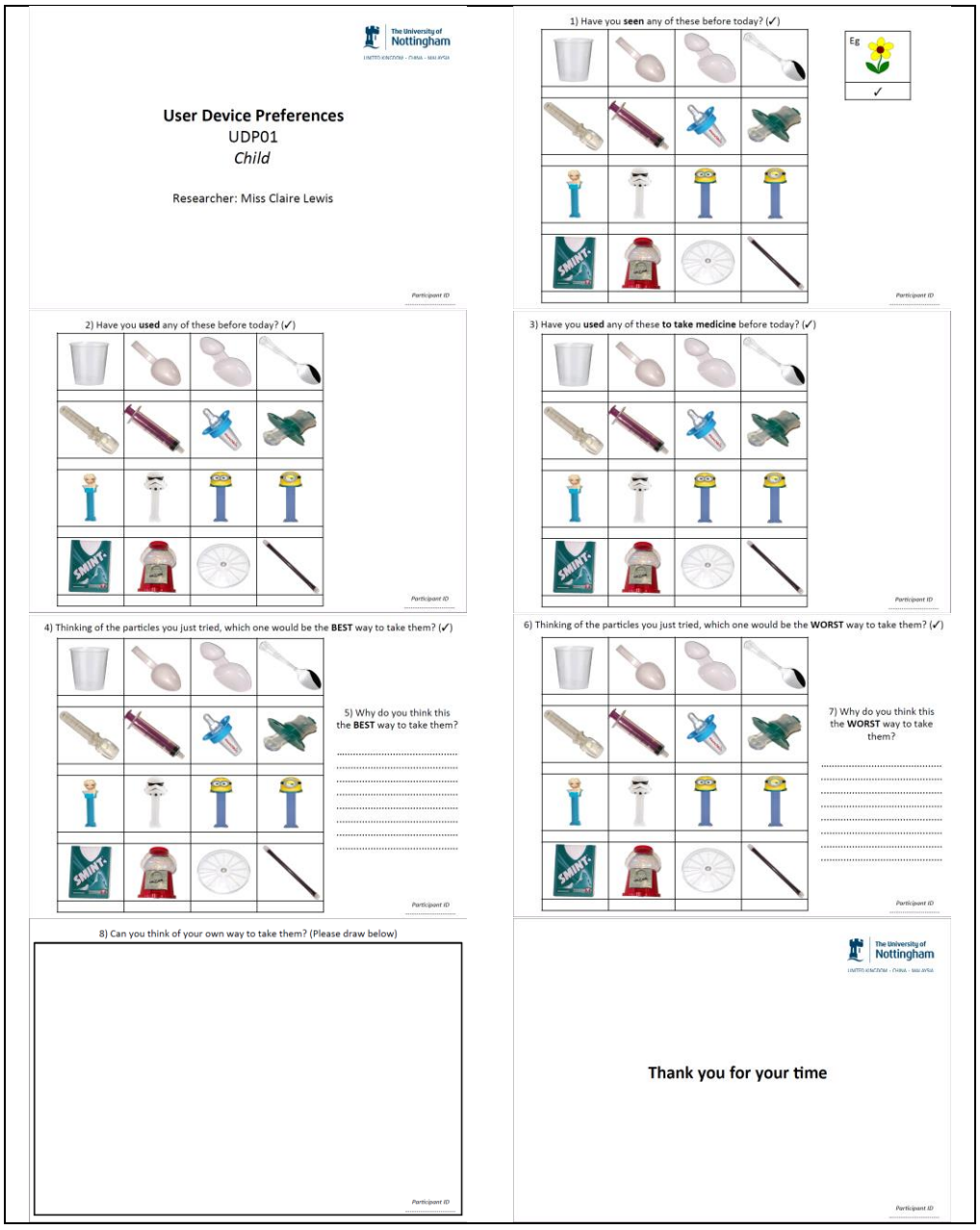
		Age (yrs)	M/F	Relationship to the child
Name(s) of child(ren)	.....	.....	.....	.....
	.....	.....	.....	.....
	.....	.....	.....	.....
Your name	.....	.....	.....	
Signature	.....			
Date	.....			

If you would like to be entered into our prize draw for a £30 Amazon voucher please leave your contact details below.

Email address: _____

Telephone number: _____

APPENDIX 2 PICTURE-BASED QUESTIONAIRRE VERSION 1



User Device Preferences
UDP01
Child

Researcher: Miss Claire Lewis

Participant ID .....

1) Have you **seen** any of these before today? (✓)

Eg ✓

2) Have you **used** any of these before today? (✓)

3) Have you **used** any of these **to take medicine** before today? (✓)

4) Thinking of the particles you just tried, which one would be the **BEST** way to take them? (✓)

5) Why do you think this the **BEST** way to take them?

6) Thinking of the particles you just tried, which one would be the **WORST** way to take them? (✓)

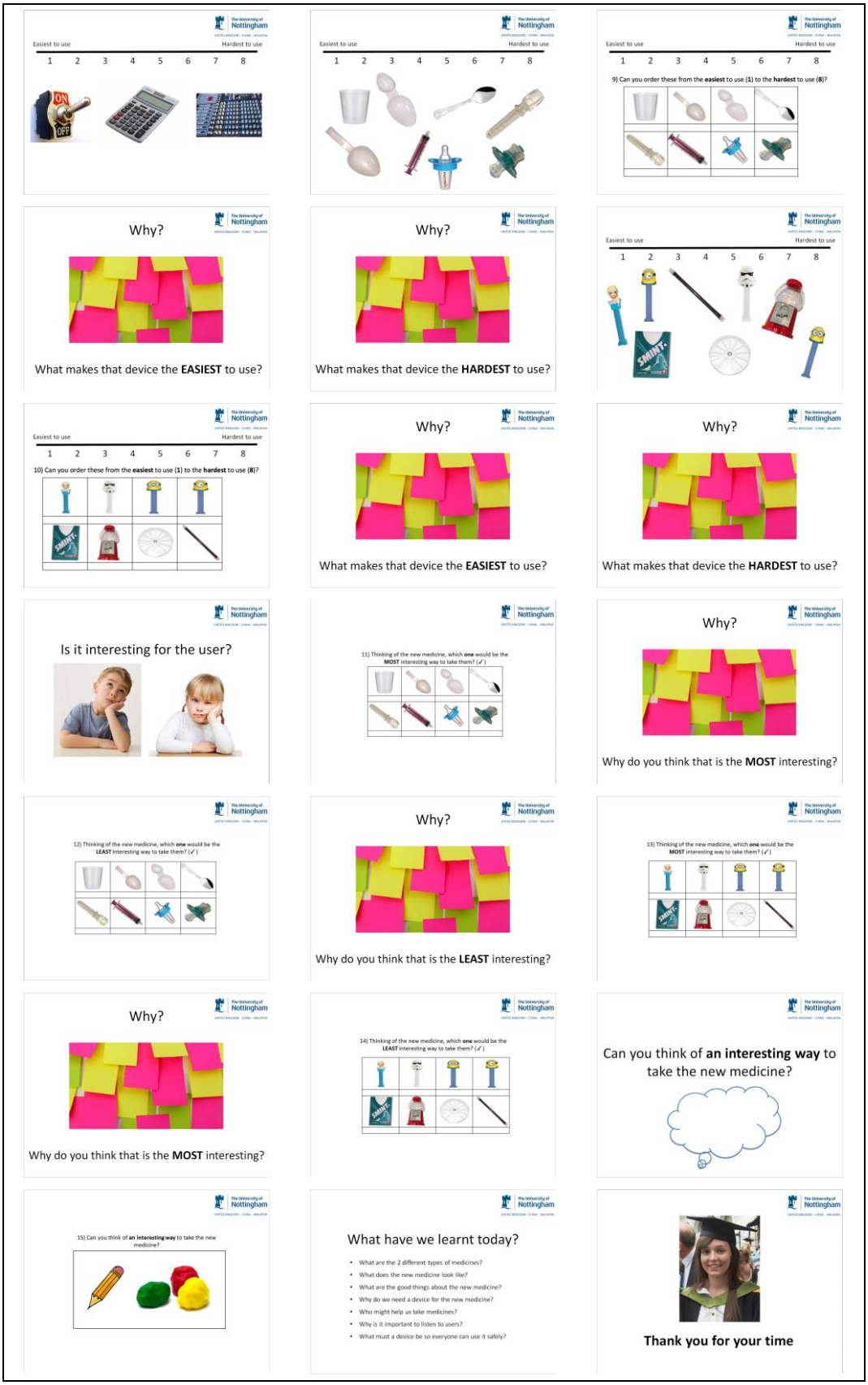
7) Why do you think this the **WORST** way to take them?

8) Can you think of your own way to take them? (Please draw below)

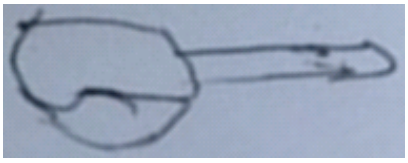
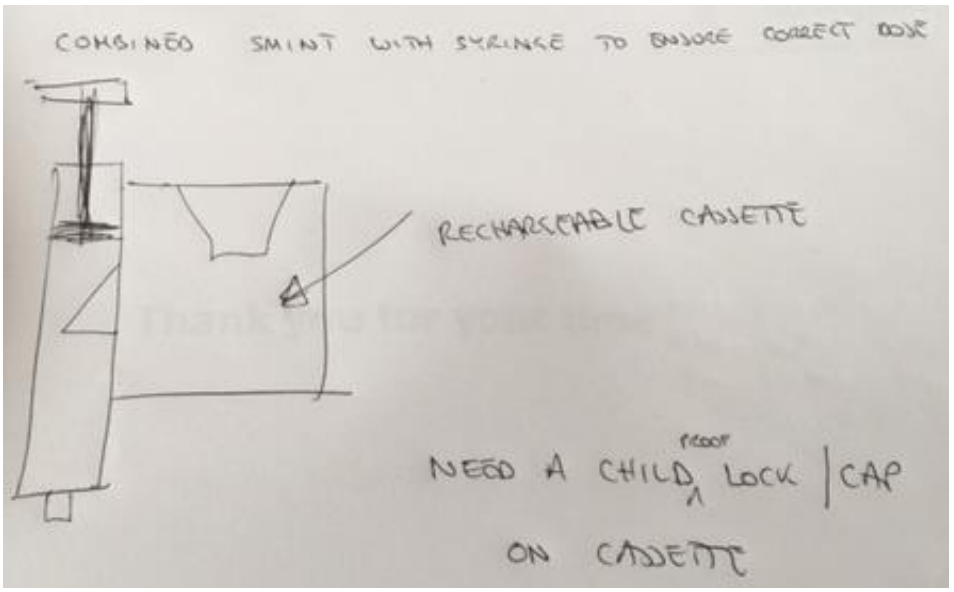
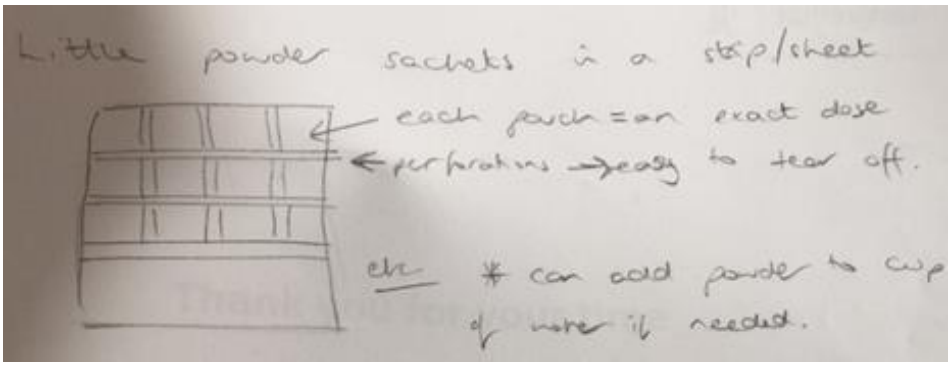
Thank you for your time

APPENDIX 3 SCHOOL-BASED PRESENTATION

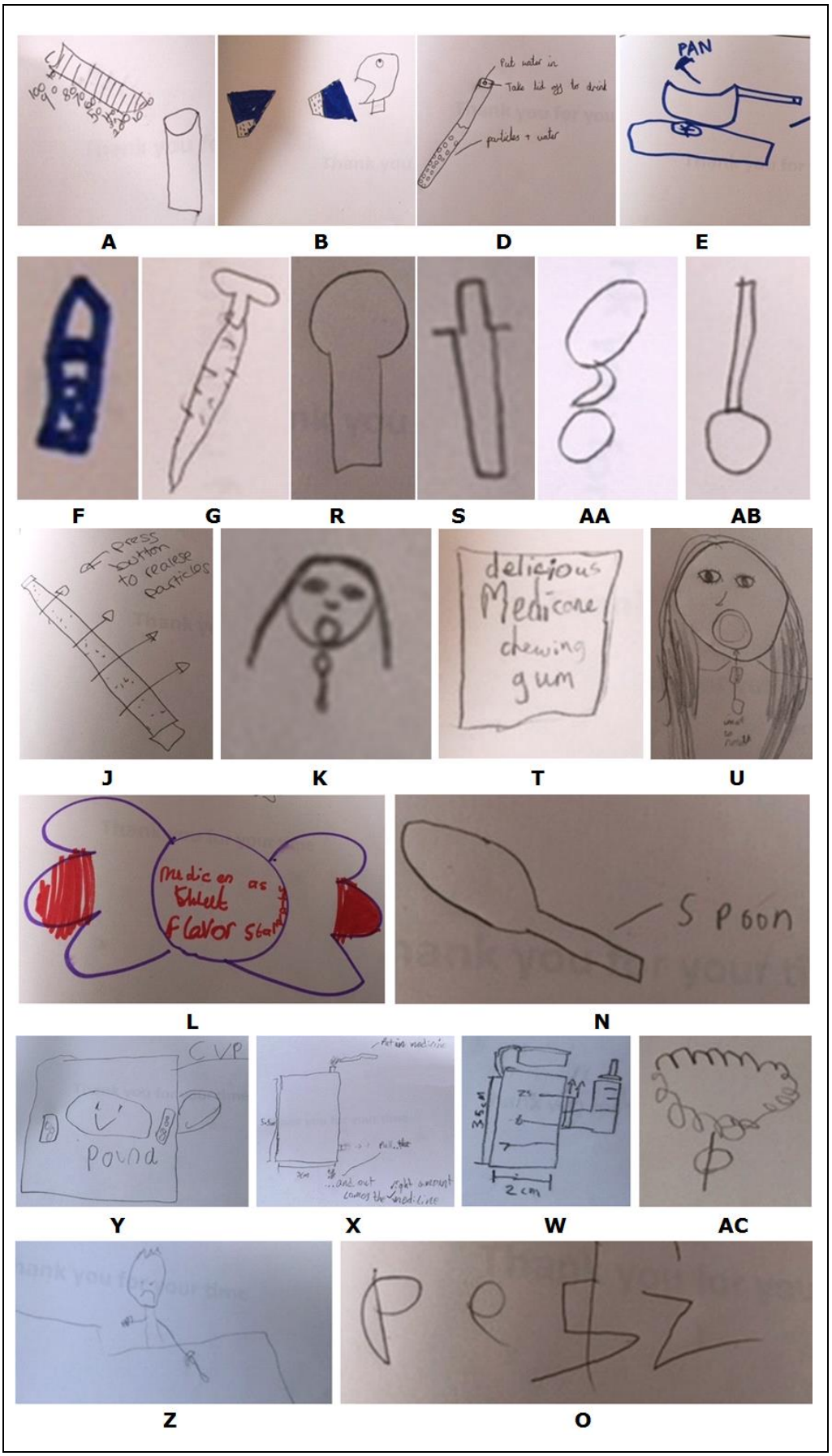



Easiest to use
Hardest to use
1 2 3 4 5 6 7 8
ON
OFF
9) Can you order these from the easiest to use (1) to the hardest to use (8)?
Why?
What makes that device the EASIEST to use?
What makes that device the HARDEST to use?
SMINT
10) Can you order these from the easiest to use (1) to the hardest to use (8)?
What makes that device the EASIEST to use?
What makes that device the HARDEST to use?
Is it interesting for the user?
11) Thinking of the new medicine, which one would be the MOST interesting way to take them? (✓)
Why do you think that is the MOST interesting?
12) Thinking of the new medicine, which one would be the LEAST interesting way to take them? (✓)
Why do you think that is the LEAST interesting?
13) Thinking of the new medicine, which one would be the MOST interesting way to take them? (✓)
Why do you think that is the MOST interesting?
14) Thinking of the new medicine, which one would be the LEAST interesting way to take them? (✓)
Can you think of an interesting way to take the new medicine?
15) Can you think of an interesting way to take the new medicine?
What have we learnt today?
What are the 2 different types of medicines?
What does the new medicine look like?
What are the good things about the new medicine?
Why do we need a device for the new medicine?
Who might help us take medicines?
Why is it important to listen to users?
What must a device be so everyone can use it safely?
Thank you for your time

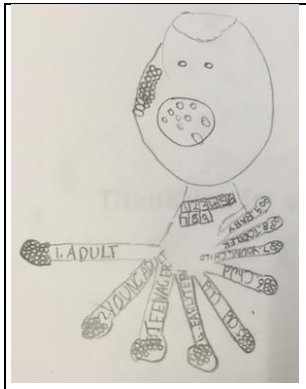
APPENDIX 4 CG'S DIY DEVICES

13		14	
18			
19			

APPENDIX 5 EC'S DIY DEVICES



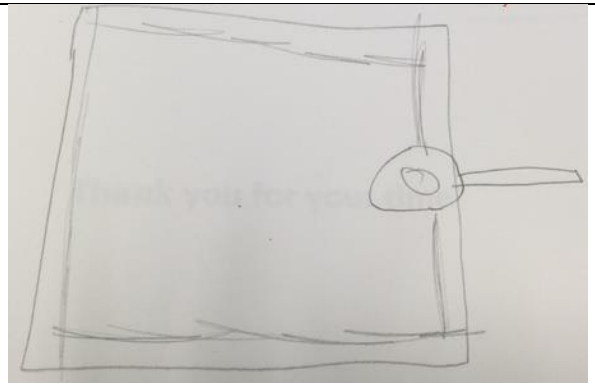
APPENDIX 6 NC'S DIY DEVICES



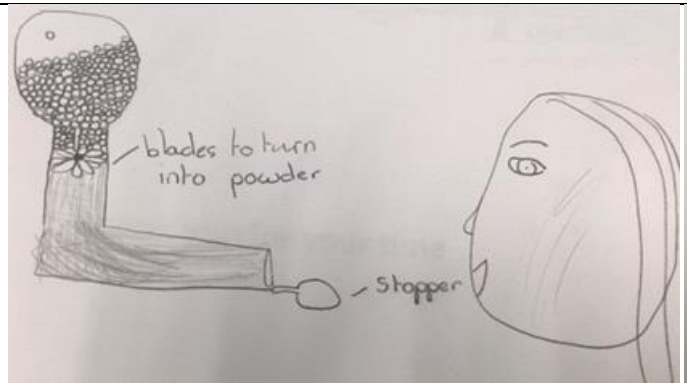
1



2



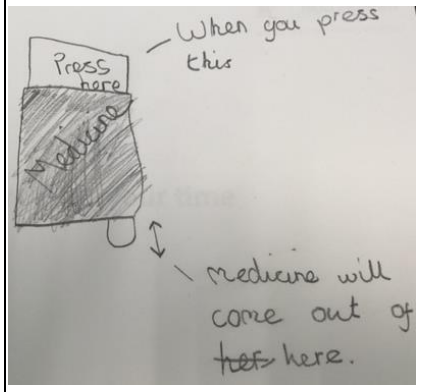
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4



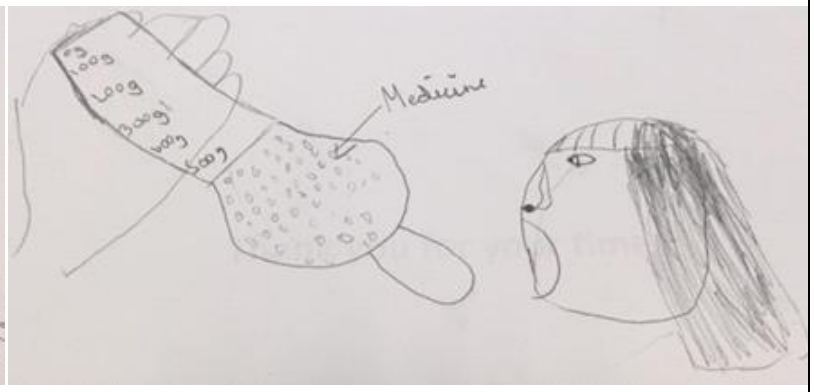
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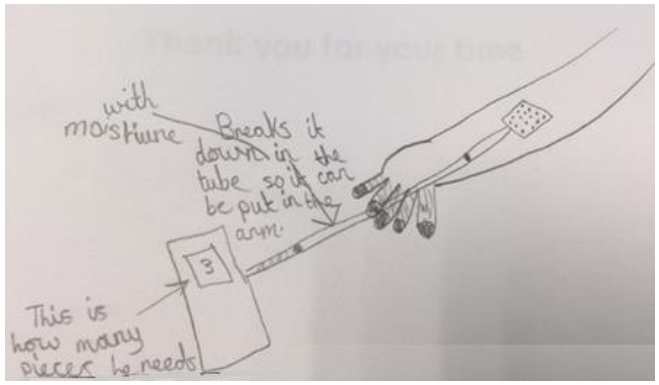
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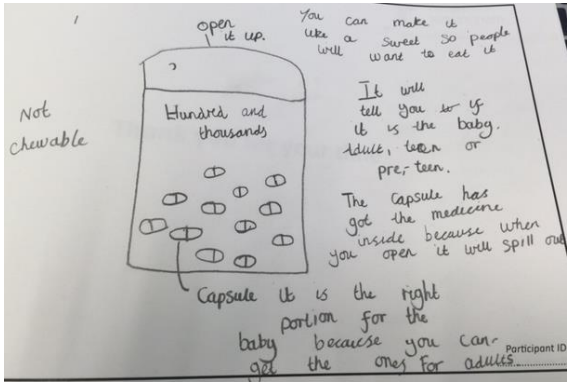
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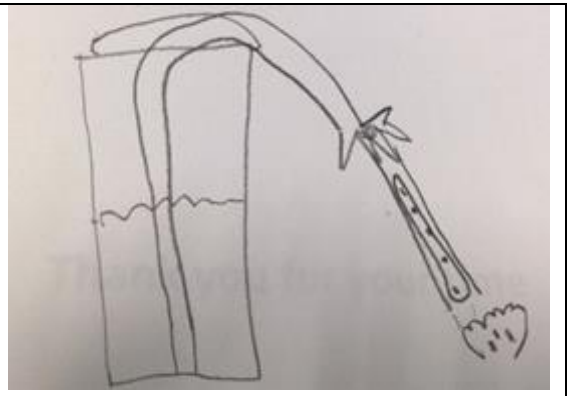
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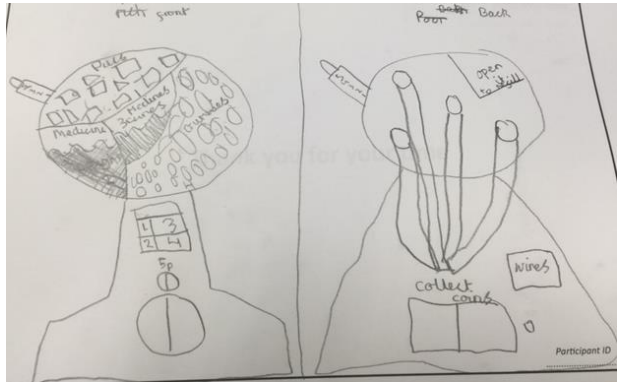
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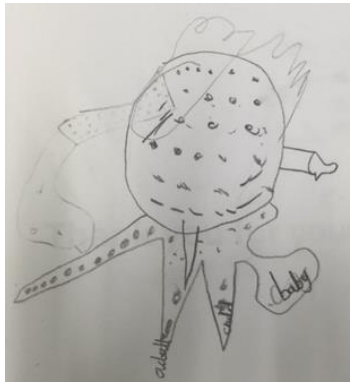
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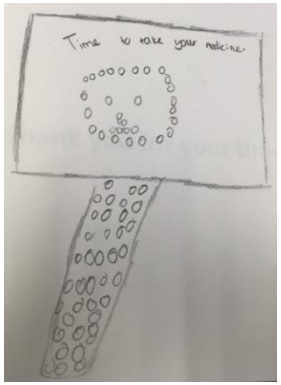
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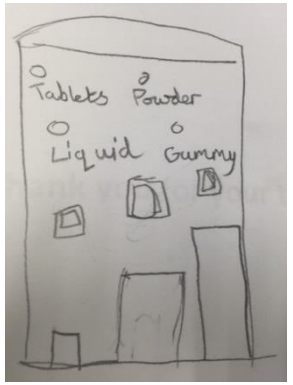
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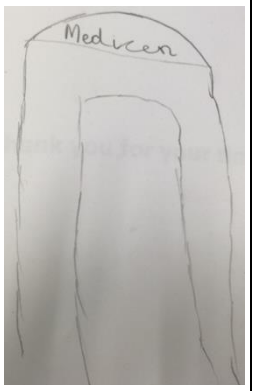
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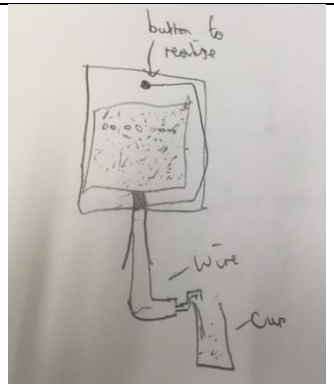
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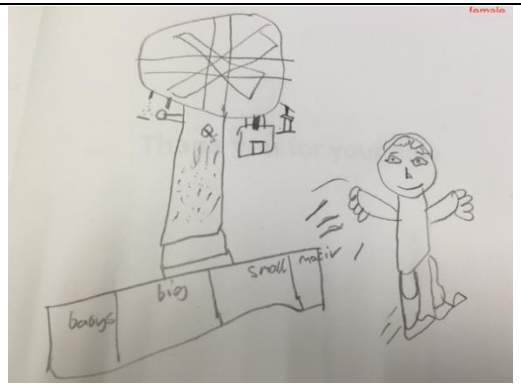
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16



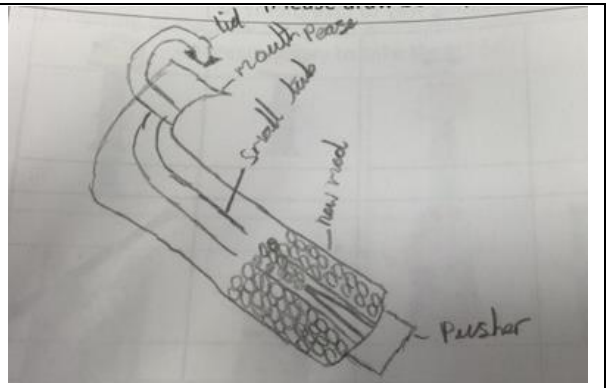
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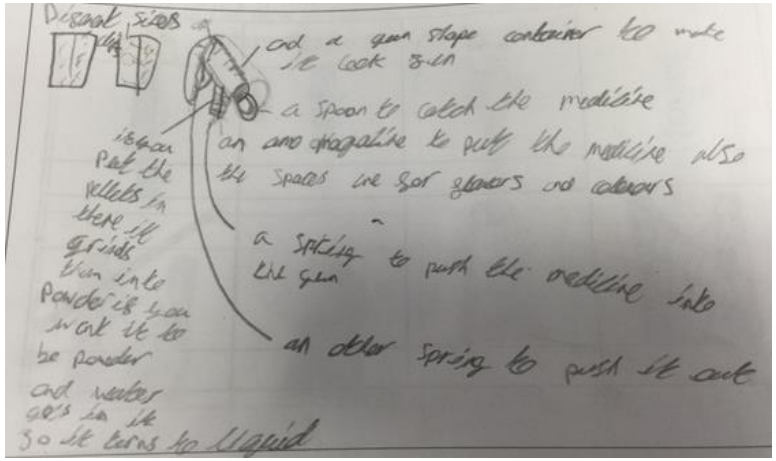
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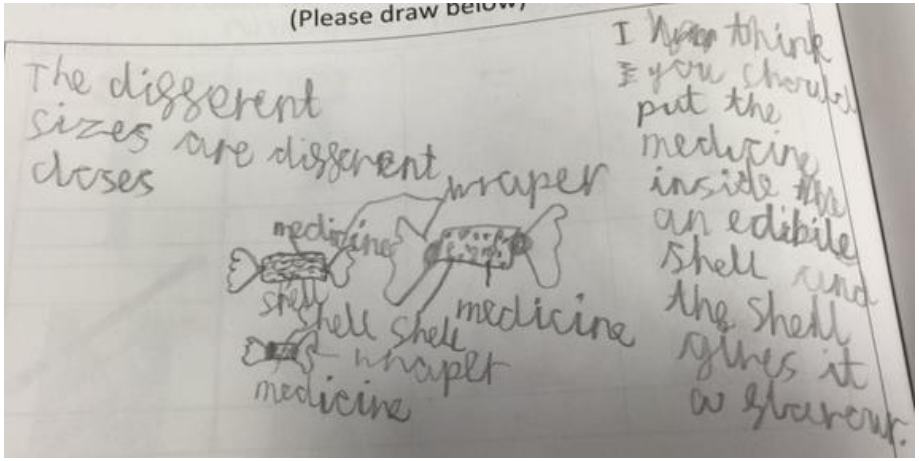
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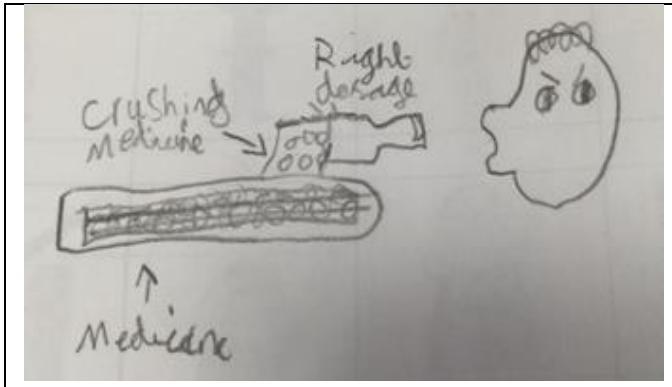
SA



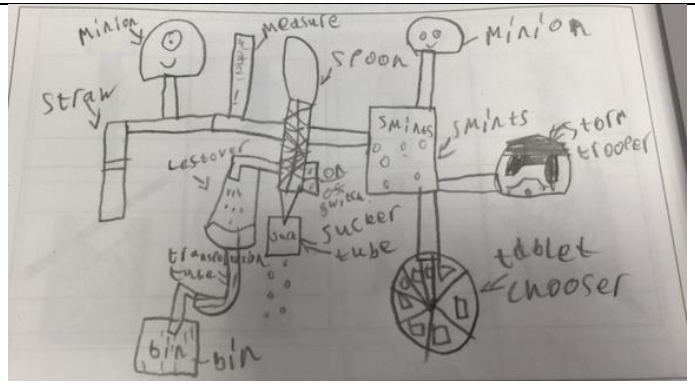
SB



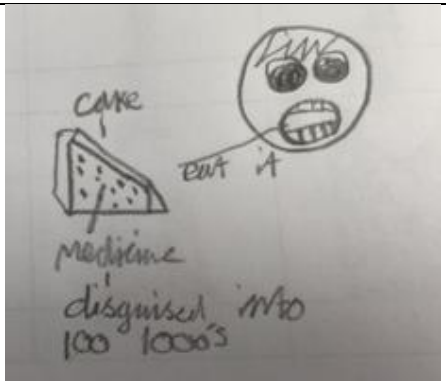
SC


Right dosage
Crushing Medicine
Medicine

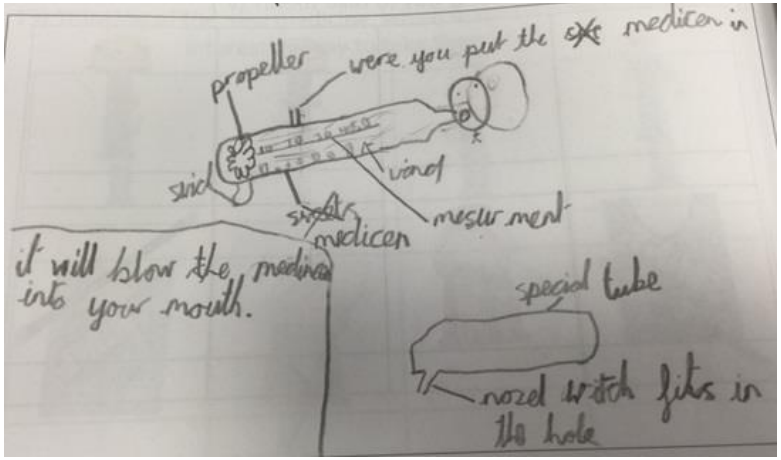
SD


Minion
measure
Minion
spoon
straw
smints
smints
storm trooper
leftovers
sucker tube
tablet chooser
bin
bin

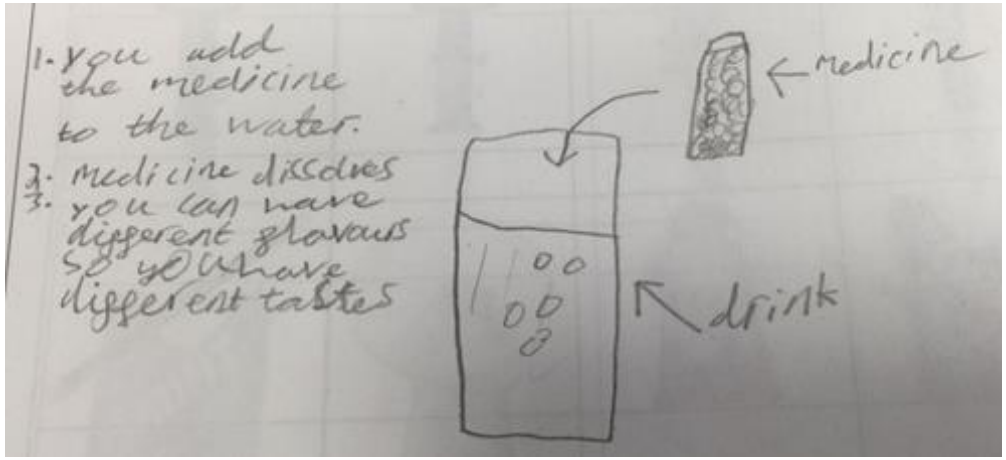
SE


cake
eat it
medicine disguised into 100 1000's

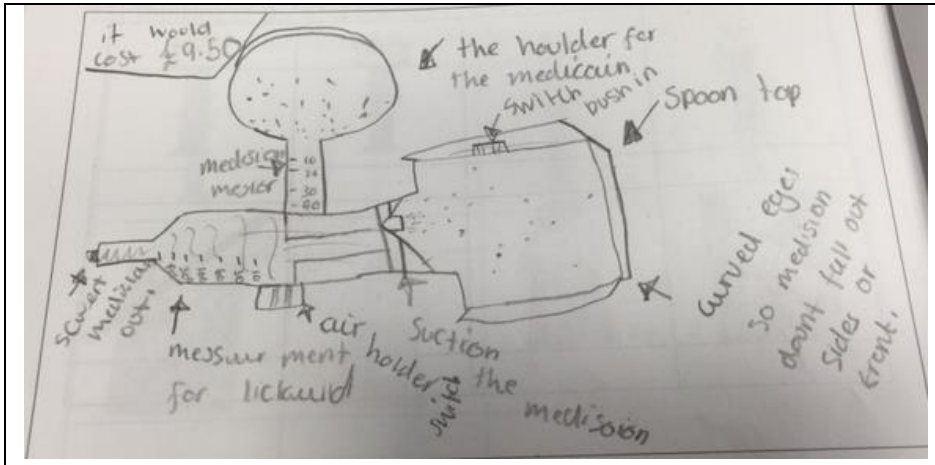
S2


propeller
were you put the medicen in
stick
vinal
mesurment
it will blow the medicen into your mouth.
special tube
nozel which fits in the hole

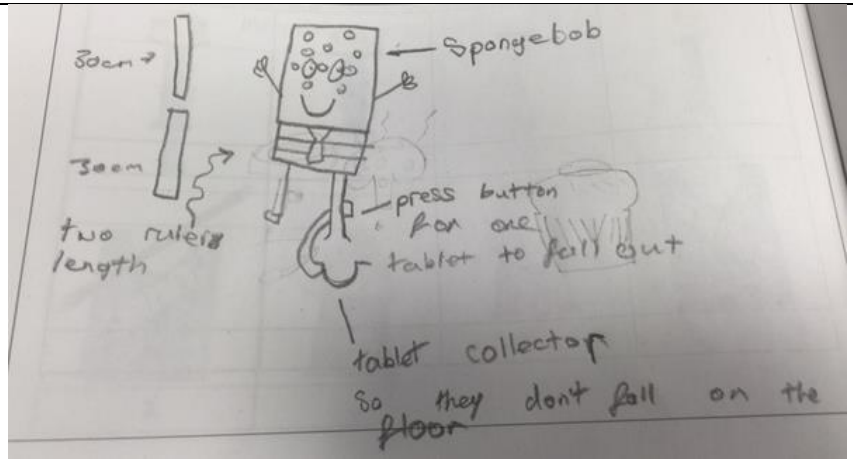
SF


1. you add the medicine to the water.
2. medicine dissolves
3. you can have different flavours so you have different tastes
medicine
drink

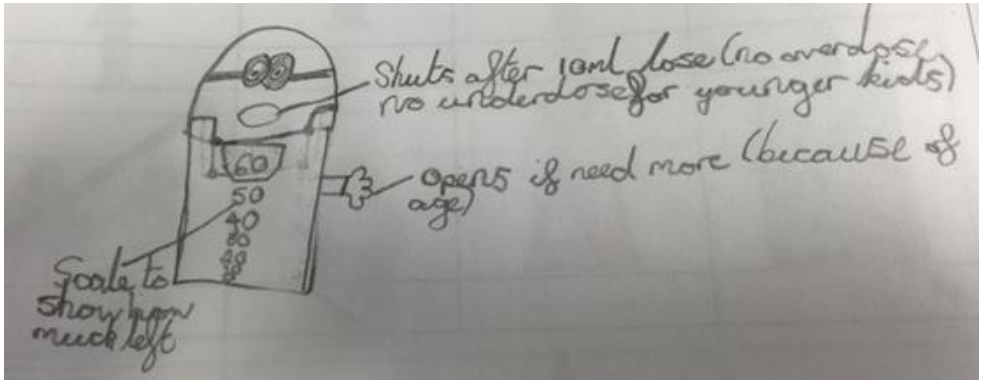
SG


it would cost £9.50
the houlder for the medicain
switch push in
Spoon top
curved edge so medsion dont fall out Side or front.
medsion meaur
Suction the medisoin
air holder
messuer ment for liquid

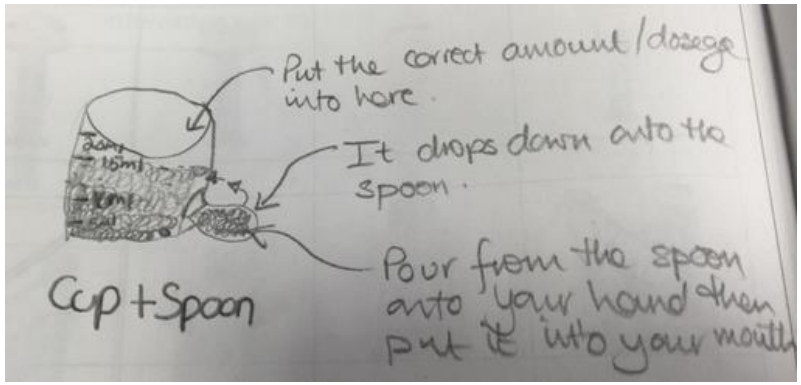
SH


Spongebob
30cm
30cm
two rulers length
press button for one tablet to fall out
tablet collector so they dont fall on the floor

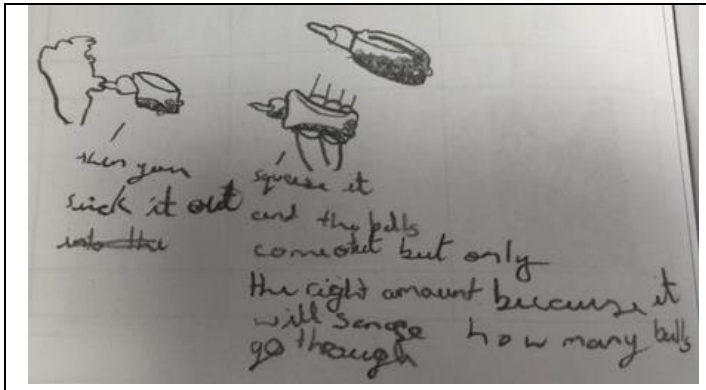
S1


Shuts after 10ml lose (no overdose) no underdose for younger kids)
opens if need more (because of age)
Scale to show how much left

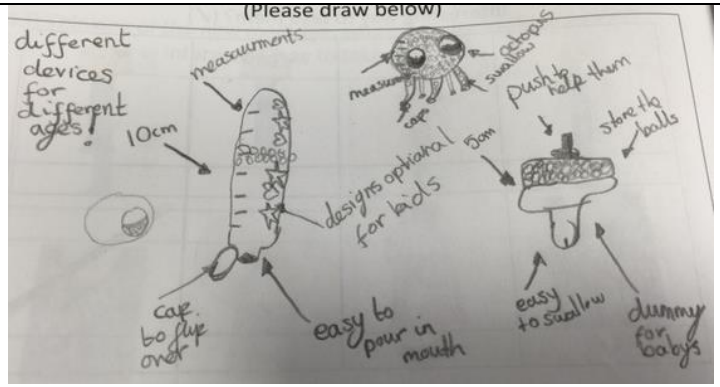
S3


Put the correct amount/dosage into here.
It drops down onto the spoon.
Pour from the spoon onto your hand then put it into your mouth
Cup + Spoon

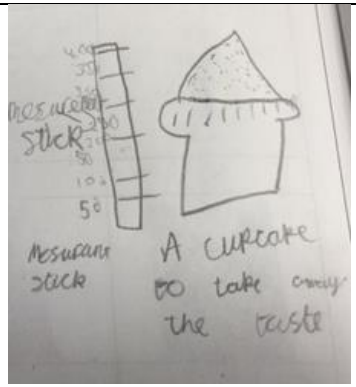
S4


then you suck it out squeeze it and the pills come out but only the right amount because it will squge go through how many pills

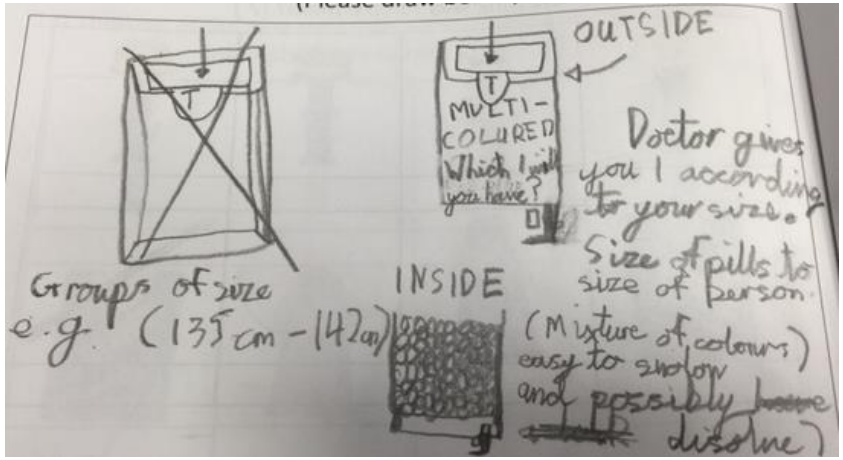
S5


(Please draw below)
different devices for different ages!
measurments
10cm
designs optimal for kids
cap to flip over
easy to pour in mouth
push to help them
store the pills
dummy for babys
easy to swallow

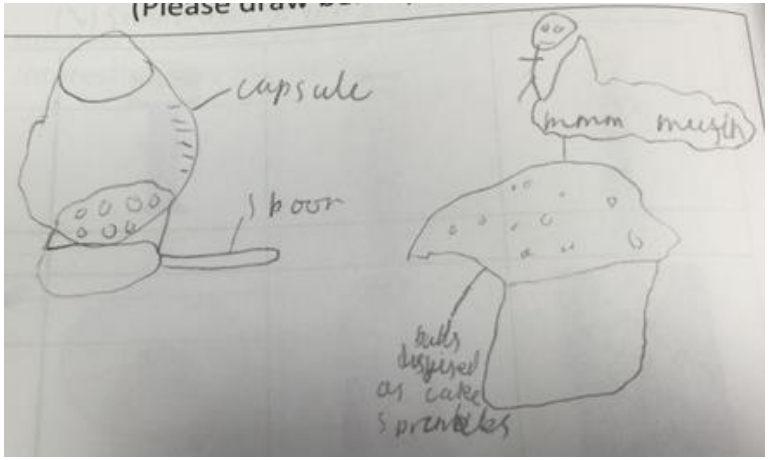
S6


measure stick
A cupcake to take away the taste

S7


OUTSIDE
MULTI-COLURED
Which will you have?
Doctor gives you 1 according to your size.
Size of pills to size of person
Groups of size
e.g. (135cm - 142cm)
INSIDE
(Mixture of colours)
easy to swallow
and possibly dissolve

S8


capsule
1 hour
mmm mmyth
pills disguised as cake sprinkles

S9

APPENDIX 7 EASE OF USE SURVEY

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

User Device Preferences_4

Participant information

My name is Claire Lewis and I am a second year PhD student at The University of Nottingham. As part of my research work, I would like to invite you/ the child(ren) in your care to take part in a brief research activity. Before you carry out this activity it is important you understand why the research is being done and what will be involved. Please take some time to read through this information sheet carefully and ask questions if anything is unclear or if you would like more information.

Purpose of the study

The purpose of this study is to understand what you/the child(ren) in your care believe makes a device easy to use. We aim to use this information in the design process to improve the administration of medicines to children.

What will happen if I/the child(ren) decide to take part?

You will be asked to complete a short questionnaire based on your opinions of using a device to take medicines. If you agree to take part you will be given the opportunity to ask any questions. You may also ask questions if you do not understand anything.

What will happen to the information?

All information provided will be captured on paper, then electronically and stored on a password protected computer. It will be destroyed seven years after any publication arising from the work, in accordance with the university data storage policy.

What will happen if we don't want to carry on with the activity?

You can withdraw from the activity at any time without having to provide a reason. If you do withdraw, please take this document home with you and destroy it.

Will our taking part in this study be kept confidential?

Yes. Your details will be kept confidential and held according to the Data Protection Act, and will not be published. They will be held on a secured database and made anonymous before sharing any information.

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Who is organising and funding the research?

This research is being conducted as a research project at The University of Nottingham. It is funded by the Engineering and Physical Sciences Research Council (EPSRC) and Pfizer; one of the world's premier innovative biopharmaceutical companies, who discover, develop and provide over 100 different medicines, vaccines and consumer healthcare products that help save and transform the lives of millions of people in the UK and around the world every year.

Who has reviewed the study?

This study has been approved by the University of Nottingham's School of Pharmacy's Ethics Committee.

Who do I contact if I have questions or require further information?

If you have any questions or concerns about the study, please contact Claire Lewis at the stand or my email: paxcl1@nottingham.ac.uk

Activity _ Pupil

Details

School .....
Age .....
Gender M / F
Who normally helps you take medicine? Parent / Family member / Doctor / Nurse / I do it myself / Other (Please state) .....

Activity

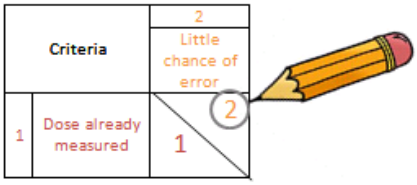
When designing a new device/gadget is it very important to listen to the users.

Whether it's an iPhone, a games console, or something to take medicine, all of these devices must be easy to use.



To understand what makes something easy to use, we are here today asking you, the users.

So... thinking about when you take medicine, is it **more important** that the dose is already measured, or that there is little chance of error?



If you think having the dose already measured is **most important**, circle 1

If you think there being little chance of error is **most important**, circle 2

Ease of use _ Pupil

Thinking of when you use a device to take medicines, work across the grid and **circle** which of the criteria is **most important** to you, as in the example.

	Criteria	2 Little chance of error	3 Size of device	4 What the device looks like	5 How simple the device is to use	6 How quick the device can give the medicine	7 If you are familiar with the device	8 Number of steps getting the medicine from the bottle to your mouth
1	Dose already measured	2 / 1	3 / 1	4 / 1	5 / 1	6 / 1	7 / 1	8 / 1
2	Little chance of error		3 / 2	4 / 2	5 / 2	6 / 2	7 / 2	8 / 2
3	Size of device			4 / 3	5 / 3	6 / 3	7 / 3	8 / 3
4	What the device looks like				5 / 4	6 / 4	7 / 4	8 / 4
5	How simple the device is to use					6 / 5	7 / 5	8 / 5
6	How quick the device can give the medicine						7 / 6	8 / 6
7	If you are familiar with the device							8 / 7



APPENDIX 8 EASE OF USE POSTER

User Device Preferences

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

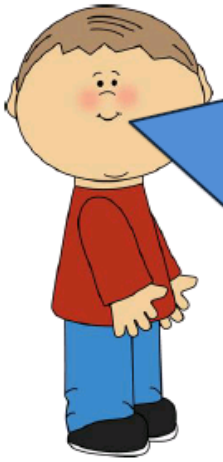
My name is Claire,
I am a second year PhD student at The University of Nottingham.
As part of my research work, I would like to invite you to take part in a brief activity.
Before you carry out this activity it is important you understand why the research is being done and what will be involved.
Please take some time to read through this poster carefully and ask questions if anything is unclear or if you would like more information .

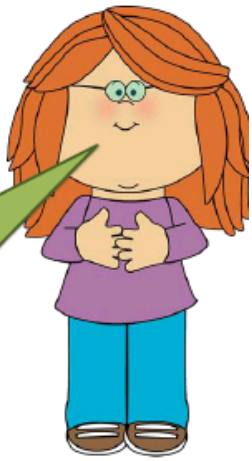


Why are you here?
The purpose of this study is to understand what you believe makes a device easy to use.
We aim to use this information in the design process to improve the administration of medicines to children.

What will happen if I decide to take part?
You will be asked to complete a short questionnaire based on your opinions of using a device to take medicines. If you agree to take part you will be given the opportunity to ask any questions. You may also ask questions if you do not understand anything.

What will happen to the information?
All information will be captured on paper, then electronically and stored on a password protected computer. It will be destroyed seven years after any publication arising from the work, in accordance with the university data storage policy.





What will happen if we don't want to carry on with the activity?
You can withdraw from the activity at any time without having to provide a reason. If you do withdraw, please take this document home with you and destroy it.

Will our taking part in this study be kept confidential?
Yes. Your details will be kept confidential and held according to the Data Protection Act, and will not be published. They will be held on a secured database and made anonymous before sharing any information.



Who is organising and funding the research?
This research is being conducted as a research project at The University of Nottingham. It is funded by the Engineering and Physical Sciences Research Council (EPSRC) and Pfizer; one of the world's premier innovative biopharmaceutical companies, who discover, develop and provide over 100 different medicines, vaccines and consumer healthcare products that help save and transform the lives of millions of people in the UK and around the world every year.

Who has reviewed the study?
This study has been approved by the University of Nottingham's School of Pharmacy's Ethics Committee.

Who do I contact if I have questions or require further information?
If you have any questions or concerns about the study, please contact Claire Lewis at the stand, or by email: paxcl1@nottingham.ac.uk

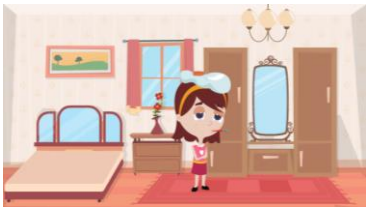
APPENDIX 9 KATY'S STORY



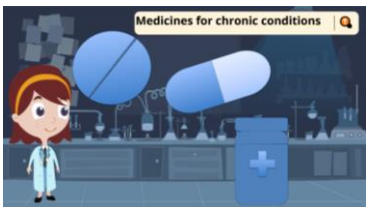








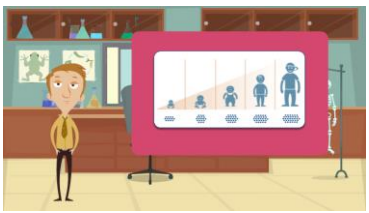


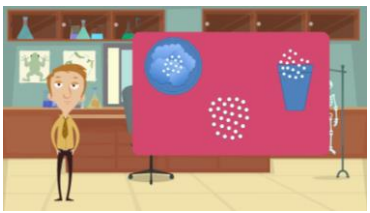
















APPENDIX 10 CO-DESIGN WORKSHEET

Design your own device for Katy

1) Why have you designed your device to **look like this**?

2) Is your device based **on something you have seen** or used before?

3) **How** does your device work?

4) How does your device **make sure it doesn't spill the medicine**?

5) How does your device **measure** the right amount of medicine?

6) **Who** would use your device to administer the medicine? Katy Her mum Both of them

KATY

6a) **What** about your device makes it good for Katy to use?

6b) **Where** would Katy use your device?

6c) What about your device makes it good for Katy to **use it there**?

6d) **How old** would Katy have to be to use your device on her own?

6e) **Why** would she have to be this age to use your device alone?

Place/draw your device here please

Please /place your device in the box and make annotations around the outside

KATY'S MUM

7a) **What** about your device makes it good for Katy's mum to use?

7b) **Where** would Katy's mum use your device?

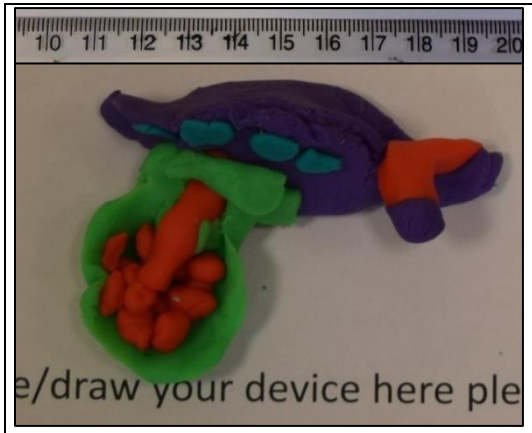
7c) What about your device makes it good for Katy's mum to **use it there**?

Thank you for your time

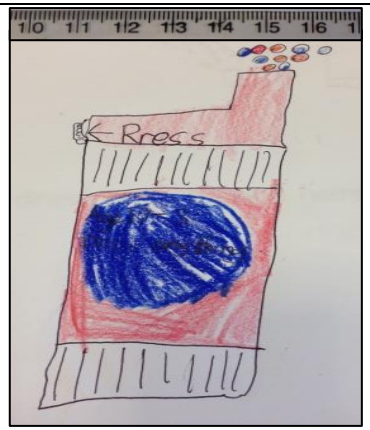
Name _____

Age _____ Gender _____

APPENDIX 11 NC'S CO-DESIGNED DEVICES



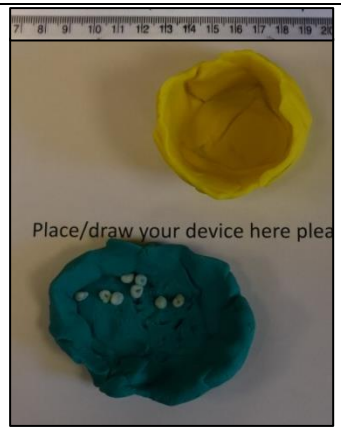
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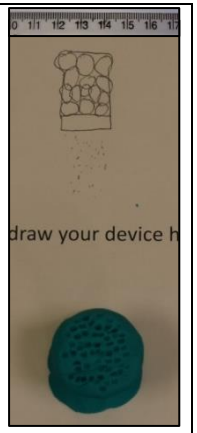
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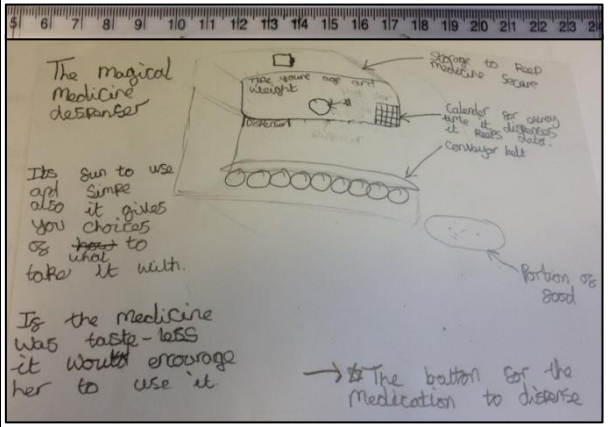
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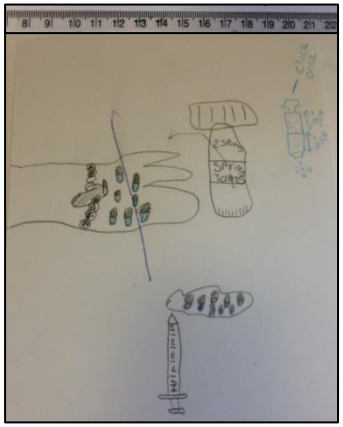
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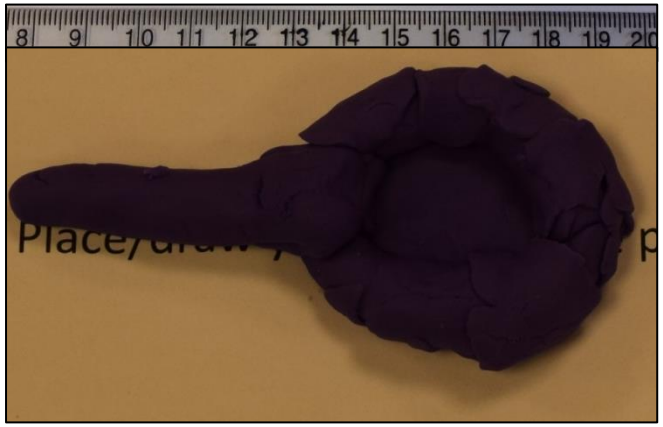
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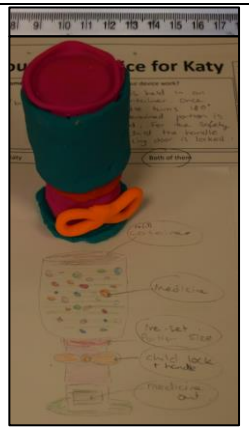
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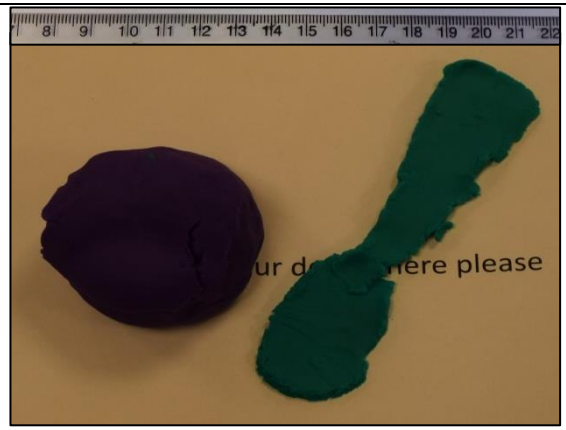
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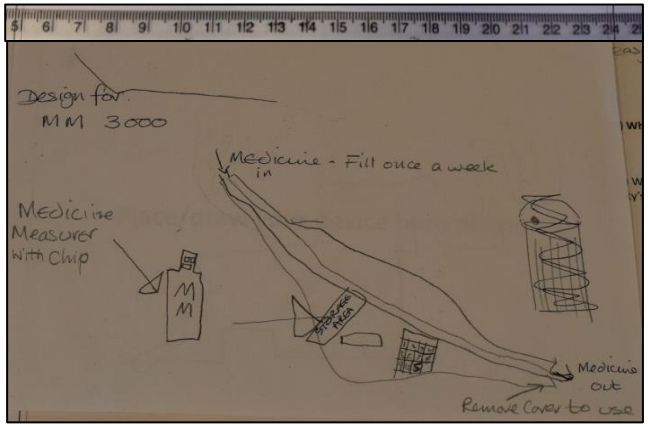
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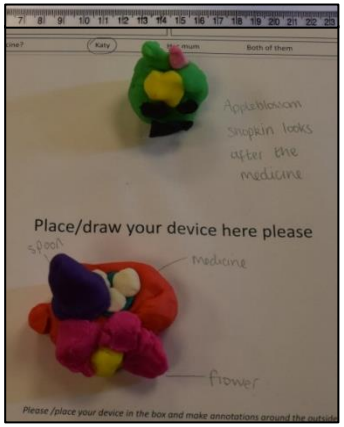
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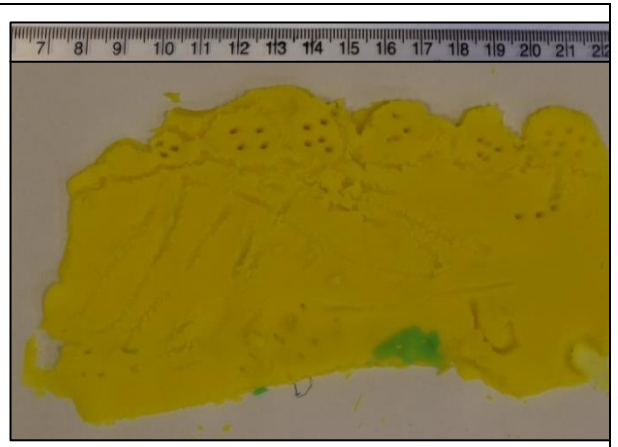
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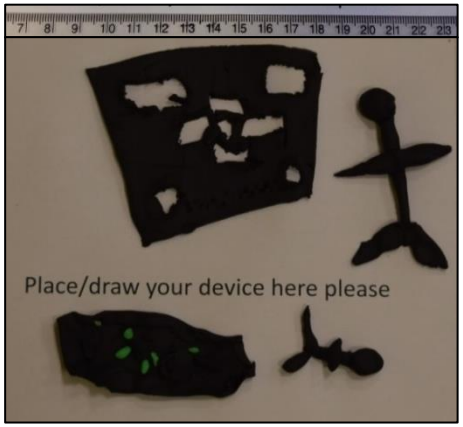
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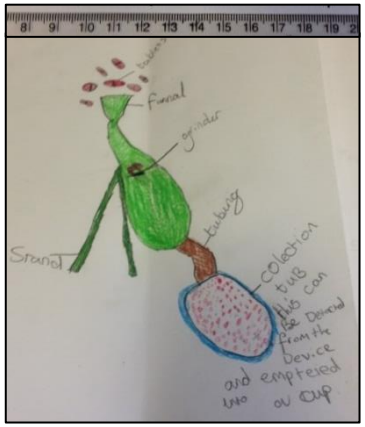
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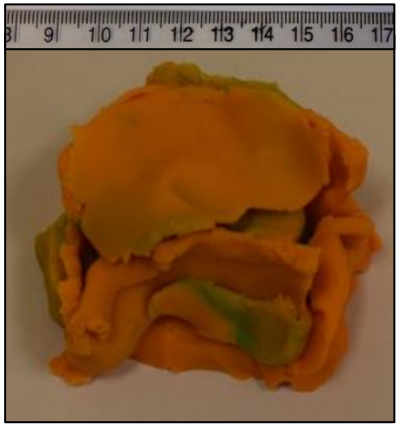
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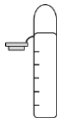
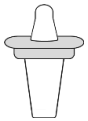
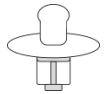
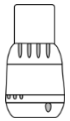


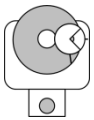
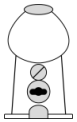
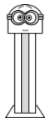
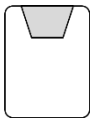
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APPENDIX 12 COMPARISON OF CURRENTLY AVAILABLE DEVICES

	Requirement	Device							
		A B C	D	E	F	G	H	I	J
									
Flexibility	Dose amount	8	16	16	16	16	16	8	10
	Admin. method	16	16	16	16	16	3	3	11
Ease of use	Simplicity	11	3	6	6	2	4	1	10
	Dose accuracy	2	6	7	6	6	6	1	16
	Chance of spillage	3	4	3	6	7	6	1	15
	Speed	9	6	16	8	2	7	1	14
	Size	15	12	5	10	13	8	14	6
	Total	**64**	**63**	**69**	**68**	**62**	**50**	**29**	**82**

Requirement		Device							
		K	L	M	N	O	PQRS	T	U
									
Flexibility	Dose amount	6	11	6	9	6	6	6	1
	Admin. method	11	6	6	11	6	11	11	3
Ease of use	Simplicity	13	7	8	10	12	16	16	14
	Dose accuracy	11	9	9	11	14	14	14	16
	Chance of spillage	11	9	9	11	15	5	15	16
	Speed	13	4	4	5	10	13	13	16
	Size	7	3	1	4	2	11	9	16
Total		**72**	**49**	**43**	**61**	**65**	**76**	**84**	**82**

APPENDIX 13 CASE STUDY SURVEY

User experience of CREON granules and capsules

Welcome

Thank you for your interest in this study.

What is the purpose of this study?

As part of my PhD research we are investigating the design and development of a device to dose granular medications. As such we are looking to understand the views and experiences of those who have administered this type of medicine.

There are currently a few granule medicines available including CREON micro and Montelukast for example.

This study aims to understand care giver experiences of **CREON micro and CREON capsules**. This study will help us understand the realities of having to use medicated granules on a regular basis.

Your involvement and experiences may contribute towards informing future medical device design and development.

The survey will take approximately 15 minutes to complete, there are no right or wrong answers and you do not have to answer any questions you do not wish to.

Your responses will be anonymous and confidential, following the completion of the survey your data is stored in accordance with the data protection act, encrypted and stored on a password protected computer.

The resulting data will be published as part of my PhD thesis as well as being disseminated through presentations, journals and posters for example. Clinicians may therefore see the results, but these will of course be anonymous and there will be no way of knowing what responses you provide.

Who is organising and funding the research?

This research is being conducted as a PhD research project at The University of Nottingham. It is funded by the Engineering and Physical Sciences Research Council (EPSRC) and Pfizer.

Who has reviewed the study?

This study has been approved by the University of Nottingham's Faculty of Engineering Research Ethics Committee.

1. I hereby confirm that I have read and understand the participant information, and I am happy to complete the survey

- ○ Yes
- ○ No

By clicking 'next' you also confirm that you have experience of CREON granules **and** capsules, and are over 18 years old.

Next >

Granules



The following 7 questions will ask you about CREON **granules**

Granules - working out the dose

2.  How do you **work out the dose** of granules you need at **home**?

a.  Is this the same when you are **out and about**?

- ○ Yes
- ○ No

i. If you selected No, please explain what you do differently when **out and about**:

Granules - measuring the dose

3.  How do you **measure the dose** of granules **at home**?

a.



Is this the same when you are **out and about**?

- ○ Yes
- ○ No

i. If you selected No, please explain what you do differently when **out and about**:

Granules - giving the dose

4.



How do you **give** the granules **at home**?

a.



Is this the same when you are **out and about**?

- ○ Yes
- ○ No

i. If you selected No, please explain what you do differently when **out and about**:

Granules - challenges

5. Did you experience any challenges using the granules?

Please don't select more than 2 answer(s) per row.

	Challenge at home	Challenge out and about	Not a challenge
Working out the dose of granules needed	☐	☐	☐
Measuring the granules	☐	☐	☐
Giving the granules	☐	☐	☐

a. If you have faced challenges with the granules please describe them here:

Granules - a device?

6. If there was a device that could accurately measure the granules how likely would you be to use it over what you currently do?

Please don't select more than 1 answer(s) per row.

	Very likely	Likely	Neither likely or unlikely	Unlikely	Very unlikely
At home	☐	☐	☐	☐	☐
Out and about	☐	☐	☐	☐	☐

Granules - a device at home?

7.  **Thinking of using a device at home, how influential would these factors be in getting you to use it over what you used to do?**

Please don't select more than 1 answer(s) per row.

	Very influential	Influential	Indifferent	Least influential	Not influential
Having the dose calculated for you	☐	☐	☐	☐	☐
Having the dose measured for you	☐	☐	☐	☐	☐
How accurate the device is	☐	☐	☐	☐	☐
There being little chance of error	☐	☐	☐	☐	☐
The size of the device	☐	☐	☐	☐	☐
How the device looks	☐	☐	☐	☐	☐
How easy the device is to use	☐	☐	☐	☐	☐
How simple the device is	☐	☐	☐	☐	☐
How quick the device gives the granules	☐	☐	☐	☐	☐
How familiar I am with the device	☐	☐	☐	☐	☐
Whether I had used the device before	☐	☐	☐	☐	☐
Number of steps getting granules from the device to the child	☐	☐	☐	☐	☐
How comfortable I am using the device	☐	☐	☐	☐	☐
How interesting the device is	☐	☐	☐	☐	☐

a. Are there any other factors that would influence whether you chose to use a device over what you used to do **at home**?

Granules - a device out and about?

8.



Thinking of using a device out and about, how influential would these factors be in getting you to use it over what you used to do?

Please don't select more than 1 answer(s) per row.

	Very influential	Influential	Indifferent	Least influential	Not influential
Having the dose calculated for you	☐	☐	☐	☐	☐
Having the dose measured for you	☐	☐	☐	☐	☐
How accurate the device is	☐	☐	☐	☐	☐
There being little chance of error	☐	☐	☐	☐	☐
The size of the device	☐	☐	☐	☐	☐
How the device looks	☐	☐	☐	☐	☐
How easy the device is to use	☐	☐	☐	☐	☐
How simple the device is	☐	☐	☐	☐	☐
How quick the device gives the granules	☐	☐	☐	☐	☐
How familiar I am with the device	☐	☐	☐	☐	☐
Whether I had used the device before	☐	☐	☐	☐	☐
Number of steps getting granules from the device to the child	☐	☐	☐	☐	☐
How comfortable I am using the device	☐	☐	☐	☐	☐
How interesting the device is	☐	☐	☐	☐	☐

a. Are there any other factors that would influence whether you chose to use a device over what you used to do **out and about**?

Capsules



The following 3 questions will ask you about CREON **capsules**

Capsules - working out the dose

9.  How do you **work out how many** capsules you need **at home**?

a. 

Is this the same when you are **out and about**?

- ○ Yes
- ○ No

i. If you selected No, please explain what you do differently when **out and about**:

Capsules - giving the dose

10.  How do you **give** the capsules **at home**?

a.



Is this the same when **out and about**?

- ○ Yes
- ○ No

i. If you selected No, please explain what you do differently when **out and about**:

Capsules - challenges

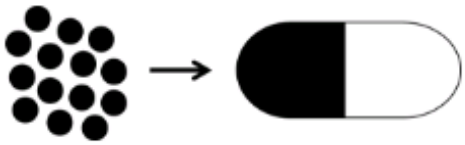
11. **Do you experience any challenges using the capsules?**

Please don't select more than 2 answer(s) per row.

	Challenge at home	Challenge out and about	Not a challenge
Working out how many capsules are needed	☐	☐	☐
Giving the capsules	☐	☐	☐

a. If you have faced challenges with the capsules please describe them here:

Moving from granules to capsules



12. At what age did the child in your care transition from granules to capsules?

- 0 - 5 months
- 6 -11 months
- 12 - 17 months
- 18 - 23 months
- 2 - 3 years
- 4 - 5 years
- 6- 7 years
- 8 - 9 years
- 10 years +
- We are yet to transition to capsules

This part of the survey uses a table of questions, view as separate questions instead?

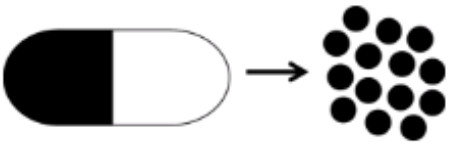
13. **Which of these factors were infleuntial when deciding to move from granules to capsules?**

Please don't select more than 1 answer(s) per row.

	Very influential	Influential	Indifferent	Least influential	Not influential
The use of food	☐	☐	☐	☐	☐
Ease of transport	☐	☐	☐	☐	☐
Ease of administration	☐	☐	☐	☐	☐
Child going to school	☐	☐	☐	☐	☐
Ease of self-administration	☐	☐	☐	☐	☐

a. Are there any other factors that influenced the move from granules to capsules?

Returning to granules



14. **Returning to granules**

Please don't select more than 1 answer(s) per row.

	Very likely	Likely	Neither likely or unlikely	Unlikely	Very unlikely
How likely are you to return to using granules?	☐	☐	☐	☐	☐

a. Why are you that likely/unlikely to return to granules?

b. Is there any scenario where you may return to granules?

Scenario - what would you do?

Please answer the questions based on the following scenario as truthfully as possible. We are trying to understand the everyday choices and challeneges of people using these medications to help in our research. All your responses are anonymous.

This part of the survey uses a table of questions, view as separate questions instead?

15.  **You are at home when your child eats a snack. The snack's fat content does not equate to a full capsule. What do you do?**

Please don't select more than 1 answer(s) per row.

	Very likely	Likely	Neither likely or unlikely	Unlikely	Very unlikely
I tailor their snacks to always be a full capsule	☐	☐	☐	☐	☐
I would round-up the dose to the nearest capsule	☐	☐	☐	☐	☐
Open and split a capsule	☐	☐	☐	☐	☐
Use granules	☐	☐	☐	☐	☐
Wait until they eat some more fat and dose then	☐	☐	☐	☐	☐
Encourage them to eat some more fat and dose as soon as possible	☐	☐	☐	☐	☐
I would do something else	☐	☐	☐	☐	☐

a. If you selected 'I would do something else', please let us know what you would do:

b.



Would you do the same thing when **out and about**?

- Yes
- No

i. If you selected No, please explain what you do differently when **out and about**:

c. **Are you happy with having to do that?**

Please don't select more than 1 answer(s) per row.

	Very happy	Happy	Neither happy or unhappy	Unhappy	Very unhappy
At home	☐	☐	☐	☐	☐
Out and about	☐	☐	☐	☐	☐

Scenario - a device?

This part of the survey uses a table of questions, view as separate questions instead?

16. **If there was a device that could accurately measure the granules for you how likely would you be to use it over what you currently do in this scenario?**

Please don't select more than 1 answer(s) per row.

	Very likely	Likely	Neither likely or unlikely	Unlikely	Very unlikely
At home	☐	☐	☐	☐	☐
Out and about	☐	☐	☐	☐	☐

This part of the survey uses a table of questions, view as separate questions instead?

17. **If there was a device that could accurately split a capsule for you how likely would you be to use it over what you currently do in this scenario?**

Please don't select more than 1 answer(s) per row.

	Very likely	Likely	Neither likely or unlikely	Unlikely	Very unlikely
At home	☐	☐	☐	☐	☐
Out and about	☐	☐	☐	☐	☐

Scenario - a device at home?

This part of the survey uses a table of questions, view as separate questions instead?

18.  **Thinking of using these devices at home, how influential would these factors be in getting you to use it over what you currently do in this scenario**

Please don't select more than 1 answer(s) per row.

	Very influential	Influential	Indifferent	Least influential	Not influential
Having the dose calculated for you	☐	☐	☐	☐	☐
Having the dose measured for you	☐	☐	☐	☐	☐
How accurate the device is	☐	☐	☐	☐	☐
There being little chance of error	☐	☐	☐	☐	☐
The size of the device	☐	☐	☐	☐	☐
How the device looks	☐	☐	☐	☐	☐
How simple the device is	☐	☐	☐	☐	☐
How quick the device gives the dose	☐	☐	☐	☐	☐
How familiar I am with the device	☐	☐	☐	☐	☐
Whether I had used the device before	☐	☐	☐	☐	☐
Number of steps getting the dose from the device to the child	☐	☐	☐	☐	☐
How comfortable I am using the device	☐	☐	☐	☐	☐
How interesting the device is	☐	☐	☐	☐	☐

a. Are there any other factors that would influence whether you chose to use the device over what you currently do **at home** in this scenario?

Scenario - a device out and about?

This part of the survey uses a table of questions, view as separate questions instead?

19.



Thinking of using these devices out and about, how influential would these factors be in getting you to use it over what you currently do in this scenario?

Please don't select more than 1 answer(s) per row.

	Very influential	Influential	Indifferent	Least influential	Not influential
Having the dose calculated for you	☐	☐	☐	☐	☐
Having the dose measured for you	☐	☐	☐	☐	☐
How accurate the device is	☐	☐	☐	☐	☐
There being little chance of error	☐	☐	☐	☐	☐
The size of the device	☐	☐	☐	☐	☐
How the device looks	☐	☐	☐	☐	☐
How simple the device is	☐	☐	☐	☐	☐
How quick the device gives the dose	☐	☐	☐	☐	☐
How familiar I am with the device	☐	☐	☐	☐	☐
Whether I had used the device before	☐	☐	☐	☐	☐
Number of steps getting the dose from the device to the child	☐	☐	☐	☐	☐
How comfortable I am using the device	☐	☐	☐	☐	☐
How interesting the device is	☐	☐	☐	☐	☐

a. Are there any other factors that would influence whether you chose to use the device over what you currently do **out and about** in this scenario?

Scenario - snacks vs meals?

20. What if there was a similar scenario at meal times? Do you do the same thing as with a snack? Please comment about anything you do differently or anything you feel is influential or an important difference between snacks and meals.

Any further comments

21. Thank you ever so much for your responses. If you would like to add anything else that you think may help with our device design, or a CREON device specifically, please state it here.

Finally, a little about you...

22. Age?

Please select ▼

23. Gender?

- Male
- Female

24. Location (country and postal/ZIP code please)

And the child in your care...

25. Age?

Please select ▼

26. Gender?

- Male
- Female

27. Condition

- Cystic Fibrosis
- Chronic Pancreatitis
- Pancreatectomy
- Other

a. If you selected Other, please specify:

Thank you

Thank you for your time and contribution.

Should you have any queries or comments regarding this survey please contact myself (claire.lewis@nottingham.ac.uk) or the case of a concerns or complaint, Dr. Robert Houghton, Chair of the Faculty of Engineering Research Ethics Committee (robert.houghton@nottingham.ac.uk).

Thank you

APPENDIX 14 STUDENT COLLABORATION DESIGN BRIEF

MM3 MDP 3
Design Project Brief
Medical device

Based on research and engineering work by:

Claire Lewis

(Supervisor Dr Joel Segal)



Context

Following recent paediatric medicine regulations (2007) pharmaceutical companies are required to investigate the paediatric application of any drug they release to market. This means companies will invest time and resource into developing medicines and administration methods suitable for children.

Brief

Research between the UoN and 'Kidditabs' is currently on going to develop a novel medical device capable of delivering free-flowing solid materials to the paediatric population. The material of interest is essentially 'Hundreds & Thousands'; small enough for children to swallow as well as being easily taste-masked to make the drugs more acceptable.

Utilising the information provided you are asked to design a medical device capable of accurately weighing different amounts of 'Hundreds and Thousands'. The device is intended for either home or pharmacy use and may be used by adults (primarily) and children (dependent on age). The product must have some degree of portability, child-proofing and a means of accurately determining the weight of material dispensed. The device should also contain a month's supply of drug and be disposable.

Manufacture

The resultant prototype for this product should be engineered from materials acceptable for drug contact, and allow storage of the material for at least 2 years.

Your design needs to be more than just a concept. You should consider which materials and manufacturing processes are appropriate for your design.

The Market

As well as the functional aspects of the product it is important that it has an **appropriate aesthetic identity** that will help to **differentiate this product in the market place and appeal to children/care-givers.** This will mean that you need to carefully identify the market, type of user and design the product specifically for their needs.

Important Task 1:

As an aid to focus and direct your design thinking you must first research and identify a brand for which your design will be targeted. This should be in the form of a brief description of that brand (max 50 words) together with 4-6 bullet points that you feel are important attributes for the product and the target market.

This must be completed within the first week of the project and submitted via email to r.tew@nottingham.ac.uk.

The brand will be used in the assessment of your design project to evaluate how well you have captured the key brand values.

Technical Resource

Available on Moodle:

- Briefing presentation slides

Interim Presentation

An interim presentation **(not a design crit**) is scheduled for the week beginning **9th February**. For this presentation you will need to prepare 2-3 concept ideas to presentation standard. The meeting will be used to guide you in the further development of your design work.

Please note that failure to present at this meeting will incur a 10% penalty on your final mark.

Submission

The design crit will be at 9am -12:00 and 12.30pm – 3:30 in the Design Studio + lecture theatre (TBC) on the 5th of March 2015.

Setting up for the crit:

- **Prepare a single PowerPoint slide showing all 4 design visuals**
- **Upload the PowerPoint slide to the MM3MDP Moodle Page before 9am on the day of the crit**

8:45 – 9:30am

Stage 1

- **Mount and present your design visuals on the wall of the design studio. Place all other work on the desk below it.**

9:30 – 3:00pm

Stage 2

- **Move to the lecture theatre for the presentation to your assessor.**
- You will present your design for 4 Minutes to your colleagues and assessors; this will then be followed by a few questions.

Assessment

As part of the assessment you are expected to submit:

- 2-3 concept presentations for use at the interim crit
- All design work bound and presented as follows:

  Research;

  Initial sketches;

  Concept proposals;

  Development sketches,

  CAD model

  A2 General Arrangement drawing with BOM table clearly identifying the component parts; materials and manufacturing process
- A set of design visuals explaining the design fully
- Any models and test rigs

Note: Sketch work should be bound with a cover sheet. Additional material that you may have produced such as rapid prototypes should also be submitted. The CAD models produced should be submitted via **CD**.

Any item too large to fit within the holdall should be clearly labelled with your student ID and module details.

Design Crit

You will present your project to one/two members of staff via a single PowerPoint slide.

You should use your chosen brand to introduce and characterise your market as well as to justify your design decisions.

Other assessors will be marking the work that you have displayed in the design studio.

When submitting your project work you will need to fill out the **self-assessment sheet** found at the back of this design brief. This should be placed inside your project folder to visibly identify your work.

The assessment sheet is identical to the one used to mark your work and indicates **the criteria that will be used to assess** your design project.

All submitted material should be contained within an A1 OR A2 Mapac Polythene Holdall (available from the engineering stores) with a cover sheet attached (available from the student office).

APPENDIX 15 STUDENT'S DEVICE CONCEPTS

a



b



c



d



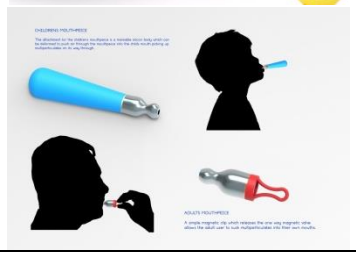
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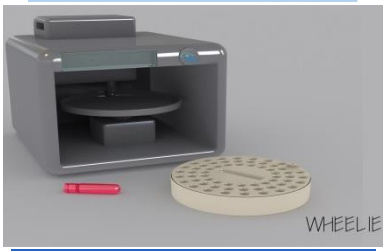
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