Drug Development and Industrial Pharmacy, 33:975–983, 2007

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040601150286

informa
healthcare

Supercritical Antisolvent Versus Coevaporation—Preparation and Characterization of Solid Dispersions

Viktor Majerik, Géza Horváth, and László Szokonya
Department of Chemical Engineering Science, University of Pannonia, Veszprém, Hungary

Gérard Charbit and Elisabeth Badens
Laboratoire de Procédés Propres et Environnement, Université Paul Cézanne Aix-Marseille, Aix en Provence, France

Nathalie Bosc and Eric Teillaud
Merck Santé sas, Lyon, France

The objective of this work was to improve the dissolution rate and aqueous solubility of oxeglitazar. Solid dispersions of oxeglitazar in PVP K17 (polyvinilpyrrolidone) and poloxamer 407 (polyoxyethylene-polyoxypropylene block copolymer) were prepared by supercritical antisolvent (SAS) and coevaporation (CoE) methods. Drug-carrier formulations were characterized by powder X-ray diffraction, Fourier transform infrared spectroscopy, scanning electron microscopy, gas chromatography, UV/VIS spectroscopy and in vitro dissolution tests. The highest dissolution rate (nearly 3-fold higher than raw drug) was achieved by preparation of drug/PVP K17 coevaporate. Oxeglitazar/PVP K17 solid dispersions were stabilized by hydrogen bonding but contained higher amount of residual dichloromethane (DCM) than poloxamer 407 formulations regardless of the method of preparation. SAS prepared oxeglitazar/poloxamer 407 dissolved more than two times faster than raw drug. However, unlike PVP K17, poloxamer 407 did not form a single phase amorphous solid solution with oxeglitazar which has been manifested in higher degrees of crystallinity, too. Among the two techniques, evaluated in this work, conventional coevaporation resulted in higher amorphous content but SAS reduced residual solvent content more efficiently.

Keywords solid dispersion; poorly water-soluble drug; oxeglitazar; supercritical antisolvent; coevaporation

INTRODUCTION

Oxeglitazar [(2E,4E)-5-(7-methoxy-3,3-dimethyl-2,3-dihydro-1-benzoxepin-5-yl)-3-methylpenta-2,4-dienoic acid] (Figure 1) belongs to a new class of diabetes drugs, the dual peroxisome proliferative activator receptor (PPAR) agonists, collectively known as the glitazars. As an orally administered active pharmaceutical ingredient (API) the bioavailability of oxeglitazar depends on its solubility and permeability in the gastrointestinal tract (FDA, 2002). Initial studies found that the absorption of oxeglitazar is limited by its poor solubility and dissolution rate. Owing to its good permeability and poor dissolution kinetics, oxeglitazar can be classified as a Class II API based on the Biopharmaceutics Classification System (BCS) (Amidon et al., 1995). In addition, conventionally crystallized oxeglitazar exists in several polymorphic forms (monotropic system) and is difficult to handle because of its needle-like habit (Majerik et al., 2007).

Many methods have been proposed in the literature to overcome such difficulties, including micronization (Miranda & Jaeger, 1998), surface modification (Cassidy et al., 1998), formation of complexes (Szente & Szejtli, 1999; Perrut et al., 2002; Lochard et al., 2004), eutectic mixtures (Yong et al., 2005), solvates, solid solutions and solid dispersions (Leuner & Dressman, 2000). In solid solutions and solid dispersions drug molecules or very fine drug crystals are dispersed in a biocompatible matrix. The therapeutic use of solid dispersions has been the focus of many recent studies (Leuner & Dressman, 2000; Van Nijlen et al., 2003; Sethia & Squillante, 2003, 2004). Although, the medical benefits associated with these formulations are evident, they are not widely used because of the manufacturing difficulties encountered with conventional techniques like spray-drying and hot melt extrusion. In the late 80's, supercritical fluids (SCFs) appeared in the pharmaceutical industry as an alternative to conventional processes (Rogers et al., 2001; Charbit et al., 2004; Majerik et al., 2004). The most common SCF is carbon dioxide ($scCO_2$) which is nontoxic, non-flammable and available in large quantities. Owing to its mild critical temperature (31.06 °C) and low critical pressure (73.8 bar), CO_2 is suitable to precipitate heat-sensitive

Address correspondence to Viktor Majerik, Department of Chemical Engineering Science, University of Pannonia, Veszprém Egyetem u. 10, H-8201, P.O. Box 158, Hungary. E-mail: majerikv@almos.vein.hu

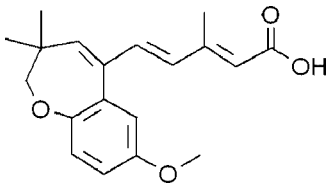

FIGURE 1. The chemical structure of oxeglitazar.

APIs. Additionally, these techniques were proved to reduce particle size and residual solvent content in one step; and in some cases crystal habit, morphology and polymorphic form of the processed drug could be controlled as well (Ruchatz et al., 1997; Beach et al., 1999; Fargeot et al., 2003; Badens et al., 2004, 2005; Pasquali et al., 2006).

In a recent study, SAS prepared solid dispersions of oxeglitazar in various excipients were compared (Majerik et al., 2007). SAS process was proved to be a viable method to prepare rapidly dissolving semi-crystalline solid dispersions which satisfied requirements on polymorphic purity and residual solvent content. In this paper, SAS and conventional coevaporation were compared. Solid dispersions containing 50 w/w% excipient (PVP K17 or poloxamer 407) and 50 w/w% oxeglitazar were prepared and characterized by powder X-ray diffractiometry (XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), gas chromatography (GC), UV/VIS spectroscopy and in vitro dissolution tests.

MATERIALS AND METHODS

Materials

Oxeglitazar was obtained from Merck Santé sas, Lyon, France; Lutrol F127 (poloxamer 407) and Kollidon 17 PF (PVP K17) were obtained from BASF, Germany; carbon dioxide (99.7%) was supplied by Air Liquide, France; ethanol (99.8%) was purchased from Carlo Erba, Italy; dichloromethane (99.95%) was purchased from SDS, France; dimethyl sulfoxide (99.8%) was supplied by 3D-Spektrum, Hungary; potassium phosphate monobasic, sodium phosphate dibasic dodecahydrate and sodium chloride were obtained from Reanal, Hungary. All chemicals were used as received.

Supercritical Antisolvent Process

The schematic diagram of the SAS apparatus is shown in Figure 2. The feed solution (6) containing 2 w/w% API and 2 w/w% excipient were dispersed through a capillary nozzle (125 μm ID) (8) in a cocurrent $scCO_2$ stream. CO_2 was compressed to 80 bar in a water-cooled membrane pump (Dosapro Milton Roy, France) (3) at a flow rate of 10 g/min, while feed solution was delivered by a reciprocating HPLC pump (Gilson 307,

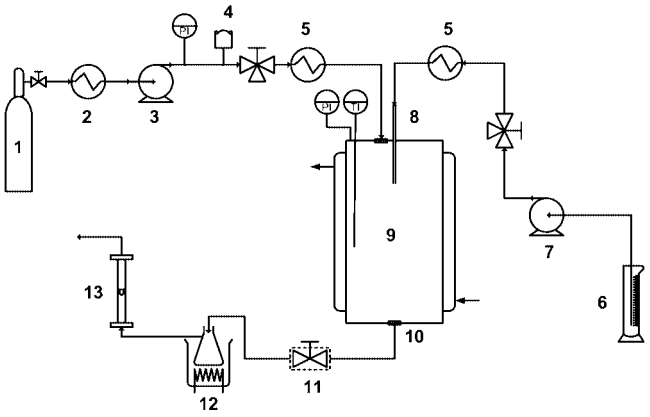

FIGURE 2. Schematic diagram of SAS apparatus. 1. CO_2 source, 2. Cooler, 3. CO_2 metering pump, 4. Bursting disc, 5. Heat exchanger, 6. Solution source, 7. Solution metering pump, 8. Capillary nozzle, 9. Precipitation vessel, 10. Frit filter, 11. Expansion valve, 12. Cold trap, 13. Gas flow meter.

France) (7) at a flow rate of 3 ml/min. Compressed CO_2 and solution were both heated (5) to 35 ± 0.5°C before entering the precipitation vessel (Top Industrie S.A., France) (9). Particles formed by the antisolvent effect were collected on 0.1 μm metal frit filter (10) and washed with pure $scCO_2$ for 30 min to remove residual solvents. A cold trap (12) was installed between the heated expansion valve (11) and the flow meter (13) to condense the organic solvents. Pressure and CO_2 flow rate were manually controlled. Solid dispersions were dried in a vacuum oven at 40°C for 24 hr so that residual solvent contents are comparable to those of coevaporates. Solid dispersions were stored in sealed glass vials under ambient temperature in the dark.

Coevaporation Process

Coevaporates were prepared by dissolving oxeglitazar and PVP K17 or poloxamer 407 in a minimum amount (~20 mL) of dichloromethane (DCM). The solvent was rapidly removed under reduced pressure in a rotary evaporator at 40°C. Coevaporates were left in the rota-dest apparatus for 2 hr, the time that a typical SAS process has taken, even though DCM had evaporated within a few minutes. Solid dispersions were ground and dried in a vacuum oven at 40°C for 24 hr. Solid dispersions were stored in sealed glass vials under ambient temperature in the dark.

Physical Mixture

Physical mixtures of oxeglitazar and PVP K17 or poloxamer 407 used in the dissolution studies and FTIR analysis were prepared by mixing the appropriate amounts of pharmaceutical ingredients in a mortar until a homogenous mixture was obtained (1 min). Physical mixtures were used immediately after preparation to avoid moisture absorption from air.

Incorporated oxeglitazar (raw drug) contained exclusively the higher melting polymorph (form A).

Scanning Electron Microscopy (SEM)

SEM micrographs were taken using Philips XL30 ESEM Environmental Scanning Electron Microscope (Philips Analytical Inc., The Netherlands). Samples were coated with gold before examination (cathode dispersion).

Powder X-Ray Diffractometry (XRD)

XRD patterns of SAS powders were obtained using a Philips Analytical X-ray diffractometer MPD3710 (Philips Analytical Inc., The Netherlands). Ground powders were placed in the cavity of an aluminum sample holder and flattened with a glass slide. Samples were scanned over the range of 4.0–47.0° 2θ with a step size of 0.020° 2θ and a count time of 2 s per step using Co Kα source with a wavelength of 1.78896 Å. Coevaporates were analyzed on Philips Analytical X-ray diffractometer B.V. PW3710 (Philips Analytical Inc., The Netherlands) over the range of 4.0–40.0° 2θ with a step size of 0.020° 2θ and a count time of 1 s per step using Cu source (λ = 1. 54056 Å).

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was carried out on a Shimadzu FTIR-8300 spectrometer (Shimadzu Corp., Japan) equipped with a DLATGS detector. KBr pellets were prepared (2 mg sample in 200 mg KBr) and scanned over a range of 400–3200 cm^{-1} with a resolution of 2 cm^{-1}. Spectra were obtained by coadding 100 scans in transmission mode. The software used for the data analysis was Hyper-IR (Shimadzu Corp., Japan).

Gas Chromatography (GC)

Residual DCM in solid dispersions was assessed using HP 8590 gas chromatograph (Hewlet Packard, Germany) with flame ionization (FID) detector. Powders were dissolved in dimethyl sulfoxide and directly injected in triplicate (2.0 μL) on a Chrompack Fused Silica column (25 m × 0.53 mm) with Poraplot Q coating (Chrompack International, The Netherlands). Samples were analyzed using Ar carrier gas at a constant oven temperature of 210°C while the injector and detector temperatures were maintained at 260°C. The method of external standardization was used to calculate the residual solvent content.

UV/VIS Spectroscopy

The drug content of formulations was determined using Metertech UV/VIS SP8001 Spectrophotometer (Metertech Inc., Taiwan). Formulations were dissolved in ethanol and analyzed at 292.0 nm in duplicate after appropriate dilution.

Solubility Measurement

An excess amount (50 mg) of oxeglitazar was added to 20 mL of pH 7.4 phosphate buffer medium (6.4 g Na_2HPO_4 $12H_2O$; 0.6g KH_2PO_4 and 5.85 g NaCl dissolved in 1000 mL distilled water) having different concentrations of PVP K17 or poloxamer 407. Solutions were rotated in water-jacketed flasks at constant temperature (37 ± 0.5°C). After 24 hr, suspensions were filtered through a disposable syringe filter (0.22 μm) and diluted with the dissolution media. The amount of dissolved oxeglitazar was quantified using Metertech UV/VIS SP8001 Spectrophotometer (Metertech Inc., Taiwan). Solubility measurements were carried out in triplicate.

Dissolution Studies

Dissolution tests were performed in triplicate in pH 7.4 phosphate buffer medium. About 100 mg of powder equivalent to ~50 mg oxeglitazar were added to 1000 ml dissolution medium. Bath temperature and paddle speed were set at 37 ± 0.5°C and 75 rpm, respectively. Aliquots of 10 mL were withdrawn through a filtering rod (2 μm) at 5, 10, 15, 30, 45, 60, and 120 min. Properly diluted solutions were analyzed on Metertech UV/VIS SP8001 Spectrophotometer (Metertech Inc., Taiwan) at λ = 292.0 nm.

RESULTS AND DISCUSSION

Particle Morphology

SEM micrograph of the raw drug prepared by cooling crystallization showed thin needle-like crystals (Figure 3). Computer simulation (GenMol software) revealed a potential hydrogen bonding between carboxylic OH and the methoxy oxygen (internal rapport). Owing to this hydrogen bonding effect, the crystal growth of oxeglitazar is preferred in one crys-

FIGURE 3. Scanning electron micrograph of raw oxeglitazar.

tallographic direction resulting in acicular crystals which is undesirable because of its poor flow properties.

SAS prepared coprecipitates formed a thick cottony layer on the vessel wall. Oxeglitazar/poloxamer 407 coprecipitate consisted of aggregated acicular particles similar to those observed for the raw drug (Figure 4a–b). Unusually large particle size was observed in comparison with other SCF processed products (Bitz & Doelker, 1996; Reverchon, 1999, 2000). One possible explanation is that poloxamer 407 could not inhibit the growth of oxeglitazar crystals which in turn have kept on growing throughout the whole precipitation process. This theory seems to be consistent with the observations of Bristow et al. (2001) who found that mean particle size of paracetamol prepared by solution enhanced dispersion by supercritical fluids (SEDS) increased linearly with the time of precipitation process. Large particle size implies low saturation ratio but this theory can not be verified in the lack of data on equilibrium solubility. Acicular particles were seen in oxeglitazar/poloxamer 407 coevaporate as well suggesting that poloxamer 407 did not form a single phase solid solution in either process (Figure 4c–d). Primary particle size of SAS prepared oxeglitazar/PVP K17 was still very large but needle-like shape was successfully changed into tabular one (Figure 4e–f). SEM micrographs showed aggregated platelets with a thickness of a few micrometers. In contrast, when solvent was removed by evaporation PVP gave a homogenous film-like precipitate (Figure 4g–h).

Crystallinity and Polymorphic Purity

Formulations were shown to have very different morphologies depending on the method of preparation and the excipient involved. The physical state of each drug-carrier formulation was investigated by XRD measurements. XRD patterns of raw drug, excipients, coprecipitates and coevaporates are shown in Figures 5 and 6. Raw oxeglitazar is crystalline with well-defined peaks at *d* values of 15.26, 8.45, 5.39, and 4.23 Å. Poloxamer 407 has two broad peaks at 3.83 and 4.65 Å while PVP K17 gave a broad background signal.

Although crystalline drug was detectable in all formulations, diffraction peaks of oxeglitazar were much weaker. The lowest intensity was measured in CoE oxeglitazar/PVP K17 followed by SAS oxeglitazar/PVP K17, CoE oxeglitazar/poloxamer 407 and SAS oxeglitazar/poloxamer 407. Consistently with previous studies PVP has successfully inhibited the crystal growth of the active substance (Delneuville et al., 1998; Van den Mooter et al., 1998; Van Nijlen et al., 2003; Sethia & Squillante, 2004), while poloxamer 407 remained crystalline after the formulation process too, and hence semi-crystalline solid dispersions were obtained instead of solid solutions (Kim et al., 2006). A comparison was made between the drug-carrier formulations prepared by the two methods. Characteristic peaks were much smaller for coevaporates than for coprecipitates using the same polymer. Thus, coevaporation seems to be more efficient in the preparation of oxeglitazar/excipient solid solutions. XRD was also used to assess the polymorphic purity of formulations. Only the form A (thermodynamically stable one) was present (data not shown) satisfying current requirements for stable polymorph.

Hydrogen Bonding Interactions

FTIR is probably the most widely used analytical method to detect hydrogen bonding in drug-carrier solid dispersions. It is known, that absorption bands of the groups, involved in hydrogen bonding, shift to lower wave numbers (Sethia & Squillante, 2004). However, in most cases only a slight broadening is observed due to the superposition of the original and the new band. Oxeglitazar contains one hydrogen donor (–OH) and three hydrogen acceptor groups (–C = O, Aryl–O–CH_3 and Aryl–O–R). The characteristic absorption bands of these groups are νC = O at 1681 cm^{-1}, νO–H in the range of 2500–3700 cm^{-1} (carboxylic group), ν_{as}C–O at 1271–1212 cm^{-1} and ν_sC–O at 1047–1029 cm^{-1} of methoxy and cyclic ether group (Figure 7a). Although the stretching vibration of OH gives a broad and intense band it was not considered because of the water residues (Kaczmarek et al., 2001). The position of νC = O band was below 1700 cm^{-1} due to the conjugation with double bonds and aromatic ring (Coates, 2000). Likewise, a broad well defined band was observed in the spectrum of PVP K17 at 1672 cm^{-1} assigned to the carbonyl stretching vibration (Figure 7b). Each pyrrole ring of the PVP polymer contains two hydrogen acceptor groups: a carbonyl group and a tertiary amine. However, the latter is not favored in hydrogen bonding due to a steric hindrance (Forster et al., 2001; Sethia & Squillante, 2004).

The FTIR spectrum of the physical mixture revealed no considerable interaction between the pharmaceutical ingredients. The spectrum shown in Figure 7c was a simple summation of those of pure compounds. In contrast, FTIR spectra of oxeglitazar/PVP K17 coprecipitate and coevaporate display different absorption bands in the carbonyl region (Figure 7d–e). A new band seems to appear at about 1650 cm^{-1} beneath the superposed νC = O bands which can be attributed to the carbonyl group of PVP K17 engaged in intermolecular hydrogen bonds with the carboxylic OH of oxeglitazar. Such interactions in drug-PVP solid dispersions were previously reported (Van den Mooter et al., 1998; Kaczmarek et al., 2001; Sethia & Squillante, 2004). The FTIR spectra of oxeglitazar/poloxamer 407 solid dispersions are shown in Figure 8. The position and intensity of the corresponding bands were similar in the spectra of physical mixture, coprecipitate and coevaporate, suggesting that poloxamer 407 did not form any hydrogen bonding with oxeglitazar.

Residual Solvent

The residual solvent content was determined with GC analysis. DCM is a Class 2 solvent with a permitted daily exposure

(PDE) of 6 mg (FDA, 1997). Two options are available when setting limits of Class 2 solvents: Option 1 may be applied if the daily dose is not known or fixed. This option assumes a high dose (10 g/day) that is rarely exceeded. Option 2 takes into account the daily dose or the maximum daily dose if the drug is not regularly administered. Assuming a maximum daily dose of 400 mg, recommended limits of DCM under Option 1 and Option 2 are 600 and 7500 ppm, respectively.

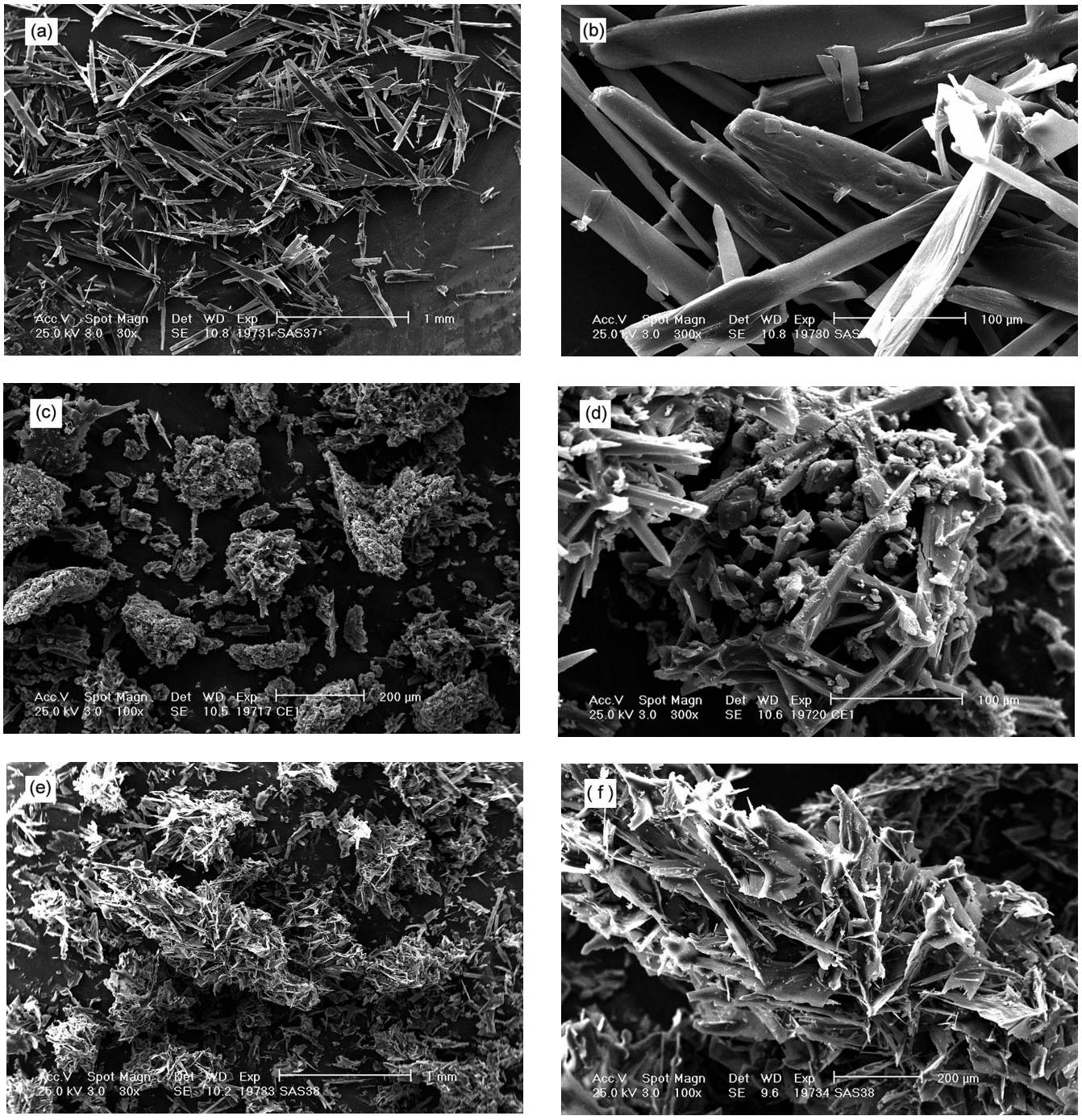

FIGURE 4. Scanning electron micrographs of drug-carrier formulations: (a–b) SAS oxeglitazar/poloxamer 407, (c–d) SAS oxeglitazar/PVP K17, (e–f) CoE oxeglitazar/poloxamer 407, (g–h) CoE oxeglitazar/PVP K17.

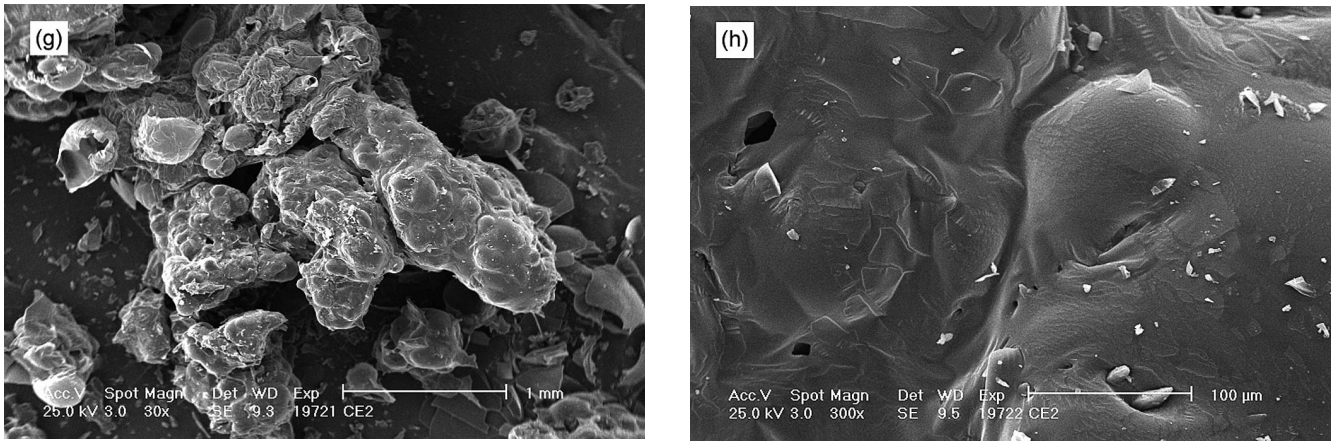

FIGURE 4. (*Continued*).

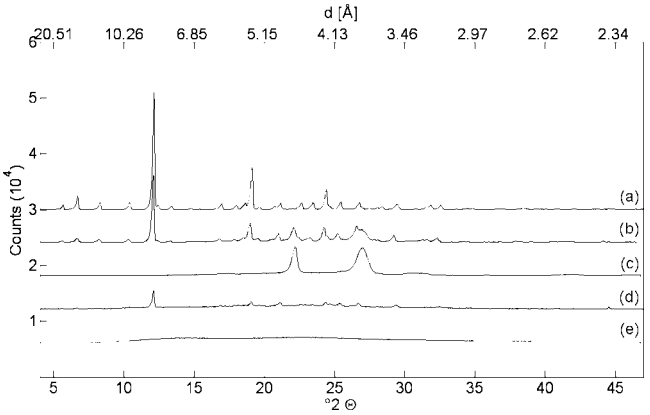

FIGURE 5. XRD patterns of (a) raw drug, (b) SAS oxeglitazar/poloxamer 407, (c) poloxamer 407, (d) SAS oxeglitazar/PVP K17, (e) PVP K17.

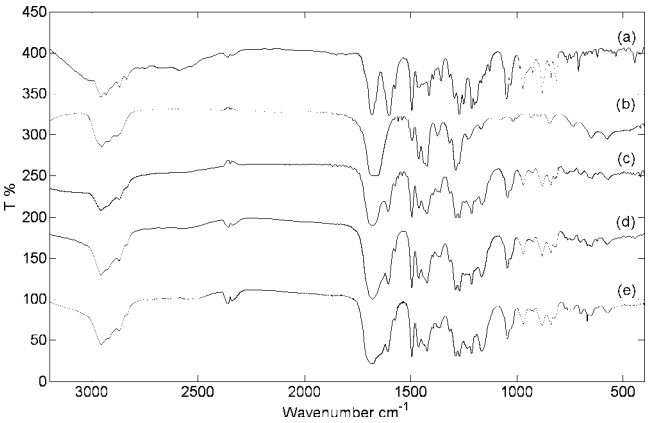

FIGURE 7. FTIR spectra of solid dispersions of oxeglitazar and PVP K17: (a) raw drug, (b) PVP K17, (c) physical mixture, (d) SAS oxeglitazar/PVP K17, (e) CoE oxeglitazar/PVP K17.

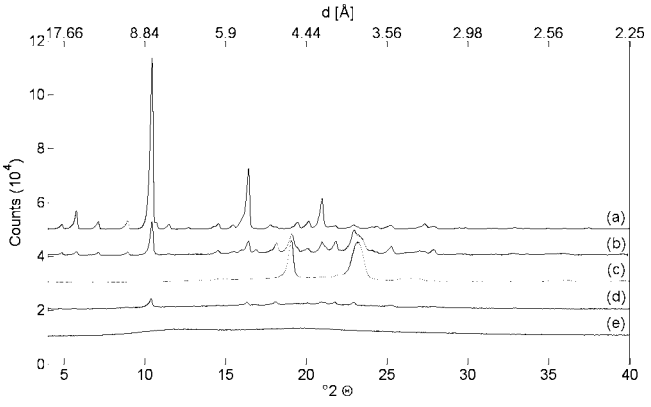

FIGURE 6. XRD patterns of (a) raw drug, (b) CoE oxeglitazar/poloxamer 407, (c) poloxamer 407, (d) CoE oxeglitazar/PVP K17, (e) PVP K17.

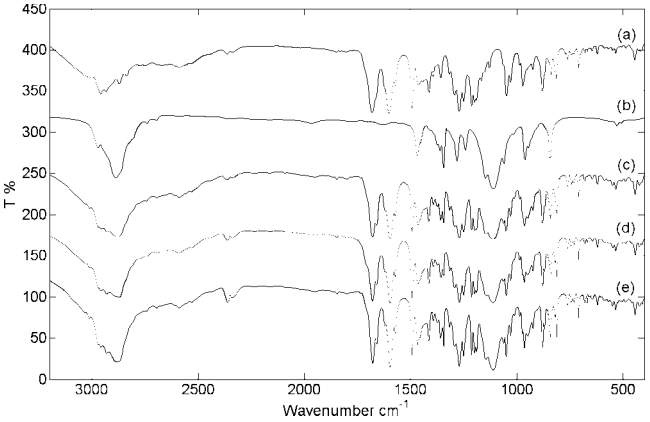

FIGURE 8. FTIR spectra of solid dispersions of oxeglitazar and poloxamer 407: (a) raw drug, (b) poloxamer 407, (c) physical mixture, (d) SAS oxeglitazar/poloxamer 407, (e) CoE oxeglitazar/poloxamer 407.

Results of GC analysis are shown in Table 1. All oxeglitazar/poloxamer 407 formulations met ICH requirements under Option 2. Residual DCM content was even lower than the stricter Option 1 limit after vacuum drying (SAS-VD and CoE-VD). In contrast, the oxeglitazar/PVP formulations have retained much more solvent. Vacuum dried coprecipitate and coevaporate met Option 2 limit but exceeded Option 1 limit. Owing to its amorphous state PVP has a high tendency to retain solvent residues during the drying or solvent stripping process. The main drawback of coevaporation is that solvent traces get trapped in the amorphous solid dispersion and further drying process is needed. The residual DCM contents in SAS prepared formulations were consistent with published works on SCF processed pharmaceutical products (Bitz & Doelker, 1996; Ruchatz et al., 1997). Ruchatz et al. found that residual solvent level and CO_2 flow rate were inversely proportional in the case of aerosol solvent extraction system (ASES). Thus, residual solvent level can be reduced by increasing the CO_2 flow rate or extending the solvent stripping.

Drug Content

Drug contents are listed in Table 2. Both SAS prepared powders contained more oxeglitazar than the nominal value (50 w/w%) suggesting that the DCM-CO_2 mixture dissolved and washed out more excipient than active substance. In contrast, drug contents in coevaporates were marginally below the nominal value. This deviation has to be taken into account in the preparation of solid oral dosage forms with high content uniformity.

Solubility Studies

Oxeglitazar solubility as a function of excipient concentration is shown in Figure 9. Solubility was measured in pH 7.4 phosphate buffer medium at 37°C. The increase in solubility was linear with respect to the weight fraction of both polymers but the curve of poloxamer 407 was much more steeper. The increase in oxeglitazar solubility was 8.7- and 3.9-fold in dissolution media with 10% w/v poloxamer 407 and PVP K17, respectively. Thus, poloxamer 407 solubilized more than twice as much drug as PVP K17. Similar results were previously reported on felodipine solubility using PVP K30 and poloxamer 407 as solubilizing agent (Kim et al., 2006).

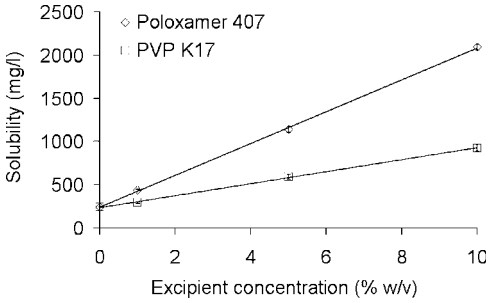

FIGURE 9. Phase solubility diagram of oxeglitazar in pH 7.4 phosphate buffer media with various poloxamer 407 and PVP K17 concentrations.

Poloxamers are highly water-soluble amphiphilic surfactants that form micelles in aqueous media and stabilize dissolved molecules or nanoparticles of hydrophobic APIs. The hydrophilic-lipophilic balance (HLB) is an empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds. The HLB value of poloxamer 407 is about 18–23 (Jannin et al., 2006), whereas surfactants with HLB value greater than about 10 are generally considered to be hydrophilic.

Dissolution Studies

Dissolution profiles are shown in Figures 10 and 11. Markers and error bars represent the mean values and the standard

TABLE 1
Residual DCM Content (ppm)

Method	Poloxamer 407	PVP K17
SAS	804 ± 189	13500 ± 248
SAS-VD	87 ± 3	618 ± 23
CoE	1294 ± 97	18770 ± 817
CoE-VD	111 ± 4	668 ± 29

TABLE 2
Oxeglitazar Content (w/w%)

Method	Poloxamer 407	PVP K17
SAS	53.5 ± 0.4	57.9 ± 0.3
CoE	47.0 ± 0.9	47.8 ± 0.7

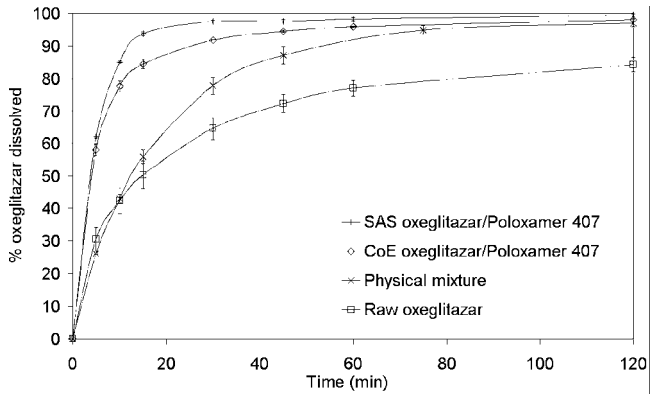

FIGURE 10. Dissolution profiles of oxeglitazar/poloxamer 407 solid dispersions, physical mixture, and raw drug.

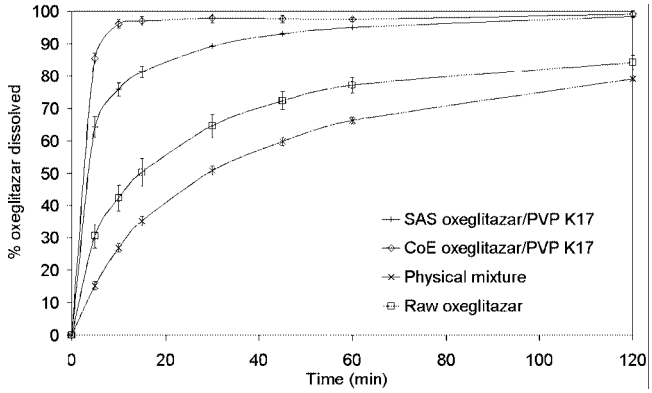

FIGURE 11. Dissolution profiles of oxeglitazar/PVP K17 solid dispersions, physical mixture, and raw drug.

error of the mean, respectively. The significance of the difference was analyzed by the Student's t-test. In all tests, a probability value of $p < 0.05$ was considered statistically significant.

Dissolution profiles were fitted with the Korsemeyer-Peppas model (Korsmeyer et al. 1983):

$$\frac{C(t)}{C_\infty} = kt^n$$

where $C(t)/C_\infty$ is the fraction of the drug dissolved to the elapsed time t, k is a constant incorporating geometric characteristics of the dosage form and n is the constant which indicates the release mechanism. Results of the linear regression are listed in Table 3. Although rapidly dissolving solid dispersions did not correlate well with the Korsemeyer-Peppas model ($R^2 = 0.5881 – 0.9361$), calculated n-values were systematically lower compared to those of raw drug and the corresponding physical mixture. Generally, low n-values ($n < 0.45$) indicate Fickian release behavior (Korsmeyer et al. 1983).

Dissolved oxeglitazar from poloxamer 407 coprecipitate and coevaporate at 5 min was 61.9 and 57.9%, respectively.

TABLE 3
Parameters of the Korsmeyer-Peppas Equation

Name	n	k	R^2
Raw drug	0.3266	0.1977	0.9598
Oxeglitazar/Poloxamer 407			
Physical mixture	0.4247	0.1586	0.9118
SAS	0.1276	0.5912	0.6759
CoE	0.1519	0.5167	0.8148
Oxeglitazar/PVP K17			
Physical mixture	0.5161	0.0787	0.9584
SAS	0.1328	0.5490	0.9361
CoE	0.0349	0.8547	0.5881

The increase in dissolution rate was roughly two-fold in both formulations compared to the raw drug (30.51% at 5 min) and the physical mixture (26.10%). Surprisingly, oxeglitazar/PVP K17 solid dispersions showed even higher dissolution rates: at 5 minutes 64.3% of the incorporated drug was dissolved from the coprecipitate and 85.6% from the coevaporate. This seems to be contradictory to the results of solubility studies. The increase in oxeglitazar solubility was more than two times higher for poloxamer 407 compared to PVP K17. However, XRD measurements and SEM micrographs confirmed that poloxamer 407 did not form a single phase solution with oxeglitazar in either process. In contrast, PVP was proved to be suitable to prepare molecularly dispersed drug-carrier systems. It can be concluded, that the two polymers have increased the dissolution rate of oxeglitazar in different manners. Poloxamer 407 exhibited excellent solubilizing effect owing to its amphiphilic nature while PVP K17 had a strong inhibitory effect on the crystallization of the API.

CONCLUSION

Supercritical antisolvent and coevaporation techniques were evaluated for their potential use in the preparation of rapidly dissolving dosage forms of Class II API. Solid dispersions of oxeglitazar in poloxamer 407 and PVP K17 were prepared and characterized by powder X-ray diffraction, Fourier transform infrared spectroscopy, scanning electron microscopy, gas chromatography, UV/VIS spectroscopy and in vitro dissolution tests. Solid dispersions obtained in both techniques were poorly crystalline and dissolved quickly in pH 7.4 phosphate buffer solution. The amorphous oxeglitazar dispersed in PVP K17 was stabilized by hydrogen bonding and dissolved faster but contained higher amount of residual DCM than poloxamer 407 formulations. SAS prepared oxeglitazar/poloxamer 407 solid dispersion satisfied all requirements concerning the residual solvent content, polymorphic purity and in vitro dissolution rate. On the other hand, oxeglitazar/poloxamer 407 formulations were semicrystalline and hence further crystallization would be faster in these system.

It can be expected that the improvement in oxeglitazar dissolution rate will increase its bioavailability, but further efforts must be made to reduce residual solvent content of the oxeglitazar/PVP solid dispersions and to verify the long-term stability of the oxeglitazar/poloxamer 407 formulations.

ACKNOWLEDGMENT

The authors kindly acknowledge the financial support from Merck Santé sas, France; and the fellowship from the French Government awarded by the Cultural and Cooperation Service of the French Embassy in Hungary. Viktor Majerik also acknowledge the financial support from the Industry for Engineering Education in Veszprém and Peregrinatio I foundations.

REFERENCES

Amidon, G. L., Lunnernas, H., Shah, V. P., & Crison, J. R. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res*., *12*, 413–420.

Badens, E., Fargeot, C., Bosc, N., Veesler, S., Teillaud, E., & Charbit, G. (2004). Polymorph control of drug in supercritical CO_2. Proceedings of the European Conference on Drug Delivery and Pharmaceutical Technology, Sevilla, May 10–12, pp. 46.

Badens, E., Teillaud, E., Charbit, G., Horváth, G., Szokonya, L., Bosc, N., & Majerik, V. (2005). Solubility enhancement of a pharmaceutical ingredient using supercritical antisolvent and spray-freezing techniques. Proceedings of The 7th International Symposium on Supercritical Fluids, Orlando, May 1–4,

Beach, S., Lathan, D., Sidgwick, C., Hanna, M., & York, P. (1999). Control of the physical form of Salmeterol Xinafoate. *Org. Proc. Res. Dev*., *3*, 370–376.

Bitz, C., & Doelker, E. (1996). Influence of the preparation method on residual solvents in biodegradable microspheres. *Int. J. Pharm*., *131*, 171–181.

Bristow, S., Shekunov, T., Shekunov, B. Yu., & York, P. (2001). Analysis of the supersaturation and precipitation process with supercritical CO_2. *J. Supercrit. Fluids*, *21*, 257–271.

Cassidy, O. E., Haskayne, L., & Rowley, G. (1998). Electrostatic charge and dissolution of surface modified phenylbutazone. *Eur. J. Pharm. Sci*., *6*, S23

Charbit, G., Badens, E., & Boutin, O. (2004). *Methods of particle production*. In *Supercritical Fluid Technology for Drug Product Development, Drugs and Pharmaceutical Sciences Vol. 138*, York, P., Kompella, U. B., Shekunov, B. Y., Ed., Marcel Dekker, Inc.: New York, pp. 159–212.

Coates, J. (2000). *Interpretation of Infrared Spectra, A Practical Approach*. In *Encyclopedia of Analytical Chemistry*, Meyers, R. A., Ed., John Wiley & Sons Ltd.: Chichester, pp. 10815–10837.

Delneuville, I., Dechesne, J. P., & Delattre, L. (1998). Preparation and study of the characteristics of dithranol:polyvinylpyrrolidone coevaporates. *Int. J. Pharm*., *168*, 109–118.

Fargeot, C., Badens, E., Charbit, G., Bosc, N., Teillaud, E., & Veesler, S. (2003). Cristallisation d'un prinicipe actif: comparaison des méthodes par voie liquide et supercritique. Proceedings of The Cristal2, Toulouse, 12–13 Novembre,, pp. 55–60.

FDA. (1997). International Conference on Harmonisation, ICH Guidance on Impurities: Residual Solvents, Federal Register., *62*, 67377–67388.

FDA. (2002). Draft—Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).

Forster, A., Hempenstall, J., & Rades, T. (2001). Investigation of drug / polymer interaction in glass solutions prepared by melt extrusion. *Int. J. Vib. Spec*. [www.ijvs.com], *5*, 6.

Jannin, V., Pochard, E., & Chambin, O. (2006). Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing Precirol® ATO 5. *Int. J. Pharm*., *309*, 6–15.

Kaczmarek, H., Szalla, A., & Kaminska, A. (2001). Study of poly(acrylic acid)-poly(vinylpyrrolidone) complexes and their photostability. *Polymer*, *42*, 6057–6069.

Kim, E. -J., Chun, M. -K., Jang, J. -S., Lee, I. -H., Lee, K. -R., & Choi, H.-K. (2006). Preparation of a solid dispersion of felodipine using a solvent wetting method. *Eur. J. Pharm. Biopharm*., *64*, 200–205.

Korsmeyer, R. W., Gurny, R., Doelker, E. M., Buri, P., & Peppas, N. A. (1983). Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm*., *15*, 25–35.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm*., *50*, 47–60.

Lochard, H., Sauceau, M., & Freiss, B. (2004). Method for the preparation of molecular complexes. World Patent WO 04096284 A1.

Majerik, V., Charbit, G., Badens, E., Horváth, G., Szokonya, L., Bosc, N., & Teillaud, E. (2007). Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. *J. Supercrit. Fluids 40*, 101–110.

Majerik, V., Horváth, G., Charbit, G., Badens, E., Szokonya, L., Bosc, N., & Teillaud, E. (2004). Novel particle engineering techniques in drug delivery: review of formulations using supercritical fluids and liquefied gases. *Hung. J. Ind. Chem*., *32*, 41–56.

Miranda, S., & Yaeger, S. (1998). Homing in on the best size reduction method. *Chem. Eng*., *105*, 102–110.

Pasquali, I., Bettini, R., & Giordano, F. (2006). Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. *Eur. J. Pharm. Sci*., *27*, 299–310.

Perrut, M., Jung, J., Leboeuf, F., & Fabing, I. (2002). Method for making very fine particles consisting of a principle inserted in a host molecule. World Patent WO 0232462.

Reverchon, E. (1999). Supercritical antisolvent precipitation of micro- and nano-particles. *J. Supercrit. Fluids*, *15*, 1–21.

Reverchon, E., Della Porta, G., De Rosa, I., Subra, P., & Letourneur, D. (2000). Supercritical antisolvent micronization of some biopolymers. *J. Supercrit. Fluids*, *18*, 239–245.

Rogers, T. L., Johnston, K. P., & Williams, III R. O. (2001). Solution-based particle formation of pharmaceutical powders by supercritical or compressed fluid CO_2 and cryogenic spray-freezing technologies. *Drug Dev. Ind. Pharm*., *27*, 1003–1015.

Ruchatz, F., Kleinebudde, P., & Müller, B. W. (1997). Residual solvents in biodegradable microparticles. Influence of process parameters on the residual solvent in microparticles produced by the Aerosol Solvent Extraction System (ASES) process. *Int. J. Pharm. Sci*., *86*, 101–105.

Sethia, S., & Squillante, E. (2003). Solid dispersions: revival with greater possibilities and applications in oral drug delivery. *Crit. Rev. Ther. Drug Carrier Syst*., *20*, 215–247.

Sethia, S., & Squillante, E. (2004). Solid dispersions of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. *Int. J. Pharm*., *272*, 1–10.

Szente, L., & Szejtli, J. (1999). Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development. *Adv. Drug Delivery Rev*., *36*, 17–28.

Van den Mooter, G., Augustijns, P., Blaton, N., & Kinget, R. (1998). Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int. J. Pharm*., *164*, 67–80.

Van Nijlen, T., Brennan, K., Van den Mooter, G., Blaton, N., Kinget, R., & Augustijns, P. (2003). Improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions. *Int. J. Pharm*., *254*, 173–181.

Yong, C. S., Lee, M.-K., Park, Y.-J., Kong, K.-H., Xuan, J. J., Kim, J.-H., Kim, J.-A., Lyoo, W. S., Han, S. S., Rhee, J.-D., Kim, J. O., Yang, C. H., Kim, C.-K., & Choi, H.-G. (2005). Enhanced oral bioavailability of ibuprofen in rats by poloxamer gel using poloxamer 188 and menthol. *Drug. Dev. Ind. Pharm*., *31*, 615–622.