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Dissolution from disintegrating tablet: separate contributions from granules and primary drug particles considered

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Summary

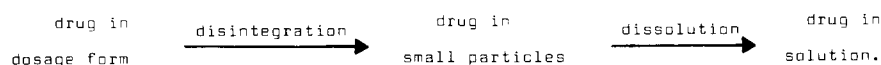
The dissolution process from a disintegrating tablet was treated mathematically so that separate contributions to dissolution from granules and primary drug particles were taken into account in a new dissolution model. Two equations were derived which were used together to describe the dissolution profile of the tablet. The applicability of the proposed dissolution model was demonstrated using published and experimental dissolution data on acetaminophen, phenylbutazone, hydrochlorothiazide and ibuprofen tablets. The apparent dependency of some of the model's parameters on certain tablet processing variables allowed the estimation of optimum values for such variables. Dissolution data of tablets prepared with increasing compaction forces and of tablets prepared with increasing disintegrant concentrations were analyzed according to theory and estimates of forces and disintegrant levels producing optimum dissolution were ascertained.

Introduction

Several investigators have used Scheme 1 to describe the dissolution process from disintegrating tablets (Leeson and Carstensen, 1975; El-Yazigi, 1981). Dissolution modeling or data interpretation based on Scheme 1 suffers from shortcomings. Scheme 1 implies that dissolution does not occur until the drug is in a fine particle form, i.e., primary drug particles (Wagner, 1969). A more realistic scheme for the dissolution process

was offered by Wagner and others (Wagner, 1969, 1971; Cadwalder, 1971). In the improved model (Scheme 2), dissolution was conceived to occur not only from primary drug particles, but also from intact tablet as well as aggregates or granules produced after disintegration of the tablet. Wagner used the modified scheme of dissolution to mathematically interpret cases of true and apparent first-order behavior of in vitro % dissolved vs time data. He also proposed the use of a distribution function to describe the in vitro % dissolution vs time data. The approach was based on the condition that % dissolved at time t was equivalent to % surface area generated to time t . However, this approach (Wagner, 1969) did not differentiate between contributions to dissolution

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Scheme 1.

from intact tablet, granules or primary drug particles. Furthermore, the description of % dissolved by a distribution function would not be applicable to cases where the above-mentioned condition of dissolution/surface area does not hold.

The present work uses Wagner's scheme for dissolution as a basis for the development of a dissolution model which takes into account separate contributions to dissolution from granules and primary drug particles. The work also reports on the application of the proposed model to arrive at optimum values for some tablet processing variables.

Theoretical

The proposed dissolution model describes the complex dissolution of a tablet as a step-wise process. The mathematical treatment of the model takes into account separate contributions to dissolution from granules and primary drug particles. The model used Scheme 2 to illustrate the different events involved in the transfer of the active agent from the disintegrating tablet to the dissolution medium. These events were as follows:

- (a) Dissolution from intact tablet (route 1).
- (b) Disintegration of the tablet to granules (route 2).
- (c) Dissolution from granules (route 3).
- (d) Deaggregation of granules to primary drug particles at a certain time $t = \tau$ (route 4).
- (e) Dissolution from primary drug particles (route 5).

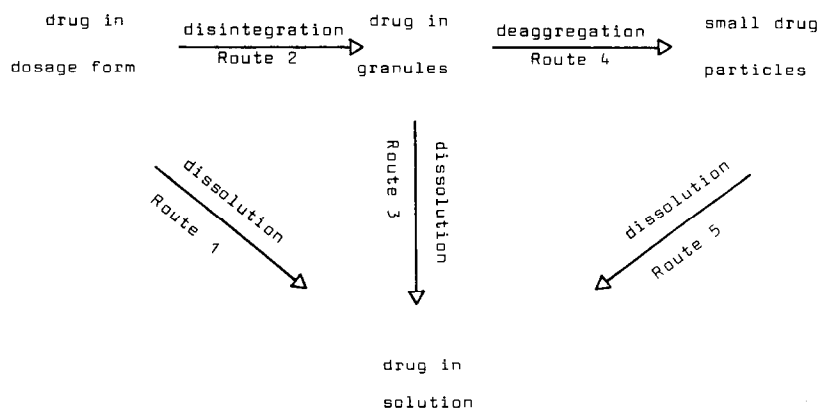
The assumptions made to assist the mathematical treatment of the dissolution model were as follows:

(1) Dissolution via route 1 is normally of minor importance and its contribution to dissolution could be ignored.

(2) The disintegration step (route 2) could be considered a first-order process.

(3) Transport of drug from granules (route 3) could be approximated by a diffusion mechanism similar to that operative under surface evaporation conditions. Therefore, at any time (t) during the life span of granules, the rate of transport of the diffusing substance would be proportional to the concentration gradient of that substance at the surface, and the surface area of granules.

(4) Surface area of granules would change exponentially with time. The rate constant of change is s and the pre-exponential factor is λ . The latter could be regarded as a measure of the



Scheme 2.

quality of the breakup of the tablet, i.e., a dispersion parameter.

(5) At a certain time $t = \tau$, the granules lose their physical integrity and deaggregate producing primary drug particles. From that time on, dissolution would continue from liberated primary drug particles.

(6) Dissolution from primary drug particles (route 5) occurs at $t > \tau$ and proceeds via a first-order process.

To simplify the mathematical treatments of the proposed model, the rate of drug appearance in solution was related to mass of undissolved drug in intact tablet, granules, etc. The use of mass dependence rather than surface dependence to describe the rate of drug appearance in solution is well documented in the literature (El-Yazigi, 1981; Carstensen et al., 1983).

Define the following:

(1) At any given time t ;

Q = amount of drug in intact tablet.

Q_g = amount of drug in granules.

Q_s = amount of drug in solution.

(2)

Q_0 = amount of drug in tablet at $t = 0$.

Q_0^* = amount of drug existing as undissolved primary particles at $t = \tau$.

Q^* = amount of drug existing as undissolved primary particles at $t > \tau$.

Q_s^* = amount of drug dissolved from liberated primary drug particles at $t > \tau$.

(3)

K_d = first-order rate constant of disintegration of tablet.

K_s = first-order rate constant of dissolution of primary drug particles.

τ = time at which granules loose physical integrity and liberate primary drug particles.

With reference to Scheme 2 and the given assumptions, the differential equation of the disintegration step and its corresponding Laplace transform are given by Eqns 1 and 2:

$$\frac{dQ}{dt} = -K_d \cdot Q \quad (1)$$

$$\bar{Q}(p) = \frac{Q_0}{(p + K_d)} \quad (2)$$

The bar above the function and p represent the Laplace transform for the function.

Assuming a diffusion mechanism for the transport of the drug from granules, the rate of drug appearance in solution from (route 3) would be a function of the concentration gradient at the surface, $(\partial C / \partial x)_{x=0}$, and the surface area of granules. Therefore, during $0 < t < \tau$, rate of change in amount of drug in granules, Q_g , would be given by Eqn 3;

$$\frac{dQ_g}{dt} = K_d \cdot Q - D \cdot \lambda \cdot (1 - e^{-st}) \cdot \left(\frac{\partial C}{\partial x} \right)_{x=0} \quad (3)$$

where D is the diffusion coefficient, and $(\lambda \cdot (1 - e^{-st}))$ describes the time dependence of the surface area of granules. From the diffusion equation of surface evaporation (Crank, 1957);

$$\frac{C}{C_0} = \operatorname{erfc} \frac{x}{2\sqrt{Dt}} - \left\{ e^{(hx + h^2Dt)} \cdot \operatorname{erfc} \left(\frac{x}{2\sqrt{Dt}} + h\sqrt{Dt} \right) \right\} \quad (4)$$

where C is the concentration in solution at time t , C_0 denotes the concentration at the surface, erfc is the complementary error function and h represents a constant term proportional to the inverse of the diffusion coefficient. Differentiate with respect to x , at $x = 0$:

$$- \left(\frac{\partial C}{\partial x} \right)_{x=0} = C_0 h \cdot e^{h^2Dt} \cdot \operatorname{erfc}(h\sqrt{Dt}) \quad (5)$$

Substitute Eqn 5 into Eqn 3.

$$\begin{aligned} \frac{dQ_g}{dt} = & K_d \cdot Q - (\lambda C_0 h) \cdot D \cdot e^{h^2Dt} \cdot \operatorname{erfc}(h\sqrt{Dt}) \\ & + (\lambda C_0 h) \cdot D \cdot e^{(h^2D - s)t} \cdot \operatorname{erfc}(h\sqrt{Dt}) \end{aligned} \quad (6)$$

$$\text{Let } (\lambda C_0 h) = \xi; \quad a^2 = \frac{(h^2D - s)}{D}$$

The Laplace transform of Eqn 6 is given by Eqn 7. To arrive at the Laplace transform of the last

term in Eqn 6, assumption was made, based on the definition of (a), that (h) could be approximated by (a) in this term.

$$\bar{Q}_g(p) = \frac{K_d Q_0}{p(p + K_d)} - \frac{\xi}{pq(q + h)} + \frac{\xi}{pq(q + a)} \quad (7)$$

where $q = (p/D)$.

Using Laplace transform tables (Crank, 1957; Selby, 1972), solve for Q_g , the amount of drug in granules at any time t ;

$$\begin{aligned} Q_g(t) = Q_0 - Q_0 \cdot e^{-K_d \cdot t} \\ - \xi \left\{ \frac{2}{h} \sqrt{\frac{Dt}{\pi}} - \frac{1}{h^2} \right. \\ \left. + \frac{1}{h^2} \cdot e^{h^2 Dt} \cdot \operatorname{erfc}(h\sqrt{Dt}) \right\} \\ + \xi \left\{ \frac{2}{a} \sqrt{\frac{Dt}{\pi}} - \frac{1}{a^2} \right. \\ \left. + \frac{1}{a^2} \cdot e^{a^2 Dt} \cdot \operatorname{erfc}(a\sqrt{Dt}) \right\} \end{aligned} \quad (8)$$

For $0 < t \leq \tau$, the amount of drug in solution is given by;

$$Q_s(t) = Q_0 - Q_g(t) \quad (9)$$

Substitute for $Q_g(t)$ in Eqn 9;

$$\begin{aligned} Q_s(t) \\ = 2\lambda C_0 h \left(\frac{1}{h} - \frac{1}{a} \right) \sqrt{\frac{Dt}{\pi}} - \lambda C_0 h \left(\frac{1}{h^2} + \frac{1}{a^2} \right) \\ + Q_0 \cdot e^{-K_d \cdot t} + \left\{ \frac{\lambda C_0}{h^2} \cdot e^{h^2 Dt} \cdot \operatorname{erfc}(h\sqrt{Dt}) \right\} \\ - \left\{ \frac{\lambda C_0 h}{a^2} \cdot e^{a^2 Dt} \cdot \operatorname{erfc}(a\sqrt{Dt}) \right\} \end{aligned} \quad (10)$$

The last two terms in Eqn 10 could be evaluated by the use of the asymptotic formula (Crank, 1957). However, these two terms vanish very rapidly and therefore, Eqn 10 could be approximated by;

$$\begin{aligned} Q_s(t) = 2\lambda C_0 h \cdot \left(\frac{1}{h} - \frac{1}{a} \right) \cdot \sqrt{\frac{Dt}{\pi}} \\ - \lambda C_0 h \cdot \left(\frac{1}{h^2} + \frac{1}{a^2} \right) + Q_0 \cdot e^{-K_d \cdot t} \end{aligned} \quad (11)$$

Eqn 11 could be rearranged to give the fraction of drug in solution, and then be rewritten in the following form:

$$f_s(t) = \alpha \sqrt{t} - \beta + e^{-K_d \cdot t} \quad \text{for } 0 < t \leq \tau \quad (12)$$

where

$$\alpha = \frac{2\lambda C_0 h}{Q_0} \cdot \left(\frac{1}{h} - \frac{1}{a} \right) \cdot \sqrt{\frac{D}{\pi}}$$

and

$$\beta = \frac{\lambda C_0 h}{Q_0} \cdot \left(\frac{1}{h^2} + \frac{1}{a^2} \right)$$

Eqn 12 calculates the fraction of drug in solution for $0 < t \leq \tau$.

For $t > \tau$, the differential equation for dissolution from primary drug particles and its corresponding Laplace transform are given by Eqns 13 and 14, respectively:

$$\frac{dQ_s}{dt} = \frac{dQ_s^*}{dt} = K_s \cdot Q^* \quad \text{for } t > \tau \quad (13)$$

$$\bar{Q}_s^*(p) = \frac{K_s \cdot Q_0^*}{p(p + K_s)} \quad (14)$$

Use Laplace transform tables and substitute the time term with $(t - \tau)$ to obtain amount dissolved from liberated primary drug particles, Q_s^* , at $t > \tau$.

$$Q_s^* = Q_0^* \cdot \{1 - e^{-K_s \cdot (t - \tau)}\} \quad \text{for } t > \tau \quad (15)$$

Substitute for Q_0^* in terms of the initial amount of drug in the tablet and amount in solution at $t = \tau$; then rearrange Eqn 15 to obtain the fraction dissolved from primary drug particles at $t > \tau$.

The fraction in solution at $t > \tau$ is given by Eqn 16 which is the summation of the fraction in solution at $t = \tau$, f_s^τ , and the fraction dissolved from primary drug particles at $t > \tau$.

$$f_s(t) = f_s^\tau + (1 - f_s^\tau) \cdot \{1 - e^{-K_s(t-\tau)}\} \text{ for } t > \tau \quad (16)$$

Thus, Eqns 12 and 16, when used together, describe the dissolution profile of the disintegrating tablet and provide estimates for several parameters controlling the dissolution process.

Materials and Methods

Ibuprofen (B.P.), lactose (B.P.) and magnesium stearate (B.P.) were supplied by A.P.M. Co., Sult, Jordan. Other ingredients were Methocel E15 (Colorcon Ltd, U.K.), Aerosil-200 (Degussa Ltd, U.K.) and Primojel (Generichem Corp., U.S.A.).

Ibuprofen tablets (200 mg)

Table 1 shows a list of ingredients of the two formulations used for preparation of the ibuprofen tablets. The active agent, lactose and methocel E 15 were mixed in a planetary mixer (Erweka Type PRS, Germany), for 30 min. Water was added to the powder mix and the wet mass was

passed through 2.00 mm screen (Erweka wet granulator type FGS, Germany). The granules were dried in a fluid bed dryer (Laboratory scale Aeromatic, Germany) at 45°C for 10 min. Granules were then passed through a 1.60 mm screen, further dried at 45°C for 2 h, and finally passed through a 1.00 mm screen before blending with disintegrant. Dry granules were mixed with Primojel and Aerosil-200 for 20 min in a powder jar using a roller (Pascal Engineering, U.K.) and finally mixed with magnesium stearate for 5 min. A single punch tablet machine (Erweka Tablet Press EKO, Germany) was used to compress tablets using 11 mm deep concave punches. Tablet hardness, friability and tablet weights were monitored during processing and were within acceptable limits.

Dissolution runs were conducted using the USP basket method (Erweka-Dissolution Tester, Type DT12R, Germany). The basket was rotated at 150 rpm in 900 ml of phosphate buffer (USP) of pH 7.2 at $37(\pm 0.5)^\circ\text{C}$. Solution concentration was monitored spectrophotometrically using a Beckman Du7 (Beckman, U.S.A.) at λ_{max} 265 nm.

Phenylbutazone and hydrochlorothiazide tablet (200 mg)

Published dissolution data (Ibrahim, 1985) were used for model assessment. The formulation used to prepare the tablets contained 49.8% phenylbutazone or hydrochlorothiazide, 10.0% partially hydrolyzed corn starch, 39.8% starch USP, 0.5% magnesium stearate USP, and water USP.

The granulations were compressed at different forces using an instrumented Colton 216 tablet press.

Acetaminophen tablets (500 mg)

Published dissolution data (Nelson and Wang, 1977) were used for model assessment. The formulation used to prepare the tablets contained 25.0 mg acetaminophen, 15.0 mg sodium carboxymethyl starch, 75.0 mg microcrystalline cellulose, 382.5 mg lactose (spray dried), and 2.5 mg magnesium stearate. The powder mix was compressed using a Model C Carver press.

TABLE 1

List of ingredients of ibuprofen tablet formulations (A and B)

Ingredients	Formulation A	Formulation B
Ibuprofen (B.P.)	200 mg	200 mg
Lactose (B.P.)	150 mg	175 mg
Methocel E15	50 mg	25 mg
Primojel	0–20% w/w	0–20% w/w
Magnesium stearate	2 mg	2 mg
Aerosil 200	2 mg	2 mg
Water (USP)	Q.S.	Q.S.

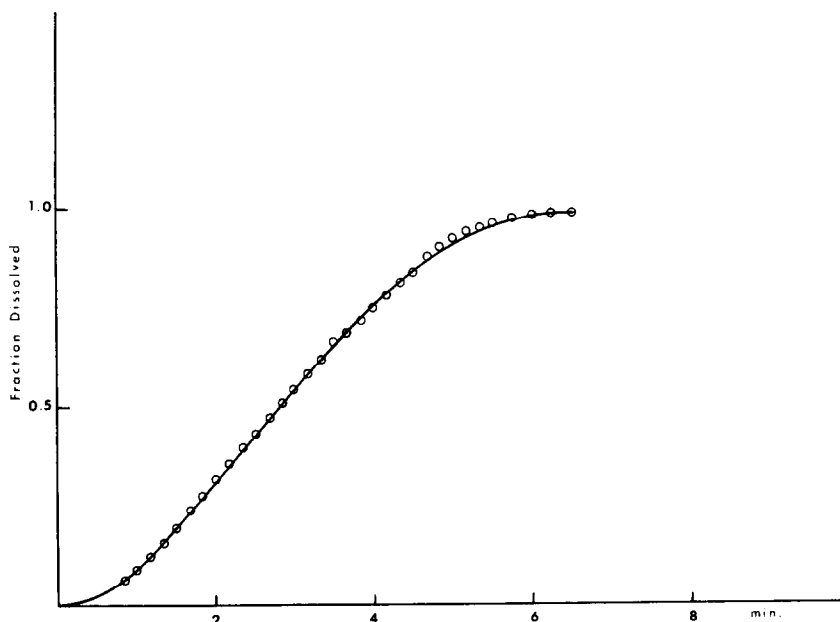


Fig. 1. Dissolution profiles of acetaminophen tablet superimposed by calculated data according to Eqns 12 and 16. (—) Experimental data (Nelson et al., 1978); (O) calculated values.

Treatment of data

The dissolution parameters α , β , τ , and K_d were obtained from a plot of the experimentally determined fraction dissolved vs square root of time. The exponential term of Eqn 12 disappears fast enough to allow estimation of α and β from the slope and negative intercept of the linear segment of the plot. K_d was calculated by substituting back into Eqn 12 for the estimated values of α and β , and fraction dissolved at time t . The time t was obtained from the intersection of the linear segment of the above plot with the time axis*. τ was estimated from the same plot and was taken as the time at which the data points started to deviate from linearity. An estimate of K_s was obtained by rearranging Eqn 16 to give;

$$\ln \left\{ 1 - \frac{(f_s(t) - f_s^\tau)}{(1 - f_s^\tau)} \right\} = -K_s \cdot (t - \tau) \quad (17)$$

The slope of the regression line of Eqn 17 gave

* In case no experimental dissolution data point was available at time t , the first next t at which experimental determination was available was used.

K_s . The estimated dissolution parameters were then substituted into Eqns 12 and 16 to calculate the fraction of drug in solution at any given time t .

Results and Discussion

Dissolution data of acetaminophen tablets (Nelson et al., 1977, 1978) prepared from a direct compaction formulation were analyzed according to the model. The dissolution parameters of the tablet were calculated from the published data, then Eqns 12 and 16 were used to calculate the fraction dissolved at any given time. Depicted in Fig. 1 is a plot of the experimentally determined dissolution profile of the acetaminophen tablet superimposed by the corresponding calculated values. Except for the very initial data points of dissolution, a very good agreement between the experimental data and the calculated values is shown in Fig. 1. The difficulty in predicting the initial data probably arises from the complexity of the dissolution process in the very early stages and from the fact that the proposed model did

TABLE 2

Dissolution data of hydrochlorothiazide tablets prepared at different compression forces and their calculated values obtained by use of Eqns 12 and 16

Time (min)	Compression force (kg)									
	1112 (± 116)		1603 (± 191)		2158 (± 204)		2638 (± 204)		3449 (± 223)	
	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
1	0.090	0.090	0.082	0.082	0.084	0.084	0.079	0.079	0.135	0.135
1.5	0.119	0.114	0.128	0.126	0.174	0.190	0.180	0.199	0.259	0.263
2	0.136	0.143	0.162	0.169	0.276	0.285	0.313	0.303	0.377	0.373
2.5	0.171	0.170	0.195	0.209	0.370	0.372	0.411	0.396	0.477	0.471
3	0.193	0.195	0.225	0.244	0.455	0.447	0.488	0.480	0.553	0.559
4	0.235	0.239	0.305	0.307	0.596	0.584	0.613	0.628	0.660	0.647
5	0.270	0.278	0.377	0.362	0.693	0.704	0.700	0.691	0.731	0.717
6	0.306	0.313	0.424	0.413	0.759	0.752	0.764	0.745	0.782	0.773
7	0.342	0.345	0.466	0.459	0.805	0.793	0.788	0.786	0.821	0.818
8	0.378	0.375	0.504	0.502	0.837	0.825	0.833	0.822	0.848	0.855
9	0.401	0.403	0.528	0.547	0.862	0.854	0.858	0.852		
10	0.428	0.430	0.567	0.588	0.882	0.878				
12	0.481	0.479	0.614	0.659						
15	0.549	0.546	0.719	0.744						
17	0.599	0.587	0.782	0.788						
20	0.644	0.644	0.848	0.841						
22	0.665	0.673								
25	0.695	0.712								
27	0.731	0.735								
30	0.760	0.766								
α	0.164		0.235		0.510		0.554		0.583	
β	0.089		0.163		0.436		0.480		0.451	
τ (min)	20.0		8.0		5.0		4.0		3.0	
K_d (min ⁻¹) ^a	4.200		4.605		4.605		5.298		5.809	
K_s (min ⁻¹)	0.042		0.095		0.177		0.184		0.222	

^a Results expressed as fraction dissolved.

K_d was calculated from data at time $t = 1$ min.

not address dissolution from intact tablets. Nevertheless, agreement between predicted values and experimental data was very good from the time where the lag period ends. This behavior was consistent with all tested data.

To further test the applicability of the model and the significance of its parameters, dissolution data of sets of tablets of phenylbutazone (PBZ) and hydrochlorothiazide (HCT) (Ibrahim, 1985) were analyzed according to the model. The tablets were prepared from a wet granular formulation and processed at different compaction forces. Shown in Table 2 are the experimental dissolution data of HCT tablets and their corresponding calculated dissolution values.

Also shown in Table 2 are the estimated values of the various dissolution parameters obtained for each set of tablets. Fig. 2 shows plots of the calculated dissolution profiles of PBZ tablets at different compaction forces, superimposed by the corresponding experimentally determined fraction dissolved at specific times. From Table 2 and Fig. 2, it is obvious that a good agreement between the experimental data and calculated values existed for the different sets of tablets. Furthermore, the ability of the model to describe satisfactorily the different shapes of dissolution curves was demonstrated in the aforementioned presentations.

The dissolution parameter (α) is a complex

term which reflects the inherent capacity of the tablet to produce certain population of dispersed granules. Higher α values indicate better disintegration patterns and more readily dissolving tablets. Profiles showing effects of applied compaction forces on α parameters and dissolution behavior of PBZ and HCT tablets are depicted in Fig. 3. The plateau regions of the α curves in Fig. 3 suggest attainment of optimum disintegration patterns from the concerned formulations. This behavior would suggest optimum dissolution of the tablets which were compressed at forces in the plateau region. While the latter statement was true in the case of HCT tablets, PBZ tablets showed a decline in their dissolution when compression forces were greater than 696 kg. There-

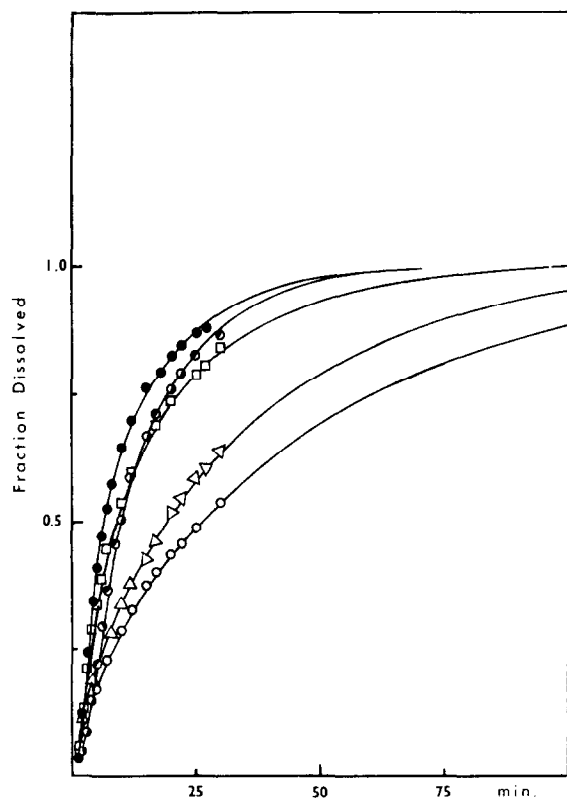


Fig. 2. Dissolution profiles of phenylbutazone tablets prepared at increasing compaction forces (curves), generated by use of Eqns 12 and 16, superimposed by experimental data (Ibrahim, 1985). (\circ) 337 kg, (Δ) 440 kg, (\square) 499 kg, (\bullet) 696 kg, and (\circ) 1528 kg. Experimental determinations were up to 30 min only.

fore, it could be concluded that, while PBZ tablets disintegrated optimally at compaction forces above 696 kg, other factors (e.g., longer lag time) adversely affected the dissolution of the tablets when compressed at forces above 696 kg.

Since the range of compaction forces used in preparing the two products produced acceptable tablets (Ibrahim, 1985), estimates of optimum forces required to prepare the products were ascertained from their α profiles. The intersection of the rising segment of the PBZ α curve with the plateau yielded a value of approx. 600 kg. From the plateau region of the HCT α curve, a force of approx. 2500 kg was determined. Therefore, using α parameter/compression force profiles, it was possible to gain a better understanding of the dissolution/compression behavior of the formulations and to recommend suitable compaction forces to prepare the two products from these particular formulations.

In the following part of the study, disintegrant concentrations in two ibuprofen formulations were varied and dissolution data of different sets of tablets were analyzed according to the model. The experimental design was aimed at testing the ability of model to: (a) choose the optimum disintegrant level, and (b) differentiate between the two formulations. As was the case with the previous examples, a good agreement between experimental data and calculated values existed for the different sets of tablets. Shown in Fig. 4 is a comparison between plots of the τ dissolution parameters of formulation A and formulation B of the ibuprofen tablets as a function of disintegrant concentration. Also shown in Fig. 4 are effects of increasing amounts of the disintegrant on the dissolution of the two formulations (inset). From Fig. 4, the presence of increasing amounts of Primojel reduced the τ values of the two formulations and shortened the time needed to achieve 90% dissolution.

According to the model, a well dissolving tablet would be characterized by a low τ value and a high α value. With this in mind, τ values of different sets of ibuprofen tablets were correlated with their corresponding α values. Results are shown in Fig. 5. From the obtained plots, it is apparent that, at disintegrant concentrations of

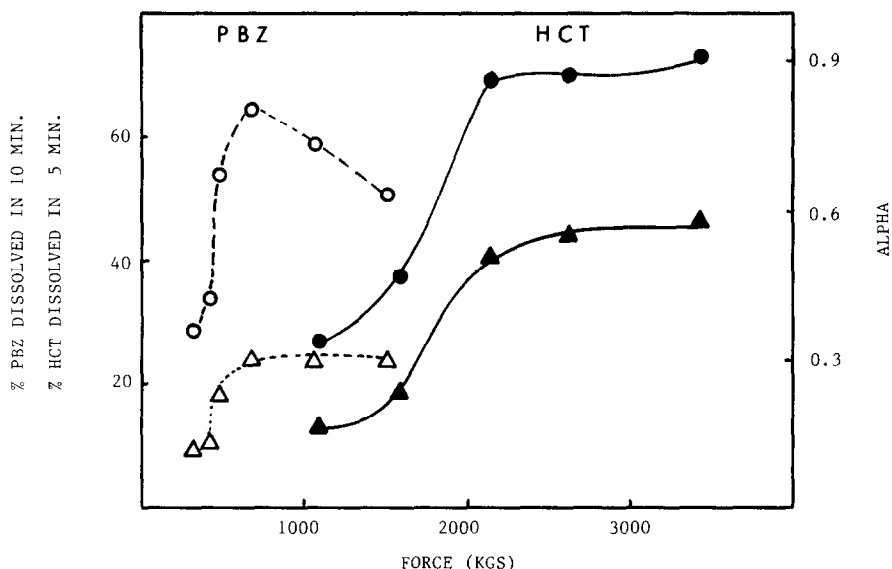


Fig. 3. Effects of compression force on dissolution and α parameter of phenylbutazone and hydrochlorothiazide tablets. (\circ , \bullet) Dissolution curves; (Δ , \blacktriangle) α curves.

10–20%, the (α, τ) data points of formula A clustered around more or less the same location. Corresponding data points of formula B, on the other hand, stretched out to lower τ and higher α

values. Therefore, while a 10% Primojel concentration could be considered as the concentration of choice for the two formulations, formula A showed a limited capacity to improve in dissolu-

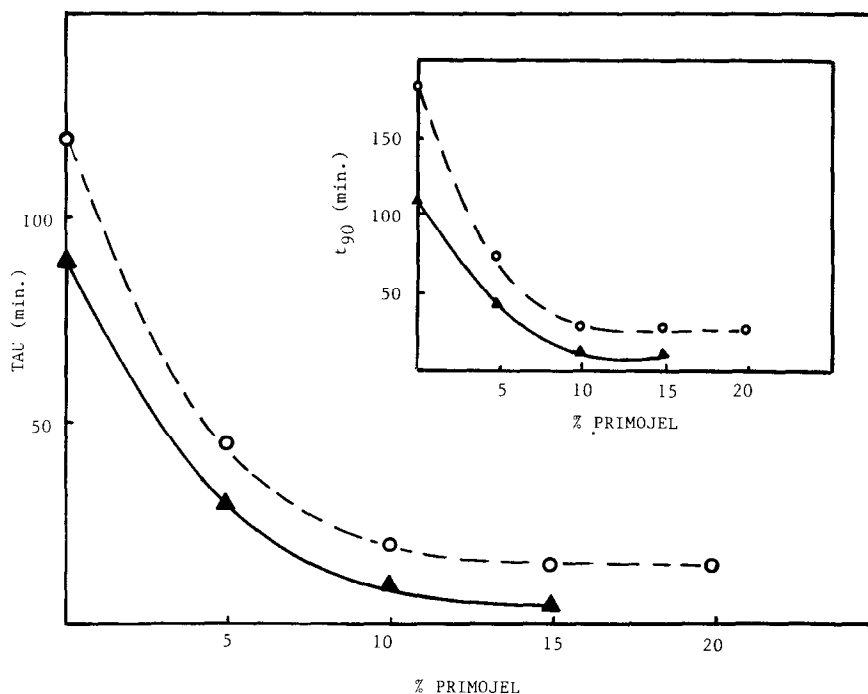


Fig. 4. Effects of increased concentrations of Primojel on the τ parameter and the dissolution (inset) of two tablet formulations of ibuprofen. (\circ) Formulation A; (\blacktriangle) formulation B.

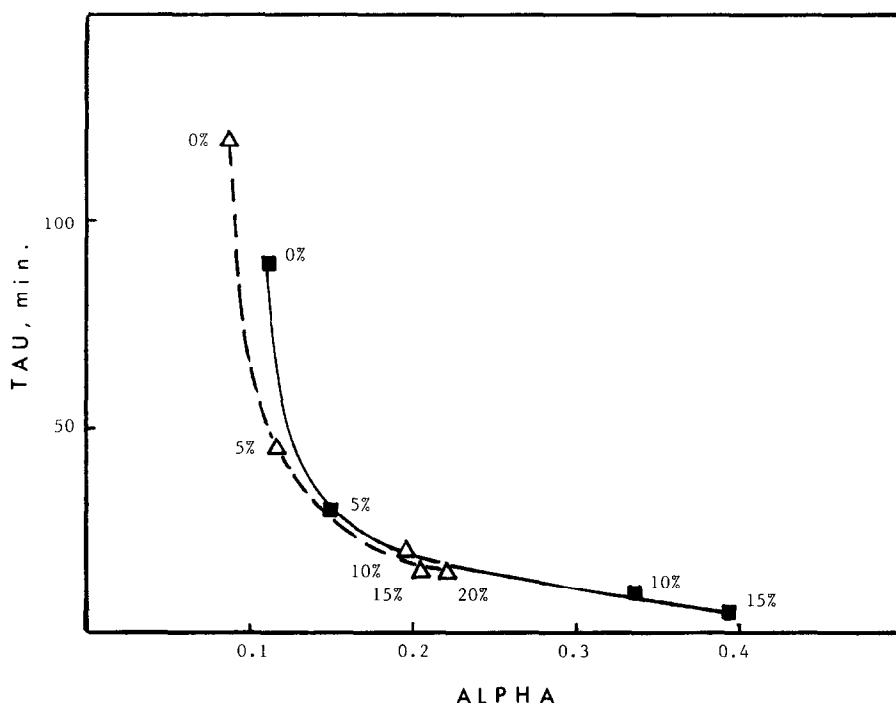


Fig. 5. Relationship between α and τ parameters for sets of Ibuprofen tablets containing different concentrations of Primojel. (Δ) Formulation A; (\blacksquare) formulation B.

tion with the increase of the disintegrant. In comparison, formula B demonstrated a good deal of inherent ability to improve in dissolution with increase in disintegrant concentration. A decision to choose formula B could thus be made based on this information. Plots similar to those shown in Fig. 5, therefore, could be useful in providing information on the inherent characteristics of the formulations.

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