Measurement of Rates of Water Penetration into Tablets by Microcalorimetry [1)]

Yasuo YOSHIHASHI,* Midori MAKITA, Shigeo YAMAMURA, Eihei FUKUOKA, and Katsuhide TERADA

School of Pharmaceutical Sciences, Toho University, 2–2–1 Miyama, Funabashi, Chiba 274, Japan.
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A method of measuring the rate of water penetration into tablets was proposed in which a heat conduction microcalorimeter was employed. Heat evolved when the tablets were immersed in water. The rate of generation of the heat was determined by a deconvolution method. The rate of water penetration into tablets when they were placed in water was determined by assuming to correspond to the generation rate of heat. For model experiments of water penetration into tablets, hydrophilic MCC was used as a basic component of the tablet, and hydrophobic phenytoin as an active ingredient. The time required for total water penetration of MCC tablets increased with tablet compression pressure, and the rate of water penetration into the tablets increased with phenytoin content.

Key words liquid penetration rate; tablets; microcalorimetry; deconvolution; microcrystalline cellulose; phenytoin

The penetration rates of liquid into powder beds and tablets have been extensively studied.[2,3)] Since the penetration of liquid into a tablet is the first step in the process of tablet disintegration, measurement of the liquid penetration rate into tablets is especially important. Various methods to measure this rate have been developed,[3)] however, these techniques are only applicable to the tablet penetration rate in one specific direction. In practice, liquid penetrates in all directions from a tablet in the gastrointestinal tract, but there has previously been no means of determining the rate at which this penetration occurs.

In a previous paper,[4)] we determined the generation rate of the heat by applying the deconvolution theory to the calorimetric curves. In this paper, the water penetration rate into tablets in water was determined quantitatively by that same deconvolution method.

MCC was used as a model compound because it is hydrophilic and has been used extensively as a disintegrant in pharmaceutical manufacturing. When the active ingredients are hydrophobic, they are believed to influence water penetration into the tablets. Accordingly, the penetration of water into solid dosage forms is an important factor influencing the bioavailability of hydrophobic active ingredients. We therefore measured the penetration rates of water into tablets containing phenytoin, a hydrophobic active ingredient. Phenytoin is practically insoluble in water and is hydrophobic in nature. Its therapeutic range is relatively narrow, and the plasma level varies from brand to brand, following oral administration in humans.[5)] Yakou *et al.*[5b,6)] suggested that low wettability of phenytoin dosage forms may delay the rate at which it is absorbed and cause this variation in plasma level. Hence, phenytoin was chosen as the active ingredient.

Experimental

Materials MCC (Avicel PH102, Asahi Chemical Industry, Japan) was of JP XII grade; the fraction that passed through a 250 mesh sieve was used. Phenytoin was of JP XII grade, and the fraction that passed through a 100 mesh sieve was used.

Preparation of Powder Samples MCC was used after being dried at 60 °C for 5 h under a vacuum with P_2O_5. Phenytoin was mixed with MCC to make 1, 3, 5 and 10% powder for 10 min in a 50 ml capacity glass micro V-type blender.

Tableting and Tensile Strength Tablets containing 0.3 g MCC or 0.3 g MCC-phenytoin mixture were prepared using an Instron Universal Testing Instrument, Model 1137 (Instron Corporation) equipped with a load cell and an upper punch. The sample powder was compressed under a pressure of 1000—5000 kg/cm^2 with flat-faced punches, in a die of 7.0 mm internal diameter, at a speed of 50 mm/min. The sample powder and tablets were stored in a desiccator containing P_2O_5 under a vacuum until used. Tablet weight was determined and tablet dimensions measured using a hand micrometer. The force causing the tensile failure of tablets under diametrical compression was measured using the above Instron instrument. Density of the powder was measured by an air comparison pycnometer (Beckman Model 930, Beckman-Toshiba, Ltd.). Porosity and the tensile strength[7)] of tablets were subsequently computed.

Microcalorimetry Calorimetric measurements were carried out using the twin type heat conduction microcalorimeter described.[4)] Fifty ml of distilled water was used as solvent. Measurements were carried out at 298.15 K in a room maintained at 298 ± 1 K. The solvent in the reaction vessels was not stirred. The heat of immersion of the powder and tablets was measured in a similar manner to that for heat of the solution described previously.[4)] The heat of immersion of the phenytoin powder itself in distilled water was negligible because little heat was generated.

Measurement of Moisture Content Moisture content was determined using a Karl Fischer titration instrument (Tsutsui Scientific Instruments Co., Ltd.). Moisture content of the sample powder and tablets was close to 0%.

Determination of Water Penetration Rate The input rate can be calculated by deconvolution of the thermogram for a tablet using the thermogram for MCC powder as a characteristic responce in the convolution equation, and is assumed to correspond to the generation rate of heat when MCC particles in the tablets are wet with water. The input rate can be converted into the water penetration rate (dW/dt), where W is the amount of MCC wet with water at time t, expressed as weight. Thus, the penetration rates of water into MCC tablets when the tablets were immersed in water were determined by the deconvolution of the thermograms as described.[4)] All measurements were carried out in triplicate and the average of three runs was used for deconvolution analysis.

Results and Discussion

Analysis of Water Penetration Rate by the Deconvolution Method Heat conduction of the endothermic reaction from the reaction vessel to the constant temperature wall in the calorimeter was earlier confirmed to occur linearly with applied heat.[4)] Therefore, we first examined the linearity for the exothermic reaction because it is well

* To whom correspondence should be addressed.

known that immersion of MCC in water is an exothermic reaction.[8]

When an ampule containing MCC powder was broken in the reaction vessel, fine particles of MCC were instantaneously dispersed into the distilled water. Therefore, the heat caused by immersion of MCC powder in water was assumed to generate instantaneously. Figure 1 shows the thermograms for the immersion of different amounts of MCC powder. They exhibited instantaneous heat evolution with maximal ΔT which was proportional to the content of MCC powder. Therefore, the exothermic reaction in the immersion of MCC powder also occurs linearly with the amount of powder.

Figure 2 shows the relationship between heat evolved with immersion of MCC powder and the amount of powder. A linear relationship was obtained in the measured weight range of 0 to 0.4 g. These results indicate that the thermogram for the immersion of MCC powder can be regarded as an impulse response, while those of MCC tablets can be viewed as a response resulting from arbitrary input.

Influence of Compression Pressure on the Penetration Profiles of Water into the MCC Tablets in Water The effect of compression pressure on the penetration profiles of water into tablets was investigated. Figure 3 shows the thermograms for the immersion of the MCC tablets prepared under various compression pressures. The maximum temperature difference (ΔT) to water penetration appeared within 3 min.

The peak time (time to reach maximum ΔT) increased with the compression pressure, indicating that the pene-

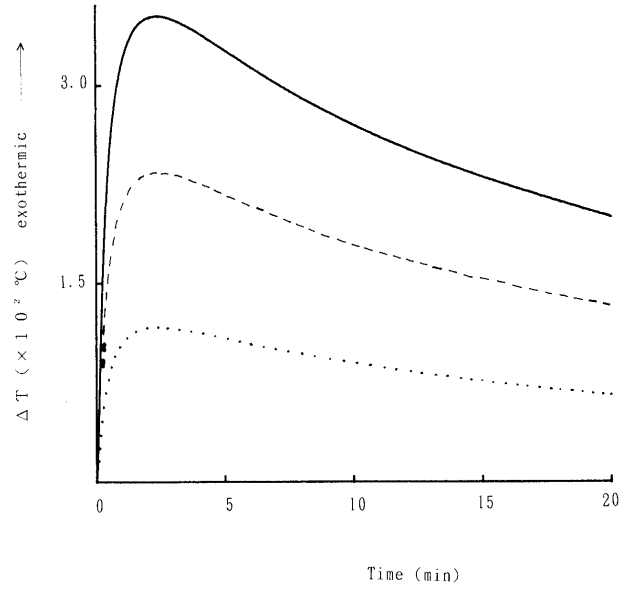

Fig. 1. Thermograms for Immersion of MCC Powder
——, 0.3 g; – – –, 0.2 g; ·····, 0.1 g.

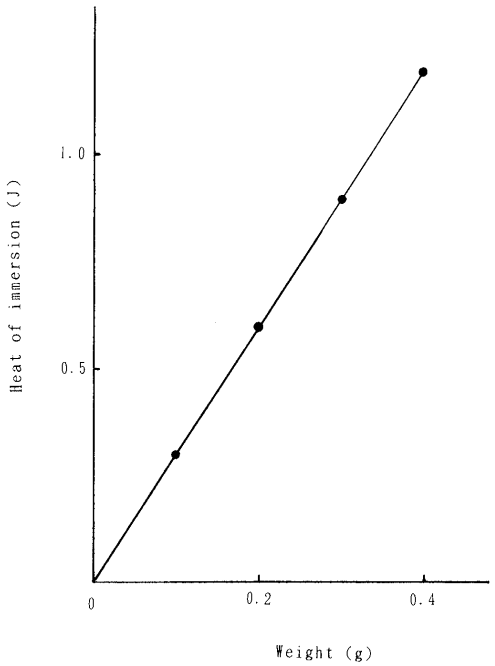

Fig. 2. Relationship between Weight and Heat of Immersion of MCC Powder

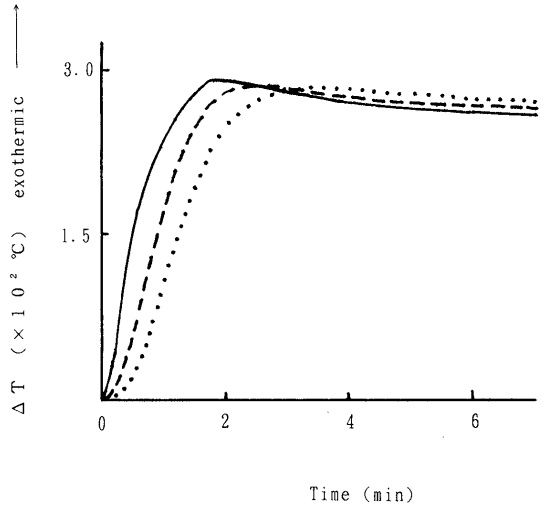

Fig. 3. Thermograms for Immersion of MCC Tablets Prepared under Various Compression Pressures
——, 1000 kg/cm²; – – –, 3000 kg/cm²; ·····, 5000 kg/cm².

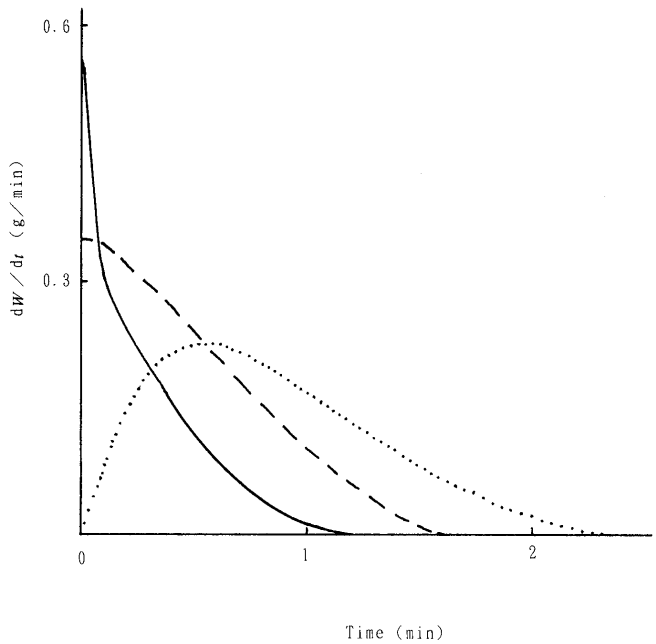

Fig. 4. Penetration Rates (dW/dt) of MCC Tablets Prepared under Various Compression Pressures
——, 1000 kg/cm²; – – –, 3000 kg/cm²; ·····, 5000 kg/cm².

tration time of water into the tablets increased with the compression pressure. The rates of water penetration into the immersed tablets obtained by the deconvolution method are shown in Fig. 4.

As expected from the thermograms shown in Fig. 3, the time required for complete water penetration increased with the compression pressure. Penetration rate thus differed with compression pressure of the tablet. $\Delta W/dt$ of the tablets prepared under compression pressures of 1000 and 3000 kg/cm^2 decreased with time. This indicates that the water penetration into the tablets was rapid with tablet disintegration. Unlike the tablets compressed under 1000 and 3000 kg/cm^2, dW/dt of the tablets compressed under 5000 kg/cm^2 increased gradually, reached a maximum, and then decreased, suggesting that tablet disintegration occurred slowly.

Since the porosity and tensile strength are largely determined by the compression pressure and this influence of the compression examined (Fig. 5).

The tensile strength increased and porosity decreased with increase in compression pressure, indicating that the capillary radius decreased and the interparticle bonding increased with compression pressure increase. Since the penetration rate decreased with compression pressure increase, this rate responds to the increase in tensile strength and decrease in porosity. Comparison of the water penetration rate between the tablets compressed under 3000 and 5000 kg/cm^2 showed the latter to be slower, although the tensile strength and porosity were slightly altered by both pressures. Therefore, it is likely that the delay in water penetration for the tablet compressed under 5000 kg/cm^2 is attributable to the smaller capillary radius.

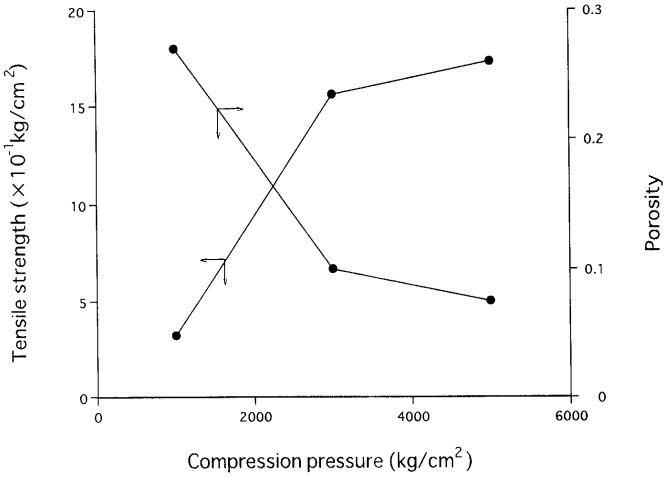

Fig. 5. Relationship between Compression Pressure and the Tensile Strength or Porosity of MCC Tablets

Influence of Compression Pressure on the Rates of Water Penetration into MCC Tablets Containing Phenytoin

Phenytoin is hydrophobic in nature, and its particles in tablets may modify the interparticle bonding during tablet compression and disintegration, so the rate of water penetration into tablets containing 10% phenytoin was determined. Figure 6 shows the thermograms for the immersion of tablets prepared under various compression pressures.

The peak times for the tablets containing phenytoin were longer than those for the MCC tablets, and the period of induction of water penetration was only observed in the tablets containing phenytoin. These results are attributable to the hydrophobicity of phenytoin. The water penetration rate for tablets compressed under 5000 kg/cm^2 was far slower than those for tablets compressed under 1000 and 3000 kg/cm^2. The thermograms on the tablets compressed under the two lower pressures resembled each other, but those compressed under 5000 kg/cm^2 differed greatly in peak time and induction period of the water. The penetration rates are shown in Fig. 7.

Comparison of the penetration profiles between MCC tablets and tablets containing phenytoin showed the latter to have a time lag; the time required for complete penetration was longer than that in MCC tablets. The effect of compression pressure on the tensile strength and porosity was also examined, and these results are shown in Fig. 8.

As can be seen from Figs. 5 and 8, the tensile strength and porosity of the tablets containing phenytoin are similar to those for MCC tablets: the tensile strength increased and porosity decreased with compression pressure. The tensile strength of tablets containing phenytoin was slightly lower at each compression pressure, while

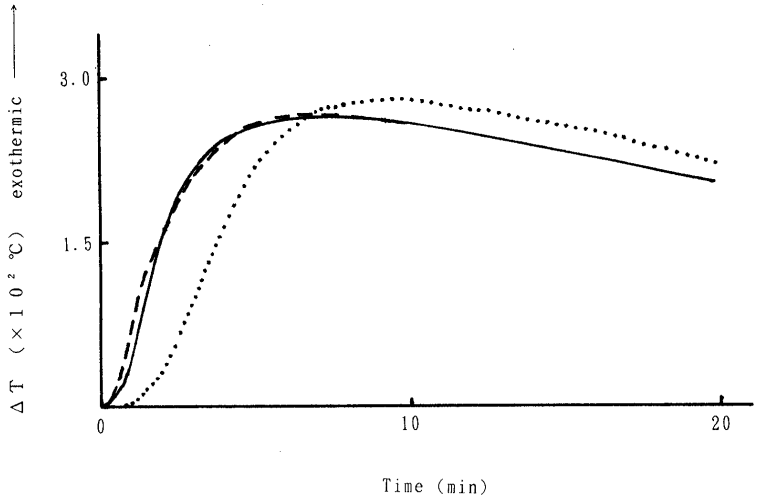

Fig. 6. Thermograms for Immersion of the Tablets Containing 10% Phenytoin Prepared under Various Compression Pressures
——, 1000 kg/cm^2; – – –, 3000 kg/cm^2; ·····, 5000 kg/cm^2.

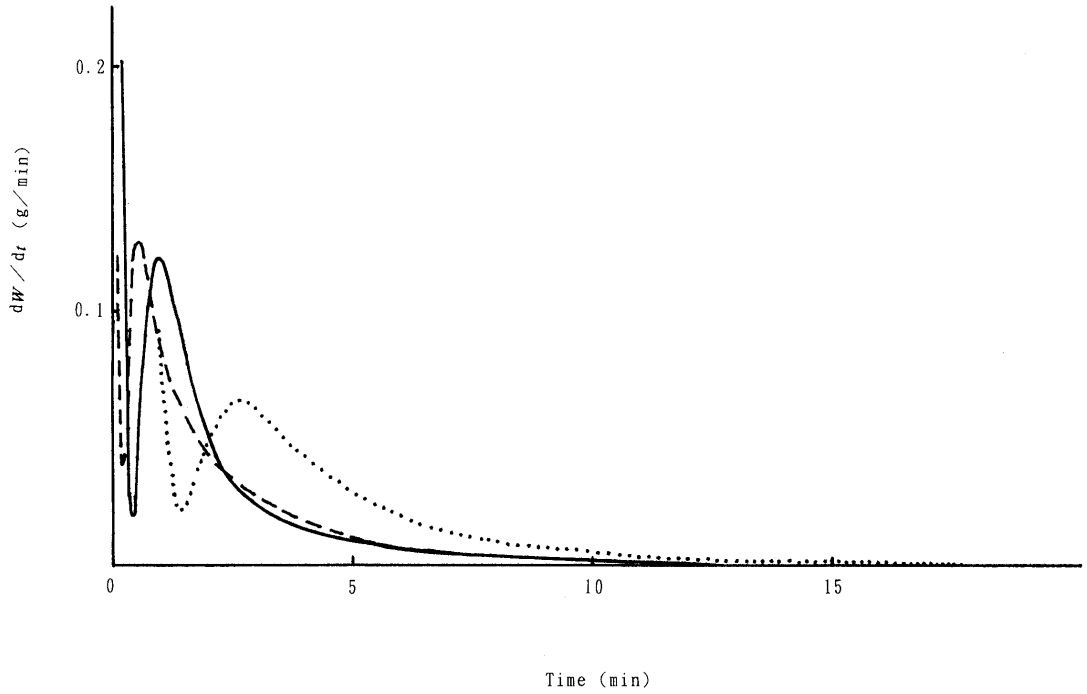

Fig. 7. Penetration Rates (dW/dt) of the Tablets Containing 10% Phenytoin Prepared under Various Compression Pressures
——, 1000 kg/cm^2; – – –, 3000 kg/cm^2; · · · · · ·, 5000 kg/cm^2.

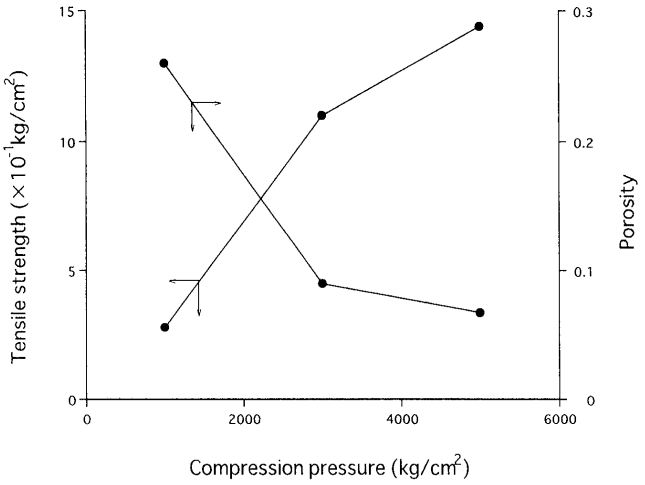

Fig. 8. Relationship between Compression Pressure and the Tensile Strength or Porosity of Tablets Containing 10% Phenytoin

porosity was similar to that for MCC tablets. The water penetration into the tablets containing phenytoin was slower than that of MCC tablets, however, indicating that the hydrophobicity of phenytoin greatly contributed to the decrease in this rate.

As shown in Fig. 7, the penetration rate profiles of the tablets containing phenytoin were similar regardless of compression pressure, and were different from those of MCC tablets. This can be explained by the change in penetration rate during tablet disintegration. In phenytoin tablets, disintegration took place relatively early (beginning at the valley in the rate profile). Initially, the penetration rates were gradually reduced; however, after tablet disintegration started, penetration occurred rapidly, then, gradually slowed again following complete tablet disintegration.

In this system, the penetration rates were not greatly influenced by the compression pressure in the range of 1000 to 3000 kg/cm^2, while the water penetration profile into tablets compressed under 5000 kg/cm^2 differed, and was similar to that for MCC tablets.

Effect of Phenytoin Amount on Penetration Rates The influence of varying amounts of phenytoin on the penetration rates of water was examined (Fig. 9).

Similar penetration profiles were obtained regardless of phenytoin content. In spite of the hydrophobicity of phenytoin, the penetration rate increased with quantity of this substance in the tablets. This can be explained by alteration of the capillary radius and interparticle bonding of the tablets. The effect of phenytoin content on the tensile strength and porosity of the tablets was then examined (Fig. 10).

As can be seen, porosity changed little with the increase in phenytoin content, although tensile strength gradually decreased. These results suggested that the radius of the capillary varied little in spite of variation in amount of phenytoin, while the interparticle bonding decreased with phenytoin increase. We cannot explain the increase in water penetration rate with phenytoin content only by the decrease in interparticle bonding, however, a theory proposed by Matsumaru[9] may help explain this. According to his theory, the force separating the two faces acts on the outside along these surfaces when the hydrophobic and hydrophilic faces are present in the neighborhood, and water penetrates into the field.

In the phenytoin tablets, the force separating the hydrophobic and hydrophilic material would have increased with phenytoin content, so that tablet disintegration would have occurred readily during the water penetration.

Conclusion

The rates of water penetration into MCC tablets and

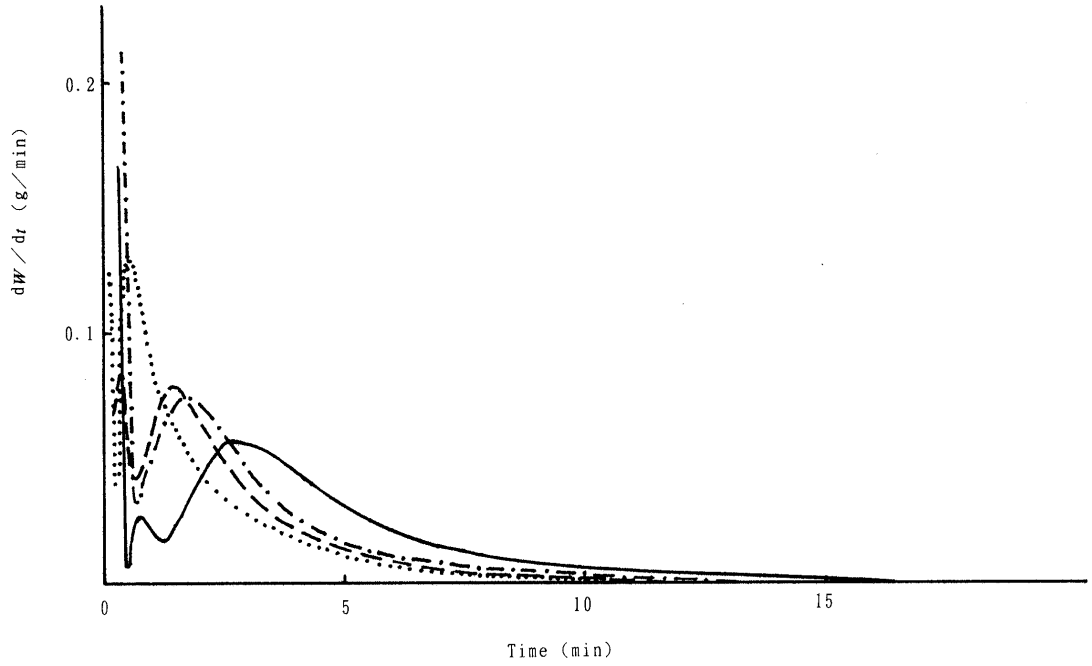

Fig. 9. Penetration Rates (dW/dt) of Tablets Containing Phenytoin of Various Concentrations Prepared under Compression Pressure of 3000 kg/cm^2

——, 1%; –·–·–, 3%; – – –, 5%; ·····, 10%.

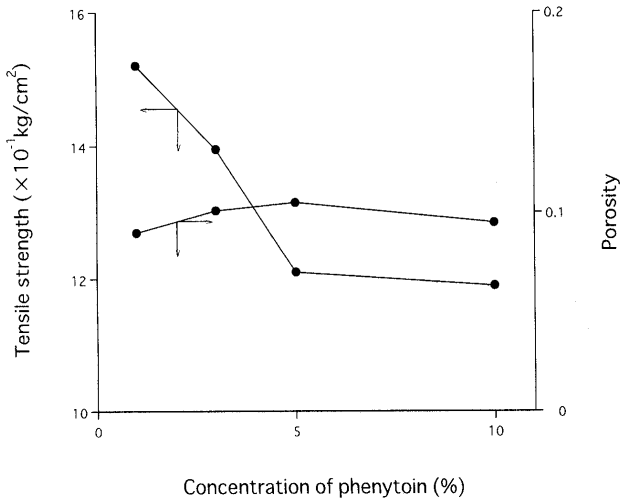

Fig. 10. Relationship between the Tensile Strength or Porosity and Phenytoin Concentrations in Tablets Prepared under Compression Pressure of 3000 kg/cm^2

those containing phenytoin as a function of tablet-compression pressure and phenytoin content were determined by the deconvolution of the thermograms obtained from microcalorimetry. The rates of penetration into MCC tablets and those containing 10% phenytoin compressed under 5000 kg/cm^2 were found to be the slowest, and this was responsible for the reduction in capillary radius of the tablets. However, abnormal water penetration behavior was demonstrated by the change of phenytoin content in tablets compressed under 3000 kg/cm^2 pressure. In spite of the hydrophobicity of phenytoin, the water penetration rates increased as its content increased. These results may be attributed to the decrease in interparticle bonding, and the increase in force separating the hydrophobic and hydrophilic material. Using this method, the water penetration behavior into tablets was quantitatively determined, and the technique has the advantage of measuring the liquid penetration into tablets under a condition simulating that of the gastrointestinal tract.

References and Notes

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