ELSEVIER

International Journal of Pharmaceutics 124 (1995) 219–229

international journal of pharmaceutics

# Buffer controlled release of indomethacin from ethylcellulose microcapsules

S. Tirkkonen *, A. Urtti [1], P. Paronen

*Department of Pharmaceutical Technology, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland*

Received 10 October 1994; revised 7 March 1995; accepted 15 March 1995

**Abstract**

The rate of release of indomethacin from ethylcellulose microcapsules prepared by coacervation was studied using internal buffer, dibasic sodium phosphate (DSP), to increase the solubility of the core. The dissolution rate of the drug was determined in phosphate buffer solutions of varying pH and concentration. The role of the stagnant diffusion layer at the microcapsule surface was also evaluated by changing the mixing in the dissolution test. Indomethacin release was accelerated considerably with increasing amounts of DSP in the core. DSP increases the pH inside the microcapsules, thus enhancing the release of the acidic drug. Increasing bulk solution pH increased the release rate of indomethacin, the enhancing effect being more pronounced with buffered microcapsules. Neither increasing phosphate concentration of the bulk solution nor increasing mixing of the microcapsules influenced the rate of release of indomethacin from unbuffered capsules. With buffered capsules the increase in phosphate concentration of bulk solution prevented leaching out of internal phosphate increasing the release rate of indomethacin. The release of indomethacin also accelerated slightly with increasing mixing.

*Keywords:* Microencapsulation; Ethylcellulose; Indomethacin; Dibasic sodium phosphate; pH-stabilized microcapsule; Buffer controlled release

## 1. Introduction

Due to their weakly acidic or basic nature, the solubility and dissolution rates of many drugs are pH-dependent (Serajuddin and Rosoff, 1984; Aunins et al., 1985; Serajuddin and Jarowski, 1985; Doherty and York, 1989; Kohri et al., 1991). This may lead to variations in drug release in the gastrointestinal tract and unpredictable drug absorption (Yamada et al., 1990; Hadzija et al., 1991; Kohri et al., 1991). For example, indomethacin, a nonsteroidal, anti-inflammatory agent, is a poorly water-soluble acidic drug with a $pK_a$ of 4.5 having a pH-dependent solubility and dissolution rate (Mooney et al., 1981; Oth and Moës, 1985; De Filippis et al., 1991; Tirkkonen and Paronen, 1992). In our previous study, the release of indomethacin from ethylcellulose microcapsules was noted to be very slow and con-

* Corresponding author. Tel. +358 71 162490; Fax +358 71 162456.

[1] Present address: School of Pharmacy, University of California San Francisco, San Francisco, CA, USA.


*SSDI* 0378-5173(95)00092-5

trolled by drug solubility (Tirkkonen and Paronen, 1992). It appears that the dissolution of indomethacin decreases the microenvironmental pH inside the microcapsules and, thus, reduces its own solubility.

The self-buffering action of dissolving species and subsequent microenvironmental pH on the hydrodynamic layer on the particle may influence substantially the dissolution rate of the drug (Doherty and York, 1989; Shah and Maniar, 1993). This has implications in the design of drug delivery systems. By incorporating appropriate

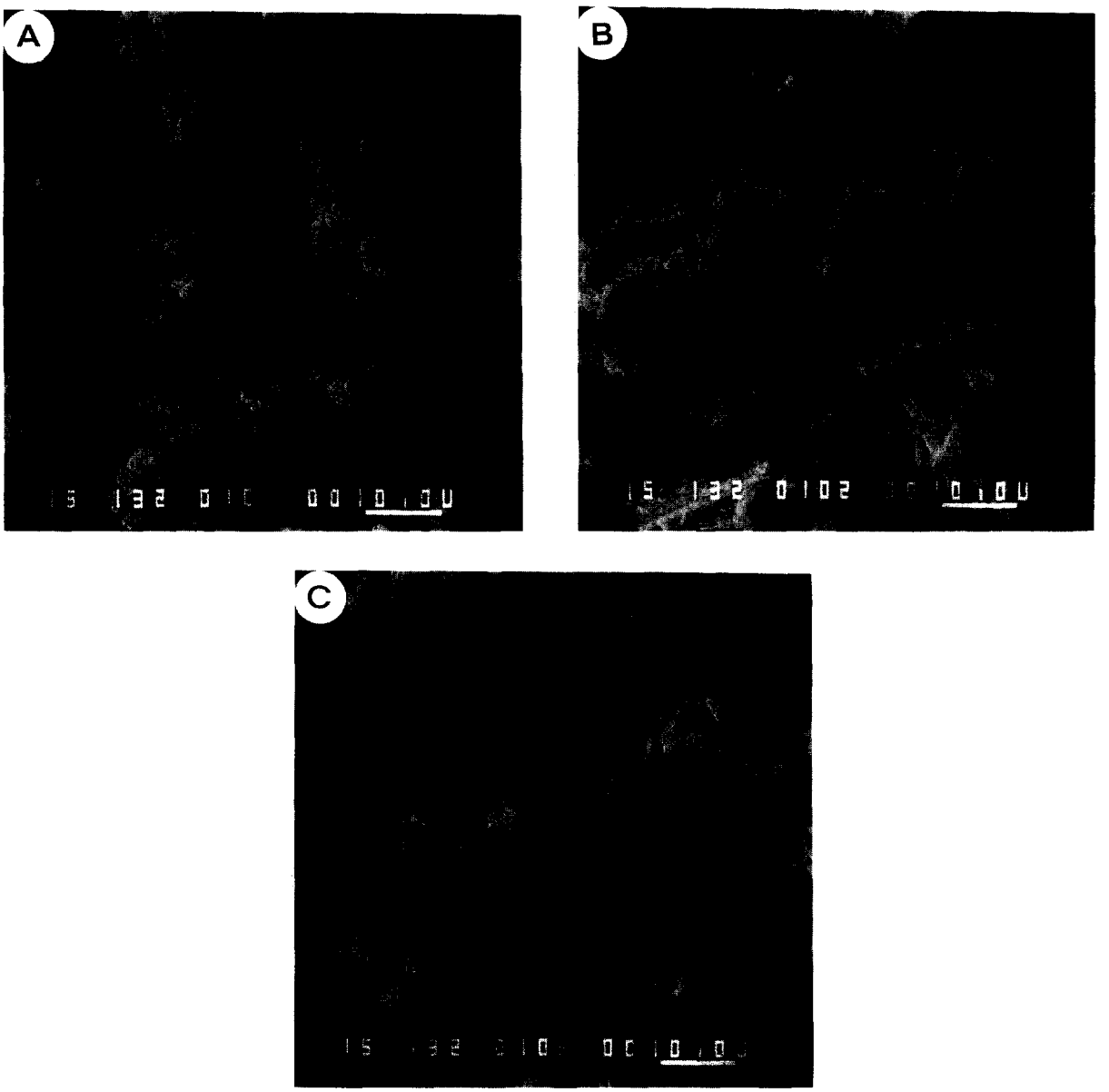


Fig. 1. Scanning electron micrographs of untreated indomethacin (A); indomethacin recrystallized from methanol (B); and powder mixture of indomethacin (90% w/w) and DSP (10% w/w) coprecipitated from methanol/water (C) (bar: 10 $\mu$m).

buffering agents, the dissolution of weakly basic (Bechgaard and Baggesen, 1980; Thoma and Zimmer, 1990; Kohri et al., 1991) or acidic drugs (Doherty and York, 1989; McGloughlin and Corrigan, 1992) can be adjusted. Furthermore, the pH dependency of drug release can be decreased by microenvironmental pH stabilization by the buffer.

Indomethacin is a very appropriate drug for microencapsulation, since it has a solubility-controlled and pH-dependent dissolution rate. The aim of this work was to prepare microcapsules in which the buffering of the microcapsule core would control the drug release rate. The release of indomethacin from ethylcellulose microcapsules containing different amounts of dibasic sodium phosphate was assessed at different pH values and external buffer concentrations. The role of the stagnant diffusion layer on drug release was evaluated by changing mixing in the dissolution test. The effect of osmotic pressure on pore formation of the microcapsule wall was examined with microcapsules containing internal sodium chloride.

## 2. Materials and methods

### 2.1. Preparation of microcapsules

For the preparation of the core of microcapsules, mixtures of indomethacin (Sigma, St Louis, USA) and dibasic sodium phosphate (DSP), $Na_2HPO_4 \cdot 2H_2O$ (Merck, Darmstadt, Germany) were made by dissolving indomethacin in methanol (BDH, Poole, UK) and DSP in distilled water (1 g of solid/60 ml of solvent). The solutions were combined and dried to a powder mixture using a vacuum evaporator. The temperature of the solutions during evaporation was 40°C. In order to break the aggregates, the powders were carefully dispersed by a mortar and pestle and sieved with a 710 $\mu$m screen before use. Due to the needle-shaped crystals and aggregated nature of the indomethacin/DSP powder mixtures (Fig. 1C), the particle size of powders was impossible to determine. According to the scanning electron micrographs, the shape and size of crystals seemed to be similar in each batch. The amount of DSP was varied from 2 to 50% w/w of the powder mixture.

Pure indomethacin, indomethacin recrystallized from methanol and coprecipitated powder mixture of indomethacin and DSP were examined by differential scanning calorimetry (Perkin Elmer DSC-7, Perkin-Elmer, Norwalk, USA). An open-pan system (aluminium pans) in an $N_2$ gas flow of 23 ml/min was used. The samples, 2–3 mg in weight, were scanned from 10 to 200°C at a heating rate of 10°C/min. Three determinations for each sample were performed. The temperature scale was calibrated using gallium and in-

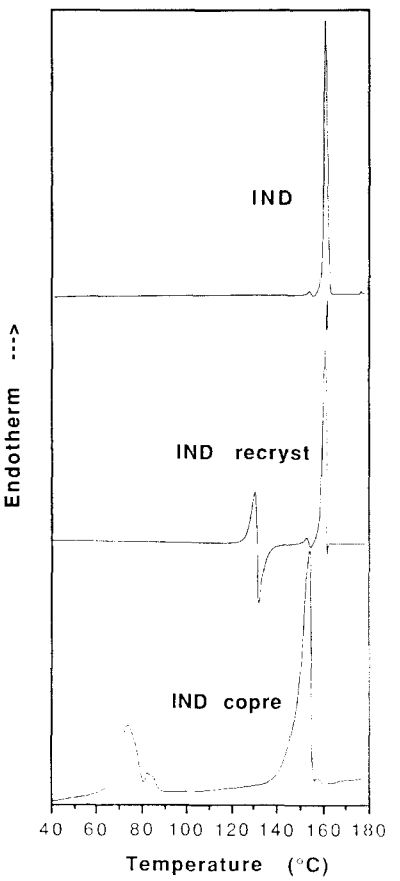


Fig. 2. Differential scanning calorimetry (DSC) thermograms of untreated indomethacin, indomethacin recrystallized from methanol and powder mixture of indomethacin (90% w/w) and dibasic sodium phosphate (10% w/w) coprecipitated from methanol/water.

dium, with melting points of 29.78 and 156.60°C, respectively.

Indomethacin, recrystallized indomethacin or coprecipitated indomethacin/DSP mixtures were microencapsulated by phase separation of ethylcellulose (Ethocel®, 45 mPa s, Fluka, Buchs, Switzerland) from cyclohexane (Merck, Darmstadt, Germany) using polyisobutylene (Mol. Wt

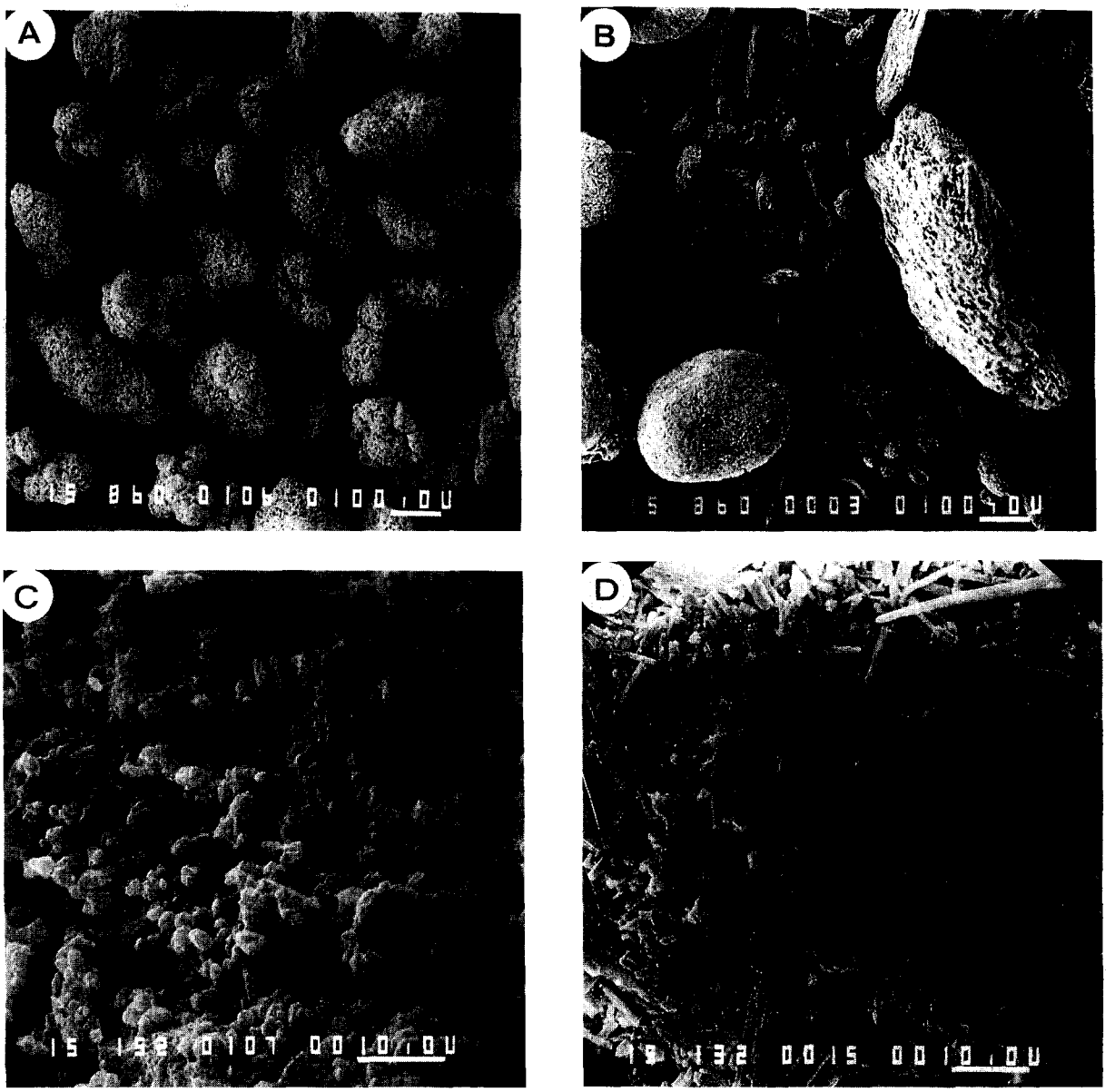


Fig. 3. Scanning electron micrographs of ethylcellulose microcapsules containing indomethacin (bar: 100 μm) (A); and powder mixture of indomethacin (90% w/w) and DSP (10% w/w) (bar: 100 μm) (B). Surface of an indomethacin microcapsule (bar: 10 μm) (C); and indomethacin microcapsule containing 10% w/w of DSP (bar: 10 μm) (D).

Table 1
Mean particle diameters ($\mu$m ± SD) of ethylcellulose microcapsules containing indomethacin and powder mixtures of indomethacin and DSP (sieve analysis performed from 1–5 different batches)

| Amount of DSP (% w/w) | Mean particle diameter ($\mu$m ± SD) | Amount of DSP (% w/w) | Mean particle diameter ($\mu$m ± SD) |
|---|---|---|---|
| 0.0 ($n$ = 3) | 212.8 ± 12.8 | 15.0 ($n$ = 5) | 242.8 ± 33.2 |
| 2.0 ($n$ = 1) | 267.5 | 17.5 ($n$ = 3) | 351.3 ± 35.4 |
| 5.0 ($n$ = 1) | 299.6 | 25.0 ($n$ = 1) | 312.9 |
| 7.5 ($n$ = 1) | 251.6 | 37.5 ($n$ = 1) | 362.8 |
| 10.0 ($n$ = 5) | 248.6 ± 27.4 | 50.0 ($n$ = 1) | 381.0 |
| 12.5 ($n$ = 1) | 272.4 | | |

380 000, Aldrich, Steinheim, Germany) as a coacervation-inducing agent. The preparation method was similar to that described in detail in our previous work (Tirkkonen and Paronen, 1992). One batch of microcapsules was prepared using a ground mixture of sodium chloride (10% w/w) and indomethacin as core material. The mass ratio of core to wall was always 10:1. The size distributions of microcapsules were evaluated by sieve analysis using standard sieves of 88, 149, 297 and 710 $\mu$m. Microcapsule sieve fractions of 88–710 $\mu$m were chosen for further studies.

The drug contents of the powder mixtures and microcapsules were evaluated by shaking a weighed sample in methanol for 10 min to dissolve indomethacin and ethylcellulose. The suspensions were filtered to remove DSP and thereafter the samples were diluted with methanol. Indomethacin was assayed spectrophotometrically (Hitachi 220, Hitachi, Japan) at 318 nm.

### 2.2. Release studies

The dissolution of indomethacin from microcapsules was studied with the rotating basket method (Sotax AT6 Dissolution Tester, Sotax, Switzerland) using baskets of a special wire netting with quadratic holes of 74 $\mu$m. The stirring rate of the baskets was 100 ± 2 rpm. The effect of various amounts of DSP in microcapsules on indomethacin release was examined in 750 ml of pH 7.2 phosphate buffer (5 and 160 mM) at 37 ± 0.5°C under sink conditions. The effect of internal sodium chloride in microcapsules on indomethacin release was also assessed in pH 7.2 phosphate buffer of 5 mM. The ionic strengths of the dissolution media were adjusted with sodium chloride to 0.5. The dissolution media were degassed with helium before tests. In each experiment 100 mg of microcapsules were used. Six parallel tests were carried out. The reproducibility of release data was evaluated from three batches of the same composition containing 10 or 15% w/w of DSP.

The effect of bulk solution pH on the release of indomethacin was studied at pH 4.6, 6.4, 7.2 and 8.0 for microcapsules without and with 15% w/w of DSP (and 25% w/w at pH 4.6) in the capsule core. The concentrations of phosphate buffer were 5 mM and ionic strengths 0.5. The release was also studied at different speeds of rotation of the baskets (50, 100 or 250 rpm) using pH 6.4 phosphate buffer. Indomethacin was analyzed spectrophotometrically at 318 nm.

### 2.3. Surface properties of microcapsules

Dried samples of the powder mixtures and of the microcapsules were coated with gold vapour using a Sputter Coater II-E 5100 (Polaron Equipment, Watford, UK). Micrographs were taken with a Jeol JSM-35 scanning electron microscope (Jeol, Japan) at an accelerating voltage of 15 kV. The topography of the microcapsules was evaluated from micrographs both before and after the dissolution test.

## 3. Results and discussion

### 3.1. Effect of internal buffer on indomethacin release

Indomethacin and the powder mixtures of indomethacin and DSP precipitated, forming needle-shaped crystals (Fig. 1A–C). According to the DSC thermograms the melting point of indomethacin (160°C) did not change after recrystallization from methanol (Fig. 2). Indomethacin recrystallized from methanol underwent an endothermic followed by an exothermic transformation at around 125–135°C. Most probably the recrystallized indomethacin existed in a methanol solvate form. The melting point of indomethacin coprecipitated with DSP decreased to 147°C. The endothermic peak was clearly broader, demonstrating a less orientated and probably more amorphous crystal structure of indomethacin in the drug-buffer coprecipitate.

The ethylcellulose microcapsules of indomethacin seem to be aggregates of smaller ones (Fig. 3A and B). Due to the very thin ethylcellulose film (core to wall ratio 10:1) the surface structure of the microcapsules (Fig. 3C and D) resembles that of the core material (Fig. 1A and C). The mean particle size of indomethacin microcapsules was smaller than that of the capsules containing indomethacin and DSP (Table 1). With greater amounts of buffer (17.5–50% w/w) the increase in microcapsule size was quite notable, probably due to the more aggregated nature of the core material. Also, the size distribution of microcapsules increased with increasing DSP concentration. The broader size distribution of buffer containing microcapsules is clearly evident in Fig. 3A and B. If the microcapsule batch contains predominantly smaller capsules, the release should be influenced more strongly (Jalsenjak et al., 1976). However, the overall release pattern is always intermediate between that of the largest and smallest fractions. Hence, the release of indomethacin is not increased as a result of the size of buffered microcapsules, the opposite probably being the case.

The release of indomethacin from microcapsules without buffering base in the core was very slow (a few percent in 7 h) (Fig. 4). The recrystallization of indomethacin from methanol did not affect the release of the drug (data not shown). Indomethacin being an acidic drug with a $pK_a$ of 4.5 decreases the pH inside the microcapsules, thus reducing its own solubility. The water solubility of indomethacin is pH-dependent amounting to only 2 μg/ml at pH 1.2 (De Filippis et al., 1991), 25 μg/ml at pH 5.1, 190 μg/ml at pH 6.0 and 1600 μg/ml at pH 7.2 (Oth and Moës, 1985).

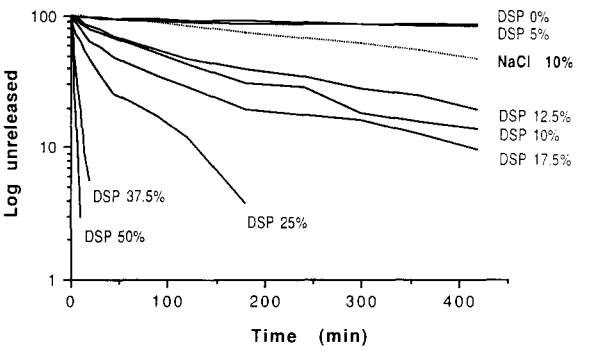


Fig. 4. Effect of internal buffer, dibasic sodium phosphate (DSP), on the release of indomethacin from ethylcellulose microcapsules in 5 mM phosphate buffer solution of pH 7.2. Effect of internal sodium chloride (NaCl 10% w/w) is also presented (dotted line). Means of 4–6 experiments are presented.

With small amounts of DSP (2–5% w/w) in the microcapsule core, the release rate of indomethacin did not increase (Fig. 4). It appears that the decrease in the melting point of indomethacin when coprecipitated with DSP did not affect the dissolution rate of the drug from microcapsules. With increasing DSP concentration (10–25% w/w), the release of indomethacin increased and was very rapid with the highest amounts of DSP (37.5–50% w/w). As a water-soluble material (> 100 mg/ml) DSP dissolves rapidly and when it elevates adequately the pH inside the microcapsule, indomethacin is dissociated sufficiently to increase its water solubility and release from the microcapsules. The drug is released via aqueous pores in the ethylcellulose wall, therefore, increasing ionization increases the extent of release. Correspondingly, the presence of a second acid, citric acid, decreases the disso-

lution rate of indomethacin from compressed discs (Ramtoola and Corrigan, 1989).

With moderate amounts of DSP the release of indomethacin is reduced after the faster initial phase (Fig. 4). Part of DSP may diffuse rapidly from the microcapsules leading to slower drug dissolution in the inner parts of the microcapsule. The greatest amounts of DSP are sufficient to overcome the self-buffering effect of indomethacin throughout the release. Internal buffer accelerated the release rate of indomethacin about 600-fold at maximum (Fig. 5). The reproducibility of the preparation method from one batch to another was assessed with three different batches containing 10 or 15% w/w of DSP. The release rates (mean ± SD) were 3.4 ± 0.59 ($\times 10E{-}3$) $min^{-1}$ and 4.8 ± 0.52 ($\times 10E{-}3$) $min^{-1}$, respectively.

Without sufficient pore formation the microcapsule wall also prevents the release of the drug. The appearance of the film did not change during the dissolution test without or with insignificant amounts of DSP in the core (Fig. 3C and 6A). In contrast, numerous holes and ruptures were formed in the coating with moderate and large amounts of DSP (Fig. 3D and 6B).

The effect of osmotic pressure inside the microcapsules on pore formation in the wall and on the release of indomethacin was examined with capsules containing 10% w/w of sodium chloride. Pore formation by osmotic pressure caused by sodium chloride increased the drug release 3-fold compared to the unbuffered indomethacin microcapsules without sodium chloride (Fig. 4). An equivalent amount of DSP enhanced the drug release 12-fold. Thus, osmotic imbibition of water into the microcapsules and subsequent ruptures in the ethylcellulose walls (Fig. 6C) increase the release rate of indomethacin, however, this provides only a partial explanation for the effects of phosphates. Indomethacin release is controlled by two factors. Firstly, solubility of the drug in the microcapsules determines the concentration gradient across the wall and, secondly, pore formation affects the diffusivity of the dissolved drug in the wall.

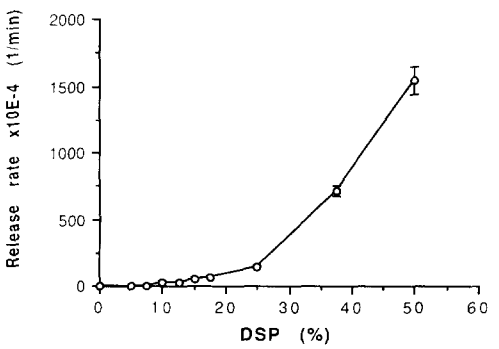


Fig. 5. Rate of indomethacin release from microcapsules as a function of internal buffer (DSP) in 5 mM phosphate buffer solution of pH 7.2 (means ± SE; $n = 4–6$).

### 3.2. Effect of bulk solution pH

The self-buffering capacity of indomethacin is low due to its very low intrinsic solubility (Aunins et al., 1985). Thus, its dissolution rate should be sensitive to the bulk solution pH. Even slight increases in dissolution medium pH markedly accelerate the dissolution of indomethacin from compressed discs (Aunins et al., 1985; Tirkkonen and Paronen, 1992). In this study, the pH of the dissolution medium affected the release of indomethacin from unbuffered microcapsules (Fig. 7). When buffering base was not used in the microcapsule core, practically no indomethacin was released into the acidic dissolution medium of pH 4.6. Increase in bulk solution pH above the $pK_a$ of indomethacin, to pH 6.4, accelerated the rate of release nearly 10-fold. Further increase in solvent pH from 6.4 to 8.0 enhanced the release of indomethacin from microcapsules only 2-fold, while the corresponding increase in the dissolution of indomethacin from compressed discs was 5-fold (Tirkkonen and Paronen, 1992). The dissolution rate in reactive media is a function of the pH at the solid/liquid interface rather than the pH of the bulk medium (Ramtoola and Corrigan, 1987). Even at pH 8.0 indomethacin release was too slow for per oral administration. The decrease in the pH inside the microcapsules due to the self-buffering action of indomethacin appears to be too strong to be overcome by increasing bulk solution pH.

The dissolution medium is able to penetrate into the microcapsules through the pores in the ethylcellulose walls (Vidmar et al., 1982). The amount and size of pores and cracks formed during the dissolution test are much greater in the buffered (Fig. 6B) than in the unbuffered microcapsules (Fig. 6A). Easier permeation of solvent enables the stronger effect of bulk solution pH on drug release in buffered microcapsules (Fig. 7). However, the effect of the external

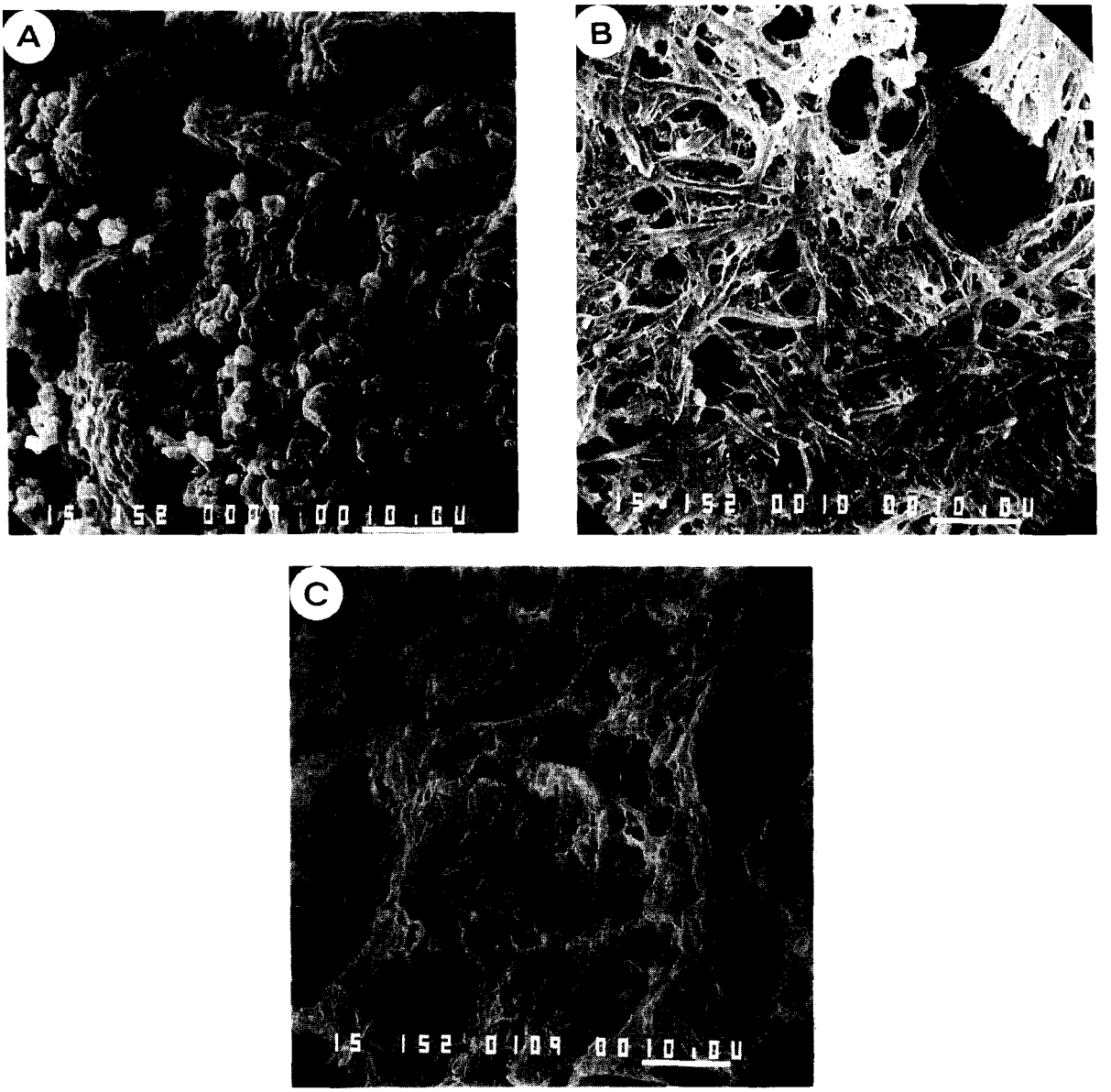


Fig. 6. Scanning electron micrographs of surfaces of microcapsules after the dissolution test, an indomethacin microcapsule (A); an indomethacin microcapsule containing 10% w/w of DSP (B); and an indomethacin microcapsule containing 10% w/w of sodium chloride (C) (bar: 10 $\mu$m).

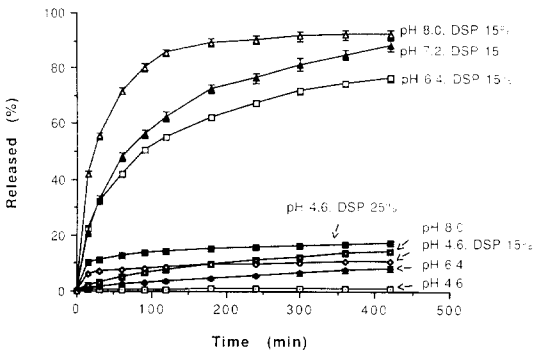


Fig. 7. Effect of phosphate buffer pH on the release of indomethacin (% ± SE) from ethylcellulose microcapsules, without or with 15% w/w (and 25% w/w at pH 4.6) of dibasic sodium phosphate (DSP) as internal buffer, in 5 mM solution ($n = 6$).

pH on drug release was weaker than that of the buffering agent inside the microcapsule. In contrast to unbuffered microcapsules, over the range of intestinal pH values the release rates from DSP buffered microcapsules were acceptable for per oral drug delivery. Furthermore, this technology might offer a way for the colonic drug release of suitable drugs.

### 3.3. Effect of buffer concentration in bulk solution

In addition to the intrinsic solubility and extent of ionisation, the dissolution rate of an acid in buffered medium also depends on the reaction between the acid and the buffer base (Ramtoola and Corrigan, 1989). The extent of the reaction depends on the buffer base concentration and the $pK_a$ of the buffer. The dissolution rate of carboxylic acids from compressed discs, at constant pH, has been shown to increase with increasing buffer concentration (Mooney et al., 1981; Aunins et al., 1985). In the present work, the effect of phosphate concentration (5 and 160 mM) on the release of indomethacin from microcapsules was studied at pH 7.2, where the buffering capacity of phosphate, $HPO_4^{2-}$ ($pKa = 7.21$) is at the maximum (Martin et al., 1983).

The buffer concentration of dissolution medium did not affect the release rate of indomethacin from the microcapsules without internal buffer (Fig. 8). The external phosphate ($HPO_4^{2-}$) could not penetrate inside the unbuffered microcapsules in sufficient amounts and react with the carboxyl groups of indomethacin. When dibasic sodium phosphate was used inside microcapsules to increase the solubility of indomethacin, the release of the drug was further accelerated with increasing buffer concentration of the bulk solution. The higher the internal phosphate concentration the greater was the degree to which drug release was affected by the external phosphate concentration. The concentration gradient of phosphate across the wall of the microcapsules decreases with increasing external phosphate concentration. Thus, the flux of internal phosphate decreases and the pH inside the microcapsules remains higher, increasing the release rate of indomethacin.

### 3.4. Effect of the diffusion layer

The role of the stagnant diffusion layer at the microcapsule surface was investigated by varying the rotation speed of the baskets used in the dissolution test. The change in stirring speed did not affect the release of indomethacin from microcapsules without base in the core (Fig. 9). During the dissolution of a solid drug the thick-

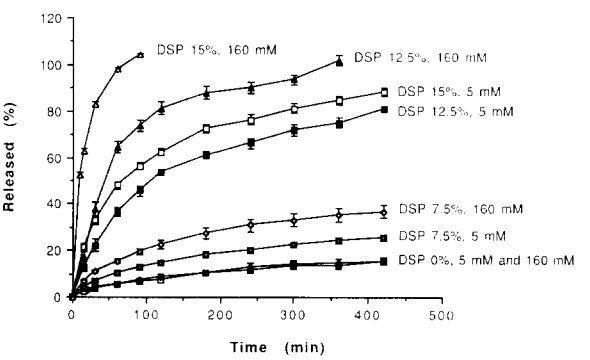


Fig. 8. Effect of phosphate buffer concentration on the release of indomethacin (% ± SE) from ethylcellulose microcapsules, without or with different amounts of dibasic sodium phosphate (DSP) as internal buffer, in pH 7.2 solution ($n = 6$).

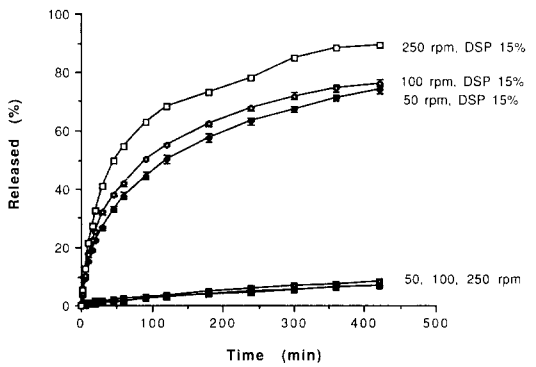


Fig. 9. Effect of mixing of ethylcellulose microcapsules on the release of indomethacin (% ± SE) from capsules, without or with 15% w/w of dibasic sodium phosphate (DSP) as internal buffer, in 5 mM phosphate buffer solution of pH 6.4 ($n = 6$).

ness of the diffusion layer decreases with increasing agitation, thus accelerating the dissolution rate of the drug. This has also been demonstrated with compressed discs of indomethacin (Ramtoola and Corrigan, 1988). Stirring of microcapsules affects only the diffusion layer outside the microcapsule wall, not the diffusion layer of solid indomethacin inside. Indomethacin release from unbuffered microcapsules may be controlled by the dissolution of the drug in the microcapsules, which is not affected by the external stirring rate. Also, in this case the ethylcellulose walls remain intact during the release process, thus providing high resistance compared to the hydrodynamic diffusion layer.

In contrast, indomethacin release from the buffered microcapsules was affected by the stirring rate. In this case, drug release is controlled by the diffusion layer from the solid drug surface to the external medium on the surface of the microcapsules. Higher stirring speed accelerates the diffusion of phosphates and $H^+$ from the microcapsules, which maintains indomethacin dissolution and drug release.

In conclusion, practically relevant indomethacin release rates from microcapsules can be obtained using internally buffered microcapsules. Without buffering the release rates are far too slow.

## Acknowledgements

The authors wish to thank Ms Aila Knuutila for assistance during the preliminary studies, Ms Minna Heikkinen and Ms Kristiina Korhonen for technical help during the final experiments and Mr Veijo Viitasaari for performing the DSC runs. The study was financially supported by the Pharmacal Research Foundation, Finland, to S.T. for the study of pharmaceutical microcapsules. P.P. was supported by the Technology Development Centre, Finland and A.U. was supported by the Academy of Finland.

## References

Aunins, J.G., Southard, M.Z., Myers, R.A., Himmelstein, K.J. and Stella, V.J., Dissolution of carboxylic acids: III. The effect of polyionizable buffers. *J. Pharm. Sci.*, 74 (1985) 1305–1316.

Bechgaard, H. and Baggesen, S., Propoxyphene and norpropoxyphene: influence of type of controlled-release formulation on intra-and intersubject variations. *J. Pharm. Sci.*, 69 (1980) 1327–1330.

De Filippis, P., Boscolo, M., Gibellini, M., Rupena, P., Rubessa, F. and Moneghini, M., The release rate of indomethacin from solid dispersions with Eudragit E. *Drug Dev. Ind. Pharm.*, 17 (1991) 2017–2028.

Doherty, C. and York, P., Microenvironmental pH control of drug dissolution. *Int. J. Pharm.*, 50 (1989) 223–232.

Hadzija, B.W., Obeng, E.K., Ruddy, S.B., Noormohammadi, A. and Beckett, A.H., Bioavailability of a controlled release indomethacin formulation in healthy subjects. *Int. J. Pharm.*, 67 (1991) 185–194.

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.

Kohri, N., Yatabe, H., Iseki K. and Miyazaki, K., A new type of a pH-independent controlled release tablet. *Int. J. Pharm.*, 68 (1991) 255–264.

Martin, A., Swarbrick, J. and Cammarata, A., *Physical Pharmacy*, 3rd Edn, Lea and Febiger, Philadelphia, 1983, p. 192.

McGloughlin, R.M.R. and Corrigan, O.I., Dissolution characteristics of benzoic acid-Tris mixtures. *Int. J. Pharm.*, 82 (1992) 135–143.

Mooney, K.G., Mintun, M.A., Himmelstein, K.J. and Stella, V.J., Dissolution kinetics of carboxylic acids: II. Effect of buffers. *J. Pharm. Sci.*, 70 (1981) 22–32.

Oth, M.P. and Moës, A.J., Enhanced in vitro release of

indomethacin from non-aqueous suspensions using indomethacin-polyvinylpyrrolidone coprecipitate. *Int. J. Pharm.*, 24 (1985) 273–286.

Ramtoola, Z. and Corrigan, O.I., Dissolution characteristics of benzoic acid and salicylic acid mixtures in reactive media. *Drug Dev. Ind. Pharm.*, 13 (1987) 1703–1720.

Ramtoola, Z. and Corrigan, O.I., Effect of agitation intensity on the dissolution rate of indomethacin and indomethacin-citric acid compressed discs. *Drug Dev. Ind. Pharm.*, 14 (1988) 2241–2253.

Ramtoola, Z. and Corrigan, O.I., Influence of the buffering capacity of the medium on the dissolution of drug-excipient mixtures. *Drug Dev. Ind. Pharm.*, 15 (1989) 2359–2374.

Serajuddin, A.T.M. and Jarowski, C.I., Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical acids and their sodium salts: II. Salicylic acid, theophylline, and benzoic acid. *J. Pharm. Sci.*, 74 (1985) 148–154.

Serajuddin, A.T.M. and Rosoff, M., pH-solubility profile of papaverine hydrochloride and its relationship to the dissolution rate of sustained-release pellets. *J. Pharm. Sci.*, 73 (1984) 1203–1208.

Shah, J.C. and Maniar, M., pH-dependent solubility and dissolution of bupivacaine and its relevance to the formulation of a controlled release system. *J. Controlled Release*, 23 (1993) 261–270.

Thoma, K. and Zimmer, T., Retardation of weakly basic drugs with diffusion tablets. *Int. J. Pharm.*, 58 (1990) 197–202.

Tirkkonen, S. and Paronen, P., Enhancement of drug release from ethylcellulose microcapsules using solid sodium chloride in the wall. *Int. J. Pharm.*, 88 (1992) 39–51.

Vidmar, V., Jalsenjak, I. and Kondo, T., Volume of water-filled pores in the ethyl cellulose membrane and the permeability of microcapsules. *J. Pharm. Pharmacol.*, 34 (1982) 411–414.

Yamada, I., Goda. T., Kawata, M., Shiotuki, T. and Ogawa, K., Gastric acidity-dependent bioavailability of commercial sustained release preparations of indomethacin, evaluated by gastric acidity-controlled beagle dogs. *Chem. Pharm. Bull.*, 38 (1990) 3112–3115.