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# Effects of Tableting Pressure on Hydration Kinetics of Theophylline Anhydrate Tablets

MAKOTO OTSUKA*, NOBUYOSHI KANENIWA, KATSUMI KAWAKAMI† AND OSAMU UMEZAWA†

*School of Pharmaceutical Sciences, Showa University and †Department of Pharmacy, Showa University Hospital, Hatanodai 1-5-8, Shinagawa, Tokyo 142, Japan*

**Abstract**—The effects of tableting pressure on hydration kinetics of types I and II theophylline anhydrate tablets at 95% relative humidity, 35°C, have been studied by using various kinetic equations. Relations between tablet expansion and hydration were studied. Samples of 2 cm diameter tablets (1 g) were compressed at 5, 10 and 20 MPa. The hydration of types I and II tablets decreased with increased tableting pressure. The time required for 50% hydration of 2 cm diameter tablets, compressed at various pressures suggests that the tablet hydration rate was affected by the tableting pressure. Types I and II tablets expanded 11·37–16·75% in volume during hydration to the monohydrate. The thickness expansion of the tablets exceeded the diameter expansion as the tablet structure was not uniform owing to the orientation of particles during the compression. The final expansion ratio of the tablets increased with increased tableting compression pressure. The Hancock Sharp constant (m) and fitting of the kinetic data to a suitable model suggested that the hydration of theophylline anhydrate tablets followed the two-dimensional phase boundary equation (type I tablets) or the three-dimensional phase boundary equation (type II tablets).

Some anhydrates of pharmaceuticals are transformed into hydrates at high relative humidity, and this affects their bioavailability through effects on the dissolution rate. Shefter & Higuchi (1963) reported that the anhydrate of theophylline was more soluble than the monohydrate. Therefore, if theophylline anhydrate transforms into the monohydrate at high humidity, in-vitro dissolution rate and bioavailability will decrease. We have shown that type I theophylline anhydrate is more stable than type II at high humidity (Otsuka et al 1990).

Lee et al (1965) reported on the stability of aspirin and ascorbic acid in tablet matrices at high relative humidity. Wakimoto et al (1969) reported moisture absorption and expansion of tablets containing starch and microcrystalline cellulose. They concluded that the expansion volume of corn starch and microcrystalline cellulose increased with increase in relative humidity, and the absorption rate decreased with increase in tableting pressure. Sangekar et al (1972) reported on the effects of moisture on tablet hardness and disintegration time. Otsuka et al (1976, 1978) reported on moisture and volume expansion of anhydrate and amorphous lactose tablets. Those authors concluded that the anhydrate tablet expanded by recrystallization of monohydrate from the solution resulting from absorption of water vapour, but the expansion of amorphous tablets at low humidity was due to hygroscopic swelling without crystallization. The hydration of anhydrate drug tablets will cause the hardness, dissolution rate, and disintegration behaviour of tablets to change, and the bioavailability of the tablets to be affected.

In the present study, we investigated the hydration and expansion of theophylline anhydrate tablets by a kinetic method, and their physicochemical stability at high humidity.

* Present address and correspondence: M. Otsuka, Department of Pharmaceutical Technology, Kobe Women's College of Pharmacy, Motoyama-Kitamachi 4-19-1, Higashi-Nada-ku, Kobe-shi 658, Japan.

## Materials and Methods

### *Materials*

Theophylline (Pharmacopeia Japonica XI) was used; saturated aqueous solution of theophylline was evaporated to dryness at 95°C for 24 h to obtain type I theophylline anhydrate, as described by Otsuka et al (1990). Type II theophylline anhydrate was converted to monohydrate by desorption at 100°C for 24 h. Sample powders were passed through a No. 42 mesh screen (350 μm). The specific surface area (Sw), average particle diameter (d), and density (D) of types I and II theophylline anhydrate were measured as described by Otsuka et al (1990) and are summarized in Table 1.

### *Preparation of tablet*

Tablets (1 g) were compressed by a 2 cm diameter punch and die for infrared spectrum analysis at compression pressures of 5, 10 and 20 MPa for a total compression time of 30 min. The surface area, volume, thickness and diameter of tablets are summarized in Table 2.

### *Powder X-ray diffraction analysis*

Powder X-ray diffraction was measured at room tempera-

Table 1. Specific surface area (Sw), particle diameter (d) and powder density (D) of theophylline anhydrate (Otsuka et al 1990).

| Material | Sw ± s.d.[a] ($cm^2 g^{-1}$) | d ± s.d.[a] (μm) | D ± s.d.[a] ($g cm^{-3}$) |
|---|---|---|---|
| Type I | 3304 ± 13 | 12·01 ± 0·07 | 1·513 ± 0·031 |
| Type II | 1954 ± 48 | 20·39 ± 0·49 | 1·499 ± 0·004 |

a, standard deviation (n = 3).

Table 2. Surface area (S), thickness (T), diameter, weight porosity and tablet expansion ratio (R) of diameter and thickness of theophylline anhydrate tablet.

| Material Compression (MPa) | S (s.d.) ($cm^2$) | T (s.d.) (cm) | Diameter (s.d.) (cm) | Weight (s.d.) (g) | Porosity (s.d.) | R (s.d.) |
|---|---|---|---|---|---|---|
| Type I | | | | | | |
| 5 | 4·917 (0·042) | 0·276 (0·005) | 2·012 (0·001) | 1·028 (0·015) | 0·2268 (0·0046) | 7·301 (0·127) |
| 10 | 4·744 (0·016) | 0·2480 (0·003) | 2·012 (0·002) | 1·013 (0·084) | 0·1521 (0·0035) | 8·121 (0·099) |
| 20 | 4·648 (0·029) | 0·2323 (0·003) | 2·011 (0·001) | 1·0120 (0·006) | 0·0985 (0·0037) | 8·637 (0·086) |
| Type II | | | | | | |
| 5 | 5·022 (0·032) | 0·291 (0·004) | 2·092 (0·073) | 1·028 (0·022) | 0·2683 (0·0052) | 6·907 (0·074) |
| 10 | 4·792 (0·035) | 0·257 (0·004) | 2·010 (0·001) | 1·029 (0·020) | 0·1674 (0·0042) | 7·807 (0·019) |
| 20 | 4·683 (0·014) | 0·239 (0·031) | 2·011 (0·020) | 1·026 (0·010) | 0·1076 (0·0019) | 8·426 (0·114) |

s.d., standard deviation (n = 3).

ture (22°C) with a type JDX 7E diffractometer (Nihon Denshi Co. Ltd). The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; time constant, 2 s; measured from $2\theta = 3°$ to $2\theta = 40°$.

*Measurement of water content, thickness and diameter of tablets*

Sample tablets were placed on a holder made of steel wire and removed from the steel plate. They were stored at 95% relative humidity in a desiccator containing saturated $K_2SO_4$ solution at 35 ± 1°C. The water content was determined by weight. The diameter and thickness of the tablets were measured with a micrometer.

## Results

*Hydration of theophylline anhydrate tablets*

Fig. 1 and Table 3 show the hydration curves and the time required for 50% hydration ($t_{\frac{1}{2}}$) of types I and II tablets compressed by various pressures at 95% relative humidity at 35°C. The anhydrate was transformed into monohydrate after 200 h in all tablets. The hydration rates of types I and II tablets decreased with increased tableting pressure. After hydration of the tablets, the powder X-ray diffraction profiles of deagglomerated tablet agreed with that of a typical monohydrate.

*Tablet expansion of types I and II during hydration*

Figs 2 and 3 show the percent tablet expansion of types I and II at 95% relative humidity and 35°C. Types I and II tablets expanded 11·37–16·75% of tablet volume during hydration to a monohydrate. The final percent expansion, porosity and expansion ratio (R) of tablets are shown in Table 4. The thickness expansion of tablets exceeded the diameter expansion. The R of the tablets increased with increased tableting compression pressure. Type I tablets expanded more than type II.

*Hydration kinetics of types I and II tablets*

The hydration process of types I and II tablets at 95% relative humidity and 35°C were analysed by the method of Hancock & Sharp (1972; see Table 5) and the results are shown in Fig. 4. The Hancock–Sharp constant (m) of various kinds of type I and II tablets was calculated by the least-squares method and the results are summarized in Table 6.

Figs 5 and 6 show the predictions of model equations (Table 5) for the isothermal hydration of various kinds of

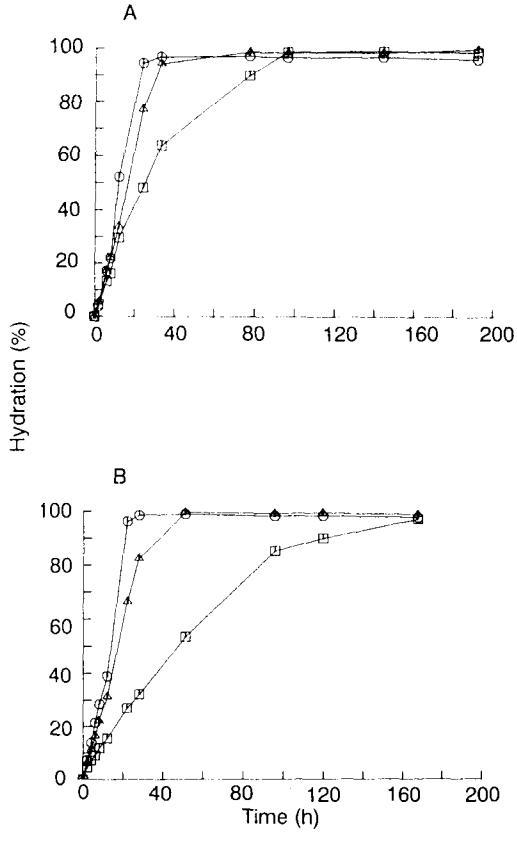


FIG. 1. Hydration profiles of types I (A) and II (B) tablets at 95% relative humidity and 35°C. □, 20 MPa; △, 10 MPa; ○, 5 MPa.

Table 3. Time required for one-half hydration ($t_{\frac{1}{2}}$) of tablets of theophylline anhydrate.

| Material Compression (MPa) | $t_{\frac{1}{2}} \pm$ s.d.[a] (h) |
|---|---|
| Type I | |
| 5 | 12·9 ± 0·4 |
| 10 | 16·5 ± 0·5 |
| 20 | 25·1 ± 0·9 |
| Type II | |
| 5 | 13·9 ± 0·4 |
| 10 | 17·4 ± 0·6 |
| 20 | 47·4 ± 2·3 |

a, standard deviation (n = 3).

type I and II tablets. Values in the range of 5–95% fractional hydration were used as data for analysis of the hydration mechanism. The plots were estimated using the least-squares method. The Hancock–Sharp constant (m) values and the kinetic model fitting suggest that the hydration of theophylline anhydrate tablets proceeded as follows: The hydration of type I tablets compressed at 5, 10 and 20 MPa followed the two-dimensional phase boundary equation (R2), but that of type II tablets compressed at 5, 10 and 20 MPa followed the three dimentional phase boundary equation (R3).

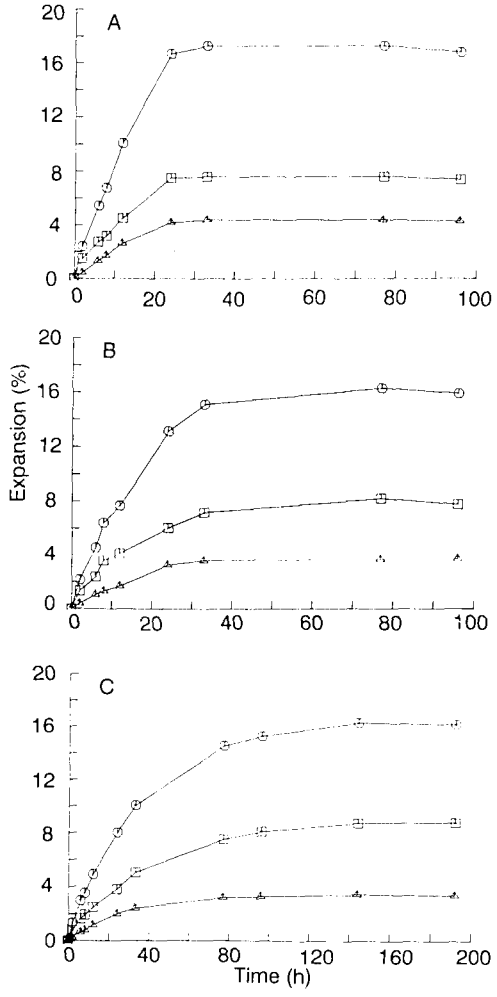


FIG. 2. Tablet expansion profiles of type I tablets at 95% relative humidity and 35°C. (A), 20 MPa; (B), 10 MPa; (C), 5 MPa. ○, Tablet volume; □, tablet thickness; △, tablet diameter.

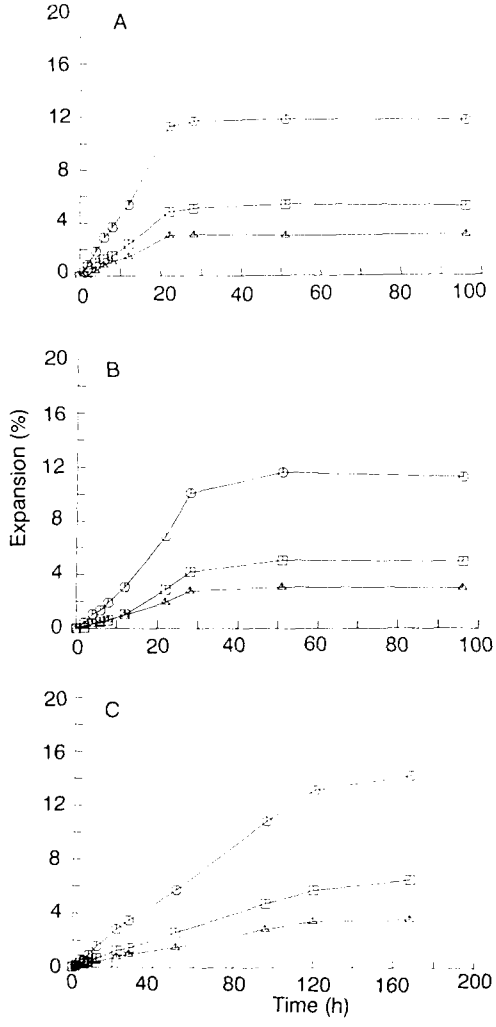


FIG. 3. Tablet expansion profiles of type II tablets at 95% relative humidity and 35°C. (A), 20 MPa; (B), 10 MPa; (C), 5 MPa. ○, Tablet volume; □, tablet thickness; △, tablet diameter.

*Relations between porosity and fractional hydration of type I and II tablets*

Fig. 7 shows relations between tablet volume and water content of type I and II tablets at 95% relative humidity and 35°C. The tablet volume of type I and II tablets increased in water content; a linear relationship was found for type II tablets but not for type I tablets.

## Discussion

*Effect of tableting pressure on hygroscopicity of type I and II tablets of theophylline anhydrate*

After Shefter & Higuchi (1963) reported the dissolution behaviour of theophylline monohydrate and anhydrate, Pharmacopoeia Japonica XI (1986) required the anhydrate crystalline form of theophylline. We reported the effects of surface character on the hygroscopicity of types I and II

Table 4. Percent expansion, porosity and final expansion ratio (R) of thickness and diameter of theophylline anhydrate tablet.

| Material Compression (MPa) | Expansion of tablet: Thickness (s.d.) (%) | Diameter (s.d.) (%) | Volume (s.d.) (%) | Porosity (s.d.) | R (s.d.) |
|---|---|---|---|---|---|
| Type I | | | | | |
| 5 | 7·38 (0·22) | 4·27 (0·06) | 16·75 (0·29) | 0·338 (0·008) | 1·73 (0·01) |
| 10 | 7·78 (0·19) | 3·73 (0·05) | 15·97 (0·142) | 0·269 (0·008) | 2·09 (0·05) |
| 20 | 8·84 (0·39) | 3·37 (0·23) | 16·31 (0·32) | 0·225 (0·010) | 2·62 (0·06) |
| Type II | | | | | |
| 5 | 4·99 (0·46) | 3·00 (0·33) | 11·38 (0·93) | 0·345 (0·010) | 1·66 (0·09) |
| 10 | 4·98 (0·07) | 3·00 (0·10) | 11·37 (0·21) | 0·252 (0·012) | 1·66 (0·04) |
| 20 | 6·54 (0·12) | 3·61 (0·24) | 14·36 (0·41) | 0·220 (0·006) | 1·81 (0·01) |

s.d., standard deviation (n = 3).

Table 5. Kinetic equations g(x) for common mechanisms of solid-state decomposition and values of Hancock–Sharp constant.

| Symbol | g(x) | m[a] | Mechanism |
|---|---|---|---|
| R1 | x | 1·24 | Zero-order (Polany–Winger equation) |
| R2 | $2(1-(1-x))^{1/2}$ | 1·11 | Two-dimensional phase boundary |
| R3 | $3(1-(1-x))^{1/3}$ | 1·07 | Three-dimensional phase boundary |
| F1 | $-\ln(1-x)$ | 1·00 | First-order |
| A2 | $(-\ln(1-x))^{1/2}$ | 2·00 | Two-dimensional growth of nuclei (Avrami equation) |
| A3 | $(-\ln(1-x))^{1/3}$ | 3·00 | Three-dimensional growth of nuclei (Avrami equation) |
| D1 | $x^2$ | 0·62 | One-dimensional diffusion |
| D2 | $(1-x)\ln(1-x)+x$ | 0·57 | Two-dimensional diffusion |
| D3 | $(1-(1-x)^{1/3})^2$ | 0·54 | Three-dimensional diffusion (Jander equation) |
| D4 | $(1-2x/3)-(1-x)^{2/3}$ | 0·57 | Three-dimensional diffusion (Ginstiling–Brounshtein equation) |

a, $\ln(-\ln(1-x)) = \ln B + m \ln t$ (x = 0·15—0·50).

theophylline anhydrate in a previous study (Otsuka et al 1990). Type II theophylline anhydrate was more hygroscopic than type I, and types I and II were transformed into the monohydrate above 66 and 82% relative humidity, respectively, at 35°C; the gas affinity balance of type I was about 7 times of that of type II. The results of gas affinity balance studies suggest that the particle surface of type II was more hydrophilic than that of type I. Since the tablets had smaller Sw and porosity than the powder beds, the hydration rates of the tablets were much slower than those of the powder beds. The hydration rates of the tablets decreased with increased tableting pressure (Fig. 1 and Table 3), because the Sw and porosity of the tablets decreased with increased pressure (Table 2). This result suggests that the geometric structure of the dosage form will affect the hydration rate. On the other hand, the hydration rate of the type II powder bed was found to be faster than that of the type I powder bed in a previous study (Otsuka et al 1990), but the hydration rates of type I tablets were faster than those of type II tablets. This suggests that the hydration rate of the tablet depends not only on the hygroscopicity of the bulk powder, but that the geometric factors of the dosage form are also important; water vapour enters the pores of a tablet, where it is adsorped on the surfaces of anhydrate crystals and then reacts with the drug. The diffusivity of water vapour in the pores of a tablet may be a rate-determining step in hydration.

The expansion of a tablet indicates the porosity increase during hydration and thereby affects its hydration kinetics. The expansion of types I and II tablets during hydration suggests that these tablets expanded more in thickness than in diameter (Figs 2, 3). Nakagawa et al (1979), using X-ray diffraction, found that aspirin crystals within a tablet after compression had a preferred orientation. They concluded that thin, plate-like crystals had a strong tendency to orient preferentially at an early stage of compression. Similarly, the tablet structures of types I and II theophylline anhydrate might not be uniform; the crystal shapes of types I and II were not spherical, but columnar. The specific plates of crystals were thus oriented in the tablet after compression, so the mechanical strength of the tablet was not uniform (Figs 2,

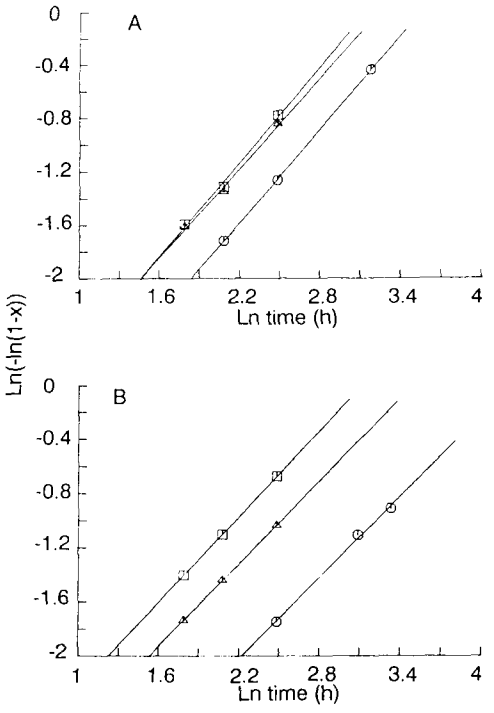


FIG. 4. Hancock–Sharp plots of type I (A) and II (B) tablets □, 20 MPa; △, 10 MPa; ○, 5 MPa.

Table 6. Hancock-Sharp constant (m) of tablets of theophylline anhydrate.

| Material Compression (MPa) | Model | m ± s.d.[a] |
|---|---|---|
| Type I | | |
| 5 | R2 | 1·194 ± 0·02 |
| 10 | R2 | 1·143 ± 0·02 |
| 20 | R2 | 1·17 ± 0·00 |
| Type II | | |
| 5 | R3 | 1·04 ± 0·07 |
| 10 | R3 | 1·06 ± 0·05 |
| 20 | R3 | 0·98 ± 0·04 |

a, standard deviation (n = 3).

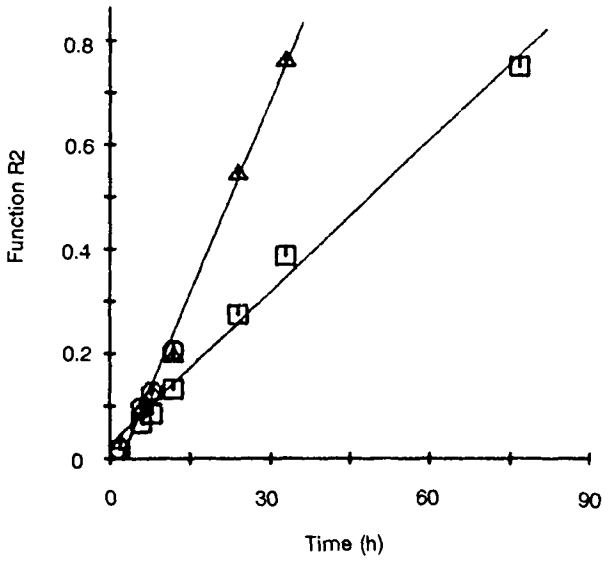


FIG. 5. Dependence of function R2 on time for hydration of type I tablets theophylline anhydrate. □, 20 MPa; △, 10 MPa; ○, 5 MPa.

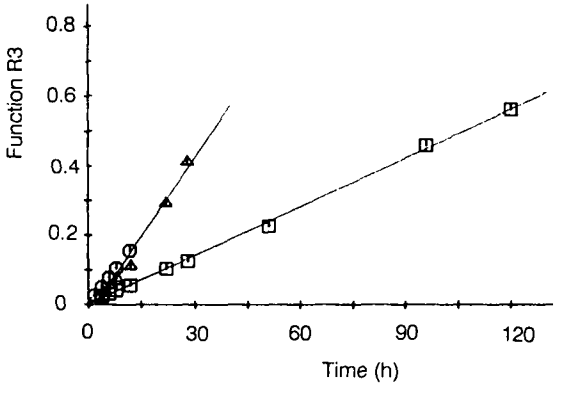


FIG. 6. Dependence of function R3 on time for hydration of type II tablets theophylline anhydrate. □, 20 MPa; △, 10 MPa; ○, 5 MPa.

3). The relations between tablet volume and water content (Fig. 7) suggest that types I and II tablets hydrated in proportion to their increased expansion. The tablet expansion of type II did depend on hydration as shown by the straight lines in Fig. 7; the non-linear relationships for type I suggested other factors were involved for type I hydration.

*Hydration kinetics of types I and II tablets of theophylline anhydrate*

The hydration kinetic results in a previous study (Otsuka et al 1990) suggested that the type I powder bed followed the A2 equation, but the type II powder bed followed the F1 equation. The kinetic results of types I and II tablets suggested that the hydration of tablets does not depend on the hydration mechanism of bulk powder, but is affected by the structure of the dosage form. The hydration of theophylline anhydrate tablets proceeded from the surface of the tablet to the inside following phase boundary kinetics. All hydration of type II tablets followed the R3 equation, and the tablet expansion depended on the hydration; the relation between expansion and hydration was almost a straight line.

On the other hand, the hydration of all type I tablets followed the R2 equation, and the tablet expansion depended not only on hydration as shown by their non-linearity (Fig. 7). This suggests that type II tablets expanded uniformly during hydration, but type I tablets did not. The expansion ratio of thickness to diameter of types I and II also suggests that the type II tablet expanded uniformly whereas the type I tablet did not. Since the rate-determining step of hydration of types I and II theophylline anhydrate tablets is diffusion of water vapour into the pores, the pattern of tablet expansion by hydration depends on the hydration kinetics of the changed tablet.

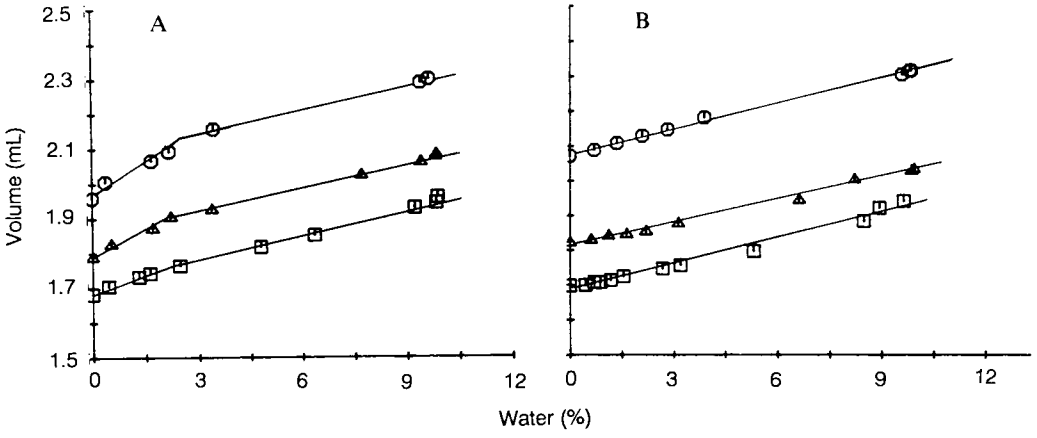


FIG. 7. Relation between the tablet volume and water content of type I (A) and II (B) tablets of theophylline anhydrate. □, 20 MPa; △, 10 MPa; ○, 5 MPa.

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