Solvent Deposition Method for Enhancement of Dissolution Rate: Importance of Drug-to-Excipient Ratio

HANS JOHANSEN * **and NIELS MØLLER** ‡x

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Abstract □ Dissolution rates and particle sizes of phenylbutazone solvent deposited on lactose, starch, and silicon dioxide, separately, and of norethindrone and digoxin deposited on lactose were investigated. Microparticulate dispersed drugs on the surface of excipients result when drug-to-excipient ratios are low. Fast dissolution rates are observed for such systems. This effect can be extended to higher ratios when silicon dioxide is used as the excipient. Because of adsorption, however, the release from silicon dioxide is more or less limited.

Keyphrases □ Dissolution rate—enhanced by solvent deposition method, effect of drug-to-excipient ratio □ Solvent deposition method—enhancement of dissolution rate, effect of drug-to-excipient ratio □ Dosage forms, solid—enhancement of dissolution rate by solvent deposition method, effect of drug-to-excipient ratio

A solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix. This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix. Biopharmaceutical aspects of this technique were considered by Termansen (1), who stated that the purpose of preparing a formulation of linguets of methyltestosterone in this way was to obtain small methyltestosterone particles having satisfactory absorption.

Solvent deposition systems were described and characterized previously (2, 3). The term "minuscular form" was introduced to describe "that the drug has undergone molecular micronization when it is dispersed on the extensive surface of a microparticulate adsorbent." It was concluded (2, 3) that fast drug dissolution is obtained from solvent deposition systems.

The purpose of the present report is to emphasize the importance of a low drug-to-excipient weight ratio when the solvent deposition technique must be considered as an optimal method of increasing dissolution rates of slightly soluble drugs.

EXPERIMENTAL

Materials—Soluble, swelling, and adsorptive excipients were used. The specific surface areas, determined by the gas adsorption technique (4), were: lactose (particles less than 50 μm), 0.50 m^2/g; lactose (particles less than 150 μm), 0.20 m^2/g; potato starch, 0.20 m^2/g; and silicon dioxide[1], 190 m^2/g.

A polyethylene 12-tridecyl ether urea complex[2] (I) was used. All solvents and other substances were pharmacopeial or analytical grade.

Solvent Deposition Systems—The preparations were made in 10–50-g portions by wetting the excipients with solutions of the drug in organic solvents. The solvents were evaporated at room temperature with frequent stirring, and the mixtures were passed through a 200-μm sieve (70 mesh).

To avoid phenylbutazone undergoing fast air-oxidation during excipient application, these systems were prepared in a nitrogen atmosphere (4). The solvent was acetone. The size of the lactose particles was less than 50 μm.

For norethindrone, the solvent was chloroform and the size of the lactose particles was less than 150 μm. For digoxin, the solvent was chloroform–methanol (1:1) and the size of the lactose particles was less than 150 μm. Aggregates of digoxin preparations were broken by passage through a 150-μm sieve (100 mesh).

Dissolution Rate—Determinations of dissolution rates, at the indicated wavelengths, of the preparations used samples equivalent to 8 mg of phenylbutazone (237 nm), 8 mg of norethindrone (248 nm), and 20 mg of digoxin (222 nm). Tests were conducted at 37 ± 0.2° in a beaker apparatus with a magnetic stirrer (3 × 0.6 cm) at 509 rpm. The dissolution medium was 1000 ml of 0.1 *N* HCl containing 0.05% of I.

Establishment of reproducible wettability, *etc.*, was done as described previously (4). The dissolution profiles given in the figures are means of six tests. On the average, the relative standard deviation was about 2%, varying from 0.6 to 4.0%.

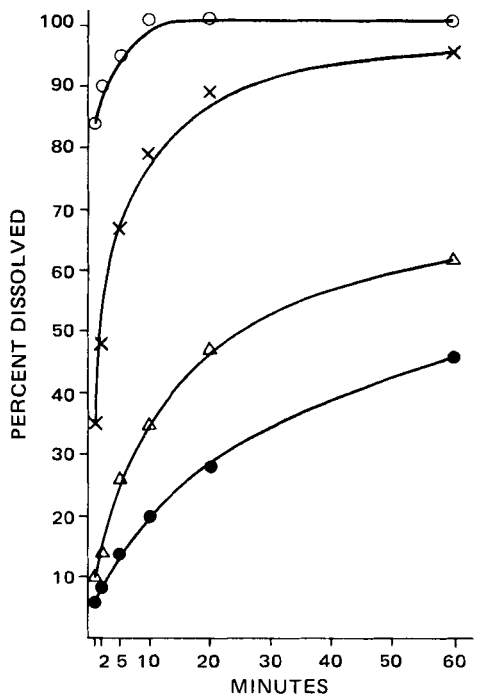


Figure 1—*Dissolution profiles of phenylbutazone solvent deposited on lactose (particle size less than 50 μm). Key: ○, 2% phenylbutazone; ×, 10% phenylbutazone; △, 50% phenylbutazone; and ●, 75% phenylbutazone.*

RESULTS AND DISCUSSION

Figures 1–3 show the influence of the drug-to-excipient ratio on the dissolution rate of systems using phenylbutazone as a model substance. It is almost insoluble in 0.1 *N* HCl (14 mg/liter, 37°), and it crystallizes into needles easily identifiable by microscopy. Figure 4 shows some typical scanning electron micrographs of the systems, indicating crystallization processes with crystals and aggregates of sizes that increase with an increasing drug content. The starch systems are preferred for the illustration since the differentiation of drug and excipient is clear. Similar

[1] Aerosil 200.
[2] Renex 35, Atlas Powder Co.

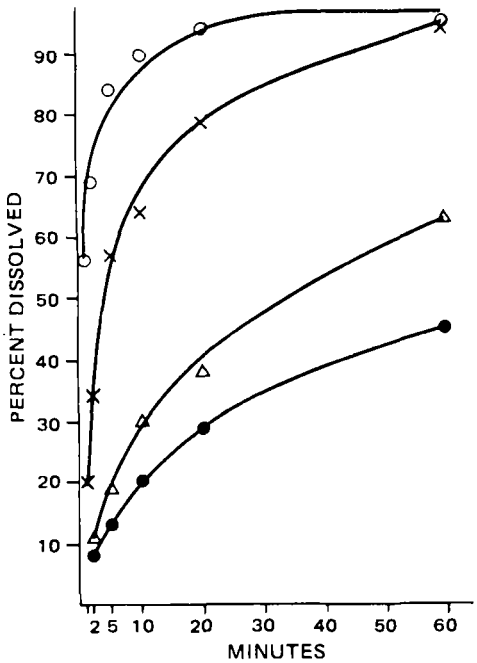


Figure 2—*Dissolution profiles of phenylbutazone solvent deposited on potato starch. Key: ○, 2% phenylbutazone; ×, 10% phenylbutazone; △, 50% phenylbutazone; and ●, 75% phenylbutazone.*

micrographs of the silicon dioxide systems show that pure minuscular preparations are obtained at the drug-to-excipient ratios of 2 and 10%, while large phenylbutazone crystals are predominant in the 50 and 75% systems.

The very extensive surface of silicon dioxide makes it possible to prepare systems with the drug present as small submicrometer particles or as a molecular coating at higher drug-to-excipient ratios than are found for lactose and starch. However, phenylbutazone adsorption onto the insoluble silicon dioxide surface takes place (Fig. 3) most evidently for the low drug-to-excipient ratio. Similar drug adsorption to silicon dioxide in 0.1 *N* HCl was observed for several drugs, particularly for diethylstilbestrol and polythiazide. Therefore, the use of silicon dioxide as an excipient in solvent deposition systems is somewhat limited.

The conclusions based on the experiments with phenylbutazone (Figs. 1–3) are valid for any drug being dissolution rate tested at varying drug-to-excipient ratios. Examples using lactose as the excipient are shown in Figs. 5 and 6. Official tablets of norethindrone or digoxin are usually prepared by solvent deposition techniques to achieve a satisfactory content uniformity for the solid dosage forms of low dosages. Both drugs are very slightly soluble in 0.1 *N* HCl, but drugs of higher water

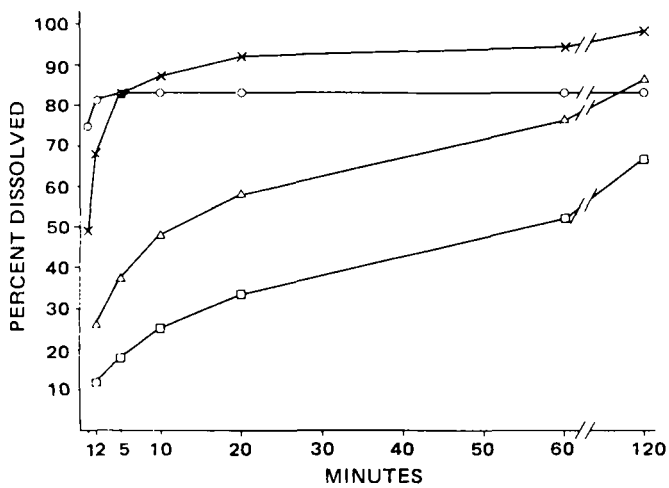
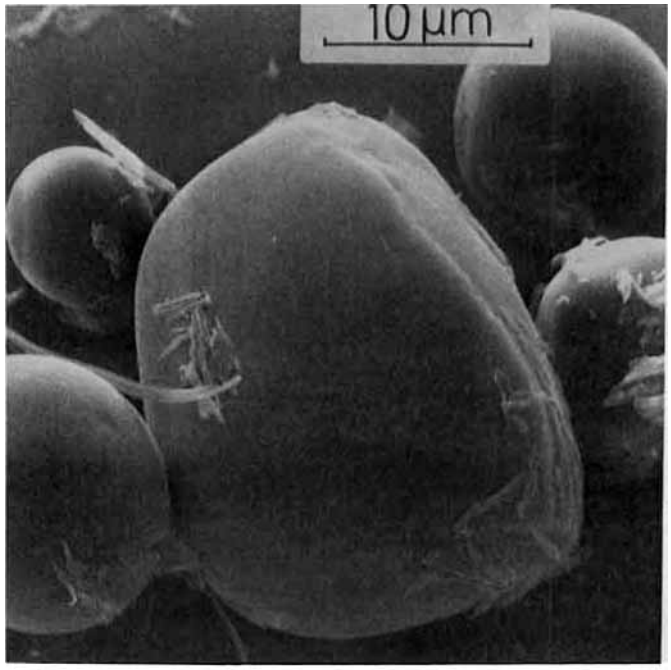


Figure 3—*Dissolution profiles of phenylbutazone solvent deposited on silicon dioxide. Key: ○, 2% phenylbutazone; ×, 10% phenylbutazone; △, 50% phenylbutazone; and □, 75% phenylbutazone.*



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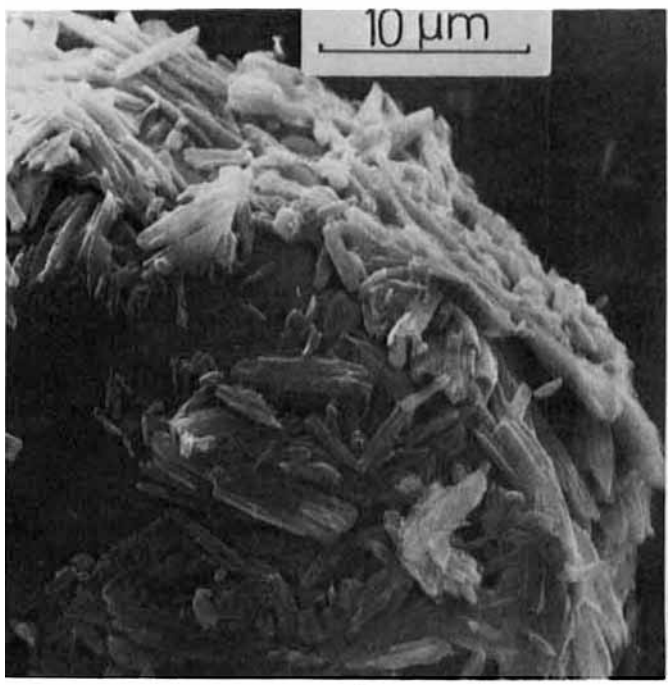

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Figure 4—*Scanning electron micrographs of phenylbutazone solvent deposited on 90% (a) and 50% (b) potato starch.*

solubility also have been examined, *e.g.*, aspirin. However, because of the higher solubility and good wettability of such solvent-deposited drugs, the dissolution rates of the systems become rather fast; even large particles of 100–200 μm are prevalent when higher drug-to-excipient ratios are used.

Results of dissolution studies on solvent-deposited digoxin and hydrocortisone on lactose were reported and compared to frictionally deposited triturations and to simple blends using a rotating-basket apparatus (60 rpm) (5, 6). The investigators found that the solvent-deposited triturations dissolved more rapidly than the simple blends but slower than the frictionally deposited triturations, although the drug-to-excipient ratio was rather low (1:20).

The dissolution profiles of solvent-deposited and frictionally deposited digoxin and hydrocortisone on lactose (1:20) gave no significant differ-

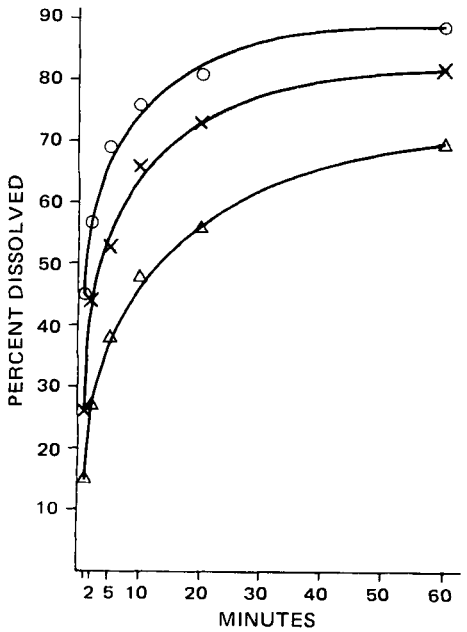

Figure 5—*Dissolution profiles of norethindrone solvent deposited on lactose (particle size less than 150 μm). Key: ○, 2% norethindrone; ×, 10% norethindrone; and △, 20% norethindrone.*

ences when the experiments were carried out in the present beaker apparatus. This result points to the need for caution in interpreting experimental data, because factors such as hydrodynamics and granule size may determine the distinguishability of different formulations.

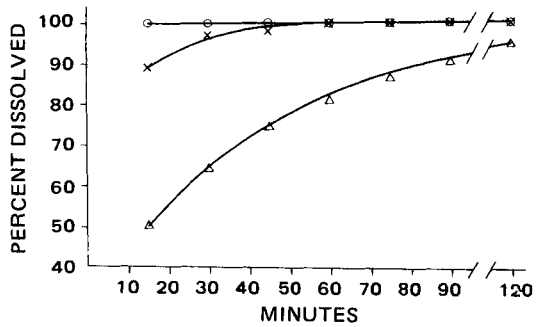

Figure 6—*Dissolution profiles of digoxin solvent deposited on lactose (particle size less than 150 μm). Key: ○, 1% digoxin; ×, 5% digoxin; and △, 25% digoxin.*

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New *In Vivo* Evidence for Narcotic Agonistic Property of Leucine-Enkephalin

HEMENDRA N. BHARGAVA

Received February 28, 1977, from the *Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612.* Accepted for publication April 7, 1977.

Abstract □ Administration of leucine-enkephalin or morphine to mice rendered dependent on morphine by pellet implantation inhibited the naloxone-precipitated abstinence syndrome. The withdrawal jumping response was inhibited by morphine or leucine-enkephalin; however, both failed to inhibit withdrawal defecation and rearing behavior. On a molar basis, leucine-enkephalin was half as potent as morphine in inhibiting the abstinence syndrome. New *in vivo* pharmacological evidence for narcotic agonist-like activity of leucine-enkephalin is provided.

Keyphrases □ Leucine-enkephalin—narcotic agonist activity evaluated, mice □ Narcotic activity—leucine-enkephalin evaluated, mice

The discovery of specific opiate receptors in brain and other opiate-sensitive tissues suggested the possible existence of endogenous ligands (1–3). Two pentapeptides, methionine-enkephalin and leucine-enkephalin, were identified (4) and postulated to be endogenous ligands for the opiate receptors in mammalian brain (5–8). Both peptides mimic the ability of morphine to inhibit electrically induced contractions of the guinea pig ileum and mouse vas deferens. These inhibitory effects are antagonized by the opiate antagonist, naloxone (4). Enkephalins also inhibit the stereospecific receptor binding of naloxone in brain homogenate (4). The binding of enkephalins to the opiate receptor is inhibited by a high sodium-ion concentration and enhanced by a high manganese-ion concentration, a response characteristic for opiate agonists (9).

Enkephalins also produce analgesia when administered into the lateral ventricles of rats (10, 11). It has been suggested that enkephalin and morphine receptor sites for analgesia may be similar or identical (12, 13). Recently, methionine-enkephalin was shown to suppress antagonist-induced morphine abstinence in morphine-dependent mice (14). The present report presents new *in vivo* evidence for the similarity of action of morphine and leucine-enkephalin.

EXPERIMENTAL

Male Swiss-Webster mice[1], 25–30 g, were maintained on food and water *ad libitum* in a room maintained on 12-hr light–dark cycles at an ambient temperature of 23 ± 1° and a humidity of 65 ± 2%. Mice were rendered

[1] Scientific Small Laboratories, Arlington Heights, Ill.