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Research paper

The combined effect of wet granulation process parameters and dried granule moisture content on tablet quality attributes

Ian P. Gabbott *, Farhan Al Husban, Gavin K. Reynolds

Pharmaceutical Development, AstraZeneca, Charter Way, Macclesfield SK10 2NA, United Kingdom.

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ABSTRACT

A pharmaceutical compound was used to study the effect of batch wet granulation process parameters in combination with the residual moisture content remaining after drying on granule and tablet quality attributes. The effect of three batch wet granulation process parameters was evaluated using a multivariate experimental design, with a novel constrained design space. Batches were characterised for moisture content, granule density, crushing strength, porosity, disintegration time and dissolution.

Mechanisms of the effect of the process parameters on the granule and tablet quality attributes are proposed. Water quantity added during granulation showed a significant effect on granule density and tablet dissolution rate. Mixing time showed a significant effect on tablet crushing strength, and mixing speed showed a significant effect on the distribution of tablet crushing strengths obtained. The residual moisture content remaining after granule drying showed a significant effect on tablet crushing strength. The effect of moisture on tablet tensile strength has been reported before, but not in combination with granulation parameters and granule properties, and the impact on tablet dissolution was not assessed. Correlations between the energy input during granulation, the density of granules produced, and the quality attributes of the final tablets were also identified. Understanding the impact of the granulation and drying process parameters on granule and tablet properties provides a basis for process optimisation and scaling.

1. Introduction

Wet high shear granulation (batch and continuous) is used in the pharmaceutical industry to improve the properties of solid dosage formulations, primarily enhancing flowability, to facilitate the production of compacts with uniform weight and therefore drug content. Additional benefits may also be obtained as a result of the granulation process, such as decreased segregation potential, reduced dusting and in some cases improved compaction behaviour. Drug substances (and some excipients) are often cohesive materials and possess poor flow properties and are therefore ideal candidates to be processed using wet granulation.

A lot of research has been conducted into granulation rate processes ([1] summarises much of this), and the impact of granulation process parameters on granule and tablet properties [2] is well documented. However, many of the experimental studies have been performed using orthogonal experimental designs, which constrain the ranges of process parameters that can be explored meaningfully. For example, a standard factorial experimental design would dictate that a batch is run with high water quantity, high impeller speed and long mixing time, which means that the maximum values of each parameter must be restricted if the batch is to avoid over-granulation. Similarly, minimum values for design points requesting low water quantity, low mixing time and low impeller speed must be considered carefully, if any size enlargement is to be achieved at all. This means that conditions such as slow impeller speeds and short mixing times but high water quantities are not commonly explored. This study aims to address this gap by using an experimental design with a constrained design space (Fig. 1). Essentially, the water quantity added will be determined as a function of impeller speed and mixing time.

The second aspect to this study is that of granule moisture content. Following wet granulation the granules must be dried, and the combined influence of the granulation parameters and the drying end point and residual moisture content in the granules has to date been somewhat overlooked in the literature.

The impact of moisture content on the compaction of powdered materials (rather than granular) has been explored [3], who found

* Corresponding author.
E-mail address: ian.gabbott@astrazeneca.com (I.P. Gabbott).

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List of symbol

M	mass (g)
P	maximum impeller power (W)
V_a	apparent volume (cc)
ρ_a	apparent density of tablets (g/cc)
ρ_t	true density of solids (g/cc)
τ_a	actual impeller torque (Nm)
τ_t	total impeller torque capability (Nm)
ω	rotational speed of the impeller (revs per second)

that water can increase compactibility of materials (see [4] for definition), through dissolution/crystallisation of the material to produce solid bridges, or by decreasing the interparticulate separation distance. They found no significant effect of powder moisture content on volume reduction of materials during compaction. It is also reported that the effect of moisture can be transformed in the presence of a polymer, depending on the degree of chemical or physical association between the water and polymer phases [5,6]. There is also some conflicting evidence about the optimum amount of moisture to be included in a specific tablet formulation from a compression point of view, and how this moisture affects the physical strength of the resultant tablets [7].

However, no research to date has examined the interplay between granule density and moisture content on the subsequent compaction process and the properties of the tablets that result. The aims of this work are:

- To examine the link between granulation process parameters, granule properties (including moisture content) and the properties of the tablets compacted from those granules.
- To determine the relative influence of granulation process parameters and residual granule moisture content on the properties of tablets produced.
- To explore whether it is possible to produce tablets with high hardness and fast dissolution.
- To explore whether tablet properties can be predicted using granule density data.
- To explore specific energy of granulation as a method for describing the batch wet granulation process across a range of production scales.

2. Materials and methods

Drug substance and excipients were dispensed according to the formulation shown in Table 1. Note that the lubricant, magnesium stearate, was included in the nominal total but was not included

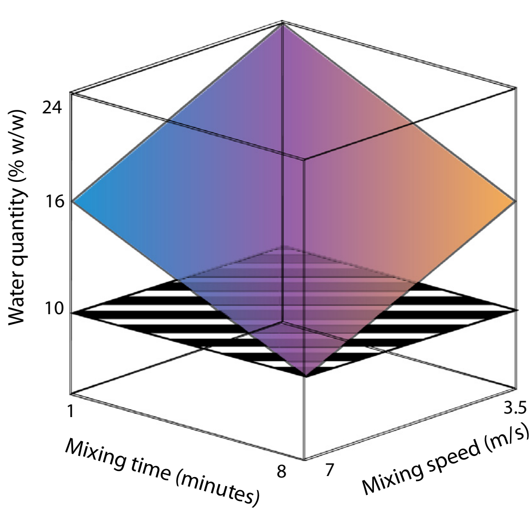

Fig. 1. Design space to be explored in this study.

during granulation. Following drying and milling, the lubricant was added to make up 2% (w/w) of the mass of dry granules.

Tablets were manufactured according to the flow diagram in Fig. 2. Equipment and parameter ranges used in this study are listed for each step. The chopper was run for the same length of time as the main impeller (indicated by 'total mixing time') for each batch.

Prior to drying, each granulation batch was divided into two sub-batches to carry out drying to two different residual moisture contents: high (2–4% w/w moisture) and low (<1% w/w moisture). Materials were double-wrapped (double-bagged in LDPE bags or stored in an overwrapped bottle) between each stage to prevent significant changes in moisture content between unit operations (see Table 2).

2.1. Specific energy of granulation

Impeller torque readings during the entire period of wet granulation were recorded and used to calculate the specific energy of granulation for each batch. The Glatt TMG 1/6 provides torque readings as a percentage from the maximum torque capability of the machine. In order to calculate the actual torque and mixing energy for each batch, the following equations were used in the calculation:

$$\tau_t = 60P/2\pi N \tag{1}$$

where τ_t is the total impeller torque capability in Nm, P is the maximum impeller power in Watts, and N is the rotational speed of the impeller in revolutions per second. A total impeller power of 1.1 kW at a rotational speed of 935 rpm as stated in the user manual of the Glatt TMG 1/6 was used to calculate the maximum torque output of the machine.

$$\tau_a = \tau_r \tau_t / 100 \tag{2}$$

where τ_a is the actual torque in Nm, and τ_r is the relative torque applied during granulation and reported by the machine as a percentage.

$$P_g = \tau_a 2\pi N/60 \tag{3}$$

where P_g is the total power of granulation in Watts.

$$E_s = \left[\int P(t)dt\right]/M \tag{4}$$

where E_s is the specific energy of granulation in kJ/kg, t is the total granulation time in seconds and M is the mass of powder in the granulator in kg.

The contribution of the chopper to the total mixing energy has been ignored for these calculations, since few research studies on the effect of the chopper during high shear granulation have been conducted. Most studies were limited to the chopper effects on granule size, shape, friability, and porosity using vertical shaft granulators and the conclusions varied [8]. In general, the chopper is considered to have limited impact. Reports have concluded that it acts only as a baffle [9], that it has no effect on the granule size distribution [10] and that it has no effect on pore size distribution of granules [11].