High shear blending with glyceryl distearate provides individually coated drug particles for effective taste masking

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ABSTRACT

Lipid coating in a high shear blender without heating and complex spray mechanism was investigated as a simplified approach to hot melt coating in a fluid bed device. Potassium chloride was coated with 20% glyceryl distearate using both processes. Microscopic images revealed that the drug surface was covered with a smooth lipid film after processing in the high shear blender as opposed to an irregular film obtained by fluid bed coating. Particle size analysis showed that blending speed had a significant impact on particle growth. Fast blending at 750 rpm resulted in particle agglomeration whereas blending at 450 rpm provided individually coated drug particles. In vitro dissolution studies indicated that both processes were able to keep potassium chloride concentration below an indicative taste perception threshold. Negative sensory characteristics were shown to be reduced in both processes. The results suggest that lipid coating in a high shear blender is as efficient as hot melt coating in a fluid bed device, but offers the benefit of being much simpler. This enables the production of high dose drugs with reduced bitter taste at low excipient concentration and therefore has the potential to improve oral treatment, in particular for pediatric patients.

1. Introduction

The development of child-appropriate medicines is a global need. This is increasingly understood by the pharmaceutical industry which has implemented pediatric investigational plans (PIP) along with the regulatory authorities to make medicine formulation more acceptable in children [1]. An often unmet need is the palatability of the drug in the final dosage form. The palatability of medicines is one of the most important factors likely to influence patients’ compliance and adherence to therapeutic regimens and outcomes [2]. The European Medicines Agency has defined palatability as “the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth), determined by the characteristics of the active substance, the way the active substance is formulated into a finished medicinal product, and by the characteristics of the excipients” (EMA/CHMP/QWP/805880/2012 Rev. 2). Effective taste masking can tremendously increase the palatability of a drug product, therefore the compliance and completion of the treatment in pediatric patients [3].

Some strategies that were reported successful for taste masking include: (i) use of sweeteners, (ii) granulation of particles using appropriate binders like solid lipids or alginates, (iii) melt extrusion or spray drying promoting physical or chemical interactions between drug and excipients, (iv) bitter blockers that interact with taste receptors instead of the administered drug, (v) ion exchange resins which bind the ionic group of the drug to that of the excipients, (vi) adsorption of the drug to a porous carrier, (vii) viscosity enhancement to reduce contact with taste receptors and (viii) complex formation with cyclodextrins [4]. However, the technology that has been investigated most in the last decade, and which appears to be most efficient at masking the bitter taste of drugs, is film coating [4,5].

Hot melt coating is an efficient approach to mask the inconvenient taste of a drug [6,7]. It is a solvent-free process in which molten lipid excipient is sprayed on to solid drug particles during fluidization in a fluid bed coating device. The lipid solidifies upon cooling and coats the particles with a film. The process is quick and no drying step is required, enabling yet coating of the pure drug substance with very high specific surface area, in reasonable time. Hot melt coating is conducted in a fluid bed coater modified to enable the spraying of molten lipid excipients. Comprehensive reviews are given by Jannin and Cuppok and Becker et al. [7,8] Although highly suitable this method did not meet industry acceptance which might be attributed to the need for
Potassium chloride was chosen as the coating agent. It is a taste- and odorless fine powder of spherical shape, with a mean particle size of 50 μm and a melting range of 50–60 °C. It is insoluble in water. Previous odorless fine powder of spherical shape, with a mean particle size of 400 μm, and freely soluble in water. High doses were administered twice a day orally (0.5–1 mmol/kg K⁺). Moreover, taste masking of potassium chloride is difficult to achieve as it is described as having a bitter and salty taste in the oral cavity and hence has more complex taste properties compared to other drugs [15]. With this in mind, potassium chloride was particularly well-suited for this investigational study.

Different high shear blending parameters were investigated using a surface response experimental design, with the objective to efficiently mask the negative sensory characteristics of potassium chloride. Nonetheless, granulation does not exclude effectiveness as it was reported that larger particles in the oral cavity can be perceived as gritty, compromising the sensory characteristics of the end product [16]. Therefore, only individually coated particles were considered for further investigation by measurements of in vitro drug release and evaluation by a trained descriptive sensory panel. Granules were excluded from evaluation. The results were compared with the conventional hot melt coating process in a fluid bed device.

2. Materials and methods

2.1. Materials

Potassium chloride (food grade, # 3316000059, Brenntag SA, Chassieu, France), glyceryl distearate (Precirol® ATO 5, # 161745, Gattefossé SAS, Saint-Priest, France).

2.2. High shear blending process

The different process steps and investigated parameters are highlighted in Fig. 2 and Table 1 respectively. (i) Pre-blending: A binary mixture of 80% potassium chloride (280 g) and 20% glyceryl distearate (70 g) was placed into a 1 L high shear blender (Diosna P1, Diosna, Osnabrück, Germany) and homogenized at 50 rpm for 3 min (ii) Generation of friction heat: The impeller was set to 900 rpm until the product temperature reached 45 °C. (iii) Particle coating: The impeller speed was reduced to 450, 600 or 750 rpm whilst setting the chopper speed to 500, 1000 or 1500 rpm. Once the product temperature reached 48 °C coating lasted for 1, 3 or 5 min (iv) Cooling and discharge: Post-process impeller and chopper speed were reduced to 50 and 100 rpm respectively to allow the product gently cooling down to 35 °C. (v) Sieving and characterization: After 30 min at room temperature the coated powder was sieved through 1250 μm. The recovery rate was defined at the fraction that passed the sieve. Only this fraction was retained for further investigation.

2.3. Design of experiment

A Box-Behnken surface response design was applied to investigate the effects of the process parameters blending speed, chopper speed and coating time on particle size. Minitab® 17 was used for the study design and statistical analyses. A total of 15 runs in random order were designed with three replicates at central point (Table 1). A second experimental design was applied to further investigate the main effect of the lipid concentration on this same response. The lipid concentration was varied from 10 to 12.5 to 15%, the investigated blending speed was 450, 600, 750 rpm and the coating time 1, 2, 3 min. The chopper speed was fixed to 500 rpm. The results were subjected to Analysis of Variance (ANOVA) at a 5% (p < 0.05) level of significance to determine which parameters had significant impact on the response. Three-dimensional response surface plots were used to examine the relationship between particle growth and two independent variables. Optimum process
parameters were identified targeting the lowest increase in particle size and in vitro drug release rates using a response optimizer (Minitab® 17).

2.4. Scale-up of the high shear blending process

The identified optimum process parameters were transferred to a larger high shear blending unit (450 rpm blending speed, 500 rpm chopper speed, 3 min coating time). A binary mixture of 80% potassium chloride (1680 g) and 20% glyceryl distearate (420 g) was placed into a 6 L high shear mixer (Diosna P6) and processed referring to the previously described high shear blending method. The geometry of the 6 L bowl was symmetrically scaled to the 1 L bowl. Therefore the sample weight was increased by a factor of six to maintain a constant ratio of mass to volume (hence the same fill ratio between the 1 L and the 6 L bowl). The impeller speed was adjusted from 450 to 364 rpm which represented the same ratio of inertial to gravity forces of the powder blend by keeping the Froude number constant (Equation (1)). This was supposed to provide similarity of the small and the larger scale therefore generating comparable friction heat and subsequent film formation [17]. Chopper speed and coating time were kept constant. During coating the impeller speed varied from 362.8 to 365.2 rpm while the product temperature increased from 48 to 50 °C.

\[ Fr = \frac{N^2 D}{g} \]  

where \( Fr \) indicates the Froude number, \( N \) the impeller speed (1/s), \( D \) the impeller diameter (m) and \( g \) the gravitational constant (m/s).

2.5. Fluid bed coating of potassium chloride

The applied coating parameters were identified in a separate experimental design. Potassium chloride (1200 g) was coated with 20% glyceryl distearate (300 g) in a top spray fluid bed coater (GPCG 1.1, Glatt, Binzen, Germany). The drug powder was placed into the preheated coating chamber and fluidized for 12 min until the product temperature attained 42 °C. Glyceryl distearate was melted and maintained at 100 °C and sprayed onto the fluidized potassium chloride particles. The spray rate was set to 10 g/min, atomization air was 100 °C, air flow rate was 18 m³/h and the spray nozzle diameter was 0.8 mm. The nozzle was positioned at the lowest level. After coating the inlet temperature was turned off to allow the powder to cool until the inlet reached the outlet temperature. After 30 min at room temperature the coated powder was sieved through 1250 μm. The recovery rate was defined at the fraction that passed the sieve. Only this fraction was retained for further investigation.

2.6. Particle size measurement

The particle size of the single materials, the physical mixture of potassium chloride with glyceryl distearate and the coated material was determined using a laser diffraction particle size analyzer (Beckman Coulter LS 13 320, Villepinte, France).

2.7. Differential scanning calorimetry (DSC)

DSC was performed with glyceryl distearate to determine the percentage of the liquid fraction during melting and the solid fraction during cooling. A Perkin-Elmer differential scanning calorimeter was used (Perkin Elmer Diamond DSC, Perkin Elmer SAS, Courtaboeuf, France). Samples of 5 mg were placed in 50 μl closed aluminum pans and heated from −20 to 120 °C at 3 °C/min. The temperature was maintained for 15 min at 120 °C and the sample subsequently cooled to −20 °C at 3 °C/min. Only the first heating and cooling cycle was considered to simulate the melting and crystallization behavior of glyceryl distearate during high shear blending.

Table 1

Randomized Box-Behnken design and response values for the high shear blending process with 20% glyceryl distearate.

<table>
<thead>
<tr>
<th>DoE</th>
<th>Blending speed (rpm)</th>
<th>Chopper speed (rpm)</th>
<th>Coating time (min)</th>
<th>Increase in PS(μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>750</td>
<td>1500</td>
<td>3</td>
<td>124.3</td>
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<tr>
<td>2</td>
<td>600</td>
<td>500</td>
<td>5</td>
<td>118.1</td>
</tr>
<tr>
<td>3</td>
<td>450</td>
<td>1000</td>
<td>1</td>
<td>33.6</td>
</tr>
<tr>
<td>4</td>
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<td>7</td>
<td>600</td>
<td>1500</td>
<td>1</td>
<td>145.5</td>
</tr>
<tr>
<td>8</td>
<td>750</td>
<td>500</td>
<td>3</td>
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<tr>
<td>9</td>
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</tr>
<tr>
<td>15</td>
<td>600</td>
<td>1500</td>
<td>5</td>
<td>146.1</td>
</tr>
</tbody>
</table>

* PS = particle size.
2.8. Field emission gun scanning electron microscopy (FEG-SEM)

The lipid film coat on the drug surface was examined using a field emission scanning electron microscope (Zeiss SUPRA55-VP SEM). The samples were deposited on an adhesive carbon tape taking care not to overload the deposit and to crush the powder. To protect samples from heat damage and maintain their integrity, observations were made at low voltage (1.2 keV), except for the pure potassium chloride sample (5.0 keV), without any carbon deposit on the sample surface. The images were recorded at a magnification of 60 × at a high resolution.

2.9. Drug release measurements

Simulation of drug dissolution in the oral cavity was modified from Ref. [18] to assess the taste masking efficiency at 20% glyceryl disaccharide. Drug release was measured 24 h after manufacturing using an electrical conductivity meter (CDM210, Hach Lange, Lognes, France). 93.75 mg of the sample (corresponding to 74.5 mg potassium chloride hence 1 mmol/kg K⁺) were placed into a 10 mL glass tube and carefully covered with 3 mL demineralized water (37°C) using a volumetric pipette. The medium temperature was maintained at 37°C by placing the tube in a heated double jacketed bowl. To prevent the sample from floating, a sieve was placed in the tube and fixed with a rubber band. Changes in conductivity upon the release of potassium chloride under gentle stirring were continuously recorded over 5 min. The drug was considered successfully coated when the release kinetics of the samples was below the reported taste perception threshold of 0.005–0.03 M [19,20] corresponding to 0.3–2.2 mg/mL potassium chloride. Measurements were run in triplicate.

Additional drug release measurements were conducted by an independent service provider (Filab, Dijon, France) using Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES, PerkinElmer, Villebon-sur-Yvette). 93.75 mg of the sample were placed in 3 mL artificial saliva at 37°C composed of 120 mg/mL urea and 10 mg/mL glucose in water. After 60 s under gentle stirring the medium was separated from the sample and analyzed for the concentration of potassium chloride. The samples were analyzed in triplicate. Significance between the means was determined with the 2-sample t-test.

3. Sensory analysis

3.1. Panel

An established qualified descriptive panel of 8 assessors experienced in sensory analysis was used for this study. The panel provided written informed consent to take part in the research and expectorated all samples, thus ethical approval and specific medical inclusion and exclusion criteria were not required. The research was not considered a medical drug trial so was carried out in accordance with IFST Guidelines for Ethical and Professional Practices for the Sensory Analysis of Foods and not specifically under The Code of Ethics of the World Medical Association (Declaration of Helsinki). The protocol for testing was divided into two distinct phases.

3.2. Phase 1 (orientation and lexicon development)

During the panel orientation phase, assessors tasted the samples and formulated a lexicon of descriptive flavor, taste, mouthfeel and after flavor/taste/feel attributes to describe them. A final vocabulary of 2 tastes, 2 mouthfeels, 2 aftertastes and 1 afterfeel were determined (Table 2). In addition, the panel agreed on the use of an attribute describing the initial impact of the samples and described it as the combined intensities for all perceived tastes/flavours/mouthfeels.

### Table 2

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Modality</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial impact</td>
<td>Initial taste/flavor/mouthfeel</td>
<td>The combined intensities for all perceived tastes/flavours/mouthfeels</td>
</tr>
<tr>
<td>Bitter</td>
<td>Taste/aftertaste</td>
<td>The basic bitter taste associated with caffeine</td>
</tr>
<tr>
<td>Salty</td>
<td>Taste/aftertaste</td>
<td>The basic bitter taste associated with sodium chloride</td>
</tr>
<tr>
<td>Gritty</td>
<td>Mouthfeel</td>
<td>Amount of gritty/grainy particles in the mouth</td>
</tr>
<tr>
<td>Tingling</td>
<td>Mouthfeel</td>
<td>A tingling and burning sensation on the tongue and mouth</td>
</tr>
<tr>
<td>Tongue numbing</td>
<td>Afterfeel</td>
<td>A feeling of decreased or loss of sensation on the tongue</td>
</tr>
</tbody>
</table>

3.3. Phase 2 (sample testing)

The products were evaluated in triplicate during three separate sessions. Due to its high sensory impact, the last sample assessed in each session was uncoated potassium chloride. For the remaining samples the presentation order was balanced to account for first position and carry-over effects. All samples were coded with randomly selected three-digit codes and served ‘blind’ to assessors. Samples were tested as follows. Assessors were instructed to take a capsule in their hand making sure that the product was flicked to the end of the capsule. The assessors gently opened the capsule by twisting the top away from the bottom of it and placed the contents (uncoated or coated drug) in the middle of their tongue. They then pressed their tongue against the roof of their mouth/palate and rubbed gently, allowing the contents of the capsule to start dissolving. The initial impact of the sample was assessed immediately. For the next 20 s, while the sample was in the mouth, assessors carried out the first evaluation (taste, flavor and mouthfeel). They then rinsed with a defined amount water (2 × 20 mL) and 60 s after sample intake, carried out the second evaluation (aftertaste, afterflavor and afterfeel). As well as having a 10-min break between samples, assessors were provided with water and unsalted crackers as a palate cleanser. The sensory attributes of the products were scored on unstructured 10 cm line scales labelled at both ends with extremes of each descriptive term. A list of definitions for each of the attributes included in the final vocabulary was also available to each panelist. Panel scores from descriptive sensory analysis were subjected to Analysis of Variance (ANOVA) at a 5% (p < 0.05) level of significance to determine which terms were effective at differentiating between the samples.

4. Results

4.1. High shear blending process

The time needed for the drug: lipid mixture to reach 45°C at 900 rpm was approximately 15 min. Further 3–9 min were required to reach the final coating temperature of 48°C at the experimental blending speeds. Cooling to 35°C lasted about 20 min. The recovery rate after sieving was found to be between 67.0 and 96.7% (Table 3). The recovery rate for the larger production scale was 97.1%, for the fluid bed coated sample 91%.

4.2. Electron microscope images

Fig. 3 shows electron microscope images of potassium chloride before and after processing. Samples prepared in a high shear blender appeared smooth at the surface. The sharp edges of the initial cubic form were rounded. The surface of the fluid bed coated drug was rough and the edges were not as rounded compared with coating in the high
4.3. DSC measurements

The DSC thermogram of glyceryl distearate and the corresponding percent liquid and solid fraction upon heating and cooling are presented in Fig. 4 and Table 4. The melting event started at 20°C with the melting onset observed at 51°C and the offset at 56°C. Complete melting appeared at 60°C. The liquid fraction of glyceryl distearate at the final coating temperature of 48°C was 14.7%. The crystallization onset was found at 52°C followed by the offset at 50°C. Crystallization was complete at 35°C.

4.4. Particle size analysis

Fig. 5 shows the mean particle size distribution of both the physical mixture of potassium chloride with glyceryl distearate (Fig. 5a) and the drug processed by high shear blending (DoE 1–13) or fluid bed coating (Fig. 5b). Fig. 5a reveals that the size fraction of glyceryl distearate disappeared after processing whereas the mean particle size of potassium chloride increased. Individual size distribution curves in Fig. 5b show that particle growth was observed for each processed drug sample and that the extent of particle growth depended on the process parameters. For DoE 9, 10, 12 and 13 also the number of larger particles increased (expressed by the higher percentage of volume). When coated in the fluid bed device with the applied process settings only the number of larger particles increased, not the mean particle size (Fig. 5b). The same pattern was obtained after high shear blending in a larger unit as depicted in Fig. 5c. No effect on the mean particle size could be noted, only the number of larger particles increased slightly.

Fig. 6 reveals that blending speed had an impact on d10, d50, d90 and the mean particle size. Low blending speed of 450 rpm resulted in an increase of the mean particle size by 34, 89, 59 and 104 μm (DoE 3, 5, 6, 10) whereas a blending speed of 750 rpm resulted in an increase by 124, 96, 173 and 154 μm (DoE 1, 4, 8, 11). The same tendency was depicted in the three-dimensional surface plot in Fig. 7a. The evolution of the mean size is presented as a function of blending speed and coating time with the chopper speed set to 500 rpm. It shows that faster blending speed and longer coating time resulted both in larger particles of the processed drug. However, a significant difference was only observed for the mean and the d50 (p < 0.05). The speed of the chopper did not significantly affect particle growth (Fig. 7b) and did not interact with blending speed.

Interestingly, the mean particle size was negatively affected when the glyceryl distearate concentration was reduced to 12.5 and 10%, although this was not significant and only relevant when processed at 600 and 750 rpm (Fig. 7c). This effect was not observed at 15% (and 20%) glyceryl distearate. To further investigate this tendency potassium chloride was processed alone, without glyceryl distearate, and the resulting mean particle size compared to potassium chloride processed with 12.5% glyceryl distearate (600 rpm for 2 min). It was found that the size of potassium chloride decreased by 22.8 μm in the presence of 12.5% glyceryl distearate, and by 108.0 μm in the absence of glyceryl distearate (data not shown), suggesting that the amount of lipid matters.

4.5. Drug release measurements

Fig. 8 shows the release kinetics of the drug samples processed at 450 rpm in the high shear blender (DoE 3, 5, 6, 10). At 450 rpm particle growth was minor suggesting individual coating (and no granulation). The results were compared to that of the fluid bed coated drug. It was found that the amount of drug released remained below the highest reported perception threshold of potassium chloride (2.2 mg/mL) within 5 min for both the high shear blended samples DoE 6 and DoE 10 and the fluid bed coated sample. Drug release above the threshold was found for DoE 3 and DoE 5. No sample released less than the lowest reported threshold (0.3 mg/mL).

Drug release measured in artificial saliva (data not shown) using ICP-AES was similar (p > 0.05) to that in deionized water using the conductivity meter (0.46 ± 0.05 and 0.34 ± 0.1 mg/mL after 1 min for sample DoE 6).
4.6. Descriptive taste analysis

A panel objectively described and quantified the sensory characteristics of DoE 6, DoE 10 and the fluid bed coated drug as well as the uncoated sample of potassium chloride. Differences in sensory characteristics between the samples obtained by high shear blending (DoE 6 and DoE 10) and the fluid bed coated drug were significantly different from the uncoated potassium chloride, as summarized in Fig. 9 and Table 5. The ‘initial impact’ experienced by the assessors when tasting potassium chloride was more than twice as high as that experienced when they tasted any of the coated samples. The sensory characteristics ‘initial impact’, ‘gritty’ and ‘tingling’ mouthfeel, ‘salty’ and ‘bitter’ taste/aftertaste as well as ‘tongue numbing’ afterfeel were significantly higher in uncoated potassium chloride. High shear blending of potassium chloride on a larger scale revealed that the larger batch was perceived as similar to the small batch for the characteristics ‘initial impact’ and ‘bitter’ aftertaste (Fig. 10). However, it was described as having significantly lower levels of the attributes ‘bitter’ taste, ‘salty’ taste/aftertaste, ‘gritty and tingling mouthfeel’ and ‘tongue numbing’ afterfeel (p < 0.0001).

5. Discussion

Hot melt coating is an efficient method for taste masking. The lipid film coat provides a taste barrier between the drug and the tongue, thus reducing the unpleasant taste of drug in the oral cavity. Improving the taste properties of drugs can ultimately improve patient compliance, both pediatric and adult. The present study aimed to investigate high shear blending as an alternative taste masking method to a ‘conventional’ hot melt coating process in a fluid bed device. For this purpose the model drug potassium chloride was blended with 20% glyceryl distearate in a high shear mixer and compared to potassium chloride coated with 20% glyceryl distearate in a fluid bed device. The advantage of this alternative technology lies in its simplicity as it eliminates the need for complex spray setups and an external heat source.

The high shear blending process was divided in 5 stages. The pre-blending stage ensured that the lipid particles were homogenously mixed with the drug particles. Blending at 50 rpm prevented projection of the smaller, less dense lipid particles (50μm, ρ 1.0001g/cm³) to the lid, thus separation from the larger and denser potassium chloride particles (ρ 1.9785g/cm³). The second stage, where the drug: lipid mixture was blended at 900 rpm, was required to generate sufficient friction heat to induce lipid melting. However, too fast blending is not recommended. It was reported that at very high blending speeds smaller particles accumulate at the upper site of the mixer, whereas the larger particles remain below [21]. This may reduce interparticulate contact therefore limiting the generation of heat. Reducing the speed where the temperature reached 45°C prevented exceeding the final coating temperature (48°C) as a result of the inertia of the system. The actual coating process with different process parameters (DoE 1–13) started at 48°C. At 48°C the glyceride was only partially melted (Table 4) and high process yields could be obtained at 450rpm indicating that particle coating took place and no granulation (Table 3). The cooling phase was run until 35°C since 100% of glyceryl distearate were solid at this temperature (Table 4), preventing sticking.

Scanning electron microscope images showed the particle surfaces of uncoated, high shear blended and fluid bed coated potassium chloride (Fig. 3). Uncoated particles had sharp edges with some irregularities on the surface. Particles appeared to be smoother and the edges rounded when processed in a high shear blender. Rounding of the edges was due to interparticulate friction and friction between the drug particles, impeller blades and process chamber wall. We suggest that these shear forces enabled formation of a smooth lipid film. In contrast to the high shear blended drug, the surface of the fluid bed coated drug particles appeared to be spotty. During fluid bed coating the melted glyceride is sprayed onto the drug surface where it immediately recrystallizes. As a consequence solid lipid droplets accumulate on the drug surface and do not fuse together to a continuous, smooth film.

DSC measurements indicate that glyceroyl distearate was not completely melted at the applied coating temperature of 48°C (Fig. 4, Table 4). However, the particle size fraction of glyceroyl distearate

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**Table 4**

<table>
<thead>
<tr>
<th>Heating temperature (°C)</th>
<th>Liquid fraction (%)</th>
<th>Cooling temperature (°C)</th>
<th>Solid fraction (%)</th>
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<tbody>
<tr>
<td>15</td>
<td>0</td>
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Fig. 4. DSC thermogram of unprocessed glyceryl distearate.
completely disappeared after processing assuming that the lipid was totally used at the end of the process (Fig. 5a). We believe that the film is created progressively, through progressive lipid melting. In the first instance it is likely that the relatively smaller lipid particles attach to the surface of potassium chloride mainly through van der Waals interactions due to the close contact during blending [12]. Subsequently however, when shear forces induce higher temperatures, the lipid particles begin to fuse progressively spreading to a thin film on the drug surface. Provided appropriate process parameters are applied progressive film formation prevents granulation, enabling coating of the individual particles. In addition, glyceryl distearate almost instantly solidifies (Table 4) further limiting particle agglomeration.

Subsequent size analysis revealed that the mean particle diameter systematically increased as a function of the process parameters (blending speed, chopper speed, coating time) (Fig. 5a/b, 6, 7a). However, statistical analysis gives evidence that only blending speed had a significant impact on particle growth: the faster the blending speed the larger the particles. The results suggest that particle coating can be achieved at a blending speed of 450 rpm whilst granulation may occur at 600 and 750 rpm (Fig. 6). Fast blending induces more shear

![Particle size distribution diagram](image_url)
forces generating more friction heat. Consequently the risk of particle agglomeration increases. Surprisingly, lower lipid concentrations (10 and 12.5%) resulted in particle size reduction at 600 and 750 rpm (Fig. 7c). This may indicate that the use of 15% or more glyceryl distearate can prevent mechanical abrasion of the drug particles during high shear blending due to its thermoplastic properties, and would strengthen the foregoing theory that close interparticulate contact enables film coating thus protection yet at low temperature. Alternatively, it could be hypothesized that agglomeration of fragments take place following particle abrasion, and that actually melt granulation occurs. In this case abrasion would not depend on the lipid concentration but on the strength of mechanical forces, consequently the speed of the
impeller. However, particle size increased with increasing impeller speed for lipid concentrations above 15% whilst it decreased at lipid concentrations below 15%. If abrasion was foregoing agglomeration relative to the speed of the impeller, particle size reduction would be expected to occur at high lipid concentrations too, where particle abrasion is most pronounced. Agglomeration of fines was also not apparent in SEM images (Fig. 3).

Particle size did not evolve when potassium chloride was coated in the fluid bed device (Fig. 5b). Clearly, the size distribution of the coated drug was similar to that of the uncoated drug, although the number of larger particles slightly increased probably due to the agglomeration of fines. However, fluid bed coating can also favor particle abrasion due to mechanical stress. Especially the outer coating layer may suffer as reported by Jannin and Cuppok [8] and Priese and Wolf [22]. This may impact the final particle size, but was not further investigated in the present study.

Drug release measurements were performed with potassium chloride processed with 20% glyceryl distearate at 450 rpm in the high shear blender. The assay indicated that taste masking could be possibly achieved with the process parameters of DoE 6 and DoE 10 since the released drug concentration was below the indicative perception threshold (Fig. 8). Drug release from the fluid bed coated sample was comparable to that of DoE 6 and DoE 10 suggesting that both processes were able to coat the drug to a similar extent. The taste masking ability hence the effectiveness of coating potassium chloride with glyceryl distearate was assessed by a panel. DoE 6, DoE 10 and the fluid bed coated sample were tasted and the results compared to that of the uncoated drug. The sensory characteristics were broken down by modality, e.g. taste/aftertaste and mouthfeel/afterfeel. In addition, and to describe the sensory characteristics experienced as soon as the samples entered the oral cavity, the assessors defined the attribute ‘initial impact’ as being the combined intensities for all perceived tastes/flavours/mouthfeels. It was clearly shown that the initial impact of the samples in the oral cavity was significantly reduced in the coated samples compared to the uncoated drug (Fig. 9). Also no significant differences were observed for the drug coated in the high shear blender and that coated in the fluid bed device. This confirms the significant effect that coating had on the undesirable sensory characteristics of potassium chloride irrespective of the coating technology applied.

The optimal high shear blending parameters for subsequent scale-up were identified using an optimization plot (Fig. 11). The target goal was defined to keeping particle growth and 2 min drug release rate minimal.
A composite desirability (D) value of one indicates that the process parameter settings may achieve favorable results for both responses, whilst a value of zero indicates that the settings will lead to results outside the acceptable limits. As shown in Fig. 11a the following settings were predicted to give the desired responses: 450 rpm blending speed, 500 rpm chopper speed, 2.4 min coating time (D: 0.9040). To enable comparison of the results with that obtained from the experimental design, the parameters of DoE 6 closest to the predicted ones were selected for scale-up: 450 rpm blending speed, 500 rpm chopper speed, 3 min coating time. The increase of coating time from 2.4 to 3 min reduced D from 0.9040 to 0.8841 which was due to the predicted increase in particle size (Fig. 11b).

It was observed that particle size did not evolve when potassium chloride was processed in a larger unit (6 L) at the set process parameter combination (Fig. 5c). This indicates that individual film coating was achieved, and no granulation. As opposed to it, the particle size increased by 59 μm for DoE 6 from the experimental design in the 1 L unit. The reason for this may be a higher ratio of the powder volume to process chamber surface in the larger equipment. This is supposed to increase the contact between the particles and reduce that with the impeller blades and the chamber wall, leading to less adhesion of the particles to the equipment surfaces. As a consequence the heat transfer and lipid distribution in the powder blend is improved which enabled individual particle coating without any evolution in particle size. In vitro drug release from the scale-up batch was slightly higher but not significantly different from DoE 6 (0.9 ± 0.6 vs 0.7 ± 0.2 mg/mL after 2 min and 2.4 ± 1.3 vs 1.9 ± 0.6 mg/mL after 5 min, Fig. 8). The sensory characteristics of the larger scale batch were similar to DoE 6.
(or significantly improved for some of them, Fig. 10 Table 5). This suggests that the process is scalable as long as the blending speed is adjusted to the size of the bowl (and geometry if different). The better sensory characteristics may again be due to a higher ratio of the powder volume to process chamber surface since this reduces the loss of lipid to the process chamber and improves lipid distribution in the powder blend.

6. Conclusion

Hot melt coating in a fluid bed device is a common approach to coat bad tasting drugs with a neutral tasting lipid film. To simplify this approach a high shear blender was used instead of a fluid bed coater eliminating the need for a complex spraying setup and the adaptation of equipment for heating. The results show that blending in a high shear mixer was equally efficient as in a fluid bed device. Individual particle coating with only minor growth in particle size was achieved at 450 rpm with 20% glyceryl distearate at 48 °C. We propose that the lipid partially melts, progressively forming a smooth film on the surface of the drug. Faster blending speed was observed to induce particle agglomeration whilst the use of lipid concentrations below 15% led to particle size reduction. The transfer to a larger production unit

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Uncoated</th>
<th>High shear blended (DoE 6)</th>
<th>High shear blended (DoE 10)</th>
<th>High shear blended (Scale-up)</th>
<th>Fluid bed coated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial impact</td>
<td>7.2a</td>
<td>3.0bc</td>
<td>3.2b</td>
<td>2.8c</td>
<td>3.0b</td>
</tr>
<tr>
<td>Bitter taste</td>
<td>4.6a</td>
<td>2.9b</td>
<td>3.0b</td>
<td>2.6c</td>
<td>3.0b</td>
</tr>
<tr>
<td>Salty taste</td>
<td>8.3a</td>
<td>6.3b</td>
<td>6.4b</td>
<td>5.6c</td>
<td>6.1b</td>
</tr>
<tr>
<td>Bitter aftertaste</td>
<td>3.7a</td>
<td>2.3 bc</td>
<td>2.5b</td>
<td>2.1c</td>
<td>2.4b</td>
</tr>
<tr>
<td>Salty aftertaste</td>
<td>4.0a</td>
<td>2.4b</td>
<td>2.5b</td>
<td>2.2c</td>
<td>2.5b</td>
</tr>
<tr>
<td>Gritty mouthfeel</td>
<td>5.7a</td>
<td>5.1b</td>
<td>5.2b</td>
<td>4.7c</td>
<td>5.1b</td>
</tr>
<tr>
<td>Tingling mouthfeel</td>
<td>5.3a</td>
<td>3.4b</td>
<td>3.2b</td>
<td>2.8c</td>
<td>3.1bc</td>
</tr>
<tr>
<td>Tongue numbing afterfeel</td>
<td>3.8a</td>
<td>2.3b</td>
<td>2.2bc</td>
<td>1.9f</td>
<td>2.3b</td>
</tr>
</tbody>
</table>

*Average score of 8 assessors measuring attributes on defined 10 cm line scales.
**Significance declared at the level p ≤ 0.05.

Fig. 8. Release kinetics of potassium chloride processed at 450 rpm in a 1L high shear blender or in a fluid bed device with 20% glyceryl distearate. The dotted line indicates the reported perception threshold of potassium chloride.

Fig. 9. Illustration of the sensory attributes differentiating between uncoated potassium chloride, the high shear blended samples DoE 6 and DoE 10 in a 1L bowl and the fluid bed coated sample (the x-axis shows the average sensory scores measured by the panel).

Fig. 10. Graphical illustration of the sensory attributes: comparison between the small batch of DoE 6 (350 g) and the larger batch sample (2.1 kg) produced by high shear blending with 20% glyceryl distearate.
appeared to be as efficient, provided the blending speed is adjusted. A trained sensory panel confirmed the taste masking effectiveness of both coating processes.

Declaration of interest

The authors declare no competing financial interest.

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References


