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Development and pharmaceutical properties of a new oral dosage form of theophylline using sodium caseinate for the possible use in elderly patients

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Abstract

As a new oral dosage form which elderly patients could handle and swallow more easily, a solid mass containing theophylline was formed by treatment of a powder mixture of sodium caseinate, microcrystalline cellulose and theophylline with moist heat in the form of saturated steam under pressure. The physical and chemical stability of theophylline in solid mass form was confirmed on the basis of data obtained by infrared spectroscopy, X-ray powder diffractometry and high-performance liquid chromatography. The solid mass containing theophylline showed lower water absorption and reduced swelling tendency compared to the theophylline-free solid mass, whereas the slope of the gel destruction curve of swollen mass containing theophylline was similar to that of the theophylline-free solid mass. Therefore, it appeared that elderly patients could swallow this dosage form easily. The rate of release of theophylline from the swollen mass decreased in the order of distilled water, JP XII disintegration test fluid no. 2 (pH 6.8), and JP XII disintegration test fluid no. 1 (pH 1.2). The profiles of theophylline release from the swollen mass demonstrated non-Fickian diffusional behavior. In JP XII disintegration test fluid no. 1, theophylline was released slowly from the whole swollen mass, but rapidly from the destroyed swollen mass. The presence of digestive enzyme (pepsin) increased the release rate of theophylline from the swollen mass gradually. Thus, the structure of the polymer network in the swollen mass was considered to influence the release profile of theophylline. Although the biopharmaceutical parameters of this new oral dosage form should be further examined, the dosage form using sodium caseinate seems to be useful for medication in elderly patients.

Keywords: Oral dosage form; Theophylline; Sodium caseinate; Solid mass; Swelling; Dissolution; Elderly patients

1. Introduction

Most medications currently in use are oral dosage forms such as tablets, powders, granules and syrups. Elderly patients frequently have many difficulties with handling and taking oral dosage forms because of physiological changes such as impaired dexterity (arthritis) and impaired swallowing (xerostomia) with aging (Kottke et al., 1989, 1990). Thus, for treatment of the elderly the development of new oral dosage forms is required (Peter and Richard, 1990). The elderly in Japan prefer oral dosage forms such as a jelly due to the ease of handling and swallowing

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(Sugihara, 1990). In the case of the formulation of jelly or gel forms, chemical and microbiological issues should be considered because of the presence of large amounts of water in these forms. Material such as xerogel is, hence, favorable for use as a dosage form appropriate for the elderly, as it contains no water during storage and changes to a gel when water is added.

In our previous paper (Watanabe and Sugihara, 1992), we reported that the treatment of a powder mixture of sodium caseinate and microcrystalline cellulose (MCC) with moist heat in the form of saturated steam under pressure formed a solid mass, and that this solid mass displayed a rapid and marked swelling behavior on addition of water. These phenomena occurred because water-soluble sodium caseinate protein powder was converted into water-insoluble polymerized protein solid mass by cross-linking. Formalin-casein powder is marketed commercially in France, and the characteristics of formalin-casein as a tablet disintegrant have been reported by Ponchel and Duchêne (1990). It seems that formalin-casein exhibits a swelling property due to the polymerization of casein on treatment with formalin. The novel characteristic of our method is the polymerization of sodium caseinate without formalin, yielding a solid mass as the final product. During storage, the solid mass is a dry mass which changes into a gel on addition of water, and thus can readily be handled and swallowed by elderly patients. In the present study, we intended to develop a new oral dosage form for use in elderly patients with chronic obstructive pulmonary diseases. We selected theophylline as a model drug because of its considerable stability to heat. The stability of theophylline, swelling behavior of the solid mass and release behavior of theophylline from the solid mass were investigated, although the solid mass containing theophylline has not yet been used clinically.

2. Materials and methods

2.1. Materials

Sodium caseinate and theophylline were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan). Microcrystalline cellulose (Avicel® PH101, Asahi Chemical Industry, Co., Ltd, Tokyo, Japan), caffeine and saccharated pepsin (Fujisawa Astra Co., Ltd, Osaka, Japan) were of JP grade. Theophylline monohydrate was obtained by recrystallization from the aqueous solution, and anhydrous theophylline was prepared by drying at 100°C for 1 h (Puttipipatkhachorn et al., 1990). Xylitol (Nacalai Tesque Inc., Kyoto, Japan) was used after grinding the crystal into powder (42 mesh pass). All the other reagents used were of reagent grade.

2.2. Preparation of solid mass

The method of preparation of the solid mass was reported previously in detail (Watanabe and Sugihara, 1992). 1 g of powder mixture, which was prepared by blending for 20 min with an automatic mortar and pestle, was transferred into a thimble filter (Polyfuron® no. 89, Toyo Roshi Co., Ltd Tokyo, Japan) and treated with moist heat in the form of saturated steam under pressure by use of a hospital automatically controlled autoclave. After cooling to about 80°C, the solid mass formed was removed from the thimble filter and dried for 24 h at room temperature in a vacuum drier. In this report, this process is referred to as moist heat (MH) treatment. MH treatment was usually performed at 115°C for 10 min. In the theophylline release test, solid mass prepared by MH treatment (115°C, 60 min) was also used.

2.3. Infrared (IR) spectroscopy

IR spectra were determined by the KBr method using an infrared spectrometer (type IR-435, Shimadzu, Kyoto, Japan).

2.4. X-ray powder diffractometry

Powder X-ray diffraction patterns were obtained using a Rigakudenki 2027 diffractometer (Tokyo, Japan) under the following conditions: target, Cu; filter, Ni; voltage, 30 kV; current, 5 mA; and scanning speed, 4°/min.

2.5. Water absorption test

The water absorption ability of the solid mass containing theophylline was examined as described previously (Watanabe and Sugihara, 1992), according to the method originally developed for the study of the water absorption ability of tablet disintegrants by Nogami et al. (1969). In brief, we placed the solid mass on a glass filter wetted with distilled water and measured the amount of water absorbed using an electrical balance.

2.6. Gel strength of the swollen mass

The gel strength of the swollen mass containing theophylline was measured using a rheometer (NMR-2001J Fudoh Kogyo Co., Ltd, Tokyo, Japan) described previously (Watanabe and Sugihara, 1992).For measurements, the solid mass was placed in the sample bottle (50 ml volume) and 10 ml of distilled water was then added. Measurements were performed 2 min after the addition of water.

2.7. Evaluations of theophylline release

Theophylline release tests from the solid mass into various fluids were performed using a JP paddle dissolution apparatus (paddle rotating speed, 100 rpm) at 37°C. We used distilled water, JP XII disintegration test fluids no. 1 and no. 2 as test fluids (500 ml). JP saccharated pepsin (1 or 3%) was dissolved in JP XII disintegration test fluid no. 1. After 1.0 g of the solid mass was added to the fluids, aliquots of the solutions were removed at suitable intervals and filtered through membrane filters (pore size 0.45 μm). The theophylline concentration was determined by UV spectroscopy at 272 nm (type UV-240, Shimadzu, Kyoto, Japan) after removing casein protein. The method for removing casein protein was similar to that by which the phenytoin concentration in casein solution was measured previously (Watanabe et al., 1990). The theophylline concentration in JP saccharated pepsin solution was determined by high-performance liquid chromatography (HPLC) as UV absorption of saccharated pepsin interfered with the measurement of theophylline. The HPLC conditions were as follows: column, Zorbax ODS (4.6 mm i.d. $\times$ 15 cm length, Shimadzu Co., Kyoto, Japan); mobile phase, CH_3CN/0.1 M KH_2PO_4 (pH 5.3) = 10:90; elution rate, 1.0 ml/min.

As the solid mass sometimes changed to a larger swollen mass in the test fluid and the swollen mass was broken down in contact with the rotating paddle, we put the solid mass into a hemisphere stainless basket (about 6.5 cm i.d. and about 10 g in weight), which was placed at the bottom of dissolution apparatus beaker.

To test for theophylline release from the crushed swollen mass, the solid mass was initially swollen by the addition of 50 ml distilled water. This swollen mass was then transferred into a 50 ml plastic syringe and pushed out into the test fluid.

3. Results and discussion

3.1. Stability of theophylline

During the process of manufacturing solid mass containing theophylline, it is possible that theophylline molecules could have undergone several chemical reactions and decomposition owing to both the high temperature and steam. The IR spectrum of the solid mass prepared by MH treatment of powder mixture (theophylline/sodium caseinate = 1:1 w/w) showed no difference from that of the powder mixture before treatment (Fig. 1). Also, on IR spectral analysis of the solid mass (theophylline/sodium caseinate/MCC = 0.1:0.36:0.54 by wt, the sample mostly used in this study), we observed no IR spectral change on MH treatment (data not shown). In the HPLC measurement of theophylline in the solid mass after MH treatment, the content of theophylline remained unchanged. Thus, it appeared that theophylline did not react with the functional groups of either protein or other theophylline molecules.

3.2. X-ray diffraction of theophylline

Fig. 2A and B shows the X-ray diffraction patterns of anhydrous theophylline and monohydrate, respectively. The diffraction patterns of intact and MH-treated theophylline (Fig. 2C-1 and C-2) were consistent with those shown in Fig. 2A, being attributed to anhydrous form II of theophylline (Suzuki et al., 1989). The X-ray diffraction pattern of theophylline monohydrate after MH treatment showed an anhydrous pattern (data not shown), since dehydration took place in the final drying process of MH treatment.

The powder X-ray diffraction patterns of the solid mass (theophylline/sodium caseinate = 1:1 w/w and theophylline/sodium caseinate/MCC = 1:1:1 by wt) are also shown in Fig. 2. In MCC-anhydrous theophylline blend granules, a crystal transition from the anhydrous to monohydrate form has been reported to occur (Herman et al., 1988, 1989). However, in the solid mass, no change in the crystal form or crystallinity of theophylline was observed (Fig. 2D,E).

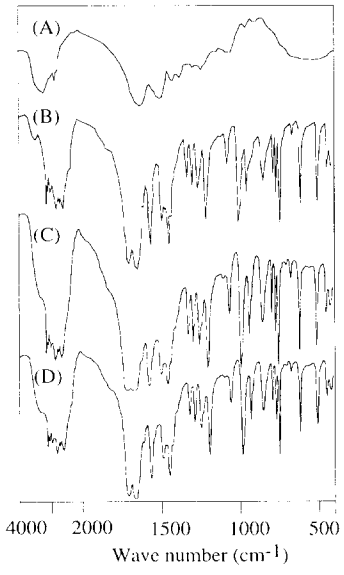

Fig. 1. Effects of MH treatment on IR spectra of the powder mixture (theophylline/sodium caseinate = 1:1 w/w). (A) Sodium caseinate, (B) theophylline, (C) powder mixture before treatment, (D) powder mixture after treatment.

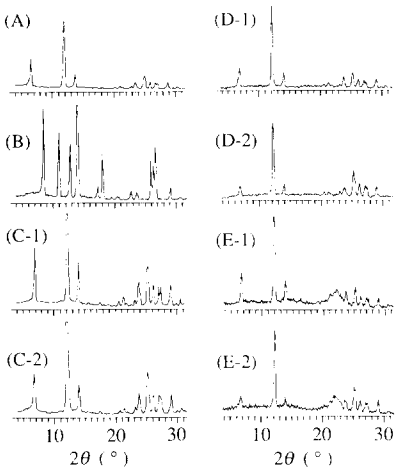

Fig. 2. X-ray diffraction patterns of theophylline and the powder mixtures. (A) Anhydrous theophylline, (B) theophylline monohydrate, (C) theophylline used in the experiment, (D) powder mixture; theophylline/sodium caseinate = 1:1 w/w, (E) powder mixture; theophylline/sodium caseinate/MCC = 1:1:1 w/w. (C-1), (D-1) and (E-1), before MH treatment; (C-2), (D-2) and (E-2), after MH treatment.

3.3. Water absorption profile of the solid mass

The results of the water absorption test on the solid mass containing various amounts of theophylline are demonstrated in Fig. 3. The solid mass absorbed water very rapidly within 30 s, and then the amount of water absorbed gradually decreased. In the solid mass containing theo-

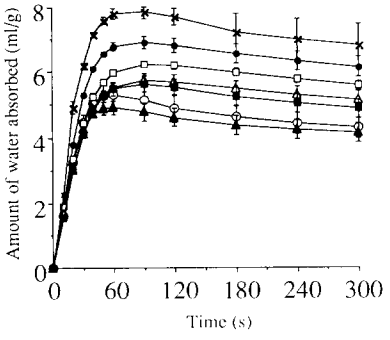

Fig. 3. Water absorption profiles of solid mass containing various amounts of theophylline. Theophylline content in 1 g solid mass: (×) 0 mg, (●) 5 mg, (□) 10 mg, (△) 20 mg, (■) 30 mg, (○) 100 mg, (▲) 200 mg. Each point represents the mean ± S.D. of three determinations.

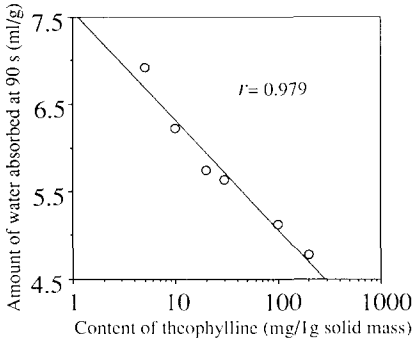

Fig. 4. Relationship between amount of water absorbed and theophylline content in the solid mass. The amount of water absorbed is shown as the value at 90 s in Fig. 3. r, correlation coefficient.

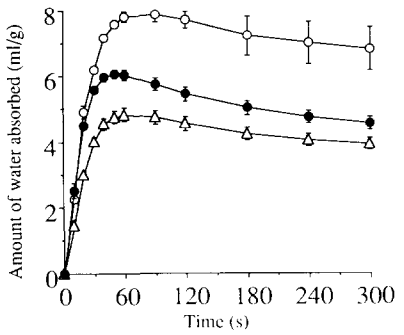

Fig. 6. Water absorption profiles of solid mass containing caffeine or xylitol. (○) Drug-free solid mass, (△) caffeine 100 mg in 1 g solid mass, (●) xylitol 100 mg in 1 g solid mass. Each point represents the mean ± S.D. of three determinations.

phylline, the amounts of water absorbed were much lower than those of theophylline-free solid mass. Fig. 4 shows the relationship between the theophylline content of the solid mass and the amount of water absorbed at 90 s. The amount of water absorbed decreased with increasing theophylline content. A plot of log theophylline content vs absorbed water gave a near-straight line over the range of 5–200 mg theophylline.

To investigate the effects of theophylline in the fluid on the water absorption behavior in the solid mass, theophylline solutions of varied concentrations were used as the test fluids. Fig. 5 depicts the influence of theophylline concentrations on the amount of theophylline solution absorbed by the theophylline-free solid mass. A greater amount of water was absorbed using distilled water than the theophylline solutions. In a previous report (Watanabe and Sugihara, 1992), we showed that the water absorption properties of the solid mass were influenced by electrolytes in the absorbed fluids, probably because electrical repulsion of the polymer might be affected by electrolytes. Thus, the reasons for the decrease in the amount of fluids absorbed with the use of theophylline solutions might be attributed to the presence of ionized theophylline in the fluids. The water absorption profiles of the solid mass containing caffeine and xylitol are illustrated in Fig. 6. Both caffeine and theophylline are xanthine derivatives and their physicochemical properties seem to be similar. Xylitol, in contrast, did not dissociate in water. If the decrease in water absorption was due only to the disappearance of electrical repulsion caused by ionized theophylline, decreased water absorption would be observed only for the solid mass containing caffeine, and not for that containing xylitol. The amount of water absorbed by the solid mass containing caffeine was as low as that by solid mass containing theophylline. While xylitol did not dissociate like theophylline, the amount of water absorbed by the solid mass containing xylitol decreased in a similar fashion to that containing theophylline. Johnson et al. (1991) reported similar phenomena in tablets formulated with superdisintegrant and lactose. Since lactose is water-

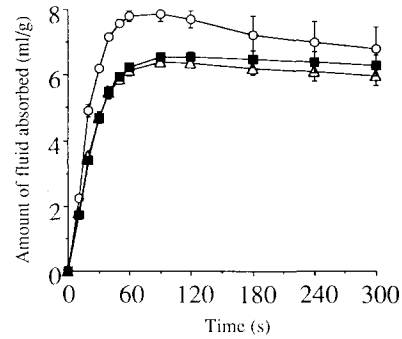

Fig. 5. Influence of theophylline concentration on fluid absorption profile of theophylline-free solid mass. Theophylline concentration of fluid: (○) 0 mg/ml, (■) 2 mg/ml, (△) 5 mg/ml. Each point represents the mean ± S.D. of three determinations.

soluble, it dissolves and forms a diffusion barrier layer of saturated lactose solution around the tablet. This diffusion layer may impede the availability of water to the super-disintegrant, thus slowing the rate of water entry. This mechanism was applicable to the solid mass containing xylitol or theophylline. Consequently, it is presumed that the decreased water absorption behavior of the solid mass containing theophylline would be due to both the blocking of pores by saturated theophylline solution formed by penetrated water and the disappearance of electrical repulsion of polymer by ionized theophylline in the fluid.

3.4. Gel strength of the swollen mass

The solid mass containing theophylline showed poorer swelling features than the theophylline-free solid mass, corresponding to the small amount of absorbed water (data not shown). No clear break point, at which a sudden drop of the load was observed, was obtained from the curve of the solid mass containing theophylline. The gel strength, defined as the load at break point, was estimated as 103.7 g for the theophylline-free solid mass, but could not be determined for that containing theophylline. The relationship between stress and strain (the slope of the curve), i.e., the elastic modulus, was similar in both swollen masses.

3.5. Theophylline release profiles

Previously, we showed that the amount of fluid absorbed by the solid mass in the test fluid decreased in the order of distilled water, JP XII disintegration test fluid no. 2, and JP XII disintegration test fluid no. 1 (Watanabe and Sugihara, 1992). The release profiles of theophylline from the solid mass containing theophylline 100 mg in 1 g solid mass are shown in Fig. 7; the fastest release was observed in distilled water, and the slowest in JP XII disintegration test fluid no. 1. The release rate of theophylline from the solid mass in distilled water was slower than that of theophylline powder in distilled water. The order of release rates of theophylline in those fluids was the same as that observed in the amount of

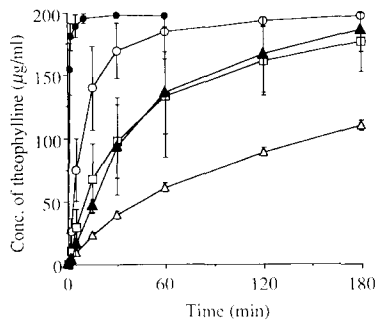

Fig. 7. Release profiles of theophylline from the solid mass at 37°C. Dissolution test fluids: (○) distilled water, (△) JP XII disintegration test fluid no. 1, (□) JP XII disintegration test fluid no. 2. (▲) Solid mass (MH treatment, 115°C for 60 min) tested in distilled water. (●) Powder of intact theophylline tested in distilled water. The theophylline content of all samples was 100 mg. Each point represents the mean ± S.D. of three determinations.

fluid absorbed. Fig. 7 also shows that the release rate of theophylline from the solid mass prepared by severe MH treatment (115°C, 60 min) was slower than that from the solid mass obtained by the usual MH treatment (115°C, 10 min). We reported previously that more severe MH treatment led to an increase in the extent of cross-linking of the peptide chain (Watanabe and Sugihara, 1992). The results shown in Fig. 7 suggest that the state of protein cross-linking within the solid mass had a significant effect on the release rate of theophylline.

Fig. 8 shows the Higuchi (1961) plots (square

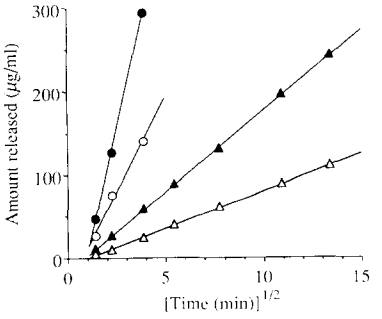

Fig. 8. Plot of the amount of theophylline released from solid mass against the square root of time. Theophylline content 100 mg: (○) distilled water, (△) JP XII disintegration test fluid no. 1. Theophylline content 200 mg: (●) distilled water, (▲) JP XII disintegration test fluid no. 1.

Table 1
Theorphylline release data fitting to Eq. 1

Test medium	Amount of theophylline of solid mass (mg)	Kinetic constant (k) (min^{-n})	Release exponent (n)	Correlation coefficient (r^2)
Water	100	8.275	0.822	0.960
Water	200	6.600	0.908	0.990
JP XII disintegration test fluid no. 1	100	1.489	0.722	0.991
JP XII disintegration test fluid no. 1	200	2.026	0.677	0.986

root of time vs the amount of theophylline released) for the release profiles of theophylline from the solid mass containing 100 and 200 mg theophylline in 1 g solid mass. The release rate of theophylline from the solid mass containing 200 mg theophylline was about twice that of the solid mass containing 100 mg theophylline. The plots showed a good linear relationship, indicating that theophylline release from the swollen mass was caused by a diffusion-controlled mechanism (Higuchi, 1961).

The fraction of theophylline released from the solid mass was analyzed using the relationship (Korsmeyer et al., 1983):

$$M_t/M_\infty = k \cdot t^n \quad (1)$$

where M_t and M_∞ are the amount of theophylline released up to time t and at equilibrium, respectively, k denotes a kinetic constant (min^{-n}), n is a release exponent, both being characteristic of the matrix-eluant system, and t represents the duration of release. The release exponent n characterizes the mechanism of release: $n = 0.5$ indicates release by a diffusive (Fickian) mechanism, $n = 1$ is characteristic of zero-order drug release, and the limit defined as $0.5 < n < 1$ indicates anomalous diffusion. The calculated values of the kinetic constant (k) and the diffusional exponent (n) are listed in Table 1. The analysis of release profile from the solid mass suggested an anomalous character of theophylline transport (n = 0.677–0.908). The non-Fickian type diffusion might be due to the swelling of the matrix and the dissolution of protein in the swollen mass.

3.6. Other factors influencing the release rate of theophylline

In practice, the solid mass was usually administered after swelling. Theophylline release from the solid mass in JP XII disintegration test fluid

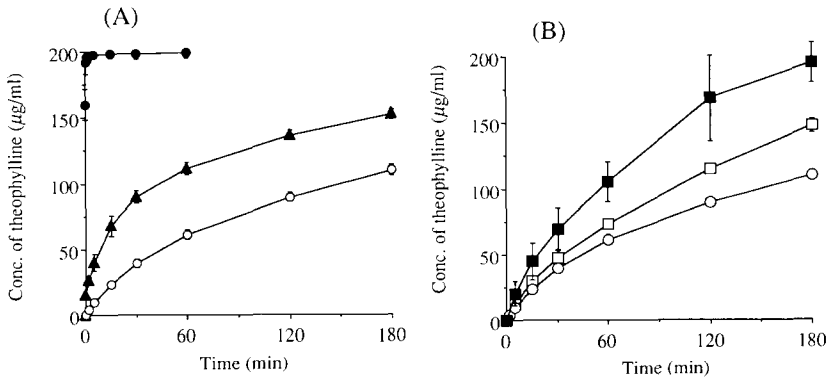

Fig. 9. Release profiles of theophylline from the solid mass (theophylline 100 mg) under various test conditions at 37°C. (A) State of solid mass: (○) intact, (▲) preswollen for 5 min, (●) destroyed swollen mass after the addition of distilled water. (B) Release profiles in JP XII disintegration test fluid no. 1. Concentration of saccharated pepsin: (○) 0%, (□) 1%, (■) 3%. Each point represents the mean ± S.D. of three determinations.

no. 1 was investigated after swelling with distilled water for 5 min. Fig. 9A shows the effects of pre-swelling and mass destruction on the theophylline release profile for the solid mass containing 100 mg of theophylline. In the pre-swollen sample, the initial release rate of theophylline was very fast and decreased gradually. The solubility of sodium caseinate is remarkably low at pH 1.5 (Millar and Corrigan, 1991). The release profile of theophylline was attributed to the change of the looser structure of the network to a tighter form and the formation of the insoluble protein. The swollen mass may be destroyed when administered or swallowed. Therefore, a release test was performed after the destruction of the swollen mass by pressing it out through a 50 ml syringe to evaluate the effect of the swollen mass size on the release of theophylline. Indeed, theophylline was released quickly from the destroyed swollen mass even in JP XII disintegration test fluid no. 1.

As the main component of the solid mass was sodium caseinate protein, it would be digested by enzymes in the stomach. To investigate the effects of digestion of the solid mass on theophylline release, the release test was performed in JP XII disintegration test fluid no. 1 containing saccharated pepsin (Fig. 9B) (Murthy et al., 1989). In the dissolution tests, we observed that the solid mass was digested peripherally, with shrinking in size. As shown in Fig. 9B, the theophylline release rate increased with the passage of time. In fluid containing a high concentration of enzyme (3%), theophylline was released more rapidly than at a low enzyme concentration (1%). These phenomena might result from a size change in the solid mass and loosening of the network caused by digestion.

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