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EFFECT OF PARTICLE SIZE AND EXCIPIENTS ON THE DISSOLUTION RATE OF METRONIDAZOLE FROM SOLID DOSAGE FORMS: II

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ABSTRACT

In-vitro dissolution tests were carried out with tablets prepared from different particle size ranges of metronidazole. Influence of tablet binding agents (Methylcellulose, polyvinyl pyrrolidone - (PVP), potato starch and gelatin) on the drug release were investigated under similar conditions. Comprimates containing PVP and drug with particle size 1.75 µm (in lactose mixture) gave optimum results. These findings may open new ways of formulating a metronidazole tablet exhibiting improved drug - liberation, subsequently with a better bioavailability than the KLION^{R}-Tablet manufactured in Hungary.

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INTRODUCTION

The influence of formulation on drug action has been carefully reviewed by Munzel (1) and Blanchard (2). Among formulation factors found to exert much effect on bioavailability of solid dosage forms e.g. tablets are t h e ones attributed to dissolution rate such as particle size, granule size (3), carriers e.g. lactose (4, 5), binding agents and their concentrations (6).

In the first part of these investigations, the effects of drug particle size and lactose on the in-vitro dissolution of metronidazole were reported. Particle size reduction plus the application of lactose as a carrier were found to increase dissolution rate.

In this paper, the effects of particle size, lactose and some tablet binders on the in-vitro release of the same drug (Metronidazole) from tablets are presented.

EXPERIMENTAL

Materials

Metronidazole (Richter-Budapest) USP- standard, potato starch, corn starch (Agena Austria), Gelatina Alba (Rousselot - Paris), Polyvinyl

pyrrolidone (GAAF- Cooperation, FRG), Methylcellulose 400cp. (Fluka AG), Lactose spray dried (HMS - Holland) All materials used were of analytical grade.

Methods:

Tablet - Formulation

All tablets formulated and tested contained equivalent amounts of the same vehicles. The tablet composition given in table 1 was used with different sizes of metronidazole named, 1.75 µm, 125 - 200 µm and 400 - 500 µm.

Tablet binders (Gelatin, Methylcellulose, Starch and Polyvinyl pyrrolidone (PVP)), were used at a weight range of 2% (w/w) of the formula. Wet granulation

TABLE 1: Metronidazole Tablet Composition

Ingredient	Quantity per tablet (mg)
Metronidazole	250.0
Aerosil	1.5
Magn. stear.	1.5
Tablet binder	7.5
Talc	10.0
Corn starch	79.5
Weight of Tablet	350.0 (mg)

was applied and the amount of moisture in the granules prior to tabletting was found to be 3.11 ± 0.17% S.E.[2] for formulations with 1.75 μm metronidazole (in metronidazole: lactose mixture), and 2.07 ± 0.08% S.E.[2] for granules containing larger crystals of the drug (i.e. d = 125 - 200 μm and d = 400 - 500 μm). From every granulate, comprimates of 10 mm in diameter, weighing 350 mg each were prepared using a single punch tabletting machine[1], and a constant force of 7.5 kg wt. (The tablet hardness was found to vary from 4.5 to 5.6 ERWEKA kg wt).

Dissolution Rate Studies

An *in-vitro* dissolution method related to that of Needham *et al* (7) was adopted. Tablets were placed in a USP Basket held stationary in distilled water (500 ml) at 37 ± 0.5°. Agitation of the dissolution medium was facilitated by a magnet stirrer (2.9 x 0.85 cm) operated 2.5 cm under the basket at a speed of 150 r.p.m. Samples were withdrawn at specified intervals of time and were immediately filtered using 0.45 μm Sartorius Filter Membranes. Replacement of the sample volume by water at the same temperature (37°) was done.

[1]Wittenberg Type KP - 2 (GDR); [2]S.E. = Standard Error

After an appropriate dilution, concentration was determined from absorbance at 320 nm, using SPECTROMOM - 204, UV-Spectrophotometer (Hungary).

In order to study the reproducibility of the method, 9 tablets from the same batch were individually tested for dissolution and the results were statistically analysed. On the basis of the obtained narrow standard errors, the method was considered reliable and the rest of the tests were repeated at least three times.

RESULTS AND DISCUSSION

The amounts of metronidazole dissolved in water at different time intervals from tablets prepared from various particle size ranges of the drug applying different tablet - binding agents are reported in figures 1 - 4. An increase in Dissolution Rate with decreasing particle size was observed. Formulations containing drug - particle size of 1.75 μm (in the lactose mixture) released the drug at the fastest rate. It is almost certain that, apart from the small particle size of metronidazole, lactose, being easily water soluble should have played a positive role in the increased rate of dissolution of the drug. From these series of tests, it was also experienced that the comprimates containing Polyvinyl Pyrrolidone

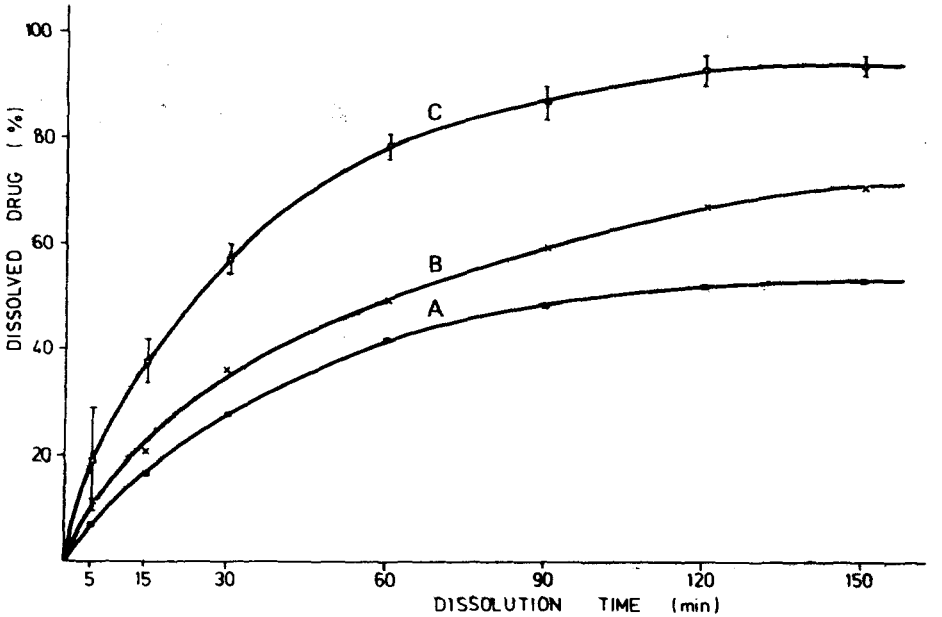

FIGURE 1

Effect of Particle Size on the Dissolution Rate of Metronidazole from Tablets with 2% Gelatin - Binder. Key: A = 400-500 μm; B = 125-200 μm; C = 1.75 μm. Vertical lines represent Rel. S.Dev. for 9 similar experiments.

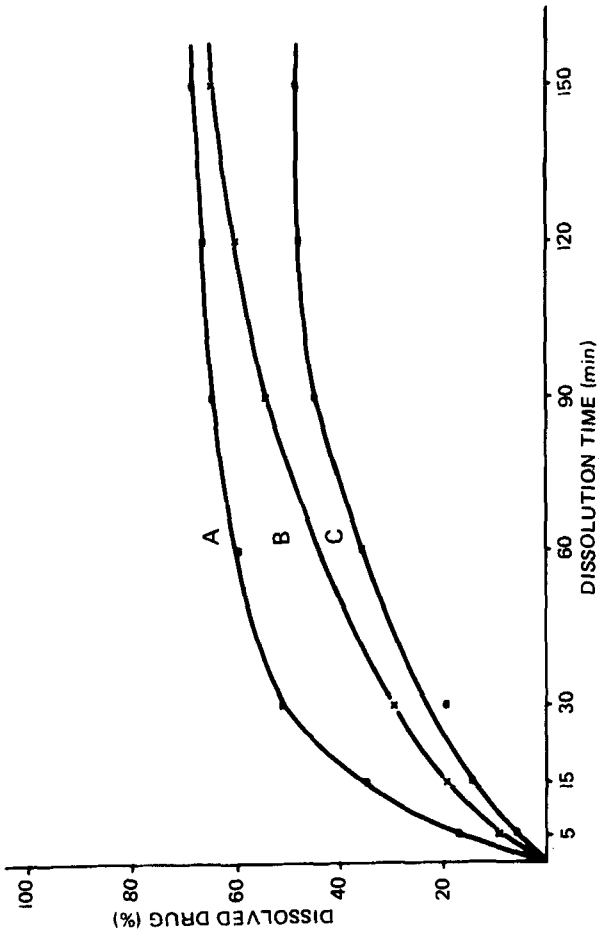

FIGURE 2

Effect of Particle Size on the Dissolution Rate of Metronidazole from Tablets with 2% Methylcellulose - Binder. Key: A = 400-500 µm; B = 125-200 µm; C = 1.75 µm.

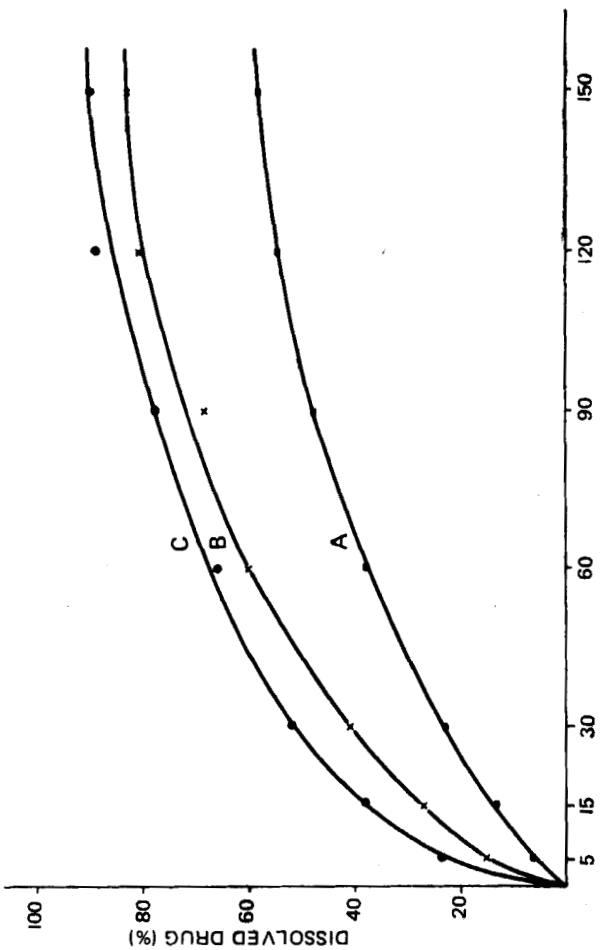

FIGURE 3
Effect of Particle Size on the Dissolution Rate of Metronidazole from Tablets with 2% Potato Starch - Binder. Key: A = 400-500 µm; B = 125-200 µm; C = 1.75 µm.

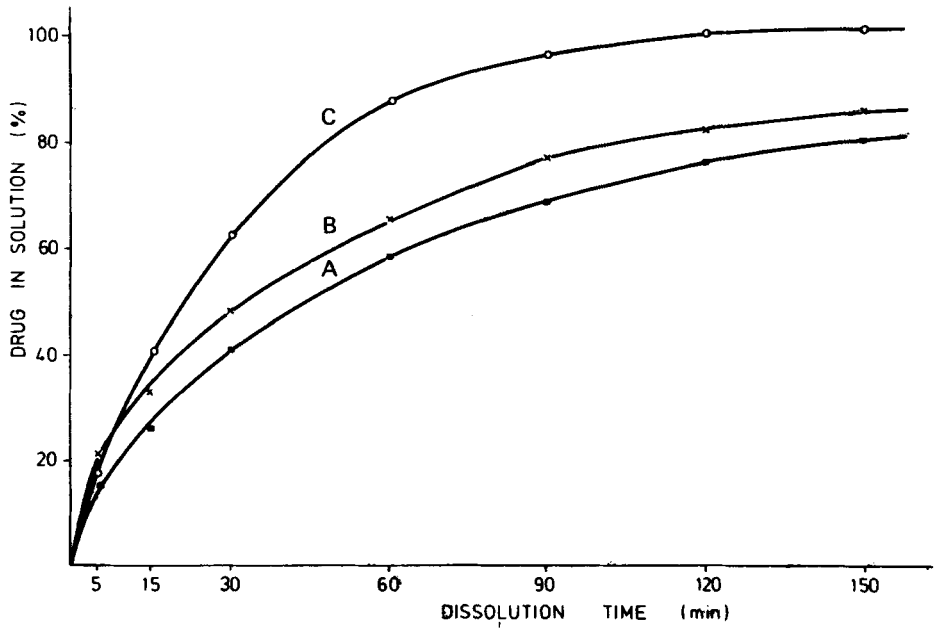

FIGURE 4

Effect of Particle Size on the Dissolution Rate of Metronidazole from Tablets with 2% PVP - Binder. Key: A = 400-500 μm; B = 125-200 μm; C = 1.75 μm.

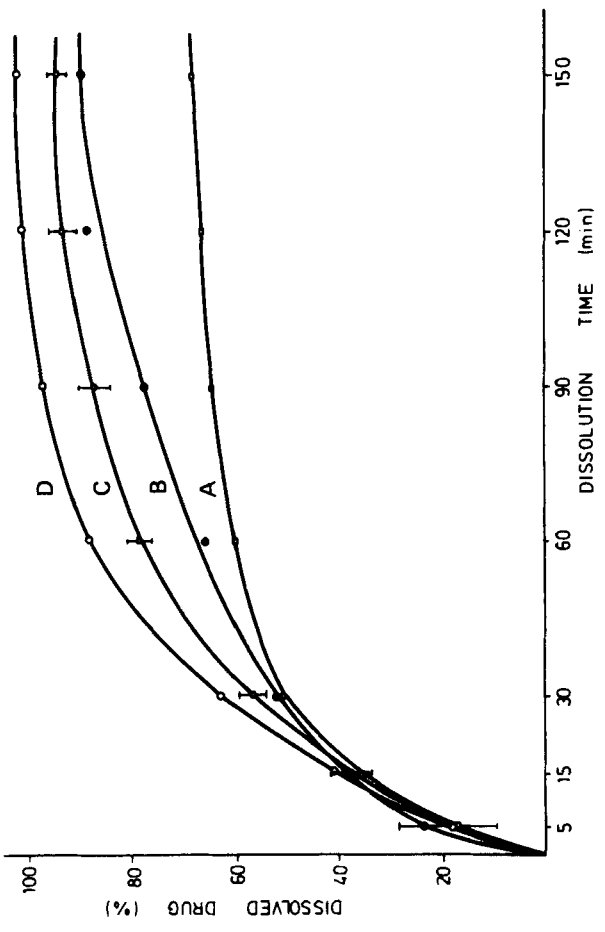

FIGURE 5

Comparative Influence of Binders on the Release of Metronidazole from Tablets. Key: A = Methylcellulose B = Potato Starch; C = Gelatin; D = PVP. Content of Each Binder was 2% (W/W). Particle Size of Metronidazole was 1.75 μm in each of the Formulations.

(PVP), liberated the drug relatively faster than those prepared from other binding materials (figure 5). Such binders e.g. potato starch gel, methyl cellulose and gelatin tend to swell in water and release the drug more slowly. However, PVP dissolves in water more rapidly and disperses the drug particles in the dissolution medium more evenly. This could explain the superiority of PVP to the other binders in the liberation of the active drug from tablets.

These findings may provide new ways of formulating a metronidazole - tablet which exhibits better dissolution and absorption properties, than the KLION ^{R} - Tablet, currently manufactured in Hungary.

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