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Characteristics of Ethylcellulose Microcapsules of Sulfisoxazole

Doo Man Oh and Min Hwa Lee

College of Pharmacy, Seoul National University, Seoul 151, Korea

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Abstract □ Sulfisoxazole, a chemotherapeutic agent, was microencapsulated with ethylcellulose by means of phase separation from cyclohexane by temperatture change. The size distribution was determined by use of standard sieves and the effect of core to wall ratio was noted. To examine their shapes and surface characteristics, the microcapsules were observed with a scanning electron microscope. Release of the drug from microcapsules into pH 7.5 buffer medium was studied. The release pattern was found to have similar properties to the release of a drug from an insoluble porous matrix reported. The apparent diffusion coefficient of sulfisoxazole was measured for the transport of the drug from the core of microcapsules into the surrounding sink condition. The apparent diffusion coefficient increased with increasing capsule size.

Keywords □ Microencapsulation, Phase separation, Sulfisoxazole microcapsules, Size distribution, Scanning electron microscopic observation, Dissolution, Diffusion coefficient.

Several general reviews of microencapsulation have been published.[1-3] The development of microencapsulation as a technique for the preparation of sustained release dosage forms has progressed steadily with the emphasis mainly on the use of gelatin-acacia coacervates as a means of microencapsulating water-insoluble drugs.[1]

Other techniques have been investigated particularly for microencapsulation of water soluble drugs.[4] A procedure for producing microcapsules of water soluble materials was outlined in the U.S. patent and involved ethylcellulose coating by means of polymer deposition from cyclohexane by temperature change[5] or by nonsolvent addition.[6] Recently, ethylcellulose microcapsules were prepared by the more flexible procedure of pan coating.[7]

Jalsenjak *et al.*[8] and Deasy *et al.*[9] have found that ethylcellulose coated microcapsules containing water soluble drugs had poor capacity to retard drug release. Therefore, coating of core was modified using various sealants in an attempt to prolong the *in vitro* release of drugs.[7,9]

The core materials microencapsulated by ethylcellulose in the literature[8-14] were aspirin, sodium phenobarbitone, magnesium aluminum hydroxide hydrate, sodium salicyate, pipethanate hydrochloride, pheneticillin potassium, and methylene blue. However, few papers have been reported on the methylcellulose micrcapsules of water insoluble drugs.

Permeability is one of the most important proporties of microcapsules when they are used in the medical and pharmaceutical fields. The permeation process of a drug through the wall of a microcapsule is closey related to the composition of the wall and/or to the method of preparation of the microcapsules. Ohta et al.[15] found that the permeability coefficient of ethylcellulose microcapsules towards sodium hydroxide increased with increasing capsule size, and Jalsenjak and Kondo[16] reported that the permeability of gelatin-acacia microcapsules

followed the same trend. In both papers, the permeability coefficients of microcapsules towards electrolytes were measured on thin-walled microcapsules, the wall thicknesses of which could be regarded as constants, whatever the particle size of microcapsules is.

The authors have investigated the preparation of microcapsules with ethylcellulose at different core to wall ratios, and the *in vitro* dissolution of a water insoluble drug, sufisoxazole, from microcapsules. Also this paper reports the wall permeability of sulfisoxazole for various capsule sizes when solute permeation takes place from the capsule core into the surrounding sink condition.

EXPERIMENTAL METHODS

Materials

Sulfisoxazole(K.P. IV) was sieved through a series of standard K.P. sieves. Particle size range was 37-74 μm. Ethylcellulose standard 10 cp and 20 cp(Ethocel, Dow Chem.), hexane (Wako Pure Chem.), and cyclohexane(Wako Pure Chem.) were used. The pH 7.5 phosphate buffer was used as dissolution medium. All materials used were of reagent grade.

Preparation of Microcapsules

The method was based on those described by Fanger et al.[5] and Jalsenjak *et al.*[8] The coating vessel used was 1 liter capacity of three-necked round bottomed flask and fitted with a stainless four bladed stirrer, a thermometer, and a reflux condenser. The lower part of the vessel was heated by immersion in an oil bath. With continuous stirring at 50°C with magnetic bar, wall material (ethylcellulose) in an amount depending upon the core to wall ratios, was added to 600 ml of cyclohexane and the temperature raised to 70°C over 20 minutes. Core material, sulfisoxazole, was then added and the temperature raised to 80°C. After being held constant for 1 hour, the system was cooled carefully. When the temperature was 78°C, the magnetic bar was removed and stirring was continued using the four bladed stirrer at 9000 r.p.m. Subsequently, the system was allowed to cool slowly to 35°C over 3 hours and then cooling accelerated to 25°C. The microcapsules were filtered, washed with cold cyclohexane, and dried in air.

Microcapsules with core to wall ratios of 1:1, 1:1.5, and 1:2, with ethylcellulose 10 cp or 20 cp, were prepared respectively. Cyclohexane was reused after redistillation.

Particle Size Separation of Microcapsules

The various battches obtained were classfied into suitable particle size ranges using a nest of standard sieves mounted on a moving sieve shaker for 5 minutes.

Dissolution Procedure

An equivalent quantity of 100 mg sulfisozazole of selected particle size ranges were weighed into a K.P. dissolution basket assembly which was then immersed in 900 ml dissolution medium, pH 7.5 phosphate buffer solution at 37$\pm$ 0.5°C. A stirring speed of 100 r.p.m. was used. Time commenced on the introduction of the basket into the medium. At intervals, 2 ml samples were removed, flitered, and assayed spectrophotometrically at 255 nm (Pye Unicam SP 1750 Ultraviolet Spectrophotometer).

An equal volume of dissolution medium was added to the dissolution vessel immediately after each sample was removed as was allowed for the calculation of the amount of drug released.[14]

Total Drug Contents of Microcapsules with 1:1 *Core to Wall Ratio*

Triplicate samples of approximately 200 mg

of microcapsules were accurately weighed, and thorougily triturated, and the powder was suspended in 1000 ml of pH 7.5 phosphate buffer solution. The mixture was filtered through a Millipore filter with a 0.22 μm pore size. A suitable dilution of the sample was made, and assayed at 255 nm. The microcapsule walls were collected, washed, and dried.

Determination of Wall Thickness

For relatively thick-walled microcapsulse, an encapsulated particle can be considered as two concentric spheres having the radius of microcapsule, r_{mc}, and the radius of core, r_c. The thickness of the wall, h, can be calculated from the volume relationships of the concentric spheres as follows; The mass of the wall, m_w, is given by

$$m_w = N\left[\frac{4}{3}\pi r_{mc}^3 - \frac{4}{3}\pi(r_{mc}-h)^3\right] d_w \cdots (1)$$

where N is the number of capsules and d_w is the density of the wall material. The number of particles per sample weight, m_{mc} grams, is given by

$$N = \frac{3m_{mc}}{4\pi r_{mc}^3 \cdot d_{mc}} \cdots (2)$$

where d_{mc} is the density of microcapsules. Therefore, the following equation is obtained;

$$h = r_{mc}\left[1-\left(1-\frac{m_w \cdot d_{mc}}{m_{mc}\cdot d_w}\right)^{\frac{1}{3}}\right] \cdots (3)$$

The thickness of wall can be calculated from the densities of wall and capsules, the mass of the wall material, m_w, in a sample of microcapsules weighing m_{mc} grams. Densities were determined from the displacement volume of a known weight of the wall material, or a sample of microcapsules, using n-hexane as the displacement fluid.[12,17,18]

Permeation Studies

The permeation process may be characterized by means of Fick's First law. For a sample of spherical microcapsules, the permeation rate is given by;

$$\frac{d_m}{dt} = Da \cdot A \cdot \frac{\Delta c}{h} \cdots (4)$$

where m is the mass of drug released, Δc is the difference in drug concentration between the inside, c_2, and outside, c_1, of the microcapsules, Da is the apparent diffusion coefficient, and h is the wall membrane thickness. The total surface area, A, is defined as the product of the number of capsules in a sample and the surface area of an individual capsule, *i.e.* $A = N \cdot 4\pi r_{mc} \cdot r_c$. Under the experimental conditions used, $c_2 \gg c_1$, thus Δc becomes c_2.

For a plot of the mass of drug transferred against time, the permeation rate is given by the slope, dm/dt, and the apparent diffusion coefficient is

$$Da = \frac{\text{slope} \cdot h}{N \cdot 4\pi r_{mc} \cdot r_c \cdot c_2} \cdots (5)$$

Slopes were calculated by the least squares methods and as the other parameters of the equation (5) were known, the apparent diffusion coefficients were calculated.[20]

Scanning Electron Microscopy

Dried samples of microcapsules were mounted onto stubs and vacuum-coated with gold film approximately 60nm thick. A JSM-35 Scanning Electron Microscope (Jeol) was used.

RESULTS AND DISCUSSION

The technique of polymer separation as a means of coating solid particles to form microcapsules is apparently easy, but slight changes in the procedure produce a marked variation in the final product. This variation is shown by the gross appearance of the microcapsules and also in their size distribution.

Factors affecting the nature and yield of the microcapsules were the viscosity of the polymer, the degree of agitation, the time of addition of

wall and core materials, and the rate of cooling. The stirring rate had the greatest effect. Different stirring rates have been used: for example, Jalsenjak *et al.*[8] used 560 r.p.m. Deasy *et al.*[9] used 750r.p.m., whereas Feinstein & Sciarra[21] used 100r.p.m., and Alpar & Walters[13] used 248r.p.m. At slow speeds large ethylcellulose-coated microcapsules were obtained as a result of aggregation. Therefore, 900r.p.m. was adopted. The behavior of the system probably depends on the materials as well as well as on the rate of stirring. The second important variable was the rate of cooling. In the rapid cooling, the core, sulfisoxazole, was coated unevenly with small particles of ethylcellulose (Fig. 1). Alhtough the rate of stirring was relatively slow, lots of fine microcapsules were sometimes obtained if the rate of cooling was very slow. The grade of ethylcellulose used was also important. Standard ethylcellulose having a high ethoxy content was preferred. The technique adopted produced microcapsules with a smooth outer wall and a size distribution which was approximately repr oducible from batch to batch (Table I).

Table I shows that the size distribution was changed when the stirring rate was reduced to 600 r.p.m. Sieving analysis results are also shown from products obtained using ethylcellulose standard 10 cp or 20 cp. The 20 cp grade produced less coarse particles. The general appearance of both samples was similar as shown in Fig. 1(A) and (B).

Fig. 1(C) shows that in part the larger microcapsules are composed of aggregates of smaller capsules, rather than single capsules with thicker walls. A similar aggregated appearance of ethylcellulose coated drugs was reported.[9,22] Fig. 1(D) shows a portion of the surface of an ethylcellulose 20 cp coated microcapsule which, like the surface of 10cp coated capsule, exhibits both rough and smooth areas with the presence of pores, some of which may extend through the coating to the core material. These pores can act as points of entry for dissolution fluid.

Fig. 1(F) shows a portion of the surface of a microcapsule after 3 hour dissolution study, which, in contrast to Fig. 1(D), shows a swollen and eroded surface with an enlarged pore present. This observation was different from the results of Alpar & Walters[13] and others.[7,8] However, the change of the surface of microcapsules after 10 minute dissolution treatment was not observed (Fig. 1E). In add-

Table I: Size distribution of sulfisoxazole microcapsules.

Size range	Mean size	% Fraction for a given core: wall ratio				
		1 : 1			1:1.5	1:2
μm	μm	A	B	C	D	E
149~297	223	4.11	13.58	2.57	8.93	7.05
297~500	398.5	46.39	30.02	54.93	46.10	51.95
500~840	670	40.01	36.19	40.98	42.13	39.75
840~2,000	1,420	9.15	19.62	1.52	1.66	1.25
2,000		0.34	0.59	0.00	1.18	0.00

A: Ethylcellulose 10 cp and the stirring rate 900 r.p.m.
B: Ethylcellulose 20 cp and the stirring rate 600 r.p.m.
C, D, E: Ethylcellulose 20 cp and the stirring rate 900 r.p.m.

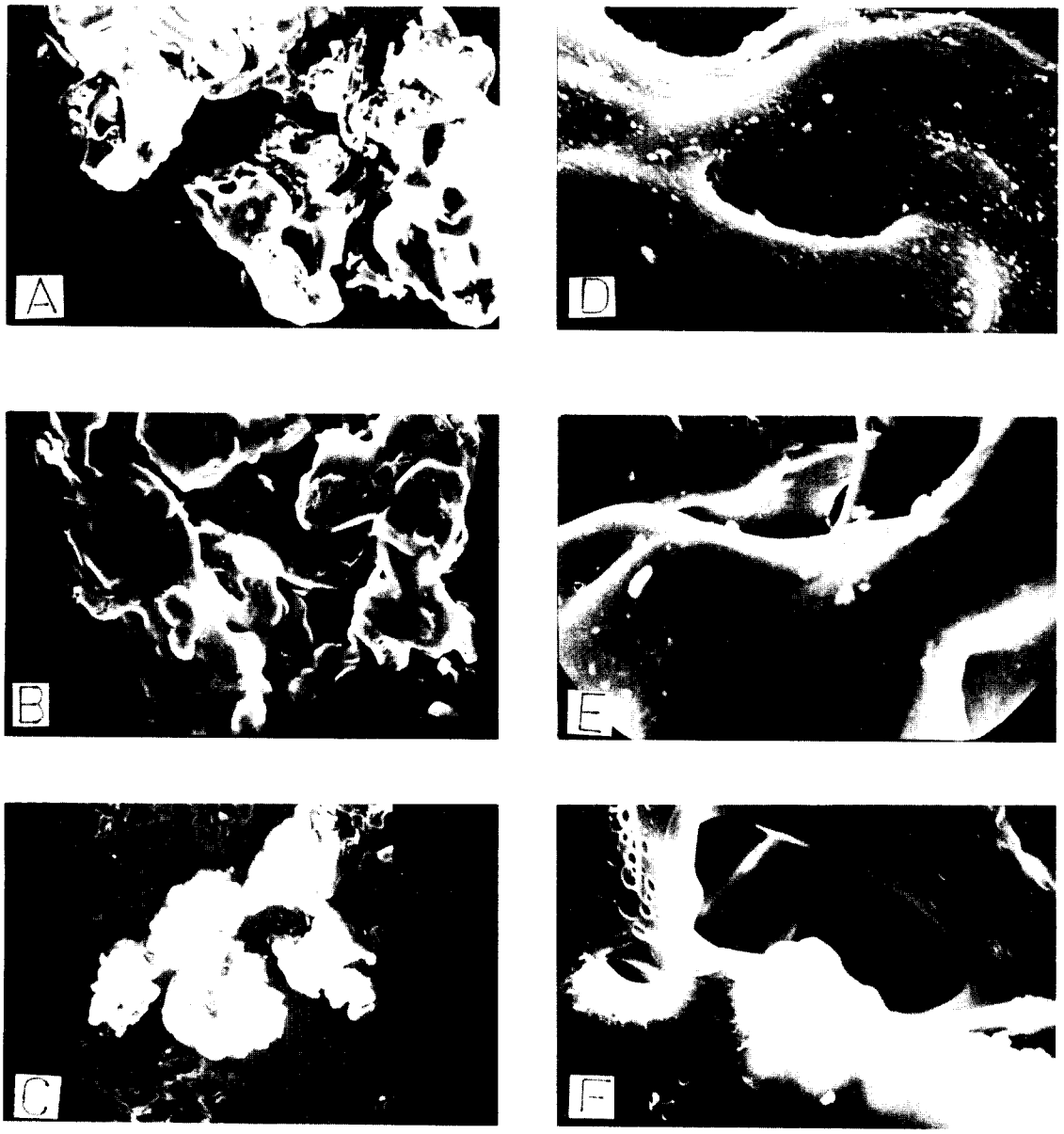

Fig. 1: Scanning electron micrographs of mean size 398.5μm microcapsules containing sulfisoxazole coated with ethylcellulose 10 cp (A) or 20 cp (B,C,D,E,F), before (A,B,C,D) or after 10 minute (E) and 3 hour (F) dissolution studies. Magnification: A,B 200×, C 48×, D,E,F, 1,000×.

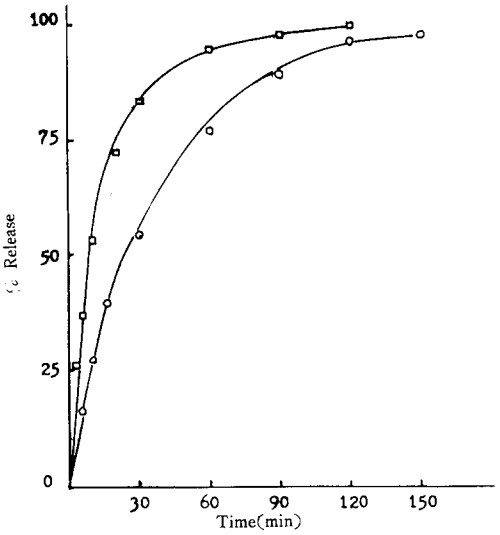

Fig. 2: Release (%) of sulfisoxazole from microcapsules prepared with ethylcellulose 10 cp microcapsule (□) and 20 cp (○), respectively. Mean size: 398.5μm.

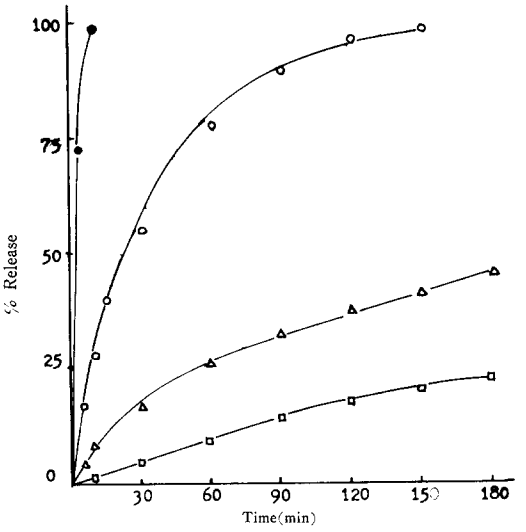

Fig. 3: Release (%) or sulfisoxazole from microcapsules prepared at various core to wall ratios. Mean microcapsule size: 398.5μm. Core to wall ratio: ●, 1:0 (sulfisoxazole only); ○, 1:1; △, 1:1; □, 1:2.

ition, some portion of microcapsules still was not changed at the surface morphology after 30 minute dissolution.

Studies of the *in vitro* dissolution are often used to indicate possible differences in bioavailability of pharmaceutical products. Fig. 2 shows the release of sulfisoxazole from 398.5μm mean size microcapsules prepared using two grades of ethylcellulose. The ethylcellulose 20cp coated capsules had the slower release. It was assumed by Deasy *et al.*[9] that the faster release of core material from the 10 cp coated microcapsules was probably due to their greater fragmentation and porosity associated with increased swelling of the polymer.

For the production of prolonged action preparations, it is desirable that the release of the encapsulated drug should be further retarded. Because of its capacity to produce a finer particulate product with a great tendency to prolong release, ethylcellulose 20 cp was chosen to prepare several batches of microcapsules.

Fig. 3 shows the release of sulfisoxazole from microcapsule fractions with various core to wall ratios. Uncoated drug dissolved completely within 10 minutes. As the core to wall ratio decreased, the release of the drug decreased considerably. It is reasonable to expect thicker walls and correspondingly greater delays in the release rate. It was also reported that the surface areas decreased as a result of increasing wall thickness and the intensity of surface pores decreased with decreasing core to wall ratios.[13]

At a constant core to wall ratio, the smaller microcapsules released their contents more rapidly (Fig. 4). As the larger microcapsules consisted of aggregates of smaller microcapsules (Fig. 1C), dissolution was confined to the outer surface and thus the relase of the drug from the center of the aggregate was inhibited. The

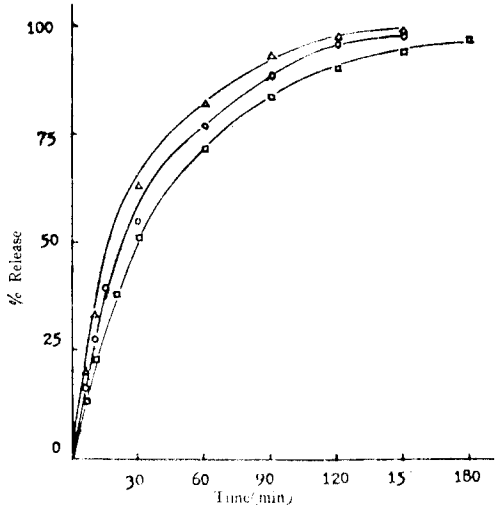

Fig. 4: Release (%) of sulfisoxazole from microcapsules of various size with 1:1 core to wall ratio. Mean size, μm, △223, ○398.5, □670.

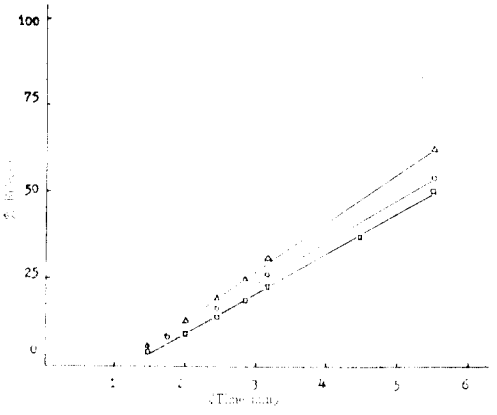

Fig. 5: Release (%) of sulfisoxazole as a function of time. Mean size, μm, △223, ○398.5, □670.

Table II: Characteristics of ethylcellulose microcapsules with 1:1 core to wall ratio.

Size fraction	r_{mc} cm	r_c cm	h cm	d_w# gcm^{-3}	d_{mc}# gcm^{-3}	m_w*# g	m_{mc}*# g	N*
1	0.0117	0.0064	0.0053	1.281	1.470	0.0965	0.1035	20,280
2	0.0199	0.0113	0.0086	1.224	1.307	0.0968	0.1032	4,636
3	0.0335	0.0193	0.0142	1.183	1.226	0.0988	0.1012	1,036

* Expressed per 0.2g samples (*i.e.* $m_{mc}=0.2g$).
\# The mean value of three determinations.

dissolution curves showed a linear part at the beginning of process and afterwards the plot showed a downward deviation from the straight line (Fig. 4). The linear relationship held for up to approximately 40% of the initial drug content in the microcapsules.

The mechanism of drug release from microcapsules is probably complex, involving leaching, diffusion, and erosion compounded by polymer swelling. With polymer encapsulated drug systems, swelling or erosion of the coating will lead to changes in drug release rate. Although the enlargement of the surface pores through which solution and diffusion would occur was observed after the overall dissolution test, the microcapsules did not fragment or alter in shape or size during the earlier dissolution stages (Fig. 1E). Therefore, release of the drug would be expected to occur partly by a diffusion controlled process.

Higuchi[23] reported the release of a drug from insoluble porous matrix was linearly related to the square root of time. The ethylcellulose coated microcapsules of sulfisoxazole show a similar straight line (Fig. 5), which is further evidence that a diffusion process is responsible for the release of the drug similar to results of Schwartz *et al.*[24]

For the purpose of size fraction characterization, it was possible to estimate the average thickness of the wall for the ideal case, that is, assuming perfect sphericity and wall uniformity by calculation. The physical characteristics of microcapsules of sulfisoxazole are given in Table II. The densities of the microcapsules and the wall material decreased with increasing capsule size, but there is insufficient evidence to suggest the cause of this.

A suggested overall permeation mechanism of the core material by solvent permeation consists of three rates: the rate of solvent penetration into the microcapsule, the rate of core dissolution, and the rate of removal of core material into solution.[12] The rate of release of the drug is determined, in general, by the solution to Fick's law.

The calculation of the apparent diffusion coefficient in this paper was carried out with certain assumptions. If a drug is enclosed within an inert membrane or wall, and if the drug concentration is maintained constant within the enclosure, then a steady state will be established, during which the permeation rate will be constant under the sink condition of the bulk solution. The most convenient method in achieving these demands is with a saturated solution of a drug with an excess of solid drug present in a microcapsule. The constant permeation rate can be maintained as long as excess pure solid phase is present. Continual loss of drug or dilution by penetrated water will eventually produce a situation where the rate will fall. It is assumed that a uniform concentration gradient in the wall holds as long as the permeation rate is constant(Fig. 6). A volume of the sink condition was 900 ml. The solubility of sulfisoxazole in pH 7.5 phophate buffer is 0.375 g litre^{-1} at 37°C. Therefore, sink conditions

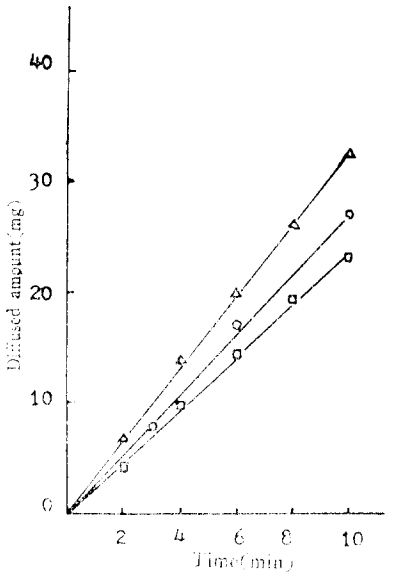

Fig. 6: Plot of amount of drug diffused into buffer medium (pH 7.5) m_{mc}=0.200g. Microcapsule size fraction: △1, ○2, □3.

were adopted in this experiment. And the difference in concentration of the drug inside and outside the microcapsules is equal to C_2. Although progressive swelling of the wall might have taken place with increase in porosity and decrease in tortuosity as dissolution proceeded, any alteration of microcapsule wall could not be observed during permeation studies (Fig. 1E). Therefore, it was assumed that the total surface area and the wall thickness were constant.

It appears that in range of experiments all of necessary requirements are met, and the apparent diffusion coefficient, Da, was calculated by using equation (5). The numerical values of Da are given in Table III. The apparent diffusion coefficient increased with increasing microcapsule size.

This finding can be compared with the results of others.[12,15] The permeability coefficient increased with increasing capsule sizeas was reported in those papers. The permeability coefficient,

Table III: Apparent diffusion coefficients for sulfisoxazole.

Size fraction	dm/dt $\times 10^5 gs^{-1}$	Da $\times 10^7 cm^2 s^{-1}$	% M.D.*
1	5.440	0.40	8.4
2	4.431	0.78	8.6
3	3.978	1.79	1.7

* % Difference of the most deviant result of four experiments from the mean.

P, can be converted to the apparent diffusion coefficient by using the equation;[25]

$$Da=P.h \quad \cdots\cdots(6)$$

The wall thicknesses of the thin-walled microcapsules were supposed to be constant independent of the size of microcapsule.[17] If this assumption holds, it may be concluded the apparent diffusion coefficient for a drug should also have the same trend as the permeability coefficient.

Structured water in and around the microcapsule wall was suggested as the possible cause of the observed size effect since the amount of structured water is grater in a dispersion containing microcapsules of small size in large numbers than in one containing microcapsules of a large size in small numbers.[26]

Another explanation of the influence of capsule size on the apparent diffusion coefficient was proposed by Senjkovic & Jalsenjak.[12] A drug diffuses in the ethylcellulose film also by the solubility process in the membrane.[20] It has been shown that the volume of pores in the wall of ethylcellulose microcapsules is small.[27] Association of those findngs with the rather high values of Da of sodium phenobarbitone allowed the postulation of parallel membrane and a queous pore pathways for the permeation of the drug through the microcapsule wall. In such a case, the increase of the apparent diffusion coefficient for larger microcapsules would be given by the volume fraction of the pores in the wall depending upon the capsule size.[12] Support for this explanation comes from the fact that the density of the wall material is lower for larger microcapsules indicating higher porosity of their walls(Table II).

Further studies of ethylcellulose-coated microcapsules will be investigated on the release of sulfisoxazole from tableted microcapsules of various core to wall ratios and mean sizes. In addition, the data of the *in vivo* release of the drug from their dosage forms will be compared with those of the *in vitro* release.

CONCLUSION

1. The important factors affecting the preparation of microcapsules were the degree of stirring, the rate of cooling, and the viscosity of the polymer.
2. Scanning electron microscopic observation of products indicated that the surface of microcapsule walls was not changed during the permeation studies (10 minutes) but changed during the dissolution test by erosion and swelling of ethylcellulose.
3. The release of sulfisoxazole from ethylcellulose microcapsules, as those of water soluble drugs, decreased with decreasing the core to wall ratio, and with increasing the particle size at a constant core to wall ratio. The ethylcellulose 20 cp coated microcapsules released the drug slower than those prepared with ethylcellulose 10 cp.
4. A diffusion process was partly responsible for the release of the drug.
5. The apparent diffusion coefficient of the drug from microcapsules increased with increasing microcapsule size.

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