DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(5), 541-557 (1993)

EFFECT OF TABLETING PRESSURE AND GEOMETRICAL FACTOR OF TABLET ON DEHYDRATION KINETICS OF THEOPHYLLINE MONOHYDRATE TABLETS

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ABSTRACT

The effect of compression pressure and geometrical factors (thickness and diameter) of tablet on the dehydration kinetics of theophylline monohydrate tablets was studied using an infrared water-content measuring instrument. The dehydration rate of 2 cm diameter tablets decreased with increase in tabletting pressure. The dehydration rates of tablets also depended on tablet shape. The 2 cm diameter tablets (thin tablets) dehydrated faster than 1 cm diameter tablets (thick tablets). Dehydration of the powder bed (loosely packed tablets) and 2 cm tablets compressed at 49 MPa followed the two-dimensional phase boundary equation, and

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that of 2 cm diameter tablets compressed at 98 MPa and 196 MPa (thin tablets) followed the three-dimensional phase boundary equation. Dehydration of 1 cm diameter tablets compressed at 98 MPa (thick tablets) followed the one-dimensional diffusion equation. It seems that the dehydration of the tablet was controlled by the porosity and the surface area of the tablet. Therefore, tablet thickness and tabletting pressure are important factors affecting the dehydration mechanism.

INTRODUCTION

The physical and chemical stability of solid dosage forms, and in particular compressed tablets, is of obvious importance to the formulation scientist because change in physico-chemical properties of tablets affects drug content and/or bioavailability through the effects on decomposition rate, disintegration time and dissolution rate, and there are many reports of solid-state chemical reactions in solid-state.[1] Carstensen et al.[2] reported that the decomposition of vitamin A in a tablet followed a first-order equation. DeRitter et al.[3] reported the effect of silica gel on the stability of ascorbic acid in multivitamin tablets in which the decomposition of ascorbic acid followed a zero-order equation. Shefter and Higuchi[4] reported the solubilities of monohydrate and anhydrate theophylline, and then studied the solid-state dehydration kinetics of monohydrate powder.[5] However, there are few reports relating tableting pressure or geometrical factors tablet to solid-state reaction kinetics. We reported the dehydration kinetics of various dosage forms of theophylline monohydrate in a previous paper,[6] and concluding that crystal shape and porosity affected the dehydration kinetics of theophylline powders and tablets. In the present study we used a kinetic method to investigate the effects of compression pressure and geometrical factors of tablet on the dehydration of theophylline monohydrate tablets.

MATERIALS AND METHODS

Materials

Theophylline (Pharmacopeia Japonica XI) was recrystallized from distilled water. Sample powder was sieved with a No. 42 mesh screen (350 μm). Crystals of the intact sample had shapes of long needles (average particle size 18.6 μm). One gram of the powder was formed into a powder bed about 3 cm in diameter (7.1 cm^2) and 0.33 cm thick. This was done on a steel plate using a 3 cm diameter glass container. In this present study the powder bed was assumed to be a model of a loosely packed tablet with 70.5% of porosity. Tablets (1 g) were compressed by a 1 cm or 2 cm diameter punch and die for infrared spectrum analysis at compression pressures of 49, 98 and 196 MPa for a total compression time of 30 min for each sample. The compressed tablet was put on a steel-wire holder and removed from the steel plate.

Characterization of powder and tablets

The specific surface area (Sw) of powder was measured by the air permeability method (SS-100; Shimadzu Co., Ltd.), assuming the particle to be a sphere, and Sw and specific surface area diameter were calculated. Powder porosity was measured by using a type PT powder tester (Hosokawa Micro. Labo. Co., Ltd.), and density was measured by using an air picnometer (Model 930, Beckman Co. Ltd.). The thickness, diameter and volume of the tablets were measured by a micrometer. Tablet porosity was calculated from the tablet volume and weight. The Sw, density and porosity of the powder bed and tablets of theophylline monohydrate are summarized in TABLE 1 and 2.

The powder X-ray diffraction profiles of theophylline tablets were checked by a diffractometer (Model JDX 7E, Nihon Denshi Co. Ltd.) at room temperature. The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA;

TABLE 1. Powder characteristics of theophylline

Material	Density ±S.D.[a] (g/cm^3)	Sw[b] (cm^2/g)	d[c] (um)
Monohydrate	1.517 ± 0.002	2160	18.6
Anhydrate	1.499 ± 0.004	-	-

a, standard deviation (n=5); b, specific surface area; c, mean particle size.

TABLE 2.Characteristics of theophylline monohydrate tablet

Sample tablet	St[a] ± S.D. (cm^2)	D.T.[b] ± S.D. (cm)
2 cm 49 MPa	8.21 ± 0.34	0.967 ± 0.034
2 cm 98 MPa	7.73 ± 0.05	0.916 ± 0.007
2 cm 196 MPa	7.74 ± 0.06	0.891 ± 0.011
1 cm 98 MPa	4.80 ± 0.02	1.662 ± 0.007

a, surface area of tablet; b, distance from surface of tablet (D.T.=Volume of tablet/Surface of tablet)

time constant, 2 sec; measured from 2θ=3° to 2θ=40°. The powder X-ray diffraction profiles before and after dehydration of theophylline monohydrate are shown in FIGURE 1.

Dehydration apparatus

The infrared water-content measuring instrument (Kyoto-Denshi Kogyo Co. Ltd.) was placed in a drying box where the humidity was kept below 10% relative humidity with dry air. The samples were placed on a steel plate under conditions described previously.(6) The sample weight was converted into current by a transducer and was recorded on chart paper.

Dehydration kinetics of powder and tablets

The fractional dehydration of theophylline powder or tablet was calculated from the theoretical water content value of theophylline monohydrate. The predictions of isothermal

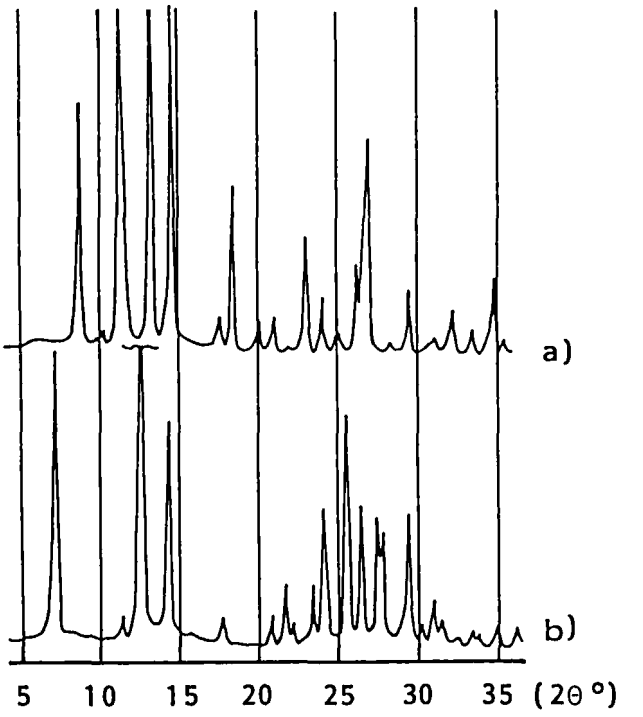

FIGURE 1. Powder X-ray diffraction profiles of theophylline monohydrate before and after dehydration (a) before dehydration (monohydrate); (b) after dehydration (anhydrate)

TABLE 3. Kinetic equations for the most common mechanisms of solid-state decomposition

Symbol	g(x)	Mechanism
R2	$2(1-(1-x))^{1/2}$	Two-dimensional phase boundary mechanism, cylindrical symmetry
R3	$3(1-(1-x))^{1/3}$	Three-dimensional phase boundary mechanism, spherical symmetry
F1	$-\ln(1-x)$	First-order mechanism, one nucleus on each particle
A2	$(-\ln(1-x))^{1/2}$	Two-dimensional growth of nuclei mechanism (Avrami equation), randon nuclation
A3	$(-\ln(1-x))^{1/3}$	Three-dimensional growth of nuclei mechanism (Avrami equation), random nuclation
D1	x^2	One-dimensional diffusion mechanism
D2	$(1-x)\ln(1-x)+x$	Two-dimensional diffusion mechanism, cylindrical symmetry
D3	$(1-(1-x)^{1/3})^2$	Three-dimensional diffusion mechanism (Jander equation), sherical symmetry
D4	$(1-2x/3)-(1-x)^{2/3}$	Three-dimensional diffusion mechanism (Ginstiling-Brounshtein equation), sherical symmetry

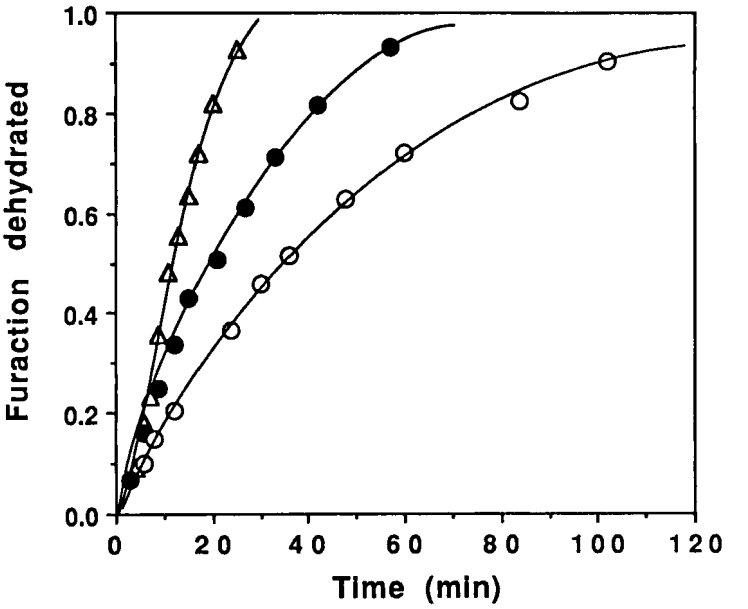

FIGURE 2. Effect of dosage forms on dehydration curves of theophylline monohydrate tablets
△, powder bed; ●, 2 cm tablet compressed at 98 MPa;
○, 1 cm tablet compressed at 98 MPa.

dehydration of the various kinds of tablets were analyzed on the basis of 9 kinds of solid-state kinetic model equations reported by Criado et al.[7] (1978) as shown in TABLE 3. Data in the range of 5 - 95% fractional dehydration were used for analysis of the dehydration mechanism. The plots were estimated by using the least-squares method.

Reaction site during dehydration of theophylline tablets

A tablet was dehydrated about 50%, and then removed, after which 50% of the weight was removed from the tablet surface by a cutter knife. The water content inside of the tablet was then measured. The water content outside of the tablet was calculated from the water content inside and that of the entire tablet.

TABLE 4. Time required for 50% dehydration (T.D.) of theophylline monohydrate tablets

Sample	T.D. (min)				
	60° C	65° C	70° C	75° C	80° C
Powder bed	24.6	16.0	12.0	8.5	-
Tablet					
2 cm 49 MPa	28.5	18.5	14.7	9.4	-
2 cm 98 MPa	-	26.1	19.1	13.9	12.8
2 cm 196 MPa	-	28.1	24.5	19.1	14.9
1 cm 98 MPa	-	46.2	34.9	24.5	21.1

RESULTS

Dehydration process of various dosage forms of theophylline monohydrate

FIGURE 2 shows the effect of dosage form on dehydration curves of theophylline monohydrate powder bed and tablets at 70° C. The times required for 50% dehydration (T.D.) of the powder bed and tablets are summarized in TABLE 4. The dehydration of the powder bed was faster than those of compressed tablets. The tablet thickness affected the dehydration rate of tablets compressed at 98 MPa, so the 2 cm diameter tablets (thin tablets) dehydrated faster the 1 cm diameter tablets (thick tablets).

FIGURE 3 shows the effect of tableting pressure on dehydration curves of theophylline monohydrate 2 cm tablets. The dehydration rate of 2 cm diameter tablets decreased with increase in tableting pressure since the porosity decreased with increased of tableting pressure.

FIGURE 4 shows the effect of temperatures on dehydration curves of theophylline monohydrate 2 cm tablets compressed at 49 MPa. The dehydration rate of tablet increased with the elevation of temperature.

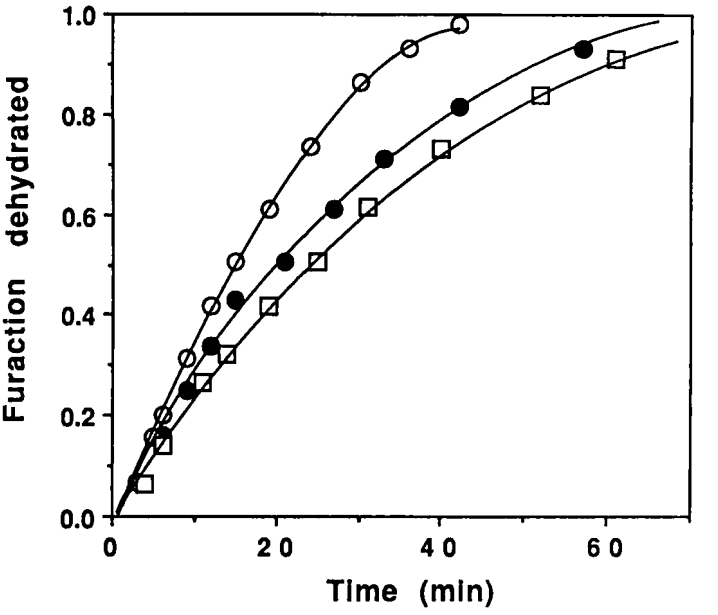

FIGURE 3. Effect of tableting pressure on dehydration curves of 2 cm diameter tablets of theophylline monohydrate at 70° C ○, tablet compressed at 49 MPa; ●, at 98 MPa; □, at 196 MPa.

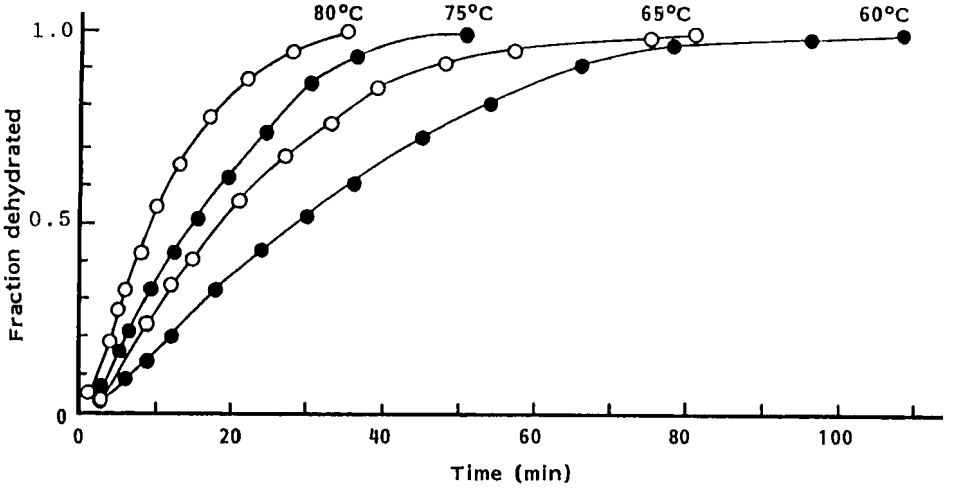

FIGURE 4. Effect of temperature on dehydration curves of 2 cm tablets compressed at 49 MPa of theophylline monohydrate

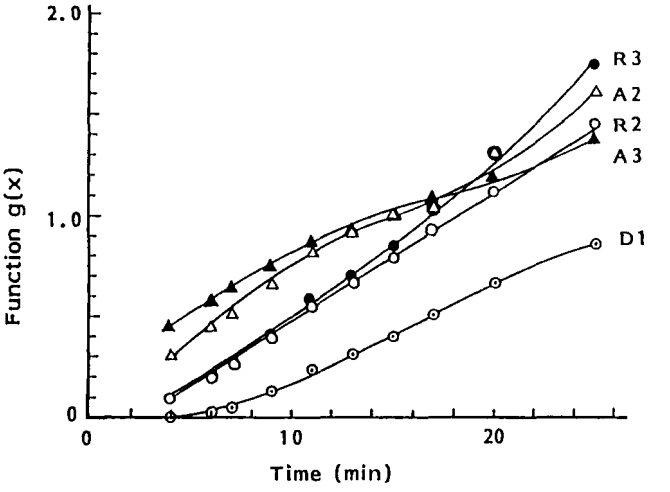

FIGURE 5. Dependence of g(x) on time for dehydration of a powder bed of theophylline monohydrate at 70° C

Dehydration kinetics of the powder bed and tablets of theophylline monohydrate

FIGUREs 5, 6 and 7 shows predictions of isothermal dehydration of various kinds of tablets at 70° C from kinetic equations.[7] The correlation coefficients of the plots of various functions g(x) and time are summarized in TABLE 5. Dehydrations of the powder bed and the 2 cm diameter tablets at a compression pressure of 49 MPa (loosely packed tablets) followed the two-dimensional phase boundary equation (R2), and that of the 2 cm diameter tablets at 98 MPa and 196 MPa followed the three-dimensional phase boundary equation (R3). Dehydration of the 1 cm diameter tablets at 98 MPa (thick tablets) followed the one-dimensional diffusion equation (D1).

Arrhenius plots for dehydration of theophylline powder and tablets are shown in FIGURE 8 and the activation energy (E) and frequency factors (A) are summarized in TABLE 6.

Reaction site during dehydration of theophylline tablets

The porosity of theophylline tablets increased about 2 - 6% after dehydration as shown in TABLE 7, but the volume decreased

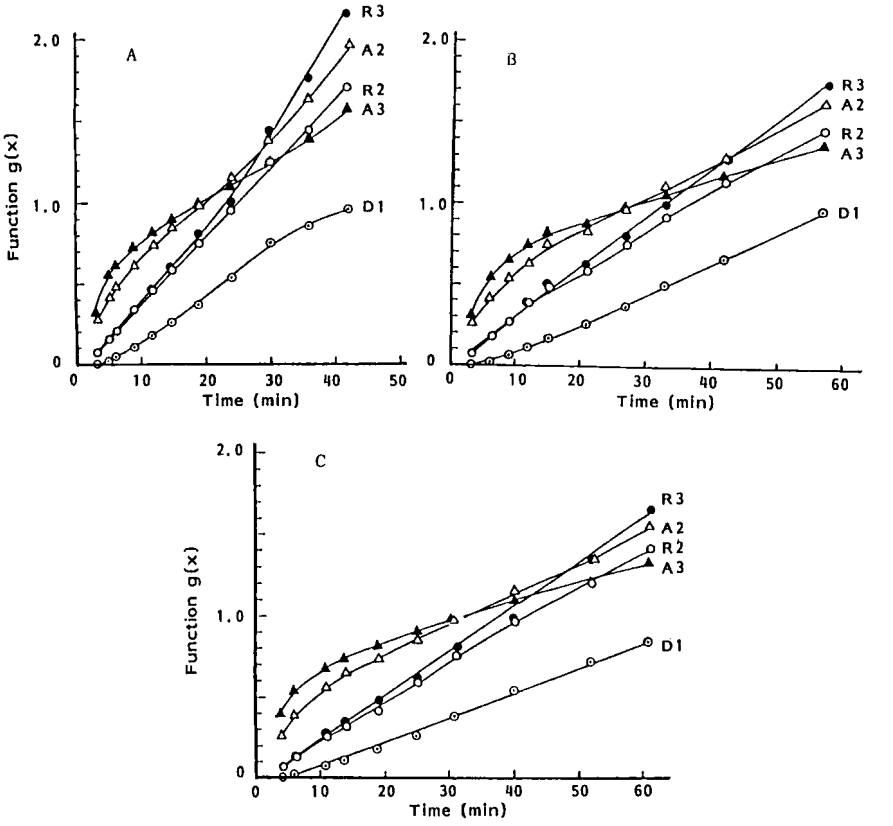

FIGURE 6. Dependence of g(x) on time for dehydration of 2 cm diameter tablet of theophylline monohydrate at 70° C A, tablet 2 cm 49 MPa; B, 2 cm 98 MPa; D, 2 cm 196 MPa.

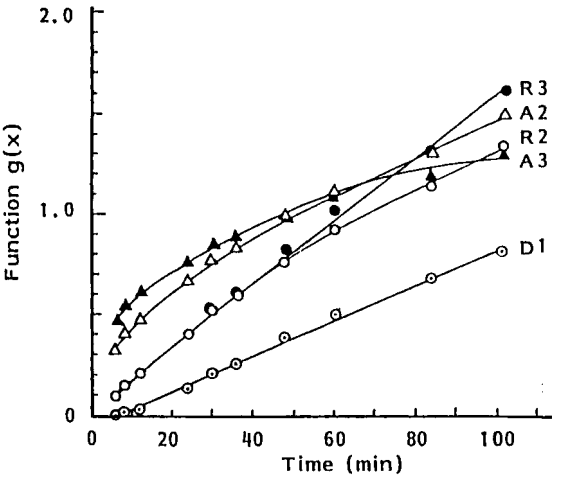

FIGURE 7. Dependence of g(x) on time for dehydration of 1 cm diameter tablet of theophylline monohydrate at 70° C

TABLE 5. Correlation coefficients of the model fitting plots

Sample	R2	R3	F1	A2	A3	D1	D2	D3	D4
Powder bed									
60° C	1.000	0.997	0.982	0.998	0.994	0.994	0.972	0.942	0.964
65° C	1.000	0.998	0.976	0.998	0.993	0.995	0.982	0.941	0.971
70° C	0.999	0.998	0.981	0.999	0.993	0.991	0.982	0.941	0.971
75° C	0.999	0.995	0.985	0.998	0.989	0.986	0.982	0.948	0.973
Mean	1.000	0.997	0.981	0.998	0.992	0.992	0.980	0.943	0.970
S.D.	0.001	0.001	0.003	0.000	0.002	0.004	0.004	0.003	0.003
2 cm 49 MPa									
60° C	1.000	0.998	0.984	0.998	0.992	0.995	0.981	0.944	0.971
65° C	0.998	1.000	0.993	0.998	0.992	0.997	0.994	0.971	0.989
70° C	1.000	0.998	0.973	0.998	0.993	0.996	0.989	0.949	0.980
75° C	0.999	0.999	0.996	0.990	0.973	0.993	0.996	0.976	0.992
Mean	0.999	0.999	0.987	0.996	0.988	0.995	0.990	0.960	0.983
S.D.	0.001	0.001	0.009	0.004	0.008	0.002	0.006	0.014	0.008
2 cm 98 MPa									
65° C	0.998	0.999	0.991	0.991	0.978	0.999	0.991	0.959	0.983
70° C	0.997	0.999	0.990	0.992	0.978	0.997	0.991	0.960	0.983
75° C	0.990	0.996	0.999	0.981	0.963	0.997	0.999	0.986	0.996
80° C	0.997	1.000	0.992	0.992	0.977	0.996	0.991	0.961	0.984
Mean	0.996	0.999	0.993	0.989	0.974	0.997	0.993	0.967	0.987
S.D.	0.003	0.002	0.004	0.005	0.006	0.001	0.004	0.011	0.006
2 cm 196 MPa									
65° C	0.999	0.998	0.987	0.992	0.981	0.999	0.990	0.957	0.981
70° C	0.999	0.999	0.992	0.993	0.980	0.998	0.989	0.962	0.982
75° C	0.997	0.999	0.993	0.990	0.977	0.999	0.992	0.964	0.985
80° C	0.999	0.999	0.988	0.994	0.984	0.997	0.986	0.955	0.977
Mean	0.998	0.999	0.990	0.992	0.981	0.998	0.989	0.960	0.981
S.D.	0.001	0.000	0.003	0.002	0.003	0.001	0.002	0.004	0.003
1 cm 98 MPa									
65° C	0.988	0.995	0.998	0.979	0.959	0.998	0.998	0.980	0.995
70° C	0.994	0.998	0.997	0.988	0.975	0.998	0.996	0.976	0.991
75° C	0.997	0.999	0.987	0.992	0.979	0.999	0.991	0.950	0.980
80° C	0.999	0.999	0.978	0.995	0.984	0.999	0.987	0.954	0.987
Mean	0.995	0.998	0.990	0.989	0.974	0.999	0.993	0.965	0.988
S.D.	0.004	0.002	0.008	0.006	0.009	0.001	0.004	0.013	0.006

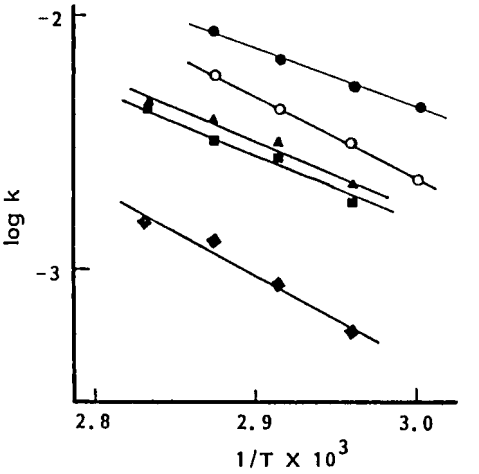

FIGURE 8. Plot of log k against 1/T for the dehydration of various theophylline tablets
●, a powder bed (R2); ○, tablet 2 cm 49 MPa (R2);
▲, 2 cm 98 MPa (R3); ■, 2 cm 196 MPa (R3);
◆, 1 cm 98 MPa (D1).

TABLE 6. Dehydration activation energy (E) and mechanism of tablets of theophylline monohydrate

Sample	E[a] (kcal/mol)	A[b] (min^{-1})	Mechanism	(r)[c]
Powder bed	15.4	4.19^{8}	R2	0.989
Tablet				
2 cm 49 MPa	14.7	1.06^{8}	R2	0.995
2 cm 98 MPa	11.5	1.06^{5}	R3	0.985
2 cm 196 MPa	13.4	4.92^{6}	D1	0.984
2 cm 196 MPa	13.3	7.06^{6}	R3	0.983
1 cm 98 MPa	11.5	3.48^{5}	D1	0.981
1 cm 98 MPa	17.0	1.07^{9}	R3	0.987

a, activation energy; b, frequency factor; c, correlation coefficient.

TABLE 7. Change of tablet porosity of theophylline monohydrate after dehydration

Sample	Porosity (%)	
	Pb^{a} ± S.D.	Pa^{b} ± S.D.
Powder bed	71.5[c] (60.7[d])	-
Tablet		
2 cm 49 MPa	21.2 ± 2.1	25.8 ± 2.0
2 cm 98 MPa	10.7 ± 2.6	16.7 ± 2.6
2 cm 196 MPa	5.9 ± 0.2	12.8 ± 0.4
1 cm 98 MPa	17.2 ± 0.4	18.9 ± 1.1

a, before dehydration; b, after dehydration; c, loose porosity; d, tapped porosity.

TABLE 8. Change of tablet size of theophylline monohydrate after dehydration

Sample	Tablet size (%)		
	Thickness ± S.D.	Diameter ± S.D.	Volume ± S.D.
Tablet			
2 cm 49 MPa	98.3 ± 0.8	99.0 ± 0.4	96.4 ± 3.5
2 cm 98 MPa	98.1 ± 0.4	99.5 ± 0.1	97.2 ± 0.5
2 cm 196 MPa	99.8 ± 0.5	98.4 ± 0.1	97.9 ± 0.5
1 cm 98 MPa	94.5 ± 0.7	99.0 ± 0.4	92.6 ± 1.2

TABLE 9. Water content of inside and outside of theophylline monohydrate tablet after dehydration

Sample	Dehydrated fraction of tablet			
	Over all	Outside	Inside	R[a]
2 cm 98 MPa	0.526	0.900	0.317	2.84
1 cm 98 MPa	0.435	0.820	0.180	4.56

a, Tablet dehydraion ratio (R=dehydrated outside / inside); each value is the average of 2 measurements.

slightly as summarized in TABLE 8. To clarify the dehydration mechanism, the water contents inside and outside of a 50% dehydrated theophylline tablet are shown in TABLE 9. Experimental results suggest that tablet dehydration proceeds from the surface to the inside of the tablet. A tablet with a diameter of 1 cm at 98 MPa (thick tablet) had higher porosity than a tablet 2 cm in diameter at 98 MPa (thin tablet). However, the dehydration ratio inside the 1 cm tablet was greater than that of the 2 cm tablets.

DISCUSSION

Effect of tableting pressure on tablet dehydration

The results of T.D. of 2 cm diameter tablets (TABLE 4) suggest that the dehydration rate of a tablet is affected by tableting pressure. This can be explained by the decrease in porosity (TABLE 7) and surface area of tablet (TABLE 2) with increase in tableting pressure. Since the powder bed and the 2 cm diameter tablet had large porosity at 49 MPa, it seemed that the diffusion of water vapor in the tablet pores was negligible, and so, the dehydrations followed the R2 equation. It seems that dehydration appears to be controlled by thermal diffusion; dehydration proceeds two-dimensionally from the outside of the tablet to the inside. A 2 cm diameter tablet at 196 MPa had

only 6% less St (TABLE 2) than a 2 cm 49 MPa tablet, but the T.D. of a 2 cm tablet at 196 MPa (TABLE 4) was 50 - 100% greater than that of a 2 cm 49 MPa tablet. This result suggests that the effect of tableting pressure on dehydration rate is mainly caused by decrease in the porosity of tablet. From this observation, the first impression was that the dehydration of the 2 cm 196 MPa tablet was affected by diffusion of the water vapor in the tablet pores. However, the dehydration kinetics results suggests that the dehydration of the 2 cm 196 MPa tablet was not controlled by the diffusion of water vapor in the tablet pores, but followed the R3 equation. It seems that these dehydration kinetics were reasonable for following reasons: (a) The tablets used in these experiments were not very thick (D.T. was low as shown in TABLE 2), which suggests short mean length of the pores, (b) The porosity of the 2 cm 196 MPa tablet increased about 2 times after dehydration (TABLE 7), which means that the diffusion rate of water vapor in the dehydrated part of the tablet was much larger than in the intact part. Consequently, it seems diffusion of water vapor in the tablet pores was not in control in the dehydrated part of the tablet, so the dehydration proceeded three dimensionally from tablet surface to inside. As a result, the dehydration of 2 cm 196 MPa and 98 MPa tablets followed the R3 equation.

Effect of geometrical factor of tablet on tablet dehydration

The T.D. changed depending on the tablet shape. The 1 cm diameter tablet at 98 MPa had smaller surface area and higher porosity than the 2 cm 98 MPa tablet. This result suggests that the St and/or the D.T. were more important factors than porosity in the dehydration of these tablets. It appeared that dehydration of the 1 cm 98 MPa tablet was controlled by the diffusion of water vapor in the pores, simply because the D.T. was very high (long pores in tablet) and porosity before and

after dehydration were not significantly different. Therefore, it seems that dehydration of the tablet was controlled by water vapor diffusion. However, the 2 cm 98 MPa tablet had smaller D.T. and its porosity increased about 60% after dehydration. From the results of kinetic analysis (TABLE 5) the dehydration of the 1 cm 98 MPa tablet followed the D1 equation, but that of the 2 cm 98 MPa tablet followed the R3 equation. This means that the dehydration of the 1 cm 98 MPa tablet was controlled by the diffusion process of water vapor in the tablet pores, whereas that of the 2 cm 98 MPa tablet was not controlled by the diffusion process, but dehydrated from the tablet surface. The dehydration ratio (TABLE 9) also supported this dehydration mechanism difference.

In a previous paper[6] we reported that the dehydration of theophylline powder changed with the dosage form of the powder bed and the particle shape of the powder. The dehydration of the powder bed under this condition was presumed to be true dehydration of the crystals with no a diffusion process in the interparticle void of the powder bed, because the 50 um thick powder beds had large surface area (50.3 cm^2) and large porosity (about 70%). It is assumed that dehydration of a tablet can be divided into two processes with both reactions on the surface and inside the tablet. When the tablet has a small surface area and little porosity, the diffusion of water vapor in the tablet pores is hindered during dehydration as shown in the dehydration of 1 cm diameter tablets. This situation was also reported by Higuchi[8] as drug diffusion from the matrix tablet, the drug release from the matrix tablet is controlled by the porosity and tortuosity of the pores.

On the other hand when a tablet has a large surface area (a thin tablet, 2 cm diameter tablets at 98 and 196 MPa) or higher porosity (a loosely packed tablet, the powder bed and 2 cm

diameter tablets at 49 MPa), the diffusion of water vapor in the tablet might be negligible. However, in the latter case thermal diffusion in the interparticle void of the tablet might not be negligible, since the tablet has a large interparticle void with poor thermal conductivity.

Arrhenius plots of dehydration of theophylline monohydrate tablets

All Arrhenius plots of dehydration of various theophylline tablets (FIGURES 5, 6 and 7) were linear. This is evidence in support of the dehydration of tablets following the model equations. The E and A of tables calculated from the Arrhenius plots are apparent parameters, but from the pharmaceutical viewpoint we can understand the dehydration mechanisms of tablets and estimate the half lives of dehydration of these dosage forms.

CONCLUSION

Dehydration of the tablets was affected by the tableting pressure through the St and porosity of the tablets. The T.D. of 2 cm diameter tablet increased with tableting pressure. The T.D. of the 2 cm diameter tablets was more than that of the 1 cm diameter tablets. The dehydration mechanism of the tablets depended on geometrical factore of tablet. The dehydrations of 2 cm diameter tablets (thin tablets), followed the phase boundary equation, but that of 1 cm tablet that had long distance from the tablet surface (thick tablet), followed the diffusion controlled equation. From these experimental results, conclude that the dehydration kinetics of tablets is affected by the tablet porosity and tablet thickness.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Miss Kyoko Kobayshi and Miss Yasuko Isono for their assistance with the experimental work.

REFERENCES

(1) J. T. Carstensen, "Pharmaceutics of solids and solid dosage forms, VII. Stability and dating of solid dosage forms, 183 - 206, A Wiley-Interscience Publications, Tront, (1977).

(2) J. T. Carstensen, E. S. Aron, D. C. Spera and J. J. Vance, J. Pharm. Sci., 55, 561 - 562 (1966).

(3) E. DeRitter, L. Magid, M. Osadca and S. H. Rubin, J. Pharm. Sci., 59, 229 - 231 (1970).

(4) E. Shefter and T. Higuchi, J. Pharm. Sci., 52, 781 - 791 (1963).

(5) E. Shefter, H. Fung and O. Mok, J. Pharm. Sci., 62, 791 - 794 (1973).

(6) M. Otsuka and N. Kaneniwa, Chem. Pharm. Bull., 36, 4914 - 4920 (1988).

(7) J. M. Criado, J. Morales and V. Rives, J. Thermal Analysis, 14, 221 - 228 (1978).

(8) T. Higuchi,J. Pharm. Sci., 52, 1145 - 1149 (1963).