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Micronization of drugs using supercritical carbon dioxide

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Abstract

Particles from gas saturated solutions, a novel method for high pressure material processing, has been used for micronization of practically insoluble calcium-channel blockers nifedipine and felodipine and the hypolipidemic agent fenofibrate with the aim of increasing their dissolution rate and hence their bioavailability. Dependent on the pre-expansion conditions, a mean particle size of between 15 and 30 μm was achieved for micronized nifedipine and 42 μm for micronized felodipine. The particle size of processed fenofibrate, on the other hand, increased due to agglomeration. The highest dissolution rate was achieved by preparation of drug coprecipitates with PEG 4000.

Keywords: Supercritical fluids; PGSS process; Micronization; Dissolution; Nifedipine; Felodipine; Fenofibrate

1. Introduction

The use of supercritical fluids (SCFs) is becoming more and more important in the pharmaceutical field. Beside their extractive, chromatographic and applications in biochemical reactions, SCFs offer interesting applications in materials processing. In recent years, processing of pharmaceuticals with SCFs, especially with supercritical carbon dioxide, has received increased attention (Subramaniam et al., 1997). Three supercritical micronization techniques, namely rapid expansion of a supercritical solution (RESS), gas anti-solvent recrystallisation (GASR) and high pressure crystallisation (HPC) have been used to date.

The first method, where particles are formed as a result of the rapid expansion of a SC solution (RESS), is suitable for substances with sufficient solubility in the SC solvent (Philips and Stella, 1993). Beside being of interest as an alternative to conventional size reduction methods (recently reported also by Allesi et al., 1995) RESS is a novel route to solvent free polymer-drug microspheres and microparticles for the controlled release of

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drugs (Debenedetti et al., 1993; Tom et al., 1993; Benedetti et al., 1995; Kikic and Alessi, 1995).

In the second method (GASR), the SCF is used as an anti-solvent that causes particle precipitation from a liquid solution. The GASR process is of interest in the formulation of fine peptide and protein powders (Debenedetti et al., 1993; Tom et al., 1993; Yeo et al., 1993) and polymer microspheres or microparticles (Debenedetti et al., 1993; Benedetti et al., 1995).

The advantages of crystallisation at supercritical conditions over conventional crystallisation becomes especially important when nonvolatile, thermally-labile drugs are to be crystallised under controlled temperature and pressure conditions (Knez, 1997).

An alternative micronization technique using aerosol solvent extraction system (ASES) was also recently described (Steckel et al., 1997). Several steroids were dissolved in an organic solvent and sprayed into supercritical carbon dioxide which was used for extraction of organic solvents from the micronized drugs.

A new method for particle generation with SCFs, known as particles from gas saturated solutions (PGSS) was used in this work (Weidner et al., 1994; Kerč et al., 1997; Senčar-Božič et al., 1997). The PGSS method shows some advantages over RESS, GASR and HPC processes. Compared to RESS the consumption of CO_2 is an important parameter being lower by an order of magnitude 10^3 for PGSS than for RESS. Since in RESS the substance has to be dissolved in the supercritical gas, sufficient solubility in SC CO_2 is the criterion which eliminates many pharmaceutical compounds from the RESS process. In PGSS on the contrary, the compressible gas is dissolved in the molten compound and the gas saturated liquid phase is further processed. When compared to GASR advantageously no organic solvent is needed in the PGSS process.

In this study, practically water insoluble nifedipine and felodipine, dihydropyridine calcium-channel blockers and the practically insoluble hypolipidemic agent fenofibrate were processed by the PGSS process with the aim to increase dissolution rate and hence bioavailability.

2. Materials and methods

2.1. Materials

Nifedipine (Lek Slovenia), felodipine (Lek Slovenia), and fenofibrate (INFA Italy) with mean particle size of 50, 60, and 7 μm, respectively, and PEG 4000 (Hoechst Germany) were used as received. Carbon dioxide (99.94%) was donated by Linde plin Celje, Slovenia.

2.2. Micronization with the PGSS process

In the PGSS process (Fig. 1), a compressible gas (i.e. CO_2) is dissolved under pressure in a melted drug (or a mixture of drug/carrier). This gas saturated solution is later expanded which causes supersaturation and fine particles precipitate. The experimental equipment has been presented in detail (Weidner et al., 1994).

The drug was placed in an autoclave (NWA-Lorrach, Germany; max. pressure 400 bar, max. temperature 400°C) and CO_2 was introduced using a high pressure pump until the desired pressure (based on process parameters-maximum pressure 200 bar (Table 1, Table 2, and Table 3) was achieved. The autoclave was then heated up to the operating temperature which was close to the melting point of the drug to be micronized.

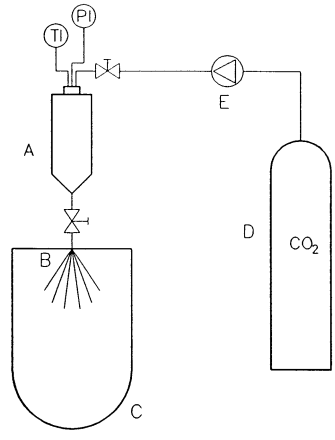

Fig. 1. Laboratory apparatus for micronization with PGSS process (A, autoclave; B, nozzle; C, expansion chamber; D, carbon dioxide reservoir; E, high pressure pump; PI, analogue manometer; TI, thermoelement with digital screen).

Table 1
Experimental conditions for micronization of drugs using PGSS process

	Nifedipine	Felodipine	Fenofibrate
Melting point of drug (°C)	171–175	141–145	79–84
Amount of drug (g)	5	5	5
Pre-expansion pressure (bar)	100, 125, 150, 175, 190, 200	200	190
Pre-expansion temperature (°C)	165, 175, 185	150	65, 70, 80
Nozzle diameter (mm)	0.4, 0.25	0.4	0.25

Simultaneously the pressure reached the operating value. After reaching the equilibrium (approximately 2 h) the gas saturated solution was expanded through the nozzle (Spraying systems, Germany; orifice 0.4 and 0.25 mm, spray angle 60°) and the compressible gas evaporated in the expanding chamber causing the micronization of drug particles.

2.3. Particle size and particle size distribution

Particle size and particle size distribution were measured with a Granulometer Cilas 920, operating on the principle of laser diffraction spectroscopy. Water dispersions of micronized particles were prepared and additional water was added in Granulometer automatically until the desired concentration of particles was achieved.

2.4. Scanning electron microscopy (SEM)

The shape and surface appearance of particles were observed with a scanning electron microscope (JEOL SM-840 A). The samples were prepared by shadowing with carbon and gold/palladium in vacuum and observed with the secundar electron technique.

2.5. Thermal analysis

A Mettler TA 300 DSC apparatus was used. All thermal analyses were performed in an inert atmosphere (N_2). The sample sizes were approximately 10 mg and the heating rate was 10 K /min.

2.6. Dissolution studies

Dissolution studies of nifedipine (10 mg) and felodipine (10 mg) were performed following the USP paddle method in 1000 ml of distilled water at 37°C and 100 rpm. The concentrations of drug in withdrawn and filtered aliquots were determined spectrophotometrically: nifedipine at 335 nm and felodipine at 364 nm.

The dissolution profile of fenofibrate (200 mg) was determined following the USP paddle method in 1000 ml 0.1 M sodium lauryl sulphate solution and the absorbance was measured at 285 nm.

3. Results and discussion

Experimental conditions for micronization of nifedipine, felodipine and fenofibrate are presented in Table 1.

Using the PGSS process nifedipine was micronized at various pressures in the range from 100 to 200 bar and at temperatures 165, 175, and 185°C. The mean particle size of the starting nifedipine was 50 μm, and it was decreased to 15–30 μm, depending on experimental conditions (Table 2). The resulting particle size was a function of process conditions. With increasing the pre-expansion pressure the mean particle size was decreased and as a result, the dissolution rate was found to be higher for samples prepared at higher pre-expansion pressures (Fig. 2). The shape of micronized particles was irregular and according to SEM pictures it was assumed that the particles were porous. With particle size re-

Table 2
Particle size and particle size distribution of micronized nifedipine

$T_{pre\text{-}exp}$ (°C)	$P_{pre\text{-}exp}$ (bar)	Mean part. size (μm)	d 10% (μm)[a]	d 90% (μm)[b]	Nozzle diameter (mm)
*	*	49.7	21.1	80.3	
165	200	**			0.4
175	100	26.2	9.4	61.7	0.4
	125	20.3	6.0	50.9	
	150	22.1	7.0	64.6	
	175	22.6	7.5	78.3	
	190	21.2	5.5	37.6	
	200	16.3	2.9	28.5	
185	125	30.0	7.7	92.9	
	150	21.9	6.6	53.3	
	175	21.8	7.2	54.6	
	190	15.4	3.1	24.5	
175	125	30.1	8.5	54.5	0.25

[a] d 10%, the size of the particles at which 10% of the particles are smaller.
[b] d 90%, the size of the particles at which 90% of the particles are smaller.
* Non-micronized nifedipine.
** At 165°C and 200 bar micronization was not achieved since expansion of gas saturated solution was not possible.

duction and, therefore, increased specific surface area (external and internal) the dissolution rate increased to some extent, but the anticipated effective surface area was probably reduced by the drug's hydrophobicity and agglomeration of the particles during and after micronization.

In order to avoid agglomeration of micronized particles and thermal degradation of nifedipine at high temperatures (175 and 185°C) hydrophilic polymer PEG 4000 was added to nifedipine to decrease its melting point. Micronization at temperatures between 50 and 70°C was possible and fine powdered nifedipine/PEG 4000 particles were obtained. Their dissolution rate was twice as high as that for pure micronized nifedipine (Senčar-Božič et al., 1997).

The mean particle size of the starting felodipine was 60 μm and decreased after micronization with the PGSS process to 42 μm. Specific surface area measured using the BET method increased from 0.33 m^2/g for the starting felodipine to 1.33 m^2/g for micronized felodipine. The starting felodipine as well as micronized felodipine practically do not dissolve in water due to the poor wettability of felodipine particles. The amount of dissolved felodipine after 1 h was only 0.26 mg and 0.29 mg for the starting felodipine and the micronized sample, respectively. Differences in dissolution rate between the starting and micronized felodipine became obvious when lactose as a wetting agent was added to felodipine particles in the form of physical mixture in the ratio 1:2 (Fig. 3).

In the DSC scans of felodipine/PEG 4000 mixtures only a melting peak of PEG 4000 at 55°C was observed and it was concluded that felodipine dissolves in the PEG 4000 melt.

According to thermal analysis results and our experience with nifedipine where the highest dissolution rate was achieved with nifedipine/PEG 4000 coprecipitates (Senčar-Božič et al., 1997) felodipine/PEG 4000 mixtures were also micronized using the PGSS process. Experimental conditions are presented in Table 3.

Samples with felodipine/PEG 4000 ratio 1:4 (C4, C5, and C6) were homogenous powders. On the contrary, the samples with lower felodipine/PEG 4000 (C1 and C3) were sticky and agglomerated. The pre-expansion temperature of 150°C was obviously too high for PGSS micronization of felodipine/PEG system since particles that were formed from the melt after expansion through the nozzle were not able to cool before reaching the bottom of the expansion chamber and agglomerated to a sticky mass on the bottom of the

Table 3
Experimental condition for micronization of felodipine/PEG 4000 mixtures using the PGSS process

$T_{pre\text{-}exp}$ (°C)	$P_{pre\text{-}exp}$ (bar)	Felodipine/PEG ratio	Nozzle diameter (mm)	Sample code
60	175	1:4	0.4	C5
60	190	1:4		C6
70	195	1:4		C4
60	190	1:3		C1
150	190	1:1		C3

chamber. The dissolution profiles of felodipine/PEG 4000 coprecipitates (C4, C5, and C6) along with the starting felodipine and its physical mixture with PEG 4000 (1:4) are presented in Fig. 4. The amount of felodipine dissolved in 1 h from felodipine/PEG 4000 coprecipitates micronized at pre-expansion pressure of 175, 190, and 195 bar is 13.5-, 10-, and 8-times higher than original felodipine, respectively. From Fig. 4 an impact of the pre-expansion pressure on dissolution behaviour of felodipine from micronized felodipine/PEG 4000 coprecipitates can be seen. Similar observations were previously noted for nifedipine/PEG 4000 samples (Senčar-Božič et al., 1997). Even at the pre-expansion pressure of 175 bar enough CO_2 was dissolved in the melt to cause a rapid precipitation of the components. The lower dissolution rate of sample C4 that was micronized at 195 bar and 70°C could be explained by the decreased solubility of CO_2 in the melt at a higher temperature (Weidner et al., 1997).

The mechanism of the enhanced dissolution rate of drugs from micronized drug/PEG 4000 coprecipitates could be explained in same way as dissolution of solid dispersions was interpreted by different

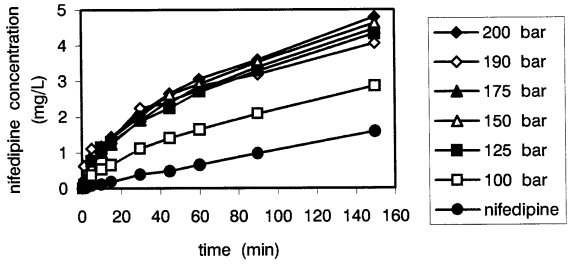

Fig. 2. Dissolution profiles of nifedipine, micronized at 175°C and various pressures compared with original nifedipine.

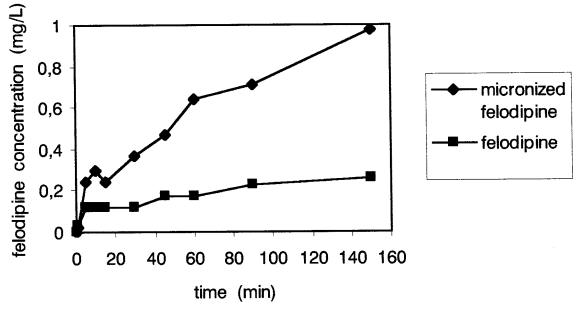

Fig. 3. Dissolution of starting and micronized felodipine in physical mixtures with lactose (1:2).

authors (for example, Sugimoto et al., 1980; Ford, 1986; Sumnu, 1986). We believe that a combination of factors including particle size reduction, interactions between the drug and PEG 4000 and the solubilization effect of the hydrophilic carrier contribute to the enhanced dissolution rates of drugs.

Fenofibrate (melting point at 78°C) with mean particle size of 7 μm was used for further micronization with the PGSS process. Unfortunately micronization at 80 and 65°C was not successful. At

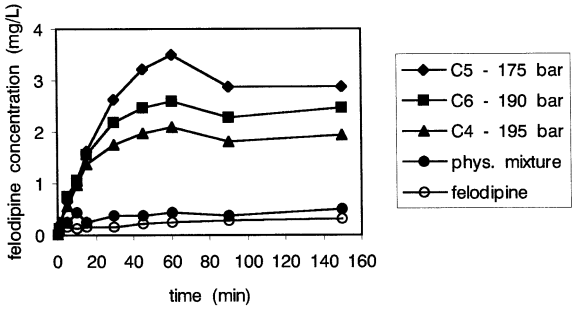

Fig. 4. Dissolution of micronized felodipine/PEG 4000 samples prepared at different pre-expansion pressures compared with original felodipine and physical mixture of the same composition (1:4).

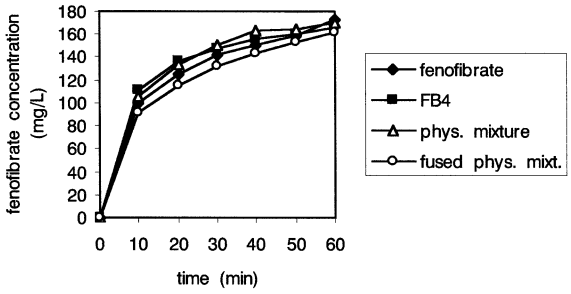

Fig. 5. Dissolution profiles of micronized fenofibrate/PEG 4000 compared with original fenofibrate, its physical mixture and fused physical mixture of the same composition (4:1).

80°C the solubility of CO_2 in the melt was probably too low and solidification of fenofibrate occurred in the nozzle. At 65°C the solubility of CO_2 in the melt was higher but the micronized particles agglomerated. After micronization at 70°C and 190 bar the particles were partly agglomerated and the particle size determination showed that the PGSS process even increased the particle size from 7 to 32 μm due to agglomeration of particles in the PGSS process.

Fenofibrate/PEG 4000 mixture was also micronized using the PGSS process at 60°C and 190 bar, but the dissolution profile does not differ significantly from the dissolution profile of fenofibrate, its physical mixture and fused physical mixture (Fig. 5).

With the PGSS process micronized drugs and drug/PEG 4000 samples were prepared in a new way, which has some advantages over classical methods for micronization of pure drugs and for drug/carrier solid dispersion preparation, namely fusion methods and solvent processes. In the PGSS process there is a melt of the drug (and a carrier), saturated with supercritical CO_2. Upon expansion the gas evaporates and therefore this solution is rapidly cooled down and the drug (or drug/carrier) precipitates in form of microparticles, thereby avoiding the comminution step. Since the cooling is rapid due to the expansion of CO_2 present fine particles with a narrow particle size distribution can be formed. On the other hand, there is no organic solvent needed. The removal of solvent is a problem of classical coprecipitation or coevaporation techniques where large amounts of organic solvents are needed and in which complete removal is often a long and difficult process (Ford, 1986). With the PGSS process, micronized drug or micronized drug/carrier can be obtained in one step with no organic solvent. The condition for successful micronization with the PGSS process is sufficient solubility of supercritical CO_2 in the melt to achieve the expandable gas saturated solution.

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