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Correlation between dissolution and disintegration rate constants for acetaminophen tablets

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Summary

The aim of this work is to study how factors such as tablet hardness, dissolution stirring rate, pH and volume of the dissolution medium, influence the disintegration- and dissolution-time profiles of ideally formulated acetaminophen tablets. It was found that for fast-disintegrating tablets, semilogarithmic plots of the disintegration and dissolution versus time were linear. The slopes of the linear plots were used to calculate the disintegration rate constant (k_d) and the dissolution rate constant (k_s). In contrast, for slow-disintegrating tablets, two lines were obtained. The point of intersection of the two lines was referred to as the lag-time, which is the time needed for the tablet to disintegrate. Similar patterns were obtained at different dissolution conditions such as stirring rates, pHs and volumes of the dissolution medium. A plot of k_s versus k_d was linear with a slope of approximately one, suggesting that dissolution is a direct function of distintegration. Similarly when $T_{90dissolved}$ was plotted against $T_{90disintegrated}$, a linear relationship was obtained with a slope of approximately one. Equations describing these relationships were deduced. The disintegration time measured in the dissolution apparatus was equal to the disintegration time measured by the BP method at a compression force 18–21 kN but much higher when the compression force was greater than 21 kN. However, the disintegration time measured in the dissolution apparatus was almost equal to $T_{90dissolved}$ at all the compression forces studied.

Introduction

The object of correlating the disintegration and dissolution rates of tablets and capsules is desirable. Several investigators demonstrated that disintegration and dissolution in the same apparatus can be correlated. Wagner (1969) has pointed out that first-order kinetics apply to the analysis of the dissolution data. Carstensen et al. (1978a and b, 1980) showed that all dissolution and disintegration data adhere to an exponential decay law. Kitazawa et al. (1975, 1977) developed an equation similar to that of Wagner (1969) without taking the surface area of the dissolving particles into consideration and in which when the dissolution data were plotted semilogarithmically versus time, two straight lines were obtained. The point of intersection of the two lines was taken as the time needed for the tablet to disintegrate into small particles. Nelson and Wang (1977, 1978) described a method for determining the time course of tablet disintegration which involves a

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numerical analysis of the experimental dissolution profile of a tablet and the dissolution characteristics of primary drug particles. El-Yazigi (1980, 1981) studied the release of drugs from an idealized tablet formulation and commercial tablets and developed a simple graphical method for disintegration–dissolution analysis of percent dissolved–time data and noted that the dissolution and disintegration are not first-order in nature. Jacob and Plein (1968) found an increase in hardness resulted in a decrease in the dissolution rate of phenobarbitone tablets but they found no correlation between the dissolution rate and disintegration time.

In view of the above variable results, this present work was undertaken in order to study the dissolution–disintegration patterns of an ideally formulated acetaminophen tablet and to determine how variables such as compression force, tablet hardness, dissolution stirring rate, pH and volume of the dissolution medium influence these patterns.

Materials and Methods

Materials

Acetaminophen direct compression grade was purchased from Hartington, U.K. Magnesium stearate was obtained from Sigma Chemicals, U.K., colloidal silicon dioxide from Degussa, F.R.G., microcrystalline cellulose from FMC, U.S.A., and disodium hydrogen phosphate from BDH Chemicals, U.K.

Methods

Tablet formulation

Acetaminophen 500 mg tablets were made by direct compression. The tablet formulation contained 84.5% acetaminophen, 3.5% gelatin, 0.2% magnesium stearate, 0.2% colloidal silicon dioxide and 11.6% microcrystalline cellulose. The tablets were tested for their thickness, friability, hardness and disintegration time (as in the BP 80). The results obtained are shown in Table 1.

Dissolution studies. Six 500 mg tablets of acetaminophen were placed each in a basket of USP dissolution apparatus in a 37 °C thermostated bath. Dissolution experiments were then performed in 500 ml of distilled water and at a stirring rate of 60 rpm unless otherwise stated. Samples were then removed at designed time intervals and assayed for their acetaminophen content spectrophotometrically at 250 nm. The experiment was continued until 100% dissolution was achieved. Percent dissolved was calculated from an established Beer's plot. Each data point is the average of 6 individual determinations. In all cases the standard deviation was less than 3%.

TABLE 1

Physical properties of the tested tablets

Compression force (kN)	Hardness (kg)	Thickness (mm)	Friability (%)	BP disintegration time (min)
18.1	7.5	5.4	2.80	2
21.1	10.5	5.0	1.40	4
22.0	18	4.6	0.57	5
23.0	20	4.4	1.23	41
24.5	> 20	4.3	2.93	51

Disintegration studies. Disintegration rate studies were determined in the same apparatus used for the dissolution studies. The disintegration test was carried concurrently with the dissolution test, in that each time a sample was taken for dissolution measurements, the stirring motor was stopped, the baskets were lifted out and the tablets were dried to a constant weight (M). Percent undisintegrated was calculated from $M/M_0 \times 100$ where M_0 is the initial tablet weight. Each data point is the average of 6 individual determinations. In all cases the standard deviation was less than 3%.

Results and Discussion

Fig. 1 shows the disintegration–dissolution data for fast-disintegrating tablets (BP disintegration time of ≤ 5 min) and for slow-disintegrating tablets (BP disintegration time of ≥ 40 min). It is clear that for fast-disintegrating tablets, the disintegration–dissolution data fall on the same line which is curvilinear in nature. However, for the slow-disintegrating tablets, the disintegration–dis-

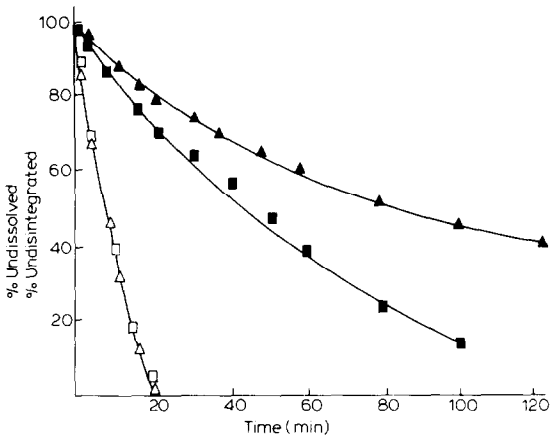

Fig. 1. Disintegration and dissolution profiles. Fast-disintegrating tablets (□, △); slow-disintegrating tablets (■, ▲).

solution data do not fall on the same curve and show a well-defined exponential decay pattern.

Fig. 2 shows a plot of the logarithm of the percent remaining (undissolved and undisintegrated) versus time for the fast-disintegrating tablets. It is evident from Fig. 2 that only one straight line is obtained contrary to what have been reported by Kitazawa et al. (1977) and El-Yazigi (1981) but similar to the findings reported by Carstensen et al. (1980). This suggests that the tablet disintegrates gradually and hence there is a

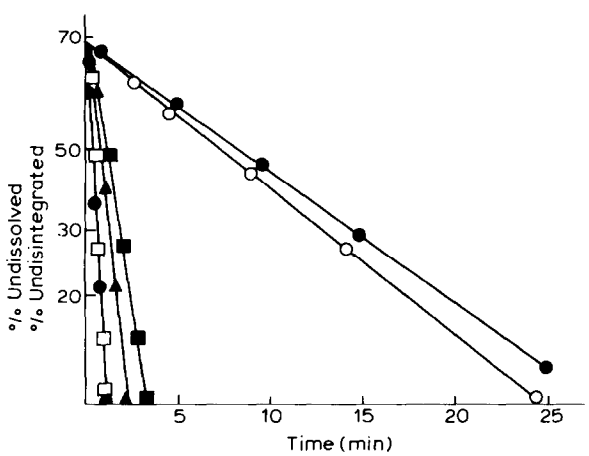

Fig. 2. Semilogarithmic plot of percent undissolved and undisintegrated versus time for fast-disintegrating tablets. Hardness 7.5 kg (●, □); hardness 10.5 kg (■, ▲); and hardness 18.0 kg (●, ○), respectively.

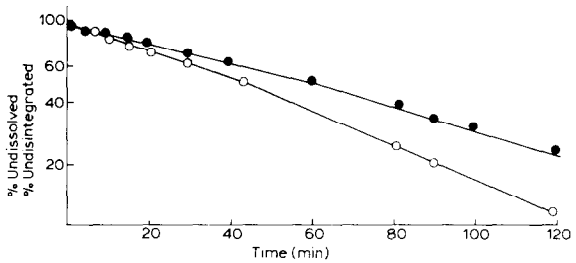

Fig. 3. Semilogarithmic plot of percent undissolved (●) and undisintegrated (○) versus time for slow-disintegrating tablets.

continuous and not a sudden increase in surface area.

Figure 3 shows the dissolution–disintegration data for the slow-disintegrating tablets plotted semilogarithmically versus time. It is evident from Fig. 3 that two intersecting lines are obtained. This behavior is similar to that reported by Kitazawa et al. (1975, 1977). The point of intersection of the two lines is referred to as the lag-time (T_i) which is the time needed for the tablet to disintegrate into small particles. At T_i there is a sudden increase in surface area resulting in a sudden increase in dissolution.

In an attempt to determine whether the above dissolution and disintegration behaviour for fast- and slow-disintegrating tablets is maintained under different experimental conditions, dissolution and disintegration data were obtained at different volumes of dissolution media, pH and stirring rates. The dissolution profiles obtained at different volumes of dissolution medium for the fast- and slow-disintegrating tablets are shown in Fig. 4. Fig. 5 shows the profiles obtained at different pHs and Fig. 6 shows the profiles obtained at different stirring rates.

It is evident from these figures that in all cases the fast-disintegrating tablets showed one-line plots, and the slow-disintegrating tablets showed two-line plots. This suggests that the dissolution behavior of a tablet of a given hardness is independent of the experimental conditions.

To quantify the relationship between dissolution rate constant (k_s) and the disintegration rate constant (k_d), k_s was correlated versus k_d for all the tablets at all experimental conditions employed. It is important to mention that a linear

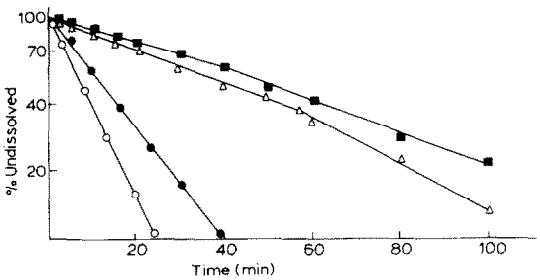

Fig. 4. Effect of volume of the dissolution medium on the dissolution profiles for fast-disintegrating and slow-disintegrating tablets. Volume 500 ml (●, ■) and volume 900 ml (○, △), respectively.

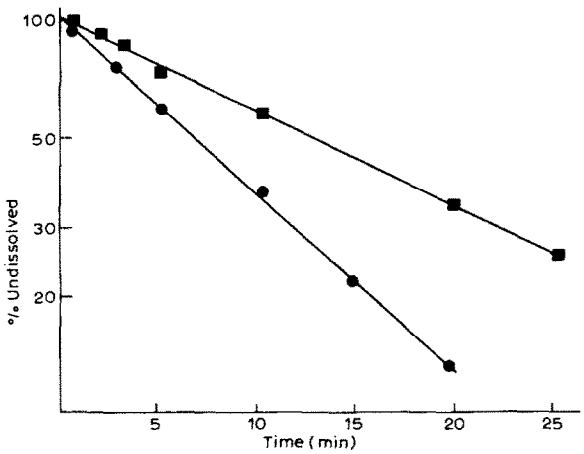

Fig. 5. Effect of pH on the dissolution of fast-disintegrating tablets. 0.1 HCl (■) and pH 5.8 (●).

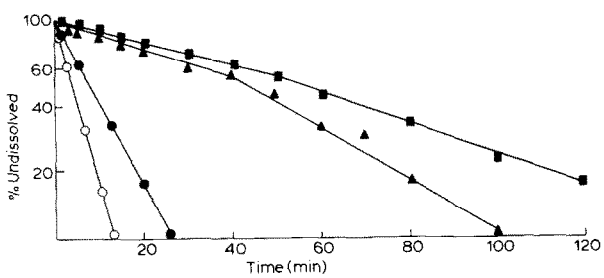

Fig. 6. Effect of stirring rate on the dissolution profile of fast-disintegrating and slow-disintegrating tablets. 60 rpm (●, ■) and 100 rpm (○, ▲), respectively.

relationship was obtained in the following equation:

$$k_s = 0.006 + 0.954k_d \quad (r = 0.998;\ n = 10)$$

This equation suggests that the slope of the k_s–k_d plot is approximately one and that the line passes through the origin.

The relationship between dissolution and disintegration of tablets, when performed in the same apparatus was also determined by correlating the time needed to dissolve 90% of the tablet (T_{90Ds}) versus the time needed for 90% of the tablet to disintegrate (T_{90DT}) at different experimental conditions. A linear relationship was obtained in the following equation:

$$T_{90Ds} = -0.515 + 1.022(T_{90DT})$$

$$(r = 0.996;\ n = 10)$$

This equation also suggests that the slope of the plot is approximately one and that the line passes through the origin. Fig. 7 shows the effect of the compression force on T_{90Ds}, the disintegration time

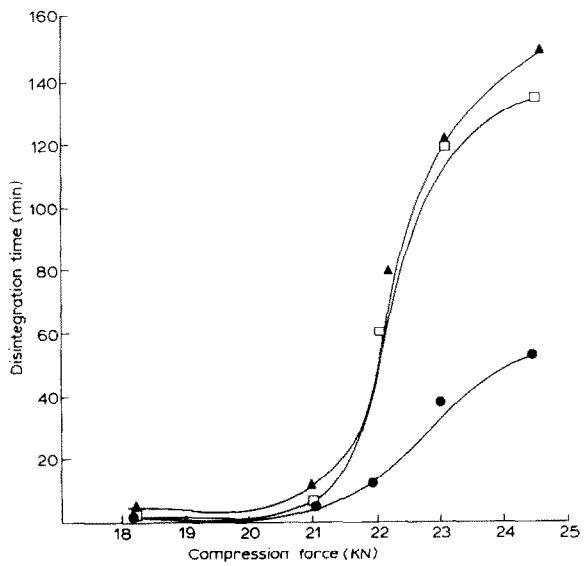

Fig. 7. Variation of T_{90Ds} (▲), DT (□) and DT_{BP} (●) with the applied compression force.

as measured in the dissolution apparatus (DT) and the disintegration time as measured in the BP disintegration apparatus (DT_{BP}). It is evident from Fig. 7 that T_{90Ds}, DT and DT_{BP} are low and almost equal at compression forces of 18–21 kN. Then small changes in the compression force result in a larger increase in all of these parameters. At compression forces greater than 21 kN, the values of DT and T_{90Ds} are almost identical and higher than the values of DT_{BP}. The difference between the values of DT and DT_{BP} could be due to the differences in the nature of the two techniques used to measure the disintegration times.

From this work it can be concluded that in the case of fast-disintegrating tablets, the dissolution and disintegration profiles follow first-order kinetics. With slow-disintegrating tablets, the theory suggested by Kitazawa et al. (1977) prevails. It was also found that the shapes of the disintegration and dissolution profiles were independent of the experimental conditions such as pH, stirring rate and volume of the dissolution medium. This work also revealed that a plot of the experimentally determined k_s versus k_d, when both dissolution and disintegration are performed in the same apparatus, was linear with a slope of unity. This suggests that dissolution is a direct function of disintegration.

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