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Use of ion-exchange resins to prepare 100 μm-sized microcapsules with prolonged drug-release by the Wurster process

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Abstract

Ion-exchange resin (IER)–drug complexes were used as core materials to explore their capability to prepare a 100 μm-sized, highly drug-incorporated microcapsule with a prolonged drug release by the Wurster process. Diclofenac sodium was loaded into Dowex 1-X2 fractionated into 200–400 mesh and subsequently microencapsulated with two types of aqueous colloidal polymer dispersion, Aquacoat® or Eudragit® RS30D. The mass median diameter and drug content of the microcapsules thus obtained were 98 μm and 46% with Aquacoat®, and 95 μm and 50% with Eudragit® RS30D, respectively. Each microcapsule was obtained at a product yield of 94%. The rate of drug release from the microcapsules was highly dependent on the encapsulating materials. For the microcapsules coated with Aquacoat®, diclofenac sodium was found to be rapidly released over 4 h, even at a 25 wt% coating level because of cracks on the microcapsule surfaces resulting from the swelling stress of the drug-loaded IER cores. In contrast, significantly prolonged drug-release was achieved in the microcapsules prepared with Eudragit® RS30D: even such a very low coating level as 3 wt% provided an exceptionally prolonged drug-release over 24 h. The results indicated that the use of IER along with a flexible coating material would be a feasible way to prepare a prolonged release type of microcapsules with a diameter of 100 μm and a drug content of more than 50% by the Wurster process.

Keywords: Coating; Diclofenac sodium; Ion-exchange resin; Microcapsule; Prolonged release; Wurster process

1. Introduction

An air-suspension coating process, often referred to as the Wurster process, has been characterized as a mechanical microencapsulation

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method (Thies, 1996). In this process, particles circulating in the coating chamber are encapsulated by a wet-spraying. Because of such a simple principle, it provides a unique method for preparing microcapsules with multi-layered and composite structures that have a potential as functional particulate materials in versatile industrial fields including pharmaceuticals.

The major drawback in this process is difficulty in processing fine particles. For usual pharmaceutical particles, the lower critical size of particles that can be individually coated without agglomeration appears around 20 μm in diameter (Fukumori et al., 1991). However, the coating process is often hampered by severe agglomeration, even for particles in the 20–100 μm size range, depending on the physicochemical properties of the particles, e.g. hygroscopicity, electrostatic charging and/or solubility to spray solvent. In this context, some of the present authors have found that an aqueous colloidal polymer dispersion can exhibit an extremely low agglomeration tendency even in such fine particles of less than 100 μm (Ichikawa et al., 1993). The observed low agglomeration tendency has been ascribed to its incomplete film formation and consequent low binding strength. This can be achieved under the specific operating conditions where the drying/layering of the colloidal polymers sprayed onto core particles is separated from the film-formation process. The resulting porous films can be cured by post-thermal treatment. The film thus established has been demonstrated to work as a permeation barrier against drug release.

Another problem encountered in spray coating of such fine particles as 20–100 μm comes from the difficulty in decreasing the coat thickness. Usually, commercially available coating materials need up to 10 μm thickness to work as a sufficient diffusion barrier for prolonged release dosage forms. For prolonged release coating of the fine particles, therefore, large quantities of the coating materials are required because of the large specific surface area. Consequently, the process becomes time-consuming. Diffusion of drugs through a microcapsule coat is primarily dependent on the thickness and permeability of coating materials employed and the drug concentration gradient across the coat. Simple coat thickening is one way to reduce the diffusion rate, but obviously, this gives rise to a size enlargement and a low drug content in the products. It is also not so easy to decrease the permeability of the coat formed by the commercial colloidal polymer dispersions with the aid of certain additives because of the delicate colloid stability. Thus, these often become a challenging problem, especially in the practical design and preparation of the fine microcapsules.

As an alternative approach, the present study focused on the design of core materials including drugs. The drug diffusion rate should be reduced even if the coat is not thickened, provided that the drug can be loaded into core materials having an ability to interact with the drug. Ion-exchange resins seemed to be a feasible candidates for this purpose because they have been well established in making complexes with ionic drugs easily (Chaudhry and Saunders, 1956; Gyselinck et al., 1981; Amsel et al., 1984; Motycka et al., 1985; Farag and Nairn, 1988; Irwin et al., 1990; Torres et al., 1995; Mohamed, 1996).

The aim of this study was to explore the capability of the ion-exchange resins as a means of circumventing problems of particle size enlargement and low drug content resulting from the increased coat thickness in the production of fine microcapsules with prolonged drug release by the Wurster process. For this purpose, prolonged release coating of IER–drug complexes with commercial aqueous colloidal polymer dispersions was carried out. The colloidal polymer dispersions employed were cellulosic and acrylic colloidal polymers widely used in the coating of pharmaceutical solid dosage forms. The coating performance of these colloidal polymers in wet-spray coating of drug–IER complexes was compared, and the drug-release properties from the drug–IER thus coated were evaluated.

2. Materials and methods

2.1. Materials

Anion exchange resins (Dowex®, Dow Chemical Co., Midland, MI) in the chloride form (1-X2,

200-400 mesh) were purchased from Nacalai Tesque, Inc., Kyoto, Japan. Ethylcellulose pseudolatex (Aquacoat®, FMC Corporation) was obtained as gifts from Asahi Chemical Industry (Japan), while Eudragit® RS30D was kindly supplied by Röhm GmbH (Germany). Diclofenac sodium was purchased from Sigma® (St. Louis, MO). Triacetin (Nacalai Tesque, Inc., Kyoto, Japan) was used as a plasticizer. Light anhydrous silica (Aerosil #200, Nihon Aerosil, Tokyo, Japan) was used as an anti-adherent. Purification of water (purified water) was carried out by deionization and, thereafter, distillation. All materials excluding the ion-exchange resins were used as received.

2.2. Purification of the ion-exchange resins

The ion-exchange resin (IER) was purified by a column method. Approximately 350 g of the IER was allowed to swell in 500 ml of purified water for 12 h. The IER thus swollen was decanted to remove some floating resin particles, washed again with purified water until the supernatant became transparent, and slurried in 500 ml of purified water. The slurry was poured into a glass column (55 mm i.d. × 860 mm) equipped with a cotton plug at the bottom. Three and a half liters of methanol were then passed through the column of the resin, followed by 17.5 l of 2 N NaOH for replacing the Cl^- with the OH^- form. Thereafter, purified water was passed through the column to wash out NaOH until the pH value of eluent became neutral. The purified IER was recovered by vacuum filtration and dried in an oven at 50°C for 72 h. The pre-dried IER was passed through a 250-μm stainless sieve and further dried to constant weight in a vacuum at room temperature.

2.3. Drug loading

The diclofenac–IER complex was prepared by a batch process. The purified IER (35 g) was suspended in a 4 w/v% of diclofenac sodium aqueous solution (1050 g) under magnetic stirring at 60°C for 24 h. After cooling, the drug-loaded IER was recovered by vacuum filtration and resuspended in 1000 ml of purified water. The suspension was stirred for 30 min at room temperature and then decanted. This washing process was repeated until the drug concentration in the supernatant became negligible (below 0.32 μg/ml). The drug-loaded IER thus obtained was dried in the aforementioned manner and placed in a desiccator prior to use.

2.4. Coating apparatus

A spouted bed coater (Grow Max (140), Fuji Paudal Co., Ltd., Osaka, Japan) assisted by a draft tube, known as the Wurster configuration, was used (Ichikawa and Fukumori, 1999). A pneumatic spray nozzle with a liquid outlet caliber of 1.0 mm, a bag filter with a 5 μm opening and a peristaltic pump (MP-03, Tokyo Rikakikai, Tokyo, Japan) were used through all experiments.

2.5. Measurement of particle-size distribution

The sieve analysis was carried out using a ro-tap shaker (Iida Seisakusho, Tokyo, Japan). The drug-loaded IER and the coated IER were premixed with 1 and 3 wt% of Aerosil #200, respectively. Ten grams of these pretreated samples were charged and sieved for 10 min by the ro-tap shaker.

2.6. Drug-release study

The release studies were performed on an NTR-VS6P dissolution apparatus (Toyama Sangyo Co., Ltd., Japan) according to the paddle method as described in the Japanese pharmacopoeia (JP XIII). JP XIII disintegration second fluid (pH 6.8) and purified water were used as dissolution fluids. Nine-hundred milliliters of the fluid were kept at 37°C and rotated at 200 rpm. The microcapsules were pre-dried in a vacuum at room temperature for 12 h and further mixed with 1 wt% of Aerosil #200. Then, they were heated at 65°C, corresponding to the softening temperature of the coating materials used here (Table 1), for 3 h in an air stream oven for curing the coat. The drug-loaded IER and the cured microcapsules, equivalent to 5 mg of diclofenac sodium, were tested. The concentration of drug released in the dissolution fluid

at predetermined time intervals was determined by measuring its absorbance at 276 nm on a spectrophotometer (UV-190, Shimadzu, Kyoto, Japan).

2.7. Drug-release kinetics

Quantitative studies of the ion-exchange process have been reported in detail (Boyd et al., 1947; Reichenberg, 1953). The rate equations suitable for analysis of the release mechanism of drug from ion exchange resinate were already developed based on those studies. In the ion-exchange process, the rate-controlling step was shown to be diffusion either in the resin particle itself, so-called "particle diffusion", or in an adherent stagnant film ("film diffusion") (Boyd et al., 1947). Since particle diffusion and film diffusion are sequential steps, the slower of the two is rate-controlling. Under conditions where particle diffusion is the rate-controlling step, the fraction of drug released, F, from spherical resin particles with uniform diameter in a solution of infinite volume as a function of time is given by the following equation:

$$F = \frac{Q_t}{Q_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{e^{-n^2 Bt}}{n^2} \quad (1)$$

where Q_t and Q_∞ are the amounts of drug released after time t and after infinite time, respectively, and n is the summation variable. B is a rate constant defined as $4\pi^2 D/d^2$, where D represents the effective diffusion coefficient of the exchanging ions (drugs) in the resin particle, and d is the mean diameter of resin particles. Depending upon the magnitude of F, Reichenberg (1953) obtained the following two equations:

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{1/2} \quad (2)$$

$$Bt = -\log_e \frac{\pi^2}{6}(1 - F) \quad (3)$$

Eq. (2) is the result of Fourier transformation and integration of Eq. (1) and used for F values lower than 0.85. Eq. (3) is for F values larger than 0.85. If a plot of the Bt values corresponding to the F values against time gives a straight line with a slope equal to B, it can be assumed that drug diffusion within the resin particles is the rate-controlling step in the diffusion process. The slope of the line yields the rate constant, B, and the effective diffusion coefficient, D, of drug can be calculated from this B value. While this theory cannot be introduced strictly to the coated IER unless the IER and the coating materials can be treated as a homogeneous ion-exchange system, it is tempting to speculate the effectiveness of the coating materials on diffusion of the drug ion within the IER in this theoretical manner. The present study followed such an assumptive treatment of the release kinetics in the microencapsulated ion-exchange resins reported by Motycka and Nairn (1978, 1979) to estimate the diffusion characteristics of the IER microencapsulated with Aquacoat® or Eudragit® RS30D.

Table 1
Formulations and operating conditions of Grow Max (140) spouted bed coater in the preparation of microcapsules

	MC-A	MC-E
Core: drug-loaded IER (g)	25	25
Release-prolonging coat		
Aquacoat® (g)	6.25	
Eudragit® RS30D (g)		2.0
Triacetin (g)	0.81	0.1
Water	ad.	ad.
Total (g)	300	100
Softening temperature of cast film (°C)	65	65
Operating conditions		
Inlet air temperature (°C)	60	60
Outlet air temperature (°C)	27	29
Inlet air flow rate (m^3/min)	0.21–0.22	0.22
Liquid flow rate (ml/min)	3.5–3.8	4.4
Spray air flow rate (l/min)	60	60
Spray air pressure (kg/cm^2)	2.6	2.7

2.8. Drug content

The drug-loaded IER and the MCs were pulverized in a mortar and pestle, respectively. Ten milligrams of each powdered sample were weighed accurately, dispersed in the JP second fluid containing 2 M KCl (300 ml), and stirred for

6 h. The dispersion was filtered through a 0.45 μm membrane filter. The concentration of diclofenac sodium in the filtrate was determined by the same method described above. The obtained drug content was used to estimate Q_∞.

2.9. Particle morphology

The morphology of the microcapsules after exposure to the JP second fluid at 37°C was assessed by an Olympus polarizing microscope (BX50, Olympus, Japan) equipped with a VH-7000 digital HD microscope (Keyence Co., Ltd., Tokyo, Japan). The photographic images were taken under a polarizing viewer, and the corresponding relief images were obtained using an image-processing function of the VH-7000 digital microscope.

2.10. Softening temperature of cast film

A thermomechanical analysis (TMA) was performed by a Shimadzu TMA-30 thermal analysis system, according to the method previously reported (Fukumori et al., 1988).

3. Results

3.1. Microencapsulation of drug-loaded IER

Formulations of microcapsules and operating conditions of the Grow Max (140) spouted bed coater are listed in Table 1. Triacetin was added to each aqueous colloidal polymer so as to adjust the softening temperature to 65°C. In order to prevent any agglomeration in the coating process, the inlet air temperature was set at 60°C, which is slightly lower than the softening temperature of each coating material plasticized by triacetin. The polymer weight percentages finally applied (based on the weight of drug-loaded IER) were 25 wt% for Aquacoat® and 8 wt% for Eudragit® RS30D, respectively. The polymer concentration in the spray dispersion was set to be low (2.0–2.1 wt% on a dry basis). This unusually low concentration was to reduce the particle adhesion to the chamber due to the electrostatic charging that often gave rise to less homogeneous coating. Indeed, at the beginning of the coating operation, the drug-loaded IER tended to adhere to the chamber wall due to the electrostatic charge, but it began to circulate steadily as the coating proceeded.

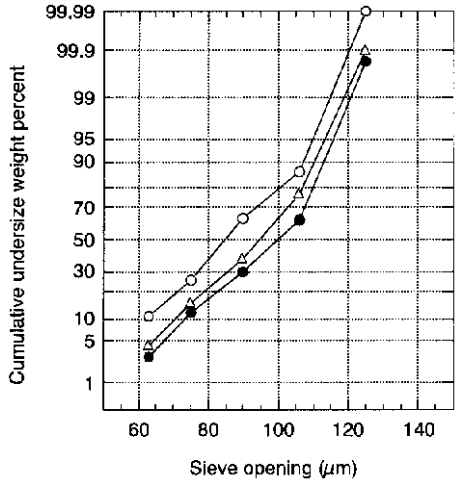

Fig. 1. Cumulative undersize distributions of drug-loaded IER particles and microcapsules. ○: drug-loaded IER particle; ●: MC-A (25% coated); △: MC-E (8% coated).

Fig. 1 shows the cumulative undersize distributions of the drug-loaded IER before and after microencapsulation. The particle-size distribution curve of each microcapsule shifted approximately parallel with that of the drug-loaded IER, indicating that each coating material did not induce any agglomeration of the drug-loaded IER during the coating process. No agglomerates were observed, even in the fraction larger than 125 μm, and thus the single-core microcapsules were obtained successfully.

The characteristics of the microencapsulated IER are listed in Table 2. Each MC was obtained at yield of 94%. The mass median diameters of the MCs ranged from 95 to 98 μm. The drug content of the MCs was more than 50% except for that of microcapsules with Aquacoat® at a 25 wt% coating level. This high drug content was approximately twice as high as that of the diclofenac sodium microcapsules prepared in our previous study (Ichikawa et al., 1997).

Table 2
Characteristics of microcapsules

	MC-A	MC-E
Product		
Yield (%)	94	94
Mass median diameter (μm)	98	95
Drug content		
Just before coating (%)	56.0	56.0
2% coating level (%)	55.6	55.6
3% coating level (%)	–	54.3
4% coating level (%)	55.1	–
6% coating level (%)	54.3	51.5
8% coating level (%)	53.6	50.4
12.5% coating level (%)	52.8	–
25% coating level (%)	45.5	–

3.2. Drug release from microencapsulated IER

Figs. 2 and 3 show the respective release of diclofenac sodium in the JP second fluid from the microcapsules coated with Aquacoat® and Eudragit® RS30D (hereafter referred to as MC-A and MC-E, respectively). For the MC-A, drug release was found to be very fast: approximately 90% of drug was rapidly released over 4 h, even in the microcapsules with a 25 wt% coating level. In contrast, the MC-E exhibited significantly prolonged drug release. The release rate depended highly on the coating level. Extremely suppressed release was achieved in the microcapsules with a 3 wt% coating level or more, though the 2 wt% coating level in the MC-E was insufficient for prolonged release. The microscopic appearances of the MC-A and the MC-E after exposure to the JP second fluid are shown in Fig. 4a and b, respectively. The Aquacoat® membrane in the microcapsules induced large cracks on their surfaces, while no cracks appeared on the Eudragit® RS30D coat. With the MC-E, small cracks on the surfaces were observed only at a 2 wt% coating level (data not shown). It was evidenced that these cracks were ascribed to the rapid release observed in the microcapsules.

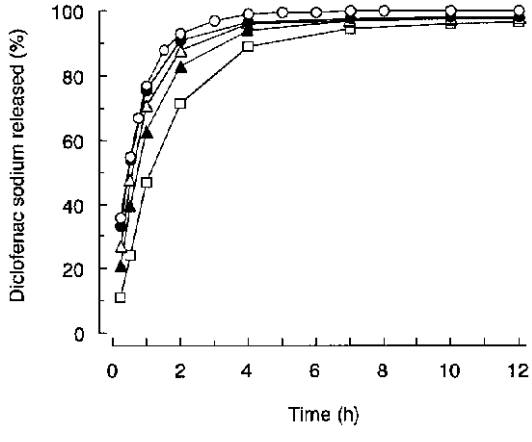

Fig. 2. Release of diclofenac sodium from drug-loaded IER and MC-A in JP disintegration second fluid (pH 6.8). Aquacoat® applied: ○: 0 wt%; ●: 4 wt%; △: 8 wt%; ▲: 12.5 wt%; □: 25 wt%.

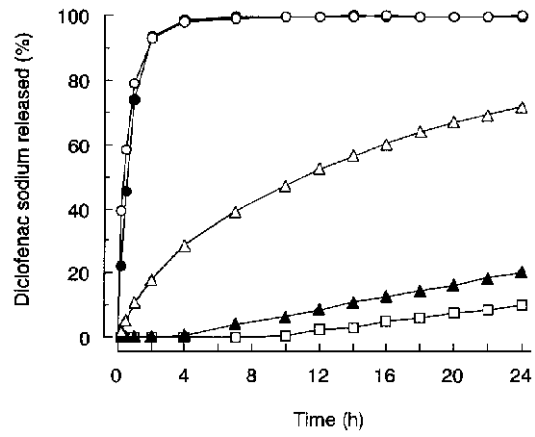

Fig. 3. Release of diclofenac sodium from drug-loaded IER and MC-E in JP disintegration second fluid (pH 6.8). Eudragit® RS30D applied: ○: 0 wt%; ●: 2 wt%; △: 3 wt%; ▲: 6 wt%; □: 8 wt%.

According to Eqs. (2) and (3), the *Bt* values were calculated from the *F* values given by the release data and plotted against time. The results are shown in Figs. 5 and 6 for the MC-A and MC-E, respectively. The *Bt* versus *t* plot shown in Fig. 5 gave straight lines with a correlation coefficient, *r*, always higher than 0.99, suggesting that the diclofenac release from the drug-loaded IER or even the microencapsulated IER (MC-A) is apparently controlled by "particle diffusion". A similar tendency was observed in the case of the drug-loaded IER coated with Eudragit RS30D, except that the plots provided straight lines with extremely low slopes at coating levels of more than 3 wt% (Fig. 6).

4. Discussion

The single-core microcapsules with a high drug content of more than 50% were obtained successfully by coating the drug-loaded IER with Aquacoat® or Eudragit® RS30D using the Wurster process. The resulting microcapsules showed a high drug content of more than 50% and a very low agglomeration tendency. This 50% of the drug content in the present microcapsules was twice as high as that of the previously developed prolonged-release microcapsules composed of a 32–44 μm calcium carbonate core with a layer of diclofenac sodium, an undercoat of Eudragit® L30D and an overcoat of Eudragit® RS30D (Ichikawa et al., 1997). The drug content of the present drug-loaded IER was comparable to the previous drug-layered particles. The observed high drug content would be, therefore, due to the fact that the amount of coating materials required for prolonging drug release was only 3% in the present microcapsules with Eudragit® RS30D.

Torres et al. (1998) have carried out microencapsulation of terbutaline–IER complexes with cellulose acetate butyrate by a solvent evaporation method. According to their report, the drug content of the drug–IER complexes was found to be 55.6%, which was comparable to that of the present case. After microencapsulation of the

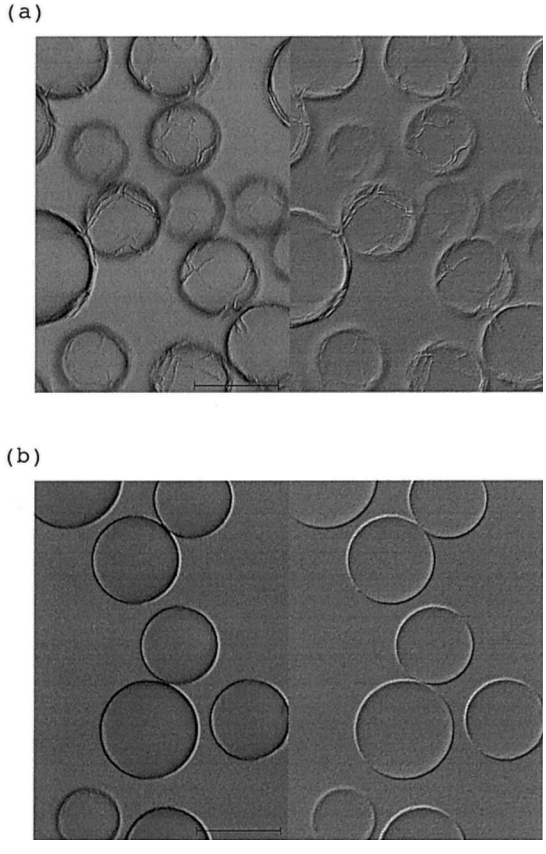

Fig. 4. Polarizing micrographs (left) and the corresponding relief images (right) of MC-A (a) and MC-E (b) after exposure to the JP disintegration second fluid. Scale bars: 100 μm. Coating level: 25 wt% for MC-A; 3 wt% for MC-E.

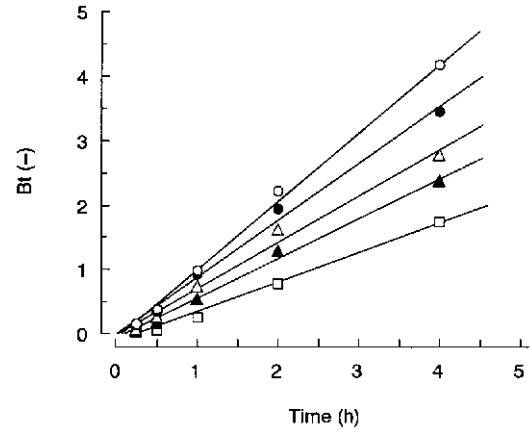

Fig. 5. Plots of *Bt* versus *t* for release data of MC-A presented in Fig. 2. Symbols are the same as those in Fig. 2.

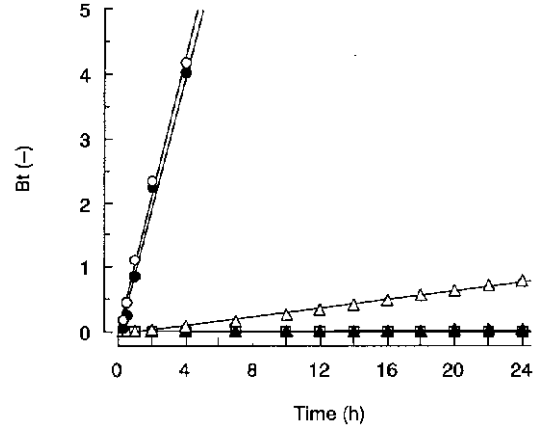

Fig. 6. Plots of *Bt* versus *t* for release data of MC-E presented in Fig. 3. Symbols are the same as those in Fig. 3.

terbutaline–IER complexes at a coat:core ratio of 2:1, the drug content decreased to 17–19%, in spite of such a high encapsulation efficiency as 92–103%. Likewise, the liquid phase processes such as solvent evaporation and an emulsion method traditionally employed as a microencapsulation technique often give a porous, non-homogeneous coat, demanding a large amount of coating material for prolonging the drug release. Consequently, this makes it difficult to achieve high drug loading without excessive size enlargement of microcapsules. In contrast, it is well known that collision of the circulating particles to the inner wall of draft tube in the Wurster process gives rise to a membrane-smoothing effect, and thus a dense coat can be achieved. This clearly saves the amount of coating material needed for a prolonged drug release. However, it is often experienced that agglomerates have a non-uniform film due to their irregular shape and thereby show a fast drug release, compared with the case of single-core microcapsules. In the present study, therefore, no generation of large agglomerates might additionally contribute to the obtained prolonged-release in the small feed amount of coating material.

Release rates of diclofenac sodium in the MC-E were remarkably different from those in the MC-A. For discussion purposes, the $Bt-t$ relationships for both MC-A and MC-E were introduced to assist in the interpretation of the effect of Aquacoat® and Eudragit® RS30D films on the release rate of diclofenac sodium. Motycka and Nairn (1979) reported the drug-release behavior of resinates coated with several types of materials including ethyl cellulose. They found that even the coated resinates showing a release rate slower than that of the uncoated resinates largely yielded a $Bt-t$ relationship close to linearity. They suggested that the encapsulating material, while decreasing the rate of release considerably, might still permit the rate to follow the particle diffusion process of ion exchange. Similarly, the release rate of diclofenac sodium was found to give the linear $Bt-t$ plots for both MC-A and MC-E (Figs. 5 and 6), though the slopes of the plots were strongly dependent on the types and the amounts of the encapsulating materials. Thus, the microencapsulation of the drug-loaded IER with either Aquacoat® or Eudragit® RS30D seemed to involve reducing the rate of drug diffusion rather than changing the mechanism of drug release.

The ability to reduce the rate of drug diffusion in the IER seemed to depend primarily on the mechanical properties of the coating material employed. As shown in Fig. 4, the Aquacoat® film resulted in large cracks on the microcapsules in the dissolution fluid. This would lead to rapid release of the drug from any resinate surfaces exposed to the dissolution fluid and thus less effectiveness of the film on the particle diffusion (Fig. 5). On the contrary, the Eudragit® RS30D film was found to retain the intact appearance during exposure to the dissolution fluid. No cracks were observed when more than 3% of the polymer on a dry basis was supplied to the drug-loaded IER. Since such a film with no crack would reduce exposure of reginate surfaces to the dissolution fluid, the exchange of the inner with the outer dissolution fluid would be largely suppressed. In addition, one possible explanation for the extremely reduced release rate with the MC-E is that in this situation, diclofenac sodium would exist in a more acidic environment within the IER due to its acidic nature and thereby give rise to the reduced water solubility of the drug itself in the microencapsulated IER (Ichikawa et al., 1997); consequently, the rate of drug diffusion in the IER would be markedly reduced (Fig. 6), unless crack formation occurred. Indeed, the MC-E with a 2% coating level where small cracks were observed on the microcapsule surfaces exhibited no significant effect on particle diffusion (Fig. 6).

According to Sun et al. (1997), the Aquacoat® film proved to be cracked even in the dry state when the swellable porous hydrogel beads were coated with Aquacoat® in a small self-designed fluidized bed spray coater with the Wurster column. In the present work, fortunately, no formation of cracks was found microscopically on the Aquacoat® film of the cured microcapsules in the dry state. Basically, the large cracks appearing in the Aquacoat® film shown in Fig. 4 would be ascribed to its weak strength and low ability of elongation in hydrated state. Bodmeier and Paeratakul (1994) reported that the elongation of

Aquacoat® cast film was shown to be 0.13% in the wet state. Obviously, such a poor ability in elongation did not allow the film to resist the strong mechanical stress resulting from the swelling of IER. Different from the cast film prepared from the aqueous colloidal dispersion, ethyl cellulose film cast from methanol can increase its elongation somewhat to be 0.5% in wet state (Bodmeier and Paeratakul, 1994). However, Raghunathan et al. (1981) noted that even organic solvent-based spray coating of ethyl cellulose for drug–resin complexes did not provide an efficient diffusion barrier due to the rupture of the ethyl cellulose coating in the dissolution medium. Eventually, in the case of ethyl cellulose films, an additional technique such as the pretreatment of the IER with polyethylene glycol will be required for preventing their rupture from the rapid swelling of the IER (Raghunathan et al., 1981). On the contrary, Eudragit® RS30D could result in very flexible films with an elongation of approximately 300 times larger than that of the Aquacoat® films in the wet state (Bodmeier and Paeratakul, 1994). The present findings indicates that simple coating of the IER with an elastic polymer in the air suspension coating process can prevent the rupture of films without any additives, even if the IER swells in the dissolution media. Thus, the use of acrylic polymer provides more advantage over the cellulosic polymer in terms of no generation of cracks of the coat during the release process. Most recently, a similar result was reported in the terbutaline-loaded IER microencapsulated with Eudragit RS/RL polymers using an oil-in-water solvent evaporation procedure (Cuña et al., 2000).

It should be noted that diclofenac release from the microcapsules could be prolonged even with such a small amount of coating material as 3 wt%. Obviously, this prevents excessive size enlargement due to the coat thickening, while it is favorable to obtain highly drug-loaded microcapsules. As a result, microencapsulated IER with a small size of 95 μm and a high drug content of 54% could be achieved. Incidentally, it was experimentally confirmed that no drug release from the drug-loaded IER and the microencapsulated IER occurred in purified water (data not shown). The best application of the microcapsules with such properties can be found in ready-made oral liquid suspensions. From a practical point of view, however, a simple coating of Eudragit® RS30D was not sufficiently permeable to provide the practically allowable prolonged drug release. Design and preparation of the microencapsulated IER with the enhanced drug release rate will be described in a subsequent paper.

5. Conclusions

The present study demonstrated that the use of drug–IER complexes as core particles in aqueous polymer coating by the Wurster process could result in prolonged-release microcapsules with a membrane of a few micrometers in thickness. The mechanical properties of polymers used in coating were found to be a primarily important factor on this processing. While Aquacoat® with a poor ability in elongation was less effective for this purpose, Eudragit® RS30D exhibited excellent mechanical properties that could resist the expansion force resulting from the swelling of IER. With the drug-loaded IER with a Eudragit® RS30D coating, the coating material necessary for prolonged release was only 3 wt% based on the weight of the drug-loaded IER. Consequently, this made it possible to achieve prolonged release microcapsules with a small diameter of 95 μm and a relatively high drug content of 54%.

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