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Micronization: A Method of Improving the Bioavailability of Poorly Soluble Drugs

J.C. Chaumeil

Laboratoire de Pharmacotechnie et Dermopharmacie, Faculté des Sciences Pharmaceutiques et Biologiques, Université René-Descartes, Paris, France

SUMMARY

For poorly soluble drugs, the digestive absorption depends on their rate of dissolution. Decreasing the particle size of these drugs improves their rate of dissolution. Fine grinding mills are use to micronize powders: either jar mills or fluid energy mills. Theses processes were applied to griseofulvin, progesterone, spironolactone and diosmin. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy. © 1998 Prous Science. All rights reserved.

Key words: Micronization - Griseofulvin - Progesterone - Spironolactone - Diosmin

BIOAVAILABILITY AND RATE OF DISSOLUTION

The bioavailability of a drug administered by the oral route depends primarily on its ability to be absorbed by the digestive tract. The main absorption mechanism is passive diffusion, which requires the active materials to retain an amphophilic structure in aqueous solution. Drugs that are absorbed in this way must dissolve in the digestive fluids before diffusion through the digestive tract. The amount of drug absorbed then depends on its solubility characteristics.

Some drugs are highly soluble and it is relatively easy to obtain a good rate of dissolution with any type of formulation. The parameter limiting the absorption, in this case, is the permeability of the digestive mucosa to the substance. However, the solubility is often low which reduces the rate of dissolution. This is especially the case for newer drugs, which may have a complex molecular structure. In these cases, the drug formulation is important because it is the main parameter dictating the rate of dissolution of active materials: digestive absorption is determined by the amount dissolved.

The bioavailability of a drug is classically defined as the fraction of the administered dose that reaches the systemic circulation of a living organism, and the rate at which it does so. The first, and often only, parameter that can improve the bioavailability of a poorly soluble drug is its rate of dissolution in the digestive fluids (1).

Noyes and Witney's law can be used to evaluate the rate of dissolution: $dc/dt=KaS(Cs-Ct)$, where dc/dt is the rate of dissolution from the powder state of a drug; Ka is a constant depending

on the dissolution conditions; S is the area of contact between the powder and the solvent; Cs is the concentration of the drug at saturation; Ct is the concentration of the amount of dissolved drug at the time of measurement. All of these parameters are constant, except for S and Ct.

Increasing S allows, to a first approximation, an improvement in the rate of dissolution. S is inversely proportional to the extent of granulation of the powder. It can thus be increased by reducing particle size.

MICRONIZATION: A METHOD OF REDUCING PARTICLE SIZE

The process used to reduce size of particles and aggregates must be chosen according to the powder characteristics (structure, hardness, and chemical stability) and the particle size required. The granulation of a powder can be defined as the average particle size measured using an appropriate device: a screen down to a few tens of micrometers, a particle size counter, or electronic or laser diffraction for smaller granules (2).

Theoretically, the smaller the particles, the higher the rate of dissolution. Practically, the energy of the process can create a disequilibrium in the electric charges of the particles and cause aggregation of the smaller particles. This means that the minimum particle size is a few micrometers.

The best devices for reducing particle size are those which spread out the energy. However, it is rarely possible to obtain the required particle size using only one operation. High-energy equipment that could reduce a raw material with large particles to one with micrometer-sized particles would release a large amount of heat, which could cause partial destruction of less stable molecules. Processes for reducing particle size must therefore be carried out in successive steps. The apparatus used for reducing particle size can be classified into three broad categories (1): i) coarse crushers; ii) intermediate grinders; iii) fine grinding mills.

Briefly, micronizers are part of the last category and can only be used with the powders that are first reduced to particles a few millimeters in size.

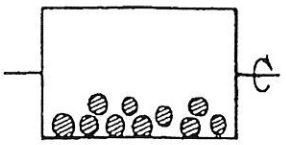

FIG. 1. Jar mill. (Reprinted with permission from Le Hir, A. Pharmacie galénique. 6th Edition. Masson 1992.)

Generally, two types of micronizers are used: First, pebble or jar mills operate by the principle of attrition or impact. The material to be ground is placed in a cylindrical jar containing pebbles or balls of flint, porcelain, or stainless steel (Fig. 1). The jar revolves horizontally on its long axis, which tumbles the pebbles or balls with the particles, which are pulverized. This grinding can be carried out with the raw material alone or in suspension in a (nonsolvent) liquid; Secondly, fluid energy mills are used to obtain extremely fine particles. The particle size is reduced by subjecting the material to high-speed jets of air or inert gas (Fig. 2).

Like the other methods of reducing particle size, micronization does not produce a powder with a uniform particle size. Size distribution is a

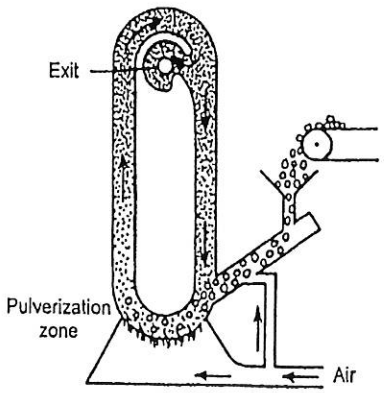

FIG. 2. Fluid energy mill (Reprinted with permission from Le Hir, A. Pharmacie galénique. 6th Edition. Masson 1992.)

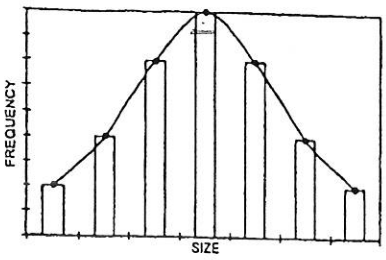

FIG. 3. Size ranges of particles.

statistical concept. For regular particles, diameter is used to define the extent of granulation, regarding the particles as spheres. The size range of the particles is usually normally distributed around a maximum, which is defined as the particle size and which is the median value of the real measured size (Fig. 3).

APPLICATION OF MICRONIZATION TO POORLY SOLUBLE DRUGS WITH A LOW BIOAVAILABILITY

The rate of dissolution of several sparingly soluble drugs has been improved by micronization. The most successful examples involve antifungal, hormonal and venotonic drugs.

Griseofulvin has a particularly low solubility and was thus studied as a micronized powder with a median particle size of 3 micrometers (3). Measurement of the amount dissolved in water *versus* time using a micronized powder showed that the rate of dissolution depended on the area of contact, which is related to the particle size. Increasing this area was the best way of increasing the rate of dissolution of this drug (4).

In the field of hormones, progesterone has had limited clinical use because of its poor digestive absorption due to its low aqueous solubility. To improve its bioavailability, progesterone was micronized and placed in soft gelatin capsules containing arachidonic oil as a dispersion excipient (5). A new formulation of progesterone is now available for hormonal therapies. A comparison of oral micronized progesterone administration (200 mg per dose) and injectable administration (intramuscular route) of an oily solution (50 mg per dose) in postmenopausal women showed that after a 1-day treatment, the relative bioavailability of the micronized progesterone was 8.6% compared with the intramuscular progesterone (Table 1). Mean C_{max} values for oral administration of progesterone were 30% of those obtained after intramuscular administration, and T_{max} occurred significantly earlier with the oral administration (6). These results could be due to the low diffusion rate of progesterone from its oily solvent after injection. After the second day of the treatment, progesterone was shown to accumulate after the multiple intramuscular doses; no such accumulation was observed after oral administration.

The use of micronization for progesterone has made it possible to administer this hormone by the digestive route, providing a significant benefit to patients.

Comparable advantages have also been obtained with micronized spironolactone, which has an enhanced *in vitro* dissolution (7). The bioavailability in 24 healthy male subjects

TABLE 1. Comparison of pharmacokinetic parameters for micronized progesterone administered orally and progesterone in oil administered intramuscularly for day 1 of a 2-day regimen.

	Micronized progesterone*	Intramuscular progesterone**
AUC_{0-24} (ng.h/ml)	87.4 ± 17.2	254.6 ± 18.2#
C_{max} (ng/ml)	17.1 ± 10.7	14.3 ± 1.0
T_{max} (h)	2.5 ± 1.6	8.7 ± 2.0#

*200 mg; **50 mg in oil; #Values after intramuscular progesterone significantly different from corresponding values after micronized progesterone treatment ($p < 0.05$). Each value is the mean ± SEM of data from 15 subjects. Reprinted by permission from the American Society for Reproductive Medicine (*Fertility and Sterility* 1993, 63: 26-33).

TABLE 2. Bioavailability of micronized spironolactone to standard spironolactone tablets.

Preparation	Bioavailability (%)*	
	By 96-hour AUC**	By 96-hour urinary canrenone excretion***
25 mg tablets	118.3 (108.0-129.7)	111.8 (99.6-125.8)
100 mg tablets	111.1 (101.8-121.5)	101.4 (87.2-117.9)
Overall	114.6 (108.0-121.6)	107.0 (98.1-116.8)

*Figures in parentheses are 95% confidence limits.

** $\frac{\text{Canrenone AUC after micronized tablets}}{\text{Canrenone AUC after standard tablets}} \times 100$

*** $\frac{\text{Urinary canrenone excretion after micronized tablets}}{\text{Urinary canrenone excretion after standard tablets}} \times 100$

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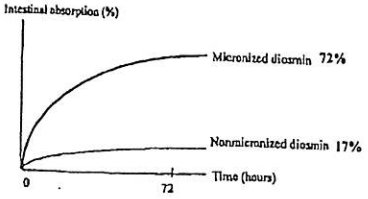

FIG. 4. Intestinal absorption of micronized and nonmicronized diosmin.

receiving tablets manufactured with either micronized material or the standard material was studied by measurement on the pharmacokinetics of the main metabolite of spironolactone, canrenone, for 96 h after treatment (8). Table 2 shows the relationship of the blood levels of canrenone (AUC) and its urinary excretion with the particle size of spironolactone; the differences are statistically significant.

A pharmacological study was carried out by Johnston *et al.* (9) to investigate the effects of micronization on the digestive absorption of a flavonoid, diosmin. This study showed that the absorption of micronized diosmin is four times greater than that of nonmicronized diosmin (Fig. 4).

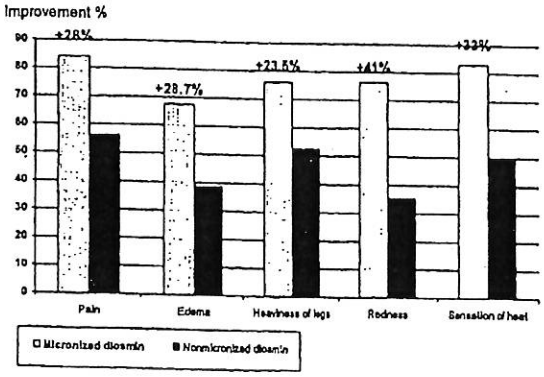

FIG. 5. Improvement in the clinical symptoms of venous insufficiency with micronized and nonmicronized diosmin.

Another study demonstrated the better clinical efficacy of micronized diosmin after 60 days of treatment ($p<0.01$) (10). Plethysmographic measurements showed a significantly higher venotonic activity for micronized diosmin, in terms of venous distensibility and emptying time. The superiority of micronized diosmin, compared with an equivalent dose of nonmicronized diosmin, has been demonstrated both pharmacologically and in terms of the clinical symptoms of venous insufficiency (Fig. 5).

CONCLUSIONS

These findings on the influence of particle size show that reducing particle size by micronization can improve the rate of dissolution of poorly soluble materials. Such *in vitro* results may be useful for optimizing drug formulations to improve the bioavailability of poorly soluble drugs.

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Address for correspondence: J.C. Chaumeil, Laboratoire de Pharmacotechnie et Dermopharmacie EAD 1597, Faculté de Sciences Pharmaceutiques et Biologiques, Université René-Descartes, 4, avenue de l'Observatoire, 75270 Paris Cedex 06, France.