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Research paper

Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers

Heike Friedrich [a], Bernd Fussnegger [b], Karl Kolter [c], Roland Bodmeier [a,*]

[a] College of Pharmacy, Freie Universität Berlin, Berlin, Germany
[b] Strategic Marketing Pharma Excipients, BASF AG, Ludwigshafen, Germany
[c] Product Development Pharma, BASF AG, Ludwigshafen, Germany

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Abstract

The dissolution rate of the model drugs carbamazepine and nifedipine was improved by adsorbing solutions of the drugs in hydrophilic non-volatile or volatile solvents onto carriers with a large surface area. This was accomplished by dissolving the drug in methanol or the non-toxic hydrophilic liquids PEG 400 or 2-pyrrolidone, and adsorbing these solutions onto the surface of silica (Aerosil®) or crosslinked polyvinylpyrrolidone (Kollidon® CL-M). The solvent binding capacities decreased in the order of methanol, PEG 400, 2-pyrrolidone for Aerosil® 200, 300, 380 and for Kollidon® CL-M. Kollidon bound less liquid than Aerosil because of the smaller surface area. Differential scanning calorimetry measurements showed higher interactions between drugs and Kollidon compared to Aerosil, suggesting a low aggregation of precipitated drug particles. The drug release from the adsorbent systems was enhanced when compared to micronized drug and independent of the drug loading in the investigated range. The drugs were also dissolved in various liquid, paste-like or solid solubilisers (polyoxyl-40-hydrogenated castor oil (Cremophor® RH 40), macrogol-15-hydroxystearate (Solutol HS®), poloxamers (Lutrol® F68, Pluronic® F87NF and Pluronic® L44NF) and adsorbed onto Kollidon. These adsorbent systems also exhibited an increased dissolution rate when compared to pure drug.

Keywords: Aerosil; Crosslinked PVP; Dissolution rate enhancement; Poorly soluble drugs; Solubilisation

1. Introduction

The poor dissolution characteristics of water-insoluble drugs are a major challenge for pharmaceutical scientists. Reduction of the particle size/increase in the surface area of the drug is a widely used and relatively simple method for increasing dissolution rates. However, micronised drugs have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area [1]. Other methods to reduce the tendency of drug agglomeration and to increase the dissolution rate include the incorporation of the drug into hydrophilic carriers (solid solutions/dispersions) or drug solution deposition onto adsorbents [2]. The surface area of the drug available for contact with the dissolution medium is increased by the use of particulate adsorbent carriers, whereby the drug is bound to the carrier and thus cannot agglomerate. This is accomplished by dissolving the drug in an organic solvent and adsorbing this solution onto the carrier. The evaporation of the organic solvent results in a rapid precipitation of the drug either on the surface or within pores of the adsorbent material. This is a simple and time-saving procedure and has been described for silica many years ago [3–8]. Other authors used microcrystalline cellulose, modified corn starch, Mg trisilicate, Al glycinate and Mg stearate [9,10]. Organic solvents, such as acetone, chloroform or methylene chloride were mostly used to dissolve the drug followed by soaking the carrier with this drug solution. However, organic solvents are not desirable because of their potential toxicity, processing hazards and environmental and solvent residual concerns.

In this study, the drug was adsorbed on the surface of two different adsorbent materials of varying surface areas from drug solutions in non-toxic and non-volatile hydrophilic fluids (PEG 400, 2-pyrrolidone), paste-like materials (Cremophor® RH, Solutol® HS, Pluronic® L44 NF) and low melting solids

* Corresponding author. College of Pharmacy, Freie Universität, Kelchstrasse 31, Berlin, Germany. Tel.: +49 30 83850643; fax: +49 30 83850692.
E-mail address: bodmeier@zedat.fu-berlin.de (R. Bodmeier).

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(Pluronic® F87, Lutrol® F68) compared to the volatile solvent methanol. Silica (Aerosil®) and crosslinked polyvinylpyrrolidone (Kollidon® CL-M), which are widely used pharmaceutical excipients, were investigated as adsorbent carriers for the hydrophilic liquids, pastes, low melting solids and methanol.

Crosslinked polyvinylpyrrolidone has not been described in the literature as an adsorbent material despite its excellent surface characteristics. The use of volatile organic solvents would result in adsorbent systems with precipitated drug, while adsorbed hydrophilic solutions would allow the drug to remain partially dissolved or at least solubilised in the presence of the non-volatile hydrophilic fluids during dissolution.

2. Materials and methods

2.1. Materials

Micronised carbamazepine and nifedipine (Sigma-Aldrich Laborchemikalien GmbH, Seelze, Germany), hydrophilic fumed silica (Aerosil® 200, 300, 380) (Aerosil) (Degussa AG, Düsseldorf, Germany), crosslinked polyvinylpyrrolidone (Kollidon) (Kollidon® CL-M), 2-pyrrolidone (Soluphor® P), polyethylene glycol (PEG 400) (Lutrol® E 400), polyoxyl-40-hydrogenated castor oil (Cremophor) (Cremophor® RH), macrogol-15-hydroxystearate (Solutol) (Solutol® HS), copolymers of ethylene oxide and propylene oxide (Lutrol) (Lutrol® F68) (BASF AG, Ludwigshafen, Germany), (Pluronic F) (Pluronic® F87 NF) and (Pluronic L) (Pluronic® L44 NF) (BASF AG, Mount Olive, New Jersey, USA), sodium dodecyl sulfate (SDS) (Texapon®) (Henkel KGaA, Düsseldorf, Germany), methanol (Merck KGaA, Darmstadt, Germany).

2.2. Binding capacity of the adsorbents for the solvents

The binding capacity of the adsorbents for the solvents was determined by mixing the adsorbent (1.0 g Aerosil or Kollidon) with increasing amounts of methanol, PEG 400 and 2-pyrrolidone (in increments of 10% w/w based on the adsorbent) in a mortar for 5 min at ambient conditions ($n=6$). The binding capacity was defined as the highest amount of solvent at which the powders were still dry and free-flowing. The powders (500 mg) were then compressed into tablets with a pressure between 6 and 7 kN (single punch excentric press, Korsch EK0, Korsch, Maschinenfabrik Berlin, Germany) with 10 mm flat-faced tooling to determine the solvent binding capacity under compression ($n=6$). The binding capacity under pressure was defined as the highest amount of solvent, at which the tablets were still dry and no fluid leaked from the tablet.

2.3. Drug solubility in hydrophilic solvents

Excess amounts of carbamazepine and nifedipine were placed into 5 ml solvent (2-pyrrolidone, PEG 400, methanol) in a glass vial. The samples were shaken for at least 5 days at 25 ± 2 °C. Two millilitre samples were taken from the saturated solution and filtered through a 0.5 μm filter (Sartorius AG, Göttingen, Germany). The drug concentration was detected UV-spectrophotometrically at $\lambda=238$ nm for nifedipine and at $\lambda=286$ nm for carbamazepine (UV 2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA) after appropriate dilution with water (1:100–1:500) ($n=6$). All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

2.4. Preparation of drug precipitates from the solvents

Drug precipitates from methanol were prepared by first dissolving excess amounts of carbamazepine and nifedipine in 5 ml methanol, followed by evaporation of the methanol and drying of the powder over silica gel under vacuum for 2 days. Drug precipitates from PEG 400 and 2-pyrrolidone were formed by placing excess amounts of carbamazepine and nifedipine in 5 ml of PEG 400 or 2-pyrrolidone. The bottles were shaken at 60 °C and a small amount of solvent was added again after 2 days under stirring at 60 °C to dissolve the remaining drug particles in order to obtain a solution close to saturation. After 2 days, the clear drug solutions were cooled to 8 °C in a refrigerator and centrifuged to obtain the drug sediment, which was dried in a vacuum desiccator for 2 days. The drug powders/sediments were analysed by powder wide angle X-ray scattering measurements.

2.5. Physical state of drug in the solubilisers

The solids Lutrol® F68 and Pluronic® F87 NF and the pastes Cremophor® RH and Solutol® HS were molten at 50 °C on a heating plate. The liquid Pluronic® L44 NF was also heated to 50 °C. Excess amount of drug was dissolved under stirring at 50 °C in the liquefied solubilisers for 5 min. The cooled drug-containing solubilisers were investigated by wide angle X-ray scattering measurements.

2.6. Drug adsorption to the adsorbents

The drugs (0.04, 0.12 or 0.16 g corresponding to 1.96, 5.66 or 7.4% w/w based on solvent/carrier amount, respectively) were dissolved in 1.0 g solvent (methanol, PEG 400, 2-pyrrolidone). The solutions were added drop wise to 1.0 g Aerosil 300 or Kollidon powder and mixed for 5 min in a mortar. The Pluronics, Solutol, Lutrol and Cremophor were heated to 50 °C, followed by drug addition and stirring for 5 min. The drugs were dissolved in each case. The clear solutions were added dropwise to the Aerosil 300 or Kollidon powder and mixed for 5 min in the mortar. The ratio between solvent and adsorbent was always 1:1. Compositions containing adsorbent/solvent/drug are called adsorbent systems. Physical mixtures (PM) containing adsorbent/drug (drug content: 2% w/w) were prepared by mixing in a mortar for 5 min. All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

2.7. Powder X-ray diffractometry

Wide angle X-ray scattering measurements were performed on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, $\lambda = 0.15418$ nm, 40 kV), fixed with a Philips PW 1710 diffraction control unit (Philips Industrial and Electro-acoustic Systems Divisions, Almelo, The Netherlands). The radiation scattered in the crystalline regions of the samples was measured with a vertical goniometer (Philips PW 1820, Philips Industrial and Electro acoustic Systems Division, Almelo, The Netherlands). Patterns were obtained using a step width of 0.02° with a detector resolution in 2θ between 4 and 40° at ambient temperature.

2.8. Differential scanning calorimetry (DSC)

DSC studies were performed using a Mettler DSC 821e (Mettler, Toledo, Giessen, Germany). Samples (4–7 mg) were weighed in 40 μl aluminum crucibles with closed covers. DSC scans were recorded at a heating rate of 10 K/min from 20 to 180 °C for nifedipine mixtures and from 20 to 200 °C for carbamazepine mixtures and all other mixtures with 80 ml/min N_2 gas flow rate. The melting transitions (T_m) were derived from the computed extrapolated peak maximum, using the Star® Software (Mettler, Toledo, Giessen, Germany).

2.9. Scanning electron microscopy (SEM)

The surface characteristics of the mixtures were studied by scanning electron microscopy. The particles were coated with gold–palladium and then observed with an electron microscope (Philips SEM 515, PW 6703, Philips Industrial Electronics, Kassel, Germany) at ambient temperature.

2.10. Drug release studies

Drug release studies were performed with freshly prepared adsorbent systems containing 5 mg drug in 400 ml water including 0.3% w/v sodium dodecyl sulfate at 37 °C in a horizontal shaker at 75 rpm (GFL 3033, Gesellschaft für Labortechnik mbH, Burgwedel, Germany). 2 ml samples were taken after 15, 30, 45 and 60 min and filtered through a 0.5 μm filter (Acryl/Copolymer/Nylon, Sartorius AG, Göttingen, Germany). The drug concentrations were detected spectrophotometrically at $\lambda = 238$ nm for nifedipine and $\lambda = 286$ nm for carbamazepine (UV 2101 PC, Shimadzu Scientific Instruments, Inc., Columbia, MD, USA) ($n = 3$). Absorbance of the adsorbents and solvents at $\lambda = 238$ and 286 nm was negligible. All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

3. Results and discussions

Particle size reduction/increasing the surface area is an important mean to improve the rate of dissolution of poorly water-soluble drugs. A simple method to increase the surface area is the mixing of the drug with carriers, which have a large surface area, resulting in an increased drug release [9]. A modification of this procedure, which was investigated in this study, was to adsorb the drug on the adsorbent (carrier) surface from solutions of the drug in suitable solvents.

Initial investigations were performed to determine the solvent uptake capacity of the adsorbents. Three types of Aerosil, namely Aerosil® 200, 300 and 380 (surface areas: 200 ± 25, 300 ± 30, 380 ± 30 m^2/g and particle sizes: 12, 7 and 7 nm) [11] and Kollidon (surface area: 3–6 m^2/g and a particle size: 10 μm) [12] were investigated as adsorbent materials. High solvent loading is a requirement for high drug loading. Table 1A lists the highest amount of solvent, which could be adsorbed and resulted in a free-flowing powder. Higher amounts of solvent resulted in wet and lumpy powders. The solvent binding capacity depended on both the type of adsorbent and the solvent and was in the range of 100–300% solvent based on adsorbent. The solvent uptake increased with increasing surface area of the Aerosil powders in the order of Aerosil® 200 < Aerosil® 300 < Aerosil® 380. Aerosil® 380 was described as being not significantly finer than Aerosil® 300, but the higher surface roughness could probably explain the higher binding capacity for solvents [11]. The adsorption of liquids correlated with the surface area and number of silanol groups, which are capable of hydrogen bonding and electrostatic interaction [12,13]. The solvent binding capacity of the three Aerosil® types decreased in the order methanol > PEG 400, 2-pyrrolidone. The binding capacities of Kollidon for the solvents were quite high, when considering the relatively small surface area of Kollidon compared to Aerosil (Table 1A). The adsorption of liquids was facilitated by electrostatic, covalent, hydrophobic and hydrogen bonding mechanisms [14,15]. The solvent binding capacity of Kollidon decreased in the order methanol, PEG 400, 2-pyrrolidone.

Solvent-loaded adsorbent powders could be either filled into capsules or be compressed into tablets as the final dosage forms. The ability of the solvent-loaded adsorbents to keep the solvent during tabletting was therefore important; it investigated by compressing the powders into tablets. The adsorption capacity of Aerosil® 300 and Kollidon for PEG 400 and 2-pyrrolidone decreased under pressure. Kollidon kept half of PEG 400 and 2-pyrrolidone compared to the uncompressed state whereas the solvent binding capacity of Aerosil under compression force was less influenced, because of the higher surface area (Table 1B). The solvent-loaded powders with methanol lost no solvent during compression, because methanol was evaporated after mixing with the adsorbent (as

Table 1
(A) Solvent binding capacity of uncompressed powders of Aerosil 200, 300, 380 and Kollidon

Adsorbent	Solvent binding capacity (g/g)		
	Methanol	PEG 400	2-Pyrrolidone
Aerosil 200	2.0 ± 0.1	2.0 ± 0.3	1.3 ± 0.2
Aerosil 300	3.0 ± 0.1	2.2 ± 0.1	1.6 ± 0.1
Aerosil 380	3.0 ± 0.2	2.4 ± 0.1	2.2 ± 0.3
Kollidon	1.3 ± 0.2	1.2 ± 0.1	1.0 ± 0.1

Table 1(B)
Solvent binding capacity of compressed powders of Aerosil 300 and Kollidon ($n=6$)

Compressed adsorbent	Solvent binding capacity (g/g)		
	Methanol	PEG 400	2-Pyrrolidone
Aerosil 300	3.0±0.1	2.0±0.1	1.3±0.2
Kollidon	1.3±0.1	0.6±0.1	0.5±0.1

determined by a weight loss). This could result in adsorbent systems with precipitated drug, whereas the drug could remain partially dissolved with the adsorbed hydrophilic non-volatile solvents.

The loading capacity of the dosage form strongly depends on the solubility of the drug in the solvent and on the uptake capacity of the adsorbent for the drug solution. Drugs have to be dissolved in the solvents prior to adsorption of the drug solutions onto the adsorbents. Carbamazepine was freely soluble in 2-pyrrolidone and methanol and soluble in PEG 400. Nifedipine was soluble in PEG 400 and sparingly soluble in 2-pyrrolidone and methanol (Table 2).

The drug could precipitate after adsorption of the drug solution onto the adsorbent, thus possibly diminishing its dissolution rate enhancing property. The potential precipitation is dependent on the solubility of the drugs in the solvents, the degree of saturation of the drug solution, potential evaporation of the solvent or interactions between components. With methanol, the drug nucleated onto or within the surface of the adsorbent upon evaporation of methanol. The precipitation of carbamazepine and nifedipine from methanol, 2-pyrrolidone and PEG 400 was therefore investigated by solvent evaporation or cooling. Carbamazepine can exist in four polymorphic forms and as dihydrates [16–18]. Form I ($T_m=191$ °C) and form III ($T_m=177$ °C), which are the commercially available, constitute an enantiotropic pair. The X-ray diffraction pattern of the untreated carbamazepine and carbamazepine crystallized from methanol showed the characteristic peaks of the polymorphic form I (Fig. 1A). Carbamazepine recrystallised from 2-pyrrolidone showed characteristic peaks at 5 and 8° 2θ, which are characteristic for the dihydrate form I [17–20]. Carbamazepine precipitated from PEG 400 showed a halo pattern indicating the amorphous drug form (Fig. 1A). It is well-known, that the amorphous form has a favorable effect on the dissolution rate when compared to the crystalline modifications. Burger and Koller have reported on the existence of two metastable polymorphs as well as four different solvates crystallized from 1,4-dioxane for nifedipine [21]. Untreated nifedipine used in this study existed in modification I (Fig. 1B). Crystallization from methanol also resulted in modification I. A slightly changed pattern to that of modification I was obtained when nifedipine was crystallized from 2-pyrrolidone. The crystallization product from PEG 400 showed a different X-ray diffraction pattern (the peaks at 8 and 10° 2θ disappeared), which was attributed to modification II.

Table 2
Solubility of carbamazepine and nifedipine in 2-pyrrolidone, PEG 400 and methanol at 25 °C ($n=6$)

Drug	Solubility (mg/ml)		
	2-Pyrrolidone	PEG 400	Methanol
Carbamazepine	100.4±0.7	74.4±0.7	159.1±3.6
Nifedipine	24.3±0.2	61.9±0.2	19.06±5.2

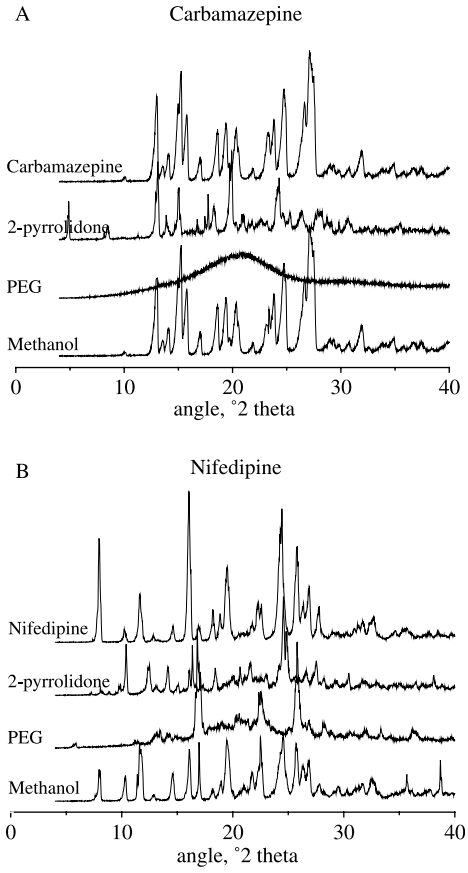

Fig. 1. Powder X-ray diffraction pattern of untreated drug and drug precipitated from methanol, PEG 400 and 2-pyrrolidone: (A) carbamazepine and (B) nifedipine.

Next, the morphological characteristics of the adsorbent systems were investigated. Aerosil 300 was selected among the Aerosil types for further studies. Pure Aerosil powder consists of spherical particles, which mostly build a loose network [11]. Kollidon is a powder of spherical particles with a porous structure [12]. The particle size of the Aerosil adsorbent systems was much larger and in the lower micrometer range when compared to the original particle size, which was in the nanometer range (Fig. 2). The solvents PEG 400 and 2-pyrrolidone connected several Aerosil particles together. For example, PEG 400-soaked Aerosil particles were in a range of 10–30 μm (Fig. 2A) and 2-pyrrolidone-soaked Aerosil particles formed lumps with a size of 10–60 μm. In contrast, the size of Kollidon particles (approx. 10 μm) remained unchanged after solvent soaking and was therefore smaller than the agglomerated Aerosil particles. The Kollidon particles had a smooth surface and appeared to be covered by PEG 400 or 2-pyrrolidone (Fig. 2B). The surfaces of Kollidon and Aerosil particles were free of precipitated carbamazepine or nifedipine with PEG 400 and 2-pyrrolidone at drug loadings of

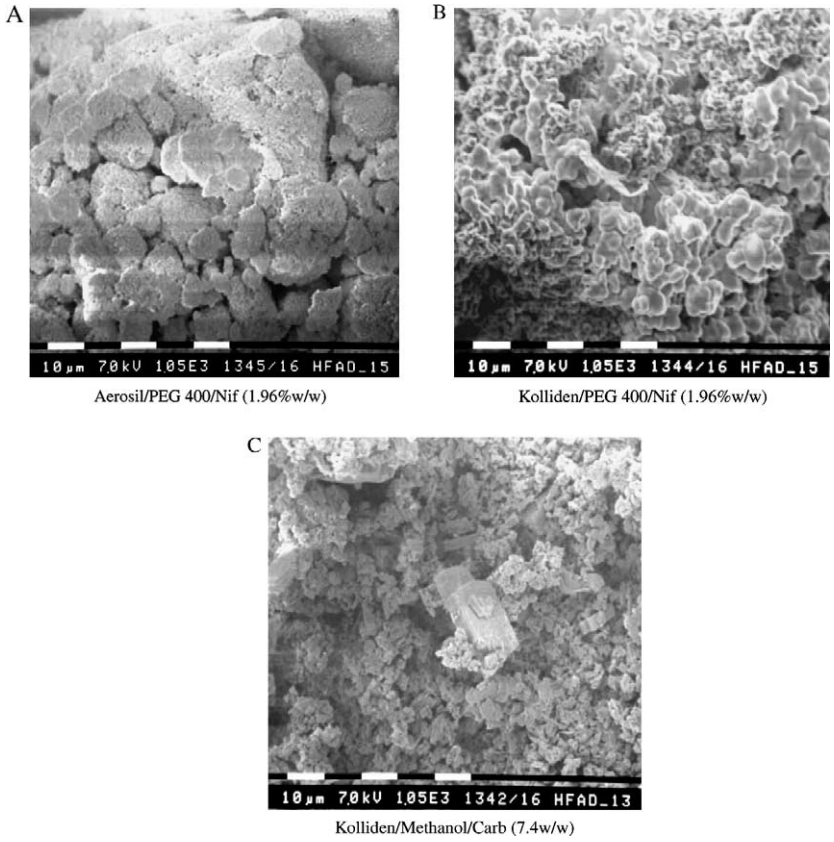

Fig. 2. Scanning electron micrographs of adsorbent systems: (A) Aerosil/PEG 400/nifedipine (1.96% w/w), (B) Kollidon/PEG 400/nifedipine (1.96% w/w); (C) Kollidon/methanol/carbamazepine (7.4% w/w).

1.96 or 7.4% w/w. The pictures of all other adsorbent systems were similar (not shown). Even with the volatile methanol, no drug crystals were visible on the surface. However, the drug could have precipitated within the pores/channels of the adsorbents. Only the higher drug-loaded methanol-soaked Kollidon system revealed drug particles in the micrometer range, probably because of the smaller surface area, when compared to Aerosil (Fig. 2C). With PEG 400 or 2-pyrrolidone, the drug could either precipitate in the nano-size range within the channels of the adsorbents or the drug remained dissolved within the non-volatile solvent. This could not be clarified by SEM or polarized light microscopy.

DSC measurements were performed to study the physical state of the drug. Freshly prepared adsorbent systems containing 1.96% w/w drug and physical mixtures of adsorbent:drug (2% w/w) were investigated (Fig. 3). Carbamazepine showed a melting transition of 191 °C indicative of modification I. The physical mixture of drug and Kollidon showed two weak transitions, which corresponded to modifications I and III. The melting transition temperatures were depressed due to interactions (Table 3). The smaller enthalpies of the melting transitions of the physical mixtures compared to the adsorbent systems could not be explained. Variations in melting peak position could be caused by different binding forces between drug molecules and adsorbent [11,15]. The larger melting point depression for Kollidon indicated stronger physical interactions between drug and Kollidon than between the drug and Aerosil. The mixtures of carbamazepine/PEG/adsorbent showed a recrystallization peak of the drug. The recrystallization peak of carbamazepine indicated that the drug was either amorphous or dissolved in PEG at the beginning of the DSC-heating run. The amorphous state of the drug could not be shown by DSC because of the low sensitivity of the DSC for detection of weak glass transition temperatures. The 2-pyrrolidone-containing adsorbent systems contained carbamazepine as crystalline drug indicated by the melting transition. The adsorbent systems with nifedipine did not show detectable

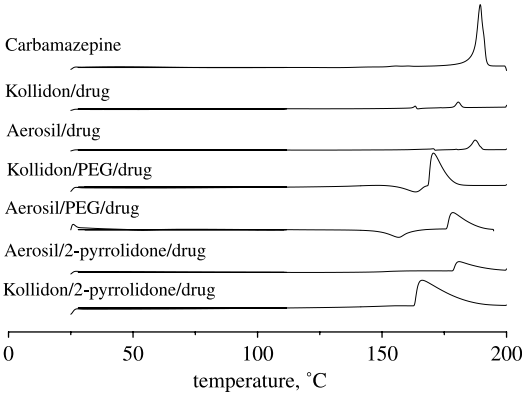

Fig. 3. Differential scanning thermograms of various adsorbent systems (1.96% w/w carbamazepine), physical mixtures of adsorbent and drug (2% w/w carbamazepine) and pure drug.

Table 3
Melting temperatures (T_m) and melting temperature depression values (T_m-depression) of the drugs, physical mixtures (2% w/w drug) and adsorbent systems (1.96% w/w drug) as determined by DSC ($n=1$)

Composition	Carbamazepine		Nifedipine	
	T_m (°C)	T_m-depression (°C)	T_m (°C)	T_m-depression (°C)
Drug	191		171	
Physical mixtures				
Kollidon/drug	180	11	162	9
Aerosil/drug	187	4	169	2
Adsorbent systems				
Kollidon/PEG 400/ drug	171	20	–	–
Aerosil/PEG 400/ drug	179	12	–	–
Kollidon/2-pyrro-lidone/drug	166	15	–	–
Aerosil/2-pyrro-lidone/drug	181	10	–	–

–, Not detectable.

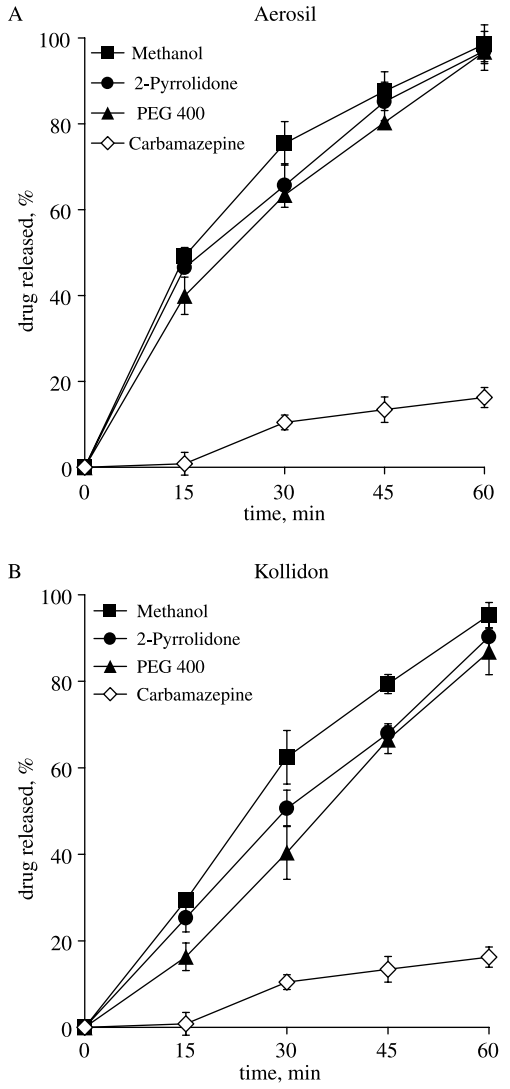

Fig. 4. Effect of solvent on the drug release from adsorbent systems (1.96% w/w carbamazepine) compared to micronized drug: (A) Aerosil, (B) Kollidon.

peaks, because nifedipine remained dissolved within the solvents during the heating process of the DSC run.

Finally, the drug release from these systems was studied. The surface area was one of the factors responsible for the increased dissolution rates of the drugs. More than 40% carbamazepine was released within the first 15 min and 100% within 60 min from the Aerosil system without significant differences between the solvents (Fig. 4A). No effects of the different solubilities of drug in the solvents or different precipitated drug modifications from the PEG 400/- or 2-pyrrolidone/Aerosil system on the drug release were seen (Figs. 1A and 4A). The dissolved part of drug precipitated in fine particles and had good wettability due to the surrounding solubilising materials, independent of the type of modification and its solubility. Kollidon was less efficient in enhancing the release of carbamazepine compared to the Aerosil systems, because of the lower surface area and probably due to the higher interactions between Kollidon, solvent and drug (Fig. 4B). The Kollidon systems released 15–30% carbamazepine within the first 15 min and the release was also mostly complete after 60 min and quite constant. The drug was released in the order of methanol > 2-pyrrolidone > PEG 400, however, the differences were minor. Probably, the drug

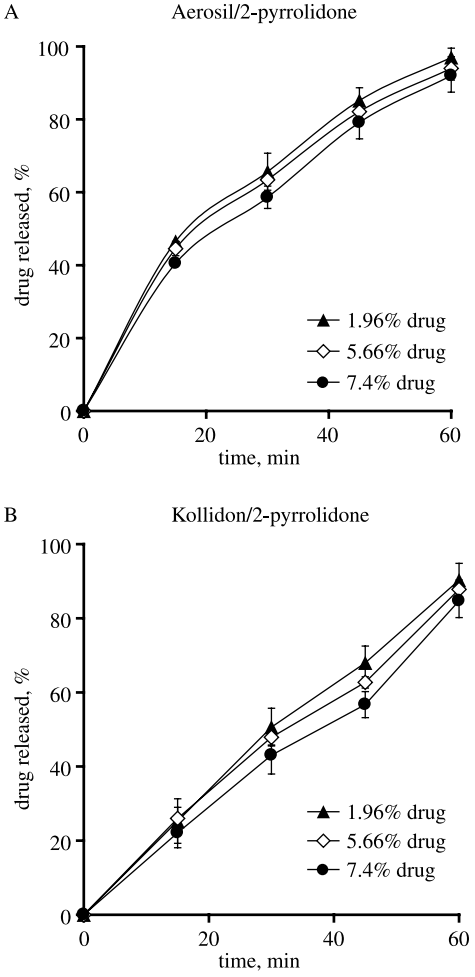

Fig. 5. Effect of carbamazepine loading on the drug release from 2-pyrrolidone/adsorbent systems: (A) Aerosil, (B) Kollidon.

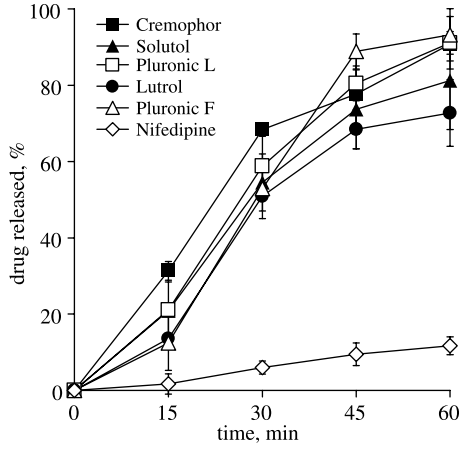

Fig. 6. Effect of solubiliser on the drug release from Kollidon systems (1.96% w/w nifedipine).

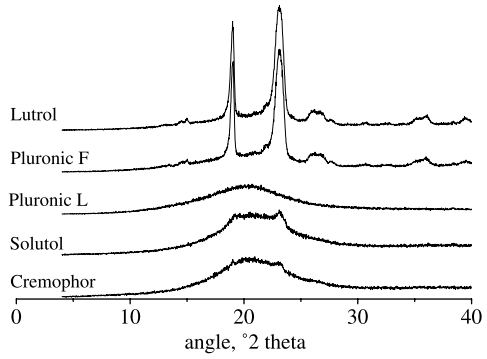

Fig. 7. Powder X-ray diffraction pattern of nifedipine precipitated from different solubilisers.

particles had good wettability due to the surrounding solubilising materials and the effect of different solubilities of different drug modifications was minor. The drug release was not affected by the carbamazepine content, as shown for 2-pyrrolidone systems (Fig. 5A and B).

Kollidon powder was also loaded with solutions of drug in various solubilisers in order to investigate the drug release of such systems. The drug release was enhanced and not significantly different among the solubilisers (Fig. 6). The drug had good wettability due to the solubilising materials. X-ray data suggested that the drug precipitated either amorphous or remained partially dissolved in the solubilisers. The peaks at 19 and 23 2θ correspond to Lutrol and Pluronic F (Fig. 7).

In summary, Kollidon is an interesting alternative adsorbent material for drugs dissolved in hydrophilic solvents or solubilizers to the established Aerosil in order to enhance the rate of dissolution. The non-volatile hydrophilic solvents and solubilisers are potential non-toxic alternatives to volatile solvents with regard to potential toxicity and processing hazards and environmental and solvent residual concerns.

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