Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations

Jennifer Walsh[a1], Sejal R Ranmal[b2], Terry B Ernest[c], Fang Liu[d]

[a] Jenny Walsh Consulting Ltd, BioCity Nottingham, Pennyfoot Street, Nottingham. NG1 1GF United Kingdom. jenny@jennywalshconsulting.com

[b] Department of Pharmaceutics, UCL School of Pharmacy, 29-39 Brunswick Square, London. WC1N 1AX United Kingdom.

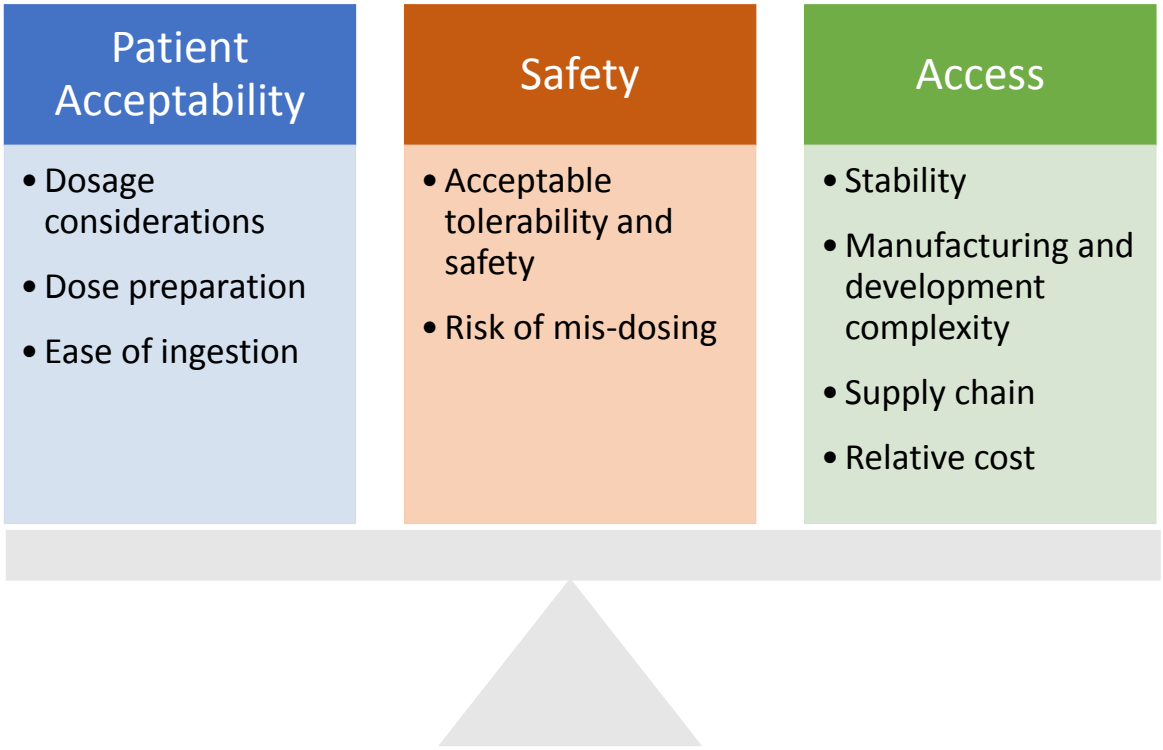
[c] GSK, Third Avenue, Harlow, Essex. CM19 5AW United Kingdom. terry.b.ernest@gsk.com

[d] Department of Pharmacy, Pharmacology and Postgraduate Medicine, School of Life and Medical Sciences, University of Hertfordshire, Hatfield. AL10 9AB United Kingdom. f.liu3@herts.ac.uk

[1] Corresponding author +44 7757 948052

[2] Current address Intract Pharma, 29-39 Brunswick Square, London. WC1N 1AX United Kingdom

Graphical Abstract



Abstract

The selection and design of age-appropriate formulations intended for use in paediatric and geriatric patients are dependent on multiple factors affecting patient acceptability, safety and access. The development of an economic and effective product relies on a balanced consideration of the risks and benefits of these factors. This review provides a comprehensive and up-to-date analysis of oral dosage forms considering key aspects of formulation design including dosage considerations, ease of use, tolerability and safety, manufacturing complexity, stability, supply and cost. Patient acceptability has been examined utilising an evidence-based approach to evaluate regulatory guidance and literature. Safety considerations including excipients and potential risk of administration errors of the different dosage forms are also discussed, together with possible manufacturing and supply challenges. Age appropriate drug product design should consider and compare i) acceptability ii) safety and iii) access, although it is important to recognise that these factors must be balanced against each other, and in some situations a compromise may need to be reached when selecting an age-appropriate formulation.

Key words Access, Acceptability, Drug product design, Formulation, Geriatric, Manufacture, Oral, Paediatric

1. Introduction

Patient centric pharmaceutical drug product design may be described as “the process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target population over the intended duration of treatment” (Stegemann et al., 2016). The selection and design of patient-centred oral pharmaceutical dosage forms continues to be one of the most significant challenges in the development of medicinal products for paediatric and geriatric populations due to the diverse needs and characteristics of these patient groups. In recent reviews, various patient related factors have been described (Drumond et al., 2017; Ivanovska et al., 2014; Liu et al., 2014; van Riet-Nales et al., 2016b; Zajicek et al., 2013)), although most have been in relation to the development of formulations for use in children. It is well acknowledged that a broad range of unique issues need to be taken into consideration in these two heterogeneous populations, some of which may not be seen to the same extent, if at all, in adults. For example, a frequently encountered issue includes determining the suitability of tablet and

capsules sizes in relation to patients' age and ability to swallow solid oral dosage forms (Ranmal and Tuleu, 2013). Age-related physiological changes and vast differences in required dose also present particular challenges. There is still very limited evidence based data which can be used to provide specific recommendations. The availability of regulatory guidance on the pharmaceutical development of paediatric medicines is welcomed (EMA, 2013), although detailed rationale for the recommendations is not provided. Similar guidance on medicines for geriatric patients has not yet been published, although a number of activities are on-going including the development of a reflection paper (Agency, 2013; van Riet-Nales et al., 2016a).

The International Conference on Harmonisation (ICH) pharmaceutical development guideline (Q8 (R2)) states "in all cases, the product should be designed to meet patients' needs and the intended product performance" (ICH, 2009). Therefore when defining the Quality Target Product Profile (QTPP) and selecting an appropriate dosage form, it is important to consider patient requirements and how the product may be taken alongside the complex technical challenges and feasibility of pharmaceutical development and manufacturing processes. In addition, the relative cost and supply of the product are important considerations..

The criteria for the selection of an age-appropriate dosage form have previously been identified as being efficacy/ease of use, safety and patient access (Sam et al., 2012). The aim of this review is to provide a comparison of different oral dosage forms according to these three criteria in order to assist pharmaceutical product formulators to select and develop the most suitable product for paediatric and geriatric patients. For the purposes of this review, it is assumed that formulators will have already considered active pharmaceutical ingredient (API) properties and other preformulation considerations, hence this topic will not be included. Diseases to be treated would have an impact on the development of pharmaceutical products for children and older adults; however, a disease-specific evaluation for developing age-appropriate formulations would render an entirely new angle of review. In this article, we discuss the general considerations in the selection of age-appropriate formulations taking into account the expected duration of treatment (short term versus long term) and severity of the condition when assessing the benefit risk balance of the excipients to be used within a formulation (EMA, 2013).

2. Factors to consider for paediatric/geriatric oral dosage form design

Choice of formulation may be affected by the properties of the API, target age group and disease to be treated (Wang, 2015), as well as culture and geographical location. In designing a drug product intended for use in paediatrics or older adults, all typical considerations of adult dosage form development apply. As for any drug product, API properties which can impact the selection of dosage form include for example biopharmaceutical classification, physico-chemical properties, stability, dose and required release rate (Kuentz et al., 2016). For instance, APIs with high solubility (BCS I and III) are generally more suitable for oral solutions and syrups compared to poorly soluble APIs, and mini tablets and oral films may not be appropriate for APIs which require high doses due to limitations in drug loading per unit dosage form. Furthermore, API properties may influence the manufacturing method and processing route that may be applied to a particular dosage form (Leane et al., 2015). The taste of an API should also be considered when selecting an oral dosage form, and approaches to minimise the interaction of an aversive-tasting API with taste receptors in the mouth should be utilised. Formulations for paediatrics and older patients add complexity to the development process due to the diverse nature of the patient population, safety and compliance considerations. Hence, additional factors need to be taken into account when developing products for these groups.

As stated above, Sam et al. (2012) previously proposed a structured framework for assessing and balancing the benefits and risks of different pharmaceutical dosage forms for paediatric use in relation to 3 key criteria; efficacy/ease of use, safety and patient access (Sam et al., 2012). The ease of use of a medicinal product (including dose flexibility), is one aspect that affects its overall acceptability to patients, and in this review, this broader concept of patient acceptability has been considered instead. The factors to consider in relation to these 3 criteria are outlined in Table 1. Patient acceptability is determined by the characteristics of the product and the user and may be defined as “an overall ability of the patient or caregiver (defined as ‘user’) to use a medicinal product as intended (or authorised)” (EMA, 2013; Kozarewicz, 2014). It can have a significant impact on patient adherence and therefore safe and effective therapy, and should be considered for all patients, including older adults. A pharmaceutical product must have acceptable safety and a positive benefit risk profile and the safety profile of a formulation may differ according to the age of the patient. To enable patient access to the drug product, manufacturability, stability, supply chain and cost need to be considered. Key features of oral dosage forms with respect to their patient acceptability, safety and access, based on pharmaceutical

development guidelines, the reflected literature and the authors' experience are summarised in Table 2, and discussed in greater detail in the following sections.

Table 1 Factors to consider for the selection of an oral dosage form

Patient Acceptability	
Dosage considerations	The ability of the formulation to be sub-divided without impact on the product's safety and efficacy to allow flexible and optimal dosing to the patient
Dose preparation	The requirement for any manipulation or measurement of a quantity of the formulation prior to administration.
Ease of ingestion	The ease with which the product may be taken by the patient, including aspects such as palatability, swallowability, size and quantity of solid dosage units, volume of liquid.
Safety	
Acceptable tolerability and safety	The product should not give rise to an unacceptably high risk of adverse effects, acute toxicity, organ toxicity or GI side effects, which are not directly caused by the API.
Risk of mis-dosing	The risk of administration of an incorrect dose, for example by incorrect handling, incorrect measurement and/or incorrect administration of the required dose.
Access	
Stability	The shelf-life of the product, including in-use if appropriate.
Manufacturing and development complexity	How complicated the required development process and manufacturing and packaging operations are, including the need to use specialised, non-routine processes.
Supply chain	How the product is stored and transported, including in resource-poor settings.
Relative cost	The estimated magnitude of cost of a dosage form compared to the other dosage forms, excluding API cost.

139 **Table 2 Comparison of key features of oral dosage forms***

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
Solution/ Syrup/ Drops	High dose flexibility for solution/ syrup Some limitation with drops	Require use of measuring device to measure and administer the required dose	Easy to swallow Palatability may be an issue Volume needs consideration	Multi dose containers require preservatives May require buffers, co-solvents, flavours and/or sweeteners	Risk of mis-dosing due to incorrect handling and use of measuring device	Generally less stable than solids Potential for microbiological contamination in-use Need to consider compatibility with primary packaging	Non-complex development process Usually routine manufacturing and packaging process with standard equipment	Bulky for transport and storage May need temperature control	Low
Emulsion	High dose flexibility	Require use of measuring device to measure and administer the required dose Require shaking prior to dosing to ensure homogeneity	Easy to swallow Palatability may be an issue Volume needs consideration	Multi dose containers require preservatives Require surfactants May require flavours and/or sweeteners	As for "Solution/ Syrup", but with higher risk of mis-dosing; requires shaking prior to measuring dose to ensure homogeneity and dose uniformity	As for "Solution/ Syrup", but thermo-dynamically unstable	Development and manufacturing process can be complex Usually routine packaging process with standard equipment	As for "Solution/ Syrup"	Medium/ high

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
Suspension	High dose flexibility	Require use of measuring device to measure and administer the required dose Require shaking prior to dosing to ensure homogeneity	Easy to swallow Palatability may be an issue Volume needs consideration Mouth feel needs to be considered to avoid a gritty sensation	Multi dose containers require preservatives May require buffers, surfactants, flavours and/or sweeteners	As for "Emulsion"	As for "Solution/ Syrup", but may be less physically stable	Development and manufacturing process can be complex, but less challenging than oral emulsions Usually routine packaging process with standard equipment	As for "Solution/ Syrup"	Medium
Effervescent/ Dispersible tablet	Low dose flexibility	Require dissolution or dispersion in a suitable volume of water	Easy to swallow Palatability may be an issue A large volume may be a challenge for young and older patients to swallow	May require flavours and/or sweeteners Sodium, potassium and bicarbonate content to be considered	Risk of mis-dosing if full volume of the solution/ dispersion is not ingested, and/or residue not ingested	Generally good stability, although can be sensitive to moisture so requires protective primary packaging Solutions/ dispersions have limited stability	Non-complex development process Usually routine packaging process with standard equipment, but may need modified tooling and low humidity conditions	Transport and storage more favourable compared to liquids	Low/ medium

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
Multi-particulates/ Granules/ Sprinkles/ Powders	Medium/High dose flexibility	Requires appropriate use of device or packaging when measuring and/or administering dose Further preparation may be required if administered with food or beverage	Easy to swallow Considered acceptable from 6 months when given with semi-solid food, from birth if dispersed in liquid Dose volume, texture (mouthfeel) and palatability require consideration	Risk of aspiration or choking (when not dispersed)	Risk of mis-dosing for products requiring dose to be measured Risk of incomplete dosing if administered with food or beverage and mixture is not fully consumed Risk of constitution errors with powders for oral suspension	Good stability Compatibility and stability with potential food or beverages should be verified (if labelled as such)	Development and manufacturing complexity depends on technology used Usually routine packaging process with standard equipment Can also function as intermediate products in manufacture of other dosage forms	Transport and storage more favourable compared to liquids	Low/ medium
Tablets	Low dose flexibility	No dose preparation required	Difficult to swallow for neonates, infants and young children and older adults may have difficulty	Risk of aspiration or choking Data on age vs. suitable tablet size required	Low risk of incorrect use and mis-dosing Greater risk if tablet manipulated	Good stability	Non-complex development process Usually routine manufacturing and packaging process with	Transport and storage more favourable compared to liquids	Low

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
			Size and shape need consideration for ease of swallowing Limited organoleptic issues				standard equipment		
Hard gelatin capsules	Low dose flexibility	No dose preparation required when swallowed whole Further preparation required if capsule contents administered with food or beverage	Difficult to swallow for neonates, infants and young children, and older adults may have difficulty Size needs consideration for ease of swallowing Limited organoleptic issues	Risk of aspiration or choking Risk of gelatin shell sticking to the mucosa of the oesophagus leading to retention Gelatin may not be accepted by some cultures/ lifestyles but alternatives available	Low risk of incorrect use and mis-dosing	Good stability	Non-complex development process Usually routine manufacturing and packaging process with standard equipment	Transport and storage more favourable compared to liquids	Low

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
Soft gelatin capsules ("Softgels") (excluding chewables)	Low dose flexibility	No dose preparation required	Difficult to swallow for neonates, infants and young children, and older adults may have difficulty Limited organoleptic issues	As for "hard gelatin capsules" Potential risk of chewing	Low risk of incorrect use and mis-dosing	Potentially less stable than tablets; may be sensitive to high temperature and humidity	Requires specialist development and manufacturing processes Usually routine packaging process with standard equipment	Transport and storage more favourable compared to liquids May be unsuitable for storage at high temperatures and humidities.	High
Mini-tablets [2] (1 - 4 mm)	Medium dose flexibility	May require counting or measuring device, or appropriate packaging for measuring/ administering multiple mini-tablets Handling may be difficult for older patients with poor manual dexterity	Easier to swallow than conventional sized tablets Limited organoleptic issues	Potential risk of choking or aspiration (especially in young children (< 2 years), if coated)	Risk of mis-dosing where multiple mini tablets are required per dose	Good stability	Non-complex development process Usually routine manufacturing and packaging process with standard equipment Content uniformity may be a challenge	Transport and storage more favourable compared to liquids	Low

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
Oro-dispersible tablet/ Melt	Low dose flexibility	No dose preparation required May be taken without water	Easier to swallow than conventional tablets Taste and mouth feel (grittiness) are main considerations	Potential risk of choking or aspiration May require flavours and/or sweeteners	Low risk of incorrect use and mis-dosing	Good stability but may require moisture protective packaging	Complexity depends on technology used Routine manufacturing process with standard equipment (compressed ODTs) or specialist process and equipment (lyophilisates)	Transport and storage more favourable compared to liquids	Low - high
Chewable dosage forms	Low dose flexibility	No dose preparation required	Should be chewed and not swallowed Not suitable for patients without teeth or those with limited chewing ability Palatability may be an issue	Risk of choking or aspiration Risk of intestinal obstruction if swallowed intact or partially chewed May require flavours and/or sweeteners	Low risk of mis-dosing	Good stability but may require moisture protective packaging	Complexity depends on technology used Routine manufacturing process with standard equipment (tablets) or specialist process and equipment (deposited	Transport and storage more favourable compared to liquids	Low/ medium.

	Patient Acceptability[1]			Safety		Access			
Feature/ Dosage form	**Dosage considerations**	**Dose preparation**	**Ease of ingestion (Organoleptic suitability)**	**Acceptable tolerability & safety**	**Risk of mis-dosing**	**Stability (shelf life & in-use)**	**Complexity of development and manufacture**	**Supply chain**	**Relative cost**
							formulations and softgels)		
Oral films (dispersible)	Low dose flexibility	No dose preparation required May be taken without water Handling of small films may be difficult for older patients with poor manual dexterity	Easy to swallow	May require plasticisers, flavours and/or sweeteners	Low risk of mis-doing	Good stability but require moisture protective packaging	Requires specialist development, manufacturing and packaging processes	Transport and storage more favourable compared to liquids	Medium/ high

* Based on pharmaceutical development guidelines, reflected literature and the authors' experience

[1] See also Table 3 for literature evidence of patient acceptability

[2] Mini tablets are defined as being 1-3 mm in diameter, however studies evaluating the acceptability of 4 mm mini tablets are included

3. Acceptability

Oral dosage forms may be divided into those which provide flexible doses, such as liquids and multiparticulates, and those which provide unit doses, such as tablets and capsules. Each have advantages and disadvantages for the user which should be carefully considered during paediatric and geriatric medicine development (Sam et al., 2012; van Riet-Nales et al., 2016b), as discussed below.

The EMA reflection paper published in 2005 provided a matrix proposing the applicability of various dosage forms in children of different ages (CHMP, 2006). However, the evaluation was based on anecdotal evidence only and the matrix was not suggested to be used as recommendations for paediatric formulation development, although it may have been used as such (van Riet-Nales et al., 2016a). A decade later, reports on the acceptability of some of the dosage forms in children have been published, yet evidence is sparse. A detailed evaluation of evidence of acceptability of oral paediatric medicines can be found in a recently published article (Mistry et al., 2017), and a recent systematic literature review analysed dosage form design features that can affect patients' acceptability or preference in both paediatric and adult populations (Drumond et al., 2017). In the current review, studies that generated evidence in dosage form acceptability are presented in Table 3 according to different age groups including children and older adults. Crucially, these studies are based on published literature evidence of patient or caregiver reported acceptability of dosage forms, rather than reasonable judgements of suitability, or the availability of licensed products. In this review, the age range of children were divided into sub-groups according to the ICH guideline (ICH, 2001). For the older population, many factors other than arbitral age affect their overall ability; however, it has been suggested to sub-divide the population into the "early-old" from 65 to 74 years, the "middle-old" from 75 to 84 years and the "late-old" starting from 85 years of
age (Swanlund, 2010). For the purpose of this review, the sub-division of the older population was not included in Table 3, due to the limited studies conducted in this patient population compared to those in children.

Acceptability is defined as the end-user ability and willingness to use a medicinal product [16], however studies reporting on comparative preferences between different formulations have also been included. Whilst comparative patient preferences between formulations, to some extent, provide an indirect indication of patient acceptability, it should be noted that they have limitations in guiding pharmaceutical development. Preference would likely be of more importance for consumer health and over-the-counter medicinal products where more

than one option may be available to the consumer. This is often not the case for New Chemical Entities (NCE's). There are significant methodological differences and complexities in published studies reporting medicines acceptability in children and the elderly. This may have contributed to the seemingly conflicting results for some dosage forms.

Oral liquids are one of few formulation types typically considered suitable from birth (EMA, 2013) and the provision of dose flexibility and ease of swallowing with liquid products are important advantages, both for children and geriatric patients. Palatability is the critical determinant of acceptability, and various studies have reported measures of this specific parameter when evaluating liquid formulations (Angelilli et al., 2000; Cote et al., 2002; Herd and Salehi, 2006; Schwartz, 2000; Tolia et al., 2005). This can present a major limitation of these dosage forms, since many APIs and excipients are known to have an aversive taste, and limited taste-masking strategies can be applied to liquids (Cram et al., 2009). The poor taste of liquid medicines has shown to be a major barrier for older patients with dysphagia (Kelly et al., 2010) and in children (Venables et al., 2015). Dose volume is another primary consideration in the acceptability of liquids. A commonly cited recommendation for paediatrics is a target volume of ≤ 5 mL for children under 5 years and ≤ 10 mL for children of 5 years and older (EMA, 2013) (Organisation, 2012). However, no studies have been identified which correlate the relationship between dose volume and patient acceptance, and little guidance is available for older patients. Similarly, there is little evidence to determine the relationship between product acceptability and other important attributes, such as viscosity, particle size, and use of delivery devices (Mistry et al., 2017). The effect of viscosity and consistency of dietary liquids on swallowing performance in dysphagic patients has been investigated (Dantas et al., 1990; Steele and Van Lieshout, 2004; Troche et al., 2008); however, the impact on acceptability and safety of liquid medicines in older patients has scarcely been studied.

Dispersible and effervescent tablets are dissolved in water prior to administration, therefore the acceptability of these dosage forms may be affected by similar factors as liquids. However, directly reported evidence is scarce in both the paediatric and geriatric populations (Table 3). Numerous sources highlight that large volumes of water that may be required to dissolve these tablets can be problematic for children and older patients. Two referenced studies involved administration of dispersible/effervescent tablets to children using small amount of water (a few drops or 5 mL) (Nasrin et al., 2005; Winch et al., 2006). Similar to liquid formulations, the effect of administration volume together with other attributes of the dosage form (e.g. palatability) on patient acceptance needs further investigation.

The acceptability of tablets (> 5 mm) and capsules in children and older adults is largely determined by the ability to swallow the dosage form intact. Even for children of the same age, this ability varies considerably between individuals, and is affected by their disease status and available training. Children with HIV as young as 3 years were able to swallow antiretroviral tablets, whereas one-third of adolescents were found to have problems swallowing tablets (Hansen et al., 2008; Nahirya-Ntege et al., 2012; Yeung and Wong, 2005). Nevertheless, studies suggest that for children of older age groups (12 years and over), tablets are a more preferred choice of medicine compared to powder and liquid formulations (MacDonald et al., 2003; McCrindle et al., 1997; Nahirya-Ntege et al., 2012). In a recent study, tablets were reported to be the preferred solid oral dosage form amongst adolescents and their caregivers (Ranmal et al., 2016). There is limited evidence available linking tablet size and shape to ability of swallowing in different age groups (Kokki et al., 2000; Meltzer et al., 2006). Difficulty in swallowing tablets in older adults, especially those with dysphagia has been reported (Schiele et al., 2013). Capsules were reported to have a greater tendency of prolonged oesophagus transit compared to tablets in older patients and oesophageal retention can occur in these patients even when administrated with a large amount of fluid (Bailey et al., 1987; Perkins et al., 1999). A better understanding of the optimum dimensions across age groups, as well as the influence of physical characteristics (such as shape or surface coating) would be highly valuable for patient-centred medicine development.

Orally disintegrating tablets (ODTs) and chewable tablets are considered to be convenient to take especially without the need for water. Palatability and retention time in the mouth are important aspects that may influence their acceptability; however, these dose forms have not been evaluated extensively in children and older adults. A recent study assessing end-user perceptions of oral dosage forms found a preference for chewables amongst school children, adolescents and their caregivers (Ranmal et al., 2016). In older patients with dysphagia, ODTs proved to be easier to swallow (Carnaby-Mann and Crary, 2005) and were well accepted for the treatment of Parkinson's disease, hypertension and hypoglycaemia (Fukui-Soubou et al., 2011; Koh et al., 2008; Nausieda et al., 2005).

Emerging evidence suggests that many children and their caregivers often show higher acceptability to solid oral dosage forms compared to liquids, if these are designed to be suitable in relation to the capabilities of the child. This is illustrated through the emergence of mini-tablets which have been studied in neonates and infants, and reported to show better acceptance than liquids (Klingmann et al., 2015b; Klingmann et al., 2013b; Spomer et al.,

2012a; van Riet-Nales et al., 2013). Administration of multiple mini-tablets has recently been studied (Kluk et al., 2015), however the effects of larger quantities and long-term acceptability requires further understanding. In addition, evidence of chewing was seen in all studies referenced. This is an important consideration for certain APIs or delivery systems, where palatability, safety, and/or bioavailability concerns may arise if the integrity of the dosage form is compromised. The use of mini-tablets accompanied by an electronic dispensing device was considered to be favourable in patients with Parkinson's disease for the potential of easy swallowing and flexible dosage (Bredenberg et al., 2003). Further investigation of the acceptability of this emerging dosage form in older patient groups needs research attention.

Multiparticulate formulations include powders, granules and pellets, and offer alternative options for administration, ranging from direct administration into mouth, to sprinkling onto food or mixing with drink. They are generally considered to be suitable from six months of age, when infants start to feed on semi-solid foods (EMA, 2013). A relatively larger numbers of studies have investigated their acceptance in children compared to other oral dosage forms; however evidence from these studies is too heterogeneous in nature to support an overall consensus, partially due to the diversity of methodologies applied. The use of sprinkles for administration of micronutrients in young children (0-5 years) has been investigated, yet mixed results in acceptability have been reported (de Pee et al., 2007; Jefferds et al., 2010; Kounnavong et al., 2011). Acceptability was often linked to whether the sprinkles changed the colour, texture and smell of food. As mentioned previously, sprinkles were generally more acceptable over oral liquids (e.g. drops, solution and syrup) in children of age ranging from 5 months to 16 years, although texture and viscosity of vehicle if used, can have an impact (Cloyd et al., 1992; Geltman et al., 2009; Lopez et al., 2016; Zlotkin et al., 2003). Particle size can be a critical aspect affecting acceptability of multiparticulates. The FDA recommends a target particle (bead) size of 2.5 mm for multiparticulate products to be labelled for sprinkle administration (Administration, 2012). Studies suggest that oral grittiness of multiparticulates increases with increasing particle sizes (Kimura et al., 2015; Lopez et al., 2016); although evidence still needs to be established, the particle size recommended by FDA might not render adequate mouth-feel and might affect patient acceptability. Evidence of the acceptability of multiparticulates in older adults is limited. A recent study investigated acceptability of oral flexible dosage forms in older patients attending community pharmacies and found that granules were the least acceptable (Liu et al., 2016). The main reason for not being favourite in this patient group was the concern for the effect of granules on food when mixed together.

Oral films are relatively new developments in oral formulations for paediatric and geriatric use. Similar to ODTs they are convenient to use and can be taken without water; however, again, investigations in their use in children and older adults are still limited. Rodd et al. reported that oral filmstrips were more acceptable in infants (aged 1.9-4.3 weeks) and their parents compared to oral drops (Rodd et al., 2011). The reasons for this were attributed to accurate dosing and easier administration for the film formulation.

In general as shown in Table 3, there is a distinct lack of information to enable age appropriate dosage form selection to be based on patient acceptability data. Although regulatory guidance indicates oral liquids and powders/granules administered as a liquid preparation are acceptable for the whole (paediatric) population from birth, there are limited data on the effect that volume, viscosity and particle size (in suspensions) can have on acceptability in different age groups. Similarly for solid oral dosage forms, there are still many unknowns in terms of for example, how multiple mini tablets and tablet size and shape can impact patient acceptability. Furthermore, there are examples where consensus on acceptability of a particular dosage form in a specific age group has not been reached between different studies, for example oral liquids in infants and toddlers, and mini tablets in pre-school aged children. However it is not known if this is due to differences in methodologies and/or other factors such as taste. Hence, although evidence is emerging in this area of research, it is still necessary to consider the patient acceptability of products on a case by case basis.

In older patient populations, considerably less evidence is available on the acceptability of medicines compared to children. There is a large variation in the quality of research conducted in this patient population and a lack of consistency in study methodologies. However there are examples of evidence emerging in recent years, such as the use of ODTs in patients with Parkinson's disease and hypertension (Fukui-Soubou et al., 2011; Nausieda et al., 2005). Whilst age is often used to sub-divide the paediatric population, more factors could affect the acceptability of medicines in older patients; frailty, co-morbidity, polypharmacy, and visual/cognitive impairments. The diseases to be treated may have a greater impact on developing appropriate formulations for older patients than for children, due to disease effects on patient characteristics, dose regimens, therapeutics/side effects and adherence. Overall, there are some similarities in acceptability considerations for paediatric and geriatric patients, for example difficulties in swallowing tablets and capsules which may impact dosage form selection. However, it should be noted that distinct differences exist between the two patient populations (Liu et al., 2014). Similar issues in medication acceptability might have different impacts in children and older patients. For

example, understanding the need for medication adherence and subsequent co-operation may differ in the two patient groups, and the taste of a medicine might influence the willingness (or unwillingness) to take a medicinal product in different ways.

332 **Table 3 Literature-based evidence for patient acceptability of oral dosage forms according to age**

Dosage form	Preterm newborn infants	Term newborn infants (od-28d)	Infants and toddlers (1m-2y)	Pre-school children (2-5y)	School children (6-11y)	Adolescents (12-18y)	Older adults (≥ 65y)
Liquid: Solution/Syrup/Drops/ Suspension/Emulsion	+ (Klingmann et al., 2015a)	+ (Cohen et al., 2009; Klingmann et al., 2015a) ±(Strehle et al., 2010) - (Rodd et al., 2011)	+ (Cohen et al., 2009; Geltman et al., 2009; Klingmann et al., 2013a; Spomer et al., 2012; van Riet-Nales et al., 2013) ± (Dagan et al., 1994; Kekitiinwa et al., 2016; Nahirya-Ntege et al., 2012; Scolnik et al., 2002) - (van Riet-Nales et al., 2015; Zlotkin et al., 2003)	+(Cohen et al., 2009; Jacobsen et al., 2015b; Klingmann et al., 2013a; Moniot-Ville et al., 1998; Mulla et al., 2016; Spomer et al., 2012) ±(Kekitiinwa et al., 2016; Nahirya-Ntege et al., 2012; Scolnik et al., 2002) - (van Riet-Nales et al., 2015; Verrotti et al., 2012)	+ (Bekele et al., 2014; Cohen et al., 2009; Jacobsen et al., 2015b; Moniot-Ville et al., 1998; Mulla et al., 2016) ±(Nahirya-Ntege et al., 2012) -(Cloyd et al., 1992; Verrotti et al., 2012)	+ (Cohen et al., 2009) (Bekele et al., 2014) ±(Nahirya-Ntege et al., 2012) -(Cloyd et al., 1992)	0
Effervescent/Dispersible tablet	0	0	+ (Nasrin et al., 2005b; Winch et al., 2006)	+ (Nasrin et al., 2005b; Winch et al., 2006)	0	0	+(Phillips et al., 1992) ±(Bayer et al., 1988; Sebert et al., 1995)
Multiparticulates/Granules/ Sprinkles/Powders	0	0	+ (Geltman et al., 2009; Munck et al., 2009b; van Riet-Nales et al., 2013; Zlotkin et al., 2003) ±(Kekitiinwa et al., 2016)	+(Munck et al., 2009b; Verrotti et al., 2012) ±(Kekitiinwa et al., 2016; Patchell et al., 2002)	+(Cloyd et al., 1992; Verrotti et al., 2012) ±(Patchell et al., 2002) -(Kekitiinwa et al., 2016)	+(Cloyd et al., 1992) ±(Patchell et al., 2002) -(Kekitiinwa et al., 2016; McCrindle et al., 1997)	+ (den Uyl et al., 2010)

			- (van Riet-Nales et al., 2015)	- (van Riet-Nales et al., 2015)			
Tablets (≥ 5 mm)	0	0	+ (Kokki et al., 2000) ±(Coleman et al., 2002; Nahirya-Ntege et al., 2012)	+ (Beck et al., 2005; El Edelbi et al., 2015a; Jacobsen et al., 2015a; Kekitiinwa et al., 2016; Kokki et al., 2000; Kreeftmeijer-Vegter et al., 2013) ±(Coleman et al., 2002; Nahirya-Ntege et al., 2012)	+ (Beck et al., 2005; Bekele et al., 2014; El Edelbi et al., 2015a; Jacobsen et al., 2015a; Kekitiinwa et al., 2016; Kokki et al., 2000; Kreeftmeijer-Vegter et al., 2013; Lottmann et al., 2007b; MacDonald et al., 2003; McCrindle et al., 1997; Meltzer et al., 2006) ±(Coleman et al., 2002; Nahirya-Ntege et al., 2012)	+ (Bekele et al., 2014; El Edelbi et al., 2015a; Jacobsen et al., 2015a; Kekitiinwa et al., 2016; Kreeftmeijer-Vegter et al., 2013; Lottmann et al., 2007b; MacDonald et al., 2003; McCrindle et al., 1997; Weinberg and Naya, 2000) ±(Coleman et al., 2002; Nahirya-Ntege et al., 2012) - (Hansen et al., 2008)	+(Perkins et al., 1994) ±(Brotherman et al., 2004; Sebert et al., 1995) -(Carnaby-Mann and Crary, 2005; Nausieda, 2005; Phillips et al., 1992; Schiele et al., 2015)
Capsules	0	0	-(Munck et al., 2009a)	+ (Beck et al., 2005; El Edelbi et al., 2015b; Garvie et al., 2007; Jacobsen et al., 2015a; Mekmullica and Pancharoen, 2003) ±(Babbitt et al., 1991)	+ (Beck et al., 2005; Bekele et al., 2014; El Edelbi et al., 2015b; Garvie et al., 2007; Jacobsen et al., 2015a; Mekmullica and Pancharoen, 2003)	+ (Bekele et al., 2014; El Edelbi et al., 2015b; Garvie et al., 2007; Jacobsen et al., 2015a) ±(Babbitt et al., 1991)	-(Bailey et al., 1987; Perkins et al., 1994; Schiele et al., 2015) ±(Bayer et al., 1988)

				- (Czyzewski et al., 2000; Munck et al., 2009a)	±(Babbitt et al., 1991) - (Czyzewski et al., 2000)		
Mini-tablets[1] (1-4 mm)	+ (Klingmann et al., 2015a)	+ (Klingmann et al., 2015a)	+ (Klingmann et al., 2013a; Spomer et al., 2012; van Riet-Nales et al., 2013; van Riet-Nales et al., 2015) ±(Kekitiinwa et al., 2016) - (Van de Vijver et al., 2011)	+ (Klingmann et al., 2013a; Spomer et al., 2012; van Riet-Nales et al., 2015) ± (Kekitiinwa et al., 2016; Kluk et al., 2015) - (Thomson et al., 2009)	-(Kekitiinwa et al., 2016)	-(Kekitiinwa et al., 2016)	0
Oro-dispersible tablet	0	±(Valovirta and Scadding, 2009)	±(Valovirta and Scadding, 2009)	±(Valovirta and Scadding, 2009)	+ (Cohen et al., 2005; Lottmann et al., 2007a) ±(Valovirta and Scadding, 2009)	+(Lottmann et al., 2007a)	+ (Carnaby-Mann and Crary, 2005; Fukui-Soubou et al., 2011; Koh et al., 2008; Nausieda et al., 2005)
Chewable tablet	0	0	0	0	+(Bukstein et al., 2003)	0	+ (den Uyl et al., 2010)
Oral film	0	- (Rodd et al., 2011)	0	0	0	0	0

Key:

+ acceptable; - not acceptable; ± both acceptable and not acceptable data reported; 0 no evidence found; reference number provided in parentheses.

In cases where no clear definition of “acceptability” was given in the article, “acceptable” of a formulation was defined as > 70% of participants support the acceptability of a product or a product scores > 70% of the scale used in the study, in analogy to Mistry et al [18].

[1] Mini tablets are defined as being 1-3 mm in diameter, however studies evaluating the acceptability of 4 mm mini tablets are included.

The data presented in the table was based on a literature search on Pubmed, Scopus and Embase, from the beginning of the source to May 2017. The search terms included a combination of “elderly, older adults, aging, ageing, geriatric, paediatric, pediatric, children, infant, newborn, adolescent, teens, youth, teenagers” AND “oral formulation, oral dosage form” AND “Satisfaction, acceptance, preference, approval, acceptability, swallow, palatability”.

4. Safety

Patient safety is of great importance, and when selecting a dosage form, the safety and tolerability of the dosage form type and the required excipients used must be assessed, in particular for the younger and older age groups. In addition, the potential for mis-dosing must be considered.

Excipients have different functional roles within a formulation and their selection is therefore closely linked to dosage form. Although they are generally considered to be pharmacologically inactive, excipients may cause adverse effects or may affect the exposure of a drug (CHMP, 2006). During infancy and childhood there are significant developmental changes including the maturation of metabolic pathways and organ systems which can impact the way in which an excipient is handled (Benedetti et al., 2005; CHMP, 2006). For example, immature alcohol dehydrogenase can lead to accumulation of ethanol in neonates and infants (Zuccotti and Fabiano, 2011), and there is the potential for propylene glycol toxicity in children below 4 years due to limited metabolic capacity and renal function (EMA, 2014a). In addition, the use of benzoates and benzoic acid is a concern in neonates, where an accumulation of unmetabolised benzoic acid may lead to the displacement of bilirubin from albumin leading to hyperbilirubinaemia (EMA, 2014b). The potential impact of excipients on organ development in neonates, infants and young children should also be considered. For example, there have been safety concerns regarding possible endocrine-disrupting effects of the preservative propyl paraben, although a permitted daily exposure limit of 2 mg/Kg body weight for both adult and paediatric patients has been calculated based on juvenile rat toxicity data (EMA, 2015). A recent re-review of animal reproductive and developmental toxicity studies has led to a new temporary acceptable daily intake (ADI) for sorbic acid and its potassium salts of 3 mg/Kg body weight (EFSA, 2015).

During the aging process there are changes in metabolising enzymes as well as a reduction in liver perfusion and renal function (Perrie et al., 2012)]. Therefore, it is conceivable that accumulation of excipients may occur in older patients, leading to toxicity and adverse effects. A list of such excipients are summarised in a review (Breitkreutz and Boos, 2007). As with evidence of acceptability, there appears to be a considerable lack of information regarding the safety profiles of pharmaceutical excipients in older adults compared to children, and hence this requires further research attention.

In addition to the preservatives and co-solvents highlighted above, other excipients which have been reported in the literature to have potential risks include sweeteners (e.g.

saccharin, aspartame, sorbitol), solubilising agents (surfactants) (e.g. polysorbate) and flavourings (Ernest et al., 2007; Ursino et al., 2011). The latter can be complex mixtures, the exact composition of which is often not known (especially natural flavours). Risk of allergies and sensitization as well as toxicity of the flavouring including the solvent or carrier used should be considered (Walsh et al., 2014).

Formulators also need to consider the salt and electrolyte content of the dosage form. For example, formulations containing high levels of sodium or potassium may not be suitable for patients with renal insufficiency (CHMP, 2006), and high salt (sodium chloride) intake has been identified as a risk factor for the development of hypertension in adults (Nutrition), 2003). Indeed, adult patients prescribed sodium-containing effervescent, dispersible and soluble formulations have been found to experience an excess of cardiovascular events compared with patients on non-sodium formulations of the same drugs, these events being largely driven by an increased risk of stroke and hypertension (George et al., 2013).

Multi-dose oral liquids such as solutions, syrups, emulsions and suspensions generally require the inclusion of a preservative system to maintain microbiological quality throughout the product shelf-life. The exception to this is traditional syrups which contain high concentrations (60 - 80 %) of sucrose, and hence low water activity. However, chronic administration of oral liquid medicines containing sucrose have been found to increase the incidence of dental caries and gingivitis in children (Roberts and Roberts, 1979). Therefore, due to the cariogenic and glycogenic properties of sucrose, "sugar-free" syrups containing sugar substitutes such as sugar alcohols (polyols) (e.g. sorbitol, maltitol, glycerol), are more commonly developed, which require preservatives. It should be noted that formulations containing high levels of polyols may potentially have laxative effects (Walsh et al., 2014) and it has been reported that a number of these osmotically active excipients can have an impact on the absorption of some drugs, although the mechanism is not known (Chen et al., 2013).

Oral liquids commonly require the inclusion of functional excipients that may have unfavourable safety and toxicity characteristics for young and older patients, as described above, depending on their level of use and duration of treatment. For example, oral solutions may require a co-solvent (e.g. ethanol, propylene glycol, glycerol) to increase the solubility of the API, and buffers (electrolytes) are often employed to optimise the pH of the solution formulation to maintain the solubility of the API. The control of pH is also required for all preserved oral liquids to ensure optimal preservative activity. Frequent use of low pH oral medicines has been reported to potentially cause dental erosion in children, especially

418 when the pH is below 5.5 (Taji and Seow, 2010). Oral suspensions and emulsions are
419 fundamentally unstable and salts including buffers, and surfactants such as dispersing and
420 emulsifying agents (e.g. polysorbates) are employed to enhance the physical properties of
421 these formulations.
422
423 As highlighted above, palatability is one of the main elements of the patient acceptance of an
424 oral medicinal product (EMA, 2013) and since many APIs have an unpleasant taste, it is
425 likely that the majority of oral dosage forms require the application of taste masking. Solid
426 oral dosage forms that are swallowed intact such as tablets or multiparticulates may have a
427 non-functional coat applied which provides a barrier between the API and taste receptors in
428 the mouth and throat. Similarly, hard and soft capsules tend to have minimal taste by virtue
429 of the materials with which the capsule shells are made (for example gelatin, hypromellose
430 or starch derivatives). In contrast, oral liquids, effervescent, (oro) dispersible and chewable
431 dosage forms, and oral films, generally require the utilisation of taste masking techniques to
432 improve their palatability. Sensory based taste masking approaches using sweeteners
433 and/or flavouring agents are commonly used for oral dosage forms (Walsh et al., 2014).
434 However, as indicated above, sweeteners and flavourings are excipient groups for which
435 some safety concerns have been raised. Older patients often take multiple medications
436 (polypharmacy) and hence there is the potential risk of additive excipient effects in these
437 patients.
438
439 Whilst the risk associated with required excipients is relatively higher for liquid products than
440 oral solid products, choking is another potential safety risk in using oral medicines for
441 paediatric and older patients. Dysphagia is a common condition in older adults due to for
442 example a weak tongue and poor control of muscles (Perrie et al., 2012). In addition,
443 nervous system disorders and some medications can have a negative impact on patient
444 swallowing ability including reduced saliva flow (Stegemann et al., 2012). This can result in
445 older adults having difficulty in swallowing conventional solid oral dosage forms, with a
446 potential risk of choking. The ability of children to swallow solid oral dosage forms such as
447 tablets is dependent on the developmental stages of individual child as discussed in the
448 previous section. Inappropriate use of these formulations may pose the risk of choking in
449 children, for example incidents of coughing were observed in young children when
450 administered coated mini-tablets (Klingmann et al., 2013b). It is possible that the size and
451 shape of tablets/capsules and the volume of multiparticulates may affect the risk of choking,
452 although no clear evidence of this could be found in the public domain.
453

Medicines that are in a liquid format such as oral solutions, suspensions, emulsions, and constituted effervescent and dispersible dosage forms may have a lower risk of choking compared to solid oral dosage forms. However, low viscosity liquids increase aspiration/penetration risks in older patients with dysphagia (Dantas et al., 1990). Indeed, it has been found that the risk of aspiration of a liquid in patients with dysphagia is affected by many characteristics of the liquid, including viscosity, texture, volume and delivery device. These factors need to be considered when developing liquid-form medicines for paediatric and older patients.

The use of solid oral dosage forms that disintegrate in the mouth or may be chewed can mitigate the risk of choking. However, it should be noted that ODTs were shown to have the same risk of choking as conventional tablets in patients with dysphagia (Carnaby-Mann and Crary, 2005). With chewable tablets, there is a risk of intestinal obstruction should the tablet be swallowed or only partially chewed (Gupta et al., 2013). In addition, care should be exercised with chewable tablets in young children below 2 years due to the risk of choking (Michele et al., 2002).

The risk of mis-dosing is highest where a patient or caregiver is required to identify and measure a specific volume of product using an administration device, or count a specific number of unit dosage forms. Unless provided in unit dose packs, oral liquids require measurement of the prescribed dose for administration and various studies have investigated the accuracy and ease of measurement of oral liquids by caregivers with different devices. Overall, dosing cups appear to have the highest error rates, although there are some conflicting results regarding the accuracy of measurement with oral syringes and measuring spoons (Beckett et al., 2012; Ryu and Lee, 2012; Tanner et al., 2014). In Europe, oral syringes are commonly supplied by healthcare professionals to paediatric patients and caregivers for the administration of oral liquids, despite being the most frequently cited problematic measuring device; key problems reported include the identification of the correct dose and having difficulty in measuring the dose (Walsh et al., 2015). Older patients may face additional difficulties in the correct use of oral administration devices due to a decrease in hand function (e.g. grip strength and hand dexterity) (Carmeli et al., 2003) and visual impairment due to a deterioration of the function of the eye tissues with age and/or ocular pathology (e.g. presbyopia, cataracts, macular degeneration) (Loh and Ogle, 2004). Clear and appropriate units of measure (e.g. mL) and simple instructions for use are important for reducing potential dosing errors (Yin et al., 2014; Yin et al., 2011).

Homogeneity of oral liquids is vital to ensure dose uniformity. There is therefore a greater risk of mis-dosing with suspensions and emulsions compared to oral solutions, where the product may not be adequately shaken by the caregiver before dose administration. Hence the ease with which the suspension or emulsion can be easily re-dispersed and the speed of sedimentation or phase separation (permitted standing time) need to be considered.

Although no measurement of volume is required for the administration of effervescent and dispersible products, there are a number considerations associated with administering these dosage forms. The product must be allowed to fully effervesce/ disperse prior to administration and the full volume of liquid must be swallowed, including any residue; it may be necessary to rinse the container to ensure any residue is ingested. Young children and adults on fluid restricted diets may struggle to ingest large volumes of liquid and so the volume required for dispersal should be kept to a minimum and indicated to the patient.

Similar risks of mis-dosing to those described above for oral liquids are applicable to multiparticulates, unless they are presented in unit dose formats such as sachets. Graduated dosing spoons have been developed for the measurement of multi particulate products (Furin et al., 2013), however, little information appears to be available in the literature on the dosing accuracy and ease of use of such administration devices. Multiparticulates, including powders may be administered directly in the mouth or mixed with a food or beverage to facilitate swallowing (CHMP, 2006; van Riet-Nales et al., 2016b). If mixed with food or beverage, the smallest quantity should be used to minimise the risk of incomplete consumption of the whole dose. In addition, using this approach for product administration has the risk of potential instability and incompatibility of the formulation with the food/beverage, as well as a potential impact on the biopharmaceutical characteristics of the product, all of which can lead to inadvertent mis-dosing (EMA, 2013). Powders for oral suspension are constituted with a specified volume of water or other vehicle prior to administration, and a high incidence of errors has been reported when this is conducted by the caregiver. For example, addition of an incorrect volume of water or failure to adequately shake the bottle leading to incorrect concentration of product has been noted (Berthe-Aucejo et al., 2016).

All other solid oral dosage forms discussed in this review are considered to have a low risk of mis-dosing, unless manipulated (e.g. cut or crushed) or requiring counting (e.g. multiple mini tablets). Tablets may be manipulated to achieve the required dose or in response to patient preference. However, such interventions can cause unknown effects on the stability and bioavailability of a product, together with a risk of inaccurate dosing (Richey et al.,

2013). Indeed, investigations into the cutting (splitting) of tablets have shown a wide variability in weight and content uniformity results, with drug content variability being attributed to weight variation in tablet halves, especially with unscored tablets (Habib et al., 2014; Hill et al., 2009). Where several mini tablets are required per dose, the use of a dispensing or counting device may be needed to facilitate accurate dosing (Aleksovski, et al., 2015). Older patients whose manual dexterity is compromised may find the handling of mini tablets challenging due to their small size, which could lead to mis-dosing.

Overall, when considering potential risks associated with excipient safety and administration errors, solid oral unit dosage forms offer a more favourable safety profile compared to oral liquids, although they provide less flexibility of dosing.

5. Access

Along with key considerations associated with patient acceptability and safety, enabling access to the medicine is fundamental, for patients of all ages. There are many factors that impact accessibility of the medicine including the product stability, the complexity associated with its manufacture and the ability to supply the product from the manufacturing site to the patient. Each of these factors may impact cost and affordability of the drug product and must be factored into the drug product design to ensure global availability. A comparison of anticipated relative cost, stability risk, manufacturing complexity and supply chain challenges of various oral dosage forms compared to conventional tablets is provided in Table 4.

Table 4 Relative cost, stability risk, manufacturing complexity and supply chain challenges of various oral dosage forms compared to conventional tablets

Feature/ Dosage form	Stability (shelf life & in use)	Manufacturing & Development	Supply Chain	Cost
Conventional tablets*	0	0	0	0
Solution/Syrup/Drops	++	0	++	+
Suspension/Emulsion	++	+	++	+
Effervescent/ Dispersible tablet	+	+	+	+
Multi-particulates/Granules/ Beads/ Sprinkles/Powders	+	+/++[1]	0	+/++[1]
Mini tablets	0	+	0	0
Hard gelatin capsules	+	0	+	0
Soft gelatin capsules (“Softgels”)	+	++	+	+

Compressed oro-dispersible tablet	0	+	0	0
Lyophilisate/ melt	+	++	+	++
Chewable dosage forms	+	+	+	+
Oral films	+	++	+	++

Key:
Conventional tablets = 0 (reference value) *
0 = equivalent risk/complexity compared to conventional tablets
+ or ++ = greater risk, complexity or cost compared to conventional tablets
[1] Depends on technology used

Traditionally, liquid oral dosage forms are selected as the dosage form of choice for dosing medicines to children due to their flexibility of dosing and ease of swallowing. Indeed, they are considered to be suitable for the whole patient population as well as geriatric patients, notwithstanding the risks highlighted in section 3 (providing the excipients are considered to have acceptable safety) (Table 2). However, the stability of such products can be very challenging and hence their shelf life may be limited. For example, physical, chemical and microbial instability can arise due to the API being solubilised or suspended in a vehicle that may cause oxidation, or an aqueous vehicle that may be prone to microbial spoilage. These formulations may consequently require storage in a refrigerator to avoid microbial spoilage and/or minimise chemical instability which may have implications for transportation and their suitability in resource poor territories. The requirement for specialised storage conditions together with a potentially relatively short shelf life may negatively impact the supply chain, since cold chain supply can be very costly and may be very difficult to control between manufacturing and receiving sites, and cold storage can be inconvenient for the end user. An additional consideration for the product supply chain is the size and dimensions of the primary and secondary packaging. Multi use packs can offer convenience to the end user but may be costly to transport due to their bulkiness, whilst single use packs e.g. sachets, are individually smaller but may increase the overall packaging requirements and consequently drive up the total cost of each unit dose.

From a manufacturability perspective, oral liquid formulations such as solutions and syrups are relatively straightforward to prepare. Solutions for example, may be manufactured using a simple process using non-complex equipment. A pH adjustment step may be required at the end of manufacture. The solution is filled into multi use or single use bottles using suitably precise filling equipment. Suspensions and emulsions, however, may require the use of an homogeniser to prepare a physically stable suspension or emulsion to avoid the risk of sedimentation or flocculation of the suspension and separation of the emulsion.

584 Suspensions and emulsions are therefore more complex to develop and manufacture than
585 solutions.
586
587 Due to the stability challenges associated with oral liquid products, there is an increasing
588 focus on the development of age appropriate solid oral products (WHO, 2008). Tablet
589 dosage forms (including effervescent, dispersible and chewable tablets), are typically more
590 stable than liquid formulations. There is less microbial spoilage risk due to low moisture
591 content levels, and being in the solid form, chemical and physical stability risk is also
592 significantly reduced. However instability as a result of API-excipient interactions can still
593 occur and may be exacerbated by the long term storage conditions that the product may be
594 subjected to post manufacture, for example temperature and humidity. ODTs and to some
595 extent dispersible/effervescent tablets may be prone to moisture absorption on storage due
596 to the design of the matrix and the excipients selected. Such products may require
597 protection from moisture (via moisture protective packaging) to enable adequate shelf life.
598
599 Typically tablet manufacture does not require the use of highly sophisticated pieces of
600 equipment or particularly advanced technologies. Tablets may be prepared using direct
601 compression or by wet or dry granulation followed by compression and film coating as
602 appropriate. API properties such as bulk density, particle size and particle shape can
603 influence the manufacturing process (Leane et al., 2015). The complexity and cost of the
604 manufacturing process depends on the number of unit operations required. An added
605 complication for the manufacture of mini tablets is the requirement to ensure content
606 uniformity of each individual unit tablet if the mini tablets are intended to be taken as
607 individual dose units, which requires strict control of particle size and powder flowability.
608 This is a significant challenge given the low compression weight of mini tablets (Aleksovski
609 et al., 2015). Due to their small size and generally superior stability, the transportation and
610 storage of tablets tends to be less costly compared to liquids. Conventional tablets often do
611 not require specialised packaging and a number of unit doses may be packed into a small
612 pack (such as a blister or bottle), which minimises volume and mass and hence reduces
613 shipping cost. Alternatively conventional tablets may be supplied in bulk format for hospital
614 settings without impact on the stability or shipping costs.
615
616 Chewable tablets may be manufactured via conventional tabletting processes, or if
617 gelatin/confectionary-based, by more complex methods which may be patented and involve
618 for example extrusion or moulding. Similarly, the complexity and hence cost of
619 manufacturing ODTs depends upon the technology used. ODTs may be manufactured by
620 direct compression of polysaccharide based excipients which is relatively inexpensive, or

may utilise relatively expensive, specialised and patented manufacturing processes such as freeze drying (lyophilisation) (Al-khattawi and Mohammed, 2013; Badgujar and Mundada, 2011; Baltzley et al., 2014). As discussed above, ODTs and in particular freeze-dried formulations are likely to require moisture protective packaging which could increase packaging cost.

Fast disintegrating oral films are a similar alternative to ODTs in that they are easy to swallow and can be taken without water, although the dose is restricted to <75mg to minimise the size of the film. The formulations are reasonably simple with the API typically being dissolved in a polymer solution. However, the manufacturing process is very specialised and the films are prone to moisture absorption and hence often packed in foil pouches for protection, leading to a higher cost compared to more conventional solid oral dosage forms (Borges et al., 2015; Hoffmann et al., 2011).

Multiparticulates are considered to offer advantages of both liquid and solid oral products in that they are easy to swallow and enable dose flexibility whilst having stability properties generally comparable to conventional tablets and low risk of microbiological spoilage. As with ODTs, complexity of manufacture depends on the technology used, and is also related to number of unit processes required. For example, the simplest multiparticulate product may comprise a mixture of powders. In contrast, multiparticulates such as granules and spheroids (beads) may require more advanced equipment and know-how (for example melt granulators, spray dryers, extruders and/or spheronisers) (Gandhi B, 2013). Non-powder multiparticulates are often coated with a polymer which can act to modify API release or to provide taste masking. Once coated, the multiparticulates require curing to ensure that the coat is completely annealed and then they are typically filled into capsules or single unit packs such as sachets. Such technology may render the process too complex and expensive for low cost manufacturing facilities although supply chain considerations are likely to be similar to those for tablets.

As stated above, hard capsules are usually filled with multiparticulates (especially powders) although they may also be filled with semi solid materials such as lipidic based formulations. The stability of both the capsule contents and shell must be considered. Hard capsules are most commonly manufactured from gelatin or hypromellose and consequently their integrity may be impacted by humidity. The inclusion of a desiccant in the primary packaging to improve overall product stability may result in gelatin capsules becoming brittle due to dehydration. Furthermore the iteration between the fill of the capsule and the capsule shell must also be considered, since gelatin can cross link with some materials resulting in a delay

in capsule disintegration (Gullapalli and Mazzitelli, 2017). Hard capsule filling is a relatively simple manufacturing process using either volume or gravimetric filling systems. Typically power blends are filled but API alone may be filled if the material has appropriate flow characteristics. Once prepared, the capsules may be packaged into bottles or blister packs and consequently this is a relatively cheap process that is routinely used for providing drug products to resource poor regions.

Soft gel capsules are generally used for liquid fill, for example lipid-based formulations for poorly soluble APIs and high potency APIs where content uniformity can be problematic. Stability can be particularly challenging for these dosage forms due to potential incompatibility between the liquid/semi-solid fill formulation and the gel capsule, as well as possible temperature and humidity effects on the capsule shell. The development and manufacture of soft gel formulations can be complex and requires the use of specialised equipment (Gullapalli and Mazzitelli, 2017). Hence the risks associated with stability and the complexity of manufacture and development significantly increase the cost of soft gel capsules.

From a manufacturability perspective, typically conventional tablet dosage forms offer the least stability risk, the simplest manufacturing processes, enable a simple and cost effective supply chain and hence are a low cost dosage form option. However, these considerations, together with those outlined for other dosage types must be evaluated in combination with patient acceptability and patient safety. Dispersible tablets offer an advantage over conventional tablets by overcoming swallowing difficulties faced by some paediatric and geriatric patients.

6. Other dosage forms and Innovations

This review has focussed on commonly used and well-known oral dosage forms, however the authors have investigated a number of other novel formats, but little information, if any, appears to be available on their patient acceptability. Although historically sugar-based medicated oral lozenges (lollipops) have been indicated for the relief of sore throats due in part to their demulcent properties, the utilisation of this dosage form for the treatment of local infections and systemic conditions has gained interest in recent years (Rao et al., 2012). For example, sugar-based lollipops (lozenges) have been developed for the local treatment of oral thrush in children and also as a means for administering the anthelmintic Levamisole to paediatric patients (Kamath et al., 2012). In addition, Actiq® (Fentanyl citrate) transmucosal lozenges are available for the management of breakthrough pain in cancer patients from 16

694 years. Lozenges/ lollipops offer the advantage of being suitable for patients who have
695 difficulty swallowing tablets since they are intended to be slowly sucked. However, there is a
696 risk of choking together with the potential to cause dental caries due to the sucrose within
697 the formulation.
698
699 Chewing gum has also been available for many years, and is now being considered for use
700 as a modified release drug delivery system. It is intended to be chewed for a certain period
701 of time to deliver the drug, after which the remaining mass should be discarded. As with
702 lozenges/ lollipops, medicated chewing gum may be taken without water and can provide
703 both systemic and local drug delivery. In addition, it is perceived to be accepted by children
704 and teenagers, although there is a potential choking risk. Different chewing styles may lead
705 to differences in drug release rates and the chewing action may not be culturally and/or
706 physically acceptable to some patients, especially the elderly (Aslani and Rostami, 2015;
707 Khatun and Sutradhar, 2012).
708
709 The use of hydrophilic oral gels (jelly) for the elderly is an area of interest, especially in
710 Japan where a number of oral jelly products are currently available. The products are
711 provided in unit dose packs and have the advantage of being easy to swallow, without the
712 need for water (Imai, 2013). Hence oral gels are likely to be appropriate for all patients who
713 have difficulty swallowing solids, including young children (Gohel et al., 2009). Oral gels
714 have also been investigated as a potential vehicle to facilitate the administration of mini
715 tablets and pellets (Kluk et al., 2015). In Japan, an agar-based jelly (Swallowing Aid Jelly
716 ("Magic Jelly")) has been developed to assist medicine administration in both elderly and
717 paediatric patients (Ryukakusan Co. Ltd, https://www.ryukakusan.co.jp/productjelly/en). In
718 European Nordic countries and Germany, a special coating (MEDCOAT®) is available that
719 can be applied to tablets and capsules by patients to assist swallowing. The coating
720 becomes very slippery in contact with water or saliva and also contains saliva stimulating
721 ingredients that further improve swallowing (http://www.medcoat.com/).
722
723 The development of printed medicines has gained interest in recent years, and may offer the
724 potential for personalised medicines whereby the dose of API and product properties are
725 tailored to the patient. For example, the feasibility of printing API onto porous substrates and
726 oro-dispersible films has been investigated, which may provide a platform technology
727 suitable for the accurate administration of low dose and poorly soluble APIs (Janssen et al.,
728 2013; Sandler et al., 2011). 3D printing may also be used for the preparation of medicinal
729 products, for example the first 3D printed medicine (Spritam®, Levetitacetam) was approved
730 by the FDA in 2015 (Prasad and Smyth, 2016). This product utilises ZipDose® technology

whereby powder blend is deposited as a single layer, and an aqueous binding fluid is applied. Interactions between the powder and liquid bind these materials together. The process is repeated several times to produce solid, yet highly porous formulations. The development of 3D-printed tablets containing multiple drugs has been investigated ("polypill"), which may offer simplified dosing regimens and hence improved adherence for those patients taking many separate tablets (Khaled, 2015a; 2015b). It is clear that printed medicines may offer many advantages to the elderly and paediatric patients, although further research is required.

Inventions and development of novel platforms should be encouraged although the three aspects i) acceptability, ii) safety and iii) patient access discussed in this review must be considered for them to be adopted by industry and accepted by patients. It should also be acknowledged that whilst it is aspirational that there is a single dosage from that can meet these defined criteria across the paediatric or geriatric populations, it is very likely that more than one dosage form will be required.

7. Conclusions

This review provides a comprehensive comparison of various oral dosage forms relating to evidence-based patient acceptability, safety and access, to assist pharmaceutical product formulators to select and develop the most suitable product for their intended patient population. The ideal age appropriate drug product design should consider i) acceptability ii) safety and iii) access.

However, the review has identified a number of knowledge gaps in terms of the impact of various dosage form attributes on the acceptability of the product in both paediatric and geriatric patients. Although the evaluation of patient acceptability of various dosage forms is gaining interest, there is still a huge lack of information, knowledge, and in some cases conflicting evidence in this area. It is therefore suggested that pharmaceutical companies and academia should be encouraged to conduct research into and publish any data they generate regarding dosage form acceptability. Furthermore, since companies are required to evaluate patient acceptability during paediatric clinical studies (EMA, 2013), it is proposed that the European Medicines Evaluation Agency (EMA) publish anonymised information on for example swallowability of different sized solid oral dosage forms according to patient age. Regulatory guidance should be updated to reflect current evidence-based knowledge. It is recognised that patient acceptability may be influenced by many factors, but the availability of such information in the public domain would facilitate pharmaceutical product design.

Despite these challenges, a valuable overview of literature evidence on patient acceptability has been provided.

Key safety considerations have been highlighted and summarised. The safety of a number of excipients has been reviewed as part of the on-going process for updating the EU guideline on excipients in the label and package leaflet of medicinal products for human use (EMA, 2012). This has provided a valuable source of information although there still appears to be a dearth of information available on the safety and tolerability of many commonly used excipients in paediatrics and the elderly, especially their long term use. In the case of neonates, infants and young children, this has often led to the need to utilise juvenile animal data (when available), to support their use. Additional data are required to support the robust assessment of excipient benefits versus their potential risks within a formulation. The publication of emerging data both from researchers and regulatory authorities is therefore encouraged to help fill the gaps. Similarly, it is suggested that companies and excipient suppliers are encouraged to make public their safety data on excipients, for example by sharing it via the EuPFI Safety and Toxicity of Excipients in Paediatrics database (Salunke et al., 2013). This would reduce the potential for duplication of excipient safety studies.

The evaluation of the accessibility (stability, ease/cost of development, manufacture and supply) of the oral dosage forms has highlighted that those with the most favourable access, for example conventional tablets, may not necessarily be the most acceptable for all patients. In a similar manner, oral dosage forms reported to have high patient acceptability, for example oral liquids, may be less favourable from a safety of excipients and supply perspective. This clearly illustrates that a single “ideal” dosage form does not exist. It should be recognised that patient acceptability, safety and access must be balanced against each other and in some situations a compromise may need to be reached when selecting an age-appropriate formulation.

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