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Influence of process variables on the properties of simvastatin self-emulsifying granules obtained through high shear wet granulation

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Abstract

Improvements of the oral bioavailability of lipophilic drugs can be obtained using lipidic formulations such as the self-emulsifying drug delivery systems. The high shear wet granulation (HSWG), using microemulsions as binder, is a viable process to produce self-emulsifying granules. However only few information is present in literature on the effect of process variables on the properties of the granules obtained with these binders. Consequently, this article compares the effects of some relevant experimental variables (impeller speed and massing time) on the final technological and pharmaceutical properties of the granules produced using simple water, or alternatively, a microemulsion as binder and containing simvastatin (SV) as model drug. The effects of the variables were determined by evaluating the granule median diameter, their particle size distribution, roundness, disintegration time and dissolution rate of SV. Results clearly demonstrated that the microemulsion-based process was less sensitive to operating conditions than the water-based process. With microemulsion the nucleation process and growth regimes were more difficult to control, resulting in products with broader PSDs. At the same operating conditions microemulsion-based granules were more brittle but rounder and showed smaller median diameter compared to water-based granules. The dissolution rate of simvastatin was not significantly affected by the operating conditions.

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1. Introduction

In order to improve the oral bioavailability of lipophilic drugs, in recent years much attention has been focused on lipidic formulations, with particular emphasis on self-emulsifying drug delivery systems (SEDDS). The clinical usefulness of the SEDDS is evident from the commercially available formulations containing cyclosporin A, ritonavir and saquinavir (Strickley, 2007; Talegaonkar et al., 2008). SEDDS are mixtures of drug, oils, surfactants and/or co-solvents which form fine oil-in-water emulsions upon dilution with aqueous medium or *in vivo* administration. The digestive motility of the stomach and intestine provide the agitation necessary for the self-emulsification process (Hauss, 2007; Gursoy and Benita, 2004). The small oil droplets produced by self-emulsification provide a large interfacial area for pancreatic lipase and promote rapid release of the drug. The surfactants are also able to improve drug bioavailability by various mechanisms including improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased P-glycoprotein-mediated efflux. The key step for SEDDS formulation is to find a suitable oil-surfactant mixture that can dissolve the drug within the required therapeutic concentrations. Liquid SEDDS can then be used to fill either soft or hard gelatine capsules (Porter et al., 2008; Costantinides, 1995).

The drawbacks of SEDDS include high manufacturing costs, interaction of the fill with the capsule shell and problems due to storage temperature (Prajapati and Patel, 2007; Pouton, 2000). These difficulties can be avoided by preparing solid self-emulsifying drug delivery systems (solid-SEDDS) involving the solidification through adsorption of SEDDS on powders or nanoparticles to create a solid dosage form. Consequently, the solid-SEDDS combine the advantages of solid dosage forms (e.g. low production costs, high stability and reproducibility) with those of SEDDS (i.e. enhanced solubility and bioavailability) (Atef and Belmonte, 2008; Balakrishnan et al., 2009; Tang et al., 2008). A versatile way to obtain solid forms is the high shear wet granulation (HSWG) process (Cavinato et al, 2010a, Cavinato et al., 2010b; Cavinato et al., 2011). Some studies have also demonstrated that it is possible to incorporate a self-emulsifying system into microcrystalline cellulose using extrusion/spheronization and high shear granulation processes (Newton et al., 2001; Franceschinis et al., 2005). It has been also found that for this to be possible, it is necessary to introduce water into the SEDDS in order to form an oil-in-water microemulsion to be used as a binding agent.

However, information about the effect of process variables on granule characteristics when a microemulsion is used as granulating liquid is very limited in the literature. Consequently, the purpose of this investigation was to compare the effect of operating variables such as impeller speed and massing time on granule properties (mean diameter, particle size distributions - PSD, shape and disintegration time) when an oil-in-water microemulsion is used as granulating liquids. For comparison also water as binder was used in parallel experiments. Since the self-emulsifying granules are designed to increase the solubility of poorly water-soluble drugs, a class II model drug, simvastatin (SV), was included in the granulating liquid. Consequently, also the influence of experimental conditions on dissolution rate of SV has been evaluated.

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2. Experimental

2.1. Materials

Simvastatin (SV) EP-grade (d_{10}=2.8 μm; d_{50}=8.9 μm; d_{90}=23.1 μm) was supplied by Polichimica (Bologna, Italy), Propylene glycol-monolaurate (Lauroglycol™ 90), Medium chain triglycerides (Labrafac™ Lipophile WL1349), Propylene glycol mono-caprylate (Capryol™ 90) and Polyglyceryl oleate (Plurol Oleique® CC 497) and Diethylene glycol-monoethyl-ether (Transcutol® HP) were obtained from Gattefossé (Saint-Priest, France). Polyoxyl-35-castor oil (Cremophor® EL) was supplied by BASF (Ludwigshafen, Germany) and Monohydrate Lactose (Lac) by Meggle (Wasserburg, Germany). Polysorbate 80 (Tween 80), Microcrystalline cellulose (MCC) and Polyvinylpyrrolidone K 90 (PVP) were obtained from Acef (Fiorenzuola D'Arda, Italy). All the other chemicals and solvents were of analytical grade and were used without further purification.

2.2. Solubility studies and pseudo-ternary phase diagram study

Solubility studies were conducted by placing an excess of SV in a 2 ml glass vial containing 1 g of each excipient. Mixtures were then vortexed and kept at 25°C for 24 h in a thermostated shaking water bath to facilitate solubilization. The samples were then centrifuged at 5000 *g* for 10 min to remove the undissolved drug. The supernatant was taken and diluted with an proper solvent for SV quantification using a high performance liquid chromatography (HPLC) system consisting of LC-6A pump (Shimadzu Liquid Chromatograph, Kyoto, Japan) and UV-vis detector (Shimadzu UV Spectrophotometric Detector SPD-6°, Kyoto, Japan). The chromatographic column was a XDB-C8 column (Eclipse, Agilent, 5 μm 150mmx4,6mm). The amount of SV was determined following the conditions reported by Alvarez- Lueje (Alvarez- Lueje et al., 2005). A mobile phase constituted of a mixture of pH 4 phosphate buffer and acetonitrile (35:65) was pumped isocratically at a flow rate of 1 ml/min. A 100 μl volume was injected onto the column and the effluent was monitored at 238 nm.

The pseudo-ternary phase diagrams of oil, surfactant/co-surfactant, and water were developed using the water titration method. Mixtures of oil and surfactant/co-surfactant at certain weight ratios were diluted with purified water in a drop-wise manner. Each mixture was observed visually. The tendency to emulsify was judged good when droplets spread easily in water and formed a fine milky emulsion. It was judged as bad when there was poor or no emulsion formation. For each phase, diagrams at a specific ratio of surfactant/co-surfactant, 1:1, 1:2 and 1:3 (w/w) were used. Each microemulsion was prepared by loading 2% (w/w) of SV.

2.3. Characterization of microemulsions

2.3.1. Stability evaluation and determination of microemulsion viscosity

The stability of microemulsions as a function of storage time was routinely evaluated by visual inspection of the samples on a daily basis over a period of 4 weeks. Stable systems were identified as those free of any physical change, such as phase separation, flocculation and/or precipitation. Stability was monitored at room temperature. Stable microemulsions were characterized by a viscosimetric analysis using a Rotovisco RV 20 viscometer (Haake, Karlsruhe, Germany) and a rheocontroller RC 20 with M5 sensor system. Measurements were taken at shear rates from 0 to 700 sec^{-1} at 20°C using NV equipment.

2.3.2. Droplet size of microemulsion

A volume equal to 1 ml of each microemulsion was diluted with 200 ml of simulated intestinal fluid and gently mixed. The droplet size distribution of the resultant microemulsions were determined using laser light scatter technique (Malvern Hydro 2000 Malvern, Worcestershire, UK). The results are averaged from three replicated experiments.

2.3.3. Interaction between powders and granulating liquid

The interaction between the powders and the granulating liquid was evaluated by measuring the liquid-solid contact angle using sessile drop method (Susana et al., 2012). Magnified videos of binder drops falling from a tube and lying on dry powder mixture (70% (w/w) of MCC, 27% (w/w) of Lac and 3% (w/w) of PVP) were filmed using a fast digital camera (FastCam PCI 1000, Photron) at 250 frames per second. The time for complete sinking of the droplet was then precisely measured and referred to as drop penetration time (Susana et al., 2012).
The liquid surface tension was estimated using the equation (Middelman, 1995):

$$\gamma_{LV} = 0.244 \frac{d^3 \rho g}{D}$$

where d and D are droplet and tube diameters, ρ and g are the liquid density and the gravity respectively.

2.4. Granulation procedure

The granules were obtained using a one-step high shear mixer Rotolab (IMA SpA, Lucca, Italy). Briefly, the main part of the apparatus is a 2 liters thermostated bowl equipped with an impeller (minimum 120 rpm, maximum 1200 rpm speed) and chopper with a working speed of 3000 rpm. The machine is also equipped with a tilting system used to move the material during drying or massing time.

<Table 1>

In order to evaluate the effect of the two experimental variables selected (impeller speed and massing time) on granule properties using both water and microemulsion as granulating liquid, the granulation experiments were planned using an experimental design technique. In particular, a factorial plan was used where two variables (impeller speed and type of granulating liquid) were studied at 2 levels and one variable (massing time) was studied at 3 levels as shown in Table 1.
The granulation procedure and composition of solid carriers were standardized on the basis of preliminary trials. A mass of 200 g of powder mixture comprising 70% (w/w) of MCC, 27% (w/w) of Lac and 3% (w/w) of PVP was dry-mixed using an impeller speed of 120 rpm for 10 min. Successively, 160 g of granulating liquid (water or microemulsion) containing 2% (w/w) of SV was dripped on dry powders at a flow rate of 10 ml/min. In particular, in preparing water-based granules, the SV was suspended in water before the wetting phase. Instead, for the microemulsion-based granules, the drug was dissolved in the oil phase before emulsification. After the wetting phase, the impeller speed and massing time were varied according to the experimental plan reported in Table 2. Finally, the granules were dried at 40°C in a ventilated oven until constant weight was

achieved. Dry granules were sieved in order to remove lumps larger than 3 mm and stored in tightly-sealed bags.

<Table 2>

2.5. Characterization of granules

2.5.1. Size and shape analysis

For the size distribution analysis, 100 g of granules were poured over a set of sieves (2000, 1000, 800, 600, 500, 400 and 300 μm). A vibrating apparatus (AS 200, Retsch, Hamburg, Germany) was used at medium vibration level for 10 min. The fractions were then collected and weighted. The results of the particle size analysis (PSD) were presented as cumulated distribution (Allen, 1997).

Fifty granules, randomly selected from the modal size fraction of each batch of granules, were used for shape characterization using a digital camera (DBK-61BUC02, 1/2" CMOS, 2048x1536, The Imaging Source, Bremen, Germany) mounted on an inverted microscope (Olympus IX51, Hamburg, Germany). Granules with a size range of 600-800 μm were analysed under a magnification of 40 times. The analysis was performed using customized software written in MATLAB. The shape of the granules was evaluated using the projected area of the particles in terms of roundness Φ_R which can be defined as:

$$\Phi_R = 4\pi A_P / P^2$$

Where A_P is the projected area and P its perimeter. Particle roundness values lie between 0 and 1 and the greater the value, the rounder is the projected area of the granule (Nazar et al., 1996).

2.5.2. Disintegration test of granules

The disintegration time of the granules was measured in 200 ml of SIF at 37°C using a disintegration apparatus (FUI XII ed., Sotax DT2, Sotax, Allschwil, Switzerland) modified with a 100 μm wire net at the base of the tubes. Granule samples of 200 mg from each formulation (600-800 μm size range granule) were tested (n=6). The endpoint was taken as the time at which no obvious particles were present on the sieve in each disintegration basket.

2.5.3. *In vitro* dissolution tests

In vitro drug dissolution tests were performed using the USP 24 method with a dissolution apparatus 2 (Sotax AT7 Smart, Sotax, Allschwil Switzerland) at 100 rpm. The dissolution tests were carried out at 37±0.5°C in 900 ml of simulated intestinal fluid (SIF, phosphate buffer pH 6.8) as dissolution medium using 600-800 μm size range granules.

During the release studies, 1 ml of dissolution medium sample was removed and filtered; SV quantification was performed using the HPLC technique as reported in 2.2. The volume removed was replaced each time with fresh medium. Results are averaged from three replicated experiments.

3. Results and Discussion

The absorption of class II molecules can be greatly improved by formulating them in SEDDS (Hauss, 2007; Gursoy and Benita, 2004; Porter et al., 2008) that are usually found in liquid

form. The drawbacks of these formulations (Costantinides, 1195; Prajapati and Patel, 2007) can be avoided by preparing solid-SEDDS. Such systems require the solidification by adsorption of SEDDS into powder/nanoparticles to create solid dosage forms. Although Franceschinis and co-worker (Franceschinis et al., 2005; Franceschinis et al. 2011) have already demonstrated that it is possible to produce solid-SEDDS by high shear granulation using a microemulsion as granulating liquid, few information is found in the literature on the link between this type of granulating liquid, the operating variables (such as impeller speed and the massing time) and the final granule properties. Consequently, the purpose of this investigation was to compare the effects of these variables on the granule properties when water or an oil-in-water microemulsion were used as granulating liquids. In order to evaluate also their effect on the drug release, simvastatin an hydroxymethylglutarylcoenzyme A (HMG-CoA) reductase inhibitors having a water solubility of 0.0010 mg/ml was selected as model drug.
The appropriate formulation to convey simvastatin (SV) was selected on the basis of a preliminary study which involved the evaluation of SV solubility in different excipients in order to identify those in which the highest drug solubility can be achieved. The results obtained are reported in Figure 1.

<Figure 1>

Among the surfactants tested, Cremophor® EL (HLB 12-14), a polyoxyl castor oil derivative, was selected because it demonstrates greater drug solubility. The literature also reports that it is able to enhance drugs intestinal absorption and inhibit P-glycoprotein (Ge et al. 2008; Rege et al., 2002).
Among the oil phase tested, Lauroglycol™ 90 was selected since it showed higher drug solubility than Labrafac™ WL1349 and Capryol™ 90 and it has a good ability to form a microemulsion with Cremophor® EL. Finally, Transcutol® HP was selected as solvent and co-surfactant because of its good drug solubility resulting in improved drug loading.
In order to identify the mixtures of Lauroglycol™ 90, Cremophor® EL, Transcutol® HP and water able to form microemulsions, pseudo-ternary phase diagrams were realized using the water titration method. In particular, three pseudo-ternary phase diagrams were constructed using a mixture of surfactant and co-surfactant (Cremophor® EL and Transcutol® HP, respectively) weight ratios of 1:1, 1:2 and 1:3. Each microemulsion was prepared by solubilizing 2% (w/w) of SV in the mixtures of Lauroglycol™ 90, Cremophor® EL and Transcutol® HP before to add water. Microemulsions were daily observed visually and those which did not show any signs of separation, flocculation and/or precipitation after a period of 4 weeks were considered stable and characterized by viscosity measurements. The viscosity values are reported in Table 3. Since preliminary trials demonstrated that microemulsions with viscosity larger than 0.030 Pa*s could not dripped with our apparatus, only microemulsions with viscosity lower than this value were analysed by laser light scattering measurements (see Tables 3 and 4).

<Table 3>

<Table 4>

Although the modal droplet size was lower (it ranged from 0.11 to 9.58 μm), the span values highlighted that the formulations A16 and C16 have polymodal distributions which could potentially lead to coalescence and instability phenomena.
Among the remaining microemulsions, formulation named C14 was selected in consideration of its small modal droplet size (0.111 μm) and of the large amount of SV which was able to vehicle thanks to the presence of 15% of Transcutol® HP.

In order to evaluate the different behavior of the granulating liquid during the granulation procedure, the two granulating liquids (water and microemulsion C14) were characterized by liquid-solid contact angle, droplet penetration time and liquid surface tension measurements. Table 5 shows that microemulsion behaved as a hydrophobic liquid (Susana et al., 2012).

<Table 5>

Even though the microemulsion surface tension was half than that of water, the resulting penetration time was two order of magnitude larger than that of water. This can be justified by the contact angle value which was larger than 90° for microemulsion, indicating a poorer wetting ability, and by the larger viscosity which may be attributed to the 40% of a mixture of oil phase, surfactant and co-solvent. These differences were expected to impact on the granulation process and on the properties of the final granules. An high value of penetration time indeed might lead to a poorer and slower liquid distribution during the wetting phase of the granulation process. Consequently, when the microemulsion was used as granulating liquid the formation of a broader nuclei size distribution and a more difficult to control agglomeration process were expected (Litster and Ennis, 2004; Litster et al., 2001; Hapgood et al., 2003).

<Figure 2>

In order to verify this hypothesis and to evaluate the effect of the two selected experimental variables (impeller speed and massing time) on the final properties of granules (mean diameter, PDS, disintegration time, roundness and drug dissolution rate), the granulation experiments were designed using a factorial plan ($3^1 \times 2^2$) consisting in 12 experiments as reported in Table 2. Granules were produced using granulation procedure described in section 2.5. At the end of the process, granules were dried until constant weight and sieved in order to evaluate mean diameter. The results of the PSD analysis are presented as cumulated distribution in Figure 2.

As expected from the penetration time values, the PSDs obtained with microemulsion were broader then that with water. Figure 2 shows indeed that for water-based granules the d_{10} and the d_{90} are roughly 500 and 3000 μm, while for microemulsion-based granules the d_{10} was always smaller than 500 μm and the d_{90} always larger than 3500 μm, meaning larger PSDs.

<Figure 3>

This behaviour indicated that at 10 ml/min of liquid addition rate, the impeller speed (600 and 800 rpm) was not sufficient to mechanically promote the homogeneous dispersion of the microemulsion. This can be better understood by looking at the nucleation regime map in Figure

3(a) (Litster et al., 2001; Hapgood et al., 2003) where the efficiency of liquid addition, represented by the dimensionless spray flux number Ψ_a, is compared with the efficiency of liquid absorption into the powder, represented by the dimensionless drop penetration time, τ_p. Because of the relatively inefficient liquid addition method (dripping) the system was surely working outside of the drop controlled region. The system probably worked in a range of Ψ_a where the penetration time can be relevant to determine the nucleation regime. So for water (with τ_p two order of magnitude lower) the nucleation probably occurred in the intermediate regime while for the microemulsion the nucleation occurred in the mechanical dispersion regime (Figure 3a), which is never optimal (Litster et al., 2001; Hapgood et al., 2003).

From Figure 2 it can be also observed that the median diameter, d_{50}, was affected by the binder type and this can be observed more clearly in Figure 4 where all the median diameters are directly compared. As a first observation, the granules produced using water resulted in a larger median diameter than those with the microemulsion. This fact could be explained in terms of number of liquid bridges. When microemulsion was used as liquid binder only the 60% in weight was represented by water available to produce firm liquid bridges between particles. It is worth remembering the lipophobic character of the powder mixture (Table 4) and so the impossibility for the oily phase in the microemulsion to establish firm capillary bridges. In agreement with these observations, Podczeck et al. (Podczeck et al., 2009) reported that using an emulsion as a binder may increase the required amount of granulating liquid. Using microemulsions therefore not only reduced the number of capillary bridges (supported only by water) but the presence of an intrinsically lubricating medium (the oily phase), generated more plastic/deformable granules. This directly affected the granule growth regime increasing the deformation Stokes number, St_{def} (Litster et al., 2001). This number is the ratio between the impact energy of two colliding granules and the work σ_y to plastically deform the granules:

$$St_{def.} = \frac{\rho v_c^2}{2 \sigma_y}$$

where v_c is the representative collision velocity of the granules within the mixer (proportional to the impeller tip speed) and ρ is the granules density.
If the granules are rigid (small St_{def}) their growth is retarded (induction regime), however if they are too plastic the impact energy will probably break them instead of promoting coalescence. Only a balance between impact energy and particle strength can provide a smooth growth of the granules.
The use of microemulsion increases the granule plasticity (since σ_y is reduced) and drive the system in the so called crumble regime, where the granules can not resist to the shear forces imposed by the impeller (Figure 3b). The growth is compromised resulting in a consolidation and reduction of granule size. Figure 4 shows indeed that for microemulsion the median size slightly reduces by increasing the granulation time and the impeller speed.

<Figure 4>

An even more interesting behaviour is given by the water-based granules. It can be seen indeed from Figure 4 that the size of the granules increases with time at the lower impeller speed (600 rpm), while it decreases at the higher impeller speed (800 rpm). This behaviour can be again

explained with the granule growth regime map of Figure 3b. At 600 rpm the system is probably in the steady growth regime and the size of the granules increase smoothly with time. However increasing the impeller speed at 800 rpm cause an increase of the St_{def} (larger impact velocity between the granules) and moves again the systems towards the crumb regime so that the size of the granules decreases with the massing time. We can also notice the contrasting effect of impeller speed on granule size. At high impeller speed and for low granulation time the size is maximum. It means that for short massing time the high impeller speed provides intense shear forces on the wet mass which contribute to consolidated the granules squeezing out the liquid contained into the pores and promoting further coalescence between the granules. However prolonging the massing time, up to the point when no further liquid is available for granule growth, becomes detrimental to granule size since breakage becomes dominant over coalescence.

The different strength of the granules can be indirectly deduced by the disintegration time test. The 600-800 μm size range of each sample was characterized by disintegration time and morphological analysis. The results obtained are summarised in Figures 5 and 6.

<Figure 5>

<Figure 6>

The disintegration test gives an indication of the internal structure of the granules, since longer times can be related to a larger strength of the granules. The data obtained show that the water-based systems have much larger values of disintegration time than microemulsion-based granules. This behaviour is coherent with the observations of Vervaet et al. (Vervaet and Remon, 1994) in preparing systems containing high concentrations of a non-ionic surfactant. In our systems, the lactose crystallization after water removal gives rise to the solid bridge. So an initially larger number of capillary bridges during the growth phase is reflected by a larger number of solid bridges after drying of the granules. The larger the number of solid bridges, the greater the time needed for the aqueous medium to migrate in the granule structure and to solubilize the solid bridges, which leads to disintegration of the granule (Ennis, 2006). Consequently, when microemulsion is used as binder the final number of solid bridges is reduced and disintegration time decreases. Furthermore, in microemulsion-based granules, the presence of an oil phase lubricating the contact points between solid particles makes the final granule soft and less resistant. Figure 5 shows that also the disintegration time has a dependence on massing time for both types of binder, in particular the longer the massing time the higher disintegration time. This effect is most evident in water-based granules. It can also be noted that for water-systems the disintegration time increases at higher impeller speed. It is evident the positive effect of the massing time on the consolidation of the granules, which is independent of the growth regime they belong to (steady growth or crumb).

Finally, the granules underwent a morphological analysis from which the roundness Φ_R was obtained. As seen in Figure 5, using both types of binder, an increase in massing time produced an increase in Φ_R. The impeller speed instead, at least in the range of speed investigated, did not affect significantly the shape of the granules. Even though with small differences, the more plastic granules (microemulsion-based) resulted in larger value of roundness.

In order to verify the effect of the process variables on drug dissolution rate, granules

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also underwent a dissolution test. Simvastatin is a poorly water-soluble drug and in the absence of a surfactant is unable to dissolve in simulated intestinal dissolution medium without enzymes. As a consequence, granules produced using water as binder are not able to release simvastatin. On the other hand, self-emulsifying granules are able to increase the dissolution rate of simvastatin, and the dissolution profiles obtained are used to extrapolate the amount of SV released after 10, 30 and 70 minutes. The results are reported in Figure 7 and show that the amount of SV released after 10, 30 and 70 min depended on massing time. In particular, data show that the lower the massing time, the greater the amount of released SV.

<Figure 7>

Also these observations agree with the results discussed so far, in particular with the disintegration time data and can be attributed to the increased level of granules consolidation occurring as an effect of longer massing times.

Conclusions

Granulation experiments were carried out in high shear wet conditions using two different binders (water and microemulsion) and operating conditions (impeller speed and massing time). The results showed that the granulation process (nucleation up and growth) are greatly influenced by the type of binder. In particular, when water is used as binder the final characteristics of the granules are influenced by all the experimental variables studied, so that it is relatively easy to control the product properties through the operating condition. In order to produce solid self-emulsifying drug delivery systems, water was replaced with an oil-in-water microemulsion. In this case (at least in the variable ranges examined), the system was relatively insensitive to impeller speed and could only be moderately modified through the massing time. On the whole the wet granulation process in a high shear mixer has proved to be a useful technique for producing self-emulsifying granules and increase drug dissolution rates obtaining products with acceptable technological characteristics. In particular product shape (roundness) was even better than that obtained for water-based granules. With microemulsion however the nucleation process and the growth regimes were more difficult to control, resulting in products with broader PSDs. Further studies will be carried out in order to verify the possibility of improving this technological property by reducing the dimensionless spray flux number (for example by spraying the emulsion instead of dripping it), or by decreasing the Stokes deformation number (for example by modifying the composition of solid carrier or reducing the impeller speed).

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Table 1

Franceschinis E. , Santomaso A.C., Benda L., Perissutti B., Voinovich D. , Realdon N., Influence of process variables on the properties of simvastatin self-emulsifying granules obtained through high shear wet granulation (2015) *Powder Technology, 274, 173-179.*
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Table 1 – Variables (X_i) and number of levels considered in this study.

Variables (X_i)	Codified levels	Experimental values
X_1- Type of granulating liquid	1	Water
	2	Microemulsion
X_2- Impeller speed (rpm)	1	600 rpm
	2	800 rpm
X_3- Massing time (min)	1	2 min
	2	3 min
	3	5 min

Table 2 - Experimental plan.

Exp. n°	X_1	X_2	X_3	Type of granulating liquid	Impeller speed (rpm)	Massing Time (min)
1	0	1	0	water	600	2
2	0	2	0	water	800	2
3	0	1	1	water	600	3
4	0	2	1	water	800	3
5	0	1	2	water	600	5
6	0	2	2	water	800	5
7	1	1	0	microemulsion	600	2
8	1	2	0	microemulsion	800	2
9	1	1	1	microemulsion	600	3
10	1	2	1	microemulsion	800	3
11	1	1	2	microemulsion	600	5
12	1	2	2	microemulsion	800	5

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Table 3. Composition of stable microemulsion containing 2% (w/w) of SV and their viscosity values *n*=3).

Formulation	Water (%)	Lauroglycol ™90 (%)	Transcutol® HP (%)	Cremophore® EL (%)	Viscosity (Pa s)
A 14	60	20	10	10	0.084
A 15	70	10	10	10	0.076
A 16	80	10	5	5	0.007
A 18	60	30	5	5	0.024
A 19	50	40	5	5	0.030
A 20	40	50	5	5	0.061
A 21	30	60	5	5	0.081
B 14	60	20	6.67	13.33	0.100
B 15	70	10	6.67	13.33	0.061
B 17	70	20	3.33	6.67	0.021
B 19	50	40	3.33	6.67	0.062
B 20	40	50	3.33	6.67	0.141
B 21	30	60	3.33	6.67	0.108
C 14	**60**	**20**	**15**	**5**	**0.019**
C 15	70	10	15	5	0.018
C 16	80	10	7.5	2.5	0.004
C 17	70	20	7.5	2.5	0.007
C 19	50	40	7.5	2.5	0.037
C 20	40	50	7.5	2.5	0.057

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Table 4. Particle size of microemulsions having viscosity less than 0.030 Pa*s
*Span is calculated as $(d_{90}-d_{10})/d_{50}$

Formulation	Amount of SV vehicled (g/g)	Modal droplet size (µm)	Span* (-)
A 16	2128.4	0.342	3.983
A 18	3221.4	9.483	1.417
A 19	3767.9	4.954	1.358
B 17	2599.4	0.159	1.848
C 14	**4482.7**	**0.111**	**0.824**
C 15	3936.2	1.079	2.736
C 16	2241.3	0.132	38.891
C 17	2787.8	8.120	1.446

Table 5 - Properties of binders containing 2% (w/w) of simvastatin obtained from experimental measurements and image analysis.

Granulating liquid containing 2% (w/w) of SV	Density (kg/m^3)	Viscosity (Pa·s)	Liquid-solid contact angle (°)	Penetration time (s)	Liquid surface tension (mN m)
Water	1000	0.003	67	0.05	73.50
Microemulsion	995	0.017	108	5.01	38.24

FIGURES

Figure 1. Screening of SV solubility in seven different excipients

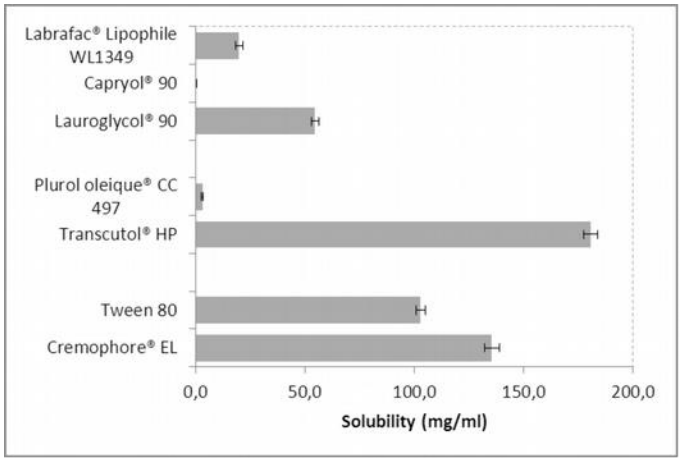

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Figure 2. Cumulated PSD of the granules obtained using water and microemulsion C14.

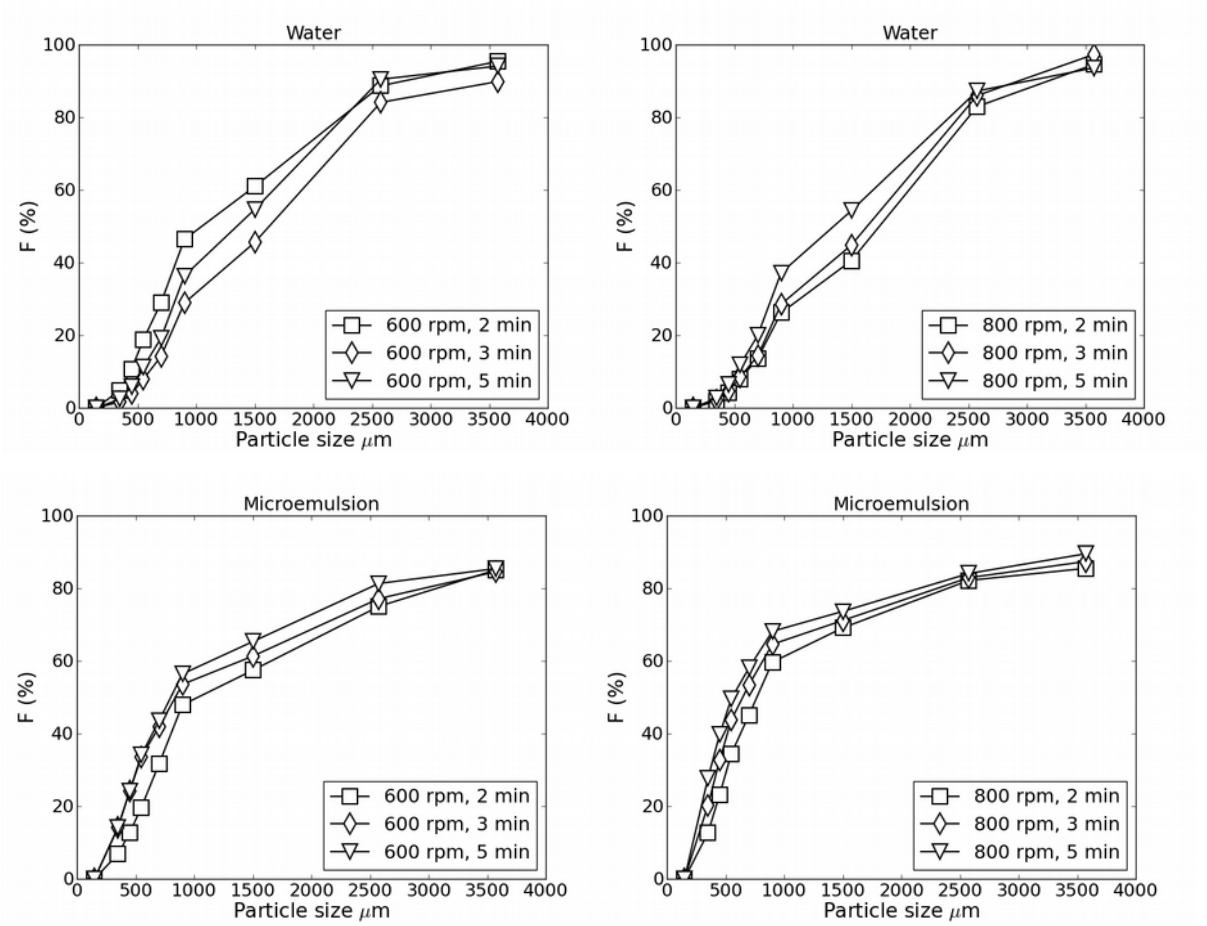

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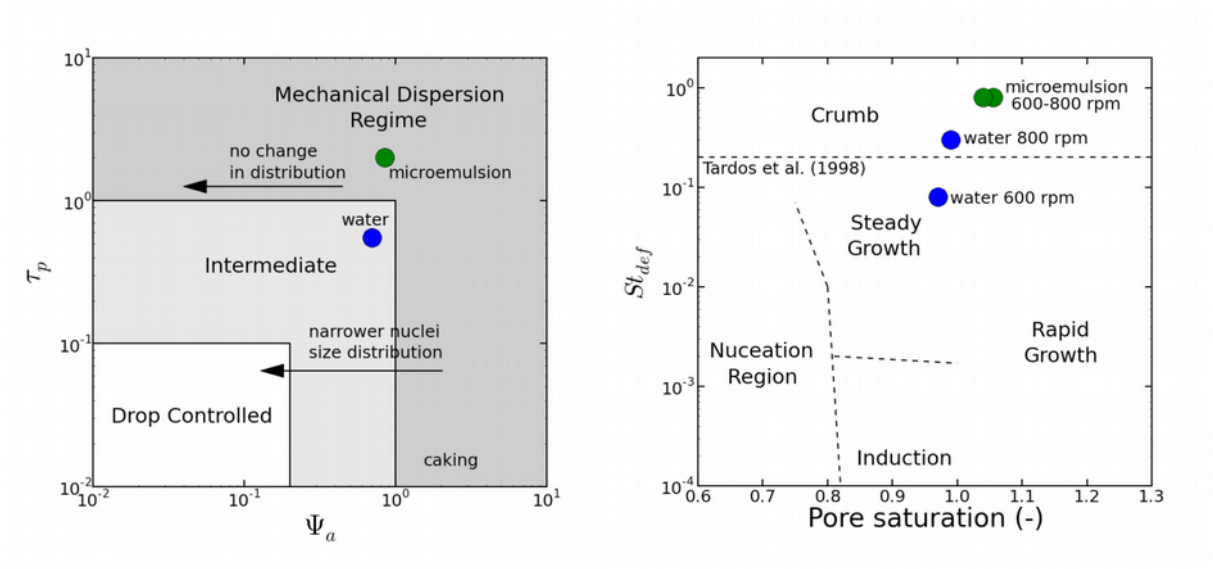
Figure 3. Nucleation (a) and growth regimes (b) maps. Comparison between water- and emulsion-based granules. The point positions are just qualitative. No attempts have been made to determine quantitatively the exact value of the dimensionless numbers. The *in situ* exact determination of the majority of the quantity involved (penetration time, recirculation time, powder surface velocity, binder viscosity in the mixture, granule yield stress and porosity) are very difficult to assess quantitatively. The dimensionless numbers have been therefore used just as an interpretative tool to explain the experimental evidences.



(a) (b)

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Figure 4. Median diameters of the granules as a function of massing time and impeller speed.

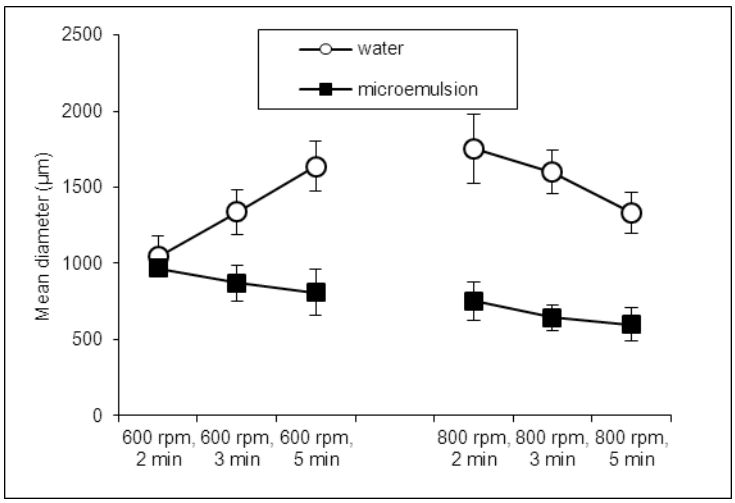

Figure 5. Disintegration time for water- and microemulsion based granules as a function of massing time and impeller speed.

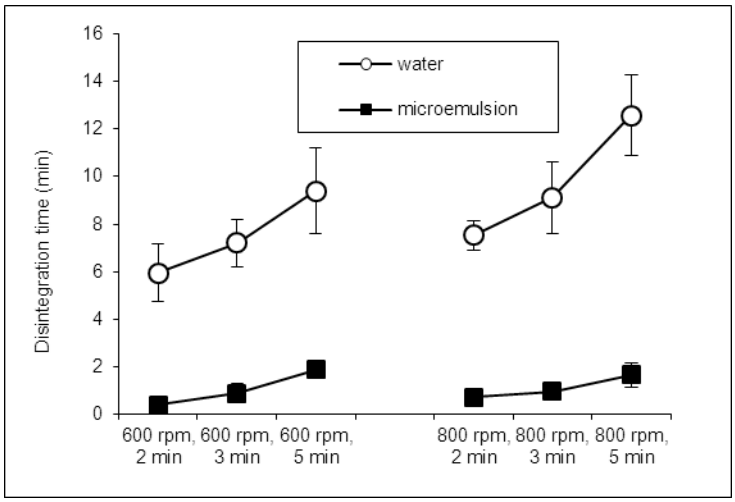

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Figure 6. Granules shape (roundness) for water- and microemulsion based granules as a function of massing time and impeller speed.

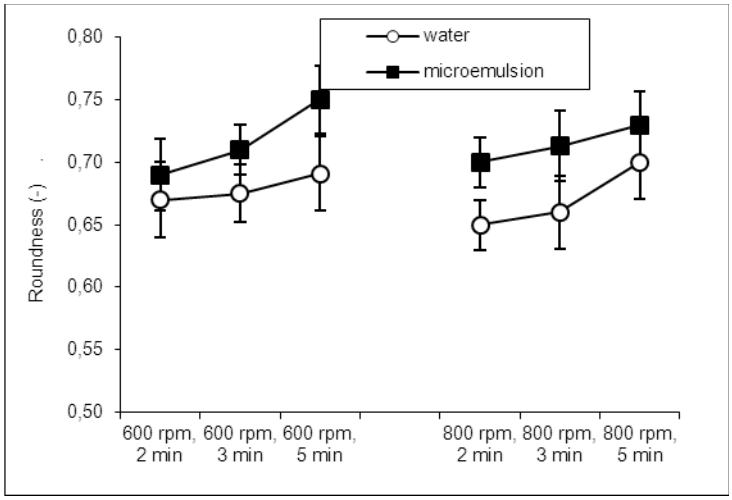

Figure 7. Dissolution rate for SV in microemulsion-based granules as a function of massing time and impeller speed.