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Report

Effect of Drug (Core) Particle Size on the Dissolution of Theophylline from Microspheres Made from Low Molecular Weight Cellulose Acetate Propionate

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Three particle sizes (450, 120, and 5 μm) of theophylline were encapsulated in low molecular weight cellulose acetate propionate (intrinsic viscosity, 1.08 dl/g) by the solvent evaporation method. The theoretical drug content for all the batches of microspheres was 50% (w/w). Particle size analysis revealed that about 50% of the microspheres containing the large theophylline crystals (average length of 450 μm) were greater than 500 μm in diameter, whereas only about 35% of the microspheres containing the medium drug crystals (average length of 120 μm) were greater than 500 μm in diameter. The drug content of the larger microspheres prepared from the large drug crystals and the medium drug crystals was much greater than the theoretical drug content (50%, w/w); however, the drug content of all the batches of microspheres containing micronized drug was close to 50% (w/w). Release of the drug in simulated intestinal fluid was very rapid from microspheres containing large and medium drug crystals, while release was slower and more predictable from microspheres made from micronized drug.

KEY WORDS: theophylline; cellulose acetate propionate; microspheres; core size; dissolution.

INTRODUCTION

Many variables can influence the preparation and properties of microspheres made by the emulsion-solvent evaporation technique (1–9). However, the effect of the particle size of the core material on the particle size distribution and dissolution properties of microspheres prepared by the technique has not been reported. Therefore, the objectives of this investigation were to evaluate the effect of the particle size of the core (theophylline) on the size distribution and drug release properties of microspheres prepared by the emulsion-solvent evaporation technique.

MATERIALS AND METHODS

Preparation of Particle Size Fractions of Theophylline

Theophylline usually consists of long crystals (~5:1 length:width ratio) which are difficult to separate into size fractions. Therefore, particle size separation of anhydrous theophylline (Sigma Chemical Co., St. Louis, Mo.) was performed by an elutriation process. In this process, 2–3 g of the drug containing a mixture of particle sizes was placed in a clean, tall 50-ml measuring cylinder and filled with a 50:50 mixture of acetone and *n*-hexane (J. T. Baker Chemical Co., Phillipsburg, N.J.). The cylinder was covered with aluminum foil and turned upside down several times. The cylinder was then allowed to stand for 8–15 sec to let the larger crystals settle to the bottom. The smaller suspended crystals in the supernatant liquid were quickly transferred to another clean 50-ml measuring cylinder. The volume in the second cylinder was adjusted to 50 ml with more *n*-hexane/acetone mixture and the cylinder was covered with aluminum foil and shaken. This process of shaking the suspension and transferring the supernatant to another clean cylinder was repeated six times. At the end of the process, the drug crystals from the first two cylinders were combined to form a batch of large crystals. The crystals in the fifth and the sixth cylinders formed a batch comprising the medium crystals. The elutriation process was repeated until the required weights of large and medium drug crystals were obtained. Micronized drug was obtained by grinding the drug particles with a glass mortar and pestle.

Lengths and widths of at least 200 particles were determined microscopically for all particle size fractions.

Preparation of Microspheres

Microspheres of different particle sizes of the drug were prepared by the emulsion-solvent evaporation method using heavy mineral oil (J. T. Baker Chemical Co., Phillipsburg, N.J.) with 1% Span 80 (Ruger Chemical Co., Irvington, N.J.) as the external phase. The internal phase consisted of the polymer (low molecular weight cellulose acetate propionate,

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Table I. Particle Size of Large, Medium, and Micronized Crystals of Theophylline

Crystals	Length range (μm)	Width range (μm)	Average length (μm)	Average width (μm)
Large	159–800	40–250	450	95
Medium	30–450	10–150	120	20
Micronized	1.25–21	1–2.5	5	2.5

Scientific Polymer Products, Ontario, N.Y.), acetone, and an appropriate particle size of the drug. After emulsification, the acetone was allowed to evaporate with continuous stirring at room temperature over 4 hr. The formed microspheres in oil were maintained at 50°C for an additional 30 min while stirring to ensure complete evaporation of residual acetone. After cooling the oil and allowing the microcapsules to settle, the clear supernatant mineral oil was decanted into a waste bottle. The microspheres were thoroughly washed three times with 100 ml *n*-hexane to remove the residual oil. The microspheres were recovered by filtration, dried in an oven at 40°C overnight, and stored in a clean glass bottle. Particle size distribution of the dried microspheres was performed by sieving through a set of standard sieves with openings of 500, 355, 250, 177, 125, 88, and 63 μm.

Drug Content Analysis

An accurately weighed (5.0-mg) sample of the microspheres was placed in a 100-ml volumetric flask. Methylene chloride (J. T. Baker Chemical Co., Phillipsburg, N.J.) was

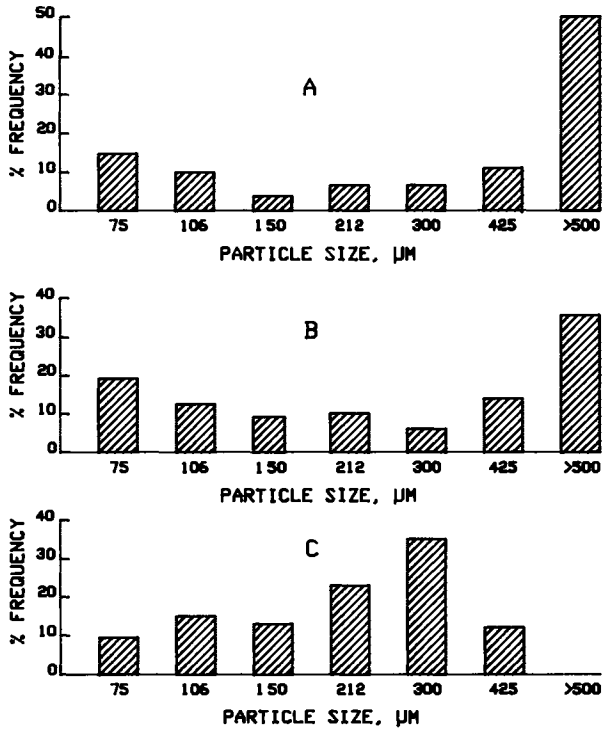

Fig. 1. Particle size distribution of microspheres made from low molecular weight cellulose acetate propionate. (A) Large theophylline crystals; (B) medium theophylline crystals; (c) micronized theophylline crystals.

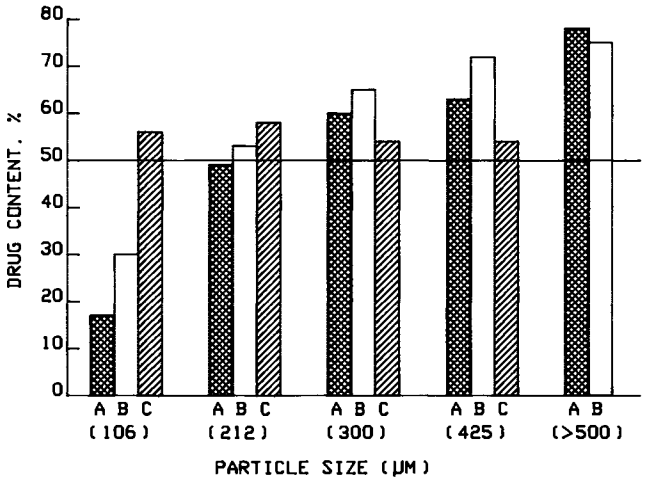

Fig. 2. Drug content of microspheres made from three different particle sizes of theophylline. (A) Large theophylline crystals; (B) medium theophylline crystals; (C) micronized theophylline crystals.

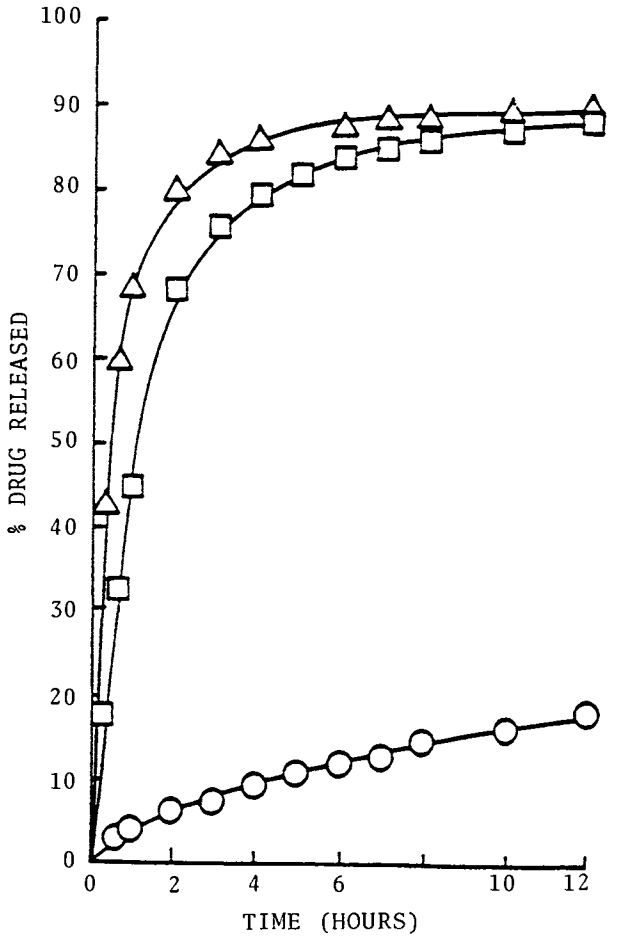

Fig. 3. Effect of drug (core) particle size on dissolution from 425-μm cellulose acetate propionate microspheres. (○) Micronized theophylline crystals (drug content, 54%); (□) large theophylline crystals (drug content, 63%); (△) medium theophylline crystals (drug content, 72%).

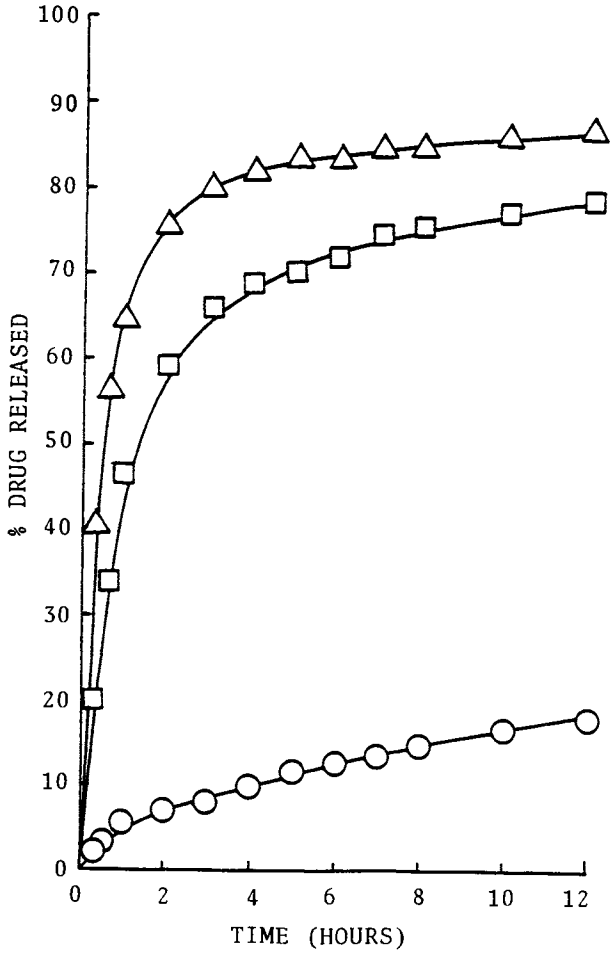

Fig. 4. Effect of drug (core) particle size on dissolution from 300-μm cellulose acetate propionate microspheres. (○) Micronized theophylline crystals (drug content, 54%); (□) large theophylline crystals (drug content, 60%); (△) medium theophylline crystals (drug content, 65%).

added to dissolve the polymer and the drug. The flask was sonicated for 10 min to facilitate the dissolution of the microcapsules. Drug concentration in the flask was determined spectrophotometrically at a 274-nm wavelength.

In Vitro Dissolution Studies

In vitro dissolution studies were carried out at 37°C in 1000 ml of Simulated Intestinal Fluid U.S.P. without enzyme at 100 rpm using a standard USP XXI dissolution apparatus with Teflon-coated paddle stirrers. Accurately weighed samples of microspheres (20–30 mg) were suspended in the dissolution media and an aliquot of dissolution fluid was withdrawn every hour for 12 hr to assay the released drug spectrophotometrically at 271 nm. The fluid was returned to the vessel after analysis.

RESULTS AND DISCUSSION

Theophylline Particle Size Analysis and Particle Size Distribution of Microspheres Made from Different Particle Sizes of the Drug

The results of microscopic examination of the drug particles separated by the elutriation method and micronization process are shown in Table I.

The mode of the particle size distribution of microspheres containing large and medium drug crystals was greater than 500 μm, whereas the mode of the particle size distribution of microspheres prepared with micronized drug was 300 μm (Fig. 1), thus indicating that increasing the particle size of the core increased the overall size of the microspheres.

Drug Content of Microspheres Prepared from Large, Medium, and Micronized Drug Particles

Drug content analysis of five particle size fractions of microspheres (ranging from 106 to 500 μm) of each of the three different particle sizes of the drug showed that the drug content of microspheres containing micronized drug was more uniform and close to the theoretical drug content of 50% (w/w) for all the different particle sizes of microspheres up to 425 μm (Fig. 2). Microspheres greater than 500 μm were not obtained when micronized drug was used. The drug content of the larger microspheres (425- and 500-μm diameter) containing either the large or the medium drug crystals

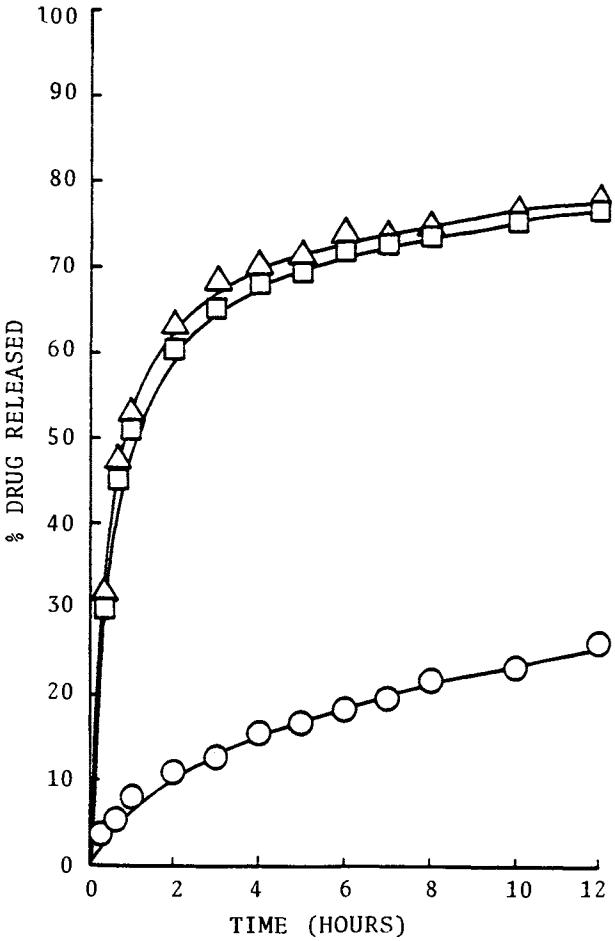

Fig. 5. Effect of drug (core) particle size on dissolution from 212-μm cellulose acetate propionate microspheres. (○) Micronized theophylline crystals (drug content, 53%); (□) large theophylline crystals (drug content, 49%); (△) medium theophylline crystals (drug content, 58%).

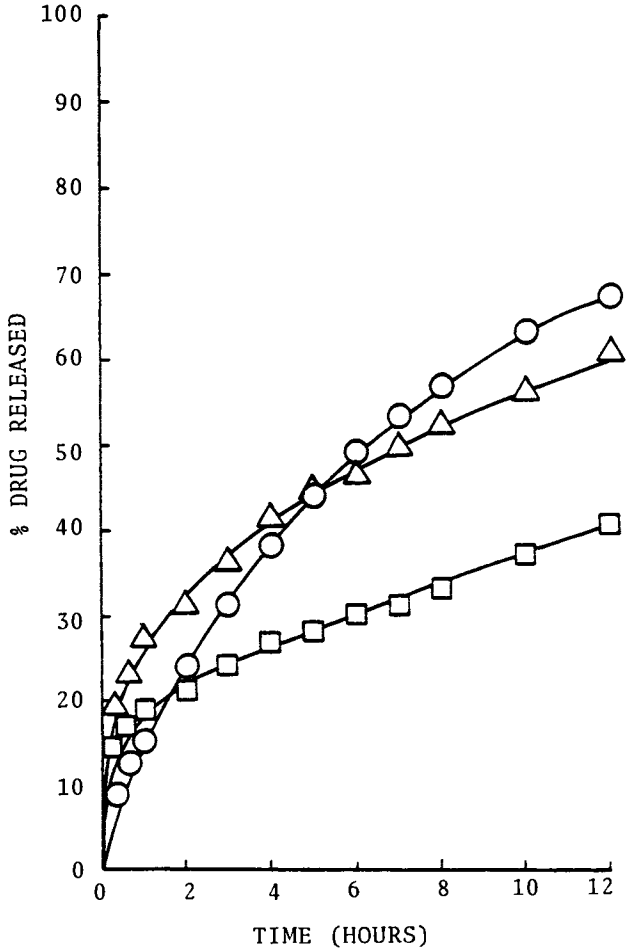

Fig. 6. Effect of drug (core) particle size on dissolution from 106-μm cellulose acetate propionate microspheres. (○) Micronized theophylline crystals (drug content, 56%); (□) large theophylline crystals (drug content, 17%); (△) medium theophylline crystals (drug content, 30%).

(78 and 75% drug content, respectively) was much more than the theoretical drug content, while the drug content for the smaller microspheres (106-μm diameter) prepared with either the large or the medium drug crystals (17 and 30% drug content, respectively) was much less than the theoretical drug content.

These results can be explained by the emulsification process, which tends to shear away polymer solution from the larger drug crystals which form the core of the microspheres. Small crystals, on the other hand, have a high surface-to-weight ratio and therefore are much more likely to be carried along with the polymer solution and not be separated from it during the shearing process.

In Vitro Dissolution Studies

In vitro dissolution profiles of the microspheres (Figs. 3–5) showed rapid drug release from microspheres containing large and medium drug crystals. The time for 50% dissolution of the microspheres was 1 hr or less, with 80–90% of the drug being released in 12 hr. This rapid drug release was due to the high drug content within the microspheres, with only slight retardation by the polymer matrix. However, drug release was more predictable and sustained from microspheres containing micronized drug and more closely resembled typical matrix microsphere release kinetics.

In Fig. 6, the drug release from 106-μm microspheres containing micronized drug appears to be faster than from those containing large and medium drug crystals. This is because the drug content (17% for large crystals and 30% for medium crystals) of the microspheres containing large and medium drug crystals is much lower than the theoretical drug content, thus slowing the release rate of the drug considerably. The drug content of microspheres containing micronized drug was 56%.

It can be concluded from this study that the drug (core) particle size must be carefully controlled in order to obtain a uniform and predictable release of the drug from matrix microspheres. Moreover, the particle size distribution of the microspheres can be more closely controlled when the particle size of the core material is much smaller than the microsphere size.

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