Inhibition of Sulfathiazole Crystal Growth by Polyvinylpyrrolidone

A. P. SIMONELLI, S. C. MEHTA, and W. I. HIGUCHI

Abstract □ The results of polyvinylpyrrolidone inhibition of sulfathiazole single crystal growth are presented. It was found that the minimum concentration of polyvinylpyrrolidone required to inhibit completely crystal growth was a linear function of the supersaturation ratio with an intercept of ~1.15 exhibited on the latter axis. It was also found that the minimum concentration of polyvinylpyrrolidone required for complete inhibition of crystal growth was a function of the molecular weight of polyvinylpyrrolidone used for the inhibition study. The results of inhibition studies using molecular weights of polyvinylpyrrolidone of 10,000, 40,000, and 360,000 are presented. The data suggest that the inhibition point depends on the relative rates of transport of polyvinylpyrrolidone and sulfathiazole to the crystal surface from the bulk of the solution. A model is presented that appears to be consistent with the data.

Keyphrases □ Sulfathiazole crystal growth—polyvinylpyrrolidone effect □ Crystal growth, sulfathiazole—mechanism, polyvinylpyrrolidone inhibition □ Polyvinylpyrrolidone molecular weight effect—sulfathiazole crystal growth □ Model, kinetic—polyvinylpyrrolidone effect, sulfathiazole crystal growth

The growth of crystals may create undesirable changes in many pharmaceutical preparations such as suspensions for intramuscular or subcutaneous injection, oral suspensions, suppositories, and ointments containing undissolved drug particles. Crystal growth may cause these preparations to change drastically their particle-size distribution. Associated crystal growth formulation problems include adverse changes in syringeability, dispersibility, and irritability to the patient upon administration (1–3).

Crystal growth may also play an important role in polymorphic reversions. When polymorphism is present, the various crystal modifications of solid drugs can exhibit drastically different physical characteristics. Most important of these characteristics from a drug-availability standpoint are differing solubilities and dissolution rates as they can significantly alter important pharmacokinetic factors such as rates of absorption, drug availability, and resulting physiological concentrations. Since the higher energy crystal form of the drug exhibits higher activity, maintaining the physical stability of the high energy polymorphic form of drugs in suspension despite their instability becomes very important and has posed many problems to formulators. The importance of this problem is compounded by the fact that the reversion of the unstable form to the more stable form produces a less soluble form of the drug and in doing so increases the rate of crystal growth due to the resulting higher supersaturations. Such changes are realized if the unstable modification is exposed to the conditions of temperature and solvent (4–7) which permit rapid crystal growth of the more stable phase. Unless there is inhibition, such changes may lead to marked variances in a formulation's performance as a physical or drug delivery system.

Crystal growth and the associated polymorphic reversions have been extensively studied, and it has been found that a number of additives such as polymers and surfactants prevent these undesirable changes in pharmaceutical preparations (8–10). A survey of the literature, however, shows that very little is known regarding the role played by these agents in these situations except for their classifications as dispersion or suspending agents. Recognizing the need for studies designed to shed some light on the mechanism of this phenomenon, this study was initiated as a logical extension of the previous investigation regarding the growth of single crystals. While this report deals only with the sulfathiazole–polyvinylpyrrolidone (PVP) system, the underlying principles are sufficiently general to be extrapolated to other drug–polymer systems. Sulfathiazole was chosen because it has exhibited polymorphic behavior and is widely used as a suspension.

APPARATUS AND PROCEDURE

The apparatus and procedure used to study crystal growth rates have been described in another communication (11). The effect of additives upon the rate of crystal growth was determined by adding polymer in increments as a function of time through a sampling hole in the container lid. A stopwatch was used to obtain the time of each measurement of the crystal dimension and the time of inhibitor addition.

RESULTS AND DISCUSSION

Since the growth of the long axis of a single crystal of sulfathiazole in the absence of inhibitor must serve as a base line and integral part of this study, Fig. 1, which illustrates the growth rate of sulfathiazole as a function of the supersaturation ratio (11), is included. The supersaturation ratio, S, is the supersaturated solution concentration of sulfathiazole divided by the solubility of sulfathiazole. Figure 1 shows that the crystal growth rate of sulfathiazole is a linear function of the supersaturation ratio at higher supersaturations and that extrapolation of the linear portion of the curve yields an intercept on the supersaturation ratio axis at about a value of 1.15. Below a supersaturation ratio of 1.15, crystal growth may occur and may be surface controlled (11). Figure 1 also clearly shows that the stirring rate exerts a strong influence on the observed crystal growth rate above this supersaturation ratio and strongly indicates that in this region the growth rate must be diffusion controlled.

The effect of addition of PVP to the supersaturated solution was next investigated. It was found that the resulting effect on the sulfathiazole crystal growth rate was dependent upon the concentration of PVP in solution. To investigate this aspect further the polymer was added in lambda increments as a function of time. Between additions of polymer, the length of the crystal was also measured as a function of time and in this way the effect of PVP on the growth rate was established. Figure 2 shows typical results of such an experiment. The crystal length is plotted *versus* time and each arrow indicates the time of an addition of a solution of PVP by means of a lambda pipet. Interestingly the direction as well as the magnitude of the PVP effect was apparently dependent on the PVP concentration.

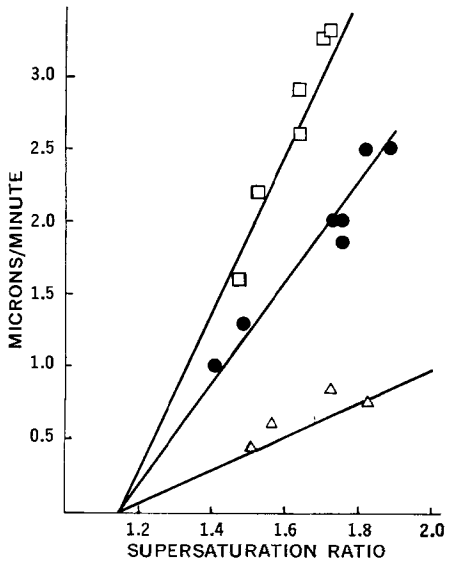


Figure 1—*Crystal growth of sulfathiazole in water along the long axis as a function of supersaturation at different stirring speeds. Key: △, 10 r.p.m.; ●, 150 r.p.m.; and □, 400 r.p.m.*

The initial additions of PVP showed no apparent effect; then further additions of PVP apparently decreased the growth rate; the rate of growth then apparently increased with other additions of PVP; and finally, still further additions of PVP caused complete crystal growth inhibition. This experiment was repeated a large number of times, and the results showed that this behavior was qualitatively reproducible, *i.e.*, the acceleration of growth before complete inhibition. The rate of acceleration, however, was not quantitatively reproducible. The reason for this becomes apparent if the growth pattern of the crystal is noted during the experiment, because the addition of PVP not only caused changes in the rate of crystal growth but also caused changes in the growth pattern. This is illustrated in Fig. 3 which shows the appearance of the crystals at various stages of the experiment. Initially the crystal face outline has smooth linear lines which converge to sharp points. This outline is maintained during its

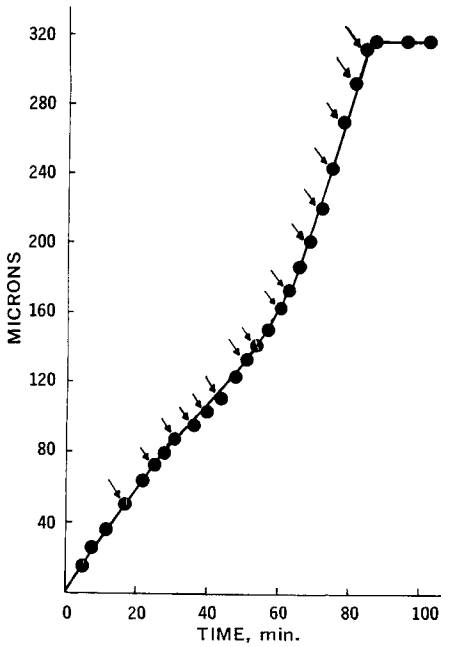


Figure 2—*A typical plot of crystal growth of sulfathiazole as a function of time, with incremental additions of PVP to the solution made also as a function of time. Each arrow indicates the time of addition of PVP solution in lambda increments.*

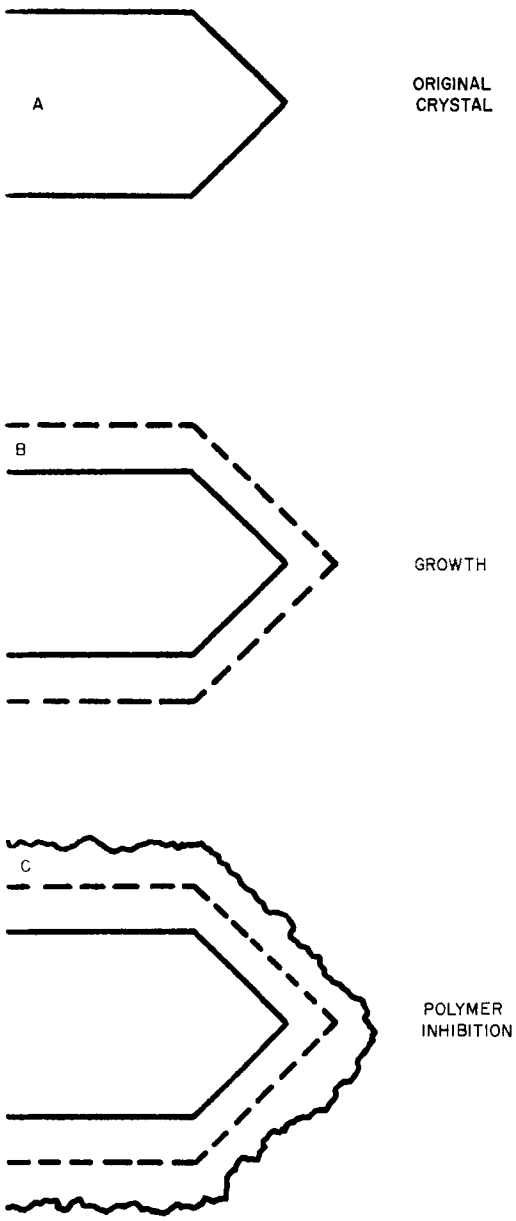


Figure 3—*Appearance of crystal surface outline at various stages of the experiment: A, original crystal at t = 0; B, after normal growth; and C, after the addition of PVP, showing polymer inhibition.*

enlargement as crystal growth proceeds in the absence of PVP. After the addition of PVP, however, the smooth linear lines during the accelerated growth period are replaced by randomly jagged lines which converge to indefinite intersection points. These intersection points are rounded as opposed to the sharp points previously observed.

Although the accelerated growth rate was not quantitative, the point of complete inhibition was reproducible and indicated that it would provide meaningful data regarding the influence of PVP. For this reason the minimum concentration of PVP for complete inhibition was noted as a function of the supersaturation ratio (Fig. 4). The relationship shown by Fig. 4 appears to be linear with an x-axis intercept and, as expected, it shows that higher PVP concentrations are needed as the supersaturation increases. It should be emphasized that each point plotted in Fig. 4 was the result of a large number of PVP additions to the solution with subsequent observation of the crystal length between additions to determine its rate of crystal growth. When the crystal ceased to grow, the sum of the PVP additions was calculated and the PVP concentration in the solution determined. This value was checked by mounting a new crystal and exposing it to the above inhibitory concentration of PVP to elimi-

Table I—Comparison of PVP Equivalent and Molar Weights Needed for Crystal Growth Inhibition

PVP Molecular Weight	Ratio of Slopes[a] Equiv. Weight Basis (ψ)[b]	Molar Weight Basis (α)[c]
10,000	1.00	1.00
40,000	1.49	0.37
360,000	4.30	0.12

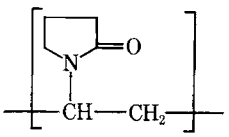
[a] Relative to the 10,000 molecular weight slope. [b] ψ, also equal to the number of equivalents needed for inhibition relative to the 10,000 molecular weight PVP. [c] α, also equal to the number of moles needed for inhibition relative to the 10,000 molecular weight PVP.

nate the possible error of dilution introduced by the frequent addition of PVP in the initial experiment.

As a result the values of the minimum concentration of PVP for complete inhibition plotted in Fig. 4 should be considered only as upper limits as the process of adding discrete amounts almost assures some degree of overshooting the minimum value. To eliminate or to decrease significantly the magnitude of this overshoot would require a countless number of additional experiments for each point. However, this was not done as the data at hand are sufficiently precise to provide firm establishment of the model which will be subsequently proposed.

This inhibition was further investigated to include the effect of PVP molecular weight. Figure 4 shows the resulting plots from different experiments using PVP molecular weights of 10,000, 40,000, and 360,000. As can be seen, the necessary grams of PVP per 100 ml. of solution to cause inhibition of crystal growth at any supersaturation ratio increases with increasing molecular weight of PVP. In addition the rate of increase of the grams of PVP per 100 ml. of solution needed as a function of increasing supersaturation ratio is much faster for PVP polymers of high molecular weight than those of lower molecular weight.

At this point of discussion, it was felt that the polymers should be compared on the basis of their relative concentrations of the recurring vinyl pyrrolidone segment,



rather than relative concentrations of molecules because it was desired to compare their effectiveness on an equivalent weight basis. For this reason, concentrations were expressed in terms of gram percent rather than moles/liter. It should be noted, however, that if the

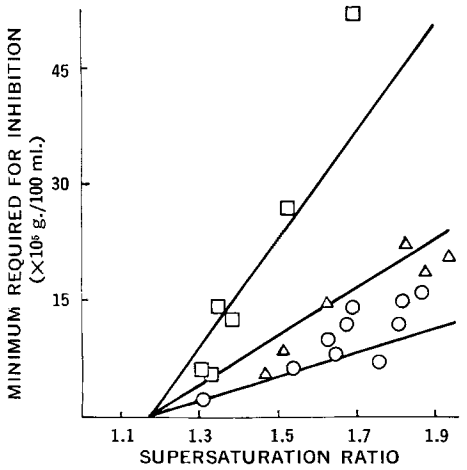


Figure 4—*Minimum concentration of different molecular weights of PVP required to cause inhibition of crystal growth of sulfathiazole as a function of supersaturation. Key: O, 10,000 molecular weight; Δ, 40,000 molecular weight; and □, 360,000 molecular weight.*

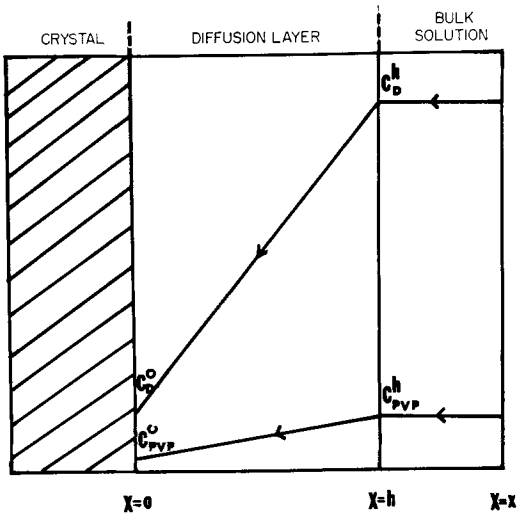


Figure 5—*Kinetic model describing the concentrations of sulfathiazole and PVP as a function of distance from the crystal surface.*

necessary concentrations of PVP were expressed in terms of molarity, the effects of polymer molecular weight would be very different from those noted using gram percent. As a matter of fact, the range of their relative molecular weights, 1:4:36, is sufficiently large to cause the relationship to be reversed, *i.e.*, the higher molecular weight PVP requires less moles for inhibition. Table I shows the results of a comparison of the slopes of best fit linear curves drawn through the corresponding data points.

These relationships imply that this is not an equilibrium process but must involve dominating kinetic factors. If an equilibrium process was in control, it would not be expected that more equivalents of the higher molecular weight PVP would be needed due to the better adsorption tendencies of the higher molecular weight polymers. This would be true if all segments have equal covering ability. This can be rationalized on the basis that a higher molecular weight PVP molecule contains more units per molecule than its lower molecular weight counterpart and therefore can make more attachments to a crystal surface with which to anchor itself.

It can be inferred that diffusional processes are controlling the effective concentration of PVP required for inhibition by considering the following:

1. The rate of crystal growth appears to be controlled by the rate of diffusion of sulfathiazole to the surface as shown by the stirring rate dependence of the crystal growth studies.

2. The PVP molecular weight dependence of the PVP inhibition suggests that the rate of PVP diffusion to the surface may be rate determining; otherwise, it whould be expected that the minimum equivalent weight of PVP needed to inhibit sulfathiazole crystal growth should be independent of the molecular weight as the PVP polymer consists of identical recurring units.

3. Finally the marked inhibition concentration dependency of PVP on the supersaturation ratio also supports the hypothesis that the rate of diffusion of PVP to the surface is rate determining. For a nondiffusional model, it would be expected that the PVP concentration needed should be invariant and not a function of the supersaturation ratio.

This rationalization prompted the proposal of the kinetic model which is illustrated in Fig. 5. It is easily seen that in this model the relative concentrations of drug and PVP at the surface of the crystal will depend on the relative concentration in the bulk of the solution and the relative rates of diffusion through the diffusion layer. If this is true the relative rates of deposition of both species on the surface of the crystal must also depend on the relative rates of diffusion to the surface, as it would be expected that the relative rates of deposition must be dependent on the relative concentrations of both species at the surface. Since the data show that a minimum concentration of PVP is needed for inhibition to occur, it can be postulated that if the rate of deposition of PVP is relatively slow as compared to that of the sulfathiazole, it is buried by the avalanche of precipitating sulfathiazole molecules. If, on the other hand, its rate is relatively rapid, it in turn can bury the precipitating sulfathiazole

molecules and sufficiently cover the crystal surface to cause inhibition of crystal growth. This model can be used to explain adequately all the results reported in this study. For example this model would predict that a higher PVP concentration would be needed to cause crystal growth inhibition at higher supersaturation ratios of sulfathiazole as the sulfathiazole molecules would increase their diffusional rate to the surface, necessitating that the PVP do so also.

Since this model readily lends itself to a mathematical treatment, quantitative relationships were derived to test the validity of the model. Assuming a steady state, the rate of diffusion of drug, G_D, and PVP, G_p, are given by the following equations:

$$G_D = K_D D_D (C_D^h - C_D^0) \quad \text{(Eq. 1)}$$

$$G_p = K_p D_p (C_p^h - C_p^0) \quad \text{(Eq. 2)}$$

where C_D and C_p denote the concentration of drug and PVP, respectively; the superscripts h and 0 denote the concentrations in the bulk of the solution and at the crystal surface, respectively; and K_D and K_p are the corresponding proportionality constants.

Since the model assumes that inhibition occurs when the relative diffusional rate of PVP to the surface is sufficiently rapid, it can be stated that for complete inhibition to occur the following condition must prevail:

$$G_p \geq k' G_D \quad \text{(Eq. 3)}$$

where k' is the proportionality constant relating the minimum PVP rate of diffusion for inhibition to the drug rate of diffusion. Substitution of Eqs. 1 and 2 into Eq. 3 and rearrangement of the resulting equation lead to the following equation for the minimum bulk concentration of PVP, $(C_p^h)_M$, needed for crystal growth inhibition of sulfathiazole:

$$(C_p^h)_M = \frac{kD_D}{D_p}[C_D^h - C_D^0] + C_p^0 \quad \text{(Eq. 4)}$$

where[1] $k = (K_D/K_p)k'$.

The supersaturation ratio, S, is defined as

$$S = \frac{C_D^h}{C_D^s} \quad \text{(Eq. 5)}$$

where C_D^s is the solubility of the drug.

Equations 4 and 5 yield

$$(C_p^h)_M = \frac{kD_D C_D^s (S)}{D_p} + C_p^0 - \frac{kD_D C_D^0}{D_p} \quad \text{(Eq. 6)}$$

Equation 6 predicts that a plot of $(C_p^h)_M$ *versus* S is a straight line with a slope of $kK_D C_D^s / D_p$ which intercepts the supersaturation ratio axis at:

$$S = \frac{C_D^0}{C_D^s} - \frac{C_p^0 D_p}{kD_D C_D^s} \quad \text{(Eq. 7)}$$

The above predicts that in the absence of PVP the intercept is equal to C_D^0/C_D^s when $(C_p^h)_M = 0$, and experimentally this appears to be equal to 1.15. In the presence of PVP, however, experimental results indicate that the intercept essentially remains unchanged and this appears to differ with the results predicted by Eq. 7. If one examines the relative magnitudes of the first and second terms of Eq. 7, however, it can easily be shown that the second term is negligible. The first term is equal to $\simeq$1.15, assuming this is independent of the presence of PVP. The second term can be set equal to C_p^0/slope. Since C_p^0 is $<<< 10^{-5}$ g./100 ml. and the slope is 1.5 to 5.5 $\times$ 10^{-6}, Eq. 7 predicts that the intercept is essentially unchanged with the addition of PVP.

Equation 6 was derived for the sulfathiazole–PVP system but will be applicable to any drug-inhibitor system that is described by this model. If the drug is changed, Eq. 6 predicts that the minimum concentration of inhibitor needed for complete crystal growth inhibition, $(C_p^h)_M$, would be directly proportional to the solubility and diffusion coefficient of the drug. Perhaps of more significance is that Eq. 6 predicts that $(C_p^h)_M$ is directly proportional to the supersaturation ratio and inversely proportional to the diffusion coefficient of the polymer.

[1] In an idealized situation, $K_D = K_p$ and therefore $k = k'$. The more general treatment presented in this discussion—*viz.*, $k \neq k'$, is preferred as it might allow for nonideal factors such as nonlinear concentration gradients and different sites of deposition.

Table II—Comparison of Experimental PVP Molecular Effectiveness to the Expected Effectiveness[a]

Relative Comparison[b]	PVP Molecular Weight Polymer 10,000	40,000	360,000
Molar slopes[c]	1	0.37	0.12
Apparent molecular effectiveness	1	2.70	8.33
Diffusion coefficient factor	1	2.11	4.37
Diffusion coefficient adjusted experimental molecular effectiveness	1	5.70	36.40
Expected molecular effectiveness	1	4.00	36.00

[a] Assuming equivalency of molecular segments. [b] Relative to 10,000 molecular weight polymer. [c] See Table I.

These predictions can be used as a test for the applicability of the model to a given system. The data previously presented in this study clearly show that $(C_p^h)_M$ is directly proportional to the supersaturation ratio. If $(C_p^h)_M$ is also inversely proportional to the respective PVP diffusion coefficients, then the slopes of the three straight lines obtained for the three different molecular weight PVP compounds should be in the same ratio as their reciprocal diffusion coefficients assuming that each segment has equal covering capability regardless of the molecular size.

For this purpose, the diffusion coefficients of the three species of PVP used in this study, 10,000, 40,000, and 360,000 molecular weight were independently determined in a diffusion cell using a membrane filter by a method previously reported (12). The diffusion coefficients were found to be 1.55 $\times$ 10^{-6}, 7.33 $\times$ 10^{-7}, and 3.55 $\times$ 10^{-7} cm.^{2}/sec. for the 10,000, 40,000, and 360,000 molecular weight polymers. A set of straight lines were simultaneously fitted to the data points of all three PVP compounds using a common intercept of 1.15 and ratio of slopes that were proportional to their respective reciprocal diffusion coefficients. A common intercept was used as predicted by Eq. 6. Figure 4 shows that the agreement is well within experimental error and lends strong support for the proposed model.

Although the diffusional rate of PVP to the surface has been established as the controlling process, it would be of interest to determine the relative effectiveness of the different molecular weight PVP molecules once they arrive at the surface. It would be expected that the 360,000 molecular weight PVP would be 9 times more effective than the 40,000 molecular weight PVP and 36 times more effective than the 10,000 molecular weight PVP. Table II shows the results of calculations which strongly support the equivalency of molecular segments in covering the surface regardless of molecular weight and that the apparent relative molecular effectiveness is due to the relative PVP rates of transport to the crystal surface.

Yet to be explained is the small amount of PVP needed for complete inhibition of crystal growth of sulfathiazole. This result suggests that the PVP must be strongly bound to the sulfathiazole crystal surface. This should not be unexpected as the PVP consists of a recurring group which allows it to form many attachments to the surface. This possibility was tested out by running an inhibited crystal from a PVP solution of a given sulfathiazole supersaturation ratio in a solution of comparable supersaturation ratio but without PVP. The crystal did not grow, indicating that the PVP was not removed from the crystal surface and therefore it was indeed strongly bound.

To investigate this further, calculations were made using Eqs. 1 and 2 to estimate the relative rates of transport of sulfathiazole and PVP from the bulk of the solution to the crystal surface. The results of these calculations confirmed the above, as they clearly showed that the relative rates of deposition of PVP as compared to sulfathiazole was not sufficiently large to provide for a tightly packed film over the sulfathiazole crystal surface.

Although no further evidence was obtained, sufficient data are at hand to permit a mechanistic speculation. It is believed that these results can be explained on the basis that the polymer forms a noncondensed netlike film over the crystal surface of sulfathiazole. This

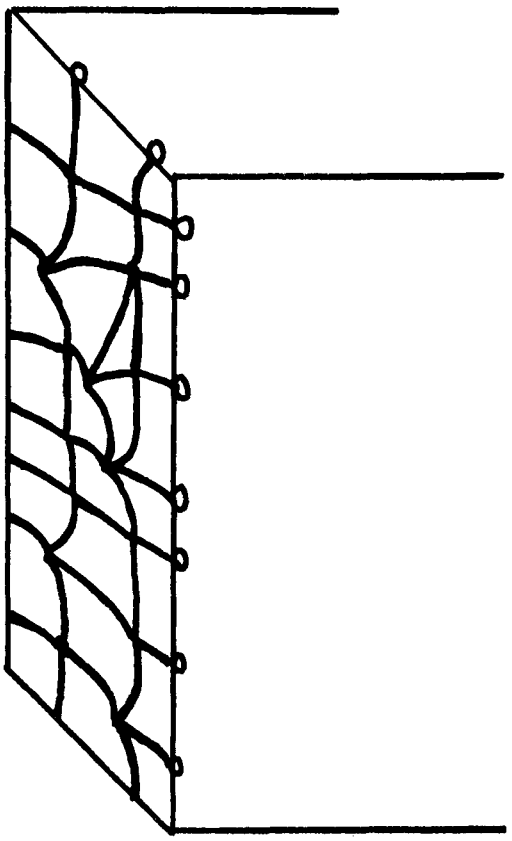


Figure 6—*Net inhibition model illustrating the inhibition by PVP on one surface of the crystal.*

is illustrated by Fig. 6. This model, of course, will permit the sulfathiazole to grow out through the openings of the net. In order to do so, however, the crystal will need to grow in fingerlike protrusions (Fig. 7). In addition the radii of these protrusions will be governed by the effective pore size of the polymer net. If this is true the curvature of these protrusions will require higher supersaturation ratios to grow, as can be shown using the Kelvin equation (12):

$$\ln \frac{P}{P_0} = \frac{2\gamma M}{RTdr} \qquad \text{(Eq. 8)}$$

where P = vapor pressure of a small drop or particle of radius r (~micron), P_0 = vapor pressure of a planar surface ($r \sim$ large), γ = interfacial tension or free energy of the crystal, M = molecular weight, d = density, R = gas constant, and T = absolute temperature.

In the case of a particle suspended in a saturated solution, it can be assumed that the ratio P/P_0 can be approximated by the ratio of the respective activities in the solution, a/a_0, where a is the activity of a small spherical particle and a_0 is the activity of a large particle. If activity coefficients of both particles are the same, the activities can be replaced by their respective solubilities. This ratio, however, defines the supersaturation ratio that a large crystal will be exposed to if placed in a solution which is saturated with respect to the small particle. This, of course, is the supersaturation ratio which has been utilized in all previous graphs, as the single crystal used in the previous experiments can be considered the equivalent of a large particle. As a result, Eq. 8 can be expressed by the following equation:

$$\ln S = \frac{2\gamma M}{RTdr_p} \qquad \text{(Eq. 9)}$$

where S is the supersaturation ratio (relative to the solubility of a large particle) of a solution in which a protrusion with a curvature that is equivalent to a particle of radius r_p will have equal probabilities of growth or dissolution.

Equation 9 shows that as the effective radius of a protrusion decreases, the protrusion will require a correspondingly larger supersaturation ratio before it will grow. This indicates that a netlike coverage of PVP that controls the effective radius of protrusions from the crystal surface can cause the crystal to require a higher supersaturation ratio than if it were absent in order for the crystal to grow. Furthermore, the tighter the net the smaller the effective radii of the resulting protrusions and the higher the minimum supersaturation ratio required for crystal growth to occur.

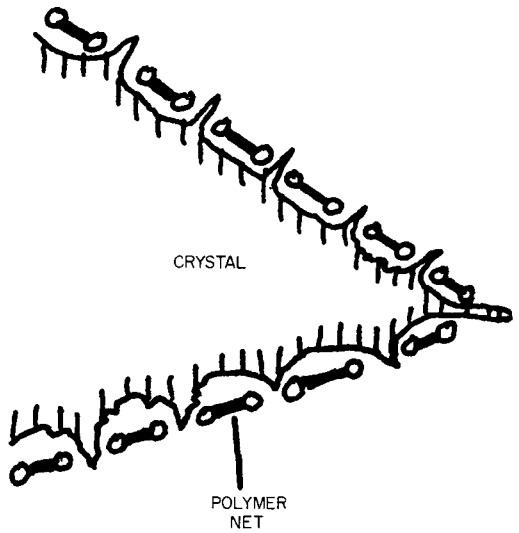


Figure 7—*Net inhibition model illustrating a cross section of the protrusions growing through the openings of a polymer net.*

This speculation can be combined with the kinetic diffusion model to describe a possible mechanism of inhibition by PVP of a sulfathiazole crystal exposed to its supersaturated solution. The experimental data previously presented in this study showed that the crystal growth inhibition of sulfathiazole by PVP is related to the relative transport rates to the crystal surface. This implies that the point of inhibition is related to the relative rates of deposition. The PVP reaching the surface forms a netlike structure (since complete coverage does not occur at the point of inhibition) which allows the sulfathiazole to grow out in fingerlike protrusions (suggested by fingerlike growth before the point of inhibition). Due to the higher curvature of these protrusions, however, the minimum supersaturation ratio for growth increases as shown by Eq. 9. This curvature, on the other hand, is determined by the effective pore size of the polymer net. The effective pore size of the net is determined by the relative PVP to sulfathiazole transport rate. Since the relative PVP to sulfathiazole transport rate governs the relative ratio of PVP and sulfathiazole deposited on the crystal surface, it follows that the higher the relative PVP rate, the smaller the effective pore size of the polymer net and the higher the supersaturation required for growth to be maintained. This model is consistent with all the data reported in this study.

REFERENCES

(1) T. J. Macek, U. S. pat. 2,671,750, Mar. 9, 1954.

(2) B. J. Magerlein and J. K. Dale, U. S. pat. 2,828,319, Mar. 25, 1958.

(3) *Ibid.*, U. S. pat. 2,841,599, July 1, 1958.

(4) H. Nogami and T. Nagai, *Yakkyoku*, **9**, 29(1958).

(5) J. Hasegawa and T. Nagai, *Chem. Pharm. Bull. (Tokyo)*, **6**, 129(1958).

(6) W. I. Higuchi and H. Y. Saad, *J. Pharm. Sci.*, **54**, 74(1965).

(7) H. Y. Saad and W. I. Higuchi, *ibid.*, **54**, 1205(1965).

(8) J. D. Mullins and T. J. Macek, *J. Amer. Pharm. Ass., Sci. Ed.*, **49**, 245(1960).

(9) J. K. Dale and S. L. Ross, U. S. pat. 2,861,920, Nov. 25, 1958.

(10) J. K. Dale and A. R. Hanze, U. S. pat. 3,062,712, Nov. 6, 1962.

(11) S. C. Mehta, P. D. Bernardo, W. I. Higuchi, and A. P. Simonelli, *J. Pharm. Sci.*, **59**, 638(1970).

(12) A. H. Goldberg and W. I. Higuchi, *ibid.*, **57**, 1583(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969, from the *College of Pharmacy, University of Michigan, Ann Arbor, MI 48104*

Accepted for publication September 10, 1969.

Presented in part to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Miami meeting, May 1968.

Supported by Contract PH 43-68-1284 with Chemotherapy, National Cancer Institute, National Institutes of Health.

The authors thank the reviewer for suggesting Table II.

Rate of Crystal Growth of Sulfathiazole and Methylprednisolone

S. C. MEHTA, P. D. BERNARDO*, W. I. HIGUCHI, and A. P. SIMONELLI

Abstract □ The results of crystal growth rate studies using single crystals of sulfathiazole and methylprednisolone are presented. The growth rate of sulfathiazole crystals growing in a supersaturated aqueous solution showed stirring rate dependence from 10 to 400 r.p.m. The same stirring rate dependence was found for all three faces studied. In alcohol solutions, however, the stirring rate dependence appeared to disappear above 150 r.p.m., suggesting that at the higher stirring rates the rate of crystal growth of sulfathiazole is surface controlled. A plot of the growth rate *versus* the supersaturation ratio appeared to be linear for all studies with intercepts exhibited on the supersaturation ratio axis. The intercept appeared to be a function of its solvent varying from 1.07 to 1.43 and to be a function of the polarity of the alcohol. The crystal growth rate of methylprednisolone, on the other hand, showed no stirring rate dependence in the range from 20 to 400 r.p.m. and appears to be surface controlled even at low stirring rates.

Keyphrases □ Crystal growth rates—single crystal method □ Sulfathiazole crystals—growth rate □ Methylprednisolone crystals—growth rate □ Stirring rate effect—crystal growth □ Refractive index—crystal axes determination

There are a number of situations where an understanding of the growth behavior of crystals may provide a basis for improving pharmaceutical formulations. Crystal growth in a suspension formulation, as a result of temperature fluctuations or Ostwald ripening, may lead to undesirable changes in its particle-size distribution. Such changes whether they affect the ease of administration, efficacy, or the esthetic appearance of suspensions constitute "physical instability." Investigations (1–5) of crystal growth behavior involving systems of pharmaceutical interest are relatively few. Furthermore, most of these studies have not been mechanistically oriented, *i.e.*, aimed at establishing the molecular mechanisms. Generally such studies have only answered the question of whether or not crystal growth occurs under the particular prevailing condition.

The present report describes the results of crystal growth studies involving the two drugs, sulfathiazole and methylprednisolone. A simple but convenient method to study crystal growth is described. The crystal growth rate data were obtained as a function of supersaturation, crystal orientation, and stirring rate and provided much insight as to the probable rate-determining processes governing crystal growth. Furthermore, this method is well suited for the screening and evaluation of potential crystal growth inhibitors.

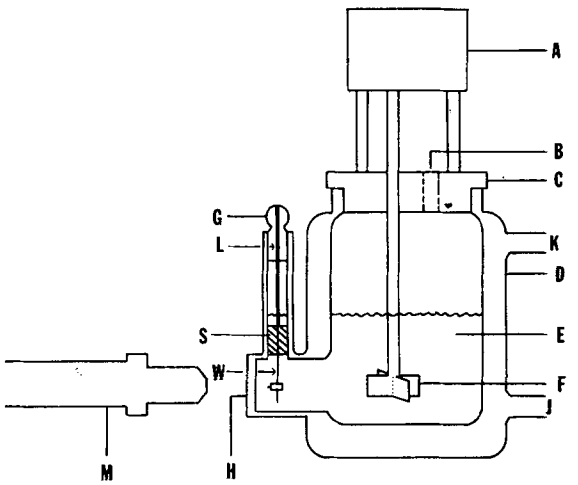


Figure 1—*Crystal growth apparatus. Key: A, synchronous motor; B, sampling port; C, Teflon lid; D, jacketed beaker; E, supersaturated solution; F, stirrer; G, glass stopper with a fused stainless steel rod (L); H, optical glass window; J, inlet for water (30°); K, outlet for water (30°); M, microscope; S, stainless steel coupling to hold removable crystal holder shown in Fig. 2; and W, tungsten wire holding crystal holder described in Fig. 2.*

GENERAL CONSIDERATIONS

Previous experiences have indicated the need to develop a technique utilizing a relatively convenient experimental system yet capable of providing much insight into the factors governing the rates of growth of crystals. Since the prime purposes of this study were the quantitation of crystal growth rates and the determination of the effect of various factors upon this growth, it was decided that a single crystal technique which measures linear growth rather than techniques which utilize gross volume changes should be employed. The single crystal technique is more reproducible and therefore more quantitative because of the following reasons:

1. Surface area is not important, as linear growth is a function of the chemical potential of the solution relative to the solid surface which can be expressed in terms of unit area. Furthermore, the