International Journal of Pharmaceutics, 12 (1982) 251–264
Elsevier Biomedical Press

Dissolution rate control of the release kinetics of water-soluble compounds from ethyl cellulose film-type microcapsules

S. Benita and M. Donbrow

Department of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, Jerusalem 91120, P.O.B. 12065 (Israel)

(Received December 2nd, 1981)
(Modified version received March 20th, 1982)
(Accepted April 5th, 1982)

Summary

Microcapsules of sodium salicylate and potassium dichromate were prepared by the temperature reduction ethyl cellulose coacervation method using polyisobutylene as a protective colloid. Film-coated microcapsules were obtained. Minute empty wall polymer spheres were also formed in amounts increasing with protective colloid concentration or core particle size and decreasing with ethylcellulose concentration, in conformity with the mechanism previously proposed.

Neither matrix diffusion nor first-order kinetics was observed by sodium salicylate experimental release data. Since small pores not initially present were formed, a dissolution model was applied; release conformed with the Hixson-Crowell cube-root law and was influenced by agitation rate in the sink solution. The effective diffusion coefficients from dissolution rate constants were near to the theoretical water value but several orders higher than the measured permeability constant through ethylcellulose cast films.

In support of a hypothesis that pore-formation was caused by the high "internal osmotic pressure developed by water-soluble core material", the release rate fell on increasing external osmotic pressure, which ultimately prevented pore-formation at 7 M LiCl. This is the first case in which a dissolution model has been shown applicable to film-coated core materials.

0378-5173/82/0000–0000/$02.75

Introduction

The nature of ethylcellulose-coated microcapsules prepared by coacervation using the differential thermal solubility method varies, depending on the experimental conditions used (Benita and Donbrow, 1981; Senjkovic and Jalsenjak, 1981). Addition of a protective colloid such as polyisobutylene favours formation of discrete, single-core, smooth-walled microcapsules (Benita and Donbrow, 1981; Merkle, 1972), which we have termed the "film-type", as opposed to the "matrix-type" consisting of multiple-core agglomerates that are generally obtained when a protective colloid is not employed. The kinetics of drug release would be expected to differ in these structurally-distinct microcapsule types. Indeed, the Higuchi matrix diffusion equation was considered applicable (Salib et al., 1971; Jalsenjak et al., 1976; Oyaalpar and Walters, 1981; Deasy et al., 1980) in typical systems prepared without protective colloid present. On the other hand, first-order release was reported in several cases in which a protective colloid had been employed (John et al., 1979; Benita and Donbrow, 1981a, b) and the present authors have in fact validated these kinetics for salicylamide and theophylline release, which also seemed to observe a square-root of time release pattern. It is of interest that most of the microencapsulated core materials were water-soluble in the studies in which matrix-type microcapsules were obtained but sparingly soluble in water with the film-type. To complete the picture of the behaviour of the latter type of microcapsule, the present work reports some studies on water-soluble core materials and the in vitro release kinetics of sodium salicylate from such single core microcapsules.

Materials and methods

Materials

Ethylcellulose (N-type) had an ethoxyl content of 4.75–49.0% and the viscosity of a 5% w/w solution in toluene–ethanol (80:20 w/w) was 100 cps (Hercules, Wilmington, DE). Polyisobutylene had an MW of 380000 (Oppanol B50, BASF, Ludwigshafen, F.R.G.). Sodium salicylate conformed to USP XIX (Baker and Adamson, Morristown, NJ) and potassium dichromate to DAB 7 (Riedel-De-Haen AG, Seelze-Hannover, F.R.G.).

Methods

Preparation of microcapsules

An abridged description is given, full details having been presented elsewhere (loc.cit.). Mixtures containing the required quantities of sodium salicylate, ethylcellulose, polyisobutylene and cyclohexane were heated to 80°C. They were allowed to cool slowly at controlled stirring rate to 45°C and were then cooled very rapidly, using ice, to 25°C and stirred for a further 15 min.

The microcapsules were separated from the solution by decantation and rinsed

with three 200 ml portions of cyclohexane to remove polyisobutylene from the microcapsule surface and also any empty wall polymer coacervate droplets present. They were collected by vacuum filtration and oven-dried at 50°C for 30 min, yielding a free-flowing powder. Sodium salicylate was the main core material investigated and potassium dichromate was found convenient as a model core substance.

All batches were duplicated or triplicated if the active ingredient content deviated more than 3–4% between batches.

Core materials, were segregated by standard mesh sieves before microencapsulation.

Drug solubility in coating solution and drug losses

Sodium salicylate was found to be insoluble in the solvent-wall polymer mixture at 80°C. The particle size distribution of the core material, checked microscopically, did not change significantly during the microcapsulation process, nor were uncoated drug particles detected in the apparatus or the batch.

Evaluation of microcapsules:

Drug content. A weighed quantity of microcapsules was disintegrated in water by means of a high-speed blender until all the core material had dissolved and filtered to remove the insoluble wall polymer fragments. Potassium dichromate and sodium salicylate were determined spectrophotometrically at 257 nm and 298 nm, respectively, against standard solutions.

Wall polymer rejected during microcapsule formation. The percent rejection, R, was calculated for each batch from the equation (Benita and Donbrow, 1981a):

$$R = 100[1 + W_0/W_{EC}(1 - 1/F)] \tag{1}$$

where R is the percent of ethylcellulose rejected, W_0 is the initial amount of drug used, W_{EC} is the initial amount of wall polymer available for microencapsulation and F is the fractional drug content of isolated product by weight, determined experimentally. For the case in which $W_0 = W_{EC}$; this simplifies to:

$$R = 100(2 - 1/F) \tag{2}$$

Wall thickness. The microcapsule wall thickness was calculated from the equation (Benita and Donbrow, 1981a):

$$r_2 - r_1 = \left\{\left[\frac{d_c}{d_{EC}}(1/F - 1) + 1\right]^{1/3} - 1\right\} r_1 \tag{3}$$

where r_1 and r_2 are the mean radii of the microcapsules and the core particles and d_{EC}, d_c are the densities of ethylcellulose and the core materials. The densities of the microcapsules and the core and wall materials were determined in cyclohexane using

a pycnometer. Dried materials were used and volume adjustment was completed in a few seconds to avoid imbibition and swelling. Results were reproducible and were within 2% of literature values.

Microscopic studies. The surface characteristics of the wall membranes obtained under different conditions, both before and after immersion in the sink solution were studied by Scanning electron microscopy (Cambridge Instruments, U.K.). The wet microcapsule shells were isolated by vacuum filtration, dried at 50°C for 2 h and lyophilized overnight prior to regular gold coating treatment.

Release of microencapsulated material. Release of active ingredients from the microcapsules was measured using a rotating basket dissolution apparatus similar to that described in the U.S.P. XIX, modified by use of a 100 ml perspex basket fitted with nylon mesh windows in place of the wire mesh (Benita and Donbrow, 1981a). The basket was rotated at 100 rpm (±3%) by means of a constant rate adjustable stirrer (Stedi speed model, Fisher, Pittsburgh, PA) using a covered beaker containing 1 litre of water at 37°C (±0.5). Drug release was determined spectrophotometrically (Unicam SP1800, Pye Unicam, Cambridge, U.K.) using a flow cell with pump (Model MHRK, Watson-Marlow, Falmouth, U.K.) and automatic recording. The sample size was 50–100 mg. There was no turbulence, as checked by measurement of dissolution rate of standard pellets of pure benzoic acid.

Measurements were at least duplicated and were closely reproducible. The sink solution was water, except in the work on pH effects, in which McIlvaine buffers were used.

Results and discussion

Microcapsule characteristics and preparation variables

The influence of polyisobutylene concentration and core particle size on microcapsule properties, previously studied using non-ionic materials such as salicylamide and theophylline, was investigated to determine whether the highly water-soluble ionic core materials behaved similarly with respect to coating efficiency, microcapsule type and release behaviour.

TABLE I

POTASSIUM DICHROMATE MICROCAPSULES: EFFECT OF POLYISOBUTYLENE CONCENTRATION ON COMPOSITION

Polyisobutylene (%)	Dichromate content (%)	Wall thickness (μm)	Ethyl cellulose rejected (%)
3	88.0	10.35	73
4	90.3	7.52	79
5	92.5	6.37	84

Initial conditions: potassium dichromate (213.5 μm, mean diameter) 10% w/w, ethyl cellulose 5% w/w in cyclohexane, 250 rpm.

TABLE 2

SODIUM SALICYLATE MICROCAPSULES: (a) EFFECT OF ETHYL CELLULOSE CONCENTRATION ON COMPOSITION AND PROPERTIES, AND (b) EFFECTIVE DIFFUSION COEFFICIENTS, D

Ethyl cellulose (%)	(a)				(b)
	Drug content (%)	Wall thickness (μm)	Ethyl cellulose rejected (%)	Hixson-Crowell release constant (10^2 mg$^{1/3}\cdot$s^{-1})	D (10^5 cm$^2\cdot$s^{-1})
1	83.7	2.75	42.8	8.30	0.30
3	77.0	6.61	50.3	5.33	0.37
5	52.8	16.30	11.1	0.55	0.20

Initial conditions: sodium salicylate (111.5 μm, mean diameter) 5% w/w, polyisobutylene 5% w/w in cyclohexane, 250 rpm.

Table 1 shows the influence of the protective colloid concentration on potassium dichromate microcapsule properties.

Increase of colloid concentration yielded microcapsules of higher dichromate content. As the initial wall polymer/dichromate ratio and the particle size were constant and there was no loss of core material, the content variation is due to varying wall membrane thickness, as indicated by the calculated values. The microcapsules were quantitatively recovered and the core particles were found to be uniformly microencapsulated. Evidently, the variation in wall polymer content and wall thickness is due to the formation of empty coacervate droplets and their removal during the washing and decantation stages[1]. The percent rejection of ethylcellulose in the last column was calculated from the difference between the polymer available and that found in the microcapsules (Eqn. 1). It represents the amount of wall polymer unavailable in the coating process under the specific conditions used and hence of the amount converted into empty coacervate droplets.

In considering the possible causes of the observed decrease of coating efficiency, it is tempting to assume that excess of wall polymer was used, so that decreasing its quantity will eliminate the amount rejected. However, as shown in Table 2a, decrease in the amount of ethylcellulose from 5% to 1% in the microencapsulation of sodium salicylate led on the contrary to an increase in percent loss. The explanation of the phenomenon must therefore be sought elsewhere.

The effect of protective colloid concentration on the apparent loss of wall polymer by formation of empty droplets closely parallels its effect on the size of stabilized coacervate droplets when core material is absent, shown in previous work (Benita and Donbrow, 1980). Such stabilized coacervate droplets, suspended in the

[1] The appearance of these empty shells is presented in Benita and Donbrow (1981a)

solvent, were unable in the present work to coat core material when the two were mixed and stirred together at room temperature. It is therefore proposed that increase in the protective colloid concentration above a critical level inhibits diffusion and growth of the ethylcellulose phase separating during cooling; this results from increase in the viscosity of the medium and the degree of adsorption of the protective colloid. As a consequence, a larger proportion of coacervate droplets are stabilized when still small, these becoming less available or unavailable for coating core particles. While on the one hand this reduces the efficiency of the coating process it may on the other hand be utilized to obtain the film-type of microcapsule, containing single discrete core particles, and also to control wall thickness.

In contrast to the results reported in the literature, the microcapsule drug content decreases with decreasing particle size of the drug, in the presence of the protective colloid (Table 3a). This is caused by more complete uptake of the wall polymer, particle size reduction leading to increase in the specific surface of the core particles of core material which, with a fixed amount, causes increased entrapment of separating coacervate droplets of wall polymer. These experimental results fit the mechanism proposed. Similar behaviour was observed in the microencapsulation of salicylamide and theophylline and it is concluded that the character of the core material does not significantly influence the nature of the microcapsules or the effects of core particle size and protective colloid concentration in the process.

Release kinetics and wall pore formation

Up to the present, drug release from microcapsules was considered to follow one of two possible kinetic models: the Higuchi diffusional equation, developed to describe the behaviour of drug dispersions in matrices (Higuchi, 1963), or the classical first-order equation.

Neither model was found to be in accord with the experimental release data for

TABLE 3

SODIUM SALICYLATE MICROCAPSULES: (a) EFFECT OF CORE PARTICLE SIZE ON COMPOSITION AND PROPERTIES, AND (b) EFFECTIVE DIFFUSION COEFFICIENTS, D

Mean particle diameter [c] (μm)	(a)				(b)
	Drug content (%)	Wall thickness (μm)	Ethyl cellulose rejected (%)	Hixson-Crowell release constant (10^2 mg$^{1/3}\cdot$s^{-1})	D (10^5 cm$^2\cdot$s^{-1})
213.5	81.9	9.50	63.2	2.94	0.37
111.5	77.1	6.70	50.5	5.34	0.37
62	62.2	6.80	1.4	8.03	0.72

Initial conditions: sodium salicylate (selected particle size) 5% w/w, ethyl cellulose 3% w/w, polysiobutylene 5% w/w in cyclohexane, 250 rpm.

[c] Segregated before microencapsulation using standard sieves.

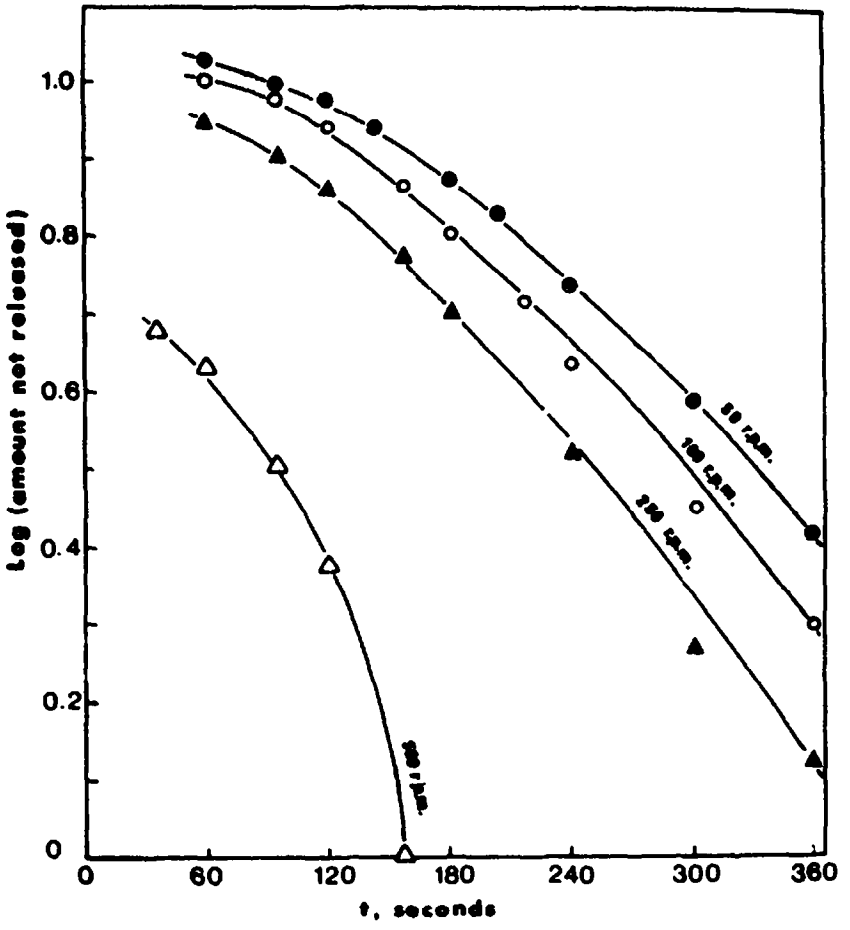

Fig. 1. First-order release plots of sodium salicylate from microcapsules at different sink solution agitation rates.

these single core particle microcapsules. The first-order plot, an example of which is given in Fig. 1, is not linear. Correlation coefficients for Higuchi equation plots treated by the least-squares linear regression method are given in Table 4. Their low values as well as the plot itself indicate non-linearity. Furthermore, the release rate,

TABLE 4

SODIUM SALICYLATE MICROCAPSULES: CORRELATION COEFFICIENTS OF HIGUCHI EQUATIONS PLOTS AT SELECTED CORE PARTICLE SIZE

Mean particle diameter (μm)	
213.5	0.981
111.5	0.964
62	0.985

Initial conditions: as in Table 3.
r = correlation coefficient.

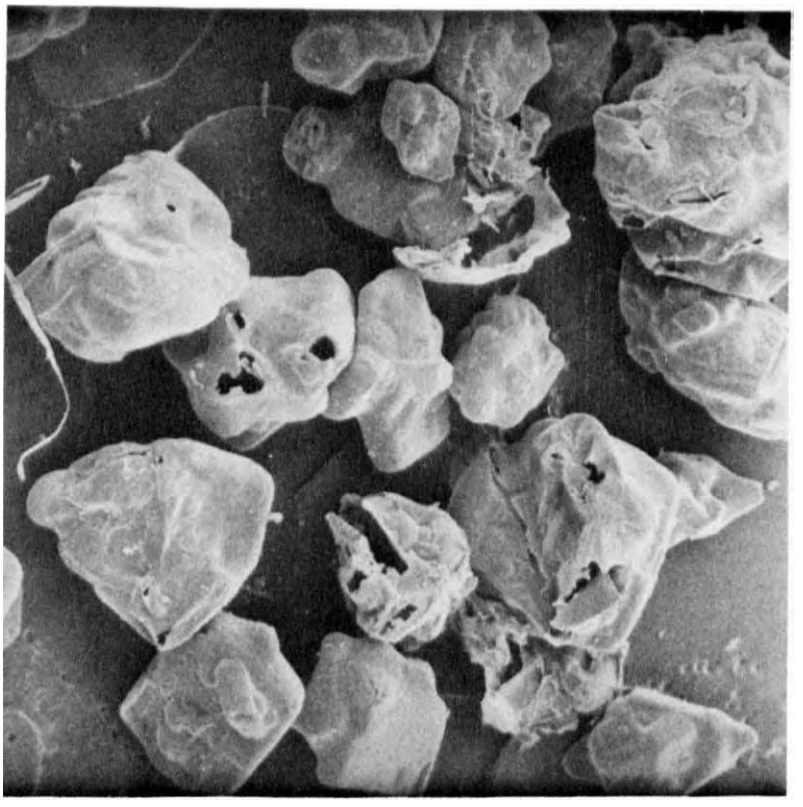

Fig. 2. Scanning electron photomicrograph of potassium dichromate microcapsules after immersion in water (magnification 1 : 100); conditions as in Table 1.

expected to be slow if the coat were intact owing to the low wall solubility of the salts, was in fact rapid. After complete release of contents, the microcapsules recovered showed the presence of minute pores or holes. These pores, which are clearly visible by scanning electron microscopy in the spent potassium dichromate microcapsules (Fig. 2) were not present in the original samples before immersion in water (Fig. 3). Similar results were obtained for sodium salicylate microcapsules before and after release (Figs. 4 and 5).

Since access of the extracting fluid to the core material would be enhanced by pore formation, it seemed possible that the release rate was controlled by the dissolution rate of the core material. For this reason, a dissolution model was used to analyze the release data, this being the first successful application of such a treatment to microcapsules. The Hixson-Crowell (1931) cube-root law (Eqn. 4) was considered suitable since the surface area of the core material decreased, the shape of the core appeared to remain unchanged and sink conditions were maintained during the entire release process.

$$W^{1/3} = W_0^{1/3} - kt \tag{4}$$

where W is the amount of drug remaining in the microcapsules at time t, W_0 is the initial amount and k is a constant containing the diffusion coefficient, D, the

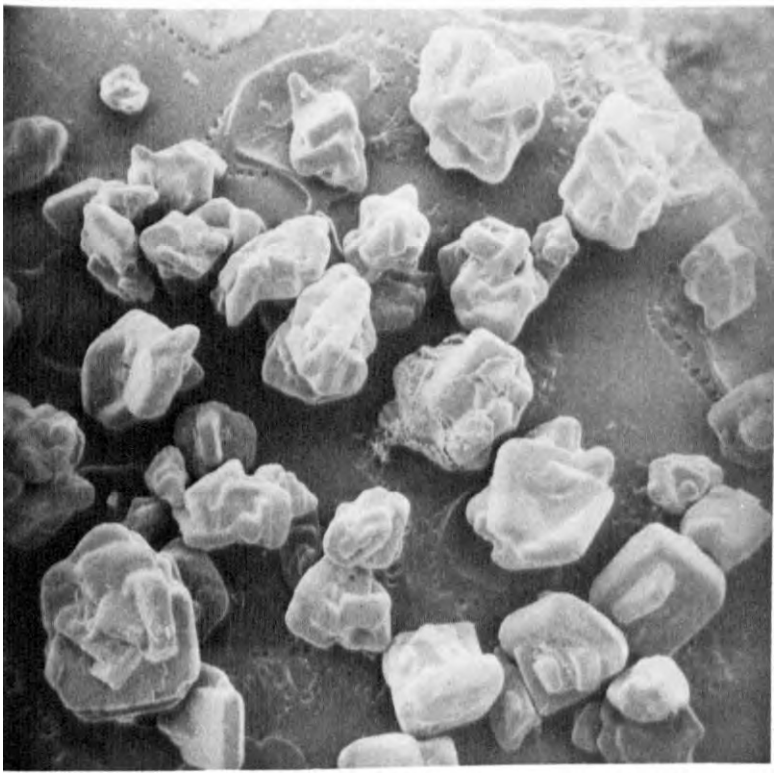

Fig. 3. Scanning electron micrograph of potassium dichromate microcapsules before immersion in water (magnification 1 : 50); conditions as in Table 1.

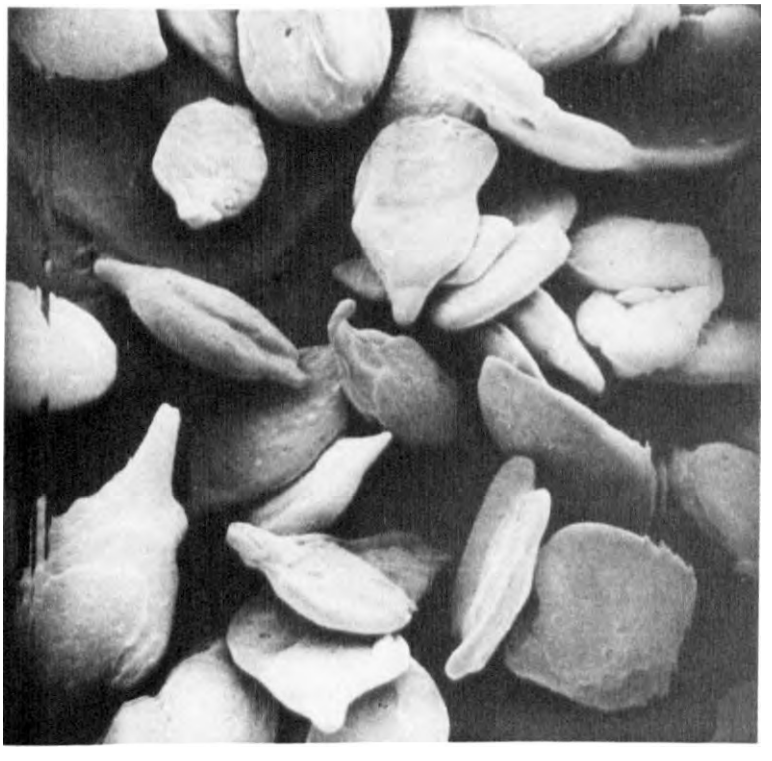

Fig. 4. Scanning electron photomicrograph of sodium salicylate microcapsules before immersion in water (magnification 1 : 100); conditions as in Table 3 for 213.5 μm mean particle diameter.

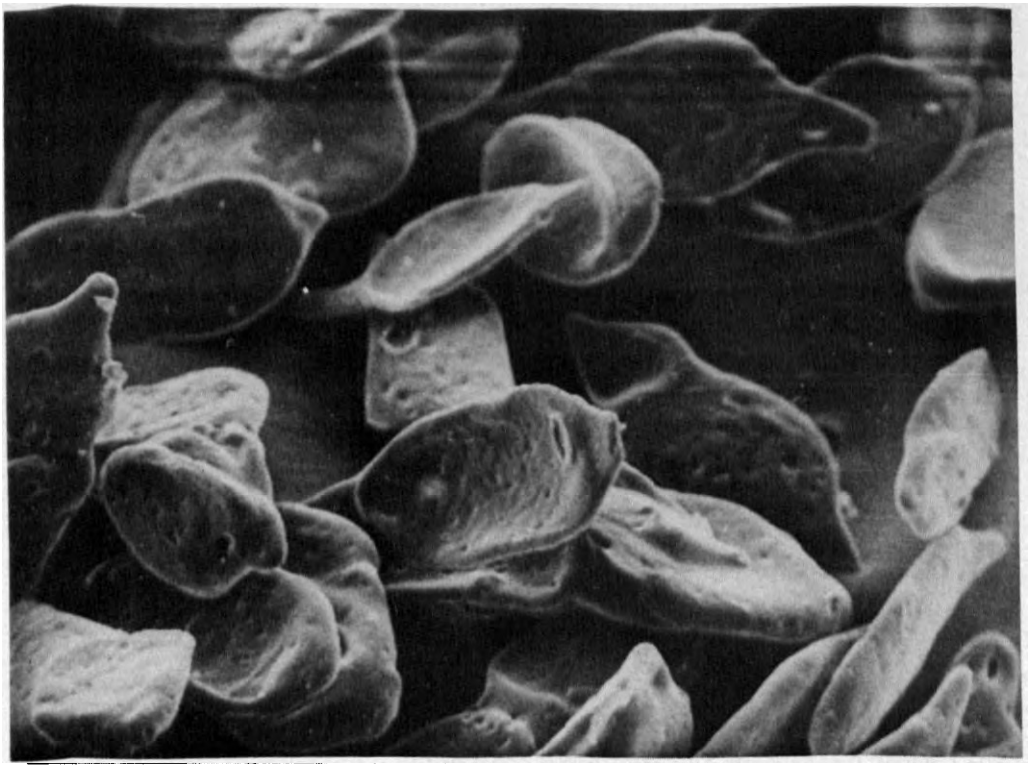

Fig. 5. Scanning electron photomicrograph of sodium salicylate microcapsules after immersion in water (magnification 1 : 150); conditions as in Table 3 for 213.5 μm mean particle diameter.

density, ρ, the solubility, C_s, and the unstirred layer thickness, h, defined by the equation:

$$k = \frac{DC_s}{\rho h}\left[\frac{4\pi\rho}{3}\right]^{1/3} \tag{5}$$

Unlike the previous treatments, the $W^{1/3} - t$ plot was linear. Again, increase of the agitation rate in the sink solution raised the slope, as expected for dissolution, since the unstirred layer thickness is reduced as the agitation rate is increased (Fig. 6).

In view of the observance of the dissolution equation, the effect of agitation rate and the microscopic evidence of pore-formation, the mechanism proposed is transport through capillary channels formed in the coat only after microcapsule immersion in the external fluid, and not present in the original wall. Perforation of the coat must be due to the high internal osmotic pressure developed inside the microcapsule on solution of the highly water-soluble core material. Confirmation is afforded by diminution of the release rate with increase in the osmotic pressure of the external solution, as shown in Fig. 7. Reduction of the osmotic pressure gradient must reduce the stress on the coat and evidently leads to lessened pore or capillary formation, bearing in mind that initially the wall is relatively free of pores except in damaged microcapsules. Further support is afforded by release experiments performed in a high concentration lithium chloride medium in which sink conditions still prevailed. Scanning electron microscopic examination of microcapsules which had been im-

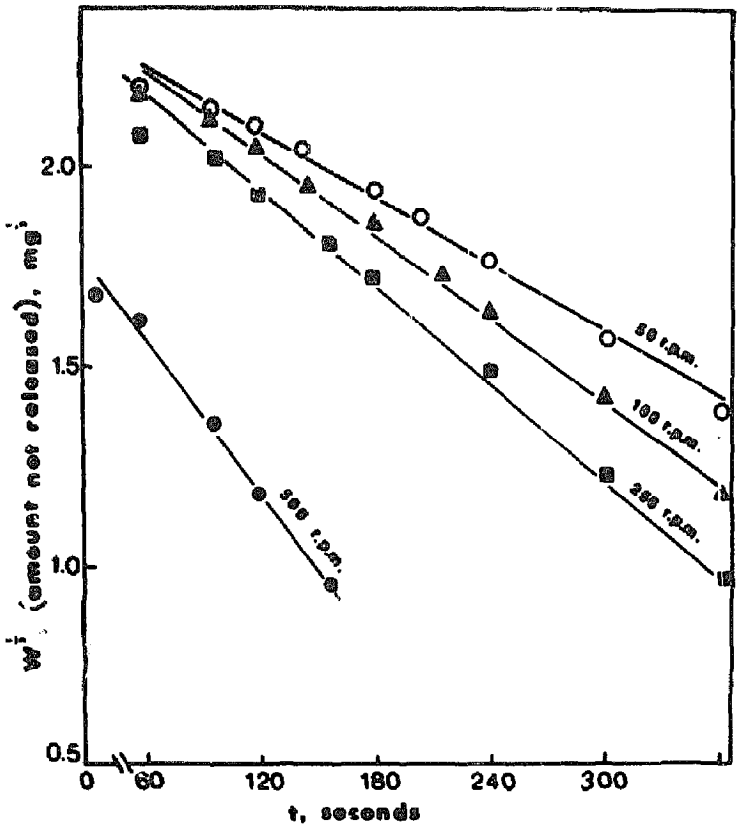

Fig. 6. Hixson-Crowell release plots of sodium salicylate from microcapsules at different sink solution agitation rates.

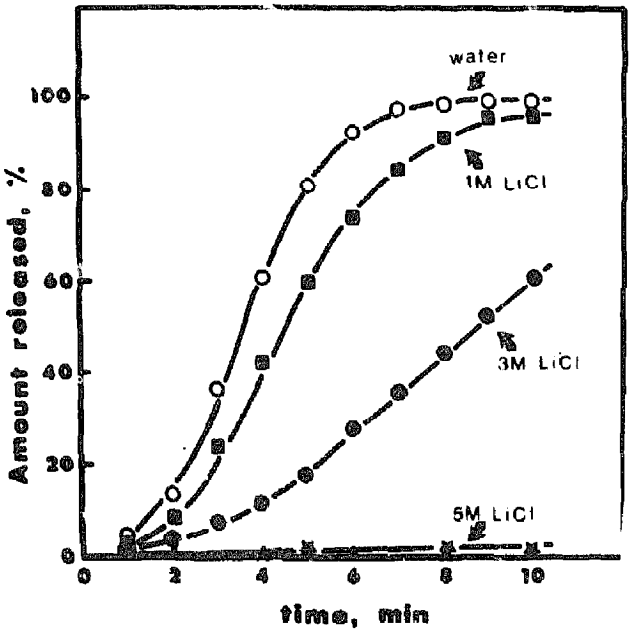

Fig. 7. Effect of increasing osmotic pressure of the external solution on sodium salicylate release from microcapsules.

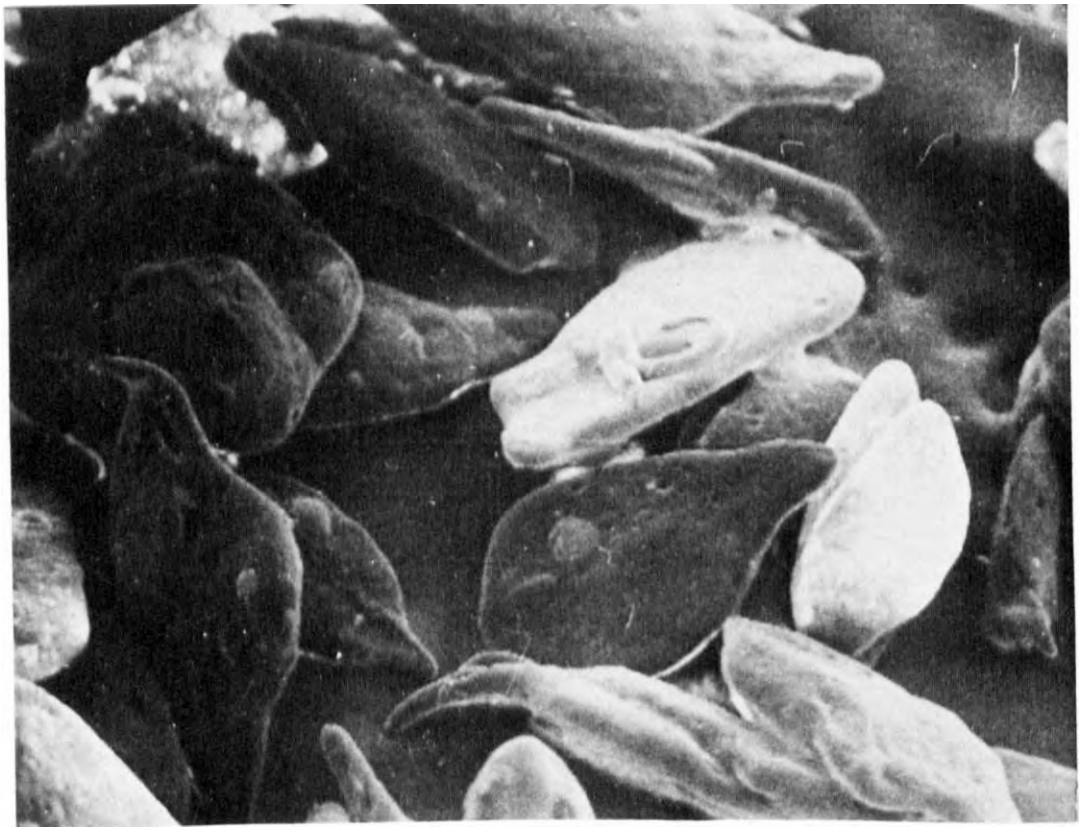

Fig. 8. Scanning electron photomicrograph of sodium salicylate microcapsules after immersion in a 7 M LiCl solution (magnification 1 : 200); conditions as in Fig. 5.

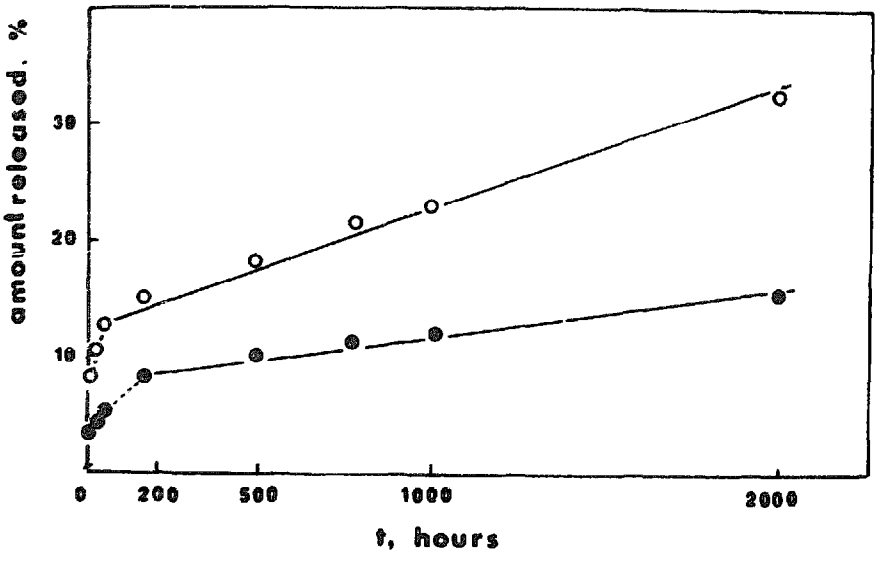

Fig. 9. Sodium salicylate release from microcapsules in 7 M LiCl sink solution.

TABLE 5

SODIUM SALICYLATE MICROCAPSULES: EFFECT OF SINK SOLUTION pH ON RELEASE USING HIXSON-CROWELL TREATMENT

pH	Correlation coefficient	Release constant (10^3 $mg^{1/3} \cdot s^{-1}$)
0.5	0.999	2.42
1	0.998	3.38
4	0.996	5.34
water (5.5–6)	0.995	5.50

Initial conditions: sodium salicylate (111.5 μm, mean diameter) 5% w/w, ethyl cellulose 5% w/w, polyisobutylene 5% in cyclohexane 250 rpm.

mersed in 7 M LiCl showed the ethylcellulose wall material to have remained unperforated (Fig. 8). Release under such experimental conditions should be dependent upon the low permeability of sodium salicylate in the wall due to its low polymer solubility. Confirmation was afforded by its slow release in 7 M LiCl, measured over a prolonged period (Fig. 9). Finally, non-integrity of the wall polymer as a barrier may be checked experimentally by measurement of release rates in sink solutions varying sufficiently in pH. Were the capillarity sufficient to allow buffer penetration, the salicylate solubility should decrease as the pH is lowered below 4, owing to the formation of an increasing proportion of salicylic acid in the diffusion layer. Consequently the dissolution rate should be decreased, according to the reduction in the effective value of C_s in Eqn. 5. The release rate constants listed in Table 5 do indeed fall with decreasing pH. It is concluded that pore-formation must have occurred after immersion in water.

Calculation of effective diffusion coefficient

For the purpose of validating that the dissolution process of sodium salicylate was the rate-determining step in the release from microcapsules, the effective diffusion coefficients were calculated for each batch using Eqn. 5 and utilizing the requisite experimental parameters. These experimental values were compared with the estimated value of the diffusion coefficient in water, calculated according to Eqn. 93 in Flynn et al. (1974), wnich was found to be 2.85×10^{-5} $cm^2 \cdot s^{-1}$.

Owing to the inaccessibility of information concerning the effective unstirred layer thickness at the drug–water boundary of the perforated microcapsules, the wall thickness value was used as an approximation in the first instance. D values obtained for the different microcapsule preparations are listed in Tables 2a and 3a. Surprisingly, they are all of approximately the same order and relatively near to the value of the theoretical D in water. The operative unstirred layer thickness should in fact be greater than the wall thickness, bringing the D values even nearer to the aqueous value.

These D values are drastically different from the permeability constant of salicylate ion through an ethylcellulose cast film, which was found to be 3.92×10^{-11} $cm^2 \cdot s^{-1}$ (Samuelov et al., 1979), eliminating the possibility that the release process is membrane-controlled.

The ethylcellulose coat thickness appears to be related to the effective unstirred layer thickness, since this calculation method yields D values showing little if any dependence on wall thickness. These results confirm that the dissolution of sodium salicylate in water must be the rate-determining step, even should the surface of the solid not be entirely exposed to the sink solution.

References

Benita, S. and Donbrow, M., Coacervation of ethyl cellulose: the role of polyisobutylene and the effect of its concentration. J. Colloid Interface Sci., 77 (1980) 102–109.

Benita, S. and Donbrow, M., Effect of polyisobutylene on ethyl cellulose walled microcapsules: wall structure and thickness of salicylamide and theophylline microcapsules. J. Pharm. Sci., 71 (1982a) 205–210.

Benita, S. and Donbrow, M., Release kinetics of sparingly soluble drugs from ethyl cellulose walled microcapsules: theophylline microcapsules. J. Pharm. Pharmacol., 34 (1982b) 77–82.

Deasy, B.P., Brophy. B., Ecanow, B. and Joy, M., Effect of ethylcellulose grade and sealant treatments on the production and in vitro release of microencapsulated sodium salicylate. J. Pharm. Pharmacol., 32 (1980) 15–20.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J., Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci., 63 (1974) 479–510.

Higuchi, T., Mechanism of sustained-action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J. Pharm. Sci., 52 (1963) 1145–1149.

Hixson, A.W. and Crowell, J.H., Dependence of reaction velocity upon surface and agitation. I-Theoretical consideration. Ind. Eng., Chem., 23 (1931) 923–931.

Jalsenjak, I., Nicolaidou, C.F. and Nixon, J.R., The in vitro dissolution of phenobarbitone sodium from ethyl cellulose microcapsules. J. Pharm. Pharmacol., 28 (1976) 912–914.

John, P.M., Minatoya, M. and Rosenberg, F.J., Microencapsulation of bitolterol for controlled release and its effect on bronchodilator and heart rate activities in dogs. J. Pharm. Sci., 68 (1979) 475–480.

Merkle, H.P., Mikroverkapselung fester arzneistoffe mittels koazervation. Ph.D. Thesis, EPF Zurich, 1972.

Oyaalpar, M. and Walters, V., The prolongation of the in vitro dissolution of a soluble drug (phenethicillin potassium) by microencapsulation with ethyl cellulose. J. Pharm. Pharmacol., 33 (1981) 419–422.

Salib, N.N., Elmen Shawy, M.E. and Ismail, A.A., Ethyl cellulose as a potential sustained release coating for oral pharmaceuticals. Pharmazie, 31 (1976) 721–723.

Samuelov, Y., Donbrow, M. and Friedman, M., Effect of pH on salicylic acid permeation through ethylcellulose-PEG 4000 films. J. Pharm. Pharmacol., 31 (1979) 120–121.

Senjkovic, R. and Jalsenjak, I., Apparent diffusion coefficient of sodium phenobarbitone in ethylcellulose microcapsules: effects of capsule size. J. Pharm. Pharmacol., 33 (1981) 279–282.