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The development of a novel formulation map for the optimization of high shear wet granulation

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ABSTRACT

With a view to describing the powder agglomeration process, particles have often been considered as inert material and the solid–liquid interactions have rarely been contemplated.

The present research aims to fill the gap in understanding how the nucleation and the early stage of the granule growth depend on some important formulation properties.

The glass transition concept coupled with on-line impeller torque monitoring and measurements of the time evolution of the particle size distribution was used to give a description of the early stage of the agglomeration process in high shear wet granulation. A mixture of commonly-used pharmaceutical powders, which are amorphous and crystalline in nature, was processed.

Accordingly, a new formulation map is presented which describes the onset of significant granule growth as a function of the key formulation components (i.e. diluent, dry and liquid binder).

From this map, the minimum amount of liquid binder required to induce appreciable granule growth is determined as a function of the type, quantity, hygroscopicity and particle size distribution of the diluent and the solid binder. This map can be obtained from a priori glass transition measurement using a static humidity conditioning system and by fitting the experimentally obtained data using a modified Gordon–Taylor equation.

1. Introduction

The pharmaceutical industry frequently applies high shear wet granulation to a powder mixture in order to improve the particle characteristics, the homogeneity and the flowability properties [1,2]. High shear wet granulation is therefore an example of particle design, since an initial powder mixture composed of a drug and some excipients can be transformed in design structured agglomerates through liquid addition and vigorous mixing [3].

In spite of the importance and the widespread use of this industrial operation, currently it is not completely clear how a change in the process conditions and formulation variables can affect the evolution of the granule properties. Many efforts have been made with a view to engineering the process, splitting up the agglomeration process into different stages, such as the initial granule formation phase or nucleation [4], the granule growth and finally breakage [5]. However, wet granulation has remained in practice more an art than a science, as pointed out by Iveson et al. [6].

Therefore our ability to control the high shear granulation process in order to establish a key factor such as the end-point conditions, for instance, is still an unsolved problem.

Several and varied methods have been explored for this purpose. Briens et al. [7] and Daniher et al. [8] proposed an end-point monitoring technique based on the acoustic emission survey. However, at present, the granulator power consumption and impeller torque monitoring are the most widespread methods to monitor the agglomeration process since they are a direct measurement of the resistance of the wet mass to mixing [9–11]. The power consumption or impeller torque profiles have been traditionally subdivided into different phases, as described by Leuenberger et al. [12]: (1) a first slight increase in the profile, usually related to nuclei formation and moisture sorption, (2) a rapid increase in the profile slope, due to the attainment of the pendular state (formation of liquid bridges), and (3) a plateau phase in the profile which indicates the transition from the pendular to the funicular state. Some authors consider this plateau region as an equilibrium stage between granule growth and breakage, corresponding to optimal granule characteristics [13].

Modern and scientific approaches to granulation understanding aim to split and analyze every single agglomeration phase. In

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Table 1
Formulation composition for the second experimental set.

Experiment	Lactose monohydrate 150 M amount (%, w/w)	Microcrystalline cellulose MCC amount (%, w/w)	Binder type and amount (%, w/w)	Croscarmellose sodium amount (%, w/w)
1	76.0%	20% constant	HPMC, 2.5%	1.5% constant
2	73.5%		HPMC, 5.0%	
3	71.0%		HPMC, 7.5%	
4	68.5%		HPMC, 10.0%	
5	76.0%	20% constant	PVP, 2.5%	1.5% constant
6	73.5%		PVP, 5.0%	
7	71.0%		PVP, 7.5%	
8	68.5%		PVP, 10.0%	

this work we focus on the early stage of the growth phase and on the potential of on-line impeller torque measurements to monitor the granule growth. Whereas most research has been primarily devoted to end-point determination, less effort has been dedicated to the understanding of the granulation onset.

In addition, particles have often been considered inert materials, i.e. interactions between solid particles and liquid have seldom been considered. Notable exceptions are those of a few authors which explained the agglomeration of different powder mixtures as a consequence of increased powder stickiness [14] or a change in the deformability and viscosity of the wet mass [15] when the powder temperature is below the material glass transition temperature.

The aim of this work is to close the gap in understanding how the main formulation properties affect the early stage in the agglomeration of a powder mixture, which is not composed by inert glass beads but by amorphous and crystalline particles. In order to achieve this result, the impeller torque profile analysis has been coupled with the binder glass transition concept. It has been demonstrated that the granulation onset can be identified as an abrupt increase in the impeller torque value when the amount of the added liquid exceeds a critical threshold indicated here as minimum liquid volume (MLV).

The experimental results have been, thus, gathered in a new formulation map which combines the key elements of the powder mixture and gives the minimum liquid volume necessary to start the agglomeration process. It has been also demonstrated how to construct the formulation map using independent measurement of the dry binder glass transition temperature.

2. Materials and methods

Variations of a common, active-free pharmaceutical formulation were considered. The resultant formulations were mixtures of amorphous and crystalline powders.

Lactose monohydrate 150 mesh (Lactochem® Regular Powder 150 M, Friesland Foods, Zwolte, The Netherlands) and microcrystalline cellulose (MCC) (Pharmacel® 101, DMV International, Veghel, The Netherlands) were used as main diluents. Croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer, Philadelphia, USA) was used as disintegrant while the solid binders were hydroxypropylmethylcellulose HPMC (Pharmacoat® 603/Methocel® E5, Shin-Etsu Chemicals, Niigata, Japan) or polyvinylpyrrolidone PVP (Kollidon® K30, BASF, Ludwigshafen, Germany). Excipients were granulated using deionized water at 20 °C.

Experiments were performed in a small scale, top driven granulator (MiPro 1900 ml, ProCepT, Zelzate, Belgium) with a stainless steel vessel, a chopper and a three bladed impeller. Granulator was equipped with a measuring/registering system for impeller torque and powder temperature values during granulation.

The volumetric fill level of the vessel was 40%, for a weight of about 400 g. A premixing stage at 1000 rpm and for 5 min was performed prior each of the granulation experiments. Granulating liquid was added through a tube with a 1 mm diameter by a computer controlled dosimeter.

Two experimental sets were performed. In the first set three granulation experiments were carried out to determine the influence of impeller speed on impeller torque profiles and on particle size distribution of the final granules. At this stage powder mixture composition was held constant and was (on weight basis): lactose monohydrate 150 M (73.5%), microcrystalline cellulose (20%), HPMC (5%) and croscarmellose sodium (1.5%). All the experiments were stopped immediately after liquid addition so that the massing phase was not carried out.

Variable conditions were: the impeller speeds at 500, 850 and 1200 rpm, whereas the total amount of liquid and liquid addition flow rate were always fixed at 100 ml and 10 ml/min, respectively.

A second set of granulation experiments was performed with different formulation compositions under the same process conditions (i.e. impeller speed of 850 rpm, chopper speed of 3000 rpm, total amount of water added of 100 ml and water addition rate of 10 ml/min).

This experimentation was designed to determine the role of the dry binder on the granule growth phase. The changes in the formulation composition involved the binder type (HPMC and PVP) and amount (in the range 2.5–10%, w/w) as shown in Table 1.

Granule samples were taken immediately after the end of the wetting time and dried. Drying was given a special care to preserve as much as possible the granules' size. A first gentle drying was carried out at constant temperature and pressure (20 °C and 1 bar) in a mildly ventilated drying room, and a second drying in an oven for 1 h with a temperature of 50 °C and a pressure of 5 mbar. The wet material was arranged as a thin layer (thickness was about 5 mm). This procedure was followed for minimizing incidental alteration in particle size distribution (PSD) due to the drying method (e.g. attrition in fluid bed dryer, caking in oven at high temperature).

The PSD was characterized by sieve analysis and image analysis. The sieving method consisted on 5 mm of vibration amplitude for a 10 min analysis time. Sieves apertures were: 45, 90, 180, 250, 355, 500, 710, 850 and 1000 μm. Image analysis of granulates was performed using a camera with a 2/3 in. CCD (Jai, CV-300) and interfaced with a Image Tool PC program (ImageTool©, Copyright 2008, Evans Technology, Inc.).

A gravimetric analysis system (IGAsorp, Hiden Isochema, Warrington, UK) was used in order to determine the water sorption isotherm for each formulation component at 25 °C.

Binder samples were kept at different relative humidity grades under nitrogen flow; the weight change of each binder sample during the time course analysis was measured by a hygrometer. The exposure time of each sample to the different humidity grade corresponded to the time at which binder sample weight did not change anymore or otherwise to a maximum time of 12 h.

Curves representing influence of water content on binder glass transition temperature were determined by DSC. HPMC and PVP duplicate samples (about 500 mg) were preconditioned in a atmosphere at given RH%. Samples were weighted and spread as a thin