Mechanism of Crystallization of Hydrocortisone by Ultrasonic Irradiation

By STANLEY L. HEM*, DONALD M. SKAUEN, and HAROLD M. BEAL

Reproducible, reduced crystal size distributions resulted from insonating a supersaturated solution, whose background particle count is controlled, at a fixed temperature. The crystallization temperature of the insonated and uninsonated samples was dependent on the number of heterogeneous nuclei present. The ultrasonic energy used in this study was in excess of the amount required to reduce the particle size. Ultrasound acted in the initial phase of crystallization. Ultrasound is believed to act by eroding, shattering, or in some way disrupting nuclei that form in a normal manner.

Ultrasound has been effective in reducing the particle size of a large number of substances. It is surprising to note the many theories which have been suggested to explain the action of ultrasound in producing small, uniform crystals. The simplest suggestion, that the reduction in particle size is due to agitation, has been rejected by several authors (1, 2).

Experimentation on supercooled Wood's metal (3, 4) led to the conclusion that friction between the solid and the melt is responsible for the reduction in grain size. It has been generalized that the increased crystallization rate of metals is due to an increased number of crystallization centers as a result of ultrasonic scattering of the microcrystals forming in the melt (5). Ultrasound may increase the number of crystal nuclei by shattering or eroding the nuclei that occur in a normal manner (6, 7). A number of reports have concluded that ultrasound accelerates the process of spontaneous crystallization and plays an essential role in the formation of nuclei (8). Brown (9) and Mazhul (10, 11) have stated that cavitation bubbles themselves act as nuclei for the crystals to initially form around.

The increased crystallization velocity of supercooled benzophenone was attributed to the localized removal of heat at the phase boundaries (12).

Evaporation from the surface of the cavitation bubble during cavity growth may cause sufficient cooling to initiate nucleation (13).

The large pressures which occur after the collapse of the cavitation cavity may cause a sufficient change in melting point to cause nucleation (14).

The effect of ultrasound was hypothesized to be analogous to an increase in the supersaturation of the solution (15).

Thus, it has been established that ultrasonic treatment during a phase change can improve the product in terms of an increased rate of crystallization and a smaller, more uniform size distribution. At present no clear understanding of the mechanism of ultrasonic crystallization is available.

EXPERIMENTAL

Cohn's (16) investigation of the factors involved in the ultrasonic crystallization of hydrocortisone was chosen as a foundation for this study. The conditions in terms of solvent, degree of supersaturation, and treatment temperature that were reported to yield the smallest particle size were used. Thus, a saturated solution of hydrocortisone in ethanol was prepared at 65°.

The solubility curve for hydrocortisone in ethanol has been reported by Cohn (17). The pertinent values for this study are given in Table I.

Table I.—Solubility of Hydrocortisone in Ethanol

Temp., °C.	Concn., mg./ml.
65	63.1
55	42.3
50	36.2
45	31.5
40	25.4
35	21.5
30	17.7
25	15.4

The solution was filtered while at 65° through either a 0.45-μ membrane filter or a Whatman No. 42 filter paper which was also maintained at 65°. A 10-ml. sample of the saturated solution was transferred by a warm pipet to the treatment vessel and covered. The solution was permitted to cool from 65° to the bath temperature.

The Sonifier, model S-125,[1] provided the ultrasonic energy. It is a high-intensity piezoelectric type source with a frequency of 20 Kc./sec.

The geometry of the treatment vessel and the Sonifier tip was the same as reported by Cohn (16). The Sonifier tip was positioned 2.3 mm. from

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[1] Branson Sonic Power Co., Danbury, Conn.

the bottom of the 20-ml. beaker. The Sonifier, model S-125, has a fully transistorized power supply; no warm-up time was required as power was available immediately. This enabled treatment times of 5 sec. to be employed. Weissler's (18) method for measuring relative cavitation intensity confirmed that this geometry provided maximum ultrasonic effects.

Weissler's (18) method for measuring relative cavitation intensity was used to calibrate the Sonifier to permit operation at several intensities. The method is based on the sonochemical liberation of chlorine from carbon tetrachloride dissolved in water. *o*-Tolidine was reacted with the liberated chlorine and yielded a yellow color suitable for colorimetry. The absorbance at 436 mμ wavelength is linear with respect to the chlorine concentration. Various ultrasonic intensities were defined by plotting the absorbance against time. The slope of the straight line was used to designate a particular intensity. Calibration curves for the 3 cavitation levels used in this study are given in Fig. 1.

Weissler's (18) method requires measurement in an aqueous system. The addition of small amounts of such chemicals as petroleum ether, ethyl ether, and ethanol completely block the sonochemical decomposition of carbon tetrachloride. It has been suggested that these substances have a protective action on the solution. They have high vapor pressures and are thought to penetrate the cavitation bubble and interfere with the electronic effects associated with cavitation (19). It has also been suggested that the presence of organic liquids reduces the thermal conductivity of the gas-filled bubbles. This may reduce the thermal reactions occurring in the cavity. The possibility exists that the presence of these compounds causes a change in the decomposition products of carbon tetrachloride (20).

The crystallizations in this study were carried out in ethanol. Cavitation depends upon the surface tension, viscosity, density, vapor pressure, cohesive strength, and heat transfer of the liquid (21). At a fixed setting the amount of cavitation in an aqueous solution will differ from the amount in an alcoholic solution. The linear nature of the absorbance *versus* time plot would indicate a fairly simple, direct relationship among these solvent variables. Thus, it can be assumed that the relative cavitation levels in an aqueous solution will be directly related to the relative cavitation levels in an alcoholic solution.

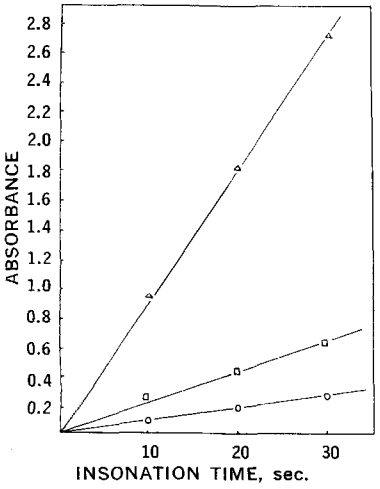

Fig. 1.—Calibration curves for measuring relative cavitation intensity. Key: △, 120 v., setting 8; □, 120 v., setting 2; ○, 100 v., setting 2.

The measurement of cavitation has been one of the major problems in ultrasonic research. There is no other satisfactory method available for measuring cavitation. Previous to Weissler's method it was impossible to accurately calibrate an instrument or monitor its day to day operation. In view of these conditions it was felt that this assumption was justified.

At a line voltage of 120 v. and a power level setting of 8 (maximum for the Sonifier), Weissler's (18) method gave a slope of 0.090. A line voltage of 120 v. and a power level setting of 2 gave a slope of 0.021. A slope of 0.009 was obtained at a line voltage of 100 v. and a power level setting of 2. These calibration curves are shown in Fig. 1.

These intensity levels are in the approximate ratio of 10:2:1. Although the cavitation levels were different in ethanol, it was assumed that these settings would also give ultrasonic intensities in ethanolic solutions in the ratio of 10:2:1.

The collection of a sample of crystals for evaluation was performed by vacuum filtration using a 0.20-μ membrane filter. Only a small sample of crystals was required for size analysis by the Coulter counter.[2] It was possible to obtain the necessary sample by quickly removing the mother liquor from 1 ml. or less of the crystallization suspension.

Particle size distributions were determined using a Coulter counter with a 70-μ aperture tube. It was found that an aqueous electrolyte of 0.9% sodium chloride saturated with hydrocortisone was suitable. The crystal sample was dispersed with 1 drop of 2% methylcellulose 400[3] prior to analysis. Enough sample was added to the counting vessel to give between 10,000 and 20,000 counts per 500 μl.

The particle size distributions were found to follow the log-normal distribution law. The geometric mean, $\overline{M}g$, the most appropriate measure of central tendency for log-normal systems, and the geometric standard deviation, σg, were used to characterize the results of the crystallizations. As these values are based on the measurement of 10,000 to 20,000 individual crystals, they are the best estimates available of the population mean and the population standard deviation for each case (22–24).

Two series of experiments were performed. In the first a saturated solution was prepared at 65°. The solution was filtered through a 0.45-μ membrane filter or Whatman No. 42 filter paper and transferred to the treatment vessel. A series was also performed on the unfiltered supernatant. Preparation of the solution, then filtering a portion through a membrane filter or filter paper was done to vary the number of heterogeneous particles present in the saturated solution. This was confirmed by the Coulter counter data in Table III.

[2] Coulter Electronics, Hialeah, Fla.
[3] Marketed as Methocel 400 by the Dow Chemical Co., Midland, Mich.

The 65° saturated solution was allowed to stand undisturbed for 2 hr., and then 10 ml. of supernatant was transferred by pipet to the treatment vessel. The Sonifier was positioned, and the solution was covered. A number of treatment bath temperatures were used varying from 55 to 30° in 5° intervals. The solution was examined 60 min. after reaching thermal equilibrium. A visual observation for the presence or absence of crystals was performed. This procedure was repeated with the application of ultrasound to the clear solution after thermal equilibrium in the treatment bath had been reached. Ultrasonic energy was applied for 1 min. at relative cavitation levels of 10 and 1. Each solution was visually examined after 1 hr. for the presence of crystals. These results are contained in Table II.

In order to evaluate the number of particles in the saturated solution before treatment, a particle count was run with the Coulter counter. Because the Coulter counter requires a conductive solution it was impossible to perform a background count on the alcoholic solutions. An aqueous 0.9% sodium chloride solution was saturated with hydrocortisone at room temperature. The clear supernatant was either taken as the sample or the solution was filtered through 0.45-μ membrane filter or Whatman No. 42 filter paper. The particle size distribution of each of these solutions was then determined by Coulter counter analysis. They are listed in Table III. The results were taken as approximations of the number of potential heterogeneous nuclei present in the crystallization solution.

TABLE II.—OCCURRENCE OF CRYSTALLIZATION IN FILTERED SOLUTIONS

Treatment Temp., °C.	Unfiltered Soln.			Whatman No. 42 Filter Paper			0.45-μ Membrane Filter		
	No US[a]	1[b]	10[b]	No US[a]	1[b]	10[b]	No US[a]	1[b]	10[b]
55	+	+	+	−	−	−	−	−	−
50	+	+	+	−	−	−	−	−	−
45	+	+	+	−	−	−	−	−	−
40	+	+	+	+	+	+	−	−	−
35	+	+	+	+	+	+	+	+	+
30	+	+	+	+	+	+	+	+	+

[a] No ultrasound applied. [b] Relative cavitation intensity.

TABLE III.—COULTER COUNTER ANALYSIS OF SATURATED SOLUTIONS AFTER FILTRATION

D(diam.), μ	No. of Particles Larger than D in 0.5 ml. of Saturated Soln. After Indicated Treatment: Unfiltered Supernatant	Whatman No. 42 Filter Paper	0.45-μ Membrane Filter
1.25	78,000	31,000	250
2.00	28,000	7,500	62
3.00	12,000	2,500	18
5.00	3,700	700	5
6.00	2,000	350	—
8.00	800	150	—
10.00	300	100	—
12.00	140	35	—
14.00	100	30	—
16.00	40	22	—
18.00	21	14	—
20.00	8	4	—

TABLE IV.—PARTICLE SIZE DISTRIBUTIONS OBTAINED AT 35°

Insonation Time, sec.	Relative Cavitation Intensity 1: $\bar{M}g$	σg	2: $\bar{M}g$	σg	10: $\bar{M}g$	σg
60	4.7 μ	2.5	4.7 μ	2.5	4.9 μ	2.3
15	4.7 μ	2.4	4.9 μ	2.2	5.1 μ	2.3
5	4.8 μ	2.4	4.7 μ	2.6	4.9 μ	3.1

Control: $\bar{M}g$ 9.5 μ, σg 2.8

TABLE V.—PARTICLE SIZE DISTRIBUTIONS OBTAINED AT 25°

Insonation Time, sec.	Relative Cavitation Intensity 1: $\bar{M}g$	σg	2: $\bar{M}g$	σg	10: $\bar{M}g$	σg
60	4.7 μ	2.5	4.6 μ	2.3	4.6 μ	2.3
15	4.4 μ	2.4	4.5 μ	2.4	4.3 μ	2.4
5	4.6 μ	2.3	4.6 μ	2.3	4.3 μ	2.4

Control: $\bar{M}g$ 9.2 μ, σg 2.7

The second experiment examined the effect of ultrasonic intensity on the crystal size distributions. A saturated solution was prepared at 65°, filtered through a 0.45-μ membrane filter, and brought to thermal equilibrium in either a 25 or 35° water bath. Thirty-five degrees was chosen as one treatment temperature because this was the highest temperature at which crystals developed after filtration through a 0.45-μ membrane filter. The solution was clear to the eye at this point. It was then treated with ultrasound at a relative cavitation intensity of either 10, 2, or 1 for 60, 15, or 5 sec. The crystals were collected and their size distributions determined with the Coulter counter. The crystal size distributions are shown in Tables IV and V.

RESULTS AND DISCUSSION

The results of the crystallizations from filtered solutions are given in Table II. Table III lists the Coulter counter analysis of these solutions. The number of particles in the solution prior to treatment represents contamination by foreign material contained in either the hydrocortisone or the ethanol, or originating from the glassware. Undissolved hydrocortisone may also contribute to the total particle count.

It was observed that the crystallization temperature of the untreated samples decreased as the number of particles in the saturated solution was reduced. This behavior is in agreement with the heterogeneous nucleation theory.

Heterogeneous nucleation refers to nucleation which occurs on particles which are present in the solution. Filtration would remove some of these potential nucleation sites and cause a reduction in the temperature at which crystals appear. A similar observation has been reported by Melia and Moffitt (25).

Heterogeneous nucleation can be better understood by comparing it with homogeneous nucleation. In supersaturated solutions there is continual formation and dissolution of molecular clusters of

solute (26). The Becker-Doring theory (26, 27) and the Christiansen-Nielsen theory (27) view this as a series of bimolecular collisions. These clusters may continue to grow by collision or may shrink due to the loss of individual molecules. When the cluster reaches a point where the tendency to dissociate is balanced by the tendency to grow (in order to decrease surface free energy) it is termed a critical nucleus. The size of the critical cluster is unknown but it is thought to be several hundred molecules for most solids (27, 28). The tendency to grow is dominant once a cluster is larger than the critical nucleus. Nucleation followed by crystal growth then proceeds.

The energy barrier to nucleation may be reduced by the catalytic effect of foreign particles in the solution. The presence of these substrates for the critical nucleus permit nucleation to occur more readily (26, 29).

The activation energy of heterogeneous nucleation, $\Delta G_{het.}$, can be related to the activation energy of homogeneous nucleation, $\Delta G_{hom.}$ An equation (26) has been derived for the nucleation of vapor drops on surfaces in terms of the contact angle, θ.

$$\Delta G_{het.} = \frac{\Delta G_{hom.}\,(2 + \cos\theta)(1 - \cos\theta)^2}{4}$$

It is seen from the equation that $\Delta G_{het.}$ will always be smaller than $\Delta G_{hom.}$ If heterogeneous nucleation is possible it will cause crystallization to occur more readily than homogeneous nucleation. In most cases crystallization will be complete before homogeneous mechanisms have begun.

It was observed that ultrasound did not cause crystallization to occur at any temperature above the crystallization temperature of the untreated samples. This temperature was dependent on the number of particles present in the solution prior to insonation. The behavior of the insonated samples is in agreement with the heterogeneous nucleation theory. There is no indication that ultrasound initiates crystallization. It only affected solutions at or below their normal crystallization temperatures.

The particle size distributions obtained at 35° with varying cavitation intensities and treatment times are given in Table IV. The results of similar experiments at 25° are given in Table V. These results were obtained by Coulter counter analysis. This instrument proved very suitable for characterizing particle size distributions. A number of problems were encountered in calibrating the instrument, finding a suitable electrolyte, obtaining complete dispersion of the crystal cake, and developing an adequate technique. However, the advantages in terms of number of particles counted, reproducibility, and speed would recommend this technique for future particle size studies.

The particle size distributions show virtually no difference for treatment times ranging from 5 to 60 sec. Cohn (17) reported that treatment times of 1 to 15 min. showed no effect on particle size. This indicates that ultrasound acts at an early stage in the crystallization process, and that continued insonation has no effect.

Little change was noted in the particle size distribution when varying relative cavitation intensities were used. An excess of energy was available for this application.

Based on this study the following mechanism of ultrasonic crystallization is visualized. A cavitation bubble collapses with great force in the proximity of a nucleus or a growing crystallite. The high pressure generated is sufficient to erode, shatter, or in some way disrupt the small particle or crystallite. This results in the formation of new nuclei. These nuclei may grow into crystals or may be further dispersed by cavitation. The net effect is a great multiplication in the number of nuclei in the supersaturated solution. This results in reduced crystal size and an increased rate of crystallization. Ultrasound does not initiate nuclei but acts on nuclei which normally appear in the solution.

SUMMARY AND CONCLUSIONS

1. Crystal size was reduced by the application of ultrasound to a supersaturated solution of hydrocortisone in ethanol.

2. Reproducible distributions resulted from insonating a supersaturated solution, whose background particle count is controlled, at a fixed temperature.

3. The crystallization temperature of the supersaturated solution was observed to depend on the number of heterogeneous nuclei present.

4. Ultrasound did not initiate crystallization above the crystallization temperature of the untreated supersaturated solution.

5. Ultrasound acts in the initial phase of crystallization. The size distributions obtained after 5-sec. insonation compared favorably with those obtained after 60-sec. insonation.

6. The ultrasonic energy used in this study was in excess of the amount required to reduce the particle size.

7. Ultrasound is believed to act by eroding, shattering, or in some way disrupting nuclei that form in a normal manner. This effect increased the number of crystal nuclei and resulted in reduced particle size.

8. The Coulter counter was adapted for measuring the hydrocortisone crystals. The advantages of this technique in terms of number of particles counted, reproducibility, and speed would recommend it for future particle size studies.

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Variability of Uniformity of Weight Test as an Indicator of the Amount of Active Ingredient in Tablets

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Fifty-four samples, embracing five drugs sold as compressed tablets, were obtained. Individual tablet weights were determined and individual chemical assays were carried out on 10 tablets from each sample. There was little or no relationship between the amount of active ingredient and tablet weight for promazine tablets in which the active ingredient formed a small proportion (15–23 per cent) of tablet weight, but this relationship was high for tolbutamide tablets in which the active ingredient formed a large proportion (73–90 per cent) of tablet weight. This observation suggests that the uniformity of weight test may sometimes be usefully employed instead of individual tablet chemical assays when the proportion of active ingredient in the tablets is high and that the emphasis in developing direct measures of content uniformity should be placed on preparations containing small proportions of active ingredient. The present data do not confirm the observation of Moskalyk *et al.* (1961) that "Greater deviations 'in active ingredient' were found to occur in lighter weight tablets" within preparations.

THE UNIFORMITY of weight test has been included in the "British Pharmacopoeia," the "United States Pharmacopeia," and the "National Formulary" for many years. Its purpose has been to provide an indication of the amount of active ingredient in each tablet. The validity of such a test depends, of course, on the assumption that the amount of active ingredient is directly proportional to the weight of the tablet. While various aspects of the uniformity of weight test have been studied previously (see for example *References 1–3*), general recognition of its inadequacy in certain situations has only recently been recognized. The 17th revision of the U.S.P. and the 12th edition of the N.F. included for the first time a content uniformity test for certain tablets. While determinations of the amount of active ingredient in individual tablets will be necessary for some preparations, there seems little point in taking these more costly observations in cases where the uniformity of weight test gives comparable results. It is the purpose of this paper to present some data which suggest that the uniformity of weight test may be satisfactory for some tablet preparations, but inadequate for others.

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MATERIALS AND METHODS

Samples of five drugs sold in compressed tablet form were procured from Canadian retail outlets in bottles of 100 tablets. A total of 54 samples from 36 different companies were obtained. In general, not more than one sample of each drug was obtained from each company, and in fact 53 of the possible 180 company-compound combinations are represented.