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REVIEW ARTICLE

Patient-Centred Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations

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Abstract Patient acceptability of a medicinal product is a key aspect in the development and prescribing of medicines. Children and older adults differ in many aspects from the other age subsets of population and require particular considerations in medication acceptability. This review highlights the similarities and differences in these two age groups in relation to factors affecting acceptability of medicines. New and conventional formulations of medicines are considered regarding their appropriateness for use in children and older people. Aspects of a formulation that impact acceptability in these patient groups are discussed, including, for example, taste/smell/viscosity of a liquid and size/shape of a tablet. A better understanding of the acceptability of existing formulations highlights opportunities for the development of new and more acceptable medicines and facilitates safe and effective prescribing for the young and older populations.

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Key Points

Appropriate pharmaceutical design of oral medicines can improve acceptability and patient outcomes in paediatric and geriatric populations.

Similar considerations should be given to physical characteristics affecting swallowability of tablets and capsules for use in children and older patients.

Whilst formulation factors such as taste and smell are important features for paediatric medicines, safe swallowing is the key formulation factor in designing medicines for older patients.

1 Introduction

Acceptability has previously been defined as “an overall ability of the patient and caregiver (defined as ‘user’) to use a medicinal product as intended (or authorised)” [1]. This

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terminology is used as the basis for this review article. Additional consideration is required in developing medicines for young and older patients as their physiological and cognitive responses may differ due to the developing and deteriorating conditions of the body, respectively. Oral administration is the most common route of drug delivery to both young and older patients. However, there are obstacles for young and older patients to accept their oral medicines, e.g. swallowing difficulties or dysphagia, the involvement of caregivers, child recalcitrance and polypharmacy in the older population, to name just a few. While these barriers may not be considered major issues for adults, they could potentially affect adherence in young and older patients. In many cases, oral medicines are modified to ease administration in these patients, ranging from simple removal from packaging to dispensing in a dosette box, to more complex alterations including crushing or splitting of solid oral dosage forms [2–6]. Altering medication dosage forms, whether for children or adults, leads to unlicensed use of medicines and can potentially change bioavailability, toxicity and stability of the medicines.

Guidance issued by the European Medicines Agency (EMA) highlighted that acceptability must be an integral part of paediatric formulation development [7]. Recently, the EMA Geriatric Expert Group has issued a concept paper on the need for a reflection paper on the quality requirements of medicines for older adults [8]. The EMA Quality Working Party is currently looking into drafting the reflection paper. Similar principles might apply to assess the acceptability of medicines in children and older adults; however, a duplicate approach might not be appropriate due to the different patient-centred issues in these two populations. The aim of this review is to highlight the similarities and differences between children and older adults in relation to the acceptability of oral medicines. A detailed analysis of barriers associated with administration of oral medicines guides the choice and development of appropriate medicines to meet the needs of both patient groups (see the Electronic Supplementary Material for a description of the search strategy).

2 Patient-Centred Factors Affecting Acceptability of Oral Medicines

Table 1 summarises the most important patient-related factors that affect oral medication acceptability in children and older adults.

2.1 Patient Characteristics

There is no such thing as a standard paediatric or geriatric patient. As the physiological and cognitive systems

continue to develop or be impaired, chronological age is not the best indicator to predict the characteristics of the patient. Frailty does not always accompany very old age nor do all infants mature at the same rate. The heterogeneity is higher in the older adult group as the definition and recognition of the physiological changes with advanced age is diverse.

2.2 Drug Therapy-Associated Factors

The duration of treatment and the required number of medicines potentially increase the complexity of acceptance to medicines in older adults. Many older adults are on multiple medications to treat their multi-morbidities [9]. The dose regimen further complicates adherence and acceptance of medicines [10]. In this respect, multi-compartment adherence aids are promising in terms of helping patients to remember to take their medicines at the right time [11].

2.3 Socio-Cultural Factors

In both populations the involvement of a caregiver is common; therefore, there is a need for the directions on usage of a medicine to be clear both to the patient and the caregiver. Older adults living in their own home may be the sole person responsible for their medicine management, whereas seniors living in nursing homes are often helped by formal carers or by nurses at hospitals. The majority of paediatric populations, except adolescents, are typically dependent on their parents/carers to take their medicines. As such, the ability and willingness of the carer to administer a medicine to these patients as intended could determine the acceptability of the medicine and outcome of the treatment [12–16].

The acceptability of medicines may be influenced by the setting in which the administration of the medicine takes place. Children with minor diseases may need to take medications during nursery/school hours. Chronically ill children may need to take their regular medicines or medicines for the treatment of acute problems at school. Peer pressure and child recalcitrance are potential factors affecting their acceptance of a medication form in these cases.

2.4 Dysphagia in Children and Older Adults

The ability to swallow determines the acceptability of conventional medication forms such as tablets and capsules. Swallowing is a rapid, albeit complex, process that involves two essential actions: bolus transport and airway protection. The process of deglutition is generally divided into three main phases: the oral phase, the pharyngeal

Table 1 The most important patient-related factors affecting acceptability of oral medications in children and older adults

Factors	Children	Older adults
Patient characteristics		
Age	0–18 years; divided into subgroups according to age [17]. A patient's cognitive development should also be considered in acceptability of medicines	>65 years; age alone is not the only determinant affecting patients' health conditions and ability to take medicines; frailty could be more important than age
Health conditions	A single condition is more common than the presence of co-morbidities in paediatric populations	Co-morbidities are common; medication handling and administration can be affected by many diseases that are highly prevalent such as dementia, Parkinson's disease, head and neck cancer, and stroke, and common functional conditions, e.g. visual and cognitive impairments and neuromuscular degeneration
Disease status	Acute conditions and long-term illnesses are both present although acute conditions are more common	Acute conditions and long-term illnesses are both present although chronic conditions are more common
Ability to swallow	Very young children may have difficulties swallowing conventional tablets and capsules	Dysphagia is common and affects ability to take oral medicines; many age-related conditions can cause swallowing difficulties
Drug therapy-associated factors		
Duration of therapy	Short- and long-term treatments are both required although short-term treatments are more common	Long-term treatments are common; acceptability to medicines can be affected by treatment outcomes of long-term therapy
Concomitant medications	A single medication for the treatment of a single disease is more common than multiple medications due to the prevalence of acute rather than chronic illness	Polypharmacy (taking more than 5 medicines at the same time) has high prevalence; the number of medicines taken can affect the preference of dosage forms, e.g. patients taking numerous tablets may prefer fixed-dose combinations
Social factors		
Responsibility for medication administration	Young children are usually helped by caregivers; older children can self-administer medicines	Independent-living older adults can self-administer medicines; in other cases they can be helped by caregivers
Caregivers	Usually adults including parents/guardians, nursery practitioners and school teachers	A mixture of different characteristics; could be older-age partners or nursing home/hospital nurses
Environments where oral medication administration occurs	Home, nursery, school, hospital	Home, residential home, nursing home, hospital

phase and the oesophageal phase. Dysphagia is defined as difficulty in swallowing and can occur in both children and older adults [18]. While swallowing reflexes can be observed as early as in utero, significant maturation related to deglutition occurs between 6 months and 3 years of age, with complete maturation generally believed to have occurred by 6 years of age [19, 20].

The prevalence of paediatric dysphagia is difficult to ascertain given the wide variations in how swallowing impairments are defined and the assessment measures used to identify them. The causes of paediatric dysphagia can be medical, developmental, behavioural, psychological, or it may indeed be a multidimensional disorder. Common aetiologies include prematurity, developmental disorders, neurological disorders, reflux and craniofacial abnormalities [21, 22]. Although the exact incidence of dysphagia is unknown, it is reportedly becoming more common given the improved prognosis of pre-mature infants and of children with chronic medical conditions [23, 24]. Nevertheless, it

has been reported that as many as 25–45 % of typically developing children and up to 80 % of children with developmental disabilities exhibit some form of feeding disorders [21].

In contrast to children, the natural process of aging is associated with a decline in swallowing function affecting all three phases of deglutition [25]. Poor dentition and reduction in masticatory strength in older age are the main causes of increases in oral-phase duration and the amount of oral residue during swallowing. Age-related neuromuscular decline contributes to a delay in triggering pharyngeal swallowing reflex and decreases in bolus movement and clearance in the oesophageal phase. It was estimated that 70–90 % of the older population experience some degree of dysphagia [26]. In one study, 87 % of residents in a care home (average age of 87 years) reported mealtime difficulties related to swallowing and 68 % showed signs of dysphagia [27]. The prevalence of dysphagia is particularly high in patients with age-related

diseases such as Parkinson's disease (80 %), Alzheimer's disease (40–70 %) and acute stroke (50 %) [28–31].

3 Factors Affecting Acceptability of Tablets and Capsules

3.1 Acceptability of Tablets and Capsules in Children

The age at which most children acquire the skills to swallow tablets and capsules safely has been the subject of much debate. Early literature widely quotes 6 years as a general age from which these dosage forms may be considered suitable for children [32]. Recent evidence suggests that some children may have already acquired the ability to swallow tablets and capsules from an earlier age, or in some cases can be taught using behavioural training interventions. For example, Yeung and Wong [33] found that children with HIV as young as 3 years were prescribed stavudine as a solid dosage form. In a recent study in Uganda and Zimbabwe, 36 % of children were able to swallow antiretroviral tablets intact (mean age 3.3 years), while 64 % required them to be crushed or dispersed (mean age 2.9 years) [34]. Behavioural techniques to aid swallowing of both tablets and capsules involving children as young as 2–3 years old have also been described; however, such reports are limited to specific diseases and small sample sizes [35–41].

Although swallowing ability may be perceived to improve with age, some studies have reported swallowing difficulties in adolescence. In a general paediatric clinic in Denmark, nearly half (43 %) of parents surveyed reported children aged 12 years and younger experienced difficulties taking both liquids and tablets, primarily due to taste and swallowability; problems in administering tablets were more pronounced [42]. In a qualitative study, Hansen et al. [43] found that more than one-third of adolescents described difficulties in taking oral medications, particularly swallowing tablets, primarily due to taste and size. Polaha et al. [44] similarly reported that around one-third of children and adolescents had refused and rejected tablets at least once; interestingly, frequent medication users were more likely to refuse them despite reportedly having better tablet swallowing skills. Difficulties in swallowing have nonetheless been implicated as a barrier to adherence in children in various chronic conditions [38, 45–47].

The ability to swallow tablets and capsules is one of the factors that influence the age at which children convert from liquid to solid formulations. Following analysis of community prescription data in Netherlands, Schirm et al. [48] found that the use of tablets and capsules exceeded liquids from the age of 7 years for licensed products, 3 years for off-label medicines and 9 years for unlicensed,

pharmacy-compounded medicines. Similarly, in the UK, the average age of conversion from liquid to solid anti-retroviral formulations was 7.3 years [33]. It is worth noting that many factors can potentially affect this conversion age, e.g. the availability of tablets of the right size and strength for paediatric use and the acceptance of prescribing an unlicensed medicine when an authorised formulation is available. Comparison of the practice in different countries would be an interesting topic for future study.

The ability of children to swallow tablets and capsules is strongly related to the size of these dosage forms, alongside age. However, current guidance on the suitability of tablet sizes for different age groups in children is based upon anecdotal feedback and perception [7]. Direct evidence in this area is scarce and future research in this area is required. Table 2 summarises the published evidence on the ability of children to swallow tablets of different dimensions based upon age. Mini-tablets (1–4 mm in diameter) are relatively new dosage forms with considerable promise in paediatrics [17, 49]. Mini-tablets can be administered directly (swallowed whole) or could be labelled for sprinkling onto food. Various research studies have recently assessed the acceptability of mini-tablets in infants and children (Table 2). While these exploratory studies demonstrate their proof of concept, each involved administration of single mini-tablets, whereas multiple mini-tablets are more likely to be used clinically to provide the appropriate dose. Further research is required to demonstrate the application of mini-tablets in practice.

3.2 Acceptability of Tablets and Capsules in Older Patients

In older patients, age- or disease-related swallowing difficulties affect their ability to take solid oral medicines. In a survey involving 17 community pharmacies from England and Northern Ireland, 60 % of patients aged between 60 and 89 years experienced difficulties in swallowing tablets and capsules [56]. A recent study reported that 37.4 % of adult patients (mean age 62 years) attending their general practices had difficulties in swallowing medicines [57]. Polypharmacy (taking ≥ 5 medicines) is common in older patients [9]. A study conducted in Switzerland showed that community-dwelling polypharmacy patients (mean age 67 years) reported ongoing (9.0 %) or past (13.4 %) swallowing difficulties that resulted in intentional non-adherence in 23 % of these patients [58].

Anxiety, previous bad experiences and disliking the idea of taking medicines could all contribute to difficulties for older patients in taking tablets and capsules [57]. Effortful swallowing, a process of swallowing 'hard' using oral and pharyngeal muscles, is commonly advised by speech and

Table 2 Literature reports on the ability of children to swallow tablets in relation to age and tablet size

Age of children	Sample size	Tablet size	Study outcomes	References
1–9 years	555	7 mm ketoprofen tablets	80 % of parents reported that their children had no problems with swallowing, although administration problems were three times more common in those under 2 years of age than in older children	[50]
2–11 years	96	5 and 8 mm	1–7 tablets were taken by children over several months. No reports of swallowing difficulties or adverse events	[51]
6–11 years	113	7 mm	91 % of children aged 6–11 years were able to swallow the tablet; 46 % without training, 38 % trained with an ordinary plastic cup and 7 % with the assistance of a patented pill cup	[41]
2–6 years	100	3 mm mini-tablets	46 % of 2-year-olds and 87 % of 5-year-olds were able to swallow a single mini-tablet	[52]
From 6 months	306	2 mm coated and uncoated mini-tablets	Children as young as 6 months old were capable of swallowing the mini-tablets, with acceptability of the mini-tablets superior to 3 mL glucose syrup. Some instances of chewing before deglutition were observed across the various age groups, with around half of children aged 1–3 years swallowing the mini-tablets intact. Two incidences of coughing were reported for coated mini-tablets, both in children below 1 year of age	[53]
6–30 months	16	2 mm enteric-coated pancrelipase mini-tablets	The mini-tablets were administered with applesauce to the children. Ease of swallowing was rated by parents on a 4-point scale (with 0 corresponding to poor and 3 as excellent). The mean score of the mini-tablets was 1 (fair) to 2 (good)	[54]
1–4 years	183	4 mm uncoated mini-tablets	The mini-tablets were significantly better accepted than 3 other dosage forms (a powder, suspension and syrup)	[55]

language therapists to help dysphagia patients and could increase the oral swallowing pressure to propel the swallowed object more effectively [59]. It was shown that targeted training using swallow-related exercises significantly improved swallowing performance of patients with Parkinson's disease [60]. Indeed, some patients with dysphagia found that concentrating on swallowing improved their ability to swallow solid dosage forms [61].

3.3 Factors Affecting Swallowability and Oesophageal Transit of Tablets and Capsules in Adults

During the swallow process, there is a risk for tablets and capsules to adhere to the oesophagus, causing prolonged or incomplete oesophageal transit. A trapped dosage form can start to disintegrate or dissolve within the oesophagus and cause oesophageal injury, often due to altered local pH or hyper-osmolarity [62]. The swallowability and oesophageal transit of tablets and capsules are affected by many physical characteristics of the dosage form. However, literature reports on swallowability of tablets and capsules were typically conducted in the adult population and data from children and older adults are scarce. Difficulties in swallowing and oesophageal retention of tablets and capsules are expected to be magnified in children and older adults; therefore, the findings of studies in adults provide useful guidance. Nevertheless, studies that are directly conducted in paediatric and geriatric populations would be

valuable to guide the design of medicines for these patients.

Tablet size was found to affect the swallowability and oesophageal transit in adults; smaller tablets were considered easier to swallow and showed faster oesophageal transit than larger tablets (Table 3). Shape, density, surface characteristics and type of formulation can all affect the swallowability and oesophageal transit of tablets and capsules (Table 3). Visual aspects of medicines such as colour can be adapted not only to provide an aesthetic dosage form that is acceptable to patients, but to aid users in recognising and differentiating medicines. The colour of tablets is associated with flavour perceptions and there are many reviews on the topic [63]. Tablet colour has been linked with taste, where pink is considered to be sweeter than red, and yellow is considered to be salty irrespective of its actual ingredients [64]. The colour of a medication has also been connected with specific ailments and can affect patient adherence. A change in tablet colour was associated with non-adherence in adult patients with epilepsy [65]. There have been reviews on the effect of colour of tablets and perceptions of efficacy [66]. Colour preferences among children have shown to be stereotypically gender dependent [67], and they seem to prefer brightly coloured medicines. In older patients, white was seen as the most popular colour choice for tablets; however, those patients who take more than ten tablets every day prefer brighter colours than patients who take fewer tablets [68].

Table 3 Factors affecting swallowability and oesophageal transit of tablets and capsules

Study population	Outcome measure	Summary of outcomes	References
Tablet size			
Male adults aged 24–33 years	Ease of swallowing	Swallowing larger tablets required significantly more swallows and more effort in swallowing than smaller tablets	[73]
Adults (age range 17–82 years)	Oesophageal transit	Smaller tablets have shown faster oesophageal transit than larger tablets	[69, 74, 75]
Adults (age range 23–77 years)	Oesophageal transit	Large tablets (11 mm) showed significantly longer oesophageal transition time than small (5.5 mm) and medium (8 mm) size tablets	[69]
Older adults (aged 59–80 years)	Oesophageal transit	Oesophageal transit of tablets as small as 4 mm in diameter can be prolonged	[76]
Tablet shape			
84 % participants aged 23–64 years and 15 % aged 65 years or older	Ease of swallowing	Arched (curved), oval and oblong tablets were generally easier to swallow than flat round tablets. Oblong tablets were considered difficult to swallow for small tablets	[68]
Male adults aged 24–33 years	Ease of swallowing	Medium or large tablets were preferred to be oblong or oval, while small round tablets were considered as easy to swallow as other shapes	[73]
Adults (age range 17–82 years)	Oesophageal transit	Oval tablets were easier to pass through the oesophagus than round tablets, especially when the tablet is large	[69, 74]
Film coating			
Male adults aged 24–33 years	Ease of swallowing	A film coating applied to the surface of the tablet was found to make swallowing easier	[73]
Adults (age range 17–82 years)	Oesophageal transit	Film coatings improve oesophageal transit of both large and small tablets compared to uncoated tablets	[69, 74]
Density			
Adults (age range 17–82 years)	Oesophageal transit	Heavy large capsules passed through the oesophagus significantly faster than light large capsules in a standing position	[74]
Type of formulation			
Older adults (mean age 66, range 50–79 years)	Oesophageal transit	The oesophageal transit time of gelatine capsules was significantly longer than enteric-coated and cellulose-based film-coated tablets	[77, 78]
Adults (age not specified)	Oesophageal transit	Barium sulphate tablets were more likely to stick to the oesophagus than capsules of the same drug	[79]
Adults (age range 17–82 years)	Oesophageal transit	Large capsules passed through the oesophagus significantly faster than uncoated oval tablets and their transit was less affected by the posture of the patient than tablets	[74]
Adults (age range 19–80 years)	Oesophageal transit	Oesophageal passage of capsules was not affected either by capsule size or the amount of water taken at the same time, both of which had significant influence on the transit of tablets	[69]
Body position of the patient			
Adults (age range 17–82 years)	Oesophageal transit	Oesophageal transit of tablets and capsules are significantly faster in patients in the standing position than in the supine position	[69, 74, 75, 80, 81]
Fluid taken			
Adults (age range 17–82 years)	Oesophageal transit	Tablets and capsules pass through the oesophagus faster when a large quantity of fluid is taken with the medication	[80–82]
Adults (age range 19–80 years)	Oesophageal transit	The most common cause of oesophageal retention of tablets and capsules was the combination of a small volume of water (25 mL) and the supine position. When a large quantity of water (100 mL) was taken, the transit time was significantly shorter for small and large tablets in the supine position and for large tablets in the standing position	[69]

The ability of a patient to swallow tablets and capsules is also affected by patient-related factors. The retention of a tablet or capsule in the oesophagus is affected by the body

position of the patient while taking the medicine and the volume of fluid taken with the medication (Table 3). It was recommended that medications should be taken with at

least 100 mL of fluid and the patient remains standing for at least 90 s to prevent oesophageal retention [69]. Although useful guidance, some older patients may not be able to follow this advice, as they may be bedridden or may have difficulty in swallowing a large amount of fluid [70]. Similarly, this volume may be too large for children to take.

3.4 New 'Easy-to-Swallow' Technologies to Aid in Swallowability of Tablets and Capsules

Several technologies have been developed to aid the swallowing of solid oral dosage forms. A disposable device called MedCoat[®] (Med Coat AB, Stockholm, Sweden) can be used by the patient to apply a thin coat on the tablet before swallowing [71]. The coating contains gelatine, sweeteners and flavouring agents and can improve the taste of the tablet. In a clinical trial (average age 30 years), the coating improved the ease of swallowing of tablets, especially bitter-flavoured placebo tablets [71]. A similar flavoured spray product Pill Glide[®] (FLAVORx Inc., Columbia, MD, USA) requires the patient to apply the spray to the back of the mouth and tongue before taking tablets or capsules [72]. The spray creates a lubricated surface in the mouth and thus facilitates swallowing. Pill Glide[®] has been found to be helpful in adolescents with difficulties in swallowing tablets.

4 Factors Affecting Acceptability of Oral Liquid Dosage Forms

Oral liquids are generally regarded to be the most appropriate dosage form for children despite having issues including taste masking, portability, stability and the inclusion of excipients that are not always appropriate for all paediatric patients. The challenge in using liquid formulations in older patients, particularly those with dysphagia, is aspiration, which is caused by inadequate protection of the airway during swallowing. The prevalence of aspiration was reported as 51 % in dysphagia patients and 36 % of healthy older adults showed some degree of aspiration during normal swallowing [83, 84].

Patient acceptability of a liquid dosage form is inevitably affected by many of its characteristics (Table 4). Modifications in these formulation factors can improve swallowing of a liquid by moderating the timing and response of oral, pharyngeal and oesophageal phases.

4.1 Taste, Smell and Palatability of a Liquid

Taste is regarded as the most important factor determining the acceptability of a liquid medicine in children. There

have been several studies undertaken that investigated the taste of liquid medicines in paediatric populations. These typically use face-rating scoring systems to evaluate the taste in this population and an example study was conducted by Cohen et al. [108]. Review articles have been published on this area and the reader is directed to the review by Ernest et al. for additional information [109].

Research has linked smell of a liquid to flavour and it has been argued that the majority of the flavour of food actually comes from its smell [110]. It is likely that certain medicines do smell unpleasant, yet there is very limited work done in this area, particularly in linking medication odour to compliance/adherence (Table 5).

The effect of taste on medication acceptability in older patients has not been extensively investigated compared to the paediatric population. However, the unpleasant taste of liquid medicines was identified as one of the barriers for older patients with dysphagia to taking their medications [61]. Swallowing is modulated by the nervous inputs generated from sensory receptors in the oral, pharyngeal and laryngeal regions via trigeminal, glossopharyngeal and vagus nerves [111]. Taste, thermal and chemical properties of the ingested fluid act as stimuli of these nerves and are known to affect swallowing activities (Table 4). However, the effect of taste was likely to decrease in older adults due to the reduced taste sensitivity in older individuals [112].

Beneficial effects of a sour bolus, consisting of 50 % lemon juice and water, on the oropharyngeal swallowing in patients with neurogenic dysphagia were reported by Logemann et al. [87] (Table 4). It was suggested that the sour taste acted as an "alerting" stimulus and enhanced or altered the sensory input to the nervous system and thus facilitated oropharyngeal swallowing in neurogenic dysphagia patients. The strong sour taste was deemed unpleasant by most participants and changing the liquid into a palatable sweet and sour taste did not significantly improve swallowing [91]. It is the challenge for future research to utilise the benefit of the sour taste and improve the palatability in the design of oral liquid medicines to promote safe swallowing in older dysphagic patients.

4.2 Texture and Viscosity of a Liquid

The texture and mouth feel of particles is acknowledged as important in food products as it affects mastication and overall taste sensation [113]. Grittiness of particles has previously been linked to particles >12 µm [113]. Texture effects on acceptability of liquid medicines have not been extensively investigated (Table 4) and it is an important subject for future research.

The consistency and rheology of the swallowed bolus affect the safety of swallowing [114, 115]. In particular, liquids and thin pastes initiate significantly different

Table 4 Factors affecting the swallowability and acceptability of liquid medicines

Study population	Outcome measures	Summary of outcomes	References
Taste			
Healthy young adults	Swallowing speed	Sweet, sour and salty tastes reduced the swallowing speed and prolonged oral and pharyngeal swallowing durations compared with neutral tastes	[85]
Healthy young adults	Swallow physiology	Sweet, sour and salty tastes generated stronger muscle contractions and shorter activation onset times during swallowing than the no-taste conditions	[86]
Older adults (aged 65–85 years)	Swallow physiology	The effects of sweet, sour and salty tastes on swallow physiology reduced	[86]
Patients with neurogenic dysphagia	Oropharyngeal swallowing	A sour bolus reduced the swallow onset time, shortened the pharyngeal delay and transit time, and improved oropharyngeal swallow efficiency	[87]
Palatability			
Healthy young adults	Swallowing physiology	Palatability of the ingested liquid had little effect on swallowing physiology and performances	[88, 89]
Adults aged 23–71 years	Oral, pharyngeal and oesophageal transit	No difference was found on the duration of oral, pharyngeal and oesophageal phases of swallowing between an unpleasant bitter bolus and a pleasant sweet bolus	[90]
Older patients with neurogenic dysphagia	Swallowing performance	A pleasant sweet–sour mixture did not significantly improve swallowing performances compared with water	[91]
Oral stimuli			
Patients with stroke (aged 41–88 years)	Pharyngeal transit	The combination of sour taste and cold stimuli was able to improve pharyngeal transit time	[92]
Healthy young adults	Swallow performance	Carbonated water was able to improve swallowing performances	[88, 93]
Adult patients with neurogenic dysphagia	Pharyngeal transit and aspiration risk	Carbonated water significantly improved pharyngeal transit and reduced aspiration and penetration risk scores compared with non-carbonated thin liquid	[94]
Smell			
Adults	5-Point scale on smell (5 being most positive score)	The smell of different liquid corticosteroid products (prednisolone 1 mg/mL; prednisolone sodium phosphate 1 mg/mL and dexamethasone 0.5 mg/5 mL) was measured. Dexamethasone scored most positively; this may be attributed to the lower concentration, as the taste was not scored more positively than prednisolone	[95]
Texture			
Adults	Effects on palatability	The texture of liquids was included in a study on the palatability of liquid anti-infectives with acknowledgement that texture can influence palatability of a liquid, although there were no additional details on what textures are acceptable or otherwise	[96]
Adults	5-Point scale on texture (5 being most positive score)	The texture of different liquid corticosteroid products (prednisolone 1 mg/mL; prednisolone sodium phosphate 1 mg/mL and dexamethasone 0.5 mg/5 mL) was measured. Prednisolone sodium phosphate 1 mg/mL was scored most positively; this may be due to the higher solubility of the salt form making the particle size smaller within the product	[95]
Children aged 1–4 years	Acceptability	Syrup was more acceptable to children than a suspension using placebo formulation and this is likely related to the taste or texture difference between these formulations	[55]
Viscosity			
Healthy young adults	Oropharyngeal transit	Increasing the viscosity of the liquid slowed the oropharyngeal transit of the bolus	[97–100]
Patients with Parkinson's disease	Timing and safety of swallow	Increasing the viscosity of the liquid slowed the oropharyngeal transit of the bolus and reduced aspiration/penetration risk scores by preventing the premature emptying from the mouth before the pharyngeal swallow response	[100]

Table 4 continued

Study population	Outcome measures	Summary of outcomes	References
Dysphagia patients with dementia or Parkinson's disease	Oesophageal transit	Both honey-thick and nectar-thick liquids were able to significantly reduce the risk of aspiration in dysphagia patients compared with thin liquids	[101]
Volume			
Healthy older adults (aged 61–70 years)	PAS score	Increasing the liquid bolus volume increased the risk of aspiration. The PAS score increased significantly with a 20 mL bolus volume compared with 5, 10 and 15 mL volumes	[83]
Healthy male adults	Oral and pharyngeal phases of swallowing	Higher liquid bolus volumes (2–20 mL) increased difficulty in swallowing, including a longer oral retention time and increased magnitude of structural movement for oropharyngeal clearance	[97]
Patients with neurogenic dysphagia	Ease of swallowing	A liquid volume of 1 mL was more difficult to swallow by stroke patients than 5 mL volume	[102]
Administration devices			
Healthy older adults (aged 61–70 years)	PAS score	No difference in PAS scores between cup and straw drinking	[83]
Older patients with neurogenic dysphagia	PAS score	Drinking from a teaspoon resulted in significantly lower PAS scores than cup drinking	[91]
Patient posture			
Patients with oropharyngeal dysphagia; head and neck surgical patients	Prevention of aspiration	Head or body postural changes (chin down, chin up, head rotated, head tilted and lying down) eliminated aspiration in 77 % of patients with oropharyngeal dysphagia and 60 % patients who had head and neck surgery	[103, 104]
Dysphagia patients	Prevention of aspiration	Chin down posture was effective to prevent 55–64 % of aspiration	[105, 106]
Dysphagia patients	Prevention of aspiration	Head rotation was useful in 29 % of patients to prevent aspiration	[105]
Healthy adults	Pharyngeal clearance	Head rotation reduced the UES resting pressure and prolongs the UES opening, and thus improved pharyngeal clearance during swallowing	[107]

PAS Penetration-Aspiration Scale, UES upper oesophageal sphincter

muscle activities during swallowing compared with thick pastes, which could be associated with a higher risk of aspiration in dysphagia patients [98]. Thin liquids pose a high risk of aspiration due to their lack of resistance to flow and they usually arrive at the hypopharynx before the onset of the pharyngeal swallow. Increasing the viscosity of the liquid slows the oropharyngeal transit of the bolus and thus prevents the premature emptying from the mouth before the pharyngeal swallow response [97–99].

4.3 Volume of a Liquid Administered

Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking. There are issues in very small volumes of oral liquids for administration in children; these are generally related to the accuracy of dosing relative to the devices available [116]. Minimal volumes are normally used when dosing very young children via enteral tubes to ensure that sufficient nutrition can be administered in addition to medication. The typical volume of medicine administered in a child is

expected to be swallowable in one unit; therefore, the maximum volume should equate to the volume of a swallow. The volume of a swallow is reported to be 4.5 mL for children from 15 months to 3.5 years of age and this equates to a typical volume of 0.27 mL/kg [117].

The volume of the liquid to be swallowed can affect the safety of swallowing in older adults. A normal sip size for healthy adults has been reported to be in the range of 17–21 mL [117, 118]. However, the sip size is much smaller ($9.8 \text{ mL} \pm 6.0$) in patients with neurogenic oropharyngeal dysphagia [91]. Increasing the liquid bolus volume has been shown to increase the risk of aspiration (Table 4). Interestingly, too small a volume can also be a problem for dysphagia patients to swallow (Table 4) [102]. This is likely due to the reduced sensory awareness in these patients and because increased bolus volume increases the sensory input into the nervous system.

4.4 Administration Devices

The device used to administer an oral liquid is critical in ensuring that the dose administered is accurate. There are

Table 5 Acceptability studies of oral flexible formulations in children and older adults

Study population	Summary of outcomes	References
Multiparticulates		
Children (aged 5–16 years)	In the crossover study comparing a valproate sprinkle formulation with syrup, 9 of 12 parents preferred sprinkles due to their ease of use, while 9 children preferred them due to enhanced palatability, despite the authors reporting a gritty texture	[13]
Children (aged 3–14 years)	Neutral-tasting sodium valproate microgranules were well-accepted and adhered to over 90 days of treatment, although one-fifth of parents reported difficulty administering the drug to their child due to the consistency or mouthfeel of the drug	[126]
Children (from 6 months old)	Microencapsulated iron sprinkles and other micronutrient powders were superior in terms of ease of use, acceptance and adherence compared with other forms such as drops and crushable tablets	[127–130]
Infants (5–7 months)	Adherence to ferrous fumarate sprinkles was slightly poorer than for drops, with some parents expressing concerns about the new product and its safety	[131]
Adults and older adults (mean age 66 years, range 34–83 years)	The majority of patients (67 %) preferred chewable tablets compared with sachet for calcium and vitamin D supplements. Sachet was considered to be more time-consuming and more difficult to take than chewable tablets	[132, 133]
Children and adults with phenylketonuria (aged 8–49 years)	11 of 12 participants preferred a ‘ready to drink’ liquid protein substitute formulation over powder. The liquid formulation was considered easy to take and more convenient to use in different environments than the powder	[132, 133]
Dispersible and effervescent tablets		
Infants and children (aged 3 months to 5 years)	90 % of caregivers reported that zinc dispersible tablets were as acceptable to their children, or more so, as other medicines, while 84 % were willing to use the medicine again in the future	[134]
Children (aged 0–5 years)	Acceptability and adherence to diarrhoea treatment was more favourable using zinc dispersible tablets. Almost 90 % of children received 10 days’ treatment and two-thirds completed the full 14 days, while only 6.5 % of caregivers reported administration problems (4 % reported vomiting and 2.5 % refusal to take)	[135]
Children (aged 4–8 years)	A citrus-flavoured effervescent tablet was preferred over peppermint-flavoured syrup by more than two-thirds of the children and their caregivers	[136]
Parkinson’s disease patients with dysphagia	The acceptability of a dispersible tablet containing levodopa-benserazide was considered advantageous with regard to ease of administration	[137]
ODTs		
Children (aged 6–11 years)	More than 90 % of the children preferred strawberry-flavoured lansoprazole ODTs over peppermint-flavoured ranitidine syrup	[138]
Children (aged 5–11 years)	The taste of the ondansetron ODTs scored lower than placebo; however, none of the children rejected or spat out the tablet and 87 % were reportedly willing to take it again in the future	[139]
Children (aged 6 months to 10 years)	A randomised clinical trial involved administration of ondansetron ODTs or placebo to children; however, patient acceptability was not assessed as part of the study	[140]
Adult patients with depression	More than 80 % of patients preferred ODTs over conventional tablets	[141, 142]
Older patients with schizophrenia	Olanzapine ODTs have been shown to improve medication compliance in acutely ill non-compliant patients in nursing homes	[143]
Depressed patients older than 85 years	Mirtazapine ODTs were used for the treatment of depression in these ‘old-old’ patients, and were found to be acceptable and well-tolerated	[144]
Older patients with Parkinson’s disease	In a multicentre, open-label study, more than twice as many patients preferred carbidopa–levodopa ODTs (45 %) compared with conventional tablets (20 %)	[145]
Chewable tablets		
Children from the age of 2 years	The review summarised chewable tablets to be safe and well-tolerated in children from this age	[146]
Children (aged 6–11 years)	82 % of the children and 87 % of their parents preferred a cherry-flavoured chewable montelukast tablet over inhaled therapy, and this formulation resulted in better self-reported adherence	[147]

ODTs orally disintegrating tablets

many alternatives available for the delivery of oral liquids including oral syringes, measuring spoons and measuring cups. In general, drinking from a spoon is considered safer for patients with dysphagia than cup and straw drinking (Table 4). The front edge of the bolus was reported to be frequently in the hypopharynx before the initiation of the swallowing during straw drinking and this distal bolus location was associated with greater occurrences of airway penetration in dysphagia patients [119].

4.5 Packaging and Storage

Preservatives are required in multidose oral preparations; however, preservatives are often associated with bitterness and this needs to be balanced with the overall palatability of the medicine. The safety and toxicity of the preservatives used need careful consideration, particularly for neonates. Packaging liquid medicines in a single-use sachet has benefits in terms of reducing the requirement for preservatives and also increasing the portability of a medicine. This packaging is used within the UK for paracetamol suspensions and Gaviscon[®] products. Anecdotal evidence suggest that carers prefer sachets of certain drugs due to the portability and also eliminating the need for an additional measuring device as the medicine can be transferred directly from the sachet to the patient's mouth. Oral liquids may require refrigeration, which is a further hurdle for patients who may require frequent administration of a liquid.

4.6 Patient Posture

Postural changes of the head and body have been frequently used as compensatory treatments for oropharyngeal dysphagia, especially for eliminating aspiration of thin liquids. The most effective postural techniques include head rotation and chin-down posture—touching the chin to the front of the neck (Table 4) [105, 106, 120, 121]. The effectiveness of the chin-down posture in reducing the risk of aspiration is related to a significant narrowing of the laryngeal entrance and a posterior shift of the epiglottis, and thus providing a more effective protection of the airway entrance [122–124]. This technique was seen to be most helpful in the oldest patients (ages 80–95 years), probably relating to the changes in the natural neck posture with age [101]. Head rotation was shown to lateralise the bolus away from the direction of the head turn during swallowing [107, 125]. This technique is therefore useful for patients with unilateral neurologic or structural damage to the pharynx, by bypassing the damaged area and improving the efficiency of swallow. The effect of posture in the very young has not been examined with respect to medicines administration but may be of significant importance for babies and infants who often feed in a horizontal position.

5 Acceptability of Other Flexible Oral Solid Dosage Forms

Alternatives to liquid medicines are often sought where liquid medicines are not acceptable to patients; for example, where taste issues cannot be overcome, more sophisticated formulation approaches such as encapsulation of drug particles may be required. Many disadvantages associated with taking oral liquids can be avoided by the use of flexible oral solid medicines that are convenient to use by patients who cannot swallow tablets and capsules. Table 5 describes studies investigating the acceptability of these formulations in children and older adults and Table 6 summarises the advantages and challenges of using these formulations in these patient groups.

5.1 Multiparticulate Dosage Forms

Multiparticulates include powders, granules and pellets and are usually presented in sachets or capsules that can be reconstituted in a drink to provide solutions or suspensions, or applied onto food as 'sprinkles'. They can also be further processed to produce other solid formulations including conventional, orally disintegrating or chewable tablets. Based on recent US FDA guidance, multiparticulates that are labelled for administration via sprinkling should have a target size of 2.5 mm, with no more than 10 % variation over this to a maximum size of 2.8 mm [160]. These formulations are typically considered as paediatric formulations; however, older patients can also benefit from their use, such as for the treatment of Parkinson's disease, osteoporosis and phenylketonuria [132, 133, 161].

5.2 Dispersible, Soluble and Effervescent Tablets

Dispersible, soluble and effervescent tablets are solid dosage forms that can be dispersed or dissolved in a liquid to form a solution or suspension. These dosage forms require effective taste masking, as reviewed in Sect. 4.1 relating to oral liquid medicines. These dosage forms are beneficial in the delivery of large doses of active drug substances as they are easier to swallow than large tablets. The acceptability and safety of using dispersible and soluble tablets in older adults, especially those with dysphagia, have not been fully studied. However, effervescent formulations may be a useful technology to promote safe swallowing in older patients due to the production of carbon dioxide in water. Carbonated water has been found to be able to improve swallowing in dysphagia patients by exciting chemical stimulation in the oral cavity (Table 4) [88, 93, 153]. A national survey in the UK showed that

Table 6 Advantages and challenges of using flexible oral solid formulations in children and older adults

Advantages	Challenges
Multiparticulates	
<ol style="list-style-type: none"> 1. Infants can start to swallow thick, semi-solid foods from the age of 6 months and administration of multiparticulates mixed with semi-solid food is considered appropriate for children above this age [17] 2. Multiparticulates can be mixed with semi-solid food for administration to older patients. Swallowing is considered safer with a lower risk of aspiration in dysphagia patients when semi-solid food, such as paste, pudding and rice is swallowed than with liquids [148–150] 	<ol style="list-style-type: none"> 1. Grittiness and poor mouth feel [13, 16, 126] 2. Lack of knowledge and experience in the use and safety of this formulation amongst parents and carers [13, 16, 126] 3. Multiparticulates are considered to be more time-consuming and more difficult to take than liquid formulations and chewable tablets due to the requirement of handling (mixing with food and drink) before administration [132, 133]. This could pose challenges to children and older adults, many of whom rely on caregivers for taking their medicines
Dispersible and effervescent tablets	
<ol style="list-style-type: none"> 1. These tablets are potentially suitable to be administered to infants under 6 months of age for drug substances and excipients that are compatible with breast milk [151]. A ‘nipple shield delivery system’ (NSDS) could facilitate this novel method of infant drug delivery [152] 2. Carbonated water generated by effervescent formulations could potentially improve safe swallowing in dysphagia patients [88, 93, 153] 	<ol style="list-style-type: none"> 1. These formulations usually require the application of a large volume of water, which could be problematic for both children and older patients who find swallowing a large amount of liquid difficult, especially in patients with dysphagia [70] 2. The risk of aspiration in dysphagia patients for swallowing thin liquids resulted from these formulations would need to be considered 3. Effervescent formulations showed high capacity for tooth erosion, even more so than sugar-containing medicines, which should be considered for long-term use in children and older people [154] 4. Soluble and dispersible formulations often contain a high quantity of sodium and the maximum daily dose of these medications could exceed the recommended daily dietary intake of sodium [155]. Prescribing sodium-containing formulations was associated with increased cardiovascular incidents [155] and the use of effervescent formulations was responsible for poor blood pressure control in older hypertension patients [156]
ODTs	
<ol style="list-style-type: none"> 1. ODTs are generally acceptable in children and older patients, which is normally associated with their taste, texture, ease of use and reduced concern about difficulties in swallowing [141, 142, 145] 2. ODTs are easier to swallow than conventional tablets in dysphagia patients [157]. Fewer numbers of swallows, shorter swallowing duration, reduced muscular effort and less fluid assistance are required in swallowing ODTs than conventional tablets 3. The use of ODTs can be beneficial for patients who are purposely non-adherent, particularly in relation to antipsychotic treatments, as it is more difficult to spit the tablet out or hide the formulation in the mouth [158] 4. The ease of administration of ODTs can be advantageous to reduce the work burden on nursing staff and caregivers who assist the administration of medicines in older patients [143] 	<ol style="list-style-type: none"> 1. The risk of aspiration remains the same in swallowing ODTs as conventional tablets in dysphagia patients [157]
Chewable tablets	
<ol style="list-style-type: none"> 1. Many chewable formulations are licensed for use in children from the age of 2 years and were found to be safe and well-tolerated in children from this age [146, 147] 	<ol style="list-style-type: none"> 1. Chewable tablets have the potential for tooth erosion over long-term use [154] 2. Use in older patients could be limited due to the decline in chewing ability 3. Adverse events are associated with the swallowing of intact or partially chewed chewable tablets, such as intestinal obstruction, ischaemia and perforation [159]. The issue can be augmented by the large variation in chewability of commercially available chewable tablets [159]

ODTs orally disintegrating tablets

90 % of the prescribed and issued over-the-counter ‘easy to swallow’ solid formulations were effervescent tablets for long-term use in older people [162].

5.3 Orally Disintegrating Formulations

Orally disintegrating formulations include tablets, films and thin wafers. These formulations are relatively new innovations in improving patient compliance and acceptance, especially for paediatric and geriatric patients. These preparations may be applicable for use across the paediatric population, including infants and young children; however, evidence of their use and acceptability in these subsets is lacking. A number of orally disintegrating tablet and film formulations have been developed for the treatment of diseases that are common in the older population such as pain, depression, Parkinson’s disease and Alzheimer’s disease [163, 164].

5.4 Chewable Tablets

Chewable tablets are another dosage form useful for paediatric and geriatric patients who are unable to swallow conventionally sized monolithic dosage forms intact. In typically developing children, deciduous (primary) teeth begin to erupt from 6 months of age and the complete set of 20 have usually erupted between the ages of 2 and 3 years. Exfoliation of deciduous teeth begins from 6 to 7 years of age, with complete replacement by permanent teeth usually completed by the age of 12–13 years. Recent research suggests continual refinement of chewing skills occurs until at least the age of 3 years, at which time chewing patterns and efficiency also stabilise [165].

Despite the recent popularity of chewable tablets in children, their usage in older adults may be limited due to the deteriorations of chewing ability in this age group. The prevalence of chewing problems was observed to be 40 % among older Tanzanian citizens (aged 50–100 years) [166]. In Finland, chewing ability was considered poor in 55 % of long-term hospitalised older individuals and 65 % could eat mashed food only [167]. The loss of teeth is regarded as the primary factor accounting for the deterioration of the chewing ability and the possession of more than 20 teeth is essential for retaining good chewing capacity. However, a survey in Japan showed that 65 % of older people (aged 75–100 years) had less than 20 teeth [168]. In Denmark, half of the 75- and 85-year-old men and women in a suburban area were edentulous and only 15 % still had more than 20 teeth [169]. As a result, chewing problems were shown in three-quarters of those very old men and women who have lost all of their natural teeth.

5.5 Films and Jellys

A film formulation provides easy swallow through the application of a dry film that turns into a jelly instantaneously in the mouth by absorbing a small amount of saliva [170]. The film consists of an inner layer that contains the active drug and two gelling layers covering the drug layer (Fig. 1). The dissolution of the drug in the mouth was limited by the gel layer which swells by absorbing water (Fig. 2). The oesophageal transit of the film was significantly quicker than gelatin capsules [170]. The technology may be difficult to use in older people with xerostomia, which is a common symptom in the older population, particularly related to the increased use of medications [171]. A drug-containing oral jelly was developed to improve swallowing for older patients [172]. The formulation comprises a jelly portion and an air portion which can be pushed to extrude the jelly when opening the package.

6 Acceptability of Dosage Forms Designed for Particular Therapeutic Effects

6.1 Modified-Release Formulations

Oral modified-release formulations enable longer and more patient-friendly dosing intervals. This can be beneficial in children to avoid the need to take medicines at school or nursery settings and to improve adherence in older patients. More simplified dose regimens with fewer daily doses have been associated with higher patient adherence [10]. It was found that patient adherence was significantly higher with once- and twice-daily regimens than three and four times daily regimens. Further evidence shows that adherence can be improved by switching from twice-daily to once-daily therapy [173]. Adherence to antiretroviral therapy was significantly improved when patients were switched from twice-daily to once-daily stavudine treatments for HIV [174]. However, for extended-release formulations,

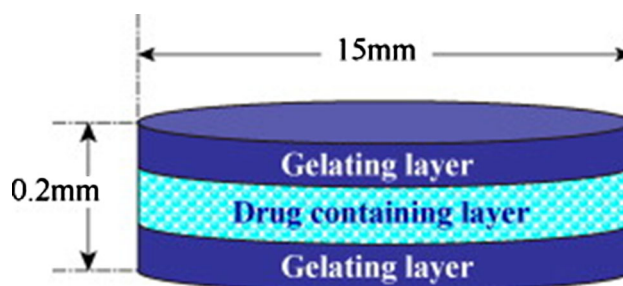
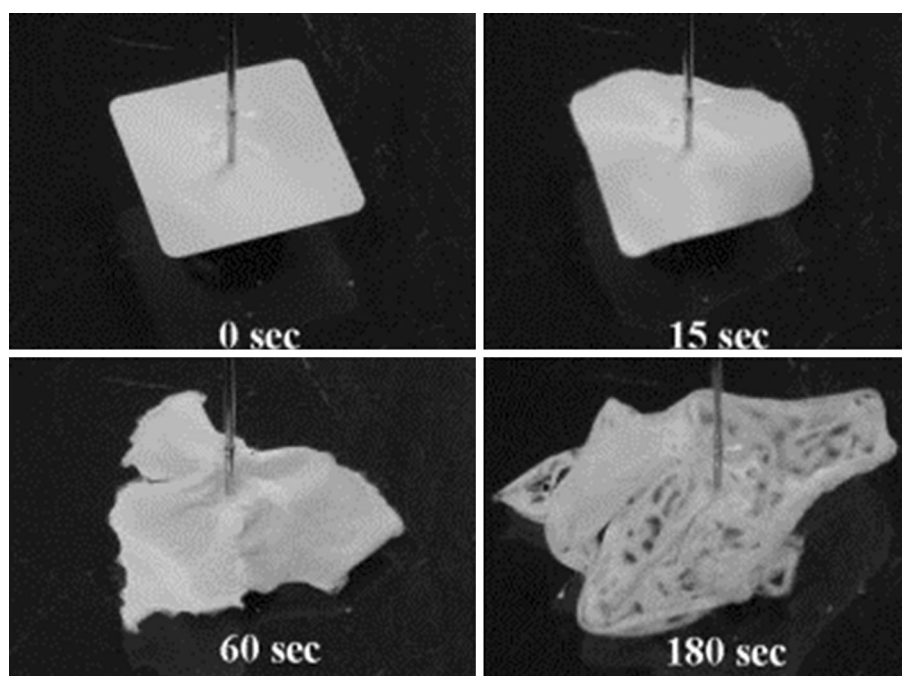


Fig. 1 Schematic structure of the easy-swallowing film formulation (reproduced from Okabe et al. [170], with permission)

Fig. 2 The swelling behaviour of the film formulation in purified water (reproduced from Okabe et al. [170], with permission)



patients need to be reminded that doses should be taken at approximately equal time intervals, e.g. the same time of the day for once-daily preparations. Taking doses too far apart or too close together for these formulations may result in decreased efficacy or increased adverse effects.

Conventionally, modified-release formulations are designed as single-unit dosage forms that contain the active ingredient in a single tablet or capsule. These formulations are challenging for children and older patients to swallow (see Sect. 3.1). Crushing modified-release tablets prior to administration poses an additional risk of toxicity due to the high level of active drug contents. There have been reports of patient deaths resulting from administering crushed modified-release tablets to older dysphagia patients [175]. Modified-release multiparticulate systems offer a more flexible method for administration to children and older patients and exist as granules, pellets, beads, mini-tablets, microspheres and microcapsules [176–179]. These multiple-unit modified-release systems can be filled into capsules/sachets or compressed into orally disintegrating tablets as the final dosage form [180, 181].

6.2 Fixed-Dose Combinations

Fixed-dose combinations could be useful to reduce pill burden in older patients and could be beneficial for paediatric patients with combined drug therapies such as treatment for HIV. However, this could increase the size of the tablet and cause further swallowing issues. A potential solution could be different coloured pellets that could be mixed together at different strengths by the manufacturer

or pharmacist. Fixed-dose combinations in the forms of oral suspensions and dispersible tablets have been proposed in paediatrics for the treatment of HIV [182]. Kayitare et al. [183] have developed a fixed-dose combination tablet of zidovudine and lamivudine for paediatric use that allows dose flexibility and easy administration to children. The rectangular tablet can be broken into eight subunits for dose adjustment according to body weight and each subunit disintegrates rapidly in a small volume of liquid to aid administration. It was suggested that the tablet is suitable for children from infants (from 1 month old) to adolescents (up to 18 years of age) [183].

7 Concluding Remarks

Children and older adults share similarities in oral medication acceptability, particularly difficulties in swallowing conventional tablets and capsules. Appropriate formulation design and selection affect the acceptability of medicines in these two age groups and have an impact on patient safety, therapeutic outcomes and adherence. However, distinct differences in relation to drug therapy are notable in children and older people, and separate considerations in prescribing and formulation development should be given to the two populations. Whilst taste, smell and palatability are major concerns in developing paediatric formulations, characteristics of a medicine affecting safe swallowing are of significant importance in older patients, especially to prevent oesophageal retention and risk of aspiration. Nevertheless, both the young and older populations benefit

enormously from the advances in pharmaceutical technology which offers bespoke and appropriate formulations of choice to meet their needs.

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