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Effect of Polyisobutylene on Ethylcellulose-Walled Microcapsules: Wall Structure and Thickness of Salicylamide and Theophylline Microcapsules

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Abstract □ Microcapsules were prepared by the ethylcellulose coacervation process which is based on the differential thermal solubility in cyclohexane. When a protective colloid, polyisobutylene, was present in adequate concentration, individually film-coated core particles formed. However, they were accompanied by small empty coacervate droplets, detectable by microscopic observation. Below the critical colloid concentration, the product had the form of an aggregate, in contrast to individual film-coated microcapsules. Increase of colloid concentration yielded microcapsules of higher drug content, because the coating became progressively thinner; there was a corresponding increase in the release rate of drugs from the microcapsules. Since the initial wall polymer/drug ratio and the particle size are constant, the drug content varied with the thicknesses of the wall membrane. This is shown here by removal of empty coacervate droplets by repeated decantations, enabling determination of drug content by chemical analysis. In contrast to results reported in the literature, in the presence of a protective colloid, microcapsule drug content decreased with decreasing particle size of the drug. This was caused by more complete uptake of the wall polymer on the increased surface of core material. The effect of protective colloid concentration on the apparent loss of wall polymer as empty droplets closely paralleled its effect on the size of stabilized coacervate droplets when core material was absent. It is proposed that stabilized droplet formation is a side reaction when core material is present, causing changes in wall thickness. This reaction not only affects the efficiency of the coating process but may be utilized to control wall thickness. First-order constants for drug release from salicylamide and theophylline microcapsules followed the same pattern as wall thickness and confirmed the validity of the measurements.

Keyphrases □ Polyisobutylene—effect on ethylcellulose-walled microcapsules □ Microencapsulation—effect of polyisobutylene on ethylcellulose-walled microcapsules, wall structure and thickness of salicylamide and theophylline microcapsules □ Coacervation—ethylcellulose effect on polyisobutylene on microencapsulation process

Although ethylcellulose is the most widely used coating material in microencapsulation, the basic coacervation process has been carried out under a variety of conditions (1, 2). Previous experimental results demonstrate that changes in the basic technique, essentially temperature reduction of a hot cyclohexane solution, markedly influence the quality and characteristics of the microcapsules formed. Among variations introduced has been the use of protective colloids such as polyethylene (2, 3), butyl rubber (4, 5), and polyisobutylene (6). Observation of microcapsules prepared in the absence of a protective colloid (7–9) reveals aggregates of coated particles, whereas individual microcapsules consisting of single core particles uniformly coated are formed when a protective colloid is present (3).

Dhruv *et al.* proposed (10, 11) that the extent and integrity of microencapsulation in the gelatin–acacia coacervation system is largely dependent on the coacervate volume, which changes with various experimental parameters in the absence of core material. The effects of polyisobutylene on the basic ethylcellulose coacervation process was recently studied (12). The polyisobutylene concentration was shown to control the phase coacervation volume and the final ethylcellulose coacervate droplet size. The present work investigated the effect of polyisobutylene concentration and particle size of core material on the wall/core ratio and drug release from microcapsules. It was attempted to relate these parameters to the underlying causes revealed by earlier studies.

EXPERIMENTAL

Materials—Ethylcellulose[1] (*N*-type) had an ethoxyl content of 47.5–49.0%. The viscosity of a 5% (w/w) solution in toluene–ethanol (80:20 w/w) was 100 cps[1]. Polyisobutylene[2] had a molecular weight of 380,000. Salicylamide[3] conformed to NF XIV and theophylline[4] conformed to BP 1973.

Preparation of Microcapsules—The method of preparation, developed with modifications from an earlier technique (1), was described elsewhere (12). The core and wall materials[5] were added to the stirred cyclohexane–polyisobutylene solution (250 or 300 rpm). The mixture was then heated to 80°, and allowed to cool at a controlled stirring rate to 45°.

[1] Hercules, Wilmington, Del.
[2] Oppanol B50, BASF, Ludwigshafen, West Germany.
[3] Sigma, Saint Louis, Mo.
[4] May and Baker, Dagenham, England.
[5] The quantities used were always adjusted to 100 g total weight with cyclohexane.

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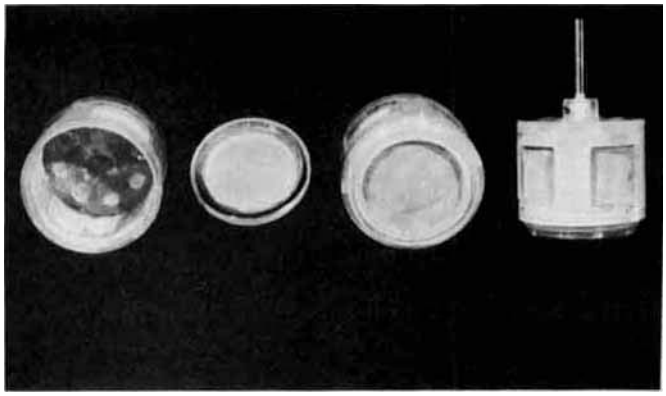

Figure 1—*Rotating basket showing dissembled parts used for release of drugs from microcapsules.*

It was cooled very rapidly using ice to 25° and stirred for another 15 min.

The microcapsules were separated from the solution by decantation and rinsed with three 200-ml portions of cyclohexane to remove any polyisobutylene adsorbed at the microcapsule interface and any empty wall polymer coacervate droplets. They were collected by vacuum filtration and oven-dried at 50° for 30 min, yielding a free-flowing powder.

All batches were duplicated. When the content of active ingredient deviated more than 3–4% between batches, a triplicate was performed. The effect of each experimental parameter was studied while the other parameters were kept constant for each drug. Segregation of the core materials was effected by standard mesh sieves.

Solubility of Drugs in Coating Solution and Drug Losses—Analysis of the clear supernatant layer obtained when the drug suspension was allowed to settle at 80° showed that the solubilities of salicylamide and theophylline in the coating polymer-protective colloid mixture were <0.02 and <0.01%, respectively. The particle size distribution of the core material, checked microscopically, did not appear to change significantly during the microencapsulation process. No uncoated drug particles were observed in the apparatus or in the batch after the process.

Evaluation of the Microcapsules Prepared—*Determination of Microcapsule Content*—The microcapsules were dissolved in chloroform and assayed spectrophotometrically at 306 and 276 nm for salicylamide and theophylline, respectively, using a calibration curve based on standard solutions in chloroform. Ethylcellulose did not absorb in chloroform at these wavelengths.

Determination of Loss of Wall Polymer—The percentage loss was calculated as follows for each batch prepared. The total weight of microencapsulated product obtained, *i.e.*, core and coating material, W_T, in a given batch was obtained from:

$$W_T = W_0/F \qquad \text{(Eq. 1)}$$

where W_0 is the initial amount of drug used and F is the fractional drug content of isolated product, by weight, determined experimentally. The assumption that none of the drug is lost or remains uncapsulated was validated earlier. The weight of the coat in the product, W_{EC}, is given by

$$W_{EC} = W_T - W_0 \qquad \text{(Eq. 2)}$$

If W_{EO} is the initial amount of wall polymer available for microencapsulation, then:

$$\text{percent loss of wall polymer} = \frac{100\,(W_{EO} - W_{EC})}{W_{EO}} \qquad \text{(Eq. 3a)}$$

$$= 100\left[1 + \frac{W_0}{W_{EO}}(1 - 1/F)\right] \qquad \text{(Eq. 3b)}$$

For the case in which $W_0 = W_{EO}$, this simplifies to[6]:

$$\text{percent loss of wall polymer} = 100\,(2 - 1/F) \qquad \text{(Eq. 3c)}$$

For an example, see Table I, 8% (w/w) polyisobutylene. The calculation for a 100-g system is as follows:

[6] The authors acknowledge the reviewer's suggestion to write the equation as a function of the fractional drug content.

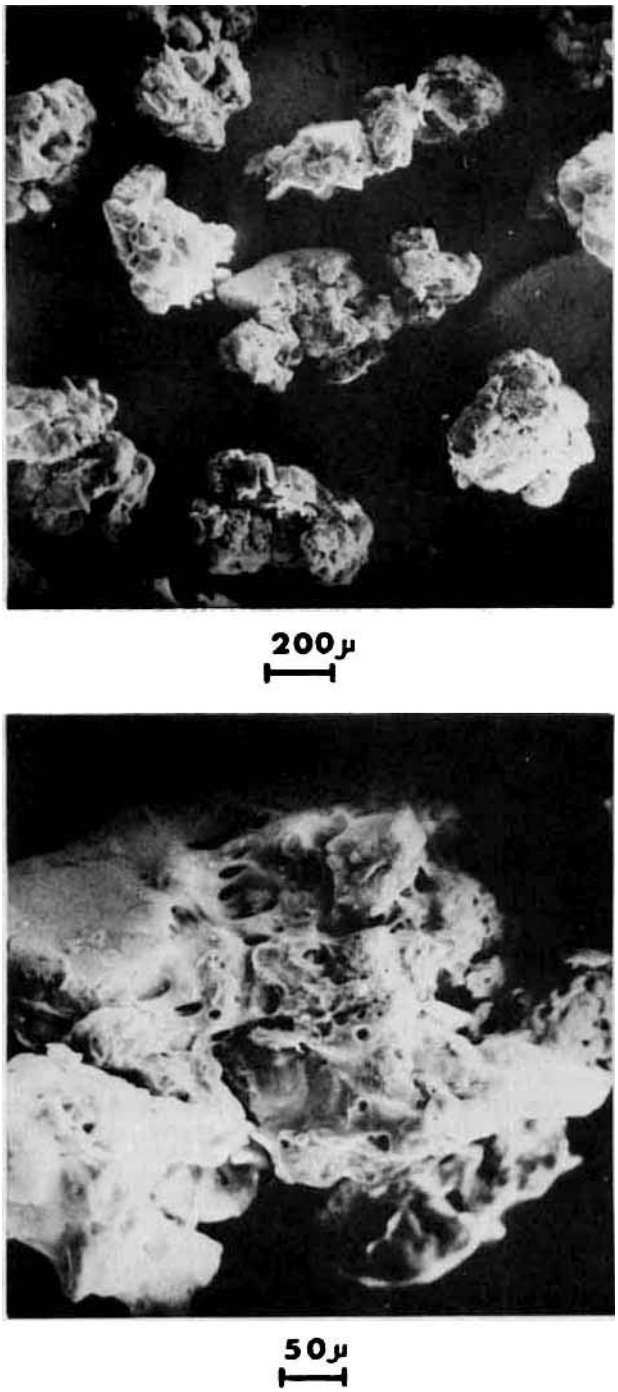

Figure 2—*Scanning electron micrographs of ethylcellulose-microencapsulated salicylamide prepared in the absence of polyisobutylene (5% salicylamide and 5% ethylcellulose at 300 rpm).*

$$W_T = \frac{5}{0.907} = 5.512$$

$$W_{EC} = 5.512 - 5 = 0.512$$

$$\text{ethylcellulose loss} = 89.76\%\ \text{(w/w)}$$

Wall Thickness—The wall thickness of the microcapsules was calculated from the particle size of the core material and the relative densities of the wall and core material. Quantitative expression of the relationship requires use of a shape factor, and because particle shape and size vary widely, even within batches of a single core material, it is generally assumed that the core particles are spherical and the capsule wall is uniform. This enables the use of a simplified model in which the microcapsule is considered to be composed of two spheres. Using the appropriate

Table I—Effect of Polyisobutylene Concentration on Salicylamide Microcapsule Contents and Properties with 5% Salicylamide [a] (100–200 mesh) and 5% Ethylcellulose [a] at 300 rpm

Polyisobutylene[a], %	Drug Content, mean percent ± *SD*	Wall Thickness[b], μm ± *SD*	Ethylcellulose Loss[c], % ± *SD*	Phase Coacervation Volume[d], ml	k_i[e], 10^3 min^{-1}
0	47.6[f]	19.2[f]	0	20	8.03[f]
3	—	—	—	48	—
5	51.2 ± 0.2	17.2 ± 0.1	4.5 ± 0.8	58	1.60
6	50.8 ± 0.9	17.4 ± 0.5	2.9 ± 3.4	59	1.55
7	51.4 ± 1.0	17.0 ± 0.5	5.5 ± 3.8	59	1.62
7.5	66.2 ± 0.4	10.3 ± 0.1	49.0 ± 0.6	—	2.04
8	90.7 ± 0.6	2.4 ± 0.1	89.8 ± 0.6	68	11.2
9	95.1 ± 1.1	1.2 ± 0.3	94.8 ± 1.3	86[g]	18.0

[a] Percentages of materials (w/w) were based on the total weight of the initial suspension containing all the components. [b] Calculated by means of Eq. 4; the standard deviation estimate was based on the drug content analyses. [c] Calculated by means of Eq. 3; the standard deviation estimate was based on the drug content analyses. [d] Parallel experiments performed in the absence of core material (12). [e] First-order release constant. [f] In the absence of polyisobutylene or at low concentrations, the wall polymer separated as an aggregate, both in the absence and presence of core material (see Ref. 12) and the microcapsules formed were of the matrix-coat type. [g] Coacervate phase volume continued to increase above 9% of polyisobutylene.

Table II—Effect of Polyisobutylene Concentration on Theophylline Microcapsule Contents and Properties at Different Particle Sizes [a] with 5% Theophylline and 5% Ethylcellulose at 250 rpm

Polyisobutylene, %	Drug content[b], %	Wall thickness, μm	Ethylcellulose Loss, %	k_i[c], 10^3 min^{-1}
	Particle size, 100–200 mesh			
5	56.7	14.2	23.5	2.58
7	66.0	9.9	48.5	4.75
8	72.0	8.0	61.1	8.15
9	82.4	4.7	78.6	16.85
	Particle size, 60–80 mesh			
5	76.2	12.7	68.7	0.50
8	94.8	2.4	94.5	26.7
9	96.8	1.5	96.7	41.5

[a] See Table I for key. [b] All data show the mean value for two batches (3–7% deviations). [c] Correlation coefficients of the first-order plot (see Fig. 7) were 0.999–0.998.

relationship (13), expressed in terms of fractional drug content[6], a mean spherical wall thickness is estimated as:

$$r_2 - r_1 = \left\{\left[\frac{d_c}{d_{EC}}\left(\frac{1}{F} - 1\right) + 1\right]^{1/3} - 1\right\} r_1 \qquad \text{(Eq. 4)}$$

where r_1, 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. The results were duplicated exactly and were within 2% of literature values.

Microscopic Studies—Optical[7] and scanning electron microscopy[8] were used to evaluate the quality of the coating obtained under the various conditions used.

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 USP XIX, modified by use of a 100-ml perspex basket in place of the wire mesh, the wall of which was pierced by four windows and covered by a nylon screen (80–100 mesh) bonded permanently by means of epoxy resin to the inner wall, to prevent exit of the microcapsules (Fig. 1). The upper side was pierced by eight holes, sealed with the same nylon screen, and the perspex hollow-ring screw-on base contained a nylon screen insert. The basket was rotated at 100 rpm (±3%) by means of a constant-rate adjustable stirrer[9], using a covered beaker containing 1 liter of water at 37 ± 0.5°. Drug release was determined spectrophotometrically[10] using a flowcell with a pump[11] and automatic recording (sample size, 50–100 mg). There was no turbulence, as checked by measurement of dissolution rate of standard pellets of pure benzoic acid.

The wavelengths used for salicylamide and theophylline were 298 and 272 nm, respectively. Dissolution experiments were duplicated and were closely reproducible.

[7] Tiyoda, Tokyo, Japan.
[8] Cambridge Instrument Co., England.
[9] Fisher Stedi-speed model, Pittsburgh, Pa.
[10] Unicam SP 1800, Pye Unicam Ltd., Cambridge, England.
[11] Model MHRK, Watson-Marlow, Falmouth, England.

Table III—Effect of Particle Size of Salicylamide and Theophylline on Coating Parameters and Release Rates of Drugs from Microcapsules [a]

Particle Size Mesh	Drug Content, %	Wall Thickness, μm	Ethylcellulose EC Loss, %	k_i[b], 10^3 min^{-1}
5% Salicylamide, 7% Polyisobutylene, and 5% Ethylcellulose at 300 rpm				
40–60	89.3	8.3	88.0	2.13
60–80	75.4	13.3	67.3	1.88
100–200	51.5	17.0	5.8	1.60
200–300	50.5	9.8	1.8	5.40
5% Theophylline, 5% Polyisobutylene, and 5% Ethylcellulose at 250 rpm				
60–80	76.2	12.7	68.7	0.50
80–100	67.5	14.1	51.9	0.55
100–200	56.7	14.2	23.5	0.58

[a] See Tables I and II for key. [b] Correlation coefficients, 0.999.

RESULTS AND DISCUSSION

Appearance of Microencapsulated Core Materials—From the preliminary experimental results, it was observed that the presence of polyisobutylene at a minimal concentration was vital to the formation of individual microcapsules. The use of concentrations between 0 and 2% failed to give good reproducible microcapsules. The final product obtained after sieving (1190–840 μm) was composed mainly of large irregular aggregated masses, which were dispersions of core material in ethylcellulose as shown by scanning electron microscopy (Fig. 2). Microscopically, it was impossible to distinguish individually coated particles inside the mass.

Deasy *et al.* (9) obtained a product with surface properties closely similar to the aggregates shown in Fig. 2. The particle size of their product ranged between 1190 and 300 μm, and although an increase in the proportion of finer aggregates was achieved by drastic increase in agitation rate and slowing down of the cooling rate, the nature of the coated particles was essentially unchanged.

The minimum polyisobutylene enabling formation of individually microencapsulated core particles was 3%. However, high turbulence in the system at this concentration, in which the viscosity was low, led to losses of wall polymer by adhesion to the container walls during the cooling phase, while reduced agitation led to adhesion to the stirrer and bottom of the vessel. Such losses were negligible under the experimental conditions used when 5% protective colloid was added.

Photomicrographs (Fig. 3) of salicylamide and theophylline microcapsules in cyclohexane show that each particle was uniformly coated and no aggregation of the microcapsules occurred even after decantation and separation (Fig. 4). The coacervated polymer droplets formed a smooth continuous coat around each particle, markedly different from the surface characteristics of pure salicylamide. Clearly, the presence of an adequate polyisobutylene concentration in the coacervation process

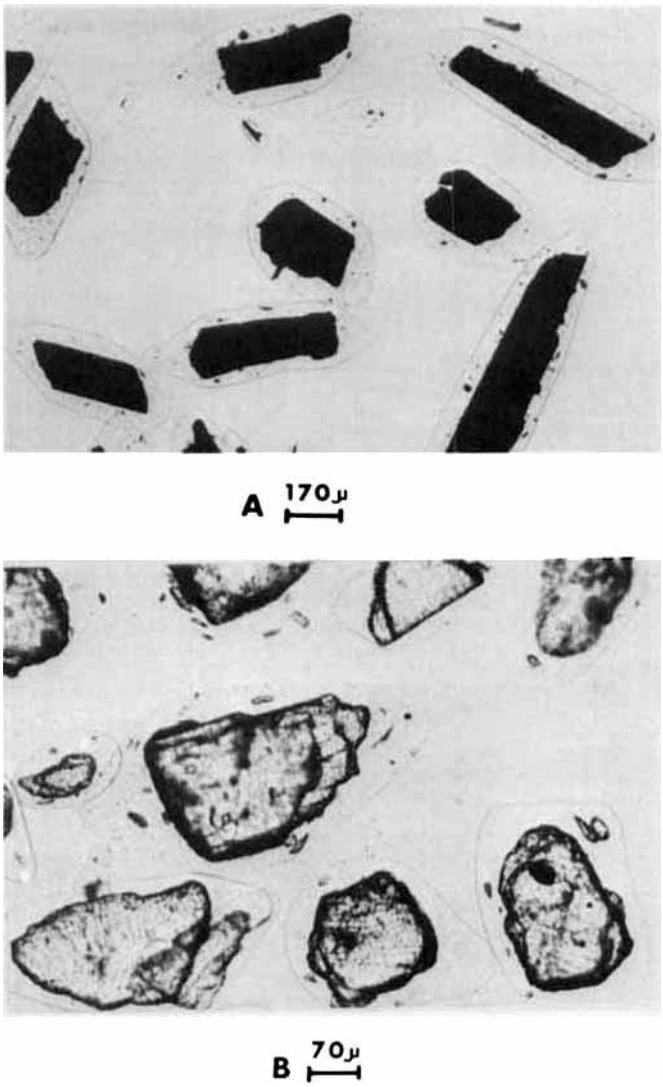

Figure 3—*Photomicrographs of theophylline microcapsules, A (5% theophylline, 5% ethylcellulose, and 5% polyisobutylene at 250 rpm) and salicylamide microcapsules, B (5% salicylamide, 5% ethylcellulose and 5% polyisobutylene at 300 rpm).*

enables formation of such a continuous wall, which may be termed a film-coat, as opposed to the spongy aggregate matrix obtained in the absence of protective colloid or at a low concentration.

These different forms have perhaps not been adequately distinguished in the literature; both are produced by the same basic cooling coacervation method according to the experimental conditions used, and both are described as microcapsules. The particle size of those possessing a matrix-type wall would be expected to be inadequate as a parameter for their characterization and their properties would be expected to vary considerably even at constant particle size, depending on porosity and shape factors and the number of core particles entrapped. On the other hand, in the film-coat type, the shape of the core particle is maintained even when these are highly asymmetrical (Fig. 5). The film thickness appears enlarged in the photomicrographs (Fig. 3) because of swelling of the coat in the original solution or pure cyclohexane. For this reason, no direct measurement of the film thickness could be performed using an optical microscope. Experiments were performed with other solvents such as glycerin and liquid paraffins, but in this case it was difficult to distinguish the wall clearly.

Effect of Polyisobutylene Concentration—In studies of the influence of the protective colloid concentrations, it is not expected that the mean drug content of the microcapsules would change if the initial amounts of wall and core material and the particle size were kept constant, provided the drugs are insoluble in the hot and cold solvent mixtures and the core and wall materials are totally incorporated in the final microcapsules obtained. Alternatively, such losses of core and wall material that do occur should be independent of protective colloid concentration. However, routine microscopic and scanning electron microscopic observation of the products led to detection of varying amounts of empty spherical particles of wall material in the different batches which evidently were solidified coacervate droplets (Fig. 6). They were removed by the repeated decantation to obtain drug-filled microcapsules alone. Since quantitative recovery of empty shells proved to be laborious and some microcapsules were lost in the separation, the drug content of the

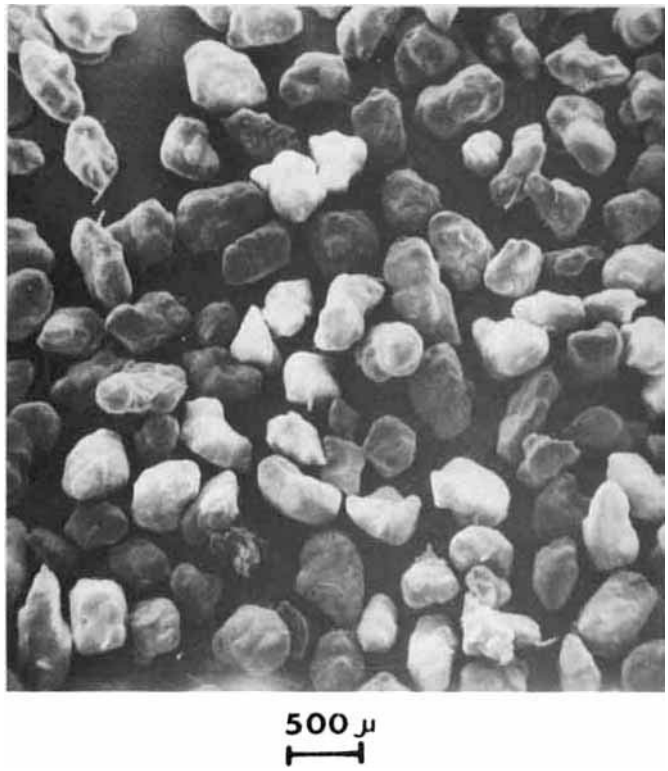

Figure 4—*Scanning electron micrograph of salicylamide microcapsules (see text).*

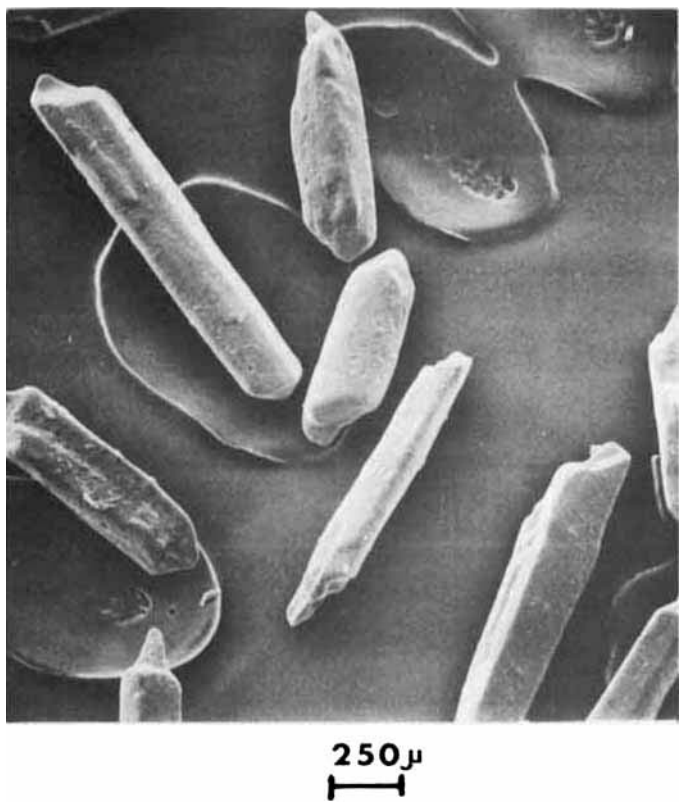

Figure 5—*Scanning electron micrograph of theophylline microcapsules (see text).*

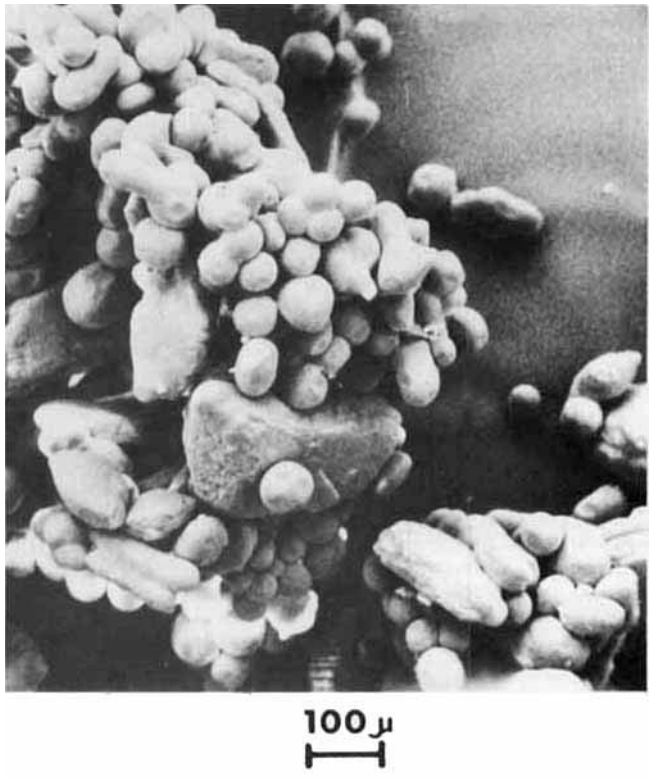

Figure 6—*Scanning electron micrograph of salicylamide microcapsules (250–300 μm) with empty spherical coacervate droplets (40–60 μm).*

purified microcapsules was determined analytically. Then, from the initial quantities of materials used, assuming that all the available drug had been microencapsulated uniformly (as was confirmed by experimental observation) the amount of wall polymer in the microcapsules was calculated and hence the amount "wasted."

This method, described in the experimental section, has not yet been applied to the microencapsulation process. Use of equations for concentric spheres (13) enabled estimation of mean equivalent sphere coat thickness. This calculation probably gives a reasonably true value for salicylamide but a hypothetical one for theophylline due to the crystal shapes (Fig. 3). Repeat batches treated in this way proved to have reproducible drug contents, indicating that stirring conditions, cooling rate, and the separation process were well controlled (Table I).

The drug content of the microcapsules, as seen in Table I, was constant up to 7% of polyisobutylene, but then rose sharply indicating decrease of uptake of wall material by the core particles, which is shown calculated as percentage ethylcellulose loss. The equivalent wall thickness also expresses this trend, and since drug release rate from the microcapsules followed first-order kinetics (Figs. 7A and 7B), release-rate constants[12] were evaluated for the series; they are inversely related to the mean wall thickness in salicylamide (Table I). The same protective colloid effects are evident in the preparation and data of theophylline microcapsules (Table II), although with this core material, the concentration effect is gradual rather than drastic.

Relation to Wall Polymer Coacervation—In considering possible causes of the observed decrease of coating efficiency, it is tempting to assume that excess wall polymer was used, so that decreasing its quantity will eliminate the losses. However, halving the amount of ethylcellulose to 2.5% (w/w) at the 5% level of polyisobutylene, with the other conditions as in Table I, yielded microcapsules which, after purification, contained 87.9% salicylamide, corresponding to 72.4% loss of ethylcellulose, compared with 4.5% loss at 5% wall polymer. Initial studies over a wider range of core and wall concentrations confirms this trend and will be reported upon completion.

In ethylcellulose coacervation studies performed in the absence of core material (12) under the same conditions used in Table I, the phase coacervation volume, which was small at low concentrations of protective colloid, rose sharply at first and flattened out to give a constant value between 5 and 7% of polyisobutylene. Above this level of additive, the

[12] A full analysis of the release kinetics of microcapsules made by this method is the subject of the second part of this investigation.

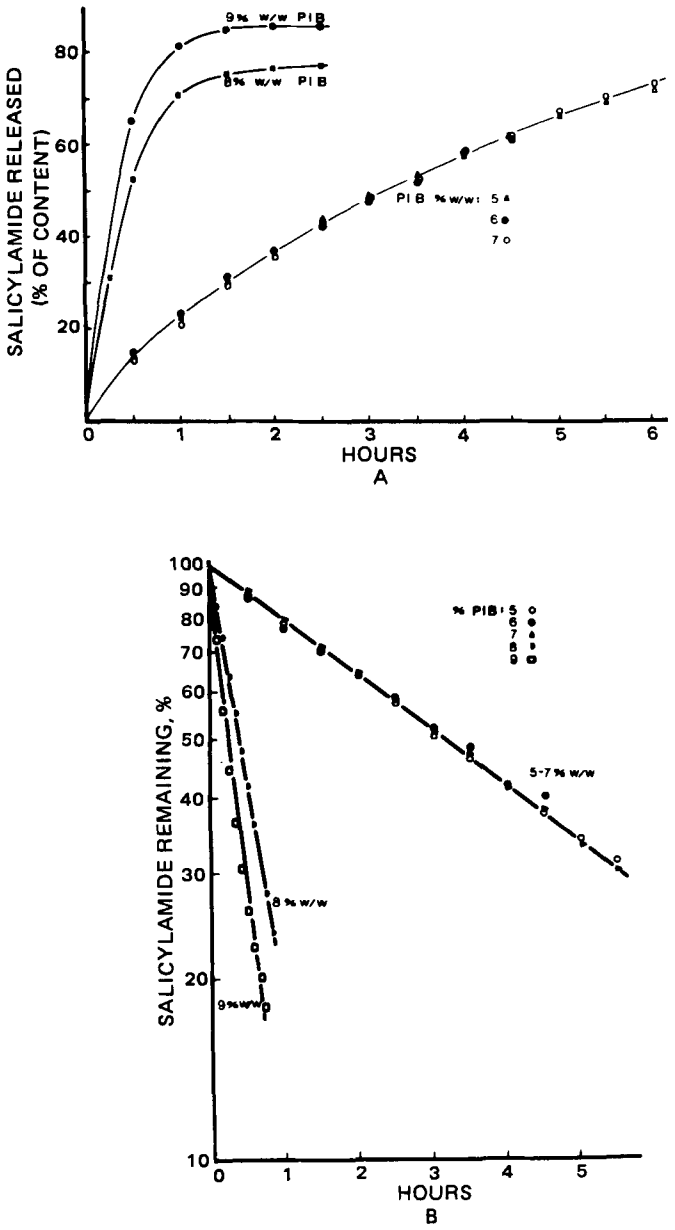

Figure 7—*Salicylamide release from microcapsules prepared using different polyisobutylene concentrations; linear plot (A) and first-order plot (B).*

coacervation volume rose very steeply toward 100% of the total volume, reached at 10% additive. Values (Table I) ran in a manner closely similar to drug content. The coacervate droplet size in the absence of core material was shown to change inversely to the phase coacervation volume (12). The relation of the effects of polyisobutylene on coacervation and microencapsulation parameters are more clearly evident graphically (Fig. 8). Microcapsule wall thickness remained relatively constant as did release rate from the microcapsules and coacervate droplet size at 5–7% polyisobutylene; above this range they changed steeply, with thickness and droplet size falling and release rate rising. The related function, loss of ethylcellulose, followed an inverse pattern to wall thickness. It is clearly indicated that the coating ability for salicylamide falls off drastically as the protective colloid concentration exceeds a critical value, at which the droplet size also undergoes drastic change and the coacervation volume rises (Table I).

It seems that the microcapsule coating process reflects more fundamental changes arising from the coacervation process.

The sudden increase in coacervation volume above 7% in the absence of core material was considered due to a combination of decrease in coacervate drop size and increase in viscosity, the former effect resulting from stabilization of the droplets by adsorption of polyisobutylene as a protective colloid at an earlier stage in droplet growth (12). Such stabi-

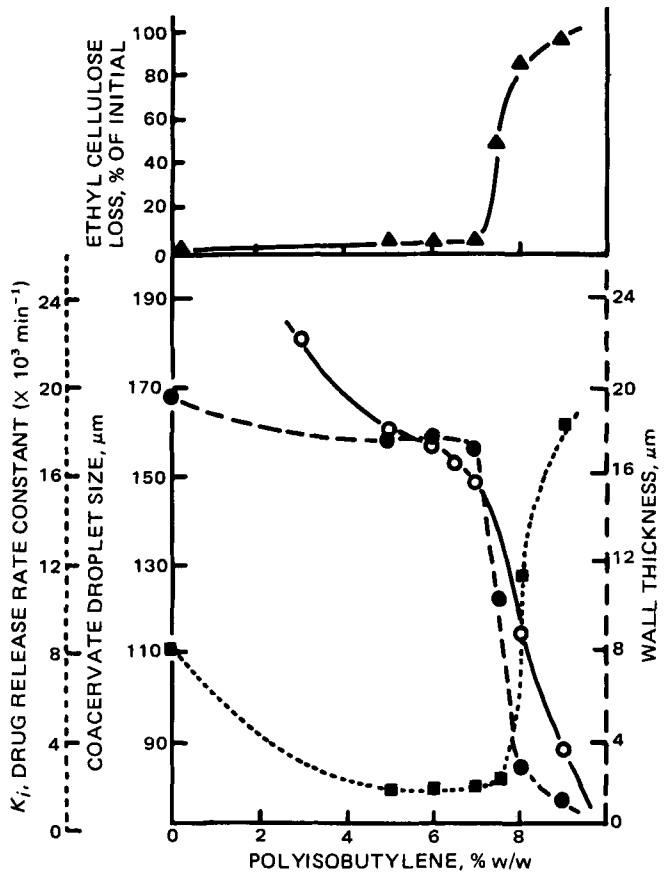

Figure 8—*Effect of polyisobutylene concentration on coacervate and microcapsule parameters (core material: salicylamide; see Table I for conditions). Key: ●, wall thickness; ○, coacervate droplet size; ▲, ethylcellulose loss; and ■, first-order release rate constant* (k_i).

lized coacervate droplets, suspended in the solvent, were unable to coat core material when the two were mixed and stirred together at room temperature. Therefore, it is proposed that the mechanism of the effects observed on increasing the protective colloid concentration above a critical level is that diffusion and growth of wall polymer from the coacervate microdroplets separating out during cooling is inhibited by increase in viscosity, and a larger proportion of droplets are stabilized when they are still small, becoming less available for use in coating.

Effect of Particle Size—The drug content of the microcapsules decreased with reduction in core particle size (Tables II and III). With a fixed amount of core material, particle size reduction leads to increase in the specific surface. The corresponding minimization in the loss of wall polymer may be attributed to the availability of the additional surface for entrapment of separating coacervate droplets. It can also be seen that at equivalent particle sizes there is a tendency for ethylcellulose loss to vary from one drug to another, probably due to differences in particle shape or surface energy[13].

The variation in drug content of the microcapsules as a function of particle size is reflected in the drug release rates, which change inversely with wall thickness[14] (Tables II, III). However, the precise quantitative relationship cannot be tested without allowing for size distribution and shape factors, considerations that are beyond the scope of this study.

The particle size effect fits the mechanism proposed. Considering the coating and stabilization of empty droplets as competitive processes, the former will be favored at the expense of the latter by surface area increase of the core material, which should enhance the rate of uptake of the separating ethylcellulose.

In fact, the results obtained in this work are in contradiction to those published in the literature. It is well accepted that at a constant ratio of coat polymer to drug, decrease of particle size leads to a decrease in wall thickness and an increase in release rate (13). This is true only if in the specific microencapsulation process all the coating polymer is used up in building the wall. Microencapsulation using ethylcellulose coacervated in the presence of protective colloid gives a unique system in which the latter prevents empty stabilized coacervated droplets from interacting with microcapsules, and encourages formation of a continuous uniform film coat which retains the shape of the core material.

The results also show that by means of particle size change, the effective coating efficiency may be varied between high and low levels with consequent change of wall thickness while retaining a true film coating. The question of whether the amount of initial wall material used is in excess or not has a different relevance in a system in which the concentration of protective colloid is one of the major controlling factors in the efficiency of the coating process. By choice of suitable protective colloid concentration or particle size, full efficiency can be achieved without changing the initial wall polymer concentration.

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[13] Although different stirring rates were employed, this factor was found insufficient to account for the differences between the two drugs.

[14] There is a tendency for release rate to rise as core particle size falls, at equivalent wall thickness, probably due to surface area increase.