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AUTOMATED DETERMINATION OF DISSOLUTION RATE:

II. FACTORS INFLUENCING VARIABILITY

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ABSTRACT

The effect of factors influencing variability on the dissolution pattern of tablets 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, or the formulation blend containing 200 mg of the drug. The tablets were pressed using a hydraulic press and employing identical compression force for the same time period for each tablet. The results showed that the inter-tablet range values obtained in each formulation were not significantly different from each other and the dissolution profiles exhibited portions indicating sudden increase in the dissolution rates. It is shown that the variability observed may have been due to the possible suction of the dissolving drug particles. The use of a fritted-glass filter tip at

the inlet end of the sampling tube reduced the variability significantly producing more reproducible dissolution curves.

INTRODUCTION

In a recent study dealing with the variability in a system for the automated determination of dissolution rate (1), it was shown that large inter-tablet variations encountered in such a system may be observed either due to possible inter-tablet 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.

In a more recent study dealing with the effect of particle size distribution on the dissolution of tablets (2), it was shown that the variability observed was due to the alteration in the particle size distribution of the tablets due to compression during tabletting. 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 also found to be due to alteration in the size distribution brought about during tabletting. In spite of the fact that 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, the inter-tablet variability was rather large. 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:

Three types of tablet formulations were investigated.

(a) Tablets prepared by direct compression and containing no excipient: Tablets were prepared by individually weighing 200 mg of the drug for each tablet and compressing the tablets using a hydraulic press. Identical compression force for the same time period was used for each tablet.

(b) Tablets prepared by direct compression and containing a disintegrant: The drug was blended with the disintegrant using a V-blender: Tablets were prepared by individually weighing a quantity of the blend containing 200 mg of the drug and the blend was compressed into tablets as described in section (a).

(c) Tablets prepared by wet granulation: The tablets prepared by wet granulation were formulated to contain the disintegrant during wet granulation. Tablets were prepared by individually weighing a quantity of the dried, blended granules containing 200 mg of the drug and compressing into tablets as described in section (a).

DISSOLUTION STUDIES:

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

RESULTS AND DISCUSSION

The efficiency of the automated apparatus was ascertained as described previously (2). The reproducibility of the apparatus was good and the fluid samples passing through the flow cell were found to be representative of the bulk media in the dissolution chamber.

In order to minimize inter-tablet differences due to particle size distribution, the tablets were prepared using a narrow size distribution of drug particles. This was accomplished by sieving out the undersize and oversize particles employing standard sieves.

TABLETS PREPARED BY DIRECT COMPRESSION AND CONTAINING NO EXCIPIENT

Fig. 1 shows the dissolution of the drug from the tablets prepared by direct compression and containing no excipients. Curve A was generated by computing the average values from the dissolution graphs of individual tablets. Curve B is a typical dissolution profile obtained with only a few tablets. Most of the tablets examined gave plots which exhibited a sudden and somewhat erratic increase in the dissolution rate similar to the one shown in Curve C. It may be pointed out that the sudden increase in the dissolution rate was not at the same point on the time-axis but varied from tablet to tablet. In the case of a few tablets the sudden increase in the dissolution rate was observed more than once.

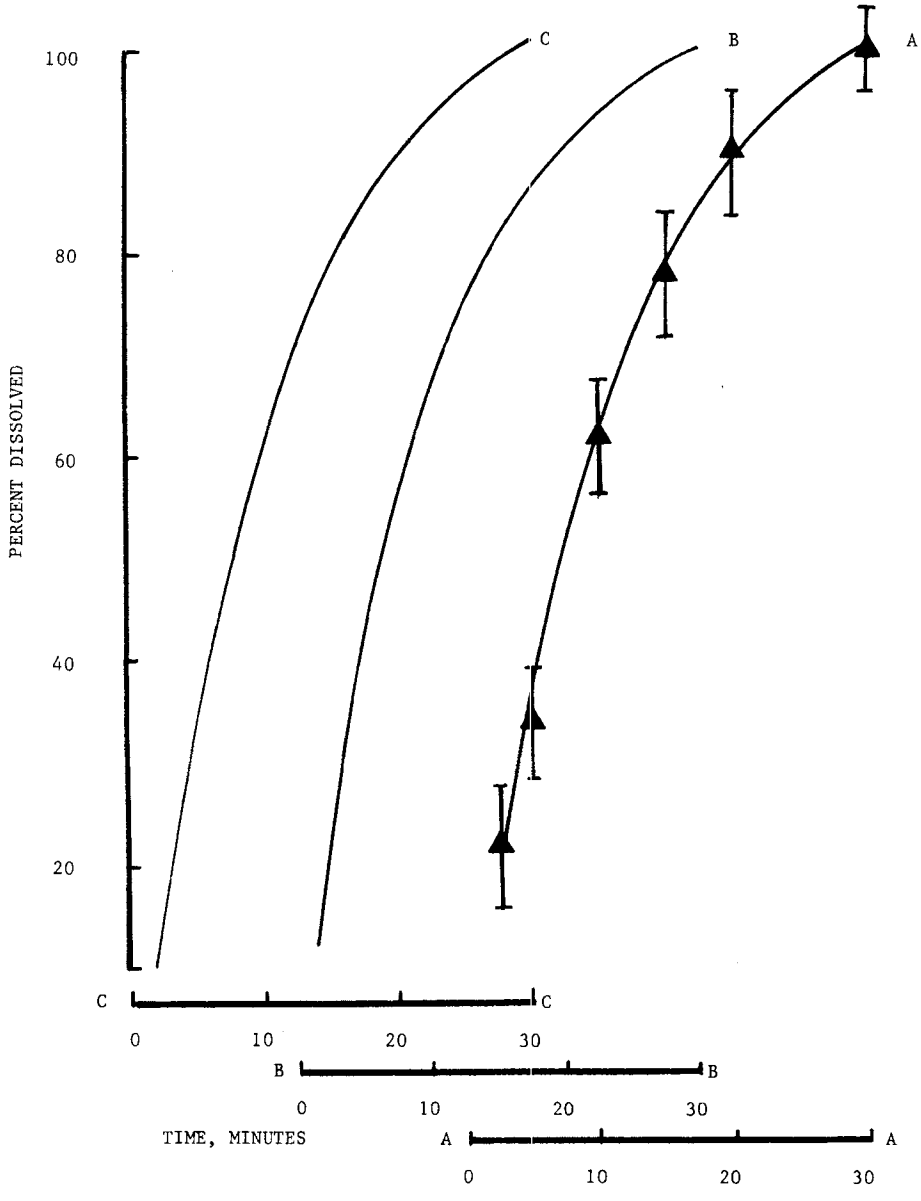

FIGURE 1

DISSOLUTION PROFILES OF TABLETS PREPARED BY DIRECT COMPRESSION

TABLETS PREPARED BY DIRECT COMPRESSION AND CONTAINING A DISINTEGRANT

The dissolution of the drug from the tablets prepared by direct compression and containing a disintegrant was found to be similar to the dissolution of the drug from the tablets containing no excipient. However, some differences were noted. Very few tablets followed the pattern found in Curve B of Fig. 1 and the number of tablets exhibiting the shape found in Curve C of Fig. 1 was more in this case than that observed in the case of tablets containing no excipient.

TABLETS PREPARED BY WET GRANULATION

The dissolution of the drug from the tablets prepared by wet granulation showed similarities in exhibiting the sudden rise in the dissolution rate as dissolution progressed but such sudden increases were few and far between. In most cases, the dissolution curve was smooth (Curve B, Fig. 2) and the majority of tablets exhibited dissolution patterns which were more or less superimposable. In addition, the inter-tablet range values (Curve A) were less than those found in the case of tablets prepared by direct compression (Curve A, Fig.1).

The results found in Figs. 1 and 2 reveal that inspite of the fact that the particle size distribution of the drug was controlled, the dissolution profiles exhibited significant inter-tablet range values in each formulation studied. The variability observed was less in the case of tablets prepared by wet formulation than that found in the case of tablets prepared by dry

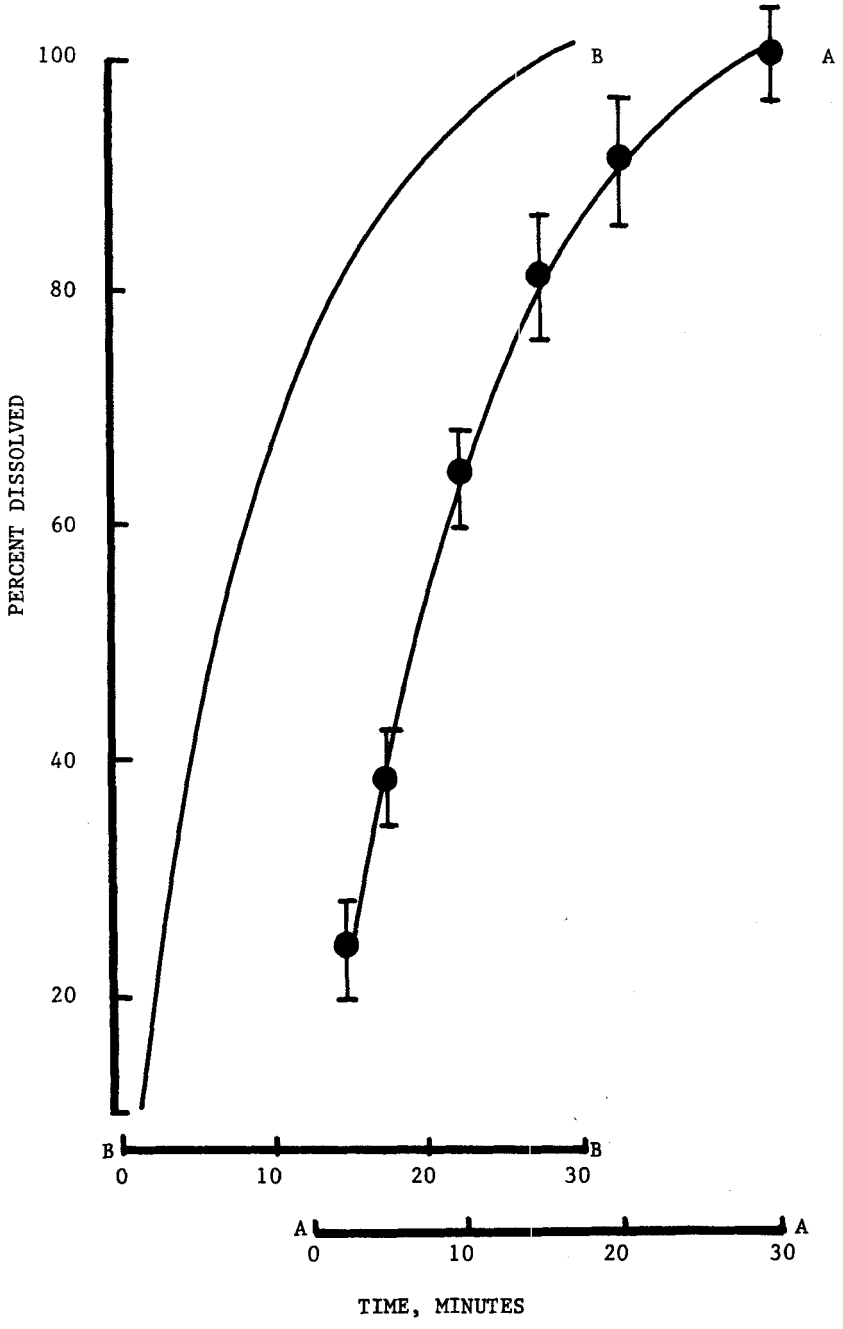

FIGURE 2

DISSOLUTION PROFILES OF TABLETS PREPARED BY WET GRANULATION

granulation. This may be due to the wetting of the drug particles during wet granulation, which may have helped in causing some degree of uniformity in the process of dissolution (3).

In order to gain a better understanding of the reasons for the variability observed, the data were examined critically. The dissolution curves for each experiment in each formulation were studied for points of similarities and differences. It was noticed that in some instances the dissolution curves were superimposable only in the initial portion but differed significantly as the dissolution progressed. Similarly, in other instances the reverse was the case and in a few cases the dissolution curves appeared to be similar both in the initial as well as in the final periods but exhibited differences in the middle segment of the dissolution pattern.

One possible explanation for this type of pattern may be attributed to the possibility of some small particles of the dissolving drug finding their way into the sampling tube and dissolving slowly thus creating a different concentration gradient. Also, these particles may have lodged themselves on the filter membrane at the end of the sampling tube and may have dissolved slowly while still adhering to the filtering device, thus representing a dissolution pattern different from the one actually taking place in the dissolution flask. Either one or a combination of both these factors would tend to exhibit variability in the system. This is because the dissolution of such particles in the sampling tube would result in

a solution more concentrated than that in the dissolution flask and may also create a possible non-sink condition within the sampling tube.

A simple experiment was performed in order to test the validity of this hypothesis. The tablets were allowed to disintegrate in a saturation solution of the drug and the particles were recovered by filtration (2). Microscopic examination of the recovered particles revealed that the tablets prepared by wet granulation yielded coarse particles which were similar to the granulation used for compression. When placed in the saturated solution of the drug and stirred gently, the particles appeared to settle down at the bottom of the container almost immediately. Thus, the chances of these particles undergoing suction in the sampling tube would be rather slim. In order for the particles to undergo suction, they would have to undergo considerable dissolution so that their size would be small enough to keep them afloat and thus prevent their settling.

On the other hand, the particles recovered from the tablets prepared by direct compression were found to be much smaller in size and exhibited a greater tendency to undergo suction in the sampling tube. This was more pronounced in the case of tablets containing a disintegrant then those which did not contain any excipient. These results appear to confirm the hypothesis that the observed variability may have been due to the possible suction of the drug particles in the sampling tube

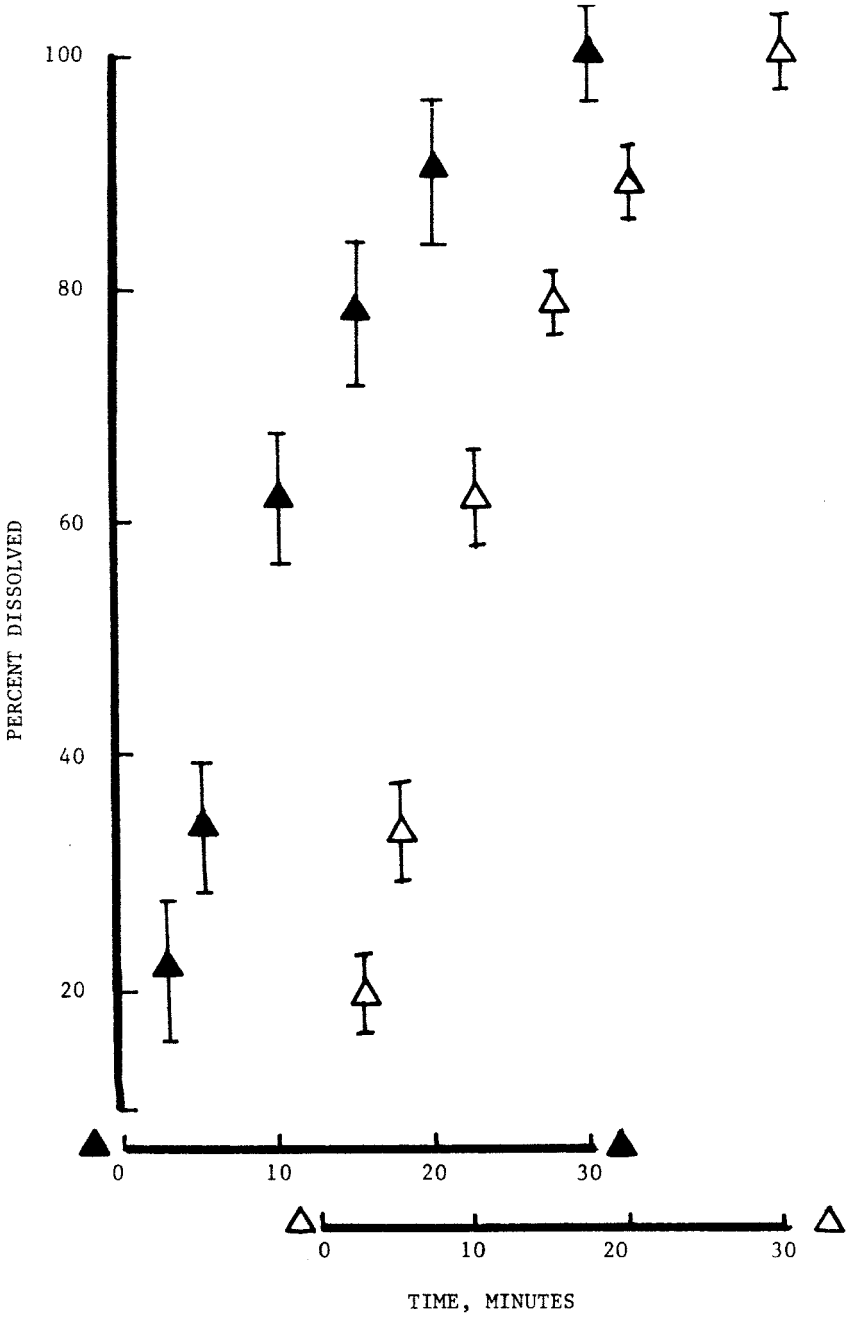

FIGURE 3

DISSOLUTION PROFILES OF TABLETS PREPARED BY DIRECT COMPRESSION.

CLOSED TRIANGLES: without fritted glass filter
OPEN TRIANGLES : in the presence of fritted glass filter

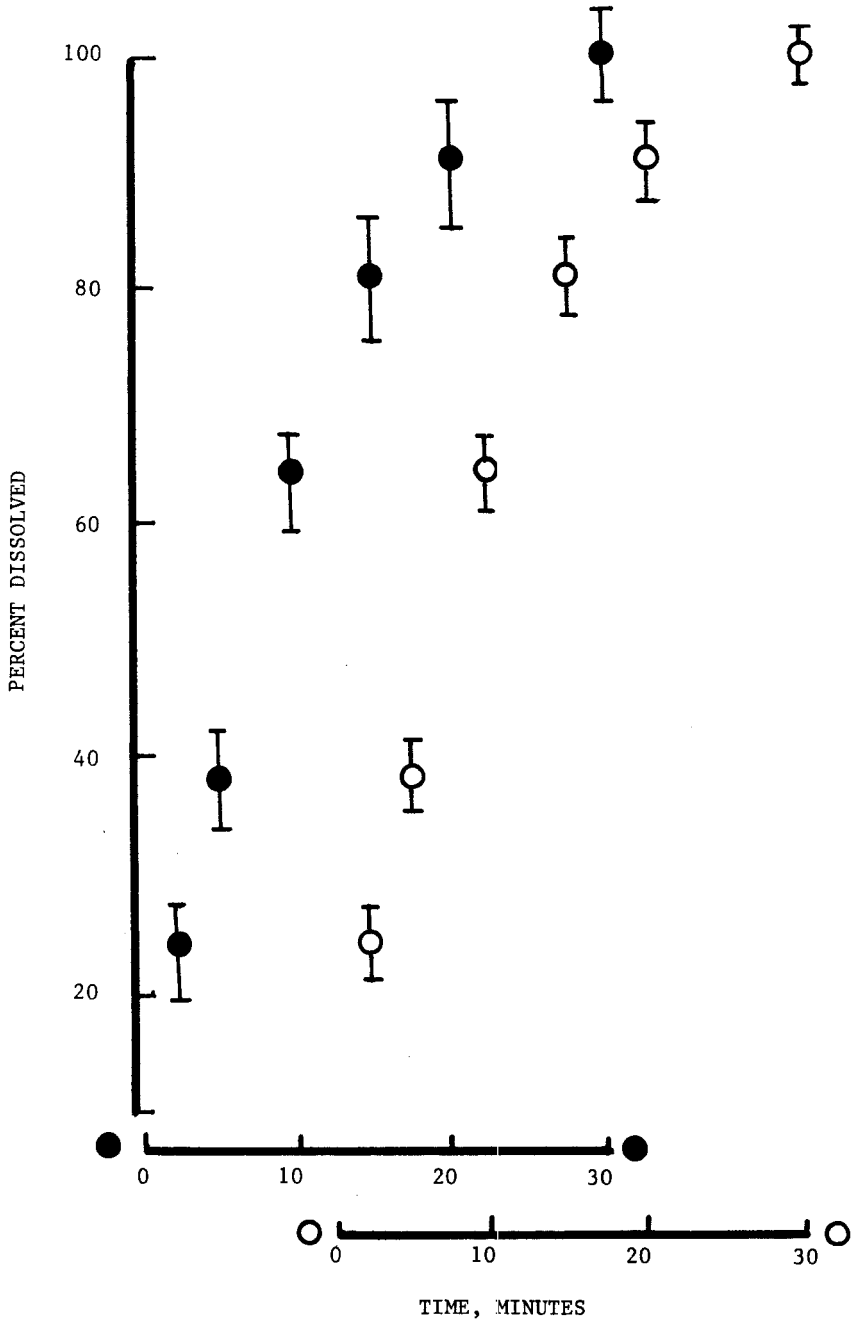

FIGURE 4

DISSOLUTION PROFILES OF TABLETS PREPARED BY WET GRANULATION

CLOSED CIRCLES: without fritted glass filter
OPEN CIRCLES : in the presence of fritted glass filter

and resulting in the creation of a variable concentration gradient.

In order to minimize the variability due to possible suction of the drug particles inside the sampling tube, the apparatus was modified slightly. A one-inch long cylinderical fritted-glass coarse filter tip having the same diameter as that of sampling tube was attached at the inlet end of the sampling tube and it was found that this modification reduced the variability significantly. The results are shown in Figs. 3 and 4. For comparison purposes the results obtained without the use of the fritted-glass filter have also been included in the figure.

From the results found in Figs. 3 and 4, it can be readily seen that the inter-tablet range values were reduced significantly in the case of tablets prepared with controlled particle size and examined for dissolution employing the modification described above. Detailed experimentation is in progress to look into the possibility of further improving the instrumentation and will be the subject of a future report.

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