Title: Sensory aspects of acceptability of bitter-flavoured 7.5 mm film-coated tablets in adults, preschool and school children.

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Abstract: There is great interest in demonstrating acceptability of solid oral formulations in paediatric populations. This study investigated the acceptability of small, 7.5 mm, bitter-flavoured, coated tablets in healthy children and adults. A randomised, double-blind acceptability test was performed involving 101 children (4–12 years) and 52 adults (18–75 years). Acceptability was measured by participants as sensory assessment of taste, mouthfeel and hedonic perception, and by researcher observations of ability to swallow the tablet and negative facial expressions. Additionally, the taste-masking effect of film coatings was assessed based on the intensity of bitterness perception. At least one tablet was voluntarily swallowed by 35.7% of 4–6-year olds, 74% of 7–12-year olds and 98% of adults. The bitterness of the tablet did not affect participants' ability to swallow it. The sensory properties determined whether the tablet was acceptable. The following factors: low bitterness, high smoothness, high slipperiness and pleasant aftertaste had a positive impact on overall palatability in both populations. The paediatric scores during sensory evaluation of tablets differed from adults, showing lower acceptability. This study demonstrates the multifactorial nature of palatability of tablets and highlights that adults' palatability evaluation cannot be directly translated to a paediatric population.

Key words: Acceptability, paediatric medicine, mouthfeel, coated tablets, sensory assessment

1 Introduction

Currently, there is much emphasis on the development of paediatric dosage forms that allow easy and convenient dosing. For a long time, the "gold standard" for age-appropriate medicines was oral liquids with each dose measured using a spoon or syringe. A recent paradigm shift has seen a move from liquids to solid dosage forms for paediatric oral medication (Drumond et al., 2017; Klingmann et al., 2018). The current European Medicine Agency (EMA) paediatric guideline does not limit the use of solid medicines in children by age (EMA, 2013).

For children, the key factors influencing acceptability of oral tablets are the ability to swallow the dosage form, the size and palatability of the tablet (EMA, 2013). A key barrier in developing acceptable and age-appropriate tablets is the lack of knowledge of what is acceptable, and what tablet features are preferred by children. In this sense, the acceptability of small tablets has not been fully established in children. Previous studies on acceptability have used placebo dosage forms, where palatability (taste-masking and mouthfeel) were not represented (Kokki et al., 2000; Meltzer et al., 2006). Furthermore, the impact of coatings on the mouthfeel and swallowing experience associated with tablets has not been explored in children.

Methodology to assess the acceptability of oral paediatric medicines is not standardized. Extensive reviews of currently used methods, conducted in 2017 found only one validated method (Drumond et al., 2017; Mistry and Batchelor, 2017), where the result of swallowing a sample was evaluated by an experienced physician (Klingmann et al., 2013; Spomer et al., 2012). In the literature, the observed ability to swallow a tablet (complete or partial swallowing) has been used as an indicator of its acceptability in young children (Klingmann et al., 2013; Sznitowska et al., 2015). In these studies acceptability has been primarily measured as per the regulatory definition, "an overall ability of the patient and caregiver to use a medicinal product as intended" (Kozarewicz, 2014) by assessing ability to swallow a tablet as an indicator of ability to use the medicine as intended. However, the simple ability to swallow a tablet is not fully representative of the patients' experience. Acceptability is multifactorial and encompasses all the positive and negative experiences of a patient and/or caregiver

which translates into the patients willingness to take the medicine (Drumond et al., 2017). Recently, a more complex observation-based tool was suggested and validated for acceptability evaluation in a paediatric population (Ruiz et al., 2017; Vallet et al., 2018). This study provided real-life data, as parents evaluated four measures ('result of intake', 'child's reaction', 'manipulation-administration time' and 'methods used to achieve administration') during routine medicine use. The tool was found to be universal for various dosage forms and has been transposed for the older population (CAST - ClinSearch Acceptability Score Test®) (Ruiz et al., 2019). However, the abovementioned tools do not collect data from children themselves.

Facial expressions are coded using a Facial Action Coding System, which is widely used, standardised, anatomically based system, where each facial movement is coded as an action unit (AU) (Ekman and Rosenberg, 2005). The system can be used as a tool to recognise emotions (Kring and Sloan, 2007). Observation of key facial features during a swallow provides additional information on the preference of medicines and has previously been shown to link to patient reported measures of the acceptance of liquids (Mistry et al., 2018). In addition, patient reported measures of mouthfeel provide insights into how formulations can be optimised.

Tablets are designed to be swallowed quickly so that the active ingredient does not interact with taste buds; yet there are several anecdotal reports of tablets that have a bitter taste (Gowthamarajan et al., 2004). This can be more significant in paediatric populations where tablet swallowing is less efficient and children have a lower threshold of bitter taste than adults which may change their taste perception of medicines (Mennella and Bobowski, 2015). Coatings are applied to tablets for many functions; to modify drug release, improve the appearance, aid identification and also to improve acceptability (El Edelbi et al., 2015; Hofmanová et al., 2019; Mahdi and Maraie, 2015; Uloza et al., 2010). The aspects of acceptability that can be tuned with a coating layer include palatability (taste and mouthfeel) and ease of swallowing. Three factors which are known to affect taste-masking efficiency of coatings are (i) coating thickness, also related to shape and size of the dosage form (Römer et al., 2008; Sauer and McGinity, 2009); (ii) coating formulation (Joshi and Petereit, 2013) and

(iii) the chemistry of the API (Vesey, 2018). The efficacy of coatings to taste-mask bitter agents has previously been reported in adults (Joshi and Petereit, 2013) yet there is currently no similar data in children.

Many drug substances are bitter, which is linked with disgust and rejection of food and drugs (Peyrot Des Gachons et al., 2011; Rozin et al., 2009). Quinine is a bitter agent commonly used in standardised gustatory tests (Landis et al., 2009; Soto et al., 2015) due to its high bitterness value and the ability of humans to detect this in the micromolar range (Soto et al., 2015). Quinine is a therapeutic agent used in the treatment of malaria; yet low levels are not associated with adverse effects. The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) concluded that quinine levels in soft drinks of up to 100 mg/litre (as quinine base) were not of toxicological concern (JECFA, 1993); thus it can be used as a bitter agent at low concentrations in sensory analysis.

In this study, the acceptability of small (7.5mm) tablets was assessed in children (aged 4-12 years) and adults with participant reported measures of taste, mouthfeel and hedonic perception of the tablet, along with researcher reported ability to take the tablet and negative facial expressions. The data was analysed to determine key attributes for the acceptability of small coated tablets in children; adults were used as a comparator population.

2 Materials and methodology

2.1 Design

The design of this study is based upon the recommendations made by Mistry and Batchelor (2017), and is also informed by a review on 'Sensory and consumer testing with children' (Guinard, 2000) and other relevant literature.

A cross-over, double-blind, single centre acceptability study was proposed to investigate the oral perception (ease of swallowing, mouthfeel and taste) of quinine flavoured tablets with five different coatings. The study was conducted in healthy children (4-12 years old) and healthy adults (18-75 years old). Ethical approval for the study was obtained from the Ethical Review Committee of the University of Birmingham (ERN_18-1782A).

2.2 Participants

The participants were recruited from the University of Birmingham and from groups and networks associated with the research team. Exclusion criteria: reported allergy/hypersensitivity to quinine, smokers, illnesses that compromise taste or smell, lactose intolerance, and swallowing impairment. Adult volunteers were asked to self-assess eligibility for the study, while for child volunteers, eligibility was assessed by the child's legal guardian. On the day of the study eligibility was confirmed by a researcher.

Each participant/their legal guardian received a detailed participant information sheet in advance. They were given adequate time to read and consider the information provided and ask questions. Before the study began, all participants/their legal guardians gave written informed consent and child participants gave verbal assent.

2.3 Materials

The study used round, biconvex, 7.5 x 2.5 mm tablets, prepared by direct compression and comprised 2.5 % (w/w) quinine sulfate as a bitter agent, microcrystalline cellulose, calcium carbonate DC, magnesium stearate, and silicone dioxide (average mass 186 mg, disintegration time 1 minute 53 seconds, hardness 113 N, friability 0.03%). Dissolution data is provided in the supplementary material (Figure S1).

The tablet size used represented the smaller end of solid dosage forms prescribed for children (Jacobsen et al., 2016). Tablets were coated with five different coatings to weight gain of 4% as stated by contracted manufacturer (actual coating thickness ~3 μm) (Table 1). The tablets were supplied with a statement of fitness for human consumption by Chrysalis Health & Beauty Ltd (Nottingham, UK).

2.4 Methods

The study was conducted on the premises of the ThinkTank Science Museum (Birmingham, UK) for the paediatric cohort, and at the University of Birmingham in a dedicated room for the adult cohort. Research data was gathered with groups of participants (between 4 – 7 participants per session). The

study flow and assessment tools were the same for adults and children (Table 2); yet, children received fewer tablets due to their limited attention span and to minimise exposure to quinine.

Following consent, demographic information was collected including age, gender, ethnicity (free text), as well as previous problems with swallowing of tablets (questionnaires are available in Appendix A). The study activity consisted of two parts: assessment of (i) ease of swallowing and (ii) palatability of quinine tablets (Table 2). For each part the tablets were presented in a randomised order. Additionally, before each tablet, participants were given a palate cleanser – room temperature drinking water (bottled spring water), followed by a piece of lightly salted cracker (Jacob's, or Schar gluten free) and water again (Lucak and Delwiche, 2009).

During the ease of swallowing assessment (part (i)) participants were asked to swallow one tablet at a time in their usual manner. Unlimited access to drinking water was provided; no suggestion on the method of swallowing or amount of water to take was given. Participants rated how easy the tablet was to swallow using a 5-point scale (Figure 1). The amount of water taken was measured as the difference in the mass of the cup of water before and after swallowing the tablet ($\rho_{H2O} \approx 1$g/mL). Researchers observed and recorded the success of the tablet administration (tablet swallowed/spat out/refused) and any verbal comments made by participants about the tablet. Researchers also recorded the facial expressions of participants on a tick chart, choosing from: lips pressed together (AU 24), nose wrinkling (AU 9), eyes squeezed shut (AU 6+43), brows pulled together and lowered (AU 4), head shake (AU 84).

During the palatability assessment (part (ii)) participants were instructed to put the tablet in their mouth, feel its surface with their tongue for 5 seconds, then spit it out. As the participants undertook this process, researchers observed and recorded participant facial expressions and any verbal comments they made about the tablet. Participants evaluated the sensory perception of each tablet using five parameters: bitterness, stickiness, smoothness, slipperiness, and aftertaste (pleasant/unpleasant) on 5-point scales (one scale per parameter). Finally, the participants expressed their overall liking of the tablet using a 5-point scale. The sample size was determined on the basis of

the effect size needed to find a difference between two tablets on a 5-point scale (Soper, 2019). An example of setting for a participant is shown in Figure 2.

2.5 Data analysis

Each participant had the right to withdraw from the study at any time. For children, there were 3 cases of discontinuation based on a child's withdrawal. The data collected up to the point of participant withdrawal was included in the analysis. No adults withdrew from the study.

Missing data represented 0.7% (49/7127) of all data points in the adult cohort, and 1.0% (57/5858) in the children cohort. The missing data was disregarded.

2.5.1 Statistical analysis

Participant marks on 5-point scales were translated into scores from 1 to 5 (where a score of 1 referred to a negative quality – sad face; and 5 to positive quality – happy face). Comparison of tablets was done using non-parametric tests, as data was not normally distributed (Shapiro-Wilk, $p<0.05$). A comparison Friedman's ANOVA test was used to screen data for sequential effects. For all tests the level of significance $p<0.05$ was used, unless stated otherwise.

In order to compare different tablet scores for the same parameter (dependent variables), Wilcoxon's signed rank test (pairwise) with Bonferroni correction was performed. When independent variables were analysed the Kruskal-Wallis test was used. Moreover, correlations between numerical parameters were assessed by calculating Spearman's correlation coefficient (r_s).

Further, the relationship between demographic data and participants' responses was examined. The correlation of categorical data was tested with the Pearson Chi-Square test ($\chi 2$). To compare participants' responses within different populations the Mann-Whitney U test was used.

Finally, for both study populations, a Mann-Whitney U test was employed to determine the association between overall liking of the tablet and other numerical parameter (e.g. sensory perception scores on a 5-point scale). The effect size was calculated to establish the strength of this association. Furthermore, for each parameter that related to tablet overall liking, the cut off value was determined. This was performed using Receiver Operating Characteristic (ROC) analysis.

Statistical analysis was performed using SPSS statistical software version 26 (IBM Corp.).

3 Results

3.1 Participant demographics

The study included 101 children and 52 adult participants in the age range 4-12, and 18-75 years, respectively (Table 3). Within the study population, 13.8% (14/101) of children 11.5% (6/52) of adults reported *previous* issues with swallowing tablets. The number reported for children may be underestimated, due to lack of exposure to or experience of tablet swallowing in this population.

3.2 Ease of swallowing assessment

It was confirmed that the sequence of taking tablets did not affect the ease of swallowing score, in both adults and children (Friedman's ANOVA, $p=0.755$, and $p=0.307$, respectively).

The vast majority of adults scored all the tablets as easy to swallow, median equalled 5 for all the tablets ($\chi2$ (4) = 3.646, $p=0.456$) (Figure 3A). The volume of water taken to swallow did not differ between the tablets ($\chi2$ (4) = 1.955, $p=0.744$). One adult participant (#63) was unable to swallow any of the five tablets. They had previously identified themselves as generally unable to swallow tablets in the pre-study questionnaire and scored all the tablets as difficult to swallow.

Sixty-three (62.4%, 63/101) children managed to swallow at least one tablet. The success of tablet swallowing (completely swallowed vs. spat out) was age related ($\chi2$ (2) = 27.977, $p<0.001$), with 35.7%, 66% and 84.4% of 4 – 6, 7 – 9 and 10 – 12-year olds, respectively, completely swallowing at least one tablet. Boys were more likely to swallow the tablet than girls ($\chi2$ (1) = 6.960, $p<0.008$) with an odds ratio of 2.2 (CI 1.22-3.97). The type of coating did not relate to the success of swallowing the tablet ($\chi2$ (4) = 2.627, $p=0.622$).

Children who managed to completely swallow the tablet tended to give higher scores for ease of swallowing than those who spat out the tablet (Figure 3B) ($U = 275$, $p<0.001$). For children no difference between ease of swallowing was found between different coated tablets (Kruskal-Wallis $H=4.237$, $p=0.375$).

3.3 Palatability assessment

In general, the sequence in which the tablets were taken did not affect the mouthfeel or palatability scores, in both adults and children (Friedman's ANOVA, $p>0.05$). Yet, some sequence effects were found for the assessment of stickiness in children. Out of two tablets presented for mouthfeel assessment, children tended to rate the second tablet as stickier than the first one (Wilcoxon test, $p<0.05$).

The median scores for all mouthfeel attributes are given in Figure 4. The tablets which received the highest scores in both populations were Coat-B and Coat-C, while the lowest scores were given for Coat-D. The statistical differences between different tablets and a variation in score between the children and adult population are available in Appendix B.

Researchers recorded negative facial expressions as an indicator of a participant's aversion to the tablet. The most observed facial expression was 'lips pressed together' (observed in 24.8%, 50/202 of tablets tested in children, and 11.5%, 30/260 of tablets tested in adults). This was followed by 'wrinkling nose' (19.8% and 13.8%), 'brows pulled together and lowered' (10.4% and 12.7%), 'voice disgust' (17.3% and 3.1%), 'eyes squeezed shut' (14.4% and 5.0%) and 'head shake' (15.8% and 1.9%), respectively. Children expressed negative facial expressions more often than adults, which suggests lower acceptability of the tablet for children and/or social conditioning in adults. The sum of negative facial expressions was also indicative of the most and least disliked tablet. Among children, the most disliked was Coat-D (72 recorded negative expressions), and least disliked Coat-C (35 negative expressions). For adults, both Coat-A and Coat-E were most disliked (34 negative expressions), and Coat-B most liked (7 negative expressions).

Spearman's correlation coefficient (r_s) for all attributes was calculated based on adult and children reponses (Table 4). Based on adult responses the largest effect size was observed for following correlations:

- The more bitter the tablet, the less liked
- The more unpleasant the aftertaste, the less liked

- The smoother the tablet, the more slippery
- The more bitter the tablet, the more unpleasant the aftertaste

3.4 Relation between participant demographics and collected data

3.4.1 Age

The ability to swallow a 7.5 mm tablet was significantly lower in children compared to adults (62.4% vs. 98.1%). Yet, both children and adults were found to use the same volumes of water to swallow the tablet, 23 mL and 21 mL (median), respectively ($U= 21116.5$; $p > 0.05$).

When the scores given by children and adults during the part (ii), palatability, were compared, both populations scored the tablets similarly for just one attribute i.e. slipperiness (Table 5). The perception of other attributes differed; adults reported tablets to be less bitter, stickier and less smooth than children. Adults also gave higher hedonic scores, i.e. overall liking and appreciation of aftertaste, than children. This was supported by anecdotal comments expressed by child participants. The majority of comments made by children concerned the taste of the tablets, e.g. *very bitter, tasteless, tasted weird,* or expressed negative hedonic opinion, e.g. *disgusting, ugh, 'thumbs down*'.

3.4.2 Gender

3.4.2.1 Adult females vs. males

Adult females are known to have higher taste sensitivity (Michon et al., 2009), in line with that, adult females scored the tablets as more bitter than males (Table 5). This was also expressed in the lower hedonic scores given and greater incidence of negative facial expressions recorded for females. Moreover, females were found to be more sensitive to mouthfeel characteristics of the tablets. Unlike males, females could differentiate between the tablets for both stickiness and smoothness (based on number of tablet pairs differentiated in the Wilcoxon test). Tablet discrimination for other mouthfeel parameters (slipperiness and aftertaste) was not different between genders. Furthermore, the volume of water needed to swallow the tablet was associated with gender, with females using more water ($p < 0.001$).

3.4.2.2 Girls vs. boys

The paediatric population in this study was evenly split across both age range (between the limits of 4-12 years) and gender ($\chi^2(2) = 4.976$; $p>0.05$). Within the ease of swallowing part (i), girls found tablet swallowing more difficult than boys ($U = 3338$; $p<0.001$). During the palatability part (ii), all the attributes were scored similarly by both girls and boys (Table 5). Several gender differences which were found in adults, were not replicated in children, i.e. perceived bitterness intensity, overall liking, expression of negative face expressions and water taken with a tablet.

3.5 Determinants of tablet acceptability – liking

The acceptability of tablets was established on the basis of the liking scores given within the palatability part (ii). A tablet which scored 3 or 4 or 5 (neutral plus positive features) on the liking scale is regarded as acceptably liked. For the attributes related to acceptable liking (based on Mann-Whitney U test) the cut off values are given (Table 6). The parameters with the most sensitive and specific cut off values were bitterness and aftertaste (for both children and adult data). Based on paediatric data the stickiness did not determine the liking of the tablet.

In addition, a relationship between the presence of aftertaste (yes/no) and liking was established. Tablets where an aftertaste was reported were disliked by both children ($\chi2\ (1) = 8.653$, $p<0.01$) and adults ($\chi2\ (1) = 43.408$, $p<0.001$).

4 Discussion

4.1 Acceptability – measure of participant's ability to take a dose

Tablet acceptability, defined as the ability of the participant to take the tablet, was measured as the number of participants who completely swallowed the tablet. Among adults 98.1% (51/52) swallowed the tablet, while among children only 62.4% (63/101) swallowed the tablet. The high swallowability rate in the adult population, relfects the age stratification of participants where the majority of adults were under 35 years old. The inclusion of older adults, where difficulties in tablet swallowing are more prevalent (Lau et al., 2015), could alter the swallowability results. In the pediatric population the success of swallowing was age dependent, where only 35.7% of 4 – 6-year olds managed to swallow the tablet.

Based on this outcome, a 7.5 mm round tablet cannot be deemed acceptable in the youngest participants within the study population. The percentage of children succesfully swallowing tablets in this study was lower than reported in the literature for the same sized tablet (80 – 91% success rate, (Kokki et al., 2000; Meltzer et al., 2006)). However, a higher tablet swallowing success rate in the literature could be attributed to the additional means undertaken to help the children to take a tablet: training, special pill cup, promise of pain-relief or a financial incentive. Taking this into consideration, the lower swallowing success may have been expected in this study, as healthy children were asked to swallow placebo tablets without any training or instructions. Previous studies, have shown that children under 6 years old are able to swallow smaller tablets - 2 mm (Klingmann et al., 2013) or 6 mm (Kreeftmeijer-Vegter et al., 2013)). Coupled with our results, it suggests that tablets over 6 mm exceed the limit of swallowability for preschool children.

In contrast to previous studies on the ease of swallowing of tablets in children, the tablets used in this study contained a bitter flavour. The bitterness of the tablet was taste-masked with different coatings which resulted in tablets of differing bitterness intensity. We hypothesised that the tablet's aversive taste may negatively impact upon the success of swallowing the tablet. Yet, based on Mann-Whitney U test the type of coating on the tablet swallowed did not relate to its swallowing success ($p=0.644$). This suggests that the success of swallowing per se does not depend on the tablet taste. However, if a bitter dose were to be given repeatedly, the taste may pose palatability issues and reduce adherence.

4.2 Acceptability – measure of tablet palatability

It is key for a medicine to be palatable in order to be acceptable. In this work, possible determinants of palatability (taste and mouthfeel) of coated tablets were analysed. The most pronounced determinant of a participant's liking of the tablet was taste. For children and adults, the greater the perceived intensity of bitterness, the more the tablet was disliked (Table 4). Sensitivity to bitterness was age- and gender-related. For both children and females, the more bitter they rated the tablets, the higher the tendency to score tablets as less liked. When children were compared to adult females, no difference in bitterness scores was found but children disliked the tablets more than adult females.

This finding suggests that adult females can give a reliable approximation of children's perception of bitterness.

Based on palatability scores of children as well as adults the most liked tablets (liking score 3, 4 or 5) were also characterised as less bitter, smoother, and more slippery. Hence, the liking of a tablet was not just a function of taste (bitterness), but a combined effect of multiple attributes. This emphasizes the impact of mouthfeel on palatability, as distinct from palatability being a function of taste alone. Studies of oral medicines which relate a specific mouthfeel attribute and palatability/liking are scarce. So far, the mouthfeel attributes found to be important for palatability/acceptability include: grittiness (ODT) (Lopez et al., 2016), stickiness (ODF) (Scarpa et al., 2018), volume of residue (ODT) (Casian et al., 2018), and rough mouthfeel (ODT) (Kimura et al., 2015). The study presented here adds to this list by showing a direct correlation between palatability and aftertaste, smoothness and slipperiness of conventional coated tablets. Further studies are required to generate a definitive list of mouthfeel attributes critical to acceptability of oral solid dosage forms.

4.3 Sensory perception of coated tablets

The way people perceive and appreciate taste changes with age (Forestell and Mennella, 2015). In agreement with previous studies (Mennella and Bobowski, 2015), within this study children were more sensitive to bitterness (i.e. gave lower scores on 5-point scale, where 1 = extremely bitter). Moreover, children tended to give lower hedonic scores than adults (5-point liking scale, where 1 = dislike very much). These findings support the fact that both sensitivity and appreciation of taste stimuli changes with age; children are more sensitive to bitterness and have a more aversive reaction to it (Mennella et al., 2014; Nu et al., 1996), whereas adults develop a tolerance of bitter taste (Drewnowski et al., 2001). The differences in taste sensitivity have important implications for the development of oral medicines. A formulation with an acceptable taste for adults may not be acceptable to children. As a consequence, adults' sensory assessment cannot be directly translated to a paediatric population, therefore adults are not a suitable substitute of children in the complete sensory evaluation of paediatric medicines.

Apart from taste, texture perception also changes with age (Song et al., 2016). Based on the mouthfeel scores, children in this study rated tablets as smoother and less sticky compared to adult scores (Table 6). Moreover, texture preferences differed between age groups, as illustrated by different cut off values between children and adults (Table 6). For example, for smoothness, a cut off value of 4 indicated that only tablets scored by children as very smooth (score 5) were regarded as liked, while for adults', tablets that scored 4 and 5 were equally liked (cut off 3). This discrepancy illustrates the difference in textural preferences between the two populations. Even larger differences in texture perception would be expected, if older adults were recruited to the study, due to the fact that the texture sensitivity diminishes with age within adult populations (Hofmanová et al., 2019; Park, 2017).

4.4 Determination of taste-masking properties of the coatings

Tablet coating taste-masking effect was measured by measurement of bitterness intensity (part (ii)). Based on the bitterness intensity, significant differences between tablets were found (Appendix B Table B. 1). The adults rated the bitterness of tablets slightly differently than children (Appendix B Table B. 1) yet results for both groups showed agreement on the two least bitter tablets, i.e. Coat-B and Coat-C.

Differences in the perceived bitterness intensity between tablets could be related to the formulation of coatings. As all tablet cores contained the same amount of quinine flavouring, the bitterness could be inhibited only by a taste-masking coating. For the two least bitter tablets, Coat-B and Coat-C, taste-masking was achieved using different approaches. Formulation Coat-B comprised lipids, which inhibited water penetration into the tablet core, and so constrained the diffusion of quinine molecules from the tablet core to the taste buds. In the case of Coat-C, taste-masking was achieved due to the increased viscosity of the coating (attributable to xanthan gum) which slowed coating dissolution. In comparison, the standard formulation without viscosity modifying ingredients, Coat-A, was perceived as more bitter than Coat-C. The tablets perceived as most bitter (Coat-D and Coat-E) had coatings based on water insoluble polymers, and as such, were expected to inhibit water penetration into the core and subsequent quinine diffusion to the taste buds. Although similar coating formulations have

previously been shown as effective in taste-masking (Drašković et al., 2017; Hughes et al., 2016), here taste-masking was not achieved. These two coatings are less flexible, than HMPC-based ones; thus, they may require a thicker layer to provide a taste-masking effect. A reliable taste-masking film coating requires a thickness of at least 10 µm (Joshi and Petereit, 2013), yet this thickness was not achieved here.

In summary, the measure of bitterness intensity showed that none of the coatings achieved an average 'not bitter at all' score following a 5 second evaluation. Hence, none of the tablet coatings taste-masked the bitterness effectively, suggesting a thicker coating layer is required.

4.5 Study limitations

There are some limitations to this study. Firstly, the tablets supplied had a thinner coating thickness than expected (see methods). Secondly, there was no reference for maximum and minimum intensity of attributes, which left the scales open to an individual's interpretation. The study did not include an uncoated tablet as previous work demonstrated that inclusion of such a distinctly different sample resulted in skewed sensory data (Hofmanová et al., 2019).

The study used placebo tablets with quinine sulfate as a bitter tasting agent, rather than actual medicines. The choice of placebo formulation was dictated by safety of the participants. The choice of excipients was regarded as safe for oral consumption in the target population at the given doses. Maximum quantities of all excipients used in the study were calculated so that they are within safe, acceptable limits, with particular concern of quinine (JECFA, 1993) and titanium dioxide (Winkler et al., 2018).

Moreover, the study involved a heterogenous aged adult population; comparison of differences between young and older adults would be of interest.

5 Conclusions

Within this study the acceptability of 7.5 mm round tablets with five different coatings was investigated in children and adults. The ability of the participant to swallow the tablet was

independent of the applied coating. Tablets were successfully swallowed by the vast majority of children 7 years and older (74%) and adults (98%). However, the ability of children between 4 and 6 years old to take this tablet was low (35.7%), which indicates low acceptability in this age group.

The type of tablet coating affected the intensity of perceived bitterness suggesting a difference between the taste-masking effectiveness of the coatings although none were 'not bitter at all'. A lipid-based coating (Coat-B) and the HPMC coating formulated with the viscosity modifier xanthan gum (Coat-C) provided the most effective taste-masking.

Bitterness of tablets is not the only determinant of palatability. This study demonstrates the multifactorial nature of palatability by showing that the sensory properties of mouthfeel are also related to palatability. In both children and adult populations, low bitterness, high smoothness, high slipperiness and pleasant aftertaste had positive impact on overall palatability. However, while the trend in palatability was similar for children and adults, children perceived the tablets as more bitter, smoother, less sticky, and less liked. This suggests that adults' palatability scores cannot be directly translated to a paediatric population.

This study broadens the knowledge of the acceptability and palatability of small coated tablets in children and adults. The findings highlight the difference in bitterness and hedonic perception of tablets between populations. Moreover, the results show direct correlation between palatability and aftertaste, smoothness and slipperiness of conventional coated tablets, which emphasizes the need to analyse medicine palatability as a multifactorial attribute, rather than a simple hedonic parameter.

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Table 1 Details of tablet coatings used on quinine tablets used within this study.

Formulation	Description	Ingredients
Coat-A	Standard reference	HPMC 5, Glycerol
Coat-B	Lipid based	Lubritab®, HPMC 5, Capmul® MCM, talc, titanium dioxide
Coat-C	Slippery	HPMC 5, glycerol, talc, titanium dioxide, xanthan gum
Coat-D	pH dependent	Eudragit EPO readymix, titanium dioxide
Coat-E	Insoluble : soluble polymer	Surelease®, HPMC 5, talc, titanium dioxide, glycerol

Table 2 Study flow and assessment tools used for both children and adults; number of tablets received is reported as children (adults); PROs - participant reported outcomes, RROs - researcher reported outcomes.

	Acceptability		**Taste-masking effect**
	PROs	RROs	PROs
Part (i) **Ease of swallowing** 2 (5) tablets	**Ability to take** ▸ Ease of swallowing *5-point scale* **Hedonic perception** ▸ Preference test	**Ability to take** ▸ Success of taking the tablet *The child swallowed/ spat out/ refused to take a tablet* ▸ Amount of water used *Volume* **Hedonic perception** ▸ Record of negative facial expressions *Tick chart*	
Part (ii) **Palatability** 2 (5) tablets	**Taste intensity** ▸ Bitterness *5-point scale* **Mouthfeel** ▸ Stickiness ▸ Smoothness ▸Slipperiness *5-point scale* **Hedonic perception** ▸ Liking ▸ Appreciation of aftertaste *5-point scale* ▸ Preference test	**Hedonic perception** ▸ Record of negative facial expressions *Tick chart*	**Taste intensity** ▸ Bitterness *5-point scale*

Table 3 Participant data collected in a background questionnaire.

	Children (n= 101)		**Adults (n= 52)**	
Number of participants	Frequency	Percent [%]	Frequency	Percent [%]
Gender				
Male	56	55.4	19	36.5
Female	45	44.6	33	63.5
Age (years)				
4-6	28	27.7		
7-9	40	39.6		
10-12	33	32.7		
<24			11	21.2
25-34			29	55.8
35-44			5	9.6
45-54			5	9.6
55-64			1	1.9
>65			1	1.9
Ethnicity*				
Arabic	1	1.0	2	3.8
Asian	18	17.8	6	11.6
Black	0	0	2	3.8
British	6	5.9	2	3.8
Mixed	17	16.8	4	7.7
White	52	51.6	34	65.5
Missing**	7	6.9	2	3.8
Problems with swallowing tablets previously				
No	84	83.2	46	88.5
Yes	14	13.8	6	11.5
Missing**	3	3.0	0	0

* Free text was permitted for participants to complete ethnicity

** Participant did not answer the question

Table 4 Spearman's correlation coefficient (r_s) for palatability parameters (part (ii)); only significant values of at least medium effect size (>0.3) are presented; values with large effect size (>0.5) are shown in bold (number of responses: adults n=260, children n=202).

Parameter	Stickiness	Smoothness	Slipperiness	Aftertaste	Overall Liking	Negative facial expressions***
Adults						
Bitterness	<0.3**	0.307**	<0.3**	**0.668****	**0.778****	-0.453**
Stickiness		0.448**	0.415**	<0.3*	<0.3**	NS
Smoothness			**0.624****	<0.3**	0.422**	-<0.3**
Slipperiness				NS	0.372**	NS
Aftertaste					**0.714****	-0.345**
Overall Liking						-0.440**
Children						
Bitterness	NS	<0.3**	<0.3**	0.485**	**0.629****	-.0386**
Stickiness		0.309**	NS	NS	NS	-<0.3**
Smoothness			<0.3*	<0.3*	<0.3**	-<0.3*
Slipperiness				<0.3*	<0.3*	NS
Aftertaste					**0.555****	-0.312**
Overall Liking						-0.470**

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level; *** minus sign expresses negative direction of the correlation; NS – not significant

Table 5 Statistical data used to evaluate relationship between participant demographics and collected data; hypotheses in bold showed statistical significance; A – adults, Ch – children, F – female adult, M – male adult, G – girls, B – boys.

Hypothesis	Data	Statistical test and significance
Taste assessment		
Children are more sensitive to bitterness than adults	*Bitterness median (mean):* A: 2 (2.53) Ch: 2 (2.35)	Mann-Whitney U = 22165.5 **(p<0.01)**
Adult females are more sensitive to bitterness than adult males	*Bitterness median (mean):* F: 2 (2.42) M: 2 (2.75)	Mann-Whitney U = 6118.5 **(p<0.005)**
Girls are more sensitive to bitterness than boys	*Bitterness median (mean):* G: 2 (2.45) B: 2 (2.28)	Mann-Whitney U = 4619 (p=0.612)
Children are more sensitive to bitterness than female adults	*Bitterness median (mean):* F; 2 (2.81) Ch: 2 (2.69)	Mann-Whitney U = 15164.5 (p=0.228)
Mouthfeel assessment		
The difference in sensitivity to mouthfeel properties between children and adults	*Stickiness median (mean):* A: 4 (3.76) Ch: 5 (4.34) *Smoothness median (mean):* A: 4 (3.61) Ch: 4.5 (4.09) *Slipperiness median (mean):* A: 3 (2.99) Ch: 3 (2.99)	Mann-Whitney U = 18717 **(p<0.001)** Mann-Whitney U = 20837 **(p<0.001)** Mann-Whitney U = 23734.5 (p=0.192)
Adult females are more sensitive to mouthfeel differences than adult males	*Stickiness median (mean):* F: 4 (3.96) M: 4 (3.67) *Smoothness median (mean):* F: 4 (3.74) M: 4 (3.68) *Slipperiness median (mean):* F: 3 (3.08) M: 3 (3.09)	Mann-Whitney U = 6777 (p=0.068) Mann-Whitney U = 7453 (p=0.546) Mann-Whitney U = 7770 (p=0.972)
Girls are more sensitive to mouthfeel differences than boys	*Stickiness median (mean):* G: 5 (4.40) B: 5 (4.30) *Smoothness median (mean):* G: 5 (4.04) B: 4 (3.95) *Slipperiness median (mean):* G: 3 (2.82) B: 3 (3.00)	Mann-Whitney U = 4684 (p=0.825) Mann-Whitney U = 4460 (p=0.486) Mann-Whitney U = 4475.5 (p=0.462)
Hedonic perception assessment		
Adults gave higher hedonic scores to the tablets than children	*Liking median (mean):* A: 3 (2.60) Ch: 2 (2.18) *Aftertaste (pleasantness) median (mean):* A: 2 (2.37) Ch: 2 (2.14)	Mann-Whitney U = 17345.5 **(p<0.001)** Mann-Whitney U = 8821.5 **(p<0.01)**

Adult males gave higher hedonic scores to the tablets than adult females	*Liking median (mean):* F: 2 (2.51) M: 3 (2.80) *Aftertaste (pleasantness) median (mean):* F: 2 (2.33) M: 2 (2.51)	Mann-Whitney U = 5811 **(p<0.01)** Mann-Whitney U = 3149.5 (p=0.200)
Boys gave higher hedonic scores to the tablets than girls	*Liking median (mean):* G: 2 (2.20) B: 2 (2.18) *Aftertaste (pleasantness) median (mean):* G: 2 (2.25) B: 2 (2.06)	Mann-Whitney U = 1783 (p=0.602) Mann-Whitney U = 3876 (p=0.097)
Children gave higher hedonic scores to the tablets than adult females	*Liking median (mean):* F: 2 (2.28) Ch: 2 (2.42) *Aftertaste (pleasantness) median (mean):* F: 2 (2.33) Ch: 2 (2.15)	Mann-Whitney U = 11873.5 **(p<0.001)** Mann-Whitney U = 6142,5 **(p<0.05)**
Adult females showed more negative facial expressions than adult males	Sum of occurrences: F: 106 M: 19	Mann-Whitney U = 5905 **(p<0.001)**
Girls showed more negative facial expressions than boys	Sum of occurrences: G: 54 B: 61	Mann-Whitney U = 4401.5 (p=0.275)
	Miscellaneous	
Adult females needed more water to swallow a tablet than adult males	*Volume median (mean):* F: 24.5 (28.9) mL M: 16.5 (20.8) mL	Mann-Whitney U = 4513.5 **(p<0.001)**

Table 6 Results of Mann-Whitney U test for influence of the mouthfeel parameter on liking (disliked = score 1 or 2; liked = score 3, 4, or 5), and the sensitivity and specificity of the cut off (n=260 adults, n=202 children).

Parameter	Mann-Whitney U	P value	Effect size	Cut off	Sensitivity	Specificity
Adults						
Bitterness (1= bitter)	1646	0.000	0.66	2	0.79	0.87
Stickiness (1 = sticky)	5390	0.001	0.21	3	0.75	0.78
Smoothness (1 = rough)	4326.5	0.000	0.34	3	0.72	0.61
Slipperiness (1 = not slippery)	4906	0.000	0.26	3	0.52	0.77
Aftertaste (1 = not pleasant)	969	0.000	0.68	2	0.78	0.89
Negative facial expressions	4224	0.000	0.43	1	0.03	0.69
Children						
Bitterness (1= bitter)	1757	0.000	0.52	2	0.77	0.71
Stickiness (1 = sticky)	4120.5	0.478	0.05	-	-	-
Smoothness (1 = rough)	3269	0.003	0.22	4	0.59	0.31
Slipperiness (1 = not slippery)	3619.5	0.044	0.15	3	0.49	0.70
Aftertaste (1 = not pleasant)	562.5	0.000	0.88	2	0.68	0.86
Negative facial expressions	2242.5	0.000	0.44	2	0.07	0.76

Figure S1

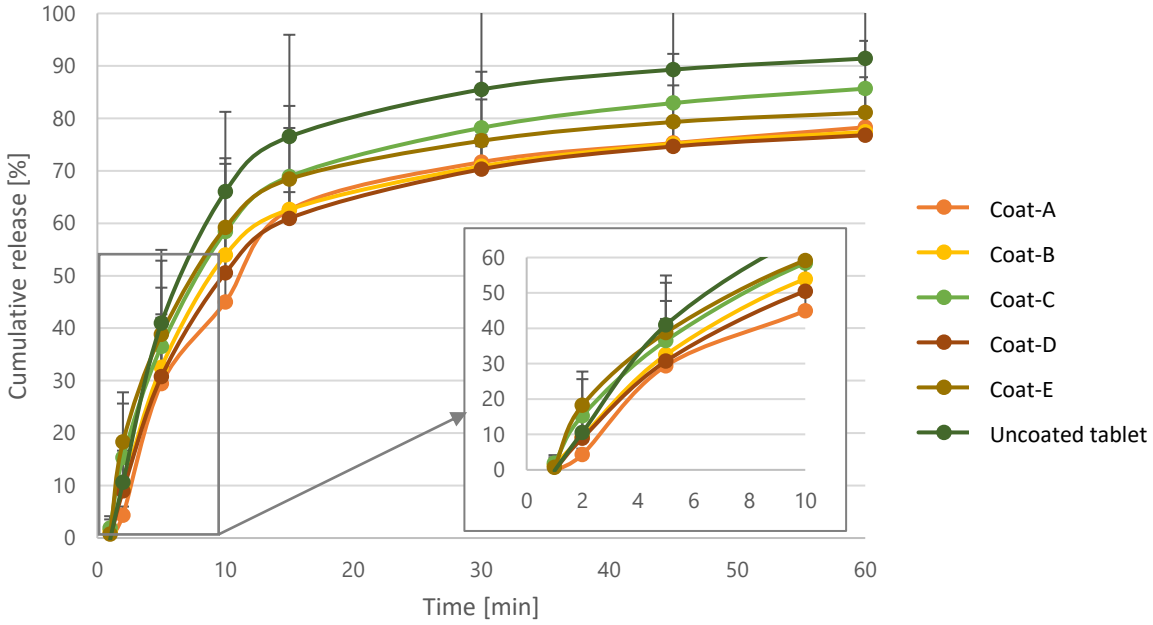


Figure S1. Cumulative drug release (quinine sulfate and dihydroquinine sulfate) for coated and uncoated tablets (n = 4); error bars represent standard deviation. Dissolution conditions: 25mL water in a small volume USP II apparatus.

Was the tablet easy or difficult to swallow?	 Very easy to swallow … Very difficult to swallow

Figure 1 Example of a 5-point scale.

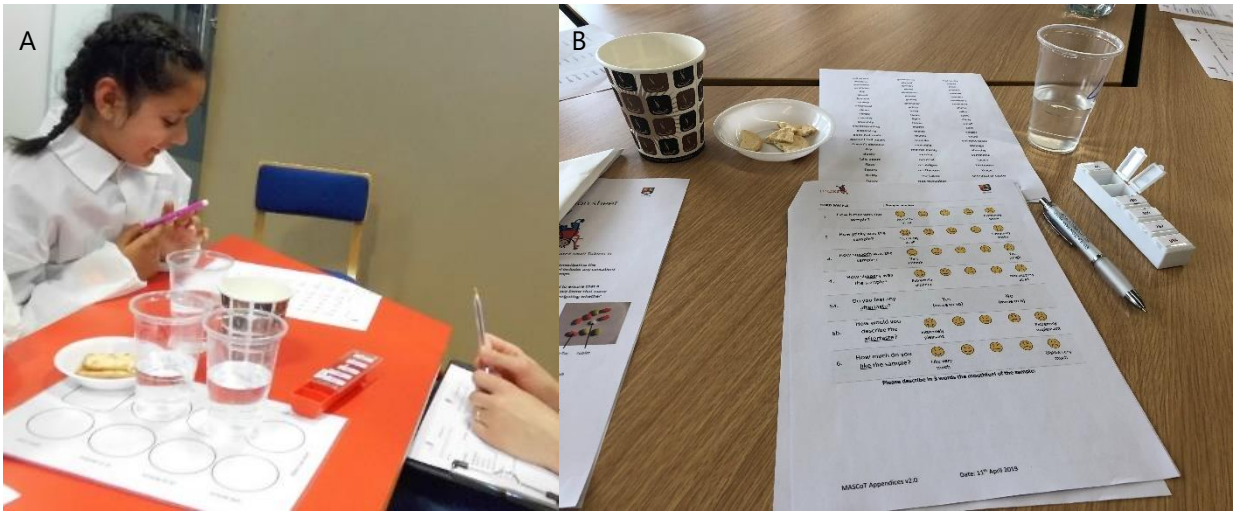
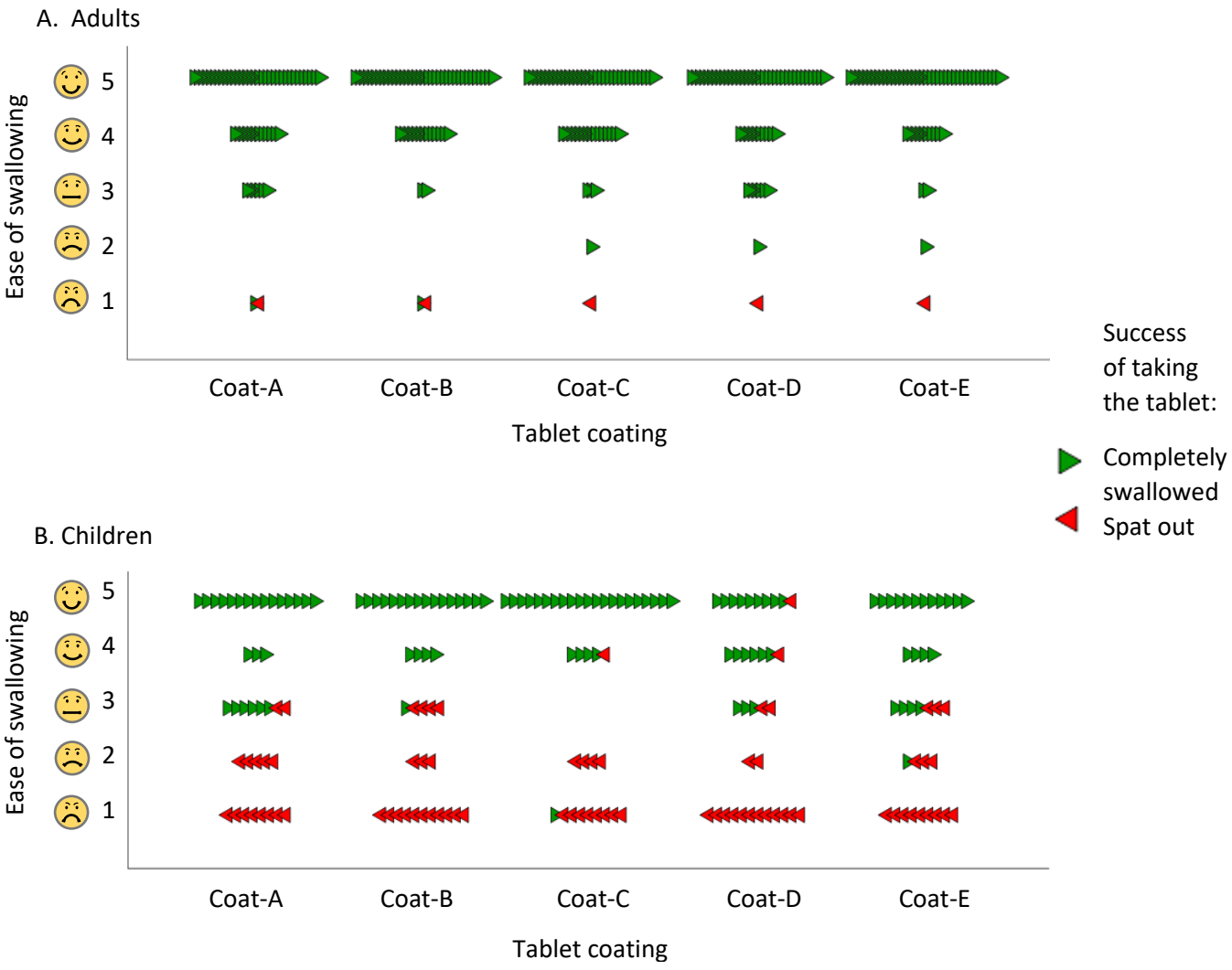


Figure 2 Child participant during the palatability part (ii) of the study (picture obtained and reproduced with a written parental consent) (A)); left: table set up for an adult participant (B).



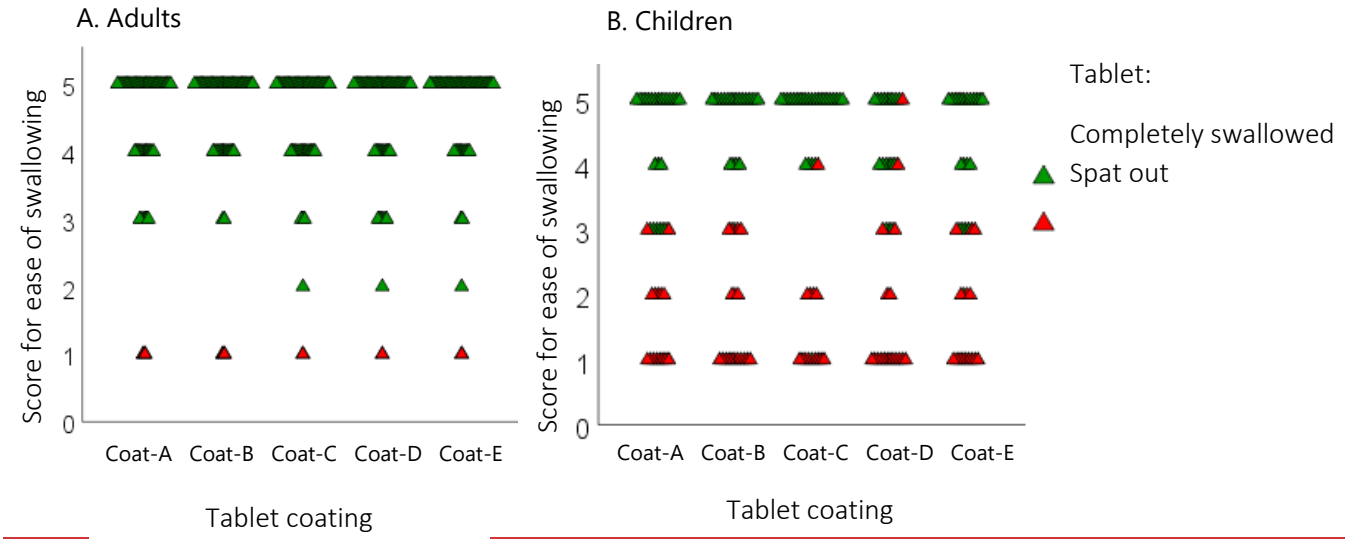


Figure 3 Participant rating of ~~E~~ease of swallowing ~~scores~~ for all the tablets; each ~~•~~ symbol represents one tablet; the tablets which were completely swallowed or spat out are distinguished; A. ~~tablets scored by~~ adult ratings~~s~~ (n=260 tablets), B. ~~tablets scored by~~ children ratings (n=193 tablets), children who refused to take the tablet did not give a score. Note that a score of 5 meant that the tablet was easy to swallow.

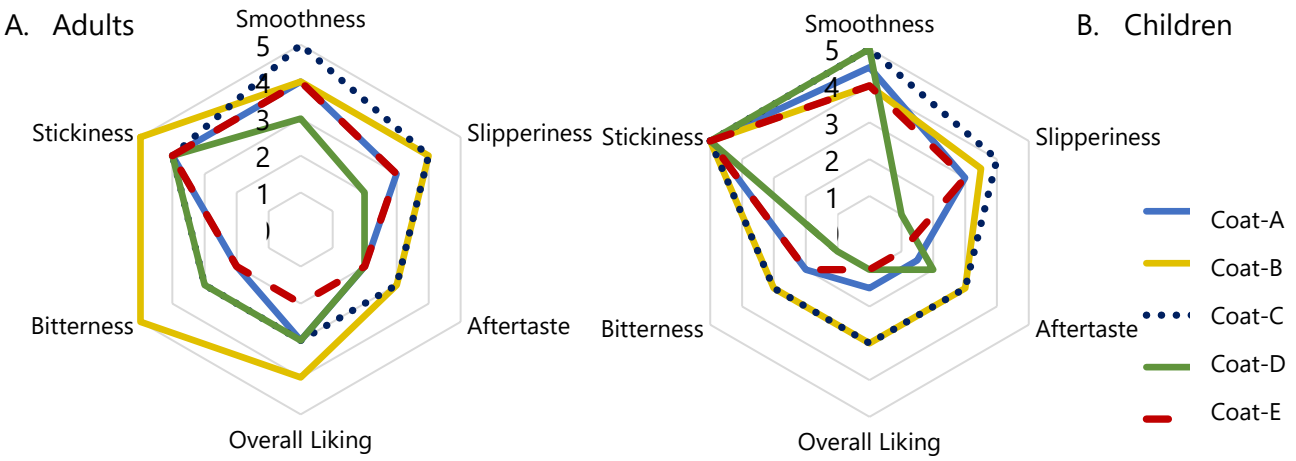


Figure 4 Comparison of the five tablet samples in the palatability test – median values for each question are given (score 1 means negative quality, 5 positive quality); A. adults (n=260); B. Children (n=202).