Importance of Viscosity in the Dissolution Rate of Cholesterol in Monooctanoin Solutions

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Abstract □ Several factors affecting the dissolution rate of cholesterol in monooctanoin were investigated. This solvent is used clinically for dissolution of residual cholesterol gallstones in the bile duct after cholecystectomy. The effect of added water on dissolution rate, measured using the static- or rotating-disk methods, was not consistent with the previously measured solubility. The discrepancy was found to be due to the decreasing viscosity of the solvent as water was added. Addition of cholesterol, however, increased the viscosity of monooctanoin. The viscosity effect on dissolution rate was investigated further by addition of polymers (povidone and poloxamer 237) which increased solvent viscosity. Dissolution rate was proportional to viscosity to the −0.4 power with these polymers. An equation was derived which predicts that dissolution rate should be proportional to viscosity to the $-\frac{2}{3}$ power. The predicted exponent was very close to reported experimental values for benzoic acid, but the dissolution rate/viscosity relationship for cholesterol in aqueous monooctanoin was nonlinear with apparent exponents of −0.65 to −2.3. Although the Arrhenius activation energies for viscosity (3.79 kcal/mol) and dissolution rate constant (3.66 kcal/mol) were almost equal for benzoic acid, a nonlinear relationship was again observed for cholesterol in aqueous monooctanoin with approximate E_a values of 5.6 10 kcal/mol. The strong influence of viscosity on dissolution rate in this system is attributed to the viscosity-increasing effect of cholesterol in the diffusion layer. The increased viscosity at higher cholesterol concentrations reduces the diffusion coefficient of cholesterol and causes the dissolution rate to be slower even though solubility may have been higher. The data suggest that it may be possible to increase cholesterol gallstone dissolution by addition of water to monooctanoin.

Keyphrases □ Cholesterol dissolution—monooctanoin, viscosity, effect of water addition □ Monooctanoin—cholesterol (gallstone) dissolution, viscosity, effect of water addition □ Viscosity—monooctanoin, cholesterol (gallstone) dissolution, effect of water addition

Monooctanoin (glyceryl monooctanoate) is being used clinically for dissolution of common bile duct cholesterol gallstones (1, 2). The solvent is infused into the bile duct through an abdominal T-tube drain inserted after cholecystectomy. Although cholesterol has high solubility in monooctanoin, most clinical studies indicate that infusion for 1–2 weeks is necessary for gallstone dissolution.

In a previous communication, the solubility of cholesterol in monooctanoin was found to be dependent on the water content of the solvent (3). With addition of water the solubility increased and then decreased with a maximum occurring at 5% water (37°C). The solubility maximum was coincident with the transition of solid cholesterol from the anhydrous to monohydrate form. Since the clinical efficacy of the solvent is primarily dependent on the dissolution rate of cholesterol, the effect of water and other factors influencing cholesterol dissolution rate in monooctanoin were investigated.

THEORETICAL SECTION

The simple Nernst diffusion layer theory is adequate for most dissolution rate studies. The dissolution rate is assumed to be proportional to the concentration gradient across an unstirred diffusion layer on the solid surface:

$$J = DA/h(C_s - C_b) \qquad \text{(Eq. 1)}$$

where J is the dissolution rate, A is the surface area of dissolving solid, D is the diffusivity of solute, C_s is the solubility of solute, C_b is the concentration of solute in bulk solution, and h is the effective diffusion layer thickness. This equation is often used with the static-pellet method for comparative dissolution rate determinations because it assumes that the dissolution rate is only affected by diffusional processes and that the factors in Eq. 1, other than solubility, are constant (4).

When diffusion and convection are both important, the Levich equation applies for a rotating dissolving disk (5):

$$J = 0.62AD^{2/3}/\nu^{1/6} \cdot \omega^{1/2}C_s \qquad \text{(Eq. 2)}$$

where ν is the kinematic viscosity and ω is the angular velocity of rotation. Since the parameters in Eq. 2 can be independently determined, the calculated dissolution rate may be compared with experimental data. Upon combination of these equations, the effective diffusion layer thickness for the rotating disk is obtained:

$$h = 1.6D^{1/2}\nu^{1/4}/\omega^{1/2} \qquad \text{(Eq. 3)}$$

EXPERIMENTAL SECTION

Dissolution Rate—Dissolution of cholesterol monohydrate from a rotating disk was measured using an apparatus similar to that reported previously (6), consisting of a synchronous motor and stirring assembly in a water-jacketed beaker. The sample was compressed in a 1.27-cm diameter die with a load of 3180 kg[1], and the die was attached to a plate on the end of the stirring shaft using cyanoacrylate glue[2] (the die was later removed by soaking the assembly in acetone). The rotation speed was changed using synchronous motors from 60–600 rpm[3]. In the static disk studies the die/disk was placed facing upward on the bottom of the beaker, and the solution was stirred at 150 rpm. To simulate the conditions of gallstone dissolution *in vivo*, 0.5-g cholesterol disks were accurately weighed and placed in screw-capped test tubes containing 40 g of solvent. The samples were left undisturbed at 37°C for 24 h and the residual cholesterol was determined gravimetrically after removing excess solvent by blotting with tissue.

Analysis—Cholesterol was analyzed by HPLC using a modification of a literature procedure (7) using an acetonitrile–methanol (5:1) mobile phase, a reverse-phase column[4], and a variable-wavelength detector at 215 nm. Dissolution samples were diluted with mobile phase and injected directly on the system. Benzoic acid was analyzed spectrophotometrically at 229 nm in 0.01 M HCl.

Water in cholesterol monohydrate and dissolution media was determined by automated Karl Fischer titrimetry[5]. Viscosity was measured using a cone-plate viscometer[6] with a circulator bath for temperature control. Cholesterol solubility was determined as previously described (3).

Fractionation of Monooctanoin—The mono- and diglyceride fractions of commercial monooctanoin were separated by column chromatography on silica gel. The diglyceride fraction was eluted with ethyl acetate–hexane (1:1) and the monoglyceride fraction was then displaced with ethyl acetate. The purity of the fractions was checked by TLC (1:1 ethyl acetate–hexane on precoated silica gel plates) and the solvent was removed by rotary evaporation. The monoglyceride melted at 36°C, and the diglyceride was an oil. The samples contained <0.5% water.

Materials—Cholesterol USP[7], monooctanoin[8], and glyceryl monolaurate[9] were obtained commercially. The ~30% diglyceride content in monooctanoin reported by the manufacturer was consistent with the column chromatography yields. Solvents were HPLC grade, and the other chemicals were reagent grade.

Cholesterol monohydrate was prepared by recrystallization from 10% aqueous acetone. The wet crystals, after filtration, were air-dried for ~1 h

[1] Fred S. Carver Inc.
[2] Krazy Glue Inc.
[3] Hurst Mfg. Co.
[4] μBondapak C_{18}, Waters Associates.
[5] Auto-aquatrator; Precision Scientific.
[6] Ferranti-Shirley, Ferranti Ltd.
[7] Sigma Chemical Co.
[8] Capmul 8210; Stokeley-Van Camp Inc.
[9] Kessco 675; Armak Industrial Chemicals.

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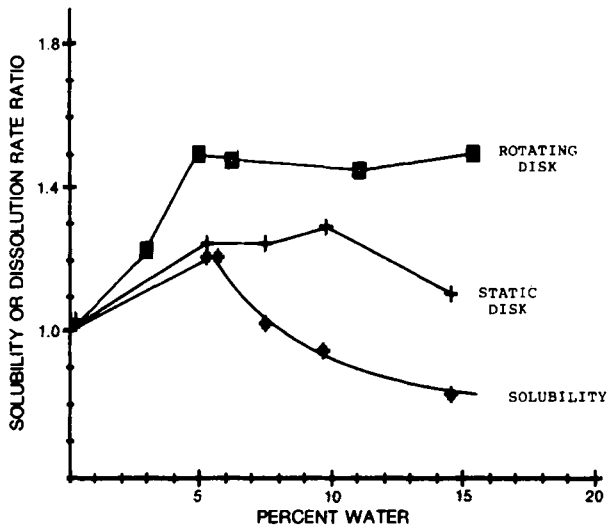

Figure 1—*Ratio of the solubilities and dissolution rates of cholesterol in aqueous monooctanoin solutions to the values in the dry solvent (37°C). Dissolution rates were measured at 150 rpm. Solubility data was taken from Ref. 3.*

and then stored in a chamber containing water. The water content of the crystals was equal to theory for a monohydrate (4.4% water). Although 95% ethanol has been widely used for preparing the monohydrate, problems were encountered in removing the residual ethanol when using this solvent. This may be due to the formation of a hemiethanol solvate (8). The vacuum drying required to remove ethanol also removed the water of hydration, so the sample was rehydrated in the water chamber. The water of hydration was quite labile. After a few hours in an open container, the water content of cholesterol monohydrate decreased to ~1%.

RESULTS AND DISCUSSION

Static-Disk Studies—Dissolution rate measurements by the static-disk method were conducted. In Fig. 1 the relative dissolution rate and solubility of cholesterol in monooctanoin solutions is plotted as a function of the water content of the solvent. At this stirring rate, there was poor agreement between the previously determined solubilities and the static-disk dissolution data. The difference was most apparent at >5% water where the dissolution rate did not decrease along with the solubility. The dissolution rate determined in the dry solvent (4.7×10^{-3} mg cm^{-2} s^{-1}) was in good agreement with the value of 4×10^{-3} reported by Thistle *et al.* (1).

Other data corroborated the poor correlation between solubility and dissolution rate. Table I shows the effect of sodium chloride on solubility and dissolution rate in 5% aqueous monooctanoin. A mixture of 0.9–2.5% aqueous NaCl with monooctanoin increased cholesterol solubility, presumably by inducing association of cholesterol with itself or the nonpolar fatty acid chains of the glycerides. As before, however, the solubility increase did not cause a corresponding change in the dissolution rate. The viscosity of the solutions was not affected by sodium chloride. Cholesterol solubility increased with addition of longer-chain glycerides. When monooctanoin was mixed with an equal amount of glyceryl monolaurate and 5% water, cholesterol solubility increased from 16.1 to 23%, whereas the dissolution rate was essentially unchanged. These data clearly show that the direct proportionality between solubility and dissolution rate expected from the Nernst equation is not being followed in this system.

Rotating-Disk Studies—Because of the uncertainty of the static-disk method with regard to hydrodynamic conditions in this system, the effect of water was redetermined using the rotating disk at 150 rpm (Fig. 1, upper

Table I—Effect of Salt on Cholesterol Solubility and Dissolution Rate (Static-Disk Method)

NaCl in Aqueous Component of 5% Monooctanoin, %	Viscosity, cP	Solubility, %	10^3 Dissolution Rate, mg cm^{-2} s^{-1}
0	37	16.1	5.7
0.9	37	18.0	5.6
1.8	38	19.1	5.5
2.5	37	18.2	5.8

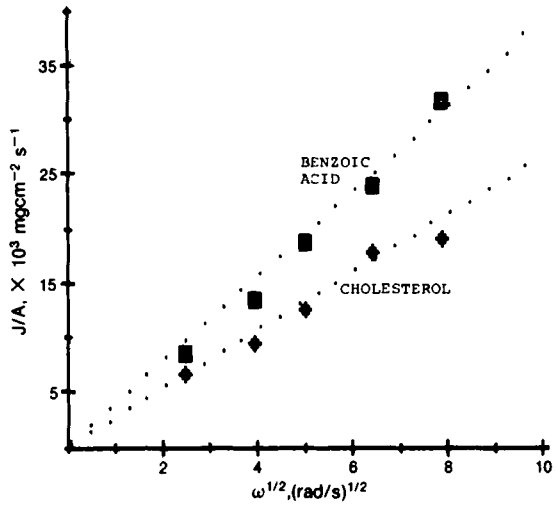

Figure 2—*Levich plots of the dissolution rate* versus *(rotation speed)*$^{1/2}$ *at 37°C for cholesterol in 10% aqueous monooctanoin and benzoic acid in 0.01 M HCl. Dotted lines were calculated using Eq. 2.*

curve). The dissolution rate and solubility data diverged still further, with an almost constant 50% increase in dissolution rate at >5% water.

The dissolution apparatus was calibrated using benzoic acid in 0.01 M HCl at 37°C. Under these conditions the dissolution rate is diffusion controlled (6). In addition, the diffusion coefficient and solubility of benzoic acid in 0.01 M HCl have been reported (4), allowing calculation of the dissolution rate according to Eq. 2. The theoretical line in Fig. 2 is in excellent agreement with the experimental data for benzoic acid.

Also shown in Fig. 2 is the dissolution rate of cholesterol in aqueous monooctanoin. The diffusion coefficient of cholesterol in the solvent was estimated to be 1.53×10^{-7} cm^2 s^{-1} using the Stokes-Einstein equation (see Eq. 4 below). With this and the other constants of Eq. 2, the theoretical line for cholesterol in Fig. 2 was calculated and found to be in good agreement with the experimental data. It may, therefore, be concluded that the dissolution rate of cholesterol under the conditions studied is a diffusion-convection-controlled process according to Eq. 2.

Effect of Water and Cholesterol on the Viscosity of Monooctanoin—During preparation of the dissolution media the viscosity of monooctanoin appeared to be reduced by the addition of water. These observations were confirmed by measuring the viscosities with a cone-plate viscometer (Fig. 3). The viscosity-lowering effect of water is generally observed with glycerol and glycols and has been attributed to the breaking of solvent-solvent hydrogen bonds by addition of water (9, 10). These data are important since viscosity changes could be an explanation for the anomalous dissolution rate results. The decreasing viscosity could be counteracting the lower cholesterol solubility, causing the dissolution rate at >5% water to be essentially constant.

Addition of cholesterol had the opposite effect on the viscosity of monooc-

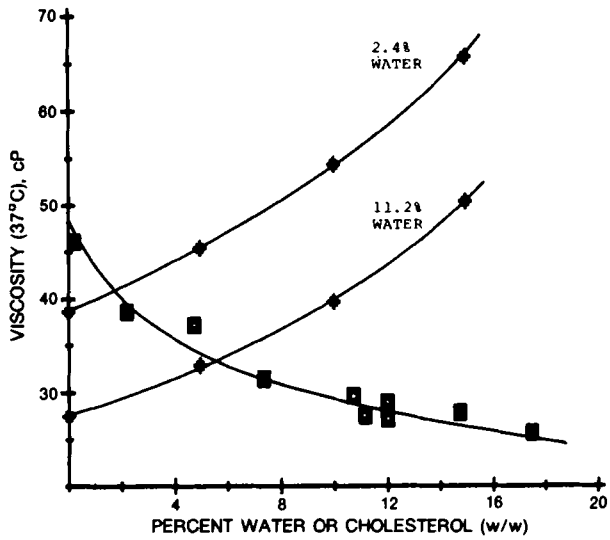

Figure 3—*Effects of water (■) and cholesterol (◆) on the viscosity of monooctanoin at 37°C.*

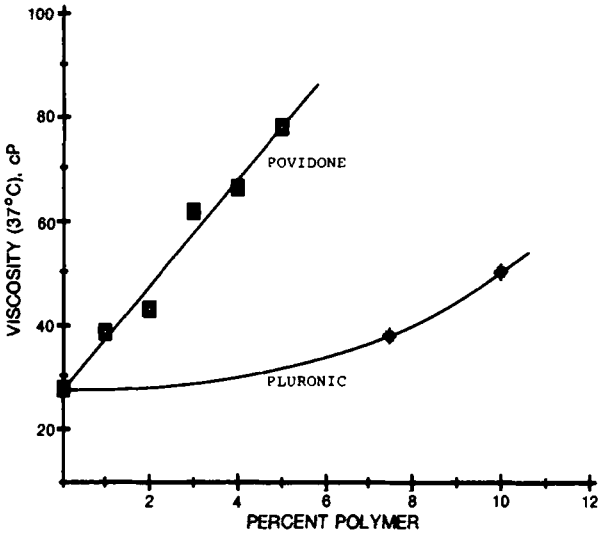

Figure 4—*Viscosity of 10% aqueous monooctanoin as a function of polymer concentration at 37°C.*

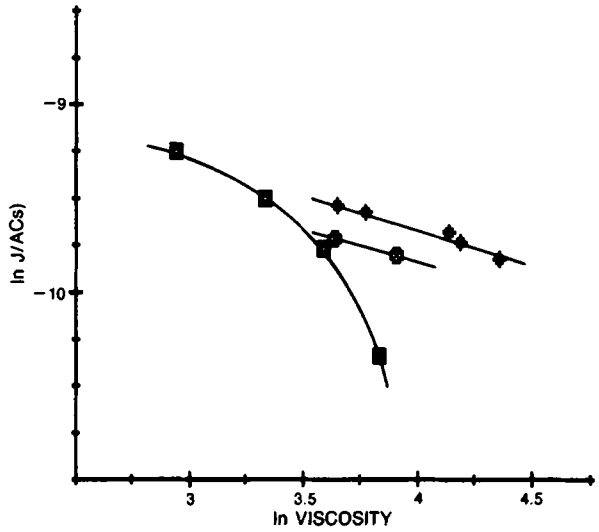

Figure 5—*Log-log plot of the dissolution rate constant* versus *the viscosity of the dissolution medium according to Eq. 5A. Key: (■) 10% aqueous monooctanoin at different temperatures; (◆) povidone in 10% aqueous monooctanoin (37°C); (◆) Poloxamer 237 in 10% aqueous monooctanoin (37°C).*

tanoin (Fig. 3). In addition, the upward curvature indicated a greater than first-order dependence on cholesterol concentration. The similarity of the two curves showed that the amount of water present had little effect on the viscosity-inducing properties of cholesterol. Since the higher concentrations in Fig. 3 are similar to the solubility of cholesterol in the dissolution experiments, the diffusion layer during dissolution must be significantly more viscous than the bulk solution. This implies also that a viscosity gradient must be present across the diffusion layer. Although it is probably not rigorously applicable to this system, the Stokes-Einstein equation predicts an inverse relationship between the diffusion coefficient and viscosity:

$$D = kT/(6\pi\eta r) \qquad \text{(Eq. 4)}$$

where k is the Boltzmann constant, T is the absolute temperature, η is the viscosity, and r is the radius of the molecule.

Viscosity Effects on Dissolution Rate—Two independent approaches were investigated for probing the effect of viscosity on dissolution rate: addition of polymers and temperature effects. The former approach has been extensively investigated in aqueous systems (11-13). In aqueous polymer solutions the exponential relationship betweeen dissolution rate and viscosity usually lies between −0.25 and −0.8 (11). The exponent was dependent on the experimental system, polymer, and dissolving solute. This specificity was proposed to be due to the difference between the measured bulk solution viscosity and the effective viscosity (resistance to solute diffusion), which controls the dissolution rate (12). In a recent study, several equations for the diffusion coefficient in polymer solutions were compared for their ability to represent benzoic acid dissolution (13). None was found to be significantly better than Eq. 4 and the average viscosity exponent was −0.62 (13).

Rearrangement of Eq. 2 gives the dissolution rate constant:

$$J/(AC_s = 0.62\nu^{-1/6}\omega^{1/2}D^{2/3} \qquad \text{(Eq. 2a)}$$

By substituting D from Eq. 4, the hypothetical effect of viscosity on dissolution rate is obtained:

$$J/(AC_s) = 0.62\nu^{-1/6}\omega^{1/2}(kT/(6\pi r))^{2/3}\eta^{-2/3} \qquad \text{(Eq. 5)}$$

$$= k'\eta^{-2/3} \qquad \text{(Eq. 5a)}$$

where $k' = 0.62\nu^{-1/6}\omega^{1/2}(kT/(6\pi r))^{2/3}$.

At constant temperature the terms of k' should be constant except for $\nu^{-1/6}$. This term, however, is almost constant over the range of viscosity usually studied. For example, a 50% increase in viscosity would change this term by only −6.5%. Equation 5 predicts that J/AC_s should be proportional to viscosity to the $-2/3$ power. This predicted value is quite similar to that experimentally determined (11-13), although previous investigators have apparently not considered this simple relationship.

In preliminary studies several polymers were screened for their effects on cholesterol solubility and monooctanoin viscosity. Povidone K-30 and poloxamer 237 were chosen because viscosity was increased without change in cholesterol solubility. In Fig. 4 the viscosity of aqueous monooctanoin is plotted as a function of polymer concentration. The povidone data are linear but the Poloxamer 237 viscosities are not, and higher concentrations were required to reach a given viscosity. Figure 5 shows the log-log relationship between dissolution rate and viscosity for these two polymers plotted according to Eq. 5a. The slopes were −0.39 for povidone and −0.36 for poloxamer 237, smaller than the $-2/3$ power predicted above.

The effect of temperature on dissolution rate has not been previously utilized for investigating viscosity effects. In Eq. 2, for the rotating disk, changing temperature affects ν, D, and C_s. Since the $\nu^{-1/6}$ term is negligible under most conditions and solubilities can be readily measured, the effect of viscosity on dissolution rate can be isolated to the changing diffusion coefficient. If Eq. 4 adequately represents the proportionality between D and η, then Eq. 5 should also be applicable for dissolution rate-temperature data. Since $T^{2/3}$ changes only 5% with the present data (20-45°C), whereas J/AC_s increases threefold, dividing J/AC_s by $T^{2/3}$ has no significant effect (Fig. 5). The slopes for this curving line are approximately −0.6 to −2.3, with the smaller value occurring at the higher temperatures (37°C and 45°C). Thus, it appears that the dissolution rate approaches theoretical behavior ($-2/3$ power of viscosity) with increasing temperature.

Activation Energies for Viscosity and Dissolution Rate—Viscosity-temperature data are commonly plotted in the Arrhenius manner to obtain the energy of activation, E_a. Figure 6 shows the temperature effect on viscosity of aqueous monooctanoin and water (14). The apparent activation energy for monooctanoin was higher than that for water. Although viscosity decreases with increasing temperature, these activation energies are reported as endothermic constants.

Previous rotating-disk dissolution rate studies reported activation energies

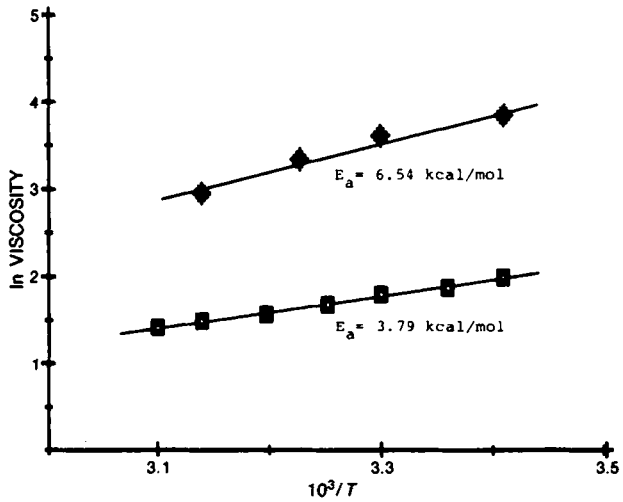

Figure 6—*Arrhenius plots of the viscosity of 10% aqueous monooctanoin (◆) and water (2 + ln η) (■) from Ref. 14.*

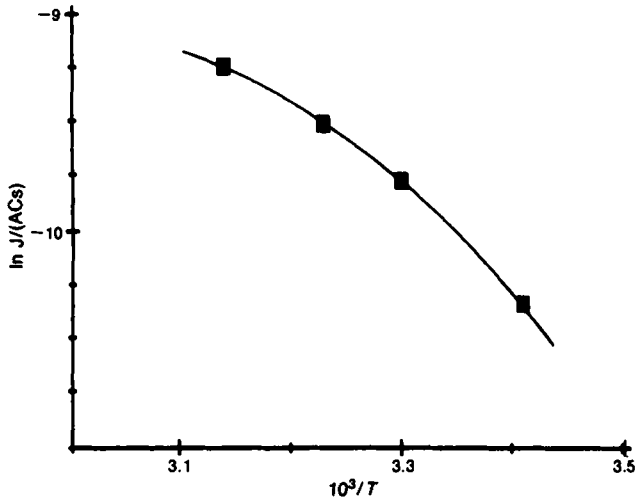

Figure 7—*Arrhenius plot for the dissolution rate constant of cholesterol in 10% aqueous monooctanoin.*

of 3.3–3.7 kcal/mol (15–17). By calculating the dissolution rate constant (J/AC_s) of benzoic acid in 0.01 M HCl from Eqs. 2 and 4, Touitou and Donbrow (17) obtained a theoretical E_a of 3.66 kcal/mol. Their experimental data showed an E_A of ~3.3 kcal/mol with some curvature in the Arrhenius plot. The difference was ascribed to the influence of interfacial kinetics at lower temperatures. The similarity between the E_a for the dissolution rate constant of benzoic acid indicates that viscosity change can almost entirely account for the change in dissolution rate.

In Fig. 7 the experimental dissolution rate constants for cholesterol are plotted against reciprocal temperature. The data again show significant curvature with an apparent range of E_a values from ~5.6 to 10 kcal/mol. As discussed previously, separation of the $T^{2/3}$ term had a negligible effect on E_a. The heat of solution for cholesterol in aqueous monooctanoin was found to be 4.1 kcal/mol (3). When ln J was plotted against T^{-1} the total heat of dissolution was ~11.5 kcal/mol. The difference in these activation energies (7.4 kcal/mol) would be the average E_a for the viscosity effect. Therefore, temperature changes exert a greater influence on dissolution rate through viscosity–diffusion coefficient effects than through solubility.

Solubility and Dissolution Rate in Mono- and Diglyceride Fractions—The monooctanoin used in these studies is a mixture containing ~30% diglyceride. The uncertainty about the individual effects of the solvent components and the previously discussed influence of viscosity prompted measurement of cholesterol solubility and dissolution rate in the mono- and diglyceride fractions of monooctanoin isolated by column chromatography. Table II compares the viscosity, solubility, and dissolution rate of the solvent and its components. The highest dissolution rates were obtained for the diglyceride fraction, even though the solubilities were the lowest. Although the data are limited, a good correlation is apparent between viscosity and dissolution rate.

A difficulty in the interpretation of Table II is that cholesterol monohydrate was used for the dissolution rate measurements, whereas the equilibrium solubility form was anhydrous (3). Curvature was not detected in the rotating-disk dissolution runs at 150 rpm, indicating that surface conversion, if occurring, was not significantly affecting the rate. This is consistent with the similar solubilities of the two forms (3). Whether conversion occurs in stirred systems depends on the hydrodynamic conditions and the potential for crystallization (supersaturation and nucleation factors).

Table II—Cholesterol Dissolution Rate in Monooctanoin and its Mono- and Diglyceride Fractions

Solvent	Water, %	Viscosity, cP	Solubility, %	10^3 Dissolution Rate, mg cm^{-2} s^{-1}
Monooctanoin	3	38	15.2	8.0
Monoglyceride fraction	3	49	15.4	7.3
Diglyceride fraction	3	18	7.3	12.1
Monooctanoin	0.4	46	13.8	6.4
Monoglyceride fraction	0.4	58	12.8	4.6
Diglyceride fraction	0.4	20	9.8	12.4

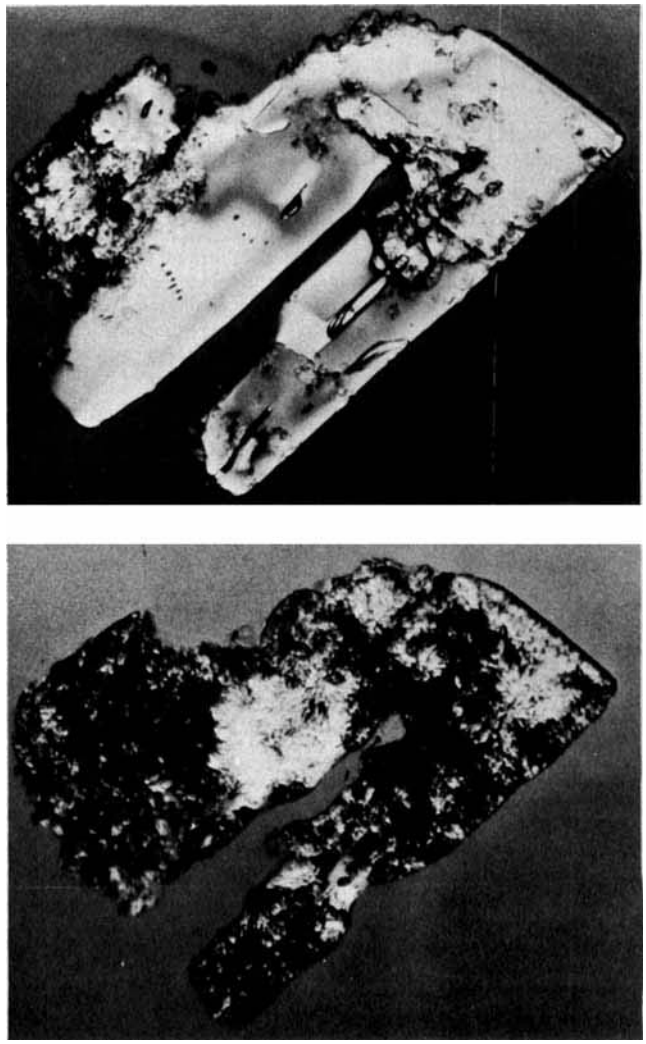

Figure 8—*Polarized light photomicrographs of a cholesterol monohydrate crystal in dry monooctanoin solution immediately upon immersion (top) and after 2 min (bottom).*

Cholesterol Dissolution in Unstirred Media—Under static (unstirred) conditions, surface transformation to the anhydrous form was observed. The photomicrographs in Fig. 8 show a cholesterol monohydrate crystal immediately and 2 min after incubation with dry monooctanoin. The darkening of the crystal is due to crystallization of the anhydrous form on the dissolving surface. In this case, the crust of anhydrous cholesterol inhibited further dissolution of the monohydrate, as shown in Table III. In the dry solvent the weight loss of tablets made from cholesterol monohydrate was less than that from the anhydrous form. The effect of water on the monohydrate in Table III parallels the results in Fig. 1, which show an essentially constant dissolution rate at >5% water. Since the conditions of these experiments are more similar to the clinical situation, which involves slow infusion into the bile duct, significant improvement in gallstone dissolution *in vivo* may be possible with monooctanoin containing water.

CONCLUSIONS

The strong effect of viscosity on dissolution rate in this system has its origin in the solute–solvent interactions which cause high solubility. These interac-

Table III—Effect of Water on Weight Loss of Unstirred Cholesterol Tablets

Water, %	Weight Loss After 24 h, %[a]	
	Monohydrate	Anhydrous[b]
0	32.5 ± 2.4	39.7 ± 1.4
5	49.8 ± 1.0	56.6 ± 3.4
10	45.8 ± 3.3	—
15	48.2 ± 4.1	—

[a] Mean ± *SD* (n = 4). [b] Dried monohydrate.

tions increase the viscosity of the diffusion layer on the dissolving cholesterol monohydrate surface. The resulting decrease in the diffusion coefficient of cholesterol in the diffusion layer causes the dissolution rate to be slower even though solubility may have been higher. For these reasons, the preferred approach for increasing the dissolution rate of cholesterol gallstones in monoglycerides would be to investigate solvents with low viscosity rather than to try to optimize solubility. The validity of this statement is supported by the data in Table II, which show that dissolution rate is greater in the diglyceride fraction of monooctanoin although cholesterol solubility is lower.

In terms of clinical applications, this study suggests that it may be possible to increase the cholesterol gallstone dissolution rate by addition of water to monooctanoin. Water may also improve local tolerance of the drug during infusion. Since the solubility of water in monooctanoin is ~15% at 37°C, the aqueous solvent would have much less potential for extraction of water from the bile duct and intestinal walls. The importance of temperature should be emphasized, since the dissolution rate of cholesterol increases 50% from 30°C to 37°C. Some of the reported variability in clinical results may be due to inadequate control of solvent temperature. Lastly, addition of water overcomes a practical problem with handling monooctanoin, *i.e.*, crystallization. By its effect on the colligative properties of the solvent, water depresses the solidification point of monooctanoin to well below room temperature.

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Effects of Acrylic Acid Polymer and Its Arrangement on Drug Release from a Wax Matrix

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Received December 23, 1982, from the *Faculty of Pharmaceutical Sciences and Institute of Colloid and Interface Science, Science University of Tokyo, 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, Japan.* Accepted for publication June 23, 1983.

Abstract □ The release of phenacetin from a wax matrix was improved by the addition of an acrylic acid polymer. Increasing the amount of polymer increased the release rate of phenacetin due to the formation of pores and channels in the matrix resulting from leaching of the polymer. The leaching was affected by the pH of the dissolution medium as well as by the methods used to prepare the granules. The polymer in ordered powder mixes behaved differently from that uniformly dispersed in a wax matrix. The drug appeared to be released by an approximate zero-order process at pH 7.5 from tablets containing the polymer.

Keyphrases □ Wax matrices, inert—release of phenacetin, effect of acrylic acid polymer □ Phenacetin release from inert wax matrices, effect of acrylic acid polymer □ Acrylic acid polymer—effect on release of phenacetin from inert wax matrices, action as a channeling agent

Recently, various methods have been developed to prolong the action of drugs by controlling their release rates. One method involves the incorporation of drugs into a wax matrix. The mechanism of drug release from a wax matrix involves the leaching of the drug by a permeating fluid that enters the drug-matrix phase through the pores, cracks, and intergranular spaces. Higuchi has treated the drug release from the matrix model in a theoretical manner (1).

Several investigators have described the incorporation of additives, such as surfactants, into the matrix (2, 3). These additives act as channeling agents and improve drug release. The drug appears to be released by a zero-order process. Others have investigated ordered powder mixes (4, 5). For example, the wettability of α-lactose powder was appreciably changed by modifying its surface with other powders (6). The purposes of this work are to evaluate an acrylic acid polymer as a channeling agent in the wax matrix and to examine the effects of powder arrangement on drug release.

EXPERIMENTAL SECTION

Materials—Carnauba wax[1] was obtained commercially, and the stearyl alcohol, sodium chloride, disodium phosphate, and hydrochloric acid were reagent grade. The phenacetin[2] was JP grade; the powder was ground with an automatic mortar[3] and then sieved to 49–105-μm particle size with stainless steel sieves. The water used in this experiment was prepared with a water purification apparatus[4]. Acrylic acid polymer[5] was cross-linked and had a viscosity of 3000 cps as a 1% aqueous solution. Molecular weight, solubility, and carboxyl group content of the acrylic acid polymer were ~2,000,000, 5% (w/w), and 60%, respectively.

Preparation of Granules—Carnauba wax (15.0 g) and stearyl alcohol (15.0 g) were mixed and melted at 90 ± 3°C. Phenacetin powder was added into the melt in small portions with constant stirring for 5 min at 90 ± 3°C, to achieve an even distribution; the mixture was then poured onto a glass plate kept at 0°C and allowed to congeal. The plate-like mass was crushed for 10

[1] Dainichi Sangyo, Ltd., Japan.
[2] Iwaki Seiyaku, Ltd., Tokyo, Japan.
[3] ANM-1000 type; Nitto Kagaku, Ltd., Nagoya, Japan.
[4] Milli-Q2; Millipore Co., Bedford, Mass.
[5] Hiviswako-104; Wako Pure Chemical Industries, Ltd., Japan.

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