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EFFECT OF MICRONIZATION OF NORFLOXACIN ON TABLET PROPERTIES

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SUMMARY

The particle size of norfloxacin was reduced through the use of an air attrition mill. Not unexpectedly, this treatment also increased the surface area of the drug. Granulations were then prepared from nonmicronized as well as micronized drug. Tablets were compressed from each of these granulations and their physicochemical properties determined. Tablets containing micronized drug showed faster in-vitro dissolution rates and an improvement in bioavailability when tested in Rhesus monkeys.

INTRODUCTION

Micronization has been used widely as a means of reducing particle size or increasing effective surface area of drugs thus

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potentially improving dissolution characteristics (Besins 1978,1980; Bumier et al;1981; Kornblum et al; 1970; Mauger et al; 1983). Spironolactone, for example, was shown to have enhanced bioavailability after micronization in spite of dissolution rate-limited absorption (Ashbury et al; 1981; d'Atis et al; 1981; McInnes et al; 1981, 1982.) Similarly the bioavailability of Griseofulvin from suspensions (Bates et al; 1975) and tablets (Lin et al; 1983) was improved when micronized drug was incorporated.

Drug/excipient interaction studies in these laboratories had indicated that the intrinsic dissolution rate of norfloxacin was likely the rate determining factor influencing the dissolution rate of norfloxacin from a tablet formulation. Since particle size, surface area and dissolution rates are usually related, a study was designed to evaluate these relationships.

More specifically, the objectives of the study were to evaluate the effect of micronized norfloxacin on tablet properties and to compare the bioavailability of micronized versus non-micronized norfloxacin (in tablet form) in Rhesus monkeys.

MATERIALS AND METHODS

Fifty grams of norfloxacin were micronized using an air attrition mill (Trost Jet Mill) coupled to a Syntron Vibra Flow Feeder (Model F-0). Particle size measurements on samples of non-micronized and micronized drug were performed by microscopy (Brinkmann Instruments, Westbury, NY). Surface area measurements were carried out using a Quantasorb sorption system (Quantachrome, Greenville, NY).

Granulations were achieved by a wet granulation technique where an aqueous solution of polyvinylpyrrolidone was used as a granulating liquid.

Tablets were compressed from these granulations on a single station press using 0.32 X 0.58 inches oval, concave, bevelled edged punches. Tablet thickness was measured (N = 10) using an Ames micrometer. The breaking strengths were determined using a Schleuniger - 2E tester (N = 10). Disintegration tests were performed with the USP apparatus in an 0.05M sodium acetate buffer (pH 4.0) at 37°C without discs (N = 6). Dissolution rates were determined in 900 mls of the same buffer at 37°C using USP dissolution apparatus II at 50 RPM (N = 4). The dissolved amounts were determined by a UV spectrophotometric method.

Bioavailability studies were carried out in a crossover design study in three male Rhesus monkeys. The standard in the bioavailability study was a suspension of norfloxacin in 5% tween 80 /5% ethanol administered by gavage. Non-micronized drug was used for preparation of this suspension. Standard dosing procedures were followed except that the monkeys were sedated with 20 mg ketamine hydrochloride injected intramuscularly about 5 minutes before the tablets were given. Blood and urine samples were collected and the serums and aliquots of the urines were examined by bioassay for level of norfloxacin. Four weeks separated the tablet doses. Data on the bioavailability of the norfloxacin suspension were obtained 8 months before the tablet bioavailability tests.

The human bioavailability study on norfloxacin was an open,

two-way, randomized, crossover, single-dose study conducted in 20 healthy male volunteers.

RESULTS AND DISCUSSION

The differences in particle size of non-micronized and micronized norfloxacin can be seen in Figure-1. Non-micronized norfloxacin can contain agglomerates up to 550 microns although 80% of typical lots is usually between 5-200 microns. After micronization, samples revealed some agglomerates up to 400 microns, but 90% of the bulk was between 1-100 microns. The surface area of non-micronized norfloxacin was measured as $1.80 m^2/g$. Micronized material, by contrast, measured $2.10 m^2/g$. The surface area data are somewhat surprising since, from particle size measurements, one could expect a much larger surface area for micronized drug as compared to unmicronized material.

Table - 1 compares the physicochemical properties of the two groups of tablets. Improvement in dissolution rates were noted in tablets made from micronized drug. The weight and thickness variations, and disintegration times were comparable although the breaking strength of tablets prepared with micronized drug were somewhat greater. This is attributed to improved bonding made possible by the increased surface area as well as an increase in fill-density.

Table - 2 shows the bioavailability in Rhesus monkeys of norfloxacin from tablets containing micronized and non-micronized drug. Absorption of micronized drug was more efficient as demonstrated by uniformly higher concentrations in serum and urine. Serum and

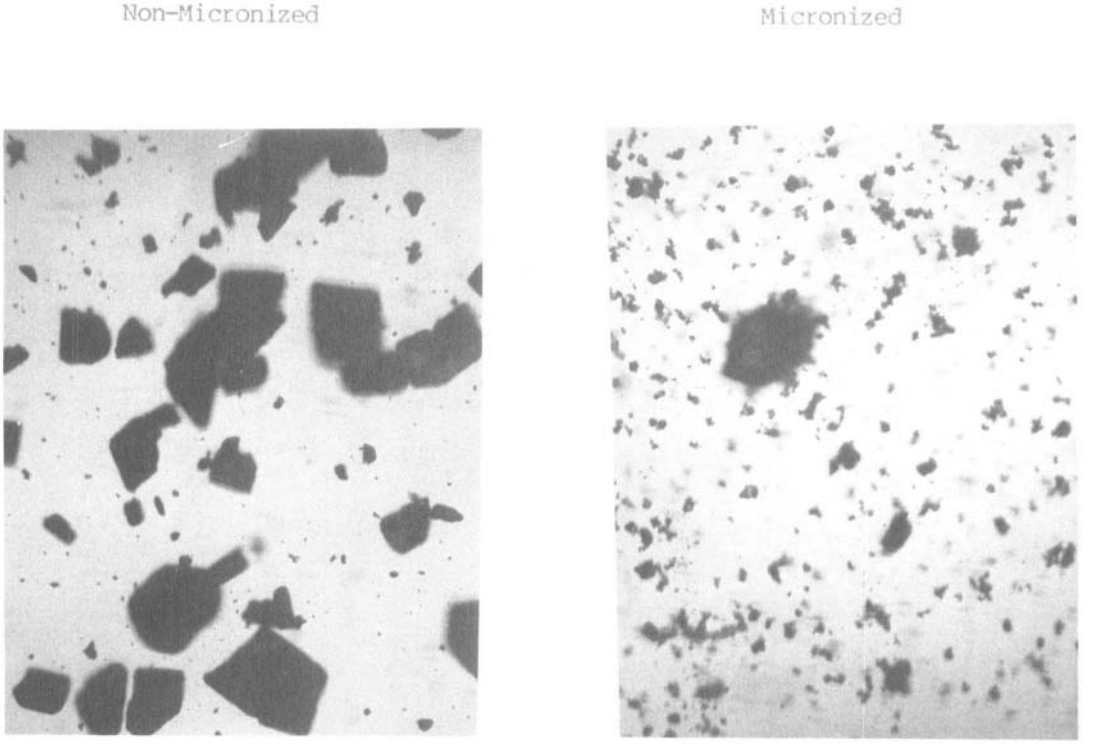

Figure 1

Comparison Between the Particle Size of Non-Micronized vs Micronized Norfloxacin

urine levels from the tablet containing micronized norfloxacin, in fact, were similar to those observed when the drug was administered as a gavage (assumed to be 100% bioavailable). It is also interesting to note that the improvement in bioavailability of micronized drug was several orders of magnitude greater than that suggested by the increase in physical parameters of particle size and surface area.

Two additional points must be considered:

1) Human bioavailability studies where a tablet formulation

Table 1

Comparison of Physical Properties of Tablets Containing Non-micronized and Micronized Drug

	Non-Micronized Drug	Micronized Drug
Weight±SD gms	0.4123±0.0029	0.4347±0.0029
Thickness±SD mm	4.957±0.011	5.291±0.0141
Breaking Strength ± SD Kg	7.54±0.34	8.84±0.54
Disintegration Time	1'48" to 3"12"	3'24" to 4'53"
% Dissolved		
15 Min.	78.8±7.6	102.2±1.0
30 Min.	96.5±3.2	103.4±0.7

containing non-micronized norfloxacin was used, showed that the drug was rapidly absorbed in humans and when compared to an oral suspension, was found 90% bioavailable.

2) All animal studies on this drug suggest that Rhesus monkeys exhibit considerably lower and variable absorption rates for norfloxacin compared to humans. Factors like retention time, fluid volume, pH of gastric fluid, stomach emptying and intestinal motility are all likely involved. The differences in bioavailability between monkeys and humans implies that a different mechanism of absorption exists between the species.

Table 2

Bioavailability of Norfloxacin in Rhesus Monkeys Following a Single Oral Dose in Suspension and in Tablet Form

Monkey	Dose	Serum				Urine		
I.D. No.	mg/kg	C_{max} (μg/ml)[a]	T_{max} (hr)	tl/2 (hr)	AUC μg.hr/ml	μg/ml[a] 0-5 hr	5-24 hr	% Dose Excreted in 24 hr
				Suspension - in Tween 80/Ethanol				
12	25.0	1.3	3	1.99	5.26	345	56	21.6
13	25.0	2.0	1	4.00	6.29	129	13	20.2
21	25.0	1.0	1	0.90	2.51	17	66	13.7
				Tablet - 200 mg Micronized Drug				
12	38.1	1.2	3	1.99	5.41	325	55	16.7
13	37.0	1.4	3	2.47	7.90	578	53	17.0
21	38.9	3.3	1	4.00	7.78	80	13	12.4
				Tablet - 200 mg Non-Micronized Drug				
12	34.5	<0.2*	-	----	----	2	22	3.9
13	32.0	0.8	3	----	----	34	9	6.8
21	35.1	<0.2*	-	----	----	13	8	3.8

[a]Determined as total bioactivity by a disk diffusion method using Klebsiella pneumoniae
*Below the sensitivity limits of the assay

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