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# PHYSICAL-CHEMICAL FACTORS AFFECTING THE PREPARATION OF A COARSE SOLID DISPERSION BY CRYSTALLIZATION OF INDOMETHACIN FROM A METASTABLE SOLID SOLUTION

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## ABSTRACT

The extent of crystallization of indomethacin as a coarse solid dispersion from a metastable solid solution was determined by three methods. An apparent critical degree of supersaturation ($C_{ss}$) was indicated by the intersection of a bilinear plot obtained from growth rate constants measured on the surface. The crystal growth rate on the surface was found to be dependent on the degree of supersaturation, storage temperature, and presence of a nucleating agent. A rank order correlation was obtained between a visual and a dissolution method for determining the extent of crystallization. The effect of adding a nucleating agent (sodium chloride) on the extent of crystallization was determined with a color difference meter.

## INTRODUCTION

The use of solid solution technology is showing increased utility in the preparation of drug delivery systems. The difficulties involved in under-

standing and evaluating these systems have been well documented and continue to exist (1,2). Systems which form true solid solutions may be characterized by their phase diagrams using conventional techniques of thermal analysis (3) It is important to realize the systems being studied may be metastable and the time required for the establishment of equilibrium may or may not be substantial. As pointed out in a review by Chiou and Riegelman (4), the effect of aging or storage of solid solutions under various conditions has not been well studied in pharmaceutical systems.

Systems that show phase changes are difficult to follow by conventional analytical methods. In this study, an interesting system was found where a phase change from the non-crystalline to crystalline state could be followed easily with simple analytical methods. A description of these methods and how they were used to monitor a phase change in a typical pharmaceutical system is presented here. The effect of several physical-chemical factors that influence the preparation of a coarse solid dispersion by crystallization of indomethacin from a metastable solid solution is discussed. A coarse dispersion is defined here as having a particle size greater than 0.5 microns (5). A solid solution is defined here as any solid system where one component is dispersed at the molecular level within another component (2).

## EXPERIMENTAL

Composition and Method of Preparation - The components and concentration ranges that were used in this study are shown in Table I. In all experiments, a standard procedure was employed; polyethylene glycol 4000 and 6000 were melted at 65-70°C. After reducing the melt temperature to 60-65°C, indomethacin was added and dissolved with high-speed agitation in the melt. Glycerin (and, where applicable, a nucleating agent) was

TABLE I

COMPONENTS AND RANGES USED IN STUDY

| Component | Range |
|---|---|
| Indomethacin[1] | 0.81-17.0% |
| Sodium Chloride USP | 0-3.22% |
| P.E.G. 4000[2]/P.E.G. 6000[2]/Glycerin USP; Ratio 10:1:1 (solution phase) | q.s. ad.100% |

[1]Merck & Co., Inc., Rahway, New Jersey.
[2]USP.

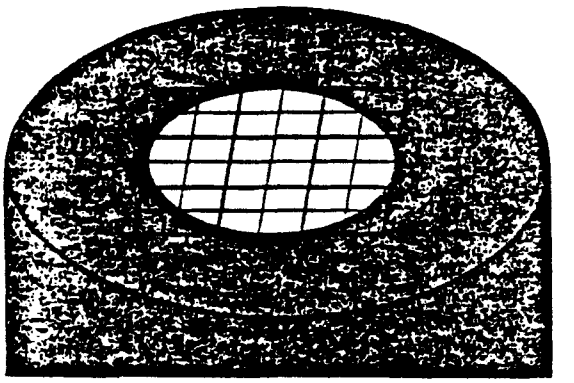
added and finally both temperature and agitation were reduced (6,7). The mixture was held at 55-60°C with slow-speed stirring to prevent the incorporation of air during subdivision. The melt was poured into plastic or metal cylindrical molds (each holding about two grams and having an exposed surface area of 0.71 $cm^2$) and allowed to solidify at room temperature. After congealing, the filled molds were transferred to air-tight glass jars, placed in a refrigerator (4-6°C) for 24 hours to induce nucleation of the indomethacin, and then stored at various controlled temperature stations (ranging from 5-50°C) for observation of crystal growth.

Determination of Extent of Crystallization - The extent of crystallization was determined by three different methods: a simple visual technique, a dissolution method described in an earlier publication (2), and a color meter measuring technique.

A simple visual method was found to have the advantage of rapidly determining the extent of crystallization. It was possible to apply it to the systems studied here only because of an apparent sharp distinction between the non-crystalline and crystalline state. When using this method, the term

zero percent crystallization is defined as the translucent yellow or amber surface appearance of the solid solution immediately after congealing. The term one hundred percent crystallization is defined as the white opaque surface appearance of the mass after its entire surface area under observation has apparently crystallized completely. Between these two extremes of the defined zero and one hundred percent crystallization, the area percent of crystallization was estimated by visual means using an overlapping transparent grid system to differentiate between the non-crystalline and crystalline areas. Figure 1 shows a diagramatic sketch of how this was accomplished.

As a further aid in determining the extent of crystallization, particularly during the early phases of growth, a portable ultraviolet lamp[1] was utilized in examining the samples to observe indomethacin crystals. Under ultraviolet light, indomethacin crystals fluoresce and appear white against



DIAGRAMATIC SKETCH OF CRYSTALLIZATION

FIG 1

[1] Mineralight USVL-13, Ultraviolet Products, Inc., San Gabriel, California.

a dark yellow background. This method was especially useful for observing initial small point sites of crystallization as they occurred on the surface.

The dissolution method and apparatus (2) reported on previously were also used here to check the validity of the visual technique described above. Dissolution rates were measured from controlled surface areas of these systems in 7.2 pH phosphate buffer (0.01M) at 25°C. Four filled dies were used only once for each determination; subsequent determinations used another set of four filled dies. The amount of indomethacin dissolved was determined spectrophotometrically as a function of time. Dissolution rates were obtained as absorbance units and transformed to mg. dissolved per ml. per minute (mg. $ml.^{-1}$ $min.^{-1}$) for plotting purposes. The initial linear portion of the plot showing the amount of drug dissolved versus time was used for calculation of dissolution rates. The disadvantage of this method is the time required for a single determination.

When using this dissolution method, the term zero percent crystallization is defined as the dissolution rate of the yellow translucent solid solution immediately after congealing. As crystallization progresses, the dissolution rate slowly decreases. The term one hundred percent crystallization is defined as the dissolution rate of the white opaque crystallized solid solution after no further reduction occurs in the dissolution rate. Typical dissolution rates for samples showing zero percent and one hundred percent crystallization are shown in Figure 2.

A color meter measuring technique was found to provide an accurate and rapid method for measuring the extent of crystallization. The samples of melt were poured into round plastic petri dishes[1] (48 mm. x 8.5 mm containing about 18 g. and having an exposed surface area of 18.1 $cm^2$) and allowed

[1] Millipore Corporation, Bedford, Massachusetts 01730, Cat. No. PD 1004700.

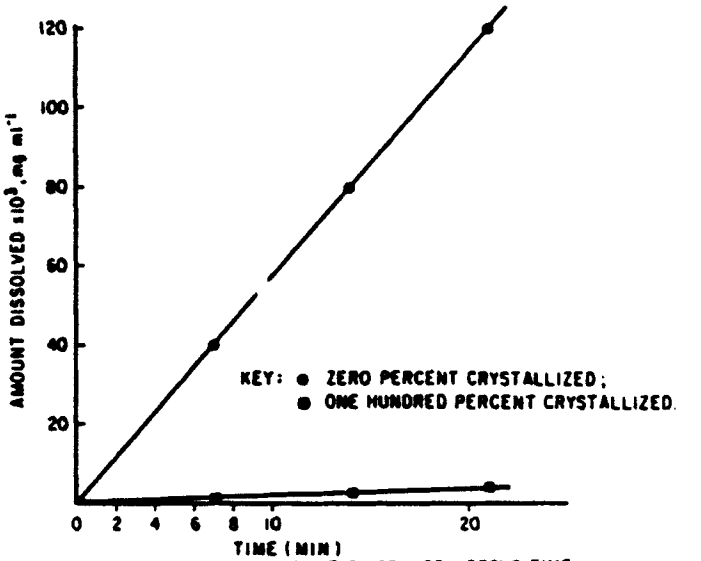



FIGURE 2-PLOT OF AMOUNT DISSOLVED VERSUS TIME

to congeal at room temperature (23°C). After congealing, the filled petri dishes were covered and placed in air-tight glass jars, placed in a refrigerator (4-6°C) for 24 hours, and then stored at temperature stations ranging from 5-50°C for observation of crystal growth.

A photoelectric color difference meter[1] was employed to measure the color values of samples freshly congealed and after storage at various temperature stations. The color value measurements are read directly as units of the L, a, and b color scales. The L scale measures the luminosity and represents a mathematical approximation of a non-linear black-white response of the eye; the a and b scales measure the chromaticity differences in the red-green and yellow-blue components, respectively. A measure of total color difference, Δ E, was calculated from the equation

$$\Delta E = \sqrt{(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2}$$

[1] HunterLab Color Difference Meter Model D25, manufactured by Hunter Associates Laboratory, Inc., 9529 Lee Highway, Fairfax, Virginia 22030.

and was used to plot the rate change of color in the sample. The use of the ΔE unit will be discussed in a subsequent section.

When using this color meter method, the term zero percent crystallization is defined as a total color difference ( Δ E) of zero, or the initial reading of the yellow translucent solid solution immediately after congealing. As crystallization progresses, the color difference ( ΔE) slowly increases. The term one hundred percent crystallization is defined as the color difference of the white opaque crystallized solid solution after no further increase occurs in this value.

*Effect of Indomethacin Concentration on Crystallization Rate* - Various levels of indomethacin were added to the polyethylene glycol 4000/polyethylene glycol 6000/glycerin mixture according to the method of preparation described. Concentrations of indomethacin ranged from 0.81% to 17.0%, the maximum solubility in the molten solvent mixture. After congealing, the samples were refrigerated overnight, then stored at 30°C as indicated in the experimental section, and examined periodically by either ultraviolet or visual observation to estimate the percent of surface area that appeared crystallized.

Effect of Sodium Chloride Concentration on Crystallization Rate - During screening tests for evaluating various additives that could act as effective nucleating agents, it was found that sodium chloride had a significant effect on the crystallization rate in this system. To assess the effect of its concentration, sodium chloride was reduced in particle size using air-attrition milling equipment[1] and screened into the desired fraction. The average particle size as estimated by microscopic examination was about 10 microns, and the particle shape was essentially spherical.

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[1] Jet-O-Mizer, Fluid Energy Processing & Equipment Co., Model 0101, Philadelphia, Pa.

## RESULTS AND DISCUSSION

Growth Rate Dependency on Indomethacin Concentration - The effect of indomethacin concentration on the crystal growth rate occurring on the surface of samples stored at 30°C was determined by visual observation and is shown in Figure 3. The data were plotted as the log of percent uncrystallized (i.e., percent remaining in solid solution) as the ordinate and time in days as the abscissa. The most rapid growth rate was achieved for the system containing 17.0% indomethacin (the maximum amount soluble in the melt) where complete crystallization on the surface occurred within six

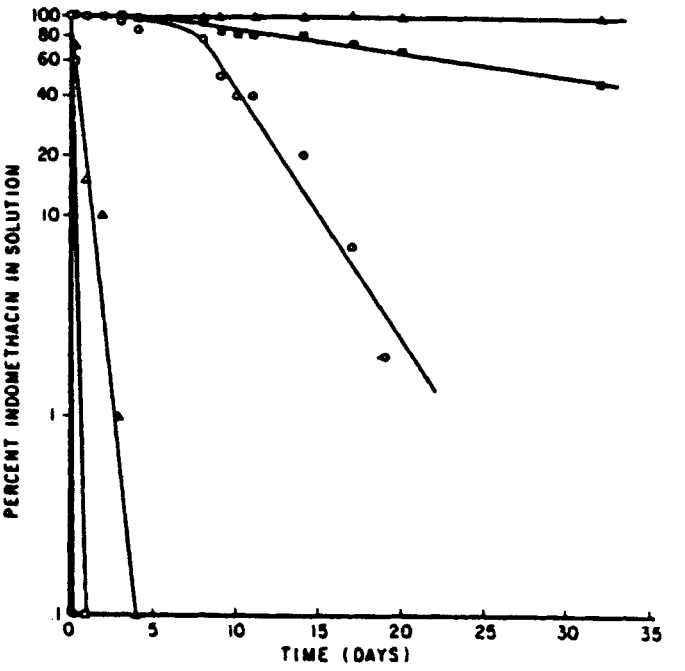


FIGURE 3 - PLOT OF LOG PERCENT INDOMETHACIN IN SOLUTION AS A FUNCTION OF TIME (DAYS)

KEY: ● 17.00%; ◘ 12.88%; △ 6.44%;
○ 3.22%; ■ 1.61%; ▲ 0.81%.

hours. These observations showed the crystallization growth rate decreased concomitantly as the indomethacin concentration was decreased. Figure 3 shows area growth rates approximate first-order growth kinetics following an induction or nucleation period, except for the solutions containing 6.44%, 12.88%, and 17.0% indomethacin because their nucleation and growth rates were so rapid. Crystallization zones were barely detectable at the lowest concentration (0.81%). Here, use of the ultraviolet light was especially useful. Observation of samples that did not completely crystallize after 32 days was discontinued.

In addition, Figure 3 also shows that the surface appeared completely crystallized within eight days for indomethacin concentration of 6.4% or higher. Solutions with an indomethacin concentration of 3.2% or lower, produced surfaces that did not crystallize completely within the observation period.

Apparent first-order growth rate constants were calculated for each of the systems using first-order kinetics where $C_0$ is defined as zero percent crystallized and $C_t$ is defined as the area percent crystallized at any time (t).

Only the linear portion of the plot for each system was used for these calculations; the induction times were ignored. Figure 4 shows the apparent area growth rate constant increases exponentially with increasing concentration. The resulting plot consists of two linear regions with two distinct slopes, $m_1$ and $m_2$. The line with slope $m_1$ shows the growth rate constants are proportional to concentrations up to slightly higher than 3.2% indomethacin where a change in slope begins to occur. The line with slope $m_2$ shows that some other parameter(s) may be affecting the increase in growth rate constants for indomethacin concentrations greater than 6.4%.

Several factors could cause this change in slope from $m_1$ to $m_2$. One possible factor is the degree of supersaturation in these systems. Indomethacin concentrations on the line with slope $m_1$ failed to crystallize completely within eight days. A critical point (or range on either side of this point) is identified in Figure 4 as $C_{ss}$; i.e., an apparent critical supersaturation concentration which is about 3.7% in this system, based on the extrapolation of the two linear regions.

Growth Rate Dependency on Temperature and a Comparison of Visual vs. Dissolution Methods for Determining the Extent of Crystallization - The effect of temperature on the surface crystal growth rate of a system containing 6.4% indomethacin was investigated using both a visual and a dissolution method on the same samples to determine the extent of crystallization. The data are plotted in Figure 5 as log K vs. reciprocal temperature in degrees Kelvin. The apparent first-order growth rate constants for the visual method were calculated using the same procedure described earlier in this report. The apparent first-order growth rate constants for the dissolution method were calculated from a plot of the log mg $ml^{-1}$ $min.^{-1}$ of indomethacin dissolved as the ordinate versus time in days as the abscissa for samples stored at each of the temperatures indicated. The initial dissolution rate for this system at zero percent crystallization was about $5.8 \times 10^{-3}$ mg $ml^{-1}$ $min.^{-1}$ and at an apparent 100 percent crystallization was about $0.2 \times 10^{-3}$ mg $ml^{-1}$ $min.^{-1}$. Both of these values compare favorably with a similar system studied earlier (2). Again, only the linear portion of the plots for each sample were used for these calculations.

The data show the most rapid growth rate was achieved at about 37°C using either method to determine the extent of crystallization. As the storage temperature was reduced, the apparent growth rates were also reduced. It is interesting to note that both plots are essentially linear

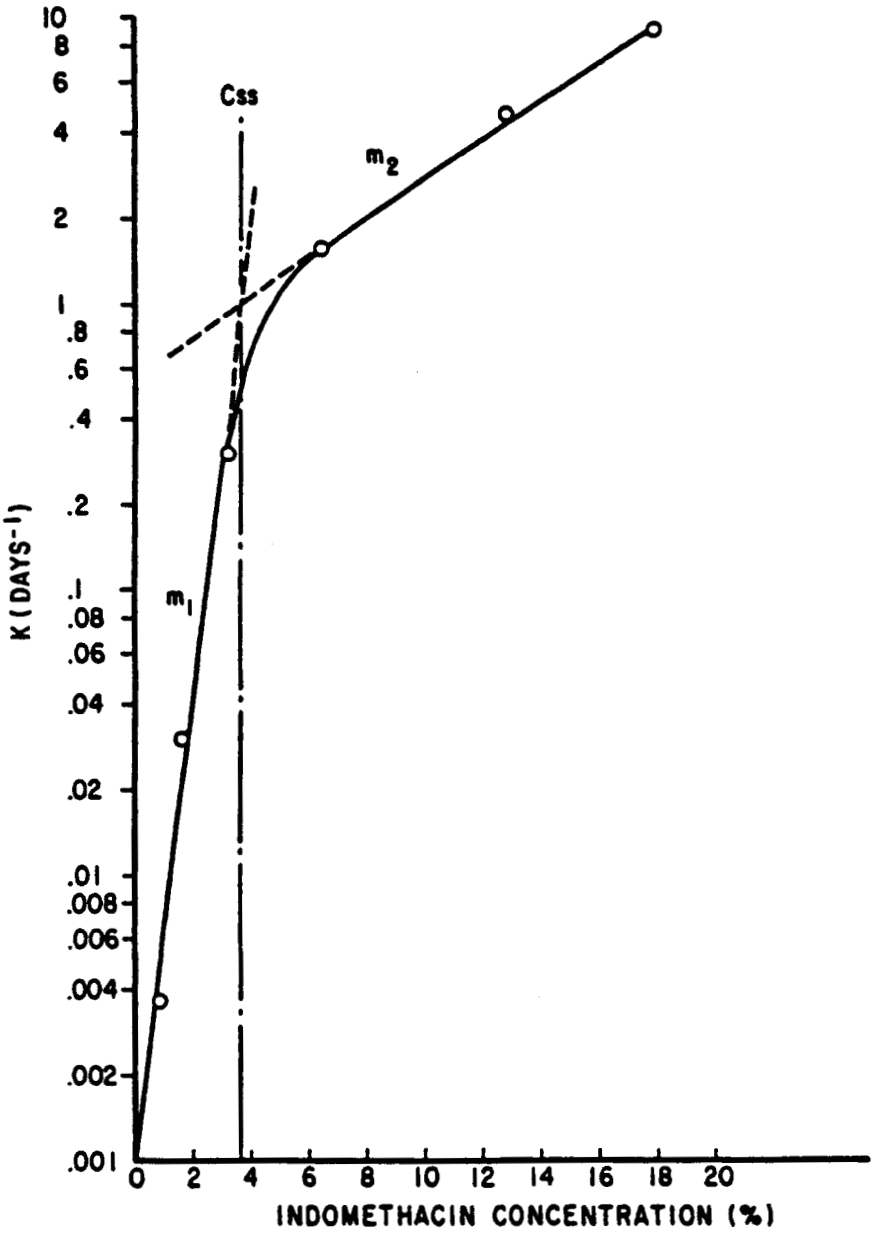


FIGURE 4 - PLOT OF LOG CRYSTALLIZATION RATE CONSTANT AS A FUNCTION OF INDOMETHACIN CONCENTRATION

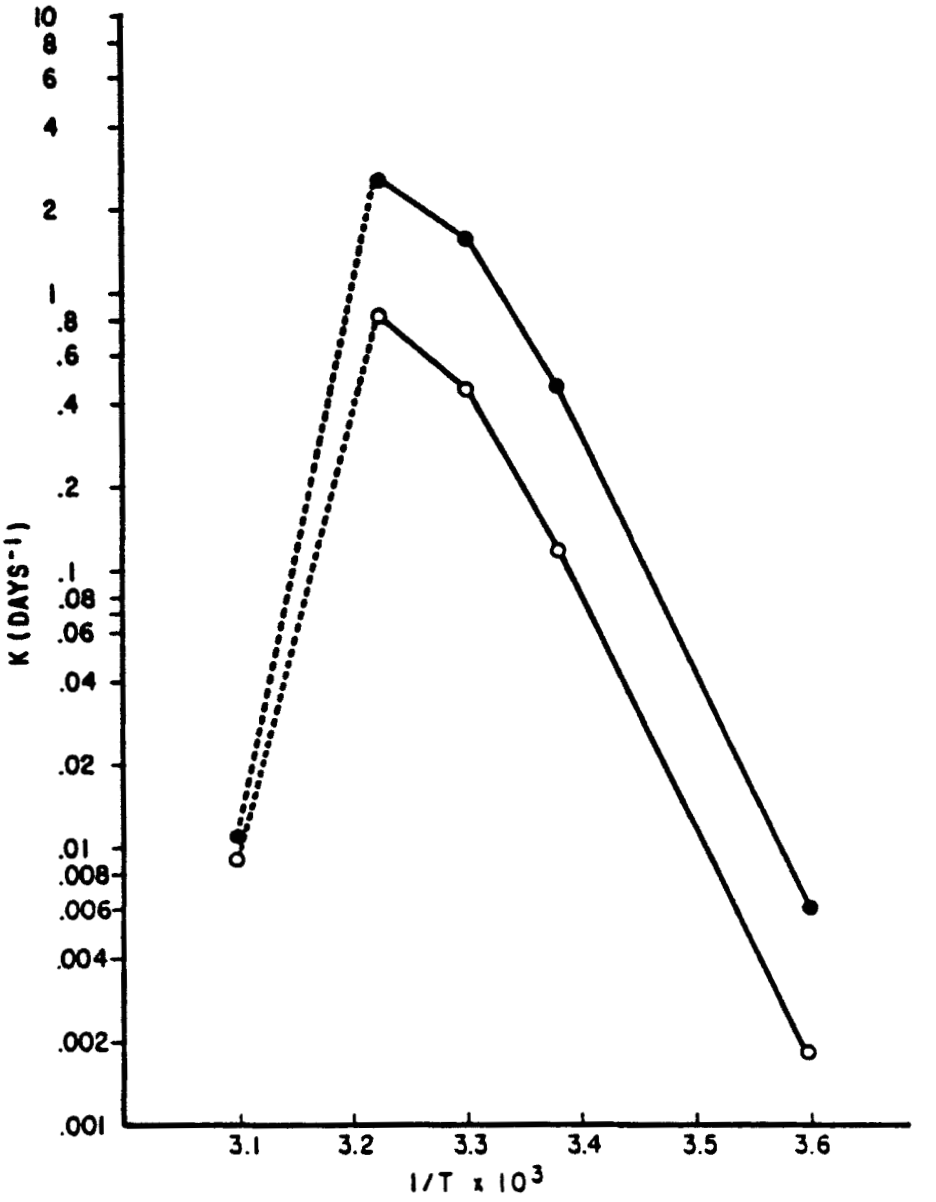


FIGURE 5 - PLOT OF LOG CRYSTALLIZATION RATE CONSTANT AS A FUNCTION OF TEMPERATURE

KEY: ● VISUAL METHOD; ○ DISSOLUTION METHOD

between 5°C and 30°C. As the storage temperature approaches 37°C, the increase in growth rate slows down and is very slow again at 50°C. This latter effect is attributed to an increase in the equilibrium solubility of indomethacin in this system as the temperature approaches its melting point.

Another interesting observation is that the linear portions of the plots between any two storage temperatures over the range of 5°C to 37°C are essentially parallel when the two methods are compared. The plot for the visual method is obviously higher as evidenced by the higher apparent growth rate constants. It would be highly unlikely that these two methods would provide identical rate constants, but the observation that they are essentially parallel indicates that a visual method, when compared to a more discriminating quantitative method such as dissolution, can provide a rank order correlation in determining the extent of crystallization.

Growth Rate Dependency on a System Containing Sodium Chloride and Use of a Color Meter Method for Determining the Extent of Crystallization - As indicated earlier, the addition of sodium chloride during screening tests was found to have a significant effect on the surface crystal growth rate. An indomethacin concentration below the apparent critical supersaturation concentration ($C_{ss}$) was selected for further investigation. The solute concentration was maintained at a constant level of 3.22% and the sodium chloride concentration was also held constant at the same 3.22% level. The effect of temperature on the extent of crystallization in this system was determined by using a color difference meter.

The data are plotted in Figure 6 as a color difference value ($\Delta E$) versus time in days. Figure 6 shows that each temperature had a different

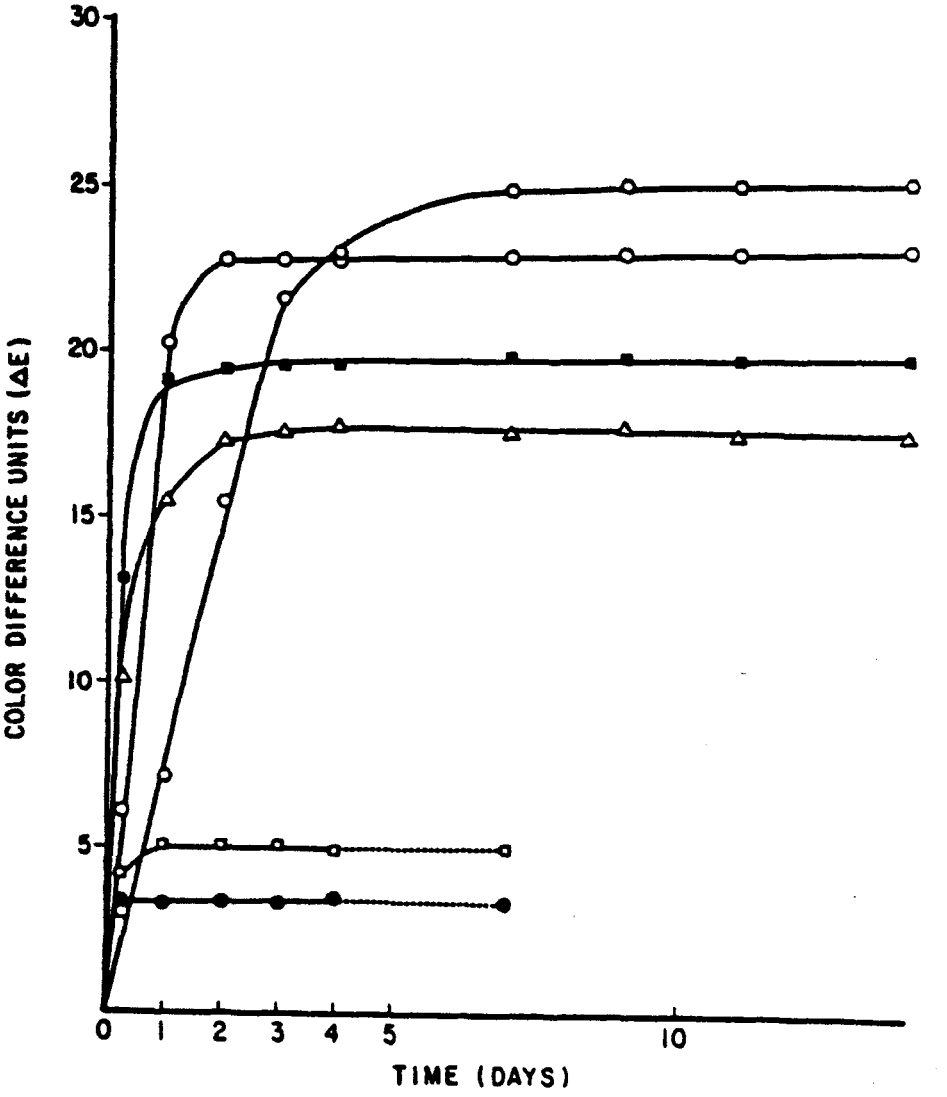


FIGURE 6 - PLOT OF THE COLOR DIFFERENCE UNITS (ΔE) AS A FUNCTION OF TIME (DAYS)

KEY: ○ 23°C; ○ 30°C; ● 40°C; △ 45°C; □ 50°C; ● 5°C.

effect on the extent and rate of crystallization. As defined in the experimental section, one hundred percent crystallization is the maximum color difference value (Δ E) obtained when no further changes occur. The data as plotted show the maximum extent of crystallization appears to occur at 23°C while the least amount of crystallization occurred at 5°C. As the storage temperature increases to 45°C, the extent of crystallization slowly decreases and then falls precipitiously at 50°. Again, this latter effect can be attributed to an increase in the equilibrium solubility of indomethacin in this system as the temperature approaches its melting point. The overall temperature effect can be seen more clearly in Figure 7 where the maximum color difference after seven days is plotted versus storage temperature.

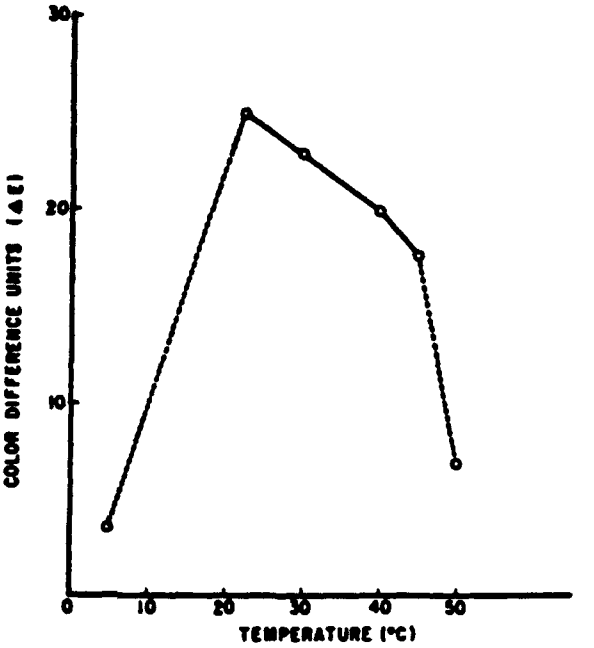


FIGURE 7 - PLOT OF THE MAXIMUM COLOR DIFFERENCE UNITS (ΔE) AS A FUNCTION OF TEMPERATURE AFTER SEVEN DAYS

The same data from Figure 6 are plotted again in Figure 8 as log percent indomethacin remaining in solution versus time in days. For this plot, one hundred percent indomethacin in solution is defined as a color difference reading of zero, and zero percent indomethacin in solution is defined as the maximum color difference reading obtained after no further changes occurred at the storage temperature being observed. The overall temperature effect is basically the same, but this procedure was followed to normalize the rate of crystallization. The apparent first order growth rate constants were calculated from the initial linear portions of the plots for each of the temperatures indicated. The plots are essentially the same as those shown in Figure 3, even though the composition of this system is different. The data show the most rapid apparent growth rate was achieved at about 40°C using this method to determine the extent of crystallization.

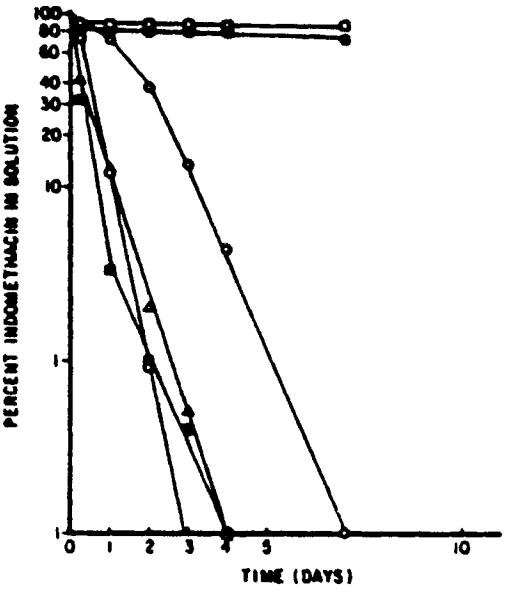


FIGURE 8 - PLOT OF LOG PERCENT INDOMETHACIN IN SOLUTION AS A FUNCTION OF TIME (DAYS)

KEY: ○ 23°C; ○ 30°C; □ 5°C; ● 50°C; ▲ 45°C; ■ 40°C.

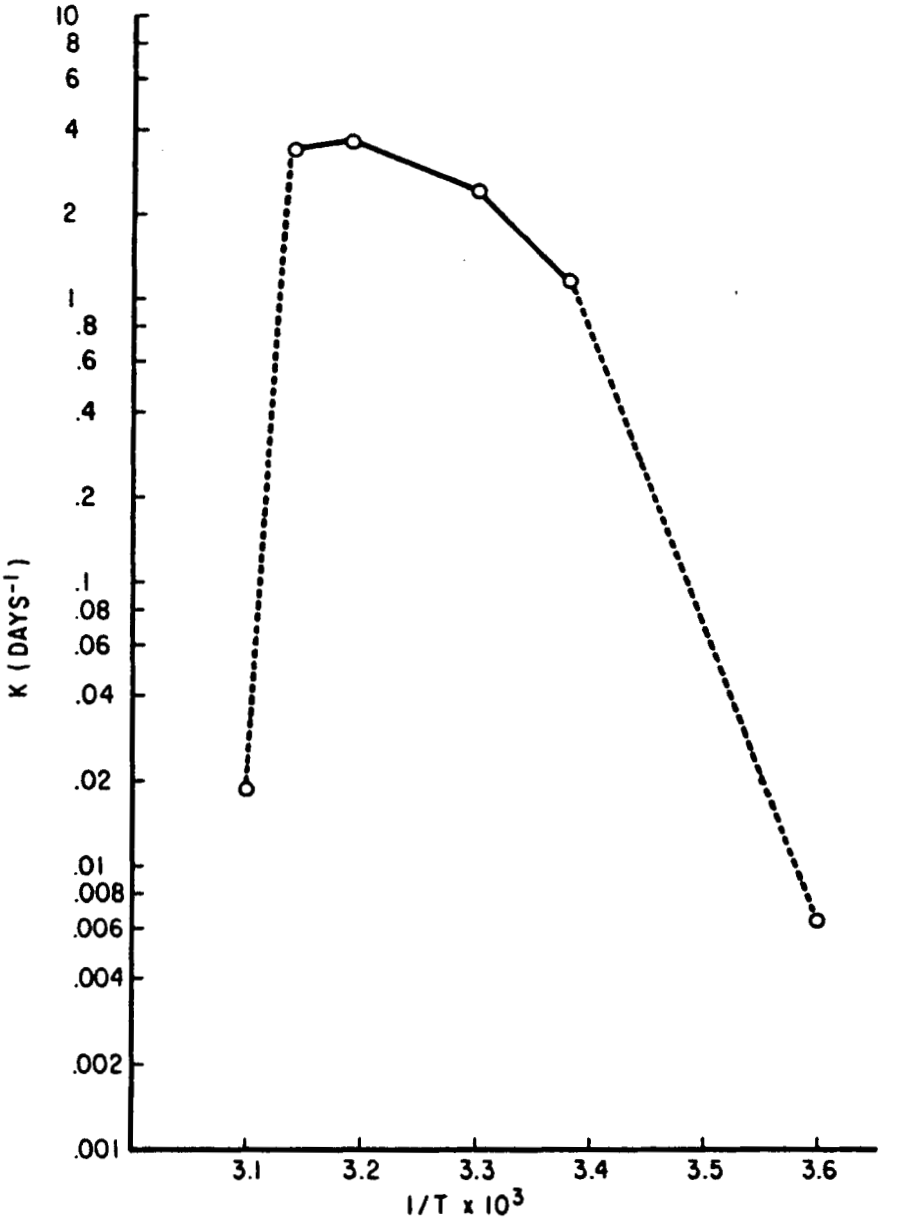


FIGURE 9- PLOT OF LOG CRYSTALLIZATION RATE CONSTANT AS A FUNCTION OF TEMPERATURE

The total temperature effect can be seen more clearly in Figure 9 where log K is plotted versus reciprocal temperature in degrees Kelvin. As the storage temperature increases, the increase in the growth rate slows down until a maximum rate is achieved at about 40°C. At 45°C, the rate tapers off and is very slow again at 50°C. This latter effect is again attributed to an increase in the equilibrium solubility of indomethacin as the temperature of this system approaches its melting point.



## ACKNOWLEDGEMENTS

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