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Enhancement of drug release from ethylcellulose microcapsules using solid sodium chloride in the wall

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Summary

Microcapsules of indomethacin and ascorbic acid were prepared by phase separation of ethylcellulose from cyclohexane using polyisobutylene as a coacervation inducing agent. Different amounts of solid sodium chloride were added to the microcapsule wall in order to alter the porosity of the film and hence to enhance the release of the core materials The microcapsules prepared were matrix type, coacervates of many drug particles and ethylcellulose. The release of the poorly water-soluble indomethacin was found to be very slow from the ethylcellulose microcapsules, but it was accelerated considerably with increasing amounts of sodium chloride Indomethacin released through the pores formed when sodium chloride dissolved from the microcapsule film The release was controlled by the solubility of the weakly acidic drug. Thus a good linearity for the release data was obtained with the Hixson-Crowell cube-root law The release of the water-soluble ascorbic acid from matrix-type microcapsules was observed to be incomplete and strongly dependent on the core/wall ratio of the microcapsules. The release of ascorbic acid accelerated in some degree as a function of sodium chloride from the microcapsules of higher core to wall ratio, but the enhancement in drug release was quite minimal with the thicker walled ones. Sodium chloride particles acted as pore formers only at the surface of the inhomogeneous microcapsule matrices The release of the drug was considered to be diffusion controlled having a biphasic release profile against the square root of time

Introduction

Water-soluble drugs permeate through lipophilic microcapsule membranes mainly by water-filled pores of the coating, while diffusion through the film dominates the permeation of sparingly water-soluble drugs (Kondo, 1986). The release of a drug of low water solubility from microcapsules having the wall polymer as a diffusion barrier consists of several steps: permeation of the polymer by water, dissolution of the drug at the inner face of the wall, permeation of the drug through the membrane and finally diffusion into the bulk phase (Nixon and Walker, 1971; Benita and Donbrow, 1982a). If the release of the drug is controlled by diffusion through the membrane, the permeability should be mainly a function of the solubility of the drug in the film (Donbrow and Friedman, 1975).

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Hydrophilic substances could increase the permeability of drugs through hydrophobic films, e.g., by changing the properties of the membrane matrix (polymer configuration, crystallinity, hydrophilicity), by introducing increased porosity into the film or by forming capillaries or a hydrated network giving direct connection between the two sides of the film (Donbrow and Friedman, 1975). Hydrophilic polymers or other polar substances have been added to hydrophobic polymer films of microcapsules in order to increase the permeability properties of the film. Vidmar et al. (1982) used polyethylene glycol 4000 in ethylcellulose films of sodium barbitone microcapsules. It introduced additional porosity into the membrane by rapid leaching out from ethylcellulose when the microcapsules were subjected to water. When the volume of water-filled pores in the membrane was increased the diffusion of the water soluble drug was also increased. Lippold et al. (1980) have reported that polyethylene glycol 1500 added to the hydrophobic microcapsule films of quaternary polymethacrylic acid esters increased their porosity and thus the release of the slightly water-soluble model drug (chloramphenicol) in water. Lippold et al. (1981) have also used glycerin triacetate, sodium chloride and dibutylphthalate to increase the pore formation of microcapsules of similar coating.

The aim of the present study was to control the permeability of the hydrophobic ethylcellulose wall of microcapsules by using solid sodium chloride to alter the porosity of the film. Two model drugs with different water solubilities were used: ascorbic acid, which is freely soluble in water and indomethacin, practically insoluble in water.

Materials and Methods

Materials

Ascorbic acid (Ph. Eur.) was micronized before encapsulation by means of an air jet mill (Fryma JM 80, Fryma-Maschinen, Switzerland) to mean particle diameter with standard error of mean of 26 ± 1.2 μm. Indomethacin (Sigma, St Louis, U.S.A.) with the mean particle diameter of 18 ± 0.9 μm was microencapsulated as received. Sodium chloride (J.T. Baker, Deventer, The Netherlands) was micronized before use by a spray dryer (Büchi Mini Spray Dryer B 190, Büchi Laboratory-Techniques, Switzerland) to the mean particle diameter of 1.6 ± 0.07 μm. The particle size distributions were studied microscopically by measuring the Feret's diameter of 200 particles.

Preparation of microcapsules

Indomethacin and ascorbic acid were microencapsulated by the phase separation method modified from that used by Samejima et al. (1982). 100 ml of cyclohexane (Merck, Darmstadt, Germany) containing 2.3% w/v of polyisobutylene (mol. wt 380000, Aldrich, Steinheim, Germany) as a coacervation inducing agent was placed in a 250 ml three-necked round-bottomed flask equipped with an air-tight stirrer, a thermometer and a reflux condenser. Ethylcellulose (Ethocel®, 45 mPas; Fluka, Buchs, Switzerland) was added to cyclohexane at room temperature. The system was stirred continuously at 310 rpm and heated to 78°C to form a solution. The core material was suspended and the mixture was cooled uniformly to 40°C within 1 h. The ratio of core to wall was 10:1 with indomethacin microcapsules and 1:1 or 1:2 with ascorbic acid microcapsules. At the temperature of 40°C different amounts (0–21% w/w of the amount of ethylcellulose) of sodium chloride were added to the microcapsule wall. The microcapsules were hardened by cooling the solution quickly to 25°C. The solution was decanted and the microcapsules were washed with cyclohexane and dried at room temperature.

Size distribution of microcapsules

The batches of microcapsules were fractioned by sieving with a mechanical shaker using standard sieves of 149, 297, 420 and 710 μm. The size fractions of 149–297 μm of indomethacin microcapsules and 149–710 μm of ascorbic acid microcapsules were used for the further studies.

Determination of wall thickness

If the microcapsules are assumed to be uniform, smooth and spherical, the average wall

thickness is given by Madan's equation (Madan et al., 1974):

$$\text{wall thickness} = \frac{W_w}{W - W_w} \cdot \frac{r}{r_w} \cdot \frac{d}{6} \quad (1)$$

where W and W_w denote the respective weights of microcapsules and wall material, r_w and r represent the densities of the wall material and core material, respectively, and d is the mean diameter of the core material particles. The densities of ethylcellulose, ascorbic acid and indomethacin were measured using a pycnometric method. The densities were calculated from the displacement volume of a known weight using cyclohexane (25°C) as displacement fluid. The calculated densities with the standard error of the mean ($n = 6$) were 0.99 ± 0.02 g/cm^3 for ethylcellulose, 1.35 ± 0.03 g/cm^3 for indomethacin and 1.87 ± 0.01 g/cm^3 for ascorbic acid.

Evaluation of surfaces of microcapsules

Scanning electron micrographs of microcapsules were taken before and after the dissolution tests. The samples were dried at room temperature and coated with gold vapor using a Jeol JFC-1100 sputter coater (Jeol, Japan). Micrographs were taken with a Jeol JSM-35 scanning electron microscope (Jeol, Japan) at an accelerating voltage of 15 kV.

Determination of drug content

Both indomethacin and ascorbic acid microcapsules were dissolved in methanol, the solutions were filtered and the samples were diluted with methanol to a suitable concentration. Indomethacin was evaluated spectrophotometrically (Hitachi 220, Hitachi, Japan) at 318 nm and ascorbic acid at 248 nm.

Dissolution studies of microcapsules

The dissolution of drugs from the microcapsules was studied with the rotating basket method (Sotax AT6 Dissolution Tester, Sotax AG, Switzerland). Baskets of wire netting with quadratic holes of 74 μm were used. The dissolution medium used was for indomethacin microcapsules pH 7.2 phosphate buffer according to USP XXI for indomethacin capsules and for ascorbic acid microcapsules pH 1.2 simulated gastric fluid without pepsin (USP XXI). The dissolution media were degassed with helium before use. 100 mg of microcapsules were placed in the basket and immersed in 750 ml of the dissolution medium at 37 ± 0.5°C. The stirring rate of the baskets was 100 rpm. Samples were taken for 7 h (or 24 h in some tests) for indomethacin microcapsules and for 30 min for ascorbic acid microcapsules. Indomethacin and ascorbic acid were analyzed spectrophotometrically at 318 and 243 nm, respectively.

Effect of pH on dissolution

The effect of pH on the dissolution rate of indomethacin was studied by the rotating disk method. 100 mg quantities of indomethacin were compressed by a hydraulic press using punches of 13 mm in diameter. A compression pressure of about 10^3 MPa was maintained for 15 min and then rapidly removed. The dissolution of the indomethacin tablets was studied in 10 mM phosphate buffer solutions (750 ml) as a function of pH (6.4, 7.2 and 8.0). The ionic strength of the

TABLE 1

Properties of ethylcellulose microcapsules containing indomethacin or ascorbic acid

Microcapsules (core/wall)	Core loading (% w/w) (±SE)	Calculated wall thickness (μm)(±SE)	Recovery (% w/w) (±SE)
Indomethacin [a] without NaCl (10:1)	90.0	0.5	90.8
Indomethacin [b] with NaCl (10·1)	89.6±0.8	0.5±0 0	88.7±0.7
Ascorbic acid [a] without NaCl (1:1)	47.8	8 9	81.0
Ascorbic acid [c] with NaCl (1:1)	45.6±0.5	9.8±0.1	88 2±4 9
Ascorbic acid [a] without NaCl (1:2)	31 6	17.7	90 8
Ascorbic acid [c] with NaCl (1:2)	30.2±0 5	18 9±0.1	91 1±1 8

[a] $n = 1$, [b] $n = 8$, [c] $n = 5$

dissolution media was adjusted with sodium chloride to 0.02. The temperature of the media was 37 ± 0.5°C and the stirring rate of the disks was 100 rpm.

Results and Discussion

Indomethacin microcapsules

The core to wall ratio of indomethacin microcapsules was high (10 : 1) because of the low water solubility of indomethacin. Consequently, the core loading of the microcapsules was high and the film was very thin (Table 1). The microcapsules formed were of the matrix type, their structure being rather loose (Fig. 1A). The shape of the capsules is not spherical and the surface is uneven. Thus, the calculated thickness of the wall of the indomethacin microcapsules is only a rough estimate. The cubic crystals of sodium chloride are clearly visible at the surface of indomethacin microcapsules (Fig. 1B). During the process of preparation of microcapsules sodium chloride was added at the temperature of 40°C, when the ethylcellulose film had already been formed, but had not hardened. The particles of sodium chloride stuck in the ethylcellulose coacervate, after which the film was hardened by cooling. If sodium

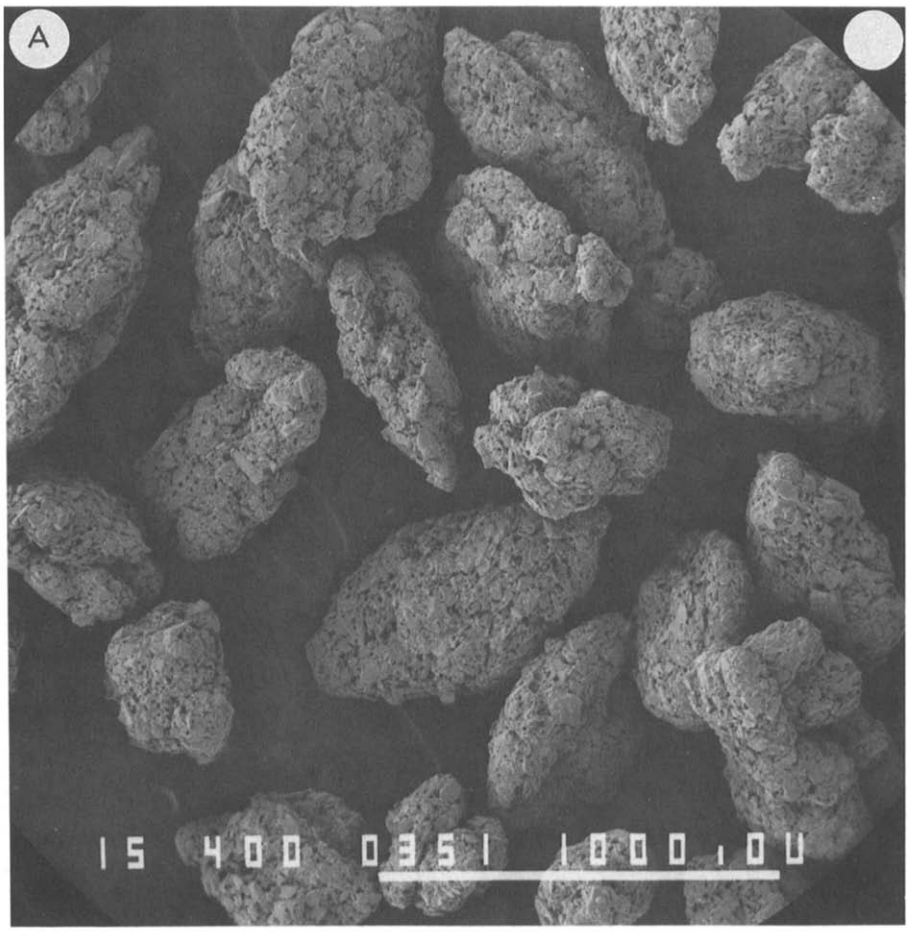

Fig. 1 Scanning electron micrographs of indomethacin microcapsules (bar: 1000 μm) (A); surface of a microcapsule with 3.5% w/w of NaCl in the film, before dissolution test (bar: 10 μm) (B); without NaCl in the film, after dissolution test (bar. 100 μm) (C), and with 3.5% w/w of NaCl in the film, after dissolution test (bar: 10 μm) (D).

chloride was added, e.g., at 35°C, it did not stick in the microcapsule film. On the other hand, if sodium chloride was added at the higher temperatures (e.g., 55 or 70°C), it probably was encapsulated inside the film and consequently had practically no effect on pore formation of the ethylcellulose wall. Although the microencapsulation process was critical with respect to the addition of sodium chloride, the method was reproducible (Tables 1 and 2). The presence of sodium chloride did not affect the amount of drug encapsulated, the microcapsule recovery or the size distribution of microcapsules. The dissolution of sodium chloride particles and pore formation in the film was detected from scanning electron micrographs after the immersion of microcapsules in water. The particles of sodium chloride dissolved during the first 10 min.

Scanning electron microscopic studies of the topography of ethylcellulose microcapsules prepared by phase separation from cyclohexane have shown that there are always pores in the ethylcellulose film made by this procedure (Senjkovic and Jalsenjak, 1981). The number and size of the pores were dependent on the small changes occurring during the process of preparation. With certain procedures, a uniform film was formed with pores of such a small size that they did not extend through the film to the core. In our studies the release of indomethacin through the ethylcellulose membrane was extremely slow (Fig. 2). Only about 35% of the drug was released over 24

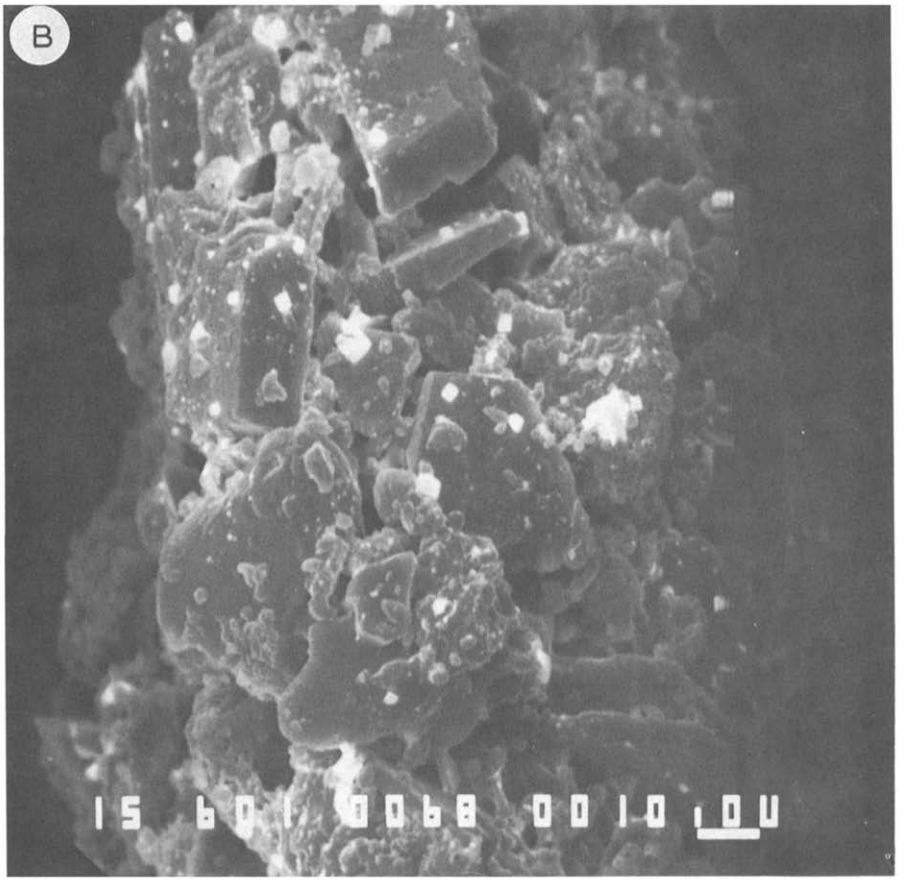

Fig 1. (B).

h when the microcapsules were prepared without adding sodium chloride to the film. Although the ethylcellulose wall of the indomethacin microcapsules was very thin, it was quite impermeable to the drug. The use of polyisobutylene in the preparation of the microcapsules could be the reason for the formation of a compact and impermeable film. Samejima et al. (1982) observed that, in addition to the reduced aggregation of microcapsules, the use of polyisobutylene resulted in the formation of smooth-walled microcapsules with a slower dissolution rate.

Koida et al. (1987) have suggested that most of the drugs are not transported through the ethylcellulose polymer phase, but rather through the water channels (i.e., fine pores and cracks) existing in the microcapsule membrane. Vidmar et al. (1982) calculated the volume of water-filled pores in the films of ethylcellulose microcapsules prepared by phase separation from cyclohexane. They obtained rather low values (0.55–2.5%) when no hydrophilic additives were used. The addition of PEG 4000 increased the volume fraction of pores in the membrane and hence the diffusion of the core material. In this study, the release of indomethacin from the matrix-type microcapsules accelerated as a function of sodium chloride concentration in the film (Fig. 2). An increase in drug release was not achieved in the case of the smallest amounts of sodium chloride (1.75–3.07% w/w), but with increasing amounts (3.28–5.25% w/w), the extent of pore formation was suffi-

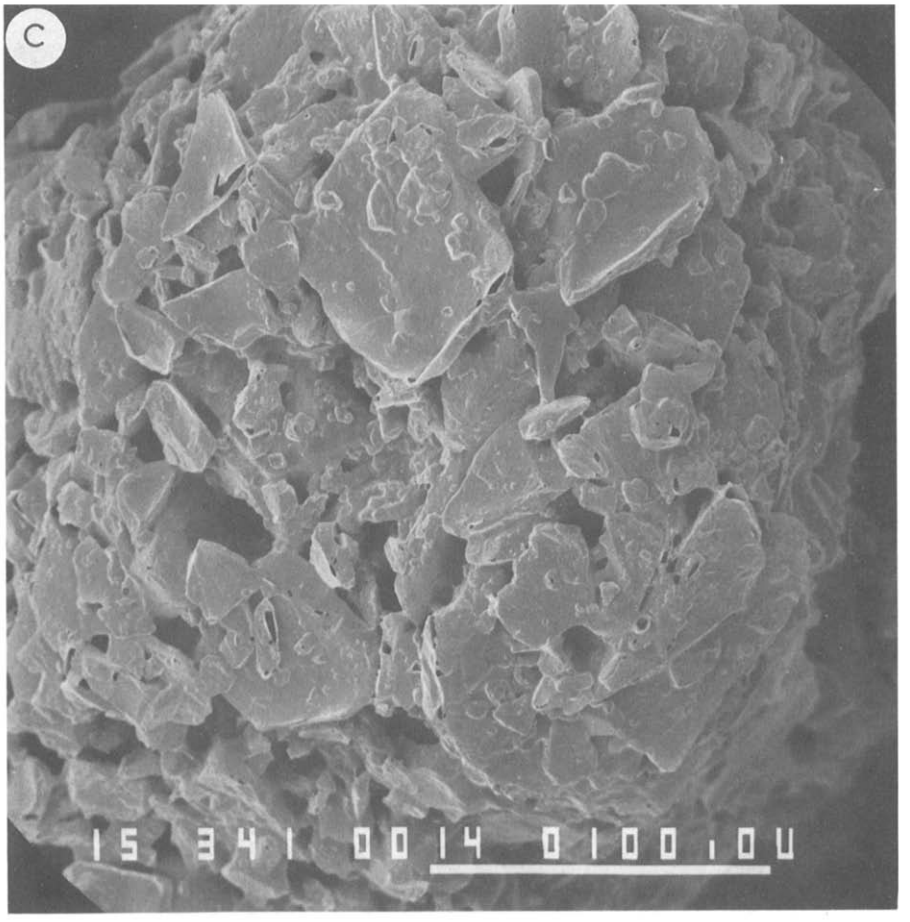

Fig 1 (C)

ciently large to bring about additional drug release. With the highest amounts of sodium chloride (7–14% w/w) indomethacin release was clearly faster and almost reached completion during the test period of 7 h. After the leaching out of sodium chloride particles (about 1.6 μm in diameter) from the thin ethylcellulose membrane, the pores formed in the film may extend through the wall to the core and therefore permit the direct transport of indomethacin into the dissolution medium. However, due to the matrix character of the microcapsules, the sodium chloride particles act as pore formers only at the surface of the capsules. Thus, the mechanism may change when indomethacin from the interior is released. Nevertheless, due to the loose aggregate structure of the matrix-type microcapsules the dissolution medium is able to penetrate effectively to the interior of the capsules.

The appearance of ethylcellulose film changes during the dissolution test. Some pores and ruptures (especially at the edges of core material particles) are evident in the film when NaCl was not used (Fig. 1C). In contrast, numerous holes and ruptures of the coating are observed for the case where sodium chloride was used (Fig. 1D). According to Salib et al. (1977), the microcapsule film does not change visually during the dissolution test if the release of drug is achieved only by diffusion through the membrane. Thus, it appears obvious that the penetration of indomethacin occurred mainly through the pores existing in the microcapsule film.

When pores have formed in the microcapsule

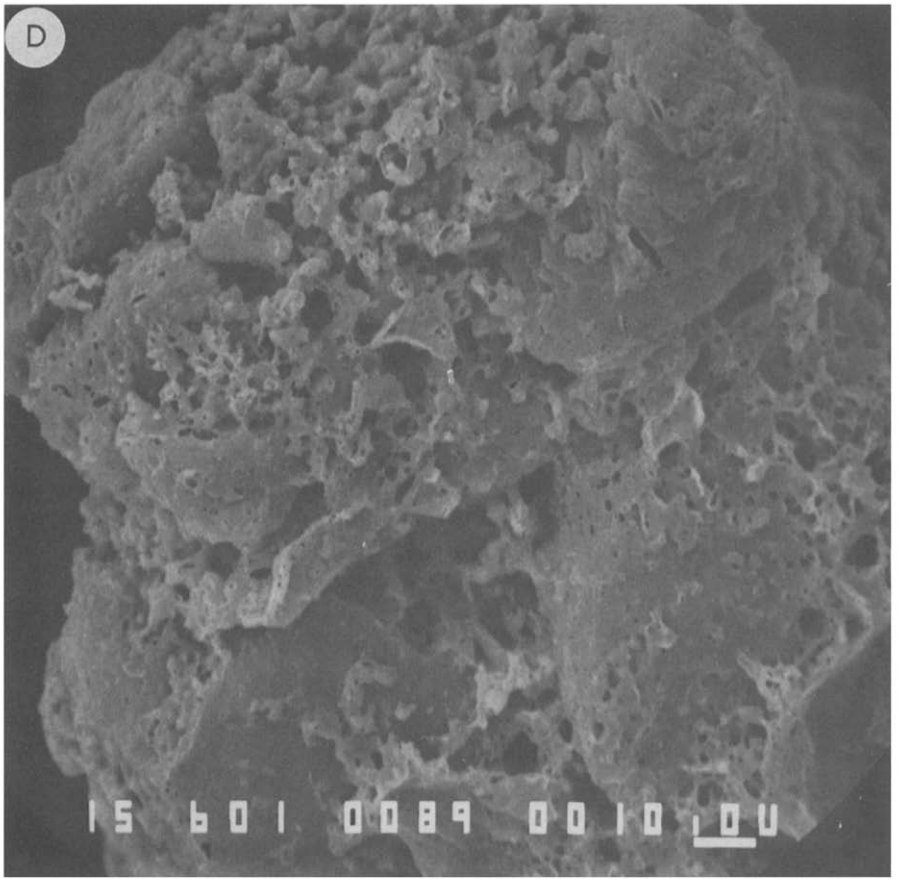

Fig 1 (D)

TABLE 2

Particle size distribution (% ± SE) of ethylcellulose microcapsules containing indomethacin or ascorbic acid

Microcapsules (core/wall)	Sieve fractions (μm)				
	< 149	149–297	297–420	420–710	> 710
Indomethacin [a] without NaCl (10 1)	47	52	1	0	0
Indomethacin [b] with NaCl (10:1)	35 ± 4 9	58 ± 2.5	4 ± 2.1	2 ± 1.1	1 ± 0 4
Ascorbic acid [a] without NaCl (1·1)	5	26	22	31	16
Ascorbic acid [c] with NaCl (1.1)	4 ± 1 3	19 ± 2.7	22 ± 1.8	35 ± 2 2	20 ± 2.2
Ascorbic acid [a] without NaCl (1:2)	1	2	6	33	58
Ascorbic acid [c] with NaCl (1:2)	1 ± 0 0	4 ± 0.9	10 ± 1.3	37 ± 2.2	48 ± 4 0

[a] $n = 1$, [b] $n = 8$, [c] $n = 5$.

film, the release of the core material is controlled mainly by the solubility of the drug (Lippold et al., 1980). The release data of indomethacin were analyzed according to several kinetic models: first-order and zero-order kinetics, the Hixson-Crowell cube-root law and the Higuchi matrix model. The best fit to the data was obtained with the Hixson-Crowell cube-root law (Hixson and Crowell, 1931):

$$m_0^{1/3} - m_t^{1/3} = kt \qquad (2)$$

where m_t represents the amount of drug remaining in the microcapsules at time t, m_0 is the initial amount and k denotes the release rate constant. Acceptable linearity was obtained with Eqn 2 for the case where sodium chloride was used in the range of 3.07–14.0% w/w.

The coefficients of determination (r^2) were between 0.992 and 0.998 up to 80% of the drug released. Thus, it appears to be possible that the rate of release was governed by the solubility of indomethacin. The slowing down of release during the final phase (Fig. 2) may be the result of either the drug reservoir being exhausted or possible inhomogeneity of the matrices. The Hixson-Crowell cube-root law is rarely applied to drug release from microcapsules. Benita and Donbrow (1982b) found that the release of sodium salicylate from ethylcellulose microcapsules behaved in conformity with the Hixson-Crowell equation. In their study, pore formation in the microcapsule film was due to osmotically active core material. The pH of the dissolution medium affected the

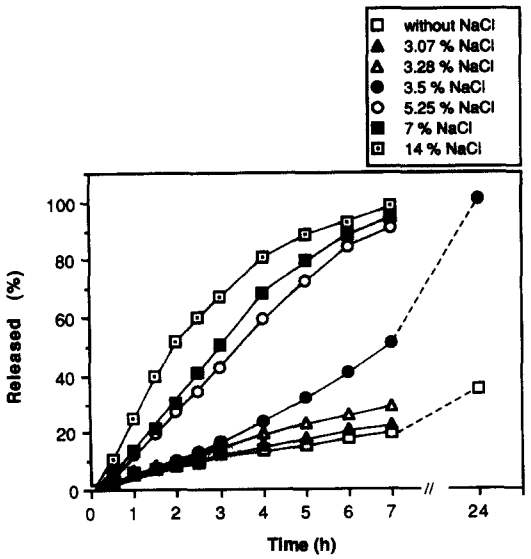

Fig. 2. Effect of sodium chloride added into the microcapsule wall on the release of indomethacin from ethylcellulose microcapsules.

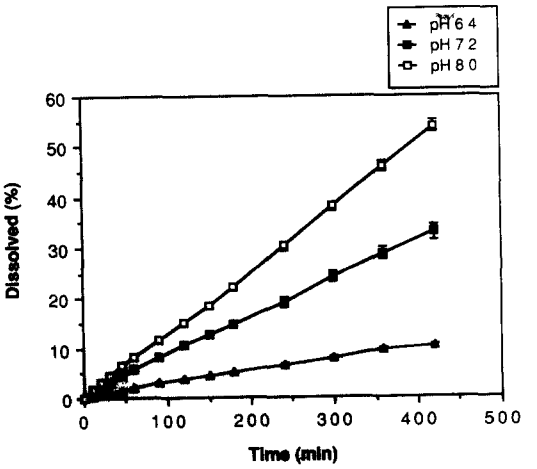

Fig. 3. Effect of pH of the dissolution medium on the dissolution of indomethacin (% ± SE) studied with rotating disk method ($n = 6$)

rate of release of the weakly acidic sodium salicylate.

Indomethacin is very slightly soluble in water but dissolves more readily in alkaline solution. The pH dependence of the solubility of indomethacin was also clearly evident from dissolution studies performed using the rotating disk method (Fig. 3). Even slight alterations in pH markedly affected the dissolution of indomethacin. The dissolution of indomethacin might decrease the pH of its environment inside the microcapsule and thus itself reduce its solubility and release. This could be the reason for the poorer linearity ($r^2 = 0.976–0.980$) resulting with the Hixson-Crowell equation, when NaCl was not used or was used in such small amounts (1.75 and 2.625% w/w) that no enhancement in drug release was achieved. With the highest amounts of sodium chloride the porosity of the film appeared to be sufficient to allow relatively free penetration of buffer solution (pH 7.2) into and out of the microcapsule. The dissolution of indomethacin increased as a result of the flushing effect of dissolution medium causing a considerable increase in drug release.

Ascorbic acid microcapsules

The ascorbic acid microcapsules were needle-shaped at both core/wall ratios (1:1 and 1:2) (Fig. 4A). The capsules appear to be of the ma-

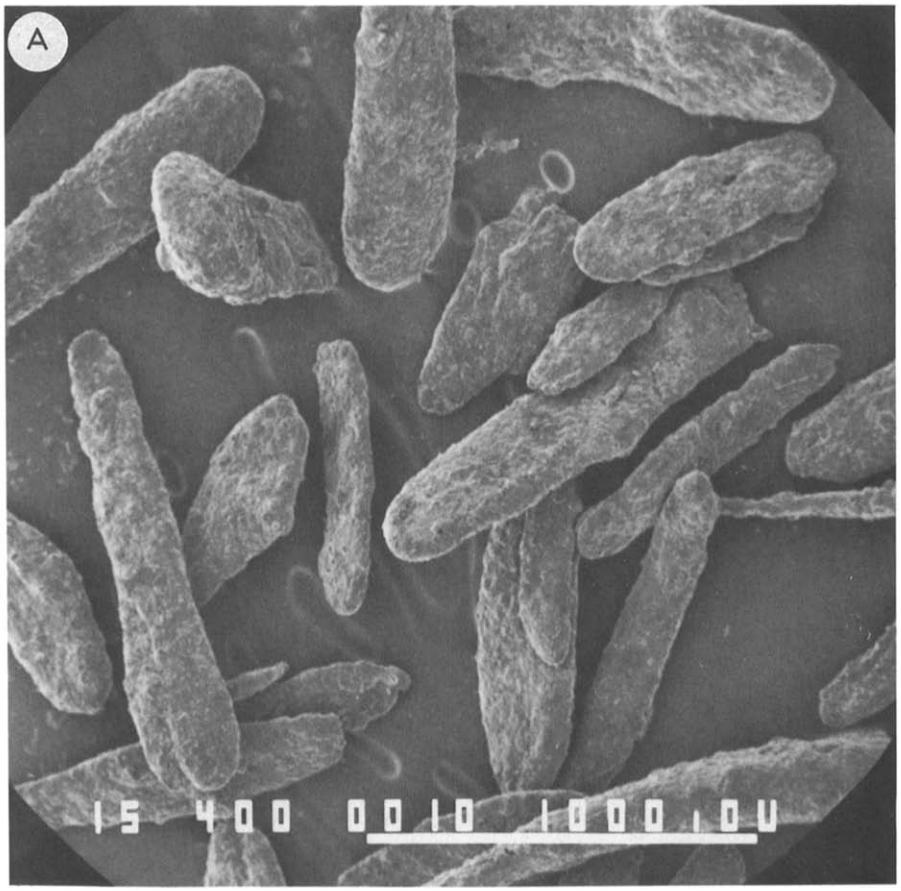

Fig. 4. Scanning electron micrographs of ascorbic acid microcapsules (bar: 1000 μm) (A); surface of a microcapsule with 7% w/w of NaCl in the film, before dissolution test (bar: 100 μm) (B); and with 0.875% w/w of NaCl in the film, after dissolution test (bar: 100 μm) (C).

trix type, having a rather dense structure. A few small pores in the microcapsule film as well as crystals of sodium chloride are observed in the scanning electron micrograph of the capsule surface before the dissolution test (Fig. 4B). The drug content of ascorbic acid microcapsules and the mathematically estimated thickness of the wall (Table 1) as well the particle size distribution (Table 2) were dependent on the core/wall ratio of the microcapsules. The presence of sodium chloride did not have any significant effect on the values of these parameters.

When no addition of sodium chloride was made to the ethylcellulose wall, about 50% of the drug was released within 30 min from the capsules with the higher core/wall ratio (Fig. 5A), whilst approx. 30% drug release occurred from those with the thicker wall (Fig. 5B). After 30 min further release of drug had practically ceased. The addition of sodium chloride was found to have some influence on the extent of overall release of ascorbic acid from the microcapsules with a core/wall ratio of 1 : 1 (Fig. 5A). However, the effect of sodium chloride was clearly weaker in the case of the microcapsules with the thicker walls (Fig. 5B). At both core/wall ratios and at every concentration of sodium chloride tested, the release of ascorbic acid did not reach completion, which could indicate the formation of dense reservoirs of drug enclosed within the intact eth-

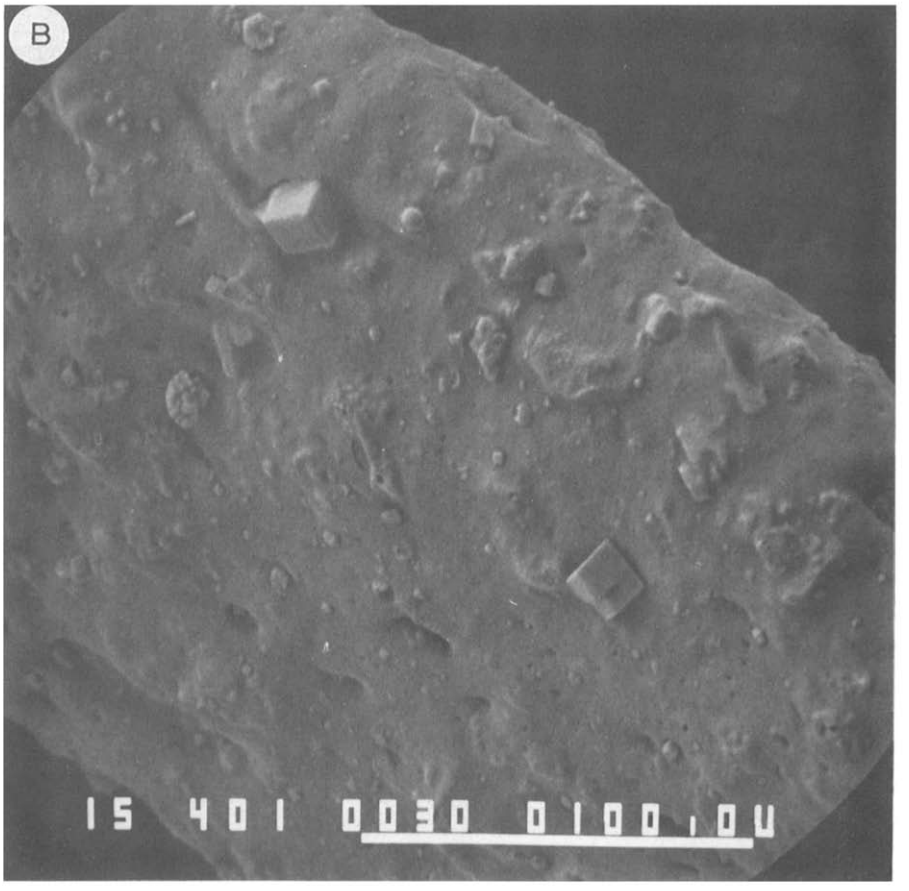

Fig. 4 (B)

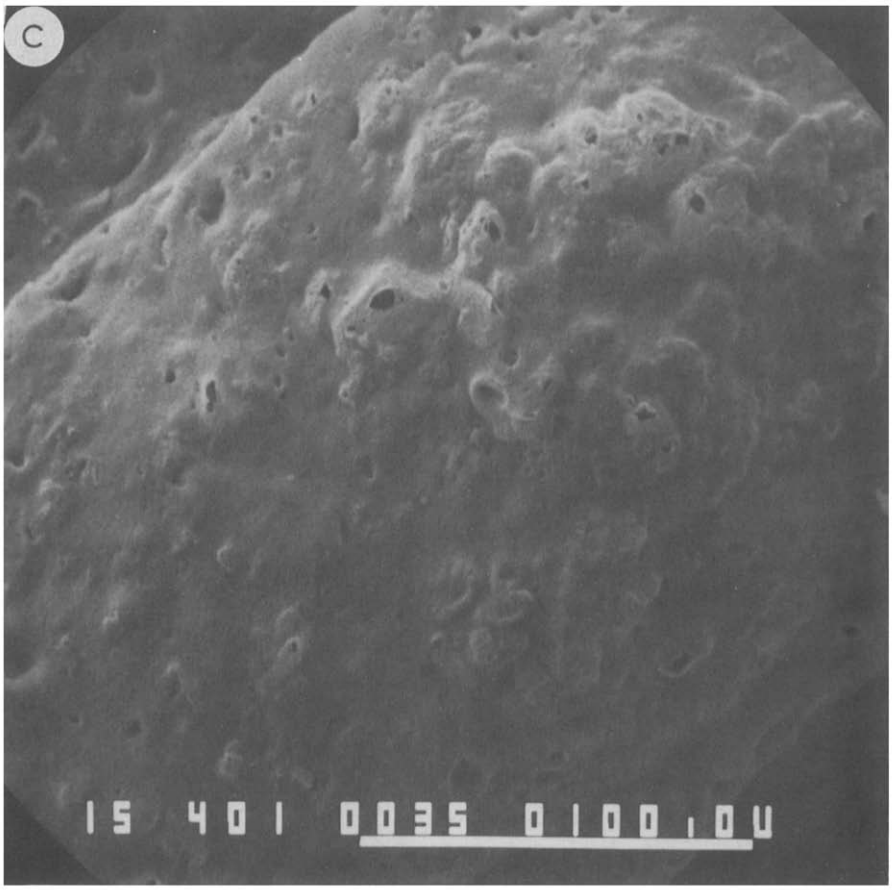

Fig 4 (C)

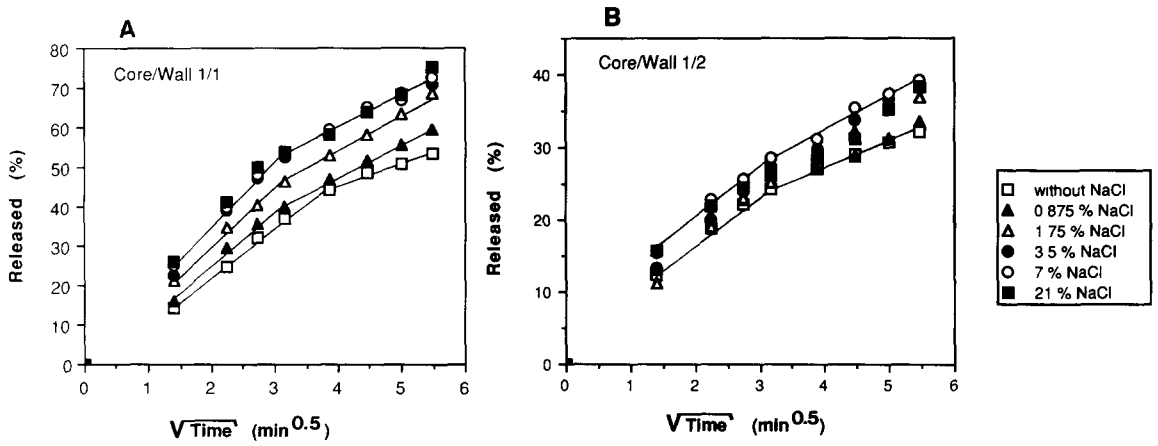

Fig 5. Effect of sodium chloride added into the microcapsule wall on the release of ascorbic acid from ethylcellulose microcapsules with core/wall ratio of 1 1 (A) and 1·2 (B)

ylcellulose walls. The relatively large ascorbic acid microcapsules (Table 2) were observed to be compact aggregates of smaller microcapsules. As in the case of indomethacin microcapsules, during preparation, the deposition of coacervate around the core material and the aggregation of microcapsules had already occurred before the addition of sodium chloride (40°C). Therefore, the particles of NaCl are connected to the surface layer of the microcapsule aggregates. Furthermore, the diameter of the sodium chloride particles used was only about one-fifth or one-tenth of the estimated wall thickness of the microcapsules. Thus, the pores formed in the ethylcellulose wall were mainly at the surface layer of the film, not extending effectively through it. That being the case, the amount of pores at the surface of microcapsule wall is not in direct relationship to the release of the drug (Senjkovic and Jalsenjak, 1981).

The overall release data of ascorbic acid did not conform well with any kinetic models tested (first-order and zero-order kinetics, Hixson-Crowell cube-root law and Higuchi matrix model). When the drug released was plotted vs the square-root of time (Fig. 5A and B), two linear portions were noted in the release profile. The biphasic matrix diffusion profile consisted of a faster release phase at the beginning followed by a slower stage. The effect of different amounts of NaCl is mainly observed during the first, rapid phase, when ascorbic acid from the outer region of the matrices is released. Subsequently, the release of drug is slower and proceeds at a nearly constant rate, irrespective of the amount of NaCl. This could be due to the fact that NaCl particles did not act as pore formers in the interior of the microcapsules. The thicker the microcapsule wall, the shorter was the initial rapid release phase and the less complete was the overall release of drug.

Drug release by matrix diffusion has also been considered to be applicable with several other coacervation-produced ethylcellulose microcapsules (e.g., Jalsenjak et al., 1976; Oya Alpar and Walters, 1981). In these cases, water-soluble core materials were typically used and the microcapsules formed were regarded as matrix-type microcapsule aggregates. In some cases, biphasic release profiles were obtained (Vidmar and Jalsenjak, 1982; Chemtob et al., 1986).

Conclusions

The film of ethylcellulose microcapsules prepared by phase separation using polyisobutylene as a coacervation-inducing agent was very impermeable in nature. It was possible to accelerate the release of indomethacin from the matrix-type microcapsules by adding NaCl to the capsule film at a convenient stage during the preparation process. Pore formation at the surface of the microcapsule wall was increased as a function of the amount of NaCl. The release of indomethacin appeared to be controlled by the solubility of the drug in the dissolution medium. When the porosity of the wall was low, the weakly acidic drug could decrease the pH of the environment inside the microcapsule and, hence, by itself reduce solubility and release. When the interconnecting network of pores was sufficient to allow the buffer solution to penetrate into and out from the microcapsules the release of the drug was considerably accelerated.

The ethylcellulose microcapsules of water-soluble ascorbic acid prepared by the same process were also of the matrix type. The effect of sodium chloride on drug release was relatively small: i.e., the thicker the microcapsule wall, the smaller the effect. The release was diffusion controlled, being dependent on the structure of the matrix around the core material. A biphasic release profile was obtained when plotting the drug release vs the square-root of time. The faster release phase at the beginning was dependent on the amount of NaCl used in the wall, while the ensuing slower phase was not. This was considered to be an indication of an incomplete capillary network, which did not extend into the interior of the microcapsule matrices.

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