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Evaluation of the composition of the binder bridges in matrix granules prepared with a small-scale high-shear granulator

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ABSTRACT

The aim of this work was to evaluate the binder bridges which can form in hydrophilic matrix granules prepared with a small-scale high-shear granulator. Matrices contained hydroxypropyl methylcellulose (HPMC) as a matrix-forming agent, together with lactose monohydrate and microcrystalline cellulose as filler. Water was used as granulating liquid. A 2^4 full factorial design was used to evaluate the effects of the operational parameters (impeller speed, chopper speed, dosing speed and wet massing time) on the granulation process. The temperature of the sample increased relevantly during the preparation in the small-scale apparatus. The same setup induced different temperature increases for different amounts of powder. This alteration enhances the solubility of lactose and decreases that of HPMC, and thus the quantities of the dissolved components can vary. Accordingly, changes in composition of the binder bridge can occur. Since exact determination of the dissolution of these materials during granulation is difficult, the consequences of the changes in solubility were examined. Differential scanning calorimetry (DSC), thermomechanical analysis (TMA) and X-ray diffraction (XRD) measurements were made to evaluate the films prepared from liquids with different ratios of soluble materials. The DSC and XRD measurements confirmed that the lactose lost its crystalline state in the film. The TMA tests revealed that increase of the quantity of lactose in the film decreased the glass transition temperature of the film; this may be attributed to the interaction of the additives. At a lactose content of 37.5%, a second glass transition appeared. This phenomenon may be indicative of a separate amorphous lactose phase.

1. Introduction

Various solid matrix systems are currently popular because of their controlling effects on the dissolution of the active ingredients [1,2]. These matrices (mainly tablets) may be hydrophobic or hydrophilic. Hydrophilic systems can influence the rate of liberation of active pharmaceutical ingredient (API) by erosion and diffusion [3–5], but they can also exhibit relevant bioadhesive properties which can affect the site of action [6,7]. The matrix-formers that are mainly used for erodable systems are polymers with good solubility, high water uptake and properties appropriate for the formation a mucilaginous (adhesive) layer. The additional pharmaceutical excipients must be hydrophilic so as to avoid inappropriate wetting of the matrix-former and to promote the action of the matrix-former polymer.

Tablets can be prepared through the direct compression of a powder mixture containing a matrix-former or through the compression of granules (generally the matrix granules) [8]. Various methods can be used to prepare granules containing the previously mentioned components [9–12]. The most widely applied method is wet granulation, where the granulating fluid is an aqueous system. The granulating fluid can contain different binder materials (mainly macromolecular agents) or it can be a solvent of the solid component, in which case the soluble and later the solidified component too form bridges between the particles and ensure the appropriate mechanical behaviour for the agglomerates [13]. The soluble component can be any member of the powder mixture, e.g. the active agent, filler, matrix-former, etc., or a mixture of them. A number of publications have demonstrated that excipients that are strongly soluble in the liquid binder play a major role in the formation and strength of solid bridges inside a granule [14–16]. Those studies additionally dealt with the evaluation of the binder bridges, focusing on the mechanical and morphological properties of the granules, but not on the exact composition of binder

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bridges. Other papers discuss the evaluation of the solubilities of the materials, the crystallization/recrystallization processes and examination of the product formed with respect to amorphism and polymorphism [17–19]. Study of the composition and crystalline state of these individual small bridges in the granules is difficult, but an understanding of their formation is critical for optimization of the granulation process. The significance of such evaluations is highlighted by the well-known phenomenon that an amorphous form can change during storage and can indicate stability problems [20].

It was mentioned above that the hydrophilic matrix-former component can be water-soluble. Conventionally, various polysaccharides/polymers are used in the tablet formulations to retard drug release. A solution of such materials (e.g. different cellulose derivatives) is often used as a coating material. Alternatively, these can be used as a binder during conventional wet granulation binders [21,22]. It is known that a solution of these polysaccharides/polymers as binders probably on drying enables the granules to be coated by them [23] and the course of drying, they form hard film bridges [24–27]. In general, these materials are applied in high concentrations in the powder mixture during the formulation of matrix systems. A proportion of these materials dissolves in the granulation liquid and so a film or binder bridges are formed during drying, but prediction of the exact quantities is difficult. Another problem inherent in the prediction is the fact that the powder mixtures contain materials with different water uptakes and solubilities. The dissolved amounts of the components can be influenced by the quantity of the liquid and also by the operational parameters, e.g. the effectiveness of mixing or the processing time. The effects of the operational parameters on the granules or pellets formed have been studied [28–30], but the composition of the binder bridges (film) has not been evaluated.

The high-speed moving of the parts of a small-scale high-shear granulator (impeller and chopper) can cause a relevant increase in the temperature of the powder/granules. This parameter can therefore be an indirect factor during the optimization. Its importance is emphasized by the temperature-sensitive nature of the solubility of the components. In the composition under evaluation, not only the rate of dissolution, but also the quantity of materials dissolved can depend on the temperature. Hence the solution formed during granulation and after drying in the binder film can exhibit different compositions. Since exact, direct measurement of the components in the fluid formed around the solid particles and in wet granules appears impossible, it is reasonable to prepare and study the properties of free films formed from different ratios of the soluble components.

Pressures to save API are driving formulation developers toward smaller-scale laboratory processes (miniaturization), while pressure to save time puts a premium on increasingly accurate laboratory-scale tools. An appreciable number of manuscripts have dealt with miniaturization of the different technological methods and its problems [31–34]. In certain cases, it is very difficult to extrapolate the results to larger systems.

In the present work the effect of operational parameters and batch size on the temperature increase during small-scale granulation were studied. Since the solubilities of the components may change as a result of this, the main aim was the evaluation of binder bridges with different ratios of soluble materials. Such data can be informative as concerns granulation scale-up.

Table 1
Values of factors

Factor	Low-level (−)	High-level (+)
Chopper speed, X_1 (rpm)	1500	3500
Impeller speed, X_2 (rpm)	500	1000
Dosing speed, X_3 (ml/min)	5	15
Wet massing time, X_4 (min)	1	4

2. Experimental

2.1. Materials

HPMC (Pharmacoat 606, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) was used as matrix-former. Our preformulation studies indicated that the optimum concentration was 30%. Microcrystalline cellulose (Vivapur 301, Rettenmaier&Söhne GmbH, Rosenberg, Germany) was applied as a filler/binder, and α-lactose monohydrate (Ph. Eur., Hungaropharma Plc., Budapest) as a filler, each of these components was in a quantity of 35%.

2.2. Preparation of matrix granules

In the first part of the granulation, 150 g of granules was prepared in a high-shear granulator (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium). This apparatus is equipped with an Infrared product temperature sensor assembly. It ensures a constant control between 20 °C and 100 °C. In accordance with our previous results [35], the quantity of liquid (water) was 35–100 g of powder mixture.

During the optimization of the granulation process, the quantities of the powder mixture and the liquid were kept the same, and the technical parameters were varied. A 2^4 factorial design was applied to study the effects of the operational factors (Table 1). The experiments were performed in a randomized sequence. The granules were dried on trays at 40 °C for 24 h.

Statistica for Windows 7.1 AGA software (StatSoft Inc., Tulsa, USA) was used for the calculations. The following linear approach, containing the interactions of the factors, was used to determine the response surface. This program can also evaluate three-factor interactions, but in this study they were not investigated. They are very difficult to interpret.

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4$$

The confidence interval in the mathematical evaluations was 95% ($p < 0.05$).

In the second part of our work, the effect of the batch size was evaluated. The same apparatus was used. The composition of the powder mixture was the same and the quantity of water was again 35–100 g of powder mixture. The operational parameters were—chopper speed: 3500 rpm; impeller speed: 1000 rpm; dosing speed: 5 ml/min; and wet massing time: 4 min. The amounts of powder taken were 50 g, 100 g, 150 g and 200 g. The dosing time had to be adjusted.

2.3. Study of granules

The sizes and the size distributions of the samples were assessed. An analytical sieve (Retsch GmbH, Haan, Germany) was used. The D10, D50 and D90 values of the samples were determined with sieving system software (Retsch EasySieve 2.0).

2.4. Evaluation of the films

Different samples were prepared for the thermoanalytical tests on the free film. Aqueous solutions containing various ratios of HPMC and lactose were produced (Table 2). They were poured into teflon dishes, and the solutions were then dried under the same