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Influence of polyethylene glycol and povidone on the polymorphic transformation and solubility of carbamazepine

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Abstract

Purpose: Influence of polymers on the polymorphic transition of drugs has received limited attention in the literature. The main objective of this study was to gain an understanding of the influence of polyethylene glycol and povidone on the crystalline modification and subsequently the solubility of carbamazepine in solid dispersions. *Methods*: The physical state of the drug within the dispersions was determined using DSC and powder X-ray diffractometer. DSC and optical microscopy was used to study the kinetics and morphology of dihydrate formation, respectively. *Results*: Both the polymeric dispersions showed an improved dissolution profile for carbamazepine. Carbamazepine was present in an amorphous form within the povidone dispersions. In contrast, the PEG dispersions showed the presence of crystalline drug. Higher ratios of drug/PEG resulted in the metastable form I of carbamazepine. Dihydrate formation from both the polymeric dispersions was higher compared with pure carbamazepine. The physical state of the drug and the amount of drug in solution accounted for the higher dihydrate formation from these dispersions. *Conclusions*: Knowledge of the factors contributing to enhanced solubility is critical to the stability of solid dispersions. Additionally, influence of polymers like povidone on the crystalline transitions of polymorphic drugs may be crucial during its use as a binder in granulation.

Keywords: Carbamazepine; Polymorphism; Dihydrate; Solid dispersions; Polyethylene glycol; Povidone

1. Introduction

Carbamazepine is a commonly used anticonvulsant drug and belongs to class II of the biopharmaceutical classification system. Compounds in this category have high intestinal permeability and low water solubility. Subsequently, the bioavailability of such compounds is limited by their solubility in water. There have been several reports concerning the polymorphism of carbamazepine and its influence on the solubility and bioavailability. At least four different anhydrates and one dihydrate form have been identified for carbamazepine (Krahn and Mielck, 1987). Differ-

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ences in bioavailability have been observed among various commercial formulations of carbamazepine as well as among the different polymorphic forms (Meyer et al., 1992). The mechanical strength and dissolution behavior of carbamazepine granules and tablets were found to be influenced by the solvent system used in the binder solution (Otsuka et al., 1999). These changes were due to polymorphic transitions occurring in the presence of solvent(s) during the granulation process.

An understanding of the polymorphism of carbamazepine and the influence of various excipients on the polymorphic transitions is critical to the development and performance of its solid dosage forms and ultimately its bioavailability. Recently, Otsuka et al. showed that hydroxypropylcellulose inhibited the dihydrate formation of carbamazepine (Otsuka et al., 2000). The presence of hydroxypropyl methylcellulose in sustained release carbamazepine tablets was also shown to affect the dissolution of the drug due to its inhibitory effect on dihydrate formation (Katzhendler et al., 1998). The solubility of the anhydrous carbamazepine is approximately twice that of its dihydrate (Luhtala, 1992). However, the anhydrous form once in contact with water converts to the dihydrate form (Laine et al., 1984; Young and Suryanarayanan, 1991). Given the differences in solubility between the anhydrous and dihydrate forms, the significance of the findings of Otsuka and Katzhendler is indisputable. The influence of polymers on the polymorphic transitions of carbamazepine, however, has received limited attention in the literature. This is especially important when dealing with solid dispersions since polymers are routinely used for their preparation.

Though solid dispersions have been known to increase the solubility of several drugs, there are not many commercial applications of this technology. One of the main reasons is the stability issue related to solid dispersions. The dissolution profile and mechanical strength of solid dispersions can often change over a period (Dordunoo et al., 1997; Ford and Rubinstein, 1980). One of the reasons for the enhanced dissolution profile of the solid dispersions may be related to the crystalline transformation taking place during its preparation. Conversion of the drug to the amorphous form or its presence as very small crystallites within the solid dispersions may lead to an increase in dissolution. It is well known that the different crystalline forms of a drug may have different solubility and mechanical properties. Thus, the stability of the dispersion in terms of dissolution may be directly related to the crystalline transitions, which may occur during the preparation of these dispersions.

In the preparation of solid dispersions with polymorphic drugs like carbamazepine, polymers such as povidone and PEG, as discussed earlier may change the crystal properties of carbamazepine. This can significantly affect not only the dissolution of the drug from the solid dispersion but also its stability. Therefore, the main objective of the present study was to investigate the role of povidone and PEG on the crystalline properties of carbamazepine in solid dispersions.

2. Materials and methods

2.1. Materials

Polyethylene glycol (Carbowax Sentry™) with molecular weight average of 4000 (PEG 4000) was obtained (as a sample) from Union Carbide Corporation, Danbury, CT. Povidone (Kollidon 30) with average molecular weight of 49 000 was obtained (as a sample) from BASF corporation, Mount Olive, NJ. Anhydrous carbamazepine was donated by BFGoodrich Diamalt GmbH, Raubling, Germany.

2.2. Preparation of solid dispersions

Solid dispersions were prepared by the solvent method. Accurately weighed quantities of anhydrous carbamazepine and the polymer in the ratio of 1:9, 3:7 and 6:4 were dissolved in methanol in a round bottom flask. The solvent was evaporated using a rotovap (Buchi Analytical Inc., New Castle, DE) under ambient temperature. The resulting solid was placed in a vacuum oven at 40 °C for 48 h to remove all the residual solvent.

The dried solid dispersion was lightly ground in a mortar and pestle and passed through US 80 sieve (180 μm). Differential scanning calorimetry (DSC) and powder X-ray studies conducted on the ground and unground dispersions did not indicate any change in physical state induced by grinding. The particle size was determined using a Malvern Mastersizer laser diffraction instrument (Malvern Instruments, Inc., Southborough, MA).

2.3. Thermal analysis

DSC of carbamazepine, PEG, povidone, and the solid dispersions was performed using a TA Instruments DSC 2920 Module, New Castle, DE. The samples were heated at a rate of 10 °C/min from 0 to 220 °C under a dry nitrogen gas purge. All measurements were conducted in sealed non-hermetic aluminum pans. Typical sample weights ranged between 5 and 10 mg. All analyses were performed in triplicate.

2.4. X-ray powder diffraction

X-ray powder diffraction for carbamazepine, PEG, and the solid dispersions with PEG was performed using a Bruker D8 X-ray diffractometer (Bruker Axs Inc., Madison, WI). Measurement conditions included target, CuKα, voltage, 30 kV, and current, 40 mA. Patterns were obtained using a step width of 0.02° 2θ between 5 and 60° 2θ at ambient temperature.

2.5. Dissolution studies

It is well established that particle size affects dissolution. The average particle size of the solid dispersions and pure carbamazepine was the same, average particle size being 100 um. An excess quantity of the solid dispersions corresponding to 20 mg of carbamazepine was added to a vial containing 20 ml of water at 37 °C. The vial was placed in a shaker bath at 37 °C and 100 RPM. The samples were withdrawn at definite time intervals and filtered through a 0.25 μm filter (GHP Acrodisc syringe filters, Pall Gelman laboratory, Ann Arbor, MI). The amount of carbamazepine in the filtrate was assayed using a UV spectrophotometer (Beckman Coulter Inc., Fullerton, CA) at 285 nm. It should be noted that the polymers, PEG and povidone, showed negligible absorption at this wavelength.

2.6. Evaluation of dihydrate formation

Accurately weighed quantities of solid dispersions and carbamazepine corresponding to 20 mg drug were placed in a vial containing 20 ml of water at 37 °C. The vial was placed in a shaker bath at 37 °C and 100 rpm. The samples were withdrawn at intervals of 5, 30, and 60 min and filtered through a filter paper. The residue (sample retained on the filter paper) was allowed to dry under identical conditions before conducting any thermal analysis. Thermal analysis was performed as described under Section 2.3.

2.7. Optical microscopy

The growth of carbamazepine crystals in water from the various solid dispersions and anhydrous carbamazepine was observed using a Nikon Eclipse 1800 microscope (Nikon Inc., Melville, NY) equipped with a camera controller (Hamamatsu model C4742-95) and IP3 software for image analysis. The residue obtained from the dehydration studies was used for the microscopy study.

3. Results and discussion

3.1. Dissolution study

3.1.1. PEG dispersions

Fig. 1a shows the dissolution profile for the PEG solid dispersions and pure carbamazepine. All the solid dispersions showed a higher amount of drug released compared with pure carbamazepine. The amount released increased with an increasing proportion of PEG with the 1:9 carbamazepine:PEG solid dispersion showing the highest amount released followed by the 3:7 and 6:4 dispersions. The dissolution from 1:9 carbamazepine:PEG showed a decline in concentration after 30 min. The reason for this decline is discussed later.

3.1.2. Povidone dispersions

The dissolution profile of solid dispersions prepared with povidone is shown in Fig. 1b. Povidone dispersions also showed a higher release compared with pure carbamazepine. Similar to the PEG dispersions, the solubility of the 1:9 povidone dispersions declined after 15 min. The 3:7 and 6:4 povidone dispersions showed approximately 8-fold increase in the dissolution profile compared with pure carbamazepine during the initial 5 min.

Since the bioavailability of carbamazepine is limited only by its dissolution rate, even a small increase in dissolution will result in a large increase in its bioavailability. Based on the results from the dissolution studies it is evident that PEG and povidone dispersions can significantly improve the dissolution and subsequently the bioavailability of carbamazepine. Several factors may account for the increased dissolution from these polymeric dispersions including: (1) the formation of amorphous carbamazepine within the solid dispersion; (2) presence of carbamazepine as very small crystallites within the dispersion; (3) inhibition of formation of carbamazepine dihydrate thus leading to higher dissolution due to the anhydrous form; and (4) an increased hydrophilic effect due to PEG and povidone. Each of these factors was individually investigated to identify the cause of enhanced dissolution from the solid dispersions containing either PEG or povidone.

The decline in drug release observed for the 1:9 solid dispersions (both PEG and povidone) may be due to the polymorphic transformation of the anhydrous carbamazepine to the more stable dihydrate form in water. Similar decline in dissolution profile have been observed for several other drugs capable of forming hydrates (Shefter and Higuchi, 1963).

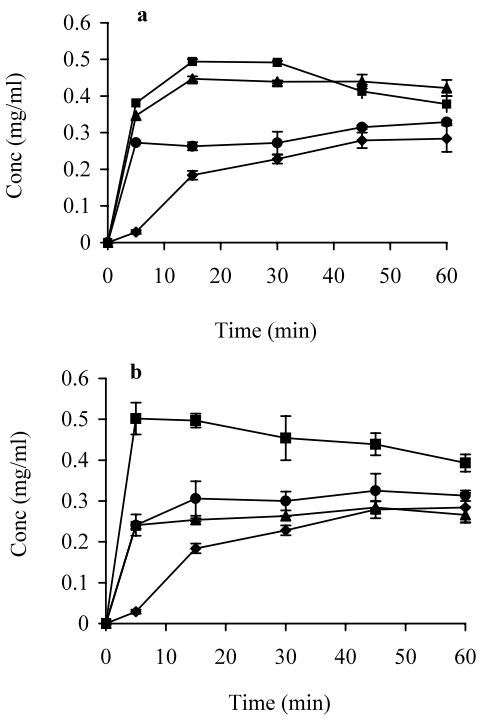

Fig. 1. Dissolution profile of solid dispersions (a) carbamazepine:PEG (b) carbamazepine:povidone (■) 1:9 (▲) 3:7 (●) 6:4 (◆) carbamazepine.

3.2. Thermal analysis

Carbamazepine exhibits enantiotropic polymorphism, i.e. there exists a transition temperature below the melting point of either of the polymorphs at which both these forms have the same free energy (Behme and Brooke, 1991). Above the transition temperature, the higher melting form I has the lower free energy and is more stable. Below the transition temperature, however, the lower melting form III is more stable since it has the lower free energy. The transition temperature of carbamazepine enantiotropic forms has been reported to be around 71 °C (Behme and Brooke, 1991). Hence, under ambient conditions form III is the most stable form.

The DSC curves obtained for the pure components and the solid dispersions are illustrated in Fig. 2. Pure carbamazepine (Fig. 2a) shows a small melting endotherm at 176 °C followed by a second endotherm at 190 °C. These two endotherms correspond to form III and I of carbamazepine, respectively (Lowes et al., 1987). The melting endotherm at 176 °C indicates that the carbamazepine used in this study was form III and this is consistent with free energy considerations.

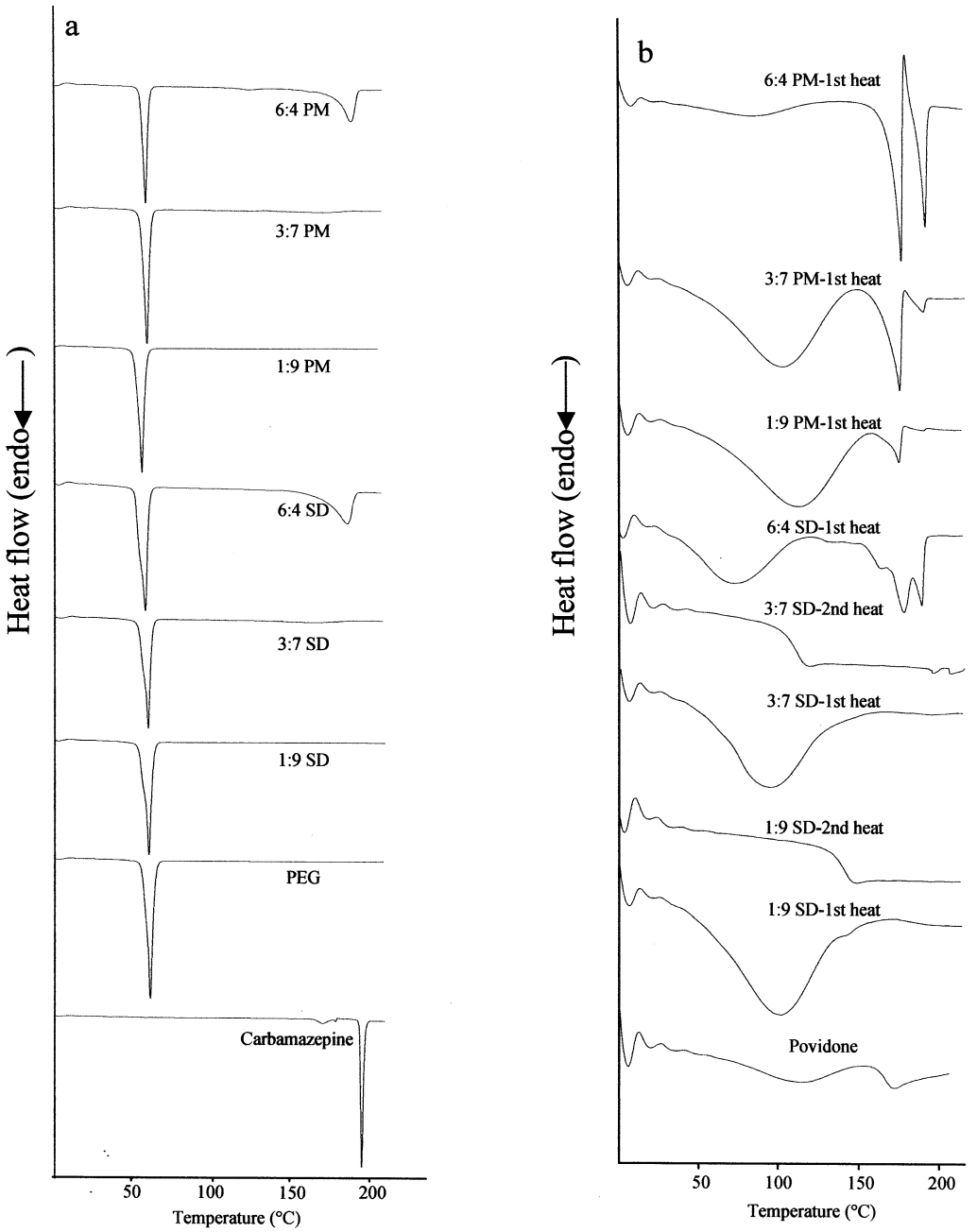

Fig. 2. DSC thermograms of solid dispersions (SD) and their physical mixtures (PM) (a) carbamazepine:PEG (b) carbamazepine:povidone.

3.2.1. PEG dispersions

Fig. 2a shows the DSC thermogram for carbamazepine dispersion with PEG. Pure PEG shows an endotherm at 67 °C corresponding to its melting point. Interestingly, the melting endotherm for carbamazepine was not evident in the DSC ther-

mograms for the 1:9 and 3:7 solid dispersions. The 6:4 dispersions, however, showed a broad endotherm between 175 and 190 °C corresponding to the melting point of the drug. DSC results on the physical mixtures of carbamazepine and PEG also reveal a lack of melting endotherm in the 1:9 and 3:7 physical mixtures. The melting peak for carbamazepine was present in the 6:4 physical mixtures similar to the 6:4 solid dispersions.

A lack of drug melting endotherm in solid dispersions usually suggests the presence of the drug in an amorphous form within the dispersions. However, the absence of a melting endotherm for carbamazepine in the PEG solid dispersions may not be indicative of the physical state of carbamazepine within the dispersion. Since PEG melts before the drug, there is a possibility that the crystalline carbamazepine might dissolve in the molten PEG during the DSC scan and convert to the amorphous form. This is similar to the 'melt method' used to prepare PEG dispersions. The absence of melting endotherm, therefore, may be due to the formation of amorphous carbamazepine during the DSC scan and not necessarily due to its presence in the solid dispersion. This is further substantiated by the absence of a melting endotherm in the physical mixtures. The 6:4 dispersions showed the presence of crystalline drug since the amount of PEG was not sufficient to inhibit the crystallization of carbamazepine.

3.2.2. Povidone dispersions

The DSC results of povidone dispersions are shown in Fig. 2b. Pure povidone shows a glass transition temperature (T_g) at 168 °C, consistent with its amorphous state. A broad endotherm around 100 °C indicates loss of water due to the extremely hygroscopic nature of povidone. The 1:9 and 3:7 carbamazepine:povidone dispersions showed a similar broad endotherm during the first heating cycle. However, on reheating the same sample, a distinct T_g was seen for both the dispersions, which may have been obscured by the evaporation endotherm during the first run. The 1:9 and 3:7 dispersions had T_g of 143 and 111 °C, respectively. The absence of drug melting endotherm and the presence of a single T_g for the 1:9 dispersion indicate that carbamazepine is present in an amorphous form within the dispersion. In addition, the drug acts as a plasticizer by lowering the T_g of povidone. In the case of the 3:7 dispersions two small distinct endotherms were observed near the melting point of carbamazepine during the second heating cycle. In contrast, the 6:4 dispersions showed a melting peak for the drug during the first heating cycle. Thus, it is apparent that carbamazepine was present in the crystalline form in the 6:4 dispersions.

Numerous studies have shown that polymers like povidone used in solid dispersions can inhibit the crystallization of drugs resulting in an amorphous form of the drug in the solid dispersions (Sekikawa et al., 1978; Yoshioka et al., 1995). The mechanism of crystallization inhibition by povidone is often due to specific interactions, especially hydrogen-bonding between the drug and polymer. The extent of inhibition depends on the proportion of the polymer in the mixture, with higher proportions resulting in more inhibition.

3.3. Powder X-ray analysis of PEG dispersions

Since DSC could not confirm the physical state of carbamazepine within the PEG matrix, powder X-ray diffraction studies were conducted on these dispersions. Fig. 3 shows the powder X-ray diffraction patterns for the physical mixtures and solid dispersions with PEG. All the solid dispersions and their physical mixtures show the presence of distinct peaks characteristic of crystallinity. This further confirms that DSC may not be useful for examining the solid state of drugs within PEG matrices. Pure carbamazepine shows peaks at approximately 13 and 15 2θ, which are specific for form III (Otsuka et al., 2000). This is in agreement with the melting point obtained with DSC. PEG reveals two distinct peaks at 19 and 23 2θ characteristic of its crystalline nature. The peaks of carbamazepine form III at 13 and 15 2θ were also evident in all the physical mixtures. Thus, simply mixing of the drug and PEG did not change the physical state

of either of the components. The diffraction profile for the 1:9 solid dispersions was similar to the corresponding physical mixture, indicating the presence of crystalline form III of carbamazepine. Interestingly, the 3:7 and 6:4 solid dispersions showed additional peaks between 5 and 8 2θ which are characteristic of form I (Krahn and Mielck, 1987; Kobayashi et al., 2000). The preparation of the 3:7 and 6:4 carbamazepine:PEG solid dispersions, therefore, results in the formation of form I of carbamazepine. This finding is extremely important from a stability aspect. As mentioned earlier under Section 3.2, form I is the metastable form of carbamazepine under ambient conditions. However, on storage form I will tend to convert to the more stable form III. The two forms differ in their solubility evidently due to differences in their free energy (Kobayashi et al., 2000). Given these differences in solubility, it is expected that a change in the dissolution profile of the 3:7 and 6:4 solid dispersion will occur with time due to the conversion of form I to III.

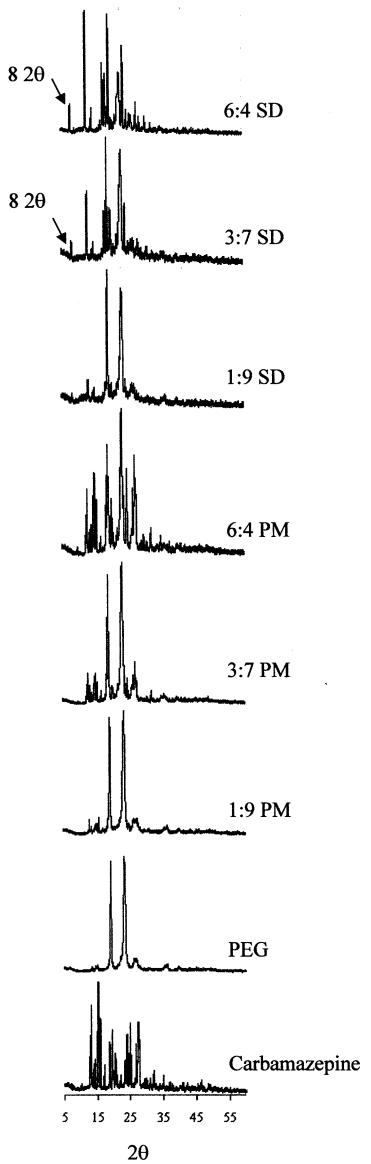

Fig. 3. Powder X-ray data for carbamazepine:PEG dispersions (SD) and their physical mixtures (PM).

The results from the dissolution, DSC, and powder X-ray diffraction studies provide an insight into the long-term stability of these dispersions. In the case of povidone dispersions, the presence of amorphous carbamazepine may present a problem. Amorphous forms of drugs usually have higher solubility compared with the crystalline forms. However, the stability of amorphous forms is low, and conversion to stable crystalline forms occurs gradually. It is probable that the rate of dissolution of the povidone dispersions may decrease over time due to the conversion of amorphous carbamazepine to the crystalline form depending on storage conditions.

The temperature of storage conditions have been reported to influence the rate of transformation of the amorphous to crystalline form. Storage above the T_g will lead to a relatively rapid conversion to the crystalline form due to the high mobility of the amorphous form above their T_g (Hancock et al., 1995). The humidity of storage conditions is also extremely important considering the hygroscopic nature of povidone. Absorbed moisture can reduce the T_g of the amorphous povidone dispersions and lead to further instability in these dispersions. Hence, the choice of appropriate storage conditions is necessary to maintain long term stability of these dispersions.

In the case of 1:9 PEG dispersions, presence of the stable crystalline carbamazepine form would not be expected to have any stability problems. However, the 3:7 and 6:4 dispersions showed the presence of the metastable (under ambient conditions) form I, which can convert to the stable

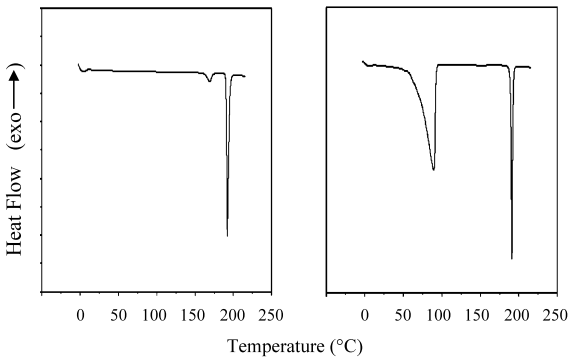

Fig. 4. DSC thermogram of (a) anhydrous carbamazepine (b) carbamazepine dihydrate obtained after suspension of solid dispersions in water.

form III. Hence, the dissolution profile of the 3:7 and 6:4 PEG dispersions may change with time due to the differences in solubility between form I and III.

3.4. Formation of dihydrate

To further investigate the mechanism of increased dissolution from the PEG and povidone dispersions, the extent of dihydrate formation from these dispersions was evaluated. On heating carbamazepine dehydrate it loses its water of crystallization and shows a dehydration endotherm between 50 and 90 °C (Kobayashi et al., 2000; Krahn and Mielck, 1987). The presence of this endotherm was considered as an indication of the dihydrate formation. The kinetics of dihydrate formation from solid dispersions and pure carbamazepine was determined using the area under the dehydration endotherm, ΔH_t. This area corresponds to the energy involved in breaking of the drug-water bonds and the vaporization of water (Khankari et al., 1992; Han and Suryanarayanan, 1997)

3.4.1. PEG dispersions

Fig. 4 shows a representative DSC thermogram for carbamazepine crystals recrystallized from PEG solid dispersions in water. All the PEG solid dispersions showed an endotherm between 70 and 90 °C after 5 min of contact with water, indicating the formation of the dihydrate. In contrast, carbamazepine did not show any endotherm during the 60 min indicating the absence of any dihydrate formation during this period. In addition to the dehydration endotherm, an additional endotherm was observed at approximately 192 °C for all the samples. This endotherm corresponds to the melting of polymorphic form I of carbamazepine.

Table 1 shows the overall energy of transition, ΔH_t for the various solid dispersions and carbamazepine. The 1:9 solid dispersions showed the highest value for ΔH_t within 5 min and this value did not vary with time. In the case of 3:7 and 6:4 dispersions, ΔH_t increased from 5 to 60 min, indicating an increase in dihydrate formation over time. Formation of the dihydrate appears to be proportional to the amount of carbamazepine in solution as seen from the dissolution results. As previously mentioned (Fig. 1a) the 1:9 dispersions showed the highest concentration after 5 min followed by a decline in concentration after about 30 min. On the contrary, the 3:7 and 6:4 solid dispersions did not show any decline in dissolution profile with time during the 60-min time period. These results are consistent with the ongoing dihydrate formation for 3:7 and 6:4 dispersions indicated by an increase in ΔH_t seen over time. Similar increases in the transition of anhy-

Table 1
Total heat of dehydration of carbamazepine and the solid dispersions

Solid dispersion	ΔH_t (J/g)		
	5 min	30 min	60 min
Carbamazepine	0	0	0
CZ:PEG (1:9)	357.7 ± 21.7	329.9 ± 15.8	363.9 ± 10.5
CZ:PEG (3:7)	191.7 ± 19.1	217.1 ± 21.4	244.0 ± 24.4
CZ:PEG (6:4)	164.6 ± 29.8	164.4 ± 7.2	218.1 ± 15.0
CZ:Povidone (1:9)	304.8 ± 21.5	328.9 ± 15.4	339.5 ± 8.4
CZ:Povidone (3:7)	329.4 ± 12.1	347.0 ± 2.9	369.6 ± 2.4
CZ:Povidone (6:4)	227.3 ± 4.7	298.4 ± 13.5	331.2 ± 16.0

Average $\pm$ S.D., $n = 3$.

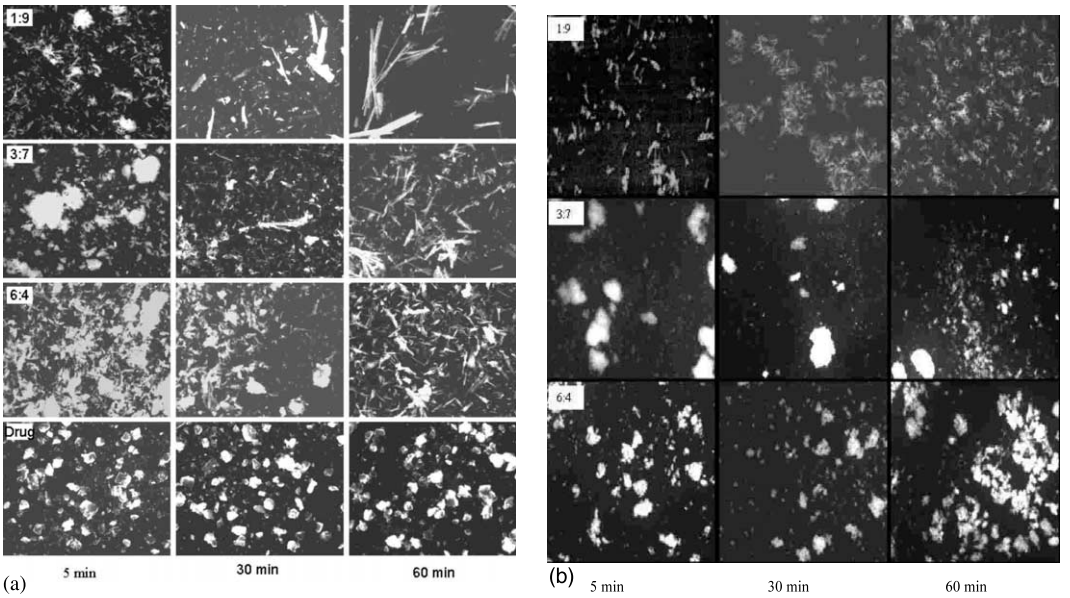

Fig. 5. Optical micrographs of carbamazepine dihydrate recrystallized from (a) carbamazepine: PEG dispersions in water (b) carbamazepine: povidone dispersions in water.

drous to dihydrate form with an increase in carbamazepine concentration in solution have also been reported in the presence of surfactants like sodium lauryl sulfate and poloxamer (Luhtala, 1992).

The dissolution data suggests that for pure carbamazepine, the amount of drug in solution may be too low to promote the growth of dihydrate crystals. Though there are studies in the literature stating that the transformation of anhydrous carbamazepine to the dihydrate occurs within 5 min of contact with water, no such conversion was observed in our study (Young and Suryanarayanan, 1991; Laine et al., 1984). This may be due to the different methods (varying speed, particle size, trituration) employed to study the solubility and kinetics of polymorphic transformation of carbamazepine. Furthermore there may have been differences in the ratio of the polymorphic forms I and III in the anhydrous carbamazepine used in these other studies.

3.4.2. Povidone dispersions

Unlike the carbamazepine:PEG dispersions, the povidone dispersions (Table 1) did not show any correlation between the dissolution data and formation of the dihydrate. The 1:9 and 3:7 solid dispersions showed similar extent of dihydrate formation despite the 1:9 dispersions having a higher dissolution profile. The physical state of carbamazepine within the dispersions and the nature of polymer may account for the differences in dihydrate formation between the PEG and povidone solid dispersions. It may be that the rate of transformation of the amorphous form to the dihydrate form is higher than that of the anhydrous to the dihydrate form. This is reasonable if one compares the dihydrate formation between the 3:7 and 6:4 povidone dispersions. Despite the similarity in their solubility profile the rate of dihydrate formation is higher in the 3:7 dispersions which show the presence of amorphous carbamazepine.

3.5. Optical microscopy

3.5.1. PEG dispersions

Fig. 5a. shows the various stages of crystal growth after suspending pure carbamazepine and the solid dispersions in water for 5, 30, and 60

min. The 1:9 and 3:7 solid dispersion show the formation of small thin needle like structures within 5 min of suspension in water. In contrast, the 6:4 dispersion and carbamazepine did not show any change in shape during this time. After 60 min of suspending the solid dispersions in water, larger needle shaped crystals were seen for all the dispersions. The length of the crystals increased as the proportion of PEG increased. Unlike the solid dispersions, pure carbamazepine did not show any change in appearance during the 60-min period. Large needle shaped crystals were, however, evident for carbamazepine at the end of 24 h indicating the formation of dihydrate. The dihydrate crystals in the PEG solid dispersions appear to form by the whisker mechanism proposed by Laine (Laine et al., 1984), which includes nucleation, crystal growth and thickening of needles.

There is distinct difference in the rate of crystal growth among the solid dispersions and carbamazepine. The crystal morphology from the optical microscopy supports the DSC data, which showed a higher dehydration energy for the 1:9 solid dispersion followed by the 3:7 and 6:4 dispersions. No dehydration endotherm was observed for carbamazepine during the first 60 min. This is in agreement with the microscopy results, which also did not show any dihydrate crystals for pure carbamazepine during this period.

3.5.2. Povidone dispersions

The photomicrographs of povidone dispersions is shown in Fig. 5b. The 1:9 carbamazepine:povidone dispersions show the formation of very small needle shaped structures at the end of 5 min, which increased in length with time. The needle shaped crystals seen in the PEG dispersions were not evident in the 3:7 and 6:4 povidone dispersions. Though both PEG and povidone dispersions showed the formation of dihydrate, the morphology of the dihydrate appears to be different in the two polymeric dispersions.

The increased solubility observed with the PEG and povidone dispersions cannot be accounted by the dihydrate formation since neither of these polymeric carriers inhibited the dihydrate formation.

3.6. Effect of polymer solution on the solubility of carbamazepine

Solubility of carbamazepine was conducted (with conditions identical to that of the dissolution studies) in PEG and povidone solutions at three different concentrations, 0.3, 0.6 and 1% (w/v). These concentrations correspond to the concentration of the polymer present on dissolution from the solid dispersion.

3.6.1. PEG solution

Fig. 6a shows the dissolution profile of carbamazepine in PEG solution. The amount of carbamazepine in solution was lower in the presence of PEG solutions. A similar effect of PEG solution on the dissolution of carbamazepine has been reported by El-Zein et al. (El-Zein et al., 1998). Thus, the increased dissolution from the carbamazepine:PEG solid dispersions cannot be attributed to the hydrophilic nature of PEG.

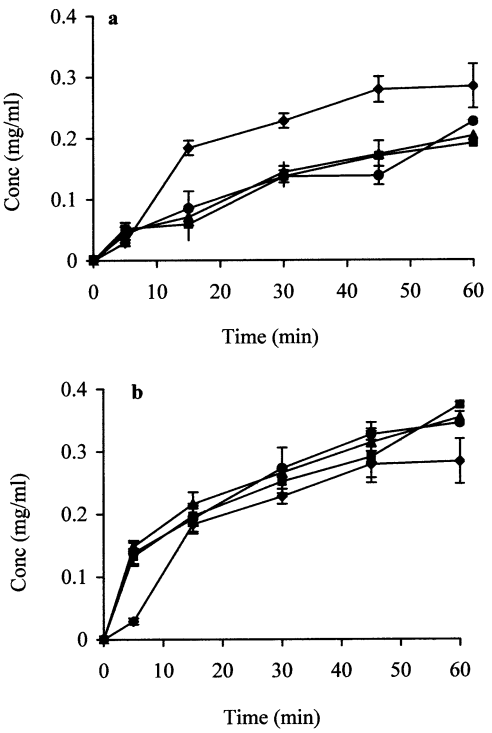

Fig. 6. Effect of various concentrations (% w/v) of (a) PEG and (b) povidone solution on the solubility of carbamazepine (○) water (■) 0.3 (▲) 0.6 (●) 1.

3.6.2. Povidone solution

The solubility of carbamazepine in povidone solution was similar to that in water (Fig. 6b). There was a small increase in solubility during the initial 5 min and at the end of 60 min. In general, though, povidone did not show any enhanced wetting effect.

4. Conclusions

Solid dispersions of carbamazepine with PEG and povidone increased the dissolution of carbamazepine by different mechanisms. Carbamazepine was present in the amorphous form within the povidone dispersions and this can account for its higher release from these dispersions. The increased dissolution from the PEG dispersions maybe due to the presence of carbamazepine as very small crystallites dispersed within the matrix. Both the polymeric dispersions also showed differences in the dihydrate formation.

Identification of the factors leading to improved dissolution in solid dispersions can help the formulator to anticipate any stability problems that can occur during the storage of these dispersions. Most importantly, knowledge of the mechanism of enhanced dissolution by these polymeric carriers will help the formulator to choose the formulation with optimum solubility and long term stability. Moreover, polymers such as povidone, which is commonly as a binder solution can alter the solid state characteristics of the drug during processing. Hence extreme care should be undertaken and the necessary studies performed to detect any solid state transformation when using such systems.

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