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

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ABSTRACT

The use of metronidazole in the treatment of Trichomoniasis, Giardiasis, Amoebiasis and infections caused by anaerobic microbes has been well established. This communication outlines efforts made to design a metronidazole formulation with better absorption properties than the "KLION-Tablet", currently manufactured by the Chemical Works of Gedeon Richter Ltd., Budapest. A relatively low solubility of the drug in water, and improper selection of vehicles contribute to low dissolution rate, hence limiting the absorption. Particle size reduction and the incorporation of lactose in the finer aggregating powder, showed increased dissolution rate.

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INTRODUCTION

After oral administration of solid dosage forms, absorption of the active substances from the gastro-intestinal tract, is closely dependent on the dissolution. Dissolution rate of solids can be explained by the Noyes-Whitney relation (1).

$$\frac{dw}{dt} = K.S.\ (Cs - Ct)$$

where $\frac{dw}{dt}$ = the dissolution rate

K = the dissolution rate constant

S = Specific surface area

Cs = solubility of the solid

Ct = concentration of solid at time, t.

Assuming that dissolution and absorption of drug in the G.I.T. do take place simultaneously then $Ct \approx 0$, $Cs \gg Ct$ i.e. dissolution rate depends mainly on the surface area and on the solubility of the drug at the given temperature. Similarly, solubility and surface area are the main factors affecting in-vitro dissolution rate if "Sink Conditions" are to be maintained. It follows that, for substances with relatively poor solubilities in water, the dissolution rate will increase with decreasing particle size (i.e. increasing surface area). Consequently, absorption will be increased provided that their absorption is rate limited by the dissolution process.

The aim of this work was to investigate the influence of particle size reduction and some excipients on the in-vitro release of metronidazole from solid dosage forms.

EXPERIMENTAL

Materials

Metronidazole (Richter G., Budapest) USP standard, Natrium choleicum (Richter G., Budapest, Lactose- spray dried (HMS - Hollandische Melksuiker Fabriek). These materials were of analytical grade.

Particle Size Classification

Five particle size classes were selected for dissolution tests. Particle size classes A (400 - 500 μm) and B (125 - 200 μm) were determined by using laboratory sieving screens. Size E (44 μm)[1] was determined by ALPINE AIR JET SCREENING, Augusburg, FRG. Size classes C (2.4 μm)[2] and F (1.75 μm)[2] were obtained after comminuting the crystalline substance in a Bantam Hammer Mill (Mikropul, Koeln) equiped with screen 3481 - 020. The first four fractions A, B, C and E contained pure drug, while the last fraction F contained

[1] The indicated size refers to geometric median diameter by mass - (dgm).

[2] Sizes in geometric median diameter by count or number - (dgc).

metronidazole: lactose in a ratio of 2.85:1 mixed and then milled together. Particle size analysis for the fine powder fractions C and F was carried out using Particle Size Micrometer and Analyser, Type 525 (Fleming Instruments Ltd., England), by applying the double image principle described by Timbrell (11).

Solubility of Metronidazole

A large excess of metronidazole was added to a series of 10 ml - ampoules containing about 5 ml of distilled water, 0.1 n HCl or artificial intestinal fluid of pH 7.3. Some of the sealed ampoules were agitated in a water bath at 22°, while others were shaken at 37° for 24 hours. Samples were then withdrawn, filtered by a 0.45 µm - Millipore membranes, and their concentrations in water and artificial intestinal fluid were determined from their absorbances at 320 nm. Drug concentrations in hydrochloric acid were assayed at 277 nm. An additional 10 hour-shaking of samples did not show any further increase in concentrations, which were now considered as the solubilities of metronidazole in the given liquids at the experimental temperatures.

Powder Dissolution

Dissolution rates of different powder samples were carried out in 200 ml. distilled water in a

250 ml. beaker at 37°. Powdered drug samples weighing 250 mg each were introduced into the dissolution medium. All samples from fractions A, B and E were found to wet readily with the exception of those from fraction C, which formed aggregates. Agitation was maintained by a magnetic stirrer (2.9 x 0.85 cm) operated at 120 r.p.m. 5 ml-aliquots were withdrawn after 1, 2, 5, 15 and 30 minutes, and were immediately filtered by a millipore membrane (0.45 μm). Sample-equivalent volumes of the dissolution medium at 37° were replaced. After appropriate dilutions, the samples were assayed for metronidazole content at 320 nm.

Initially, the experiment was repeated 11 times with fraction E alone, with the intention of determining the relative standard deviation of the results. Having found a good reproducibility of the experiments, the rest of the fractions were examined using the same method, and repeating each test at least three times.

RESULTS AND DISCUSSION

The solubility of metronidazole in various solvents or fluids is listed in Table 1. The solubility of this drug in 0.1 n hydrochloric acid was about twice as much that in water or artificial

TABLE 1: Solubility of Metronidazole (w/v)% at 22 and 37°

Solvent media	Solubility at 22°	Solubility at 37°
Water	0.94	1.41
0.1 n HCl	2.02	2.76
art. intest. fluid (pH 7.3)	0.87	1.28

intestinal fluid (pH 7.3). Probable hydrogen binding between the highly polar HCl and the tertiary N-atom of metronidazole is likely to account for the increased solubility of the drug in the acid.

In figure 1, dissolution rate profiles of metronidazole of various size ranges in water are reported. Generally, a reduction of particle size produced an increased dissolution rate as expected. However, an unexpected low dissolution rate was observed with fraction C (2.4 μm), which dissolved at a lower rate than that of fraction E (44 μm). Such a reduced dissolution rate was apparently attributed to the formation of poorly wetting and subsequently slowly dissolving aggregates. An attempt to break the aggregates by a tenside (Sodium Cholate) was not successful. This can be seen from the insignificant difference between

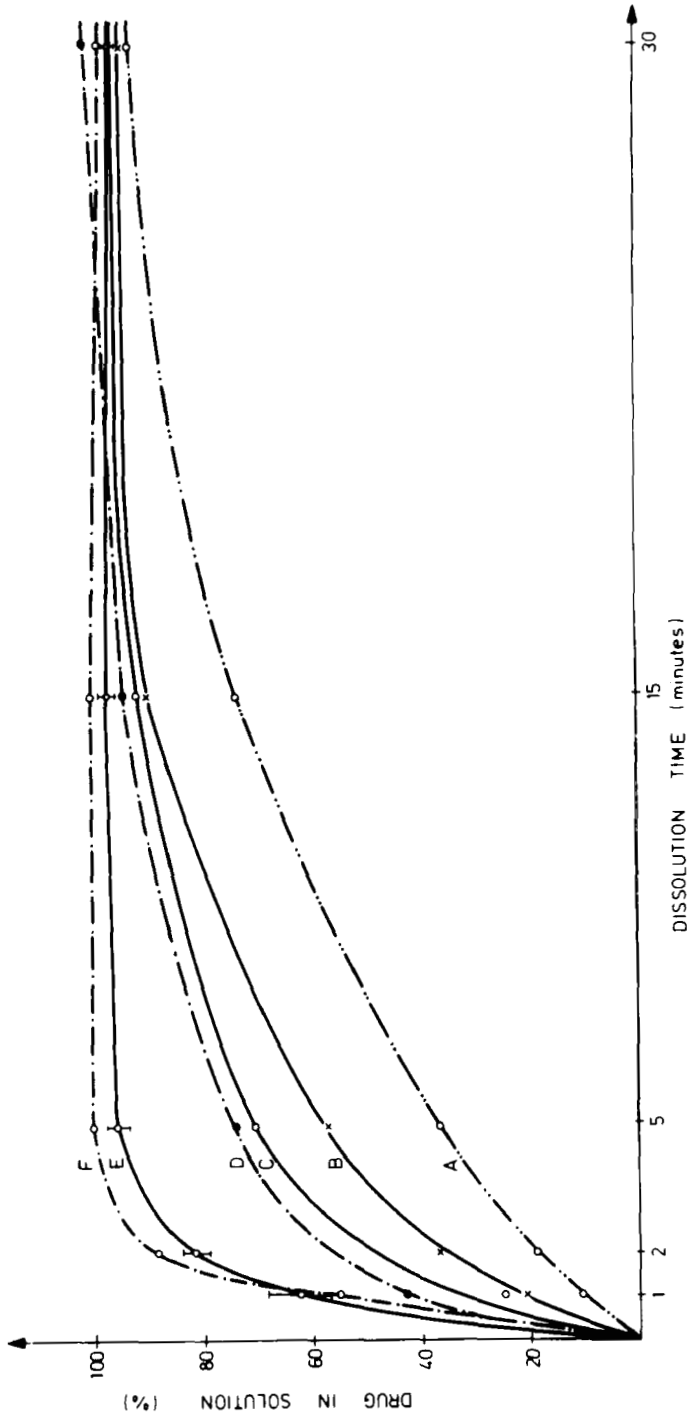

FIGURE 1
Influence of Particle Size on the Dissolution Rate of Metronidazole in Water at 37°. Key: A = 400-500 µm; B = 125-200 µm; C = 2.4 µm; D = 2.4 µm (Dissolution in 0.05% Aqueous Sodium Cholate); E = 44 µm; F = 1.75 µm. Vertical lines represent Relative Standard Deviation for 11 Repeated Measurements.

curves D and C (figure 1), the dissolution profiles of metronidazole in a solution of sodium cholate and water respectively.

However, the influence of lactose on the enhancement of dissolution of drugs from drug-lactose triturations has been reported in the literature by a number of workers. Shah et al (10) found a remarkable increase in the dissolution of digoxin and hydrocortisone from lactose triturations as compared with that of the pure drugs.

Considering such finding(s) metronidazole and lactose (3:1) were mixed and milled together. This mixture contained 2.85:1 (metronidazole:lactose)[3]. After particle size analysis, samples from this mixture designated as fraction F (1.75 μm) were tested for dissolution. The dissolution rate of metronidazole from the lactose mixture was markedly increased, and was the highest among all other fractions examined, (figure 1). The fact that lactose wets and dissolves rapidly in water explains the stepped-up dissolution.

The dissolution rate constants based on the slopes of the profiles in figure 2, and the variations in dissolution times for 60% of the drug

[3]Analytically determined.

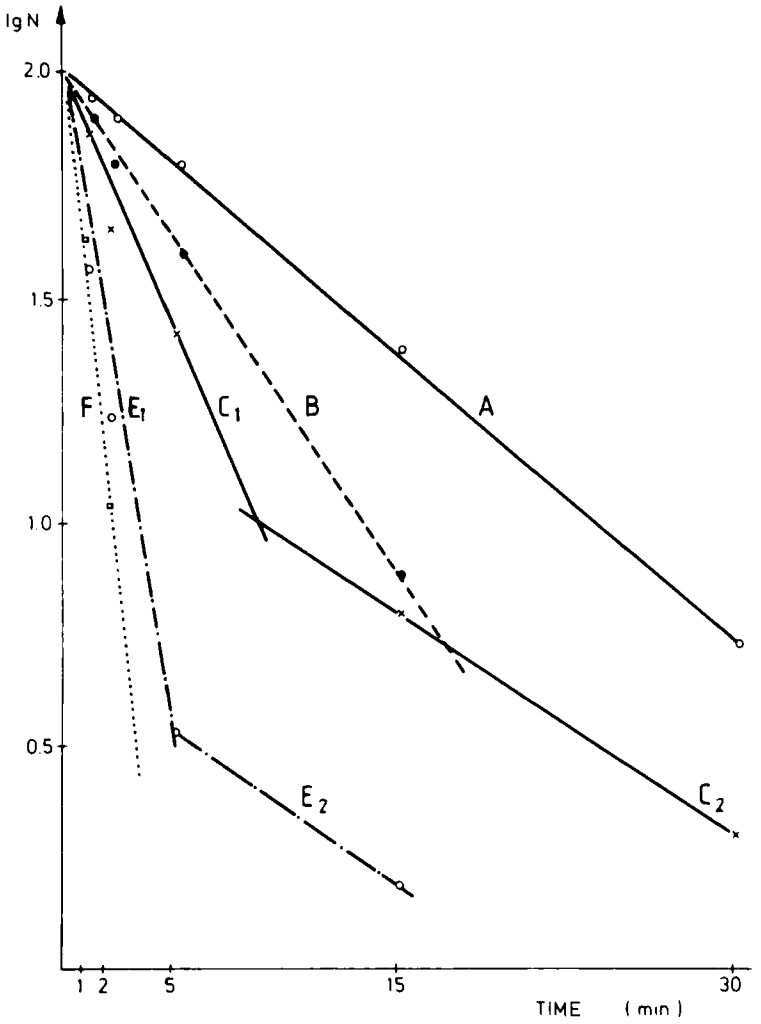

FIGURE 2

Semi-log Plots of Percent Drug Undissolved (lg N) vs. Dissolution Time. Key: A = 400-500 μm; B = 125-200 μm; C_1, C_2 = 2.4 μm; E_1, E_2 = 44 μm; F = 1.75 μm; N = Percent Undissolved Drug.

TABLE 2: Dissolution Rate Constants and Dissolution Times for 60% of metronidazole

Fraction	Size (μm)	K x 10^2 (min^{-1})	$t_{60\%}$ (min)
A	400-500	4.2	10.5
B	125-200	7.5	5.5
C	2.4	11.3 (C_1)	3.0
		3.4 (C_2)	
E	44	30.0 (E_1)	<1.0
		3.4 (E_2)	
F	1.75	45.0	<1.0

(Table 2), confirm the importance of particle size reduction in the enhancement of dissolution of metronidazole. On the basis of these findings, it should however be appreciated that particle size reduction alone (e.g. milling up to very fine powders) may not necessarily bring about desired high dissolution effects. The inclusion of water soluble carriers is likely to cause interaction with the interparticulate attractions thereby hindering aggregation and promoting dissolution.

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