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The effect of primary particle surface energy on agglomeration rate in fluidised bed wet granulation

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Abstract

The effect of primary particle surface wettability by a binder solution on the rate of agglomeration in a fluid-bed top-spray granulation process was investigated. A model system consisting of hydrophilic and hydrophobic spherical primary particles with a narrow size distribution, and an aqueous solution of hydroxy propyl-cellulose (HPC) as binder, was used. The surface energy of the primary particles was measured by inverse gas chromatography (IGC) and their wettability was characterised by static and dynamic contact angle. Granulation was carried out in a desktop fluid-bed granulator and the resulting granule size distribution and granule microstructure were analysed. The hydrophobic particles gave a wider granule size distribution (larger maximum granule size) than hydrophilic ones under otherwise identical conditions, and the granules were notably rounder and more compact. However, the fraction of un-granulated fines was also higher in the case of hydrophobic primary particles. SEM analysis of granule microstructure revealed that the hydrophilic particles were coated by the binder solution, which left a smaller amount of binder available to form bonds at particle contacts. On the other hand, all of the binder was found to form solid bridges in the case of hydrophobic primary particles. A population balance model was used to explain the observed granulation behaviour.

Keywords: Wetting; Spreading; Surface energy; Inverse gas chromatography; Population balance model; Monte Carlo simulation

1. Introduction

The wet granulation of pharmaceutical materials typically involves the co-agglomeration of small crystals of a drug substance (active pharmaceutical ingredient, API) with particles of an excipient by means of a liquid binder [1]. The main objectives of granulation in the pharmaceutical context are to improve powder flow and compaction behaviour before tabletting, and to ensure composition uniformity. It is well known that granulation behaviour can be rather sensitive to the properties of the primary solid particles [2–7]. Even different batches of nominally the same material can granulate differently, and considerable amount of time is often spent on identifying granulation conditions (binder type and level, temperature, etc.) each time a new API is introduced. It would be desirable if quantitative or qualitative guidelines existed for the selection of robust granulation process conditions based on a set of particle physico-chemical properties that can be measured on a small sample early on in the formulation and process development cycle [8].

The change of granulation behaviour when a new solid material is introduced can be caused by several factors: a different material will generally have not only different surface properties (surface energy, wetting characteristics) but also different particle morphology, density, and size distribution. The objective of our present work was to investigate the sole effect of particle surface properties on granulation behaviour, and specifically to confirm or otherwise the widely held assumption that “better wetting means better granulation”. To this end a model system consisting of uniformly sized hydrophilic and hydrophobic glass beads has been chosen. Although highly idealised, such a system allows us to keep constant all process conditions and material properties except the surface energy, thus carry out a true single-parameter sensitivity study.

The rate of granule growth by agglomeration is proportional to the collision frequency between the particles present in the granulator, and the fraction of collisions that are successful, i.e. the fraction of collisions that lead to coalesce rather than rebound [9]. For a collision to be successful, two conditions

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must be met: (i) the particles must contact each other by a binder-wet region, and (ii) the viscous binder layer in this region must be able to dissipate the kinetic energy of the particles. Depending on the surface energy, a liquid binder droplet deposited on a smooth particle will either spread completely and form a film coating (total wetting case), or, in the case of partial wetting, take the shape of spherical cap whose base radius, *a*, and height, *h*, can be related to the volume, *V*, and contact angle, *θ*, by the following equations [10] if we assume the droplet size to be relatively small compared to the particle size, and so neglect the curvature of the particle surface:

$$a = \left[\frac{3V}{\pi}\frac{\sin^3\theta}{2-3\cos\theta+\cos^3\theta}\right]^{1/3} \quad \text{and} \quad h = a\left[\frac{1-\cos\theta}{\sin\theta}\right] \qquad (1)$$

The dependence of *a* and *h* on *θ* is plotted in Fig. 1. As can be seen, for a fixed binder volume a hydrophobic particle (i.e., larger contact angle *θ*) will have a smaller fraction of its surface covered by the liquid than a hydrophilic one, and therefore smaller probability of hitting another particle with a wet region during a certain number of random collisions. On the other hand, if it does hit another particle with the binder-wet area, the local thickness of the liquid layer will be larger than for a corresponding hydrophilic particle, and so will its ability to dissipate the kinetic energy of the impact. This trade-off will be central to further analysis. An illustration of the liquid configuration on a hydrophilic and a hydrophobic particle is shown in Fig. 2. A detailed numerical analysis of droplet morphologies on non-spherical particles can be found in Ref. [11].

The critical conditions for the dissipation of kinetic energy by a viscous layer of given thickness (so-called viscous coalescence) have been derived [12–14] in the form of the Stokes number, defined as

$$\mathrm{St_v} = \frac{2mu_0}{3\pi\mu d^2} \qquad (2)$$

where *m* is the particle mass, u_0 is the collision velocity, *μ* is the viscosity of the liquid, and *d* is the particle diameter. In the case of a collision between particles of unequal size, the reduced mass and radius, respectively, are used in place of *m* and *d*:

$$m = \frac{2m_1m_2}{m_1+m_2} \quad \text{and} \quad d = \frac{2d_1d_2}{d_1+d_2} \qquad (3)$$

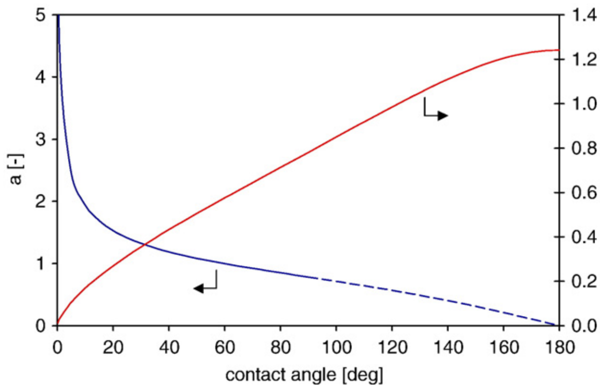

Fig. 1. Dependence of the base radius, *a*, and the height, *h*, of a spherical cap with a nominal volume of *V*=1, on contact angle.

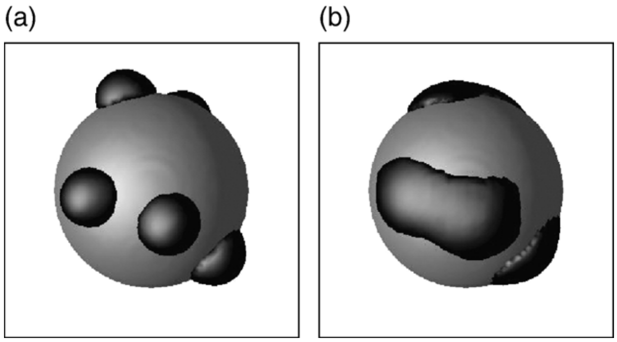

Fig. 2. Illustration of liquid droplet morphologies on a spherical particle with a contact angle of 75° (a) and 15° (b). The binder volume and the initial position of the droplets were the same. The final liquid configuration was obtained by a Volume-of-Fluid (VOF) simulation, as described in Ref. [24].

A collision is deemed successful if the Stokes number is below a critical value (the critical Stokes number, $\mathrm{St_v^*}$)

$$\mathrm{St_v^*} = \left(1+\frac{1}{e}\right)\ln\left(\frac{h}{h_\mathrm{a}}\right) \qquad (4)$$

where *e* is the coefficient of restitution, *h* is the thickness of the binder layer at the collision point, and h_a is the characteristic size of surface asphierities [12]. The value of the Stokes number determines whether coating or granulation occurs [15,16], and the maximum granule size that can still lead to coalescence for a given volume of binder with certain viscosity [17]. Of specific interest in our present work is the influence of the particle surface properties on the agglomeration rate, which we will seek to interpret in terms of the dependence of the critical Stokes number on contact angle, via the binder layer thickness — i.e. the combination of Eqs. (1) and (4).

2. Materials and methods

2.1. Granulation

Two types of commercially available glass beads (Sovitec Cataphote, Belgium) were used as primary solid particles in granulation: hydrophilic (grade AF) and hydrophobic (grade AF-225) glass beads. The glass beads were spherical and practically mono-disperse, with a mean diameter of 110 μm and a true density of 2170 kg $\mathrm{m^{-3}}$ for both grades. The binder liquid was a 2% (wt.) aqueous solution of hydroxypropyl cellulose (Fisher Scientific, UK). The viscosity of a 2% solution of HPC is approximately 0.013 Pa s and its surface tension 50 mN $\mathrm{m^{-1}}$. Granulation was performed in a desktop fluid-bed granulator (Pro-C-epT, Belgium) using a top spray arrangement. In each case, a batch of 400 g of solids was granulated with a total of 110 ml of binder solution added at a