DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(18), 2439-2455 (1991)

THE SWELLING OF CORE TABLETS DURING AQUEOUS COATING I: A SIMPLE MODEL DESCRIBING EXTENT OF SWELLING AND WATER PENETRATION FOR INSOLUBLE TABLETS CONTAINING A SUPERDISINTEGRANT.

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ABSTRACT

A simple mathematical model was established to describe changes of tablet thickness due to swelling and water penetration during aqueous coating process. The model was illustrated by a simple linear equation, i.e.; $D = -(\alpha/(1+\varepsilon))l_1+(\alpha/(1+\varepsilon))l_0$; where D, l_0, l_1, α and ε are the depth of water penetrating into tablets, initial tablet thickness, the remaining dried core tablet thickness, swelling and porosity parameters, respectively. The data from dicalcium phosphate dihydrate(Ditab) tablets containing a super-disintegrant may be fitted into the model showing significant statistical correlation. The model was valid for describing the extent of tablet swelling and water penetration during aqueous coating.

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INTRODUCTION

To achieve the goal of drug release, a certain amount of disintegrant is employed in tablets. One of its mechanisms of action is swelling(1, 2). Sodium carboxymethyl cellulose, for example, swells, in contact with water, up to 200% of its original volume(3). This is undesirable when an aqueous film coating is to be applied to tablets containing a considerable amount of disintegrant. The coating process variables such as water removal efficiency, tablet bed temperature, etc., have been utilized to overcome the undesirable effect(4). There has not been, however, any study in terms of the tablet bed approach.

BASIC ASSUMPTIONS AND MATHEMATICAL DERIVATION

As analogous to the model of swelling of a hydrocolloid tablet(5), a simple mathematical model is established based on the following assumptions;

1. there is a unidirectional penetration of water into a tablet matrix,
2. the model is confined to flat faced tablets,
3. a thermodynamically quasi-static coating process has been achieved,
4. the volume of swelling (V_g) is considered as an additive quantity,
5. the shrinkage due to water removal is negligible, and
6. the overall rate of water penetration is constant as well as the degree of swelling.

Two parameters, namely, swelling(α) and porosity(ε), are introduced. They are defined as change of swelling volume(V_g) and of pore volume(V_p) with changing dried core volume(V_m), i.e.; $\alpha = (dV_g/dV_m)$, and.$\varepsilon = (dV_p/dV_m)$, respectively.

Let l_0, l_1, l_2 denote initial tablet thickness, thickness of remaining dried core after processing, and tablet thickness after processing, respectively. As seen in Figure 1, the depth of water penetrating into a tablet is;

$$D = l_2 - l_1 \qquad (1)$$

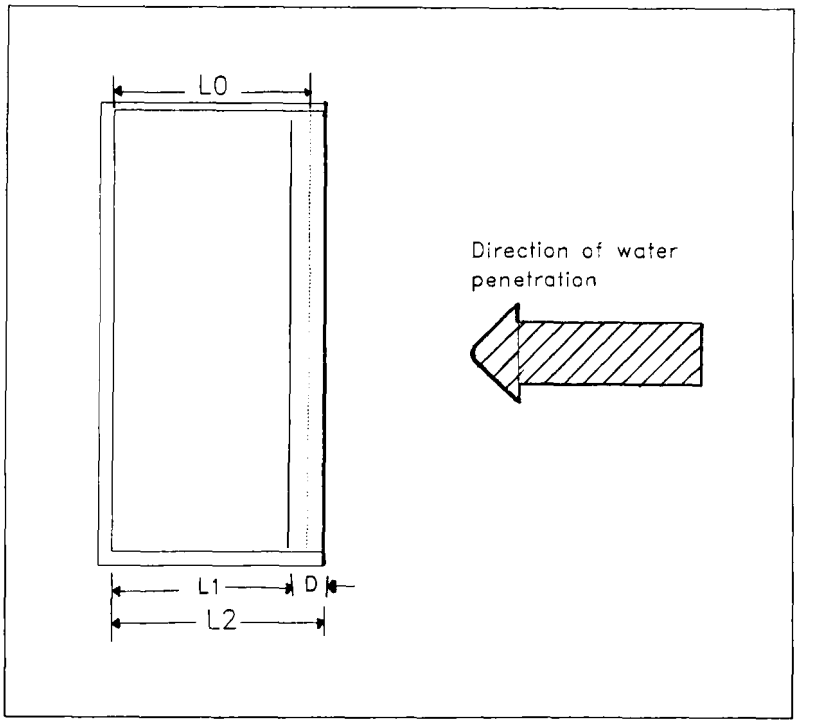

FIGURE 1: The scheme illustrating the mathematical model in operation.

Form assumption 4, swelling volume is additive volume of the core matrix wetted by sprayed water(V_m) and volume associated with water(V_w);

$$V_g = V_m + V_w \quad (2)$$

The loss of volume of dried core and pore volume during contacting water can be described as;

$$d(V_m + V_p) = -A\, dl_1 \quad (3)$$

where A is surface area which remains fixed in this case. An increase in volume due to swelling is then;

$$d(V_w - V_p) = A\, dl_2 \quad (4)$$

Differentiating equation (2) by dV_m and introducing α value yields;

$$\alpha = 1 + (dV_w/dV_m) \quad (5)$$

By using the same technique for equation (3) as well as inserting ε gives equation (6);

$$1 + \varepsilon = -A\,(dl_1/dV_m) \quad (6)$$

Then, substituting (dV_w/dV_m) from equation (5) into the differential form of equation (4);

$$\alpha - 1 - \varepsilon = A\,(dl_2/dV_m) \quad (7)$$

By assumption 6, both (dl_1/dV_m) and (dl_2/dV_m) are constant, thus, from equations (6) and (7);

$$(dl_2/dl_1) = -[\alpha-(1+\varepsilon)]/(1+\varepsilon) \quad (8)$$

From equation (1); $$(dD/dl_1) = (dl_2/dl_1) - 1 \quad (9)$$

Then, equations (8) and (9) yield;

$$(dD/dl_1) = -[\alpha/(1+\varepsilon)] \quad (10)$$

Rewriting equation (10) in the integral form with boundaries of D from 0 to D and those of l_1 from l_0 to l_1. The equation becomes;

$$D = -[\alpha/(1+\varepsilon)]\,l_1 + [\alpha/(1+\varepsilon)]\,l_0 \quad (11)$$

EXPERIMENTAL

Five disintegrants, which included corn starch, cross-linked carboxymethyl starch(Primojel, GeneriChem), microcrystalline cellulose(Avicel PH102, FMC Corp.), cross-linked carboxymethyl cellulose(Ac-di-sol, FMC Corp.), and cross-linked polyvinyl pyrrolidone (Polyplasdone XL, GAF Corp.), were employed at 2 concentration levels of 5 and 15% w/w. Each of the disintegrants was blended with dicalcium phosphate dihydrate(Ditab, Rhone-Poulenc) and 2% w/w povidone U.S.P., which acted as a directly compressible insoluble filler and a binder, respectively. In order to visually determining the extent of water penetration, 3% w/w cobalt chloride, anhydrous, was also presented in each formulation which, in the presence of water at 52-56 degrees C, changes in color because of dihydrate formation(6).

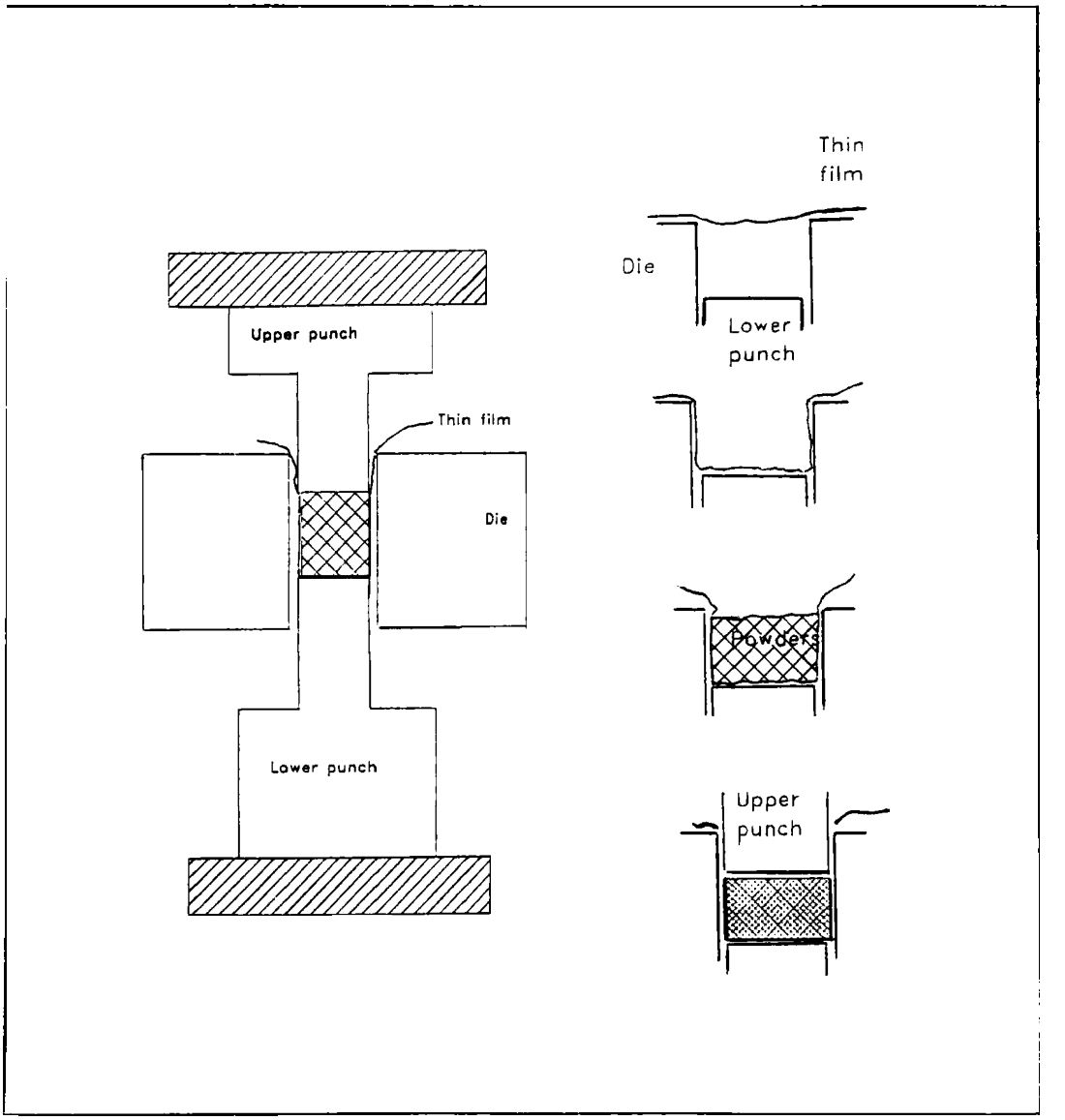

FIGURE 2: The method of preparation of wrapped tablet for single surface studies.

Table 1: Test of homogeneity of tablet populations.

Tablets	Ditab series	n	624
Mean	506 mg.		
Std.Dev	4.55 mg.	Variance	20.71
Skewness	-1.60	Kurtosis	10.38
t:Mean=0	2778.63	Prob>t	0.0001
W:normal	0.95	Prob<W	0.0001

Prior to compression, a thin polyethylene film (0.0063 mm. in thickness) was lined inside a half-inch-die. The tablets, which were prepared using a carver press, were wrapped during compression and had only one face that would contact with water(Figure 2).

The compression force was controlled in the range of 2000 $\pm$ 50 kg. to ensure the uniform compaction porosity. Tablet weight variation from 624 tablets was done to evaluate the homogeneity of the tablet population. Table 1 and Figure 3 present the statistical test which showed no effect of thin film on population variation.

A conventional pan coating system was employed. All spraying was done using an ultrasonic spray nozzle(Sonicore, model 035H, Sonic development Corp.). As assumed earlier, the process should achieve thermodynamic quasi-stasis. The coating conditions were set and the process was monitored by determining tablet bed surface temperature. Table 2 shows the conditions used during coating process. Figure 4 illustrates quasi-static tablet bed surface temperature measured by an infared pyrometer(Omegascope 600, Omega Engineering, Inc.).

To a quantity of blank tablets, the "wrapped" tablet samples with a thickness(l_0), were added to the coating pan. The coating process was initiated. Instead of coating

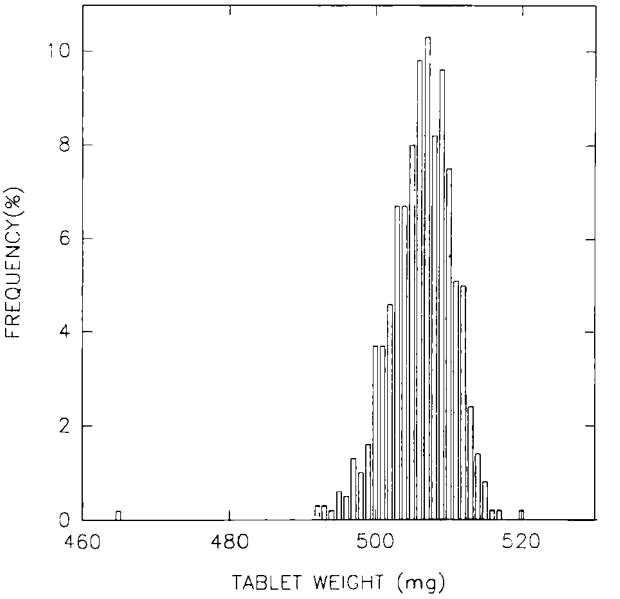

FIGURE 3: Tablet weight distribution indicating no effect of the thin film on tablet weight variation.

Table 2: Tablet coating conditions.

Tablet load	2 Kg.
Pan speed	20 rpm.
Inlet air temp	54.5 C
Tablet surface temp	40-55 C
Spray solution	Water
Spray rate	10 ml/min.
Spray pressure	15 psi.

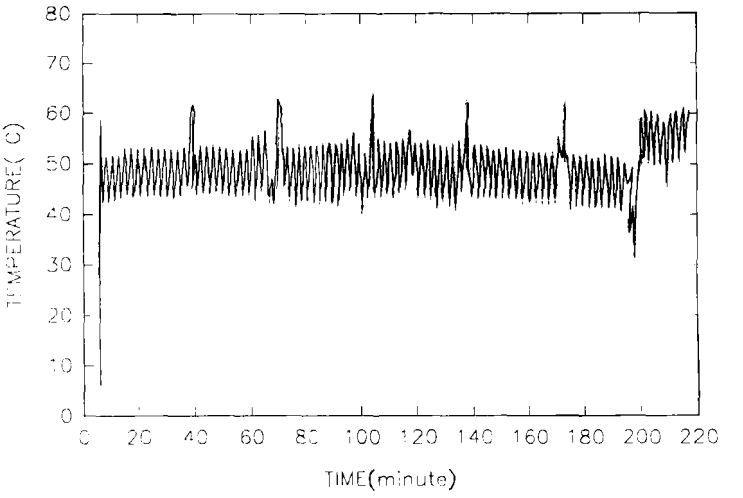

FIGURE 4: Tablet bed surface temperature–time profile detected by IR probe, showing quasi–static coating process.

Table 3: Parameters drawn from simple linear regressions between D's and l_1's.

Tablets	Slope(b_1)	Intercept(b_0)	r
Ditab, only	1.011	2.286	0.986
5% Avicel PH102	0.974	2.231	0.961
5% Polyplasdone XL	0.858	2.022	0.958
5% Primojel	1.029	2.344	0.996
5% Ac-di-sol	1.084	2.488	0.980
5% Corn starch	0.953	2.204	0.939
15% Avicel PH102	1.384	3.108	0.993
15% Polyplasdone XL	1.327	3.386	0.980
15% Primojel	1.195	2.918	0.913
15% Ac-di-sol	2.319	5.545	0.972
15% Corn starch	1.355	3.210	0.927

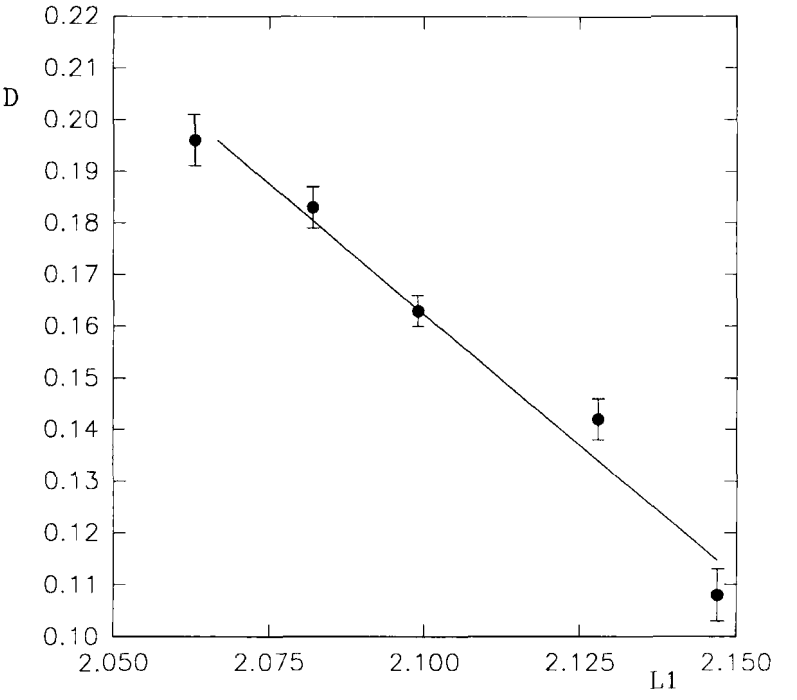

FIGURE 5.a: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness(L1) of dicalcium phosphate dihydrate tablets.

solution, water was sprayed onto the tumbling tablet bed. After 250 ml. of sprayed water were added, the process was paused to collect samples. The process continued for 5 to 6 intervals, i.e.; the amount of water was between 1250 ml. and 1500 ml., depending upon the undesirable effects seen such as tablet breakage, and the loss of quasi-static period due to the excess amount of water accumulated on tablet surface which unbalances the drying process. Then, the tablet thickness(l_2) of the wrapped tablet was measured. On each tablet surface, there was a thin blue layer of cobalt chloride dihydrate representing the extent of water penetration. This layer was microscopically measured to obtain the distance(D). These results were statistically

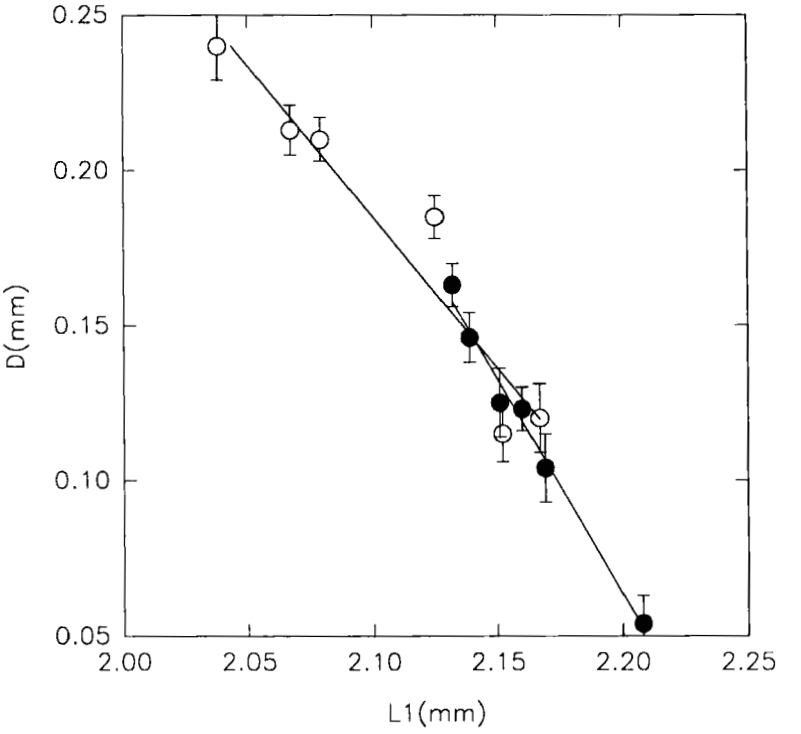

FIGURE 5.b: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness (L1) of microcrystalline cellulose(5% for open circles and 15% for filled circles) in dicalcium phosphate dihydrate tablets.

fitted according to the previously described model. Paired t-tests were performed to determine the significance of each parameter.

RESULTS AND DISCUSSION

The results of this study were statistically evaluated. All data are able to be fitted into the model with very high correlation(the correlation coefficients(r's) are tabulated in table 3.).It is seen from the mathematical derivation that the slope of fitted line, β_1 mathematically equals the value of its intercept divided by initial tablet thickness, β_0/l_0.

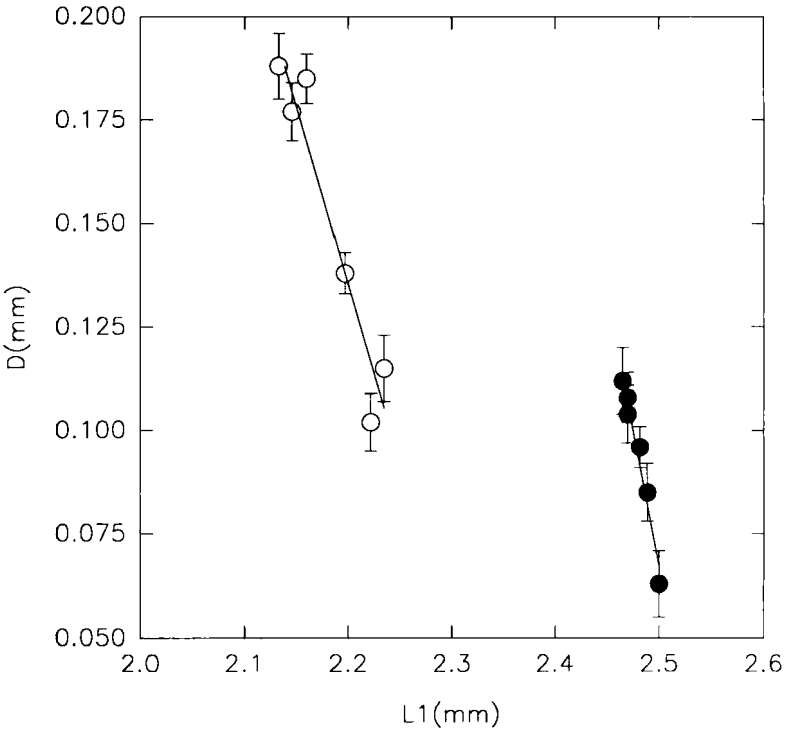

FIGURE 5.c: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness(L1) of cross-linked polyvinyl prrolidone (5% for open circles and 15% for filled circles) in dicalcium phosphate dihydrate tablets.

The model, therefore, can be simply validated by comparing either regressed slope(β_1) with the based-on model calculation ($\beta_1' = (\beta_0/l_0)$) or actual initial thickness(l_0) with calculated one($l_0' = (\beta_0/\beta_1)$). As seen in table 4, both actual and calculated values agree statistically to be the same.

THE MEANING OF β_1

From the model derivation point of view, the slope of fitted lines, $\beta_1 = [\alpha/(1+\varepsilon)]$, is, simply; $(dV_m+dV_w)/(dV_m+dV_p)$. If water penetrates into the pores of a tablet matrix

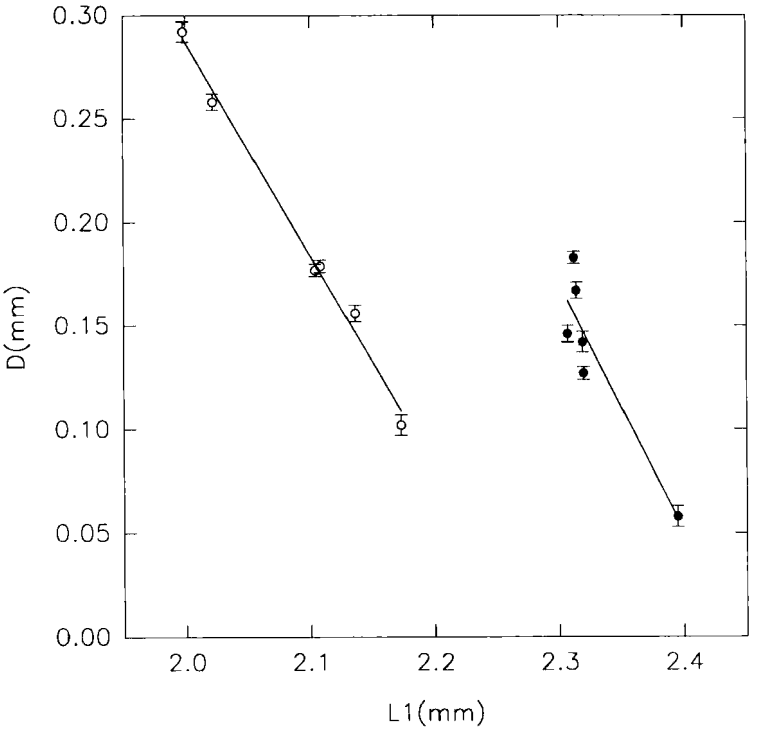

FIGURE 5.d: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness(L1) of cross-linked carboxymethyl starch (5% for open circles and 15% for filled circles) in dicalcium phosphate dihydrate tablets.

without swelling, i.e.; $dV_w = dV_p$, then β_1 approaches unity. Ditab tablets, as illustrated in figure 5. a, undergoes the so-called non-swelling condition because the slope approaches unity(see also table 3). As seen in table 3, the presence of a disintegrant causes the slope to deviate from unity. On one hand, if the tablets containing a disintegrant which show a slope greater than one, they are said to be in swelling predominated condition. On the other hand, if their slope is less than one, they undergo water penetration as a dominate condition. β_1 will be used for describing the performance of tablet disintegrant presenting in a tablet matrix.

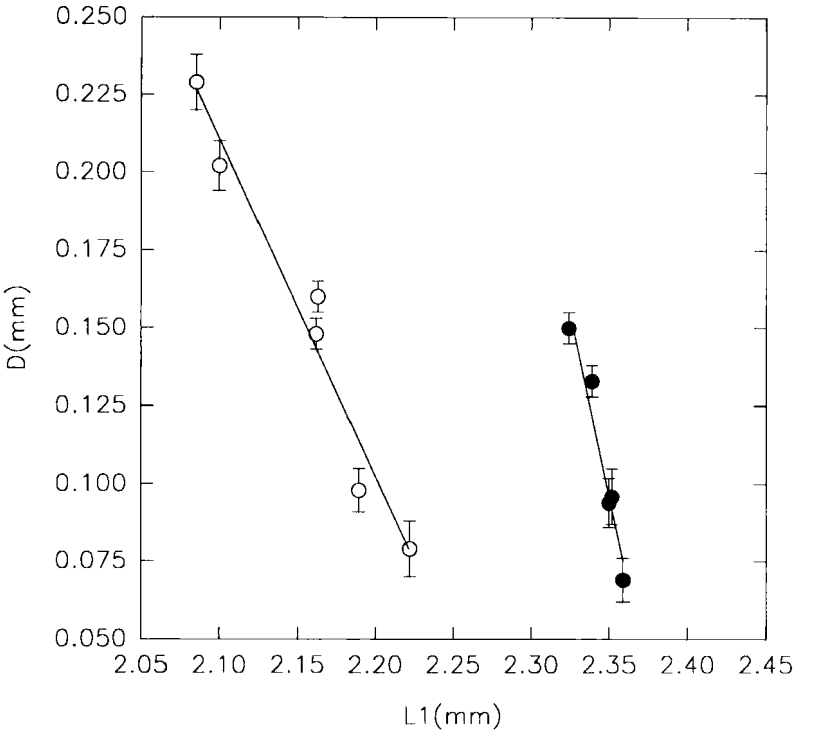

FIGURE 5.e: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness (L1) of cross-linked carboxymethyl cellulose(5% for open circles and 15% for filled circles) in di-calcium phosphate dihydrate tablets.

Table 5 illustrates the p-values of paired t-tests compared between the β_1 values of tablets containing a disintegrant and that of plain Ditab tablets. At 95% confidence, 15% Polyplasdone XL, 15% Avicel PH102, and 15% Ac-di-sol tablets exhibit significant swelling with p-values of 0.042, 0.007, and 0.002, respectively. In spite of being less than unity β-values for some disintegrants in 5% level, the results show non-significant difference between their β's and Ditab's β. The presence of a disintegrant caused the swelling effect which overshadows the water penetration.

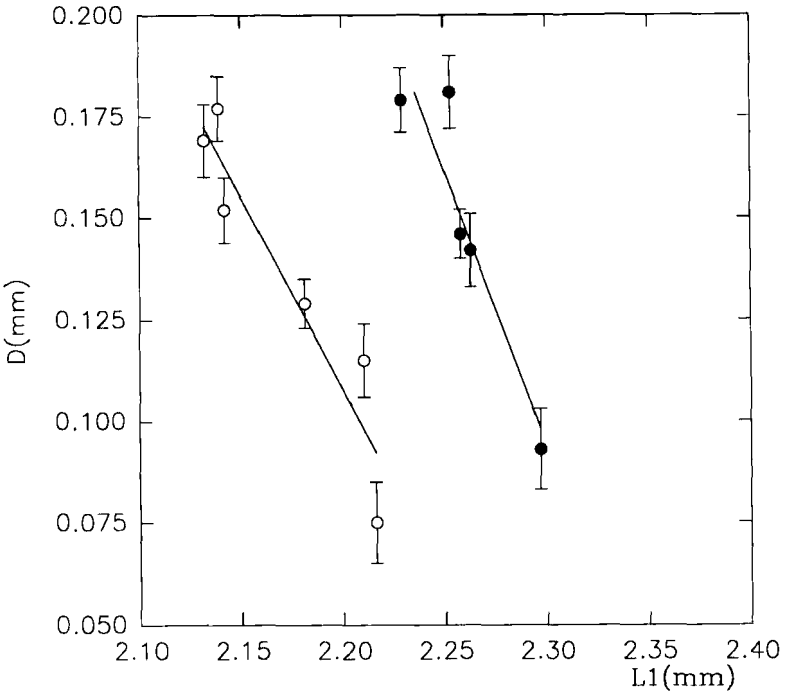

FIGURE 5.f: The plot between the depth of water penetrating into tablets(D) and the remaining dried core thickness(L1) of corn starch(5% for open circles and 15% for filled circles) in dicalcium phosphate dihydrate tablets.

Among the disintegrants, the β_1 parameters are compared at the same level of concentration. These p-values are tabulated in table 6. Only 15% Ac-di-sol present in the tablet matrices significantly swells to a greater extent compared to the others. And, the significance of swelling can not be clearly seen in the case of the lower concentration.

The amount of disintegrant presenting in a tablet matrix seems to have a significant role in tablet swelling. As seen in Figures 5, 15% disintegrant formulations, generally, tends to have a steeper slope. The increase in slopes with increasing amount of disintegrant in a tablet matrix is seen in the cases of Polyplasdone XL, Avicel PH102, and Ac-di-sol with statistical significances(p-values of 0.014, 0.014, and 0.002, respectively).

Table 4: Comparisons between actual and predicted parameters.

tablets	b_1	b_1'[1]	t-statistic[2]	l_0	l_0'[3]	difference[4]
Ditab, only	1.011	1.033	0.160	2.214	2.260	-2.11%
5% Avicel PH102	0.974	0.997	0.118	2.238	2.290	-2.33%
5% Polyplasdone XL	0.858	0.885	0.157	2.284	2.358	-3.25%
5% Primojel	1.029	1.013	-0.244	2.313	2.279	+1.49%
5% Ac-di-sol	1.084	1.099	0.096	2.264	2.294	-1.35%
5% Corn starch	0.953	0.980	0.110	2.250	2.313	-2.81%
15% Avicel PH102	1.384	1.346	-0.339	2.309	2.246	+2.73%
15% Polyplasdone XL	1.327	1.346	0.097	2.516	2.551	-1.39%
15% Primojel	1.195	1.221	0.069	2.391	2.443	-2.17%
15% Ac-di-sol	2.319	2.276	0.094	2.436	2.392	+1.80%
15% Corn starch	1.355	1.365	0.024	2.351	2.369	-0.78%

Note:

1. $b_1' = b_0/l_0$,

2. $t = (b_1-b_1')/SE$, $SE(\text{standard error})=[(SE_{b1})^2+(SE_{b0}/l_0)^2]^{1/2}$

Critical value of t-statistic at 0.05 a level and 9 degree of freedom is $\pm$ 1.833,

3. $l_0' = b_0/b_1$, and

4. difference is $100\ (l_0-l_0')/l_0$.

Table 5: Paired t-tests for significance of b_1 from that of b_1 of Ditab tablets.

Disintegrant	%	d.f.[1]	t-value[2]	p-value[3]
Avicel PH102	5	10	-0.215	0.417
	15	10	2.943	0.007
Polyplasdone XL	5	10	-0.953	0.181
	15	10	1.915	0.042
Ac-di-sol	5	10	0.497	0.315
	15	9	3.874	0.002
Primojel	5	10	0.162	0.437
	15	10	0.646	0.266
Corn Starch	5	10	-0.291	0.388
	15	9	1.035	0.164

Note:

1. degree of freedom = $n_1 + n_2 - 1$,
2. $t = (b_1 - 1.011)/SE$,
   Standard Error(SE) = $[(SE_{b1})^2 + (0.097)^2]^{1/2}$, SE of Ditab tablets is 0.097
3. $p = 1\text{-}2\ [p[(t), d.f.)]$.

Table 6: p-values for swelling comparisons among disintegrants

(pairwise comparisons between disintegrants listed by column and row.)

6.1 5% Disintegrant.

	p-value				
	Polyplasdone XL	Corn Starch	Avicel PH102	Primojel	Ac-di-sol
Polyplasdone XL	-	0.334	0.276	0.119	0.104
Corn Starch	0.334	-	0.463	0.341	0.269
Avicel PH102	0.276	0.463	-	0.361	0.276
Primojel	0.118	0.342	0.361	-	0.326
Ac-di-sol	0.104	0.269	0.276	0.326	-

6.2 15% Disintegrant.

	p-value				
	Primojel	Polyplasdone XL	Corn Starch	Avicel PH102	Ac-di-sol
Primojel	-	0.333	0.354	0.256	0.001
Polyplasdone XL	0.333	-	0.469	0.362	0.009
Corn Starch	0.354	0.469	-	0.466	0.031
Avicel PH102	0.256	0.362	0.466	-	0.009
Ac-di-sol	0.011	0.009	0.031	0.009	-

Overall, the results suggest that cross-linked carboxymethyl cellulose present in tablets causes significant swelling when in contact with sprayed water used in aqueous coating process. This result agrees with the data previously presented(3).

CONCLUSION

The established mathematical model is able to describe the extent of swelling and water penetration during aqueous coating. With controlled compression force, increasing the amount of disintegrant present in the tablets increases the $[\alpha/(1+\varepsilon)]$ value. The amount of disintegrant present should play an important rule in changing the swelling observed. Further work will be done on evaluating the effect of porosity on swelling and water penetration by varying compression force.

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