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Dissolution rate studies using the B.P. disintegration apparatus

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The application of the B.P. disintegration apparatus in dissolution rate studies has been examined. The dissolution profiles of some brands of chloramphenicol capsules and tolbutamide tablets have been examined at various tube speeds with and without the guided disc. For both drugs a tube speed of 20 strokes/min gave the optimum difference in dissolution rates. The effect of the guided disc depended on the disintegration time of the product tested. For poorly disintegrating products the use of the guided disc resulted in about twofold increase in dissolution whilst insignificant effect was found for products with fast dissolution rate.

It is well recognized that the dissolution of solid drugs can be the rate limiting step in the absorption process. Various types of dissolution apparatus have been suggested (Hersey, 1969) in an attempt to introduce a dissolution test for routine work. The widespread availability of the disintegration apparatus makes it ideally suited for providing constant and reproducible agitation necessary for a dissolution test. Many workers have used the U.S.P. disintegration apparatus in dissolution studies (Schroeter, Tingstad & others, 1962; Middleton, Davies & Morrison, 1964; Withey & Mainville, 1969). No data were reported on the optimum conditions of the test.

This paper examines the effects of tube speed and the guided disc on the dissolution rates of some brands of chloramphenicol capsules and tolbutamide tablets. These drugs were selected because of the reported variations in absorption and dissolution rates (see Aguiar, Wheeler & others, 1968, for choramphenicol capsules and Levy, 1964, and Varley, 1968, for tolbutamide tablets).

MATERIALS AND METHODS

Materials

Four commercial brands of chloramphenicol capsules and three brands of tolbutamide tablets were purchased. These were designated as products A, B, C, D for the capsules and I, II, III for the tablets.

Apparatus

The apparatus used was a standard unit of the B.P. distintegration apparatus equipped with a variable speed motor to control the tube speed.*

The dissolution medium (800 ml) was placed in 1 litre beaker (18 cm high and 10·5 cm i.d.). The tube, at its highest position, just touched the liquid and at the lower position it was 5 cm from the bottom of the beaker. During one complete stroke, the tube travelled 7 cm.

* M. R. Suppliers Ltd., London: rev/min 20, B.S.S. 170 + rheostat. The motor needed running about 30 min to give controlled speeds of 45 ± 2, 30 ± 2, 20 ± 2, 15 ± 1, 10 ± 1 rev/min (as checked every 10 min).

Dissolution media

Hydrochloric acid (0·1N) and a 0·05M phosphate buffer (pH 6·8 ± 0·02) were used for chloramphenicol and tolbutamide respectively. The buffer was used on account of the poor solubility of tolbutamide in 0·1N hydrochloric acid.

All experiments were made at 37° ± 0·1°.

Procedure

At zero time one capsule (or tablet) was placed in the tube and the apparatus operated. At various time intervals, a 5 ml aliquot was sampled using a pipette fitted with a glasswool filter. No solid particles were observed in the aliquots when examined microscopically. Fresh volumes of either 0·1N hydrochloric acid or the phosphate buffer at 37° ± 0·1° were added to compensate for the aliquots withdrawn. Adjustments were made in the calculation for removal and replacement. Determinations of chloramphenicol and tolbutamide were made spectrophotometrically at 278 and 227 nm respectively. The 100% dissolution was obtained by stirring the content in the beaker at the end of the experiment. Four replicate experiments were made and averaged.

RESULTS

Fig. 1 shows representative plots showing the dissolution rates of the various brands of chloramphenicol capsules and tolbutamide tablets examined at a tube speed of 30 strokes/min. No correlation was found between the disintegration time of a brand and its dissolution rate. This is shown in Table 1, where both tablets I and II have approximately the same disintegration times but differed widely in their dissolution rates (Fig. 1b). However, delayed disintegration was often coupled with

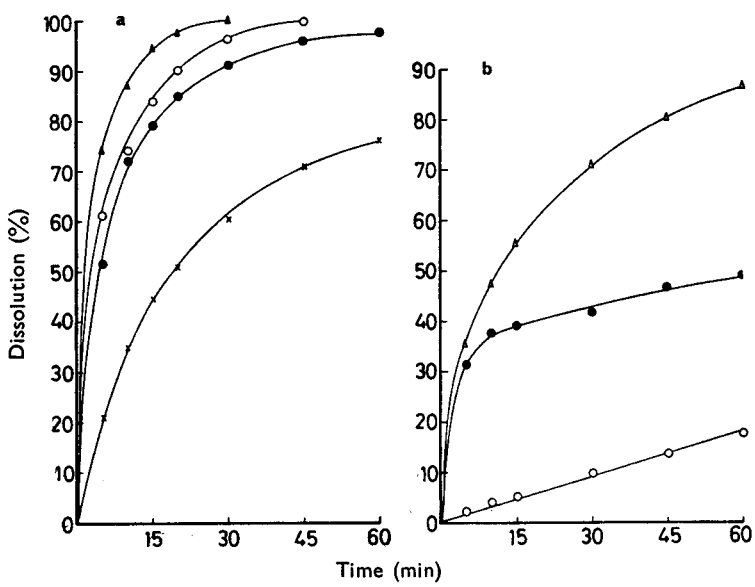

FIG. 1. a. Dissolution rate of chloramphenicol capsules in 0·1 N HCl at 37° ± 0·1°. Speed: 30 strokes/min (no guided disc). ▲—▲ capsule A; ○—○ capsule B; ●—● capsule C, ×—× capsule D. b. Dissolution rate of tolbutamide tablets in a 0·05M phosphate buffer (pH 6·8) at 37° ± 0·1. Speed: 30 strokes/min (no guided disc). △—△ tablet I; ●—● tablet II; ○—○ tablet III.

Table 1. *Disintegration times (in min) at various tube speeds with and without the guided disc*

Tube speed*	Capsules A	B	C	D†	Tablets I	II	III‡
10	12	—	—	>60	2·5	—	>60
15	9	—	—	>60	2·5	—	>60
20	7	5	14	>60	2·5	2	>60
30 without disc	5	5	11	35	2	1·5	>60
30 with disc ..	3	2·5	6	5	1	1	>60
45	5	4	7	35	1·5	1	>60

* No. of complete strokes/min.
† This brand gave large aggregates on disintegration at all speeds.
‡ This brand remained as a non-disintegrating disc at all speeds.

poor dissolution as with capsule D and tablet III. Capsule D yielded on disintegration few large aggregates which settled at the bottom of the beaker whilst tablet III failed to disintegrate over 1 h. For tablet III the dissolution curve was linear (Fig. 1b) similar to the data reported for the dissolution of non-disintegrating discs.

Effect of tube speed

The effect of tube speed on dissolution was studied on capsules A and D (Fig. 2a) and tablets I and III (Fig. 2b). An increase in tube speed resulted in a faster dissolution and consequently shorter times for a particular percentage of dissolution. Table 2 shows, at various tube speeds, the calculated values for t90%, t50% and t10% (times for the respective percentages of dissolution). The increase in the tube speed also affected the initial dissolution. Fig. 2a shows that, for capsule A, about 30%

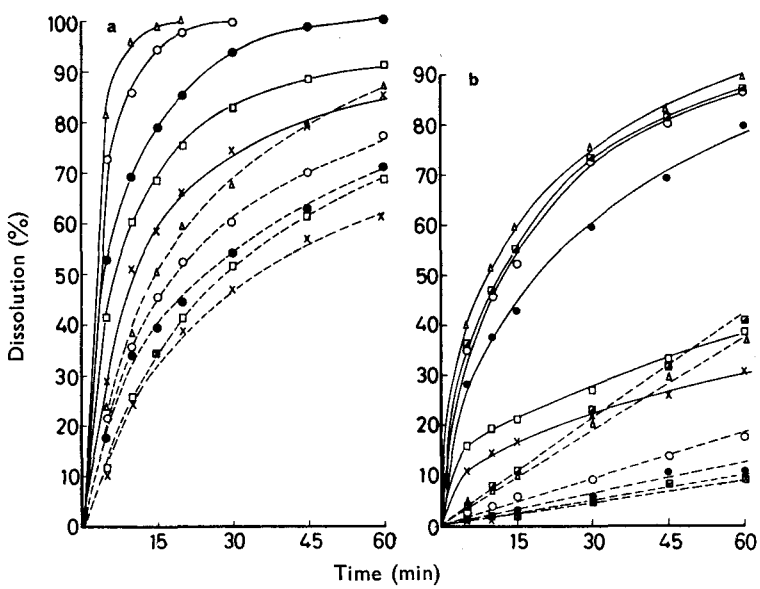

FIG. 2. a. Effect of tube speed on the dissolution rate of chloramphenicol capsules A (——) and D (– – –). Tube speed in strokes/min. (×) 10; (□) 15; (●) 20; (○) 30; (△) 45.
b. Effect of tube speed and the guided disc on the dissolution rate of tolbutamide tablets I (——) and III (– – –). Tube speeds in strokes/min. (×) 10; (□) 15; (●) 20; (○) 30; (△) 45; (◪) 30 with disc.

Table 2. *Calculated values of the times (in min) for 90%, 50% and 10% dissolution at various tube speeds*

Tube speed*	*t* 90% Capsule A	*t* 50% Capsule D	Tablet I	*t* 10% Tablet III
10	>60 min	35	>60	57
15	50	28	>60	~57
20	25	25	21	48
30 without disc	12	19	12	31
30 with disc	7	11	11	14
45	7	15	9	15

* No. of complete strokes/min.

increase in dissolution occurred after 5 min when the tube speed was increased from 20 to 45 strokes/min. The poorly disintegrating capsule D, on the other hand, showed only about 7% increase. It is probable that the increase in tube speed has aided the dispersion of the fine particles produced from capsule A but did not affect significantly the dispersion of the quickly sedimenting aggregates of capsule D. The dissolution of the non-disintegrating tablet III followed the same pattern at various tube speeds, where linear plots were obtained (Fig. 2b). This suggests that variations in the tube speed did not influence the mechanism of dissolution of this brand. The increase in dissolution at higher tube speeds may be attributed to the rapid erosion of the tablet surface.

Effect of the guided disc

The effect of the guided disc on dissolution rate was studied on tablets I and III (Fig. 2b) and capsule A, B and D (Fig. 3). The tube speed selected was 30 strokes/min as specified in the B.P. test for disintegration. As shown in Fig. 2b, the use of the guided disc resulted in an insignificant effect on the dissolution of the fast dissolving tablet I. For capsules A and B only a slight increase in dissolution occurred (Fig. 3). The effect of the disc, however, was well pronounced in the dissolution of the non-

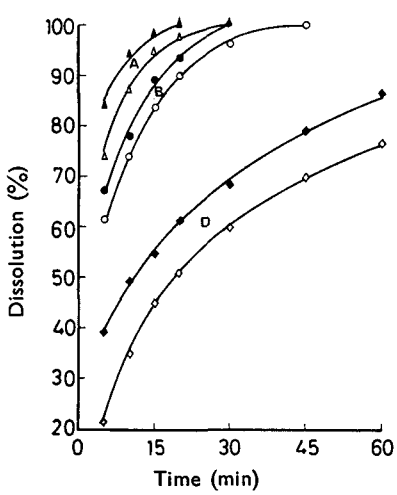

FIG. 3. Effect of guided disc on the dissolution rate of chloramphenicol capsules A, B and D. Speed: 30 strokes/min. △, ○, ◇, without the disc; ▲, ●, ◆, with the disc.

disintegrating tablet III and the poorly disintegrating capsule D. For tablet III about twofold increase in dissolution was observed. The mechanical effect of the guided disc may be responsible for this increase. It was observed that although the use of the disc did not affect the disintegration time of this brand III (Table 1), yet fragments of the tablet were formed and passed into the dissolution medium.

Area under dissolution curve at various tube speeds with and without the guided disc

The areas under the dissolution curves were calculated for the fastest and slowest dissolving products (capsules A and D and tablets I and III). Area measurement was made on graph paper by counting squares. Fig. 4 shows at various tube speeds, the ratios of area for capsule A to that of capsule D and for those of tablet I to tablet III.

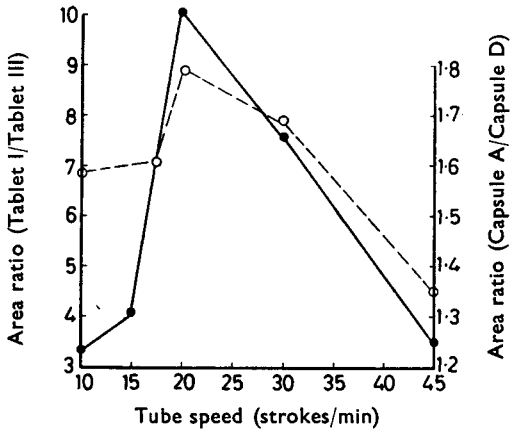

FIG. 4. Effect of tube speed on the area ratio of tablet I/tablet III (●—●) and capsule A/capsule D (○ - - ○).

A tube speed of 20 strokes/min gave the highest ratios for both drugs and therefore it was regarded as the best discriminating speed. When the guided disc was used at tube speed 30 strokes/min the ratio: area for tablet I to area for tablet III was decreased from 7·51 (Fig. 4) to 3·10. This is due to the pronounced increase in the dissolution of tablet III compared to tablet I (Fig. 2b), in the presence of the disc. The ratio for capsules A/D fell from 1·68 (Fig. 1) to 1·46 with the disc.

DISCUSSION

The suitability of the B.P. disintegration apparatus in discriminating the dissolution rates of the various brands tested is seen from Fig. 1. Although the U.S.P. disintegration apparatus has been used by many workers, no critical evaluation of the speed of agitation was reported. A tube speed of 30 strokes/min, as specified in the disintegration test, has been currently used without justification. In the study of Marcus (1969) the speed produced by the U.S.P. apparatus could not differentiate between the dissolution rates of four tablet formulations of different absorption characteristics. When a milder agitation technique was used, variations in the dissolution rates were observed. In the present work a tube speed of 20 strokes/min gave the best discrimination between the dissolution rates of the brands tested. This speed, therefore, is regarded as the optimum speed. Speeds higher than twenty pro-

duced marked agitation of the particles in the beaker. This enhanced dissolution of both fast and slow dissolving brands and subsequently the area ratios were low (Fig. 4). At speeds lower than twenty the particles resting at the bottom of the beaker were not subjected to visible agitation and remained unstirred. This suppressed dissolution particularly of the brands with good dissolution characteristics. Brands with poorer dissolution, on the other hand, were less affected and therefore lower area ratios were obtained (Fig. 4).

Although the B.P. permits the repeat test using the guided disc in the disintegration test for tablets, its use is not permitted for the capsules (B.P. 1968). In the dissolution test, it appears that the use of the guided disc increases the dissolution of both tablets and capsules through its mechanical effect. This effect was more pronounced in the poorly disintegrating products as tablet III (Fig. 2b). The use of the guided disc may, therefore, lead to poorer discrimination between fast and slow dissolving products. The ratios of the areas under dissolution curves produced, at 30 strokes/min, with (1·46 for capsules A/D 3·10 for tablets I/III) and without (1·68 for capsules A/D and 7·51 for tablets I/III) the guided disc show this effect. Campagna, Cureton & others (1963) have also found that omission of the disc of the U.S.P. apparatus gave dissolution data for prednisone tablets which agreed with *in vivo* results.

Beside the tube speed and the guided disc, other factors may affect the dissolution test using disintegration apparatus. Of these factors mention may be made to the mesh number of the wire of the tube and the distance between the bottom of the tube and the beaker on the downward stroke. This latter factor seems to markedly influence the stirring action imparted to the particles which have passed through the mesh to the beaker.

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