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The influence of various excipients on the conversion kinetics of carbamazepine polymorphs in aqueous suspension

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Abstract

The influence of various excipients on the conversion of carbamazepine polymorphs to the dihydrate in aqueous suspension has been investigated. Ten excipients having functional groups which were potentially able to form hydrogen bonds with carbamazepine (group 1: methylcellulose, hypromellose (hydroxypropyl methylcellulose), hydroxypropylcellulose (HPC), 2-hydroxyethylcellulose (HEC), carmellose sodium (sodium carboxymethylcellulose), cellobiose; group 2: povidone (polyvinylpyrrolidone), povidone-vinyl acetate copolymer (povidone/VA) and N-methyl-2-pyrrolidone; group 3: macrogol (polyethylene glycol) and polyethylene oxide–polypropylene oxide copolymer (PEO/PPO)) were selected. Carbamazepine polymorphic forms III and I were dispersed separately into each aqueous excipient solution (0.1%, w/v) for 30 min at room temperature. The inhibition effect of each excipient was quantified using Raman spectroscopy combined with multivariate analyses. The solubility parameter of each excipient was calculated and used for categorizing excipients. Excipients in groups 1 and 2, which had both low solubility parameters (< 27.0 $MPa^{1/2}$) and strong hydrogen bonding groups, inhibited the conversion completely. With increasing solubility parameter, the inhibition effect decreased for group 1 excipients, especially for carbamazepine form I, which had a higher specific surface area. Also, the excipients of group 3, lacking strong hydrogen bonding groups, showed poor inhibition although they had low solubility parameters (< 21.0 $MPa^{1/2}$). This study indicated the importance of both hydrogen bonding interaction and a suitable hydrophobicity (expressed by the solubility parameter) in the inhibition of the conversion of carbamazepine to the dihydrate.

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Introduction

Carbamazepine is an important anti-convulsant drug which has been in routine use for over 20 years (Hartley et al 1990). Although carbamazepine has a high intestinal permeability, the bioavailability is limited by its low water solubility (0.11 mg mL^{-1}). Carbamazepine is known to crystallize into at least four polymorphic forms and one dihydrate, and its solubility and dissolution rate have been found to be influenced by the polymorphic form (Kahela et al 1982; Kaneniwa et al 1987; Kobayashi et al 2000). The dissolution rates of two commonly existing polymorphic forms (forms I and III) and the dihydrate have been reported to be in the order of form I > form III > dihydrate, and the solubilities calculated for the anhydrates were 1.5–1.6 times that of the dihydrate according to dissolution tests (Kobayashi et al 2000), indicating a further decrease in solubility and thus bioavailability of carbamazepine forms once they convert to the dihydrate.

Efforts have been focused on improving the solubility and dissolution of carbamazepine form III using various excipients and formulation methods (Bettini et al 2001; Moneghini et al 2001; Naima et al 2001; Nair et al 2002; Hu et al 2003; Koester et al 2003; Marchais et al 2003; Perissutti et al 2003; Sethia & Squillante 2004), where the formation of carbamazepine form I or the amorphous form was induced due to its interaction with excipients such as macrogol (polyethylene glycol) and povidone (polyvinylpyrrolidone) during the preparation. However, all these studies were carried out in the solid state, and much less

attention was given to the conversion of carbamazepine in aqueous suspension in the presence of excipients. Recently, it has been found that the conversion of carbamazepine to the dihydrate was facilitated when carbamazepine was dissolved in solutions containing various surfactants such as sodium lauryl sulfate (SLS) and sodium taurocholate (STC) (Rodríguez-Hornedo & Murphy 2003). This was explained by the enhanced dissolution of carbamazepine in the presence of these surfactants. Carbamazepine solubility was also markedly increased in various nonionic surfactants such as Tweens, Myrjs and Brijs (Samaha & Gadalla 1987; Shah et al 1987). Hypromellose (hydroxypropyl methylcellulose) and egg albumin on the other hand have been reported to inhibit the conversion of carbamazepine to the dihydrate in aqueous suspension, with hypromellose showing a much higher inhibition ability than egg albumin (Katzhendler et al 2000a, b). This group suggested that the strong inhibition ability of hypromellose was due to structural complementarity between hypromellose and carbamazepine. The bond spacing distance (3.69 Å) between the oxygen and hydrogen atoms in the carbamazepine dimer (indicated by * in Figure 1, CBZ dimer) was similar to the distance between the oxygen and the hydrogen atoms in the cellulose ring of hypromellose (indicated by # in Figure 1, cellulose) (Katzhendler et al 1998).

The fact that there are only a few studies of the effect of excipients on the conversion of polymorphs of carbamazepine to the dihydrate may be a consequence of the difficulties in studying such compounds in an aqueous suspension using standard solid state techniques such as X-ray powder diffraction (XRPD). However, Raman spectroscopy is well suited to monitor polymorphic conversion in aqueous medium due to the weak water scattering signal and simple sample preparation, where preparation for XRPD such as filtration and grinding are avoided. Previously, we characterized the conversion process of pure carbamazepine forms III and I to the dihydrate in aqueous suspension (Tian et al 2006). This study was conducted to obtain an insight into the mechanism of interaction between carbamazepine and various excipients in aqueous suspension.

Materials and Methods

Materials

Carbamazepine form III obtained from Sigma-Aldrich Chemie (Munich, Germany) was used as received. Carbamazepine form I was prepared by heating form III at 150°C for 3 h as described by Grzesiak et al (2003). Dihydrate was prepared from carbamazepine as received by recrystallization from an ethanol–water mixture as reported by Krahn & Mielck (1987). All forms were confirmed by X-ray powder diffraction as reported previously (Krahn & Mielck 1987; Grzesiak et al 2003). The particle size of carbamazepine forms III and I was controlled by sieving to the range 180–250 μm (Test sieves, Endecotts Ltd, UK). The specific surface areas of form III and I were estimated based on their respective scanning electron microscopy (SEM) images. Adobe Photoshop 7.0 (San Jose, CA) was used to remove the background from SEM photos and the two-dimensional specific surface area of particles was calculated by AnalySIS Pro 3.1 (Soft Imaging System GmbH, Germany) (100 particles were randomly selected for each form).

Methylcellulose with molecular weights of 14 000, 41 000 and 88 000; hypromellose (hydroxypropyl methylcellulose) with a molecular weight of 26 000; hydroxypropylcellulose (HPC) with a molecular weight of 80 000; 2-hydroxyethylcellulose (HEC) with a molecular weight of 720 000; carmellose sodium (sodium carboxymethylcellulose) with a molecular weight of 700 000; and cellobiose were purchased from Sigma Chemical Co. (St Louis, MO). Povidone (polyvinylpyrrolidone) with molecular weights of 24 500 and 44 000, and macrogol (polyethylene glycol) with a molecular weight of 6000 were obtained from BDH Chemicals Ltd (Poole, UK). Povidone (Kollidon 90F) with a molecular weight of 1000 000–1500 000, povidone–vinyl acetate copolymer at a weight ratio of ~6:4 (povidone/VA) and a molecular weight of 45 000–70 000, and polyethylene oxide–polypropylene oxide copolymer (PEO/PPO) with a molecular weight of 8400 were obtained from BASF, Germany. *N*-Methyl-2-pyrrolidone was purchased from ISP Technologies, Inc. (Wayne, NJ). All excipients were used without further purification. Molecular weights of the polymers were supplied by the respective companies.

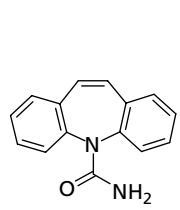
The chemical structures of carbamazepine and the various excipients used in this study are presented in Figure 1. The excipients could be classified into three groups according to their molecular characteristics. Group 1, cellulose derivatives and cellobiose–having both hydrogen bond donor and acceptor groups in their ring structure. Group 2, povidone/VA, povidone and methylpyrrolidone–only having hydrogen bond acceptor groups. Group 3, macrogol and PEO/PPO–having hydrogen bond donor groups only at the two ends of the polymer chain, and weaker hydrogen bond acceptor groups than those in group 2.

X-ray powder diffraction (XRPD)

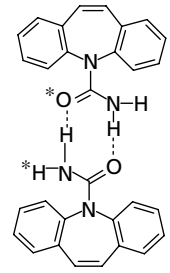
XRPD measurements were performed using a Philips PW 1130/00 X-ray generator (Philips, Almelo, The Netherlands), and a Phillips PW 1050 goniometer (Philips, Almelo, The Netherlands). The X-ray generator was set to an acceleration voltage of 40 kV and a filament emission of 20 mA. The diffraction patterns were collected over the range of 5–35° (2θ) at a step size of 0.02° (2θ). The diffractograms were displayed using Mac Diff version 4.0.5 software (A. J. Hall, Applied Geology, University of Strathclyde, UK).

Differential scanning calorimetry (DSC)

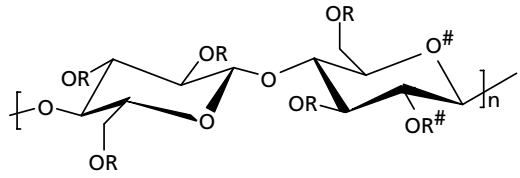
Thermal analyses of the different carbamazepine forms and the recovered samples were performed using a DSC – Q100 (TA instruments, New Castle, DE). Samples were weighed into aluminum pans and sealed with a crimper. The thermal behaviour of the samples was studied under a dry nitrogen purge (20 mL min^{-1}) at a heating rate of 10°C min^{-1} over a temperature range of 40–200°C.



CBZ



CBZ dimer

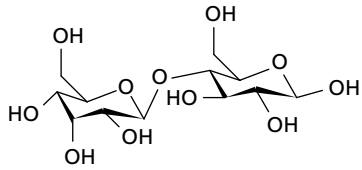


Cellulose (R = H) or cellulose derivatives (R from the list below)

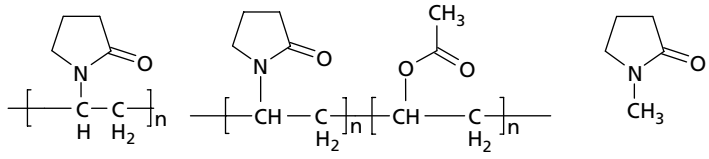
Cellulose derivatives	–R	DS†
Methylcellulose	$-CH_3$	1.50–1.90 (1.70)
Hypromellose (Hydroxypropyl methylcellulose)	$-CH_2CH(OH)CH_3$, $-CH_3$	~0.50 (0.50), ~2.50 (2.50)
Hydroxypropyl cellulose (HPC)	$-CH_2CH(OH)CH_3$	~2.00 (2.00)
Hydroxyethyl cellulose (HEC)	$-CH_2CH_2OH$	1.50 (1.50)
Carmellose sodium (sodium carboxymethylcellulose)	$-CH_2COONa$	0.86 (0.86)

†DS (Degree of Substitution) were obtained from Sigma information sheets.

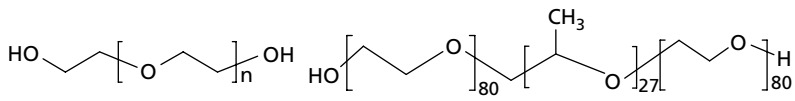
Values in parentheses are the DS values used for the solubility parameter calculations.



Cellobiose (2-β-D-glucose)



PVP PVP / VA N-methyl-2-pyrrolidone



PEG PEO / PPO

Figure 1 Structures of carbamazepine (CBZ) and excipients used in this study. PVP = povidone, PEG = macrogol.

FT-Raman spectroscopy

The FT-Raman instrument consisted of a Bruker FRA 106/S FT-Raman accessory (Bruker Optik, Ettlingen, Germany) with a Coherent Compass 1064–500N laser (Coherent Inc, Santa Clara, CA) attached to a Bruker IFS 55 FT-IR interferometer, and a D 425 Ge diode detector. Analysis was carried out at room temperature utilizing a laser wavelength of 1064 nm (Nd:YAG laser) and a laser power of 105 mW. Back-scattered radiation was collected at an angle of 180°. Samples were measured in aluminum cups and 16 scans were averaged for each sample at a resolution of 4 cm^{-1}. Sulfur was used as a reference standard to monitor the wavenumber accuracy. OPUS 5.0 (Bruker Optik, Ettlingen, Germany) was used for all spectral analysis.

Solubility parameter calculation

The Hansen solubility parameters of all the excipients were calculated according to their chemical structures using the approach of Hoftyzer/Van Krevelen (Van Krevelen 1990).

Scanning electron microscopy (SEM)

SEM micrographs were taken for the initial carbamazepine forms III and I. Samples were mounted onto a strip of double-sided carbon tape and sputter coated with a thin layer of gold–palladium under argon vacuum before analysis. SEM (Cambridge Instrument, Stereoscan 360) was performed using a 15 kV beam acceleration voltage. Micrographs were recorded using a PGTE Mitsubishi video/copy processor.

Mixture quantitation

Binary mixtures for the calibration models carbamazepine anhydrate forms I and III were blended separately with dihydrate to form binary physical mixtures at 20% (w/w) intervals from 0 to 100% carbamazepine anhydrate in dihydrate (20 mg per sample). Each concentration was prepared in triplicate and measured by Raman spectroscopy.

Multivariate analyses

Multivariate analyses were performed using the Quant2 package that accompanies OPUS software (Bruker Optics, Germany). The spectral regions for calibration were selected, and all spectra were mean centered. Multiplicative scattering correction and/or first derivative calculation were used for processing spectra when necessary to correct for sample packing and baseline differences. The calibration models were calculated using the PLS algorithm and cross-validation (one sample removed per cycle). Details of the method were reported by Tian et al (2006).

Conversion of carbamazepine in various excipient solutions

Carbamazepine (40 mg) was dispersed independently in triplicate into each 2 mL aqueous excipient solution (0.1%, w/v) for 30 min at room temperature, and then recovered by pouring the whole dispersion onto two layers of filtration paper to remove excess water. The carbamazepine residue was then transferred into three sample holders consecutively, and analysed immediately. Carbamazepine was also dispersed into pure distilled water under the same conditions and recovered using the same method.

Results and Discussion

Characterization of the initial carbamazepine polymorphs and the recovered samples from dispersing carbamazepine in various excipient solutions for 30 min

XRPD

Dihydrate was the most stable form of carbamazepine in aqueous suspension, and both carbamazepine forms III and I started converting to the dihydrate upon contact with water. The X-ray diffractograms of the initial carbamazepine forms III, I and the dihydrate are shown in Figure 2 (diffractograms a, b and c).

XRPD was carried out for the recovered samples of forms III and I dispersed separately in the excipient solutions for 30 min. The results obtained for some carbamazepine/excipient combinations are also shown in Figure 2 (diffractograms d–i). All diffractograms had two common features. Firstly, no peaks due to excipients could be observed. This was due to the very low concentration (0.1% w/v) of excipient in the preparation, and the amorphous nature of most of the excipients used. Secondly, all peaks could be attributed to the dihydrate and form III or I, respectively, indicating the absence of other polymorphic forms of carbamazepine.

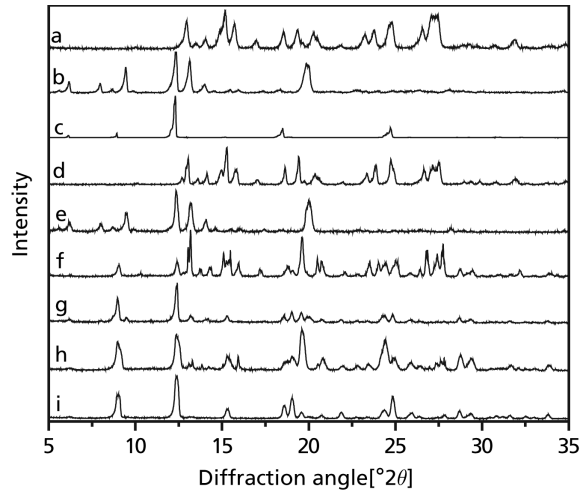


Figure 2 X-ray diffractograms of different carbamazepine forms and of recovered samples (rec) from various excipient solutions (0.1%, w/v). a, Carbamazepine form III; b, carbamazepine form I; c, carbamazepine dihydrate; d, rec from form III in povidone solution; e, rec from form I in povidone solution; f, rec from form III in HEC solution; g, rec from form I in macrogol solution; h, rec from form III in PEO/PPO solution; i, rec from form I in cellobiose solution.

Since the samples were measured directly after recovery without further drying and grinding, inhomogeneous particle size distribution might have induced some differences in the peak pattern of XRPD due to preferred orientation, which is especially common for needle like crystals such as carbamazepine form I and dihydrate. However, there were clear differences in the degree of the dihydrate formation between the recovered samples. The samples recovered from povidone solutions (Figure 2d and e) were similar to their initial forms (Figure 2a and b), indicating a complete inhibition of conversion after 30 min dispersion. The characteristic dihydrate peaks at 9.0 and 12.3° (2θ) appeared in the samples recovered from form III dispersed in HEC solution and form I dispersed in macrogol solution (Figure 2f and g), and became dominant for the samples recovered from carbamazepine dispersions containing PEO/PPO and cellobiose, respectively (Figure 2h and i). There appeared to be a decrease in the ability of the excipients to protect against dihydrate formation in the sequence povidone > HEC or macrogol > PEO/PPO or cellobiose.

DSC

The thermal behaviour of the initial carbamazepine forms III, I and pure dihydrate is shown in Figure 3 (thermograms a, b and c). Recovered samples from various excipient solutions were also characterized by DSC. Figure 3 shows the thermograms of the same carbamazepine/excipient systems as shown in Figure 2. There was no apparent conversion to the dihydrate for the samples recovered from povidone solution since no water endotherm can be seen in Figure 3 (thermograms d and e). However, water evaporation started to appear in the carbamazepine samples with excipients that showed less ability to protect against hydration such as HEC, macrogol, PEO/PPO and cellobiose (thermograms f–i).

Some differences in the thermal behaviour of form III and dihydrate in the recovered samples compared with their pure forms were found as shown in Figure 3. The water loss endotherm of dihydrate in the recovered samples was approximately 9°C lower than that in the pure dihydrate, and the form III transition peak was broad and around 164°C, i.e. approximately 11°C lower than for the pure form III. These differences were possibly due to the presence of the respective other form as described above in these recovered samples. Similar changes in the form III thermogram have been reported for mixtures of forms III and I (Bettini et al 2001).

Raman spectroscopy

Raman spectra of the carbamazepine forms and the recovered samples of forms III and I dispersed separately in various excipient solutions are shown in Figures 4 and 5, respectively. Two excipients were randomly selected from each group, and again no peaks belonging to the excipients or other polymorphic forms of carbamazepine were found, confirming the results obtained from XRPD and DSC. However, the different conversion extent of carbamazepine form III or I to the dihydrate due to the influence of the excipients in the solution could be clearly observed, especially in the spectral features indicated by the arrows in Figures 4 and 5.

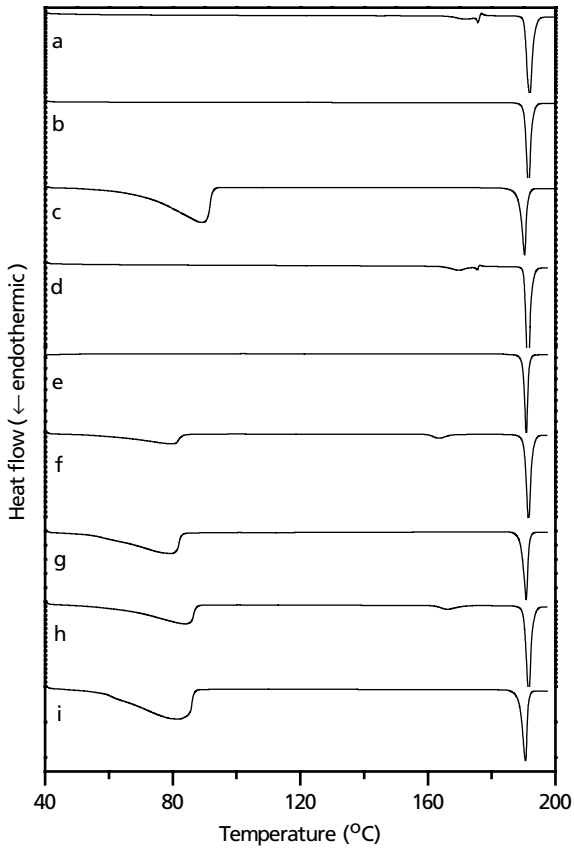


Figure 3 DSC thermographs of different carbamazepine forms and of recovered samples (rec) from various excipient solutions (0.1%, w/v). a, Carbamazepine form III; b, carbamazepine form I; c, carbamazepine dihydrate; d, rec from form III in povidone solution; e, rec from form I in povidone solution; f, rec from form III in HEC solution; g, rec from form I in macrogol solution; h, rec from form III in PEO/PPO solution; i, rec from form I in cellobiose solution.

Quantitative studies

Quantitation of binary mixtures

Since there was no interference from the excipients or other polymorphic forms of carbamazepine, calibration models built of binary mixtures of carbamazepine forms III or I, respectively, with the dihydrate were used for quantifying the conversion of carbamazepine in each excipient solution. The generation of these calibration models was described in detail by Tian et al (2006).

Conversion of carbamazepine dispersed in various excipient solutions

To show the effects of the excipients on the conversion of carbamazepine, the conversion of carbamazepine forms III and I was plotted as the percentage of remaining carbamazepine vs the solubility parameter calculated for each excipient (Figure 6).

It has been reported that hypromellose can completely inhibit the conversion of carbamazepine form III to the dihydrate

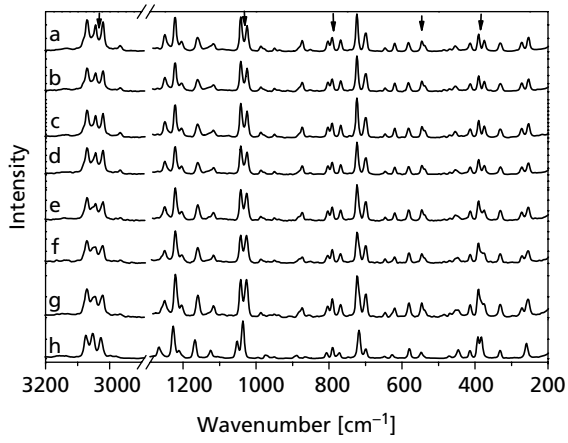


Figure 4 Raman spectra of different carbamazepine forms and of recovered samples (rec) from form III dispersed in various excipient solutions (0.1%, w/v) for 30 min. a, Carbamazepine form III; b, rec from hypromellose solution; c, rec from povidone solution; d, rec from HEC solution; e, rec from carmellose sodium solution; f, rec from cellobiose solution; g, rec from PEO/PPO solution; h, carbamazepine dihydrate. Arrows show area of spectral differences between the samples.

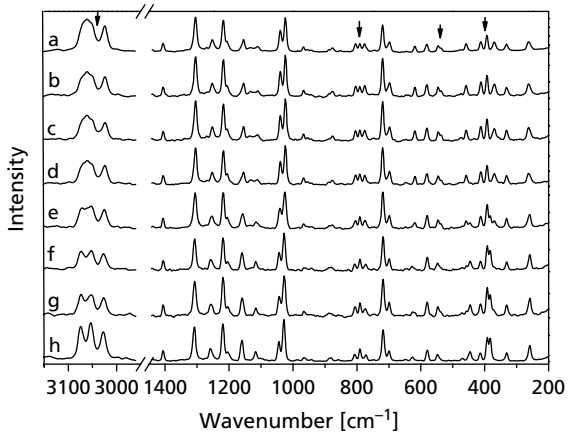


Figure 5 Raman spectra of different carbamazepine forms and of recovered samples (rec) from form I dispersed in various excipient solutions (0.1%, w/v) for 30 min. a, Carbamazepine form I; b, rec from hypromellose solution; c, rec from povidone solution; d, rec from HEC solution; e, rec from PEO/PPO solution; f, rec from carmellose sodium solution; g, rec from cellobiose solution; h, carbamazepine dihydrate. Arrows show area of spectral differences between the samples.

in aqueous suspension, because of a structural match between form III and hypromellose as mentioned above (Katzhendler et al 1998). Excipients in group 1 were selected based on the criterion of having a similar cellulose ring structure to hypromellose, and thus should have the potential to completely inhibit the conversion.

As shown in Figures 4 and 6A, the Raman results for hypromellose agreed well with those published by Katzhendler et al (1998). There was no conversion to the dihydrate after dispersing form III in hypromellose solution for 30 min, and this was the same for two other excipients in group 1, methylcellulose and HPC, which had higher solubility parameters than hypromellose. However, partial conversion to the dihydrate occurred when carbamazepine was dispersed in HEC (especially for form I), and there appeared to be a trend of increasing conversion with increasing solubility parameters of the group 1 excipients used.

The difference in the inhibition ability of these excipients was unlikely to be caused by a modulation of their ability to H-bond with carbamazepine, since there were no structural differences in the cellulose ring structure present in this class of excipients. Also, since the polymer solutions had a very low concentration (0.1%, w/v) and carbamazepine is a neutral drug, factors such as pH and viscosity were unlikely to play an important role. Therefore, the difference may be mainly related to the solubility of these excipients in water. Polymers such as hypromellose, methylcellulose, HPC or HEC, which have lower solubility parameters and thus higher hydrophobicity than carmellose sodium or cellobiose, can provide stronger protection for the carbamazepine particles against water attack, because they are less likely to be present in the aqueous phase rather than being adsorbed on the carbamazepine particle surface. Simonelli et al (1970) reported the inhibition of the crystal growth of sulfathiazole by povidone, suggesting both binding and/or adsorption of povidone to the crystal surface. Also, Lechuga-Ballesteros & Rodriguez-Hornedo (1993) reported the inhibition of L-alanine crystal growth by excipients (L-amino acids) due to the excipients' adsorption.

The importance of structural matching for the cellulose derivatives, however, is highlighted by the fact that cellobiose, which may be regarded as the monomer unit of cellulose despite its high solubility parameter, was still able to partially inhibit carbamazepine form III conversion.

A similar trend could also be seen for carbamazepine form I dispersed in the excipients of group 1 (Figure 6B). However, the conversion extent greatly increased when solubility parameters became higher than that of HEC, which may have been caused by the higher specific surface area of form I (approximately 43 mm^{-1}) than form III (approximately 17.2 mm^{-1}). This could also be seen from their morphology (Figure 7), where form I consisted of needle-like aggregates whereas form III consisted of separate prism like crystals. The inhibition of conversion of form I was thus more difficult than for form III.

For the excipients in group 2, complete inhibition of forms III and I conversion was observed for povidone and povidone/VA, which had similar solubility parameters to hypromellose, but lacked the strong structure matching to carbamazepine. Povidone and povidone/VA however, are strong hydrogen bond acceptors due to the oxygen of their carbonyl group, which can bind to one of the hydrogens attached to the nitrogen of carbamazepine. This hydrogen bonding is likely to be formed as one hydrogen atom of carbamazepine is not involved in the carbamazepine dimer formation. Therefore, a high structure match as for hypromellose may not be necessary when the excipients have appropriate hydrophobicity (solubility parameters lower than 27.0 $MPa^{1/2}$) and can form relatively strong hydrogen bonds with carbamazepine.

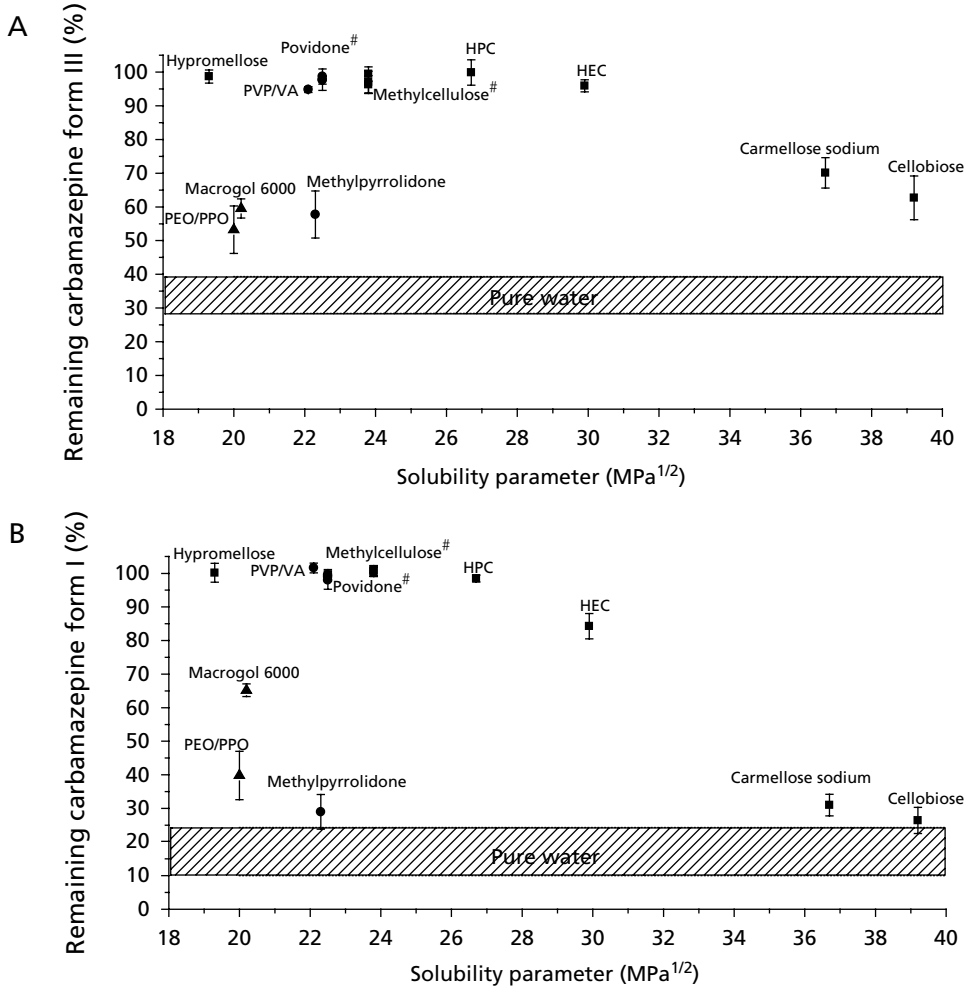


Figure 6 Percentage of remaining carbamazepine forms III (A) and I (B) after 30 min of dispersion vs the solubility parameter of excipients in group 1 (■), group 2 (•), group 3 (▲), (the conversion extent of forms III and I in aqueous suspension containing no excipient is shown by the two hatched bars). #Three different grades of methylcellulose and povidone were used.

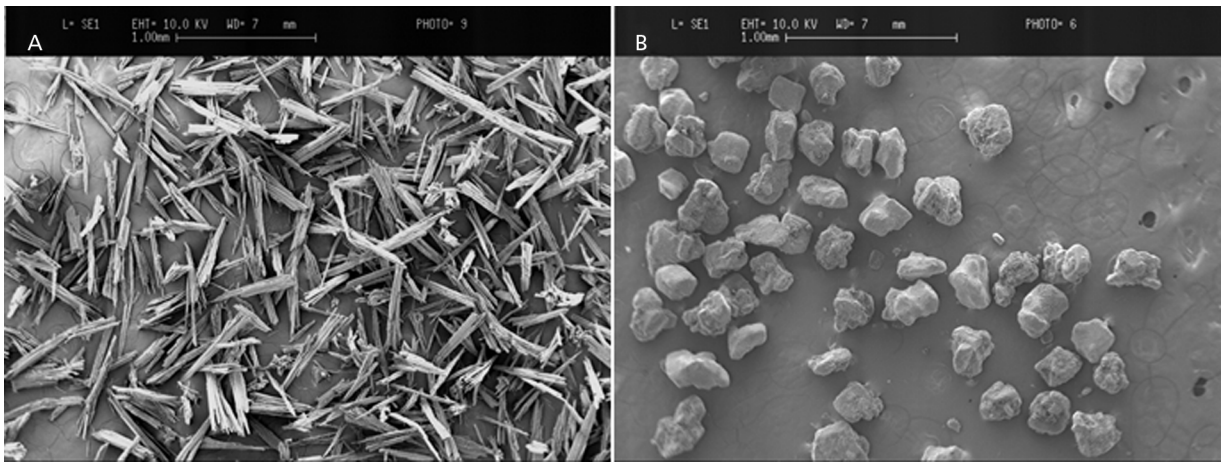


Figure 7 SEM micrographs of carbamazepine polymorphs. A, Form I; B, form III (horizontal scale bars: 1.00 mm).

Methylpyrrolidone, which might be regarded as a "povidone monomer", was also used in this study. It showed much less inhibition ability even though it has a similar solubility parameter to povidone. This is explained as being a consequence of size difference between the "monomer" and polymer. It is plausible that povidone can undergo several interactions with the surface of the carbamazepine crystals. Methylpyrrolidone, as a single molecule, cannot do this, thus it only partially inhibited the conversion and showed an especially low inhibition ability for the bigger surface area samples of form I.

It must be mentioned that differences in the diffusion rate may also have been a factor inducing the differences in inhibition ability between povidone and methylpyrrolidone. However, under the current conditions, while the influence of polymer size on the conversion could be observed when the size difference was significant such as between polymer and monomer, polymers with different molecular weights showed the same inhibition ability. As shown in Figure 6, there was no difference in the conversion extent of carbamazepine among the three grades of povidone, or among the three grades of methylcellulose.

The excipients in group 3, macrogol and PEO/PPO, both showed weak inhibition ability although they have low solubility parameters. This may be explained by their weak hydrogen bonding with carbamazepine. As shown in Figure 1, macrogol and PEO/PPO have hydrogen bond donor groups only on the two ends of their polymer chain. Moreover, the oxygen atom of carbamazepine is already involved in the carbamazepine dimer formation. Although there are oxygen atoms in macrogol and PEO/PPO, which are hydrogen bond acceptors (Greenhalgh et al 1999; Cao et al 2002), the hydrogen bonding interaction with carbamazepine to the ether oxygen is likely to be weaker than to the carbonyl oxygen of povidone or povidone/VA.

From this study, it could be concluded that there were two important prerequisites for the inhibition of polymorphic transition of carbamazepine forms III and I to the dihydrate by excipients in dilute (0.1% w/v) aqueous solution. Firstly, the possibility of hydrogen bonding between the drug and excipients, where hydrogen bond acceptor groups (as in povidone) appeared to be of some importance for the inhibition. Secondly, the excipients must have sufficient hydrophobicity (expressed in this study by the solubility parameter) to increase the likelihood of interactions with the carbamazepine crystal surface. Investigations under different conditions that may influence the solution mediated conversion of carbamazepine forms III and I to the dihydrate, such as seeding, temperature, concentration of excipient solution and dispersing time, are required.

Conclusion

The influence of various excipients on the conversion of carbamazepine to the dihydrate in aqueous solution was investigated, in an attempt to clarify the mechanisms underpinning the effect of polymeric excipients on the polymorphic conversion in aqueous dispersion. Katzhendler et al (1998) emphasized hydrogen bond formation through a significant structural matching between the excipient and drug as important, while Simonelli et al (1970) suggested surface adsorption as the only necessity for complete inhibition of povidone to the growth of sulfathiazole crystals. For the selection of excipients in this study, we found that both hydrogen bonding ability and a sufficient hydrophobicity were important to the inhibition ability of excipients, although it was difficult to compare the relative importance of the two factors. Furthermore, Raman spectroscopy was used successfully to investigate the polymorphic conversion of a drug in suspensions containing various excipients, offering the potential of fast and reliable excipient screening.

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