Reduction of Agglomeration and Production Optimization for Enteric Pellet Coatings

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Introduction

Pellets are versatile dosage forms for many actives. To control drug dissolution profiles, they can be prepared with different coatings. Coated multiparticulate systems are known to show less variation in drug release than single unit formulations. Furthermore, dose dumping effects due to damaged coatings can be avoided due to the spread of the dose over the multiparticulate system. Enteric coatings are often used coatings for pharmaceutical pellets if the active substance requires protection from the gastric environment or protection from the API is required. Commonly inert pellets are provided in a size range from 0.1 to 2.0 mm. Especially in the case of smaller pellets the coating process becomes challenging due to extensive agglomeration. Agglomeration of pellets can lead to compromised release profiles and thus the requirement for removal of the agglomerated pellets. This in turn is increasing overall production costs. Furthermore, agglomeration tendencies are often addressed by reduced spray rates, adding to production costs due to prolonged production times.
Furthermore, the functionality of the coating is often governed by the thickness of the coating. Due to the fact that the overall surface area of the same mass of pellets will increase rapidly with reduced sphere volumes, the mass of coating needed increases in the same manner. This effect increases the prolonged production times, outlined above, further and can lead to economic challenges.
For the presented work pellets were layered with a thin film of an immediate release film containing a highly soluble food colorant followed by application of an insulation film of the same polymer. The pellets were then coated with an enteric coating and the point of gastric resistance was determined. Spray rate, solid content of the dispersion and the composition of the coating was varied within a DoE framework. Agglomeration was evaluated by sieving as well as analysis of images generated with a flatbed scanner. The generated data was used to model the processing time required to reach gastric resistance and the corresponding minimum required film thickness as well as the percentage of non-agglomerated goods. Finally, the parameters were extrapolated to process conditions on production scale equipment. Including the costs for energy consumption, raw material costs and human resources allowed for an approximation of overall production costs.

Materials

All materials were used as supplied by the manufacturers without further conditioning.
Kollicoat® MAE 100 P and Kollioat® IR / BASF SE; Triethyl Citrate / Jungbunzlauer Ladenburg GmbH; Talc / Imerys S.A.; Mesoporous Silica / W.R. Grace & Co-Conn.; Allura Red / Extrachem GmbH + Sensient Food Color Europe GmbH; Titanium Dioxide / Kronos Worldwide, Inc; PharSQ Spheres CM S (D50 300 – 500 µm) / Chemische Fabrik Budenheim KG).

Methods

Particle Size and Agglomeration

Particle size parameters for uncoated and coated pellets at all coating stages were measured by laser diffraction with a Helos KR system of Sympatec GmbH. Agglomeration was evaluated using a RS 200 control sieving machine (Retsch GmbH) with 355 µm and 400 µm sieves. Furthermore, an Epson V600 flatbed scanner (Seiko Epson Corp.) was used to detect agglomerates by image analysis using the public domain software Image J.

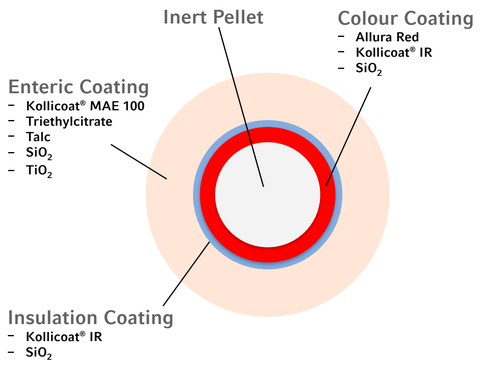

Figure 1: **Schematic overview of applied coating layers**

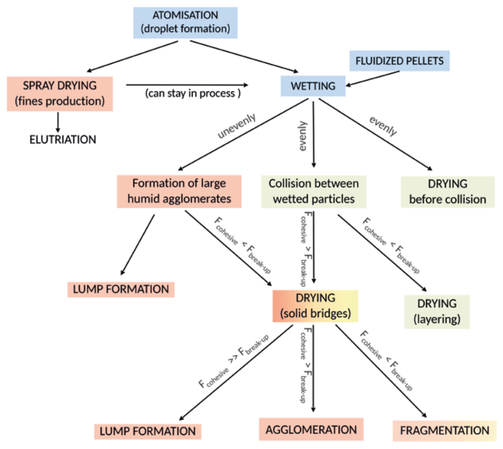

Figure 2: **Agglomeration during coating process (modified from [2])**

Pellet Coating

All coatings were carried out on a Ventilus V 2.5 (Romaco Innojet GmbH) fluid bed coater with 250 g of pellets. Color layers and insulation layers were applied from low viscosity dispersions at 8 % solid content to reduce agglomeration (spray rate 1.5 g/min; spray pressure 2.5 bar; product temperature 47 °C) Agglomerates created at these stages were removed by sieving.
Enteric coatings with a fixed ratio of plasticizer (triethyl citrate) to methacrylate polymer (Kollicoat® MAE 100 P) were applied within a DoE framework created with MODDE 13 PRO (Sartorius AG) as shown in Table 1 and equivalent settings to the application of the lower layers if not stated otherwise.

Parameter	Range
Spray Rate (SpRt) [g/min]	2–4
Dispersion conc. (DispCo) [%]	22–32
TiO_2 conc. [%]	5
Talc conc.[%]	confidential
SiO_2 conc. [%]	confidential
Polymer system conc. [%]	50–90

Table 1: **DoE Settings**

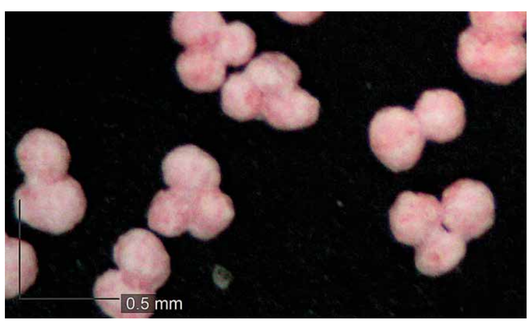

Figure 3: **Microscopic image of agglomerated pellets at 75 x magnification**

Results

On average, the films were 5 µm in thickness for the colored layer and 1 µm for the insulation layer. The film thickness to reach gastric resistance varied from 15 µm to 35 µm. It was found that there are two main drivers that increase the production costs. On one hand the amount of coating required to achieve gastric resistance governs the time requirements and thus energy and human resources costs. Figures 4 + 5 show the modelled time and film thickness responses. It can be observed that an increased talc content and a moderate silicon dioxide content help to obtain films that achieve gastric resistance at a thinner layer faster. On the other hand, production of a poor-quality product with view on agglomeration is significantly driving up costs, considering that the agglomerated product needs to be discarded. Figure 6 shows the degree of agglomeration in relation to spray-rate, dispersion concentration and talc content at a moderate SiO_2 content. High spray rates and a high solid content in the dispersion increase the level of agglomeration. Increasing the talc content to the ideal level helps to reduce the agglomeration effect.
Figure 7 shows the combined effects on the overall costs with the ideal compromise reached using the ideal coating composition, lower dispersion concentration and moderately high spray rate (that might necessitate removal of some agglomerates).

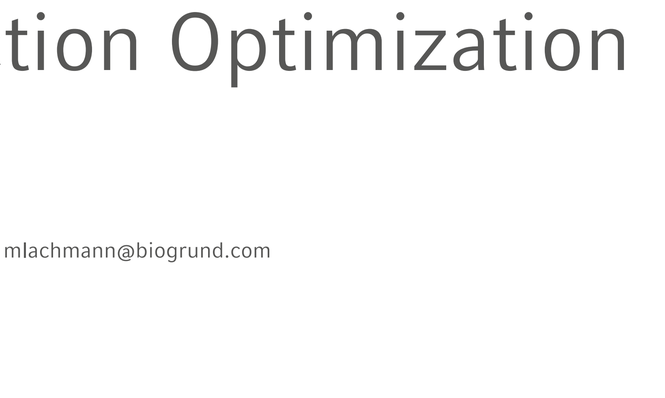

Figure 4: **Production-time to reach gastric resistance of pellets**

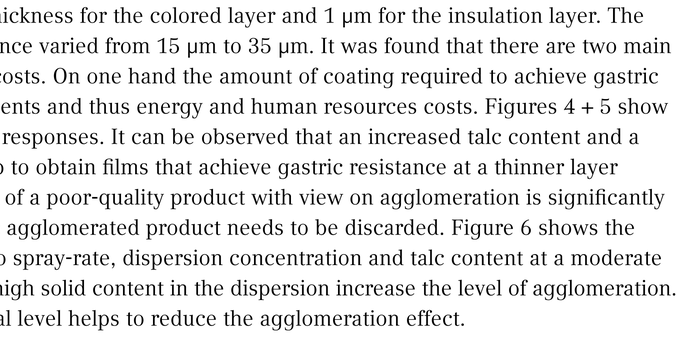

Figure 5: **Film thickness to reach gastric resistance of pellets**

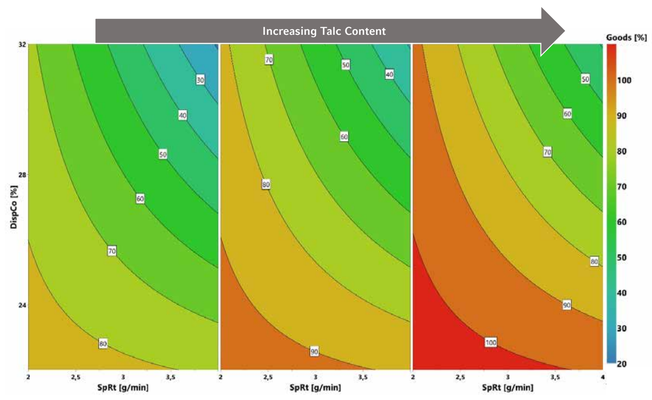

Figure 6: **Non agglomerated pellets produced in %**

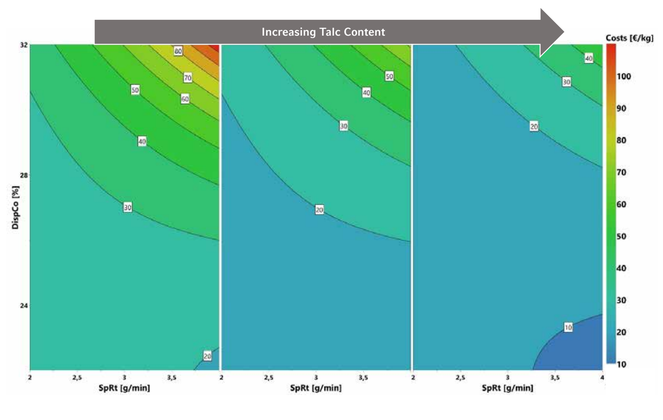

Figure 7: **Approximation of overall production costs**

Conclusion

Coating of pellets is a challenging task, especially if pellets in the smaller size range are used as substrate. Adding a thick layer of poorly suitable coating might help to obtain the desired functionality but this strategy will by a costly one. Large quantities of agglomerated product will need to be removed and long production times are inefficient. The new AquaPolish® E composition of BIOGRUND can reduce the production costs significantly.

References:

[1] P. Kleinebudde, Pharmazeutische Pellets - Herstellung, Eigenschaften und Anwendung, Heinrich-Heine-Universität Düsseldorf, 2004, pp. 162-174
[2] Saleh, K. and P. Guigon, Chapter 7 Coating and encapsulation processes in powder technology, in Handbook of Powder Technology, A.D. Salman, M.J. Hounslow, and J.P.K. Seville, Editors. 2007, Elsevier Science B.V. p. 323-375)

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