Powder Technology 274 (2015) 173–179

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

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

E. Franceschinis [a,*], A.C. Santomaso [b], L. Benda [a], B. Perissutti [c], D. Voinovich [c], N. Realdon [a]

[a] PharmaTeG - Pharmaceutical Technology Group, Department of Pharmaceutical and Pharmacological Science, University of Padova, Via Marzolo 5, 35131 Padova, Italy
[b] APTLab - Advanced Particle Technology Laboratory, Department of Industrial Engineering, University of Padova, via Marzolo 9, 35131 Padova, Italy
[c] Department of Chemical and Pharmaceutical Sciences, University of Trieste, P.le Europa 1, 34127 Trieste, Italy

ARTICLE INFO

Article history:
Received 1 October 2014
Received in revised form 8 January 2015
Accepted 10 January 2015
Available online 15 January 2015

Keywords:
Self-emulsifying systems
Wet granulation
High shear mixer
Simvastatin
Microemulsion

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 are present in the 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.

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 [26,28]. 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 provides the agitation necessary for the self-emulsification process [13,15]. 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 gelatin capsules [8,22].

The drawbacks of SEDDS include high manufacturing costs, interaction of the fill with the capsule shell and problems due to storage temperature [23,24]. 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) [3,4,29]. A versatile way to obtain solid forms is the high shear wet granulation (HSWG) process [5–7]. 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 [11,20]. 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

* Corresponding author. Tel.: +39 049 8275339; fax: +39 049 8275366.
E-mail address: erica.franceschinis@unipd.it (E. Franceschinis).

http://dx.doi.org/10.1016/j.powtec.2015.01.026
0032-5910/

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

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.

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), and 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 a 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 an XDB-C8

Table 2
Experimental plan.

Exp. no.	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

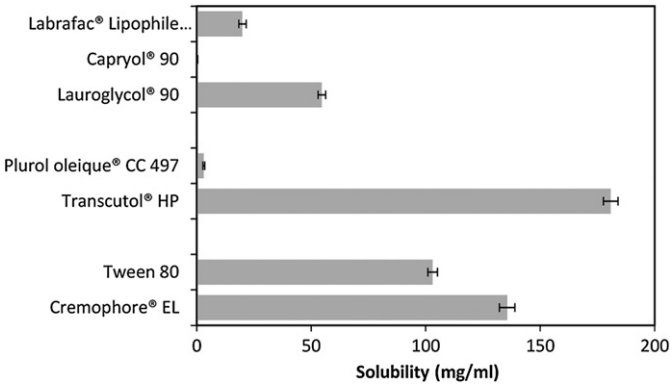

Fig. 1. Screening of SV solubility in seven different excipients.

column (Eclipse, Agilent, 5 μm 150 mm × 4.6 mm). The amount of SV was determined following the conditions reported by Alvarez-Lueje [2]. A mobile phase was composed 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

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

Data in bold indicates select formulation.