

Evidence of acceptability of oral paediatric medicines: a review

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Abstract

Objectives The aim of this review was to map the currently available evidence on acceptability of oral paediatric medicines to aid in the selection of suitable platform formulations for the development of new acceptable paediatric products.

Methods This process used a defined search strategy of indexed publications and included methods to assess the quality of the evidence retrieved.

Key findings Taste/palatability was the most extensively studied area of paediatric medicine acceptability yet standard methods or criteria that define what is classed as acceptable to children is still to be defined. There have been many reports on the acceptability of medicines to paediatric populations yet major gaps in the acceptability knowledge base exist including the shape and dimensions of tablets, minitab; and capsules swallowed whole in infants and children; size and overall volume of multiparticulates; volume of liquids completely swallowed in infants and children; duration of retention within the oral cavity, size and taste of orodispersible tablets, lozenges and chewable tablets and the number of solid units dosed at each time point.

Conclusions The review highlights where further information is required to support knowledge around acceptability of age-appropriate medicines. An algorithm to aid in selection of a formulation that is likely to be acceptable based on the age range to be treated by the medicine is presented as a result of this review.

Introduction

There is much evidence to support the need for age-appropriate medicines to treat paediatric patients. Pharmaceutical products for the paediatric population have a number of considerations that may not apply to adult products. In particular, the acceptability of a product needs to be clearly defined for paediatric populations and this is currently an area of great interest.

The importance and incentive to study the acceptability, including palatability, of paediatric formulations was discussed in the reflection paper^[1] and endorsed in the latest European Paediatric guideline on pharmaceutical development of formulations for paediatric use.^[2] Before this regulatory change, there was no requirement for medicines to be demonstrated to be acceptable to children. Guidance issued by the European Medicines Agency (EMA) in 2013

states that patient acceptability must be an integral part of paediatric formulation development and described in the paediatric investigation plan (PIP).^[3] 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)'.^[4] The palatability of paediatric medicines is one of the most important formulation factors in the acceptability of liquid medicines with potential to influence adherence to therapeutic regimens and outcomes.^[5] Palatability has been defined as, 'the overall appreciation of a (often oral) medicine by organoleptic properties such as vision (appearance), smell, taste, after-taste and mouth feel (e.g. texture, cooling, heating, trigeminal response), and possibly also sound (auditory clues)'.^[4]

A better understanding of acceptability of paediatric medicines offers advantages to the pharmaceutical industry and patients. The pharmaceutical industry will benefit from

a standardisation of approaches to the development of paediatric medicines, a reduction in duplication of efforts, and reduced development times and the associated costs for the development of paediatric medicinal products. Patients benefit by having access to medicines known to be acceptable both during clinical evaluation and for subsequent therapy with a better clinical outcome and improved quality of life. Furthermore, an understanding of acceptable formulations reduces the barrier to the development of new age-appropriate formulations of existing medicines.

A lack of knowledge about what is currently considered to be acceptable to paediatric patients hinders the development of acceptable, age-appropriate medicines. Regulatory guidelines have been published although these have been criticised as they are not based on scientific evidence (e.g. Ref. [2]). This review article gathers the available evidence to provide a much needed, single source of information on which paediatric formulations should be selected based on their acceptability to children. The wide range of evidence from a broad spectrum of study types was effectively mapped, thereby highlighting areas where acceptability is understood and where possible future reviews or primary research is required. Presentation of these results in an accessible and summarised format assists policy makers for guideline development and those working in pharmaceutical industry.^[4]

Methods

Information on acceptability of medicines was sought from a literature search and also 'grey' literature including conference proceedings. Overall, the methods for the review protocol were informed by the Cochrane Handbook for Systematic Reviews of Interventions.^[6] This review was limited to the primary critical attributes in acceptability testing as identified by Kozarewicz^[4] and was limited to oral dosage forms (Table 1).

Relevant data on each critical parameter were sought from the literature to gather evidence on what is currently known or suggested to be acceptable. The literature search identified indexed publications by searching Scopus, PubMed, Embase and Medline. Search key words included the following: acceptability OR preference AND medicine AND (child OR infant OR paediatric OR paediatric) AND (palatability OR taste OR smell) OR (size OR shape OR appearance OR swallowability) OR (dose adjustment OR manipulation OR device) OR dose frequency.

The process to identify the most relevant research included the following: screening of titles and abstracts; selection of studies based on inclusion criteria with checks from a second reviewer; searching of reference lists of included studies and contacting experts for the details of any unpublished or ongoing studies (EuPFI network

Table 1 Critical acceptability attributes in oral pharmaceutical formulations for children as identified by Kozarewicz⁴

Dosage form	Critical acceptability attributes
Monolithic solid dosage forms to be swallowed	Size and shape, taste and aftertaste for uncoated dosage forms
Multiparticulate solid dosage forms to be swallowed	Particle size, shape, texture (surface aspects) and hardness (grittiness); taste and aftertaste for uncoated multiparticulate; dose volume (quantity of multiparticulate that needs to be taken); need for a measuring/counting device and ease of administration
Solid dosage forms to be chewed	Taste and aftertaste and the mouth feel, smell, time needed to chew and effort required to chew (duration of administration)
Solid dosage forms to be dispersed (solubilised) in the mouth (e.g. tablets and lozenges)	Taste and aftertaste and the mouth feel, smell, time needed to dissolve/disperse (duration of administration)
Liquid dosage forms – solution, suspension	Taste and aftertaste; smell; volume, viscosity and the mouth feel; need for a measuring device and ease of preparation/administration; visual aspects (overall appearance)

(www.eupfi.org) and consortium members within SPaeDD-UK); and finally data extraction using a bespoke data extraction table.

Only papers where information that specifically related to acceptability attributes, as measured in paediatric populations, was extracted and included in the results; many papers described the acceptability of dosage forms but did not contain sufficient details on product parameters could not be included. In addition, information about medicines that are used clinically, yet approved before the need to demonstrate acceptability, is included where relevant to highlight current medical practice in paediatric populations.

The quality of the conclusions of this review is dependent on the quality of studies included in the evidence base, as poor quality studies are more likely to generate inaccurate results. Many reviews that map the available evidence do not include a quality assessment which is critical in the use of this review to guide development of paediatric medicines. The customised data extraction table used within this review included a quality section where the robustness of the evidence collected was categorised according to the type of data presented. A summary of the criteria used to categorise evidence in terms of setting acceptability criteria is presented in Table 2.

Table 2 Categorisation of evidence to support defining acceptable limits for paediatric medicines

Type of evidence	Category of evidence	Setting acceptable limits
Peer-reviewed study specifically evaluating evidence of acceptability in children	Strong	Appropriate to set acceptability criteria
Data from a paediatric investigation plan (PIP) or PIP review suggesting acceptability in children	Medium	Likely to be appropriate to set acceptability criteria
Peer-reviewed study evaluating acceptability in a non-paediatric population		
Data from paediatric medicines approved before the need for a PIP	Weak	Although used in clinical practice may be insufficient to set acceptability criteria
Unsupported statements within the literature	No evidence	Insufficient to set acceptability criteria

Several literature sources include statements about the acceptability of particular medicines in paediatric populations, many of these are based on the authors' experience, as clinical practitioners or in other roles and there are no reported data to support these statements. In terms of regulatory requirements, it is considered essential to demonstrate acceptability; therefore, such assumptions based on experience are unlikely to be appropriate in setting acceptability criteria.

Results

Literature reports that define acceptability

Figure 1 shows the results of the search and the screening of literature to identify studies to include in this review. Twenty-nine papers were found that met the criteria to be classified as strong evidence in determining the acceptability of paediatric medicines; full details of these studies are included as Table S1.

Scale methods were typically used to assess acceptability or palatability with visual analogue scales and hedonic scales being the most common. Other methods used focused on a forced choice or preference between multiple products to rank order in terms of taste or a simple question as to whether the child would be prepared to take the medicine again (e.g. Refs [7,8]). One study evaluated the

time taken for a nurse to administer the medicine as a measure of acceptability where it was stated that the average administration time was 60 s.^[9] Although measures of acceptability and palatability are reported, there are very few studies that define the limits or criteria for 'acceptable' products. The information in Table 3 reports the information available on what the criteria for definition of acceptability was within published literature.

Interpretation of acceptability data is complex as there are many different tools and criteria reported in the existing literature.

Analysis of strong literature evidence on acceptability

Monolithic solid dosage forms

Seven sources of strong evidence on the acceptability of conventional monolithic dosage forms were identified and a further five that related to minitables (Table S1). Only one study compared the acceptance of two different-sized dosage forms (capsules size 2 vs size 0) as anticipated the smaller capsule was preferred and resulted in increased compliance.^[20] Studies investigating solid dosage forms that are small in size (2–3 mm), recognised as minitables, indicate that such formulations may be accepted by children from birth (see Table 4).

Tablets up to 8 mm in diameter were demonstrated to be acceptable (able to be swallowed whole) in children as young as 2 years of age.^[16,21,22] The number of tablets that could be swallowed was only investigated for the minitables, where Kluk *et al.*^[15] demonstrated that up to 10 minitables were acceptable to children from 2 years of age when they were suspended in jelly to aid administration. About 58% of children aged 2–3 were able to swallow 10 minitables without chewing; many other children chewed the tablets, which may limit their use to palatable immediate release formulations.

Tablets were demonstrated to be preferred to alternative formulations (powders and liquids) in four studies.^[14,23–25] In a study conducted by Musiime *et al.*,^[26] minitables of lopinavir/ritonavir were preferred by children (aged 6 months–6 years) in comparison with a syrup and a conventional tablet. Children who could swallow conventional tablets preferred these to minitables due to the taste of the minitables. The dimensions of the conventional and minitables were not reported by the authors.^[26]

Multiparticulate solid dosage forms to be swallowed

Five sources of strong evidence were identified (Table S1) all of which concluded that sprinkle/granule formulations

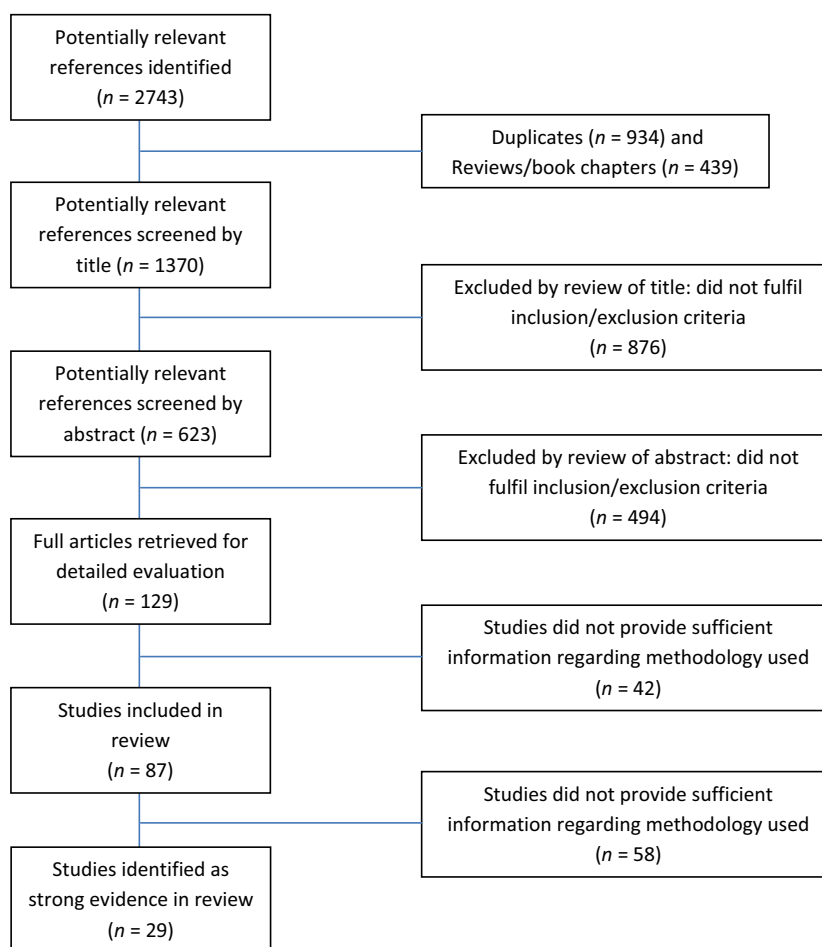


Figure 1 Flow diagram of study identification and selection.

were well-accepted by children from 3 months of age.^[10,26–29] The studies also showed a preference for multiparticulates over oral liquids. The size of multiparticulates or volume administered was not reported within most of the studies.

Motte *et al.*^[10] reported a study to measure the acceptability of prolonged release multiparticulates of sodium valproate; the particles had a diameter of <400 µm; although these were well-accepted in children (84.1% of under 5s and 78.4% of over 5s reported it as acceptable) in cases where parents struggled to treat children, 90% reported that the consistency of the product was the main issue.

In a study to compare iron oral drops to multiparticulate sprinkles in children, 92% expressed a dislike for the drops by closing their mouth tightly or pulling a face, whereas only 6.5% objected to taking the multiparticulate product,^[28] and this difference is attributed to the preference of taste of multiparticulates. A study on 53 children (mean age 6.7 years) revealed that multiparticulates were judged to be significantly more palatable compared to the oral liquid both by children and their parents.^[27]

Solid dosage forms to be retained/dispersed/solubilised in the mouth (tablets, films, wafers, lozenges)

Dosage forms to be retained/dispersed in the mouth are becoming more popular as a formulation for children. Strong evidence identified included the following: three studies on orally dispersible tablets^[7,30,31] and one on a lozenge.^[13]

Orally dispersing tablets (ODT) of desmopressin were favoured compared to conventional tablets in a study of 211 children aged 5–15 years.^[30] This preference was related to age with those under 12 years showing a statistically significant preference for the ODT product.^[30] A strawberry flavoured ODT was preferred to a peppermint flavoured syrup in children aged 4–8 years; this difference may be associated with the flavour rather than the dosage form itself.^[31] Cohen investigated the taste and acceptability of ondansetron ODT compared to a placebo ODT. Each child was asked to evaluate the tablet according to taste, sensation and willingness to take the medication in future.

Table 3 Summary of criteria for acceptability as defined within studies

Defined limit of acceptability (or equivalent)	Study reference
In a 2 face hedonic, these were considered as acceptable or not; in the 4 face hedonic, this was also the case for the negative two being unacceptable and positive 2 being acceptable	[10]
Carers needed to state that the product was equally or more acceptable to their child than other medicines (70% of population agreeing was used as basis for statistical powering)	[11]
Two products were included that were stated to be acceptable and unacceptable in terms of taste using a 5 point hedonic scale from 1 worst to 5 best	[12]
Acceptable taste = mean score of 3.4 in a five-point hedonic scale	
Unacceptable taste = mean score of 2.1 in a five-point hedonic scale	
Primary endpoint (of acceptability) was % of participants with a score of >4 on the seven-point hedonic scale	[13]
Ability to swallow the dosage form whole (observed to look for chewing, choking, aspiration)	[14–19]

About 87% of the 31 children aged 5–11 stated that they would be willing to take the ondansetron tablet again which was the measure of acceptability of this dosage form used within this study.^[7] Overall ODTs appear to be an acceptable dosage form in children over 5 years of age provided they include appropriate flavouring agents.

Thompson *et al.*^[13] compared the taste of strawberry vs orange lozenges in children aged 6–12 years. Both were judged to be acceptable, where the product was ranked as 'good', 'really good' or 'supergood' by 85.3% of participants for strawberry and 49% for orange flavour; in addition, 94% were willing to take strawberry product again and 56% willing to take orange product again.

Liquid dosage forms, solutions, suspensions

Dispersible, soluble and effervescent tablets are solid dosage forms which can be dispersed or dissolved in a liquid to form a solution or suspension. These dosage forms require effective taste masking and have similar critical quality attributes for acceptability as liquids as they are administered as a liquid to the patient. Administration of tablets predispersed on a spoon was reported in two studies; this type of formulation has the benefits of stability of a tablet with the administration being akin to a liquid which is more familiar to some children and offers benefits to younger children. The overall acceptability was good although there were reports of dispersion on the spoon being awkward for parents.^[32]

The acceptability criteria for taste varied between studies: a hedonic score greater than neutral was considered

Table 4 Literature data on acceptability of tablet/capsule size (including minitables) by age in paediatric populations

Age (years)	Dimensions swallowed (including chewing/splitting)	Dimension swallowed whole
Neonate (under 28 days)	2 mm ^[23]	82.2% can swallow 2 mm ^[23]
0.5	2 mm ^[14,17]	70% can swallow 2 mm ^[17]
1	4 mm ^[24]	60% can swallow 2 mm ^[17]
2	2–3 mm ^[15]	40% can swallow 2 mm ^[17] ~60% can swallow 2–3 mm ^[15] 46% can swallow 3 mm ^[18] >80% can swallow 5 mm ^[16] Can be trained to swallow tablets up to 7–8 mm ^[16]
3		50% can swallow 2 mm ^[17] 53% can swallow 3 mm ^[18] >80% can swallow 17.6 mm (size 2 capsule) ^[20]
4		>75% can swallow 2 mm ^[14] 80% can swallow 2 mm ^[17] >80% can swallow 7 mm ^[21]
5		100% can swallow 2 mm ^[17] 85% can swallow 3 mm ^[18]
6		91% can swallow 7 mm ^[22]

acceptable in one case,^[8] whereas a hedonic score of 2.7/5 (which is beyond neutral) was reported for a product known to be unacceptable in another study.^[12] Hedonic scores were also used to rank the smell of four antibiotic suspensions: cefdinir, amoxicillin/clavulanate, cefprozil and azithromycin.^[33] The resulting mean scores (of 5) for each drug were the following: cefdinir = 3.97, amoxicillin/clavulanate = 3.37, cefprozil = 3.95 and azithromycin = 3.95, and all products were rated as having an acceptable smell within this study. The percentage of participants agreeing a product was acceptable was also used as a measure within studies, and the lowest percentage in agreement where the product was concluded to be acceptable was 70.5%.^[32]

The volumes of liquid reported to be acceptable were 0.5 ml for neonates,^[23] 2.5 ml for children from 1 to 4 years^[24] although only 36–72% of children aged 0.5–6 years were able to fully swallow 3 ml of syrup.^[14]

In studies where the liquid was a comparator, the alternative formulations were typically preferred: ODTs,^[31] multiparticulates^[10,26–29] and minitables.^[17]

Discussion

Analysis of all evidence on acceptability

For this review, strong evidence was defined (Table 2) as a peer-reviewed study that included data that specifically

evaluated acceptability of medicines within a paediatric population; the definition did not explore methodology, sample size, settings, etc. as this was outside of the scope of this review (although some study details are included in Table S1). This evidence was judged to be strong as the study required ethical approval as well as peer review before publication; therefore, the results and conclusions have been externally validated.

Monolithic solid dosage forms

Size and shape

Problems relating to the sizes of solid dosage forms or swallowing medicines have been reported in several studies,^[34–39] yet the dimensions of the solid dosage forms were not specified in these reports. ‘Pill-swallowing’ studies conducted in children and young people with HIV have identified that young people fear that solid dosage forms may ‘get stuck’ or cause choking.^[40,41] Solids are only usually acceptable postweaning.^[42] The age at which most children acquire the skills to swallow tablets and capsules safely has been subject of much debate. Paediatric literature widely quotes 6 years as a general age from which solid monolithic dosage forms are considered suitable for children.^[43] Some children may already have acquired the ability to swallow tablets and capsules from an earlier age or can be taught using behavioural training interventions. For example, Yeung and Wong^[44] 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).^[45]

In a review of approved PIPs for children aged 0–11 years, 37 approved PIPs for monolithic tablets were reported.^[46] Size data were available on 24 of these tablets, where two were small (0–4 mm), 15 were medium-sized (5–9 mm) and four were large (>10 mm). There was little information on how age correlated to tablet size within this article although it was stated that two PIPs have been agreed with tablets from 0 to 4 mm for children aged 2–5 years. The shape of tablets in approved PIPs was reported for 21 of the 37 approved monolithic tablets, 12 were round, eight were oblong/caplet/oval and 1 was a specified other shape.^[46]

An evaluation of PIPs conducted by regulators concluded that it is now increasingly accepted that small (0–4 mm) tablets may be applicable in young children (2–5 years), yet the use of medium-sized tablets (5–9 mm) in this age group (2–5 years) is still discouraged, whereas the use of large-sized tablets (>10 mm) is generally considered unacceptable because of swallowing difficulties and the

risk of choking.^[46] Minitablets are often chewed by children; therefore, it may be prudent to consider the development of harder tablets if chewing is to be discouraged (although it is important to also recognise the risk of dental damage or choking with harder non-chewable tablets). The EMA Paediatric Committee’s (PDCO’s) Formulation Working Group (FWG) recommend that for younger patients, those aged 6–8 years, tablets of 6–7 mm with appropriate shape are acceptable.^[47]

It is reported to be acceptable for patients/carers to split tablets if score lines provide equal amounts^[48]; there is evidence from PIPs that tablets with a score line have been approved.^[46] PIPs have been approved for tablets larger than 5 mm for children aged 2–5 years and tablets larger than 10 mm for children aged 6–11 years.^[46] The majority of these larger tablets were reported to be immediate release and film-coated tablets that may be broken, crushed or chewed, unless bioavailability or patient acceptability is affected.

Number of units per dose administration

Problems associated with the quantity of solid dosage forms in children have been reported previously, typical issues raised were tablet quantity or too much medication (e.g. Refs [34–36,49–51]). The quantity of solid dosage forms was reported as a main problem when administering medicines to patients with HIV.^[51]

In a study by Adams *et al.*,^[52] the number of tablets that parents/caregivers and healthcare workers thought was acceptable for children in Tanzania to take as a single dose was reported. Typically, one tablet was felt to be most appropriate for children in early years of primary school (under 8 years) rising to two tablets in last years of primary school (9–12 years). The total number of tablets per day rose to 3–6 for those in early years at primary school and up to 6–9 for older children.

Van de Vijver *et al.*^[53] reported that the overall acceptability of Creon capsules (capsule size not stated) decreased as the number of capsules to be taken increased, although the actual number of capsules was not reported. The PDCO FWG state that the number of tablets, capsules or particles to be administered must be easy to count and to administer (e.g. 1–3 tablets).^[47]

Taste and aftertaste of uncoated dosage forms

There are limited reports of the poor taste of solid dosage forms; an example is the taste of nelfinavir tablets,^[54] although these are coated rather than uncoated tablets. Typically neutral tasting medicines have been proposed by the EMA for use in children particularly in the treatment of chronic conditions.^[3]

Acceptable parameters for monolithic solid dosage forms

In terms of evidence to support acceptability of monolithic dosage forms, the information in Table 5 provides a summary of parameters likely to be acceptable to paediatric populations.

Multiparticulate solid dosage forms to be swallowed

Particle size, texture and hardness

For solid oral multiparticulate dosage forms, important texture attributes include roughness, hardness, fracturability and cohesiveness, depending on the specific form.^[55]

Based on recent FDA guidance, multiparticulates which 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.^[56] They report that this size should ensure adequate mouthfeel and reduce the risk of inadvertent chewing although it is not stated whether this is based on adults or a paediatric population. The multiparticulate sizes used in approved modified release capsules labelled for sprinkling on food was reported; the majority of products had multiparticulate sizes of <1.5 mm.^[57]

The administration may also impact upon the mouthfeel, for example products administered directly into the mouth are likely to feel more gritty than those

mixed with soft food before administration. Lopez *et al.*^[58] assessed the mouthfeel of spherical cellulose multiparticulates dispersed in liquids in young adults using a VAS from very smooth to very gritty. As anticipated, the grittiness perception increased with both concentration and particle size and the most pleasant samples were associated with a low grittiness score. Kimura *et al.*^[55] evaluated the mouthfeel of particles of a range of sizes in adults; the results showed that the score of roughness increased within increasing particle size; typically particles >300 µm were scored poorly.

Taste and aftertaste

The modified release granule formulation of valproate (Depakine® Chronosphere®) was designed to be a tasteless multiparticulate product to avoid issues with palatability that were observed with the liquid product.^[27] Several studies have investigated the acceptability of micronutrient powders delivered as a multiparticulate sprinkle (e.g. Refs [59,60]); a major finding in these studies are that parents like the product as it is neutral tasting with a neutral smell and does not affect the taste of food with which it is administered.

Dose volume (quantity)

Children with cystic fibrosis (CF) are recommended to take lipase doses of 400–800 units per gram of ingested fat; in an infant of 10 kg (2 years old), this equates to eight scoops of

Table 5 Proposed acceptable tablet/capsule parameters based on ages of paediatric populations. Strong evidence is coloured green; medium evidence is orange; weak evidence blue and no evidence is grey

Product attribute	Available evidence of acceptability			
	Neonates (<1 month)	Infants (1 month – 2 years)	Child (2–5 years)	Child (6–11 years)
Size	2 mm ^[23]	2 mm ^[17]	2 mm ^[14,17] 3 mm ^[18] 5 mm ^[16] 7 mm ^[21] 17.6 mm ^[20a]	3 mm ^[18] 7 mm ^[22] 9 mm ^[46] 12.1 × 4.2 mm
Shape	Not appropriate	Round ^[46]	Round ^[46]	Round/oblong/caplet/oval ^[47]
Number of units per dose	Not appropriate	1 ^[52] 3 ^[47]	1 ^[52] 3 ^[47] 10 (minitablets in jelly; total volume < 5 ml) ^[15]	1–2 ^[52] 3 ^[47]
Taste and aftertaste of uncoated dosage forms	Not appropriate	Neutral ^[27]	Neutral ^[27]	Neutral ^[27]

^aThis size capsule was acceptable to children with cystic fibrosis who are used to taking monolithic dosage forms; there is no evidence on acceptability in other paediatric populations.

multiparticulates (each scoop holds 100 mg) of Creon[®] for children to be administered daily with meals. Nelfinavir is administered in large volumes, for instance, at the dose of 55 mg/kg BID, an average 6 year old is required to take 25 scoops (each scoop contains 50 mg; total administered is 1250 mg) of Nelfinavir powder, twice a day with food. This 'large volume' of Nelfinavir powder was reported to be challenging for parents to administer.^[61]

Delivery device

The EMA Paediatric Committee's (PDCO's) Formulation Working Group (FWG) recommend that an appropriate dispensing device should be available to enable measurement of the required doses and to count multiparticulates.^[47] Infants and children with CF are recommended to take lipase doses of 400–800 units per gram of ingested fat; this is delivered either using Creon[®] capsules (often split and emptied in part) or Creon[®] for children is a bulk container of mini multiparticulates with a dosing scoop that delivers 5000 lipase units per scoop (each scoop holds 100 mg). A study that compared parents (of children aged 6–36 months) preference for each dosage form reported that the use of the scoop with the Creon[®] product was easier than opening capsules and that it was easier to measure the correct dose.^[62]

Dose sipping technology has been developed to deliver a single dose of small-sized pellets, overcoming swallowing issues.^[17,63] This technology incorporates small-sized pellets in a straw; when the child holds the straw in a beverage and sips, the drug is delivered in a 'user friendly' way. The Coni-Snap[®] sprinkle capsule has been developed which is easy to open providing a useful delivery device for multiparticulates.^[64]

Acceptable parameters for multiparticulate solid dosage forms

The parameters for multiparticulates that are likely to be acceptable in paediatric populations are summarised in Table 6.

Solid dosage forms to be chewed

Size and shape

No strong evidence was identified on the acceptable size of tablets designed to be chewed (as compared to conventional tablets that may be chewed by patients). Commercially available chewable tablets range from 9.5 mm for montelukast tablets^[65] for children over 2 years to 14.7 mm for simethicone tablets for children over 6 years.^[66]

Taste, aftertaste and mouthfeel

Historically, the majority of oral chewable dosage forms have been hard and leave residual particles in the mouth and teeth, which are features that children find unpleasant. Wiet *et al.*^[67] reported that softer chewy textures are preferred by children to harder, crunchier OTC medicine forms, although this study was based on opinions and not exposure to dosage forms.

There are many over the counter fruit-flavoured vitamin tablets for children that are soft and designed to be chewed. These are generally acceptable to children and they constitute a significant commercial market.

Time needed to chew and effort required to chew

In typically developing children, primary teeth begin to erupt from 6 months of age and the complete set of

Table 6 Proposed acceptable multiparticulate parameters based on ages of paediatric populations. Strong evidence is coloured green; medium evidence is orange and no evidence is grey

Product attribute	Available evidence of acceptability			
	Neonates (<1 month)	Infants (1 month–2 years)	Child (2–5 years)	Child (6–11 years)
Size			<400 µm ^[10] <300 µm ^[55] 2.5 mm ^[56]	<400 µm ^[10] <300 µm ^[55] 2.5 mm ^[56]
Shape		Round	Round	Round
Number of units				
Taste and aftertaste of uncoated dosage forms		Neutral ^[27]	Neutral ^[27]	Neutral ^[27]
Texture (grittiness)				
Dose volume				
Measuring device		Scoop preferred to capsule ^[62]	Scoop preferred to capsule ^[62]	Scoop preferred to capsule ^[62]

20 have usually erupted between the ages of 2 and 3 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.^[68] It has been reported that soft chewable dosage forms such as gelatine gummy sweets may be easier, more appealing and natural to chew for children, compared to a chewable tablet.^[69]

Researcher observational analysis discovered that children under 2 years with neuroblastoma found it easier to chew tablets as they were unable to swallow the tablets whole.^[70] Chewable tablets of Montelukast were preferred to inhale cromolyn in a study of 266 children aged 6–11 years, although there were no details on the formulation to report whether this was just a preference for oral therapy compared to inhale or whether the chewable tablet was particularly preferred.^[71]

Solid dosage forms to be dispersed/solubilised/eroded in the mouth (tablets, films, wafers, lozenges)

Size and shape

No data exist on the acceptable size of orodispersible tablets. Commercially available ODT have diameters ranging from 9 to 17.5 mm. Products licensed for use in children have diameters of 9.5 mm for acyclovir used in children over 2 years^[72]; Ondansetron dispersible tablets are licensed for use in children over 6 months and the Ratiopharm product has a diameter of 6.5 mm.^[73] FDA guidance suggests that the weight of ODTs should be <500 mg, this is based on all ODTs and not just those designed for use in paediatric populations.^[74]

There are limited published data on acceptable sized dosage forms that can be retained within the mouth for erosion. There are several marketed medicinal products that are used in paediatric populations as well as nutraceutical and vitamin products. Confectionary is known to be well-accepted in children and there may be extensive knowledge on preferred size and shape by age that could be used to inform the development of paediatric formulations. The size of the dosage form should be appropriate for the size of the oral cavity of the child.

Ondansetron oral films (Setofilm[®]) are listed in the BNF-C for use in children over 6 months; these are 3 cm² films that contain 4 mg drug^[75]; fentanyl buccal films are also listed in the BNF-C which range up to 3.11 cm².

Flurbiprofen lozenges are licensed for use in children and these are 19 mm in diameter, although they are only licensed for use in children over 12 years of age.^[76]

Taste and aftertaste and mouthfeel

The taste of ODTs is important in maintaining acceptability for children. There have been very few studies on the taste of this type of dosage form.

The mouthfeel of ODTs has not been reported in the literature although it would seem sensible to consider similar-sized particles to those delivered as multiparticulate dosage forms are likely to be acceptable. The granule size within ODT formulations was acceptable up to 244 µm based on a study conducted in adults.^[55]

Over the counter lozenges and films are available for children, and these are typically fruit-flavoured products containing vitamins and other supplements rather than medicines.

Time needed to dissolve/disperse

FDA guidance defines an ODT as, 'A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue'. The time taken for disintegration must be 30 s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative.^[74] No literature was found on in-vivo dispersion times in children although studies conducted in adults have reported times of 29.4 s for complete oral disintegration of risperidone tablets^[77,78] and 58 s for olanzapine tablets.^[78] Although orally dispersible tablets can be taken without water, a study on Desmopressin revealed that 13% of children did take the ODT with water^[30] compared to 77% with the conventional tablet formulation.

The European Pharmacopoeia states that orally dispersing films should 'disperse rapidly', no further information is provided regarding timelines for disintegration *in vivo* and how the disintegration should be affirmed *in vitro*.^[79]

Orally eroding dosage forms can be manufactured to provide a range of erosion times to suit drug release and subsequent therapy. There are no data on acceptable erosion times in paediatric populations.

Liquid dosage forms, solutions, suspensions

Taste and aftertaste

The taste of medicines and how this is evaluated has previously been reported.^[80] There are several examples of work has been carried out on the assessment of medicine taste (e.g. Refs [81–84]). Brand names are rarely reported within the literature which limits the direct comparison between studies as it is already known (and the focus of several studies) that therapeutic equivalents can have very different tastes (e.g. Refs [12,13,85–94]). Evaluating an acceptable

taste is difficult, the consensus from previous data seems to suggest that a better than neutral response to a taste is an acceptable taste.

Smell

The literature evidence on perceptions regarding the smell of medicines is limited. Esteban Gomez *et al.*^[95] reported problems with smell on an average scaled measure ranging from 0 to 5 (0 = causing no difficulties 5 = causing maximum difficulties with adherence). The average smell scores were reported for the liquid: reverse transcriptase inhibitors and protease inhibitors as 0.3 and 2.1, respectively. The study found that the smell of protease inhibitors caused moderate difficulties with adherence.^[95]

Volume

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.^[96] 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.^[97]

The EMEA report that typical target dose volumes should be <5 ml for children under 5 years and <10 ml for those 5 years and older.^[43] Yet, there are examples of larger volumes used with children routinely. Paracetamol suspension is available as 120 mg/5 ml or 250 mg/5 ml products, and the recommended dose for a child of 2–3 years is 180 mg; this is likely to be administered as 7.5 ml of the 120 mg/5 ml product.^[75]

Yeung and Wong^[44] postulated that it may be the volume of liquid that is taken that drives the conversion to solid dosage forms for children with HIV. The data in Table 7 provide some support that large volumes are not well-accepted, although there are other factors including the taste of the liquids as well as its portability that also need to be considered. In addition, there was no report as to whether the tablets/capsules were taken whole or manipulated before administration once the child converted to the solid dosage form.

The major difference in products that require reconstitution by the patient is the volume of liquid consumed as this is typically much larger than ready to use liquid products. Research conducted in oral rehydration and activated charcoal preparations has shown that children struggle to

swallow large volumes of unpleasant tasting liquids.^[98,99] Typical instructions for reconstitution are to disperse into a glass of water before drinking; therefore, a reasonable volume would be 100 ml or smaller if possible.

Mouthfeel/texture

There are very limited reports on the influence of texture of medicines; Allué *et al.* (2012) evaluated the organoleptic properties of oral rehydration solutions in children, including the influence of texture by comparing a 'gelatine' and 'gel' texture; their results showed that the 'gel' texture was preferred, although no further details on this finding were provided.^[100] The need to improve the texture of medicines was also highlighted for antiretroviral therapies,^[50,95] although details on textural issues were not explicitly reported.

There are no reports on the ideal mouthfeel of a liquid medicine; yet it is intuitive to suggest that this needs to be smooth and in the case of a bad tasting medicine, a product that is swallowed rapidly and leaves minimal residue on the oral cavity surfaces. Positive attributes of oral formulations reported in a recent study described good textures as being 'sherbet' and 'fizzy'.^[101]

A recent study investigated barriers to medicines administration in children and although taste was the most reported issue in medicines, refusal texture was the next most frequent reason for refusal.^[102] Specific medicines identified with textural issues included lactulose which was described as 'oily' and co-trimoxazole liquid described as 'thick and gelatinous'.^[101]

Need for a measuring device and ease of preparation

Liquids are typically administered via an oral syringe or medicine spoon. It is essential that the dose is measurable for all patients; there have been literature reviews published recently on this topic (e.g. Ref. [103]). The device supplied must be appropriate for the product and the doses required by the patient.

Acceptable parameters liquid dosage forms

In terms of evidence to support acceptability of liquid formulations, the information in Table 8 provides a summary of parameters likely to be acceptable to paediatric populations.

Conclusions

Although there have been many reports on the acceptability of medicines to paediatric populations, there are still major

Table 7 Formulation factors and the age of conversion from a liquid to a solid formulation as reported by ref. [44] Product details and doses are based on a 6-year-old, 20-kg child referenced from the BNF-C^[75]

Drug	Dose	Age of conversion (years)	Solid product details	Liquid product details
Stavudine	20 mg twice daily	3.6	20 mg capsule 17.5 × 6.1 mm	1 mg/ml solution 20 ml twice daily
Abacavir	150 mg twice daily or 300 mg once daily	9.2	300 mg tablet	20 mg/ml 7.5 ml twice daily
Didanosine	250 mg daily	7.2	250 mg capsule 19.3 × 6.7 mm	20 mg/ml 12.5 ml daily
Lamivudine	75 mg twice daily or 150 mg once daily	10	150 mg tablet (scored) 13.9 × 6.9 mm	50 mg/5 ml 7.5 ml twice daily
Zidovudine	100 mg in the morning 200 mg in the evening	6.9	100 mg capsule 15.7 × 5.8 mm	50 mg/5 ml 10 ml in the morning 20 ml in the evening

Table 8 Proposed acceptable liquid parameters based on ages of paediatric populations. Strong evidence is coloured green and no evidence is grey

Product attribute	Available evidence of acceptability			
	Neonates (<1 month)	Infants (1 month – 2 years)	Child (2–5 years)	Child (6–11 years)
Volume	<0.5 ml ^[23] <5 ml ^[43]	2.5 ml ^[24] ≤5 ml ^[43]	2.5 ml ^[24] ≤5 ml ^[43]	≤10 ml ^[43]
Mouthfeel Taste and aftertaste			Score >50 mm on a VAS or neutral to positive in a hedonic scale in at least 70% of test population ^[10,12,104]	Score >50 mm on a VAS or neutral to positive in a hedonic scale in at least 70% of test population ^[10,12,104]
Smell	Neutral smell	Neutral smell	At least 70% of test population score smell as good or really good ^[33] Neutral smell	At least 70% of test population score smell as good or really good ^[33] Neutral smell

gaps in the knowledge base. The findings from this review highlight the gaps in knowledge where additional research is required to better understand acceptability of paediatric medicines.

Although taste/palatability has been the most extensively studied area of paediatric medicine acceptability, there are still no recommended standard methods or criteria that define what is classed as an acceptable liquid or what flavours are acceptable to children. A defined methodology or standard needs to be identified to support acceptable palatability claims in paediatric products. Many palatability studies have been conducted in Western populations, and there is a need to ensure that flavours are acceptable where products will be distributed globally. It is also essential to recognise that palatability is broader than taste, and the impact of smell and texture should not be ignored.

Studies undertaken that assess the acceptability of dosage forms in paediatric populations often do not report key

critical attributes of the formulation under test which limits the breadth of their utility. Studies should report a greater level of detail on formulation attributes. Primary research is required to define the acceptability of the following: the volume of liquid administered, the volume of multiparticulates administered, the dimensions of tablet and minitables (including those designed to be retained in the mouth), the size of multiparticulate granules, the time that products should be retained in the mouth and the number of tablets dosed at each time point.

Major gaps exist in the dimensions and number of monolithic solid oral dosage forms that are acceptable to children across all age ranges. Further primary research is required to best understand the minimum age at which tablets are likely to be accepted as this option often offers a simple option in providing medicines to children.

Multiparticulate dosage forms are typically of interest as they combine the stability of solid dosage forms with the flexibility of liquids. Research is required to better

	Liquid (including dispersible tablet or granules for reconstitution)	Conventional or mini monolithic tablet	Multi-particulate	Orodispersible tablet	Chewable tablet
Will the medicine be used to treat neonates? →Yes→ ↓ No ↓	<0.5 mL volume Neutral taste	2 mm minitab acceptable	X	X	X
Will the medicine be used to treat infants? →Yes→ ↓ No ↓	<2.5 mL volume Neutral taste	<3 mL tablet Up to 3 tablets per dose	Neutral taste	<6.5 mm tablet Neutral taste	X
Will the medicine be used to treat children aged 2-5 years? →Yes→ ↓ No ↓	<2.5 mL volume Neutral taste	Up to 10 minitab acceptable <4 mm tablet Up to 3 tablets per dose	Neutral taste	<9.5 mm tablet Neutral taste	<9.5 mm tablet Neutral taste
Will the medicine be used to treat children aged 6-12 years? →Yes→	<10 mL volume Neutral taste	<7 mm tablet Up to 3 tablets per dose	Neutral taste	<9.5 mm tablet Neutral taste	<14.7 mm tablet Neutral taste

Figure 2 Proposed (based on the evidence in this review) algorithm to select an acceptable age-appropriate medicine.

understand the impact of particle size, volume administered and method of administration in determining the acceptability of multiparticulates to children although the evidence to date looks promising.

Dispersible tablets, such as multiparticulates, offer benefits of both solid and liquid dosage forms. There are products that disperse in a small volume (<5 ml), directly within the mouth or within a glass of water. The taste of these products is typically the key attribute investigated, yet it is important to also consider additional aspects of orally disintegrating products including the dimensions and duration for retention. The evidence suggests that with appropriate taste masking, orally dispersible tablets can be acceptable to children over 5 years of age.

The PDCO FWG recommend that acceptability, including palatability testing, should be performed during clinical trials in target patients’ population.^[47] This encourages acceptability testing to be conducted as part of the clinical development of a product, yet it is important that product

development follows the path where the final product is likely to be acceptable to the relevant population to avoid delays in the availability of age-appropriate medicines to children.

The evidence within this review was used to create an algorithm that may help in the design of age-appropriate medicines (Figure 2). It is envisaged that this algorithm will be useful to those developing oral medicines for children to ensure they select a formulation that is likely to be acceptable to the patient. It is anticipated that this algorithm will be developed further as more evidence becomes available.

It is essential that high-quality research is undertaken to address current gaps in knowledge to ensure that efforts in development are focussed on products that are highly likely to be acceptable to the relevant paediatric population. The output of studies on acceptability needs to be disseminated in peer-reviewed journals and include sufficient detail on the formulation attributes to understand acceptability of medicines to children.

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References

1. EMEA. Reflection paper: formulations of choice for the paediatric population EMEA/CHMP/PEG/194810/2005. London, 2006 [Feb 2015]; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf. (accessed May 2016).
2. EMA. Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012. London, 2013 [31/04/2013]; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf (accessed May 2016).
3. EMA. Guideline on pharmaceutical development of medicines for paediatric use. Draft. 2013; EMA/CHMP/QWP/805880/2012 Rev. 1, Committee for Medicinal Products for Human Use (CHMP); Paediatric Committee (PDCO). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137023.pdf (accessed May 2016).
4. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm* 2014; 469: 245–248.
5. Salunke S *et al.* European Paediatric Formulation Initiative's (EuPFI) 2nd conference commentary – formulating better medicines for children. *Int J Pharm* 2011; 419: 235–239.
6. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration, 2011 Version 5.1.0 [updated March 011]. Available at: www.cochrane-handbook.org. (accessed May 2016).
7. Cohen IT *et al.* Ondansetron oral disintegrating tablets: acceptability and efficacy in children undergoing adenotonsillectomy. *Anest Analg* 2005; 101: 59–63.
8. Mulla H *et al.* 'Acceptability' of a new oral suspension formulation of mercaptopurine in children with acute lymphoblastic leukaemia. *J Oncol Pharm Pract* 2015; 22(3): 387–395.
9. Uhari M *et al.* Acceptance of antibiotic mixtures by infants and children. *Eur J Clin Pharmacol* 1986; 30: 503–504.
10. Motte J *et al.* Acceptability and tolerance of sodium valproate, a new sustained-action granule formulation, in monotherapy for epileptic children from 3 years old. *Arch Pediatr* 2005; 12: 1533–1539.
11. Nasrin D *et al.* Acceptability of and adherence to dispersible zinc tablet in the treatment of acute childhood diarrhoea. *J Health Popul Nutr* 2005; 23: 215–221.
12. Sjövall J *et al.* Methods for evaluating the taste of paediatric formulations in children: a comparison between the facial hedonic method and the patients' own spontaneous verbal judgement. *Eur J Pediatr* 1984; 141: 243–247.
13. Thompson A *et al.* Open-label taste-testing study to evaluate the acceptability of both strawberry-flavored and orange-flavored amylmetacresol/2,4-dichlorobenzyl alcohol throat lozenges in healthy children. *Drugs R D* 2013; 13: 101–107.
14. Klingmann V *et al.* Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. *J Pediatr* 2013; 163: 1728–1732.e1.
15. Kluk A *et al.* Can preschool-aged children swallow several minitables at a time? Results from a clinical pilot study. *Int J Pharm* 2015; 485: 1–6.
16. Kreeftmeijer-Vegter AR *et al.* Development and evaluation of age-appropriate film-coated tablets of levamisole for paediatric use (2–18 years). *Expert Opin Drug Deliv* 2013; 10: 293–300.
17. Spomer N *et al.* Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch Dis Child* 2012; 97: 283–286.
18. Thomson SA *et al.* Minitables: new modality to deliver medicines to preschool-aged children. *Pediatrics* 2009; 123: e235–e238.
19. Mekmullica J, Pancharoen C. Acceptability of oral typhoid vaccine in Thai children. *Southeast Asian J Trop Med Public Health* 2003; 34: 334–336.
20. Patchell CJ *et al.* Creon 10,000 Minimicrospheres vs. Creon 8,000 microspheres – an open randomised crossover preference study. *J Cyst Fibros* 2002; 1: 287–291.
21. Kokki H *et al.* The feasibility of pain treatment at home after adenoidectomy with ketoprofen tablets in small children. *Paediatr Anaesth* 2000; 10: 531–535.
22. Meltzer EO *et al.* Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr* 2006; 45: 725–733.
23. Klingmann V *et al.* Acceptability of uncoated mini-tablets in neonates – a randomized controlled trial. *J Pediatr* 2015; 167: 893–896.e2.
24. Van Riet-Nales DA *et al.* Acceptability of different oral formulations in infants and preschool children. *Arch Dis Child* 2013; 98: 725–731.
25. McCrindle BW *et al.* Acceptability and compliance with two forms of cholestyramine in the treatment of

- hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr* 1997; 130: 266–273.
26. Musiime V *et al.* The pharmacokinetics and acceptability of lopinavir/ritonavir minitab sprinkles, tablets, and syrups in african HIV-infected children. *J Acquir Immune Defic Syndr* 2014; 66: 148–154.
 27. Verrotti A *et al.* Effects of the abrupt switch from solution to modified-release granule formulation of valproate. *Acta Neurol Scand* 2012; 125: e14–e18.
 28. Zlotkin S *et al.* Use of microencapsulated iron(II) fumarate sprinkles to prevent recurrence of anaemia in infants and young children at high risk. *Bull World Health Organ* 2003; 81: 108–115.
 29. Cloyd JC *et al.* Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference. *J Pediatr* 1992; 120(4 Pt 1): 634–638.
 30. Lottmann H *et al.* A randomised comparison of oral desmopressin lyophilisate (MELT) and tablet formulations in children and adolescents with primary nocturnal enuresis. *Int J Clin Pract* 2007; 61: 1454–1460.
 31. Tolia V *et al.* Taste comparisons for lansoprazole strawberry-flavoured delayed-release orally disintegrating tablet and ranitidine peppermint-flavoured syrup in children. *Clin Drug Investig* 2005; 25: 285–292.
 32. Moniot-Ville N *et al.* The acceptability, efficacy and safety of a new paediatric oral suspension of roxithromycin in respiratory tract infections. *J Int Med Res* 1998; 26: 144–151.
 33. Powers JL *et al.* Comparison of the palatability of the oral suspension of cefdinir vs. amoxicillin/clavulanate potassium, cefprozil and azithromycin in pediatric patients. *Pediatr Infect Dis J* 2000; 12(Suppl): S174–S180.
 34. Buchanan AL *et al.* Barriers to medication adherence in HIV-infected children and youth based on self-and caregiver report. *Pediatrics* 2012; 129: e1244–e1251.
 35. Christiansen N *et al.* Oral chemotherapy in paediatric oncology in the UK: problems, perceptions and information needs of parents. *Pharm World Sci* 2008; 30: 550–555.
 36. Marhefka SL *et al.* Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP). *AIDS Care* 2004; 16: 323–338.
 37. Paranthaman K *et al.* Factors influencing adherence to anti-retroviral treatment in children with human immunodeficiency virus in South India – a qualitative study. *AIDS Care* 2009; 21: 1025–1031.
 38. Roberts KJ. Barriers to antiretroviral medication adherence in young HIV-infected children. *Youth Soc* 2005; 37: 230–245.
 39. Tucker CM *et al.* Associations with medication adherence among ethnically different pediatric patients with renal transplants. *Pediatr Nephrol* 2002; 17: 251–256.
 40. Czyzewski DI *et al.* Teaching and maintaining pill swallowing in HIV-infected children. *AIDS Reader* 2000; 10: 88–95.
 41. Garvie PA *et al.* Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics* 2007; 119: e893–e899.
 42. EMA. *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*. Draft. 2013;EMA/CHMP/QWP/805880/2012 Rev. 1; Committee for Medicinal Products for Human Use (CHMP); Paediatric Committee. (PDCO): Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137023.pdf (accessed May 2016).
 43. EMEA. Reflection paper: formulations of choice for the paediatric population. EMEA/CHMP/PEG/194810/2005. 2006. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf (accessed May 2016).
 44. Yeung VW, Wong ICK. When do children convert from liquid antiretroviral to solid formulations? *Pharm World Sci* 2005; 27: 399–402.
 45. Nahirya-Ntege P *et al.* Young HIV-infected children and their adult caregivers prefer tablets to syrup antiretroviral medications in Africa. *PLoS One* 2012; 7: e36186.
 46. Van Riet-Nales DA *et al.* Oral medicines for children in the European paediatric investigation plans. *PLoS One* 2014; 9(6): e98348.
 47. EMA. List of criteria for screening PIPs with regard to paediatric specific Quality issues and referring them to the PDCO FWG for discussion. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/01/WC500159380.pdf. (accessed May 2016).
 48. EMA. DRAFT Guideline on Pharmaceutical Development of Medicines for Paediatric Use EMA/CHMP/QWP/180157/2011 Committee for Medicinal Products for Human Use (CHMP), 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107908.pdf. (accessed May 2016).
 49. Boni S *et al.* Compliance to combination antiretroviral therapy in HIV-1 infected children. *Int J Antimicrob Agents* 2000; 16: 371–372.
 50. Gibb DM *et al.* Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J* 2003; 22: 56–62.
 51. Pontali E *et al.* Adherence to combination antiretroviral treatment in children. *HIV Clin Trials* 2001; 2: 466–473.
 52. Adams LV *et al.* Children's medicines in Tanzania: a national survey of administration practices and preferences. *PLoS One* 2013; 8(3): e58303.
 53. Van de Vijver E *et al.* Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. *J Pediatr Gastroenterol Nutr* 2011; 53: 61–64.

54. Reddington C *et al.* Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 2000; 19: 1148–1153.
55. Kimura S *et al.* Effect of granule properties on rough mouth feel and palatability of orally disintegrating tablets. *Int J Pharm* 2015; 484: 156–162.
56. Guidance for Industry Size of Beads in Drug Products Labeled for Sprinkle. 2012. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm240243.pdf> (accessed July 2016).
57. Nagavelli LR *et al.* Analysis of bead sizes for MR capsules labeled for sprinkle. *AAPS PharmSciTech* 2010; 11: 1508–1510.
58. Lopes F *et al.* Perception of oral grittiness: Influence of formulation variables. EuPFI annual meeting. 2014; Poster presentation.
59. Adu-Afarwah S *et al.* Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. *Am J Clin Nutr* 2007; 86: 412–420.
60. Tripp K *et al.* Formative research for the development of a market-based home fortification programme for young children in Niger. *Matern Child Nutr* 2011; 7: 82–95.
61. Van Dyke RB *et al.* Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics* 2002; 109: e61.
62. Munck A *et al.* Pancreatic enzyme replacement therapy for young cystic fibrosis patients. *J Cyst Fibros* 2009; 8: 14–18.
63. Ziegler IM. *Dose Sipping Technology – A Novel Dosage Form for the Administration of Drugs*. CRC Press, Boca Raton, Florida, USA: Modified-Release Drug Delivery Technology: 217–230.
64. Capsugel. Coni-Snap(R) sprinkle Qualitative Survey, 2013. Available at: <http://www.capsugel.com/ihc/coni-snap-sprinkle> (accessed January 2016).
65. Limited MSaD. Summary of Product Characteristics: Singulair Paediatric 5 mg chewable tablets, 2016. Available at: <https://www.medicines.org.uk/emc/medicine/17717> (accessed May 2016).
66. Limited FLU. Patient Information Sheet: Wind-Eze Tablets, 2014. Available at: <https://www.medicines.org.uk/emc/medicine/26521> (accessed May 2016).
67. Wiet SG, Bunick F. Paediatric oral solid dosage form preferences: A quantitative analysis among children and their parents. 3rd EuPFI annual conference, 2010; Available at: <http://www.eupfi.org/downloads/2nd%20conference%20Abstracts%20for%20Publication.pdf>.
68. Delaney AL, Rudolph C. Nascent oral phase. In: Shaker R, Belafsky PC, Postma GN, Easterling C, eds. *Principles of Deglutition*. New York: Springer, 2013: 151–162.
69. Mok M, Tuleu C. Development and Analysis of Medicated Soft Chew Dosage Form Suitable For Paediatric Use. EuPFI 3rd Annual Conference. 2010. Available at: <http://www.eupfi.org/downloads/2nd%20conference%20Abstracts%20for%20Publication.pdf> (accessed May 2016).
70. Veal GJ *et al.* Adaptive dosing approaches to the individualization of 13-cis-retinoic acid (isotretinoin) treatment for children with high-risk neuroblastoma. *Clin Cancer Res* 2013; 19: 469–479.
71. Volovitz B *et al.* Comparison of oral montelukast and inhaled cromolyn with respect to preference, satisfaction, and adherence: a multicenter, randomized, open-label, crossover study in children with mild to moderate persistent asthma. *Curr Ther Res* 2000; 61: 490–506.
72. Tillomed Laboratories Ltd. Aciclovir dispersible tablets. Patient information sheet. Available at: <http://www.mhragovuk/home/groups/spcpil/documents/spcpil/con1427432156757.pdf> (accessed May 2016).
73. Spirit Pharmaceuticals Pty Ltd. Onsetron(R) ODT Product Information. Available at: http://www.actavis.com.au/nr/rdonlyres/5197cdc7-0dd7-4ed6-a15d-ffeb2eab923/0/onsetronodt_.pdf (accessed May 2016).
74. FDA. *Guidance for Industry. Orally Disintegrating Tablets*. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2008. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf> (accessed May 2016).
75. Joint Formulary Committee. London: BMJ Group and Pharmaceutical Press. Available at: <http://www.medicinescomplete.com> (accessed January 2016). British National Formulary for Children (online) (accessed May 2016).
76. Reckitt Benckiser Healthcare UK Limited. Summary of Product Characteristics: Flurbiprofen 8.75 mg Lozenges. Available at: <http://www.mhragovuk/home/groups/spcpil/documents/spcpil/con1444367913253.pdf> (accessed January 2016).
77. Chue P *et al.* Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorder. *Can J Psychiatry* 2004; 49: 701–703.
78. Chue P *et al.* Dissolution profile, tolerability, and acceptability of the orally disintegrating olanzapine tablet in patients with schizophrenia. *Can J Psychiatry* 2002; 47: 771–774.
79. European Pharmacopoeial Commission. *Oromucosal Preparations. European Pharmacopoeia – edition 80* Strasbourg, France: European Directorate for the Quality of Medicines (EDQM), 2013: 793–796.
80. Davies EH, Tuleu C. Medicines for children: a matter of taste. *J Pediatr* 2008; 153: 599–604.
81. Somasiri UL *et al.* Antiepileptic drugs for children: availability, suitability and acceptability. *Sri Lanka J Child Health* 2013; 42: 38–39.

82. Smith CJ *et al.* A prospective study to assess the palatability of analgesic medicines in children. *J Adv Nurs* 2013; 69: 655–663.
83. Rieder M. How sweet it isn't: a new formulation of sodium phenylbutyrate and the challenge of palatability for medicines for children. *Arch Dis Child* 2012; 97: 1080.
84. Baguley D *et al.* Prescribing for children – taste and palatability affect adherence to antibiotics: a review. *Arch Dis Child* 2012; 97: 293–297.
85. Ameen VZ *et al.* Ranitidine (Zantac[®]) syrup versus ranitidine effervescent tablets (Zantac[®] EFFERdose[®]) in children: a single-center taste preference study. *Pediatr Drugs* 2006; 8: 265–270.
86. Bagger-Sjoberg D, Bondesson G. Taste evaluation and compliance of two paediatric formulations of phenoxymethylpenicillin in children. *Scand J Prim Health Care* 1989; 7: 87–92.
87. El-Chaar GM *et al.* Randomized, double blind comparison of brand and generic antibiotic suspensions: II. A study of taste and compliance in children. *Pediatr Infect Dis J* 1996; 15: 18–22.
88. Herd DW, Salehi B. Palatability of two forms of paracetamol (acetaminophen) suspension: a randomised trial. *Paediatr Perinat Drug Ther* 2006; 7: 189–193.
89. Jahnsen T, Thorn P. An acceptability study of two pivampicillin mixtures in children in general practice. *Scand J Prim Health Care* 1987; 5: 241–243.
90. Kim MK *et al.* Vomiting of liquid corticosteroids in children with asthma. *Pediatr Emerg Care* 2006; 22: 397–401.
91. Martínez JM *et al.* A taste comparison of two different liquid colecalciferol (vitamin D 3) preparations in healthy newborns and infants. *Clin Drug Invest* 2006; 26: 663–665.
92. Stafford L *et al.* Comparison of paediatric steroid mixtures. *Aust J Hosp Pharm* 1998; 28: 246–249.
93. Stevens R *et al.* A randomized study of ondansetron syrup in children: evaluation of taste acceptability and tolerance. *Pediatr Hematol Oncol* 1996; 13: 199–202.
94. Ubaka CM *et al.* Palatability of oral paediatric antibiotics commonly prescribed in a Nigerian specialist hospital. *Eur J Hosp Pharm: Sci Pract* 2013; 20: 122–124.
95. Esteban Gomez MJ *et al.* Influence of antiretroviral therapy characteristics on pediatric patient adherence. [Spanish] Influencia de las características del tratamiento antirretroviral en la adherencia del paciente pediátrico. *Farmacia Hospitalaria*. 2004; 28(6 Suppl. 1): 34–39.
96. Morecroft CW *et al.* Prescribing liquid medication: can the dose be accurately given? *Arch Dis Child* 2013; 98: 831–832.
97. Jones DV, Work CE. Volume of a swallow. *Am J Dis Child* 1961; 102: 427.
98. Cheng A, Ratnapalan S. Improving the palatability of activated charcoal in pediatric patients. *Pediatr Emerg Care* 2007; 23: 384–386.
99. Dagnone D *et al.* Assessment of the palatability of vehicles for activated charcoal in pediatric volunteers. *Pediatr Emerg Care* 2002; 18: 19–21.
100. Polanco-Allué I *et al.* New routes of administration of salt solutions (oral rehydration solutions) in the treatment of acute gastroenteritis: prospective, controlled and organoleptic study of satisfaction. *Acta Paediatrica Espanola*. 2012; 70: 87–92.
101. Venables R. Determining the prevalence and nature of oral formulation-related barriers to medicines administration in paediatric patients suffering from chronic conditions. University of Birmingham, 2014.
102. Venables R *et al.* Oral formulation-related barriers to medicines administration in children with chronic conditions: views of parents and young people. *Arch Dis Child* 2014; 99(Suppl1): A169–A170.
103. Richey RH *et al.* Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatr* 2013; 13: 81–89.
104. Schwartz RH. Enhancing children's satisfaction with antibiotic therapy: a taste study of several antibiotic suspensions. *Curr Ther Res* 2000; 61: 570–581.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Twenty-nine papers were found that met the criteria to be classified as strong evidence in determining the acceptability of paediatric medicines.