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Relationship between particle shape and some process variables in high shear wet granulation using binders of different viscosity

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ABSTRACT

The effects on granule shape of binders of different viscosities have been compared in the high shear wet granulation process. Water and different emulsions were used as liquid binders. The observed differences in shape have been explained in terms of the granule growth regime map and show that it is easier to control the shape of granules obtained using emulsions as binder. Moreover, evidences have been collected showing that high shear wet granulation is a viable solution for solid self-emulsifying drug delivery systems.

1. Introduction

There is evidence in the literature that lipid-based systems are successful in enhancing the bioavailability of Class II Active Pharmaceutical Ingredients (APIs), which are poorly water-soluble but highly permeable drug molecules [1]. One of the most popular approaches of lipid formulations is the self-emulsifying drug delivery system (SEDDS). SEDDSs are mixtures of oils and surfactants, sometimes containing co-solvents, which are able to spontaneously emulsify and produce fine oil-in-water emulsion when introduced into aqueous phase under gentle agitation.

Upon peroral administration, these systems form fine oil-in-water emulsions (or microemulsion) in the gastro-intestinal tract with mild agitation provided by gastric motility [2,3].

However, SEDDSs are mostly prepared as liquid dosage forms such as emulsions. They can be contained within soft capsules and present some disadvantages especially in the manufacturing process with consequent high production costs. Moreover, incompatibility problems with the capsule shell such as leaking of components are usual. Accordingly, the new drug delivery technology solid SEDDS started to interest researchers because it combines the advantages of SEDDS with those of solid dosage forms [4]. Various methods were used to incorporate lipids into solid matrices, which were summarized in a recently published review [5] and high shear wet granulation (HSWG) is a promising solution. Some researchers [6,7] demonstrated that it is possible to incorporate a self-emulsifying system into cellulose microcrystalline by extrusion–spheronization and high shear wet granulation. Moreover, they found that to make this possible it is necessary to incorporate water into the SEDDS in order to form an oil-in-water emulsion and to ensure that the process work.

However, the use of emulsions in wet granulation results in binders of increased viscosity which give granules with physical characteristics different from those obtained with simple water. In particular the attention is here focused on the shape of the granules. Controlling granule shape may be desirable for many reasons; among these are for example the flow properties. A spherical shape possesses a minimum surface area to volume ratio resulting in reduced cohesive forces and mechanical interlocking thereby resulting in improved flowability of the bulk powder [8]. Obtaining more spherical shape is a desired prerequisite also when a subsequent coating or drug layering of the granules is necessary.

The advantage of HSWG is that mixing, massing and granulation are performed in a few minutes in the same equipment. However HSWG does not always warrant more spherical granules. The process variables need to be controlled with care as the granulation progresses so rapidly and usable granules can be transformed very quickly into unusable ones.

A certain number of works dealing with granule shape were performed in the past on pharmaceutical powders granulated using water or aqueous polymer solutions as granulating liquid.

For example some authors have used a granulation map in order to discriminate between different growth/breakage mechanisms as a function of formulation and process variables [9,10–12]. As a result of a specific growth/breakage mechanism, final granule shape has been correlated with a particular area in the growth

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Table 1
Process and formulation variables studied and their codified values.

Variable	Levels
X1 – impeller speed (rpm)	800 1200
X2 – massing time (min)	3 5
X3 – binder or viscosity	Water Empty emulsion (E1) Emulsion with API (E2)

regime map [11,12]. A similar approach will be here adopted for solid SEDDS. Differences in the granule shape will be explained in the light of the Stokes deformation number approach and the comparison with classical water-bound granules will be presented as well. The results of granule characterization will be also compared with those obtained by other researchers [6,13].

2. Experimental set-up

The granules were obtained using a 2 l one-step mixer granulator Rotolab® (Zanchetta SpA, Italy). Granulation procedure was standardized on the basis of preliminary trials. 250 g of a fixed powder mixture composed by 70% of microcrystalline cellulose (Acef, Italy), 27% of monohydrate lactose (Meggle, Germany) and 3% of polyvinyl pyrrolidone K-90 (Acef, Italy) was dry-mixed using an impeller speed of 150 rpm for 10 min. Successively binder solution was added on dry powders through a tube with a 0.5 mm internal diameter, using a constant rate of 10 ml/min.

Two different liquid binders were considered: water and emulsions. Emulsions were chosen in order to study the effect of an increasing viscosity on pellet performances and to evaluate the possibility to produce self-emulsifying pellets containing the model drug. Formulation of emulsions was selected using a pseudo-ternary phase diagram constructed using the water titration technique. Emulsion 1 (E1) contained: Lauroglycol 90 (Gattefossè, France), Transcutol (Gattefossè, France), Cremophore EL (BASF, Germany) and water. A second emulsion was considered: Emulsion 2 (E2) had the same composition of the first one and contained also 5% of Simvastatine (Polichimica, Italy) as model drug.

Viscosity for the three liquid binders were determined by the viscosimeter Rotovisco RV 20 (Haake, Karlsuhe, Germany) and resulted: 0.001, 0.009, 0.017 Pa s for water, E1 and E2, respectively. The amount of binder solution used to prepare pellets was fixed at 80% (w/w) of total weight of powders. To reduce the number of experiments needed to obtain the highest amount of information on granule characteristics, the screening was planned using an experimental design technique, in particular a factorial plan was used were two variables were studied at 2 levels and one variable was studied at 3 levels as shown in Table 1. The factorial plan is reported in Table 2.

During massing time impeller speed was increased according to Table 2. Massing time was 3 or 5 min. At the end of granulation process the granules were dried in oven at 40 °C until constant weight was achieved. Dry granules were sieved in order to remove lumps larger than 3 mm and stored in well closed bags before characterizations.

For size distribution analysis 100 g of granulation product was poured over a set of sieves (300, 500, 600, 800, 1000, 2000 and 3000 μm). A vibrating apparatus (Retsch AS200, Germany) was used at medium vibration level for 10 min. The fractions were collected and then weighted. Resulting PSDs will be here represented by the normalized-sectional frequency distribution (mass-based) [14,15] in order to perform a more reliable and reproducible comparison between the PSDs.

Table 2
Experimental plan.

Experiment number	Impeller speed (rpm)	Massing time (min)	Liquid binder
1	800	3	Water
2	1200	3	Water
3	800	5	Water
4	1200	5	Water
5	800	3	E1
6	1200	3	E1
7	800	5	E1
8	1200	5	E1
9	800	3	E2
10	1200	3	E2
11	800	5	E2
12	1200	5	E2

Shape analysis of granulates were performed using a camcorder equipped by CCD 2/3 in. (mod CV-300, Jai) and interfaced with Image Tool PC program (ImageTool©, Copyright 2008, Evans Technology, Inc.). Typically 40–50 granules from each experiment were analyzed.

Porosity and density of final granules were measured using respectively a mercury porosimeter (Pascal 140, Thermo Scientific, Italy) and a helium pycnometer (Pycnomatic ATC, Thermo Scientific, Italy).

The measurements of compression strength were performed using a computer controlled uniaxial mechanical testing instrument (TA-XT2i Texture analyzer, Stable Micro Systems, UK) equipped with very sensitive force and motion transducers mounted to the upper probe of the instrument and a fixed lower fulcrum that forms the base of instrument. A monolayer of granules (600–800 μm size range) was placed on the instrument plate and then pressed for 80% of the monolayer height. The resultant stress–deformation plot links the total measured force depending on the press displacement. The last and highest compression force value was recorded as the sample compression strength and plotted. Each experiment was repeated more than 50 times in order to obtain a reliable compression strength value.

Binder/powder wettability was also taken into account by measuring liquid surface tension and liquid–solid contact angle with the drop pendant and the sessile drop methods respectively: magnified movies of binder drops dropping from the tube and lying down on dry formulation were taken using a fast digital camera (FastCam PCI 1000, Photron, UK) at 250 frames per second.

3. Results

Experimental data concern four main aspects of the problem:

- liquid binder properties and powder wettability;
- final granule shape;
- particle size distribution of the final product;
- granule compression strength.

Liquid drop size and liquid–solid contact angle were measured using image analysis.

A sample of the initial dry formulation was poured into a Petri dish and the surface gently levelled.

Magnified movies of droplets detaching the dosimeter tube and lying on the dry formulation within the Petri dish were taken. The droplet detachment can be described by the following force balance, which represents the force required to contracts the droplet