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RESEARCH PAPER

Evaluation of Two Dextrose-Based Directly Compressible Excipients

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ABSTRACT

The objectives of this research were to evaluate the physical properties and compaction behavior of two dextrose-based directly compressed excipients. Anhydrous theophylline (10% w/w) was used as a drug model, Emdex and or Maltrin M510 (89.5% w/w) were used as diluent, and magnesium stearate (0.5% w/w) was used as lubricant. Direct compression and wet granulation methods were used for preparing the compacts. In general, the wet granulation method reduced the density of the mixture and consequently its flow rate compared to the mixture prepared only by solid–solid mixing. All formulations were compressed at four different compressional forces and at a target weight of 450 mg ± 5%. Tablets obtained were different in physical properties and mechanical strength based on type of excipient used and methods of tablet preparation (direct compression versus wet granulation). Compacts prepared from Maltrin M510 had a longer disintegration time and slower drug release than compacts of the same composition but prepared with Emdex. Disintegration time and drug dissolution from tablets containing Maltrin M510 as diluent and prepared by wet granulation appeared to be controlled by a "gel" layer formation around the tablets and not by the tablets porosity. This study demonstrates that full characterization of excipients is needed because a different manufacturing process for the same excipients may produce differences in the pharmaceutical products.

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INTRODUCTION

Over the last 25 years considerable research activity has occurred on tablet product design and the data show the imperative necessity of a complete excipient characterization including functionality or physicochemical testing and assessment of compaction, because these factors may exert a profound influence on the stability, bioavailability, and manufacturing process of a formulated drug (1–6).

Tablets can be compacted by direct compression or after a granulation step. Direct compression involves the mixing of several ingredients of the powder mass before compaction. Direct compression is widely accepted by the pharmaceutical industry; it is economical because of the reduction of labor, cost, time, operational space, and machinery utilized (7). The process of wet granulation involves the agglomeration of several ingredients prior to tableting. Granulation is designed to improve tableting properties including flowability, compressibility, and compatibility of the blend ingredient. The various steps involved in the process of granulation have a significant effect on the particulate characteristics of the resulting granulation.

However, relatively few studies have been performed concerning the relation between the primary properties of the ingredients, characteristics of the blend or granules, and the properties of the final tablets. The goal of this study was to demonstrate the importance of the physical properties of blends or granules such as density, porosity, flowability, particle size distribution, surface morphology, and surface area on the compressibility and properties of the final tablets. The relationship among compressional forces, tablet hardness, crushing strength, porosity, and dissolution was also investigated. Another goal was to compare the physical properties of tablets prepared by direct compression and those of the same composition but prepared by wet granulation (8).

MATERIALS AND METHODS

Materials

Except when noted, all chemicals were analytical grade and used as received. Theophylline anhydrous was generously supplied by Searle Pharmaceutical Inc. (Puerto Rico), Emdex (Dextrates, NF Hydrated) was supplied by Mendell (Patterson, NY), Maltrin M510 (fine granules Maltodextrin) was kindly supplied by Grain Processing Corp., and magnesium stearate was supplied by Amend Drug and Chemical Co.).

Preparation of Blends

Four formulations were prepared. Two were prepared by direct compression and the remaining formulations were prepared by wet granulation. The batch size for each formulation was 2 kg. A 10% w/w anhydrous theophylline was used as a drug model, 89.5% w/w of Emdex or Maltrin M510 was used as diluent, and 0.5% w/w magnesium stearate was used as lubricant. All materials were sifted manually through no. 12 screen and the lubricant was sifted through no. 30 screen.

The powder mixing was performed by preblending the drug (200 g) and equal quantity of the diluent (200 g) in a Turbula mixer (Willy A. Bachafen, model T 2C, Switzerland) at a speed of 90 rpm for 10 min. The preblend was transferred to a V-blender (PK processor, Patterson Kelly, model LB-5322) and the remaining amount of the diluent was mixed with the preblend by geometric dilution for 10 min. The lubricant (10 g) was added before compression and the blend was mixed for an additional 5 min.

Wet Granulation for Emdex Formulations

The wet granulation process was performed in a Hobart planetary mixer by adding a sufficient quantity of water as the granulating liquid. Water was added to the already blended drug–excipient mixture until a suitable consistency was achieved. The wet agglomerates were hand screen-sifted through a no. 12 mesh size and introduced in a hot air oven for drying at 40°C for 15 hr.

Wet Granulation for Maltrin M510 Formulations

The wet granulation process was also performed in a Hobart planetary mixer and the water was added by dripping from a sterile piggyback device because of the large agglomerates with large lumps formed immediately when water was added directly to the mixture. The dripping rate of the water was adjusted and the water was dropped slowly until a mass of good consistency was obtained. The wet granules were sifted through a no. 12 screen after drying since it was difficult to hand screen before drying.

Bulk and Tapped Density

Samples of 50 g each were evaluated for bulk and tapped density (g/ml) in duplicate. For bulk density determination each sample was poured into a 100-ml graduated cylinder using a large funnel and the volume

occupied was measured. The sample weight was then divided by the bulk volume to obtain the bulk density.

The tapped density was determined using the Vandekamp tap density tester. The samples were poured into a 100-ml measuring cylinder and placed in the tester, each sample was tapped 200 times, and the number of taps was increased until no change in powder bed volume was observed. In order to obtain tapped density, the weight of the sample was divided by the tapped volume (volume occupied after tapping in milliliters).

True Density and Porosity

A helium pycnometer was used to calculate the true density and porosity of the samples. The empty sample cup was initially weighed and a sample of 15–20 g was placed in the cup and purged for 1 min with helium to allow the air to be purged from the instrument. The change in pressure caused by a finite change of the system is a function of its total volume. The chamber was filled to 19.5 ± 0.2 psig, then the valve was closed and the pressure was allowed to equilibrate and was recorded as p_1. The pressure immediately after expansion was recorded as p_2. For accurate density measurement, four determinations for each sample were performed. The general equation for computing sample volume is

$$V_{SAMPLE} = V_{CELL} - V_{EXP}/\{(p_1/p_2) - 1\}$$

where V_{SAMPLE} is true volume of the sample; V_{CELL} is empty volume of the sample with empty sample cup in place; V_{EXP} is expansion volume added; p_1 is recorded charge pressure; and p_2 is recorded pressure after expansion. The V_{CELL} and V_{EXP} were 37.125 and 20.874 ml, respectively, at a full scale range of 35 cm^3.

Sample density (ρ_{SAMPLE}) was computed as follows:

$$\rho_{SAMPLE} = W_{SAMPLE}/V_{SAMPLE} = \frac{\text{gross weight} - \text{cup weight}}{V_{sample}}$$

Percent porosity can be calculated from true volume (V_t) and bulk volume (V_b) as follows:

$$\% \text{ porosity} = \frac{(1 - V_t)}{V_b} \times 100$$

Dynamic Flowability

Three samples each of 100 ml were tested for flow rate (g/min) in the Vankel Flow Meter. The sample was poured in a fixed-position calibrated cylinder which contained a seal below it to prevent the powder from flowing. A 200-ml beaker was placed over the equipment scale and tared to record the weight of the sample after completion of the test. A velocity of 20 cm/min and a voltage of 20 A were set for the instrument. The seal under the calibrated cylinder was removed to allow the particles to flow freely into the beaker and when the flow of the particles stopped, the weight was recorded and the distance between starting point and end point was measured on the paper of the recorder. The flowability time was calculated from distance measured on the graph paper of the recorder and instrument velocity, and the flow rate (g/min) for the powder was calculated by dividing the weight of the sample over flow time to obtain flow rate.

Scanning Electron Microscope

Surface morphology for the different formulations prepared under various conditions were examined by the scanning electron microscope. A small sample was mounted on a stub (aluminum mounts) and stock with colloidal silver liquid gum and left to dry. The sample was put in the Auto Sputter Coater (Biorad E5200) and covered with gold layer for 80 min. Argon gas was used for the vacuum. Each second, 3 Å of gold was applied on the sample. For this photo, 10 mV was used and the photomicrographs were taken at 20× and 150× magnifications for each sample.

Particle Size Distribution

Three samples each of 60 g were placed on a Tyler sieve shaker with a set of no. 20, 40, 60, 80, 100, 200, 325 sieves and pans were arranged in descending order. The sieves were shaken for 5 min. The granules retained on each sieve were weighed and data were plotted on log probability paper as percent cumulative under size on a probability scale versus mean diameter of two successive screens on log scale. The geometrical mean diameter of each sample was calculated, which represents the size of 50% of the particles.

Friability of Granules

An Erweka friabilator fitted with an abrasion wheel was used for measuring friability of granules obtained from the wet granulation process. A 10-g sample of mesh fraction 18/40 was introduced in the friabilator and processed at 250 rpm. The percent friability was calculated by using the following formula:

$$\text{Percent friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \times 100$$

Surface Area Determination

A sample cell was filled with a sample of 0.9 ± 0.1 g, which allowed adequate space for the unimpeded flow of gas above the sample surface. For each formulation a differential scanning calorimetry determination was done to determine the appropriate temperature to outgas the sample prior to analysis to ensure that the temperature used during outgassing did not promote any physical or chemical changes within the sample. The Emdex formulations were outgassed by heating the cell at 65°C for 120 min, and using nitrogen flow as a purged gas to carry away the contaminants on sample surface. Maltrin M510 formulations were outgassed by heating the cell at 35°C overnight with nitrogen. The Quantasorb equipment was used to obtain data needed to calculate surface area of the powders and granulated formulations. The process of adsorption of a mixture of 10% nitrogen/helium and desorption was monitored by measuring the change in thermal conductivity of the gas mixture that passed through a cell containing the powder. To determine a single point surface area of pharmaceutical powders, the Brunarer–Emmett Teller (BET) formula was used.

$$S_t = (1 - P/P_0) \times A/A_c \times V_c\ (NA_{cs}P_a)/RT)\ m^2$$

where p is partial pressure of adsorbate; N is Avogadro's number; P_0 is saturated pressure of adsorbate; R is gas constant (82.1 cm^3 atm/K mole); A is signal area; A_c is area of calibration; V_c is volume of calibration; A_{cs} is cross-sectional area of adsorbate molecule in square meters (for $N_2 = 16.2 \times 10^{-20}$ m^2); and T = temperature of calibration volume (ambient temperature) in Kelvin.

Tablet Compression

The blends were compressed into tablets using a single-punch instrumented tablet press (Korsch, EKO) equipped with 12/32-in. round, flat-faced tooling. Target tablet weight was 450 mg ± 5% and tablets were compressed at four different compressional forces to give target hardness between 2 and 3 kp, 4 and 6 kp, 7 and 9 kp, and 10 and 12 kp, respectively. Compression of compacts was maintained at least 1 min during experiments (at each force level) in order to increase the probability of a series of compacts having nearly identical properties. During compression of the different formulations, the following was recorded: upper and lower main compression forces; upper and lower forces displacement; ejection force; tablet thickness; total work; frictional work; elastic work, and net work. Tablet hardness was obtained using Schleuniger hardness tester.

Crushing Strength

The tablet crushing strength (T_s) was calculated from the thickness (H), diameter (D), and crushing force (F_c) measurement using the following equation:

$$T_s = 2\ F_c/\Pi/DH$$

Disintegration Time

A total of six tablets were tested separately for disintegration (Erweka disintegration apparatus). The test was performed using 900 ml of distilled water maintained at 37 ± 2°C as the immersion fluid. For the purpose of this investigation, disintegration was completed when no fragment of the six tablets remained on screen. The disintegration time for each tablet was recorded and the mean was calculated.

Dissolution Testing

The dissolution of theophylline from all tablet formulations was measured in 900 ml distilled water at 37 ± 0.5°C using a rotating basket apparatus (Hanson Research model SR2) at a speed of 50 rpm. Filtered samples were withdrawn and assayed using a UV spectrophotometer (Beckman Instruments, model DU 65) at 271 nm. The number of replicates for each formula was six tablets.

RESULTS AND DISCUSSION

Theophylline formulation containing Maltrin M510 produced by wet granulation gave higher density, better flow, and lower porosity than the directly compressed formulation of the same composition. These results are expected and Table 1 shows the data for bulk density, tapped density, and porosity for the mixture prepared by wet granulation or blending.

The flow rates of both Emdex and Maltrin M510 formulations are shown in Table 2. Formulations with high bulk density and low porosity such as Emdex blend and Maltrin M510 granules gave higher flow rate than formulations with low bulk density and high porosity (Emdex granules and Maltrin M510 blend).

Table 1

Density and Porosity of the Different Emdex and Matrin M510 Formulations

Test ($n = 3$)	Emdex Direct Compression	Emdex Wet Granulation	Maltrin M510 Direct Compression	Maltrin M510 Wet Granulation
Bulk density (g/ml)	0.70	0.52	0.45	0.68
Tapped density (200 taps)	0.84	0.57	0.61	0.82
Tapped density (400 taps)	0.85	0.58	0.61	0.84
Tapped density (600 taps)	0.85	0.59	0.62	0.84
Tapped density (800 taps)	0.86	0.59	0.62	0.85
Tapped density (1000 taps)	0.86	0.59	0.63	0.85
Percent porosity	83.3	90.03	90.82	83.71

Table 2

Flow Rate of Emdex and Maltrin M 510 Formulations

Formulations	Flow Rate (g/min) $n = 3$
Emdex direct compression	472.17
Emdex wet granulation	288.18
Maltrin M510 direct compression	[a]
Maltrin M510 wet granulation	416.36

[a]Flow rate could not be measured.

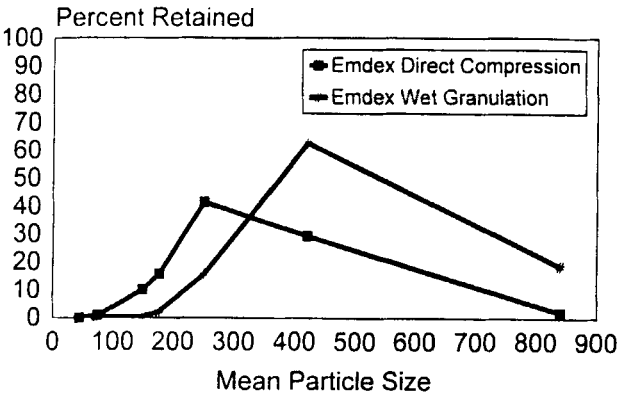

Figure 1. Percent retained on the screen versus mean particle size for Emdex formulations.

The mean particle diameters for all formulations prepared by Emdex or Maltrin M510 were obtained from the cumulative frequency plots on probability paper. For Emdex granules most of the particle sizes fell in the range of 250–420 μm and for Maltrin M510 granules most of the particle sizes were between 74 and 177 μm, and particle sizes of 250–840 μm resulted in bimodel distribution. In general, the particle size for granules was higher than that of the blend of the same composition. Figures 1 and 2 show the different plots for particle size distribution of all formulations.

Theophylline formulations containing Maltrin M510 and prepared by wet granulation were more friable than Emdex granules (Table 3). A significant difference in

Table 3

Granule Friability for Emdex and Maltrin M510 Formulations

Test ($n = 3$)	Emdex Wet Granulation	Maltrin M510 Wet Granulation
Mean percent friability	7.67	23.0
Standard deviation	1.53	13.86

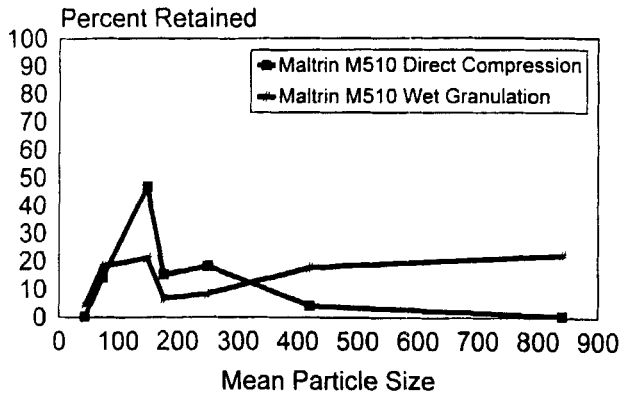

Figure 2. Percent retained on the screen versus mean particle size for Maltrin M510 formulations.

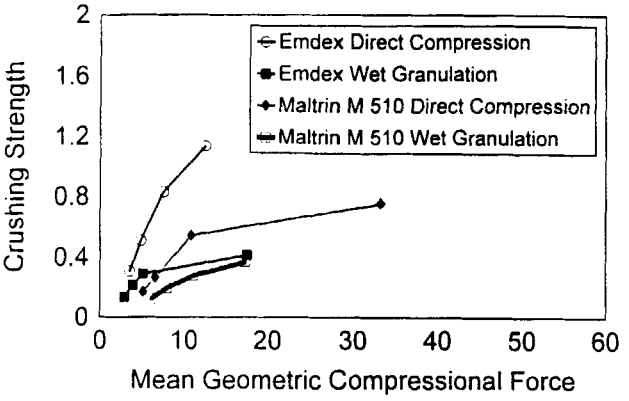

Figure 3. Crushing strength versus mean geometric compressional force.

friability data was observed among different mesh fractions of Maltrin M 510; this may indicate poor powder wetting during the wet massing and consequently some of the granules were not firmly formed.

The surface area was determined for all formulations by the single-point BET method. Initially the degassing procedure was performed at 100°C for 90 min, because this method is usually performed at elevated temperature (above 100°C) to accelerate the rate at which contaminants can leave the surface. However, the appropriate temperatures and durations for degassing Emdex and Maltrin M 510 were between 60 and 65°C for 2 hr and 30 and 35°C overnight, respectively, and volume of gas used for calibration in all formulations was 0.1 ml of nitrogen. In general, powder blends show higher specific area than wet granulation mixtures. The specific surface areas are shown in Table 4.

The effect of compressional force (kN) versus crushing strength (kp/mm^2) for different diluents and different manufacturing processes was investigated. As depicted in Fig. 3, all formulations showed an increase in crushing strength as the compressional force was increased. In general, the wet granulation method for both diluent Emdex or Maltrin M510 exhibited low crushing strength compared to the direct compression method. Both Emdex and Maltrin M510 tablets prepared by the wet granulation method produced tablets with low crushing strength value compared to tablets of the same composition but prepared by wet granulation.

A linear relationship was found between compressional force and percent porosity for formulations containing Emdex prepared by direct compression and formulations containing Maltrin M510 prepared by wet granulation, as indicated in Fig. 4. The formulation prepared with Maltrin M510 and wet granulation method exhibited the lowest percent porosity.

The effect of compressional force on disintegration time for tablets prepared by using different diluents and

Table 4

Specific Surface Area for Emdex and Maltrin M510 Formulations

Formulations	Specific Surface Area (m^2/g) (n = 3)
Emdex direct compression	0.26
Emdex wet granulation	0.17
Maltrin M 510 direct compression	0.21
Maltrin M 510 wet granulation	0.12

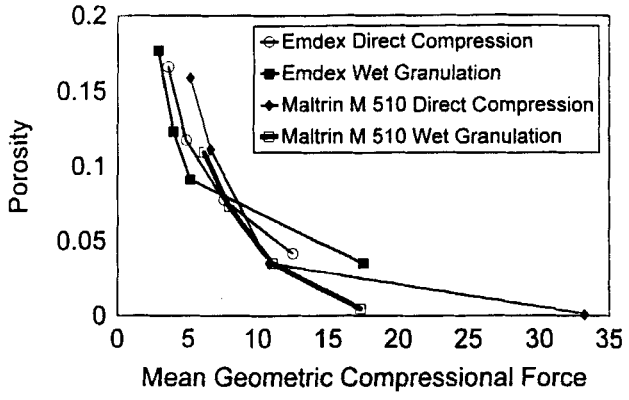

Figure 4. Porosity versus mean geometric compressional force.

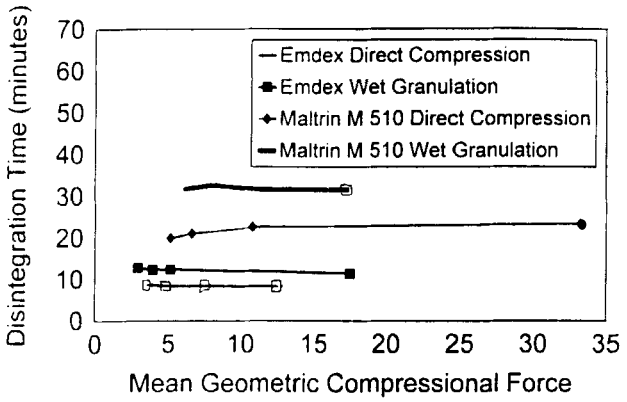

Figure 5. Disintegration time versus mean geometric compressional force.

different manufacturing processes is shown in Fig. 5. In general, tablets prepared with Emdex diluent were of lower disintegration time than those of the same composition but prepared with Maltrin 510. None of the formulations showed an increase in disintegration time as the compressional force was increased except for the formulation prepared with Maltrin M510 and direct compression. Maltrin M510 formulations prepared with direct compression showed a viscous gel layer around the tablets during the disintegration and disintegration of these tablets appeared to be controlled by the gel layer and not by porosity of the tablets.

The effect of compressional force on dissolution of theophylline from the different formulations is shown in Fig. 6. In general, the time for 50% ($T_{50\%}$) of theophylline to be released from all formulations was increased by increasing compressional force to a certain level after which there was no increase in $T_{50\%}$ by increasing compressional force. However, Emdex and Maltrin M510 wet granulation formulations showed the opposite behavior; the $T_{50\%}$ decreased as the compressional force was increased. Maltrin tablets prepared by wet granulation showed a significantly higher $T_{50\%}$ value than tablets of the same composition but prepared from Emdex granules. This result is probably because the gel layer formed over and around tablets prepared with Maltrin M510 as diluent, which retarded dissolution. This gel layer was observed during disintegration and dissolution testing.

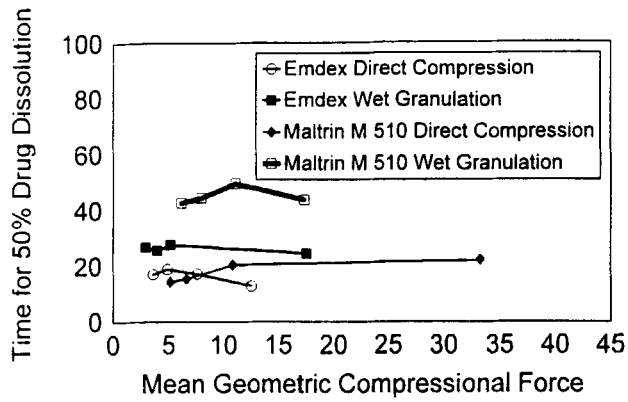

Figure 6. Time for 50% of the drug to dissolve versus mean geometric compressional force.

CONCLUSIONS

The relationship between primary physical properties, characteristics of blends, methods of manufacturing (wet granulation versus direct compression), and the properties of the final tablets were investigated. This study showed that physical properties of the blends or the granules such as density, porosity, flowability, particle size distribution, and surface area influence the physical properties of tablets. The manufacturing process such as direct compression or wet granulation also dramatically affects the properties of the produced tablets, particularly when the wet granulation process is accomplished with directly compressed excipient.

The formulation prepared with Emdex and direct compression produced tablets of the highest mechanical strength and highest dissolution rate compared to other formulations prepared with Maltrin M 510 or prepared by a different manufacturing process.

Disintegration time of formulations containing Maltrin M510 appears to be controlled by a gel layer formation and not by the porosity of the tablets. $T_{50\%}$ appears to be affected by the compressional forces applied. Formulations prepared by wet granulation gave higher $T_{50\%}$ than those of the same composition but prepared by the direct compression method. In general, the formulation prepared by using Maltrin M510 gave higher $T_{50\%}$ than those of the same composition but prepared with Emdex.

REFERENCES

1. Z. E. Chowhan, Pharm. Technol., September, 72 (1993).
2. M. Celik and E. Okutgen, Drug Dev. Ind. Pharm., 19, 2309 (1993).
3. H. G. Brittain, Pharm. Technol., 66 (1993).
4. M. Celik and C. E. Driscoll, Drug Dev. Ind. Pharm., 19, 2143 (1993).

5. L. Chiu Li and G. E. Peck, Drug Dev. Ind. Pharm., 16, 1491 (1990).
6. J. Mollan Jr. and M. Celik, Drug Dev. Ind. Pharm., 19, 2335 (1993).
7. M. J. Snavely, T. C. Price, and H. Won Jun, Drug Dev. Ind. Pharm., 19, 729 (1993).
8. A. M. Juppo, L. Kervinen, J. Yliruus, and E. Krisfferson, Drug Dev. Ind. Pharm., 47, 543 (1995).