Tablet Formulation Study of Spray-Dried Sodium Diclofenac Enteric-Coated Microcapsules

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Sodium diclofenac enteric-coated microcapsules were prepared by a spray-drying technique with Eudragit L 30D as enteric-coating material. The spray-dried powder, mixed with neocel or flo-starch, or the mixture of neocel and flo-starch (weight ratio, 1:1) was directly compressed into a tablet. The micromeritic properties of the spray-dried powder and the mixed powder for tableting were investigated. The flowability of the spray-dried powder was poor but improved after incorporating the excipients. The release rates of sodium diclofenac from the spray-dried powder, the mixed powder before tableting, and the tablets were determined in 0.1 *N* HCl solution, pH 6.8, phosphate buffer solution, distilled water, and pH-changed medium. The results indicated that the spray-dried powder, the mixed powder before tableting, and the tablets all exhibited enteric-coated release properties; these powders and tablets showed some resistance to simulated gastric acid and then released drug more rapidly in pH 6.8 buffer solution. The weight ratio of neocel to flo-starch plays an important role in controlling the release of sodium diclofenac from enteric tablets. The 1:1 weight ratio of neocel to flo-starch was more suitable for designing the microdispersed sodium diclofenac enteric-coated tablets.

KEY WORDS: sodium diclofenac; spray drying; enteric coating; microcapsules; neocel-to-flo-starch ratio.

INTRODUCTION

Sodium diclofenac is a widely used nonsteroidal antiinflammatory drug to treat rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis (1–4). In order to eliminate the gastrointestinal (GI) adverse effect of sodium diclofenac, effective enteric-coated products have been developed and commercialized (5,6). They may allow a drug dosage form to pass through the acid environment of the stomach without irritation, to disintegrate in the upper intestine, and to release the drug. Thus multiple-unit and single-unit enteric-coated preparations have been developed (7–9). Advantages of the multiple-unit products include ready distribution over a large surface area, thus minimizing the risk of local damage caused by the dumping effect of the single unit. Further, multiple units are also less variable and less dependent on gastric transit time. They may attain more constant plasma levels, achieve a slow-release effect, give higher accuracy in reproducibility dose by dose, and make less decrease in bioavailability (10–13). In particular, a single unit of enteric-coated product may be significantly influenced by the physiological pH condition and digested food, possibly leading to poor bioavailability (14–16). Therefore, the microdispersed or multiple-unit enteric-coated products were recently developed (9,11,12,17). Takenaka *et al.* have developed a spray-drying aqueous formulation to prepare enteric-coated microcapsules and devised a new *in vitro* release simulator to study the drug release from encapsulated tablets in the GI tract (18). However, we found interactions between the enteric-coating material and the drug during spray-drying, which did not occur with wet granulation to prepare enteric-coated granules (19,20).

Recently, an aqueous polymeric latex or pseudolatex as enteric-coating material has been used for coating, to replace the organic solvent system (21,22). Although the latter system offers some processing advantages such as low heat of vaporization, stability of water-soluble or moisture-sensitive drugs, and short processing time, safety precautions, environmental pollution, and economic advantages favor the use of water used as a solvent. The aqueous polymers often used for enteric coating are methacrylic acid and ethylacrylate copolymers (Eudragit L 30D), cellulose acetate phthalate (Aquateric), and polyvinyl acetate phthalate (Coateric) (23). These aqueous polymers are insoluble in acidic media but dissolve rapidly when the coating material is contacted with neutral or weak alkaline solution. Because water has a higher heat of vaporization, appropriate equipment must be selected to offer good drying efficiency. Fluid-bed dryer and coating pan are more often used than spray-dryer to coat tablets or pellets with aqueous polymeric system to prepare sustained-release or enteric-coatic products.

In the present study, the spray-drying technique to prepare enteric-coated microcapsules with aqueous acrylic latex was used. The powder properties of the spray-dried powder were determined. Tablet formulation with enteric action was designed by mixing the spray-dried products with neocel or flo-starch, or the mixture of neocel and flo-starch, and compressed them to form a microdispersed enteric tablet. The effect of different weight ratios of neocel to flo-starch (1:0, 1:1, 0:1) on the dissolution behavior of microencapsulated tablets with enteric action was also estimated.

MATERIALS AND METHODS

Materials

Sodium diclofenac (Syn-Tech Chem. & Pharm. Co., Ltd., Hsin-Ying, Taiwan, ROC) was obtained. Voltaren (Ciba-Geigy Ltd., Basle, Switzerland) and Voren (Yung Shin Pharm. Indus. Co. Ltd., Taichung, Taiwan, ROC) are commercially, sodium diclofenac 25-mg enteric-coated tablets. Eudragit L 30D (Rohm Pharm, Darmstadt, West Germany), neocel (microcrystalline cellulose, Cheng Chyi Co. Ltd., ROC), and pure flo-starch (pregelatinized starch, CPC Intern. Co., Australia) were used. All other excipients and reagents were commercial products.

Preparation of Spray-Dried Products

Table I shows the spray-drying formulations. Sodium diclofenac was dissolved in distilled water, and the appropriate amount of excipients was added to the solution to

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Table I. Formulations for Preparation of Enteric-Coated Microcapsules by Spray-Drying Technique

Component	Spray drying formulations (%)				
	I	II	III	IV	V
Sodium diclofenac[a]	37.50	37.50	37.50	37.50	37.50
Eudragit L 30D	3.75	7.50	11.25	18.75	26.25
PEG 6000	2.50	2.50	2.50	2.50	2.50
Aerosil	6.25	6.25	6.25	6.25	6.25
Soluble starch	30.00	26.25	22.50	15.00	7.50
Lactose	25.00	25.00	25.00	25.00	25.00
Symbol	(△)	(▲)	(○)	(●)	(□)

[a] An additional 5% of sodium diclofenac was added.

form a suspension and, finally, comix with Eudragit L 30D and its plasticizer, PEG 6000. The slurries were fed by a roller pump to the spray-dryer (GA 32, Yamato Sci. Co. Ltd., Japan) and atomized into a drying chamber by a spray nozzle. The spray-dryer was operated under the following conditions: inlet temperature, 160 ± 5°C; outlet temperature, 80 ± 5°C; drying air, 0.40 m^3/min; and atomizing air, 1.0 kgf/cm^2. The yields of all spray-dried products are >84%. The drug entrapped in each spray-dried product is listed in Table II.

Micromeritic Properties of Spray-Dried Products

Packing property of the spray-dried products and the mixed powder before tableting was measured by a tapping powder method. Bulk density (ρ_b), tapping density (ρ_t), and compressibility index ($\rho_t - \rho_b/\rho_t$) were obtained, as listed in Table II. The Kawakita equation was used to estimate the packing property.

$$N/c = 1/ab + N/a \quad (1)$$

$$c = (V_0 - V_n)V_0 \quad (2)$$

where a and b are constants representing the proportion of consolidation at the closest packing attained and packing velocity index, respectively. N is the number of taps, V_0 is the volume of powder in a measuring cylinder at the loosest packing, and V_n is the volume after the Nth tapping. The compressibility index of the different weight ratio of neocel to flo-starch without drug was also investigated. The shape and surface topography of the excipients and the spray-dried products were observed by a scanning electron microscopy (S-520, Hitachi, Japan).

Preparation of Tablets

The spray-dried products containing sodium diclofenac equivalent to 25 mg were mixed with the mixture of neocel and flo-starch in a vinyl bag. The weight ratio of neocel to flo-starch (N:F) was 1:0, 1:1, or 0:1. After adding aerosil (1.5%), talc (1.5%), and magnesium stearate (1%), the mixed powder was directly tableted on a rotary tableting machine equipped with a concave punch. The tablet weighed 150 mg, and the thickness and diameter of tablet were 3.33 and 8.0 mm, respectively. The hardness of tablets was determined by hardness tester (NT-1M, Toyama SanGyo Co. Ltd., Japan).

Dissolution Studies

The dissolution rates of the spray-dried products, the mixed powder before tableting, and the tablets were determined using USP XXI Apparatus 2 at 37 ± 0.5°C with paddle, and rotation was set at 50 rpm. The dissolution medium was 0.1 N HCl solution, pH 6.8 phosphate buffer solution, and water (pH 5.7). In order to simulate the pH change of GI tract, pH-changed dissolution procedure specified in USP XXI/NF XVI for enteric-coated articles, Method A, was fol-

Table II. Micromeritic Parameters of Powdered and Tableted Spray-Dried Powders

Parameters	I	II	III	IV	V
			Powdered spray-dried powders		
Bulk density	0.2697	0.2351	0.2172	0.2566	0.2238
Tapping density	0.5226	0.5007	0.4594	0.5237	0.4360
Compressibility index (%)	48.39	53.05	52.72	51.01	52.68
a[a]	0.5382	0.5764	0.5938	0.5608	0.5897
b[a]	0.0178	0.0182	0.0186	0.0185	0.0184
Drug content (%)	34.41 ± 1.34	32.23 ± 1.08	28.15 ± 0.97	25.56 ± 1.01	24.02 ± 0.89
			Tableted spray-dried powders[b]		
Bulk density	0.3005	0.2969	0.3216	0.3184	0.2839
Tapping density	0.5961	0.5568	0.5655	0.5795	0.4986
Compressibility index (%)	49.59	46.68	43.12	45.05	43.06
a	0.5238	0.4873	0.4506	0.4721	0.4516
b	0.0448	0.0615	0.0604	0.5000	0.0461
H (kg)[c]	19.04 ± 1.92	20.36 ± 1.76	19.32 ± 1.48	17.34 ± 1.13	17.44 ± 1.91

[a] a and b are the parameters of Kawakita equation.
[b] The mixture of spray-dried powders and other excipients.
[c] H is the hardness of tablets.

lowed: 2 hr of exposure to 750 ml of 0.1 *N* HCl solution followed by testing in 1000 ml of pH 6.8 phosphate buffer solution and adjusting with 250 ml of 0.20 *M* tribasic sodium phosphate solution. The releasing amount of sodium diclofenac was periodically determined by UV spectrophotometer (UV-320, Jasco, Japan). Voltaren and Voren tablets were also investigated as a comparison. The mean of six tablets was calculated.

RESULTS AND DISCUSSION

Solid particles can be directly formed by spray-drying the droplets. Since this technique combined the drying and agglomeration processes into one step, it may be time and cost saving and under better process control (24–26). Figure 1 shows the scanning electron microphotographs of the spray-dried products. The surface of the spray-dried powder seemed to be entirely covered with polymeric materials, since the spray-dried products were capable of retarding drug release below 10% for 2 hr in 0.1 *N* HCl solution (Fig. 4). Apparently, there was no significant difference in their superficial topographs, although Eudragit L 30D was used in a different amount. Spherical particles with a smooth surface or some surface shrinkages and folds were observed. The shrinkages of the surface wall were due to the entrapped air bubbles expanding considerably at higher drying temperature, a process that was offset partially by the loss of water. Deep indentations in the microcapsules were also found occasionally, which was probably the result of water loss from the drying drop during the early stage of processing (27).

Results shown in Table II of measurements of bulk density and compressibility index suggest that all the spray-dried materials are likely to have poor flow characteristics, as a result of the low value of bulk density and high value of compressibility index. The microstructure and the extremely small particles of the spray-dried products might result in lower bulk density and higher porosity, leading to the poor flow property of the spray-dried powder. However, the flowability of spray-dried products could be improved by adding the excipients used for direct tableting. Since the compressibility index of the mixture of neocel to flo-starch was less than 30%, as shown in Fig. 2, the flowability of the tableted mixtures was probably improved. The parameters *a* and *b* of the Kawakita equation were also decreased and increased, respectively, by adding the excipients to the spray-dried products, as shown in Table II. The low value of *a* and high value of *b* suggest a better flowability and packability of the powders. Figure 3 shows the surface topographs of excipients and the cross section of tablets made from the mixture of spray-dried powder and excipients. Spherical particles of the spray-dried products were distributed and embedded into the excipient mixture, and the wall material of the spray-dried particles acted as a dry binder to combine the excipients to form exceptionally hard tablets. These tablets exhibited a 17- to 20-kg hardness, which contrasted markedly with the 8- to 10-kg hardness of polymer-free tablets.

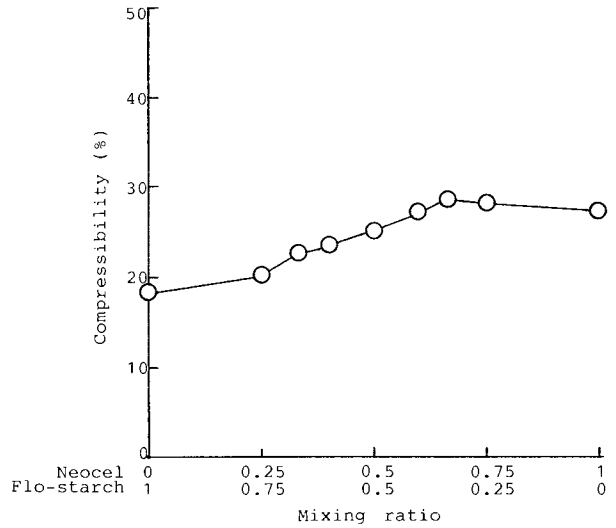

Fig. 2. Compressibility index of the mixture of neocel to flo-starch.

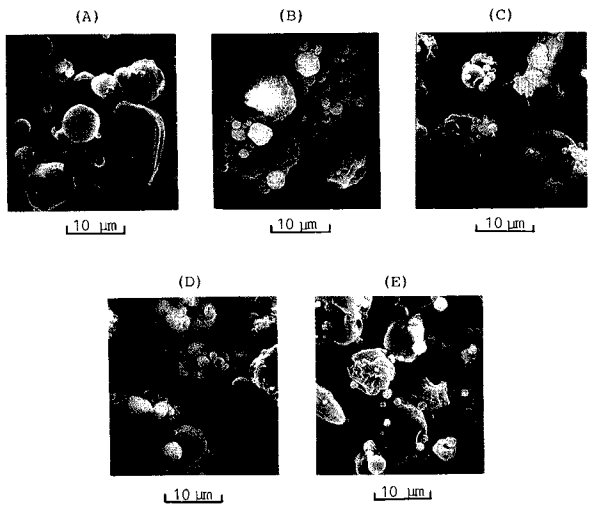

Fig. 1. Scanning electron micrographs of spray-dried products with the different amounts of Eudragit L 30D. (A) Formulation I; (B) Formulation II; (C) Formulation III; (D) Formulation IV; (E) Formulation V.

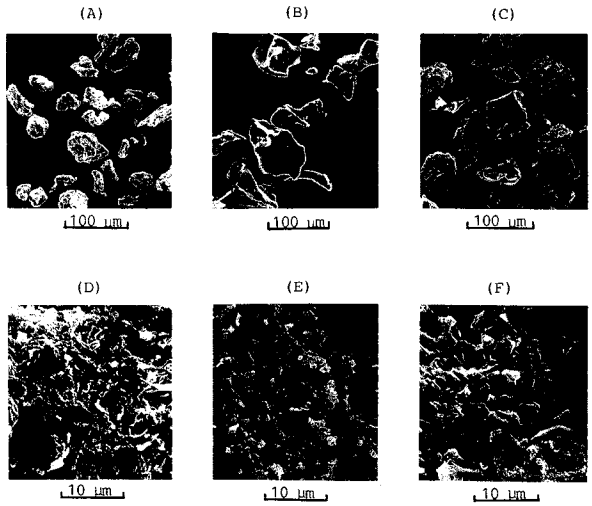

Fig. 3. Scanning electron micrographs of excipients and their mixtures with spray-dried products. (A) Neocel; (B) flo-starch; (C) mixture of neocel and flo-starch; (D–F) tablet texture made by excipients and spray-dried products—(D) Formulation I, (E) Formulation III, and (F) Formulation V.

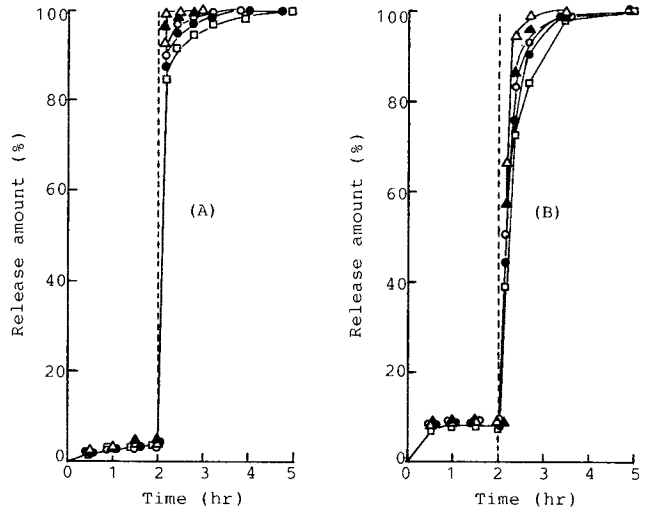

Fig. 4. Sodium diclofenac released from the spray-dried products (A) and the powdered mixtures of excipients (N:F = 1:1) and spray-dried products (B) in pH-changed dissolution medium. See Table I for symbols. Dashed line indicates the pH change.

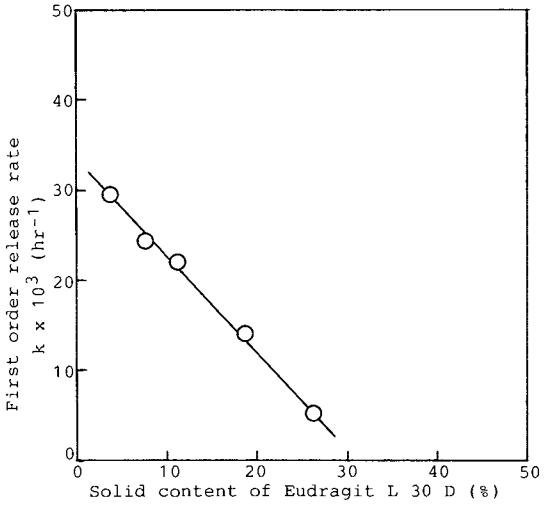

Fig. 6. Relationship between first order release rate of sodium diclofenac and the solid content of Eudragit L 30D.

The pH-changed dissolution profiles of spray-dried powder and the mixed powder before tableting (N:F = 1:1) are shown in Fig. 4. The release rate of both powder products was relatively slow in acidic pH media within the initial 2 hr. After tribasic sodium phosphate was added, the medium pH changed from acidic to 6.8 and the release rate of drug increased rapidly. The other powdered mixtures, whether N:F was 1:0 or 0:1, exhibited the same release behavior. This suggests that all the spray-dried powders were thoroughly encapsulated in enteric-coating polymer and possessed enteric-action properties. The results of the dissolution study also indicate that the release rate in pH 6.8 medium can vary with the amount of Eudragit L 30D added. The more Eudragit L 30D used, the slower the release of drug.

The cumulative amount of sodium diclofenac released from tablets (N:F = 1:1) in distilled water (pH 5.7) and 0.1 *N* HCl solution is shown in Fig. 5. The tablet was immediately disintegrated to fine particles in distilled water and started to release, leading to the release of more sodium diclofenac (>90%) after 1 hr of dissolution, probably because the Eudragit L 30D was soluble at pH 5.5 and because the dissolution of sodium diclofenac could make a higher concentration of ionic strength in the dissolution medium. On the other hand, when the tablet (N:F = 1:1) was exposed to the simulated gastric acid (0.1 *N* HCl solution), it did not disintegrate and showed a considerable slower release behavior—up to 5 hr, only 2–11% of the drug was released. The releasing amount of sodium diclofenac also depended on the levels of Eudragit L 30D used in the spray-drying formulations. The release rate of sodium diclofenac from tablets in 0.1 *N* HCl solution was fitted to the first-order release kinetic. Figure 6 shows the relationship between first-order release rate (Y) and solid content of Eudragit L 30D used (X). A linear relation, $Y = -1.0558X + 33.3112$, $r = 0.9971$, was found. This indicates that the more Eudragit L 30D was used, the slower the release rate of the tablet in simulated gastric acid; in other words, the enteric-coating action depends on the amount of Eudragit L 30D used in the spray-drying formulation. In order to investigate the dissolution behavior of the commercialized enteric-coated tablets, two

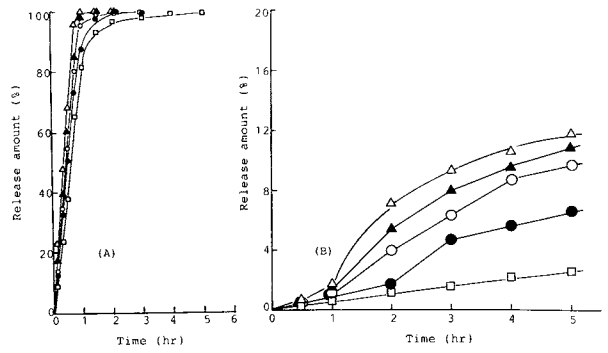

Fig. 5. Dissolution profiles of sodium diclofenac tablets made by the mixture of excipients (N:F = 1:1) and spray-dried products in distilled water (A) and 0.1 *N* HCl solution (B). See Table I for symbols.

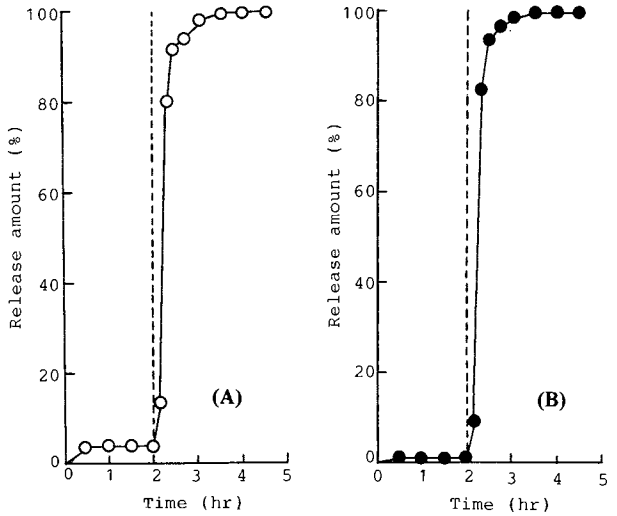

Fig. 7. Dissolution profiles of Voltaren (A) and Voren (B) in pH-changed dissolution medium.

enteric-coated sodium diclofenac products, Voltaren and Voren, were studied. Both products were carried out with the pH-changed dissolution method, as shown in Fig. 7. In the initial acidic phase (<2.0 hr), only a small amount of sodium diclofenac was released from each product. When the medium pH changed to pH 6.8, the tablet immediately disintegrated and rapidly released its inner drug content. This suggests that both commercial products possessed enteric function.

The influence of the weight ratio of neocel to flo-starch (N:F = 0:1, 1:1, 1:0) on the release rate of sodium diclofenac enteric tablets in pH-changed medium is shown in Fig. 8.

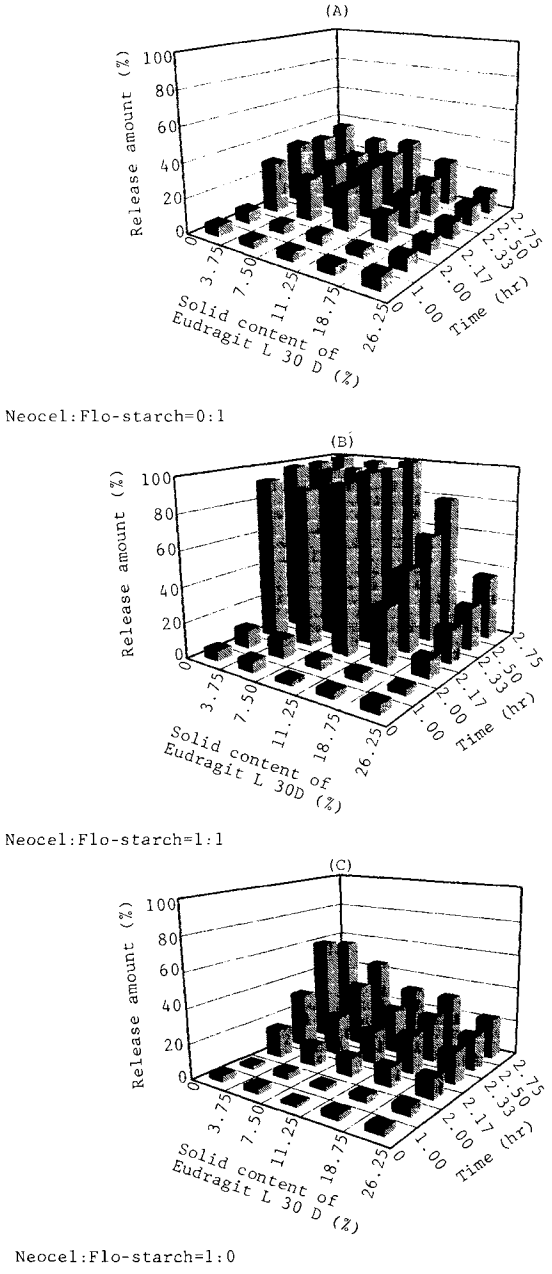

Fig. 8. Dissolution profiles of sodium diclofenac tablets made by the mixtures of spray-dried products and excipients. Weight ratio of neocel (N) to flo-starch (F) is (A) N:F = 0:1, (B) N:F = 1:1, and (C) N:F = 1:0.

When the weight ratio of N:F in the tablet was 0:1, the amount of sodium diclofenac released from the tablets was less than 10% in 0.1 *N* HCl solution 2 hr later, and only 15–40% of the amount released could be obtained, although the medium pH changed to pH 6.8 for 1 hr. Perhaps the tablet did not disintegrate and therefore resulted in a lower release. For the same reason, the release amount of sodium diclofenac from the tablets prepared with a 1:0 ratio of N:F also exhibited only 20–60% of the release amount in pH 6.8 phosphate medium. The weight ratio of N:F was 1:1, however, the release amount of drug in the pH 6.8 phosphate solution was greater than 80% except for formulation V. The rapid disintegration of the tablets after the shift of pH might be responsible for this higher dissolution rate. Being independent of such a weight ratio, the release amount of sodium diclofenac from the tablets in pH 6.8 phosphate solution still depended on the amount of Eudragit L 30D used.

If a sodium diclofenac tablet is designed as an enteric-coated dosage form, it must obey the USP XXI specification: no individual value should exceed 10% when dissolved in the acid phase after 2 hr of operation, and no less than 75% should release in buffer solution after continuous operation on the apparatus for 45 min. Figure 9 summarizes the dissolved amount of sodium diclofenac released from tablets designed by mixing the spray-dried products with the different weight ratio of neocel to flo-starch. Apparently the sodium diclofenac tablet made from the mixture of spray-dried products with neocel or flo-starch alone did not meet the USP XXI criteria. The released amount of sodium diclofenac was less than 75% in the buffer phase after 45 min, but 2 hr later this amount became less than 10% in the acid phase. For the tablet prepared by the spray-dried products and the mixture of neocel and flo-starch (N:F = 1:1), the dissolved sodium diclofenac made from formulation I or II was more than 75% in buffer solution, but their initial dissolved amount exceeded 10%, thus failed to conform the USP criteria. The released amount of sodium diclofenac tablet made from formulation V also did not meet the requirements of USP XXI since the dissolved level was less than 75%, although the release amount was less than 10% in the acidic phase. On the other hand, the tablet prepared by formulation III or IV was found to meet the USP XXI criteria in both the acid phase and the buffer phase. The release amount was not

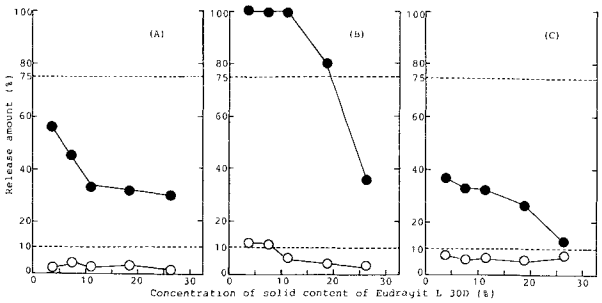

Fig. 9. Assessment of the released amounts of sodium diclofenac from tablets made from the mixtures of spray-dried products and excipients by using the criteria specified in USP XXI. See the legend to Fig. 8. (○) Released amount in acidic phase; (●) released amount in buffer phase. Dashed line indicates the criteria specified in USP XXI Acceptance Table for enteric-coated articles.

only less than 10% in the acid phase but also more than 75% in the buffer phase.

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