Teaser This review presents a systematic analysis on methods employed for assessing acceptability of oral medicines in children and older adults, to provide insights and recommendations regarding the design of reliable instruments in future studies.

Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review

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Acceptability of medicinal products in children and older populations is pivotal in ensuring adherence and therapeutic outcomes. This review systematically identifies studies reporting on formulation aspects of oral medications that affect their acceptability in these patient groups. Particular emphasis is placed on the evaluation of the methodologies employed in the studies. Sixty-eight studies were included for analysis, with 51 (75%) in children and 17 (25%) in older populations. The studies evaluated a range of oral formulations; however, the methodologies used differ considerably in participants' characteristics, study settings, tools, acceptability definitions and criteria. It is evident that there is a lack of standardisation in study design as well as the assessment methods used in assessing acceptability of medicines in children and older populations.

Introduction

Global regulatory initiatives are fostering the development of patient-centric pharmaceutical products that accommodate the needs of all users, including children, older adults and their caregivers. The lack of suitable formulations for children and older patients is increasingly acknowledged by the regulatory and scientific communities given the prevalence of unlicensed and off-label medicine use, undocumented modifications of dosage forms, patient-reported administration difficulties and rates of non-adherence [1–10]. In addition to being burdensome to patients and their caregivers, these practices can be detrimental to the safety and efficacy of medicines [11–14]. As an example, tablets are often subdivided (split) into smaller segments to aid swallowing or to acquire a more suitable dose; however, this might be inappropriate for certain drug products. For example, subdivision of a tablet could lead to unequal segments with

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nonuniform drug doses [15–18]. When a whole tablet has been coated with an enteric or modified release coating, breaking the tablet could compromise the functionality of the coating and hence alter bioavailability.

The European Medicines Agency (EMA) and Food and Drug Administration (FDA) have adopted legislations to promote the timely development and authorisation of medicines for use in children (between birth and 16 years in the USA and up to 18 years in Europe) [19–22]. To support this, the EMA released a reflection paper in 2005 broadly outlining factors to be considered in the development of formulations for children [23]. As knowledge, opinion and experience in the field developed, the agency issued another guideline in 2014 further capturing considerations in the development of age-appropriate paediatric medicines [24]. At present, a draft reflection paper on the pharmaceutical development of medicines for use in the older people (defined as adults from 65 years of age) has also been released for public consultation [25]. Although not exhaustive, these documents emphasise the importance of recognising the distinct needs of children and older adults when designing drug products.

Particular emphasis is placed on establishing 'patient acceptability' of pharmaceutical products, defined as: 'the ability and willingness of a patient to use and its caregiver to administer the medicine as intended' [24,25]. Ensuring that formulations are suitably designed and acceptable to end-users reduces the risks that medicine quality could be compromised, supports patient adherence and consequently leads to safer and effective use of medicines [9,10]. Acceptability is influenced by factors related to pharmaceutical product design (such as route of administration, dosage form design, dosing frequency and features of administration and product packaging), as well as the characteristics of end-users [26,27]. A patient's ability to use formulations as intended can vary, and is often dependent on several physiological, physical and psychological factors. Physiological functions and cognitive and motor skills inherently develop and mature from birth to adulthood. At the other end of the spectrum, aging is characterised by the decline and deterioration in the functional capacity of organs, with elderly patients often presenting with physical and cognitive impairments, multiple comorbidities, polypharmacy and frailty [28]. As such, development of medicines suitable for use in children and older patients raises unique and related challenges around drug disposition, safety of excipients and limitations with practical usability of dosage forms. In both populations, caregivers often play an important part in facilitating the administration or management of medicines – in children before they can be given responsibility for their own medication intake and in older people if they become unable to manage their medicines. Collectively, these aspects increase the complexity of patient-centric pharmaceutical product design.

The lack of empirical evidence on suitability and end-user opinions of pharmaceutical formulations across both populations is well documented [29–31]. Consequently, the current EMA guidelines advocate that patient acceptability is evaluated as an integral part of pharmaceutical and clinical development [24], and over the product lifecycle [25]. Ideally, this pivotal data should be sought from patients and caregivers themselves as a fundamental outcome of well-designed clinical studies with the proposed medicine. Alternative sources could provide indications of adequate patient acceptability, such as human factor studies with patients or healthy volunteers, using existing clinical trial data, or market experiences and literature reports [8,32–34]. However, knowledge regarding suitable methodologies for testing acceptability is sparse and fragmented, and a harmonised approach between industry and regulators is lacking [35]. Recent reviews have presented literature evidence of acceptability of pharmaceutical formulations in children and older patients [29–31]. This review aims to identify studies reporting on formulation aspects of oral medications that have been shown to influence their acceptability in paediatric and older populations, with a specific emphasis on the evaluation of the methodological approaches to provide insights and recommendations to the design of reliable instruments in future studies.

Methods

Search strategy

Indexed publications were identified by searching three electronic databases: Pubmed, Scopus and Embase, with coverage from the start date to May 2017 for all sources. The search strategy combined Boolean operators ('AND') using any of the search terms shown in Table 1. In addition, a manual search of references within publications included from the electronic search was conducted to complement the electronic search. Literature collections from expert members of the European Paediatric Formulation Initiative (EuPFI) were also reviewed.

Selection criteria

Four reviewers (F.L., S.R.R., F.L.L. and F.R.) independently conducted initial screens of identified abstracts and titles. Abstracts were excluded if they were not in the English language, did not report original data (e.g., review papers) or were duplicates. Articles were included in the review if the age of the study population was in the ranges between 0 and 18 years and >60 years. Although the WHO has used the chronological age of 65 years as the definition of 'an older or elderly person' [36], historically 60 years of age has been applied as the cut-off age for 'older population' or 'geriatrics' and was therefore adopted in the inclusion criteria of this review. Where a study had a population with a mixture of age ranges, the study was included if (i) the mean/median age was between 0 and 18 years or >60 years, (ii) separate results were presented for age groups of 0–18 years old or >60 years old, or (iii) >50% of participants were between 0 and 18 years or >60 years old.

Studies were included if patient acceptability of an oral formulation was evaluated, as defined by the EMA as 'an overall ability of the patient and caregiver (defined as 'user') to use a medicinal

TABLE 1

The applied search terms

Keywords	Synonyms
Populations	Elderly, older adults, aging, ageing, geriatric, paediatric, pediatric, children, infant, newborn, adolescent, teens, youth, teenagers
Route	Oral
Formulations	Formulation, dosage form
Assessments	Satisfaction, acceptance, preference, approval, acceptability, swallow, palatability

product as intended (or authorised)' [24,25]. Assessments included measures of swallowability (the capacity to ingest an oral formulation upon administration into the oral cavity) [25] and key organoleptic properties such as shape, size, colour, texture and palatability. Because this review focuses on the pharmaceutical formulation itself, studies evaluating aspects such as packaging, medicine administration devices and the impact of dosing frequency were not included. Studies that solely focused on taste assessment or taste comparisons of different formulations were also excluded because this has been reviewed elsewhere [37,38]. However, studies were included if taste assessment was part of the overall acceptability evaluation of the formulation. Evaluation of medicine adherence (or compliance) applies different definitions and assessment methods to acceptability [39] and studies solely investigating these outcomes were also excluded. Disagreements about the eligibility of studies were resolved by consensus, including, where necessary, with the input of additional reviewers.

Data extraction

Data were extracted by each reviewer into structured summary tables and cross-checked for accuracy. Discrepancies were resolved by consensus, including, where necessary, with the input of additional reviewers. Key details extracted for each study included formulation characteristics (e.g., dosage form type, size, shape and drug content), participant age and health condition, reporting persons (i.e., self-report or report by caregivers or observers), sample size, study setting (country location and data collection setting), design and acceptability assessment and primary outcomes.

Results

The electronic search identified 2590 records potentially eligible for inclusion (Fig. 1). Following a manual screening of titles, abstracts and full-texts, 44 publications were eligible for inclusion. An additional 24 papers were included after manual screening of references within eligible publications and through studies identified by the expert panel. Therefore, a total of 68 publications were included for analysis. The characteristics of the included studies are summarised in Table 2. A total of 51 (75%) publications were paediatric-population-based studies and 17 (25%) were based on the older population. The earliest study identified was published in 1987, whereas 42 articles (62% of the combined total) were published in the past decade from 2007 to 2017, showing increasing research intensity in this area. Sixty studies (88% of the combined total) were conducted in European and Northern American countries.

Tables 3 and 4 summarise the methodology and outcomes of each eligible study with regards to the acceptability assessment. Thirty studies (44%) assessed the acceptability of one single type of oral dosage form, for example tablets, capsules or suspensions (Table 3), whereas the remaining studies ($n = 38$, 56%) evaluated or compared more than one type of dosage form, for example the acceptability or preference of tablet versus oral suspension (Table 4). For paediatric-based studies ($n = 51$), the individual who provided the responses to the acceptability assessment included children ($n = 21$, 41% of the total paediatric studies), caregivers including parents and carers ($n = 19$, 37% of the total paediatric studies), children and caregivers ($n = 10$, 20% of the total paediatric studies) and observers or investigators ($n = 1$, 2% of total paediatric studies). Thirty-five percent (24/68) of the studies evaluated the acceptability of medicines already being prescribed to the patients, whereas in the rest of the studies (65%) patients received medicines for the purpose of testing their acceptability.

Further details on the methodology directly related to the acceptability assessment were extracted and are listed in Table 5. Questionnaires ($n = 41$, 60%) were the most commonly applied method in assessing acceptability of formulations, followed by observations ($n = 16$, 24%) that mostly related to observing the ability of the participant to swallow oral formulations. A variety of terms were used to describe or measure the acceptability (Table 5); 'acceptability' was the most commonly used term ($n = 17$, 25%) followed by 'preference' ($n = 13$, 19%). More than one-third of the studies ($n = 26$, 38%) lacked a clear definition on acceptability or other synonymous terms used. It is noteworthy that no studies included in the analysis provided standardised criteria for acceptability assessment, for example the 'acceptability rate' or the minimum % rate that would deem the formulation to be considered acceptable to patients.

Discussion

Study types and settings

In assessing formulation aspects of oral medications that influence their acceptability in the paediatric and older populations, this review examined 68 studies with 51 paediatric- and 17 older-population-based studies. Evident from examining these studies is the lack of standardisation in study design and the assessment methods used. Table 6 summarises study design considerations for dosage form acceptability assessments in children and older adults. All aspects of study design differ considerably in the reviewed studies. The types of the studies include clinical trials evaluating efficacy and tolerability of treatments, standalone investigations into acceptability of medicines such as post-marketing surveys and swallowability evaluation of solid dosage forms [3,8,34,57–72] (Table 2). The settings where the studies took place ranged from hospitals and specialised clinics to community-based environments (e.g., home, school, community centres) (Table 2). It is acknowledged that patient acceptability is influenced not only by formulation attributes but also characteristics of the patient (e.g., disease type and stage). In this regard, acceptability studies performed in the targeted patient population during prospective studies such as clinical trials and observational studies in post-marketing surveys could provide a more representative insight into the true acceptability of the formulation compared with studies conducted in healthy volunteers. However, it should be noted there could potentially be a selection bias in clinical trials because only patients who are willing to participate are included. In addition, in studies nested to clinical trials, it can be difficult to deconvolute the effect of the dosage form design from the effect of the efficacy or safety balance of the medicine (e.g., appearance of adverse events). Although clinical trials are often conducted in standardised conditions, the translation of the outcomes to patients taking the medicines at home or at school might not be straight forward. Studies conducted in healthy subjects using placebo formulations can provide fundamental understanding of the acceptability of different dosage form designs. Equally, it might not be possible to generalise acceptability findings of a

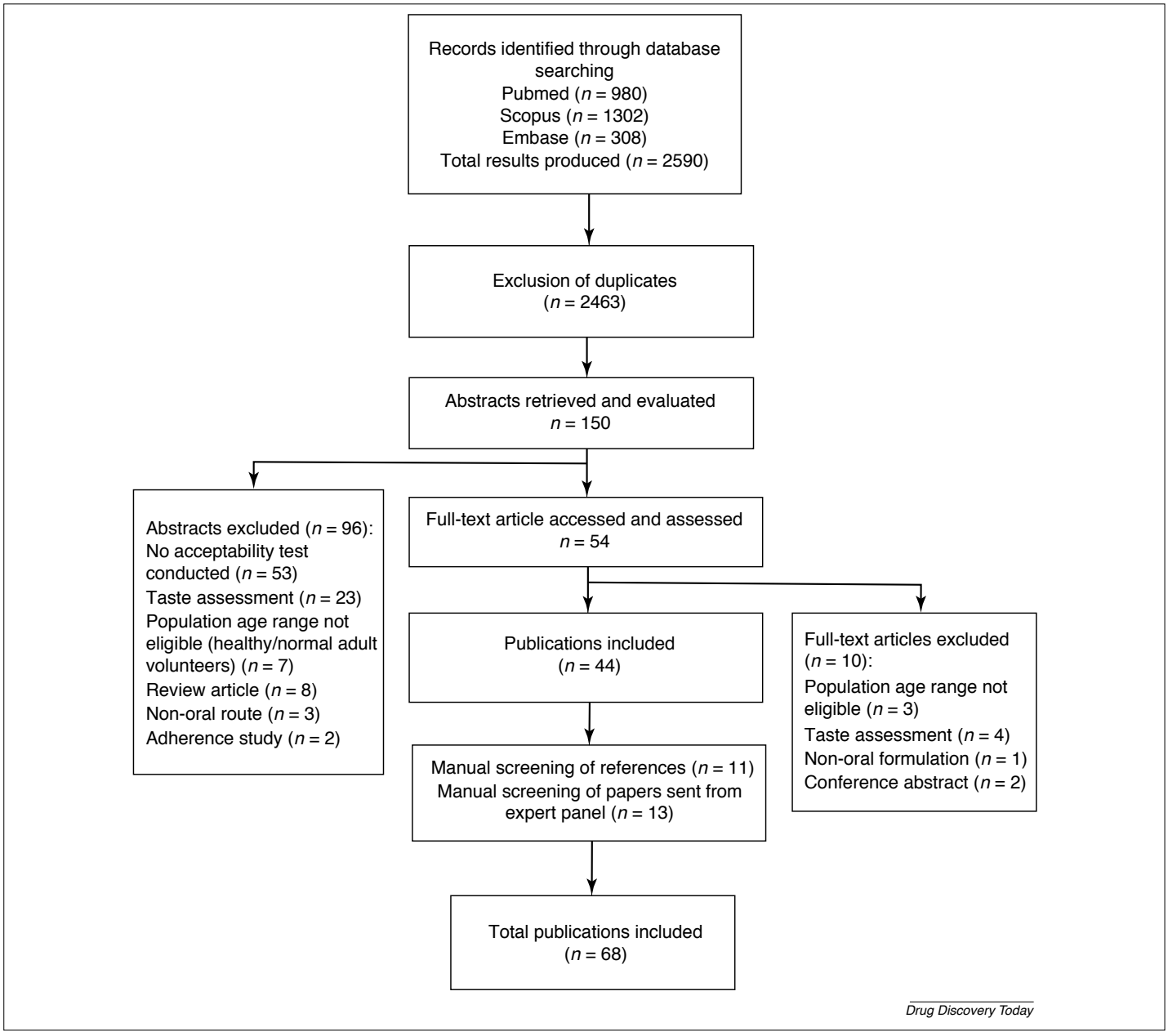

FIGURE 1

Literature search results on studies reporting acceptability of oral medicines in paediatric and older patients.

formulation, for example swallowability of a certain dosage form in a certain patient group, to other settings and patient groups because it can be influenced by the environment and the characteristics of the patient. For example, a substantial discrepancy in the prevalence of dysphagia symptoms between older patients in nursing homes (68%) and community-dwelling older adults has been found (11%) [73,74].

Participant characteristics

The participant characteristics varied in terms of age, disease status, developmental stages and/or age-related impairments in the reviewed studies. Age is often used in the classification of the paediatric and older populations. Although guidance is available to define paediatric subgroups according to age (ICH E11), this was not followed by the majority of paediatric-based studies with a wide variety of age ranges used, for example 0–26 years in one study [75] and 6 months to 14 years in another [76]. Although arbitrary age was suggested to be used to divide subgroups of the older population, numerical age alone scarcely correlates with physiological functions of the older individual or outcomes of interventions. Classification of the frailty status of older patients was proposed to be a more accurate reflection of physiological activities and abilities [77]. Healthy volunteers and patients with a range of diseases were recruited into these studies (Tables 2–4). Disease conditions, especially the presence of multiple morbidities in the older patient, might affect the experience and acceptance of patients to take their medicines. Similar effects might be seen from patients' past experiences in taking medicines and the nature of

TABLE 2

Study characteristics across the paediatric and older adult populations: data are number (%) of studies

Study characteristics	Paediatric-population-based studies (*n* = 51)	Older-adult-population-based studies (*n* = 17)
Year of publication		
2017–2007	34 (66)	8 (47)
2006–1997	14 (27)	4 (24)
1996–1987	3 (6)	5 (29)
Journal field		
Nutrition	3 (6)	–
Medical	42 (82)	11 (65)
Pharmacy	6 (12)	6 (35)
Location of study		
Europe	28 (55)	10 (59)
North America	18 (35)	4 (24)
Asia	2 (4)	3 (18)
Africa	3 (6)	–
Type of study		
Clinical trials	12 (24)	3 (18)
Swallowability evaluation	18 (35)	6 (35)
Other	21 (41)	8 (47)
Study setting		
Specialist clinics/centres	9 (18)	4 (24)
Community based[a]	16 (31)	2 (12)
Hospital based	20 (39)	8 (47)
Multi-settings	5 (10)	1 (6)
Not specified	1 (2)	2 (12)
Population size		
0–50	17 (33)	5 (29)
51–99	7 (14)	2 (12)
100–199	10 (20)	5 (29)
200–299	3 (6)	–
300–399	5 (10)	1 (6)
400–499	2 (4)	–
500+	7 (14)	4 (24)
Health conditions of participants		
Healthy volunteers	9 (18)	4 (24)
Taking medicines – reason unknown	2 (4)	1 (6)
In hospital – reason unknown	8 (15)	–
With disease conditions[b]	32 (63)	12 (71)

[a] Include: homes, general practitioners, schools, pharmacies and preventive health centres.

[b] Disease conditions include acute childhood diarrhoea, after surgery, allergies, Alzheimer's disease, asthma, cystic fibrosis, dysphagia, eligible for typhoid vaccination, epilepsy, HIV, hyperactivity disorder, hypercholesterolaemia, hypertension, infections requiring prescription of antibiotics, iron deficiency, malnutrition, nephrotic syndrome, oesophageal obstruction, osteoporosis, Parkinson's disease, phenylketonuria, primary nocturnal enuresis, respiratory tract infections, sickle cell disease, type 2 diabetes and undergoing adentonsillectomy.

their current medications (including the likeliness of polypharmacy in the older patient). For instance, differences were reported in the preference of tablet colours between older patients taking small and large numbers (>10) of tablets each day [78]. To add to the complexity, variations in children's development and age-related impairments in the older population (e.g., visual, cognitive and motoric functions) could also affect patient handling and taking their medicines.

Study methods and tools

The selection of the applied study methods and tools reflected the purpose of the studies. For example, assessing the swallowability of tablets and capsules was often done by direct observation or instrumental examination (e.g., videoendoscopy), whereas general acceptability of a formulation or medicine was conducted by interviews and questionnaires accompanied by facial and visual analogue scales (Tables 3 and 4). Age-appropriate facial scales have been developed for taste assessment in paediatrics and can be adapted for acceptability studies [37], although careful consideration must be given to the choice of scales and response options to avoid bias [79]. Two studies have used multiple endpoints to report the acceptability; for example, using the combination of children and parent reporting on acceptability and direct observation on the outcome of the intake [41,80]. These combinations of endpoints might minimise the bias of using one method for reporting the acceptability. In the majority of the studies (65%), patients received medicines or placebo formulations for the purposes of assessing their acceptability and a smaller proportion of studies (35%) evaluated acceptability of medicines that have already been prescribed to the patients. Although using patients' own medicines gives a real-world judgement on the use of the medicines, it is necessary to conduct perspective studies such as randomised trials to compare the acceptability of newer types of medicines or formulations to conventional ones.

With regards to methodological details, differences were observed between studies in terms of number of participants, study duration, number of administration attempts and who was responsible for answering the questions. In paediatric-based studies, feedback on acceptability or otherwise of the formulations was given almost equally by the children and their parents or caregivers (Tables 3 and 4). However, it is interesting to note that in certain studies caregiver or parental response was used for children older than 12 years (up to 26 years old) [34,75,81]. In most of the older-population-based studies, acceptability was evaluated by the patients themselves, with the exceptions of caregivers' satisfaction for medicines used in the treatment of Alzheimer's and Parkinson's diseases. This was probably because of the disease-related decline in patients' capacity in participating in the studies [82,83]. However, the acceptability of the patient might differ from that reported by caregivers.

Clarification is required regarding circumstances under which the caregiver's (parent's or partner's) response should be used instead of the patient's in the paediatric and older populations. FDA guidance on patient-reported outcome (PRO) measures could provide some valid insight into this question [22]. This guidance highlights the challenge of PROs in children and in patients who have cognitive impairment or are unable to communicate. For these populations, especially patients who cannot respond for themselves, the FDA encourages observer reports that include only those events or behaviours that can be observed, and discourages proxy-reported outcome measures. As an extension of this guidance, in 2013 an International Society for Pharmacoeconomics and Outcomes Research (ISPOR) taskforce proposed good practices for paediatric PRO research, which is conducted to inform regulatory decision-making and support claims made in medical product labelling [84]. These recommendations propose that there is no clear evidence of child-report reliability and validity in children

TABLE 3

Methods and acceptability results in studies that assessed a single dosage form[a]

Formulation type	Drug content	Participant age range	Persons who gave the acceptability response	Acceptability assessment method	Acceptability synonym and definition	Summary of acceptability results	Refs
Tablets (7 mm, cylinder)	Placebo	6–12 years	Children	Observation and six-point visual scale	'Ability in swallowing the tablet', not defined; and 'ease of swallowing', not defined	91% of children were able to swallow a tablet; 89.5% subjects performed the task without difficulty and 10.5% exhibited a little difficulty	[70]
Tablets	–	11–20 years	Children	Semi-structured qualitative interview	'Capability to swallow medicines', not defined	Over one-third (n = 32) of adolescents expressed difficulty in taking oral medicines mostly owing to their taste and size	[3]
Tablets (7 mm round)	Ketoprofen	1–9 years	Parents	Questionnaire	'Problems in administering tablets', not defined	14% parents reported problems in administering the tablets to their children which related to difficulty in swallowing the tablets	[94]
Tablets (film coated, 5–8 mm, round)	Levamisole	2–18 years	Children	Observation	'Ability to swallow the medicine', not defined	Children swallowed 1–7 tablets every other day for several months and no problem with swallowing tablets was reported	[95]
Minitablets (3 mm, uncoated)	Placebo	2–6 years (divided into four age groups)	Children	Observation	'Success in swallowing', defined as the tablet being swallowed whole; chewing, spitting out and refusal were defined as 'nonswallowed'	The proportion of children who successfully swallowed the mini-tablet was 45–55%, 76% and 87% for 2–3 years, 4 years and 5 years old, respectively	[71]
Mini-tablets (2 mm and 3 mm)	Placebo	2–3 years	Children	Observation	'Ability to swallow', defined as complete deglutition including 'smooth swallowing', 'swallowing with a choking reflex or cough', or 'biting or chewing followed by swallowing'	83% of children were able to swallow five or ten mini-tablets of the tested sizes with the aid of fruit jelly on a spoon. However, only 57% of all children were capable of swallowing the tablets without chewing	[69]
Capsules containing microtablets	Pancrelipase MT	6–30 months	Parents	Questionnaire with four-point palatability scale (0 being poor and 3 being excellent)	'Palatability', defined as ease of swallowing	The median palatability score was 2.6 during the randomisation period	[51]
Gelatin capsules from 'sprinkle' size, through 4,3,2, and 1, to 1000 IU capsule sizes	Placebo	3–13 years	Children	Observation	'Success in swallowing pills'; not defined	17 children learned to swallow the pills through training and 11 failed to learn to swallow the pills	[62]
Gelatin capsules of increasing sizes	Placebo	4–21 years	Children	Observation	'Success in pill swallowing', not defined	95.7% children were successful in swallowing the pills through training	[64]

TABLE 3 (*Continued*)

Formulation type	Drug content	Participant age range	Persons who gave the acceptability response	Acceptability assessment method	Acceptability synonym and definition	Summary of acceptability results	Refs
Gelatin capsules (#5 to #00 in size)	Placebo	3.5–17.5 years	Children	Observation	'Success in swallowing', defined as pill ingestion and in clean mouth after swallowing	Training was performed on four disabled children and had varied degree of success in improving capacity in swallowing capsules	[57]
Tablets and capsules of various sizes	Placebo	4–9 years	Children	Observation	'Success in pill swallowing', not defined	Seven out of eight children improved pill swallowing by training	[59]
Tablets of various shapes and capsules	Placebo	67–95 (mean 81) years	Patients	Video-endoscopy	'Penetration Aspiration Scale (PAS)'	Compared with administration of milk alone, swallowing the tablets and capsules significantly increased the PAS values in patients with stroke-induced dysphagia	[8]
Enteric coated capsules	Typhoid vaccine	4–6, 7–9, 10–12 years	Children	Observation	'Success in swallowing the medicine', defined as ability to swallow the capsule without breaking them	The success rates for swallowing the capsules were 84.4%, 94.2% and 100% for the age groups of 4–6 years, 7–9 years and 10–12 years	[96]
Capsules	Radiolabelled placebo gelatin capsule, sized #1, #0 and #00	70–81 years	Radio scintigraphy	Radio-scintigraphy	'Oesophageal clearance', defined as the radioactivity in the oesophagus returned to 10% of peak value	Capsule retention in the oesophagus can occur in older patients even when the dosage form was ingested with a large amount of fluid (three out of nine elderly subjects)	[58]
ODTs[b]	Placebo and ondansetron	5–11 years	Children	Observation and questionnaire	'Acceptability', observational acceptance defined as not reject or spit out; questionnaire assessed taste, sensation and willingness to take the medication in the future	100% observational acceptance; however, a significantly larger number of the subjects in the ondansetron group found the tablet not tasting 'good' compared with the control group; 13% in the ondansetron group stated that they would not be willing to take the medication in the future	[41]
ODTs	Amlodipine	58.3% aged $\geq$65 years	Patients	Interview	'Palatability', defined as easiness to ingest	99.6% found the formulation 'easy to ingest'	[54]
ODTs	Voglibose	64.4 $\pm$11.2 years	Patients	Questionnaire assessed using comparison to conventional tablets as 'easier', 'no difference' or 'more difficult'	'Convenience of taking the medicine', not defined	53.1% reported that taking the ODT was easier than taking conventional tablet	[56]

TABLE 3 (*Continued*)

Formulation type	Drug content	Participant age range	Persons who gave the acceptability response	Acceptability assessment method	Acceptability synonym and definition	Summary of acceptability results	Refs
Dispersible tablets	Zinc	0–60 months	Caretakers	Interview	Problems in administrating the tablets	Eight caretakers (6.5%) reported problems with administering the tablet to their child	[97]
Dispersible tablets	Zinc	3–59 months	Caretakers	Questionnaire, assessed using comparison to other medicines as 'better', 'same' or 'worse'	'Acceptability', measured on the basis of child's behaviour when given the medication	93.1% of caretakers reported that the tablets were equally or more acceptable to their children than other medicines	[98]
Dispersible tablets	Fixed-dose combinations (FDC) of antimalaria drugs, artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP)	6–59 months	Caregivers	Questionnaire	'Ease of use' and 'acceptability', not defined	Caregivers reported that the two dispersible FDC tablets to be simple to use (82%, 67%), having good palatability (72%, 56%) and preferred the dispersible tablet over syrup (76.8%, 62.3%) for both products	[48]
Suspensions	Antibiotics	Median range 18–22 months	Parents	Telephone interview using three- or five-point scales	'Acceptance', defined using willingness to swallow and occurrence of vomiting; 'satisfaction', defined as 'extremely satisfied' and 'satisfied' on the scale	Percentage satisfaction was reported as 89, 81, 74 and 67% for four suspensions, respectively	[99]
Suspension	Mercaptopurine	3–12 years	Children and parents (for children below the age of 6)	Questionnaire using five-point facial hedonic scale	'Acceptability', not defined	77% children rated the taste of the formulation between 'okay' to 'good'; 82% reported that it was 'easy to take all the time'	[100]
Suspensions reconstituted from tablets	Roxithromycin	2–8 years	Investigator	Observation using a six-point scale	'Acceptability', defined as child smiling or without making a face during taking the medicine	The investigator reported the acceptability as good, fairly good or acceptable in 70.5% of children	[47]
Oral drops	Vitamin K	Infants	Midwives	Questionnaire	'Acceptability', not defined	56% of midwives reported the use of the oral drop as 'quite acceptable' or 'completely acceptable' with 33% undecided and 11% reporting it as 'not very acceptable'	[101]
Oral formulations in general	Hydroxyurea	5–17 years	Parents	Questionnaire	'Ability to swallow medicines', not defined	98% of children could swallow liquid medications; 75.5% and 72.5% could swallow tablets and capsules, respectively	[34]

TABLE 3 (*Continued*)

Formulation type	Drug content	Participant age range	Persons who gave the acceptability response	Acceptability assessment method	Acceptability synonym and definition	Summary of acceptability results	Refs
Oral formulations in general	Antibiotics	0–12 years	Parents	Questionnaire	No specific terms were used. The use and the problems related to the use of the formulations were measured	11% of the parents had difficulty in administering the medicines to their child. Fewer administration-related problems were associated to tablets and capsules than to suspensions and soluble tablets	[102]
Oral formulations in general	All medicines included	0–26 years	Parents	Questionnaire	'Acceptance', defined as history of medication rejection, frequency of use and ability to 'easily' swallow tablets and capsules	33.5% and 39.2% of children/adolescents had rejected liquid and pills, respectively, at least once	[75]
Tablets or capsules using *in situ* coating (MedCoat®) as an aid	Patients' own medications	2–17 years (mean 9 years)	Children or parents	Questionnaire	'Tolerance', defined as the facilitation of drug treatment, swallowing ability and drug palatability	The ability to swallow tablets or capsules improved in 68 of 78 children after *in situ* coating	[72]
Oral formulations (including liquids, tablets and capsules) using Pill Glide as an aid	Patients' own medications	6–17 years	Children	Self-reporting diaries, using six-point numeric or facial hedonic scale (0 indicating not difficult to 5 most difficult)	Medicine Taking Difficulty Score (MTDS) indicating 'difficulty/ease of swallowing medications'	Pill Glide decreased 0.93 overall MTDS for swallowing solid medications	[66]
Tic tac (candy) using Pill Glide as an aid	Candy	9–17 years	Children	Observation	'Success in pill swallowing', not defined	Seven of the 11 adolescents were successful in swallowing the pill using Pill Glide as an aid	[63]

[a] Single dosage form assessed: only one type of dosage form, e.g., tablet or capsule, was investigated. Drug-containing and placebo formulations can be assessed; however, they are presented as the same dosage form.
[b] ODT: orally disintegrating tablets.

TABLE 4

Methods and acceptability results in studies that compared two or more dosage forms

Small (0.287 × 0.710 inches) vs large (0.360 × 0.760 inches) tablets	Dietary supplements	Above 50 (mean age 68) years	Patients	Questionnaire using VAS[b] (100 mm, higher scores mean more preferable)	'Preference' ranked based on eight aesthetic characteristics and overall preference	Significantly more patients preferred smaller than larger tablets	[60]
Two different tablet formulations (Ketovite and RSM)	Micronutrient	1–16 years (mean 10 years)	Children and family	Questionnaire using a Likert scale from 1 (liked) to 7 (disliked)	Opinion about the medication, with respect to appearance, smell, texture, ease of administration, taste, size and acceptability	Children generally swallowed Ketovite tablets because of their smaller size; the RSM was chewed by most children owing to larger size. 53% of families were in favour of changing Ketovite to the RSM, especially if its size were reduced	[42]
Tablets vs film-coated dispersible tablets	Acyclovir	71–94 (mean 82) years	Patients	Questionnaire	'Ease of swallowing'	Standard tablets and film-coated dispersible tablets were swallowed whole with 200 ml water. 50% of subject did not have any preference between the formulations. Of those who had expressed a preference, 79% preferred the film-coated dispersible tablet	[103]
Tablets (fixed dose combination) vs effervescent calcium tablets plus vitamin drops	Calcium and vitamin D	70–95 years	Patients	Questionnaire	'Acceptability', defined as overall satisfaction, taste and presentation	A significantly higher proportion of patients were satisfied with their treatments with the fixed dose combination tablet formulation; no significant differences were found for other acceptability parameters such as taste and presentation between the two formulations	[50]
Tablets (1.3 g) vs other commonly used forms (powder, drink and capsules)	Protein substitute	Median 15 years, ranging 8–25 years	Patients	Questionnaire using VAS (100 mm, higher scores mean more acceptable)	'Acceptability', defined as palatability, smell, ease of swallowing and gastrointestinal intolerance	70% patients preferred tablets over their previously used protein substitute formulations	[45]
Tablets vs oral lyophilisate formulation (MELT)	Desmopressin	5–15 years	Patients	Questionnaire using VAS (100 mm with 0 means very easy and 100 very difficult to use)	'Preference' and 'ease to use' which is not defined	56% preferred MELT vs 44% preferred tablets; VAS scores were 22.2 ±28.3 mm and 22.6 ±27.0 mm for MELT and tablets, respectively	[44]
Tablets vs powder	Cholestyramine	10–18 years	Patients	Questionnaires with six-point Likert scales	'Acceptability', defined as preferences at the end of the study	82% participants preferred tablets and 16% preferred powder	[46]
Tablets (4 mm) vs powder vs suspension vs syrup	Placebo	1–4 years	Parents	Questionnaire using VAS (0–10 cm; 0 means very unpleasant and 10 not at all unpleasant)	'Acceptability', defined using VAS score by parents' observation and result of the intake (whether or not swallowed); and 'preference' defined as the single most preferred formulation by child and parent	The mean VAS scores were 9.01, 8.20, 7.90 and 8.19 for the tablet, powder, suspension and syrup, respectively; children and parents preferred the tablet and syrup over the suspension and the suspension over the powder	[80]

Film-coated tablets (5.7 × 11.6 mm) vs gelatin capsule (#3, 5.8 × 15.9 mm)	Placebo	Mean age 66 years	–	Gamma scintigraphy	'Oesophageal transit'	Prolonged oesophageal transit was observed for the capsules compared to the film-coated tablets	[104]
Tablets vs ODTs[a]	Carbidopa-levodopa	71.8 ±8.3 years, with Pakinson's disease	Patients	Global Preference Questionnaire	'Preference'	45% of patients preferred ODTs compared to 20% preferred conventional tablets	[105]
Tablets vs ODTs	Placebo	64.5 ±11.8 years	–	Videoendoscopy	'Swallowing performance', assessed by number of swallows, total time of swallow, use of liquid to assist swallowing, residue in the hypopharynx and airway compromise	Significantly more numbers of swallows and longer duration of swallowing were required to swallow tablets compared to ODTs in patients with dysphagia	[61]
Halved scored tablets vs syrup	Antiretroviral drugs	3 months to 17 years	Parents	Questionnaire	'Acceptability', defined as preference, difficulties and associated problems	The proportion of caregivers and children who preferred tablets over syrup was 97% and 59%, respectively. All children who preferred syrup were under 4 years old. 64% of children took the tablets dissolved or crushed and administered with a small amount of liquid	[81]
Minitablets (2 mm, uncoated) vs syrup	Placebo	0.5–6 years (divided into six age groups)	Children	Observation	'Acceptance', defined as swallowing and chewing with subsequent swallowing for the minitablet, and not defined for syrup	Overall acceptance of the mini-tablet was higher or equal to that of the syrup in all age groups	[106]
Uncoated and coated 2 mm minitablets vs syrup	Placebo	6 months to 1 year, 1–2 years, 2–3 years, 3–4 years, 4–5 years and 5–6 years	Children	Observation	'Acceptability', defined as swallowed and chewed before swallowing for the mini-tablets and everything swallowed and small trickle or left over for the syrup	78.4–100% acceptability for the uncoated minitablets; 84.3–100% acceptability for the coated minitablets and 64.7–90.2% acceptability for the syrup; two incidents of coughing were observed for the coated minitablets	[68]
Mini-tablets (uncoated, 2 mm) vs syrup	Placebo	Median 4 days (range 2–28 days)	Children	Observation	'Acceptability' defined as complete or partial swallowing; 'swallowability', defined as complete swallowing	100% acceptability was obtained for the mini-tablet and syrup formulations. Swallowability was significantly higher for mini-tablets (82.2%) than syrup (72.2%). No serious adverse events (coughing or coking) were observed for both formulations	[67]
Tablets, pellets (minitablets) vs syrup	Lopinavir	3 months to 13 years (divided into three age groups)	Caregivers	Questionnaire	'Acceptability', reported as caregivers' preference	For children below 12 months and 4 years old, 44% and 36% preferred pellets over syrup after 48 weeks' usage; for older children (4–13 years), only 13% preferred pellets to tablets after 48 weeks	[107]

Chewable tablets vs sachet	Calcium and vitamin D_3 supplement	Mean age 66 years	Patients	Questionnaire using a 0–10 rating scale for assessing acceptability, higher score indicating higher acceptance	'Preference' and 'acceptability' which is defined using five questions relating to the convenience of use of the medicines	67% patients preferred chewable tablets compared to 19% preferred sachet; chewable tablets received significantly higher acceptability scores for all five questions	[108]
ODTs vs oral solution	Desloratadine	0–12 years	Parents	Questionnaire	'Preference' measured using likelihood of trying ODT and relative preference to current medicines	65% of parents in Spain preferred the ODTs compared to 55% in Italy, 48% in France and 26% in The Netherlands	[109]
Sprinkles vs syrup	Valproate	5–16 years	Parents and children	Questionnaire	'Preference', direct comparison of the formulations	Nine out of 12 parents preferred sprinkles over syrup; similarly nine out of 12 children preferred sprinkles over syrup	[40]
Sprinkles vs oral drops	Iron supplement	5–7 months	Parents	Questionnaire	'Ease of administration', not defined	Parents were significantly more likely to be concerned about using sprinkles as a new product (12% vs 0%) and about safety of sprinkles for infants (14% vs 1.3%) than oral drops; parents in the oral drop group were more likely to report difficulty in integrating administration of the supplement to daily routine than (38% vs 17%)	[43]
Sprinkles vs oral drops	Iron supplement	8–20 months	Parents	Questionnaire	'Ease of use', not defined	92.9% of children expressed dislike of the oral drops and 6.5% objected to take the sprinkles	[53]
Granules vs capsules	Pancreatic enzyme replacement	6–36 months	Parents	Questionnaire	'Preference'	51% parents preferred the granules and 23% preferred the capsules	[55]
Dispersible tablets vs capsules	Levodopa/ benserazide	Parkinson's disease patients, mean age 79.5 years	Patients	Not defined	Not defined	Of eight participants, two patients preferred the dispersible tablet, three had no preference and three preferred capsules for reason of convenience	[33]
Modified release granules vs oral solution	Valproate	6.7 $\pm$3.6 years (acceptability in children was assessed in those older than 4 years)	Children and parents	Questionnaire with five-point facial hedonic scale	'Palatability', defined as taste of the medicine; 'ease of administration', defined as no problem in giving the medicine to the child	The overall palatability score of granules was significantly higher than the solution in children and parents; parents reported significantly fewer problems in giving the granules to their children than the solution	[52]
Creon® 10 000 microspheres (0.7–1.6 mm in a 50% smaller capsule) vs Creon® 8000 microspheres (1.0–2.0 mm)	Pancreatic enzyme replacement	3–17 years	Children	Questionnaire	'Preference', with reference to ease of swallowing, presence of an aftertaste and feeling of fullness after taking the medicine	87% preference for Creon® 10 000 over 7.4% preference for Creon® 8000	[110]

Syrup vs suspensions vs oral solutions	Antibiotics	0.5 months to 14 years (median age 2 years)	Parents or children if old enough to understand	Questionnaire using five-point facial scale	'Acceptability', defined using completion of treatment, taste, spitting out of product and acceptance to use in the future	A higher favourite was expressed towards amoxicillin–clavulanic-acid princeps over generics. 22.45% children spat out at least one dose of antibiotic	[76]
Oral drop vs oral filmstrip	Vitamin D	1.9–4.3 weeks	Infants and parents	Observation in infants and questionnaire for parents using a 1–10 Likert scale	'Acceptability', 'acceptance' and 'preference' were all used. Infant acceptance was assessed using reactions to the administration	An overall preference of 85.4% was observed for the filmstrips; however, it was not clear how this was calculated	[89]
Oral liquid, small tablet (5 mm in diameter), medium tablet (10 mm in diameter) and large gelatin capsule (22 mm × 7 mm)	Placebo	3–17 years	Children	Observation, using the Pediatric Oral Medication Screener (POMS)	Ability to swallow oral medications, with set criteria for different age groups (swallowing liquid for 3–5 years, liquid and small/medium tablets for 6–10 years and all formulations for 11–17 years)	28 out of 34 children passed their age-specific swallowing criteria. Of the six children who did not pass the criteria, three improved pill swallowing ability after intervention	[65]
Oral solid formulations	Placebo	6–11 years and 12–17 years	Children and caregivers	Questionnaire	'Acceptability', defined as 'ability' and 'willingness' to take the formulation	Favourable attitudes towards tablets and capsules increased with age until around 14 years. Chewable and orodispersible tablets were seen to be preferable across ages, whereas multi-particulates were less favourable	[111]
Oral solid formulations	Placebo	Over 65 years	Patients	Questionnaire using 0–10 scoring, with 10 being the most acceptable	'Acceptance'	Dispersible/effervescent tablets and orally disintegrating tablets were considered to be the most acceptable, followed by mini-tablets. Chewable tablets and granules were the least favoured	[4]
Tablets vs metered dose inhaler	Zafirlukast tablets and inhaled beclomethasone dipropionate	12–17 years	Children	Questionnaire	'Preference' and 'ease of use' which is not defined	70% children preferred the tablets compared with 27% preferred the inhaler; 71% preferred the tablets for ease of use compared with 29% preferred the inhaler for ease of use	[112]
Chewable tablets vs metered-dose inhaler	Montelukast sodium tablets and inhaled cromolyn sodium	6–11 years	Parents and children	Questionnaire using six-point rating scale	'Preference' and 'satisfaction'. Satisfaction was assessed using seven questions including overall satisfaction on treatment outcome and medication used, convenience and difficulty in administration, interference with life style and taken as instructed	Significantly more parents and children preferred the oral formulation compared with the inhaler (87% vs 12% and 82% vs 17%, respectively). Parents and children expressed greater overall satisfaction with the oral formulation than with the inhaler	[113]
Oral formulations (tablets or syrup) vs inhaler	Asthmatic drugs	0–5, 6–10,11–15, 16–30 and 31–60 years	Patients and parents for children under 5 years old	Questionnaire	'Preference'	55–65% children below 15 years old preferred oral formulations over inhaler. There was a significant trend favouring inhaler with increasing age	[114]

Tablets vs transdermal patches	Methylphenidate	Median age 12, ranging 5–17	Parents/ carers	Online survey	'Preference'	59.5% parents preferred for their child to take one tablet per day compared with 33.0% preferred transdermal patches and 12.5% preferred three tablets taken per day	[115]
Oral formulations vs transdermal patches	Anti-Alzheimer's disease drugs	Mean age 77 years	Caregivers	Questionnaire	'Preference'	For patients who were exposed to oral and transdermal treatments, caregivers showed higher preference for transdermal patches (82.4%) compared with oral therapy (17.6%); for patients only treated with one therapy, caregivers preferred the treatment to which the patient was exposed	[116]
Oral formulations vs transdermal patches	Anti-Alzheimer's disease drugs	Mean age 77 years	Caregivers	Questionnaire using 0–10 rating scale	'Satisfaction', ease of administration, global compliance, satisfaction relative to treatment received	Satisfaction was significantly higher for transdermal patches compared with oral medications; over 60% of caregivers of patients treated with patches reported a score between 9 and 10 compared to 46% of caregivers of patients on oral medications	[82]
Oral formulations vs transdermal patches	Rotigotine	74.6 $\pm$ 8.3 (patients with Parkinson's disease)	Caregivers and physicians	Questionnaire using five-point rating scale	'Advantageous', comparison of advantages of transdermal patches with oral formulations	Caregivers and physicians caring for patients with Parkinson's disease rated the transdermal patch to be more advantageous compared with oral formulations	[83]
Oral liquid vs rectal formulations	Acetaminophen	6 months to 6 years	Parents	A single 10 cm VAS	'Satisfaction', not defined	There was no significant difference in parental satisfaction between oral and rectal routes of administration	[49]

[a] ODT: orally disintegrating tablets.
[b] VAS: Visual Analogue Scale.

TABLE 5

Summary of methodology directly related to acceptability assessments

	Number of studies	% of studies (total *n* = 68)
Formulation type evaluated		
Tablet (including mini-tablet)	30	44
Capsule	13	19
Sprinkle/powder/sachet/granule/microspheres	9	13
Oral solution/drop/liquid not defined	8	12
Syrup	8	12
Oral formulation vs other delivery routes (transdermal patches/inhaler)	8	12
ODT[a]	7	10
Oral formulation in general	6	9
Suspension	5	9
Dispersible/effervescent tablet	5	7
Chewable tablet	2	3
Oral film strip	1	1
Candy as mock formulation	1	1
Methodology directly related to acceptability assessment		
Questionnaire/survey	41	60
Observation	16	24
Interview	4	6
Scintigraphy/videoendoscopy	4	6
Other (diary entrance/not defined)	2	3
Acceptability synonym used		
'Acceptability'	17	25
'Ability/capability to swallow'/'success in swallowing'/'oesophageal transit'/' penetration aspiration score'	17	25
'Preference'	13	19
'Convenience/ease/problems of administration/use'	6	9
'Acceptance'	4	6
'Palatability'	3	4
'Satisfaction'	2	3
'Tolerance'	1	1
'Medication taking difficulty score'	1	1
'Opinion'	1	1
'Advantageous'	1	1

[a] ODT: orally disintegrating tablets.

TABLE 6

Study design considerations for acceptability assessments of pharmaceutical dosage forms in children and older adults

Study types	Clinical trials (randomisation, open/blind, single/multi-centred) vs other types of studies (e.g., standalone acceptability investigation, post-marketing survey)
Study settings	Hospital vs special clinics vs community e.g., home, school, children centre **for children** or home, nursing home, residential home, health centre **for older adults**
Population characteristics	- Age (division into subgroups according to age) - Health volunteers vs **children** or **older adults patients** with diseases (disease status) - Developmental disabilities **for children**- - Co-morbidity **for older adults** - Swallowing difficulties Age-related impairments (e.g., visual/cognitive impairments) **for older adults** - Past experiences in taking medicines - Current medications and whether or not polypharmacy **for older adults**
Study methods and tools	- Interviews/focus groups/questionnaires/ observations/diary entries - Facial scale/Likert scale/visual analogue scale
Details in methodology	- Number of participants - Study duration (short vs long term use) - Number of administration attempts - Person who answers the question e.g., children vs parents/carers/healthcare professionals **for children** or e.g., patients vs partners/carers/healthcare professionals **for older adults** - Carers experiences when giving/administering medicines
Dosage forms to be studied	- Acceptability of a single dosage form or comparison between more than one - Placebo vs drug-containing medicines - Number of dosage forms to be taken at the same time - Administration as labelled or unlicensed use
Acceptability definition	Standardised terms/definitions to be used vs a variety of terms needed
Acceptability criteria	Universally agreed acceptability standard (e.g., 70%) vs case by case basis

aged below 5 years. Between the ages of five and seven, responses are questionable but their validity improves between 8–11 years of age. This taskforce considered that self-reports should be preferred only for children older than 11 years. In addition, the ASTM 'Standard Guide for Sensory Evaluation of Products by Children', although developed for food products, provides guidance on the development of studies in children of different ages [85]. The EMA has also expressed a view that it is preferable for acceptability studies to be conducted in the most relevant patient population as an integrated part of clinical trials [24,26].

Acceptability definitions and criteria

Although attempts were made to evaluate acceptability of dosage forms in the two patient populations, a common definition of acceptability was not applied in the studies. In several studies, terms such as 'acceptability', 'ease of administration', 'ease of use', 'preference', 'ability in swallowing', 'ease of swallowing', 'problems in administering tablet' and 'success in swallowing pills' were used as the evaluation for the success or otherwise of the study without clear definition of these terms (Table 6). 'Acceptability' has been defined in recent guidelines [24,25], which has been a key step forward in improving the understanding in acceptability testing as researchers start designing their studies to explore the ability and willingness of the patients to take their medicine as intended. In other words, the definition enables researchers to identify and focus to achieve the same aim. Recent reviews have proposed specific definitions of the terms relevant to acceptability such as preference and usability [29]. However, it needs to be noted that these terms differ from the regulatory definitions of 'acceptability'. For example, 'preference' is not used as a part of the terminology in regulatory guidelines. Patient preference of one medicine over another gives only the relative comparison and not the actual acceptability of the medicine. Overall acceptability is the combined effect of several contributing

factors such as appearance, palatability, swallowability and ease of administration [26]. Consequently, the definition of acceptability is open to interpretation and the way it is translated into practice might differ between studies (i.e., different outcome measures and data collection tools). There is a need for a stream of work to harmonise the study design as well as the collection and analysis of data to be able to compare the outcomes of different studies.

A first attempt to consider simultaneously the contributing factors of acceptability has been described recently [86], whereby acceptability has been approached as a multidimensional concept. An acceptability reference framework, map and profiles have been designed using evaluations of medicine use in real-life conditions. For each evaluation, a set of contributing factors has been observed and the data have been treated with multiple correspondence analysis to define an acceptability map. Utilising a clustering process, evaluations reflecting treatments positively accepted emerged in a different cluster than those that were negatively accepted. The first results showed that in 70% of the treatment evaluations performed the medicines were positively accepted (234 children, 109 medicines) [86]. A further larger scale application of the tool showed similar results with 72% positive acceptability in 850 children and 80% positive acceptability in 950 older patients (unpublished data from F.R.). The reliability of the model has been validated in a paediatric population [87].

Other tools might be considered in adaptation for acceptability assessment, such as the Medication Acceptance Scale (MAS) which evaluates a child's reaction to medication based on facial expressions, reactions upon ingestion and amount of dose swallowed [88]. This tool could be useful for patients with difficulties using scales (e.g., young children, older patients with certain diseases). However, it needs to be noted that the MAS has been specifically designed for infants and certain items (e.g., crying and body movement or level of agitation) might not be suitable for other populations such as older patients. In the studies analysed in this review, Rodd *et al*. modified the MAS by deleting the section regarding gross motor movements and the authors stated that ''it was not deemed appropriate for newborns" [89]. Other tools used in PRO measures include the Treatment Satisfaction Questionnaire for Medication (TSQM) [90], Treatment Satisfaction with Medicines Questionnaire (SATMED-Q) [91] and ACCEPT [92] and those recommended by the Equator Network (http://www.equator-network.org/reporting-guidelines/), which could be considered for adaptation in acceptability assessment. However, these PRO instruments are proposed to assess 'satisfaction', which includes other factors of interest (e.g., side effects, symptom relief and effectiveness) other than acceptability of the formulation. Moreover, these tools have been validated in adult populations and their appropriateness for use in children (especially aged under 12 years) and older patients needs to be carefully evaluated. Correspondingly, the criteria used for determining whether or not a formulation is acceptable is missing from the studies. Again, a universally agreed arbitrary limit or standard (e.g., 70% or 80% acceptance) might be considered; however, in certain circumstances a risk:benefit-based approach might be more appropriate on a case-by-case basis. One solution would be to join the efforts of key stakeholders to prepare a reporting guideline for medicine acceptability testing as for other main study types such as observational studies and randomised trials. The standardisation of study methodology and data reporting will assist researchers to publish high-impact health research and generate evidence-based information towards better medicines for children and older people. It is to be acknowledged that scientific publications could be used as supportive evidence in the approval of new medicines, although regulatory bodies might still require the original data to be submitted and reviewed as part of regulatory procedures.

Limitations of the study

This review has focused only on formulation aspects of the pharmaceutical product design and does not include other aspects such as packaging or device used. It should be acknowledged that aspects of a medicinal product other than formulation also have profound impacts on patient acceptability, as shown by Drumond *et al*. [29]. Data extraction did not consider the effects of the study settings, such as the presence of caregivers or the researcher or observer on the outcome measures on acceptability. However, this might change the behaviour of the child or older patient and alter the overall acceptability results.

Concluding remarks

The development of medicines that are appropriate and acceptable to paediatric and older patients is of paramount importance in ensuring adherence and medication safety [93]. However, assessing the acceptability of medicines in these patient groups is challenging, considering the complexity of the study population and the diversity of the end goal of the individual investigation. Published methods reporting acceptability of oral medicines in children and older adults show a lack of standardisation in terms of participant characteristics, the study settings, evaluation tools and endpoint criteria. A consensus agreement between academia, the pharmaceutical industry and regulators would be welcomed to harmonise and standardise the methodology for acceptability assessment of pharmaceutical products.

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