Release Profiles of Phenytoin from New Oral Dosage Form for the Elderly

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Utilization of the solid mass containing phenytoin, sodium caseinate and microcrystalline cellulose (MCC) as a new dosage form for the elderly was studied. The solid mass was prepared by treatment of the powder mixture with high pressure steam at 115 °C for 10 min. The stability of phenytoin in the solid mass was confirmed by infrared spectroscopy and high performance liquid chromatography. The extent of swelling of the solid mass containing phenytoin was investigated by water absorption test and gel strength test, and the swelling property was almost independent of the presence of phenytoin. The release profile of phenytoin from the solid mass was determined under various conditions, and was found to be influenced by the extent of swelling and the swollen state. It was observed that the protein adsorption to the phenytoin crystal surface and the addition of digestive enzyme also affected the release profile. In water, the solid mass prepared from a ground mixture of phenytoin and MCC showed remarkable improvement of release profile of phenytoin.

Keywords   elderly; new oral dosage form; phenytoin; stability; dissolution; sodium caseinate

The authors have been studying the utilization of a solid mass formed by treating powder of sodium caseinate and microcrystalline cellulose (MCC) with moist heat in the form of saturated steam under pressure, as a new dosage form for the elderly.[1] In the preceding paper,[2] we selected theophylline as a model drug and investigated the swelling and dissolution characteristics of the solid mass containing theophylline. In this study, poorly water soluble phenytoin was selected as a model drug. The stability of phenytoin, swelling behavior of the solid mass and release behavior of phenytoin from the solid mass were investigated. We also attempted to improve the phenytoin release from the solid mass.

Experimental

Materials Sodium caseinate (Wako Pure Chemical Industries, Ltd., Osaka, Japan, lot No. ECL5496), phenytoin (Fujinaga Seiyaku, Co., Ltd. Tokyo, Japan), JP saccharated pepsin (Fujisawa Astra Co., Ltd., Osaka Japan) and MCC (Avicel® PH101, Asahi Chemical Industry, Co., Ltd., Tokyo, Japan) were used as received. All other chemicals were of reagent grade.

Preparation of Solid Mass The preparation method of the solid mass was previously described in detail.[1] One gram of powder mixture was treated with moist heat in the form of saturated steam under pressure (115 °C, 10 min) using an automatically controlled autoclave for hospital use. After cooling to about 80 °C, the formed solid mass was taken out from the thimble filter and dried for 24 h at room temperature in a vacuum drier. We called this process MH (moist heat) treatment.

Preparation of Ground Mixture The ground mixture was prepared by grinding of 1.5 g of phenytoin and 6.0 g of MCC for 15 h with a Nitto Kagaku ANM-200 automatic mortar (170 mm diameter) and pestle (40 mm diameter).

Infrared (IR) Spectroscopy IR spectra were determined by KBr method using an IR spectrometer (Shimadzu IR-435).

Water Absorption Test Water absorption behavior of solid mass containing phenytoin was evaluated by the manner described previously.[1] In brief, the solid mass was placed on a glass filter which was dampened with water, and the decreased amount of water caused by absorption in swelling of the solid mass was weighed with an electrical balance.

Gel Strength of Swollen Solid Mass Gel strength of swollen mass containing phenytoin was measured with a rheometer (NMR-2001J Fudoh Kogyo Co., Ltd., Tokyo, Japan) as described.[1]

Evaluation of Phenytoin Release Phenytoin release tests from the solid mass were performed by the JP paddle method (paddle rotating speed, 100 rpm) at 37 °C.[2] Water and the first fluid of the JP XII disintegration test were used as test fluids (500 ml). Various amounts of JP saccharated pepsin were dissolved in the first fluid of JP XII disintegration test. After 1 g of the solid mass was added to each test fluid, aliquots of the solution (1 ml) were removed at suitable intervals and filtered through a membrane filter (pore size 0.45 μm). Phenytoin concentration was determined by high performance liquid chromatography (HPLC) as described previously.[3] Analytical conditions of HPLC were as follows: column, Zorbax ODS (4.6 mm i.d. × 15 cm); mobile phase, a mixture of acetonitrile and distilled water (2:3); flow rate, 1.5 ml/min; detector, ultraviolet 200 nm.

In the dissolution test, the solid mass absorbed water and changed to a large swollen mass, which collided with the rotating paddle and was broken. Disintegration of the swollen mass made it difficult to analyze the mechanism of drug release. One gram of solid mass used in this experiment was too large to be tested with the JP XII rotating basket method. Then, in order to prevent the destruction of the swollen mass by collision with the rotating paddle, we put the solid mass into a hemisphere stainless basket as described previously.[2] In the experiment of phenytoin release from the crushed swollen mass, the solid mass was initially swollen by the addition of 50 ml of water: it was then transferred into a 50 ml plastic syringe and was pushed out into each test fluid.

X-Ray Powder Diffractometry Powder X-ray diffraction patterns were obtained using a Rigakudenki 2027 diffractometer. Conditions: target Cu, filter Ni, voltage 30 kV, current 5 mA and scanning speed 4°/min.

Results and Discussion

Stability of Phenytoin after MH Treatment In IR spectra of the powder mixture (phenytoin : sodium caseinate = 1 g : 1 g and phenytoin : sodium caseinate : MCC = 0.1 g : 0.36 g : 0.54 g), no spectral difference was recognized between before and after MH treatment (data not shown). Quantitative analysis of phenytoin in the solid mass was performed by HPLC, and no loss of phenytoin content was observed after MH treatment. It was recognized that during MH treatment phenytoin was extremely stable.

Changes in Water Absorption Behavior of Solid Mass Containing Phenytoin Results of water absorption test of the solid mass are shown in Fig. 1. The amount of absorbed water in the solid mass containing phenytoin (pheny-

toin : sodium caseinate : MCC = 0.1 g : 0.36 g : 0.54 g) was a little less than that of the solid mass containing no phenytoin. In the preceding report,[2] the solid mass containing theophylline showed a significant decrease in amount of absorbed water, because of both the disappearance of the electrical repulsion of the polymer of the mass by the ionized theophylline and the blockade of the pores of the mass for water penetration by saturated solution of theophylline. In the mass containing phenytoin, phenytoin was dissociated little in water and pores needed for water penetration might not have been affected because phenytoin solubility was poor. Consequently, the solid mass containing phenytoin showed only a slight change in the amount of absorbed water compared to the drug free solid mass.

Effect of Phenytoin in Solid Mass on Gel Strength of the Swollen Mass In the swollen mass containing phenytoin (phenytoin : sodium caseinate : MCC = 0.1 g : 0.36 g : 0.54 g) the gel destruction curve profiles were almost the same as in the phenytoin free swollen mass (data not shown). Gel strength and the relationship between stress and strain, that is elastic modulus, of the swollen mass containing phenytoin were thus similar to that of the phenytoin free swollen mass. This suggests that the presence of phenytoin has no effect on the gel strength of swollen mass.

Phenytoin Release Profiles Figure 2a shows release profiles of phenytoin from intact crystalline powder in water and in 0.02% Tween 80 solution. Figure 2b shows release profiles of phenytoin from 1 g of solid mass containing 100 and 200 mg of phenytoin in water and the first fluid of JP XII disintegration test. Release rates of phenytoin in this fluid were significantly smaller than those in water. In an earlier report,[1] the swelling of the solid mass in the first fluid was lowered to as little as one-third that in water. The extent of swelling of the solid mass in various fluids might influence the release profile of phenytoin. In both test fluids, the amount of phenytoin released from the mass containing 200 mg phenytoin was not significantly greater than that from the mass containing 100 mg. As only a very small part of the phenytoin contained in the solid mass could dissolve due to the low solubility of phenytoin ($30.75 \pm 0.04\,\mu g/ml$ in water, $n=3$ and almost the same as in the first fluid of the JP XII disintegration test), the amount of dissolved phenytoin in the mass containing either 100 or 200 mg phenytoin was also almost similar. If the state of the mass was similar, it seemed that the release rate of phenytoin from the solid mass was dependent on the amount of dissolved phenytoin in the mass. The content of phenytoin in the mass thus had no influence on the release profiles from the solid mass.

In contrast with the initial release rate of phenytoin from intact powder in water, the initial release rates from the solid mass were greater (Fig. 2), and decreased gradually. We have already reported that the dissolution rate of phenytoin powder in sodium caseinate solution decreased owing to the adsorption of sodium caseinate protein on the hydrophobic surface of phenytoin crystal.[4] Recovery of the dissolution rate was also reported when Tween 80 was added to the test fluid.[4] As phenytoin crystals within the swollen mass might easily be wet by water, the initial release rate of phenytoin from the solid mass was faster than that of phenytoin powder. This rate gradually decreased, however, because part of the protein dissolved and adsorbed to phenytoin crystals. From Fig 2b, it is also found that addition of Tween 80 to water increased the release rate. In the swollen mass, adsorption of protein to phenytoin crystals might be inhibited by Tween 80 as in phenytoin powder. Higuchi plots (square
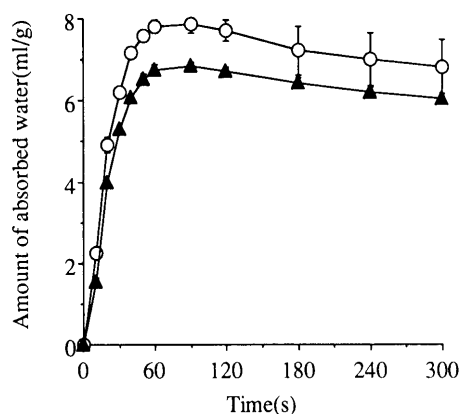

Fig. 1. Water Absorption Profiles of a Solid Mass Containing Phenytoin

Phenytoin content in 1 g solid mass: ○, 0 mg; ▲, 100 mg. Each point represents the mean ± S.D. of three determinations.
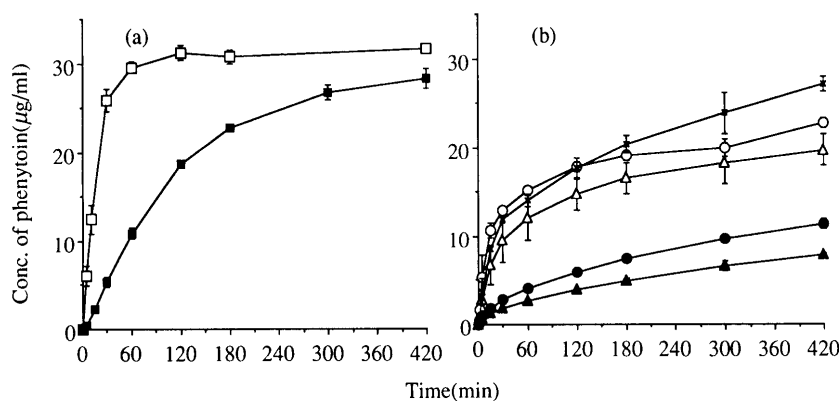

Time(min)

Fig. 2. Release Profiles of Phenytoin from a Solid Mass at 37 °C

(a) Phenytoin crystals 100 mg: ■, water; □, 0.02% Tween 80 solution. (b) The solid mass containing 100 mg phenytoin: △, water; ▲, the first fluid of JP XII disintegration test; ×, 0.02% Tween 80 solution. Solid mass containing 200 mg phenytoin: ○, water; ●, the first fluid of JP XII disintegration test. Each point represents the mean ± S.D. of three determinations.

TABLE I. Fitting of Phenytoin Release Data to Eq. 1

Test medium	Amount of phenytoin of solid mass	Kinetic constant k, h^{-n}	Release exponent n	Correlation coefficient r^2
Water	100 mg	1.872	0.860	0.975
Water	200 mg	3.127	0.915	0.963
JP XII disintegration fluid No.1	100 mg	0.833	0.564	1.000
JP XII disintegration fluid No. 1	200 mg	1.292	0.557	0.999

root of time $vs.$ the amount of phenytoin released) of release profiles showed good linear relationship (data not shown), and indicated that phenytoin release from swollen mass was controlled by the diffusion mechanism.[5]

The phenytoin release data were analyzed using the relationship[6]:

$$Mt/M_{\infty} = k \cdot t^n \qquad (1)$$

where Mt is the amount released at time t, M_{∞} is the total amount released, t is the time (h) and k is a kinetic constant (h^{-n}). The release exponent n characterizes the mechanism of release: exponent takes the value of $n = 0.5$ for Fickian diffusion, value of $0.5 < n < 1$ for anomalous diffusion, and the value of $n = 1$ for zero-order drug release. The values of kinetic constant (k) and the diffusional exponent (n) are listed in Table I. Analysis of the release profile from the solid mass suggested an anomalous nature of phenytoin transport $(n = 0.557 - 0.915)$. A non-Fickian type diffusion of phenytoin from the solid mass might be due to the swelling of the matrix and dissolution of the protein of the swollen mass.

Effect of Destruction of Swollen Mass on the Release Profile of Phenytoin Assuming that destruction of the swollen mass occurred with administration of the solid mass, a release test was carried out after finely destruction of the swollen mass by pressing it out through a 50 ml syringe in order to evaluate the effect of its size on the phenytoin release. The release rate of phenytoin from the destroyed swollen mass was very rapid in the initial dissolution stage, but became very noticeably slow after 30 min (Fig. 3). The concentration of phenytoin at 30 min in tests of the destroyed swollen mass was only about two-thirds of the saturated solubility. For this reason, the decreasing release rate after 30 min seemed not to be due to solubility, but to the adsorption of protein to phenytoin crystals.

Influences of Various Concentrations of Pepsin on the Release Rate of Phenytoin Release tests were carried out in the first fluid of the JP XII disintegration test containing saccharated pepsin (1% and 3%) to investigate the influence of digestive enzyme on phenytoin release rate from the solid mass.[7] As shown in Fig. 4, the initial release rate of phenytoin was similar among 3 test fluids until the network of the swollen mass was destroyed by enzymatic digestion (ca. 30 min). The digestion of casein by pepsin caused the release of phenytoin crystals from the mass, and the released crystals received agitation directly as well as in case of phenytoin powder. With the passage of time, the release of phenytoin increased in terms of protein digestion. No effect of increase in enzyme concentration
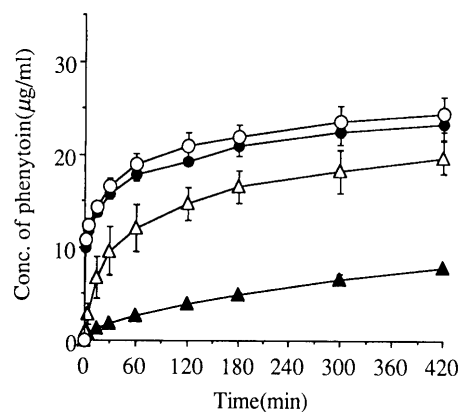

Fig. 3. Release Profiles of Phenytoin from Various Solid Mass States (Phenytoin 100 mg) in Various Test Fluids at 37 °C

Solid mass; △, in water; ▲, in the first fluid of JP XII disintegration test; destroyed state of swollen mass after the addition of water; ○, in water; ●, in the first fluid of JP XII disintegration test.
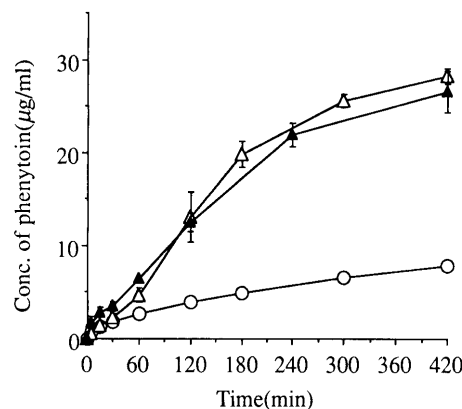

Fig. 4. Effect of Pepsin on Release Profiles of Phenytoin from the Solid Mass (Phenytoin 100 mg) in the First Fluid of JP XII Disintegration Test at 37 °C

Concentration of JP saccharated pepsin: ○, 0%; △, 1%; ▲, 3%. Each point represents the mean ± S.D. of three determinations.
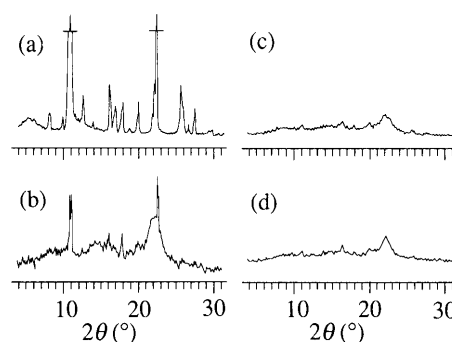

Fig. 5. X-Ray Diffraction Patterns of Phenytoin and Solid Mass

(a) Phenytoin crystals. (b) Physical mixture; phenytoin : sodium caseinate : MCC = 0.1 : 0.36 : 0.54 weight ratio. (c) Powder mixture; phenytoin : sodium caseinate : MCC = 0.1 : 0.36 : 0.54 weight ratio, one part phenytoin was ground with 4 parts MCC. (d) Solid mass prepared by MH treatment of the powder mixture (phenytoin : sodium caseinate : MCC = 0.1 : 0.36 : 0.54 weight ratio, one part phenytoin was ground with 4 parts MCC).

on the release profile of phenytoin was observed.

Improvement of Phenytoin Release from Solid Mass It was reported that the phenytoin ground with MCC showed an improved dissolution profile and bioavailability.[8] MCC was a component of the solid mass and played an
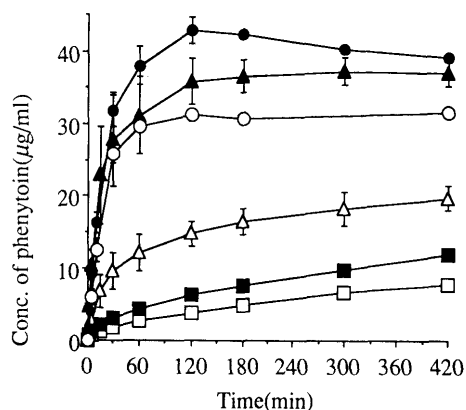
Fig. 6. Release Profiles of Phenytoin from Solid Mass Containing Ground Mixture of Phenytoin and MCC at 37 °C

Phenytoin content was 100 mg. Crystalline phenytoin powder: ○, 0.02% Tween 80 solution. Ground mixture powder of phenytoin and MCC: ●, water. Solid mass containing crystalline phenytoin powder: △, water; □, the first fluid of JP XII disintegration test. Solid mass containing ground mixture of phenytoin and MCC: ▲, water; ■, the first fluid of JP XII disintegration test. Each point represents the mean ± S.D. of three determinations.

important role in its absorption of water.[1] We prepared a ground mixture of phenytoin and MCC (1:4 weight ratio). A solid mass was then prepared by MH treatment of a powder mixture of the ground mixture, MCC and sodium caseinate (0.5:0.14:0.36 weight ratio). The results of powder X-ray diffractometry are shown in Fig. 5. In Fig. 5c, the diffraction peak of phenytoin crystals at $2\theta = 11.0°$[9] has disappeared. Figure 5d shows the diffraction pattern of the solid mass prepared by MH treat-

ment of the powder mixture containing the ground mixture; as in the powder mixture of the ground mixture, the phenytoin crystalline peak was not observed.

It was recognized that phenytoin crystals were in an amorphous state after co-grinding process and MH treatment.

Figure 6 shows the release profiles of phenytoin from the solid mass prepared using the ground mixture of phenytoin and MCC. The release rate in water was remarkably improved and supersaturation of phenytoin was observed. In the first fluid of the JP XII disintegration test, however, the release profile of phenytoin was little improved. This might be attributed to both the insolubility of sodium caseinate and the low swelling property of MH treated sodium caseinate in the first fluid of JP XII disintegration test.

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