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Carvedilol dissolution improvement by preparation of solid dispersions with porous silica

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ABSTRACT

Impregnation of porous SiO_2 (Sylysia) with carvedilol from acetone solution was used to improve dissolution of this poorly water-soluble drug. Solvent evaporation in a vacuum evaporator and adsorption from acetone solution were the methods used to load various amounts of carvedilol into the Sylysia pores. The impregnated carriers were characterized using nitrogen-adsorption experiments, X-ray diffraction, wettability measurements, attenuated total reflectance FTIR spectroscopy and thermal analysis. The impregnation procedures resulted in a significant improvement of drug release compared to dissolution of pure carvedilol or its physical mixtures with Sylysia. The results showed that when the drug precipitated in a thin layer within the carrier the dispersion retained a high specific surface area, micropore volume, and drug-release rate from the solid dispersion. Increasing the amount of drug in the solid dispersion caused particle precipitation within the pores that decreased the carrier's specific surface area and pore volume and decreased the release rate of the drug. The results also suggest that the amorphous form of carvedilol, the improved wettability and weak interactions between the drug and carrier in the solid dispersion also contribute to improved dissolution of the drug from the dispersion.

1. Introduction

The number of poorly soluble drug candidates has risen sharply over the last two decades due to the developments in hit-identification strategies (Amidon et al., 1995) and the discovery of new drug targets that require higher compound lipophilicity for adequate interaction (Alsenz and Kansy, 2001). Enhancing the oral bioavailability of poorly water-soluble drugs by increasing the dissolution rate is one of the most challenging tasks in drug development. Salt formation, solubilization, particle-size reduction, and solid dispersion formation are the approaches most often used to reach this goal. The formulation of hydrophobic drugs as solid dispersions is a significant area of research aimed at improving their dissolution and bioavailability. Solid dispersions consist of a poorly water-soluble drug and a hydrophilic excipient that may be water-soluble or water-insoluble. In both cases, the carrier properties influence the dissolution rate of the drug. Adsorption onto insoluble, non-porous, high surface-area carriers is a well-known technique to enhance drug dissolution and was already described for silica-based excipients in the early 1970s (Monkhouse and Lach, 1972a,b). A group of insoluble porous excipients that can be found in the pharmaceutical literature for solid dispersion production consists of porous silicon dioxide (Unger et al., 1983; Takeuchi et al., 2004, 2005a,b; Uchino et al., 2007), polypropylene foam powder (Streubel et al., 2003), porous calcium silicate (Kinoshita et al., 2002; Sharma et al., 2005), porous aluminometasilicate (Ito et al., 2005), controlled pore glass (Okonoi et al., 1999), zeolites (Ali et al., 1992), and porous ceramic (Kawanabe et al., 1998). Ordered mesoporous materials with pores between 2 and 50 nm in diameter are also being explored as carriers for oral drug delivery. The most frequently used of these, mesoporous silicates, show great promise in the dissolution enhancement of a wide variety of poorly soluble drugs (Heikkilä et al., 2007; Mellaerts et al., 2005; Tozuka et al., 2005; van Speybroeck et al., 2009).

Sylysia is an amorphous SiO_2 with high specific surface area and porosity and is generally recognized as safe (GRAS) under United States FDA (Food and Drug Administration) regulations (Product brochure). It is primarily used as a tablet excipient to improve the ease of powder flow through the tableting process, which provides more accurate dosages. It can be also used for powderizing liquids, to increase viscosity of liquids and gels, or to protect sensitive compounds from moisture, in research it is used as a drug carrier in solid dispersions to improve dissolution. Spray-drying indomethacin and Sylysia resulted in an amorphous form of indomethacin in the solid dispersion, probably due to its incorporation into mesopores that inhibit crystallization of the drug

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(Takeuchi et al., 2005a,b). This amorphous structure was stable for at least 2 months at increased temperature and humidity. Similar results (dissolution rate improvement and drug amorphous structure in the dispersion) were also obtained with tolbutamide and spironolactone (Takeuchi et al., 2004; Uchino et al., 2007).

Solid dispersions obtained by using hydrophilic and water-soluble excipients (e.g., polyethylene glycols or surfactants) can be soft and tacky, with the powders thus prepared exhibiting poor flow and mixing properties. Some reports show that large amounts of various excipients that improve the disintegration and sticking of solid dispersion to dies and punches must be used (Kaur et al., 1980; Sjökvist and Nyström, 1991; Owutsu-Ababio et al., 1998). The use of such a high ratio of added excipients, however, greatly increases the tablet size and is therefore impractical in most cases. On the other hand, Takeuchi et al. showed that only filler and disintegrant are needed to prepare rapidly dissolving tablets containing a solid dispersion of indomethacin and Sylysia (Takeuchi et al., 2005a,b).

Carvedilol (±)-1-(carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol is an α_1, β_1, and β_2 adrenergic receptor antagonist (Ruffolo et al., 1990, 1993; van Zwieten, 1993). It is used to treat mild-to-moderate essential hypertension, mild-to-severe heart failure, and patients with systolic dysfunction after myocardial infarction (Colucci et al., 1996; Packer et al., 1996; Dargie, 2001). Carvedilol is practically insoluble in water and exhibits pH-dependent solubility. Its solubility is <1 μg/ml above pH 9.0, 23 μg/ml at pH 7, and about 100 μg/ml at pH 5 at room temperature (Brook et al., 2007). The solubility of carvedilol in aqueous solutions with pH ranging from 1 to 4 is limited due to its protonation, resulting in "in situ" hydrochloride salt formation, which exhibits lower solubility in media containing chlorine ions due to the common-ion effect (Brook et al., 2007). Its extremely low solubility at alkaline pH levels may prevent the drug from being available for absorption in the small intestine and colon, thus making it a poor candidate for an extended-release dosage form (Chakraborty et al., 2009). Carvedilol undergoes significant stereoselective first-pass metabolism, resulting in low absolute bioavailability (30% or less) (Neugebauer et al., 1990; Chen and Chow, 1997; Morgan, 1994). However, some sources suggest that this low bioavailability is the result of poor aqueous solubility (Chen and Chow, 1997; Morgan, 1994). Improving the dissolution rate of carvedilol with self-emulsifying drug delivery systems (SEDDS) led to the improvement of drug bioavailability by 413% following oral administration compared to commercially available tablets (Wei et al., 2005). Other approaches used to improve carvedilol dissolution are self-nanoemulsifying tablets (Mahmoud et al., 2009), formation of inclusion complexes with cyclodextrins (Bhutani et al., 2007; Hirlekar and Kadam, 2009), and buccal sprays or capsules (Dugger, 2003).

It is well known that a poorly water-soluble drug requires more time to dissolve in the gastrointestinal fluid than it takes to be absorbed (Horter and Dressman, 1997). Limited solubility or dissolution in the gastrointestinal tract results in insufficient and variable absorption (Martin, 1993). This study set out to achieve an improved dissolution rate for carvedilol by impregnating Sylysia 350 particles with the drug. Two different solid dispersion preparation methods of carvedilol and Sylysia were used and compared. Firstly, carrier was impregnated in vacuum evaporator from carvedilol-acetone solution. This method is industrially applicable since it is fast and no drug is lost. Secondly, carvedilol was adsorbed after equilibration in acetone solution, filtered and dried. This method is expected to produce dispersions with best possible distribution of the drug within the Sylysia in thin layer and as a consequence best possible drug release. Changes in the molecular state of carvedilol in dispersions were investigated by powder X-ray diffractometry (PXRD) and differential scanning calorimetry (DSC). The carvedilol's release behaviour from solid dispersions was correlated with results of the methods mentioned above, as well as wettability, specific surface area, helium pycnometric density and pore-volume measurements.

2. Materials and methods

2.1. Materials

Carvedilol was obtained from Krka Pharmaceuticals (Novo Mesto, Slovenia). Porous SiO_2 Sylysia 350 was obtained from Fuji Silysia Chemicals (Kasugai, Japan). All other materials used in the study were of reagent grade.

2.2. Preparation of solid dispersion particles and drug content determination

Solid dispersions of carvedilol and Sylysia were prepared using two methods:

Method A: To prepare solid dispersion particles using evaporation, 2 g of Sylysia was suspended in 100 ml of carvedilol solutions in acetone (1%, 2%, and 4%, w/v). The suspensions obtained were evaporated in a vacuum evaporator (IKA RV 05, Staufen, Germany) at a rotation speed of 50 rpm at 50 °C for about 30 min. Two zirconium oxide balls (diameter 20 mm) were put into a stoppered 250 ml round-bottom flask in order to prevent agglomerate formation during solid dispersion preparation. The dispersions obtained – denoted as EV – contained 33%, 50%, and 67% of the drug.

Method B: 2 g of Sylysia was added to 100 ml of carvedilol solutions in acetone (2%, 3%, and 10%, w/v; solubility of carvedilol in acetone at 25 °C is 10.4 g/100 ml) in a stoppered 250 ml flat-bottom flask. After 24 h of equilibration using a magnetic stirrer (IKA Big Squid, Staufen, Germany) at room temperature, suspensions were filtered through a 0.2 μm membrane filter (Sartorius Minisart-SRP, Göttingen, Germany) and dried in a vacuum drier. The dispersions obtained – denoted as EQ – contained 35%, 46%, and 65% of the drug respectively. For EQ solid dispersions, various drug concentrations in acetone solution were tested with the aim of preparing solid dispersions with the same concentration of carvedilol as in EV dispersions. This enabled investigation of possible different ways to pack the drug in the carrier due to different methods used for solid dispersion preparation. It is believed that during preparation of EV dispersions precipitation of the drug in the form of particles dominates adsorption in a thin layer during evaporation of the solvent. In the case of EQ dispersions, it is expected that a high proportion of the drug adsorbs onto the carrier's surface in the form of a thin layer and that after filtration only the remaining solution in the carrier's pores causes precipitation of the drug particles during final drying of the dispersion.

Separate samples were prepared to measure the adsorption of carvedilol onto Sylysia using the solution depletion method after 24 h of equilibration at room temperature.

All solid dispersions were dried at room temperature in a vacuum chamber for 5 h and kept over silica gel at room temperature before their physicochemical properties were tested. Physical mixtures of carvedilol and Sylysia were prepared in proportions equivalent to solid dispersions by weighing and mixing the necessary amount using a mortar and pestle.

The dried solid dispersion particles were weighed and extracted in acetone using an ultrasound bath (Sonis 4, Iskra, Ljubljana, Slovenia) for 10 min. After filtration through the membrane filter and sufficient dilutions, samples were analyzed spectrophotometrically at 332 nm (Hewlett Packard HP 8453, Waldbronn, Germany). The drug content was calculated from the carvedilol-in-acetone calibration curve. Solubility of carvedilol in acetone at 25 °C and 50 °C acetone was determined in similar manner. Excess amount of the

drug crystals was added into 50 ml of acetone, termostated and stirred on a magnetic stirrer-hot plate for 5 h and filtered. Saturation concentration was determined spectrophotometrically.

2.3. Preparation of amorphous carvedilol

Amorphous carvedilol was prepared by melting the crystalline form at 130 °C in a thermally resistant container and quenching it with liquid nitrogen. The samples were stored in a desiccator over silica gel at room temperature.

2.4. Scanning electron microscopy

Powder samples were analyzed by scanning electron microscope (SEM). The particles were deposited on double-sided carbon tape (diameter 12 mm, Oxon, Oxford Instruments, UK). A SEM (Supra 32 VP, Zeiss, Oberkochen, Germany) was used with an acceleration voltage of 0.8 kV and a secondary detector. Samples were scanned with magnifications of 10,000×.

2.5. Differential scanning calorimetry

DSC curves were recorded with a calorimeter DSC 1, (Mettler Toledo, Schwerzenbach, Switzerland). A 3–5 mg sample was weighed and sealed in an aluminium pan. Samples were heated from 273 to 448 K at a rate of 20 K/min under nitrogen flow (40 ml/min). The calorimeter was calibrated with indium.

2.6. Powder X-ray diffraction

Samples were characterized using an X-ray diffractometer (Philips PW3040/60 X'Pert PRO, Philips Electronic Instruments, Mahwah, NJ, USA) with Cu K_0 radiation (l = 1.5418 Å) at 40 kV and 30 mA. The scanning angle ranged from 2° to 70° of 2θ, steps were 0.04° of 2θ, and the counting time was 10 s/step.

2.7. Specific surface area

The nitrogen adsorption–desorption isotherms of the Sylysia and solid dispersions were recorded using a Micromeritics Tristar 3000 (Norcross, GA, USA) apparatus at 77 K. The samples' specific surface area was calculated using multipoint Brunauer–Emmett–Teller (BET) equation from the adsorption data in the relative pressure interval from 0.05 to 0.3 (Brunauer et al., 1938).

The total pore volume was estimated using the *t*-plot method of Lippens and De Boer (1938). The pore-size distribution was derived from the adsorption branches of the nitrogen isotherms using the BJH model (Barrett et al., 1951).

Prior to the measurements, samples were outgassed in a vacuum oven at room temperature for 12 h. Between 150 and 250 mg of the sample was used for each measurement.

2.8. Wettability measurements

The contact angle was measured using micro-observation of the static drop with a Krüss DSA100 (Hamburg, Germany) static contact angle analyzer. A 200 mg sample was weighed and compressed using a circular stainless steel punch and die assembly (diameter 13 mm) in a Specac hydraulic press (Kent, UK) with a 10 s dwell time at a pressure of 4×10^8 Pa. A 1-μl drop of a phosphate buffer (pH 6.8) was put on the compressed plate and the initial contact angle was measured. The results are an average of at least five measurements.

Another wettability test was performed by measuring the penetration time of a 1 μl drop of a phosphate buffer (pH 6.8) using the DSA-100 and video-recorder software. Shorter penetration times corresponded to improved wettability.

2.9. Attenuated total reflectance (ATR) Fourier transform-infrared spectroscopy (FTIR)

A Nicolet Nexus FTIR Spectrometer (Nicolet Instruments, Madison, WI, USA) equipped with a DTGS (deuterated triglycine sulphate) detector was employed for powder-sample measurements. A diamond ATR accessory (DuraSample IR Technologies, Danbury, CT, USA) was employed for the ATR FTIR experiments. Each spectrum comprises 32 co-added scans measured at a spectral resolution of 4 cm^{-1} in the 4000–500 cm^{-1} range with an aperture of 36. Spectral data were acquired with Omnic E.S.P. software version 5.2 (Nicolet Instruments).

2.10. Helium pycnometric density

Prior to the analysis, the helium pycnometer AccuPyc 1330 (Micromeritics, Norcross, GA, USA) was calibrated against the standard volume. Between 1 and 2 g of the sample was accurately weighed for helium density determination. Each determination included five purges with helium and three analytical runs.

2.11. Dissolution studies

The pharmaceutical performance of the drug alone and the Sylysia formulations was evaluated using in vitro dissolution studies. Drug release from the solid dispersions was compared to that of crystalline carvedilol, amorphous carvedilol, and physical mixtures. Dissolution experiments were conducted in 900 ml phosphate buffer (pH 6.8) using a USP II dissolution test apparatus (Vankel 7000, Cary, NC, USA). Our goal was to illustrate the advantage in dissolution rate of various solid dispersion formulations over pure drug and physical mixtures. At pH 1.2, where sink conditions are assured, carvedilol release discrimination between formulations was impossible (rapid release of the drug from the all solid dispersions was observed). Reduced "sink capacity" of the medium was achieved by using a phosphate buffer. Another reason for evaluation of solid dispersion formulations under these conditions is the variability of gastric pH, depending on the stomach state (fasting/fed) and its content. In addition, it is not necessary that sink conditions be assured at pH 1.2 when there is little liquid in the stomach. Some researchers have also reported that gastric residence times of solid dosage forms such as pellets or hard gelatin capsules are variable and can be extremely short (i.e., under 3 min or even only 15 s) when taken into an empty stomach, preventing the drug from dissolving in acidic media (Weitshies et al., 2005).

Powders containing 25 mg of carvedilol were put into the dissolution vessel at 37 ± 0.5 °C and stirred at 100 rpm. Samples of 5 ml were collected periodically and replaced with a fresh dissolution medium. The concentration of carvedilol was determined spectrophotometrically at 241 nm.

3. Results and discussion

3.1. Physicochemical properties of solid dispersions

Fig. 1 shows particles of (a) crystalline carvedilol, (b) amorphous carvedilol, (c) pure Sylysia, (d) a physical mixture of drug and Sylysia containing 33% carvedilol, and (e and f) two solid dispersions containing 67% and 65% (w/w) of drug. The crystalline and amorphous drug particles obtained by quench cooling are larger than Sylysia particles and can be distinguished in the physical mixture (Fig. 1d). Solid dispersion particles containing the highest amount of drug show the same morphology as pure Sylysia

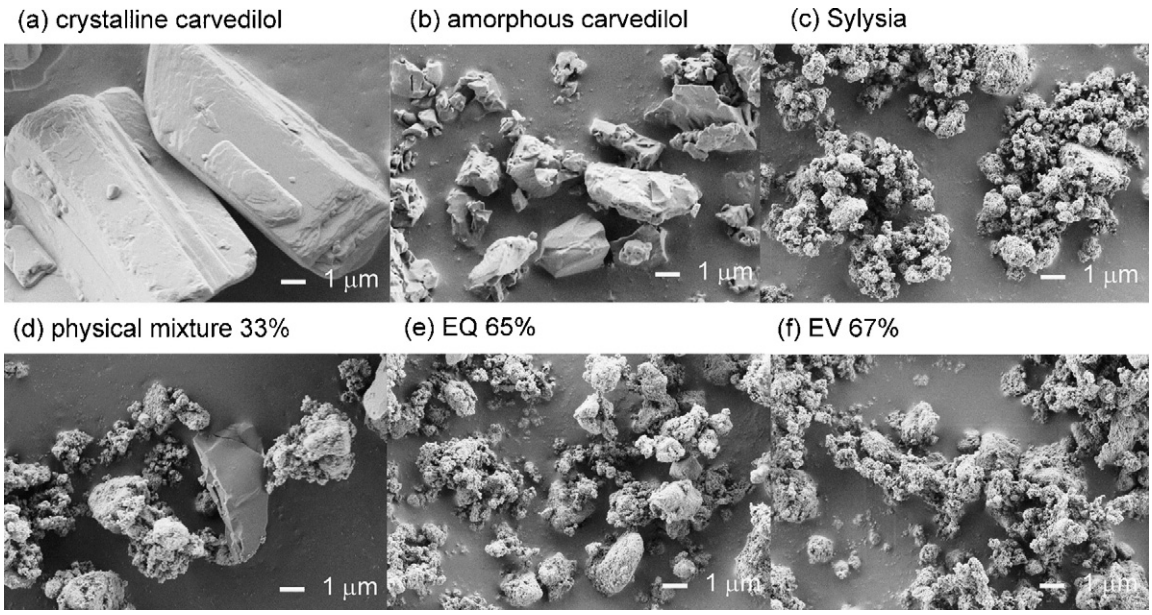

Fig. 1. SEM photos of (a) crystalline carvedilol, (b) amorphous carvedilol, (c) Sylysia, (d) physical mixture containing 33% amorphous carvedilol, and (e and f) solid dispersions containing the highest concentrations of carvedilol. Magnification 10,000×.

particles, suggesting that carvedilol is well dispersed within the particles. No separated particles of the drug were observed in the solid dispersions.

DSC curves of crystalline carvedilol, amorphous carvedilol, the physical mixture containing 33% drug, and solid dispersions containing the highest concentrations of the drug are shown in Fig. 2. The carvedilol melting peak with an onset temperature of 110 °C can be observed for crystalline carvedilol and the physical mixture. The absence of a melting peak for the solid dispersion DSC curves clearly indicates the amorphous state of the drug. The glass transition at 39 °C obtained for these samples is in agreement with the literature values (Pokharkar et al., 2006), confirming that carvedilol is amorphous in all solid dispersions prepared (DSC results of the samples containing lower concentrations of the drug are not shown). PXRD patterns of crystalline, amorphous, and EV 67% solid dispersion are shown in Fig. 3. It was confirmed that carvedilol is amorphous in all solid dispersions prepared (the PXRD results of other solid dispersions are not shown). The amorphous state of carvedilol can be a result of carrier pore size, its interactions with the silanol groups on the pore surfaces (Rupprecht et al., 1974; Vrečer, 1992), and rapid evaporation of the solvent. According to the literature (Godec et al., 2007), the pore-restricted nucleus for crystallization is in the range of a few nanometers. Because a large portion of the pores in Sylysia is larger than 20 nm, it can be concluded that other mechanisms are also likely involved in stabilizing the drug's amorphous state. It can be hypothesized that the interaction of carvedilol with the silica pores surface prevents crystallization of the drug. This inhibition of crystallization, probably due to various mechanisms involved, is also supported by the temperature of solid dispersion preparation by the evaporation method (50 °C), which was well above the drug glass transition temperature. On the contrary, additional experiments showed complete crystallization of pure carvedilol after rotary evaporation from acetone solution without the addition of Sylysia. From thermal analysis measurements it can be concluded that, at higher concentrations when the smallest pores are already full, carvedilol still precipitates as the amorphous form in larger pores and outer surfaces of the Sylysia particles.

Average pore diameter, specific surface area, and pore volume of pure Sylysia and solid dispersions are listed in Table 1. It is expected that specific surface area and pore volume decrease when the drug concentration in the dispersion increases. However, only relatively small changes of pore diameter are detected here. Pore-volume measurements suggest that in addition to its adsorption on the car-

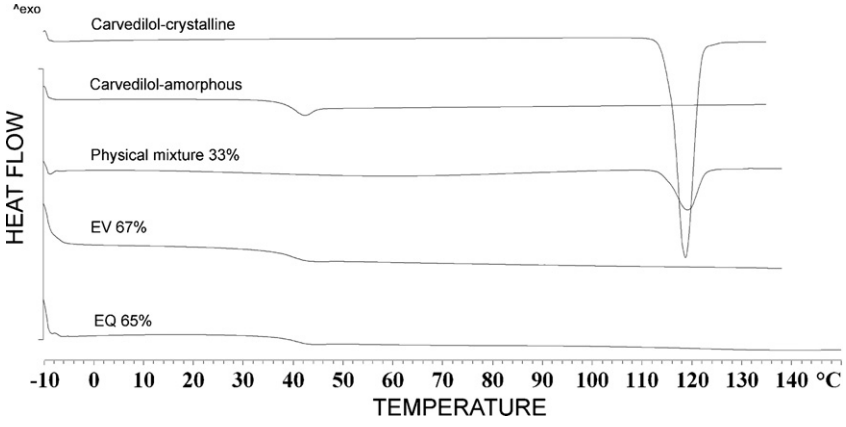

Fig. 2. DSC curves of crystalline carvedilol, amorphous carvedilol, the physical mixture with Sylysia containing 33% carvedilol, and solid dispersions containing the highest concentration of the drug prepared.

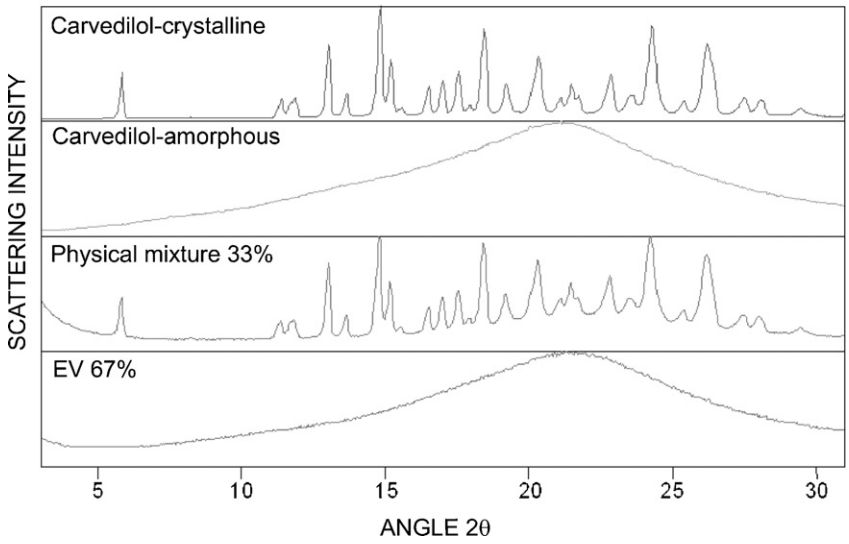

Fig. 3. XRPD data of crystalline and quench-cooled carvedilol, physical mixture with Sylysia containing 33% carvedilol, and solid dispersions containing the highest concentration of the drug prepared.

Table 1
Average pore diameter, specific surface area, and micropore volume (pore sizes from 1.7 to 300 nm) for Sylysia and the solid dispersions prepared.

Sample	Average pore diameter (nm)	BET surface area (m^2/g)	Micropore volume (cm^3/g)
Sylysia	25.3	277.5	1.76
EV 33%	25.6	134.1	0.85
EV 50%	24.4	49.3	0.34
EV 67%	22.6	6.9	0.04
EQ 34%	28.0	217.8	1.52
EQ 46%	26.3	198.7	1.31
EQ 65%	27.1	86.8	0.72

rier surface, carvedilol also precipitates in the form of particles at higher concentrations in the EV dispersion. The particles that precipitate during evaporation of the solvent occlude SiO_2 pores, which also leave behind void spaces. This results in greater reductions in volume and specific surface area with increasing drug content in EV dispersions compared to EQ dispersions. In the case of EQ dispersions, drug molecules can adsorb in the pores more evenly, probably in several layers. The theoretical content of carvedilol in Sylysia in the form of a monolayer was calculated by measuring the specific surface area of Sylysia using the nitrogen adsorption method and the molecular radius of dissolved carvedilol (0.6 nm) that was published by Almeida et al. (2004). According to this calculation, the mass concentration of carvedilol in Sylysia with a surface area of 277 m^2/g is 15%. It is believed that a small amount of carvedilol also precipitates in the form of particles in EQ dispersions, especially during drying, because some drug solution is still present in the carrier after filtration. Micropore volume and specific surface area may also be influenced by the adsorption tendency of the drug for the carrier surface from different solvents. Charnay et al. measured the amount of adsorbed indomethacin from a solution onto two SiO_2 powders (MCM41 and Aerosil) using various solvents (Charnay et al., 2004). It was determined that adsorption varies as a function of the solvent polarity, whereby higher amounts were adsorbed from nonpolar solvents. The experimental results of carvedilol adsorption from acetone solutions with different concentrations onto Sylysia are presented in Table 2. The amount of carvedilol adsorbed increases with the solution concentration, expressing a relatively high affinity for the carrier surface. These results support the hypothesis that the drug adsorbs onto the carrier surface in a thin layer because the EQ dispersion has more surface area than the EV dispersion with a similar concentration of carvedilol. The actual measured drug concentrations in the EQ dispersions that were higher than the theoretically expected ones (calculation of theoretical drug concentration in solid dispersion is based on the difference between the initial drug concentration and the measured equilibrium concentration after 24 h) confirm that a certain amount of solution remains in the dispersion after filtration and precipitates during drying. Most probably particles are formed in the dispersion from this residual solution. As the concentration of the solution increases, more particles are formed and the micropore volume of the dispersion decreases, from 1.52 cm^3/g for the EQ 34% dispersion to 0.72 cm^3/g for the EQ 65% dispersion.

As shown below, differences in specific surface area and pore volume between different solid dispersions are also reflected in different releases of the drug from these dispersions.

It was calculated theoretically that, given the micropore volume of pure Sylysia (1.76 cm^3/g) and helium density of crystalline carvedilol (1.26 g/cm^3) or amorphous (1.24 g/cm^3) carvedilol, about 2.2 g of the drug could be incorporated into 1 g of Sylysia, which is up to 70% by weight. The EV 67% and EQ 65% dispersions are close to this limit. According to these calculations, the Sylysia pores should be completely filled with the drug. This limit was

Table 2
Adsorption of carvedilol onto Sylysia at concentrations used for solid dispersion particles prepared with the equilibration method (C_{eq}).

Starting solution concentration (%)	Solution concentration in equilibrium (%)	Theoretical drug concentration in solid dispersion (%)	Measured drug concentration in solid dispersion (%)
2.0	1.34	24.8	33.6
3.0	1.96	34.2	46.1
10.0	8.14	48.2	64.9

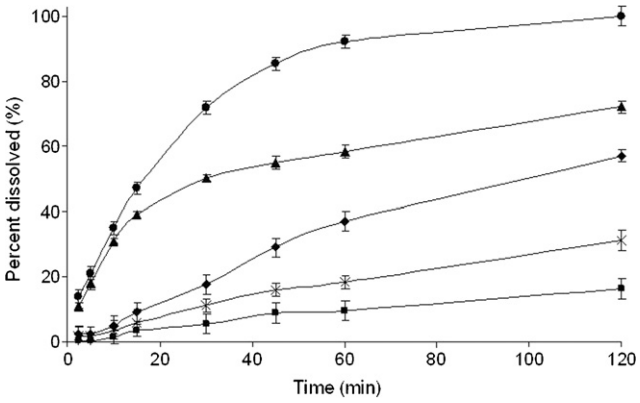

Fig. 4. Dissolution profiles of powders in buffer at pH 6.8. Crystalline carvedilol: ×, amorphous carvedilol: ■, and solid dispersions EV 33%: ●, EV 50%: ▲, and EV 67%: ♦.

reached in the EV dispersions but not the EQ dispersions. Despite the fact that the true density of the drug in solid dispersions is not known, these calculations and pore-volume measurements suggest that carvedilol also precipitated in pores larger than 300 nm and on the outer surfaces of the particles. This hypothesis is supported with additional approximate calculation since exact concentration of the drug in acetone at 50 °C, when particles start to form during EV process is not known. It can be higher than equilibrium solubility of 18.7 g/100 ml if supersaturation is needed for precipitation or lower, if silica surface promotes carvedilol particles precipitation. 1 g of Sylysia accepts 1.76 ml of carvedilol-acetone solution in its pores, which at predicted saturation point at 50 °C contains 0.33 g of the drug. Additional amount of carvedilol should according to this calculation precipitate in pores larger than 300 nm. These particles are most probably responsible for physical instability of the solid dispersion which will be an important topic in further investigations.

3.2. Release of carvedilol from solid dispersions and mechanisms involved

Figs. 4 and 5 represent a comparison of the dissolution profiles of crystalline carvedilol, amorphous carvedilol, the physical mixture containing 50% of the drug, and solid dispersions in phosphate buffer (pH 6.8). As already published in the literature, the formation of amorphous carvedilol failed to improve its dissolution rate (Pokharkar et al., 2006), which our results also confirm. The explanation for this was the conversion of the amorphous drug to a cohesive supercooled liquid at 37 °C, which is a temperature

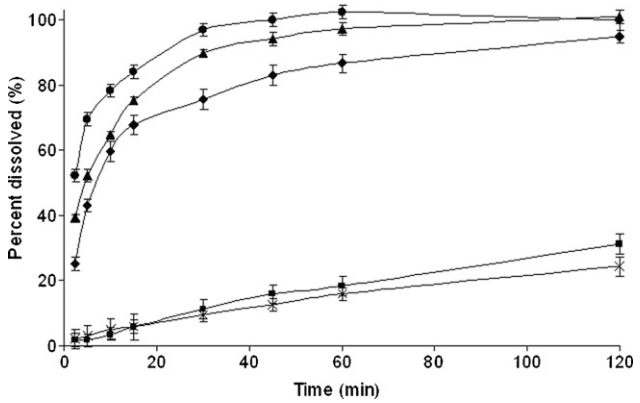

Fig. 5. Dissolution profiles of powders in buffer at pH 6.8; Crystalline carvedilol: ×, physical mixture with Sylysia containing 50% carvedilol: ■, and solid dispersions EQ 34%: ●, EQ 46%: ▲„ and EQ 65%: ♦.

Table 3
Initial contact angle and penetration time of phosphate buffered (pH 6.8) into powder compacts.

Sample	Contact angle (°)	Penetration time (s)
Sylysia	–[a]	–[a]
Crystalline carvedilol	72 ± 3	–[b]
Amorphous carvedilol	74 ± 4	–[b]
EV 33%	47 ± 3	40 ± 2
EV 50%	57 ± 2	120 ± 4
EV 67%	57 ± 4	180 ± 5
EQ 34%	46 ± 3	6 ± 2
EQ 46%	49 ± 3	9 ± 2
EQ 65%	53 ± 4	84 ± 3

[a] Not measurable, complete wetting.
[b] Infinitely long time.

close to the glass transition temperature of amorphous carvedilol. Formation of the physical mixture did not influence dissolution of the crystalline carvedilol as expected. However, drug release from solid dispersions prepared using the two different methods was significantly improved compared to the dissolution of crystalline samples. Comparing the solid dispersions prepared by evaporation shows decreasing release rates with increasing drug content. This can be explained by decreases in surface area available for dissolution due to pore filling, and decreases in wettability due to increases in drug content in the dispersion. Also, the proportion of larger drug particles that precipitate in Sylysia pores and need more time to dissolve probably increases along with increasing drug content in the dispersion. Table 3 shows that the initial contact angle measured for powder compacts and the time required for a 1 μl drop to penetrate into these compacts increases with the carvedilol content. However, these values are still much lower compared to pure carvedilol.

The rapid release of carvedilol from solid dispersions prepared using the equilibration method can be explained by the rapid desorption of the drug from silica surface as already hypothesized by Monkhouse and Lach (1972b). The addition of water to the solid dispersion results in desorption of the drug from the silica surface. This is the result of stronger interactions between the silica and water than those between the silica and drug. Interactions between carvedilol and Sylysia in the solid dispersions were evaluated with ATR FTIR. The spectra of Sylysia, crystalline carvedilol, amorphous carvedilol, the physical mixture, and the solid dispersion containing 50% drug are shown in Fig. 6. Generally, due to the lack of long-range order and the possibility of a range of molecular conformations and intermolecular arrangements, the vibrational spectra of amorphous samples exhibit broader merged bands compared to crystalline carvedilol. Band broadening and merging can be observed in the CH stretching region between 2900 and 3100 cm^{-1} and also between 3300 and 3400 cm^{-1}. No differences were found between spectra of the physical mixture and solid dispersion. It can be postulated that only weak van der Waals or hydrogen forces are involved in binding carvedilol onto Sylysia surfaces, thus enabling easy desorption of the drug during dissolution. In the Sylysia pores, the drug is adsorbed to a certain extent as a thin layer or small particles of the drug. The high specific surface area of these particles contributes to improved dissolution compared to pure drug. Additional parameters influencing dissolution are the amorphous drug structure together with the improved wettability of the dispersion particles that is observed from the accelerated penetration rate of the dissolution medium into the capillaries of these particles.

Comparing the carvedilol release rates from dispersions prepared by evaporation or equilibration shows that equilibration yields better results. These results can again be explained by the greater specific surface area exposed for release and better wettability of the particles prepared by equilibration. The faster release

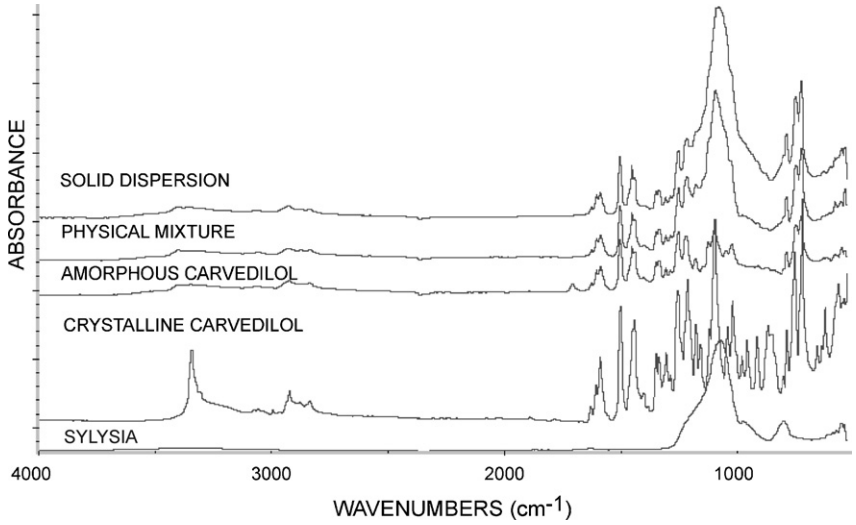

Fig. 6. IR spectra of Sylysia, crystalline carvedilol, amorphous carvedilol, the physical mixture, and the solid dispersion containing 50% drug in the spectral range between 500 and 4000 cm^{-1}.

of the drug from EQ dispersions compared to EV dispersions with similar carvedilol content correlates with the lower contact angle and shorter penetration time of the dissolution media into the particles. As mentioned above, in the EQ dispersions a large amount of carvedilol is relatively homogeneously distributed in a thin layer. In a monolayer no work is needed to break the bonds between solute (drug) molecules, as explained by Sinko (2006). The result is higher apparent solubility of the drug compared to the solubility of the drug in particle form.

From the industrial point of view for solid dispersion production the evaporation method is favoured over the equilibration method, which yielded better results in release behaviour in this study. Evaporation of the solvent during dispersion preparation prevents any drug loss. Improved adsorption and prevention of particle precipitation could be achieved by using the lowest volume of the drug solution that completely impregnates the carrier, as suggested by Ohta et al. (2005). The limitation on the amount of drug content in the dispersion would then be the solubility of the drug in the solvent. Additional attention should also be dedicated to the influence of the solvent on preventing crystallization of the drug in the solid dispersion.

4. Conclusion

Preparation of solid dispersions by impregnation of porous SiO_2 (Sylysia) was successfully used to increase the dissolution rate of poorly soluble carvedilol. It was confirmed that various mechanisms are involved in this improvement. Decreases in particle size and increases in surface area in comparison to pure drug were confirmed by specific surface-area measurements and electron microscopy. The contact angle and solvent penetration into compressed samples confirmed the improved wettability of the pure drug. Another mechanism that may contribute to improving the release rate of carvedilol from solid dispersions compared to the pure drug is amorphous structure, confirmed by thermal analysis and PXRD. In addition, the weak interactions between silica and carvedilol in solid dispersions detected by ATR spectroscopy also contributes to rapid desorption of the drug from the carrier surface upon contact with the dissolution media. The relatively large amount of the drug that can be incorporated into carrier particles confirmed that Sylysia is a promising universal carrier for further studies, including stability studies.

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References

Ali, A.S., Yamamoto, K., El-Sayed, A.M., Habib, F.S., Nakai, Y., 1992. Molecular behaviour of flufenamic acid in physical and ground mixtures with fluorite. Chem. Pharm. Bull. 40, 1289–1294.
Almeida, D.R.P., Gasparro, D.M., Martinek, T.A., Fulop, F., Csizmadia, I.G., 2004. Resolution of carvedilol's conformational surface via gas and solvent phase density functional theory optimizations and NMR spectroscopy. J. Phys. Chem. A 108, 7719–7729.
Alsenz, J., Kansy, M., 2001. High throughput solubility measurements in drug discovery and development. Adv. Drug. Deliv. Rev. 46, 3–26.
Amidon, G.L., Lennernäs, 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.
Barrett, E.P., Joyner, L.G., Halenda, P.P., 1951. The determination of pore volume and area distribution in porous substances. J. Am. Chem. Soc. 73, 373–380.
Bhutani, S., Hiremath, S.N., Swamy, P.V., Raju, S.A., 2007. Preparation and evaluation of inclusion complexes of carvedilol. J. Sci. Ind. Res. 66, 830–834.
Brook, C.S., Chen, W., Spoors, P.G., 2007. Carvedilol phosphate salts and/or solvates there of, corresponding compositions and/or methods of treatment US Patent 7,268,156.
Brunauer, S., Emmett, P.H., Teller, E., 1938. Adsorption of gases in multimolecular layers. J. Am. Chem. Soc. 60, 309–319.
Chakraborty, S., Shukla, D., Jain, A., Mishra, B., Singh, S., 2009. Assessment of solubilization characteristics of different surfactants for carvedilol phosphate as a function of pH. J. Coll. Interface Sci. 335, 242–249.
Charnay, C., Tourné-Péteilh, C., Nicole, L., Lerner, D.A., Devoiselle, J.M., 2004. Inclusion of ibuprofen in mesoporous templated silica: drug loading and release property. Eur. J. Pharm. Biopharm. 57, 533–540.
Chen, B.P., Chow, M.S.S., 1997. Focus on carvedilol: a novel beta-adrenergic blocking agent for the treatment of congestive heart failure. Formulary 32, 795–805.
Colucci, W.S., Packer, M., Bristow, M.R., Gilbert, E.M., Cohn, J.N., Fowler, M.B., Krueger, S.K., Hershberger, R., Uretsky, B.F., Bowers, J.A., Sackner-Bernstein, J.D., Young, S.T., Holcslaw, T.L., Lukas, M.A., 1996. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 94, 2800–2806.
Dargie, H.J., 2001. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 357, 1385–1390.
Dugger, H.A., 2003. Buccal sprays or capsules containing cardiovascular or renal drugs, US Patent 20030077229-A1.
Godec, A., Maver, U., Bele, M., Planinšek, O., Srčič, S., Gaberšček, M., Jamnik, J., 2007. Vitrification from solution in restricted space: formation and stabilization of amorphous nifedipine in a nanoporous silica xerogel carrier. Int. J. Pharm. 343, 131–140.
Heikkilä, T., Salonen, J., Tuura, J., Kumar, N., Salmi, T., Murzin, D.Y., Hamdy, M.S., Mul, G., Laitinen, L., Kaukonen, A.M., Hirvonen, J., Lehto, V., 2007. Evaluation of mesoporous TCPSi, MCM-41, SBA-15 and TUD-1 materials as API carriers for oral drug delivery. Drug Deliv. 14, 337–347.

Hirlekar, R., Kadam, V., 2009. Preparation and characterization of inclusion complexes of carvedilol with methyl-β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. 63, 219–224.
Horter, D., Dressman, J.B., 1997. Influence of physicochemical properties on dissolution of drugs in the gastrointestnal tract. Adv. Drug. Deliv. Rev. 25, 3–14.
Ito, Y., Arai, H., Uchino, K., Iwasaki, K., Shibata, N., Takada, K., 2005. Effect of adsorbents on the absorption of lansoprazole with surfactant. Int. J. Pharm. 289, 69–77.
Kaur, R., Grant, D.J.W., Eaves, T., 1980. Comparison of poly(ethylene glycol) and polyoxyethylene stearate as excipients for solid dispersion systems of griseofulvin and tolbutamide II: dissolution and solubility studies. J. Pharm. Sci. 69, 1321–1326.
Kawanabe, K., Okada, Y., Matsuse, Y., Ilida, H., Nakamura, T., 1998. Treatment of osteomylitis with antibiotic-soaked porous ceramic. J. Bone Joint Surg. 80B, 527–530.
Kinoshita, M., Baba, K., Nagayasu, A., Yamabe, K., Shimooka, T.I., Takeichi, Y., Azuma, M.I., Houchi, H., Minakuchi, K., 2002. Improvement of solubility and oral bioavailability of a poorly water-soluble drug, TAS-301, by its melt-adsorption on a porous calcium silicate. J. Pharm. Sci. 91, 362–369.
Lippens, B.C., De Boer, J.H., 1938. Studies on pore systems catalysts. V. The t-method. J. Catal. 4, 319–323.
Mahmoud, E.A., Bendas, E.R., Mohamed, M.I., 2009. Preparation snd evaluation of self nanoemulsifying tablets of carvedilol. AAPS PharmSciTech 10, 183–192.
Martin, A., 1993. Physical Pharmacy, fourth edition. Lea & Febiger, Philadelphia, p. 13.
Mellaerts, R., Aerts, C.A., van Humbeeck, J., Augustijns, P., van den Mooter, G., Martens, J.A., 2005. Enhanced release of itraconazole from ordered mesoporous SBA-15 silica materials. Chem. Commun. 13, 1375–1377.
Monkhouse, D.C., Lach, J.L., 1972a. Use of adsorbents in enhancement of drug dissolution, I. J. Pharm. Sci. 61, 1430–1435.
Monkhouse, D.C., Lach, J.L., 1972b. Use of adsorbents in enhancement of drug dissolution, II. J. Pharm. Sci. 61, 1435–1441.
Morgan, T., 1994. Clinicalpharmacokinetics and pharmacodynamics of carvedilol. Clin. Pharmacokinet. 26, 335–346.
Neugebauer, G., Akpan, W., Kaufmann, B., Reiff, K., 1990. Stereoselective disposition of carvedilol in man after intravenous and oral administration of the racemic compound. Eur. J. Clin. Pharmacol. 38, S108–S111.
Ohta, K.M., Fuji, M., Takei, T., Chikazawa, M., 2005. Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content. Eur. J. Pharm. Sci. 26, 87–96.
Okonoi, S., Oguchi, T., Yonemochi, E., Puttipipatkhachorn, S., Yamamoto, K., 1999. Physicochemical properties of ursodeoxacholic acid dispersed in controlled pore glass. J. Colloid Interface Sci. 216, 276–284.
Owutsu-Ababio, G., Ebube, N.K., Reams, R., Habib, M., 1998. Comparative dissolution studies for mefenamic acid-poly(ethylene glycol) solid dispersions systems and tablets. Pharm. Dev. Technol. 3, 405–412.
Packer, M., Bristow, M.R., Cohn, J.N., Colucci, W.S., Fowler, M.B., Gilbert, E.M., Shusteman, N.H., 1996. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N. Engl. J. Med. 334, 1349–1355.
Pokharkar, V.B., Mandpe, L.P., Padamwar, M.N., Ambike, A.A., Mahadik, K.R., Paradkar, A., 2006. Development, characterization and stabilization of amorphous form of a low Tg drug. Powder Technol. 167, 20–25.
Product Brochure and Sylysia, Product Brochure, Sylysia FCP, Fuji Sylysia Chemical Ltd., Kozoji-cho, Kasugai-shi, Aichi-ken, Japan.
Ruffolo Jr., R.R., Boyle, D.A., Venuti, R.P., Lukas, M.A., 1993. Preclinical and clinical pharmacology of carvedilol. J. Hum. Hypertens. 7, S2–S15.
Ruffolo Jr., R.R., Gellai, M., Hieble, J.P., Willette, R.N., Nichols, A.J., 1990. The pharmacology of carvedilol. Eur. J. Clin. Pharmacol. 38, S82–S88.
Rupprecht, H., Biersack, M.J., Kindl, G., 1974. Freigabe schwer löslicher Substanzen von den Oberflächen partiell belegter Kieselsäuren. Colloid Polym. Sci. 252, 415–416.
Sharma, S., Sher, P., Badve, S., Pawar, A., 2005. Adsorption of meloxicam on porous calcium silicate: characterization and tablet formulation. AAPS PharmSciTech 6, E618–E625.
Sinko, P.J., 2006. Martin's Physical Pharmacy and Pharmaceutical Sciences. Lippincott Williams & Wilkins, Philadelphia, p. 244.
Sjökvist, E., Nyström, C., 1991. Physicochemical aspects of drug release IX. Tableting properties of solid dispersions using xylitol as carrier material. Int. J. Pharm. 67, 139–153.
Streubel, A., Siepmann, J., Bodmeier, R., 2003. Floating matrix tablet based on low density foam powder: effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci. 18, 37–45.
Takeuchi, H., Nagira, S., Tanimura, S., Yamamoto, H., Kawashima, Y., 2005a. Tabletting of solid dispersion particles consisting of indomethacin and porous silica particles. Chem. Pharm. Bull. 53, 487–491.
Takeuchi, H., Nagira, S., Yamamoto, H., Kawashima, Y., 2004. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray drying method. Powder Technol. 141, 195–197.
Takeuchi, H., Nagira, S., Yamamoto, H., Kawashima, Y., 2005b. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int. J. Pharm. 293, 155–164.
Tozuka, Y., Kimura, A., Moribe, K., Yamamura, S., Yamamoto, K., 2005. Effect of pore size of FSM-16 on the entrapment of flurbiprofen in mesoporous structures. Chem. Pharm. Bull. 53, 974–977.
Uchino, T., Yasuno, N., Suzuki, H., 2007. Solid dispersion of spironolactone with porous silica prepared by the solvent method. Pharmazie 62, 599–603.
Unger, K., Rupprecht, H., Valentin, B., Kircher, W., 1983. The use of porous and surface modified silicas as drug delivery and stabilizing agents. Drug. Dev. Ind. Pharm. 9, 69–91.
van Speybroeck, M., Barillaro, V., Thi, T.D., Mellaerts, R., Martens, J., van Humbeeck, J., Annaert, P., van den Mooter, G., Augustijns, P., 2009. Ordered mesoporous silica material 26 SBA-15: a broad-spectrum formulation platform for poorly soluble drugs. J. Pharm. Sci. 98, 2648–2657.
van Zwieten, P.A., 1993. Pharmacodynamic profile of carvedilol. Cardiology 82, 19–23.
Vrečer, F., 1992. Physicochemical properties of piroxicam and its bonding onto different silicas, PhD Thesis, University of Ljubljana, Slovenia.
Wei, L., Sun, P., Nie, S., Pan, W., 2005. Preparation and evaluation of SEDDS and SMEDDS containing carvedilol. Drug. Dev. Ind. Pharm. 31, 785–794.
Weitshies, W., Kosch, O., Mönnikes, H., Trahms, L., 2005. Magnetic marker monitoring: an application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms. Adv. Drug. Deliv. Rev. 57, 1210–1222.