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AUTOMATED DETERMINATION OF DISSOLUTION RATE: EFFECT OF PARTICLE SIZE DISTRIBUTION

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ABSTRACT

The effect of particle size distribution on the dissolution of salicylic acid in an automated dissolution apparatus has been studied. Tablets were prepared by individually weighing 200 mg of the drug particles having a narrow size distribution, compressing the tablets using a hydraulic press and employing identical compression force for the same time period for each tablet. The results showed that the range values obtained were not significantly different from those obtained when the particle size was not controlled. However, the range values obtained from the dissolution of drug particles recovered from the tablet formulation were found to be similar to the range values obtained from the dissolution of the tablet formulation, indicating that compression during tabletting was responsible for observed differences.

INTRODUCTION

In recent years a number of devices for the automated determination of dissolution rate have been reported in the literature. With the introduction of the dissolution test in the eighteenth revision of the USP, much of the emphasis on such devices has been in the development of an apparatus meeting the official test requirements. At the same time, the applicability of the system to various other agitational systems in common usage is considered a definite advantage.

Recently, Johnson et al. (1) described an automated dissolution apparatus meeting the requirements of USP-NF dissolution test and applicable to various other agitation systems in common usage. The authors claimed high precision and reproducibility within the measuring system which were achieved by maintaining low volumes and flow rates, thus allowing measurements of real differences in dissolution characteristics between dosage forms, if these exceeded $\pm$ 2.8%. Good agreement was reported between the dissolution rates obtained by the automated system and those obtained by manual measurements. The intertablet variations obtained with typical batches of 500-mg levodopa tablets and with 2-mg benzodiazepine tablets (Table V, ref. 1) were also studied. For example, at 2.5 minutes, percent levodopa dissolved showed a range value of 17% and percent benzodiazepine dissolved showed a range value of 21%. These results indicate that the variability

observed might have been due to a number of reasons, including: (a) differences in the active ingredient content of the tablets, (b) differences due to manufacturing variables, including variability in the compression force employed and the presence of excepients etc., and (c) uneven distribution of drug particle size among tablets.

In a more recent study dealing with the variability in a system for automated determination of dissolution rate (2), the differences due to active ingredient content of the tablets and the differences due to manufacturing variables were minimized. Tablets were prepared by individually weighing 200 mg of salicylic acid for each tablet, compressing the tablets using a hydraulic press and employing identical compression force for the same time period for each tablet (2). Dissolution was followed in an automated apparatus similar to the one described by Johnson et al. (1) and it was found that inspite of controlling these parameters the intertablet variations were rather large (2). It was shown that large intertablet variations encountered in such a system may be observed either due to possible intertablet differences, e.g., differences in the disintegration properties of the tablets and/or uneven distribution of drug particle size among the tablets, or due to the non-reproducibility of the apparatus. This report investigates the possible contribution of these factors in such a dissolution determination system.

EXPERIMENTAL

MATERIALS:

All materials were of USP or reagent grade and were used as received from the manufacturer without further purification or recrystallization.

PREPARATION OF TABLETS:

Tablets were prepared by individually weighing 200 mg of salicylic acid for each tablet, compressing the tablets using a hydraulic press and employing identical compression force for the same time period for each tablet.

DISSOLUTION STUDIES:

Dissolution of salicylic acid from the tablets was followed in an automated apparatus described previously (2).

EFFECT OF PARTICLE SIZE:

Effect of particle size was evaluated by using a narrow size distribution of drug particles. The undersize and oversize particles were removed using a nest of standard sieves and the tablets were compressed as described above.

RESULTS AND DISCUSSION

The efficiency of the apparatus was ascertained by introducing 25 ml volumes of standard salicylic acid solutions and studying the time for the entire system to reach equilibrium. The results shown in Table I indicate that the reproducibility of the apparatus

TABLE I

Equilibration Time to Indicate 100% Dissolution in the Dissolution Flask

mg salicylic acid added (as 25 ml solution)	Time (in Sec) to indicate complete diffusion			
	1	2	3	average
30	113	121	97	110 ± 13
40	100	124	113	112 ± 12
50	127	119	99	115 ± 15

was good and that the fluid samples passing through the flow cell were representative of the bulk media in the dissolution flask.

EFFECT OF PARTICLE SIZE:

A narrow size distribution of drug particles was used in order to minimize intertablet differences. Dissolution, using the automated dissolution apparatus (2) revealed that the range of percent salicylic acid dissolved was reduced somewhat indicating that the intertablet variations due to uneven distribution of drug particles might have been a contributing factor in the variations observed in the dissolution rate of the tablets. However, it is possible that although the particle size distribution of salicylic acid was sufficiently narrow to start with, such may not have been the case in the final product, perhaps because

of crushing of some of the particles due to pressure employed for the compressing of the tablets. The experiments were repeated using tablets prepared with coarser as well as with finer particles but in each case maintaining a narrow size distribution. In each case studied the results showed a slight reduction in the range values of percent salicylic acid dissolved as compared to the values obtained in cases where particle size was not controlled.

A critical examination of the data shown as a bar graph in Fig. 1 reveals that in some instances (e.g., experiments No. 2 and 12) the dissolution rates were identical in the initial stages but substantial differences were observed as the dissolution progressed. Similarly, in some other instances (e.g., experiments No. 7 and 8) the reverse was the case, and yet in a few instances (e.g., experiments No. 1, 4 and 11) the dissolution rates appear to be similar in the initial and final periods but show variations in the middle portion of the dissolution process.

One possible explanation for the type of pattern observed may be attributed to the possibility of modification in particle-size distribution due to compression during tabletting. Four possibilities exist:

(a) if the large particles only were fractured the resulting distribution would be narrower, and the range values would tend to reduce.

(b) if both the large and the small particles were fractured, the resulting distribution would be essentially unaltered and the range values would also be expected to be unaltered.

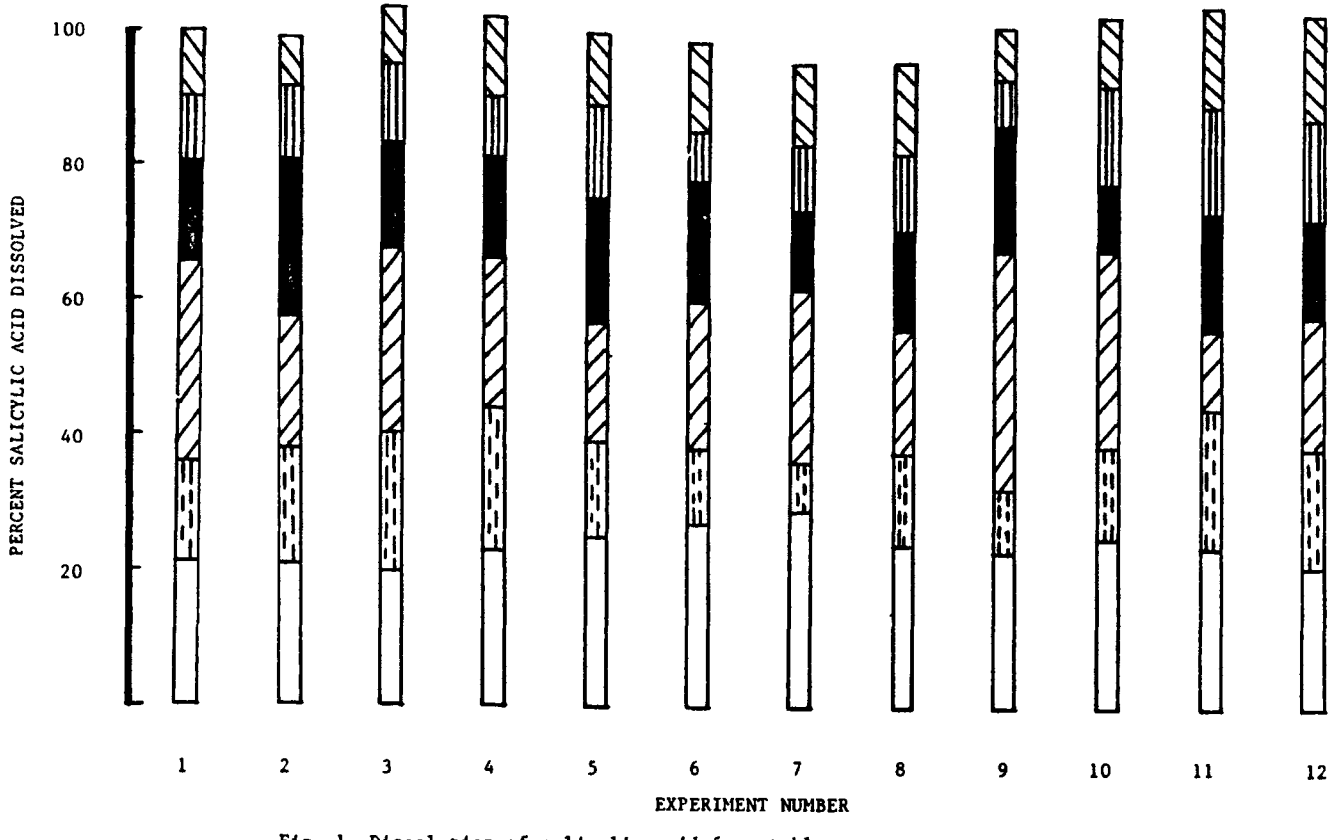

Fig. 1. Dissolution of salicylic acid from tablets at 2.5; 5; 10; 15; 20; and 30 minutes

(c) if the larger particles were fractured but the smaller particles fused into each other then the distribution would alter depending on the degree of crushing and fusion taking place.

(d) if some of the particles were fractured while others were only deformed then the resulting distribution would be a function of the extent of deformation and fracture produced and the range values would be a function of the new distribution.

In order to examine whether the particle-size distribution had been modified during compression, the tablets were allowed to disintegrate in a saturated solution of the drug and the particles recovered by filtration. It was found that compression had indeed altered the distribution which appeared to be more pronounced in the case of tablets prepared with coarser particles than those prepared with finer particles indicating that the coarser salicylic acid particles possessed greater flaw than that present in finer particles.

It is therefore conceiv ble that the failure to achieve significant reduction in the range values in the dissolution of tablets prepared with drug particles having a narrow size distribution was due to alteration in the size distribution brought about during tabletting. To test the validity of this assumption, the dissolution profile of drug particles having a narrow size distribution was compared with that of drug particles recovered from the disintegration of a tablet in a saturated solution of the drug. The results are shown in Fig. 2.

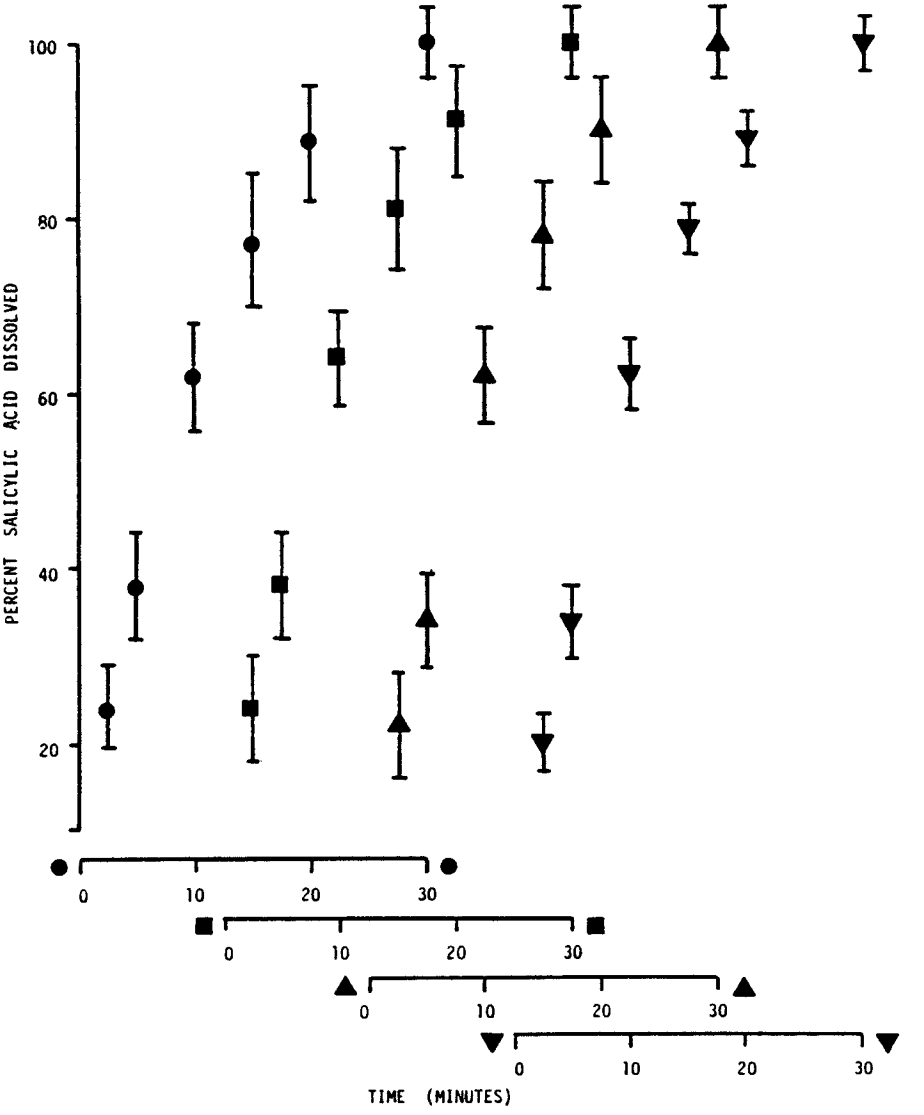

Fig. 2 Dissolution Rate of Salicylic Acid [a]

● Tablets prepared without controlling particle size

■ Tablets prepared with controlled particle size

▲ Particles recovered from tablets prepared with controlled particle size

▼ Particles having a narrow size distribution

[a] Each point represents an average of 12 experiments

From the results found in Fig. 2 it can be readily seen that the range values obtained from the dissolution of drug particles having a narrow size distribution were much smaller than those obtained from similar particles which had undergone compression. Interestingly, the range values obtained from the dissolution of drug particles recovered from the tablet formulation were found to be similar to the range values obtained from the dissolution of the tablet formulation, confirming the view that compression during tabletting was indeed the factor responsible for observed differences.

REFERENCES

1. J. B. Johnson, P. G. Kennedy, and S. H. Rubin, J. Pharm. Sci., 63, 1931 (1974).

2. P. L. Madan, J. Pharm. Sci., 64, 1080 (1975)