DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(10), 1777-1794 (1994)

THE ROLE OF LIQUID WATER UPTAKE BY AN INSOLUBLE TABLET CONTAINING A DISINTEGRANT

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ABSTRACT

The hydration capacity of each of four disintegrants including microcrystalline cellulose (Avicel PH102), corn starch, croscarmellose sodium (Ac-di-sol) and sodium starch glycolate (Primojel) was determined to express the hydrophilicity. The complete pore structure, and the water uptake of unmilled dicalcium phosphate dihydrate (Di-Tab) tablets containing one of above disintegrants at 15% w/w level were studied. It was found that the majority of the tablet porosity was made up by macropores which were accessed by mercury intrusion. There was no statistically significant difference among pore volume-size distributions of tablet samples. The water uptake results were treated by the empirical form of Washburn liquid penetration equation with appropriate experimental setup. It was possible to determine the significance of the empirical parameters drawn from the equation. It was found that the hydrophilic nature of excipients present in a tablet played a major role in water uptake phenomenon. It was suggested that the disintegrant swelling narrowed the pore sizes in the beginning and then the pores were widened due to the repelling pressure exerted causing the tablet to collapse which made the amount of liquid uptake actually smaller in the beginning and then greater later. Finally, the water penetration is impeded by gelling formation of a disintegrant present in a tablet matrix.

INTRODUCTION

When a tablet comes in contact with water, the following phenomena, respectively, occur, wetting, water penetration, and tablet disintegration with or without significant swelling. One of the driving force for liquid water penetration is that according to the fundamental phenomenon of capillary (1). Washburn (2), in 1921, used the Poiseuille's law of

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flow through the duct and developed the equations to describe the dynamics of capillary flow in two different configurations, i. e., horizontal and vertical The validity of the Washburn equation was confirmed by Fisher and Lark (3), and they found that the equation could be adequately applied to the range of capillary sizes between 3 and 400 μm.

Some tableting excipients (e g microcrystalline cellulose) are cylindrical in shape Therefore, it is useful to examine the capillary phenomena in assemblies of parallel cylinders Princen (4-5) developed the equations of capillary rise in both vertical and horizontal configurations He applied the equilibrium conditions, and geometry to set up the equations The concept, however, was more theoretical.

Kinetics of Water Penetration into a Tablet Matrix

Considering the capillary system which is so small that the Poiseuille's law covers the whole flow, the rate of liquid volume flow (dV/dt) is written as (2),

$$\frac{dV}{dt} = \frac{\pi \sum P}{8\eta l}\left(r^4 + 4\varepsilon r^3\right) \tag{1}$$

where $\sum P$, η, ε, l, and r are the sum of driving pressures, viscosity, the coefficient of slip, the length of the column of liquid in capillary at time t, and capillary radius, respectively The driving pressures consist of the unbalanced atmospheric pressure, P_A, the hydrostatic pressure, P_h, and the capillary pressure, P_s, which obeys Laplace-Young equation (1) for a hemispherical interface Considering that the capillary is wettable, i.e., ε is equal to zero, and P_A is negligible compared to P_s, there are two cases of experimental setup depending on the configuration of capillaries, i.e., horizontal and vertical cases When the setup is horizontal, only capillary rise is counted. Equation 1 has a simple form as follows,

$$\frac{dl}{dt} = \frac{r^2}{8\eta l}\left(2\,\gamma/r\,\cos\theta\right) \tag{2}$$

with its integral form of, $l^2 = (r/4hl)\gamma\cos\theta$ For a vertical configuration, the rate equation, on the other hand, can be written as,

$$\frac{dl}{dt} = \frac{r^2}{8\eta l}\left(2\,\gamma/r\,\cos\theta - \rho g l\right) \tag{3}$$

In this case, it is seen that not only the capillary rise, but the rate of liquid flow is also dependent on the amount of liquid that is already in the capillaries due to the gravity. This will counter-balance the capillary force Until the equilibrium is reached, the rate of liquid penetration will be zero The general solution of equation 3 has been solved by Washburn (2) and is shown as follows,

$$\frac{r^2 \rho g}{8\eta} t + 1 = -\frac{(2\frac{\gamma}{r}\cos\theta)}{\rho g}\ln[1 - \frac{\rho g l}{\frac{2\gamma}{r}\cos\theta}] \qquad (4)$$

The equation will be valid as long as a porous matrix does not collapse

Many workers who set up the vertical penetration apparatus (e g , 6, 9), however, mentioned the 'classical' horizontal Washburn equation that was not valid as an equation of phenomenon But, the equation had not yet applied to the results This might mislead to the understanding of the capillary rise phenomenon

The hydrophilicity of excipients also plays an important role in water uptake of a tablet (7) It was noted that a tablet disintegrant usually showed a high value of hydration capacity (8-9) and that of hygroscopicity (10) The disintegrant, when present in a tablet, could draw the liquid water into the tablet Therefore, it is of importance to determine a relationship between tablet porosity and/or hydrophilicity and tablet water uptake In addition, the empirical form of Washburn equation for the vertical configuration setup is employed in the study due to the fact that not only capillary rise but the hydrophilicity of pore system contributed in water uptake of a tablet matrix (7)

EXPERIMENTAL

Four disintegrants including microcrystalline cellulose (Avicel PH102, FMC Crop), corn starch (A E Staley Mfg Co), croscarmellose sodium (Ac-di-sol, FMC Crop), and sodium starch glycolate (Primojel, GereiChem Crop) were employed Their hydration capacities were individually determined using the method previously described (8) Each of the disintegrants was mixed with unmilled dicalcium phosphate dihydrate (Di-Tab, Rhone-Poulenc Basic Chemical Co) at 15 % w/w level

Tablet Porosity Determination: Nitrogen Adsorption

Since a pellet sample cell with the stem's internal diameter of 4 millimeters was used in the nitrogen adsorption study, Di-Tab with or without 15% disintegrant powder mixture was compressed by the hydraulic press to form 20 mg. flat-faced pellets with a $\frac{1}{8}$ -inch tooling set The compression force was controlled at 500 Kg -level Six pellets for each formulation were employed to determine the pore volume-size distribution using nitrogen adsorption method previously described (11) Pore sizes between 10 Angstroms and 0 3 microns were obtained from the instrument software calculations based on the Kelvin equation (12)

Tablet Porosity Determination: Mercury Porosimetry

A 0 5-inch-flat-faced formulated tablet with or without a disintegrant at the 15% level was made To maintain the uniformity of the results from different methods of porosity determination, the compression force had to be compensated With controlled

Table 1 Mercury contact angles on tablet surfaces.

Tablet	θ degrees(s.d.)
Di-Tab^R, only	167.5(0.71)
with 15% Avicel^R PH102	166.5(2.12)
with 15% Ac-di-sol^R	167.0(2.83)
with 15% corn starch	161.0(4.24)
with 15% Primojel^R	163.5(2.12)

compression force of 1200 ±50 kg., the tablets were made using the hydraulic press. They were dried at 80 degrees C. for 24 hours following their compaction.

In order to obtain the accurate pore volume-size distribution, the contact angle of mercury on the tablet surface was required. A drop of mercury was directly placed on the tablet surface. The equilibrium mercury contact angle was measured using a goniometer (Rame-Hart Inc.). Two duplicates were done for each tablet sample. The data are shown in Table 1.

The measurement of tablet pore volume and pore distribution having pore sizes between 0.0045 and 543 micrometers was conducted using an automated mercury intruder (Autopore II Model 9220, Micromeritics Instrument Corp.). The tablets were dried to remove sorbed moisture and other contaminants at 100 degrees C. for 12 hours. They were then placed in a penetrometer cell. It was first evacuated and then filled with mercury. The low pressure measurements (pressure range of 0.5-30 psia) were conducted. When the maximum negative intrusion was reached, the high pressure measurement which attained a maximum pressure of 60,000 psia began. Accompanied with the volume measurement, the pore diameter corresponding to the pressure was calculated. The complete pore volume-size distribution for each sample was constructed by totaling up the distributions obtained from nitrogen adsorption and mercury intrusion methods.

Dynamic Liquid Water Uptake Study

The apparatus for liquid water uptake study was set up vertically as similar to that described elsewhere (9). It consisted of a 15 ml buchner funnel fitted with a sintered glass, connected to a 1 ml pipette (0.01 ml. divisions) via Tygon tubing. It was set vertically in place with stands and clamps. Distilled water was filled into the apparatus and adjusted to zero reading on the pipette prior to measurement. To avoid the driving force due to unbalanced atmospheric pressure, the menisci of both ends were leveled to each other

Table 2 Hydration capacity of individual disintegrants.

Excipient	Hydration Capacity	MC* (%w/w)
Di-Tab	0.691	00.90
Avicel PH102	3.138	11.16
Ac-di-sol	7.859	31.31
corn starch	1.286	18.92
Primojel	21.630	37.08

*Moisture content (MC) is the equilibrium moisture content of materials, in grams of moisture per 100 grams of dry material, exposed to 90% relative humidity, at 25 degrees C for 7 days (13).

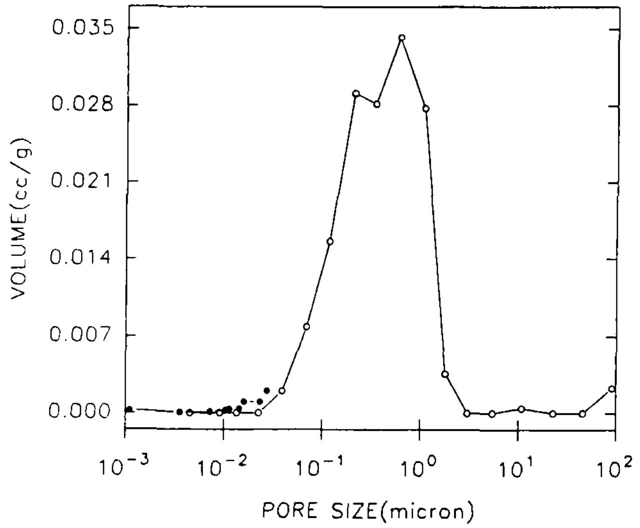

Figure 1 The complete pore volume-size distribution of Di-Tab tablets.
Key: (empty circles), the data from mercury intrusion; (filled circles), the data from nitrogen adsorption

Immediately after a tablet was place in the funnel, water was drawn into the tablet and water uptake was recorded as a change in the level of water in the pipette. Three replicate volume measurements were carried out for each time interval. The average volume for each time interval was calculated, and the volume-time profile for each tablet formulation was evaluated using the appropriate Washburn equation.

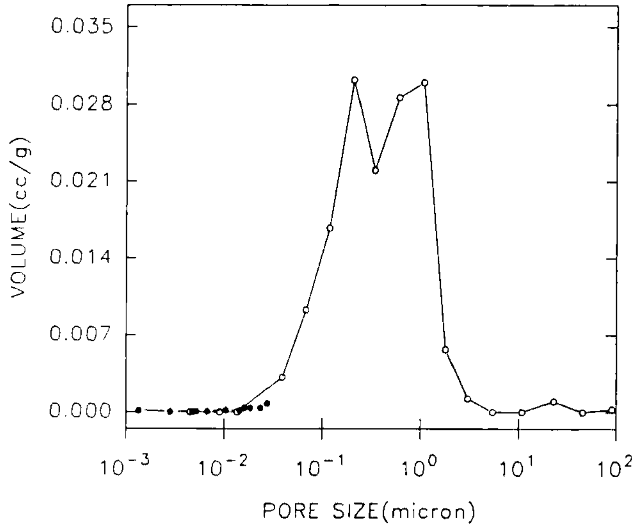

Figure 2 The complete pore volume-size distribution of Di-Tab tablets containing 15% Avicel PH102
Key: (empty circles), the data from mercury intrusion; (filled circles), the data from nitrogen adsorption

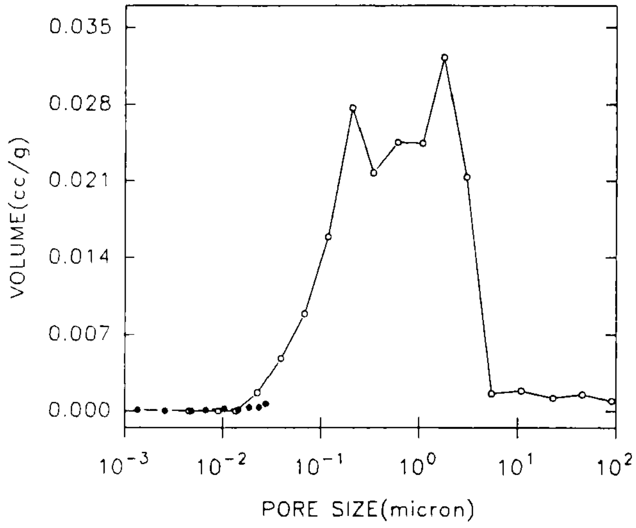

Figure 3. The complete pore volume-size distribution of Di-Tab tablets containing 15% Ac-di-sol.
Key: (empty circles), the data from mercury intrusion, (filled circles), the data from nitrogen adsorption.

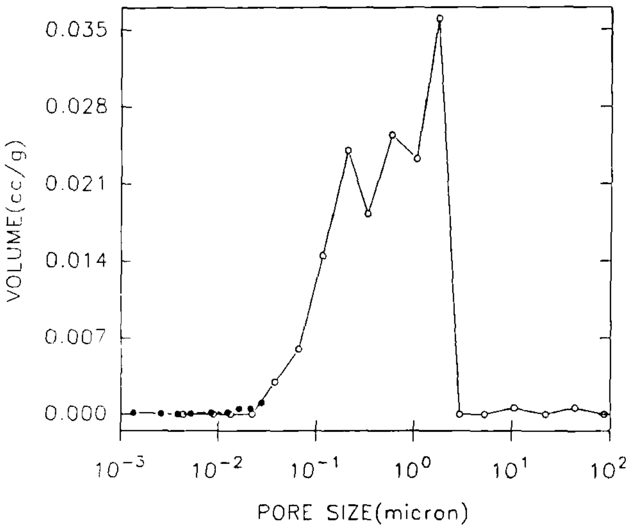

Figure 4 The complete pore volume-size distribution of Di-Tab tablets containing 15% corn starch
Key: (empty circles), the data from mercury intrusion; (filled circles), the data rom nitrogen adsorption

RESULTS AND DISCUSSION

Hydration Capacity

The hydrophilicity of individual disintegrants was expressed as a hydration capacity previously defined in the literature (8). The results are summarized in Table 2.

The hydration capacities of superdisintegrants (Ac-di-sol, and Primojel) were high compared to those of the conventional disintegrants (Avicel PH102, and corn starch), as well as their equilibrium moisture contents (Table 1). This consistency shows the evidence of the superiority in the hydrophilicity of superdisintegrants over the conventional disintegrants. The same trend was found in the moisture uptake study (13).

Tablet Porosity

According to the Kelvin equation, the nitrogen adsorption was able to analyze the pores up to 0.03 micrometers. On the other hand, mercury intrusion allows one to determine the pores in the range categorized as macropores, i.e., range of porosity between 0.0045 and 550 micrometers that covered the normal tablet pores.

An attempt to determine the complete pore volume-size distribution of the formulated tablets was made. It is probable that this could be determined by combining the distributions obtained from nitrogen adsorption and mercury intrusion. Figures 1-5 illustrate

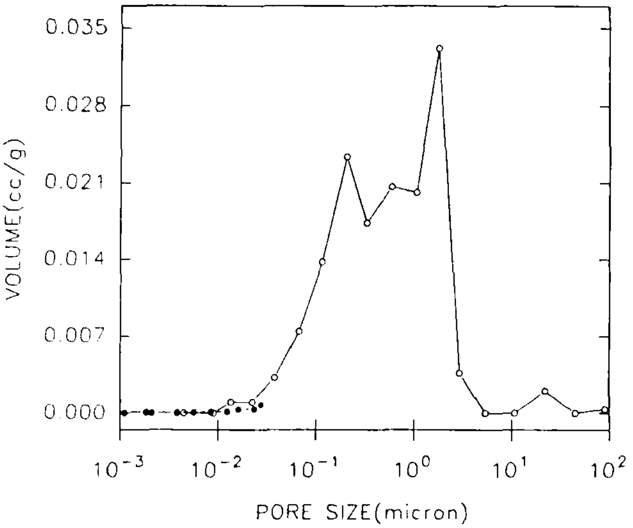

Figure 5 The complete pore volume-size distribution of Di-Tab tablets containing 15% Primojel
Key (empty circles), the data from mercury intrusion, (filled circles), the data from nitrogen adsorption

the complete pore volume-size distributions of such formulated tablets disregarding the fitted distribution model The two results are fairly agreeable in the range of overlapping pore sizes It is noted from the figures that macropores made up the majority of the pores of the tablet and the macropore volume distributions are complex The complication may be the result of the pore structural change under high pressure (14).

Using the log-normal distribution model, disregarding the meso- and micro-pores from nitrogen adsorption which are not significant in the volume-size distribution, and using an appropriate contact angle previously measured (Table 1), the pore volume-size distribution of each of the formulated tablet samples was determined. Each of pore distributions was shown in Figures 6-10. It is noted that the complications found in Figures 1-5 are no longer significant when using the fitted log-normal distribution model The geometric means and medians of pore sizes for each of the formulated tablet samples are calculated and summarized in Table 3.

With the presence of different disintegrant, the pore sizes of such systems are not statistically significant different from each other (Table 3). It may be because the majority of the tablet mass is made by Di-Tab. The deformation of Di-Tab powder to form a tablet matrix made up the pore structure in a similar fashion for all systems.

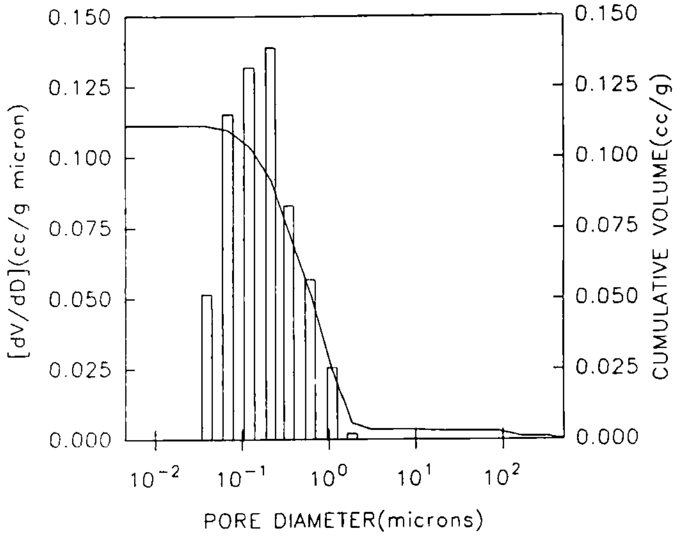

Figure 6. Mercury intrusion pore volume-size distribution of a Di-tab tablet.

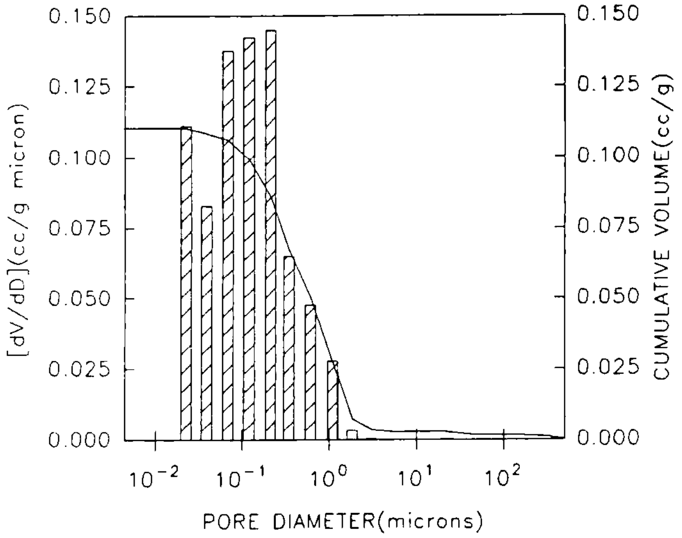

Figure 7. Mercury intrusion pore volume-size distribution of a Di-tab tablet containing 15% Avicel PH102

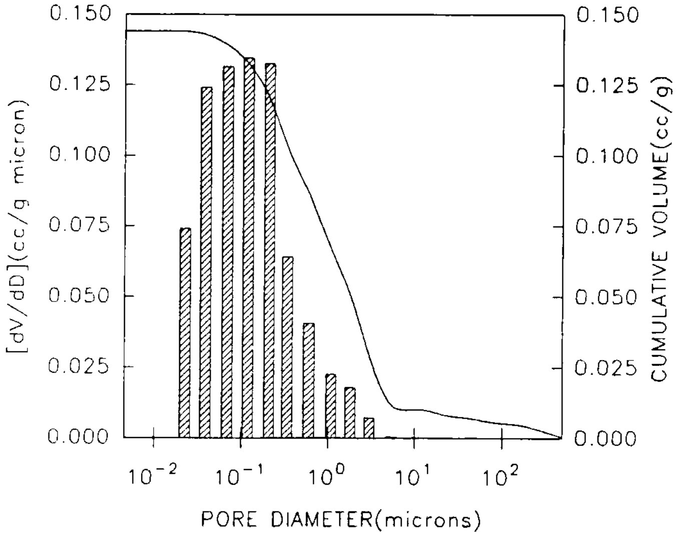

Figure 8 Mercury intrusion pore volume-size distribution of a Di-tab tablet containing 15% Ac-di-sol.

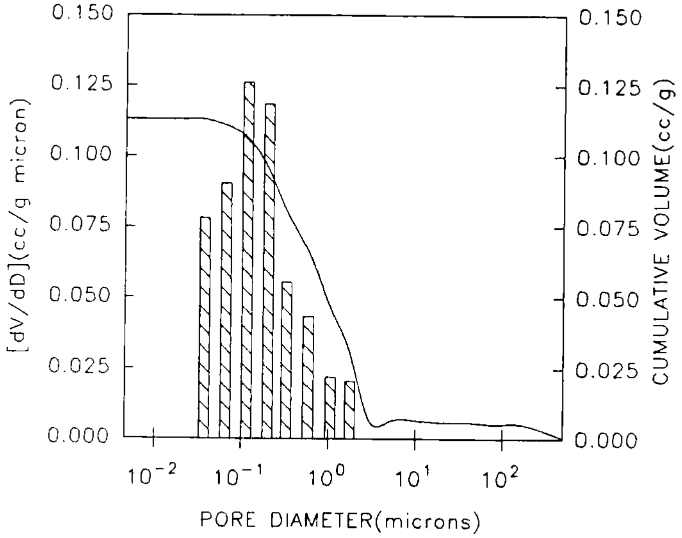

Figure 9 Mercury intrusion pore volume-size distribution of a Di-tab tablet containing 15% corn starch

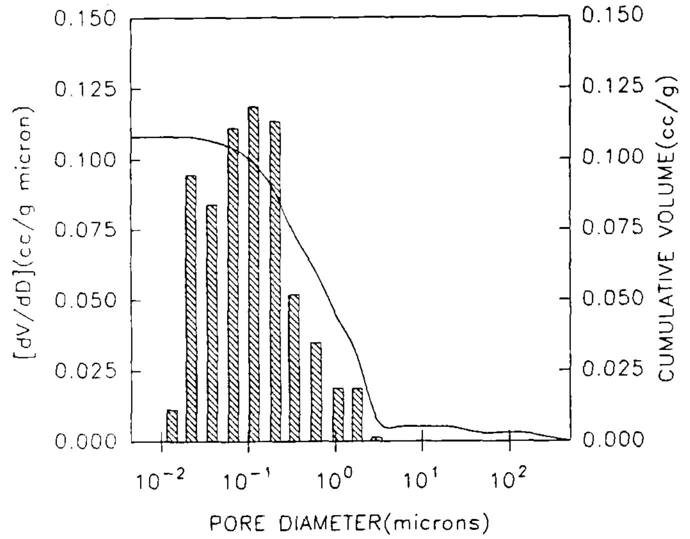

Figure 10 Mercury intrusion pore volume-size distribution of a Di-tab tablet containing 15% Primojel.

Table 3 Geometric means and medians of Di-Tab tablets porosity containing different disintegrants

Tablet	Mean* (s.d.)	Median**
Di-Tab, only	0.239(.2537)	0.164
with 15% Avicel PH102	0.191(.2731)	0.107
with 15% Ac-di-sol	0.218(.3419)	0.117
with 15% corn starch	0.253(.3297)	0.154
with 15% Primojel	0.203(.3344)	0.105

*Geometric mean of sizes in micrometers obtained from log-normal distribution fitting.
**The size in micrometers at 50th percentile of population

Dynamic Liquid Uptake Study

An attempt in applying the Washburn equation describing the liquid flow in vertical direction, which the experiment was set up, to the liquid uptake by a formulated tablet was made. Since the capillary in a tablet is far too complex to used the phenomenological equation, the empirical one will be used in stead.

Table 4. The comparisons among parameters independently obtained from two statistical models of liquid uptake by tablets

	Model*		t**-
	5.a	5.b	statistics
a	360.71(48.28)	7.50(131.3)	2.5250
b	27.672(.075)	27.754(1.841)	-0.0445
(*a* *b*)or *c*	13.04(48.28)	8.51(1.84)	0.0938

*The degrees of freedom for model 5.a and 5.b are 4 and 3, respectively.

**Based on paired t-test, the degrees of freedom is 4+3-1=6. The critical value for α-level of 0.025 (2-tail test) is 2.447.

To avoid the complications, it is assumed that the change of tablet pore sizes is negligible, i.e., the tablet does not collapse. Since this assumption is never met in actual experiment, The data will be taken in very first beginning, or in other words, before the tablet collapses. Beginning with the model setup, equation 4 could be empirically arranged as follow

$$t = -\frac{1}{k1}V - \frac{k2}{k1}\ln[1 - \frac{1}{k_2}V] \qquad (5)$$

The meaning of each of the empirical constants (k_1 and k_2) will be discussed later. The obtained empirical equation can be separately set up to 2 models, i.e.;

$$t = -aV - \frac{a}{b}\ln[1 - bV] \qquad (5.a)$$

or,

$$t = -aV - c\ln[1 - bV] \qquad (5.b)$$

where, a, b, and c are $(1/k_1)$, $(1/k_2)$, and $(a\ b)$, respectively. These two models allow one to verify equation 5 since they came from the same origin. With the aid of statistical non-linear fitting, the model equations 5.a, and 5.b are separately applied to a set of data. The independently obtained parameters from these models could be matched to each others, for examples, a or b should be the same, and c should be $(a\ b)$. Table 4 shows the matching results using the data set of liquid uptake from Di-Tab tablets. As seen in the table, there is no statistical significant difference among the parameters from these two different models at a 95% confidence interval except that for a-parameter. The t-statistic value for a-parameter lies on the border cut by the critical value, and its standard error in

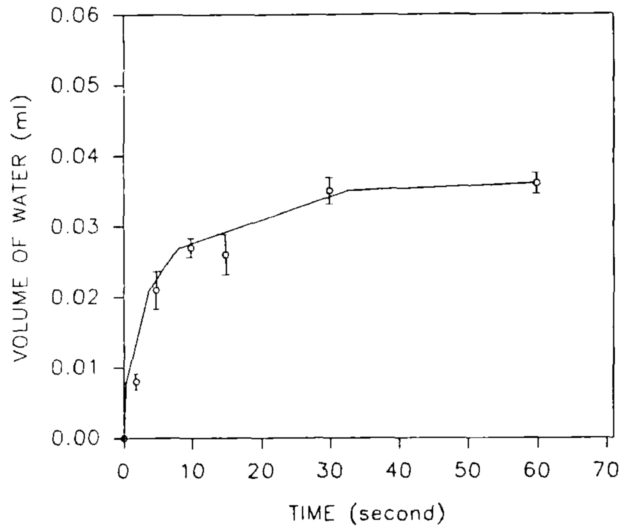

Figure 11. Water penetration-time profile of Di-Tab tablets. The solid line is based on model 5.a discussed in the text.

model 56 b is too high to accept (standard error of 131.3 compared to the estimated value of 7.5). Thus, it is still probable that the empirical equation (equation 5) is applicable to the liquid uptake data. Unfortunately, the complete verification of the phenomenological equation could not be done because of the complexity of the tablet pore structure as well as liquid penetration mechanism. Model 5.a is preferred due to the fact that the standard errors of the estimated parameters are acceptable and significantly less than the other model.

The typical pattern of liquid penetration profiles flatten off after rising because the gravitational and other forces balance capillary rise, and the tablet becomes saturated with water. It was postulated that the curve would be reflected by two different mechanisms of liquid uptake, i.e., a capillary penetration accompanied by a process of pore widening which triggers a more rapid penetration (15). In practice, it is difficult to study these mechanisms separately. It is assumed that the pore widening would come after an acceptably long period of time (which is not always valid such as in cases of tablets containing a superdisintegrant). The liquid water penetration-time profiles shown by the fitted curves using model equation 5.a for such formulated tablets are shown in Figures 11-15. The estimated parameters were extracted and presented as empirical constants appearing in equation 5. They are summarized in Table 5.

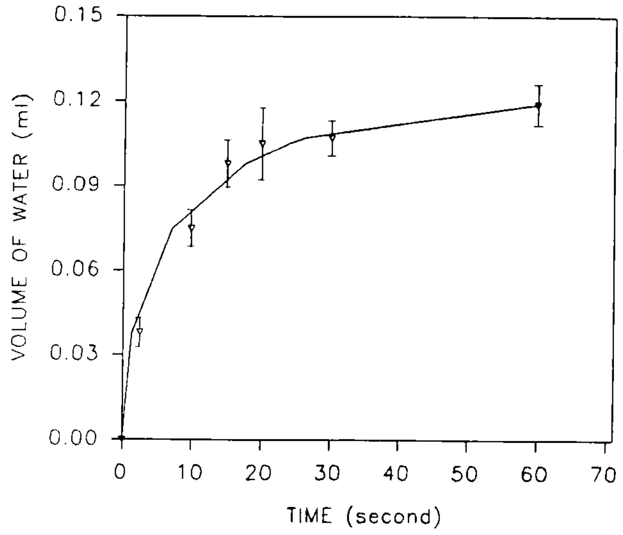

Figure 12. Water penetration-time profile of Di-Tab tablets containing 15% Avicel PH102. The solid line is based on model 5.a discussed in the text.

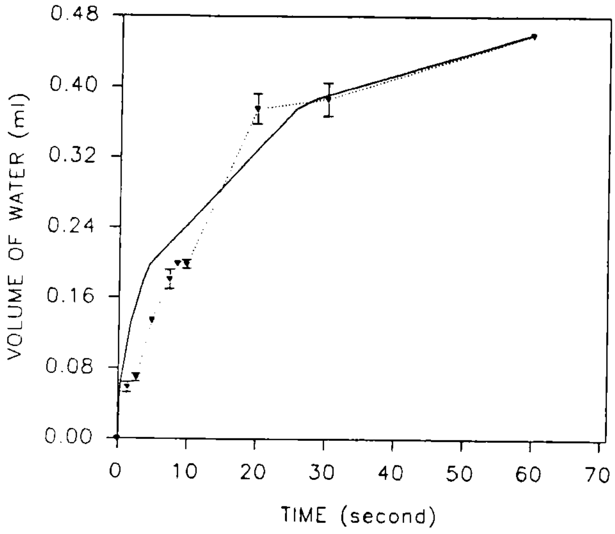

Figure 13. Water penetration-time profile of Di-Tab tablets containing 15% Ac-di-sol. The solid line is based on model 5.a discussed in the text, and the dotted line shows the actual profile.

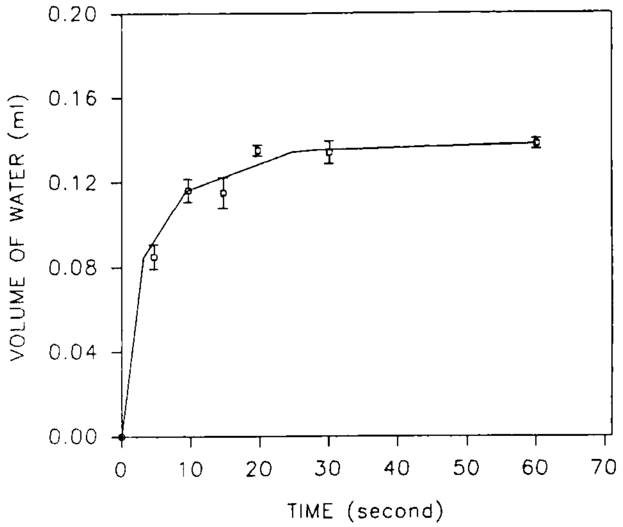

Figure 14 Water penetration-time profile of Di-Tab tablets containing 15% corn starch. The solid line is based on model 56.a discussed in the text.

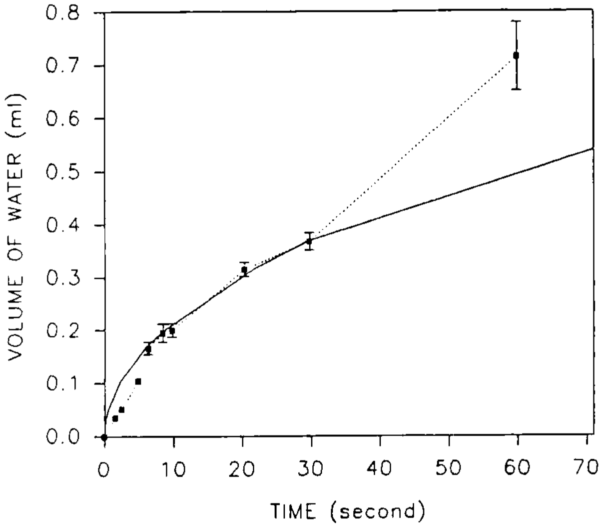

Figure 15. Water penetration-time profile of Di-Tab tablets containing 15% Primojel. The solid line is based on model 5.a discussed in the text, and the dotted line shows the actual profile.

Table 5 The liquid uptake empirical parameters extracted from model 5.a

Tablet	k_1, cm^3/sec	k_2, cm^3	*V'_{max}
Di-Tab. only	0.003	0.036	0.035
with 15% Avicel PH102	0.006	0.122	0.119
with 15% Ac-di-sol	0.012	0.513	0.468
with 15% corn starch	0.014	0.138	0.134
with 15% Primojel	0.0002	12.077	1.357

*The estimated maximum liquid uptake volume in cm^3 using statistical model of $V' = V'_{max}[1-\exp(-kt)]$, where, V', and k are volume uptake at time, t, and a constant, respectively.

By comparison between equations 4 and 5, it could be noted that the empirical constants are related to the phenomenological constants as follows

$$k_1 = \frac{\rho g A^2}{8\pi\eta} \quad \text{and} \quad k_2 = \frac{2\gamma A \cos\theta}{\rho g r} \tag{6}$$

where, A is the cross sectional surface area of a cylindrical pore having a radius, r. ρ, g, η, and θ are those factors previously denoted. As seen in equation 6, k_1 implies the relative contributions between gravity and viscosity of liquid, whereas, k_2 implies the contribution between capillary rise and gravity. Since the pore structure of the tablet does not follow exactly the cylindrical shape as stated by Washburn (2) and there is the hydrophilicity contribution, the significance of each constant could be drawn empirically. Assuming that the pore volume-size distributions of Di-Tab tablets containing a disintegrant are not significantly different from each other, which was actually true in this experiment (see the previous section), the k_1-value for liquid uptake into tablets containing 15% Ac-di-sol is higher than that for those containing 15% Avicel PH102 due to the fact that Ac-di-sol may be able to draw the liquid to a greater extent than Avicel PH102. The k_1-value for liquid uptake into tablets containing 15% Primojel is significantly low compared to the other disintegrant. It may be because Primojel undergoes a gel formation which builds up the viscosity of the penetrating liquid. The gelatin of Ac-di-sol, on the other hand, may not be sufficient to see the significance.

The k_2-values for Di-Tab tablets containing a disintegrant are significantly higher than that for Di-Tab tablet without any disintegrant, even though it seems that there is no significant difference in the pore sizes (Table 3). It may be because the hydrophilicity of the disintegrant eases the wetting of the tablet pores which makes the capillary rise overwhelm the porosity contribution. The magnitude of the k_2-value as well as the maximum uptake volume (Table 5) tends to coincide with the corresponding hydration capacity (Table 2). This finding was previously discussed by Choong and Wan (7). They suggested that water penetration into tablets could be due mainly to absorption of water by hydrophilic disintegrants (e.g. starch) whereas the porous capillary network only plays a minor role. And, these driving forces were opposed by the viscous force developed by the soluble excipient and swelling (16).

As seen in Figures 13 and 15, the model could only be partially applicable to the penetration results for tablets containing Ac-di-sol or Primojel. A superdisintegrant causes a change in tablet porosity. The disintegrant swelling narrows the pore sizes in the beginning and then the pores are widened due to the repelling pressure exerted causing the tablet to collapse which makes the amount of liquid uptake actually smaller in the beginning and then greater later. Finally, the water penetration is impeded by gelling formation of a superdisintegrant present in a tablet matrix.

CONCLUSION

It was demonstrated that the hydrophilic nature of the excipients, e.g. a disintegrant, present in a tablet played a major role in water uptake of the tablet. The empirical treatment of the Washburn liquid water penetration equation with the appropriate setup could be applied to determine the significance of the factors affecting water uptake by a formulated tablet. However, the model showed some limitation due to the complexity of the tablet pore system and the water penetration mechanism.

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