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Membrane transport of hydrocortisone acetate from supersaturated solutions; the role of polymers

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Abstract

Permeation of hydrocortisone acetate (HA) from supersaturated solutions was studied across a model silicone membrane. Supersaturated solutions were prepared using the cosolvent technique with propylene glycol and water (or aqueous polymer solutions) as the cosolvents. In the absence of the polymer, the flux of HA was similar at all degrees of saturation and was not significantly different from the value obtained for a saturated solution. Flux enhancement, as a result of supersaturation, was observed with all the polymers. The flux increased with increasing polymer concentration, reached a maximum and decreased at higher polymer percentages. The amount of polymer required for maximum enhancement differed for each polymer. The decrease of flux at high polymer concentrations is attributed to changes in microviscosity and a marginal increase in solubility. The infrared spectroscopic and differential scanning calorimetry data suggest that HA–polymer interactions occurred through hydrogen bonding thus explaining the proposed mechanism of the anti-nucleant properties of the polymers.

Keywords: Supersaturation; Cosolvents; In vitro permeation; Hydrocortisone acetate; Antinucleant polymers; Silicone membrane; ATR-IR spectroscopy

1. Introduction

Delivery of drugs through the dermal route is often limited by the excellent barrier properties of the skin. There is a constant search for improving drug delivery through the skin. Supersaturated states have been used to enhance permeation of drugs (Davis and Hadgraft, 1991; Pellett et al., 1994; Pellett et al., 1997; Megrab et al., 1995; Schwarb et al., 1999; Raghavan et al., 2000; Iervolino et al., 2000, 2001) since they can be used to enhance permeation without the use of specific enhancers which may be potentially irritant on sensitive skins.

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According to Fick's first law, the flux of a drug (J) is proportional to the concentration of the drug in the vehicle. The flux of the drug is hence limited by its saturated solubility. More correctly, the flux is related to the chemical potential gradient of the drug. Supersaturated systems can therefore increase the thermodynamic activity and the flux but they are also inherently unstable. Crystallization from the unstable state leads to a decrease in the activity and hence flux. Some polymers are known to inhibit crystallization and sustain supersaturation; for example, hydroxpropyl methyl cellulose (HPMC) and methyl cellulose (MC) were found to act as antinucleating agents for hydrocortisone acetate (HA) (Raghavan et al., 2000).

HA is a corticosteroid which has an estimated log P of 1.98 (Advanced Chemistry Development Labs. (Toronto, Canada) software). It has been established that optimum transdermal flux is achieved for compounds with log P in the range of 1–2.5 (e.g. Yano and Noda, 1986). In spite of HA having an optimum log P, it has a very low flux. This can be attributed to its very low solubility. Using supersaturated solutions of HA was found to enhance its penetration through silicone membranes. HPMC concentrations of 0.5–1% were found to be the optimum concentration required to obtain maximum enhancement of flux (Raghavan et al., 2000).

In this paper, several other polymers are examined for possible use as nucleation inhibitors for the crystallization of HA. Also their influence on modulating the HA flux across silicone membranes was studied. Silicone membranes were chosen as initial model membranes because they facilitate the investigation of the stability of supersaturated states and their influence on permeation. With skin, the interpretation would be more difficult because of its complex structure.

2. Materials and methods

2.1. Materials

Hydrocortisone acetate (HA) was purchased from Sigma (Germany). Propylene glycol and HPLC grade methanol were obtained from Fisher Scientific International Company (UK). Hydroxypropyl cellulose (HPC) grade 65SH-viscosity 50cP was obtained from Shin-Etsu (Japan), polyvinyl pyrollidone K30 (PVP), polyvinyl alcohol (PVA) and polyethylene oxide (PEO) from Sigma (USA), polyethylene glycol 400 (PEG400) from Fisher Scientific (UK), and polyacrylamide (PAA) from BDH Ltd (UK).

Silicone membranes with a nominal thickness of 300μm were obtained from Samco (UK).

2.2. Methods

2.2.1. Preparation of supersaturated solutions

Supersaturation was produced using the cosolvent method described previously by Davis and Hadgraft (1991). The cosolvents used were PG and water. Supersaturated systems were formed by mixing a saturated solution of hydrocortisone acetate in PG with either water or polymer solution. The degree of supersaturation (DS) was calculated from the cosolvent solubility plot, reported earlier (Raghavan et al., 2000), by dividing the concentration of the drug in the solution by its saturated solubility in the cosolvent mixture.

2.2.2. HPLC analysis

The HPLC analysis of HA was performed using a Milton Roy Constametric III pump, set at a flow rate of 1.5 ml/min, with a Perkin–Elmer ISS-100 auto-sampler, a Varian 2550 variable wavelength UV detector set at 240 nm and a Milton Roy CI-4100 computing integrator.

The stationary phase was an Apex reverse phase ODS 5 μm packed column (250 mm × 4.6 mm). The mobile phase of methanol/water was 65:35% v/v. Calibration curves were constructed on the basis of the peak area measurements using standard solutions of known concentration. The retention time was 4.5 min.

2.2.3. Microscopy

The solutions were analysed for the presence of crystals by observing them on microscope slides using a Vicker's microscope at a magnification of 400 × .

2.2.4. Diffusion studies

Diffusion experiments were conducted using all glass Franz-type diffusion cells that have a receptor volume of approximately 3.9 ml and a diffusional surface area of about 0.95 cm^2. The receptor chambers had side arms through which samples could be taken. To ensure sink conditions and to avoid bubble formation, a sonicated solution of water/PG (75:25) was used as the receptor phase. The silicone membrane was cut to the appropriate size and allowed to soak overnight in IPM (isopropyl myristate). Silicone grease was used to produce a leakproof seal between the flanges of the two halves of the cell held together with a screw clamp. The solutions were introduced in the donor compartments and occluded using microscopic cover slips. The receptor compartment of the cells was maintained at 37°C in a water bath. Magnetic followers were used to stir the receptor compartments. The arms were closed with caps to prevent evaporation. At 2-h intervals over 10 h, 0.4 ml of the receptor phase was removed and replaced with an equal volume of pre-thermostated receptor phase. The final samples were taken after 24 h and then assayed by HPLC.

2.2.5. Preparation of solid dispersions and recrystallized HA

Solid dispersions (SD) of HA and PVP were prepared using a solvent evaporation technique reported by Taylor and Zografi (1997). Predetermined ratios of the two components were dissolved in methanol at 50°C. The solvent was then removed under vacuum at 50°C. Any residual solvent was then removed under vacuum at room temperature for at least 24 h.

Recrystallized HA was prepared by slow evaporation to dryness of a saturated solution of HA in methanol, either in the absence of, or in the presence of, a known amount of PVP at room temperature. Complete evaporation occurred over a period of 3–4 days depending on the amount of PVP used.

2.2.6. Infrared spectroscopy and differential scanning calorimetry

FT-IR spectra were measured using an Equinox-55 FTIR spectrometer (Bruker) with MCT detector at a resolution of 2 cm^{-1}. Attenuated total reflectance (ATR) accessory Golden Gate (Specac, Ltd.) was used for measuring the spectra of PVP, HA, and their solid dispersions and physical mixtures. The Golden Gate accessory uses a diamond as the ATR crystal and is designed for measuring IR spectra of hard or non-easily deformed materials. Hence it is a suitable tool for the characterisation of polymeric materials (Kazarian et al., 1999). This accessory does not require sample preparation such as KBr powder pellets (Tantishaiyakul et al., 1999), thus allowing the acquisition of the IR spectra without any sample modifications. The procedure of measuring spectra includes placing the sample on the surface of the diamond and using the clamp to make good contact. In addition, the temperature of the diamond ATR crystal (and also the sample) can be easily varied from room temperature to 200°C, thus allowing heating of the sample for its in situ drying if necessary. This is especially important in the case of hydrophilic polymers, such as PVP, which are known to absorb water vapour from the atmosphere very easily (Kusanagi and Yukawa, 1994).

Differential scanning calorimetry was performed using a Perkin–Elmer DSC7 calorimeter. Samples were heated in hermetically sealed aluminium pans at a heating rate of 10°C/min in a nitrogen atmosphere.

3. Results and discussion

Transport measurements were performed on the supersaturated solutions of HA without and with the addition of the polymers. The steady-state flux of HA from the solution was determined by plotting the amount of HA transported across the membrane against time and calculating the slopes for the steady state region ($n = 4$). Fig. 1 shows the flux of HA as a function of the degree of saturation (DS) from solutions without and with 1% PVP as additive. The flux data for HA with 1% HPMC additive reported earlier (Raghavan et al., 2000) are also

provided for comparison. The flux of HA from a saturated solution was found to be 0.39 ± 0.06 $\mu g/cm^2/h$. In the absence of the additive, the flux of HA from supersaturated solutions was similar to the value from a saturated solution. This demonstrates that supersaturation is not maintained and the concentration of the HA solution drops to the saturated value due to rapid precipitation. Hence the flux also drops to the value of the saturated solution. This was also confirmed by the presence of crystals as soon as the HA in PG was mixed with water. In solutions containing 1% PVP as the additive, flux enhancement was not observed because of the instability of the supersaturated solution. This also led to rapid crystallization and decrease in the thermodynamic activity whereas 1% HPMC is effective in inhibiting crystallization.

Raghavan et al. (2001) has reported that by increasing the amount of polymer, the nucleation time is increased. It is possible that, in the case of PVP, 1% polymer concentration was not sufficient to inhibit crystallization. By increasing the amount of PVP in 4.8x-saturated solutions to 10% (Fig. 2a), flux enhancement was observed indicating that the amount of polymer required is dependent on its ability to inhibit crystallization.

Several other polymers were used as additives in order to ascertain the feasibility of their use in different formulations. Permeation measurements were conducted at a constant degree of saturation ($4.8\times$) and in solutions containing different polymer concentrations. The polymers chosen were PVA, PVP, PEG400, PEO and PAA. It was established that the $4.8\times$ saturated preparations were stable for the duration of the experiments. The data are provided in Fig. 2a and b.

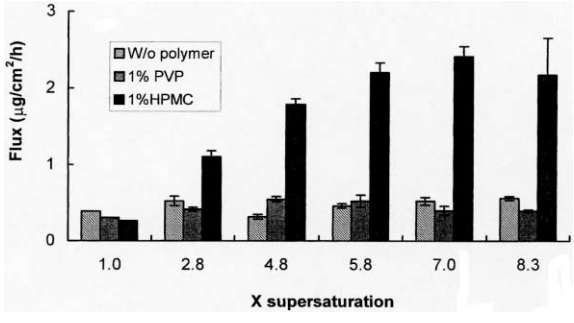

Fig. 1. Flux of HA as a function of DS from solutions containing no polymer, 1% PVP and 1% HPMC.

In the presence of the polymer, the flux was, in general, higher than the value for a solution without the polymer. The flux increased with increase in the polymer concentration, reached a maximum and decreased at higher concentrations. The results show that even though increases in flux can be obtained with lower concentrations of the polymer, an optimum polymer concentration is required to obtain maximum flux. This concentration was different for the different polymers. For example, for HPC the optimum polymer concentration was 1% whereas for PVP it was 10%.

The maximum enhancement in flux was polymer dependent (Fig. 3). As stated earlier, the flux of a drug should be proportional to the concentration of the drug in the vehicle. For a $4.8\times$ saturated solution, the flux should be 4.8 times that of a saturated solution (shown in Fig. 2a and 2b). With HPC, this enhancement was obtained while with all the other polymers the flux was lower. Using HPMC and MC, similar effects have been reported, i.e. these two polymers are effective at maintaining stability (Raghavan et al., 2000). The cellulose polymers appear to act similarly in inhibiting the crystallization process. Polyacrylamide was found to have the least ability to stabilise supersaturation and therefore produce enhancement of the flux. The lower flux results from crystallization of the drug.

At some concentration, all the polymers stabilised the supersaturation of HA. Differences may be due to, for example, molecular weight. Megrab et al. (1995) found that the flux of oestradiol varied with variations in the molecular weight of PVP. They also observed that the flux decreased at very high molecular weights. It was difficult, with the present set of polymers, to calculate the exact molecular weight of all the polymers. However, it is of interest to compare the results of the two polymers, PEO and

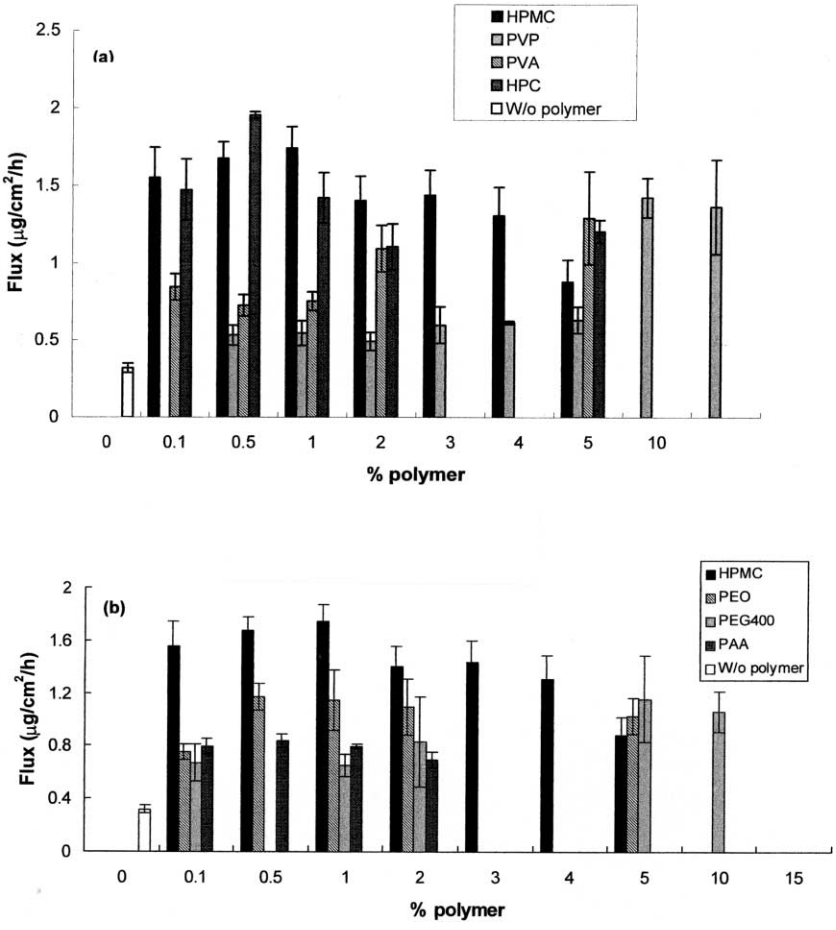

Fig. 2. Flux of HA from 4.8 × saturated solutions as a function of polymer percentage for (a) HPMC, HPC, PVP and PVA and (b) HPMC, PEO, PEG400 and PAA.

PEG400. The structures of the two polymers are similar and the only difference is their molecular weight. The flux of HA with PEO as the additive was always higher than that of HA with PEG400. Moreover, maximum enhancement of flux was obtained for solutions with 1%PEO while a 5% concentration of PEG400 was required to obtain similar stabilization. This indicates that the molecular weight may play a role in the mechanism of inhibition of crystallization.

The increase in flux at low polymer concentrations is due to the increased inhibition of crystallization and hence increased stability of the supersaturated solutions. One would expect the solutions to become more stable with further in-

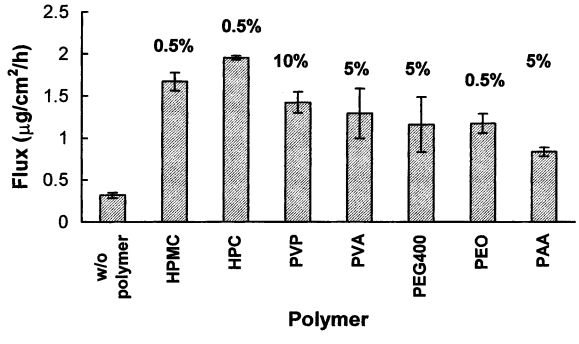

Fig. 3. Percentage of polymer needed to achieve maximum enhancement for the different polymers.

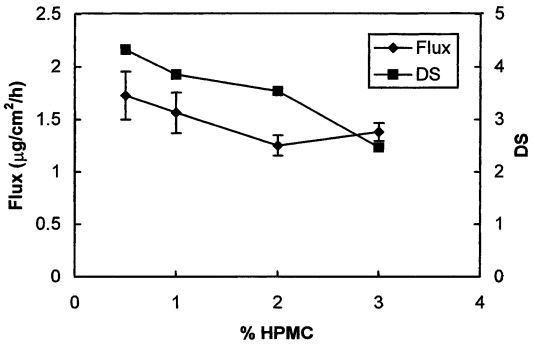

Fig. 4. Flux and modified DS as a function of HPMC percentage.

creases in the polymer concentrations. Absence of nucleation was also confirmed from the crystallisation studies, which showed that the nucleation time increased with increase in polymer concentration. Therefore the decrease in flux at high polymer concentrations must be due to other mechanisms.

The addition of a polymer to a solution increases the viscosity of the solution. According to the Stoke–Einstein's equation, the diffusion coefficient is inversely proportional to the viscosity of the system. If transfer to the membrane occurs at a comparable rate to diffusion through the membrane, an increase in viscosity would be reflected as a decrease in permeation rate. However, a recent comparative study on the permeation of HA from a solution and polymer gel showed that the fluxes were similar in both the cases (Raghavan et al., 2000). The macroscopic viscosity did not appear to influence the permeation. This is not surprising since the macroscopic viscosities of the solutions do not necessarily reflect the environment through which the drug diffuses. The microviscosity would be a dominant factor in such cases.

Addition of a polymer could increase the solubility of the drug. The increase in solubility will decrease the DS and hence the thermodynamic activity (for a given concentration of the drug). Therefore, solubility studies were performed at 32°C (the temperature of the surface of the membrane) on saturated solutions of HA in a 50%PG/50%water cosolvent mixture containing different amounts of HPMC. The HPMC concentrations used were 0.5, 1, 2 and 3%. Solutions containing 5% HPMC were very viscous and could not be analyzed with accuracy. The solubility data obtained were used to calculate the DS and are provided in Fig. 4. The DS marginally decreases with HPMC concentration up to 2%. For 3% HPMC concentration, a significant change in the DS is observed. The marginal decrease of flux at high polymer concentrations can be ascribed to the marginal increase in the solubility value. For 5% HPMC concentration, the solubility would be expected to decrease even further and hence the further small decrease in flux. In order to determine if the solubility values at low HPMC concentrations were significantly different, ANOVA was performed. The analysis showed that they are not significantly different (95% confidence).

Inhibition of crystallization of drugs by polymers has been effectively used for a variety of applications over many years but their mechanism of action has been rarely discussed (Simonelli et al., 1970; Ziller and Rupprecht, 1988, Ma et al., 1996; Lipp, 1998; Raghavan et al., 2001). Raghavan et al. (2001) recently proposed that polymers influence the crystallization processes both by adsorption of the polymer onto the crystal surface and the associated hydrodynamic boundary layer in which the polymers accumulate. The extent to which adsorption occurs may be dependent on the hydrogen bonding between the drug and the polymer. The stronger the hydrogen bonding the greater will be the crystallization inhibition. HA has three carbonyl and two hydroxyl functional groups (Fig. 5a) capable of hydrogen bonding with those of the polymers. PVP, for example, has a carbonyl group that can form hydrogen bonds with the hydroxyl groups of HA whereas HPMC has hydroxyl groups that could form hydrogen bonds with the carbonyl groups of HA (Fig. 5b and c).

In order to investigate the possibility of hydrogen bonding interactions, HA–PVP combinations were studied by infrared spectroscopy. The drug–polymer interactions should result in a shift of the IR bands corresponding to the hydrogen bonding

groups of the drug and the polymer. Fig. 6 shows IR spectra of HA and, as received, PVP. The bands corresponding to the three carbonyl groups of HA are 1741, 1720 and 1624 cm^{-1} and those corresponding to the hydroxyl groups are 3418 and 3319 cm^{-1}. The IR spectrum of, as received, PVP shows the carbonyl band around 1648 cm^{-1} and another broad band around 3398 cm^{-1}. PVP does not have any hydroxyl groups and hence one would not expect a band in this region. However, being hydrophilic, PVP easily absorbs water vapour from atmosphere, which could give rise to the OH band for PVP.

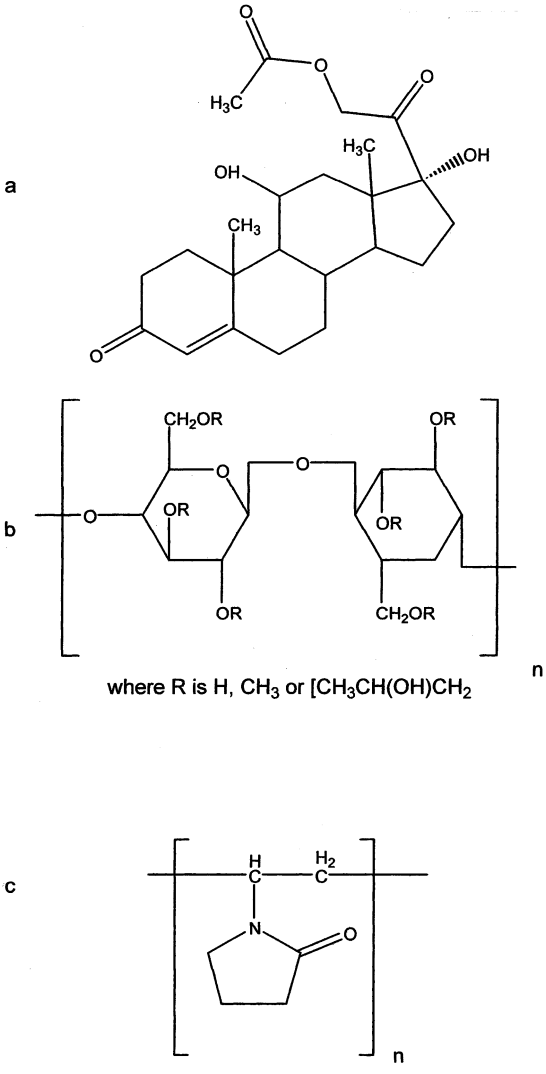

Fig. 5. Molecular structures of (a) HA, (b) HPMC and (c) PVP.

Samples of HA in the presence of PVP were prepared either by slow recrystallization from a solvent or as solid dispersion using the solvent evaporation technique following the method of Taylor and Zografi (1997). The crystals obtained from slow recrystallization were quite large ($\sim$ 500 μm) and well separated from the polymer film formed on evaporation. In the case of the solid dispersion, the drug was homogeneously distributed within the polymer film.

The IR spectrum of HA recrystallized from ethanol was similar to the pure drug irrespective of the presence or absence of PVP during the recrystallization process. This is to be expected; when the drug slowly recrystallizes, the polymer cannot be incorporated into the crystal lattice due to its incompatible size and structure. This prevents the possibility of any significant drug–polymer complex formation. Hence a solid dispersion of HA/PVP (50/50) was chosen for the present studies.

Since PVP has only a C=O band, it was decided to follow the changes in the OH bands of HA occurring due to H-bonding. However, to establish the presence of H-bonding between HA and PVP one needs to exclude an effect of H-bonding between water and PVP because stretching modes of water absorb in the same region where bands of the hydroxyl groups of HA appear. Therefore, extra care was taken to dry the samples in situ at 90°C for 30 min to ensure the absence of water absorption in the spectra. Fig. 7 shows the ATR-IR spectra of PVP at room and 90°C temperatures. There is a striking difference in the spectra: the broad band centred at ca. 3500 cm^{-1} disappears after heating the sample of PVP. This disappearance can be attributed to water removal at the higher temperature.

Fig. 8 shows the ATR-IR spectra of HA and the solid dispersion of HA with PVP (50/50). The distinct feature of the two spectra is the replacement of the two OH-bands of HA by a broad absorption band at ca. 3350 cm^{-1} for the solid dispersion. The band is retained even after the

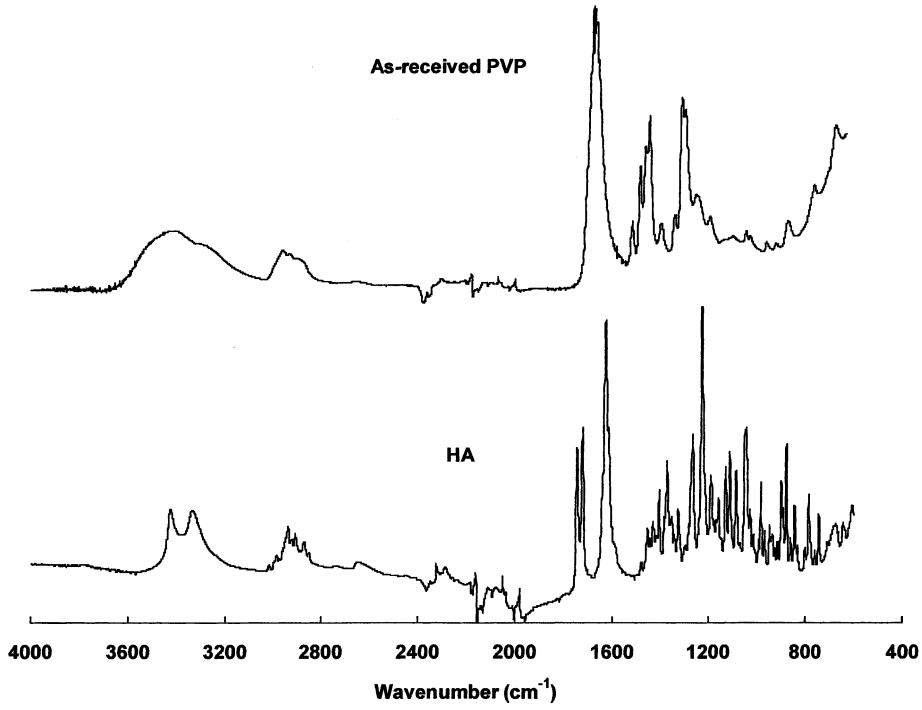

Fig. 6. ATR-IR spectra of as received PVP (upper trace), and HA (lower trace).

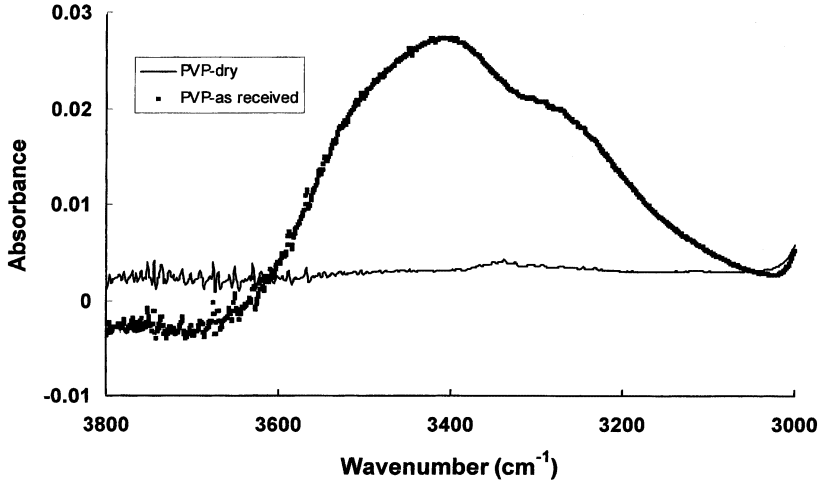

Fig. 7. ATR-IR spectra of PVP in the ν(O–H) stretching region: spectrum of PVP as supplied (solid line) and spectrum of PVP after drying (dashed line).

moisture was removed by heating the sample at 90°C. This distinct band can therefore be assigned to the ν(O–H) vibrations of HA molecules that are hydrogen-bonded to the carbonyl groups of PVP. It is important to remember that while crystals of HA have a distinct geometry, the dis-

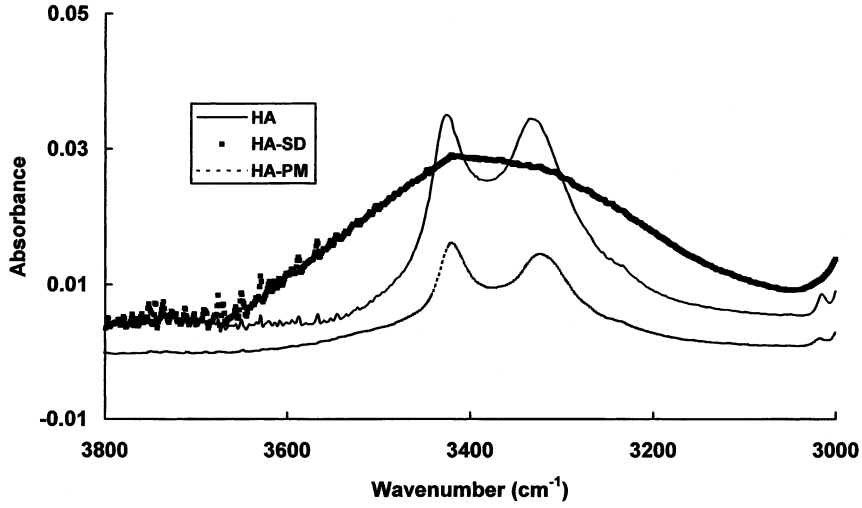

Fig. 8. ATR-IR spectra of HA, solid dispersion (HA-SD) and physical mixture (HA-PM) in the ν(O–H) stretching region.

tribution of alignments of HA molecules towards basic sites in PVP (carbonyl groups) may vary thus contributing further to the width of the broad band which is characteristic of H-bond formation. Assignment of the band to the hydrogen bonding between the HA and PVP is consistent with observation using FTIR spectroscopy of the H-bonding between PVP and piroxicam in solid dispersions (Tantishaiyakul et al., 1999). However, in their studies, the apparent presence of water was not taken into account while assigning the band. As confirmation, the FT-IR spectra of physical mixtures of HA and PVP (Fig. 8) were recorded and compared with the spectra of HA and the solid dispersion. The two OH bands of HA were still present in the physical mixtures. Moreover, no broad band at 3350 cm^{-1} was observed indicative of the absence of H-bonding between HA and PVP in the physical mixtures. The presence of H-bonding in the solid dispersion also leads to a shift of the carbonyl band. In fact a small shift of ν(C=O) band of PVP to the lower wavenumber region in the solid dispersion compared to the ν(C=O) band in pure PVP was observed (not illustrated).

Fig. 9 shows the DSC curves of solid dispersions and physical mixtures for the HA/PVP sysem. HA has a single melting endotherm around 223°C with an enthalpy of 136 J/g. On melting the samples became brownish yellow in colour indicating the decomposition of HA. A broad dehydration endotherm observed in the region of

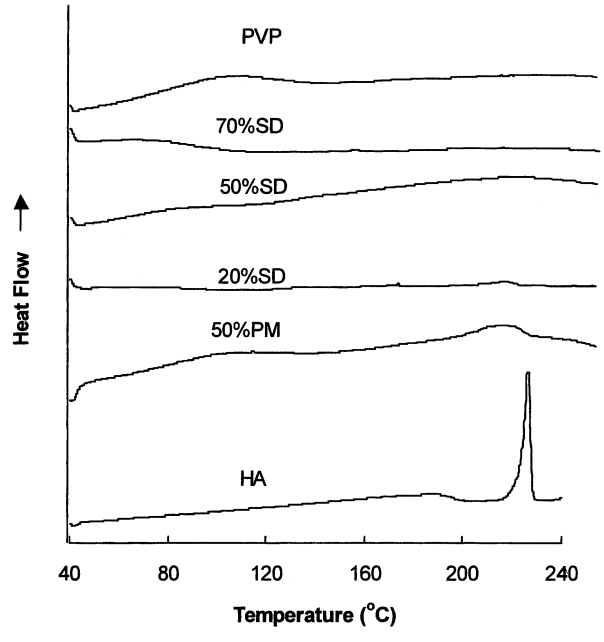

Fig. 9. DSC thermograms of HA, 50:50 HA/PVP physical mixture (PM), and solid dispersions of HA with PVP (SD).

60–120°C for PVP and the physical mixtures, confirms the IR data for the presence of water. In the physical mixture containing 50:50 HA/PVP (w/w), melting occurred over a broad range between 192 and 223°C with a melting peak around 209°C. The enthalpy also decreased significantly to 52 J/g. This might be a consequence of PVP acting as an impurity for the melting of HA. It has also been suggested in literature that this behaviour is caused by thermally induced HA–PVP interaction (Tantishaiyakul et al., 1999).

The melting peak of HA samples which were slowly recrystallized from ethanol was the same as the pure samples, as received (not shown in figure). The enthalpy of fusion was however slightly lower (118 J/g). This is probably due to some solvent inclusion during the growth of the HA crystals. The melting of HA was found to occur at a lower temperature for a 20% PVP solid dispersion and was completely absent at higher PVP concentrations. This absence has been attributed in the literature to possible interactions between the drug and the polymer (Tantishaiyakul et al., 1999). The IR spectroscopic data in the present studies provide evidence for such an interaction through hydrogen bonding.

4. Conclusions

Permeation of hydrocortisone acetate (HA) from supersaturated solutions was studied. In the absence of a polymer, the flux of HA was similar at all DS and was not significantly different from the value obtained for a saturated solution. The flux from a supersaturated system increased with increasing polymer concentration, reached a maximum and decreased at higher polymer percentages. The amount of polymer required for maximum flux differed between the polymers. The decrease of flux at high polymer concentrations could be attributed to changes in microviscosity and a marginal increase in solubility. The IR spectroscopy and DSC results show that the drug and the polymer interact through hydrogen bonding, which could explain the anti-nucleating properties of the polymer.

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