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Developing methodology to evaluate the oral sensory features of pharmaceutical tablet coatings.

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Abstract

Acceptability of medicines is critical for effective pharmacotherapy. The aim of this study was to investigate the oral sensory properties of tablet coatings to determine how mouthfeel can improve acceptability. A randomised double-blind study was performed in 84 adult volunteers (51% ≥55 years). Each participant received 4 placebo tablets (3 coated and 1 uncoated) to evaluate (i) ease of swallowing and (ii) palatability. Visual analogue scales (VAS) were used to capture sensory parameters. Acceptability was assessed using the following parameters: ease of swallowing; amount of water taken with the tablet; rank order of preference; roughness; adhesiveness and slipperiness. Ease of swallowing was determined to be the most sensitive measure of acceptance. The best coating was the one that was reported to be the most slippery and smooth.

The presence of a coating improved ease of swallowing, mouthfeel and overall palatability. This study demonstrates that slippery coatings improve acceptability of tablets. The study also demonstrates the value of VAS to measure the sensory attributes of coated tablets.

Keywords: patient acceptability; swallowability; sensory analysis; palatability; mouthfeel; coated tablets

1 Introduction

Patient acceptability of medicines is fundamental in the development of pharmaceutical dosage forms (Liu et al., 2014). Assessing acceptability of medicinal products in their target population is a requirement of the European Medicines Agency in order to obtain a marketing approval (EMA, 2006; 2017). For oral drug delivery, tablets are the most common and preferred choice of dosage form (Mohr, 2009). For any oral formulation, ease of swallowing is an important determinant of patient acceptability. Ease of swallowing is affected by both medicinal product features (i.e. dosage size, shape, slipperiness of the coating), as well as the patient's ability (physiological and/or psychological) to swallow (EMA, 2017). In general, larger solid oral dosage forms are reported to be more difficult to swallow but shape also has an influence. Round tablets have been reported to cause fewer difficulties compared to oblong and oval tablets (Schiele et al., 2013).

Another determinant of acceptability is palatability. The main factors that affect palatability of solid oral dosage forms are taste, texture and mouthfeel (Fields et al., 2015; Liu et al., 2016; Schiele et al., 2013). While taste is a sensation caused by chemical interaction of formulation components with taste buds on the tongue, texture and mouthfeel are more complex and multifactorial in nature. Texture embraces "all the mechanical, geometrical and surface attributes of a product perceptible by means of mechanical, tactile, and, where appropriate, visual and auditory receptors", as defined by the International Standards Organisation (ISO, 1994). Whereas mouthfeel encompasses the tactile properties perceived from the point a formulation is placed in the mouth to when it is swallowed (Guinard and Mazzucchelli, 1996)

Many manufacturers apply film coatings to tablets. Reasons for this include: aiding identification; improved stability; control of drug release rates and taste masking of bitter drugs (Joshi and Petereit, 2013). Typical polymers used include hydroxypropyl methylcellulose (HPMC); polyvinyl alcohol (PVA); polyvinyl alcohol - polyetheylene glycol graft copolymer (PVA-PEG); acrylic copolymers with plasticizing agents such as polyethylene glycol, triacetin or others. Film coatings can make a tablet

more palatable by taste masking and provision of a smooth outer surface texture (Fields et al., 2015) to improve mouthfeel, which can improve acceptability. In addition, they can improve ease of swallowing of a tablet. By inhibiting the disintegration of the tablet in the mouth, a polymer film coating enables a tablet to be swallowed intact and the polymer layer can enhance the gliding properties of the tablet surface within the mouth during the swallowing action i.e. provide a slippery layer (Mahdi and Maraie, 2015). Multiple studies have confirmed that coating a solid dosage form can improve the swallowing experience and taste (El Edelbi et al., 2015; Mahdi and Maraie, 2015; Uloza et al., 2010).

Unpleasant taste and mouthfeel have been found to impact patient adherence in paediatric (Venables et al., 2015) and adult populations (Schiele et al., 2013). Yet, there is limited understanding of which mouthfeel attributes have the largest impact on the acceptance of solid dosage forms. Similarily, awareness of tablet sensory characteristics that are discernible by patients is needed. Evaluation of taste and texture is typically undertaken using sensory analysis. Whilst food sensory analysis is well studied, the field of pharmaceutical sensory analysis lacks clear guidance (Tuleu, 2016). Pharmaceutical sensory studies conducted to date use a range of methodologies and some levels of discrepancies exist amongst them, such as: the number of subjects involved, type of control sample, scales and measures used, definition of acceptance criteria, and level of training of the participants. Further work is needed to determine methodology for testing the appropriateness of drug products (Drumond et al., 2017).

Previous clinical swallowing studies used various methods, to collect data: as observations (Kluk and Sznitowska, 2014); using a descriptor scale (El Edelbi et al., 2015) or VAS (visual analogue scale) (Hayakawa et al., 2016). The VAS provides continuous data, which is suitable for statistical analysis and allows detection of small differences between samples (Mistry et al., 2017). Similar methodologies have been used to assess the mouthfeel of medicines. Notable examples include *in vivo* evaluation of perceived grittiness and roughness of oral dosage forms depending on the

formulation factors (i.e. particle size) (Kimura et al., 2015; Lopez et al., 2016). Lopez et al. (2016) concluded that the perceived oral grittiness of solid multi-particulate formulations is significantly reduced when particles are dispersed in a viscous vehicle, while Kimura et al. (2015) established that a rough mouthfeel was more intense for ODT with granule size ≥200 μm. There are very few reports of studies performed that evaluate the palatability, excluding taste, of oral dosage forms. The objective of this study was to investigate the ease of swallowing and oral sensory properties of tablet coatings applied to placebo tablets. The study used a crossover, single centre design to assess the ease of swallowing and sensory perception of the mouthfeel of placebo tablets coated with different film coatings vs. uncoated ones. The oral sensory perception of tablet-coating attributes that are critical to improve swallowing and acceptability are as yet unexplored. This study investigates the effect of tablet coatings on swallowability and mouthfeel in an adult population with an emphasis on older (>55 years) adults. These data will inform the application of coatings which optimise acceptability of tablets.

2 Materials and methods

2.1 Study population and setting

The study was approved by the Ethical Committee of the University of Birmingham (ERN_17-0883 (17-1074)). All sessions were conducted within the premises of the School of Pharmacy at the University of Birmingham. The participants were recruited from the University of Birmingham and associated networks via advertisements and newsletters. The eligibility criteria included non-smoking, healthy adults between 18 and 75 years of age, who did not self-report any conditions that might compromise their taste or smell, nor any issues in ability to swallow a tablet. Prior to the study written consent was collected from all participants.

The sample size analysis showed that to detect a 10 point difference on the scale with a power of 80% and $\alpha = 0.05$ there was a need for 38 evaluations per sample. An older population (≥55 years)

was targeted to better reflect the population who take the most medication and may have a higher incidence of swallowing disorders (NHS Digital, Baijens et al., 2016; 2017).

2.2 Background questionnaire

Participants completed a background questionnaire to record demographics including: age range; gender; and previous problems with swallowing tablets including what caused these difficulties. Information on current tablet/capsule intake was also recorded. (The background questionnaire is available in Appendix A).

2.3 Materials

White capsule shaped placebo tablets (caplets) were manufactured under GMP conditions and used in this study. The caplet shape and large dimension tablets, 19 x 9 x 7 mm, were selected for this study to reflect the tablet features most likely to cause swallowing problems (Schiele et al., 2013). Tablets were prepared by direct compression on a 27-station compression machine (CMBGD-27/MT, CADMACH, India) fitted with 12 sets of D-tooling and 950mg target weight. Tablet properties were as follows, hardness: 125 ± 4 N, average weight: 951.6 mg ± 3.0%, friability: 0.1% and disintegration time: 1 min 53 seconds. These placebo tablets were composed of: lactose monohydrate (69%), microcrystalline cellulose (15%), Starch 1500® (Partially Pregelatinized Maize Starch, 15%), colloidal silica (0.5%) and magnesium stearate (0.5%).

The average porosity (P) of the tablets was 23%, as calculated from density (ρ): $P = \left(1 - \frac{\rho_{apparent}}{\rho_{true}}\right) \times 100$, where $\rho_{apparent} = 1.18\ {}^{g}/_{cm^3}$, and $\rho_{true} = 1.54\ {}^{g}/_{cm^3}$. Tablets were then coated (coating equipment: NEOCOTA 40D dual pan coater) under GMP conditions using the Opadry® film coating systems; (Opadry white, Opadry EZ white and Opadry EZ clear (Colorcon, USA) (Table 1). These aqueous based film coatings were sprayed onto tablets providing a weight gain of 3% (w/w) film coat, and 1% (w/w) clear top coat (in one case), under the process conditions shown in Table 2.

2.4 Tablet sample assessment

Both (i) ease of swallowing and (ii) palatability of placebo tablets were assessed within a single visit. In both aspects of the study participants received four tablets. To reduce carry over and sequential bias the following methods were used: four samples were presented in a randomized order in all possible sequences, and a palate cleanser was given before each sample. Palate cleansing entailed drinking room temperature spring water, followed by a piece of lightly salted cracker (Jacob's, or Schar gluten free) and followed again by room temperature spring water (Lucak and Delwiche, 2009).

During the evaluation of ease of swallowing, the participants swallowed tablet samples in their usual manner, with unlimited access to room temperature spring water. The participants were not given specific instruction on the amount of water they should drink but advised to take the tablets as they would normally. The amount of water consumed for each tablet swallowed was recorded. This was calculated by subtracting the weight of the cup of water before and after taking the sample ($\rho_{H2O} \approx 1$ g/mL). For each sample, participants measured the time taken to swallow each tablet using stopwatches. The time taken to swallow each tablet was measured by each participant from the moment the tablet was put into mouth until the perception of complete swallowing. The ease of swallowing was assessed by each participant using a 100 mm visual analogue scale (VAS) as shown in Figure 1 (the assessment form is available in Appendix B). Additionally, incidents of tablet arrest in the mouth or throat were recorded. After swallowing of all four samples, participants ranked the tablets on an ordinal scale of 1–4 (score 1 corresponding to the easiest to swallow, score 4 to the hardest to swallow), ties were not allowed. Then participants indicated which tablets were acceptable as a yes/no option for each of the four tablets.

During the palatability part of the study, participants were instructed to hold the tablet in their mouth for minimum of 10 seconds and feel the tablet surface with their tongue and palate. After each sample, the mouthfeel was assessed using 3 VAS with the following anchor phrases: roughness

("Smooth" vs. "Rough"), adhesiveness ("Doesn't stick at all" vs. "Tablet is very sticky"), slipperiness ("Tablet slips easily" vs. "Stays in place"). Finally, overall palatability was assessed on a VAS ("Pleasant" vs. "Unpleasant") (the assessment form is available in Appendix C).

2.5 Data analysis

Statistical analysis was conducted to explore differences between samples, and the relationship between demographic data and participants' responses. The participants' marks on the VAS were transcribed into scores (from 0 to 100). Firstly, Friedman's ANOVA test (non-parametric test for related samples) was performed to screen for differences between samples ($p<0.05$ was deemed significant). Further, Wilcoxon's signed rank test was used to determine differences between individual sample pairs. For a pairwise comparison of the 3 coated samples (excluding the uncoated tablet) $p<0.0167$ level was used (derived from $p=0.05$ divided by 3 combinations of pairs).

Furthermore, the participants were divided into two groups, ≤54 years and ≥55 years, to analyse the effect of age. Pearson Chi^2 test was used to analyse demographic data ($p<0.05$ was deemed significant). For comparison of VAS scores between different populations the Mann-Whitney U test was used (non-parametric test for independent samples), $p<0.05$ was deemed significant. The probability of the tablet arrest in relation to the sample taken was evaluated as odds ratio (OR) with 95% confidence intervals (CI).

The relationship between acceptability of a sample and given VAS score was evaluated using the Mann-Whitney U test ($p<0.05$ was deemed significant). Finally, Receiver Operating Characteristic (ROC) analysis was used to determine the cut off VAS value for each parameter that defined as acceptable product. Data analysis was undertaken with SPSS statistical software version 24 (IBM Corp.).

3 Results

3.1 Participant demographics

The study recruited 84 non-smoking, healthy adults between 18 and 75 years of age. All participants finished both parts of the study. One subject was excluded from data analysis as they did not adhere to the study protocol (i.e. did not undertake palate cleansing between samples) and generated multiple outliers (defined as values >1.5x interquartile value). Data from a total of 83 participants was analysed, 49 of them (59.0%) were female (Table 3). Participants over 55 years old accounted for the 51% of the study population. The number of medications taken daily was found to be age-related ($\chi 2$ (2) = 11.899, $p<0.01$). Sixteen (19.5%) participants reported taking four or more medicines daily, with a majority of them being over 55 years old.

3.2 Ease of swallowing assessment

Prior to subsequent analysis of data, it was confirmed that the order of taking tablets did not influence the VAS score given by the participant (Friedman's ANOVA test, $p>0.05$). VAS data was not normally distributed (Shapiro-Wilk test, $p<0.05$), therefore median values were compared. The VAS results showed that the uncoated tablet (median VAS: 66 mm) was more difficult to swallow than any of the coated tablets (median VAS: 85-87 mm), $\chi 2$ (3) = 52.545, $p<0.001$ (Figure 2). While the coated tablets were all similarly easier to swallow [$\chi 2$ (2) = 4.315, $p=0.116$]. The rank of ease of swallowing placed tablet samples in the following order: EZ-EZ > EZ > Opadry > Uncoated. Most participants ranked the coated tablet samples as their first choice, EZ-EZ (37.8%), EZ (25.6%), and Opadry (22%). Only 14.6% of participants ranked the uncoated tablet first, with the majority (64.6%) ranking it as the most difficult to swallow of all the tablets.

Participants drank between 0 mL to 125 mL of water to swallow each tablet. The median volume of water needed to swallow coated tablets was 28.8 mL, compared to 35.9 mL for the uncoated ones [$\chi 2$ (3) = 20.678, $p<0.001$]. The time taken to swallow tablet samples ranged from 1 to 49 seconds with uncoated tablets taking longer to swallow than coated ones [$\chi 2$ (3) = 14.855 $p<0.01$].

With a fifth (20.5%) of the 332 tablets tested, participants reported tablet arrest i.e. the feeling that the tablet was stuck, either in their mouth or during the swallow. For the uncoated tablets 41% were reported, whereas the incidence for all coated tablets was only 14% (OR 0.229, CI 0.130-0.404). The incidence of tablet arrest inversely correlated with the ease of swallowing VAS and rank ($U = 2119$, $p<0.001$, and $U = 3111$, $p<0.001$, respectively). Moreover, in the event of tablet arrest more water and more time to swallow the tablet were necessary ($Z(1) = -2.349$, $p<0.05$, and $Z(1) = -4.160$, $p<0.001$, respectively). The occurrence of tablet arrest was neither age nor gender related ($\chi2(1) = 0.127$, $p=0.722$, and $\chi2(1) = 0.123$, $p=0.726$, respectively).

3.3 Mouthfeel and palatability assessment: quantitative analysis of scales

Comparison of the median VAS scores for smoothness, stickiness, slipperiness and palatability of all samples are presented in Figure 3. All four parameters showed the uncoated tablet to be statistically different from the coated tablets (Wilcoxon's test, $p<0.01$). With the exception of slipperiness, participants were not able to perceive differences between the three coated tablets.

3.4 Demographic related aspects of ease of swallowing and palatability

3.4.1 History of issues with swallowing tablets

Over a quarter of the study population reported previous issues in swallowing tablets (n= 22/83). The reasons why participants reported issues in swallowing tablets previously are shown in Table 4. Those, who reported issues in tablet swallowing, rated the tablets on VAS as more difficult to swallow than those who did not declared any issues ($U = 8633.5$, $p<0.05$).

3.4.2 Age

The occurrence of problems with swallowing tablets was found to be age related, with younger participants (≤54 years) reporting the difficulties more often than older participants (≥ 55 years) ($\chi2(1) = 4.530$, $p<0.05$). Older participants took more time (median 7.5 s vs. 6 s), but less water to swallow the tablet (median 26.4 mL and 34.2 mL respectively) compared to the younger

participants. Also, the instances of using no water at all were more common amongst the older than the younger population (10 cases (6.1%) vs. 4 cases (2.5%)).

The ability to distinguish between the samples differed between age groups. Both, young and old, could differentiate the coated from uncoated tablets. The younger group could distinguish between coated samples using scales of roughness, adhesiveness, slipperiness and palatability. However, the older population could only differentiate the roughness between EZ-EZ and EZ coated sample, where EZ-EZ samples had lower roughness.

3.4.3 Gender

The study found no correlation between gender and occurrence of problems with swallowing tablets ($\chi 2$ (1) = 0.004, p=0.951). Neither, the time or water needed to take the tablet was gender related. Looking at the scores given on the VAS scale, there was no influence of gender, except for the palatability scale. Males tended to score the uncoated tablet as more pleasant than females did (median 50 vs. 36; U = 545, $p<0.01$). In general, females were better able to differentiate the tablets than males. While females rated the uncoated tablet significantly less pleasant than coated ones (Wilcoxon's test, $p<0.0167$), males gave similar palatability scores to all of the samples (Wilcoxon's test, $p>0.0167$).

3.5 Determinants of the acceptability

In contrast to the uncoated tablet (66%), almost all of the participants reported that the coated tablets would be acceptable to take on a daily basis (EZ-EZ 96%, EZ 93% and Opadry 95%). The score comparison of the acceptable and unacceptable tablets showed an association with the following parameters: ease of swallowing; amount of water taken with the tablet; rank; roughness; adhesiveness and slipperiness (Table 5). The VAS scores that best separated the parameters listed above into scores for acceptable vs non-acceptable tablets were calculated. For example, for ease of swallowing the cut off value of 60 mm divided acceptable and unacceptable tablets on the basis of

VAS score given. Ease of swallowing was the parameter with the most sensitive and specific cut off (Table 5).

4 Discussion

Acceptability of solid oral dosage forms is driven by the ease of swallowing and palatability. Yet, there is limited understanding of the sensory parameters which have the largest impact on the acceptance of solid dosage forms. This study explored sensory attributes that relate to patient experience during the swallowing of a tablet. The participants' responses were collected on VAS, as it is known to be a sensitive tool to measure small differences in sensory perception. Furthermore, the acceptability of samples was compared with the VAS results, to define the acceptable and unacceptable qualities of tablets.

The ease of swallowing assessment showed that the addition of a coating onto a tablet enhances the ease of swallowing compared to an uncoated one. Also, the uncoated tablet was reported to get stuck more often and required more water to swallow, which may relate to its capacity to absorb liquid. The liquid penetration of the tablet is directly proportional to its porosity (Esteban et al., 2017). Thus the high porosity of uncoated tablet favours the effect of capillary ingress of the liquid. As a result, lubricant and air are removed from the tablet/mouth interface, which increases the risk of adhesion.

Additionally, the tablet cores contained insoluble excipients, hence the surface of the uncoated tablet is rough in contact with a wet surface. This results in greater friction associated with swallowing these tablets. In contrast, a layer of polymer coating reduces the amount of water absorbed, thereby maintaining lubrication and reducing friction. In addition, on hydration they form a slippery layer that further reduces friction. This hypothesis is supported by a study showing how coatings improved the ease of swallowing *in vitro*, where coated discs with lubricating properties needed a reduced force to be moved across *ex vivo* porcine oesophageal tissue (Smart et al., 2015). This explains the fact that the uncoated tablets are perceived to get stuck more often than coated

tablets. Age was found to be an important factor in the process of taking tablets. The older population (≥ 55 years) reported difficulties with swallowing tablets less often; also they required less water to take the sample. As the older population consumes more medicines (Eurostat, 2017), it may be argued, that this is a function of experience and training with a range of solid oral dosage forms. Compared to the younger group, older participants had a longer duration of swallow. Published literature confirms that the passage of the tablet down the throat is longer in older adults (Pongpipatpaiboon et al., 2018). The results in this study may have been confounded by difficulties with using a timer or dexterity problems, rather than the slowness of swallowing itself. Despite the longer duration of the swallow, tablet arrest was not different between the older and younger populations.

The suggested volume of water taken with solid oral medicines is a full glass (Tamboli et al., 2010). In the literature, the typical amount consumed with medicines was reported as of 115 mL out of 150 mL provided (Fuchs, 2009). In this study, the median volume taken was 26.4 mL for coated and 34.2 mL for uncoated tablets. In all cases the total volume of water used to swallow tablets was less than generally recommended. The low volume consumed might be a consequence of the study set up. As the participants knew they would have to swallow a number of tablets one after another, so they may have tried to minimise their fluid intake.

Overall, the uncoated tablets in this study were regarded as inferior in terms of palatability to the coated ones. The VAS scores showed that the uncoated tablets had a rough, sticky, not slippery mouthfeel and unpleasant palatability. Whereas coated tablets showed the opposite sensation. The EZ-EZ tablet coating was superior across all parameters. The EZ-EZ coating was reported to be the most slippery and smooth, while EZ-EZ and EZ were less sticky than the Opadry coating. This was expected, as coatings based on HPMC polymers are known to have muco-adhesive properties (Washington, 2001). EZ-EZ and EZ coatings were designed to have low adhesion and high slipperiness by addition of polymer combinations and MCT which is oily, to the formulation. Thus,

the differences observed in the slipperiness of the tablets were formulation dependent. In line with previous reports, addition of a glide-enhancing excipient (xanthan gum) into the coating, it enhances slipperiness *in vivo* (Mahdi and Maraie, 2015). The coated tablets were consistently ranked as more slippery than the uncoated one.

In this study, several parameters were associated with acceptability: ease of swallowing; amount of water taken with the tablet; rank order; roughness; adhesiveness and slipperiness. Thus, these parameters can be used as a measure of acceptability. A highly sensitive and specific measure is one that accurately separates acceptable from unacceptable tablets. Ease of swallowing and rank order were highly sensitive and specific measures of tablet acceptance. Stickiness and roughness were the mouthfeel attributes most strongly linked to tablet acceptance. The scaling with the use of cut offs provides an insight into what drives the acceptability. Some attributes were more critical than other. For example, the VAS cut off of 70 mm for roughness suggested that only samples which were undoubtedly smooth were acceptable. While a VAS cut off of 20 mm for stickiness indicates that only highly sticky tablets were unacceptable, and slightly sticky tablets were acceptable. Remarkably, palatability was not associated with acceptability in this study. The palatability is often related to the appreciation of taste. Yet the tablets were designed to be tasteless which may explain why palatability was less sensitive measure. This was also shown by the fact that the VAS scores on the palatability scale were clustered in the middle of the scale. Importantly, in a presence of bitter drug in a tablet the palatability should have significant impact on the acceptability.

5 Study Limitations

There were a number of limitations associated with this study. First, the study recruited only participants self-assessed as healthy and excluded dysphagic patients or people with diagnosed swallowing difficulties. Second, the use of an untrained, non-expert panel has the potential to increase the variability of responses to the sensory attributes of tablets. All data were collected on a single visit, hence the repeatability of results within a single subject could not be determined. Finally,

although visually the tablets were alike the uncoated tablet performed very differently to the coated tablets. Therefore, by comparing only coated tablets, a more differentiated picture of the preferred coatings might have been achieved.

6 Conclusions

This study aimed to investigate the ease of swallowing and oral sensory properties of coated tablets to determine how mouthfeel can improve acceptability. It was found that the oral sensory properties can be assessed by visual analogue scales. In particular, the presence of a tablet coating improved the ease of swallowing, mouthfeel and overall palatability. Uncoated tablets were perceived as rough, sticky and not slippery, while the coated tablets were predominantly slippery, smooth and pleasant. The extent of palatability improvement was film coating formulation dependent with the greatest improvement achieved with the most slippery coating (Opadry EZ white coated with clear Opadry EZ). Opadry coating was generally accepted, but had inferior mouthfeel scores compared to both Opadry EZ coating options.

In summary, sensory analysis based on VAS can improve understanding of the factors that influence overall acceptability of medicines. The oral sensory features, when related to acceptability using cut off values, could be used as references for the testing of new coatings in the future. Specifically, ease of swallowing and stickiness were found to be a highly sensitive and specific measure to predict tablet acceptance. Notably, palatability was not associated with acceptability, though this case is specific for placebo tablets, containing no substance with aversive taste.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Author Contribution statements

Hannah Batchelor, Ali Rajabi-Siahboomi and Jason Teckoe conceived the idea presented. Hannah Batchelor and Justyna Hofmanova planned and undertook the practical work. Justyna Hofmanova undertook the analysis with statistical input from Sayeed Haque. Justyna Hofmanova and Hannah Batchelor wrote the manuscript with input from Julie Mason, Daniel To, Ali Rajabi-Siahboomi and Jason Teckoe. All authors provided critical feedback on the manuscript draft and revisions to shape the analysis and manuscript.

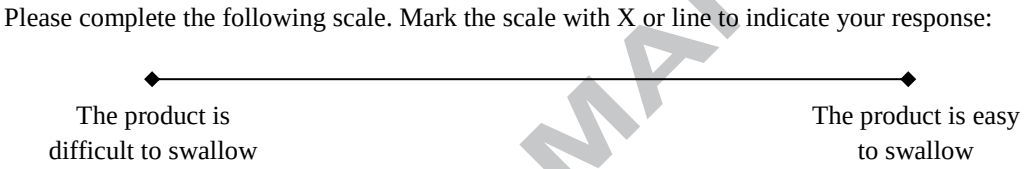

Figure 1 Example of 100 mm unmarked Visual analogue scale (VAS)

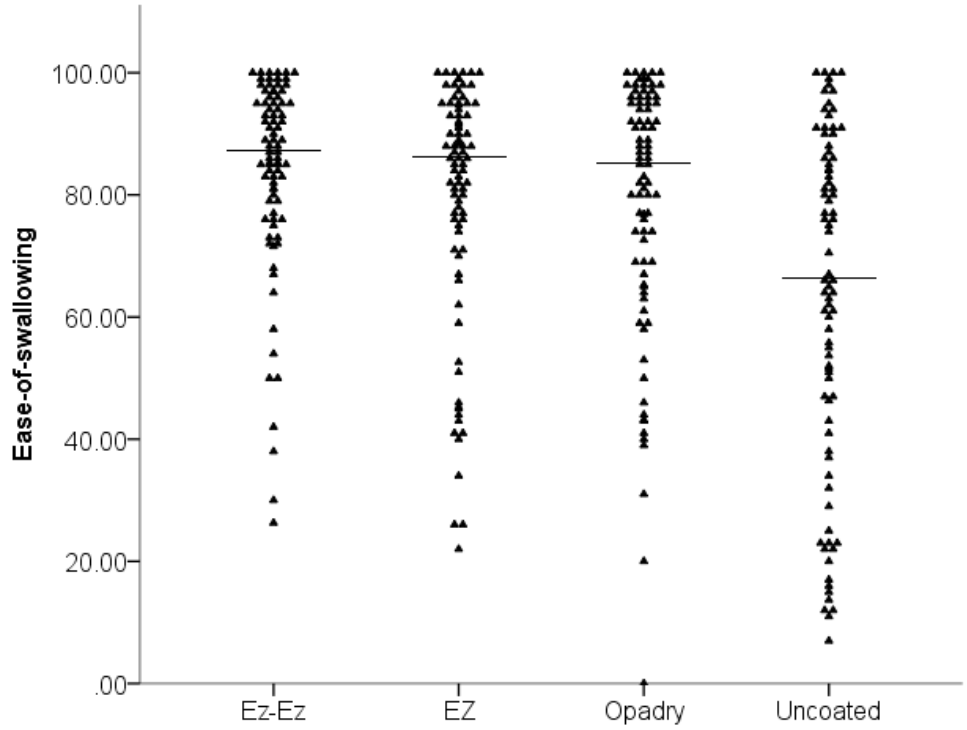

Figure 2 Ease of swallowing VAS scores for all the samples; each ▲ represents one participant, line depicts median score (n=83)

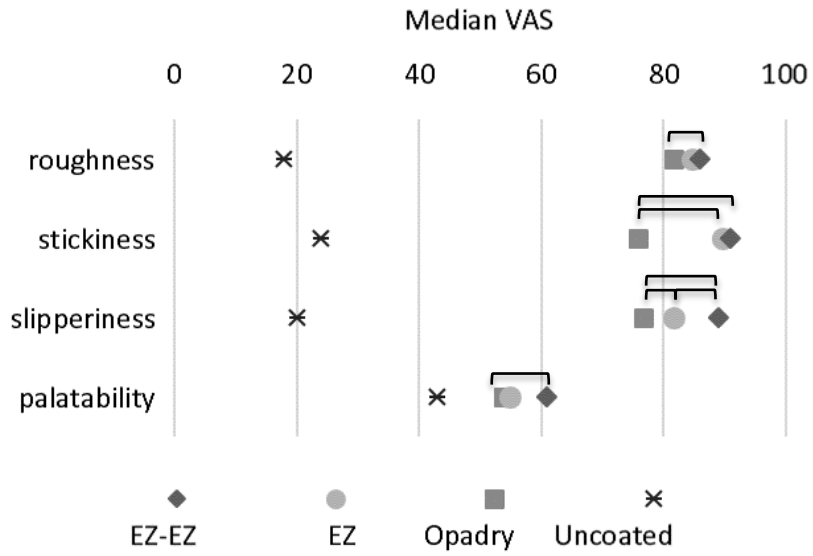

Figure 3 Comparison of the four tablet samples in the mouthfeel test (score 0 means negative quality, 100 positive quality). Brackets indicate statistical significance ($p<0.0167$)

Table 1.

Film coating systems (Opadry®) used in this study

Abbreviation used	Film coat	Top coat	Main ingredients
Uncoated	-	-	-
EZ-EZ	Opadry EZ white	Opadry EZ clear	HPMC + polysaccharide + MCT*
EZ	Opadry EZ white	-	HPMC + polysaccharide + MCT*
Opadry	Opadry 03F white	-	HPMC

* MCT - medium chain triglycerides

Table 2

Film coating process conditions used to coat the placebo tablets (if roughness was observed in tablets, an adjustment in spray rate and pan speed was made to ensure tablets appear similar)

Parameter	Batch 1	Batch 2	Batch 3	
Film Coating	Opadry® White	Opadry EZ White	Opadry EZ White	Opadry EZ Clear top coat
Solids (% w/w)	15	15	15	8
Inlet Temperature (°C)	50	50	50	50
Bed temperature (°C) - actual	44.6	44.8	46.2	45.5
Exhaust temperature (°C)	43.3	44.7	44.0	42.2
Pan speed (rpm)	2.0 - 4.0	3.0 - 4.0	3.0 – 3.5	3.0 - 4.0
Atomizing pressure (bar)	2.5	3.0	3.0	3.0
Spray rate (g/min)	24	16	17	21
Weight gain (%)	3	3	3	1
Batch size (kg)	8.3	8.3	8.3	8.3

Table 3.

Participant demographics

Number of participants (n=83)	Frequency	Percent [%]
Gender		
Male	34	41.0
Female	49	59.0
Age (years)		
<24	10	12.0
25-34	13	15.7
35-44	11	13.3
45-54	7	8.4
55-64	10	12.0
>65	32	38.6
Problems with swallowing tablets previously		
No	60	73.2
Yes	22	26.8
Missing*	1	
History of taking medicines		
None daily	34	41.5
Between 1-3 daily	32	39.0
4 or more daily	16	19.5
Missing*	1	

* Participant did not answer the question

Table 4.

Problems reported with swallowing tablets

	Frequency*	Percent of whole study population (n=83)	Percent of those who stated that have problems with swallowing (n=22)
Size of tablet	18	21.7	81.8
Taste of tablet	4	4.8	18.2
Texture of tablet	6	7.2	27.3
Aftertaste	3	3.6	13.6
Dry mouth	6	7.2	27.3
Other	1	1.2	4.5
Total	38		

* Multiple answers were possible

Table 5.

Results of Mann-Whitney U test for the influence of the parameter on the acceptability, the sensitivity and specificity of the cut off (n=83)

Parameter	Mann-Whitney U	P value	Cut off	Sensitivity	Specificity
Ease of swallowing (0 = difficult)	153.5	0.001	60	0.88	0.82
Water (mL)	214	0.018	40	0.64	0.64
Time (sec)	263.5	0.186	-	-	-
Rank (1= best)	71.5	0.000	3	0.81	1
Roughness (0 = rough)	145	0.017	70	0.65	0.75
Stickiness (0 = sticky)	136	0.011	20	0.89	0.63
Slipperiness (0 = not slippery)	149	0.020	30	0.80	0.63
Palatability (0 = not pleasant)	258	0.522	-	-	-