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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ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grant No. AM31603. The technical assistance of R. Perrone is gratefully acknowledged.

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.

0022-3549/84/0700-0910$01.00/0

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Table I—Formulations for Method 1

Acrylic Acid Polymer Conc. % (w/w)	Weight, g			
	Carnauba Wax	Stearyl Alcohol	Acrylic Acid Polymer	Phenacetin
1.0	14.775	14.775	0.45	15.0
3.0	14.325	14.325	1.35	15.0
6.0	13.650	13.650	2.70	15.0
9.0	12.975	12.975	4.05	15.0

min in a ceramic mortar and then screened to prepare a granule size of 420–590 μm.

Incorporation of Acrylic Acid Polymer into the Wax Matrix—*Method 1*—When a homogeneous melt carnauba wax and stearyl alcohol was attained at 90 ± 3°C, the polymer powder was gradually added to the melt followed by phenacetin powder, which was added in small portions at the same temperature while stirring. After pouring the mixture onto a cold glass plate, the plate-like mass was crushed and sieved to obtain the required granule size. The formulations are shown in Table I

Method 2—A 30.0-g portion of phenacetin powder and various loadings (1.0, 2.0, 3.0, and 6.0 g) of acrylic acid polymer were thoroughly blended in an automatic mortar for 5 min. Figure 1 shows scanning electron micrographs of the phenacetin and blended powders. Samples equivalent to 15.0 g of phenacetin were homogeneously incorporated into the melted mixture of carnauba wax and stearyl alcohol according to the formulations shown in Table II. The 420–590-μm granules were obtained by the same procedure described in method 1.

Preparation of Tablets—A KBr disk press[6] was used to compress the granules into tablets using a compression force of 100 kg/cm^2. The average tablet weight was ~500 mg, with a thickness and diameter of ~3.6 and 13 mm, respectively.

Dissolution Procedures—The fluids of pH 1.2 and 7.5 included in JP IX were used as the dissolution media. The former was prepared by mixing 2.0 g of sodium chloride, 24.0 mL of 10% (w/w) HCl, and a sufficient amount of water to give 1000 mL of solution; the latter was prepared by mixing 35.8 g of disodium phosphate, 6.0 mL of 10% (w/w) HCl, and water to give 1000 mL of solution.

The apparatus shown in Fig. 2 was used for the dissolution tests. The dissolution flask was covered during the experiment to prevent water evaporation. A paddle with six blades was set at 3 cm from the bottom of the flask and rotated at constant rate of 200 rpm. A stirring speed of 200 rpm was adequate to disperse the granules uniformly in the fluid. Granules (0.3 g) were added into the flask containing 500 mL of a dissolution medium maintained at 37 ± 0.1°C. After adding the granules, 3-mL aliquots of the test fluid, containing granules, were withdrawn with syringes at intervals over a 10-h period. The sample was then filtered through 0.6-μm pore membrane filter[7].

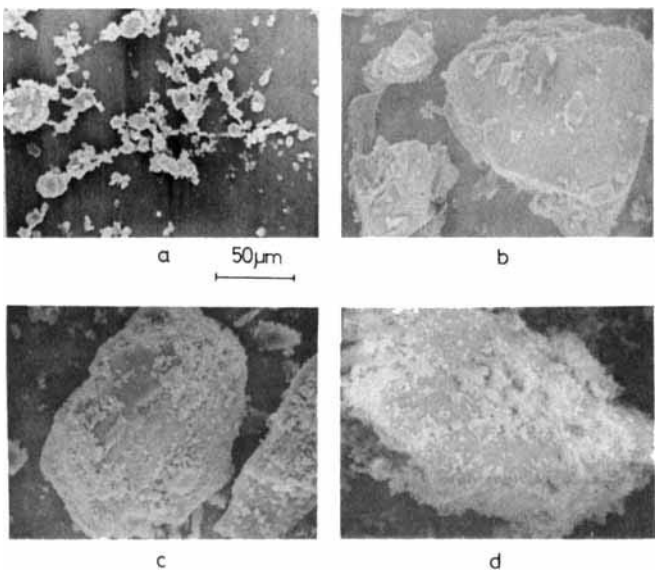

Figure 1—*Scanning electron micrographs of the powders used. Key: (a) acrylic acid polymer; (b) phenacetin; (c) polymer–phenacetin (1:10); (d) polymer–phenacetin (1:15).*

[6] Hitachi, Ltd., Tokyo, Japan.
[7] BDWP02500; Millipore Corp., Bedford, Mass.

Table II—Formulations for Method 2

Acrylic Acid Polymer Conc. % (w/w)	Acrylic Acid Polymer–Phenacetin Ratio (w/w)	Weight, g		
		Carnauba Wax	Stearyl Alcohol	Acrylic Acid Polymer–Phenacetin[a]
1.1	1:30	14.75	14.75	15.50
2.2	1:15	14.50	14.50	16.00
3.3	1:10	14.25	14.25	16.50
6.6	1:5	13.50	13.50	18.00

[a] Mixed powder.

A method similar to the USP rotating-basket method was used to investigate drug release from the tablets. A basket, in which a tablet was placed, was immersed into a flask containing 600 mL of a dissolution medium maintained at 37 ± 0.1°C. The basket was set at a height of 3 cm from the bottom of the flask and rotated at a rate of 200 rpm; this was necessary to prevent air bubbles from adhering to the basket and the tablet surface. Aliquots (3 mL) of the test fluid were then withdrawn at intervals over a 10-h period. Each sample was replaced with 3 mL of fresh dissolution medium kept at 37 ± 0.1°C to maintain the constant volume of the test fluid. The amount of phenacetin released was determined by direct measurement of the absorbance at 245 nm.

RESULTS AND DISCUSSION

Effect of Acrylic Acid Polymer Added According to Method 1 on Phenacetin Release—The release of phenacetin from the wax matrix containing acrylic acid polymer made according to method 1 was investigated. The particle sizes and concentration of phenacetin were 49–105 μm and 33.3% (w/w), respectively, the granule sizes were 420–590 μm, the compression force was 100 kg/cm^2, and acrylic acid polymer concentrations were 1.0, 3.0, 6.0, and 9.0% (w/w).

Figure 3a and b illustrates the drug release profiles at pH 1.2 from granules and tablets, respectively. The addition of acrylic acid polymer into the wax matrix affected the drug release. As is evident from Fig. 3, there was a slight increase in the release rates, in both cases, with increasing amounts of added polymer. A similar observation has been reported for a water-soluble nonelectrolytic polymer by Dakkuri *et al.* (3). The drug release from tablets for the initial 1.5 h at pH 1.2 seemed to be in accordance with the Higuchi equation, but a negative deviation was seen when the added polymer concentrations were 0, 1.0, 3.0, and 6.0% (w/w) and a positive deviation was noted when the polymer concentration was 9.0% (w/w).

The release profiles from granules and tablets at pH 7.5 are shown in Fig. 3c and d, respectively. For granules, the addition of the polymer markedly increased the drug release as compared with the polymer-free formulation. A 100% release was achieved in 10 h for the 6.0% (w/w) and in 2 h for 9.0% (w/w) polymer concentrations. Also, in the case of tablets at pH 7.5, an obvious increase in the drug release rate was associated with the amount of polymer added. The drug release appeared to follow a quasi-zero-order kinetics at high polymer concentrations (6.0 and 9.0%). Similar observations were reported by Dakkuri *et al.* (2). The deviation from a straight line after 7 h for the 9.0% (w/w) polymer concentration (Fig. 3d) could be explained by the total exhaustion of the solid drug phase.

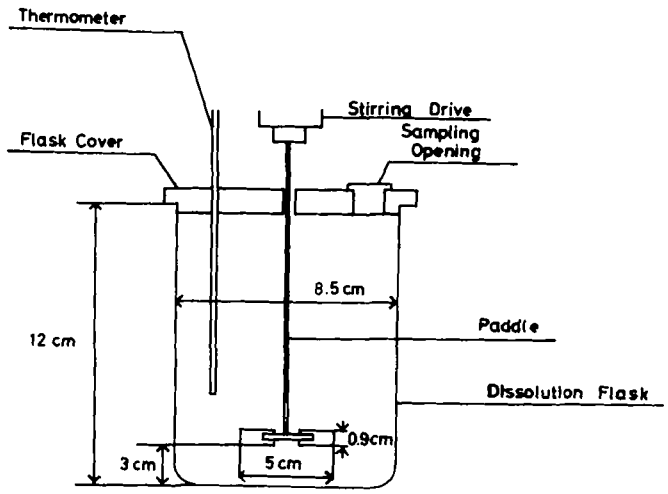

Figure 2—*Schematic diagram of apparatus for the dissolution test of granules.*

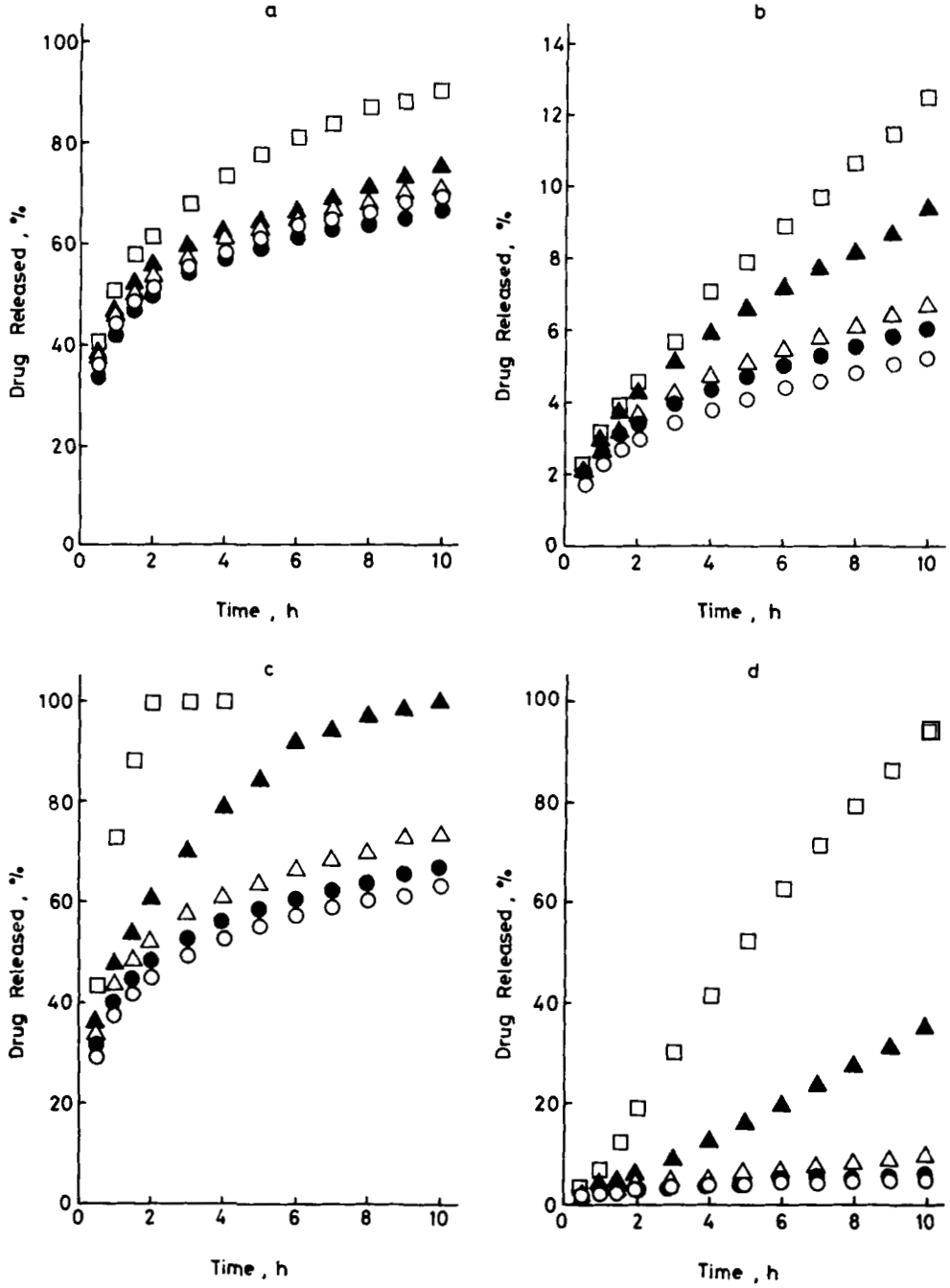

Figure 3—*Effect of acrylic acid polymer concentration on the release of phenacetin from granules at pH 1.2 (a) and pH 7.5 (c) and from tablets at pH 1.2 (b) and pH 7.5 (d), using method 1. Key: (○) 0% (w/w); (●) 1% (w/w); (△) 3% (w/w); (▲) 6% (w/w); (□) 9% (w/w).*

These distinct effects of the polymer were due to the formation of pores and channels in the matrix, which resulted from swelling and leaching of the polymer powder. The degrees of swelling and leaching of the polymer were controlled by a change in the dissolution medium pH. When the polymer in the matrix was hydrated by the dissolution medium, the degree of ionization of the carboxyl groups of the acrylic acid polymer was lower at pH 1.2 than at pH 7.5. As a result, the partially hydrated polymer molecules at pH 1.2 formed a dense jelly structure, which caused most of the polymer molecules dispersed in the matrix to be held in the pores and channels. Therefore, the drug molecules were released slowly through the pores and channels that were filled with the less-hydrated polymer molecules.

At pH 7.5, however, because the polymer chains were extended due to the repulsion of negatively charged carboxyl groups, the fully hydrated polymer became swollen. Consequently, the hydrated polymer molecules in the matrix were liberated into the dissolution medium. Leaching out of the polymer increases the internal porosity and decreases the tortuosity, as suggested by Samuelov *et al.* (7). Therefore, the drug was released rapidly at pH 7.5. The apparent quasi-zero-order kinetics of drug release from tablets at pH 7.5 and high polymer concentrations can be attributed to the increase of the diffusion rate of the drug in the channels and to the increasing number of channels after leaching of the polymer.

Effect of Acrylic Acid Polymer Added According to Method 2 on Phenacetin Release—The release of phenacetin from the wax matrix containing acrylic acid polymer made according to method 2 was studied. The particle sizes and the concentration of phenacetin were 49–105 μm and 33.3% (w/w), respectively, the granule sizes were 420–590 μm, and the compression force was 100 kg/cm^2.

The release profiles at pH 1.2 and 7.5 from granules are shown in Fig. 4a and c, respectively. These results indicated that the increase in the polymer concentration increased the release rate of phenacetin. It is also obvious that the addition of the polymer into the matrix according to method 2 significantly improved the drug release as compared with method 1. Higher release rates were also observed at pH 7.5 than at pH 1.2. Figure 4b and d illustrates the release profiles from tablets at pH 1.2 and 7.5, respectively. As described above, leaching of the polymer into the pH 1.2 dissolution medium was slight, and the effect of the addition of the polymer on the drug release at pH 1.2 was

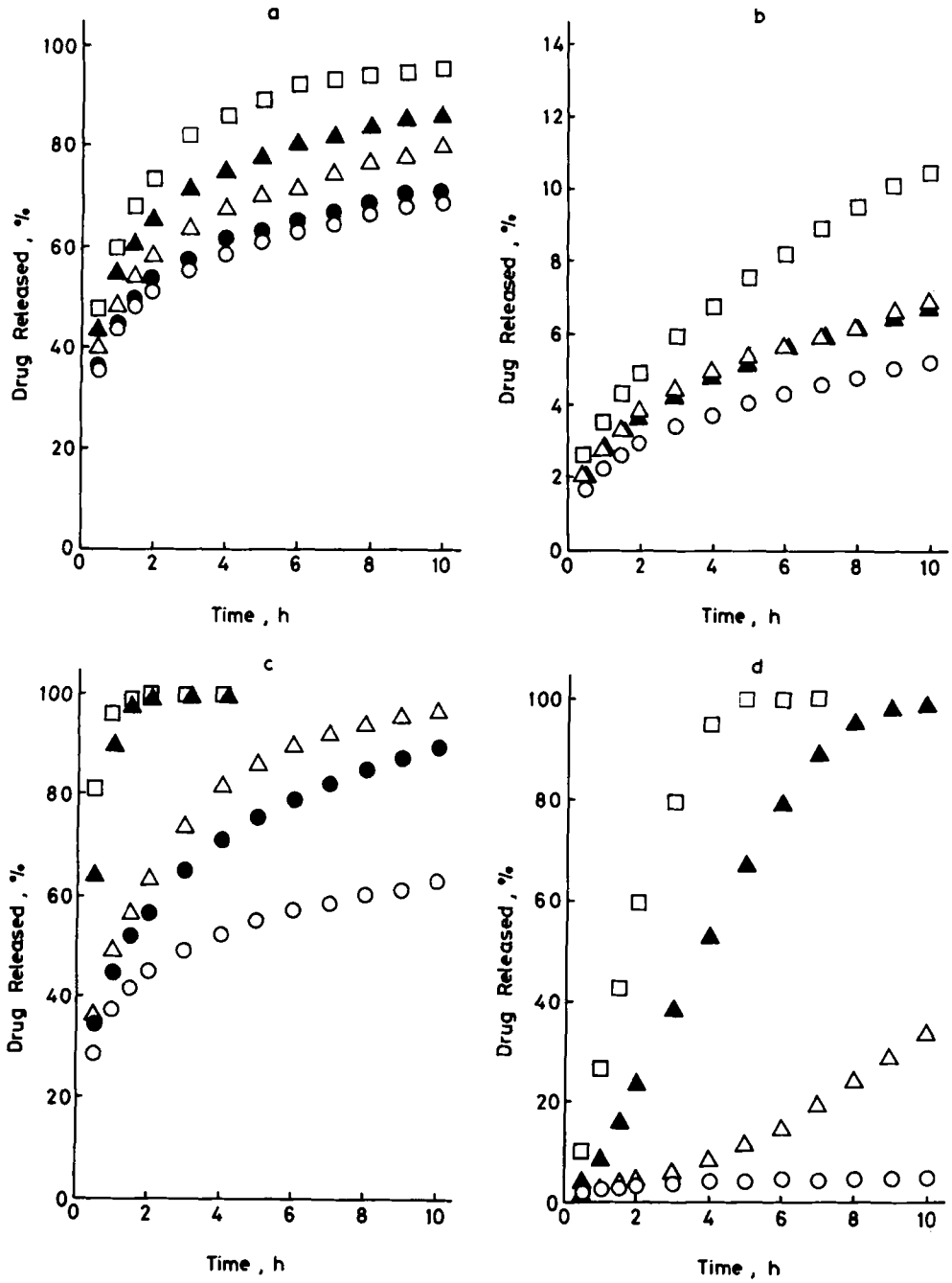

Figure 4—*Effect of acrylic acid polymer concentration on the release of phenacetin from granules at pH 1.2 (a) and pH 7.5 (b) and from tablets at pH 1.2 (b) and pH 7.5 (d), using method 2. Key: (○) 0% (w/w); (●) 1.1% (w/w); (△) 2.2% (w/w); (▲) 3.3% (w/w); (□) 6.6% (w/w).*

also negligible. At pH 1.2, the drug release from tablets in the initial period seemed to be in accordance with the Higuchi equation, and then a negative deviation was observed. However, at pH 7.5, the addition of the polymer markedly increased the drug release from tablets. The drug release followed quasi-zero-order kinetics at high polymer concentrations (3.3 and 6.6%). Moreover, tablet disintegration was observed in some cases at this pH. The drug release at a polymer concentration of 2.2% (w/w) had two zero-order rate constants, caused by slow tablet disintegration after 5 h. The tablets containing 3.3 and 6.6% (w/w) acrylic acid polymer began to disintegrate after ~1 h and 30 min, respectively. However, no burst phenomenon was observed with all the tablets. The change of the release pattern (to quasi-zero-order kinetics) at pH 7.5 and at high polymer concentrations could be caused by an increase in the diffusion rate of drug molecules through channels that resulted from leaching of the polymer and also by a shortening of this channel length due to tablet disintegration.

Differences Between the Two Methods—When the release data obtained using the two methods of polymer addition are compared (Figs. 3 and 4), it was shown that method 2 gave a more rapid release of drug than method 1

Table III—Effects of Acrylic Acid Polymer Concentration on the Zero-Order Release Rate Constant (k) for Tablets at pH 7.5

Acrylic Acid Polymer Conc., % (w/w)	k, mg/h	r
	Method 1	
1.0	0.60	0.998
3.0	1.29	0.999
6.0	6.00	0.999
9.0	18.22	0.998
	Method 2	
2.2	2.97[a]	0.998
	4.75[b]	1.000
3.3	22.89	0.999
6.6	51.63	1.000

[a] For the period up to 5 h. [b] For the period after 5 h.

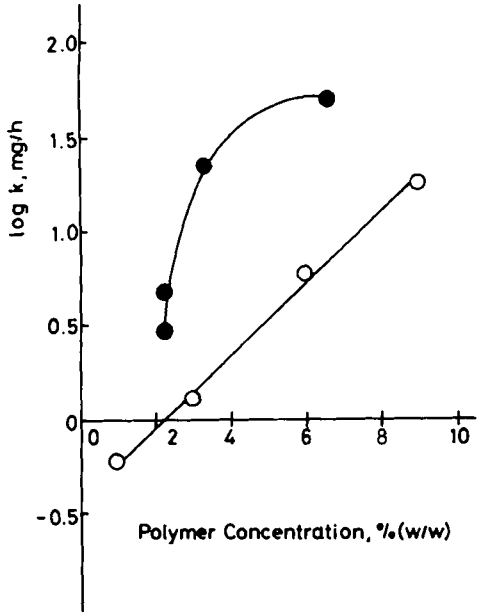

Figure 5—*Relationships of log k to the concentration of acrylic acid polymer at pH 7.5. Key: (○) method 1; (●) method 2.*

for both granules and tablets. For example, those tablets which were prepared by method 1 and contained 6.0% (w/w) polymer released only 17% of the drug in 5 h at pH 7.5, while those prepared by method 2 released 100% at pH 7.5.

The zero-order release rate constant (k) at pH 7.5 for the tablet increased with increasing polymer concentration, as shown in Table III, where k was calculated from the plots in the initial period of the test at low polymer concentrations. Attempts to relate mathematically the zero-order release rate constant, k, to the polymer concentration yielded the best results when log k was plotted against polymer concentration, giving an empirical equation similar to that suggested by Borodkin and Tucker (8). Plots of log k against polymer concentration for method 1 were linear, as shown in Fig. 5. However, log k for method 2 suddenly increased as the polymer concentration increased; there was no linear relationship between the two quantities. This difference could be explained by the formation of a polymer particle layer which adhered physically around phenacetin particles in the matrix prepared by method 2. Leaching of the polymer would, therefore, result in the formation of larger pores and channels around the phenacetin particles, increasing the surface area of the drug particle in contact with the dissolution medium. Slow disintegration of the matrix, coupled with the enhanced pore formation, would affect the drug release rate since the polymer added according to method 2 acts as a disintegrator at high concentrations (see the previous section).

Scanning electron micrographs of the tablet surface are shown in Figs. 6, 7, and 8, where the particle sizes and the concentration of phenacetin were 49–105 μm and 33.3% (w/w), respectively, the granule sizes were 420–590 μm, and the compression force was 100 kg/cm². After dissolution tests at pH 1.2 and 7.5, small pores (which had not been observed before the tests) were formed on the surface of a polymer-free tablet, as shown in Fig. 6. This was the result of phenacetin dissolution. In the case of tablets containing the polymer, larger pores were seen on the tablet surface after dissolution tests at pH 1.2 and 7.5. Figure 7 shows a tablet prepared by method 1 containing 3.0% (w/w) of the polymer. A tablet made by method 2 containing 3.3% (w/w) of the polymer is shown in Fig. 8. The pores in both tablets were formed by leaching of the polymer; the pore size was larger at pH 7.5 than at pH 1.2, and for method 2 than for method 1. The above results are in accordance with the results obtained for drug release.

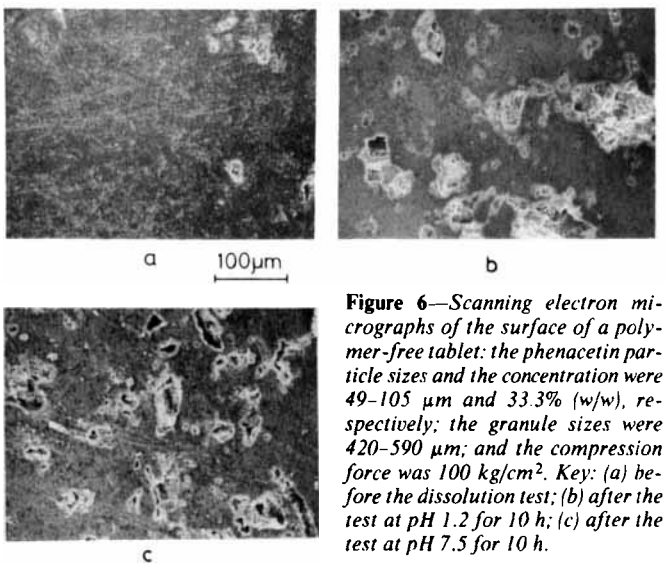

Figure 6—*Scanning electron micrographs of the surface of a polymer-free tablet: the phenacetin particle sizes and the concentration were 49–105 μm and 33.3% (w/w), respectively; the granule sizes were 420–590 μm; and the compression force was 100 kg/cm². Key: (a) before the dissolution test; (b) after the test at pH 1.2 for 10 h; (c) after the test at pH 7.5 for 10 h.*

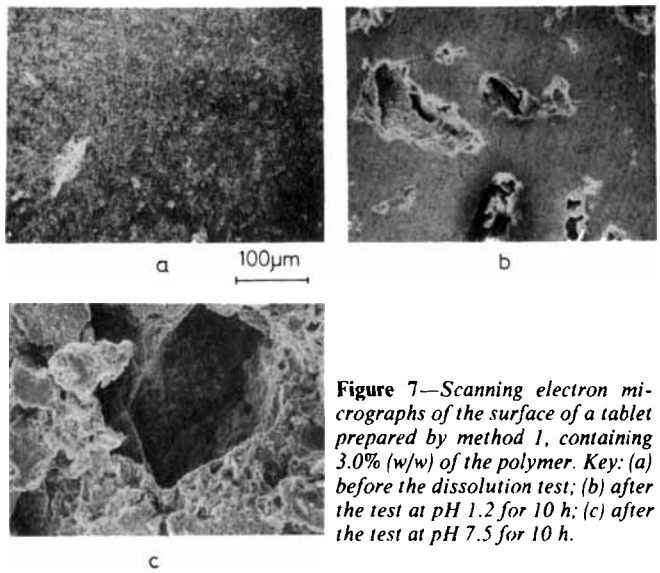

Figure 7—*Scanning electron micrographs of the surface of a tablet prepared by method 1, containing 3.0% (w/w) of the polymer. Key: (a) before the dissolution test; (b) after the test at pH 1.2 for 10 h; (c) after the test at pH 7.5 for 10 h.*

CONCLUSIONS

Acrylic acid polymer added to inert wax matrices by methods 1 and 2 acts as a channeling agent, enhancing the drug release. At high polymer concentrations, the drug release from tablets at pH 7.5 appears to follow quasi-zero-order kinetics. For both methods, the drug release rates increased with increasing polymer concentration, but method 2 was more effective than method 1. In this regard, the location of acrylic acid polymer relative to the drug particles is important, *i.e.*, leaching of the uniformly dispersed polymer in the wax matrix causes the formation of more pores and channels in addition to those formed by leaching of the drug, whereas leaching of the polymer when physically adhered around the drug particles makes the pores and channels produced by drug release larger. Therefore, the effects of powder arrangement could be one of the important factors in pharmaceutical formulation. Since addition of acrylic acid polymer to the inert wax matrix, as a channeling agent and a disintegrator, enhances the controlled release of the drug at alkaline

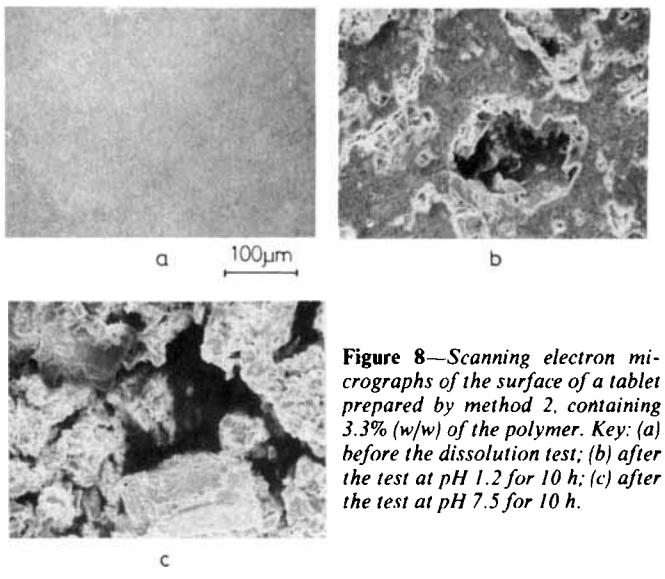

Figure 8—*Scanning electron micrographs of the surface of a tablet prepared by method 2, containing 3.3% (w/w) of the polymer. Key: (a) before the dissolution test; (b) after the test at pH 1.2 for 10 h; (c) after the test at pH 7.5 for 10 h.*

pH, the polymer could be useful in preparing an orally administered wax matrix product which releases most of its drug content in the intestinal tract.

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Particle Size Analysis of Latex Suspensions and Microemulsions by Photon Correlation Spectroscopy

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Received December 20, 1982, from the *Department of Pharmaceutics, Christian-Albrechts University of Kiel, Gutenbergstrasse 76-78, D-2300 Kiel 1, West Germany.* Accepted for publication June 7, 1983.

Abstract □ The particle size in microemulsions and other highly dispersed systems was determined by means of photon correlation spectroscopy (PCS). As PCS cannot be applied to highly concentrated dispersed phases, the measurement accuracy was tested for its dependence on the particle concentration using latex suspensions. The data obtained by clipping and scaling were compared. The particle size determination was expected to provide information about the influence of the structure of the surfactant system on microemulsions, using a homologous alcohol series as cosurfactant and potassium oleate as surfactant. In this system the region of solubilization is characteristically divided from the region of microemulsification by a zone of instability. Furthermore, there are distinct differences in mean particle sizes between microemulsions (9–30 nm) and micellar solutions (4–6 nm).

Keyphrases □ Particle size analysis—photon correlation spectroscopy, latex suspensions, microemulsions □ Photon correlation spectroscopy—particle size analysis, latex suspensions, microemulsions □ Microemulsions—particle size analysis, photon correlation spectroscopy, latex suspensions

Microemulsions appear as monophasic, more or less stable and transparent or slightly translucent, systems. They have been defined as dispersed liquid–liquid systems in which the particle size of the dispersed phase is <2000 Å. Shinoda and Friberg (1) assumed the existence of discrete micelles (oil-in-water) and reverse micelles (water-in-oil). According to the emulsion theory of Prince and co-workers (2, 3), these systems can be described as emulsions with highly dispersed internal phases. This definition includes the premise that there are essential differences between the microemulsion and the solubilization regions. The description of the structure of microemulsions as droplets is only valid for low concentrations of the internal phase. For high concentrations, Scriven (4) postulates bicontinuous microstructures. This bicoherence of microemulsions was confirmed by Lindman *et al.* (5).

These are of interest since drugs applied topically are liberated more efficiently from microemulsions than from ointments composed of the same ingredients (6). Up to now most of the known microemulsions were made with toxic surfactants or with surfactants in very high concentrations, precluding pharmaceutical use. Therefore, an attempt is made herein to determine the dependence of microemulsion formation on the structure of the emulsifier system and on other such factors, in order to find suitable excipients in suitable concentrations.

Table I—Particle Radii of Latex Suspensions (19 nm)

Particle Conc., μg/L	Radius, nm[a]	Measuring Error, %
0.05	19.3	1.6
0.1	19.2	1.1
0.25	19.4	2.1
0.5	18.9	−0.5
1	18.7	−1.6
2.5	17.8	−6.3
5	17.2	−9.5
10	16.4	−13.7
25	15.3	−19.5
50	13.8	−27.4

[a] Determined by photon correlation spectroscopy.

THEORETICAL SECTION

Light-scattering techniques are used extensively when testing microemulsions (7–12). In the following, the mean particle diameter was determined by photon correlation spectroscopy (PCS) (13, 14). A laser beam is sent through a sample and the scattered light is detected by a photomultiplier at a certain angle. The time-dependent periodical fluctuations of the scattered light are analyzed. Smaller particles diffuse faster than larger ones and, thus, cause a more rapid fluctuation of the intensity of the scattered light. The signal received by the photomultiplier is evaluated by a correlation function $C_{(\tau)} = e^{-\tau/tc}$, where τ stands for the time and tc for the correlation coefficient that describes the decay of this correlation function. The correlation coefficient is related to the diffusion coefficient D by $tc = 1/2DK^2$, where K is the absolute value of the scattering vector. As tc and K can be calculated, the diffusion constant D can be obtained; this is related to the particle radius by the Einstein relationship:

$$\bar{r} = \frac{k \cdot T}{6\pi D\eta}$$

Table II—Particle Radii of Latex Suspensions (54 nm)

Particle Conc., μg/L	Radius, nm[a]	Measuring Error, %
0.1	62	14.8
1	51	−5.6
5	50	−7.4
10	50	−7.4
20	49	−9.3
50	49	−9.3
100	50	−7.4
250	46	−14.8
500	46	−14.8
1000	44	−18.5
2500	32	−40.7

[a] Determined by photon correlation spectroscopy.

0022-3549/84/0700-0915$01.00/0

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