



## Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers



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### ABSTRACT

Multiparticulate formulations are composed of multiple solid dosage units which can be administered directly to the mouth or sprinkled on food. Oral grittiness (i.e. rough mouthfeel) may arise from the presence of particles in the mouth, limiting palatability. In this work, multiparticulate formulations were prepared by dispersion of spherical granules into orange flavoured vehicles thickened with hypromellose (HPMC) at different viscosities in order to assess oral perception of grittiness by a panel of thirty adults through direct scaling on a 100 mm visual analogue scale. The effect of formulation factors such as particle size (90, 127, 263  $\mu\text{m}$ ), amount of particles per 10 ml (0.25, 0.50, 1.00 g) and viscosity of the vehicle (0.08, 0.43, 2.80 Pas) were investigated. Grittiness was increasingly perceived with increasing amount and size of particles. Increasing viscosity of the administration media had a masking effect on the perception of particles. Less gritty samples were generally regarded as 'more pleasant' by the participants of the study. However, samples dispersed in thickened vehicles seemed to be less preferred despite being less gritty; which could be ascribed to an unpleasant mouthfeel of the vehicle. In the design of multiparticulate formulations acceptable for a targeted patient group all these formulation factors will need to be considered and optimised.

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## 1. Introduction

Multiparticulate drug delivery systems are composed of multiple solid dosage units, such as granules, pellets or minitablets, which are filled in a suitable primary packaging system (e.g. capsules or sachets). A popular technology for the preparation of these systems is active layering, whereby a drug solution or suspension is sprayed onto inert pellets (cores or seeds) by fluidised bed coating (Priese et al., 2014). Inert seeds made of sugar, microcrystalline cellulose or starch (among other materials) are commercially available for this purpose. Alternatively, the drug can be incorporated into the starter cores during the pelletisation process, followed by one or multiple layers of film coating (Priese et al., 2014). Based on the physicochemical properties of the drug and the targeted release profile many variations of the manufacturing process have been investigated (Abbaspour et al., 2014; Ahmad et al., 2014; Maniruzzaman et al., 2012; Otero-Espinar et al., 2010; Priese et al., 2014; Zolkefeli and Wong, 2013). Recently, multiparticulates have attracted a great deal of attention for the preparation of medicines suitable for paediatrics as they offer a range of advantages for the delivery of drugs to these patients. These include improved ease of swallowing and flexible dose titration compared to

conventional tablets and capsules, suitability for taste masking, controlled drug release and multiple drug delivery in the form of fixed dose combinations (Desai et al., 2013; Lopez et al., 2015). In addition, other patient populations with similar needs such as older patients could also benefit from this drug delivery approach.

Despite the fact that multiparticulates have been used for some time and now thought to ease administration of medicines in children, little is known about their acceptability and patient preferences. Multiparticulates can be reconstituted in a suitable drink to provide a suspension or added onto soft food as a sprinkle for ease of administration. Alternatively, vehicles for the oral administration of multiparticulates could be designed, manufactured and supplied to patients for a more standardised administration (Kluk and Sznitowska, 2014). The administration vehicle is expected to have a great influence on the overall patient experience by affecting various parameters such as the rate of sedimentation of the dispersed particles and the perception of particles in the oral cavity upon ingestion. In this regard, the viscosity of the vehicle could be adjusted appropriately in order to hinder sedimentation hence improving dose uniformity and, potentially, reducing perception of particles in the mouth (Kluk and Sznitowska, 2014). The reconstituted product could then be easily administered to paediatric patients with the aid of a suitable dosing device, such as a measuring spoon. Nevertheless, in the instance of co-administration with food or other vehicles the potential impact of this practice on the

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drug's bioavailability needs to be considered and evaluated (Batchelor et al., 2014).

Palatability is a critical parameter of oral formulations and especially those intended for paediatric patients. Poor palatability is likely to be linked to reduced patient compliance to a therapeutic regime, which will have a detrimental effect on the outcomes of the drug therapy (Baguley et al., 2012; Mennella et al., 2015). The current regulatory framework for development of medicines for paediatric use advise of the need for evaluating palatability and acceptability, defined as the overall ability and willingness of the patient to use a medicinal product as intended (European Medicines Agency, 2013). However, there is no official guidance for the assessment of palatability and acceptability of oral dosage forms. Most of the work that has been conducted is based on the utilisation of visual analogue scales (VAS) (van Riet-Nales et al., 2013). Taste is often considered the most important factor affecting palatability of oral medicines. In the case of multiparticulate drug delivery systems, an unpleasant (usually bitter) taste of the active pharmaceutical ingredient (API) could be overcome by application of a polymeric coating around the drug-loaded granules (Stange et al., 2014). Therefore, taste of the API would likely become less of an issue whereas oral grittiness (i.e. a rough feeling in the mouth) could turn out to be the major determinant of palatability and acceptability of the formulation. Grittiness and poor mouthfeel due to the presence of particles in suspension have been reported as a likely constraint in the administration of multiparticulates (Liu et al., 2014). However, the relationship between different formulation variables and the perception of oral grittiness has not been established yet.

In this study, perception of oral grittiness from placebo multiparticulate formulations was evaluated by a panel of healthy adult participants. For the purpose of this study, it was assumed that multiparticulate formulations would be prepared as a solid product filled into a suitable primary packaging system (e.g. sachets) which can be opened by the patient to disperse the contents in a vehicle prior to administration. Multiparticulate formulations were prepared using commercially available granules of different particle size in narrow size ranges. Variable amounts of these particles were dispersed in orange flavoured oral hydrogels (containing HPMC as viscosity modifier) and administered to the participants of the study with a suitable spoon. The aim was to determine the effect of particle size, quantity of particles and viscosity of the suspending media on perception of oral grittiness and patient preferences of multiparticulate formulations.

## 2. Materials and methods

### 2.1. Materials

Hydroxypropyl methylcellulose (HPMC, hypromellose) (4000 cP, substitution type 2906, grade 65SH-4000) was obtained from Shin-Etsu Chemical Company Ltd. (Tokyo, Japan). Microcrystalline cellulose spheres (Cellets®, type Cellets 90, Cellets 127, Cellets 263 and Cellets 500) were kindly provided by Pharmatrans Sanaq (Basel, Switzerland). Details of the particles are provided in Table 1. Orange Flavour Givarome Permaseal and Orange Flavour Permaseal were received from Givaudan (Vernier, Switzerland). Sucralose Granular NF (Emprove, NF) was purchased from Merck KGaA (Darmstadt, Germany).

**Table 1**  
Particle size descriptors of Cellets (≥85% of particles within given range).

Commercial ID	Size range (µm)
Cellets 90	63–125
Cellets 127	100–160
Cellets 263	212–300
Cellets 500	500–710

### 2.2. Physical characterisation of multiparticulates

The morphological features of the particles were imaged using Scanning Electron Microscopy (SEM). Samples were adhered onto aluminium stubs (TAAB Laboratories, Reading, U.K.), sputter coated with gold under vacuum and then imaged at different magnification levels using a Quanta 200F instrument (FEI, Hillsborough, OR, USA). Images were collected before and after dispersion of Cellets in deionised water for 24 h to assess the effect of water on particle morphology (wet samples were filtered and oven dried at 30 °C for 4 h before imaging). The aspect ratio of the particles was calculated as  $d_{\min}/d_{\max}$  (where  $d_{\max}$  is the major diameter and  $d_{\min}$  is the minor diameter) and the circularity factor was calculated as  $4\pi A/P^2$  (where  $A$  is the area and  $P$  is the perimeter) using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

The particle size distribution of the granules was assessed by laser diffraction using a Mastersizer 3000 fitted to an Aero S and a Hydro MV feeding systems for dry and wet dispersion, respectively (Malvern Scientific, Worcestershire, UK). The air pressure and feeding rate were optimised to allow dry dispersion of the particles. Wet dispersion method was carried out using deionised water as dispersant; samples were pre-dispersed in deionised water for nearly 60 min before analysis to allow water sorption equilibrium. Six replicates of each sample were tested.

### 2.3. Preparation and rheological assessment of suspending media

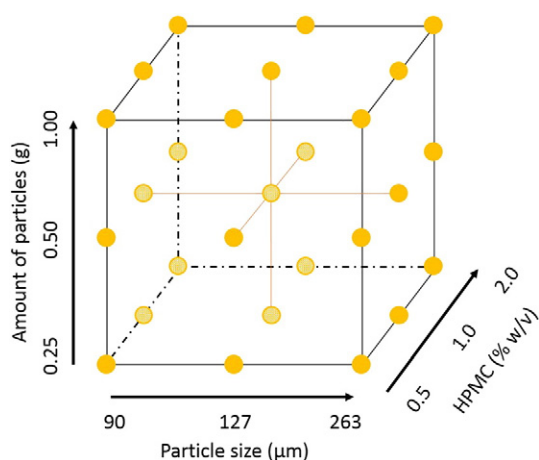
HPMC aqueous vehicles were prepared by addition of HPMC (0.5%, 1.0% or 2.0% w/w) to 100 ml of distilled water under continuous stirring at 80–100 °C followed by a rapid cool down on ice to form the gel structure. HPMC vehicles were sweetened with 0.10% (w/v) of sucralose and flavoured with 0.4–0.5% (w/v) orange flavour. Samples were autoclaved at 121 °C for 20 min and then stored in closed containers at room temperature for 24 h before viscometry and sensory evaluation. A Bohlin Gemini HR rotational rheometer system (Malvern Instruments Ltd., Malvern, UK) was used to investigate the rheological properties of the samples using a cone and plate geometry (55 mm diameter, 2° angle). A 2 ml sample approximately measured with a plastic spoon was placed onto the plate, the gap width was adjusted to 200 µm and the sample excess was removed. Samples rested for 180 s before each measurement to minimise the effect of sample shear history. A 'shear sweep' measurement mode was used whereby the shear rate of the sample is controlled by the rheometer and advanced in increments across the desired range (0.9–200 s<sup>-1</sup>). This procedure was repeated three times for each sample. Throughout testing the temperature of the sample was maintained at 25 °C. The range of shear rates was chosen to represent the flow conditions experienced by the sample in practice, from manipulation in the spoon to swallowing (O'Leary et al., 2010). However, a shear rate of 50 s<sup>-1</sup>, often taken as a representative shear rate of the mouth cavity, was used as a benchmark to compare samples (Zargaraan et al., 2013).

### 2.4. Oral sensory evaluation of multiparticulate formulations

#### 2.4.1. Experimental design and sample preparation

Samples for oral sensory evaluation were composed of 10 ml of sweetened, orange flavoured HPMC oral gels in which Cellets were dispersed by automated inversion (32 rpm). Homogeneous dispersion of particles in the media was confirmed by visual inspection immediately before sensory evaluation.

In the study of oral grittiness perception of placebo multiparticulate formulations three different variables were considered: amount of particles per sample, particle size and concentration of HPMC in the oral vehicle. A three-factor, three-level full factorial design was conducted, as shown in Fig. 1. All possible combinations of each factor were investigated, resulting in a total of 27 samples (3 particle sizes × 3 amounts of



**Fig. 1.** Experimental design space: all possible combinations of three factors (amount of particles, particle size and concentration of HPMC) at three different levels (0.25, 0.50, 1.00 g; 90, 127, 263  $\mu\text{m}$ ; 0.5, 1.0, 2.0% w/v; respectively) were investigated.

particles  $\times$  3 concentrations of HPMC). In addition, a negative control consisting of 0.5% (w/v) HPMC without particles and a positive control consisting of 0.5% (w/v) HPMC with 1 g of Cellets 500 were prepared and evaluated.

#### 2.4.2. Measurement of oral grittiness in adult volunteers

Thirty young adults aged between 20 and 25 years old (median 23; 14 men and 16 women) were enrolled in a randomised single-blind study. Participants were recruited by internal advertising at The School of Pharmacy, University of London, and included university staff and students. All participants provided written consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Research Ethics Committee at The School of Pharmacy, University of London (REC/A/09/01). The sensory evaluation was carried out in a designated room at The School of Pharmacy free from any distracting noises or smells. The study was conducted over two sessions, taking place on separate days to minimise participants discomfort and fatigue. At the start of each session, participants were presented with non-blinded negative and positive controls as references for samples to be considered “least gritty” and “most gritty” respectively. Thereafter, participants received the blinded samples (labelled with a randomised 3-digit code) in an individually randomised order. Each participant tested 27 samples in between the two session plus blinded negative and positive controls which were also given in a randomised order during the course of the sensory evaluation.

Samples were evaluated following a ‘swirl and spit’ methodology by which participants placed each 10 ml sample in their mouth, keeping it moving for about 15 s before spitting it out. Samples were administered with a flat bottom plastic dosing spoon with sufficient capacity for 10 ml. Immediately upon expectoration of the sample participants rated the intensity of the test stimuli on paper-based questionnaires with a bipolar 100 mm visual analogue scale (VAS) labelled from “very smooth” to “very gritty” on the left and right ends, respectively. Participants had free access to water and rinsed their mouth before and after each sample. After testing all the samples on each session, participants were asked to rate the “two most pleasant formulations” in order to evaluate their formulation preferences.

#### 2.5. Statistical analysis of the data

The measurement on the VAS scale in mm (where very smooth is 0 mm and very gritty is 100 mm) was used for data processing. Data

obtained was expressed as mean  $\pm$  standard deviation ( $n = 30$ ). The factor delta ( $\delta$ ) was calculated as the difference between the maximum and minimum mean response across levels of a factor. Box plots were produced for visual interpretation of the data, where centre lines represent the median, box limits indicate the 25th and 75th percentiles, whiskers extend 1.5 times the interquartile range, and outliers are represented by dots.

Differences between genders and between both sessions of the study were evaluated by Mann-Whitney  $U$  test using the blinded controls (as these were assessed on both days). Then, data from both sessions was combined and statistical analysis was performed using Kruskal-Wallis one-way analysis of variance followed by Xin Gao’s test as post-hoc analysis (Gao et al., 2008).

The obtained responses for each factor level combination were fitted to a model by multiple linear regression analysis. The model was simplified by a stepwise process and insignificant terms ( $p > 0.01$ ) were removed from the model equations. The model was validated by one-way analysis of variance (ANOVA) and lack of fit test. Simplified models were used to map out the influences of independent variables on the response via 2-D contour plot analyses.

The number of times each formulation was selected as “most pleasant” was recorded. A ‘sample preference’ factor was calculated as the percentage of participants who selected each sample as one of the two most pleasant. Non-parametric association between grittiness VAS score and sample preference was measured by Spearman’s rank correlation coefficient.

Data analysis was performed using Minitab 17 software (version 17.2.1, Minitab Inc., Pennsylvania, U.S.A.) and R software (open source).

### 3. Results

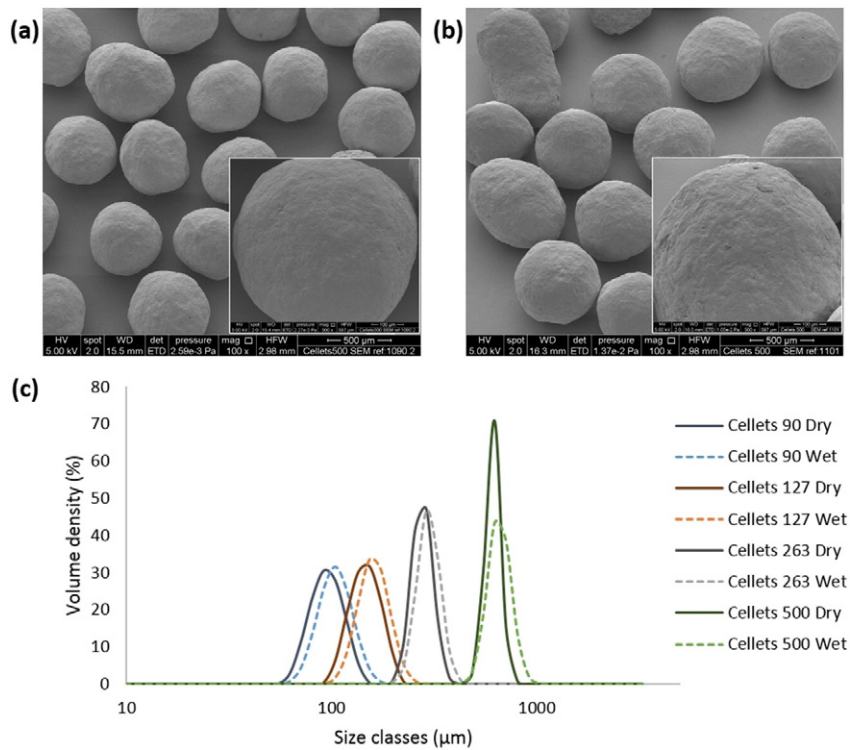
#### 3.1. Physical characterisation of the particles

SEM images of Cellets revealed their spherical morphology and smooth surface as shown in Fig. 2. Average particle circularity was determined to be  $\geq 0.85$  and the aspect ratio  $\geq 0.90$  for all particle size fractions. As the values approach 1 the spherical morphology of the particles was confirmed. Cellets retained their spherical shape when dispersed in an aqueous environment for up to 24 h and no significant disintegration of the particles occurred. The suitability of Cellets for dispersion in an aqueous vehicle prior to administration was thus confirmed.

All samples exhibited a narrow, symmetric, unimodal particle size distribution, as shown in Fig. 2. When assessed by dry dispersion method, the median particle size of Cellets 90, 127, 263 and 500 was ca. 90, 128, 263 and 605  $\mu\text{m}$ , respectively. When Cellets were dispersed in water a subtle increase in particle size was found, which was attributed to water sorption and moderate swelling of the particles. The median particle size of Cellets shifted to ca. 99, 141, 285 and 620, respectively; that is around 10% increase with respect to their original size.

#### 3.2. Rheological properties of the suspending media

The HPMC aqueous gels used as media for oral administration showed shear thinning behaviour, this means that the apparent viscosity of the sample decreased as the shear rate was increased (Fig. 3). The viscosity of the aqueous gels increased with increasing HPMC concentration, as expected. The vehicle containing 0.5% HPMC showed an apparent viscosity of  $0.08 \pm 0.01$  Pas, the 1.0% HPMC vehicle showed an apparent viscosity of  $0.43 \pm 0.06$  Pas and the 2.0% HPMC vehicle showed an apparent viscosity of  $2.80 \pm 0.04$  Pas, measured at a shear rate of  $50 \text{ s}^{-1}$ . The consistency of the three vehicles prepared could be classified as nectar-thick (51–350 mPas), honey-thick (351–1750 mPas) and spoon thick ( $> 1750$  mPas), respectively, according to the National Dysphagia Diet (NDD) guidelines (Zargarraan et al., 2013).



**Fig. 2.** SEM images of (a) dry and (b) wet Cellets 500 at 100× and 500× (inlet) magnification; and (c) particle size distribution of Cellets assessed by laser diffraction using dry dispersion and wet dispersion methods.

3.3. Oral sensory analysis of grittiness of multiparticulate formulations

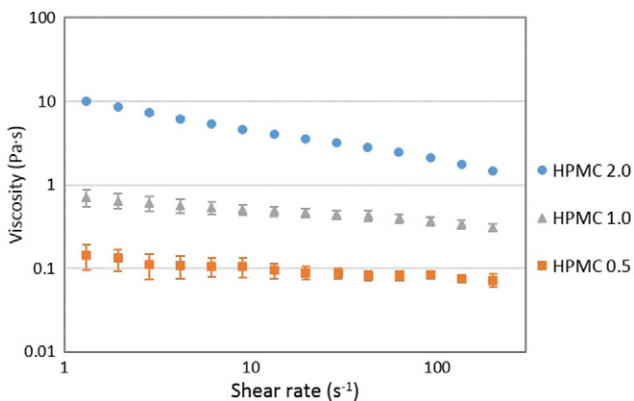
The results obtained in the trial are presented in Fig. 4. Average grittiness VAS scores were below 60 for all samples tested with exception of the positive control (the median grittiness VAS score was 24.6). Grittiness VAS scores tended to be higher with increasing particle size and also with increasing amount of particles. On the contrary, grittiness VAS scores tended to be lower with increasing HPMC content in the vehicle (i.e. with increasing viscosity of the suspending media). In agreement to this trend, the sample with the highest grittiness VAS score ( $57 \pm 24$ , disregarding the positive control) contained the highest level of particle size (263 µm) and amount of particles (1.00 g) dispersed in the vehicle of lowest viscosity (0.5% HPMC); whereas the sample with the lowest grittiness VAS score ( $12 \pm 15$ ) contained the smallest particles (90 µm) at the lowest amount (0.25 g) dispersed in the vehicle of highest viscosity (2.0% HPMC). No significant differences in grittiness

perception were found between men and women and no significant differences were found between both sessions of the study.

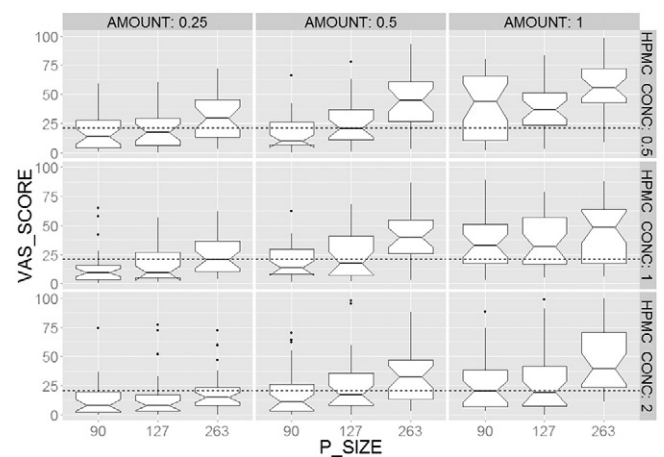
The blinded positive control containing 1.00 g of particles with a median particle size ca. 605 µm scored an average grittiness VAS score of  $87 \pm 12$ , whereas the blinded negative control (no particles) scored an average grittiness VAS score of  $1.6 \pm 2.3$ . As it can be expected, these were the two most extreme values recorded during the study, which confirms their appropriateness as positive and negative controls, respectively.

3.3.1. Effect of particle size on oral grittiness perception

Oral grittiness perception increased with increasing particle size. Particles of 90 µm scored an average VAS score of  $22 \pm 9$ , compared to



**Fig. 3.** Shear sweep measurements of autoclaved, flavoured and sweetened HPMC suspending media showing apparent viscosity of samples over a range of shear rates.



**Fig. 4.** VAS scores of oral grittiness for samples containing 90, 127 and 263 µm particles (P\_SIZE), in amounts of 0.25, 0.50 and 1.00 g (AMOUNT), dispersed in 10 ml of orange flavoured oral gels with HPMC at a concentration of 0.5, 1.0 and 2.0% w/w (HPMC\_CONC); administered with a spoon to young adults. The dotted lines represent the population median VAS score as a reference.

26 ± 8 scored by particles of 127 µm and 38 ± 12 scored by particles of 263 µm (δ = 16). However, all these samples scored an average grittiness VAS score below 50, which indicates low perception of grittiness regardless of the particle size in the range of 90–263 µm. In contrast, samples containing particles of 605 µm (positive control) scored a much higher grittiness VAS score on average (87 ± 12, when given as a blinded sample).

### 3.3.2. Effect of amount of particles on oral grittiness perception

Three different amounts of particles were evaluated, 0.25, 0.50 and 1.00 g of particles in 10 ml samples, which correspond to concentrations of 125, 250 and 500 mg/5 ml, respectively. The amount of particles per sample was a significant driver of the perception of grittiness. As expected, grittiness perception increased as the amount of particles in the sample increased. Samples containing 0.25, 0.50 and 1.00 g of granules scored an average VAS score of 19 ± 6, 28 ± 10 and 39 ± 9, respectively. The difference between maximum and minimum mean response (δ) was 20, which means that a change in the amount of particles had a bigger impact on grittiness perception than a change in particle size (δ = 16), within the ranges studied.

### 3.3.3. Effect of media viscosity on oral grittiness perception

Increasing the viscosity of the oral vehicle was shown to reduce the grittiness VAS score of the samples. Samples dispersed in the vehicle of lowest viscosity (0.08 Pas) scored an average grittiness VAS score of 32 ± 13, when dispersed in the vehicle of intermediate viscosity (0.43 Pas) the average score was 28 ± 11, and when dispersed in the vehicle of highest viscosity (2.80 Pas) the average score was 26 ± 10. Within the ranges studied, the impact of media viscosity on grittiness perception (δ = -6) was smaller than that of the amount of particles and their size. Nevertheless, the effect of media viscosity on grittiness perception was significant. This suggests that soft food (i.e. “thick” fluid) would be more effective than a drink (i.e. “thin” fluid) in terms of “masking” the presence of particles in the sample.

### 3.3.4. Interaction between factors and modelling of grittiness perception

A multiple linear regression analysis was applied to fit full polynomial equations with added interaction between factors (amount of particles, particle size and HPMC concentration). All possible interactions between factors were not significant ( $p > 0.05$ ), thus the model was simplified through a stepwise process to a first order polynomial equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$$

where  $X_1$ ,  $X_2$  and  $X_3$  represent the three factors evaluated and  $\beta_1 - \beta_3$  their coefficients, with  $\beta_0$  representing the intercept. Statistical analysis showed significant  $p$ -values ( $p < 0.01$ ) for all the studied factors and insignificant lack of fit for the measured response ( $p > 0.05$ ), indicating adequate model fit.

The fitted model was employed to generate contour plots via interpolation of data within the design space. Individual contour plots of VAS score vs. amount of particles and particles size are depicted in Fig. 5 for each level of HPMC concentration. Contour plots allow a visual interpretation of results. As shown in the graphs, relatively large amounts of particles up to 1 g can be better tolerated if particles are small and dispersed in a high viscosity vehicle to mask the presence of particles. Similarly, particles larger than 200 µm could be better tolerated when given at a low concentration and dispersed in a vehicle of high viscosity. However, a simultaneous increase of particle size and amount of particles results in a significant increase of grittiness perception, particularly in vehicles of lower viscosity.

### 3.3.5. Participants' preferences in relation to oral grittiness

After testing the corresponding number of samples during each of the two sessions of the study, participants were asked to select the two “most pleasant” samples among those tested in that particular

session. This served as a method to evaluate participants' preferences towards different formulations of multiparticulates. A list of the most preferred formulations (i.e. those more frequently selected as being “most pleasant”) is shown in Table 2.

Not surprisingly, the most preferred sample was the blinded negative control which consisted of 10 ml of the 0.5% HPMC vehicle containing no particles. In contrast, the blinded positive control containing 1 g of large particles (605 µm) was not selected by any of the participants. After the blinded negative control, the most preferred samples were those containing a low amount of small-sized particles (e.g. F4 and F1). As a general trend, samples selected as “most pleasant” could be correlated with lower grittiness VAS score. Indeed, a significant association was found between grittiness VAS score and sample preference (Spearman's rho = -0.83).

However, samples dispersed in the vehicle of highest viscosity were less preferred in spite of being less gritty. Remarkably, none of the top 5 most selected samples were prepared using the vehicle containing 2% (w/v) HPMC. These results indicate that vehicles of lower viscosity were preferred over the vehicle thickened to the highest consistency. Nevertheless, the three administration media were not assessed on its own (i.e. without particles), therefore the previous hypothesis could not be confirmed. In addition, preference for vehicles containing less HPMC could be due to an unpleasant mouthfeel of HPMC and not necessarily explained by a change in viscosity.

## 4. Discussion

MCC spherical granules were used as a model for a multiparticulate drug delivery system. These inert particles were an ethically sound model as the participants were not exposed to any drug. The insoluble particles were dispersed in vehicles of varying viscosity and administered with the aid of a spoon. HPMC was employed to modify the viscosity of the suspending media in order to make it representative of a broad range of potential vehicles used in practice. HPMC hydrogels showed shear thinning behaviour, which is commonly seen in food products and in commercial vehicles for the administration of medicines (Kluk and Sznitowska, 2014; Selway and Stokes, 2013; Zargaraan et al., 2013). The rheological properties of HPMC gels prepared at three different consistencies account for a variety of potential vehicles ranging from poorly viscous fluids ( $\leq 350$  mPas) such as juice to thicker fluids and soft-food ( $> 1750$  mPas) such as yogurt. The oral gels were sweetened and flavoured to create a more palatable vehicle, which would be more representative of the proposed real life situation where patients mix the drug product with food or drinks.

Oral grittiness of multiparticulate formulations was assessed by healthy adults using a VAS score system. In general terms, grittiness VAS scores were low; the vast majority of the samples scoring an average VAS score below 60. The low VAS score values obtained were attributed to the effect of the sweetened and flavoured vehicles which improved the feeling of the sample in the mouth. The three formulation factors assessed, viz. particle size, amount of particles and viscosity of the administration media, were shown to have a significant effect on perception of oral grittiness. Oral grittiness increased with increasing amount and size of the particles, whereas increasing viscosity of the administration media masked perception of grittiness. Within the ranges studied, the amount of multiparticulates given per sample seemed to be the most significant factor, closely followed by particle size. The effect of media viscosity on grittiness perception was moderate compared to the other two factors, but still significant. Furthermore, samples preferred by the participants of this study (i.e. those selected as being “most pleasant”) were correlated with a low VAS score for oral grittiness.

The amount of multiparticulates per sample was a significant factor in the perception of oral grittiness. As expected, samples containing larger amounts of particles were perceived to be grittier with respect to samples containing less particles. In practice, the amount of

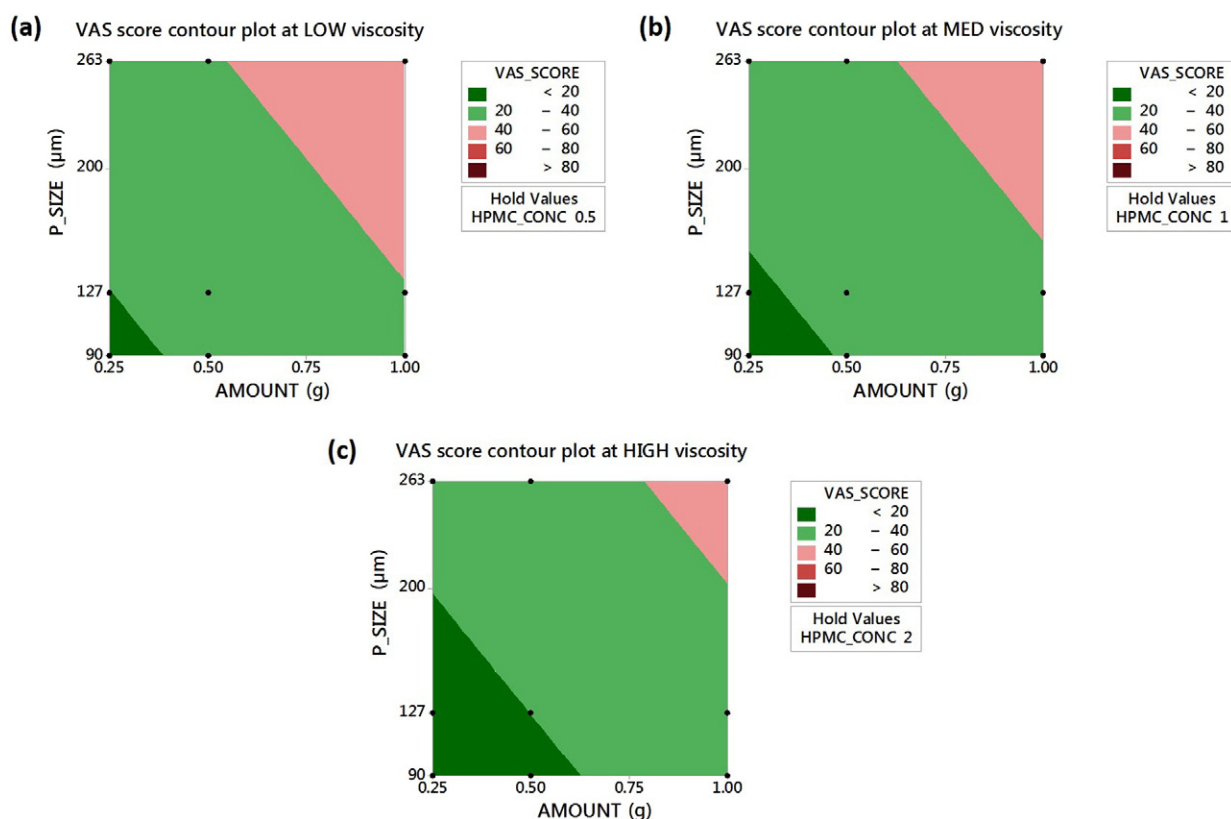


Fig. 5. Contour plots of VAS score vs particle size and amount of particles, at low (a), medium (b) and high (c) viscosity levels.

multiparticulates per sample (i.e. the amount that needs to be taken by the patient) would be greatly determined by the required therapeutic dose. The three situations assessed in this study (i.e. 0.25, 0.50 and 1.00 g of particles) aimed to cover a range of different dosing requirements, which may vary depending on the drug potency and the targeted patient population. Another important determinant of the amount of multiparticulates per sample would be the maximum drug loading per particle that can be achieved, which is dependent on the manufacturing process. The maximum drug loading of multiparticulate formulations is often low (Gandhi and Baheti, 2013), which means that the amount of particles required will be relatively high and, in turn, this would be detrimental in terms of oral grittiness and overall patient acceptability. From a formulation development point of view, manufacturing approaches with a capability for high drug loading should be prioritised to enable dosing of medicines for pain relief (e.g. ibuprofen) or antibiotics (e.g. amoxicillin) (World Health Organisation, 2013).

Particle size was found to be an important determinant of oral grittiness, as demonstrated in previous studies (Engelen et al., 2005; Imai et al., 1995; Kimura et al., 2015; Mishra et al., 2009). Multiparticulates of smaller particle size were considered less gritty than larger particles

and, in turn, samples containing smaller particles were regarded as more pleasant. In this regard, a reduction of particle size could be a potential strategy to improve palatability of multiparticulate products. However, a reduction of particle size might also have a major impact in other characteristics of the formulation, such as drug release. For instance, the release rate from coated granules has been shown to be directly proportional to the surface area of the coated core granules; thus, four times more coating solution was needed to maintain the same drug release rate when particle size was reduced by half (Ragnarsson and Johansson, 1988). Moreover, the particle size of the final product will increase after film coating, with this step needed for taste masking, controlled release or other purposes. Therefore, the particle size of multiparticulate formulations must be carefully balanced in order to achieve the desired quality target product profile, including appropriate palatability and drug release.

The viscosity of the oral vehicle used as a platform for the administration of multiparticulates was modified in order to assess the influence of media viscosity on the perception of oral grittiness. Samples suspended in vehicles of thicker consistency received lower values on the grittiness VAS scoring system than samples suspended in vehicles of thinner consistency. However, samples prepared with low viscosity vehicles were often judged to be more pleasant than those prepared in the thicker vehicles, despite of the increased grittiness perception in the former. This can be attributed to participants' preferences concerning the palatability and in particular mouthfeel of the suspending media. Although thinner vehicles were preferred in this study, a different situation might be seen in children (who usually consume food products of thicker consistency than adults) and older people with swallowing difficulties who use thickened fluids for nutrition (O'Leary et al., 2010). Although viscosity was considered to be the primary parameter that influences the perception of particles dispersed in the vehicle other physical properties of the oral vehicles such as stickiness, ductility and lubrication capacity can influence mouthfeel and

Table 2

List of samples that were selected most times as being "most pleasant" in the sensory evaluation of multiparticulate preparations by healthy adult participants ( $n = 30$ ).

ID	Amount (g)	Particle size (µm)	HPMC (% w/w)	Times ranked "most pleasant"
Negative control	–	–	0.5	27
F4	0.25	90	1	10
F1	0.25	90	0.5	9
F10	0.25	127	0.5	9
F2	0.50	90	0.5	7

palatability and thus might be important determinants of the overall acceptability of the product (Batchelor et al., 2015; Kluk and Sznitowska, 2014).

Assessment of palatability and acceptability of oral formulations is a growing area of interest for formulation scientists. The lack of validated methodology for the assessment of palatability and acceptability of oral dosage forms has been highlighted as an important barrier for the development of new age-appropriate formulations for paediatric patients (Venables et al., 2015; Walsh et al., 2014). Current guidance suggests that, when possible, palatability testing should be conducted using the final formulation and in the targeted population group (European Medicines Agency, 2013). This study has been conducted in a small population of young adult participants in a controlled setting, using a swirl and spit methodology. Naive participants took part in the study but were calibrated with negative and positive controls prior testing. The actual samples could then be assessed with respect to these references, and participants became familiar with the tasting protocol and measurement scales. Differences in oral grittiness perception can be expected with respect to other population groups, such as paediatrics or geriatrics. Therefore, evaluation of oral grittiness and preferences of multiparticulate formulations in these patient groups is much needed, especially as they are the ones that could benefit most from multiparticulate products.

## 5. Conclusion

Multiparticulate formulations represent an interesting alternative to conventional solid dosage forms for the delivery of drugs to patients with swallowing difficulties such as paediatric and geriatric patients. However, a rough or gritty feeling in the mouth may be perceived upon oral administration of multiparticulates depending on their size and amount, limiting palatability and acceptability. This study, in agreement with previous work, suggests that smaller particles would be more appropriate than larger particles in terms of mouthfeel and overall product palatability. However, the data indicated that particles larger than 200 µm receive low grittiness scores if used at a low concentration and dispersed in a vehicle of high viscosity. In conclusion, the combined influence of particle size and amount of multiparticulates on the perceived grittiness should be reflected into formulation optimisation. Further consideration should be given to the selection of a suitable vehicle for oral administration in order to maintain appropriate palatability of the reconstituted product.

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