Effect of Polyisobutylene and Sealant Treatments on Ethylcellulose-Walled Methyldopa Microcapsules

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폴리이소부틸렌 및 밀폐제 처리가 메칠도파의 마이크로캅셀화에 미치는 영향

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For the prevention of the aggregation during microencapsulation, the effects and role of polyisobutylene (PIB), as a protective colloid, were studied. The effects of sealant treatment on the microencapsulation were studied. Methyldopa was microencapsulated with ethylcellulose (EC) by polymer deposition from cyclohexane by temperature change using PIB. The EC-microencapsulated methyldopa was sealed with spermaceti. The dissolution of methyldopa was influenced by the drug to wall ratio. When PIB was used, low aggregation of microcapsules occurred and the surface was smooth with a few pores. Treatment of microcapsules with spermaceti retarded the release of methyldopa, the release being affected by the percentage of sealant used and the particle size of the product.

Keywords—microencapsulation, coacervation, methyldopa, **polyisobutylene, sealant, spermaceti**

Microencapsulation is a useful technique to alter the physical and pharmaceutical properties of a drug without changing its essential properties. In the pharmaceutical field, microencapsulation techniques have been widely investigated[1-21].

The process of coacervation is recognized as an effective method of microencapsulation of drugs because of the ability of the coacervate to coat insoluble particles present in the equilibrium liquid. Coacervation from an organic solvent vehicle (ethylcellulose-cyclohexane solution) by the change of temperature is a useful method for microencapsulation of the water-soluble drugs. Changes in the basic technique, essentially temperature reduction of a hot cyclohexane solution, markedly influence the quality and characteristics of microcapsule formed. Although ethylcellulose (EC) is the most widely used coating material in the microencapsulation by coacervation[1-8] from an organic solvent vehicle, the basic coacervation process has been carried under a variety of conditions.

Microcapsules prepared using EC as a wall formaing agent showed aggregates of coated particles and many trials have been made to prevent the aggregation during preparation of microcapsules. Among variations introduced has been the use of protective colloids such as polyethylene[9-11], polybutadiene[12], butyl rubber[13] and polyisobutylene (PIB)[3,12,15-18] in order to induce coacervation

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from EC-cyclohexane solution. Several workers[15-19] studied the effects of PIB on the basic EC coacervation and the importance of a protective colloid in forming individually film-coated core particles as opposed to aggregates. The PIB concentration was shown to control the phase coacervation volume and the final EC coacervate droplet size. However, the role and effect of the mentioned coacervation inducing agents have scarcely been studied in detail.

The present work investigated the effects of molecular weight and concentration of PIB, the core to wall ratio, and drug release from various macrocapsules. EC was used as a wall-forming material among water-insoluble polymers and methyldopa (MD), antihypertensive agent, was selected as a model core drug. An attempt has been made to prolong the *in vitro* drug release from EC-encapsulated MD by the application of spermaceti solution as a sealant.[22]

EXPERIMENTAL

Materials

Ethylcellulose (20cp, 45cp) was purchased from Dow Chemical Company. Polyisobutylene (low, medium molecular weight) was obtained from Aldrich Company. All other chemicals used were reagent grade and used as received. MD and spermaceti used were KP grade.

Preparation of Microcapsules

The method of preparation was modified from those described by Miller *et al.*[13] EC was added to the stirred PIB-cyclohexane solution and MD was then added to the above solution, and with constant stirring, the system was heated to 80 °C to form a homogeneous suspension. The system was allowed to cool to 40 °C slowly with continuous stirring and then cooled quickly to 25 °C. During this cooling period, separated droplets coated the suspended particles. The microcapsules were separated from the solution by decantation and washed at least three times with 50m*l* portions of cyclohexane to remove any PIB adsorbed on the microcapsule interface and any empty wall of polymer coacervate droplets. They were collected by vacuum filtration and solvent traces were finally removed on paper towel at room temperature and air dried, yielding a free-flowing powder. The quantity of EC, PIB and MD used varied depending on the previously designed core to wall ratios.

Dissolution Studies

Microcapsules of 297-500 μm diameter were used to obtain the dissolution pattern of MD using the artificial gastric fluid. The release of MD from the microcapsules was measured using a rotating basket dissolution apparatus similar to that described in the USP XX, modified by use of nylon screen insert in place of the wire screen, the wall of which was covered by a nylon screen (80-100 μm) bonded permanantly by means of epoxy resins to the inner wall of the basket to prevent the escape of microcapsules.

The dissolution test of MD from the different microcapsules was carried out at 37 °C and 50rpm in KP IV artificial gastric fluid (pH 1.2). Each test preparation equivalent to 500mg of MD was transferred to 500 m*l* of dissolution medium. At suitable time intervals, a 3.0 m*l* aliquot was withdrawn and filtered through 0.45μm Millipore filter and immediately replaced with an equal volume of fresh dissolution medium. The concentration of MD were calculated by determining the absorbance of the solution at 264nm.

Size Distribution Test of Microcapsules

The different sizes of microcapsules present in a batch were separated into suitable fractions by sieving on a mechanical shaker using a KS standard sieve for 5 min.

Scanning Electron Microscopy

Samples of microcapsules were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film approximately 30 nm thick. Their surface characteristics were observed using a scanning electron microscope (JCM-35C, Jeol, Japan) at a magnification of 1000×.

Sealant Treatments

Samples of 3g of EC-microencapsulated drugs were agitated at 150rpm in 50m*l* of spermaceti

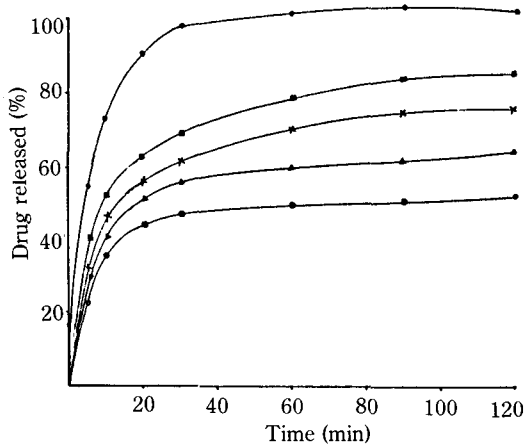


Figure 1—Release of MD from microcapsules coated with EC (45cp) at different MD-EC ratios.
Key: ●, uncoated MD; ■, 1:0.5 ratio; ×, 1:1 ratio; ▲, 1:2 ratio; ○, 1:3 ratio

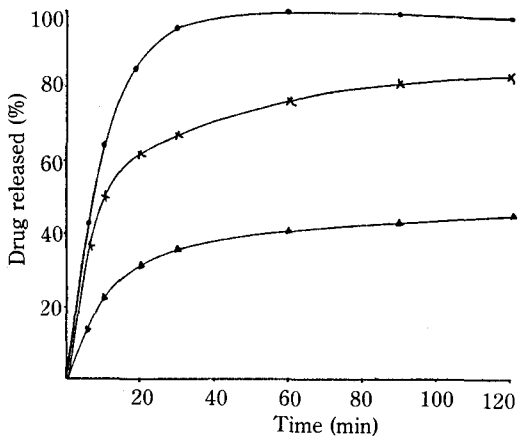


Figure 2—Release of MD from 1:0.5 ratio microcapsules coated with EC of different viscosity.
Key: ●, uncoated MD; ▲, 20cp; ×, 45cp

solution having different concentrations in cyclohexane at room temperature, filtered and air-dried overnight.

RESULTS AND DISCUSSION

Effect of Different Grades of Ethylcellulose on Drug Release

The preparation of microcapsules using EC by polymer deposition following cooling below the critical phase separation temperatures requires careful attention to details of the procedure in order to avoid obtaining a product that is largely comprised of coarse aggregated masses of the starting materials. To obtain a fine wall coated product, vigorous agitation and slow rate of cooling around the phase separation temperature must be employed. Also, washing the product with cold cyclohexane tends to lessen aggregation.

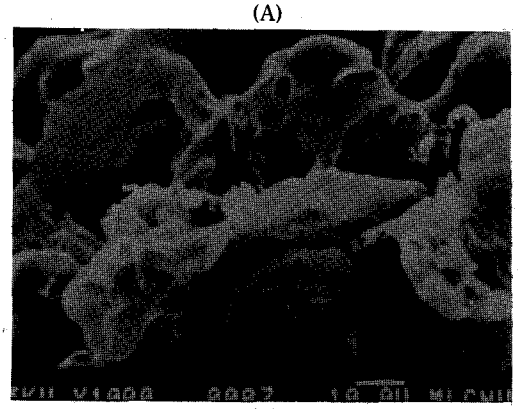
The dissolution of MD from microcapsules coated with 45 cp EC at different MD to EC ratios is shown in Fig. 1. The release rate of MD was retarded as the MD to EC ratio decreases.

Fig. 2 shows dissolution curves for the release of MD from equal size ranged microcapsules prepared using the two grades of EC. The 20cp EC-coated capsules showed the slower release. The faster release of core material from the 45cp EC-coated capsules is probably due to their greater fragmentation and porosity associated with increased swelling of the polymer. A similar rapid release of sodium phenobarbital from EC microcapsules was reported by Jalsenjak *et al.*[2] and from EC-coated granules containing various drugs by El-Sayed *et al.*[23]

The final product obtained after sieving (257-500 μm) was composed mainly of large irregular masses, which were dispersions of core material in EC as shown by scanning electron microscopy (Fig. 3). Microscopically, it was impossible to distinguish individually coated particles inside the mass. Figs. 3 and 4 show a portion of the surface of an EC-coated capsules which exhibit both rough and smooth areas with the presence of pores, some of which may extend through the coating to the core material. In contrast, microcapsules after dissolution show swollen rough surface with enlarged pores (Figs. 3B and 4B). Watanabe *et al.*[24] reported a similar aggregated appearance of EC-coated aspirin prepared by a polymer precipitation method. Figs. 3B and 4B show a portion of the surface of microcapsule after dissolution.

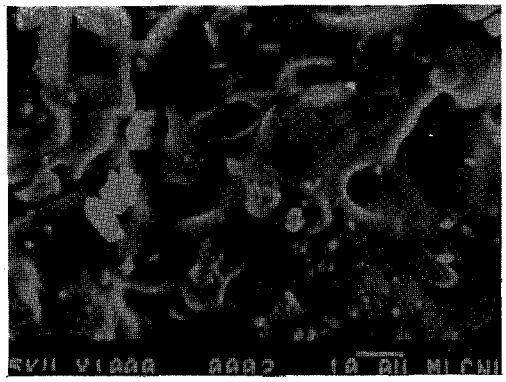
Effect of Molecular Weight and Concentration of PIB

(A)

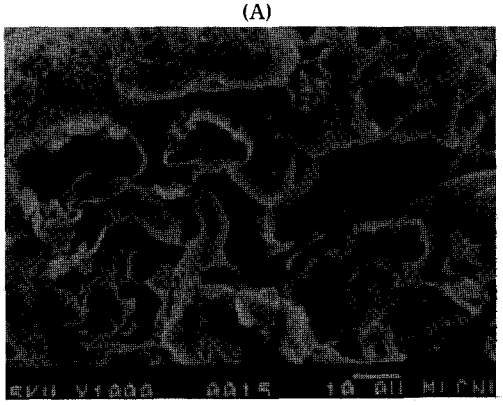


(B)

Figure 3—Scanning electron micrographs of microcapsules coated with EC (20 cp) at 1:0.5 MD-EC ratio. Key: (A), before dissolution; (B), after dissolution



(A)



(B)

Figure 4—Scanning electron micrographs of microcapsules coated with EC (45cp) at 1:1 MD-EC ratio. Key: (A), before dissolution, (B), after dissolution

The effects of PIB as a coacervation-inducing agent were studied. As shown in Fig. 5, about 90% of MD was dissolved in dissolution medium within 20 min from intact MD. But, dissolution of MD was retarded significantly in all EC-microcapsules prepared using PIB of different molecular weight. The greater delays in dissolution was shown in EC-microcapsules prepared using PIB of higher concentration (Figs. 5 and 7) and using PIB of low molecular weight (Fig. 8). It is seen that the release was decreased with increasing PIB concentration (Figs. 5 and 7), while the particle size is comparatively reduced, indicating the increased stabilization of coacervates with increasing amount of PIB. PIB stabilized the individual microcapsules during the process since in its absence large sticky mass was obtained. The stabili-

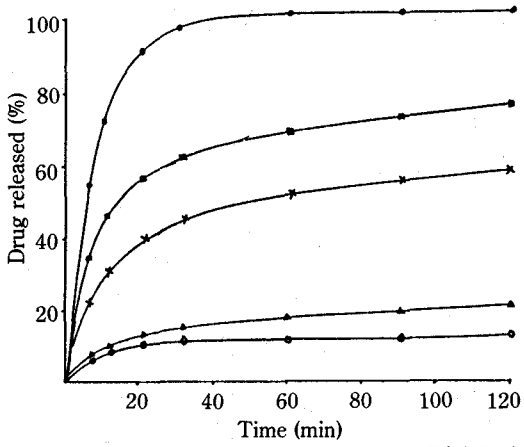


Figure 5—Release of MD from 1:1 ratio MD-EC (45cp) microcapsules prepared using low molecular PIP of various concentrations.
Key: ●, uncoated MD; ■, 0% PIB; ×, 1% PIB; ▲, 2% PIB; ○, 3% PIB

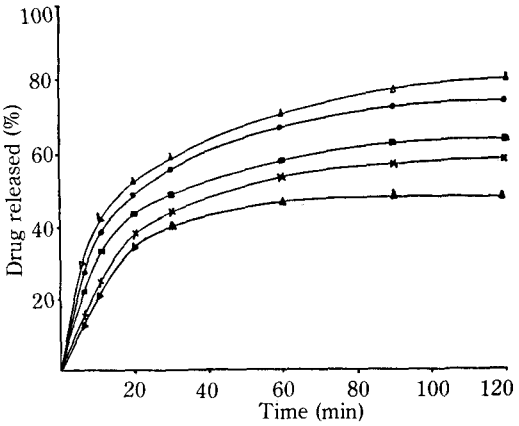


Figure 6—Effect of mean partical size on the release of MD from 1:1 ratio MD-EC(45cp) microcapsules prepared using 1% low molecular PIB solution.
Key: ▲, 223 μm: ×, 398 μm: ■, 605 μm; ●, 855 μm; △, 1,200 μm

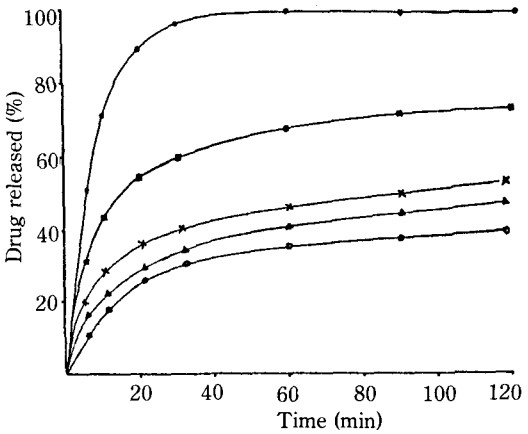


Figure 7—Release of MD from 1:1 ratio MD-EC (45cp) microcapsules prepared using medium molecular PIB of various concentrations in cyclohexane.
Key: ●, uncoated MD, ■, 0% PIB; ×, 0.5% PIB; ▲, 1% PIB; ○, 1.5% PIB

zer, a linear polymer, evidently acts by forming a high energy barrier through adsorption of anchor groups onto the droplet surface.

It is thought that the stabilization of droplets at an earlier stage in the growth of droplets and the presence of an adequate concentration of stabilizer have the effect of maintaining the coacervate droplet surface in the form of a smooth layer during solidification. Low surface coverage of PIB would permit molecular bridging between adjacent EC droplets, and result in reduced stabilizing efficacy.

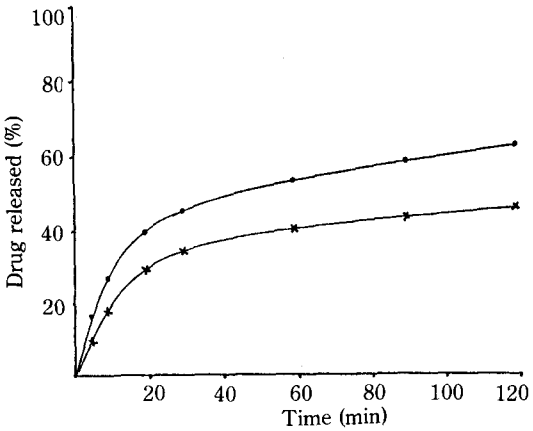


Figure 8—Release of MD from EC-coated microcapsules coacervated with different grades of PIB.
Key: ●, low molecular PIB; ×, medium molecular PIB

Scanning electron micrographs of microcapsules are presented in Fig. 9. The coacervate polymer droplets formed a smooth continuous coat and the surface of microcapsules was markedly different from the surface characteristics of pure MD. The surface of the microcapsules prepared without coacervation-inducing agent was rough and irregular like spongy aggregated matrices. The microcapsules prepared with PIB were covered with EC all over the particle surface, but the surface was smooth with a few small holes.

It is reasonable to assume that another factor in the above mentioned difference of the dissolution rates is the difference of the surface characteristics of microcapsules.

Effect of Particle Size of Microcapsules

From a commercial point of view, it is very important to obtain free-flowing discrete microcapsules. MD microcapsules coated with EC using PIB solutions having different concentrations were fractionated into six particle size ranges by means of standard sieve shaker. The results of sieving analysis of the microcapsules prepared using various concentrations of PIB are shown in Table I. The yield of microcapsules having a diameter of 297-500 μm could be used as an indicator

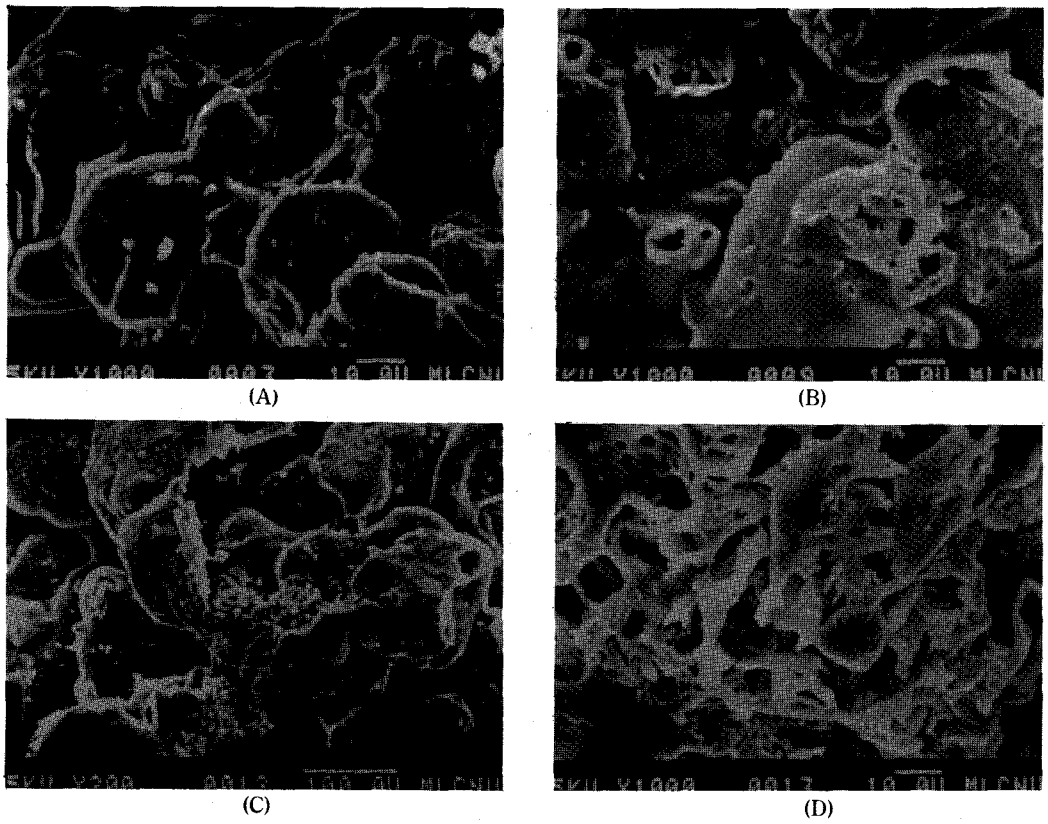


Figure 9—Scanning electron micrographs of 1:1 ratio MD-EC (45cp) microcapsules prepared using PIB of low (L-PIB) and medium (M-PIB) molecular weights.
Key: (A), L-PIB-before dissolution; (B), L-PIB-after dissolution; (C), M-PIB-before dissolution; (D), M-PIB-after dissolution

Table I—*Size distribution of 1:1 MD-EC Microcapsules Prepared Using Low Molecular PIB of Various Concentrations in Cyclohexane.*

Size range (μm)	Mean size (μm)	Size distribution (%)			
		0%PIB	1%PIB	2%PIB	3%PIB
297	297	1.34	6.68	10.55	10.87
297-500	398	1.28	13.29	17.90	23.35
500-710	605	1.90	21.21	25.32	16.13
710-1,000	855	13.12	30.85	18.29	15.54
1,000-1,400	1,200	14.52	21.29	12.96	12.43
1,400	1,400	67.83	6.04	4.96	4.65

of the degree of aggregation. Microcapsules prepared using high concentration of PIB had a narrower and finer size range. A remarkable preventive effect on the formation of aggregates of microcapsules was seen with PIB. When coacervation-inducing agent was not used, the diameter of 67.83% of the microcapsules was at least bigger than 1,400 μm. Fig. 6 shows the influence of particle size on the release of MD from microcapsules prepared using PIB. As the particle size decreases, the release of the drug increases because small microcapsules have more drug molecules close to their surface. In the view of its preventive effect on the aggregation of microcapsules and sustained release effect, PIB seemed to be suitable for the preparation of EC-microcapsules. The technique adopted produced microcapsules with a smooth outer wall and a size distribution which was approximately reproducible from batch to

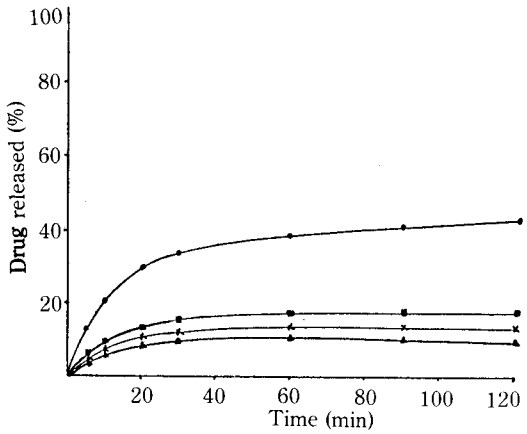


Figure 10—Release of MD from 1:0.5 ratio MD-EC (20cp) microcapsules sealed with spermaceti solutions of various concentrations.
Key: ●, unsealed; ■, 5% spermaceti solution; ×, 10% spermaceti solution; ▲, 20% spermaceti solution

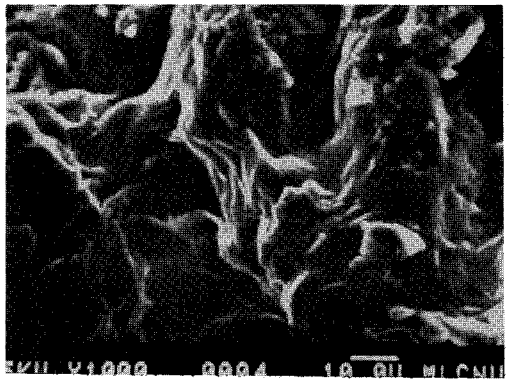
batch.

It may therefore be concluded that the manufacturing process described for microencapsulation of MD with EC using PIB yields coatings of reproducible permeability character over a wide range of core particle sizes and wall thickness indicating the suitability of these microcapsules for sustained release products on the basis of variation of these two products.

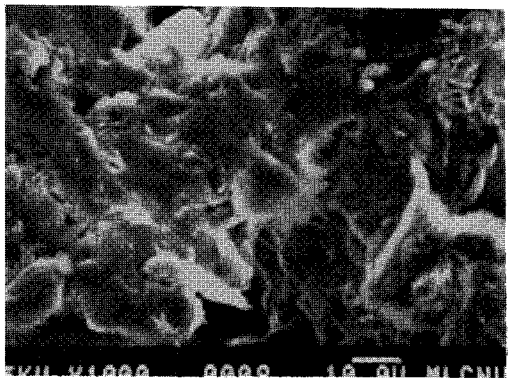
Effect of Sealant Treatments

For the production of prolonged action preparations, as distinct from other applicaitons of microencapsulation, 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 greater tendency to prolong the release, 20cp-EC microcapsules was chosen to prepare several batches of sealant treated microcapsules. Samples of the mixed microcapsules were then sealed by agitating in solutions having various concentrations of spermaceti in cyclohexane.

Fig. 10 shows the release rate of MD for 297-500 μm microscpsules sealed with spermaceti solutions. The release of the drug decreased with increasing the concentration of spermaceti in cyclohexane solution. It was shown that the release



(A)



(B)

Figure 11—Scanning electron micrographs of 1:0.5 ratio MD-EC (20cp) microcapsules sealed with 10% spermaceti solution.
Key: (A), before dissolution; (B), after dissolution

of the core material from the equal size ranged microcapsules was delayed.

Sealant treatment of the microcapsules with 20% spermaceti solution tended to produce a product which was greasy and adhesive. A similar treatment was obtained by Powell[7] for the EC-encapsulated microcapsules of N-acetyl-*p*-aminophenol.

Fig. 11(A) shows a scanning electron micrograph of a 10% spermaceti treated microcapsule, which is obviously composed of an aggregate of smaller particles. A protion of the surface having a wax impregnated appearance and no obvious pores are present. Fig. 11(B) shows a microcapsule which after 3 hour dissolution had a swollen surface containing several pores and became porous but was not appreciably fragmented. It is

probable that the mechanism of the drug release from microcapsules is complex, involving leaching, diffusion and errosion, compounded by polymer swelling, the incorporation of air in the coating and drug binding. The initial lag in release increases with treatment of spermaceti solution of high concentration and probably corresponds with the time required for the dissolution medium to penetrate the surface and capillaries of the wax-impregnated coating layer and for the drug to diffuse outward from the core.

CONCLUSIONS

1. As the methyldopa to ethylcellulose ratio decreases, it is reasonable to expect the formation of thicker walls, and correspondingly greater delays in the release rate.
2. The surface of the ethylcellulose-encapsulated microcapsule presented a rough appearance with the increased swelling of the pores of polymer extending through the wall to the surface of methyldopa inside.
3. Microcapsules prepared using polyisobutylene (PIB) of higher concentrations in cyclohexane had a narrower and finer size ranges. A remarkable preventive effect on the formation of aggregates of microcapsules and sustained release effect was shown from microcapsules prepared using PIB.
4. The surface of the microcapsules prepared without coacervation-inducing agent was irregular and rough with holes, but microcapsules prepared using PIB were smooth with a few holes.
5. Microcapsules after 3 hour dissolution was swollen and became more porous, but were not appreciably fragmented.
6. Treatment of microcapsules with spermaceti solution retarded the release of methyldopa, the release being affected by the concentration of spermaceti in cyclohexane.
7. The technique using PIB as a coacervation-inducing agent produced microcapsules with a smooth outer wall, resulting in low aggregation of microcapsules and sustained release.

REFERENCES

1) I. Jalsenjak, J.R. Nixon, R. Senjkovic and I. Stivic, *J. Pharm. Pharmacol.*, **32**, 678 (1980)
2) I. Jalsenjak, C.F. Nicolaidow and J.R. Nixon, *ibid.*, **28**, 912 (1976)
3) S. Benita and M. Donbrow, *ibid.*, **34**, 77 (1982)
4) R. Senjkovic and I. Jalsenjak, *Pharm. Acta Helv.*, **57**, 16 (1982)
5) Y. Koida, G. Hirata and M. Samejima, *Chem. Pharm. Bull.*, **31**, 4476 (1983)
6) N.N. Salib, M.E. El-Menshawy and A.A. Ismile, *Pharmazie*, **31**, 721 (1975)
7) T.C. Powell, *U.S. Patent* 3,623,997 (1971)
8) D. Fanger and R.G. McNiff, *U.S. Patent* 3,531,418 (1971)
9) W.M. Holliday, M. Berdick, S.A. Bell and G.C. Kiritsis, *US. Patent* 3,524,910 (1970)
10) L.D. Morse, *U.S. Patent* 3,557,279 (1971)
11) P.M. John, H. Minatoya and F.J. Rosenberg, *J. Pharm. Sci.*, **68**, 475 (1979)
12) M. Samejima, G. Hirata and Y. Koida, *Chem. Pharm. Bull.* **30**, 2894 (1982)
13) R.E. Miller and I.L. Anderson, *U.S. Patent* 3,155,590 (1964)
14) S. Benita and M. Donbrow, *J. Colloid Interface Sci.*, **77**, 102 (1980).
15) M. Donbrow and S. Benita, *J. Pharm. Pharmacol.*, **29**, 4 (1977)
16) S. Benita and M. Donbrown, *Int. J. Pharm.*, **12**, 251 (1982)
17) M. Donbrow and S. Benita, *J. Pharm. Pharmacol.*, **34**, 547 (1982)
18) S. Benita and M. Donbrow, *J. Pharm. Sci.*, **71**, 205 (1982)
19) W. Feinstein and J.J. Sciarra, *ibid.*, **64**, 408 (1975)
20) L.A. Luzzi, M.A. Zoglio, H.V. Maudling, *ibid.*, **59**, 338 (1970)
21) J.D. Scheu, G.T. Sperandio, S.M. Shaw, R.R. Landolt, R.E. Miller and G.D. Peck, *ibid.*, **66**, 172 (1977)

22) P.B. Deasy, M.R. Brophy, B. Ecanow and M.M. Joy, *J. Pharm. Pharmacol.*, **32**, 15 (1980)
23) A.A. El-Sayed, A.A. Badawi and A.M. Fouli, *Pharm. Acta Helv.*, **57**, 61 (1982)
24) A. Watanabe and T. Hayashi, *Microencapsulation*, Marcel Dekker, pp. 13-18