HUNGARIAN JOURNAL
OF INDUSTRIAL CHEMISTRY
VESZPRÉM
Vol. 34. pp. 41-49 (2006)

SOLID DISPERSIONS OF OXEGLITAZAR IN PVP K17 AND POLOXAMER 407 BY SUPERCRITICAL ANTISOLVENT AND COEVAPORATION METHODS

V. MAJERIK[1]✉, G. HORVÁTH[1], G. CHARBIT[2], E. BADENS[2], L. SZOKONYA[1], N. BOSC[3] and E. TEILLAUD[3]

[1]Department of Chemical Engineering Science, University of Pannonia, Veszprém Egyetem u. 10
PO Box 158, H-8201, HUNGARY ✉E-mail: majerikv@almos.vein.hu
[2]Laboratoire de Procédés Propres et Environnement, UMR6181 Université Paul Cézanne Aix-Marseille 3,
Europôle de l'Arbois BP 80 13545 Aix en Provence Cedex 4, FRANCE
[3] Merck Santé sas, 37 rue St Romain 69379 Lyon Cedex 08, 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 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 belongs to a new class of diabetes drugs, the dual peroxisome proliferative activator receptor (PPAR) agonists, collectively known as the glitazars *(Fig. 1)* [1]. As an orally administered Active Pharmaceutical Ingredient (API) the bioavailability of oxeglitazar depends on its solubility and permeability in the gastrointestinal (GI) tract [2]. Initial studies found that the absorption of oxeglitazar is limited by its poor solubility and dissolution rate. The API has to dissolve in the GI fluid prior to absorption but such drugs remain in suspension and cannot cross the membranes of the epithelial cells in the GI tract. Solubility enhancement of hydrophobic active substances is an important area of drug delivery science because one out of four orally administered APIs is concerned [3]. To overcome these difficulties, new formulation techniques were developed comprising micronization, surface modification, formation of complexes, solvates, solid solutions and solid dispersions. Micronization is an attractive method because no additional excipient is needed but it improves only the dissolution rate by increasing the specific surface area and has no effect on the solubility. In contrast, excipients were shown to increase both dissolution rate and solubility of poorly water-soluble APIs. Cyclodextrines were successfully used to form inclusion complexes with drug molecules of appropriate size [4-6]. Beside cyclodextrins non-ionic surfactants are also widely used foremost in the precipitation of surface-modified drug-carrier systems [7,8], solid solutions and solid dispersions[9]. In solid solutions and solid dispersions drug molecules or very fine drug crystals are dispersed in a biologically inert and biocompatible matrix. The therapeutic use of solid dispersions has been the focus of many recent studies [9-12]. Although, the medical benefits associated with solid dispersions are known for long time, they are not widely used because of the manufacturing difficulties encountered with conventional techniques. Spray-drying was proved to be efficient in the preparation of micrometer sized solid solution powders but particle collection is still a challenging task [13]. Formulations prepared by solvent evaporation and hot melt method may contain impurities coming from solvent residues or thermal decomposition of the API. Additionally, if the active substance exists in several polymorphic forms it is recommended that formulation contains the thermodynamically most stable form [14]. Metastable forms may convert to a more stable one which in turn may have different bioavailability or, in extreme cases, catastrophic health effects [15]. However, most of these drug-carrier systems contain the active substance in amorphous form which is known to be thermodynamically

unstable with respect to its crystalline counterpart above the glass transition temperature. Although, pharmaceutical products are supposed to contain only the most stable polymorph, the use of stabilized amorphous form can be justified by medical benefits if there is no provable risk to the patient [14]. Several medical benefits have been reported in the literature including better wettability, enhanced dissolution rate and solubility [10,11,16]. However, conventional methods i.e. spray-drying, solvent evaporation and hot melt method are known to have inherent limitations, like poor particle recovery yield, high residual solvent content or thermal degradation of the API. Residual solvent traces and degradation products might be highly toxic to the patient and should comply with very low recommended levels. In spite of the tendency to replace toxic solvents or limit their application in the pharmaceutical industry these solvents are not always avoidable.

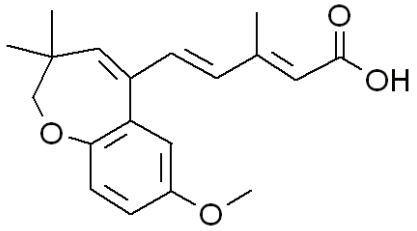

Fig. 1. The chemical structure of oxeglitazar.

In the late 80's, supercritical fluid (SCF) processes appeared in drug formulation as an alternative to conventional processes [17-21]. The most common SCF is carbon dioxide ($scCO_2$) which is non toxic, non flammable, cost efficient and available in large quantities. Owing to its mild critical temperature (31.06 °C) and critical pressure (73.8 bar), CO_2 is suitable to precipitate heat-sensitive 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 [21-26]. Unlike liquid solvents, $scCO_2$ is easy to separate from solid products and it causes no adverse health effect. Furthermore, if the SCF plays the role of antisolvent, residual solvent traces can be efficiently removed with SCF extraction [22,27].

More than ten different techniques were published and/or patented in the field of particle formation using SCFs. The most important are: Rapid Expansion from Supercritical Solution (RESS) [11,28]; Gas Antisolvent (GAS) [11,29-31], Supercritical Antisolvent (SAS) [28,32-36], Aerosol Solvent Extraction Sysytem (ASES) [13,22], Solution Enhanced Dispersion by Supercritical Fluids (SEDS) [16,37,38] and Particles from Gas-Saturated Solution (PGSS) [39].

In this study, supercritical antisolvent and conventional coevaporation was compared using PVP K17 and Poloxamer 407 as excipient and oxeglitazar as model drug. Oxeglitazar is one of the newly developed dual PPAR alpha/gamma agonists, of which the oral bioavailability is limited by its low aqueous solubility. In addition to potentially low absorption in patients, conventionally crystallized oxeglitazar is difficult to handle because of its needle-like habit. Thus, we aimed to improve both bioavailability and manufacturability of the model drug. Solid dispersions were characterized by powder X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), gas chromatography (GC), UV/VIS spectroscopy and in vitro dissolution tests.

Experimental

Oxeglitazar was obtained from Merck Santé, France; 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; dimethylsulfoxide (99.8 %) was supplied by 3D-Spektrum, Hungary; potassium phosphate monobasic, sodium phosphate dibasic dodecahydrate and sodium chloride were obtained from Reanal, Hungary.

Supercritical antisolvent process

The schematic diagram of the SAS apparatus is shown in *Fig. 2.* Feed solutions containing 2 wt. % API and 2 wt. % excipient were prepared by dissolving the calculated amount of pharmaceutical ingredients in 50 ml DCM. Feed solution (6) was dispersed through a capillary nozzle (125 μm ID) (8) in a cocurrent $scCO_2$ stream. Feed solution was delivered by a reciprocating HPLC pump (Gilson 307, France) (7) at a flow rate of 3 ml/min, 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. 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).

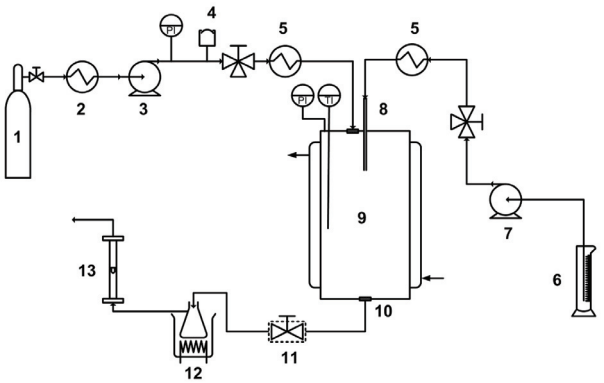

Fig. 2. Schematic diagram of SAS apparatus. 1. CO_2 source, 2. Cooler, 3. CO_2 metering pump, 4. Bursting disc, 5. Heat exchanger, 6. Solution source, 7. Solution metering pump, 8. Capillary nozzle, 9. Precipitation vessel, 10. Frit filter, 11. Expansion valve, 12. Cold trap, 13. Gas flow meter.

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 h so that residual solvent contents are comparable to those of coevaporates.

Coevaporation process

Coevaporates were prepared by dissolving oxeglitazar and PVP K17 or Poloxamer 407 in a minimum amount (~20 ml) of DCM. The solvent was rapidly removed under reduced pressure in a rotary evaporator at 40 °C. Solid dispersions were ground and dried in a vacuum oven at 40 °C for 24 h.

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 mortal until a homogenous mixture was obtained. 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 diffraction (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° 2 θ 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° 2 θ with a step size of 0.020° 2 θ 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 DMSO and directly injected in triplicate (2.0 µl) on a Chrompack Fused Silica column (25 m x 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 $Na_2HPO_4 \cdot 12\ H_2O$; 0.6 g 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 h, 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. 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. Error bars represent the standard error of the mean.

Results

Particle morphology

SEM micrograph of the raw drug prepared by cooling crystallization showed thin needle-like crystals *(Fig. 3a)*. 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 crystallographic direction resulting in acicular crystals. This habit was found undesirable because of its poor flow properties.

SAS prepared coprecipitates formed a thick cottony layer on vessel wall. Oxeglitazar/Poloxamer 407 powder consisted of aggregated acicular particles ranging from 0.5 to 1.5 mm in length *(Fig. 3b*). In contrast, coprecipitation of drug and PVP K17 resulted in aggregated tabular particles with a mean diameter of less than 200 μm and a thickness of a few micrometers *(Fig. 3c)*. Aggregates of rod-like crystals and irregular particles were observed for oxeglitazar/Poloxamer 407 coevaporate *(Fig. 3d)*. Unlike the above mentioned formulations, PVP has precipitated as a film rather than particulate powder *(Fig. 3e)*.

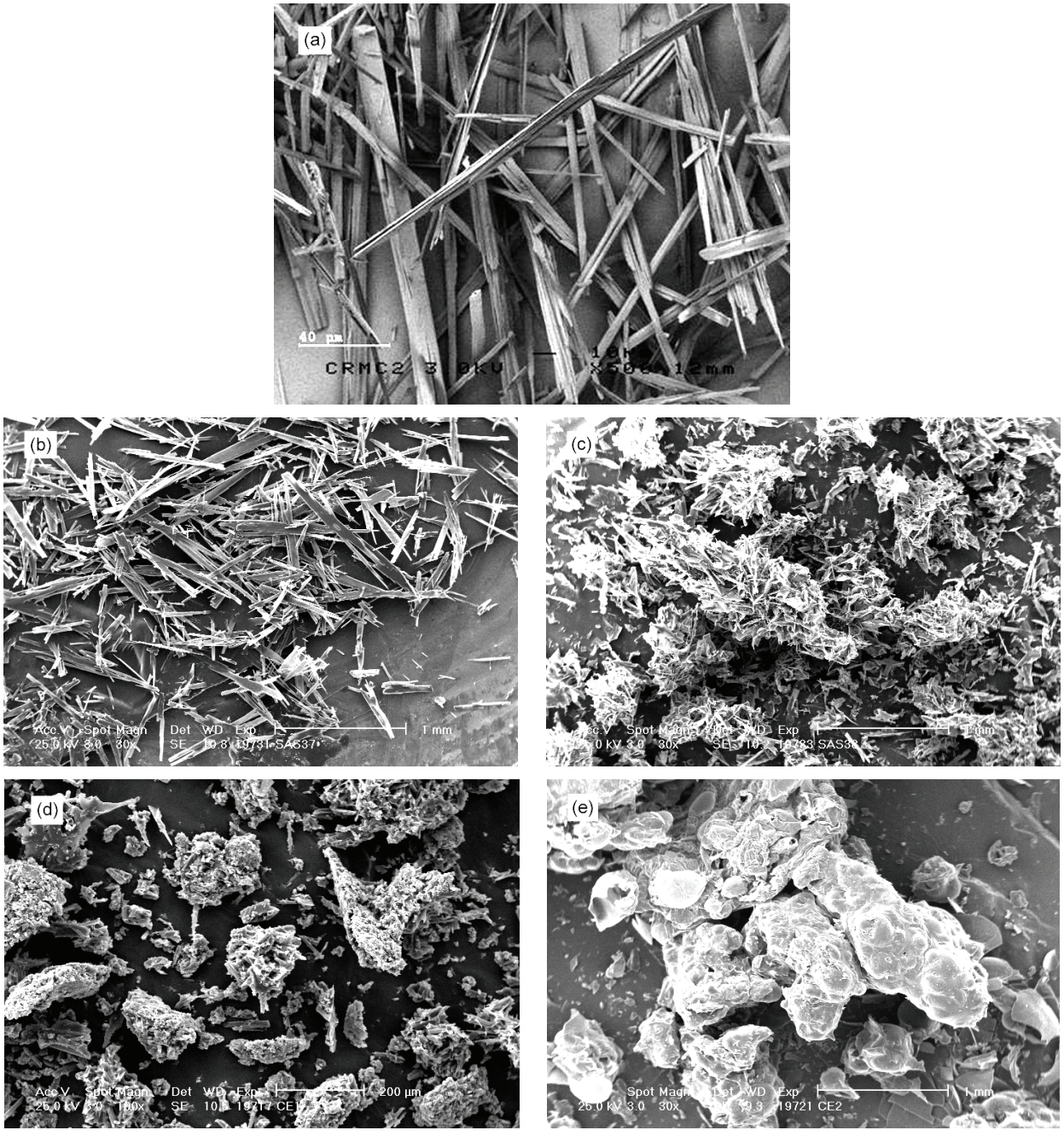

Fig. 3. Scanning electron micrographs of raw oxeglitazar (a), SAS oxeglitazar/Poloxamer 407 (b), SAS oxeglitazar/PVP K17 (c), CoE oxeglitazar/ Poloxamer 407 (d), CoE oxeglitazar/PVP K17 (e).

Crystallinity and polymorphic purity

XRD patterns of raw drug, excipients, coprecipitates and coevaporates are shown in *Fig. 4* and *Fig. 5*. Oxeglitazar and Poloxamer 407 are crystalline compounds with well-defined peaks while PVP K17 is amorphous and shows no diffraction peak. Although crystalline drug was detectable in all formulations, considerably lower peak intensities were observed suggesting that semi-crystalline solid dispersions were obtained in both techniques. The highest amorphous content was measured in CoE oxeglitazar/PVP K17 followed by SAS oxeglitazar/PVP K17, CoE oxeglitazar/Poloxamer 407 and SAS oxeglitazar/Poloxamer 407. Preliminary XRD and differential scanning calorimetric studies (data not shown) revealed that oxeglitazar has two polymorphic forms of which the higher melting form (A) is the thermodynamically stable one at all temperatures (monotropic system). However, the metastable form was not detectable in any formulation.

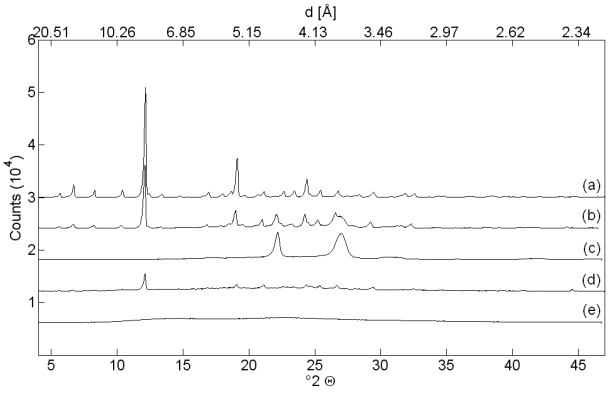

Fig. 4. XRD patterns of raw drug (a), SAS oxeglitazar/Poloxamer 407 (b), Poloxamer 407 (c), SAS oxeglitazar/PVP K17 (d), PVP K17 (e).

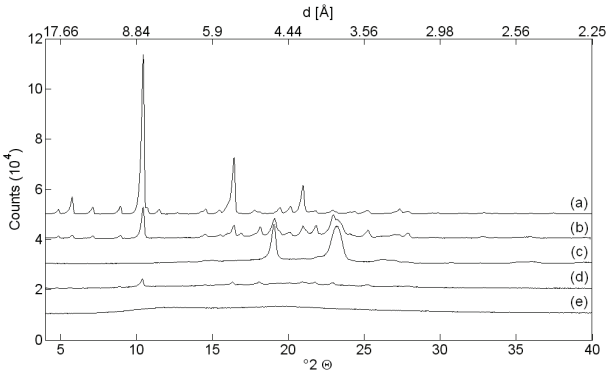

Fig. 5. XRD patterns of raw drug (a), CoE oxeglitazar/Poloxamer 407 (b), Poloxamer 407 (c), CoE oxeglitazar/PVP K17 (d), PVP K17 (e).

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 [11]. However, the new band appears only when the ratio of bonded to non-bonded group is high enough. When non-bonded groups dominate over hydrogen-bonded ones, only a slight broadening is observed due to the superposition of the two bands.

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 *(Fig. 6a)*. Although the stretching vibration of OH gives a broad and intense band it was not considered because of the water residues [40]. The position of νC=O band was below 1700 cm^{-1} due to the conjugation with double bounds and aromatic ring [41]. Likewise, a broad well defined band was observed in the spectrum of PVP K17 at 1672 cm^{-1} assigned to the carbonyl stretching vibration *(Fig. 6b)*. Each pyrrole ring of the PVP polymer contains two hydrogen acceptor groups: a carbonyl group and a tertiary amine. However, this latter is not favored in hydrogen bonding due to a steric hindrance [11,42]. The FTIR spectrum of the physical mixture revealed no considerable interaction between the pharmaceutical ingredients. The spectrum shown in *Fig. 6c* 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 *(Fig. 6d-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.

FTIR spectra of oxeglitazar/Poloxamer 407 solid dispersions are shown in *Fig. 7*. 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.

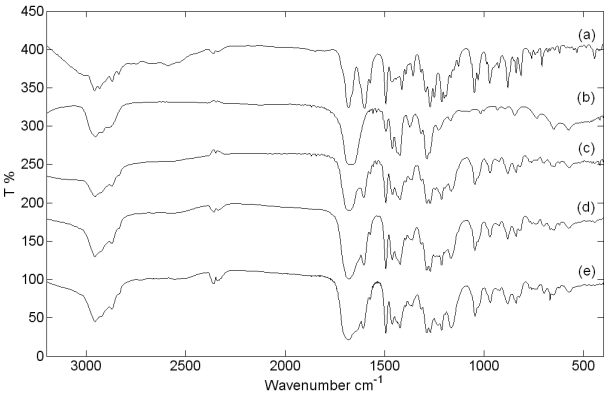

Fig. 6. FTIR spectra of solid dispersions of oxeglitazar and PVP K17: (a) raw drug, (b) PVP K17, (c) physical mixture, (d) SAS oxeglitazar/PVP K17, (e) CoE oxeglitazar/PVP K17.

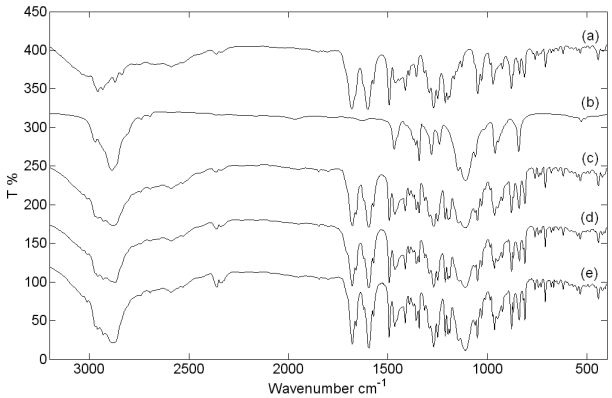

Fig. 7. FTIR spectra of solid dispersions of oxeglitazar and Poloxamer 407: raw drug (a), Poloxamer 407 (b), physical mixture (c), SAS oxeglitazar/Poloxamer 407 (d), CoE oxeglitazar/Poloxamer 407 (e).

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 [43]. 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.

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). The oxeglitazar/PVP formulations have retained much more solvent. Vacuum dried coprecipitate and coevaporate met Option 2 limit but exceeded Option 1 limit.

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

Drug content

Drug contents are listed in *Table* 2. Both SAS prepared powders contained more oxeglitazar than the nominal value (50 wt. %) 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.

Table 2 Oxeglitazar content (wt. %).

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

Solubility studies

Oxeglitazar solubility as a function of excipient concentration is shown in *Fig. 8.* 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.

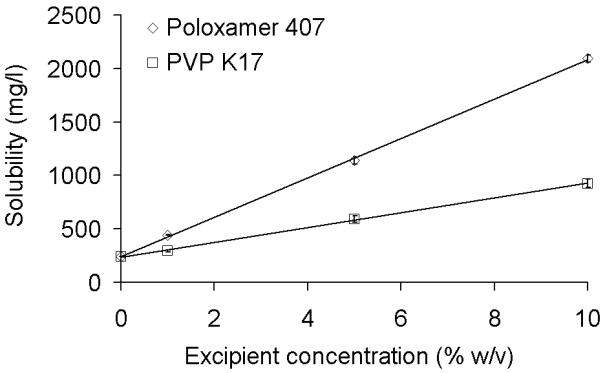

Fig. 8. Phase solubility diagram of oxeglitazar in pH 7.4 phosphate buffer media with various Poloxamer 407 and PVP K17 concentrations.

Dissolution studies

Dissolution profiles in *Fig. 9* and *Fig. 10* illustrate the dissolution kinetics of drug-carrier solid dispersions, physical mixtures and raw drug in pH 7.4 phosphate buffer medium. Coprecipitates and coevaporates exhibited significantly higher dissolution rates compared to conventionally crystallized oxeglitazar and physical mixtures. At 5 min, dissolved oxeglitazar from PVP K17 coevaporate and coprecipitate attained 85.6 and 64.3 %, while only 30.5 % of the raw drug were dissolved. Remarkable improvements were achieved with Poloxamer 407 as well. 61.9 and 57.9 % of the incorporated oxeglitazar were dissolved from the SAS prepared solid dispersion and the coevaporate, respectively.

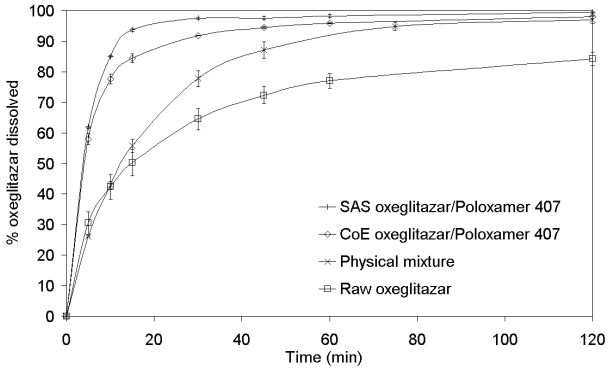

Fig. 9. Dissolution profiles of oxeglitazar/Poloxamer 407 solid dispersions, physical mixture and raw drug.

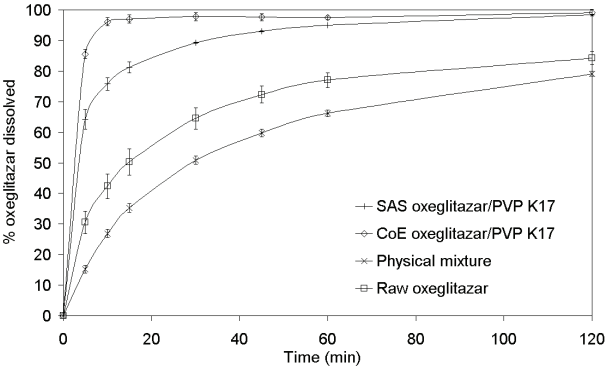

Fig. 10. Dissolution profiles of oxeglitazar/PVP K17 solid dispersions, physical mixture and raw drug.

Discussion

Formulations were shown to have very different morphology depending on the method of preparation and the excipient involved. Oxeglitazar/Poloxamer 407 coprecipitate consisted of aggregated acicular particles similar to those observed for the raw drug. Unusually large particle size was observed in comparison with other SCF processed products [13,33,34]. 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. who found that mean particle size of SEDS prepared paracetamol increased linearly with the time of precipitation process [44]. 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. Primary particle size of SAS prepared oxeglitazar/PVP K17 was still very large but needle-like shape was successfully changed into tabular one. SEM micrographs showed aggregated platelets with a thickness of a few micrometers. In contrast, when solvent was removed by evaporation PVP gave a film-like precipitate wherein dispersed drug was not distinguishable from the excipient matrix in SEM micrographs.

The physical state of each drug-carrier formulation was investigated by XRD measurements. The high-intensity diffraction peaks of oxeglitazar (form A) at *d* values of 15.26, 8.45, 5.39 and 4.23 Å were hardly detectable in solid dispersions. Consistently with previous studies PVP has successfully inhibited the crystal growth of the active substance [10,11,45,46] while, Poloxamer 407 remained crystalline after the formulation process too, and hence semi-crystalline solid dispersions were obtained instead of solid solutions. 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.

In fact, the amorphous form that predominantly constitutes the solid dispersions is also metastable above or near the glass transition temperature. The amorphous to crystalline phase transition is even faster if micro or nano-crystals are present in the formulation. The use of pharmaceutical excipients is often sufficient to inhibit crystallization and improve long-term stability. An amorphous polymer matrix may reduce considerably the molecular mobility of the incorporated API which is in most cases linked by weak interactions such as hydrogen bonding to the polymer [47,48]. FTIR studies were performed in order to detect possible hydrogen bonding interactions. Such interaction was not found in either physical mixture according to our expectations. Absorption bands have simply superposed when pharmaceutical ingredients were mixed dry. In the FTIR spectra of oxeglitazar/PVP K17 solid dispersions the νC=O band is split into two frequencies. A new band seems to appear at about 1650 cm^{-1} beneath the broad absorption band of physical mixture at 1680 cm^{-1}. The shift of carbonyl stretching band to higher frequency implies its engagement in hydrogen bonding with the only hydrogen donor group, the carboxylic OH of oxeglitazar. Such interactions between the carbonyl group of PVP and the carboxylic OH of another molecule was previously reported [11,40,46]. In the case of Poloxamer 407, possible hydrogen bonding could be expected between the carboxylic OH of the drug and the ether oxygen of the polymer, or between the terminal OH of Poloxamer and one hydrogen acceptor group of oxeglitazar. However, FTIR studies showed no evidence of such interactions. The spectra of oxeglitazar/Poloxamer 407 solid dispersions were virtually identical to that of physical mixture.

GC analysis revealed that residual DCM content in oxeglitazar/Poloxamer 407 formulations met recommended limits under Option 2 and it can be easily reduced below Option 1 limit by vacuum drying [43]. Unlike the crystalline Poloxamer 407, the oxeglitazar/PVP K17 coprecipitate and coevaporate exceeded the higher Option 2 limit and formulations did not meet Option 1 limit even after drying for 24 h. The main drawback of

coevaporation is that solvent traces get trapped in the amorphous solid dispersion and further drying process is needed. Coevaporates were left in the rota-dest apparatus for 2 h, the time that a typical SAS process has taken, even though DCM had evaporated within a few minutes. Thus residual solvent contents in coprecipitate and coevaporate are comparable.

Residual DCM contents were consistent with published works on SCF processed pharmaceutical products. Bitz and Doelker compared spray-drying, solvent evaporation and ASES processes [13]. Residual DCM concentrations in L-poly(lactic acid) (L-PLA) and L-PLA/tetracosactide powders after 4 hours of solvent stripping were 5283 and 758.3 ppm, respectively. Powders were further dried under reduced pressure for 3 day after which residual DCM contents decreased below 6 ppm. Ruchatz et al. studied the effect of spraying rate and CO_2 flow rate on the residual solvent content, particle size, yield and morphology of ASES prepared L-PLA particles [22]. The authors achieved low residual concentrations of DCM (71.5 – 449.9 ppm) after 5 hours of solvent stripping by varying the CO_2 flow rate in the range of 2 – 11 kg/h. Experiments, carried out at constant spraying rate and drying time revealed that residual solvent level and CO_2 flow rate were inversely proportional. Thus, residual solvent level can be reduced by increasing the CO_2 flow rate or extending the solvent stripping. Among the two techniques, assessed in this work, SAS was more favorable in terms of residual solvent content, while among the excipients, Poloxamer 407 was proved to be easier to dry. Owing to its amorphous state PVP has a high tendency to retain solvent residues during the drying or solvent stripping process.

All drug-carrier formulations exhibited improved dissolution properties that allow more of the drug to be absorbed. Dissolved oxeglitazar from Poloxamer 407 coprecipitate and coevaporate at 5 min was 61.9 and 57.9 %, respectively. The increase in dissolution rate was roughly two-fold in both formulations. Surprisingly, oxeglitazar/PVP K17 solid dispersions showed even higher dissolution rates: 64.3 and 85.6 % of the active substance prepared by SAS and coevaporation process were dissolved within 5 min. 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. Poloxamers are highly water soluble amphiphilic polymers that form micelles in aqueous media and stabilize dissolved molecules or nanoparticles of hydrophobic APIs. 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. The dissolution of oxeglitazar/PVP solid dispersion is governed by the disintegration of the polymer matrix which was found to be very fast. Although, Poloxamer 407 exhibited better drug solubilizing properties, the absorption of an orally administered drug is governed by kinetic rather than thermodynamic factors. In addition to better dissolution kinetics, oxeglitazar/PVP K17 solid dispersions are expected to be more stable due to the hydrogen bonding revealed by FTIR studies. On the other hand, residual solvent contents were much lower in oxeglitazar/Poloxamer 407 formulations. The concentration of DCM was below the Option 1 limit after 24 h drying. Among the two techniques SAS was found to be more efficient in residual solvent removal. DCM concentrations were 38 % lower for oxeglitazar/Poloxamer 407 coprecipitate and 28 % lower for oxeglitazar/PVP K17 coprecipitate than for corresponding coevaporates.

Conclusions

Supercritical antisolvent and coevaporation techniques were evaluated for their potential use in the preparation of immediate release solid oral dosage forms. 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.

However, one must keep in mind that the results obtained with these techniques are highly specific to a particular formulation. Other drug-carrier systems have different characteristic properties; thus, it's recommended to perform new experiments in all cases. SAS process is influenced by several operating parameters that might allow better control over the physical properties of the prepared formulations.

Acknowledgements

The authors kindly acknowledge the financial support from Merck Santé, 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 foundations „Industry for Engineering Education in Veszprém" and „Peregrinatio I".

REFERENCES

1. MAJERIK V., CHARBIT G, BADENS E., HORVÁTH G., SZOKONYA L., BOSC N., TEILLAUD E.: J. Supercrit. Fluids, In press
2. FDA, 2002. Draft – Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products. U.S. Department of Health and Human Services, Food and Drug

Administration, Center for Drug Evaluation and Research

3. LINDENBERG M., KOPP S., DRESSMAN J. B.: Eur. J. Pharm. Biopharm., 2004, 58, 265-278
4. SZENTE L., SZEJTLI J.: Adv. Drug Delivery Rev., 1999, 36, 17-28
5. World Pat. 0232462
6. World Pat. 04096284
7. CASSIDY O. E., HASKAYNE L., ROWLEY G.: Eur. J. Pharma. Sci., 1998, 6, S23
8. RASENACK N., STECKEL H., MÜLLER B. W.: Powder Tech., 2004, 143-144, 291-296
9. LEUNER C., DRESSMAN J.: Eur. J. Pharm., 2000, 50, 47-60
10. VAN NIJLEN T., BRENNAN K., VAN DEN MOOTER G., BLATON N., KINGET R., AUGUSTIJNS P.: Int. J. Pharma., 2003, 254, 173-181
11. SETHIA S., SQUILLANTE E.: Int. J. Pharm., 2004, 272, 1-10
12. SETHIA S., SQUILLANTE E.:. Crit. Rev. Ther. Drug Carrier Syst., 2003, 20, 215-247
13. BITZ C., DOELKER E.: Int. J. Pharm., 1996, 131, 171-181
14. SINGHAL D., CURATOLO W.: Adv. Drug Del. Rev., 2004, 56, 335-347
15. BAUER J., SPANTON S., HENRY R., QUICK J., DZIKI W., PORTER W., MORRIS, J.: Pharm. Res., 2001, 18, 859-866
16. World Pat. 0115664
17. YORK P.: Pharma. Sci. Tech. Today, 1999, 11, 430-440
18. JUNG J., PERRUT M.: J. Supercrit. Fluids, 2001, 20, 179-219
19. CHARBIT G., BADENS E., BOUTIN O.: Methods of Particle Production. In: York P., Kompella U. B., Shekunov B. Y.: Supercritical Fluid Technology for Drug Product Development, Drugs and Pharmaceutical Sciences Vol. 138, Marcel Dekker Inc., New York, pp. 159-212, 2004
20. MAJERIK V., HORVÁTH G., CHARBIT G., BADENS E., SZOKONYA L., BOSC N., TEILLAUD E.: Hun. J. Ind. Chem., 2004, 32, 41-56
21. PASQUALI I., BETTINI R., GIORDANO F.: Eur. J. Pharm. Sci., 2006, 27, 299-310
22. RUCHATZ F., KLEINEBUDDE P., MÜLLER B. W.: Int. J. Pharm. Sci., 1997, 86, 101-105
23. BEACH S., LATHAN D., SIDGWICK C., HANNA M., YORK P.: Org. Proc. Res. Dev., 1999, 3, 370-376
24. 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. The Cristal2, Toulouse, 2003
25. BADENS E., FARGEOT C., BOSC N., VEESLER S., TEILLAUD E., CHARBIT G.: Polymorph control of drug in supercritical CO_2. European Conference on Drug Delivery and Pharmaceutical Technology, Sevilla, 2004
26. BADENS E., TEILLAUD E., CHARBIT G., HORVÁTH G., SZOKONYA L., BOSC N., MAJERIK V.: Solubility enhancement of a pharmaceutical ingredient using supercritical antisolvent and spray-freezing techniques. 7th International Symposium on Supercritical Fluids, Orlando, 2005
27. JUNG J., CLAVIER J. Y., PERRUT M.: Gram to kilogram scale-up of supercritical Anti-solvent process. 6th International Symposium on Supercritical Fluids, Versailles, 2003
28. PERRUT M., JUNG J., LEBOEUF F.: Int. J. Pharm., 2005, 288, 11-16
29. U.S. Pat. 5,360,478
30. MONEGHINI M., KIKIC I., VOINOVICH D., PERISSUTTI B., FILIPOVIC-GRCIC J.: Int. J. Pharm., 2001, 222, 129-138
31. CORRIGAN O. I., CREAN A. M.: Int. J. Pharm., 2002, 245, 75-82
32. FALK R. F., RANDOLPH T. W., MEYER J. D., KELLY R. M., MANNING M. C.: J. Cont. Rel., 1997, 44, 77-85
33. REVERCHON E., 1999. Supercritical antisolvent precipitation of micro- and nano-particles. J. Supercrit. Fluids, 15, 1-21.
34. REVERCHON E., DELLA PORTA G., DE ROSA I., SUBRA P., LETOURNEUR D.: J. Supercrit. Fluids, 2000, 18, 239-245
35. TAKI S., BADENS E., CHARBIT G.: J. Supercrit. Fluids, 2001, 21, 61-70
36. WON D.-H., KIM M.-S., LEE S., PARK J.-S., HWANG S.-J.: Int. J. Pharm., 2005, 301, 199-208
37. World Pat. 9,501,221
38. JUPPO A. M., BOISSIER C., KHOO C.: Int. J. Pharm., 2003, 250, 385-401
39. KERC J., SRCIC S., KNEZ Z., SENCAR-BOZIC P.: Int. J. Pharm., 1999, 182, 33-39
40. KACZMAREK H., SZALLA A., KAMINSKA A.: Polymer, 2001, 42, 6057-6069
41. COATES J.: Interpretation of Infrared Spectra, A Practical Approach. In: Meyers R.A.: Encyclopedia of Analytical Chemistry, John Wiley & Sons Ltd., Chichester, pp. 10815-10837, 2000
42. FORSTER A., HEMPENSTALL J., RADES T.: Int. J. Vib. Spec., [www.ijvs.com] 2001, 5, 6
43. FDA, 1997. International Conference on Harmonisation, ICH Guidance on Impurities: Residual Solvents, Federal Register. 62(247), 67377-67388
44. BRISTOW S., SHEKUNOV T., SHEKUNOV B. Y., YORK P.: J. Supercrit. Fluids, 2001, 21, 257-271
45. DELNEUVILLE I., DECHESNE J. P., DELATTRE L.: Int. J. Pharm., 1998, 168, 109-118
46. VAN DEN MOOTER G., AUGUSTIJNS P., BLATON N., KINGET R.: Int. J. Pharma., 1998, 164, 67-80
47. KHOUGAZ K., CLAS S.-D.: J. Pharm. Sci., 2000, 89, 1325-1334
48. MATSUMOTO T., ZOGRAFI G.: Pharm. Res., 1999, 16, 1722-1728