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Crystal growth studies involving phase transitions in aqueous drug suspensions

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The growth of oxyclozanide crystals in quiescent suspensions has been monitored using the Coulter Counter. Increase in particle size is the result of an isothermal, solvent-mediated phase transition between two unsolvated polymorphs, one having a lower solubility than the other. Effects due to Ostwald ripening and temperature cycling are absent. Theophylline, which shows crystal growth in suspension by hydration, has been studied by photomicrography. Preliminary results indicate that the initial rate of growth in such systems may be qualitatively described in terms of steady-state diffusion theory.

The physical stability of pharmaceutical suspensions has long been a formulation problem, and the effect of particle size and fluctuating temperature on crystal growth is well known (Wagner, 1961; Carless & Foster, 1966; Varney, 1967). Recent experience of pronounced crystal growth in suspensions which were virtually unaffected by temperature has directed attention to a third mechanism of growth, that of isothermal, solvent-mediated phase transitions between different polymorphs or solvates of a substance. A prime consideration is the difference in solubility between the various crystal forms, and instability may be expected whenever the production of a less soluble form of the solid phase is possible.

Some examples of the effect of solvation on the solubilities of several pharmaceutical compounds have been described by Higuchi & Shefter (1963). Carless, Moustafa & Rapson (1966) have described the morphology of cortisone acetate and more recently (1968) the effect of the various polymorphic forms on crystal growth in suspensions.

Most of the previous studies of crystal growth involving phase transitions from an existing solid phase in suspensions, have either been concerned with characterizing the solid phases involved (Eanes, Gillessen & Posner, 1965; Arakwa, Kobayashi & Suito, 1966), or have used stirred systems. Since pharmaceutical suspensions are quiescent under typical storage conditions there is scope for practical investigations into the mechanism of changes in the absence of agitation. A disadvantage is that more complicated systems have to be used, but the results are of direct relevance to many formulation problems.

Ideally the growth problem can be solved by selecting the most stable form of a drug for formulation. However, it is important to consider the kinetics of phase transitions in such systems for the following reasons: (i) Conditions of plant production, such as economy, ease of filtration, production time, may make production of a desired physical form difficult. Seeding with quantities of the desired polymorph may help but is not invariably successful. (ii) The most stable forms may not be the

most effective physiologically (e.g. slower dissolution rates). In such cases it would be desirable to formulate a suspension of a less stable form and to reduce the rate of phase transition sufficiently to produce an acceptable shelf life.

The purpose of this paper is to describe some preliminary results which have been obtained for theophylline (1,3-dimethylxanthine), which shows growth by hydration, and for oxyclozanide (2,2′-dihydroxy-3,3′5,5′,6-pentachlorobenzanilide) in which a polymorphic phase change is involved.

THEORETICAL

Under conditions of constant temperature and pressure, the stable or equilibrium configuration for a crystal will be that for which the total (Gibbs) free energy is a minimum. The unit volume free energy is taken to be independent of shape, and the surface free energy is assumed to be constant over each face, though its value may be different for each different type of face. No free energy is assigned to the edges or to the corners of crystals. The Gibbs free energy (G) for a crystal of N faces may therefore be expressed as

$$G^{\alpha} = Vg_v^{\alpha} + \sum_{i}^{N} A_i g_i^{\alpha} \quad .. \quad .. \quad .. \quad (1)$$

$$G^{\beta} = Vg_v^{\beta} + \sum_{i}^{N} A_i g_i^{\beta} \quad .. \quad .. \quad .. \quad (2)$$

where V is the crystal volume, g_v is the free energy per unit volume, A_i is the area of the i'th face and g_i is the free energy per unit area of that face. The superscripts refer to polymorphs (or solvates) α and β respectively.

If $G^{\alpha} \neq G^{\beta}$ there exists a thermodynamic potential to establish equilibrium by an appropriate change of phase or crystal habit. In the dry state a solid phase change may not be possible unless favoured by suitable proximity to a transition temperature. In the presence of a suitable solvent, however, the rearrangement of molecules in the crystal can occur through selective dissolution and redeposition between crystals of different chemical potential. By this mechanism the less soluble phase grows at the expense of the more soluble phase. During growth the equilibrium crystal habit for the given environment is developed, which, in the presence of surface-active substances, often appears in an extreme form such as plates or needles.

Three stages are involved: (i) Solute molecules transfer from crystals of the more soluble phase and pass into solution. (ii) Solute migrates through solution to the surface of crystals of the less soluble phase. In the absence of fluid currents, migration takes place by diffusion along the concentration gradient between the two phases. (iii) Solute molecules deposit on the crystal lattice of the less soluble phase, adopting the same structure and thereby continuing the process until all the dissolving phase has disappeared.

With adequate wetting, the dissolution rate for a given quiescent system is not readily varied. However, stages (ii) and (iii) can be modified to control the rate of crystal growth, an obvious example being the use of surface-active agents to inhibit (iii). Consideration of diffusion kinetics will show the factors controlling the rate of stage (ii).

The steady-state laws of vapour diffusion through a membrane between two fixed vapour pressures are readily adapted to the present case of solute diffusion along an inter-particle solvent path between two fixed concentration levels. Steady-state diffusion applies since the concentration at the crystal surfaces are constant. The rate of transfer, F, of solute through the solution under these conditions is given by Fick's First Law:

$$F = -D\, dc/dx \quad .. \quad .. \quad .. \quad .. \quad (3)$$

where D is the diffusion coefficient and dc/dx is the concentration gradient of the diffusing species. On integration (3) becomes

$$\int_0^x F dx = -\int_{C_1}^{C_2} D\, dc \quad .. \quad .. \quad .. \quad .. \quad (4)$$

Since we are concerned with a steady state, F is the same through each section of the membrane, i.e. F is independent of x, resulting in a linear concentration gradient between dissolving and growing crystals. Hence,

$$\int_0^x F dx = F\int_0^x dx = Fx \quad .. \quad .. \quad .. \quad .. \quad (5)$$

and therefore,

$$F = -1/x \int_{C_1}^{C_2} D\, dc \quad .. \quad .. \quad .. \quad .. \quad (6)$$

Since at the low concentration levels considered D may be assumed constant,

$$F = -D/x \int_{C_1}^{C_2} dc = -D(C_2 - C_1)/x \quad .. \quad .. \quad .. \quad (7)$$

where x is the average inter-particle distance and $C_2 - C_1$ is proportional to the difference in concentration between the solution immediately adjacent to the two types of crystal. To a close approximation this is equal to the difference in solubility of the two phases.

The above equations apply to diffusion in one dimension. However, it is readily shown that the solutions of many problems in radial diffusion in three dimensions can be deduced immediately from those of the corresponding linear problems (Crank, 1967).

Since the rate of crystal growth is proportional to F, it can be seen from equation (7) that stability problems are increased as the solubility difference is increased or the inter-particle distance is decreased. Concentrated suspensions should therefore be less stable than dilute ones and the stability should decrease further on addition of materials which enhance the solubility difference.

EXPERIMENTAL

Preliminary considerations

The requirements for an ideal suspending medium for investigating diffusion-controlled growth presented several practical difficulties. Eventually, aqueous

systems gelled with Carbopol 940* were found to be suitable for the following reasons: (i) The Carbopol systems ensured permanent suspension of particles with the absence of fluid currents. (ii) The open network of dilute gels permits free diffusion. There is an increasing volume of literature on the growth of crystals in such media. Halberstadt & Henisch (1968) have given a status report on various aspects of the technique, and Heyrovsky, Kratochvil & Sprusil (1968) have stated that the method is particularly suitable for growing crystals isothermally. (iii) Carobopol gels can tolerate large quantities of organic solvents, enabling the solubility of the solid phases to be varied within wide limits. (iv) The viscosity is only slightly affected by temperature. (v) Since the gelling properties of Carbopol are obtained by neutralization with alkali, dispersion of the solid can be produced without difficulty in a mobile system and the pH adjusted subsequently.

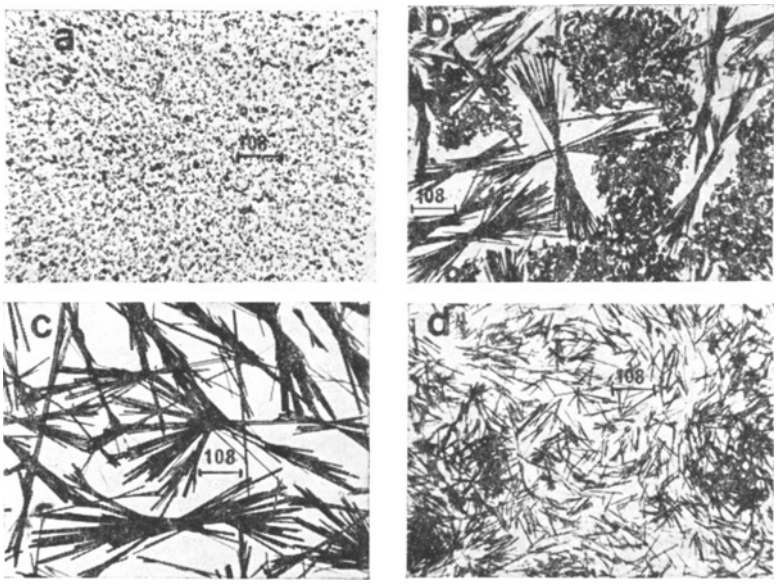

FIG. 1. (a) Micronized theophylline, anhydrous. Initial aqueous suspension. (b) Crystal growth after 5 min. (c) Crystal growth after 15 min. (d) Aqueous theophylline suspension, solid phase "seeded" with 5% w/w hydrated form. Crystal growth after 15 min. Measurements are in μm.

Studies using theophylline

As a demonstration of crystal growth by solvation, an aqueous suspension of anhydrous micronized theophylline was prepared and microphotographs taken at several intervals (Fig. 1a–d). The system provided striking visual evidence of the isothermal growth of one phase at the expense of another. Fig. 1a shows the initial suspension; Fig. 1b shows growth in progress after 5 min. Trace particles of hydrate served as nuclei, and the subsequent growth of these apparently held the supersaturation below the level required for further nuclei generation. Therefore, only a small number of very large crystals were formed. Anhydrous crystals could be seen to dissolve in the neighbourhood of the hydrated ones while the latter grew out as long needles into the voids formed. After 15 min the transformation was

* A polycarboxylic acid resin producing a gel in solution on neutralization with alkali (Goodrich Ltd.).

complete (Fig. 1c) and the final photograph (Fig. 1d) shows the effect of including 5% w/w of the hydrated phase in the initial suspension. A large number of smaller crystals were formed due to the higher nuclei concentration.

Studies using oxyclozanide

Certain production batches of bead-milled oxyclozanide concentrates, 25% w/w, exhibited pronounced crystal growth (Fig. 2a, b). Long, interlocking needle crystals were formed giving a viscous and lumpy suspension. The rate of growth varied with the batch of concentrate, the most extreme case showing virtually complete transformation after several days, while some batches appeared stable indefinitely. In no case was it possible to accelerate growth by temperature cycling. Examination by X-ray, infrared and elemental analysis showed that the crystal growth was produced by a phase transition between two unsolvated polymorphs, the final form "B" having a lower solubility than the initial form "A".

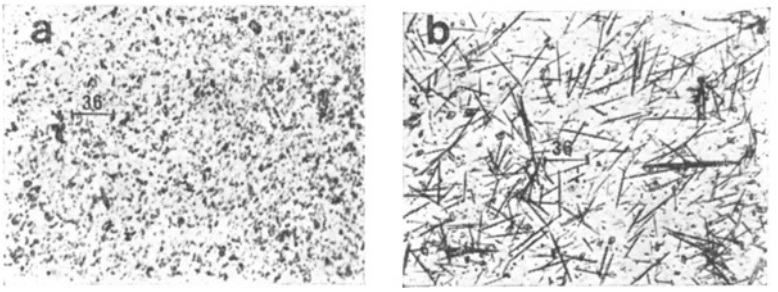

FIG. 2. (a) Oxyclozanide 25% w/w concentrate, selected batch, before polymorphic change. (b) Same batch after polymorphic change. Pronounced growth of needle crystals is shown. Measurements are in μm.

Measurement of crystal growth

A Coulter Counter "Model A", fitted with a 50 μm orifice tube and a 0·05 ml manometer (Coulter Electronics Limited, Dunstable) was used. The instrument was calibrated using polyvinyltoluene latex spheres, diameter 2·68 μm (Dow Chemical Company, Michigan). The technique for rapid monitoring of growth was as described by Carless, Moustafa & Rapson (1968). The Coulter Counter had the considerable advantage for the present work of being a volume sensing device, so that variation of crystal habit during growth would not seriously affect the results.

The counting electrolyte was a 0·9% w/v solution of sodium chloride in distilled water containing 0·02% w/v Perminal BXN (sodium alkylnaphthalene sulphonate, ICI Ltd.) as wetting agent and saturated with oxyclozanide. The solution was clarified through filter paper and then through 0·45 μm pore size Millipore filters under light vacuum.

Samples of the test suspensions were transferred to the stirred counting electrolyte by means of a glass rod. The Carbopol gel rapidly dissolved from the rod, releasing the particles into the electrolyte for counting. Measurements were then taken at only four threshold levels for speed of operation. Since all counts were related to a total count for a given series of measurements, it was not necessary to measure an exact quantity of gel into the electrolyte solution. The time taken to complete a size analysis rarely exceeded 10 min. Background and coincidence corrections were made as usual.

Effect of different polymorphs on counting technique

It is conceivable that some dissolution or growth of the test suspension could take place in the counting electrolyte, depending on which polymorph of oxyclozanide was used for saturation. Batches of counting electrolyte saturated with forms A and B were therefore prepared and size distributions of micronized samples of each polymorph obtained. In both cases there was no noted effect with change of electrolyte. It was therefore concluded that for the present system the selection of specific batches of oxyclozanide to saturate the counting electrolyte was not necessary.

The disperse phase

The micronized oxyclozanide used in the growth trials was a 10% w/w mixture of the less-soluble polymorph B in the more-soluble form A, the former serving as nuclei for the growing phase. Too low an initial nuclei concentration produced overlarge crystals with resultant blockage of the Coulter orifice, whereas at higher concentrations growth was insufficient before the phase change was complete. 10% was about the optimum, producing needle crystals of about 20 μm maximum length.

Solubility

Oxyclozanide has a very low solubility in water, less than 5 ppm at room temperature. Addition of methanol increased the solubility over a wide range, enabling the period of phase transition to be adjusted to a convenient value for measuring. The advantages of using methanol were that complete miscibility at all concentrations was assured, and the gelling properties of Carbopol were retained. From several screening tests a final concentration of 25% w/w methanol in a solution gelled with 0·3% w/w Carbopol 940 and containing 0·1% w/w Lissapol NX (a nonylphenol ethylene oxide condensate, ICI Ltd.) as wetting agent, was found to produce complete oxyclozanide conversion within about 8 h. It has however, been possible to vary the period of phase change from seconds to several days by increasing or decreasing the methanol concentration respectively.

The solubility of oxyclozanide has been determined in an aqueous solution containing 25% methanol and 0·1% w/w Lissapol NX by the method of Higuchi and Shefter (1963). Carbopol was omitted due to experimental difficulties. The values determined were 4·8 and 2·4 mg/100 ml for the "A" and "B" polymorphs respectively. The assumption was made that the presence of 0·3% w/w Carbopol did not materially alter the solubilities. Evidently solute transfer can occur under very small concentration gradients.

Preparation of suspension

The order of mixing the constituents is critical. In the presence of large amounts of methanol any attempt to disperse the solid phase by rapid agitation caused initial growth, presumably by accelerating solute diffusion. Dispersion by ultrasonics degraded the Carbopol and prevented gel-formation. It was finally found most convenient to disperse the solid mechanically in a simple aqueous Lissapol solution since no change in particle size was detected after several hours of such treatment. Only gentle mixing was then necessary to ensure a homogeneous blending with the remaining constituents. It was essential to ensure complete dispersion since any residual aggregates tended to break down as the more soluble phase dissolved, producing an initial dip in the growth curves.

The dispersion of micronized oxyclozanide in aqueous Lissapol was prepared by mechanical agitation using a stainless steel perforated piston moving inside a 25 ml measuring cylinder. The piston head had a total diameter of 11/16 inch and 12 individual holes of 1/16 inch diameter, equidistant from each other, drilled in it. Spot checks with the Coulter Counter indicated complete dispersion after about 15 min, provided the Lissapol concentration was not lower than 0·1% w/w. Microscopic examination confirmed the absence of residual aggregates. A weighed quantity of a solution of Carbopol 940 in aqueous methanol was added and the system mixed by several gentle strokes of the piston. Finally a standard solution of sodium hydroxide was added to gel the system at pH 7. The addition of the methanolic solution caused weak flocculation, possibly due to some desorption of the Lissapol. Complete dispersion was obtained however with a few seconds agitation of the gelled suspension. The amounts of the various constituents used in the preparation were chosen to give a final suspension of the following composition (% w/w): oxyclozanide, 4; Lissapol NX, 0·1; Carbopol 940, 0·3; methanol, 25; distilled water up to 100.

A further two suspensions were prepared to the above specification but containing 2 and 1% w/w oxyclozanide respectively. In each of these suspensions the solid phase was a mixture of 10% w/w polymorph B in A, but a 4% w/w suspension was prepared containing exclusively polymorph A. All tests were made at room temperature (23 $\pm$ 1°). Crystal growth in the suspensions was taken to begin on addition of the methanol.

Infra-red measurements

At intervals during the growth process samples of oxyclozanide were extracted from the suspensions and examined for polymorphic change by infrared spectroscopy. A portion of the suspension was diluted with water to thin the gel and arrest further crystal growth. The system was then centrifuged to precipitate the solid phase and the liquid decanted off. The precipitate was washed by stirring in water and centrifuging again. After washing three times the precipitate was dried over silica gel under vacuum for 48 h.

RESULTS AND DISCUSSION

The Coulter plots at four different threshold levels for the 4% w/w suspension are given in Fig. 3. Taking the 4 μm plots for reference, the growth of the 4, 2 and 1% w/w suspensions are compared in Fig. 4. The results require some caution in their interpretation, but a definite increase in the rate of growth with suspension concentration is shown. The infrared spectra (Fig. 5) confirmed that the crystal growth was accompanied by a progressive polymorphic transformation from A to B. There was no change in the infrared spectra, or detectable growth, in the suspension prepared without nuclei, confirming that the phase transition was effected by interparticle migration of solute rather than by molecular rearrangement within the solid phase. The unseeded suspension also showed that "Ostwald ripening", i.e. growth of the larger particles at the expense of the small ones was not responsible for the change observed.

It is unlikely that interaction with the solvent had any net effect on the energy balance in favour of the transformation from form A to B since no solvation product

was formed. Conceivably the production of crystals of higher surface energy than the disappearing ones could retard the phase change, and vice versa, but much more data will be required to produce evidence of this effect in the present system.

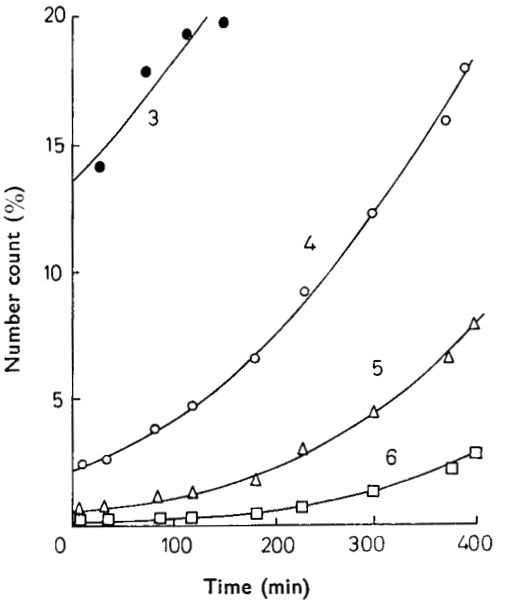

FIG. 3. Change in cumulative counts with time, representing crystal growth in a 4% w/w suspension of oxyclozanide. Counts taken at 3, 4, 5 and 6 μm threshold levels. Numbers on the curves are μm.

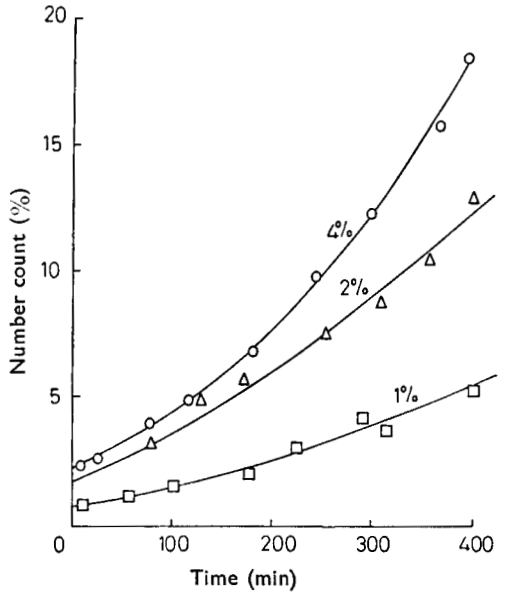

FIG. 4. Change in cumulative counts with time, representing crystal growth in 4, 2 and 1% w/w suspensions of oxyclozanide. All counts taken at 4 μm threshold level.

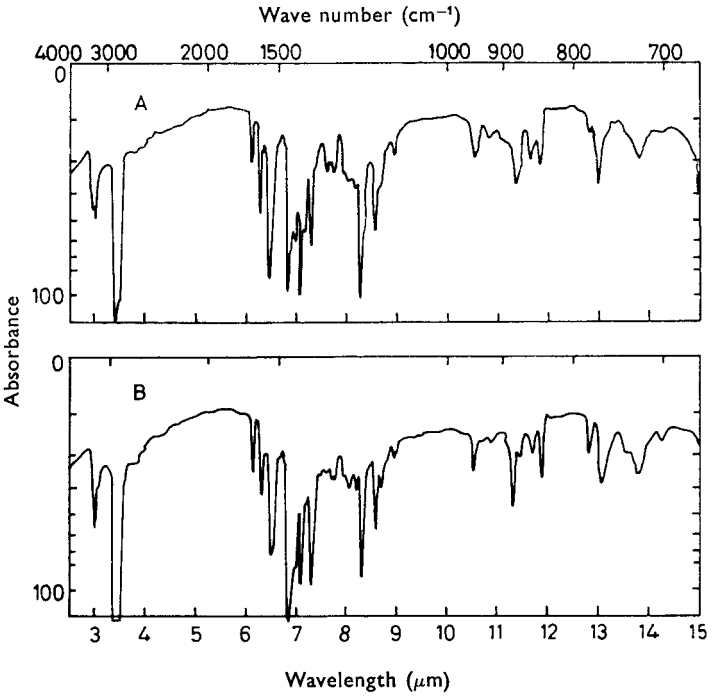

FIG. 5. A. Infrared spectrum of oxyclozanide used in crystal growth trials: 10% w/w mixture of the less soluble polymorph B in polymorph A.
B. Infrared spectrum of solid phase from 2% w/w oxyclozanide suspension extracted three days after preparation. No further growth apparent, spectrum corresponding to 100% polymorph B. Both spectra were obtained from micronized samples mulled in Nujol and read on a Perkin Elmer Infracord.

The difference between the respective bulk or lattice free energies is at present regarded as the fundamental driving force for the phase transition. The opportunity for molecules to re-orientate themselves in a crystal lattice by dissolution from one type and deposition on another evidently results in a lower energy barrier to the change than exists for re-orientation entirely within the solid phase. It was in fact impossible to induce changes in either polymorph of oxyclozanide in the dry state at temperatures between −80° and 150°. Such facilitation of phase changes by solvent mediation would account for many precipitation and filtration problems, particularly in the dyestuffs industry when unwanted colour changes may occur.

Although many stirred systems are said to be diffusion-controlled owing to a stationary layer of solution surrounding each particle, the thickness of the layer and hence the rate of dissolution, varies with the speed of stirring. In some cases the term "surface-controlled" has been applied to crystals growing in fast-streaming solutions, and there is some loose terminology in the literature on this point. In quiescent suspensions the "diffusion layer" extends throughout the disperse medium, and in the absence of surface inhibitors the system may truly be termed "diffusion controlled".

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