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Design of prolonged-release microcapsules containing diclofenac sodium for oral suspensions and their preparation by the Wurster process

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Abstract

Prolonged-release microcapsules of diclofenac sodium (DS), an acidic drug, applicable as an oral suspension for twice-a-day administration were designed. The microcapsules with a mass median diameter of around 100 μm and a high drug content were intended to exhibit a preferably prolonged release of highly water-soluble DS when prepared by the Wurster process–a spray coating method using a spouted bed assisted with a draft tube. The microcapsule was composed of a calcium carbonate core of 32–44 μm, a drug-layer of DS, hydroxypropyl cellulose and polyethyleneglycol 6000, an undercoat of Eudragit L30D and a release-sustaining coat of Eudragit RS30D. Eudragit L30D films were undercoated to decrease the solubility of DS within the environment of the microcapsules and thereby to prolong the drug release. This made it possible to decrease the amount of Eudragit RS30D membrane required to prolong the drug release, leading to decrease in the particle size of products and achievement of high drug content. As a result, prolonged release microcapsules with a mass median diameter of 92 μm and a drug content of 29% could be obtained. © 1997 Elsevier Science B.V.

Keywords: Microcapsule; Oral suspension; Diclofenac sodium; Controlled release; Coating; Wurster process

1. Introduction

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug commonly employed in the long-term treatment of rheumatic disorders, such as osteoarthritis, rheumatoid arthritic and ankylosing spondylitis. This drug is completely absorbed following oral administration, but its elimination half-life is relatively short, i.e. 1–2 h (Skoutakis et al., 1988). It is also known that repeated oral administration of DS in the long-

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term therapy causes gastrointestinal disturbances (Brogden et al., 1980). Due to these biopharmaceutical and pharmacological properties of the drug, a controlled-release formulation has been desired.

Many formulation studies for controlling DS release have been reported so far. Vyas and coworkers have prepared various dosage forms containing DS such as water-soluble matrix tablets (Vyas et al., 1989), magnetically responsive erythrocytes (Jain and Vyas, 1994), multiple w/o/w emulsion systems (Nakhare and Vyas, 1994) and poloxmer-coated three-ply-walled microcapsules (Bhatnagar et al., 1995). Hirotani et al. (1987) used a phospholipid to produce controlled-release granules. While Acartürk (1989) employed chitosan to prepare the prolonged-release matrix tablet by direct compression, Açikgöz et al. (1995) prepared the sustained-release microspheres by using the same material. Spray-dried microcapsules with an enteric coat for directly tabletting were produced by Lin and Kao (1991). Vilivalam and Adeyeye (1994) developed controlled-release diclofenac microspheres and tabletted microspheres with glyceryl monostearate and stearic acid by using the congealable disperse-phase encapsulation method. Preparation of controlled-release microspheres composed of an acrylic polymer or ethyl cellulose by spherical crystallization technique was reported by Gupta et al. (1994). Torres et al. (1995) designed a system based on the microencapsulation of diclofenac-resin complexes with hydroxypropyl methylcellulose phthalate.

There are many cases where an oral suspension is a favorable dosage form because of the ease in swallowing liquids and in adjusting the dose. These are particularly advantageous for pediatric or elderly patients. A controlled-release suspension of DS would be one of the desirable dosage forms, since the drug is often used in the elderly patients for treatment of a chronic disease such as rheumatic disorders.

Some of the present authors have been developing the microencapsulation technologies for fine particles in the range of 10–100 μm, by applying a spouted bed coating process with a draft tube, the so-called Wurster process (Fukumori et al., 1991, 1993a,b; Ichikawa et al., 1993, 1994, 1996). In this study, preparation of prolonged-release microcapsules containing DS applicable for an oral suspension was attempted on the basis of our previous studies. In order to apply the microcapsules to a prolonged-release suspension, it was required that the particle size had to be small enough to be easily suspended in an aqueous vehicle. In addition, the content of DS in the microcapsules had to be as high as possible. However, it was anticipated that loading a large amount of the drug into the fine microcapsules would make prolonged release difficult because DS is highly water-soluble; its solubility in water is 39.09 mg/ml (Sheu et al., 1992). Obviously, simple coat-thickening for suppressing release leads to enlargement of the product particle size. Therefore, the attention in this study mainly addresses how to construct the thin coat which could sufficiently prolong release of such a highly water-soluble drug with keeping a small particle size and a high drug content.

2. Materials and methods

2.1. Materials

All materials were used as received. Calcium carbonate was kindly supplied from Maruo Calcium (Hyogo, Japan). Hydroxypropyl cellulose (HPC, HPC-SSL) and Eudragit® (L30D-55 and RS30D) were also obtained as gifts from Nihon Soda (Japan) and Röhm (Germany). Diclofenac sodium was purchased from Sigma (St. Louis, MO), while polyethyleneglycol 6000, triethyl citrate and dibutyl sebacate were from Nacalai Tesque (Kyoto, Japan). Anhydrous silica (Aerosil no. 200) was obtained from Nippon Aerosil (Tokyo, Japan).

2.2. Drug-layering and coating

A spouted bed coater (Grow Max (140), Fuji Paudal, Osaka, Japan) assisted with a draft tube, a pneumatic spray nozzle with a liquid outlet caliber of 1.0 mm and a peristaltic pump (MP-3, Tokyo Rikakikai, Tokyo, Japan) was used. A

laminated bag-filter with about 1-μm opening and a filter with 5-μm opening were set for drug-layering and coating, respectively.

2.3. Measurement of particle size distribution

The sieve analysis was performed. For the drug-layered particles, an air jet sieve (Alpine 200LS) equipped with a microsieve was operated at a charged weight of 3 g, and the sieving was repeated until a constant weight was reached after 2 min of operation. For the microcapsules, a row-tap shaker (Iida Seisakusho, Tokyo, Japan) was used; the shaking time was 10 min and the charged weight was 10 g.

2.4. Drug release study

The release studies were performed on an NTR-VS6P dissolution apparatus (Toyama Sangyo, Japan) according to the paddle method as described in the Japanese pharmacopeia (JP XIII). JP XIII disintegration 2nd fluid (pH 6.8) was used as a dissolution fluid. A total of 900 ml of the fluid was kept at 37°C and rotated at 200 rpm. The prepared microcapsules were dried in a vacuum at room temperature for 12 h. To make a film-formation complete, these microcapsules were further mixed with 1% anhydrous silica and then heated at a temperature (60°C) closed to the softening temperature of RS30D coat prepared here (62°C) for 3 h in an air stream oven. The cured microcapsules equivalent to 80 mg of diclofenac sodium were tested, and concentration of drug released in the dissolution fluid at predetermined time was determined by measuring the absorbance at 276 nm on a spectrophotometer (UV-190, Shimadzu, Kyoto, Japan).

2.5. Drug content

Assays of the drug content in microcapsules were carried out by pulverizing microcapsules in a mortar and pestle, placing 10 mg of the powder in a glass tube containing 8 ml of dissolution fluid, sonicating for 30 min, centrifuging at 3000 rpm for 15 min, filtering with a 0.22-μm filter and spectrophotometrically measuring the UV absorbance of the diluted portion at 276 nm. The measured drug content was also used to estimate the value of 100% release in dissolution tests and layering efficiency. The layering efficiency was estimated from the measured content of diclofenac sodium in drug-layered particles multiplied by the total amount of produced drug-layered particles and divided by the charged amount of drug.

3. Results

3.1. Design of microencapsulation process

Formulations of spray dispersion and operating conditions of Grow Max (140) spouted bed coater are listed in Table 1. In order to produce drug-layered particles with a high drug content, it was necessary to spray a large amount of drug (50 g) dispersed in binder solution of 500 ml onto 25 g of core particles charged into the coating chamber. In this process, the liquid flow rate had to be adjusted to 1.2–2.3 ml/min, because particle adhesion to the inner wall of draft tube, possibly due to high hygroscopicity of the drug, happened when the liquid flow rate was elevated above 2.3 ml/min. The 25 g of the drug-layered particles thus produced were recharged into the coating chamber, and then directly coated with Eudragit RS30D up to 100% coating level (based on weight of the drug-layered particles). Additionally, another type of microcapsules were prepared by undercoating the drug-layered particles with Eudragit L30D up to 12.5% level and subsequently coating the undercoated particles with Eudragit RS30D up to 50% level without a break of operation. Thus, two kinds of microcapsules were obtained. The former and the later were denoted as R-MCs and LR-MCs, respectively. In the microencapsulation process, inlet air was kept at a temperature lower than the softening temperature of Eudragit RS30D cast film (62°C) to avoid agglomeration of circulating particles due to the softening of the polymer coat (Ichikawa et al., 1993). Therefore, no significant adhesion of circulating particles onto the wall of coating chamber arising from an electrostatic charge and/or the softening of the coat was observed during the operation.

Table 1
Formulations and operating conditions in preparation of microcapsules

	Drug-layering	Undercoating	Release-sustaining	
			R-MCs	LR-MCs
Formulation				
Core:calcium carbonate[a] (g)	25	25[b]	25[b]	28.6[c]
Diclofenac sodium (g)	50			
HPC-SSL (g)	10			
Polyethylene glycol 6000 (g)	2			
Eudragit L30D-55 (g)		3.13		
Eudragit RS30D (g)			25	12.5
Triethyl citrate (g)		0.47		
Dibutyl sebacate (g)			1.25	0.63
Water	ad.	ad.	ad.	ad.
Total (ml)	500	62.5	250	125
Operating conditions				
Inlet air temperature (°C)	50	50	50	50
Outlet air temperature (°C)	25–26	30	21–22	26–29
Inlet air flow rate (m^3/min)	0.08–0.14	0.28	0.22–0.24	0.28
Liquid flow rate (ml/min)	1.2–2.3	3.5	4.2	4.4
Spray air flow rate (l/min)	58	61	60	61
Spray pressure (atm)	2.9	2.9	2.8	2.9

[a] 32–44 μm.
[b] Drug-layered particles.
[c] Undercoated particles.

The characteristics of the produced particles are listed in Table 2. For the drug-layered particles, the yield, the drug content and the layering efficiency were 95, 55 and 91%, respectively, which were satisfactorily high, and the mass median diameter was 71 μm. By coating the drug-layered particles, the mass median diameter increased up to 104 μm for R-MCs and up to 92 μm for LR-MCs, respectively. The drug contents in both microcapsules at the final coating level showed more than 20%.

Fig. 1 shows cumulative undersize distributions of the drug-layered particles and the microcapsules. For the drug-layered particles, the agglomeration tendency was very low; agglomerates composed of two or three core particles were produced only by 2% when the fraction of agglomerates was conveniently estimated from the broken point on the distribution curve in the figure. For the R-MCs and LR-MCs, significant agglomeration was not induced and the size distributions were still kept narrow.

Scanning electron micrographs of the microcapsules (LR-MCs) and the related particles are shown in Fig. 2. Core particles with an angular shape were sphered by layering a large amount of drug (Fig. 2a, b). By undercoating Eudragit L30D the surfaces of the obtained particles became smoother than those of the drug-layered particles. However, they had some pores of 3–5 μm on their membranes (Fig. 2c). The large pores apparently disappeared when the undercoated particles were coated with Eudragit RS30D, but small pores around 1 μm still remained (Fig. 2d). Such porous membranes as shown in Fig. 2d were also observed in R-MCs (data not shown). On the other hand, the surfaces of final products cured by heating were well covered with anhydrous silica (Fig. 2e).

3.2. Release of drug from microcapsules

The release of DS from R-MCs and LR-MCs in JP XIII disintegration 2nd fluid (pH 6.8) are

Table 2
Characteristics of drug-layered particles and microcapsules

	Drug-layered particles	R-MCs	LR-MCs
Product			
Yield (%)	95	96	95
Mass median diameter (μm)	71	104	92
Drug content			
Just before coating (%)	55.2		51.0[a]
25% coating level (%)		—	36.5
38% coating level (%)		—	31.7
50% coating level (%)		32.4	28.9
75% coating level (%)		25.1	—
100% coating level (%)		20.7	—
Layering efficiency (%)	91		

[a] Undercoated particles.

shown in Fig. 3 and Fig. 4, respectively. R-MCs showed bimodal drug release curves; after drug was rapidly released following short-term lag, its release rate became slow during 1–2 h and then increased again (Fig. 3). This release profile did not essentially change even if the coating level of Eudragit RS30D was increased up to 100%. When R-MCs at 100% coating level were immersed in dissolution fluid and microscopically observed, one-fifth of the microcapsules showed rupture of their membranes at the time corresponding to the end of the initial lag in drug release. On the other hand, LR-MCs did not show the bimodal release profile (Fig. 4). The drug release was simply prolonged as the coating level of Eudragit RS30D increased. Moreover, the release rate highly depended on the amount of release-sustaining coat applied, compared with the case of R-MCs.

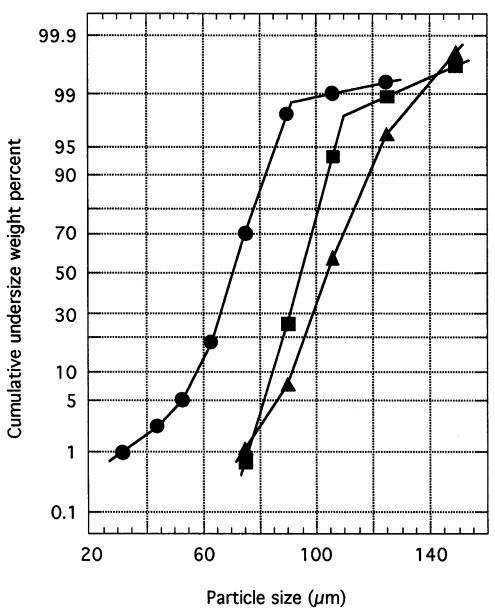

Fig. 1. Cumulative undersize distributions of drug-layered particles and microcapsules. (●) Drug-layered particle; (▲) R-MCs (100% coated); (■) LR-MCs (50% coated).

4. Discussion

The requisites in preparation of diclofenac sodium microcapsules studied here were as follows: (1) particle size of products was to be small enough to be stably suspended in an aqueous dispersing medium; (2) release of drug from microcapsules was to be prolonged for an adequate time required for twice-a-day administration; (3) the content of diclofenac sodium had to be as high as possible; (4) the microcapsules could be prepared by using the water-based polymeric systems.

With regard to the particle size, Shah and Chafetz (1994) reported that an oral suspension requires the use of particles less than 200 μm in diameter to avoid a gritty sensation during administration. In addition, particles for oral sus-

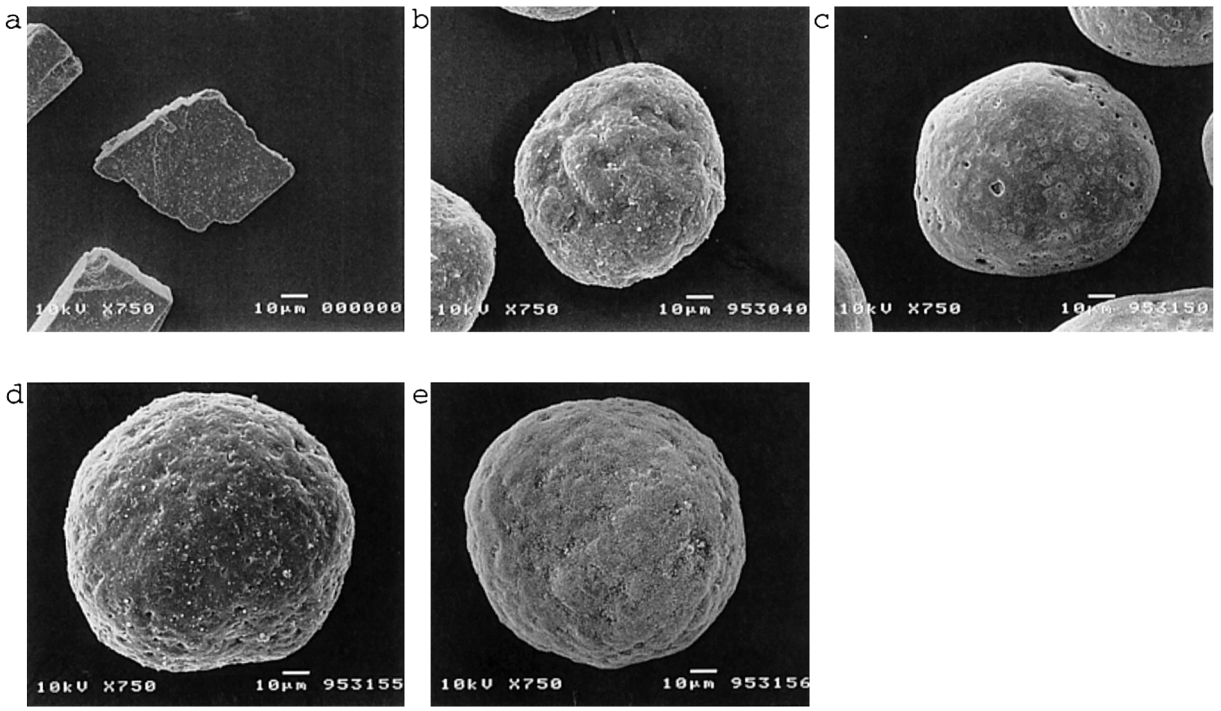

Fig. 2. Scanning electron micrographs of microcapsules (LR-MCs) and the related particles. (a) Calcium carbonate core; (b) drug-layered particle; (c) undercoated particle; (d) just after coated; (e) after heated for curing.

pension should easily be redispersed in an aqueous medium upon the gentle shaking of a container in order to avoid the fluctuation of dose in administration. Considering these given conditions, microcapsules were designed to be smaller than 100 μm in diameter. Although the Wurster process has been characterized by a microencapsulation method suitable for fine powder processing, particles smaller than 100 μm tend to exhibit unsteady circulation in the coating chamber due to their low inertia. This unsteady particle flow often leads to the production of largely agglomerated particles or imperfectly coated fine particles (Fukumori et al., 1991). To steadily maintain the circulation flow of particles even if the size of core particle was small, calcium carbonate, whose density is very high (2.93 g/cm^3), was, therefore, chosen as a core material and its fractionized powder (32–44 μm) was used. In a preliminary test, it was confirmed that this high density particles could be steadily circulated in the coating chamber. Although the use of smaller cores was desirable to achieve a high drug content, smaller than 32 μm cores could not be processed without agglomeration in this study.

From a practical point of view, water-based polymeric systems are preferable in development of coated pharmaceutical dosage forms to organic solvent-based polymeric systems because of their environmental and economic disadvantages. In this study, water-soluble HPC was selected as a binder for drug-layering. While the polymer has to exhibit a sufficient binding strength for drug-layering, an excessive binding strength unavoidably leads to agglomeration. Since HPC-L, higher viscosity grade, induced significant agglomeration in the coating of 53–63 μm lactose cores in a previous study (Fukumori et al., 1993a), a very low viscosity grade (HPC-SSL) was employed in the present study. In addition, PEG 6000 (20 wt.%) was added to HPC aqueous spray solution to suppress agglomeration as less as possible (Fukumori et al., 1993a). In the drug-layering process, particles containing a large amount of

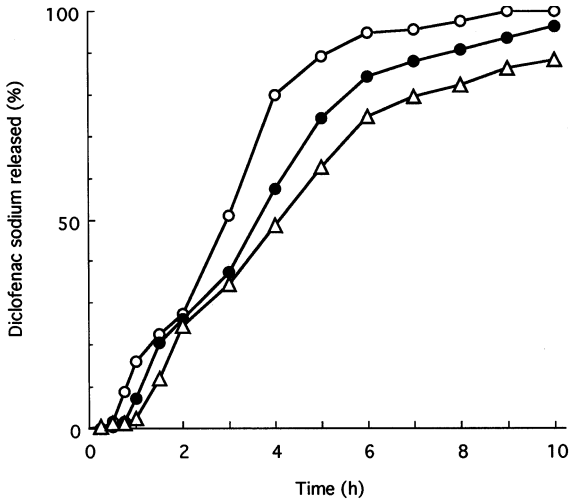

Fig. 3. Release of diclofenac sodium from R-MCs in JP disintegration 2nd fluid (pH 6.8). Eudragit RS30D applied: (○) 50%; (●) 75%; (△) 100%.

drug could be successfully prepared. The high layering efficiency indicated that drug particles well adhered onto cores. Spraying of drug suspension against fine particles frequently results in very low efficiency of layering in comparison to spraying of drug solution. In the present study, high hygroscopicity of DS seemed to contribute to

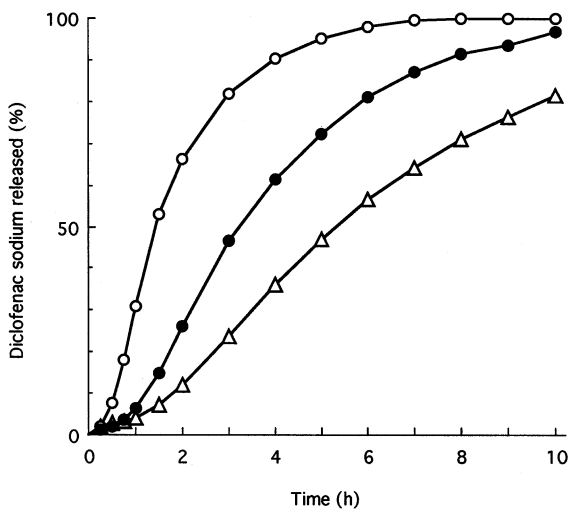

Fig. 4. Release of diclofenac sodium from LR-MCs in JP disintegration 2nd fluid (pH 6.8). Eudragit RS30D applied: (○) 25%; (●) 38%; (△) 50%.

adhesion of drug particles. On the other hand, such a high hygroscopicity of drug particles often tends to induce an agglomeration of core particles (Fukumori et al., 1993b). However, the degree of agglomeration in the present system, fortunately, remained very low (Fig. 1), suggesting that the hygroscopicity of DS would not be high enough to induce the agglomeration and/or addition of PEG 6000 into spray dispersion would be effective for suppressing the agglomeration as expected.

The thickness of drug-layer was estimated to be 17 μm, under the assumption that the density of the drug was the same as that of HPC used as binder (1.22 g/cm^3) and that the drug and the binder were homogeneously coated on the spherical cores of 38 μm (mean of sieve openings used in preparing the cores) with no pore. Theoretically, the diameter of the product without agglomeration should be 72 μm. This value was comparable to the mass median diameter of the produced drug-layered particles (Table 2). This meant that agglomeration tendency in drug-layering process was quite low and calcium carbonate cores were compactly covered with binder and drug particles.

Eudragit RS30D, an aqueous acrylic pseudolatex, was chosen as a film-coating material for prolonged release. A water-soluble plasticizer might change the properties of RS30D coat due to its leaching from the coat during the dissolution process (Bodmeier and Paeratakul, 1993). In this study, DBS was used as a lipophilic plasticizer to minimize its leach from the coat which might lead to rapid drug release.

In order to incorporate the drug into the products at a high content, layering of a large amount of the drug was necessary. However, this would induce more rapid release because of the physicochemical properties of DS, that is, its high water-solubility and high hygroscopicity. On the other hand, thickness of the coat had to be as thin as possible to reduce size-enlargement of products. It is known that solubility of DS in an aqueous medium is pH dependent: it is very slightly soluble in an acidic medium, though highly dissolves in a neutral or weak alkaline medium (Fini et al., 1985). Incorporation of an acidic compound into the microcapsules was therefore undertaken to

lower the water-solubility of DS within the microcapsules, possibly leading to prolongation of drug release. Since acidic compounds of low molecular weight would diffuse across the coat during dissolution process, it was anticipated that their effect on lowering of the solubility might become weak with time. Furthermore, it was reported that organic acids enhanced the water-permeability of Eudragit RS30D films by their migration into the films and consequent physicochemical interaction (Narisawa et al., 1996). Thus, Eudragit L30D-55, an acidic polymeric latex whose pH value is 2.1–3.1 (Japanese Pharmaceutical Excipients, 1993), was introduced between the drug-layer and the release-sustaining coat of Eudragit RS30D. As previously reported, polymeric latices could exhibit a very low agglomeration tendency, depending on the operating conditions used (Ichikawa et al., 1993), unlike polymer solution systems. Hence, Eudragit L30D was preferentially a membrane material which did not induce a significant agglomeration.

As seen in Fig. 1, a very low agglomeration tendency was also achieved in the preparation of both R-MCs and LR-MCs. The fraction of agglomerates produced was only 3% for LR-MCs and 4% for R-MCs. These are practically allowable. As a result, the mass median diameters of both microcapsules were kept around 100 μm and they could satisfy at least a requisite for oral suspension proposed by Shah and Chafetz (1994).

The release of DS from controlled release preparations is strongly dependent on the pH of dissolution medium used (Sagara et al., 1992; Sheu et al., 1992; Wilder et al., 1991). It has been demonstrated that the amount of drug released in an acidic medium was likely to be almost negligible while the release rate in a neutral or weak alkaline medium changes depending on the additives employed and the structure of dosage forms. Such a pH dependent release profile has been ascribed to pH dependent solubility profile of DS. This pH dependent release was also observed in this study. Both R-MCs and LR-MCs more slowly released DS into the pH 1.2 fluid; the fractions of the drug released over 10 h were only 31% for R-MCs and 19% for LR-MCs (data not shown). In practice, therefore, some particulate designs for improvement of pH dependency of drug release may be required in the future to avoid the fluctuation of drug release rate due to change of gastric pH value.

R-MCs in the pH 6.8 fluid exhibited a complicated drug release pattern. As can be seen in Fig. 3, approximately 20% of contents in the R-MCs with 100% coating level was rapidly released in the early stage of dissolution. Similar phenomena have been demonstrated in commercial sustained-release capsule of DS (oral Voltaren® capsule) (Sagara et al., 1992); however, the authors did not refer to the detailed mechanism in their report. The little burst after 1-h lag observed in this study would be ascribed to the membrane rapture in some microcapsules due to expansion by the osmotic pressure generated within the microcapsules, since the proportion of microcapsules whose membranes were ruptured well coincided with the fraction of drug released at the initial burst. However, the reason why the microcapsules equivalent to 20% of the product exhibited membrane rapture, weakly depending on the coating level, is still unknown. As previously reported, film thickness of coated particles varied with particle size within a batch in the Wurster process (Fukumori et al., 1991). This might be ascribed to that smaller particles might tend to receive less amount of membrane materials because of the intrinsic particle flow pattern in the Wurster process and, consequently, they might exhibit a faster release due to their thinner film. Such a size dependency in the release properties of R-MCs, however, did not seem to predominantly contribute to the initial burst as seen in Fig. 3, because the burst was similarly observed even in the fractionized microcapsules (90–106 μm) which should be sufficiently coated (data not shown). The formation of many small pores observed on the microcapsule surfaces (Fig. 2) suggested that their spanning through the thin coat might occur with a certain probability. Although the detailed mechanism of the initial burst could not be elucidated, it was at least found from Fig. 3 that simple coat of Eudragit RS30D was not acceptable practically without further coat thickening.

In contrast, LR-MCs did not show the bimodal release curve observed in the case of R-MCs. It was found on microscopic observation that LR-MCs slightly expanded in the dissolution fluid and no membrane rapture was generated by the osmotic pressure due to drugs dissolved within the microcapsules. Since DS has poor solubility in an acidic medium (Fini et al., 1985), its solubility in the microcapsules would presumably be lowered due to L30D coexisting with it. This would lead to prolongation of the drug release from LR-MCs in spite of their thinner membrane than those of R-MCs: the amount of membrane material required for prolongation of drug release became about one half of that of the R-MCs. With LR-MCs, the prolonged release of diclofenac sodium over 10 h could be achieved at more than 38% coating level of RS30D, but the release was delayed for 1 h. DS undergoes extensive metabolism and it has a relatively short elimination half-life in plasma (Skoutakis et al., 1988). It is commonly said that prolongation of release of such a drug leads to a poor bioavailability. In practice, therefore, further optimization of the release profiles by some additional strategies, for example, saturation of the metabolic processes by the combination of microcapsules having fast release profile with prolonged release microcapsules as prepared here, will be needed to improve bioavailability and to get a well maintained plasma diclofenac concentration.

The solid content in a suspension depends on the dose to be administrated and the drug content in the solid particles. It also depends on the ability of the dispersion medium to allow the suspensions to easily flow. The usual oral suspension for adults is frequently designed to supply the dose in a convenient measure of 5 ml or one teaspoonful. DS is usually used at 25, 50 or 75 mg dose. When one takes 75 mg (the maximum dose) of the drug and the solid content is 250 mg/5 ml that is often found in commercial oral suspensions, the lower limit of drug content in the microcapsules becomes 30%. The drug content of the LR-MCs with 38% levels of the release-sustaining coat of RS30D, which showed preferably prolonged drug release (Fig. 4), was 31.7% (Table 2). This value was reasonable for the above-mentioned dose plan.

5. Conclusion

In this study, prolonged-release microcapsules containing DS applicable for oral suspensions were prepared by the Wurster process. The requisite in preparing the microcapsules was how to prolong the release of highly water-soluble DS while the microcapsules had to have a mass median diameter around 100 μm and a high drug content. Simple coat of Eudragit RS30D could not work as a sufficient permeation barrier for the drug. On the other hand, undercoating of an acidic polymer, Eudragit L30D, on the drug-layered particles and subsequent coating of Eudragit RS30D were effective to prolong release of the drug. The release rate was controllable by adjusting the thickness of the release-sustaining coat of Eudragit RS30D. As a result, these could permit the mass median diameter and drug content to be smaller than 100 μm and around 30%, respectively.

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