

**Age-appropriate and acceptable paediatric dosage forms:
Insights into end-user perceptions, preferences and practices from the Children's Acceptability
of Oral Formulations (CALF) Study**

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Abstract

A lack of evidence to guide the design of age-appropriate and acceptable dosage forms has been a longstanding knowledge gap in paediatric formulation development. The Children's Aceptability of Oral Formulations (CALF) study captured end-user perceptions and practices with a focus on solid oral dosage forms, namely tablets, capsules, chewables, orodispersibles, multiparticulates (administered with food) and mini-tablets (administered directly into the mouth). A rigorous development and testing phase produced age-adapted questionnaires as measurement tools with strong evidence of validity and reliability. Overall, 590 school children and adolescents, and 428 adult caregivers were surveyed across hospitals and various community settings. Attitudes towards dosage forms primarily differed based on age and prior use. Positive attitudes to tablets and capsules increased with age until around 14 years. Preference was seen for chewable and orodispersible preparations across ages, while multiparticulates were seemingly less favourable. Overall, 59.6% of school children reported willingness to take 10mm diameter tablets, although only 32.1% of caregivers perceived this size to be suitable. While not to be taken as prescriptive guidance, the results of this study provide some evidence towards rational dosage form design, as well as methodological approaches to help design tools for further evaluation of acceptability within paediatric studies.

Keywords

paediatric; medicine; solid oral dosage forms; age-appropriate; patient acceptability; preferences

1. Introduction

The maturing field of clinical pharmaceuticals has steered a drive towards patient-centered formulation development (Liu et al., 2014, Florence, 2010, Stegemann et al., 2016). This is particularly evident in the area of paediatrics, where evolving regulatory reforms have strengthened a global focus to
5 facilitate authorisation and access to safe and high quality medicines for children. These drivers have transformed this once niche area into an integral part of the drug development process, with both the European Medicines Agency (EMA) and Food and Drug Administration (FDA) obligating investigators to outline comprehensive formulation development strategies through Paediatric Investigation Plans (PIPs) and Pediatric Study Plans (PSPs), respectively. The rationale for choice,
10 including advantages and disadvantages of dosage form design needs to be discussed and justified, with a demonstrably positive benefit-risk balance (EMA, 2013).

In its pivotal pharmaceutical development guideline, the EMA defines an age-appropriate paediatric medicine as one “whose pharmaceutical design makes it suitable for use in the target age group(s)”,
15 with pharmaceutical design encompassing factors such as composition, dosage form, dosing frequency, and packaging (EMA, 2013). A strong emphasis is placed on ensuring that formulations are acceptable to patients, by demonstrating “the overall ability and willingness of the patient to use and its caregiver to administer the medicine as intended” (EMA, 2013, Kozarewicz, 2014). Indeed, designing formulations that are both suitable and favourable for end-users can benefit patient
20 adherence and ultimately therapeutic outcomes; thus, it is just to insist that this is evaluated during pharmaceutical and clinical development. However, there is often limited information available about the taste characteristics of the active pharmaceutical ingredient (API) when a PIP is submitted, to give indications about taste masking techniques required for a paediatric dosage form. This is coupled with a well-acknowledged paucity of evidence-based data to help define key formulation characteristics
25 that are shown to be age-appropriate or acceptable across this highly heterogeneous population (Ranmal and Tuleu, 2013, van Riet-Nales et al., 2011, EMA, 2006). Therefore, it can be particularly challenging for formulation scientists to propose suitable approaches for clinical investigations, including preliminary or enabling preparations, as well as for final commercial products. In 2009,

nearly half of all PIP applications were referred to a specialised Formulation Working Group of the Paediatric Committee (PDCO FWG). Overall 92% of the 125 pharmaceutical formulations proposed had at least 1 issue; 96 were related to the pharmaceutical form, including 21 regarding appropriate choice of dosage form, while patient acceptability of 12 oral dosage forms was either not addressed or considered inadequate (Quijano Ruiz et al., 2014).

With the aim of addressing this important knowledge gap, the Children's Aceptability of Oral Formulations (CALF) study involved eliciting the unique views of school children, adolescents, and their caregivers, with a specific focus on solid oral dosage forms (SODFs). Suitability of dosage form design is one of the foremost challenges in paediatric drug delivery research, and this aspect can influence other important factors such as the need and choice of excipients or the necessity of devices. There has been a notable shift towards the development of solid formulations over liquids, given the limitations with stability, palatability, and costs associated with the latter (Lajoinie et al., 2014, Venables, 2013, Walsh et al., 2014). Rapidly advancing innovative technologies such as (oro-)dispersible, multiparticulate and chewable preparations offer the key advantages of solid dosage forms, together with the flexibility of dosing and ease of ingestion traditionally associated with liquids. Development of appropriate formulations is a global health challenge and the distinct requirements in resource-limited settings also requires due consideration (Craig et al., 2009, Sosnik et al., 2012). The World Health Organization (WHO) has spearheaded various initiatives in the area of paediatric medicines, including the aptly named "Make Medicines Child Size" campaign. In their key points to consider document, the WHO advocates the development of flexible SODFs, defined as those that can be administered in more than one manner, for example, tablets that can be dispersed in water or breast milk, or alternatively, be swallowed intact (WHO, 2012). Nevertheless, prior to adopting these changes in policy, there is a critical need to understand end-user attitudes and preferences to ensure that these proposals are truly patient-centric.

2. Material and methods

55 2.1. Development and testing of research instruments

A quantitative data collection approach was used in the CALF study, primarily using age-adapted questionnaires for children aged 6 to 9 years (CQ: children's questionnaire) and 10 years and over (YPQ: young people's questionnaire), and a separate questionnaire for caregivers (AQ: adult questionnaire). Based on the principles of patient and public involvement (PPI) in research, the
60 development, pre-testing and piloting of all research materials was completed through an iterative, systematic process involving 140 contributors. This mixed-method approach included study conceptualisation with a multi-disciplinary focus group, cognitive and observational interviews, and quantitative assessments of validity and reliability (Table 1).

65 Figure 1 illustrates the six SODFs of interest and the scale used to assess end-user attitudes. The 3-item, 5-point scale evaluated distinct but inter-related components: affective - whether the dosage form was liked or disliked; behavioural - willingness to take the dosage form; and cognitive - whether the dosage form was perceived as easy or difficult to take. This theoretical tripartite model derived from attitude psychology research has been utilised across various disciplines to capture an overall
70 'global evaluation' of an object based on the synergism of these components. The multicomponent scale demonstrated high internal consistency, as assessed by Cronbach's alpha ($\alpha = 0.782 - 0.903$). Importantly, this approach enabled the *acceptability* of each dosage form to be captured, a construct that is distinct from *preference*. Moreover, the scale accurately reflected the EMA's definition of acceptability as a measure of both *ability* and *willingness* (EMA, 2013). Children themselves
75 preferred the multicomponent scale over single-item measures, and it was found to be appropriate with respect to comprehension, respondent burden, and sensitivity in capturing attitudinal differences.

In addition to attitudes and acceptability, the questionnaires addressed preferences for dosage forms and their attributes, as well as current experiences and practices with medicines. Demographic
80 variables captured included age, gender, ethnicity and socioeconomic status (SES). To enable young people to self-report SES, the validated Family Affluence Scale (FASII) developed for the

international WHO Health Behaviour in School-Aged Children (HBSC) study was used with the permission of the research team (Currie et al., 2008a, Currie et al., 2008b). Presence of a chronic health condition (CHC) was captured using a dichotomous question and defined as “symptoms, diseases or conditions that affect [respondents] for 3 months or longer”. For younger respondents completing the CQ, ethnicity and SES were proxy-reported by caregivers. Overall, test-retest reliability of the instruments was found to be acceptable as assessed by Cohen’s kappa, ranging from $K = 0.43 - 0.77$ for individual questionnaire items.

2.2. Study design

In the main study, large-scale data collection was completed via opportunistic, purposive sampling across various hospitals, pharmacies, schools, and community settings in the UK, and a smaller sub-study in Montreal, Canada. Questionnaires were self-completed independently by children and their caregivers under the supervision of the researchers. Items were read out verbatim to younger participants where necessary. As a requirement of ethical approval, questionnaires used in Canada were translated into French to cater to Quebec’s francophone population. Forward translation was initially completed by the researcher completing fieldwork in the setting, and translated drafts were reviewed independently by two bilingual French speakers.

Following completion of the questionnaires, participants’ perceived acceptability of tablet and capsule sizes was assessed using physical models of varying dimensions. Specifically, these were round, white, flat-faced tablets of 5mm, 8mm, 10mm and 13mm diameter, and white, capsules in sizes #3, #1, #0 and #00. Children and young people selected the largest size they would be willing to swallow intact, while caregivers reported the sizes that they would deem most suitable for their child. Participants were not required to swallow the sizes that they had selected.

2.3. Ethical approval

In the UK, research conducted in community settings was approved by the local university research ethics committee (REC), while data collection in hospitals was approved by the National Research

110 Ethics Service (NRES) REC (ref: 12/YH/0121). In Canada, approval was granted by the Central
Committee of Ethics Research (CCER) of the Ministry of Health and Social Services (MSSS) in
Quebec. All participants were provided with information sheets, and written assent and consent was
obtained from both children and adults respectively, where needed as a requirement of ethical
approval. Based on guidance from NRES, five sets of age-adapted information and consent forms
115 were designed, appropriate to various age ranges and styles, including pictorial content for the
youngest participants (NRES, 2011).

2.4. Data management and analysis

During fieldwork, researchers administered laminated copies of questionnaires to respondents, which
120 were then photocopied or transcribed to identical pages. Data was uploaded to Qualtrics (Provo, Utah)
for cleaning and two-step verification. Descriptive and statistical analysis completed using Microsoft
Excel (version 14.4.1, Microsoft Corporation) and SPSS (version 22, SPSS Inc., Chicago). Mean
scores from scaled items were compared using t-tests and ANOVA, with non-parametric Kruskal-
Wallis H tests and Mann-Whitney U tests used for sensitivity analysis. A univariate general linear
125 model (GLM) analysis was completed to determine whether there was an interaction effect between
demographic variables and mean attitudinal scores. Chi-square tests for association (χ^2) were used for
statistical comparisons of categorical data. Since data analysis involved multiple hypothesis testing,
the Bonferroni method was used to correct for multiple comparisons. A p-value significance threshold
of 0.05 was used throughout.

130 **3. Results and discussion**

3.1. Participant demographics

In the main CALF study, 590 school children and adolescents were surveyed, 48% in hospital settings, 36% in pharmacies or other community settings, and 16% in schools. School children are defined as those aged 6 to 11 years and adolescents aged 12 to 17 years. Participants' demographics and health backgrounds are summarised in Table 2. As intended, research across various clinical and non-clinical settings ensured that the sample of participants was diverse, including patients with a CHC or acute illness, as well as healthy or medicines naïve children. A further 428 questionnaires were completed by adult caregivers, 284 as caregivers of school children and 144 of adolescents. The majority of these were female (78.5%) and parents (94.2%). In Canada, over three-quarters of the questionnaires were completed in English, 92 by children and adolescents, and 83 by caregivers.

3.2. Attitudes and preferences

The CALF study has been unique in directly comparing attitudes and preferences towards six different SODFs. To capture overall attitudes, ratings for each item on the tripartite scale (Figure 1) were scored from 1 to 5, and summated to produce an attitudinal score between 3 and 15. Figure 2 illustrates the rank order of acceptability based on mean summated attitudinal scores. Additionally, the results from the behavioural component of the scale are illustrated, reported as the willingness to take the dosage form for children and adolescents, and willingness to purchase the dosage form as an over the counter (OTC) paediatric medicine among caregivers. Mean attitudinal scores from school children and adolescents were compared for different demographic and healthcare variables (Table 3). This analysis demonstrates that attitudes were most significantly affected by age and prior use of dosage forms. Univariate general linear model analyses showed no interaction effect between attitudinal scores and the three independent demographic variables, age, sex and SES (completed for UK respondents for whom SES data was reported).

3.2.1 Tablets and capsules

As shown in Table 3, mean attitude scores for tablets and capsules increased with age ($p < 0.001$) indicating more favourable perceptions, whereas scores for more novel dosage forms tended to decrease. Tukey's post-hoc analysis highlighted a significant difference in attitudes to these dosage forms until the age of 12 to 13 years; from the age of 14 years, attitudes towards both remained stable. Interestingly, the same trend was observed among caregivers, with no significant difference in mean scores from the age of 14 years. Related to this, prior use of these dosage forms increased in early adolescence; only 38.8% of 10 to 11 years olds reported prior use of tablets versus 63.6% of 12 to 13 year olds. This difference was less pronounced for capsules (20.1% and 36.5% respectively). Similar rates of prior use have been reported elsewhere, including a US survey which found that nearly all respondents aged 12 years and over had used SODFs in the past (Polaha et al., 2008).

In the present study, mean attitudinal scores among caregivers tended to be lower and more variable than paediatric scores for all SODFs. T-tests confirmed statistically significant differences in mean scores among school children and their caregivers for tablets ($p < 0.001$) and capsules ($p < 0.001$), illustrated by the wider difference in means in Figure 2. Parents and caregivers play an important role in paediatric medicines use, from purchasing OTC medicines to taking primary responsibility for medicines administration. Nevertheless, caregiver perspectives of acceptability should be considered in a complementary manner, rather than as data that takes precedence or substitutes children's own views. Additionally, adults have previously shown inaccurate preconceptions that can affect their ability to predict children's behaviour and choices, including autonomy of medicines use (Hämeen-Anttila and Bush, 2008) and ability to swallow small placebo tablets (Meltzer et al., 2006).

Children's age has conventionally been seen as the primary factor when considering dosage form suitability, with 6 years historically cited as the age from which tablets and capsules may be considered suitable (EMA, 2006). Nevertheless, evidence has shown that children as young as 3 years old are able to swallow conventional tablets and capsules (Nahirya-Ntege et al., 2012, Kaplan et al., 2010, Czyzewski et al., 2000). On the other hand, older children and adolescents have reported swallowing difficulties, including as a barrier to adherence in chronic conditions (Hansen et al., 2008,

185 Polaha et al., 2008, Hommel and Baldassano, 2010, Modi et al., 2013). The present study highlights that while age is a critical factor, other aspects such as health background are also important characteristics to consider. While prior use of dosage forms was effective at capturing differences in attitudes, presence of a CHC showed less sensitivity. Overall, tablets and capsules were ranked the least favoured dosage forms for school children (Figure 2); nevertheless, school children reporting
190 frequent prior use had mean scores comparable to those of adolescents. Feedback from some of the youngest participants revealed positive perceptions, including for example, that “*tablets are adult medicines [which are] stronger and will make me better quicker*” (female participant aged 6 years old).

195 In addition to determining attitudes, participants’ preferences were captured through direct comparison of dosage forms (Figure 3). Both school children and adolescents showed a stronger preference for tablets over capsules, and indeed, tablets were ranked the most acceptable of all six SODFs among adolescents and their caregivers. The reasoning behind positive attitudes to tablets included familiarity, as well as ease and rapidity of ingestion. Barriers to the acceptability of capsules
200 included their large size, and in some instances, the misconception that they are made from plastic. A small proportion of school children (12.7%) preferred neither dosage form, though nearly half reported a neutral or negative response to the behavioural component of the scale. It is important to note that barriers to acceptability are not limited solely to the paediatric population. Incidences of medication related swallowing difficulties might have contributed to these findings, as this a well-
205 known problem across all ages. A small number of studies investigating this issue in the general adult population have reported prevalence rates between 9% to 40% (Marquis et al., 2013, DeRoche et al., 2003, Schiele et al., 2013). Remarkably, these studies have indicated a gender effect, with a significantly higher frequency of difficulties among females compared to males. In the CALF study, male respondents tended to have more positive mean scores for all dosage forms; however, the
210 superior scores for tablets and capsules in adolescents were the only differences to reach statistical significance.

Collectively, this evidence suggests that a useful approach to help guide pharmaceutical development is to assess the attributes of currently available commercial products, and determine whether these are acceptable and capable of being administered as authorised in practice. Specifically, such research should focus on capturing patients' actual experiences and practices. Moreover, this assessment should be completed for different age groups, and across diseases and indications, to help determine the extent to which unique, novel paediatric dosage forms are required. Indeed, in many cases, dosage forms developed for the paediatric population may be suitable for older adults, as well as the seemingly large number of adult patients who struggle to swallowing medicines. In certain chronic conditions, patients may have acquired the ability to swallow monolithic dosage forms intact. In such cases, tablets of appropriate dose strengths or with functional score lines may present a suitable and beneficial option for paediatric patients. Flexibility with capsules may be achieved if they are labelled for administration intact or via sprinkling of the contents. Indeed, tablets and capsules offer important advantages including accuracy of dosing, taste-masking, and ease and cost-effectiveness of manufacture. These benefits should be acknowledged in cases where these dosage forms are a potential option for paediatric medicinal products.

3.2.2 Novel dosage forms

Multiparticulates and mini-tablets show considerable promise in the paediatric population, as they offer the coveted goal of ease of administration and dose flexibility, and potentially have wide applicability through adjustment of dose quantity or volume. Recent studies assessing the acceptability and swallowability of placebo mini-tablets have been a notable emergence in the field, particularly as a dosage form for neonates and infants (Klingmann et al., 2013, Klingmann et al., 2015, Thomson et al., 2009, van Riet-Nales et al., 2013, Kluk et al., 2015). An important objective of the CALF study was to determine acceptability and perceptions of these dosage forms in older children, since very little is reported in the literature. A critical factor to note is the respective descriptions used to effectively discriminate both dosage forms; mini-tablets were presented as multiple discrete units administered directly into the mouth, while multiparticulates were described as being administered with soft food. While both dosage forms can potentially be administered either

way, this differentiation was included for clarity and brevity. Future research evaluating these dosage forms should assess the impact of these modes of administration on end-user acceptability.

245 In the CALF study, mini-tablets were relatively well accepted across ages, whereas multiparticulates became markedly less favourable with increasing age. Post-hoc analysis showed the decrease in mean attitude score for multiparticulates at the age of 10 to 11 years (Table 2) was most significant (p=0.004). Anecdotal feedback identified various factors as potential barriers to acceptability, including perceptions that they were infantile (particularly among older children), reservations about administering medicines with food (particularly in terms of consequent adverse effects to taste), and 250 concerns about knowing whether the whole dose had been administered. This is an important consideration during the development and eventual labelling of multiparticulate products.

Administration of powders and granules with soft, semi-solid foods has been deemed to be suitable for infants from the age of 6 months (EMA, 2013); however, to ensure the widest applicability, both direct administration in the mouth and mixing with food should be investigated. Adequate assurance 255 of taste-masking and palatability should be ensured, as participants' concerns are not unfounded. In the case of micronutrient sprinkle products for example, acceptability rates of over 90% have been reported by caregivers of infants (Zlotkin et al., 2003, Adu-Afarwuah et al., 2008). However, in one study, nearly of all caregivers reported that sprinkles had an unpleasant smell or taste, and that they changed the colour of food, both of which may negatively impact acceptability (Kounnavong et al., 260 2011).

In the present study, over 60% of school children and adolescents reported a willingness to take mini-tablets; however, in direct comparison, nearly half of all adolescents preferred to take a single tablet over mini-tablets (Figure 3). As part of a recent clinical study, Musiime et al. reported that older 265 children aged 4 to 13 years old who were able to swallow tablets found these more acceptable than mini-tablets that were administered with food (Musiime et al., 2014). Problems with taste and swallowing difficulties were reported by 50% and 13% of the cohort respectively for the mini-tablet product, while neither problem was reported with tablets. Concerns raised about mini-tablets in the

CALF study included handling difficulties, risk of aspiration or choking, and perceptions that they
270 would become “stuck” in teeth or tonsils. An important evidence gap with both mini-tablets and
multiparticulates is determining acceptability relative to dose quantity, and organoleptic properties
including mouthfeel or grittiness. Future research assessing these dosage forms should also consider
the modality for drug delivery and use of devices to facilitate administration. The CALF study
captured some preferences with regards to administration, with 44.9% of young people, and 45.3% of
275 caregivers favouring stickpacks or sachets. A further 22.8% and 14% respectively favoured capsules
that could be opened, while the remaining respondents stated no preference.

Age showed little effect on attitudes to orodispersible dosage forms, whereas with chewables,
attitudinal scores decreased with age but remained highly favourable for both school children and
280 adolescents. Chewables were also specifically preferred over orodispersibles and multiparticulates
(Figure 3). From an anthropological perspective, this may be instinctive; the importance of chewing
food is widely reiterated to children and mastication before swallowing is an innate mechanism for
articles which enter the mouth (Mrsny, 2012). The natural tendency to chew was evidenced in the
recent studies assessing acceptability and swallowing of mini-tablets, especially amongst those aged 2
285 to 3 years old (Thomson et al., 2009, Klingmann et al., 2013). A large market research study found
that parents in the US predominantly preferred chewables over other oral dosage forms in children
aged 1 to 15 years, while German parents showed a stronger preference for effervescent tablets and
lozenges. (Hermes Pharma, 2015). In contrast, Adams et al. found that caregivers in Tanzania
preferred pills to be swallowed intact, over chewable forms for school aged children (Adams et al.,
290 2013). Notable differences in parental attitudes to orodispersible tablets have also been shown
between European countries (Valovirta and Scadding, 2009). This disparity may be attributable to
difference in familiarity and prior use of dosage forms, an important contributing factor identified
from the CALF study.

295 Based on this emerging evidence, chewables can be considered a preferred dosage form in cases
where satisfactory organoleptic properties such as taste and mouthfeel can be achieved. Many

chewable medicines have been licensed and shown to be safe and well-tolerated in children from the age of 2 years (Michele et al., 2002). For younger participants, orodispersibles offer more potential with regards to ease of ingestion, while orodispersible mini-tablets or multiparticulates may add an important degree of dose flexibility or wider dose range where required. Multiparticulates and mini-tablets should be considered to be evaluated to be administered with food or directly via suitable, age-appropriate devices or packaging. Based on recent FDA guidance, multiparticulates labelled for administration via sprinkling should have a target size of 2.5mm (with no more than 10% variation over this to a maximum size of 2.8mm) to ensure adequate mouthfeel and reduce the risk of inadvertent chewing (FDA, 2012). In all cases, decisions regarding oral dosage form choice will often be principally governed by the taste profile and properties of the API and excipients.

3.3. Dosage form attributes

Attributes of dosage forms, such as size, shape and colour can be adapted to provide aesthetic final products that are acceptable to the end-user. Nevertheless, care must be taken to ensure that medicinal products do not appear too attractive or strongly resemble confectionary, and use of colouring agents is generally discouraged (EMA, 2013). Whatley et al. assessed the ability of healthy children aged 4 to 11 years old to identify medicines; red and white bi-coloured capsules were more correctly identified as medicines compared to tablets, while 53% of children incorrectly identified pink tablets as “sweets” (Whatley et al., 2012). In the present study, dosage form size and taste were rated as very important by 56.8% and 55.3% of young people respectively. Interestingly, colour was ranked the least important attribute with 70.7% rating it as not important. Almost half of all young people (48.8%) showed no specific preference for colour, whereas 25.6% preferred white medicines and 25.6% preferred coloured medicines. Anecdotal feedback highlighted that young children themselves had concerns that medicines should not look too appealing, for example, one 12 year old male respondent stated “*I’d prefer them [medicines] to be white [otherwise] I’d feel like I was taking something I wasn’t supposed to.*” From a regulatory perspective, other strategies are preferred for purposes of product differentiation, such as variability in size, shape, and embossing (EMA, 2013).

325 As part of the overall CALF study design, acceptability of tablet and capsule sizes was assessed using
physical models, with participants selecting the largest size they perceived to be able to swallow, or
that their child would be able to swallow. Notably, responses were based on perceived acceptability,
as actual swallowability data was not captured within this or a follow-up study. Nevertheless, these
findings present some indication of potential geometric characteristics to consider for further
330 evaluation in larger studies. As illustrated in Figure 4, 59.6% of school children reported the
willingness to take tablets of 10mm diameter or larger, while only 32.1% of caregivers found this size
suitable. In comparison, 82.9% of adolescents and 77.1% of their caregivers found tablets of this
diameter to be acceptable. Kokki et al. reported that 80% of children aged 1 to 9 years old were able
to swallow 7mm tablets, while in their study, Meltzer et al. reported 84% of school-aged children
335 could swallow tablets of the same size, with or without ordinary training (Kokki et al., 2000, Meltzer
et al., 2006). For capsules, 15% of school children chose none, while the majority (43.9%) chose the
smallest size presented. These findings are supported by evidence from practice; one study involving
observed administration by nurses reported that 84% of children aged 4 to 6 years were able to
swallow size #3 capsules intact (Mekmullica and Pancharoen, 2003). Similarly, Patchell et al. found
340 that over 87% of children aged 3 to 17 years could swallow size #2 capsules, while Green et al. found
that 73% of children could swallow hydroxyurea capsules, including over half by the age of 10 years
(Patchell et al., 2002, Green et al., 2013).

Using a similar approach with physical models, Batchelor et al. reported that over 97% of children 6
345 to 7 years old and 85% of children aged 8 to 10 years old found 10mm caplet shaped tablets
acceptable (Batchelor et al., 2013). Differences in the shape of tablet models (caplet versus round)
may contribute to these differences in findings. In the present study, 46.4% of school children and
34.1% of adolescents preferred round shaped tablets, versus 17.6% and 29.4% for oval or oblong
shapes (the remaining participants showed no preference). Conversely, nearly half of all adults
350 preferred oval or oblong shaped tablets.

A previous draft version of the EMA guideline proposed that tablets up to 10mm in diameter (medium tablets) would be deemed appropriate for school aged children and tablets up to 15mm in diameter (large tablets) for adolescents; however, this guidance was later removed for lacking a strong
355 evidence base (Ranmal and Tuleu, 2013, EMA, 2011). This study suggests that 10mm diameter tablets would be unacceptable for around 40% of a general sample of children aged 6 to 11 years, while 13mm tablets would be unacceptable for nearly half of all adolescents. Research analysing reports of swallowing difficulties among adults suggest that this can arise when tablets are greater than approximately 8mm in diameter (Schiele et al., 2013, FDA, 2013). A review of all agreed PIPs
360 by the end of 2011 found that tablets larger than 5mm had been approved for children aged 2 to 5 years and tablets larger than 10mm for children aged 6 to 11 years; studies assessing the effect of modifications were not included in the list of binding terms, and details of the therapeutic indications for these products were not included in the review (van Riet-Nales et al., 2014b). However, as highlighted from this study, the therapeutic condition and availability of existing medicinal products
365 should be considered alongside age. A recent US survey highlighted the vast differences in tablet and capsule sizes for the most commonly used paediatric medicines of the same dose, frequently between 1 and 10mm in length, but in some cases even greater than this (Jacobsen et al., 2016). Due consideration of dosage form size is equally important for generics and off-patent medicines for use in paediatric patients, which may fall outside of the current regulatory remit.

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3.4. Practices

In addition to attitudes and preferences, little is reported on the pragmatic approaches adopted by children and their caregivers to aid the administration of formulations that are not optimally designed for use in this population. Modifications include physical alterations to dosage forms, such as
375 crushing or splitting tablets, opening capsules or mixing medicines with food or drink. This can be with the aim to improve acceptability, to facilitate administration, provide an appropriate dose, or a combination thereof. The nature, motives and consequences of these practices remains an under researched area; however, they have been widely reported amongst healthcare professionals (Skwierczynski and Conroy, 2008, Akram and Mullen, 2012, Richey et al., 2013) and as “coping

380 strategies” among children and their caregivers (Hansen et al., 2008, Adams et al., 2013, Bryson, 2014).

Overall, modifications were reported by 19.1% of school children and 17.1% of adolescents who had taken tablets or capsules in the two weeks preceding questionnaire completion. The most common
385 modifications included crushing or splitting tablets and/or mixing medicines into food or drink. One limitation of the CALF study is that the purpose of modifications was not captured, for example, whether for provision of the appropriate dose, to aid administration, or both. Fewer than 10% of school children and adolescents taking tablets and capsules during the two weeks reported missing a dose due to swallowing difficulties. Among school children reporting modifications or non-
390 adherence, 75% were female, and one-third had a CHC. In adolescents, 60% were female and nearly half had a CHC. These rates highlight the need to further research the potential aforementioned gender effect. Evidence providing a scientific basis for such dosage form modifications is frequently lacking, though concerns about safety and efficacy are not unfounded. Potential and proven risks include calculation and practical errors (Wong et al., 2009), inaccuracy of dosing (Quinzler et al.,
395 2006, van Riet-Nales et al., 2014a) and harm to the individual who alters the medicine (Akram and Mullen, 2012). Altered bioavailability and palatability issues can also be of significant consequence (Best et al., 2011, Ferrarini et al., 2013).

It is important for healthcare professionals to view children as autonomous social actors and provide
400 relevant information directly to them as patients and consumers. In support of this, healthcare professionals were reported as the preferred source of information about medicines, with 80.4% of young people reporting that they would ask a doctor nurse or pharmacist if they had any questions or needed information. Just over half (56.3%) would ask family or friends, while 47.4% would look on the Internet. However, only 38.5% of respondents said they would read the patient information leaflet
405 (PIL) and 13.6% would consult other written information about the medicine. This further emphasises the need for all elements of medicinal products to be adapted in consideration of the needs of children.

3.5. Child-centred research: from subjects to participants to contributors

Despite the proposed paradigm shift towards child-centred research, there is much less empirical and methodological knowledge to guide this with younger populations compared to adults. Regulators suggest that acceptability of medicinal products should be preferably assessed with children themselves (EMA, 2013, Kozarewicz, 2014). This is advocated given sensory and perceptual differences across ages, and increasing evidence highlighting that attitudes and experiences are most accurately and reliably obtained from children themselves. However, it is imperative that the instruments developed are thoroughly tested and piloted in the intended population. As highlighted from this and other studies, children and young people's active involvement and contribution early in development can facilitate the construction of age-appropriate instruments that are consistent with their competence, abilities and understanding (Stocks and Lum, 2016).

3.6. Limitations

While this study has addressed an important knowledge gap in the field, certain limitations are acknowledged. Given the paucity of evidence available, gaining insights into dosage form acceptability warranted exploratory, qualitative methods; however, for the same reason, collecting data from large representative samples was also needed, to help address the limit in information that currently hinders early paediatric formulation development. Nevertheless, further qualitative approaches are encouraged. Additionally, it is important to highlight the demographic of present study, which included a large proportion of respondents of Caucasian ethnicity and with a medium to high socioeconomic status. This may need to be considered in relation to the generalisability of findings, particularly in comparison to global and cross-cultural research.

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Importantly, this study has explored attitudes and perceived acceptability of dosage forms, which inherently may not capture actual habits in acute or chronic settings. The initial design involved comparing choices of tablet and capsule sizes with participants' administration practices with current prescribed medicines, including collecting data around the specific dosage form attributes of these.

435 Unfortunately, this was difficult to complete in practice within hospital settings and therefore

responses were based on perceptions rather than actual swallowability data. A follow-up study to assess the swallowability of capsules in school children was also difficult to set-up, and capturing such data on end-user acceptability may be difficult outside of clinical trials. The CALF study had some potential advantages, in that respondents could openly disclose their opinions and views
440 (including barriers to acceptability) without any potential social desirability bias associated with reporting their own behaviours or practices with actual medicinal products. Nevertheless, there is further need for observed, tangible evidence to demonstrate acceptability, particularly in relation to swallowability of conventional tablet and capsule sizes. Access to wider evidence of swallowability in different age groups would help accelerate the development of medicines and avoid additional
445 acceptability studies in children.

5. Conclusions

Children have the right to access medicines that are appropriate to their unique needs and have
450 adequate assurance of their quality, safety and efficacy. Likewise, they should also be entitled and
encouraged to express their beliefs and opinions on matters that are pertinent to them, and this study
reinforces the need for evidence-based research with children themselves, rather than solely relying
on adult proxy reports. Children as young as 6 years old provided invaluable feedback which
benefited the design and development of the study as well as informing the research outcomes. Thus,
455 it is feasible to undertake such research provided methodological approaches are adapted and
structured, and due consideration is paid to children's skills and abilities rather than perceived
limitations. Moreover, data collection instruments should be comprehensively evaluated to provide
assurance of the integrity of research findings.

460 Age-appropriateness and acceptability are influenced by the characteristics of the target patient
population and pharmaceutical properties of the medicinal product. As this facet of formulation
development is in its infancy, there is little evidence to guide the specific aspects of assessment,
appropriateness of methodologies, and expectations of satisfactory outcomes. The EMA guideline
currently states that initial development should "focus on a minimum number of acceptable dosage
465 forms which are capable of meeting the needs of the majority of the children in the target age
group(s)" (EMA, 2013). Given the extensive physiological and developmental differences across the
population, it is unlikely that one single formulation could fulfil the needs and be deemed appropriate
for all intended ages. Rather than a "one size fits all" approach, investigators should aim to tailor each
formulation to cover the widest age range, ensuring pharmaceutical development strategies are
470 effective and economical whilst providing authorised products for all target subsets.

The need for systematic and transparent regulatory evaluation is well established, and understandably,
465 developers seek to follow duly endorsed scientific advice. However, the impetus of this study was not
to outline prescriptive criteria or recommendations in relation to specific patient parameters, and it
475 does not eliminate the need for age-appropriateness and acceptability to be evaluated during

pharmaceutical development. The study findings aim to provide some guidance and rationale towards a formulation strategy for PIPs and PSPs that are submitted early in the drug development process. Provision of a suitable dosage form is fundamental in ensuring safe and effective pharmacotherapy, and this evidence can help inform industrial dosage form design and clinical choice.

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Table 1 Overview of mixed-method studies and pre-testing techniques used to develop and evaluate the research material.

Development Stage	Setting	Number of contributors/ participants	Age (years)
Multi-disciplinary expert focus group	University	8	[Adults]
Focus groups with children and young people	MCRN YPAG	7	13 - 18
	MCRN YPAG	10	8 – 17
	School	5	6 – 10
	School	6	12 -15
Pre-testing: cognitive and observational interviews	MCRN YPAG	4	8 - 11
	School	7	6 - 11
	School	7	12 - 14
Assessment of test-retest reliability	MCRN YPAG	10	8 - 17
	School	5	6 - 11
	School	27	16-17
Triangulation (convergent validity) using participants' current medication practices	Hospital	44	7-17
	Hospital		

Table 2 Demographics and health backgrounds of school children and adolescent participants

	Overall [N=590] (%)	School children aged 6-11 years [n=267] (%)	Adolescents aged 12-17 years [n=323] (%)
Age subgroup (years)			
6-7	16.1	35.5	
8-9	15.6	34.5	
10-11	13.6	30.0	
12-13	14.4		26.3
14-15	14.4		26.3
16-17	25.9		47.4
Gender			
Male	47.1	51.3	43.7
Female	52.9	48.7	56.3
Ethnicity*			
White/Caucasian	48.7	55.1	43.3
Asian	19.7	12.0	26.0
Black	18.1	16.5	19.5
Mixed/Multiple	9.8	11.2	8.7
Other	3.7	5.2	2.5
Socioeconomic status (SES)			
FASII Low	17.1	21.0	13.9
Medium	39.2	38.2	39.9
High	28.1	20.2	34.7
Not reported [†]	15.6	20.6	11.5
Chronic health condition			
Reported	37.3	36.7	37.8
Not reported	62.7	63.3	62.2

FASII: Family affluence scale

* For brevity Canadian ethnicities have been combined with the broader UK groups: n=9 'East or Southeast Asian', n=7 'West Asian/Arab' and n=1 'South Asian' have been classified as 'Asian' and n=1 'Latin, Central or South American' has been classified as 'Other'.

[†] This data was not collected from Canadian respondents in keeping with the requirements for ethical approval.

Table 3 Mean summated attitudinal scores for each dosage forms among school children (SC) and adolescents (A). Attitudes were measured using 3-item 5-point scale measuring affective, behavioural and cognitive components.

	Tablets		Mini-tablets		Capsules		Chewables		Orodispersibles		Multiparticulates	
	SC	A	SC	A	SC	A	SC	A	SC	A	SC	A
Age subgroup (years)												
6-7	9.9		10.8		8.3		12.2		11.7		11.0	
8-9	10.0		11.0		9.0		12.0		11.8		11.5	
10-11	10.3		10.7		8.8		12.4		11.4		9.9	
12-13		11.0		10.8		9.5		11.4		11.2		9.3
14-15		11.8		10.5		10.2		11.1		11.0		8.8
16-17		11.7		11.1		10.3		11.1		10.9		9.6
	p<0.001		ns		p<0.001		p=0.002		ns		p<0.001	
Gender												
Male	10.1	12.1	10.8	11.2	8.8	10.8	12.4	11.4	11.9	11.1	10.8	9.5
Female	9.9	11.1	10.9	10.6	8.6	9.5	12.0	11.0	11.4	10.9	10.9	9.2
	ns	p=0.001	ns	ns [†]	ns	p<0.001	ns	ns	ns	ns	ns	ns
Prior use												
Never	9.3	7.7	-	-	8.2	8.3	11.3	10.2	11.3	10.4	10.8	9.3
Rarely	9.3	10.4	-	-	9.1	9.3	11.9	11.4	12.1	11.3	11.0	9.3
Several times	10.8	11.9	-	-	10.0	11.4	13.0	12.0	12.2	12.3	12.1	11.4
Almost daily	11.5	12.5	-	-	9.8	10.0	14.0	13.7	12.3	14.5		3.0
	p<0.001	p<0.001	-	-	p=0.012	p<0.001	p<0.001	p<0.001	p<0.001	p=0.003	ns	p<0.001
Chronic health condition												
Reported	10.9	12.0	11.4	11.0	8.6	10.5	12.2	11.1	11.9	10.9	10.9	9.5
Not reported	9.5	11.3	10.5	10.7	8.9	9.8	12.1	11.2	11.2	11.1	10.7	9.0
	p<0.001	p=0.015	p<0.001	ns	ns	p=0.040	ns	ns	ns	ns	ns	ns

ns: not significant

-: prior use of mini-tablets was not captured given the paucity of commercially available products

[†] parametric test reached statistical significance but not corroborated by equivalent non-parametric test.

Figure 1 (a) Descriptors of the six solid oral dosage forms (SODFs) evaluated in the study; (b) the 3-item, 5-point tripartite scale used to assess attitudes to dosage forms, including an affective component (like or dislike), cognitive component (easy or difficult to take), and behavioural component (willingness to take for children and young people, and willingness to purchase as an over-the-counter medicine for caregivers). Illustrated scale is from the young people questionnaire (YPQ); wording was adapted for the children's questionnaire (CQ) and adult questionnaire (AQ).

Figure 2 Attitudes and behavioural intent towards dosage forms in (a) school children and their caregivers and (b) adolescents and their caregivers. The lines indicate mean summated attitudinal scores from the tripartite scale. Bar graphs indicate the percentage of respondents reporting willingness to take the dosage form for school children and adolescents, and willingness to purchase the dosage form as an over-the-counter paediatric medicine among caregivers.

Figure 3 Comparative preferences for dosage forms amongst school children and adolescents (a) Tablets or capsules, to compare single-unit dosage forms to be swallowed intact; (b) tablets or mini-tablets, to compare single-unit versus multi-unit dosage forms administered directly; (c) chewables, orodispersible or multiparticulates, to compare specific preferences for more novel dosage forms.

Figure 4 Acceptable (a) tablet and (b) capsule sizes that school children and adolescents perceived to be able to swallow, and that caregivers perceived that their child could swallow. The single largest size was selected for each dosage form.