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Crystallization of hydrocortisone acetate: influence of polymers

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Abstract

The influence of hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG400) on the crystallization of hydrocortisone acetate (HA) was studied. Supersaturation was created by the cosolvent technique. Spontaneous nucleation was observed when no polymer was used as the additive. In the presence of the polymer, nucleation was delayed. The nucleation time decreased with increasing supersaturation at a particular polymer concentration and increased with increasing polymer concentration at a particular supersaturation. Habit modification from a well-defined polar prismatic morphology to a wing-shaped morphology was observed when HPMC was used as the additive. The effect of PVP and PEG400 on the morphology of HA was less pronounced compared to the cellulose polymers. The mechanism of nucleation retardation by the polymers is explained in terms of association of HA with the polymer through hydrogen bonding. The growth may be inhibited by the hydrodynamic boundary layer, in which the polymers accumulate as well as by the adsorption of the polymer onto the crystal surface. The habit modification of HA by HPMC is due to different extents of adsorption on different faces of the crystal, the extent of which is dependent on the hydrogen bonding functional groups that are exposed at each face of the crystal.

Keywords: Crystallization; Cosolvents; Nucleation time; Hydrocortisone acetate; Polymers; Hydrogen bonding; Diffusion mechanism

1. Introduction

The control of crystallization processes is often crucial in the production, as well as processing, of pharmaceutical drug materials. The crystallization process, as well as the nature of the crystalline product, is determined by the way that they are produced, i.e. the prehistory of the material. The control of particle size and shape, for example, is essential for the control of downstream processes such as dissolution, compaction and milling. This may be achieved by variation of operational conditions, such as degree of supersaturation, temperature, impurity and pH.

One of the applications, where inhibition of crystallization processes has been effectively used,

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is in dermal delivery. Supersaturated states have been used to enhance permeation of drugs, both through model silicone membranes as well as human skin (Davis and Hadgraft, 1991; Pellett et al., 1994, 1997; Megrab et al., 1995; Schwarb et al., 1999; Raghavan et al., 2000). The degrees of supersaturation involved in these systems are high and they tend to crystallize by spontaneous nucleation. However, added polymers act as anti-nucleating agents inhibiting nucleation as well as growth. Some of the polymers, which have been found to inhibit crystallization, are methylcellulose, hydroxypropyl methylcellulose and polyvinyl pyrrolidone. The mechanism of growth inhibition by polymers appears to be poorly understood.

The presence of foreign impurities can drastically affect the crystallization process, especially when there is some form of affinity between the impurity and the crystallizing species. Small amounts of fatty acids used as additives alter the physicochemical properties of adipic acid significantly by incorporating into the crystals (Fairbrother and Grant, 1978; Chow et al., 1984). Tailor-made additives are also known to inhibit nucleation and growth. Para-acetoxy acetanilide has been found to inhibit the growth of paracetamol (Chow et al., 1985).

The anti-nucleant polymer molecules are incompatible in both size and structure to the host molecules of the growing crystal surface. Therefore, their incorporation into the lattice, which would alter the growth characteristics of the host molecule, is extremely difficult. The primary aim of this paper is to address the role of polymers in the crystallization process. Hydrocortisone acetate (HA), a corticosteroid was chosen as a model drug. Various polymers, such as HPMC, MC, PVP and PEG400 were used as additives in the crystallization studies. Nucleation time and morphology of HA were examined both in the absence and presence of polymer additives. The mechanism of nucleation and growth are discussed based on the interaction between the drug and the polymer molecules through hydrogen bonding.

2. Materials and methods

2.1. Materials

Hydrocortisone acetate was purchased from Sigma (Germany). Propylene glycol (PG) and HPLC grade methanol were obtained from Fisher Scientific International Company (UK). Hydroxypropyl methylcellulose grade (65SH-viscosity 50cP) and methylcellulose (grade SM viscosity 100cP) — both with the brand name 'Metolose' — were obtained from Shin-Etsu Chemical Co Ltd. (Japan). PVP and PEG400 were obtained from Sigma, UK. Carbopol was purchased from Goodrich Inc.

2.2. Solubility studies

HA was added to a series of PG–water mixtures varying from 100% water to 100% PG and stirred in a water bath maintained at 32°C for 48 h. After ensuring that the solute–solvent equilibrium had been reached, the solution was centrifuged and the supernatant solution diluted and assayed using HPLC following a procedure described by Raghavan et al. (2000).

2.3. Creation of supersaturation

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 HA in PG with either water or 1% polymer (HPMC, PVP, PEG400) solution. The degree of saturation was calculated from the cosolvent solubility plot (Fig. 1) by dividing the concentration of the drug in the solution by its saturated solubility in the cosolvent mixture.

2.4. Microscopy

The gels and solutions were analysed for the presence of crystals by observing them on microscope slides using a WILD Heerbrugg microscope (Switzerland) at a magnification of 160 × .

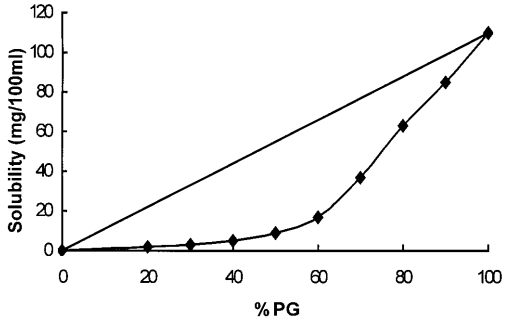

Fig. 1. Cosolvent solubility plot of HA in PG–water mixtures at 32°C. The straight line indicates the HA concentrations achieved by mixing different ratios of the two solvents.

2.5. Viscosity measurements

The viscosity measurements were performed on solutions and gels of HA using a TA instruments CSL^2 100 Carrimed rheometer. The geometry of the spindle used was a 4 cm 0° acrylic flat plate. The viscosity was obtained at different shear rates and the values reported are for a shear rate of 35 s^{-1}.

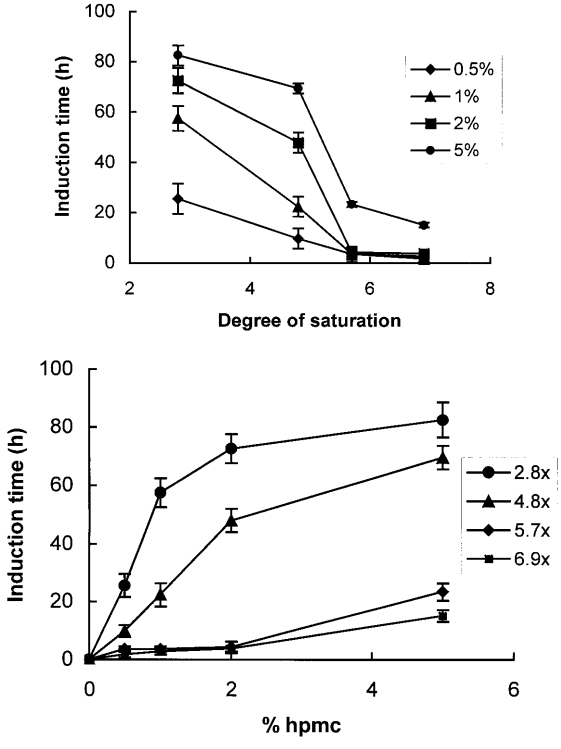

Fig. 2. Crystallization time of HA as a function of (a) degree of supersaturation at different HPMC concentrations; and (b) HPMC concentration at different degrees of supersaturation (x refers to times the saturated solubility value).

3. Results and discussion

3.1. Nucleation time

Fig. 1 shows the solubility of hydrocortisone acetate in the cosolvent mixture of PG and water. The data show that HA is almost insoluble in water and exponentially increases as the amount of PG is increased. The saturated solubility in PG is 115 mg/100 ml, which is very low. Due to the extremely low solubility values, HA does not crystallize and grow easily.

Fig. 2(a,b) shows the crystallization times as a function of supersaturation at different HPMC concentrations and as a function of HPMC concentrations at different degrees of supersaturation respectively. The crystallization times were measured as the time interval when crystals were first observable under the microscope. This technique was used as being most relevant to dermal and transdermal drug delivery, where the formulations after preparation are left unstirred.

When no polymer was present, spontaneous nucleation was observed as soon as the cosolvents were mixed at all degrees of supersaturation studied. This indicates that the supersaturated solutions are in the labile zone. This is not surprising since the degrees of supersaturation were high.

In solutions containing the polymers, the onset of crystallization was delayed. The polymers inhibit the crystallization process. At any polymer concentration, the crystallization time (t_{ind}) decreased with degree of supersaturation. As the degree of supersaturation is increased, the solutions become unstable thermodynamically and tend to crystallize faster. The nucleation probability, J, $(J\alpha(t_{ind})^{-1})$ is proportional to $\exp(-E_c/RT)$

$$E_c = \frac{16\pi v^2 \sigma^2}{3kT(\log S)^2}$$

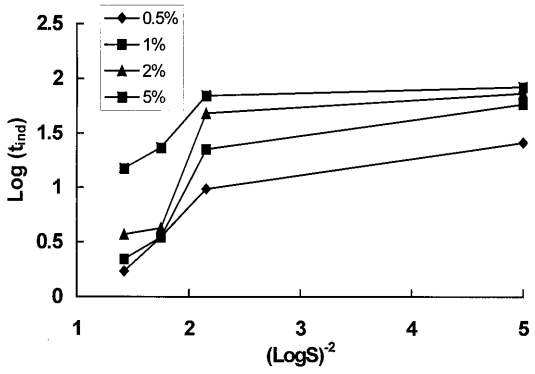

Fig. 3. Crystallization time (t_{ind}) of HA as a function of $(\log S)^{-2}$ for different HPMC concentrations.

E_c is the activation energy for nucleation. σ is the surface energy per unit area, v is the molecular volume, k the Boltzmann constant, T the absolute temperature and S the degree of supersaturation (Henisch, 1970). As supersaturation is increased, the diminishing E_c increases the nucleation probability and hence, the crystallization times are reduced.

Rearranging the above equation, it can be seen that a plot of $\log t_{ind}$ as a function of $(\log S)^{-2}$ should give straight line provided the nucleation process is completely homogeneous. This equation assumes that the probability factor is a constant. However, the probability factor could change with supersaturation (Rodriguez-Hornedo and Murphy, 1999) and the linear relationship may not hold. Fig. 3 shows a plot of $\log t_{ind}$ as a function of $(\log S)^{-2}$ for all the polymer concentrations studied. Even with limited number of points, it can be seen that there are two distinct regions, which are usually interpreted as regions of homogeneous and heterogeneous nucleation. It should be noted, however, that homogeneous nucleation is practically rare to achieve since nucleation can often be induced by external stimuli, for example, the presence of foreign bodies such as dust or even by a small scratch in the container.

It is possible to suppress the nucleation by increasing the amount of the polymer in the solution. This can be seen in Fig. 2(b) where the crystallization time is plotted as a function of polymer concentration at different degrees of supersaturation. As the polymer content increases, the crystallization time increases.

3.2. Morphology of hydrocortisone crystals

The morphology of a hydrocortisone acetate crystal grown in a 50% PG/50% water system over a period of 10 days is shown in Fig. 4(a). The crystal shows a habit with a well-facetted polar morphology. Due to the extremely small sizes (≈ 10 μm) of the HA crystals, it was not possible to identify the different planes representing the various faces. As far as the authors are aware, the morphology of hydrocortisone acetate crystals has not been reported in the literature.

The morphology of a crystal is determined by the slowest growing faces (often referred to as the morphologically important faces) as a consequence of the relative growth rates of the various faces of the crystal (Mullin, 1993). The growth rates of the different faces are dependent on the internal structure of the crystal, as well as external factors imposed on the crystal by crystallization conditions, such as supersaturation, impurities, temperature and the choice of solvents. The individual face growth kinetics depends to a different extent on supersaturation. At all degrees of supersaturation studied, with all other parameters remaining constant, the morphology of HA crystals were the same indicating that the morphology is influenced only by the solvents used at these degrees of supersaturation.

HA crystals grown in the presence of different polymers over a period of 10 days are shown in Fig. 4(b–d). It is striking to note that the habit is modified in the presence of HPMC, while PVP and PEG400 do not significantly alter the habit. In addition, the crystal surfaces and edges were very rough. The rough faces indicate that the growth takes place by a predominantly diffusion mechanism. A significant increase in the viscosity of the solutions containing the polymer might affect the growth rate in diffusion controlled growth, the viscosity of the solutions with and without HPMC was measured. With the spindle geometry used, zero shear rate viscosity could not be obtained. Hence, the viscosity for the lowest shear rate of $\approx 35\ s^{-1}$ was used for comparison.

The viscosity values obtained for solutions with/without HPMC were found lie in the range 0.02–0.04 Pa.S and were not significantly different from each other.

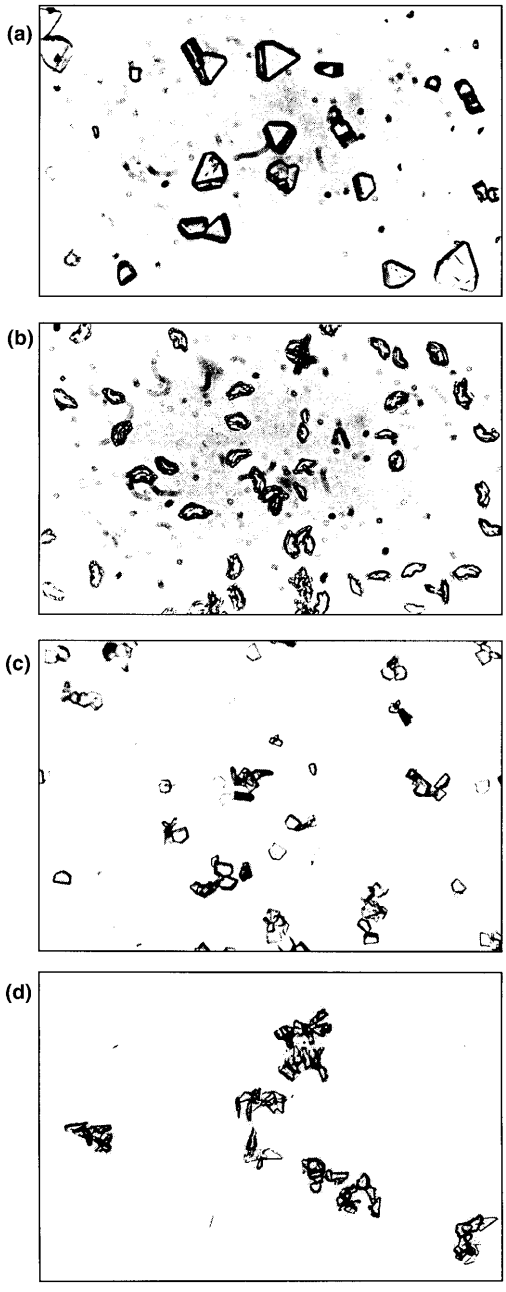

Fig. 4. Morphology of HA crystals grown in the (a) absence of the polymer and the presence of (b) HPMC, (c) PVP, and (d) PEG400. The magnification is the same for each of the pictures.

In the presence of the cellulose polymers, the crystals exhibited a wing or boomerang-shaped morphology. A similar boomerang-shaped morphology has been reported for paracetamol crystals grown in the presence of agar (Femi-Oweyo and Spring, 1994). In addition, crystals grown in the presence of the polymers were, in general, smaller than the crystals grown without the polymer during the same period. While the cellulose polymers act both as growth inhibitor and a habit modifier of HA, PVP and PEG400 act predominantly as growth inhibitors.

As mentioned earlier, the presence of foreign impurities can greatly influence the growth as well as morphology. This is a surface phenomenon whereby the impurity molecules or ions are either physically adsorbed or chemisorbed on the surface. During the crystal growth process, molecules which are similar in size and structure to the host molecule, can lock themselves preferentially onto certain faces of the crystal, thus inhibiting growth in those directions. β-lactose, which is inherently present in solution during the growth of α-lactose monohydrate, has been shown to influence the well-known tomahawk shape of the α-lactose crystal (Raghavan et al., 1999). The polymers in the present study are however neither similar in size or structure and hence it is difficult for them to be incorporated into the crystal. The habit modification, however suggests, that there are strong interactions between HA and the polymer molecules.

3.3. Gel growth of HA

A gel medium is often used to grow good quality crystals. The main advantage of this technique is that there are no convection currents present and the growth is predominantly diffusion-controlled. The principal role of the gel is to suppress nucleation by limiting the diffusion process. Moreover, many of the applications in topical drug delivery involve use of gels for drug transport.

HA crystals were grown in a Carbopol gel medium to determine the feasibility of growing

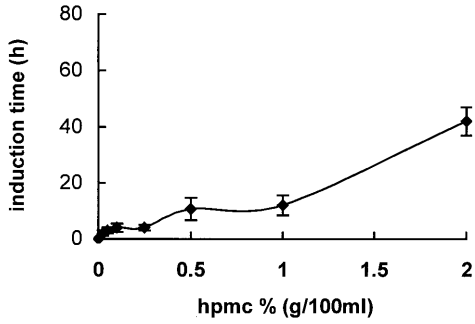

Fig. 5. Crystallization times of HA in a Carbopol gel as a function of HPMC concentration at 4.8 × saturation.

large crystals. The gel was prepared by dissolving Carbopol in aqueous solutions of HPMC. An excess of HA was added to the solvent (PG) and the solution was agitated with a Teflon coated magnetic bar and left in a water bath at 32°C for 48 h. The resultant saturated solution of HA in PG was centrifuged for 10 min and the supernatant added to the Carbopol–polymer solution. This solution was left to hydrate for 30 min. The final step was to stir the solution and add a drop of triethanolamine to form the gel. The size and shape of the crystals obtained were similar to those obtained from solutions indicating that the growth mechanism in the gel medium is similar to that of a stagnant solution. Crystallization times were measured in Carbopol gels, both in the absence and presence of HPMC. When no HPMC was present, as for the solutions, crystals were observed as soon as the cosolvents were mixed. This shows that the diffusion of the drug molecules in the bulk is too fast to be rate-limiting.

In the presence of HPMC, the crystallization was delayed. The crystallization time increased with increasing polymer concentration (Fig. 5). The crystallization times obtained were quite similar to those obtained with solutions up to 2% HPMC concentration. For 5% HPMC, the crystallization time was much higher. Crystals were eventually observed after ≈ 3 months.

The results of the crystallization data for gels containing lower concentrations of HPMC ($\leq 2\%$ HPMC) are quite surprising since the gel medium would be expected to provide diffusional resistance for the mass transport of drug molecules and decrease the nucleation probability. One reason for this could be that the viscosities of the gels and solutions could be similar. In order to establish the influence of viscosity on the crystallization process, the viscosity of the gels were measured and compared with those of the solutions. The viscosity of the gels were found to fall in the range 8–15 Pa.s at a shear rate of $\approx 35\ s^{-1}$, whereas the viscosity of the solutions were of the order of 10^{-2} Pa.s for the same shear rate, which is two orders lower in magnitude. The results suggest that the macroscopic viscosity does not influence the crystallization process and the mechanism of nucleation and growth of HA in gel medium is the same as that in a stagnant solution. It is also possible that the induction rate is controlled by either by the nucleation rate or by the step integration rate during the crystal growth depending on which process is influenced by the viscosity.

3.4. Mechanism of influence of polymer additives on crystallization

Crystallization of a material involves: (i) creation of supersaturation; (ii) formation of stable nuclei (nucleation); and (iii) growth of the crystals. The nucleation process involves the diffusion of molecules through the bulk of the solution, collision with each other and formation of nuclei of a critical size. Once the critical size is reached, growth takes place. If the diffusion is sufficiently rapid, then the nucleation process is not diffusion controlled. This is the case especially at high degrees of supersaturation. In the present studies, when no polymer was present, the nucleation of HA took place instantaneously as soon as the cosolvents are mixed. This indicates that the nucleation process is not diffusion controlled.

In the presence of the polymer, the onset of crystallization was delayed and the lag time increased as the polymer concentration was increased. In this case, the nucleation process becomes increasingly diffusion controlled with increasing polymer concentration. In addition, it is possible that the surface free energy and the collision probability factor may be changed in the presence of the additive and could influence the

nucleation rate. The mechanism of nucleation inhibition in the presence of the additive can be explained on the basis of hydrogen bonding between the drug molecule and the polymer. HA has five functional groups, three carbonyl and two hydroxyl groups (Fig. 6a), which can form hydrogen bonds. The cellulose polymers (Fig. 6b) have high levels of hydroxyl functional groups capable of hydrogen bonding. In solution, HA molecules associate with the polymer molecules to form HA–polymer hydrogen bonds. These types of drug–polymer interactions have been reported in literature (Taylor and Zografi, 1997). For nucleation to occur, this HA–polymer hydrogen bond has to be broken for the HA molecules to diffuse and form a critical nucleus. These drug–polymer interactions may inhibit or retard the formation of nuclei through collision. The strength of the drug–polymer association determines the time required for the nucleation to take place. The association is likely to be stronger with HPMC compared to the other polymers. PVP, for example with only one hydrogen bonding carbonyl group per monomer unit (Fig. 6c), will need a high amount of PVP for the same inhibiting effect. The crystallization data suggest that the nucleation process is dependent on the hydrogen bonding functional groups of not only the drug but also the polymer.

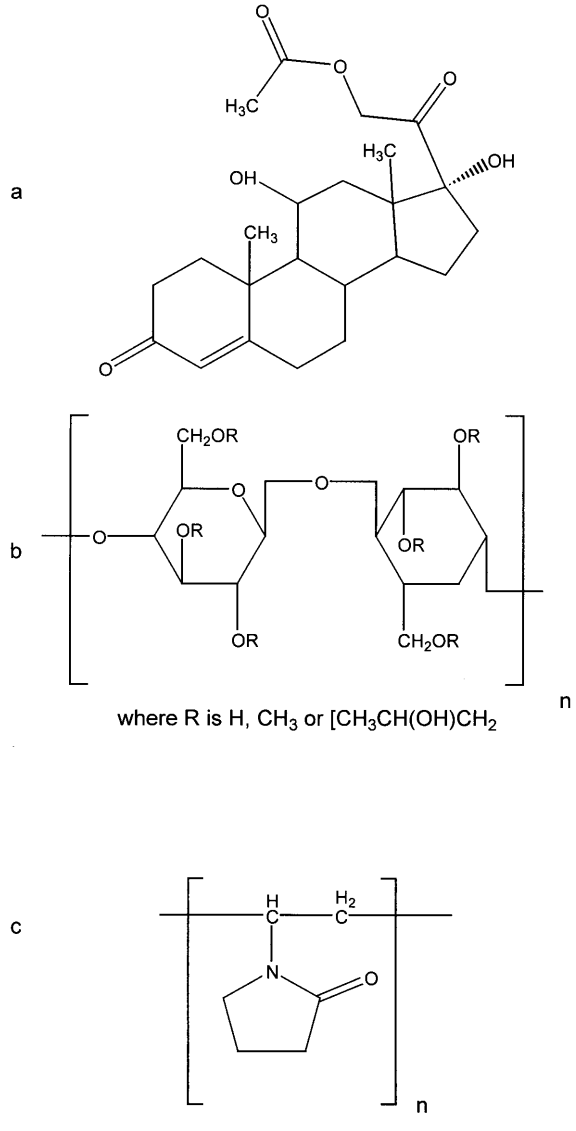

Fig. 6. Molecular structure of (a) HA, (b) cellulose (MC and HPMC), and (c) PVP.

Once the critical nucleus is formed, the HA crystal begins to grow. The growth process involves transport of growth units from the bulk solution to the crystal surface, diffusion to the growth site and incorporation into the crystal surface. Any of these processes may be rate limiting depending on the growth conditions such as supersaturation, solvent, impurities, temperature and hydrodynamics of the system. All these factors can have an influence on the growth as well as the habit of the growing crystal.

Although there have been several reports in the literature on the inhibition of crystallization by polymers (Simonelli et al., 1970; Sekikawa et al., 1978; Ziller and Rupprecht, 1988; Davis and Hadgraft, 1991; Lipp, 1998; Ma et al., 1996; Usui et al., 1997; Femi-Oweyo and Spring, 1994; Pellett et al., 1994, 1997; Taylor and Zografi, 1997; Raghavan et al., 2000), the mechanism of inhibition is rarely discussed. Simonelli et al. (1970) suggest that the polymer reaching the crystal surface forms a net-like structure which allows the drug to grow out in finger-like protrusions leading to a growth with a rough surface. According to Ziller and Rupprecht (1988), the polymer inhibits the introduction of drug molecules from solution into the crystal lattice by occupying adsorption sites and the adsorbed polymer forms a mechanical barrier against crystallization.

There is also a suggestion that the polymers do not inhibit nucleation but just decrease the supersaturation (Rodriguez-Hornedo and Murphy, 1999). This is unlikely since the in vitro permeation experiments have shown that the rate of permeation is proportional to the degree of supersaturation (Davis and Hadgraft, 1991; Pellett et al., 1994; Megrab et al., 1995; Pellett et al., 1997; Schwarb et al., 1999; Raghavan et al., 2000). Any significant changes in the supersaturation will lead to deviation from this behaviour. Moreover, no significant changes in solubility were observed with added HPMC for ibuprofen (Iervolino et al., 2000).

The present results show that growth inhibition as well as habit modification is achieved by the use of polymers. The mechanisms of both these processes can be explained by the presence of a hydrodynamic boundary layer surrounding the crystal as well as anisotropic adsorption of the polymer molecules on the growing crystal faces.

As the growth proceeds, there is a stagnant layer at the interface between the crystal face and the solution, through which the molecules have to diffuse. The thickness of the stagnant film is dependent on the relative velocities of the solid and liquid. In agitated systems, the layer can almost be non-existent. In a stagnant solution, as is the present case, this layer can be very thick. In fact, the thickness of this layer of up to 150 μm has been reported (Mullin, 1993). As the solution approaches the crystal surface, the HA growth units and the polymer molecules compete for the growth sites. HA growth units are more favourable for the incorporation into the lattice site, the large differences in molecular size and structure of the polymer molecules preclude the possibility of their incorporation. However, due to their ability to hydrogen bond with the HA molecules, the polymer molecules may adsorb onto the crystal surface. This leads to a retardation in the growth of HA crystals.

Moreover, the non-adsorbed polymer molecules are rejected at the crystal face. These molecules are not washed away but accumulate at the boundary region (Fig. 7). This provides higher resistance for drug molecules to diffuse through the barrier leading to growth inhibition.

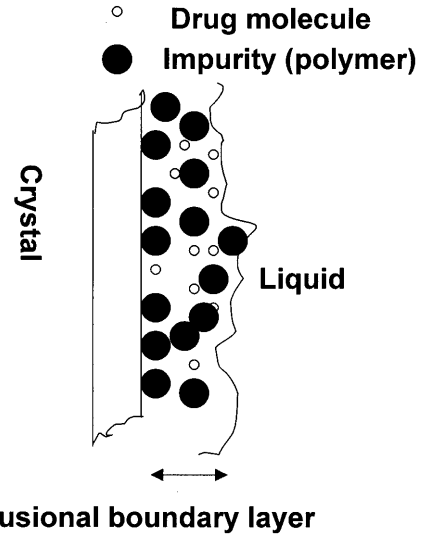

Fig. 7. Schematic diagram showing the mechanism of growth inhibition and habit modification of HA crystals by polymers.

If the adsorption was similar on all the faces, then only a growth inhibition will be observed and the morphology will remain the same. The changes in morphology of HA crystals would require that the level of adsorption is different on different faces of the crystal. The extent of adsorption on each of the growing faces would depend upon the hydrogen bonding functional groups that end at each of these faces. The polymer will adsorb onto the faces that have more hydrogen bonding groups and will lead to growth inhibition. The growth of the faces that have no or less hydrogen bonding functional groups will be relatively less influenced by the polymer adsorption. The changes in the relative growth rates of the various faces will eventually produce crystals with a modified crystal habit. This can be clearly seen in the case of HPMC, which contains a large number of hydrogen bonding groups, where the polymer strongly influences the modification of the crystal habit. Polymers like PVP, with only one hydrogen bonding functional group per monomer unit are not strongly adsorbed onto the crystal faces and are less likely to influence habit modification.

Thus, the crystallization inhibition and habit modification of drug crystals by polymer depends

upon the hydrogen bonding ability of not only the drug but also the polymer.

4. Conclusions

Crystallization of hydrocortisone acetate in the absence and presence of polymers as additives was studied. When no polymer was present, spontaneous nucleation occurred whereas nucleation was suppressed when HPMC was used as the additive. The induction time increased with increasing polymer concentration at a particular degree of supersaturation. The crystal morphology is modified by the cellulose polymers and remained unchanged with other polymers. The nucleation is retarded by the adsorption of the drug to the polymer through hydrogen bonding. The hydrodynamic boundary layer surrounding the crystal and adsorption of polymer molecules onto the crystal surface leads to the growth inhibition as well as habit modification in hydrocortisone acetate crystals.

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