The cumulative amounts of non-I compounds (as percentage of administered radioactivity in the [^{14}C]I dose) are plotted against time in Fig. 9 for the 1017-mg (A) and 43.1-mg (B) doses. The lines drawn through the values were calculated from:

$$\Sigma U = \Sigma U_\infty (1 - e^{-\lambda t}) \qquad \text{(Eq. 13)}$$

The respective half-life values (0.693/λ) in min were: (A) ΣU_{II}, 266; ΣU_{ETAC}, 266; $\Sigma U_{Rf}^{0.2}$, 152; $\Sigma U_{Rf}^{0.5}$, 578; $\Sigma U_{Rf}^{0.62}$, 277; and (B) ΣU_{II}, 231; ΣU_{ETAC}, 300; $\Sigma U_{Rf}^{0.5}$, 278; and $\Sigma U_{Rf}^{0.62}$, 193. Most of these half-lives were approximately the same as I and may indicate the facile renal elimination of these compounds.

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In Vitro Drug Release from Egg Albumin Microcapsules

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Abstract □ The *in vitro* release of phenacetin from microcapsules prepared using egg albumin as the membrane material was investigated. It was shown by scanning electron microscopy that the albumin microcapsules have nonsmooth surfaces. The amount of phenacetin released is proportional to the square root of time up to 50–70% drug release. Increases in the albumin concentration and 1-vinyl-2-pyrrolidinone polymer content in the aqueous phases used in the microcapsule preparation have an effect on matrix porosity and channel tortuosity in the matrix of albumin microcapsules. The *in vitro* release rate was found to decrease with increasing albumin concentration and 1-vinyl-2-pyrrolidinone polymer content in the aqueous phases. The *in vitro* release rate per unit area also decreased with decreasing capsule size.

Keyphrases □ Phenacetin—albumin microcapsules, release rate, controlling factors □ Microcapsules, albumin—release rate of phenacetin, effects of albumin concentration, 1-vinyl-2-pyrrolidinone polymer content, capsule size □ Delivery systems—albumin microcapsules, release rate of phenacetin, effect of albumin concentration, 1-vinyl-2-pyrrolidinone polymer content, capsule size

Delivery of a chemotherapeutic agent to desired target sites with drug carriers could achieve effective local drug concentration and minimize systemic side effects by reducing the therapeutic dose of the chemotherapeutic agent. When a drug carrier, such as liposomes, microcapsules, and microspheres, is injected into the circulatory system, its distribution in the body is an important factor in drug delivery. The tissue distribution of albumin microspheres has been studied in detail (1–3). In addition, alteration in the tissue distribution of albumin microspheres was examined using magnetic guidance (4, 5). Albumin microspheres prepared using a water–oil emulsion have a hydrophilic matrix structure, consisting of albumin molecules, that is similar to that in albumin microcapsules (6).

However, despite many reports on the tissue distribution of albumin microspheres, the mechanism of drug release from minute drug carriers that have a hydrophilic matrix structure is not well known because there are few reports on drug release (7, 8). This paper describes *in vitro* drug release from albumin microcapsules having a hydrophilic matrix structure and some controlling factors.

EXPERIMENTAL

Materials—Isooctane, dibasic potassium phosphate, monobasic sodium phosphate, acetic acid, hydrochloric acid, and sodium acetate were reagent grade. Phenacetin powder (250–300 mesh) was used for microencapsulation as the core drug.

Egg albumin[1] solution was prepared as follows: Albumin was dissolved in buffer solution [0.033 *N* KH_2PO_4–0.033 *N* Na_2HPO_4, 1:16 (v/v); pH 8.0], and the solution was filtered after centrifugation at 16,000 × *g* for 30 min to remove the undissolved materials. The albumin concentration was either 10 or 20% (w/w). 1-Vinyl-2-pyrrolidinone polymer[2] was dissolved in the same buffer solution at 70°. The solution thus obtained (50% w/w) was stored in a refrigerator overnight and used for the preparation of aqueous albumin solutions containing the polymer.

Measurement of Viscosity—Viscosities of both the albumin and mixed polymer solutions [prepared from 20% (w/w) albumin solution and 50% (w/w) 1-vinyl-2-pyrrolidinone polymer solution] were measured at 25° with a cone-plate type viscometer[3] in a shear rate range of 50–3950 sec^{-1}. Viscosity values were calculated from the straight lines in rheograms.

Preparation of Microcapsules—Albumin microcapsules were prepared by a method similar to that described in a previous paper (6). Phenacetin powder (10% v/v) was previously dispersed in albumin solutions with and without the polymer. To 100 ml of isooctane containing 5.0% (v/v) sorbitan trioleate[4] as an emulsifier, in a three-necked flask, was added 15 ml of each of the aqueous dispersions, with stirring. After further stirring for 10 min, the flask was immersed in a water bath maintained at 85° for a given period to denature the egg albumin. The resultant dispersion was cooled to room temperature.

[1] Tokyo Kasei Kogyo Co., Tokyo, Japan.
[2] K-30; Tokyo Kasei Kogyo Co., Tokyo, Japan.
[3] Rheomat 30; Contraves AG, Zurich, Switzerland.
[4] Span 85; Nikko Chemicals Inc., Tokyo, Japan.

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Table I—Effects of Albumin Concentration and Release Medium on Drug Release [a] from Albumin Microcapsules [b]

Release Medium	Cs^c, g/liter	Sample	Albumin, % (w/w)	Diameter, μm	Phenacetin Content, % (w/w)	$10^4 v_i$, g/sec	t_h, min	K, %/sec$^{1/2}$
Simulated gastric fluid	1.26	A-1	10	76.1 ± 25.9	56.4	3.75	1.1	7.69
		A-2	10	70.1 ± 22.3	55.8	3.64	0.9	8.09
		B-1	20	74.7 ± 25.3	43.5	2.80	1.8	6.60
		B-2	20	83.9 ± 31.5	44.1	3.16	1.6	6.74
Water	1.30	B-2	20	83.9 ± 31.5	44.1	2.53	2.4	5.22
Simulated intestinal fluid	1.10	B-2	20	83.9 ± 31.5	44.1	2.58	2.0	6.04

[a] Microcapsules containing 40 mg of phenacetin were dispersed in 200 ml of a test medium to obtain v_i, t_h, and K. [b] Each group of microcapsules was prepared on the same day. Speed setting and heating time in microencapsulation were 512 rpm and 10 min, respectively. [c] Solubility of phenacetin.

Table II—Size Effect on Drug Release [a] from Albumin Microcapsules [b]

Sample	Speed Setting, rpm	Diameter, μm	Phenacetin Content, % (w/w)	$10^4 v_i$, g/sec	t_h, min	K, %/sec$^{1/2}$	$10^7 V_i$[c], g·cm/sec	$10^3 K'$[d], %·cm/sec$^{1/2}$
D-1	313	239.9 ± 100.0	45.7	1.34	5.0	3.45	7.13	18.30
D-2	512	95.2 ± 28.0	46.9	2.60	2.1	5.10	4.87	9.55
D-3	848	55.6 ± 15.9	49.4	3.33	1.5	6.93	3.70	7.70

[a] Microcapsules containing 40 mg of phenacetin were dispersed in 200 ml of the simulated gastric fluid to obtain v_i, t_h, and K. [b] Microcapsules were prepared on the same day. Albumin concentration and heating time in microencapsulation were 20% (w/w) and 10 min, respectively. [c] $V_i = v_i/S_v$, where S_v is the specific surface area of the microcapsules. [d] $K' = K/S_v$.

The microcapsules separated by filtration were dispersed in 10 ml of buffer solution [0.1 *N* CH_3COOH–0.1 *N* CH_3COONa, 1:1 (v/v); pH 4.7], which was saturated with phenacetin and contained 10% (v/v) polyoxyethylene sorbitan monolaurate[5], with gentle agitation. The microcapsules were washed once with the pH 4.7 buffer solution and several times with water saturated with phenacetin. The microcapsules collected by decantation were freeze-dried.

Size measurement of the microcapsules was performed in the saturated phenacetin solution before freeze-drying. One thousand microcapsules were photographed under an optical microscope. Each of the developed film strips was projected onto a large-section paper by a slide projector. Enlarged images of the microcapsules were measured to the nearest 1.0 μm. The scale in the micrometer was used for calibration. To eliminate fluctuation in the denaturating procedures of egg albumin, the microcapsules in all experimental series (A–E) were prepared on the same day.

A scanning electron microscope[6] was used to observe the surface appearance of the albumin microcapsules. The original microcapsules and those sampled from a release test medium were dried at 50°. The dried microcapsules were vacuum-coated with gold in an ion coater[7].

Determination of Solubility of Phenacetin—Finely ground phenacetin powder was dispersed in three release test media in Erlenmeyer flasks. The dispersion in the stoppered flask, which was immersed in a water bath thermostated at 37 ± 0.1°, was vigorously agitated with a magnetic stirrer overnight to attain equilibrium. Membrane filters[8], holders, and syringes (maintained previously at 37 ± 0.1°) were used for the separation procedure of undissolved phenacetin particles. The phenacetin concentration in the filtrate was determined spectrophotometrically at 245 nm.

***In Vitro* Release of Microencapsulated Phenacetin**—The cylindrical glass cell used for the release test, 62 mm in diameter and 88 mm in depth, was equipped with a plastic cover to minimize the influence of vaporization. In the cell, 200 ml of a test medium was maintained at 37 ± 0.1°. At time zero, a given weight of albumin microcapsules containing 40 mg of phenacetin was added with stirring to this thermostated medium. Stirring was carried out with a six-blade impeller (50 mm in diameter) at a fixed rotation speed. The amount of phenacetin (40 mg) encapsulated was previously calculated to maintain the same sink condition for each *in vitro* release experiment during the test period. The dispersion was sampled at scheduled intervals and immediately filtered to remove the microcapsules. The drug concentration in the filtrate was determined by the same spectroscopic method described for the phenacetin analysis.

In release experiments, test media similar to those described in JP IX were employed. Simulated gastric fluid (pH 1.2) was a hydrochloric acid solution containing 0.1% (v/v) polyoxyethylene sorbitan monolaurate and 2 g/liter of sodium chloride; simulated intestinal fluid (pH 7.5) contained hydrochloric acid and 35.8 g/liter of monobasic sodium phosphate. Water obtained from a water purification apparatus[9] was also used as a test medium.

To attain reproducibility of the release experiments, a stirring rate of 313 rpm was employed. At stirring rates <200 rpm, no dispersion of microcapsules was observed, and the measured values were scattered widely. At rotating speeds >200 rpm, the release rates were reproducible.

RESULTS AND DISCUSSION

Properties of Microcapsules—As reported previously (6), the viscosity of the aqueous phase in the preparation of egg albumin microcapsules and microspheres markedly affects their size. Stirring speed in this experiment was determined for each preparation to obtain microcapsules within a given size range (70–110 μm) except for the microcapsule samples for the study of size effect on phenacetin release. Tables I–III show the preparation conditions of microcapsules, microcapsule size, and phenacetin content. Both the microcapsule size and phenacetin content were approximately constant in each series.

Surface Appearance of Microcapsules—Scanning electron micrographs of albumin microcapsules before and after the release experiments are shown in Fig. 1. Figure 1a–d shows that the increase of albumin concentration and the addition of 1-vinyl-2-pyrrolidinone polymer change the membrane appearance as compared with the original microcapsules (Fig. 1a). All albumin microcapsules had nonsmooth surfaces. Scanning electron micrographs (10,000×, unpublished) from a portion of the surfaces of four samples (Fig. 1a–d) showed no evidence of appearance changes due to the increase in albumin concentration and the addition of 1-vinyl-2-pyrrolidinone polymer in the preparation. Pores similar to those seen in polystyrene microcapsules prepared by an interfacial polymer deposition technique (9) could not be found in the albumin microcapsules. But a few microcapsules having some small cracks on their surfaces, which may be caused by shrinking in the freeze-drying process, existed in samples A-1 and A-2 (Table I). The undesirable surface cracks were not found in microcapsules prepared using 20% (w/w) albumin solution (B, C, and D series) or mixed polymer solutions (E series). Accordingly, increase of the albumin concentration and use of 1-vinyl-2-pyrrolidinone polymer should strengthen the microcapsule membrane.

The surface appearances of the microcapsules collected after *in vitro* release experiments were not different from those of the original capsules (Fig. 1e–h). As observation under a light microscope showed, the mixed polymer solution [10% (w/w) albumin, 20% (w/w) 1-vinyl-2-pyrrolidinone polymer], in contrast to the other solutions, gives a homogeneous

[5] Tween 20; Nikko Chemicals Inc., Tokyo, Japan.
[6] JSM-T20; JEOL, Tokyo, Japan.
[7] JFC-1100; JEOL, Tokyo, Japan
[8] Millipore filter BDWP02500; Millipore Co., Bedford, Mass.
[9] Milli-Q2; Millipore Co., Bedford, Mass.

Table III—Effect of 1-Vinyl-2-pyrrolidinone Polymer Concentration on Drug Release [a] from Albumin Microcapsules [b]

Sample	Polymer Concentration, % (w/w)	Viscosity of Aqueous Phase, cp	Speed Setting, rpm	Diameter, μm	Phenacetin Content, % (w/w)	$10^4 v_i$, g/sec	t_h, min	K, %/sec$^{1/2}$	$10^7 V_i$[c], g·cm/sec	$10^2 K'$[d], %·cm/sec$^{1/2}$
E-1	0	1.90	512	81.5 ± 27.5	62.9	3.27	1.6	6.30	5.48	1.06
E-2	5	5.22	512	94.3 ± 33.6	61.8	2.87	1.8	5.94	5.55	1.15
E-3	10	14.7	848	107.5 ± 35.0	59.4	2.40	2.4	4.88	5.21	1.06
E-4	20	68.5	1360	114.5 ± 40.7	62.7	2.02	3.0	4.34	4.72	1.01

[a] Microcapsules containing 40 mg of phenacetin were dispersed in 200 ml of the simulated gastric fluid to obtain v_i, t_h, and K. [b] Microcapsules were prepared on the same day. Albumin concentration and heating time were 10% (w/w) and 10 min, respectively. [c] $V_i = v_i/S_v$, where S_v is the specific surface area of microcapsules. [d] $K' = K/S_v$.

stripe-pattern. Many pores would be expected to be produced by the swelling and subsequent release of 1-vinyl-2-pyrrolidinone polymer dispersed in the membrane matrix during the *in vitro* release experiments; but, no pore was found in the membrane (Fig. 1g and h). On the other hand, fine white crystalline particles adhered to the outer surfaces of the microcapsules, as observed in Fig. 1e–h, which when collected from the release test medium were confirmed to be phenacetin particles.

Each of the albumin microcapsules shown in Fig. 1a, c, e, and g possessed a folded and invaginated surface. A similar surface structure has been reported by Matthews and Nixon with gelatin microcapsules prepared by a simple alcohol coacervation (10). Contrary to the findings with gelatin microcapsules, it was confirmed by light microscopy that the albumin microcapsules dispersed in the release test media appear almost spherical, suggesting hydration of the membrane materials; *i.e.*, folding and invaginating of the surfaces were caused by shrinking in the drying process. Therefore, as the membrane of the microcapsules was fully hydrated in the release test media and remained intact after release experiments, it was concluded that the drug molecules are released through channels in the fully hydrated albumin matrix.

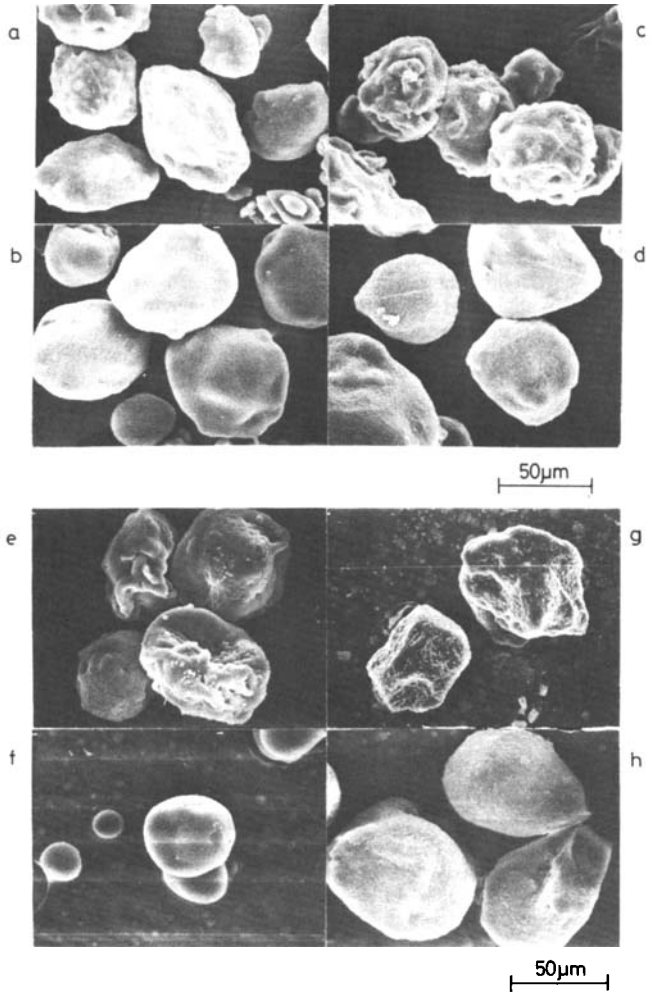

Figure 1—*Scanning electron micrographs of microcapsules prepared using (a,e) 10% (w/w) albumin solution (A-1); (b,f) 20% (w/w) albumin solution (B-1); (c,g) 10% (w/w) albumin solution containing 5% (w/w) 1-vinyl-2-pyrrolidinone polymer (E-2); and (d,h) 10% (w/w) albumin solution containing 20% (w/w) 1-vinyl-2-pyrrolidinone polymer (E-4) before and after the release tests.*

Effects of Albumin Concentration and Release Test Medium—The results of *in vitro* dissolutions of phenacetin powder and microencapsulated phenacetin prepared using a high albumin concentration [20% (w/w)] are shown in Fig. 2. In the simulated gastric fluid, a slower dissolution of phenacetin from the microcapsules in the initial stage was found, as expected. This observation suggests that the drug would be released effectively in drug diffusion. The Higuchi equation may be applied to the *in vitro* release of drugs from microcapsules if diffusion through their membranes is the rate-limiting step (11). Of the four samples of albumin microcapsules used in this study, series A and B gave a linear relationship in the initial stage of phenacetin release in the simulated gastric fluid when the percentage of drug released was plotted against the square root of time, sec$^{1/2}$ (Fig. 3). However, once 50–70% of phenacetin was released, the plots deviated negatively from linearity. This result was unexpected because, with the method of manufacture employed, these microcapsules have a suitable protective wall. But, after the initial stage of release, the core drug content appeared to have little effect on the total percentage of drug released. Accordingly, it is considered that this deviation in Fig. 3 could be attributed to exhaustion of the drug suspension phase, as described by Borodkin and Tucker (12), that is, the number of vacant microcapsules may increase in the latter stage of release.

As analysis over the whole release is difficult in this study, the initial release rate (v_i, g/sec) and the 50% release time (t_h, min), which are obtained by plotting the amount of drug released *versus* time (in min), and the slope (K) of the straight line obtained by plotting the percentage of drug released against the square root of time, sec$^{1/2}$, are used for evaluation of the *in vitro* drug release from albumin microcapsules. Table I shows v_i, t_h, and K obtained from the release profiles of the drug in the three test media. Although the difference was slight, the drug is released in the simulated gastric fluid faster from series A than from series B. As described above, the drug molecules appear to be released through the hydrated and intact membranes. Therefore, this result would be caused by decreased porosity in the membrane matrix and increased tortuosity of channels in which drug molecules diffuse.

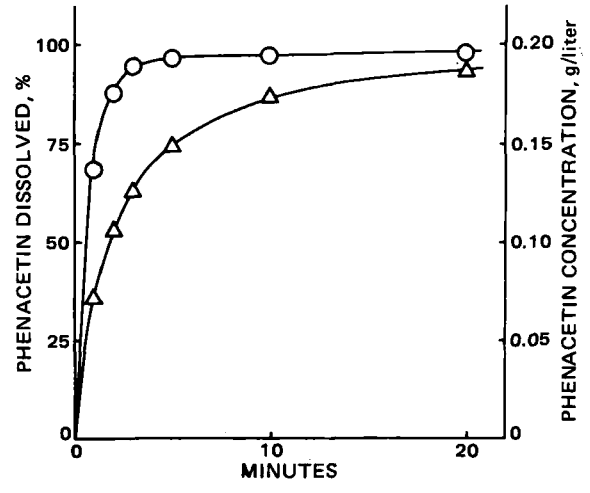

Figure 2—*Dissolution of phenacetin in the simulated gastric fluid. Key: (○) phenacetin; (△) phenacetin microencapsulated using 20% (w/w) albumin solution (B-2).*

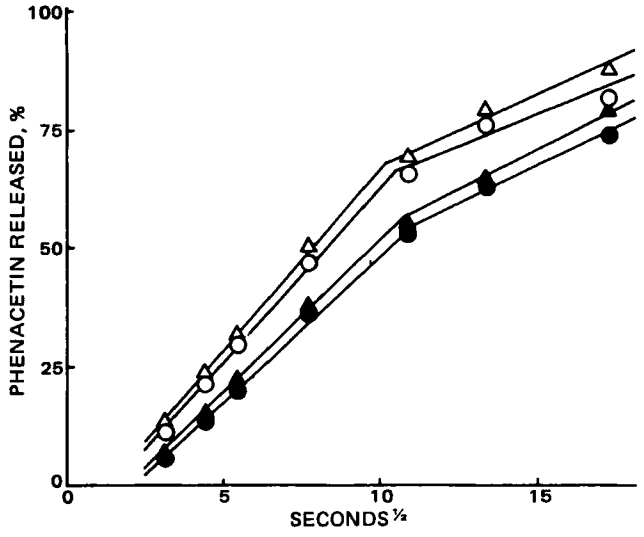

Figure 3—*Relationship between the percentage of drug release in the simulated gastric fluid and the square root of time. Microcapsules were prepared using 10% (w/w) albumin solution (○) A-1; (△) A-2 and 20% (w/w) albumin solution (●) B-1; (▲) B-2.*

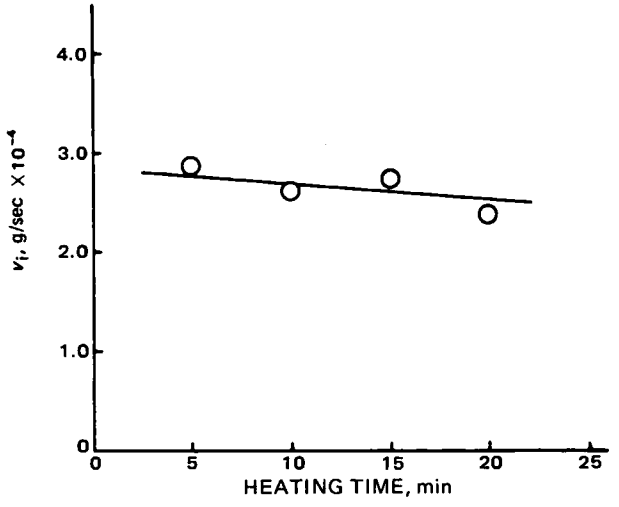

Figure 4—*Effect of heating time in the microencapsulation process on the drug release from albumin microcapsules prepared using 20% (w/w) albumin solution. As samples in the heating process at 85° were separated at scheduled intervals from the same batch (C series), capsule size was not measured. The phenacetin contents were 54.9% (w/w) at 5 min, 46.3% at 10 min, 42.9% at 15 min, and 42.7% at 20 min.*

The albumin microcapsules in sample B-2 released the drug faster in the simulated gastric fluid, though the release rates in both the simulated intestinal fluid and water were similar. Since the solubilities of phenacetin in the three test media were nearly equal, the sink condition was held constant in all *in vitro* release tests. Therefore, the condition for the albumin matrix in which drug molecules diffuse in the simulated gastric fluid seems to be different from those in the simulated intestinal fluid and in water. Furthermore, it is well known that the isoelectric point (pI) of egg albumin is 4.7. When the pH differs greatly from the pI, electrostatic repulsion of the ionized groups change the porosity and tortuosity of channels in the albumin matrix.

Effect of Heating Time in Microencapsulation—Albumin microcapsules were prepared using 20% (w/w) albumin solution. In a microcapsule dispersion sampled 2 min after the flask was immersed in a water bath maintained at 85°, albumin was still insufficiently denaturated in isooctane, and the particles collected by filtration resembled soft-boiled egg membranes. Albumin microcapsules having rigid membranes were obtained if heated >4 min. The microcapsules sampled at 5 min were white in isooctane; those obtained at 10, 15, and 20 min were light yellow.

Figure 4 shows the relationship between the initial release rate v_i and heating time in the microencapsulation. Prolonged heating time produced no appreciable difference in the release rate. Sugibayashi *et al.* have reported that an increase in the denaturing temperature of the microsphere preparation decreases matrix porosity and increases channel tortuosity in the matrix, leading to decreased drug release (8). However, the denaturing temperature of 85° in the microencapsulation used in this study is low when compared with those employed in their work (100–180°), and prolonged heating time may not affect the matrix porosity and channel tortuosity, as previously mentioned.

Effect of Capsule Size—Jalšenjak and Kondo found that the permeability of gelatin–acacia microcapsules toward sodium chloride decreased with increasing capsule size (13). The same trend was observed with the albumin microcapsules.

The effects of capsule size on drug release are given in Table II. The values of v_i and K decreased with increasing capsule size. These results are expected because (*a*) the total volume of the microcapsules containing 40 mg of phenacetin is almost constant and (*b*) the total surface area of the microcapsules increases with decreasing capsule size. But, V_i and K', which are obtained by dividing v_i and K by the specific surface area of the albumin microcapsules, increase with increasing capsule size. Contrary to the gelatin–acacia microcapsules, the albumin microcapsules are multinuclear and their membrane thickness cannot be determined theoretically. And if phenacetin particles are dispersed uniformly in the albumin matrix, it cannot be assumed that the distance along which solute molecules diffuse is shortened as the capsule size increases.

The explanation for V_i increasing with increasing capsule size is as follows: Water structure plays an important role in drug release from microcapsules, as reported previously (14). The structured water in and around the membrane affects the transport of solute molecules, and the amount of structured water is greater in a dispersion containing a large number of microcapsules than in that containing a small number of microcapsules. Another reason would be differences in the denatured state of albumin, due to increased capsule size. It can be assumed that the denaturation affects matrix porosity and channel tortuosity in the matrix.

Effect of Added 1-Vinyl-2-pyrrolidinone Polymer—The effects of the concentration of 1-vinyl-2-pyrrolidinone polymer added to the aqueous albumin solution in the microencapsulation process are shown in Table III. The values of v_i and K decrease, while t_h increases with increasing amounts of 1-vinyl-2-pyrrolidinone polymer. V_i decreases at high 1-vinyl-2-pyrrolidinone polymer concentrations, (10–20%, w/w; samples E-3, E-4). A slight increase in the capsule size due to increased viscosity of the aqueous polymer phase is also shown in Table III. However, even if V_i and K' decrease with increasing capsule size, as described in the previous section, it would be concluded that the increase in the 1-vinyl-2-pyrrolidinone polymer concentration decreases the *in vitro* release rate. Addition of the polymer to the aqueous albumin solution makes the matrix dense (Fig. 1c, d, g, and h), leading to a decreased matrix porosity and increased channel tortuosity in the matrix. Also, hydration of 1-vinyl-2-pyrrolidinone polymer may play an important role in controlling the diffusion of drug molecules. Nakagaki and Shimabayashi reported that the hydration number (water/base, mole) of 1-vinyl-2-pyrrolidinone polymer was calculated to be 2–5 by conductometry (15). Therefore, it is possible that the increase of polymer content decreases the amount of free water in unit volume of the matrix, making channels narrow and channel tortuosity higher.

CONCLUSIONS

Higuchi's equation could be applied to the phenacetin release from albumin microcapsules that have a hydrophilic matrix structure in their membranes, except in the later stages of drug release. The *in vitro* release rate was affected by capsule size, egg albumin concentration, and 1-vinyl-2-pyrrolidinone polymer content used in the microencapsulation process. It decreased with increasing capsule size and albumin and polymer concentrations. Matrix porosity and channel tortuosity in the albumin matrix played an important role in the phenacetin release.

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Systematic Error Associated with Apparatus 2 of the USP Dissolution Test IV: Effect of Air Dissolved in the Dissolution Medium

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Abstract □ Acceptable concentrations of gases in a medium are not well defined in USP dissolution tests. A sample of 10-mg prednisone tablets, known to be sensitive to dissolved gases, was tested with batches of purified water that contained different concentrations of air. The data suggest that results from Apparatus 2 can be influenced by the concentration of air in the dissolution medium unless the medium remains unsaturated with air for the duration of the test. The repeatability of means of six results was markedly improved when the air concentration in the medium was accurately controlled at the beginning of the test.

Keyphrases □ USP dissolution test—correlation of air concentration in medium to dissolution results, Apparatus 2 □ USP Apparatus 2—repeatability of dissolution results, prednisone tablets, effect of dissolved air in medium □ Prednisone—dissolution, USP Apparatus 2, effect of dissolved air in medium

The USP (1) recognizes that gases dissolved in the dissolution medium may influence dissolution test results. In such cases the analyst is directed to remove the dissolved gases before conducting the test; however, no guidance concerning acceptable gas concentrations is given. Since purified water is used to prepare dissolution media, the dissolved gases are those found in air. Complete removal of air from water is not easy; even if "air-free" water were available, air would begin to redissolve as soon as the water again contacted the atmosphere. Thus, one must assume that the air in the dissolution medium is to be reduced to a concentration that no longer influences the dissolution results—a concentration which can be determined only by experiment.

In addition to the USP calibrator tablets, this laboratory has used a sample of commercial 10-mg prednisone tablets, identified as Tablet 2 in previous papers of this series (2, 3), as a "performance standard" for Apparatus 2. Tablet 2, which was also used as a practice sample in a recent collaborative study (4), is very sensitive to excess air in the dissolution medium. A dissolution medium whose air concentration does not influence dissolution results was desired. Various methods for controlling the concentration of dissolved air were studied, and the data are presented in this paper.

BACKGROUND

The first USP dissolution test for prednisone tablets (5) specified the use of deaerated water. Deaerated water (6) is purified water that has been treated to reduce the content of dissolved air by suitable means, such as by boiling it vigorously for 5 min and cooling or by applying ultrasonic vibration. This laboratory interpreted (7) the specification to mean that the water could not be supersaturated with air at 37°, the temperature at which the dissolution test is conducted, because this condition might result in the gradual formation of bubbles on all immersed solid objects, including the product being tested. For several years, dissolution media were prepared from purified water which was boiled, cooled to room temperature, and used within a 24-hr period. A vacuum technique (3) was then developed and used. The two treatments appeared to give equivalent results; however, boiling was less convenient and was gradually replaced by the vacuum treatment.

When the dissolution test for prednisone tablets was revised (8), the specification for the medium was changed from deaerated water to purified water. The USP monograph on purified water does not specify the quantity of dissolved air allowed. Freshly prepared purified water obtained by distillation contains only a fraction of the air contained in freshly prepared purified water obtained by ion-exchange or by reverse osmosis. Dissolution results for certain products are substantially changed when purified water obtained by ion-exchange treatment is substituted for deaerated water (9). The USP later inserted the current specification for dissolved gases in the dissolution medium in the general chapter on dissolution.

EXPERIMENTAL

The test conditions were those used in a recent collaborative study (4) with these exceptions. The six-spindle dissolution drive[1] was not commercially available. The volumes of dissolution medium were measured in volumetric flasks[2]. The dissolution test system was allowed to equilibrate for only 1–2 min before the test was started. Purified water was

[1] Built by the Winchester Engineering and Analytical Center, Food and Drug Administration, Winchester, MA 01890.
[2] 500-ml flasks marked T.D./T.C.; Kimble Products, Vineland, NJ 08360.

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