Evaluation of Low-Molecular Gelatin as a Pharmaceutical Additive for Rapidly Absorbed Oral Dosage Formulation

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The dissolution behavior of ibuprofen from a kneaded mixture with low-molecular gelatin (LM gelatin) has been studied in comparison to kneaded mixtures prepared with other additives. Their *in vivo* absorption behaviors were also examined. The LM gelatin markedly enhanced the dissolution rate of ibuprofen compared to that with polyethylene glycol (PEG) 6000, dextran T10 or pullulan. Oral administrations of the kneaded mixture to beagle dogs showed the LM gelatin to be most effective in accelerating the absorption rate of ibuprofen among the additives used.

Keywords low-molecular gelatin; pharmaceutical additive; dissolution; absorption; kneaded mixture

Very recently we reported that low-molecular gelatin (LM gelatin), a hydrolysate of common gelatin, enhanced the absorption rates of some drugs by improving their dissolution characteristics because of its high aqueous solubility.¹⁻³ In this continuing investigation, we have evaluated LM gelatin to be one of the most useful additives for rapidly absorbed solid drug formulation in comparison with other additives such as polyethyleneglycol (PEG) 6000, dextran T10 and pullulan which were used as references having approximately same molecular weights and high aqueous solubilities as the LM gelatin.

Experimental

Materials Low-molecular gelatin (mean molecular weight (MW)=6000) was kindly supplied by Nitta Gelatin Co., Ltd. (Osaka). Polyethylene glycol (PEG) #6000 (MW=7800—9000) was obtained from Nacalai Tesque, Inc. (Kyoto). Dextran T10 (MW=10200) was obtained from Pharmacia LKB (Sweden). Pullulan (MW=5500) was kindly supplied by Hayashibara Co., Ltd. (Okayama). Ibuprofen (Nisshin Flour Milling Co., Ltd., Tokyo) was used as supplied. All other reagents and solvents were of analytical grade.

Sample Preparation A kneaded mixture of ibuprofen with each additive was prepared by the kneading method. Ibuprofen and additives in a weight ratio of 1:1 were weighed and placed in a mortar, and each mixture was kneaded with the same amount 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.

Dissolution Studies Dissolution of ibuprofen from the samples was measured according to the paddle method (JP XI). A volume of 900 ml deionized water was kept at 37°C and rotated at 100 rpm. Sample powders each equivalent to 80 mg of ibuprofen with or without filling in hard capsules were put into the test solution. An aliquot was withdrawn periodically and immediately filtered through a 1.0 µm membrane filter (Toyo Roshi Co., Ltd., Tokyo). The filtrate was extracted with organic solvent to remove additives. The drug concentration in the organic phase was determined spectrophotometrically at 220 nm. All studies were done in triplicate.

In Vivo Absorption Studies Beagle dogs (10—13 kg, 2—3 years old) were given a liquid diet (Besvion®; Snow Brand Milk Co., Ltd., Tokyo) for 2 d before being fasted for 24 h. The powders (equivalent to 80 mg of ibuprofen) were put into hard capsules of size 0. Each preparation was given orally to the dogs together with 20 ml of water. Blood samples were taken at appropriate intervals from the forefoot vein and centrifuged for 15 min at 3000 rpm to obtain serum fractions. To 1 ml of serum was added 1 ml of 1 N HCl, and the serum was then extracted with 5 ml of cyclohexane containing 3 µg/ml of flurbiprofen as an internal standard. The organic phase was evaporated. The residue was dissolved in 100 µl of acetonitrile and assayed by reversed phase high-performance liquid chromatography (HPLC). The HPLC conditions were as follows: pump, Hitachi 655A-11 type; detector, Hitachi 655A-21 type; column, LiChrosorb RP-18 (250 × 4 mm i.d.); mobile phase, acetonitrile–water–phosphoric acid 275:225:0.5; flow rate, 1 ml/min; detection, 220 nm.

Pharmacokinetic Analysis Bioavailability parameters were calculated

from the serum concentration–time curve up to 5 h post-administration. Moment analysis was employed to calculate the area under the serum concentration–time curve (*AUC*), the mean residence time (*MRT*) and the variance of residence time (*VRT*).⁴

Results and Discussion

Figure 1 shows the dissolution profiles of ibuprofen from

Fig. 1. Dissolution Profiles of Ibuprofen from Its Kneaded Mixture with Several Additives in Water at 37°C

○, ibuprofen alone; ●, LM gelatin kneaded mixture; △, dextran T10 kneaded mixture; ▲, PEG 6000 kneaded mixture; □, pullulan kneaded mixture.

Fig. 2. Mean Serum Levels of Ibuprofen Following the Oral Administration of Ibuprofen Powder and Its Kneaded Mixture with Several Additives to Beagle Dogs

Each point represents the mean ± S.E. (*n*=4). ○, ibuprofen alone; ●, LM gelatin kneaded mixture; △, dextran T10 kneaded mixture; ▲, PEG 6000 kneaded mixture; □, pullulan kneaded mixture.

TABLE I. Bioavailability Parameters Following Oral Administration of Ibuprofen Kneaded Mixtures

Preparation	AUC_{0-5h} (h · μ g/ml)	MRT (h)	VRT (h ²)
Ibuprofen alone	104.66 ± 11.40	2.35 ± 0.11	1.58 ± 0.07
Kneaded mixture			
LM gelatin	103.55 ± 16.86	1.99 ± 0.16 ^{a)}	1.62 ± 0.07
PEG 6000	115.41 ± 20.31	2.34 ± 0.13	1.58 ± 0.06
Dextran T10	105.64 ± 10.08	2.43 ± 0.28	1.57 ± 0.08
Pullulan	110.34 ± 15.60	2.51 ± 0.17	1.40 ± 0.21

Values represent the mean ± S.D. (n = 4). a) Significantly different from ibuprofen alone at $p < 0.05$.

Fig. 3. Dissolution Profiles of Ibuprofen Powder and Its Kneaded Mixture with Several Additives from Gelatin Capsule in Water at 37°C
○, ibuprofen alone; ●, LM gelatin kneaded mixture; △, dextran T10 kneaded mixture; ▲, PEG 6000 kneaded mixture; □, pullulan kneaded mixture.

its kneaded mixtures with several additives in water 37°C. All kneaded mixtures exhibited faster dissolution patterns than ibuprofen alone, and that with LM gelatin showed a particularly higher dissolution rate than other additives. The surface of ibuprofen might become more hydrophilic through the dispersion in LM gelatin, compared with other additives.¹⁾

Figure 2 shows the mean serum levels of ibuprofen following the oral administration of kneaded mixtures to the beagle dogs. It is evident that the LM gelatin significantly enhanced the initial serum concentration of ibuprofen and

reduced the peak concentration time (T_{max}). The other additives affected the serum concentration of ibuprofen only insignificantly. These distinct differences of additive effects were confirmed from the bioavailability parameters (Table I). As shown in Table I, the mean residence time (MRT) value, the index of rate of bioavailability, for the ibuprofen-LM gelatin kneaded mixture following oral administration was significantly reduced in comparison with those of others. However, the AUC was almost the same for all samples. The differences in the rate of bioavailability between the LM gelatin and other additives may be explained by the dissolution and absorption characteristics from the kneaded mixtures. That is, the enhanced dissolution of the kneaded mixtures with the other additives was less or cancelled out due to the negative effect imparted by the interaction such as complexation of the drug and the additives that retarded permeability, resulting in decrease in the apparent overall absorption rate of the drug. Moreover, the slow dissolution of the kneaded mixture from the capsule may be considered due to the interaction of the drug or the additive in the kneaded mixture with gelatin, the capsule component which causes less dissolution than drug alone. In fact, the dissolution of ibuprofen from the kneaded mixture in the gelatin capsule was slower than the ibuprofen alone (Fig. 3). However, the dissolution of drug from the capsule containing LM gelatin was markedly higher than the drug alone.

We have already reported that LM gelatin was very effective in accelerating the rate of absorption of a variety of drugs from the gastrointestinal tract after oral administration.^{1,2)} The data presented here further emphasized that LM gelatin was very effective as an additive providing fast dissolution and absorption of a drug.

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References

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