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European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 173–175
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Note

Nano- and micro-particulate formulations of poorly water-soluble drugs by using a novel optimized technique

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Received 9 November 2005; accepted in revised form 13 February 2006
Available online 6 March 2006

Abstract

A novel technique for the production of nano- and micro-particulate formulations of poorly water-soluble drugs has been developed. This technique involves the use of static mixer elements to provide fast precipitation by continuous turbulent mixing of two liquid flows, an aqueous phase and an organic phase, respectively. The objective of this study was to develop the mixer technique by investigating the influence of the element number on the particle size of the resulting dispersions. Four model active pharmaceutical ingredients (APIs) with a variety of polymers, lipids or surfactants underwent intensive mixing and the final suspensions showed a narrow size distribution. Parameters such as the flow rate and the temperature of the precipitated organic–aqueous phases were also significant in the reduction of particle size. Further development of the mixing technique led to reproducible and stable formulations with minimal excipient amounts. These formulations were spray- or freeze-dried to improve stability.

Keywords: Mixer technique; Poorly water soluble drugs; Precipitation; Microparticles; Nanoparticles

More than 40% of active substances during formulation development by the pharmaceutical industry are poorly water soluble [1]. There is a critical need to develop formulations for oral, injectable, inhalation and other delivery routes. A substantial factor that prevents the development of such substances is the limited dissolution rate. Therefore, several studies have been performed to overcome this hurdle. The aim of all these attempts is to increase the dissolution rate and thus to enhance absorption and bioavailability. This can be achieved by reducing the particle size in the micro- or nano-scale according to the Noyes–Whitney equation. Therefore, for this particular purpose, several approaches are used such as jet-milling, high pressure homogenization, supercritical fluid technology and spray-drying. Furthermore, the in situ micronization [2,3], spray-freezing into liquid (SFL) [4], continuous mixing chamber [5], grid mixer [6] and recently a microstructural mixer [7,8] have been also reported.

In this study, we further developed a precipitation technique by using a static mixer (Sulzer Chemtech AG, Switzerland) with 10–30 mixing elements. The main scope was to investigate the influence of the elements on the reduction of the particle size. The static mixer technique has been used by Gassmann and Sucker [9,10] to produce hydrosols followed by spray-drying but the study of critical parameters and further development was not disclosed.

In brief, the method comprises two steps: dissolution of the drug in a water miscible solvent and mixing of the resulting solution with an aqueous phase, composed of distilled water, with or without stabilizing agents. The drug precipitates as micro- or nanoparticles and the resulting dispersion is called a hydrosol.

Each loose element of the selected static mixer (SMX DN3) has a 3.2 mm diameter and 3.2 mm length. The mixer elements were welded into a stainless steel tube (Fig. 1) with 3.3 mm internal and 7.3 mm external diameter, respectively. They should be offset 90° to each other,

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doi:10.1016/j.ejpb.2006.02.004

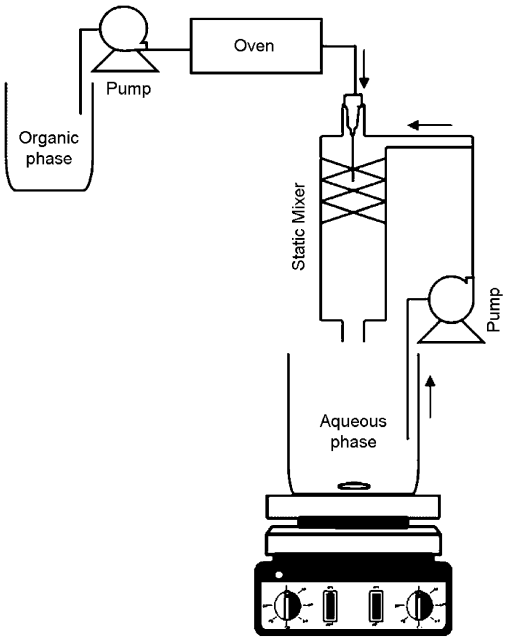

Fig. 1. Schematic diagram of static mixer set-up.

in order to obtain homogeneous mixing over the entire pipe cross-section. Although the horizontal or vertical installation attitude of the elements has no influence on the mixer efficiency, the vertical arrangement was chosen to ensure the entire wetting of the cross-section. The design of the tube is in such a way that the confluence of the two liquid flows takes place in the middle of the first element. This configuration ensures no mixing prior to the mixer entry. The tube was designed with two inlets at the upper side and an outlet at the bottom. Two peristaltic pumps (Ismatec, Zurich, Switzerland, and Millipore, Bedford, USA) control the flow rate of each phase. In order to control the temperature, particularly of the organic phase, an oven was adjusted between the pump and the inlet. The mixing was performed by the recirculation of the aqueous phase.

The precipitation of the aqueous–organic flows presumes very intensive and rapid mixing down to small length scales that the system is homogeneously mixed before particle formation initiates [11,12]. Several attempts have been made to achieve homogeneity as rapidly as possible by turbulent mixing. The great advantage of this assembly is the narrow time distribution and turbulent, homogeneous and reproducible mixing of the two liquids even with high viscosities. The latter characteristic gives the option to produce long-term stable formulations for different administration routes. Four APIs, progesterone (PRG), β-methasone valerate-17 (BMZ), carbamazepine (CBZ) and oxcarbazepine (OXC), each with different log *P* (Table 1), were used as model substances for the current study.

In the mixer technique, the organic phase is composed of a water miscible solvent, e.g., ethyl alcohol, acetone and optionally stabilizing agents such as surfactants and lipids (Table 2). The concentration of the drug depends on its solubility properties. Due to the mixer's capability for mixing high viscosity liquids, lipids or surfactants were dissolved in the organic phase. Organosoluble polymers could be also used in the aforementioned phase. As depicted in Table 2 several different polymers such as gelatine A (Sigma–Aldrich, Germany), hydroxypropylmethylcellulose (Metolose 90SH-100, HPMC 60SH-50, Shin–Etsu Chemical, Japan), lipids (Lipoid S75), and surfactants (Lutrol F-127, BASF, Germany – PEG-5 soy sterol, BPS-5, Nikko Chemical Japan) were used to produce nano- or micro-dispersions. The Lipoid S75 was used as a lipid carrier and the poloxamer F-127 as a surfactant in the organic phase.

Table 1
Partition coefficients and aqueous solubility of model APIs

Drugs	log *P*	Aqueous solubility (mg/100 ml)
Progesterone (PRG)	4.03	0.7
β-Methasone valerate 17 (BMZ)	3.98	0.6
Carbamazepine (CBZ)	2.67	13.0
Oxcarbazepine (OXC)	1.24	8.40

The decrease of the particle size and the formulation stability correlate with the effectiveness of the stabilizer. The use of the appropriate stabilizer is equally important to the above physical parameters [2].

In this study, the organic phase was mixed rapidly with the recirculating aqueous phase with different flow rates for each drug. One of the critical process parameters is the flow rate of both phases. When precipitation of the confluent phases occurs on high rates, the obtained particle size decreases significantly. Another important parameter was the temperature of the organic phase. The use of higher organic phase temperatures resulted also in lower particle sizes. By altering simultaneously the aforementioned parameters it was possible to manipulate the particle size (Table 2).

A rotary evaporator (Büchi, Switzerland) was used to evaporate the solvents. After the removal of the solvents, the particle size distribution of each formulation was measured by laser diffractometry using a Coulter LS230 (Coulter Electronics, Miami/USA) in connection with polarized intensity differential scattering (PIDS) assembly. The stability over time was evaluated as well. All formulations were stable between 1 and 3 days depending on the drug substance. Fig. 2 shows the decrease of the obtained particle size of each drug by increasing the number of mixer elements. The number of elements was 10, 20 and 30 and all experiments were repeated in triplicate. As it can be seen the mixer elements significantly alter the particle size.

Fig. 3 shows the cryo-transmission electron image of the BMZ nano-dispersion. It is obvious that BMZ is loaded within the nanosphere core.

Up to this point the static mixer technique has been used for poorly soluble drugs with 0.1 mg/100 ml water solubility [9,10]. The developments in this study have been proved also capable for CBZ and OXC with solubility greater than 1 mg/100 ml. The ratio of the organic/aqueous phase and finally the obtained particle size depends on the solubility

Table 2
Composition of aqueous/organic phase and experimental details of the Mixer technique for the model APIs (Temperature, 25 °C; organic flow rate, 50 ml/min, pH 7)

Organic phase drug/excipient	Aqueous phase	Flow rate$_{(aq)}$ (ml/min)	Temp$_{(org)}$ (°C)	$V_{org/aq}$	$R_{drug/excipient}$	Final drug loading (mg/ml)	Size ± SD (μm)
PRG, F127, S75	–	400	40	1/32	1/5.0	1.25	1.45 ± 0.17
BMZ, S75	HPMC	300	25	1/16	1/2.9	2.5	0.25 ± 0.03
CBZ, BPS-5	Gelatine	500	50	1/6	1/4.6	10	4.09 ± 0.47
OXC, BPS-5	HPMC	450	45	1/3	1/4.5	8.3	0.97 ± 0.11

The particle size corresponds to the mean volume diameter. $V_{org/aq}$, ratio of solvent/dispersion agent volumes; $R_{drug/excipient}$, ratio of drug/excipients; SD, standard deviation.

of the API in water. More hydrophilic drugs like CBZ and OXC require higher solvent volumes. It is important to remove the solvent because it could enhance the crystal growth of the dispersions. The dispersions were stable for several days. However, for long-term stability freeze- or spray-drying is required to obtain more stable forms. By increasing the mixer elements we managed to diminish the drug/excipient ratios. The maximum drug/excipients ratio is 1:5 (PRG).

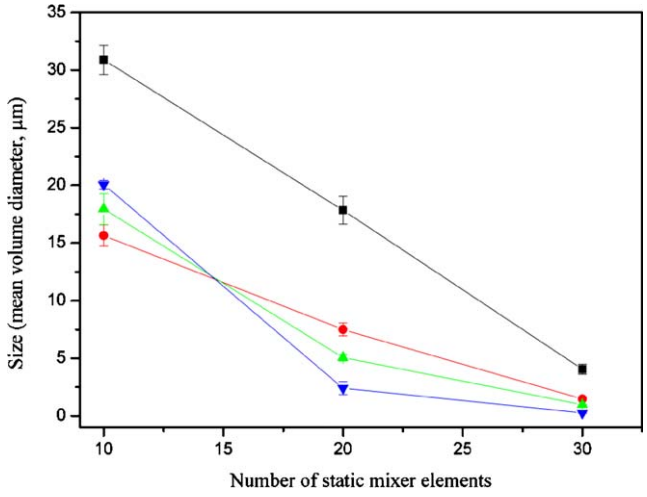

Fig. 2. Influence of mixer elements on the obtained particle size (■ CBZ, ● PRG, ▲ OXC and ▼ BMZ).

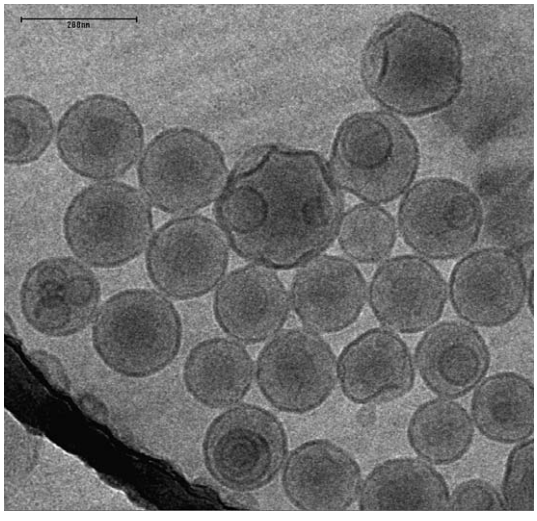

Fig. 3. Cryo-TEM image of BMZ formulation produced with the static mixer technique (30 elements).

In conclusion, the developed static mixer technique has been proved sufficient to produce formulations for different administration routes in the nano- or micro-scale by increasing the number of elements resulting in all the advantages we mentioned above. Additional improvement, except the number of elements, might be achieved by increasing the confluent flow rates and the organic phase temperature followed by a structured experimental design or a response surface methodology [12].

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