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Adsorption of carbamazepine onto crospovidone to prevent drug recrystallization

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ABSTRACT

The adsorption mechanism of the poorly water-soluble drug carbamazepine onto crosslinked polyvinylpyrrolidone (crospovidone) was investigated by adsorption isotherms in different solvents and Fourier-transformation infrared spectroscopy (FTIR). The drug adsorption was a result of hydrogen bonds between carbamazepine's amine group and crospovidone's carbonyl group. Solvents with a hydrogen donor site competed with the drug for binding sites on crospovidone and thereby decreased the extent of drug adsorption. To optimize the drug–carrier ratio, adsorbates with different drug loadings were prepared by the solvent deposition method and analyzed for drug crystals using differential scanning calorimetry, X-ray diffraction, scanning electron microscopy and polarized light microscopy. Adsorbates with a drug loading of 9.1% or less did not show drug crystals. The drug release increased in the order of micronized drug < physical mixture < adsorbate. This was attributed to wetting and deagglomeration effects in both the physical mixture and the adsorbate and the molecularly dispersed state of the drug in the adsorbate. The findings allow for a more rationale design of immediate release formulations and of transdermal patches containing drug adsorbates onto crospovidone.

1. Introduction

The oral bioavailability of a drug depends on its permeability and its aqueous solubility. Over the last decades, modern techniques like high-throughput screening of potential therapeutic agents have led to an increasing number of drug candidates with unfavorable solubility characteristics (Lipinski et al., 2001). Hence improving the dissolution behavior of poorly water-soluble drugs is a major challenge of formulation development. Different approaches like micronization or salt-formation of the drug, complexation and solubilization of the drug with surfactants and the preparation of solid dispersions/solutions have been investigated.

In solid solutions, the drug is molecularly dispersed in a hydrophilic carrier. These formulations possess enhanced dissolution characteristics as a result of the drug's higher internal energy (Bruno and Hancock, 1997). On the other hand, the high-energy state of the drug may also lead to spontaneous recrystallization during storage which can decrease the drug release. The main factors preventing drug recrystallization in solid solutions are thought to be drug–carrier interactions and the viscosity of the formulation (Bhugra and Pikal, 2008; Doherty and York, 1987; Taylor and Zografi, 1997).

Solid solutions can either be prepared by the hot melt method or the solvent method (Leuner and Dressman, 2000). In the hot melt process, drug and hydrophilic polymer are molten together and subsequently cooled whereby they solidify as a uniform mass. Limitations of this method are miscibility gaps in the phase diagram and thermostability issues of drug and carrier. Furthermore, carriers with a high melting point like linear polyvinylpyrrolidone can normally not be used. In solid solutions prepared by the solvent method, the drug and the hydrophilic polymer are dissolved in a volatile solvent. One difficulty of this method is finding a solvent which dissolves both the poorly water-soluble drug and the hydrophilic polymer. Often large quantities of solvent and sometimes additional heating have to be employed. This poses an environmental risk and is cost-intensive. A general problem of most solid solutions is their poor processability. Stickiness of the pulverized mass often requires the use of additional excipients (Serajuddin, 1999) to improve the powder flowability. These problems limit the wider commercial use of solid solutions.

The solvent deposition method, first mentioned by Monkhouse and Lach, 1972, can be seen as a modification of the abovementioned solvent method. The difference is that an insoluble polymer (e.g., silica) is soaked with a concentrated organic drug solution. The solvent evaporates and the drug is adsorbed to the surface or is absorbed in the bulk of the carrier which prevents its crystallization and facilitates its dissolution. Drug and carrier are therefore not exposed to high temperatures. Furthermore, the amount of solvent is reduced since it only has to dissolve the drug.

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Crospovidone (CPVP) is a synthetic insoluble polymer prepared from the monomer vinyl-pyrrolidone by popcorn polymerization (Haaf et al., 1985). It has pronounced swelling properties and is mainly used as disintegrant in tablets and capsules. Furthermore it is known for its adsorption properties: CPVP is used to clear fruit juices and beer (Mitchell et al., 2005) and as adsorbent material in chromatography (Percival, 1986). It was also suitable as polymeric carrier in the above described solvent deposition method (Friedrich et al., 2006) and as recrystallization inhibitor in transdermal matrix patches (Schulz et al., submitted).

Possibly, these adsorption phenomena are a result of hydrogen bonding between drug molecules and crospovidone. The present studies were undertaken to test this hypothesis. Carbamazepine was used as a poorly water-soluble model drug to investigate the optimum drug–CPVP ratio to prevent the drug from recrystallization. Finally, the optimized adsorbate was released and compared with the corresponding physical mixture and the pure drug to gain insights into the mechanism of dissolution enhancement.

2. Experimental

2.1. Materials

Micronized carbamazepine (average particle size: approximately 5 μm) (Sigma–Aldrich Laborchemikalien GmbH, Seelze, Germany), micronized crosslinked polyvinylpyrrolidone (CPVP) (Kollidon® CL-M) (BASF AG, Ludwigshafen, Germany), chloroform, ethanol, ethyl acetate (Carl Roth GmbH, Karlsruhe, Germany), methanol (Merck KGaA, Darmstadt, Germany) (all solvents: analytical grade), sodium dodecyl sulfate (Texapon®) (Henkel KGaA, Düsseldorf, Germany) were used as materials in the studies.

2.2. Adsorption isotherms

The classical batch method (Seidel-Morgenstern, 2004) was used to determine adsorption isotherms of carbamazepine onto CPVP in ethyl acetate and ethanol. In 2.0 ml Eppendorf cups, 1.0 ml carbamazepine solution was added to accurately weighed amounts (approximately 50 mg) of CPVP ($n = 3$). The carbamazepine concentrations ranged from approximately 5–90% of the carbamazepine solubility in the respective solvent. The cups were vortexed and shaken at 25 ± 2 °C for 3 h. After centrifugation (Heraeus Biofuge 13 Haemo, Heraeus Instruments, Osterode, Germany) at 13,000 rpm for 30 min, the carbamazepine equilibrium concentration (c_{eq}) in the supernatant was analyzed UV-spectrophotometrically at $\lambda = 285$ nm (UV 2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA) after appropriate dilution with the solvent. The adsorbed amount of carbamazepine onto CPVP was calculated using the following equation:

$$\frac{x}{m} = \frac{(c_0 - c_{eq}) \cdot v}{m}$$

where x is the amount of carbamazepine adsorbed onto CPVP, mg; m the amount of CPVP, g; c_0 the initial carbamazepine concentration, mg/ml; c_{eq} the concentration after equilibration with CPVP, mg/ml; v the volume carbamazepine solution, ml.

To obtain adsorption isotherms x/m was plotted against c_{eq}.

2.3. Solvent uptake and solvent binding capacity of CPVP

Approximately 200 mg dried (80 °C to constant weight) CPVP were accurately weighed in a 2.0 ml Eppendorf cup and 1.0 ml water, ethyl acetate, ethanol or methanol was added ($n = 3$). The suspensions were vortexed and afterwards shaken for 1 h at 25 ± 2 °C using a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). After centrifugation at 5000 rpm for 3 min (Heraeus Biofuge 13 Haemo, Heraeus Instruments, Osterode, Germany), the excess solvent was decanted/removed with a filter paper. The solvent uptake was defined according to the following equation:

$$U_s = \frac{m_{eq} - m_0}{m_0 \cdot \rho}$$

where U_s is the solvent uptake, ml/g; m_{eq} the mass of CPVP + solvent (after equilibration with solvent), g; m_0 the initial mass of the dried powder, g; ρ the density of the solvent at 25 °C, g/ml.

The binding capacity of CPVP for the abovementioned solvents was determined by mixing 1.0 g of thoroughly dried (80 °C to constant weight) CPVP with increasing amounts of water, ethyl acetate, ethanol or methanol (in increments of 100 mg) in a mortar with a pestle at ambient conditions. The solvent addition was stopped when CPVP was no longer capable of binding the entire solvent and changed into a paste ($n = 3$). The binding capacity was calculated according to the following equation:

$$BC = \frac{m}{m_0 \cdot \rho}$$

where BC is the binding capacity, ml/g; m the amount of solvent added, g; m_0 the initial mass of the dried powder; ρ the density of the solvent, g/ml.

2.4. ATR-FTIR spectroscopic investigation

2.4.1. Equilibration at different relative humidities

Pure water (10 ml) or saturated salt ($MgCl_2$, K_2CO_2, NaCl, KNO_3) solutions (10 ml) plus excess salt were filled into 100 ml plastic containers equipped with a mesh in the head space. Approximately 500 mg CPVP was accurately weighed into tared aluminum pans and placed on the mesh. The plastic containers were closed tightly and equilibrated at 25 ± 2 °C for at least 48 h to constant weight (Mettler AT 261 Delta Range, Greifensee, Switzerland). Dry CPVP and dried carbamazepine adsorbates onto CPVP were prepared by heating the polymer for approximately 4 h at 80 °C (UT 6060, Heraeus Instruments, Hanau, Germany) to constant weight.

2.4.2. Preparation of CPVP-solvent pastes

Dried (80 °C to constant weight) CPVP (200 mg) and 500 μl water, ethanol, ethyl acetate or chloroform were mixed in a 5 ml glass vessel with a spatula for 10 s until a homogeneous mass was formed. The vessels were closed and incubated for 10 min before the measurement took place.

2.4.3. ATR-FTIR spectroscopy

FTIR-spectra were generated with an Excalibur 3100 FTIR spectrophotometer (Varian Inc., Palo Alto, USA). The spectra were collected using a horizontal ATR accessory with a single reflection diamond crystal (Pike MIRacle, Pike Technologies, Madison, USA). 16 scans at 4 cm^{-1} resolution were averaged using Varian software (Resolution Pro 4.0).

Measurements were performed within 5 s after opening the containers to minimize the influence of the ambient humidity.

2.5. Solubility of carbamazepine in different solvents

Excess amounts of carbamazepine were added to 5 ml solvent (methanol, ethanol, ethyl acetate, water) in glass vials ($n = 3$). The samples were shaken for at least 5 days at 25 ± 2 °C. 2 ml 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 (blank value: pure solvent) at $\lambda = 285$ nm (UV 2101 PC, Shimadzu Scientific Instru-

ments Inc., Columbia, MD, USA) after appropriate dilution with the solvent.

2.6. Preparation of carbamazepine adsorbates onto CPVP

Adsorbates of carbamazepine onto CPVP (drug loading: 4.8, 9.1, 13.0, 23.1, and 33.3%, w/w, based on the total weight) were prepared by the solvent deposition method. 1000 μl methanolic carbamazepine solution (50 mg/ml) were added to 1000 mg CPVP in a mortar and immediately mixed with a pestle. Methanol was evaporated at 65 °C for 10 min (UT 6060, Heraeus Instruments, Hanau, Germany) and the procedure was repeated for adsorbates with higher drug loadings.

2.7. Differential scanning calorimetry (DSC)

DSC studies were performed using a Mettler DSC 821e (Mettler Toledo, Giessen, Germany). Samples (approx. 5 mg) were weighed into 40 μl aluminum crucibles with three pinholes in their lid. DSC scans were recorded at a heating rate of 20 °C/min from 25 to 110 °C and 5 °C/min from 110 to 240 °C under nitrogen atmosphere. The melting transitions (T_m) were derived from the computed extrapolated peak maximum using the Star® Software Version 8.10 (Mettler Toledo, Giessen, Germany).

2.8. X-ray powder diffraction (XRPD)

Wide angle X-ray scattering measurements were performed on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, λ = 0.15418 nm, 40 kV) and a Philips PW 1710 diffraction control unit (Philips Industrial and Electro-acoustic Systems Division, Almelo, The Netherlands). The scattered radiation 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.

Freshly prepared physical mixtures of carbamazepine form III and CPVP (drug content: 4.8, 9.1, 13.0, 23.1, and 33.3%) were investigated and their crystallinity was plotted against the sum of the AUCs of carbamazepine form III's three main peaks (at 13.0°, 15.2°, and 27.2°). This correlation was used to calculate the crystallinity of the adsorbates.

2.9. Polarized light microscopy (PLM) and scanning electron microscopy (SEM)

The adsorbates were investigated using a polarized light microscope (Axiotrop, Carl Zeiss Jena GmbH, Jena, Germany) connected with a digital camera. The images were evaluated using the Easy Measure Software (Version 1.0.15; INTEQ Informationstechnik GmbH, Berlin, Germany).

For SEM analysis (Philips SEM, PW 6703, Philips Industrial Electronics, Kassel, Germany) the specimens were coated with gold–palladium prior to observation. All microscopic experiments were conducted at ambient temperature.

2.10. Preparation of direct-compressed tablets and dissolution study

Tablets for dissolution testing were prepared using a hydraulic press (Specac 25.011, Specac Limited, Orpington, UK) at 1.0 t for 20 s. The tablets consisted of either 300 mg freshly prepared adsorbate with 9.1% carbamazepine or the corresponding freshly prepared physical mixture.

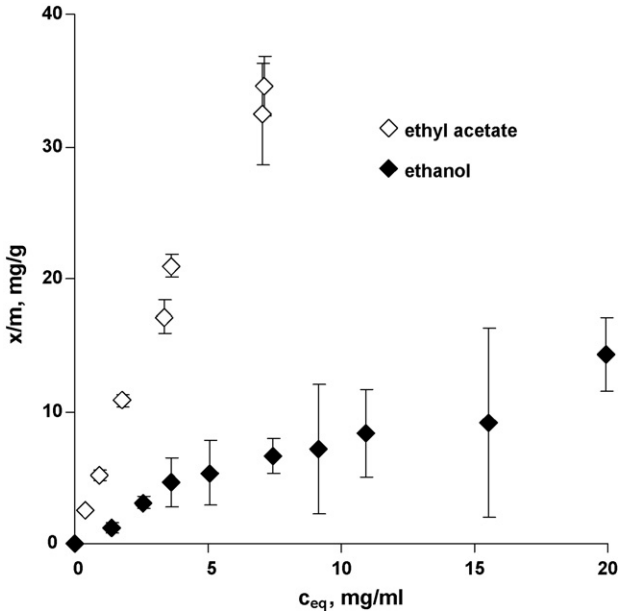

Fig. 1. Adsorption isotherms of carbamazepine onto CPVP in ethyl acetate and ethanol.

A dissolution test (release medium: 250 ml water, 100 rpm, 37 °C, non-sink conditions) with the tablets and pure micronized carbamazepine was performed (PTW 2, Pharma Test Apparatebau GmbH, Hainburg, Germany) (n = 3). Samples were taken after 5, 15, 30, 45 and 60 min and filtered through a 0.22 μm filter (Acryl/Copolymer/Nylon, Sartorius AG, Göttingen, Germany). The drug concentration was determined UV-spectrophotometrically (blank value: pure water) (UV 2101 PC, Shimadzu Scientific Instruments, Inc., Columbia, MD, USA) at λ = 285 nm).

3. Results and discussion

Drug adsorption onto carrier materials is an easy way to increase the dissolution rate of poorly water-soluble drugs by increasing their surface area and preventing their recrystallization. An understanding of the adsorption mechanism and the knowledge of the optimum drug–carrier ratio allow for a more rational development of these formulations.

3.1. Investigation of the adsorption process onto CPVP

To determine adsorption isotherms, carbamazepine solutions of varying drug concentrations were added to CPVP in Eppendorf cups. The resulting equilibrium drug concentration was measured and correlated with the amount of drug that was bound to the adsorbent. Ethanol and ethyl acetate were investigated as solvents because they possess different hydrogen bonding abilities. The solubility of carbamazepine is 160.4 ± 4.2 mg/ml in methanol, 23.4 ± 0.9 mg/ml in ethanol, 10.1 ± 0.5 mg/ml in ethyl acetate and 0.1 ± 0.1 mg/ml in water. The amount of carbamazepine bound to CPVP at a certain equilibrium concentration was significantly smaller in ethanolic solution than in ethyl acetate (Fig. 1). The relatively large standard deviation in case of ethanol was a result of the small difference between c_0 and c_{eq}. Thus fluctuations of the UV signal were amplified. Physical adsorption phenomena are often the result of specific interactions, primarily hydrogen bonds, between the drug and the adsorbate. Since CPVP's only functional group is the cyclic amide (Fig. 2), the polymer can only be the hydrogen acceptor in such a bond. The drug–polymer interaction could occur with carbamazepine's NH_2-group as hydrogen donor

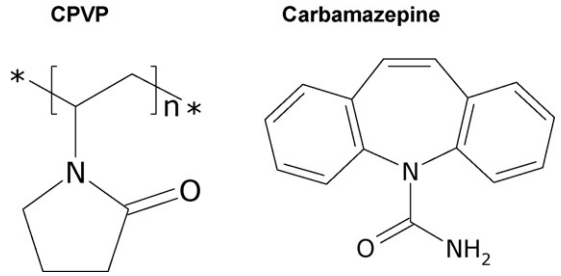

Fig. 2. Chemical structures of CPVP and carbamazepine.

site. Ethyl acetate is also only able to act as a hydrogen acceptor and thus cannot interact with CPVP in this way. This could be the reason why carbamazepine molecules adsorb onto CPVP to a greater degree when ethyl acetate is used as a solvent. Ethanol, on the other hand, participates in hydrogen bonds as both hydrogen acceptor and donor. The lower binding of carbamazepine onto CPVP in ethanolic solution could be related to ethanol competing with carbamazepine for binding sites on CPVP.

Attenuated total reflection Fourier-transformation infrared (ATR-FTIR) spectroscopy is one method of choice to investigate the nature and extent of interactions between two compounds. Since CPVP is a highly hygroscopic substance, the influence of CPVP's water content on its IR spectrum was investigated. CPVP samples were dried at 80 °C to constant weight and stored above orange gel or equilibrated at different relative humidities [21]. The spectra showed shifts of the carbonyl stretching vibrational band of from 1671.5 cm^{-1} for thoroughly dried CPVP to 1638.5 cm^{-1} for CPVP equilibrated at 100% relative humidity (Fig. 3). This result indicated a hydrogen bond formation between CPVP and water. CPVP possesses two hydrogen acceptor sites: the nitrogen and the oxygen atom of the cyclic amide. Since only the frequency of the carbonyl band shifted, the oxygen atom was apparently preferred. That seems reasonable, since steric constraints of the molecule might favor molecular interactions of this moiety and is similar to interactions between linear polyvinylpyrrolidone and ibuprofen (Sekizaki et al., 1995).

The ambient humidity had a tremendous influence on the frequency of CPVP's carbonyl group in the IR spectrum. Thus humidity effects had to be excluded when interactions between CPVP and other substances were investigated. This was achieved by using CPVP which was dried to constant weight at 80 °C in subsequent studies.

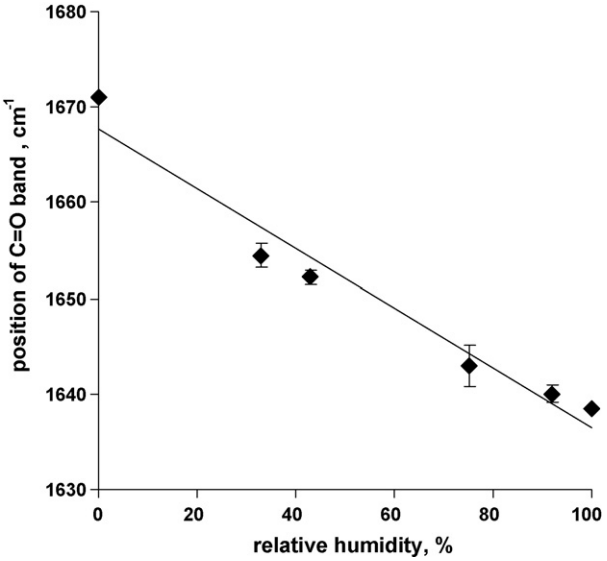

Fig. 3. Influence of relative humidity on the position of the C=O stretching vibrational band of CPVP.

To investigate interactions of CPVP with solvents, the ATR-FTIR-spectra of thoroughly dried CPVP and CPVP wetted with various solvents were compared. The extent of the carbonyl band shift was correlated to the strength of the formed hydrogen bond (Fig. 4).

Dry CPVP and ethyl acetate-CPVP pastes both showed the carbonyl band at 1671.5 cm^{-1}. Ethyl acetate's only functional group is an ester group which cannot provide a hydrogen atom for a hydrogen bond. Chloroform can act as a hydrogen donor because the electronegative chloride atoms attract and decentralize the electron cloud from the hydrogen nucleus and thereby leave the atom with a positive partial charge. As a consequence, the carbonyl band of CPVP shifted by 4.7 cm^{-1} in the ATR-FTIR spectrum of the chloroform-CPVP paste. Ethanol and water are well-known hydrogen donors due to their OH-moiety. This property led to a shift of CPVP's carbonyl band by 11.8 and 35.2 cm^{-1} in ethanol–CPVP and water–CPVP pastes, respectively.

To investigate the solid-state adsorption onto CPVP, a thoroughly dried carbamazepine adsorbate onto CPVP with 9.1% drug loading was investigated by ATR-FTIR spectroscopy (Fig. 5). CPVP's carbonyl band shifted by 3.2 cm^{-1}, indicating a hydrogen bond formation between carbamazepine and CPVP. Carbamazepine's only group able to act as hydrogen donor is the NH_2-group of the

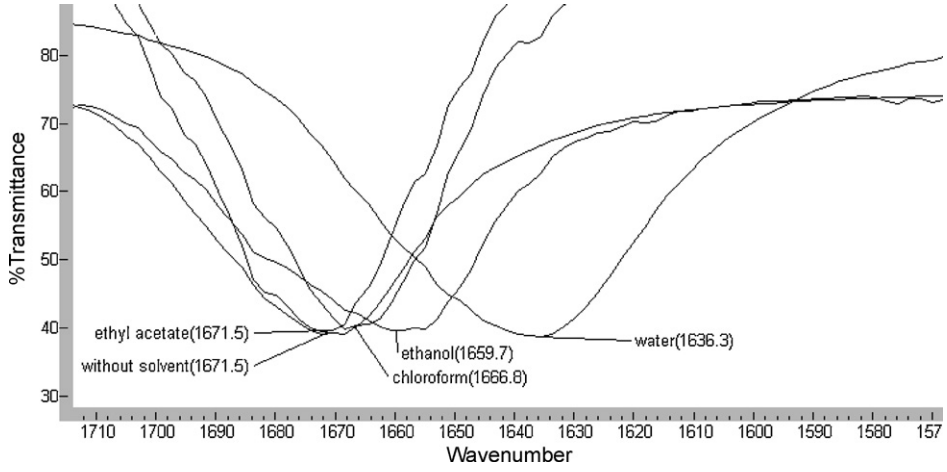

Fig. 4. FTIR spectra of dry CPVP and pastes of CPVP with different solvents.

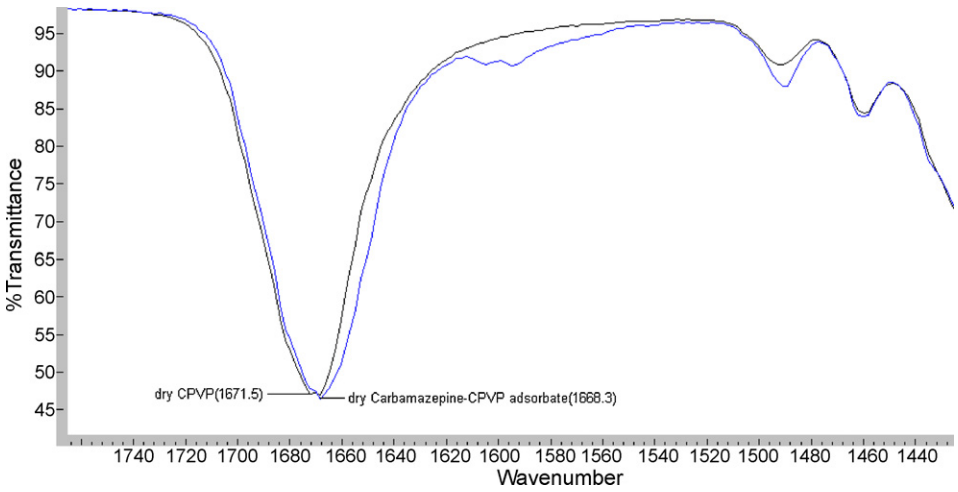

Fig. 5. Comparison of the FTIR spectra of dry CPVP and dry carbamazepine adsorbate onto CPVP.

urea function (Fig. 2). Interactions like this can immobilize drug molecules (Bhugra and Pikal, 2008) and prevent them from forming nuclei and thus crystal formation (Lipp, 1998). The small extent of the C=O shift of the carbamazepine adsorbate onto CPVP indicated a relatively weak bond formation between carbamazepine and CPVP. This is favorable, since a strong bond could impede the drug release from the adsorbate.

3.2. Optimization of the drug–carrier ratio

CPVP is capable of preventing drugs from recrystallization and of increasing drug dissolution (Friedrich et al., 2006). To find the optimum drug–CPVP ratio, adsorbates with different drug loadings were prepared by the solvent deposition method and analyzed for drug crystals by differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM) and polarized light microscopy. The solvent uptake and binding capacity of CPVP for different solvents was determined by centrifuging CPVP suspensions in different solvents (Fig. 6). Solvents capable of acting as hydrogen donors (ethanol, methanol and water) caused CPVP to take up more solvent than ethyl acetate. The significant ethyl acetate uptake of CPVP determined with this method is probably the result of the mild centrifugation conditions and hence the presence of ethyl acetate in spaces between the carrier particles.

The solvent binding capacity of CPVP is a measure of how much solvent the carrier can absorb before it becomes paste-like. The solvent binding capacity showed the same trends as the solvent uptake. However, the effects were more pronounced because only the amount of solvent that was taken up by the particles was measured. Interactions between methanol, ethanol and water and CPVP resulted in swelling of the polymer and thereby increased its binding capacity. Methanol was used for the preparation of the carbamazepine adsorbates onto CPVP for drug solubility reasons as well as CPVP's good binding capacity for this solvent. These properties are beneficial for the loading procedure of the carrier because a higher drug amount can be loaded onto the polymer in one step. Concentrated drug solutions could be problematic when they are not completely taken up by the adsorbent; the evaporation of the volatile solvent may lead to recrystallization of the drug that does not have intimate contact with the polymer.

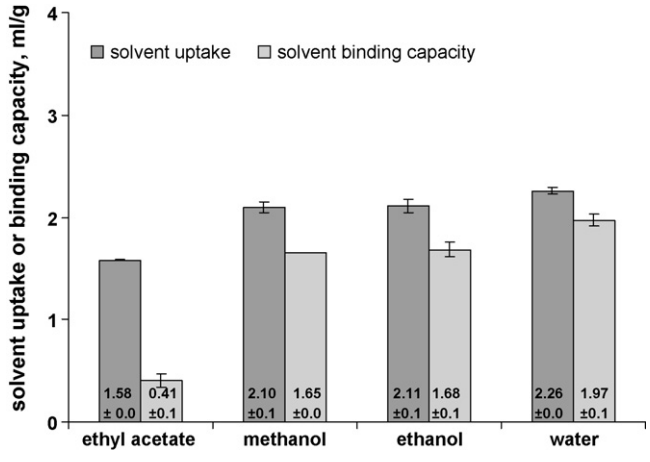

Fig. 6. Solvent uptake determined with the centrifuge method and solvent binding capacity determined with mortar/pestle and of CPVP in various solvents.

The thermograms of carbamazepine–CPVP physical mixtures showed the characteristics of carbamazepine's P-monoclinic form III (Fig. 7), which melted at 176.1 °C. Form III is the most stable polymorph of carbamazepine based on DSC analysis and the density rule (Grzesiak et al., 2003). This event was immediately followed by an exothermic peak which corresponded to the crystallization to form I. The last peak coincided with the melting of form I (191.3 °C). Due to insufficient sensitivity of the DSC method, the latter two events could not be detected in physical mixtures with lower drug loadings. The thermograms of carbamazepine–CPVP adsorbates with 33.3, 23.1 and 13.0% drug loading showed a melting point depression of 15–25 °C compared to the melting of form III in the physical mixtures. The melting point depression increased in the order of 33.3 < 23.1 < 13.0% drug loading. Furthermore, the thermal event was much broader than in the corresponding physical mixtures. Melting point depression and broadening of melting peaks have been described in the literature for drug adsorbates onto silanol (Monkhouse and Lach, 1972) and were attributed to interactions of the drug with the polymer and the minuscular form of the drug crystals. These factors facilitate the melting of the drug. Higher melting point depressions are thought to indicate increased drug–polymer interactions. The melting point depressions were more pronounced for adsorbates with lower carbamazepine loadings because the drug was more finely distributed in these formulations compared to adsorbates with higher drug loadings. Adsorbates with 9.1 and 4.8% drug loading did not show thermal events that indicated the melting of crystalline carbamazepine.

The adsorbates and the physical mixtures were investigated by XRD (Fig. 8). If the spectra showed crystallinity, they always exhibited the characteristic main peaks of carbamazepine form III at 13.0°, 15.2°, and 27.2° (Grzesiak et al., 2003).

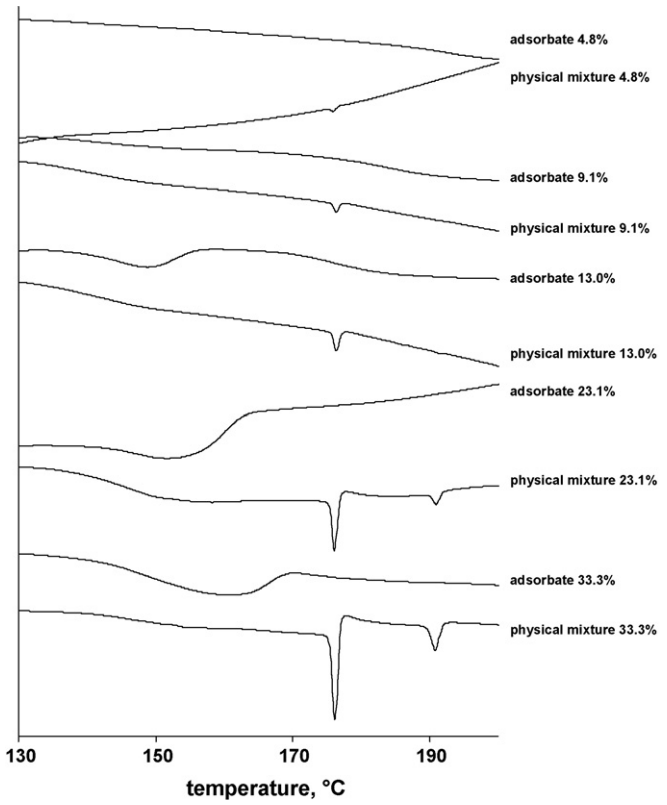

Fig. 7. DSC thermograms of carbamazepine–CPVP adsorbates and the corresponding physical mixtures with 33.3, 23.1, 13.0, 9.1 and 4.8% drug loading.

From the spectra of physical mixtures (crystalline carbamazepine form III plus CPVP, which is 100% amorphous), a correlation between the sum of the AUCs of carbamazepine's three main peaks and the total crystallinity of the mixture was obtained (Fig. 9). This relationship was used to determine the crystallinity of carbamazepine in the adsorbates (Table 1). XRD did not detect carbamazepine crystals in adsorbates with 4.8 and 9.1% drug loading, while adsorbates with higher drug loading contained crystalline carbamazepine. The total "non-crystallinity" of carbamazepine (drug loading (%) – total crystallinity (%)) yielded similar values for drug loadings from 13.0 to 33.3%. This showed the capacity of CPVP to inhibit drug recrystallization when drug crystals were

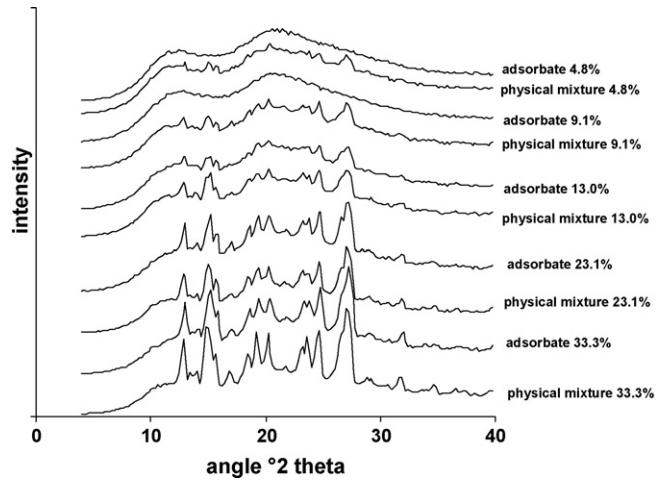

Fig. 8. XRPD of carbamazepine–CPVP adsorbates and the corresponding physical mixtures with different drug loadings.

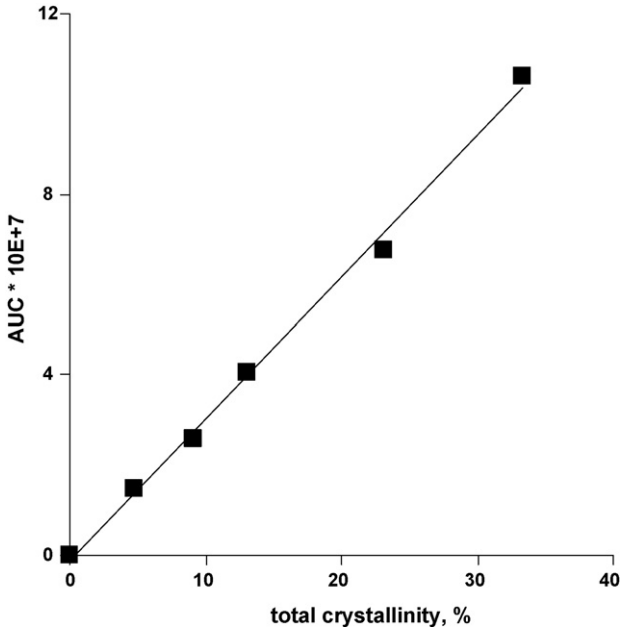

Fig. 9. Correlation of $\sum$AUCs of the three main XRPD peaks (at 13.0°, 15.2°, and 27.2°) in carbamazepine–CPVP physical mixtures and the total crystallinity of the physical mixtures.

present. The drug loading of 9.1% showed a higher capacity of CPVP to inhibit the recrystallization of carbamazepine, probably because in this case, no seed crystals were available.

SEM (Fig. 10) pictures showed carbamazepine crystals as thin needles which formed in adsorbates with drug loadings >9.1%. At lower drug loading, no carbamazepine crystals were observed. Polarized light microscopy gave similar results as SEM.

In conclusion, drug crystals were not detected by any method when the drug loading was 9.1% or less. In these adsorbates, the drug probably existed in a molecularly dispersed form. Studies of more complicated systems with ethinyl estradiol and levonorgestrel adsorbed onto CPVP in a polyisobutene matrix were conducted in another study (Schulz et al., submitted). These systems were crystal-free up to similar drug loadings (12%) as determined with carbamazepine.

3.3. Drug release

The adsorbate with 9.1% drug loading and the corresponding physical mixture were compressed into tablets without further additives. The compression step was performed because the carbamazepine adsorbates onto CPVP tended to agglomerate when added to the release medium. This led to irreproducible results. These tablets and pure micronized carbamazepine were released in a dissolution tester. Disintegration of these tablets occurred within seconds after contact with the release medium due to the pronounced swelling properties of CPVP. The drug release was faster

Table 1
Crystallinity of carbamazepine in carbamazepine–CPVP adsorbates determined by XRPD.

Drug loading (%)	AUC formulation	Total crystallinity (%)	Drug crystallinity (%)	Drug loading–total crystallinity (%)
33.3	90216955	29.1	87.3	4.2
23.1	57669697	18.7	80.5	4.4
13.0	25451563	8.5	64.2	4.5
9.1	Not detectable	0	0	9.1
4.8	Not detectable	0	0	4.8

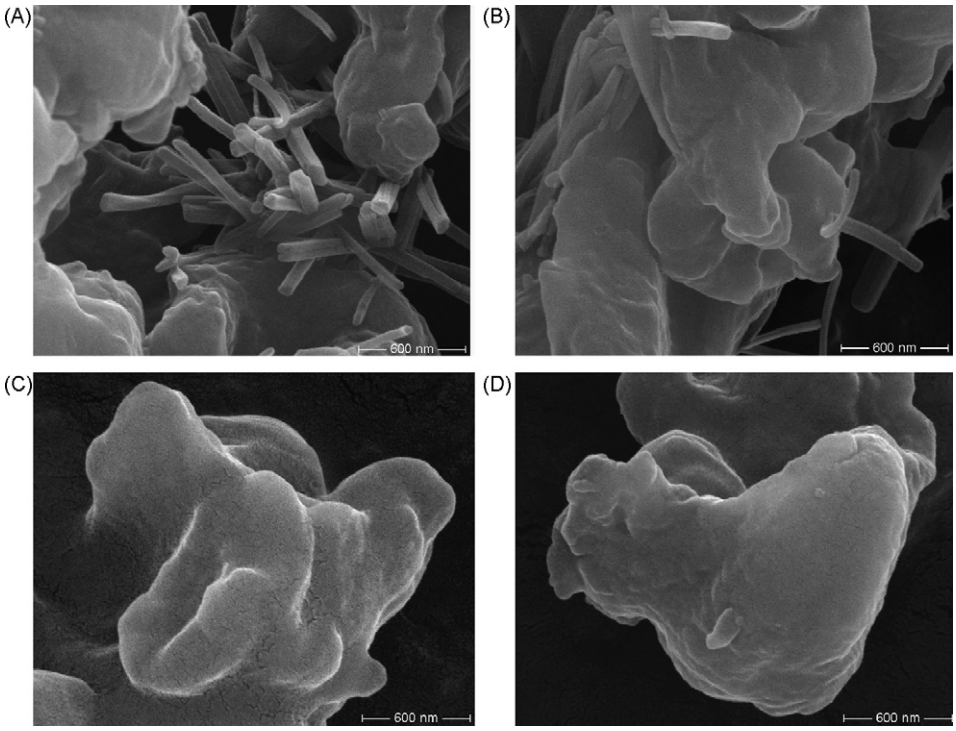

Fig. 10. SEM pictures of carbamazepine–CPVP adsorbates with (A) 33.3%, (B) 13.3%, (C) 9.1% and (D) 4.8% drug loading.

from tablets comprised of adsorbates compared to tablets comprised of physical mixture (Fig. 11). The molecularly dispersed state in which the drugs were present in the adsorbate tablets represents the ultimate reduction in particle size and the maximum increase in drug surface area. This correlates, according to the Noyes–Whitney equation, directly with the dissolution rate. Furthermore, in this physical state, no energy is required to break up crystal structures before the drug can dissolve (Leuner and Dressman, 2000). The drug release from tablets containing the physical mixture was faster than the dissolution of pure micronized carbamazepine. There are two possible explanations for this result: firstly, micronized drugs tend to agglomerate, which significantly hampers their dissolution (Aguiar et al., 1967). It is likely that CPVP in the tablets containing physical mixtures helped to disperse and disaggregate the drug particles. Secondly, it is known that even carriers that are not surface active (but hydrophilic), like linear PVP, can improve the wetting of hydrophobic drugs, e.g., in solid dispersions (Leuner and Dressman, 2000). Since the wetting is a prerequisite for dissolution, this effect probably contributed to a faster drug release kinetic.

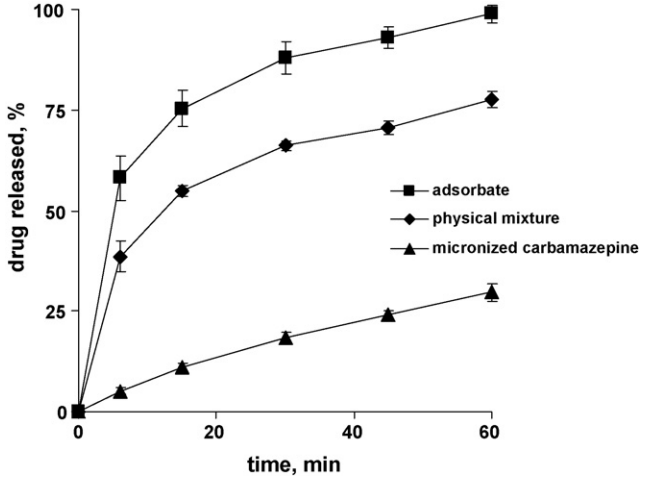

Fig. 11. Drug release from tablets prepared from the carbamazepine–CPVP adsorbate (9.1% drug loading) and the corresponding physical mixture (9.1% drug content) and pure micronized carbamazepine.

4. Conclusions

The adsorption process of carbamazepine onto CPVP is probably mainly governed by hydrogen bonds, which form between the NH_2-group of carbamazepine's urea function and CPVP's carbonyl group. This is a favorable mechanism for immediate release formulations because it ensures the complete and fast drug release from the polymeric network in aqueous environments due to the strong hydrogen donor properties of water. The interactions between carbamazepine and CPVP in the adsorbates prevented the drug from recrystallization when the drug loading did not exceed 9.1%. This adsorbate showed increased dissolution kinetics compared to the physical mixture and the pure drug. Two mechanisms of dissolution enhancement seemed to play a role: firstly, the molecularly dispersed state of carbamazepine, which explains the faster release from the adsorbate than from the physical mixture and secondly, deagglomeration and wetting effects, which explain the faster release from the physical mixture compared to the pure drug powder.

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