Enhancement of Dissolution Rates of Several Drugs by Low-Molecular Chitosan and Alginate

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The dissolution behaviors of acidic, basic and neutral drugs from kneaded mixtures with low-molecular chitosan or alginate (LM chitosan or LM alginate) have been studied in comparison with that of the drug alone. The results revealed a significant increase of dissolution rate of drugs from kneaded mixtures. Although essentially no interaction of any drug with LM chitosan or LM alginate was observed in an aqueous solution, changes of drug crystals in the kneaded mixtures were apparent. In addition, the contact angle of kneaded mixtures was obviously reduced in comparison with that of the corresponding drug powder and physical mixture.

Thus, the enhanced dissolution rate of kneaded mixtures may be due to improvement of wettability and to changes of the crystallinity, microcrystal size and shape.

Keywords low-molecular chitosan; low-molecular alginate; kneaded mixture; enhanced dissolution; wettability; crystallinity

Recently, the use of natural polymers as carriers has received much attention in the pharmaceutical field from the viewpoint of safety. In particular, natural polysaccharides such as chitosan and alginate have been studied for potential utilization in the preparation of dosage forms of commercial drugs.[1-5] However, most of these studies using chitosan and alginate have been limited to sustained-release preparations.[6-8] This limited application of these polysaccharides in the pharmaceutical field seems to be related to their low aqueous solubility. Recently, the hydrolysis products of the polymers have received considerable attention, because their physicochemical properties are different from those of the original polymers.[9,10] For example, the hydrolysis product of chitosan, so-called low-molecular chitosan, is extremely soluble in water (more than 50% (w/v)). Thus, the present study was undertaken to survey the possible utility of low-molecular chitosan and alginate (LM chitosan and LM alginate) for improving drug dissolution. Phenytoin, diazepam, betamethasone, prednisolone and digoxin were tested as acidic, basic and neutral model drugs, because they can show poor bioavailability when formulated into solid forms.

Experimental

Materials Low-molecular chitosan (LM chitosan) and low-molecular sodium alginate (LM alginate) were kindly supplied by Kurita Water Industries Ltd. (Kanagawa) and Kimitsu Chemical Ltd. (Tokyo), respectively. Phenytoin (Dainihon Pharm. Co., Ltd., Osaka) and diazepam (Nippon Roche Co., Ltd., Tokyo) were used as supplied. Betamethasone, digoxin and prednisolone were purchased from Japan Uclaf Co., Ltd. (Tokyo), Sigma Chemical (U.S.A.) and Nakarai Chemical Ltd. (Kyoto), respectively. All other reagents and solvents were of analytical grade.

Sample Preparation The kneaded mixtures of drugs with LM chitosan or LM alginate were prepared by the kneading method. A drug and LM chitosan in a weight ratio of 1 : 1, 1 : 2, 1 : 3 or 1 : 5 were weighed and placed in a mortar, then the mixtures were kneaded with 1.2 times their amount of water for 1 h. For example, in the case of drug–LM chitosan (1 : 2) kneaded mixture, 1 g of drug and 2 g of LM chitosan were weighed and kneaded with 3.6 ml of water for 1 h. Drying was carried out *in vacuo* at room temperature for 48 h. The fraction that passed through a 100 mesh sieve was used in the following experiments. The physical mixture of a drug with LM chitosan or LM alginate was prepared by mixing of the powders (< 100 mesh) in a mortar.

Dissolution Studies Dissolution of drugs from samples was measured according to the paddle method (JPXI). The dissolution medium was 500 ml of water at 37 ± 0.5 °C and the stirring speed was 100 rpm. The amounts of sample powders were 13 mg (phenytoin), 20 mg (diazepam, betamethasone), 19 mg (digoxin) and 100 mg (prednisolone) equivalent. Each sample powder (< 100 mesh) was transferred directly into the dissolution medium and stirred with a stainless-steel paddle at 100 rpm. At appropriate intervals, 3 ml samples were removed from the flask, and filtered through a 0.45 μm membrane filter. The filtrate (1 ml) was extracted with 5 ml of chloroform to remove LM chitosan and LM alginate. The drug concentration in the organic phase was determined spectrophotometrically at λ_{max} of each drug. All studies were done in triplicate.

Solubility Studies Solubility measurements were carried out according to Higuchi and Connors.[11] Excess amounts of drug were added to aqueous solutions containing various concentrations of LM chitosan or LM alginate and were vigorously shaken at 25 ± 0.5 °C for 7 d. The suspensions were centrifuged and filtered through a 0.45 μm membrane filter. The filtrate (1 ml) was extracted with chloroform and analyzed spectrophotometrically.

Powder X-Ray Diffraction Studies The powder X-ray diffraction patterns were obtained by scanning at 1°/min through the 2θ angle on a Rigaku Denki Geigerflex-2012 diffractometer (Tokyo), using CuK_α radiation.

Wettability Wettability measurements were carried out by means of the compressed disk method.[12] The sample powder was compressed into a cylindrical tablet (diameter 1.3 cm) using a single-punch tableting machine (Riken Seiki Co., Ltd., Tokyo) at a pressure of 90 kg/cm^2 for 1 min. A 25 μl drop of water was added on the flat tablet surface using a microliter syringe. After 2 s, the drop was photographed, and the contact angle was measured from the photographs.

Results and Discussion

Figure 1 shows the dissolution profiles of betamethasone from its kneaded mixtures with LM chitosan or LM alginate in water at 37 °C. The kneaded mixtures exhibited a significantly higher dissolution rate than that of betamethasone alone or the physical mixtures. The dissolution rate of the physical mixtures was slightly higher than that of betamethasone alone. The dissolutions of betamethasone preparations containing LM chitosan or LM alginate at 4 different amounts were evaluated. The disso-

TABLE I. Physicochemical Properties of LM Chitosan and LM Alginate

	LM chitosan	LM alginate
Molecular weight	3800	< 10000
Decomposition temperature (°C)	180	204
Viscosity (cP)[a]	1.02	2.64
pH[a]	6.66	6.89
Aqueous solubility (g/100 ml)[b]	> 50	> 10
Surface tension (dyn/cm)[a]	70.7	58.7
Charge density (meq/g)	2.8	—

a) 1% aqueous solution at 25 °C. *b*) Solubility at 25 °C.

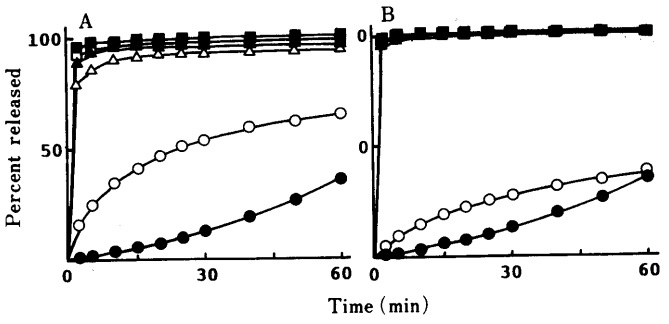

Fig. 1. Dissolution Profiles of Betamethasone (BM) and Its Kneaded Mixtures with LM Chitosan (A) or LM Alginate (B) in Water at 37 °C

●, BM alone; ○, BM : LM chitosan or LM alginate (1 : 2) physical mixture; △, BM : LM chitosan or LM alginate (1 : 1) kneaded mixture; ▲, BM : LM chitosan or LM alginate (1 : 2) kneaded mixture; □, BM : LM chitosan or LM alginate (1 : 3) kneaded mixture; ■, BM : LM chitosan or LM alginate (1 : 5) kneaded mixture.

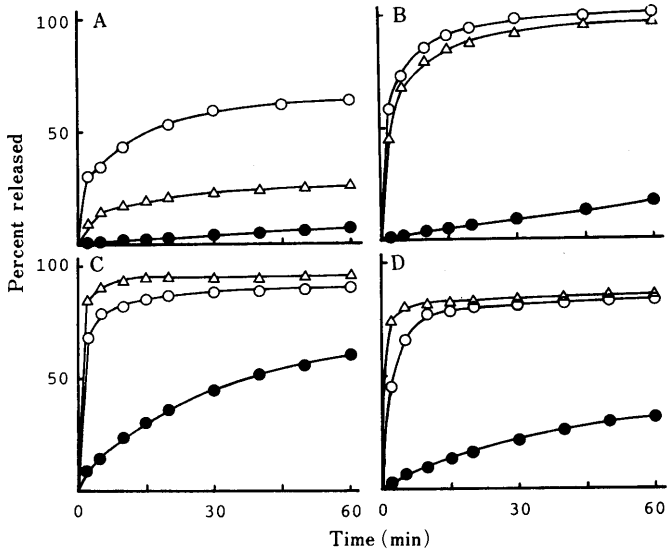

Fig. 2. Dissolution Profiles of Drugs and Their Kneaded Mixtures with LM Chitosan or LM Alginate in Water at 37 °C

A, phenytoin; B, diazepam; C, prednisolone; D, digoxin. ●, drug alone; ○, drug : LM chitosan (1 : 2) kneaded mixture; △, drug : LM alginate (1 : 2) kneaded mixture.

lution rate of betamethasone from the kneaded mixtures showed a tendency to be slightly enhanced with increasing amount of LM chitosan. LM alginate, as well as LM chitosan, gave rapid dissolution of betamethasone. The dissolution profiles for all the kneaded mixtures with LM alginate were almost the same, being independent of the LM alginate content. However, in the case of LM chitosan, the dissolution slightly depended upon the LM chitosan content; the 1 : 1 kneaded mixture showed slightly slow dissolution, compared with other preparations. The initial and final pH values of the dissolution medium were almost the same, showing 6.20, 6.37 (LM chitosan kneaded mixture) and 6.22, 6.43 (LM alginate kneaded mixture), respectively. This clearly indicates that the enhanced dissolutions of drug by LM chitosan and LM alginate could not be explained on the basis of pH effect. This implication is supported by the findings that the dissolution rates of the physical mixtures were much smaller than those for the kneaded mixtures. The dissolutions of the kneaded mixture with LM chitosan or LM alginate at a 1 : 2 weight ratio of

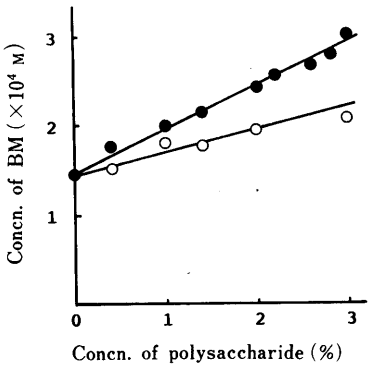

Fig. 3. Effect of LM Chitosan or LM Alginate on Solubility of Betamethasone (BM) in Water at 25 °C

●, BM–LM chitosan systems; ○, BM–LM alginate systems.

TABLE II. Solubility of Drugs in the Absence and the Presence of LM Chitosan and LM Alginate in Water at 25 °C

Drug	Solubility ($\times 10^4$ M)				
	Alone	1% LM chitosan		1% LM alginate	
	S_0	S_1	(S_1/S_0)	S_1	(S_1/S_0)
Phenytoin	1.48	2.39	(1.6)	1.94	(1.3)
Diazepam	1.33	1.41	(1.1)	1.55	(1.2)
Betamethasone	1.43	2.00	(1.4)	1.80	(1.3)
Prednisolone	5.90	8.50	(1.4)	6.60	(1.1)
Digoxin	0.35	0.37	(1.1)	0.44	(1.3)

drug to low-molecular polymer were also evaluated for other drugs. Each kneaded mixture exhibited a higher dissolution rate than that of drug alone, as shown in Fig. 2. Virtually no differences of dissolution behaviors between the kneaded mixtures with LM chitosan and LM alginate were observed for diazepam, prednisolone and digoxin, although there was a difference in the case of phenytoin. The difference in phenytoin dissolutions observed for LM chitosan and LM alginate can be ascribed to the difference in wettability, as will be described later. The enhanced dissolution behaviors of drugs from the kneaded mixtures may be explained by the increase in solubility and wettability, and/or the decrease of crystallinity of the drug caused by dispersion in LM chitosan or LM alginate. The drug solubilities were measured in the presence of LM chitosan or LM alginate.

Figure 3 shows the phase solubility diagrams obtained from betamethasone with LM chitosan and LM alginate. The solubility of betamethasone increased slightly with increasing concentration of LM chitosan or LM alginate. Table II lists the solubility of drugs in 1% LM chitosan or 1% LM alginate aqueous solution. Increases of solubility were observed for all drugs in the presence of LM chitosan or LM alginate. However, the solubilities were only 1.1—1.6 times as high as those of the drugs themselves. In addition, the ultraviolet (UV) and fluorescence spectra of the tested drugs were scarcely changed in the presence of LM chitosan or LM alginate. These data suggest that the interactions of the drugs with LM chitosan or LM alginate in aqueous solution are very weak. Therefore, it is difficult to explain the rapid dissolution rate of the drugs solely in terms of increased solubility.

Next, the crystallinity of drugs in the kneaded mixtures

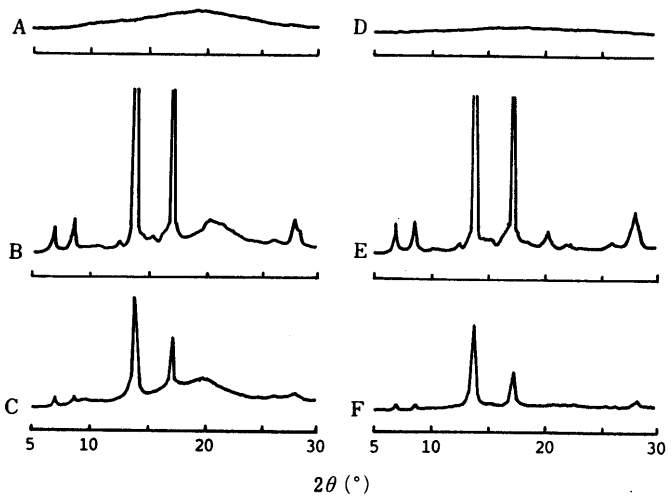

Fig. 4. Powder X-Ray Diffraction Patterns of Betamethasone (BM)–LM Chitosan or LM Alginate Systems

A, LM chitosan alone; B, physical mixture (BM : LM chitosan = 1 : 2); C, kneaded mixture (BM : LM chitosan = 1 : 2); D, LM alginate alone; E, physical mixture (BM : LM alginate = 1 : 2); F, kneaded mixture (BM : LM alginate = 1 : 2).

with LM chitosan or LM alginate was compared with that of drugs in the physical mixture by means of powder X-ray diffraction. Figure 4 shows the powder X-ray diffraction patterns of the kneaded mixture and the physical mixture composed of betamethasone and LM chitosan or LM alginate (1 : 2). Since the diffraction patterns of LM chitosan and LM alginate showed a halo pattern, the diffraction peaks in the physical mixture were characteristic of betamethasone. The diffraction peaks of betamethasone in each kneaded mixture, however, were broader than those in the physical mixture. The half-widths of each peak in kneaded mixtures were about 1.20 and 1.31 times those in the physical mixtures with LM chitosan and LM alginate, respectively. Similarly, peak broadening was observed in each kneaded mixture containing phenytoin, diazepam, prednisolone and digoxin (not shown). These data can be explained by considering that the drug powder is dispersed as separated crystals in the kneaded mixtures. Moreover, the kneading seems to cause decreases of crystallinity and microcrystal size, and changes of the paracrystal lattice and microcrystal shape.[13] The decrease of crystallinity and/or crystal size in kneaded mixtures may enhance drug dissolution rates. However, the rapid dissolution rates observed may not be fully explained by the crystal changes, and further investigation of the mechanism is needed. Since LM chitosan and LM alginate are very soluble in water, they may improve the wettability of drug particles by water through dispersion of the drug particles in LM chitosan or LM alginate. Thus, the effects of ligands on the wettability of the drugs were examined. As can be seen in Table III, the contact angle of the kneaded mixtures was obviously reduced in comparison with that of the corresponding drug powder and physical mixture. The contact angles of physical mixtures were smaller than those of the drugs alone, but greater than those of the kneaded mixtures. No differences of the contact angle was observed between the kneaded mixtures with LM chitosan and LM alginate, except in the case of phenytoin. The wettability of phenytoin, an acidic

TABLE III. Contact Angle of Sample Powder Measured by the Compressed Disk Method

Drug	Contact angle (°)				
	Alone	LM chitosan		LM alginate	
		KM	PM	KM	PM
Phenytoin	75	40	60	50	61
Diazepam	65	40	49	42	53
Betamethasone	65	37	55	41	60
Prednisolone	58	38	46	39	49
Digoxin	62	39	50	40	51

KM, kneaded mixture (drug : LM chitosan or LM alginate = 1 : 2). PM, physical mixture (drug : LM chitosan or LM alginate = 1 : 2).

drug, is improved by LM chitosan more than by LM alginate, possibly due to finer dispersion. The rapid dissolution of phenytoin by LM chitosan (Fig. 2) was mainly explained by the improvement of wettability. These results indicate that the kneaded mixture with LM chitosan or LM alginate improved the wettability of the drug, and consequently enhanced the dissolution rate of the drug.

In conclusion, LM chitosan and LM alginate enhanced the dissolution rates of drugs owing to the improvement of wettability and the decrease of the crystallinity and crystal size. High-molecular chitosan and alginate, the original polysaccharides, have been mainly applied to the sustained-release preparations. Therefore the present data also suggest that the release rates of drugs from kneaded mixtures with polysaccharides and their partially hydrolyzed derivatives, including chitosan and LM chitosan, may be subtly controlled by changing the relative contents of the high-molecular and the low-molecular polysaccharides.

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