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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

Table 3
Liquid properties resulting from experimental measurements and image analysis.

Liquid binder	Density (kg/m^3)	Viscosity (Pa s)	Liquid surface tension (mN/m)	Contact angle liquid–solid (°)
Water	1000	0.001	73.54	67.7
E1	888	0.009	38.78	105.8
E2	995	0.017	38.24	108.1

surface against the gravitational force:

$$\gamma_{LV}\pi d\ \cos\theta = \rho g\left(\frac{\pi D^3}{6}\right), \quad (1)$$

where γ_{LV} is the surface tension, θ is the angle between the droplet and the tube, ρ is the liquid density, g is the gravitational constant, d is the tube diameter and D is the droplet diameter.

Assuming $\theta = 0$ just before the droplet detachment [16], the ratio between the droplet and the tube diameters can be expressed as:

$$\frac{D}{d} = \left(\frac{6\gamma_{LV}}{d^2\rho g}\right)^{1/3} = \left(\frac{6}{\mathrm{Bo}}\right)^{1/3} = k\mathrm{Bo}^{-1/3}, \quad (2)$$

where k results to be 1.82 and Bo is the Bond number:

$$\mathrm{Bo} = \frac{d^2\rho g}{\gamma_{LV}}. \quad (3)$$

which is a dimensionless group describing the relative magnitude of forces due to gravity and surface tension. The presence of residual liquid on the tube after droplet detaching suggests an experimental correction to k in Eq. (1), so that it results to be around 1.6 [16]. Accordingly, liquid surface tension was calculated using the equation:

$$\gamma_{LV} = 0.244\frac{d^3\rho g}{D}, \quad (4)$$

where d and D_d are droplet and tube diameters, ρ is the liquid density.

Table 3 summarizes liquid properties and drop characteristics (tube with a 0.5 mm diameter).

Table 3 shows that liquid E1 and E2 present a contact angle larger than 90°: for this reason it is possible to consider them as hydrophobic liquids [17].

Even though the experimental plan contains a relatively small number of variables (the three variables of Table 1), it can be complex to synthetically describe them. We start by considering their effects on the shape of the granules expressed in terms of roundness and elongation. Roundness is computed as:

$$R = \frac{4\pi A}{P^2}, \quad (5)$$

where A is the granule area and P is the granule perimeter. Roundness resulting values are included between 0 and 1. The larger the value, the rounder the object.

Elongation, or aspect ratio, is defined as the ratio between the length of the major axis L and the length of the minor axis W:

$$E = \frac{L}{W}. \quad (6)$$

Elongation takes values larger than 1: the closer the value to 1, the rounder the object. All measurements in this work were carried out on granules belonging to the 600–800 μm size fraction.

Average roundness values with corresponding error bars are represented in Fig. 1. Data are presented in the following order: each set of data (diamonds, square and triangles) correspond to a different binder and is plotted presenting first the experiments with shorter massing time (3 min) at 800 and 1200 rpm respectively and then the same for experiments with longer massing time (5 min) as indicated in Fig. 1. This order has been followed also for all the other figures in the paper.

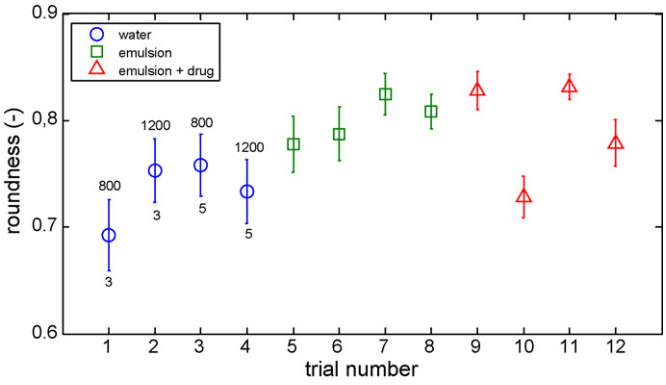

Fig. 1. Data obtained from image analysis of the granules (600–800 μm size range): roundness index as a function of the liquid binder type and the process conditions. Massing times (3 and 5) and impeller speeds (800 and 1200) are reported in just one case for sake of clarity. The sequence is the same in all the other cases.

As can be seen in Fig. 1, water-based granules present, on average, lower roundness values. It can be also observed that at lower impeller speed (800 rpm), roundness increases with viscosity both for short and long massing time. At higher impeller speed the trend is different instead: the roundness value reaches a maximum for the intermediate binder viscosity. As can be deduced from the error bars extent, the standard deviation values decrease with increasing the binder viscosity. In particular granules obtained with E2 as granulating liquid show the lowest standard deviation values: this might be a sign of strengthening properties due to the higher viscosity and more homogeneous shear stress conditions in the bulk.

Summarizing, the use of E1 or E2 seems to lead to the formation of rounder granules, especially if the massing phase is performed with the lowest impeller speed.

On the other hand, Fig. 2 shows the average elongation values with corresponding error bars. Mean elongation values roughly decrease with binder viscosity, thus indicating a lower deformability of the granules. On the whole however the effects of the chosen variables are less definite on elongation than on roughness which therefore should be chosen as the reference shape factor. The standard deviation of elongation values slightly decreases with increasing the binder viscosity. The variability of elongation values is furthermore noticeably higher than for roundness values.

Some researchers performed shape and surface roughness analysis of granules obtained using SEDDSs as liquid binders: Newton et

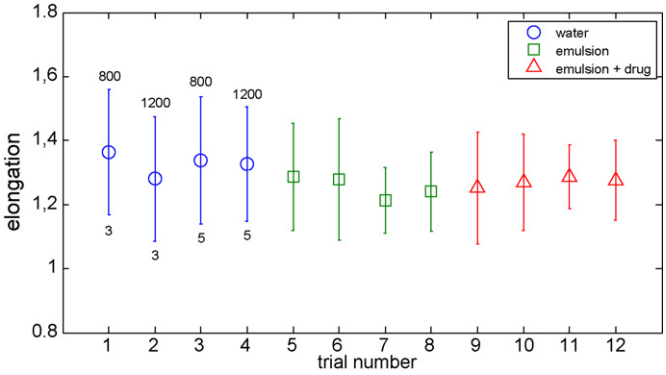

Fig. 2. Elongation values obtained from the image analysis, considering different liquid binders and process conditions.

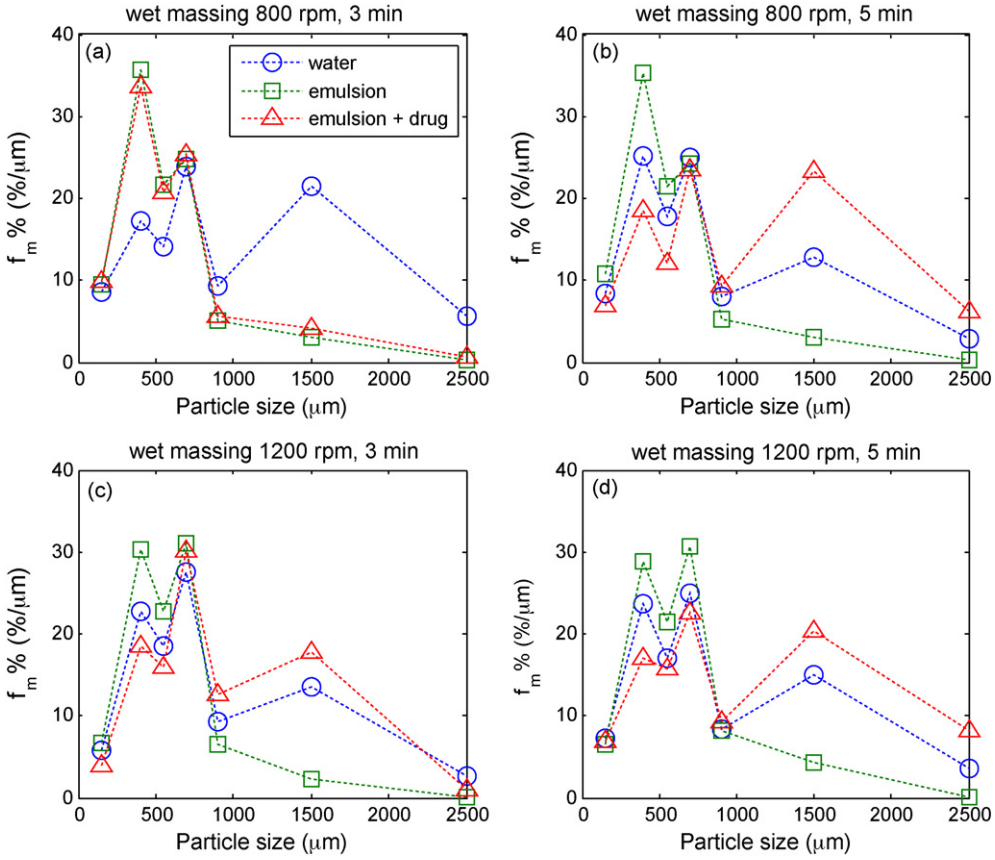

Fig. 3. Particle size distribution of the final product, comparison between different liquid binders and process conditions during the wet massing phase: (a) 800 rpm for 3 min, (b) 800 rpm for 5 min, (c) 1200 rpm for 3 min and (d) 1200 rpm for 5 min.

al. [6] and Abdalla et al. [13] turned to extrusion/spheronization in order to produce pellets containing SEDDSs. Even if the analysis of aspect ratio and eccentricity did not show considerable differences between water-based granules and those produced using SEDDSs, both of these authors reported surface roughness values noticeably lower when SEDDS was used. Thus, the use of an emulsion as binder seems to give smoother granule surface. As explained in the same papers [6,13], the presence of the oil phase within the cellulose crystalline structure might lead to a more "fluid-like" and hence smoother surface.

The final PSDs obtained using the three different liquid binders are shown in Fig. 3. The PSDs obtained using E1 and E2 as liquid binders tend to be narrower than the PSD of the water-based granules: the narrowest PSDs were obtained after 3 min, using the lowest impeller speed – see Fig. 3(a). Moreover, the PSDs obtained using water and E1 do not greatly depend on the process conditions. Contrarily both the impeller speed during the wet massing and the massing time affect the PSDs of the E2-based granules. The higher is the impeller speed and the massing time, the broader is the PSD of the E2-based granules and the higher is the mean size value.

Both particle shape and size are connected to the structure of the granule so that the compression strength of the dry granules was measured in addition. The compression test has been frequently applied to granules, tablets or wet samples in order to achieve some information about the sample structure strength [18,19]. In this work, the final dry granule was compressed with a view to describing the compression strength as a function of the process parameters-liquid binder type combination.

Fig. 4 shows the strength values for the granules and the corresponding standard deviations. As Fig. 4 clearly denotes, the longer is the massing the higher is the granule compression strength of the water-based granules. On the contrary, the breakage behaviour of granules obtained using E1 or E2 as liquid binders does not tightly depend on the operative conditions during the massing phase.

This behaviour might be explained in terms of the existence of persistent liquid bridges between primary particles after the drying process because of the oily phase in the emulsion and the consequent reduced final number of solid bridges due to lactose crystallization after water removal. The presence of lubricated contacts makes the final granule strength only slightly dependent on the operating conditions.

The average compression strength for each liquid binder is represented by a plain-dotted line. As can be appreciated in Fig. 4, the difference between the average strength values is not very remark-

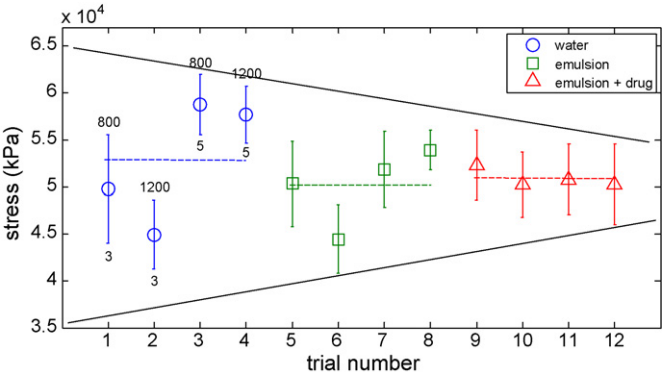

Fig. 4. Compression strength test on the granules (600–700 μm size range).

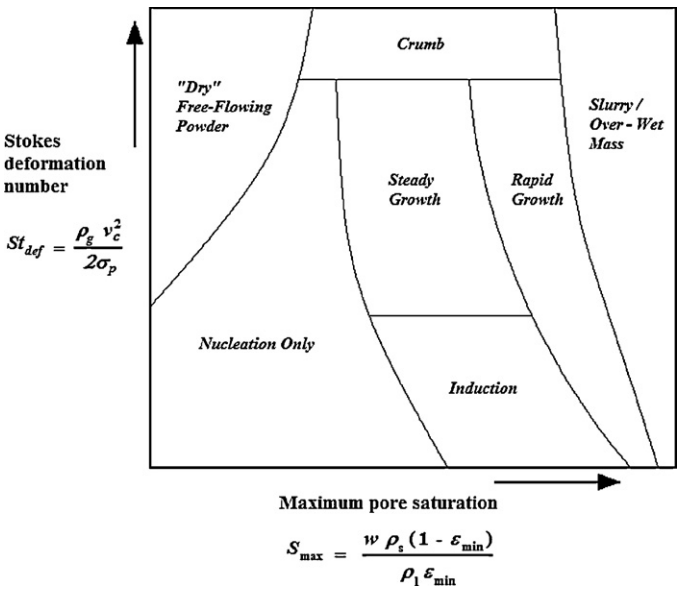

Fig. 5. Granule growth regime map [10].

able: only a very slight decrease in the mean compression strength can be noted for the granules obtained using E1. These results can be compared with those obtained by Abdalla et al. [13] and Newton et al. [6]. These authors found that the friability of granules increases with increasing the oil phase percentage in the liquid binder. They explained this phenomenon by considering the weaker interactions within the pellets in the presence of the oily phase, which was not absorbed by the cellulose solid matrix. Compression strength values in Fig. 4 are of the same order of magnitude as those presented in other literature works [20,21].

4. Discussion

Some authors correlated final granule properties (e.g. shape and size) with process and formulation variables, using granulation maps to describe particular growth/breakage mechanisms [11,12]. This approach considers the existence of two broad granule growth regimes [15,22]: steady growth and induction growth.

Steady growth regime is typical of granulation system with weak, deformable granules with coarse, narrowly sized particles and low surface tension and/or low viscosity binder liquids. In this case, two moving granules absorb impact kinetic energy during collision through plastic deformation of their structure. Liquid might be squeezed onto the granule surface forming a bond which can be strong enough to link the granules and form a new larger granule [15].

On the other hand, induction growth regime occurs in granulation systems with strong, non-deformable, slowly consolidating granules composed of fine particles and/or viscous binders. An induction time is usually necessary to allow granules to consolidate sufficiently, then the liquid might be squeezed to their surface. Thus, granules coalescence occurs without the application of large amounts of deformation and rapid granule growth is often observed [15].

If the system is too weak or the mixing energy too high, a non-granular "crumb" material will be formed [23].

A granule growth regime map was developed in order to define these different growth behaviours (see Fig. 5) as a function of two important dimensionless numbers: the Stokes deformation number and maximum granule pore saturation [10].

Granule deformation during impact can be characterized by Stokes deformation number, which is the ratio between impact energy and granule dynamic strength [10,23,24]:

$$St_{def} = \frac{\rho_g v_c^2}{2\sigma_p}, \tag{7}$$

where ρ_g is the granule density and v_c is the representative collision velocity for the granulator.

Granule dynamic strength can be identified as following [24]:

$$\sigma_p = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\mu\pi v_p}{16 d_{3,2}}, \tag{8}$$

where ε is the granule porosity, $d_{3,2}$ is the Sauter mean diameter of the granules' constituent particles, μ is the granulating liquid viscosity and v_p is the relative velocity of moving particles after impact.

Maximum granule pore saturation can be used as a measurement of liquid content [10,25]:

$$S_{\max} = \frac{w\rho_s(1-\varepsilon_{\min})}{\rho_l \varepsilon_{\min}}, \tag{9}$$

where w is the ratio between liquid and solid masses, ρ_s and ρ_l are solid particles and liquid density respectively, $\varepsilon_{\min}$ is minimum porosity for the particular set of operating conditions.

The boundary between breakage behaviour and no breakage behaviour (i.e. steady growth–crumb regime boundary) was experimentally established by Tardos et al. [23] and resulted to be $St_{def} \sim 0.2$. Iveson et al. [10] found that this boundary occurred at $St_{def} \sim 0.04$. The boundary between steady and induction growth occurred at St_{def} between 0.001 and 0.003.

The Stokes deformation number was therefore estimated for each granulation experiment in Table 2. The procedure aims at locating the granulation system conditions in the growth regime map, in order to identify the state related to granulation with water, or rather, E1 and E2.

The ratio between liquid mass and powder mass can take the place of maximum granule pore saturation for sake of simplicity in the comparison between the three different systems [10]. The velocity v_c and v_p are assumed to be 15% of the impeller tip velocity during the wetting phase [25].

ε and ρ_g are assumed to be respectively the average granule porosity and density of the final granules (see Table 4). Mercury porosimeter and helium pycnometer were used for characterizing the granules belonging to the 600–800 μm size fraction. Several samples of about 1 g each were analyzed. As can be noted from the values in Table 4, E1- and E2-based granules show lower porosity and density values.

The conditions related to the three different granulation systems are represented in the growth map of Fig. 6. Stokes deformation numbers were estimated using Eqs. (7) and (8).

The comparison in Fig. 6 can be considered a first qualitative estimation since some approximations are involved in the derivation of Stokes deformation number, but a considerable difference can be noted between conditions related to water-granulation and E1 or E2 granulation.

As described by Bouwman et al. [11], different material exchange mechanisms are exhibited increasing the Stokes deformation number: distribution, deformation (respectively steady growth and induction area in Fig. 5, lower Stokes deformation num-

Table 4
Average granule porosity, granule density and mean pore diameter for the granules obtained using the three different liquid binders.

Liquid binder	Granule porosity (%)	Granule density (kg/m^3)
Water	60.7 ± 1.3	1470.6 ± 0.5
E1	53.9 ± 0.9	1365.6 ± 0.2
E2	53.5 ± 1.0	1361.3 ± 0.3

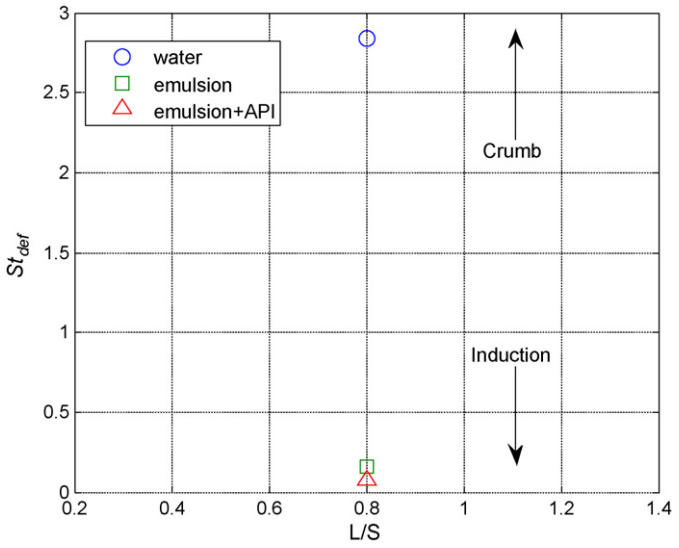

Fig. 6. Growth regime map with points related to the three different systems: granulation using water, emulsion and emulsion containing the drug (SEDDS) as liquid binders.

ber) and disintegration mechanism (crumb areas in Fig. 5, higher Stokes deformation number).

Water-granulation conditions seem to belong to the disintegration mechanism area: granules tend to be less spherical, as can be deduced from Figs. 1 and 2. This mechanism occurs when granules quickly grow and break in fragments. The causes are mainly the low viscosity of water and the granules brittleness.

E1 and E2 granulation conditions are very close to each other in the growth map. High viscosity binder promotes a distribution/deformation mechanism: granules grow more slowly and the fragmentation propensity is lower due to a higher shear resistance. Results show more spherical granules which are slightly dependent on the operating conditions during the massing phase (see Figs. 1 and 2).

Similar results were obtained by Bouwman et al. [11]: in this work a formulation mainly composed of cellulose or lactose was processed using high-shear granulation with water or viscous binders. The viscous binder strongly lowered the Stokes deformation number, thus leading to rounder granules with smoother surface. On the other hand, granules obtained using water as liquid binder resulted to be less spherical and presented rougher surface.

As can be noted in Fig. 6, St_{def} for water-granulation results to be higher than breakage/non-breakage boundary [10,23]. Similar or higher St_{def} values were obtained for similar systems using water as liquid binder [11]. Notwithstanding this discrepancy, agglomeration clearly occurred during all the experiments. This fact might be due to the presence of a small amount of viscous polymer (PVP) within the initial formulation. Accordingly, the actual viscosity in Eq. (8) might be higher, thus lowering the Stokes deformation number.

Another explanation of this discrepancy might consider possible errors in (over)estimating impact velocity in Eq. (7). As suggested by Litster and Ennis [15], it is difficult to estimate the characteristic speed to use to characterize a high shear mixer granulator and any error is greatly magnified, since St_{def} is proportional to impact velocity squared.

5. Conclusions

A study on the shape of granules obtained with three different liquid binders was performed. The analysis showed that increasing the viscosity using oil-in-water emulsions resulted in granules that were more spherical than those obtained with addition of simple water. The growth regime map was used to explain this observation. Water-based granules resulted to have higher Stokes deformation number and therefore resulted to be more deformable and brittle during their growth. Because of the intense breakage irregular granules were obtained. The opposite was obtained for emulsion bound granules. An analysis of the strength of dry granules revealed that those obtained with the emulsions were not weaker than those obtained with water, as it could be expected from the presence of a second oily phase. On the contrary the strength of emulsion based granules appeared to be independent of the operating variables such as massing time and impeller speed. This was particularly true for the case with emulsion plus API and represents a potential advantage for the production process. The collected observations show that using HSWG to obtain solid SEDDS is a viable solution which merit further consideration since many points still need to be disclosed. The role of the binder surface tension for example was not considered here but just as an anticipation of future research directions let notice that the trends of binder surface tension in Table 3 and of the Stokes deformation number in Fig. 6 are the same indicating a possible important role of this variable on the granule growth mechanism.

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