

## **Dosage form preference consultation study in children and young adults: paving the way for patient centred and patient informed dosage form development**

Hamad Alyami<sup>1</sup>, Eman Dahmash<sup>1</sup>, Fahad Alyami<sup>2</sup>, Dania Dahmash<sup>3</sup>, Chi Huynh<sup>4</sup>, David Terry<sup>1,4</sup>, Afzal R Mohammed<sup>1</sup>

<sup>1</sup> Aston Pharmacy School, School of Life and Health Sciences, Aston University, Birmingham, UK

<sup>2</sup> Najran Maternity and Children Hospital, Saudi Arabia

<sup>3</sup> College of Medical and Dental Sciences, Birmingham University, Birmingham, UK

<sup>4</sup> Pharmacy Academic Practice Unit, Birmingham Children's Hospital, Birmingham, UK

Correspondence to

David Terry, Aston Pharmacy School, Aston University, Birmingham, B4 7ET, UK;  
[d.terry@aston.ac.uk](mailto:d.terry@aston.ac.uk); [+44-121-204-3941](tel:+441212043941)

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## **ABSTRACT**

**Objectives:** The current study aims to evaluate dosage form preferences in children and young adults together with identifying the key pragmatic dosage-form characteristics that would enable appropriate formulation of orally disintegrating tablets (ODTs).

**Methods:** International, multisite, cross-sectional questionnaire of children and young adults aged from 6-18 years. Eligibility was based on age, ability to communicate and previous experience in taking medications. The study was carried out at three locations; United Kingdom, Saudi Arabia and Jordan. The questionnaire instrument was designed for participant self-completion under supervision of the study team.

**Results:** 104 questionnaires were completed by the study cohort (n=120, response rate 87%). Results showed that ODTs were the most preferred oral dosage forms (58%) followed by liquids (20%), tablets (12%) and capsules (11%). The preferred colours were pink or white while the preferred size was small (< 8mm) with a round shape. With regards to flavour, strawberry was the most preferred (30.8%) while orange was the least preferred (5.8%). The results also showed that the most important physical characteristics of ODTs were disintegration time followed by taste, size, and flavour respectively.

**Conclusions:** The results of our study support the World Health Organisation's (WHO) claim for a shift of paradigm from liquid towards ODTs dosage forms for drug administration to young children older than 6 years. Data from this study will also equip formulators to prioritise development of key physical/performance attributes within the delivery system.

## INTRODUCTION

Paediatric drug administration has gained significant attention over the last 5–7 years. Pharmacists and other healthcare professionals in the pharmaceutical industry face a myriad of challenges facing drug development is the appropriate choice of the dosage forms for drug administration to this important target population.<sup>1</sup> For this reason, the common trend has been the manipulation of adult dosage forms into a form that can be administered to overcome difficulties with regard to administration of drugs to children and young people. However, existing knowledge in this field is limited, making it difficult to identify viable solutions. The European Regulation on medicinal products<sup>2</sup> stipulates that all formulations produced for young people should include safety measures such as assessment of excipient toxicity, appropriate delivery system capable of offering dose flexibility and should generally be acceptable to the target population.

The term paediatric dosage forms need to suffice for a wide age range including neonates to adolescents (0 to 16 yrs). The common oral paediatric dosage forms in use are: solid dosage forms (such as tablets), powders, solutions, and syrups.<sup>3</sup> For oral paediatric medicines to be acceptable to young patients there are a number of factors that need to be considered, especially elegance and palatability. Elegance refers to the outward appearance of the dosage form and its appeal to the end user. This may be particularly important for children and their adherence to medication regimens.<sup>2</sup> Palatability is closely related to elegance and is a factor related to acceptability. Children will rarely take drugs that are bitter tasting.<sup>4</sup> Therefore, any active ingredients with a bitter taste are often coated with a sweet tasting substance. If the unacceptable taste is not masked, such drugs may predispose the child to reject the medicine. If the smell of the drug is unpleasant, it may also negatively influence the acceptability of the drug. The term convenience refers to the method by which it is administered, for instance, as a tablet, syrup or as a powder. Oral liquid drug preparations, including solutions, syrups, emulsion and suspension, are considered as the most suitable oral formulation for children, since they are developed for younger new-borns unable to swallow tablets and accommodate palatability and dose adjustment changes required by children.<sup>5-6</sup>

Nonetheless, liquid formulations present several drawbacks, such as low stability, difficulties in taste masking, inappropriate excipients for children (e.g. propylene glycol, benzyl alcohol,) and low transportability.<sup>2,7</sup> The World Health Organisation (WHO) recognizes the need to develop drugs and formulations that specifically target children. According to WHO, the dosage form should be both acceptable and palatable.<sup>8</sup> Furthermore, whenever possible the drug formulation should be palatable without the need to further mask the taste. Dosage form acceptability, which encapsulates a multitude of factors including preference, palatability, presentation and ease of use, has a significant influence on paediatric patient

compliance<sup>2</sup>. ODTs may increase bioavailability and faster onset of action in adults and children, since dispersion in saliva in oral cavity causes pre-gastric absorption from some water soluble actives. Taste and flavour together primarily determine the acceptability of ODTs.<sup>9</sup> Any pre-gastric absorption avoids first pass metabolism and can be of a great advantage in drugs that undergo extensive hepatic metabolism. The study described in this paper was designed with two key objectives: (1) to evaluate dosage form preferences for a wide range of formulations (liquids, injections, suppositories, solid dosage forms, patches) among children and young adults who have a history of taking medicines. The study was conducted in three regions (UK, Saudi Arabia and Jordan) at five different centres. These were Birmingham Children's Hospital (UK), Nottingham Children's Hospital (UK), Najran maternity and children hospital (Saudi Arabia), General Thar Hospital (Saudi Arabia) and Speciality Hospital (Jordan). Countries were chosen based on diverse geographical regions and ethnic mix, ease of access to suitable subjects, lack of published data regarding children preferences of dosage forms. In addition, (2) the study would provide pragmatic and translatable outcomes to support formulating stable and acceptable dosage forms. It is recognised that commonly prescribed liquid formulations used in hot and humid middle eastern countries can present significant stability issues.<sup>10</sup>

## **METHODS**

### **Study Design**

Multi-national, five-site, participant-supported questionnaire of children aged 6–18 years following a demonstration of orally disintegrating tablets. The questionnaire was conducted in both English and Arabic languages.

### **The Questionnaire**

A suitable method to collect and understand a stance to a hypothesis is a Questionnaire.<sup>11</sup> The questionnaire was developed by an iterative process between the study team and paediatric based healthcare professionals. The final questionnaire consisted of four sections. These were: demographic and educational data including gender, age, and education; participant experience of taking medicines and their preferences for various oral dosage forms (liquids, tablets, capsules and ODTs); preference for colour, shape, size, thickness, taste, flavour and disintegration time of tablets; participant feedback about the questionnaire.

## **Ethical approval**

The study was conducted at five centres; in England (2 hospitals), Saudi Arabia (2 hospitals) and Jordan (1 hospital). Birmingham Children's Hospital Research and Development provided the necessary research governance approval. The Pharmacy Academic Practice Unit at the Birmingham Children's Hospital oversaw the study. Consultation centres in Saudi Arabia and Jordan received a copy of the approved letter for the study.

## **Exclusion criteria and some challenges**

Exclusion criteria included:

- Under 6 years of age
- Over 18 years of age
- Perceived difficulty in age appropriate communication (e.g. the capacity to understand and responding to the questionnaire questions).
- No history of taking any medication

## **Statistical analysis**

Participant responses were entered into MS Excel 2007 for analysis. The  $\chi^2$  test was used to examine the independence in the data that was collected. The level of significance was chosen to be 0.05. Two-way analysis of variance (ANOVA) was used to compare data per age groups and per gender. Statistical analysis was performed using Graph Pad Prism software.

## **RESULTS**

A total of 104 questionnaires (study cohort n=120, response rate 87%) were completed. The objective of the study was to determine the preference for pharmaceutical dosage forms in the study population. A presentation concerning the different dosage forms was delivered to the participants in an open-forum style, prior to completion of the questionnaire. This allowed for both proactive and interactive contribution from the participants. The participants were allowed to ask questions concerning dosage formulations

### **Questionnaire results**

Section one: Demographic and educational background of participants

Table 1 summarises the demographic characteristics of participants. It gives the breakdown of their gender, age and educational level. Jordan had the highest percentage of participants

who had basic education as their highest educational level (100%). This was followed by Saudi Arabia (97%) and the United Kingdom (69%). This is a significant difference between the participant countries (p=0.0001).

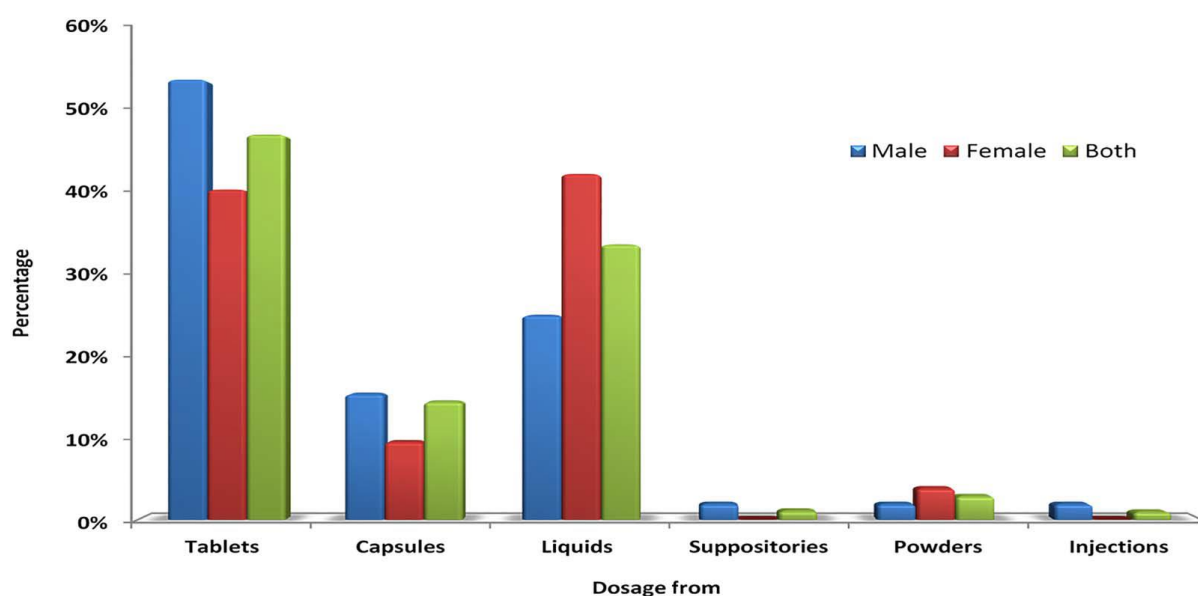
**Table 1.** Demographic characteristics of participants

Characteristics		UK N=29 (%)	Saudi Arabia N=41 (%)	Jordan N=34 (%)	Total N=104 (%)	P value
Gender	Male	8 (27.6%)	26(63.4%)	18(52.9%)	52(50%)	>0.05**
	Female	21(72.4%)	15(36.6%)	16(47.0%)	52(50%)	
Age in years	6-8	0 (0%)	7(17.0%)	10(29.4%)	17(16.3%)	p>0.05 for age group p=0.001 for regions)*
	9-11	4 (13.8%)	14(34.2%)	14(41.2%)	32(30.8%)	
	12-14	8 (27.6%)	12(29.3%)	10(29.4%)	30(28.8%)	
	15-18	17(58.6%)	8(19.5%)	0 (0%)	25(24%)	
Educational level	School	20(69%)	40(97.6%)	34(100%)	94(90.4%)	0.0001**
	Higher education	9 (31%)	0 (0%)	0 (0%)	9 (8.7%)	
	Working	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	0 (0%)	1(2.4%)	0 (0%)	1(0.9%)	

\*Two way- ANOVA \*\*Chi-Square

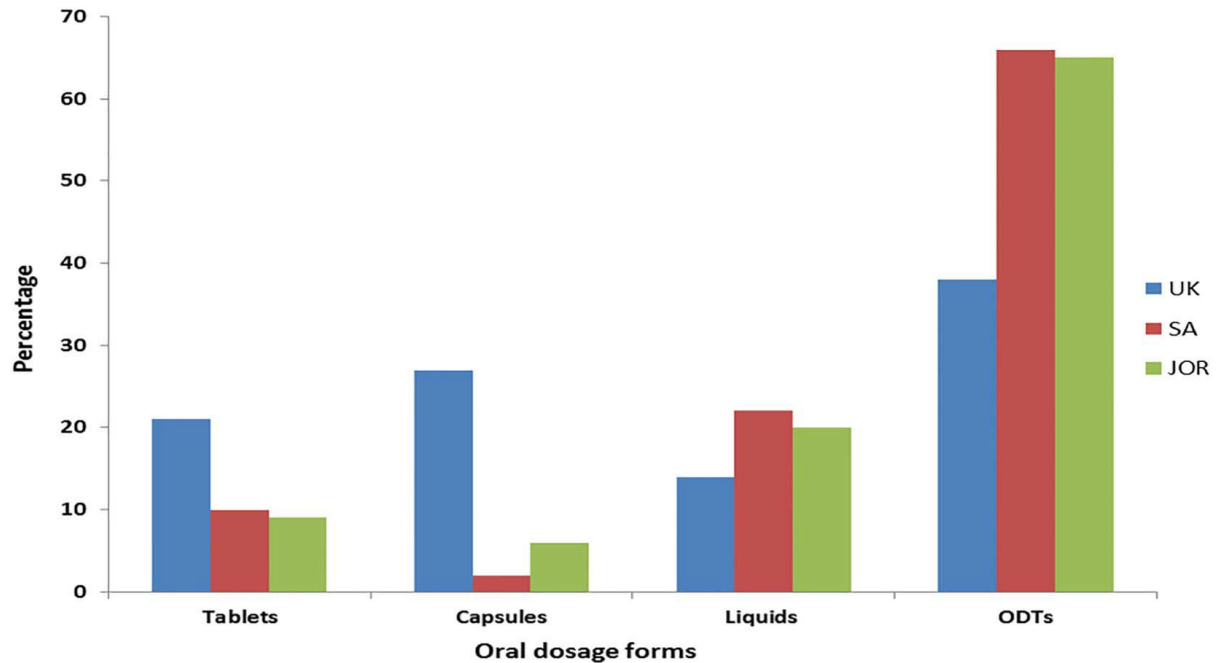
## Section two: experience of taking medicines and preferred dosage forms

Females had the highest frequency of taking daily medicines (28.6%). On a weekly and monthly basis, the male participants recorded a higher frequency of taking medicine than females (27% and 31% respectively). Figure-1 demonstrates that oral route (tablets) was more popular across both the genders compared to liquids, capsules, powders and other dosage forms.



**Figure 1** Distribution of the patients' preferences of dosage forms according to gender for all regions.

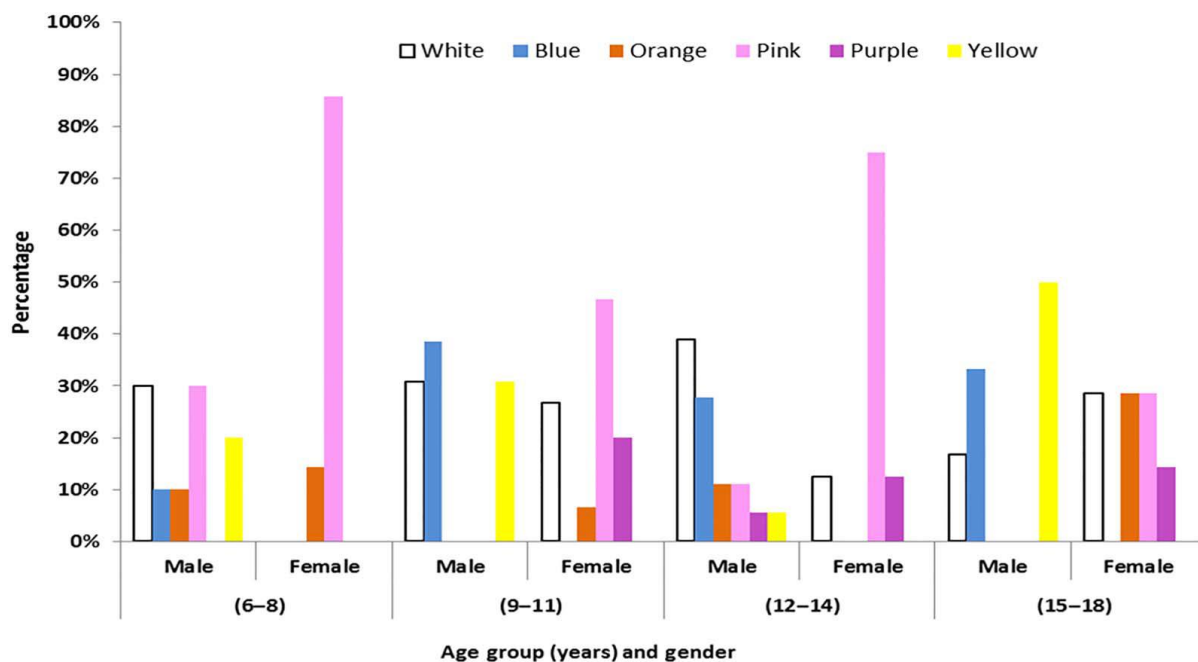
Furthermore, male participants (54%) registered their preference for tablets as compared to the female participants. In order to explore further their preference for oral route, the participants were asked for their preferred oral dosage forms. The results showed (Figure 2) that orally disintegrating tablets scored higher than tablets, capsules and liquids across the various different centres.



**Figure 2** Distribution of paediatrics who preferred oral dosage form according to regions.

### Section three: Physical characteristics results for orally disintegrating tablets (ODTs)

As the first part of the study concluded that the orally disintegrating tablets were the preferred dosage forms, the next set of investigations were centred around evaluating the preference of different attributes of ODT such as colour, taste, shape, flavour and disintegration time. Pink was the preferred colour for ODTs by more than a quarter of the respondents (30.8%) followed by white (26.0%), blue (14.4%), yellow (11.5%), orange (7.7%) and finally purple (7.7%). The majority of the participants preferred ODTs that are round in shape. This accounted for 35.6% of the responses while the heart shape was second with a preference of 22.1%. Least preferred shapes were square (4.7%) and diamond (1.9%). With regard to flavour, strawberry was the most preferred (30.8%) while orange was the least preferred (5.8%).



**Figure 3** Distribution of the preferred colour by age group and gender.

#### *Preferred Oral Dosage Forms*

In our study, results show that ODTs were the most popular oral dosage forms (58%) followed by liquids (20%), tablets (12%) and capsules (11%).

Regional analysis of the data from preferred oral dosage forms indicated that ODTs was the most preferred by the majority of respondents (66%, 65%, and 38%) for Saudi Arabia, Jordan and UK respectively (Figure-2). Analysis of distribution of responses for ODTs as preferred oral dosage form according to age group and gender in all regions showed a highest percentage of the children were male between 12-14 years of age who preferred ODTs (44.83%) followed by females between age group of 11-13 years (38.7%). However, there was no significant difference according to age group and gender ( $p=0.503$ ).

Our study exposed an interesting result in which genders and age group have different colour preferences for ODTs. For example, 28 out of 33 female participants preferred pink colour ODTs while 17 out of 28 male participants prefer white.<sup>12</sup> An extremely significant difference was detected by Chi- square test in colour preferences ( $p=0.0001$ ). Similarly, results showed that there was a significant level of distribution of the preferred colour by age group and gender ( $p=0.0351$ ). The majority of female (6-8 years) respondents (85.7%) preferred pink colour ODTs while the highest percentage preference for white was recorded for male participants (12-14 years) (38.9%) see (Figure 3).



With respect to the regional preferences, English and Jordanian participants did not prefer square shaped tablets while around 12% from Saudi preferred square shape.

The size and thickness of a dosage form is vital in its acceptability.<sup>14</sup> Small sized ( $0.15 \text{ cm}^3 \pm 0.002$ ) ODTs were most preferred (64.42%) compared to the medium  $33.65\%$  ( $0.27 \text{ cm}^3 \pm 0.006$ ) or large  $1.92\%$  ( $0.33 \text{ cm}^3 \pm 0.006$ ) ODTs.

Our results demonstrate that the preference for small sized ODTs cuts across all age groups ( $p > 0.05$ ) and gender for all study regions.

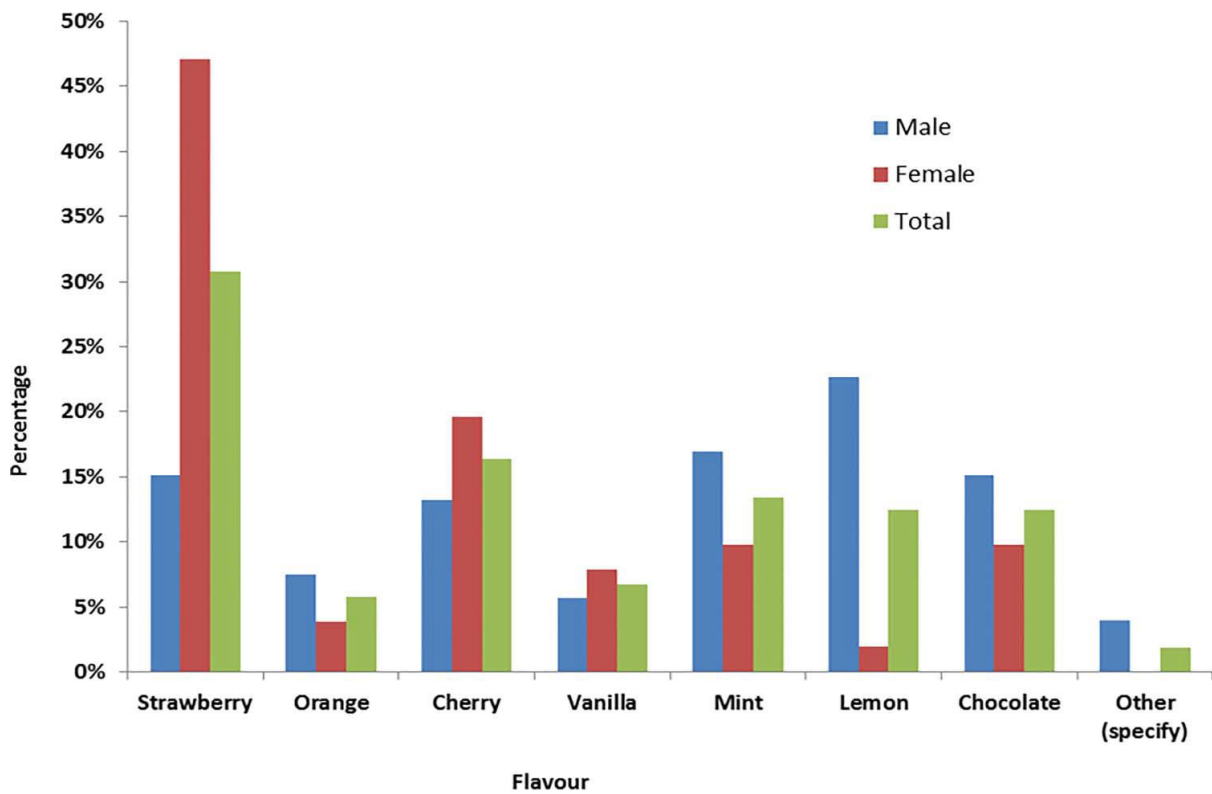
Analysis of thickness of ODTs also, highlights the preference of the participants for thin formulations at the expense of thick ODTs. The majority of respondents (66.35%) preferred thinner ODTs ( $1.14 \text{ mm} \pm 0.002$ ); however, 33.65% of the participants preferred thicker ODTs ( $2.47 \text{ mm} \pm 0.03$ ).

#### *Taste and flavour Preferences*

The taste of a drug is the result of a perception initiated by afferent sensors in the tongue; and may be sweet, neutral, bitter or salty. Flavour is usually a result of the addition of excipients. In this present study the majority of the participants (76.9%) preferred sweet taste.

With regard to flavour, strawberry was the most preferred (30.8%) while orange was the least preferred (5.8%).

When considering flavour preference by gender, it was found that strawberry was the most preferred flavour by female participants (47.1%). On the other hand, 22.6% of male participants preferred lemon followed by mint (17%), then chocolate and strawberry with 15.1% each (Figure-4).

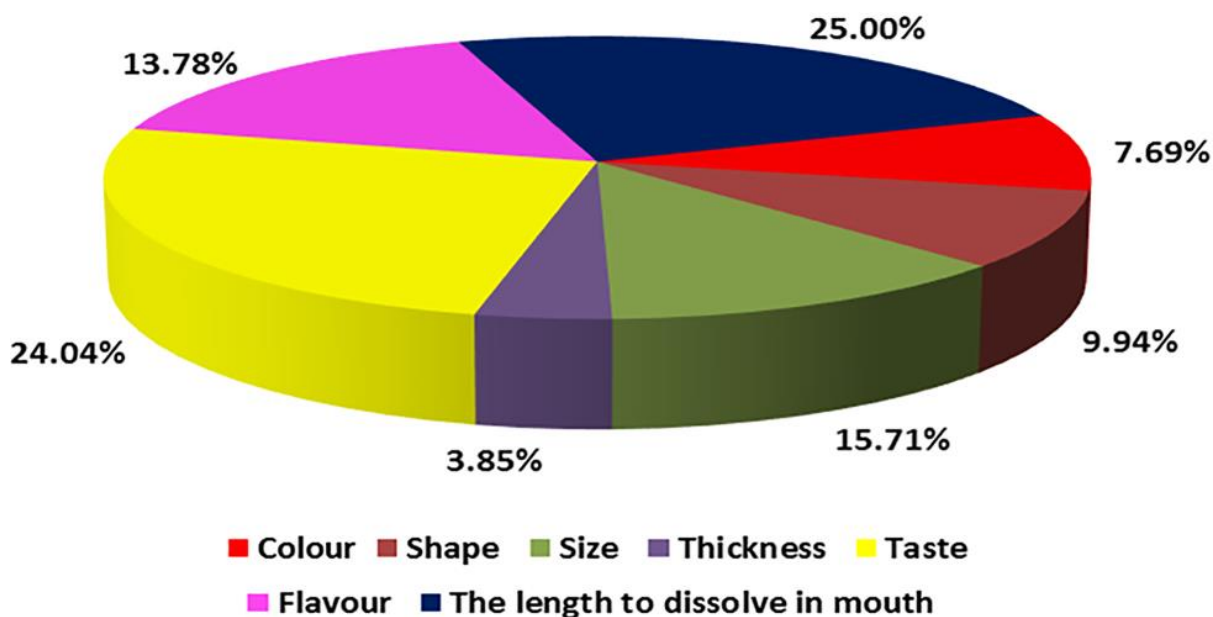


**Figure 4** Distribution of preferred orally disintegrating tablet (ODT) flavours for all regions by gender.

Although, overall strawberry was the most preferred flavour, significant differences were found among participant preferences according to the geographical regions. Lemon was the second most preferred flavour in Saudi children (24%) while it was the least with British (3%) participants.

The majority of the participants (87.5%) preferred very rapidly (<30sec) disintegrating ODTs followed by rapidly (10.6%), and the least preference was for ODTs that would disintegrate between 1.5 and 3 minutes (1.9%) respectively.

The results obtained for the analysis of the physical characteristics of ODTs showed that 25.0% rated the duration for tablet disintegration in the mouth as the most important characteristic, followed by the taste (24.1%), size (15.7%), and flavour (13.8%) respectively as shown in Figure-5. Nearly, similar results were found by Ibrahim *et al.* with respect to the importance of the physical characteristics of oral solid dosage forms, with slightly more than half (52%) of the respondents ranking the size as the most important followed by taste (40%), shape (13.6%), and colour (13.4%) respectively.



**Figure 5** Distribution of the most preferred characters of orally disintegrating tablets (ODTs) for all regions.

## Discussion

The current study explores the preference of children not only for the route of administration of medicines but also investigates the preferred oral dosage form. This study for the first time also incorporates elements of pharmaceutical development attributes that should be taken on board when developing medicines for children.

Alhaddad *et al.* cross-sectional study for people above 18 years found that tablets (69.6%) and capsules (37.6%) represented the highest preferred dosage forms. It was recommended that prescribers should prescribe to patients their preferred dosage forms, to improve medication adherence, and hence improve outcomes.<sup>14</sup> Interestingly, in our study there was no significant difference among gender  $p > 0.05$  (Chi square test) in their preferences. However, there is a significant difference according to dosage where suppositories and injections were the least preferred dosage forms  $p < 0.05$ .

The popularity of ODTs in the pediatric population is possibly due to a number of factors including ease of administration, stability and convenience of storage (as opposed to liquids). However, a study by Ibrahim<sup>15</sup> showed that capsules were the most preferred oral solid dosage forms when compared to tablets, caplets and soft gel. Ibrahim results also showed that ethnicity and age group directly influenced the participants preferences of oral dosage forms. For example, capsules were preferred by both Malays and Chinese.<sup>15</sup>

The superiority of ODTs as a preferred alternative to capsules and conventional tablets is possibly due to better patient compliance as it does not require water for administration and the tablet disintegrates and dissolves in the oral cavity within seconds.<sup>16</sup> Capsules were the second preferred form by UK respondents; possible explanation for this preference includes the ability to distinguish it from dosage forms as well as easier to swallow.<sup>17</sup> Another possible explanation for the preference of capsules could be attributed to the previous experience of the participants in taking capsules over liquid or tablet dosage forms.

As for the preferences of the white colour, followed by blue oral dosage forms, investigations by Ibrahim *et al.*<sup>15</sup> Among 350 participants in Malaysia, the study found that white was the preferred colour by more than half of the respondents (55%) followed by blue (20%). While round shape was the preferred in our results, similarly, in another study in the adult population, 53% preferred round shape tablets.<sup>15</sup> Surprisingly, in-vitro studies recommended that flat tablets have greater adherence to the oesophagus than caplets.<sup>18</sup> Furthermore, oval tablets may be easier to swallow and have faster oesophageal transit times than round tablets.<sup>19</sup>

In this study, participants felt that small ODTs are easier or more comfortable to swallow than larger ones. In 2001, Overgaard *et al.*<sup>20</sup> results showed that difficulty in swallowing increased with an increase in tablet size. The size of dosage forms may affect the transit through the pharynx and oesophagus and may directly affect a patient's ability to swallow. Larger tablets and capsules have been reported to extend oesophageal transit time. This can give rise to disintegration of the product in the oesophagus, resulting in pain and localized oesophagitis.<sup>21</sup> Sweet taste preference in our study for paediatric population is contrasted in another published study evaluated the most preferred oral solid dosage forms (OSDF) in adult participants. More than half (55.0%) of participants preferred their OSDF to be without taste while 40.7% preferred sweet taste.<sup>15</sup> According to other studies, the preference for sweet taste remains high throughout childhood<sup>22</sup> and then switches to neutral during late adolescence.<sup>23</sup> Furthermore, Pepino *et al.* reported that not only do children prefer sweet taste, but sweet tasting solutions in the oral cavity supposedly decreases pain in both infants and children, probably via the involvement of the endogenous opioid system. Therefore, it is not surprising that many oral formulations for children are sweetened.<sup>24</sup>

Strawberry preference in our study group was confirmed by other studies. For example, a study was carried out in 48 healthy schoolchildren in Tanzania and results showed that cherry flavour appeared favourable to ensure a high acceptability of anti-malarial dispersible tablets in small infants and children.<sup>25</sup>

A possible explanation could be that strawberry is found as a common flavouring in various food additives and is effective even at low concentration.<sup>26</sup>

According to the European Medicines Agency (EMA),<sup>2</sup> cherry and strawberry flavours were most preferred in medication for pain and infectious diseases within the European paediatric population; whereas lemon, peppermint and orange were recommended for indigestion remedies.

Upon in-depth analysis of the most preferred ODT's properties particularly speed of disintegration, taste and flavour, most participants believed that some tablets have a bad taste and that rapid disintegration would ensure unpleasant taste can be reduced by quickly swallowing the contents of the tablet. Additionally, pleasant flavour and taste will support their whole experience particularly those on chronic medications – and may ultimately support adherence. This study has identified the favoured medication characteristics as expressed by the participants. However it has not been tested whether these desirable characteristics are deliverable due to the physical properties of the active ingredients. Similarly the potential benefits in terms of patient adherence are implied only, and have not been tested in this present study.

## **CONCLUSION**

The general outcome was that solid dosage forms are the preferred dosage forms and orally disintegrating tablets are a preferred dosage form for children and young adults. The benefits that accrue to ODTs include safety, higher compliance, dose accuracy, stability and ease of swallowing. Within the paediatric population, orally disintegrating tablets are more convenient because they combine the advantages of both solid and liquid dosage forms but without incorporating their disadvantages such as difficulty in swallowing and lack of stability. From the results in the current study, it can be concluded that the most preferred colours were pink and white, the most preferred size is the small sized tablets and the most preferred shape was round with strawberry flavoured. Similarly, physical characteristics in order of priority with regard to the acceptability of ODTs included disintegration time, taste, size and flavour.

## **Key messages**

### **What is already known in this subject**

- The main challenge facing drug development in paediatric dosage forms is the appropriate choice of the dosage forms for drug administration to this important target population
- There are many dosage forms available for children, and it's safety and dosage flexibility is important
- Acceptance of medicines by children needs to be considered by drug formulation designers, as factors such as palatability and elegance may affect this

- Orally disintegrating tablets is a dosage formulation design available and possible for paediatric medicines

### What this study adds

- Based on a questionnaire from paediatric patients across five centres in three countries internationally, orally disintegrating tablets are the preferred dosage form for children and young adults in comparison to tablets, capsules and liquids
- Formulation of ODTs and their physical characteristics are of high importance in supporting patient adherence for children to use a particular medicine.

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Ethics approval: Research and Development Department of BCH.

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