Abstract

“DEVELOPMENT OF A FAST, LEAN AND AGILE DIRECT PELLETIZATION PROCESS FOR THE PRODUCTION OF MODIFIED RELEASE SPHEROIDS, USING EXPERIMENTAL DESIGN TECHNIQUES.”

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INTRODUCTION

The therapeutic and technical advantages of pellets which are attributed to their increased surface, enhanced flowability and uniform size and shape have been well established in the literature (Ghebre-Sellassie, 1989, Gu et al, 2004). The direct pelletization process is characterized as an attractive alternative to other pelletization techniques (Gu et al, 2004, Heng et al, 1996) as it is a single pot, quick and efficient method, using powders as a starting material. However, its successful application requires thorough understanding of its critical parameters in order to achieve a predictable process.

This is one of the major objectives of Design of experiments (DoE), a set of powerful techniques that leads to the characterization and optimization of a process, through the determination of the most important factors and interactions that influence the important quality characteristics (responses) of the finished product (Montgomery, 1976).

The use of melt materials for the production of pellets also receives significant attention, especially for applications utilizing Active Pharmaceutical Ingredients (APIs) that are unstable in aqueous environments (Rahman et al, 2009). Significant formulation work has been done focusing on the melt extrusion methods (Crowley et al, 2007, Repka et al, 2007), in contrast to the efforts on the hot melt direct pelletization processes.

The objective of this study was to develop, characterize and optimize a hot melt direct pelletization process, providing the potential of producing both immediate and sustained release pellets using the same technology.

EXPERIMENTAL METHODS

Materials

HPMC K100M (Methocel® K100M, Colorcon, UK), Gelucire 50-13 (Gattefosse France), Carnauba Wax (Kahl Germany), Colloidal Silicon Dioxide (AEROSIL® 200, Degussa, UK), Magnesium Stearate (Mosselman, Belgium).

Hot melt direct pelletization process

The pellets were prepared with the tangential spray technique in a rotor granulator (Glatt GPCG3, Glatt GmbH, Dresden, Germany) equipped with a powder feeder. Powder mixtures of Carnauba Wax (CW) and HPMC K100M were prepared at ratios varying between 0:100 and 100:0. 500g of the powder mixture were inserted in the product chamber, while a specific quantity of the same mixture was added via the powder feeder (PF), while spraying the melt material. The inlet air temperature was set at 60ºC, resulting to product temperature between 52-55ºC. A 1.2mm binary nozzle was used. The atomizing air was preheated at 85ºC and its pressure was set at 3bar. Gelucire 50-13 was selected as the binding material.
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(BM), after it was melt at 80°C, using a heater circulator and a jacketed glass container, allowing for continuous measurement of the spraying rate. The addition of the melt material was performed through a tube heated at 100°C, in order to prevent its solidification prior to spraying. At the end of spraying and the addition of the powder from the feeder, the inlet air temperature was gradually reduced to 40°C and room temperature respectively. Additional spheronization was carried out before the end of the process.

Estimation the process yield

After the completion of the process the product was sieved using a 2.0mm sieve and all agglomerates were removed. The remaining product was weighted and the % yield of the process was calculated, with reference to the amount of the raw materials used for each experiment.

Evaluation of the pellets characteristics

The evaluation of the pellets was performed using an Image Analysis System (Leica Qwin V. 2.3, Leica Imaging Systems, Cambridge, England). The Geometric Mean Diameter (GMD), the Geometric Standard Deviation (GSD) and the sphericity factor $e_R$ were estimated by the analysis of samples comprising 200 pellets.

Experimental Design

The process was initially studied using a resolution IV fractional factorial design with 16 runs. The screened factors and their levels are presented in Table 1. During screening the CW:HPMC K100M ratio was set at 50:50. The results were evaluated with both DoE and EDA techniques, in an attempt to clarify the main effects and the contribution of each factor to the responses. The DoE analysis was performed using Design Expert® V. 8.0.1, Stat-ease Inc, Minneapolis. A 17 run Central Composite Design (CCD) was then executed varying the selected significant factors (A:spray rate, B: Quantity sprayed and C:PF rate) retaining their levels as presented in Table 1.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Low Level</th>
<th>High Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Spray rate (g/min)</td>
<td>35,0</td>
<td>40,00</td>
</tr>
<tr>
<td>B Quantity of BM (g)</td>
<td>320,0</td>
<td>360,00</td>
</tr>
<tr>
<td>C Rotor speed (rpm)</td>
<td>1000</td>
<td>1400</td>
</tr>
<tr>
<td>D Rotor plate type*</td>
<td>ribbed</td>
<td>smooth</td>
</tr>
<tr>
<td>E Lubricant glidant*</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>F PF rate (g/min)</td>
<td>17,5</td>
<td>20,0</td>
</tr>
<tr>
<td>G Quantity from PF (g)</td>
<td>220,0</td>
<td>240,0</td>
</tr>
<tr>
<td>H Speronization time (min)</td>
<td>3,0</td>
<td>4,0</td>
</tr>
</tbody>
</table>

*Categoric factors. The lubricant was Mg Stearate and the Glidant colloidal silicon dioxide, at a proportion of 1%

Moreover, three additional designs were executed at CW:HPMC K100M ratios of 100:0, 75:25 and 0:100, altering appropriately the levels of the quantity of the binding material and the amount of powder added via the feeder.

Dissolution testing

A water soluble Active Pharmaceutical Ingredient (API) was incorporated at a proportion of 3% in three formulations using CW:HPMC K100M ratios of 100:0, 50:50 and 0:100 (pellet formulations named as R100, R50 and R0 respectively).
The pellets (filled in 12mg caps) and tablets prepared via compression of the pellets were tested for their dissolution profile using USP apparatus I and II respectively. The tested formulations were based on a simplex lattice mixture design, combining R100, R50 and R0 pellets. Especially for tablets, a mixture-amount design was performed studying also the effect of tablet weight (200 and 400mg, incorporating doses of 6 and 12mg respectively).

RESULTS AND DISCUSSION
Process characterization
The screening experiments were analyzed using EDA (Exloratory Data Analysis) and DoE techniques and it was decided to select the smooth rotor plate, exclude the lubricant and glidant and fix the rotation speed at 1000rpm and the quantity added from the PF at the lower level.

The CCD performed at a CW:HPMC K100M ratio of 50:50 showed the important factors and interactions affecting each response. Concerning GMD, all three factors were found to be significant (p=0.0041 for the spray rate and p<0.0001 for the quantity sprayed and the PF rate). As expected, the PF rate was the only factor with a negative effect on pellet growth, while GSD was not significantly affected.

Concerning the sphericity factor e_R, a reduced quadratic model was best fitted to the data. All main effects were significant and PF rate was found to reduce the sphericity of the pellets (C² was also significant). Two important interactions were identified, AB (p=0.0309) and BC (p=0.0006).

The yield of the process was found acceptable since in all cases it ranged between 88 and 97%. Factors A and B had a statistically significant effect on the yield of the process.

Similar effects were also identified from the analysis of the designs using the different CW:HPMC K100M ratios. However, as the CW:HPMC K100M ratio increased, less binding material was necessary in order to produce pellets of similar size. Longer spheronization times and larger binding material quantities (combined with the decreased CW:HPMC K100M ratio) lead to smoother pellets.

The process was compared to its alternatives (high shear mixing and extrusion spheronization) and its advantages and disadvantages were recognized.

Drug Release
The release was accelerated when the proportion of pellets with high CW:HPMC K100M ratio increased. The large differences in t50 and t80 values between the different formulations showed that a variety of release profiles is feasible, ranging from practically immediate release formulations, to sustained release dosage forms. This was predictably achieved by the combination of pellets with different CW:HPMC K100M ratios at proportions deriving by the model equations.

Conclusions
Challenging processes such as hot-melt direct pelletization can be approached successfully through experimental design techniques. The number of factors can be screened during the preliminary steps of process development, while the important factors may be further studied, leading to process knowledge, the main objective of the current ICH Q8 guideline (“Product Development”). The novel process (Politis and Rekkas, 2010) can be considered appropriate for use in lean and agile manufacturing settings.
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References
Montgomery DC, 1976, Design and analysis of experiments, Wiley.