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EFFECT OF DIFFERENT BINDERS ON RELEASE CHARACTERISTICS OF THEOPHYLLINE FROM COMPRESSED MICROSPHERES

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ABSTRACT

Microspheres with 60% w/w drug loading were prepared by the solvent-evaporation method using cellulose acetate butyrate as the encapsulating polymer and micronized anhydrous theophylline as the core material. Four different binders - microcrystalline cellulose, glyceryl palmito-stearate, glyceryl stearate and glyceryl behenate were used to compress three different particle sizes of microspheres. Comparison of the in vitro drug dissolution profiles revealed that drug release was fastest from all the microspheres compressed with microcrystalline cellulose as the binder followed by those compressed with glyceryl palmitostearate, glyceryl stearate and glyceryl behenate.

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INTRODUCTION

Microencapsulation is a well developed and extensively studied technology. Several reports on controlled drug delivery from compressed microspheres have been published since the 1970s (1-8). However, most of them describe drug release from compressed microspheres without any additives. Most free flowing drug-loaded microspheres can be used as granulation and can be compressed into controlled release tablets with appropriate additives such as binders and lubricants. Lately, the solvent evaporation method of microencapsulation has been extensively used in the preparation of microspheres. Hence, this study investigates preparation of theophylline microspheres using the solvent-evaporation technique and also evaluates drug release characteristics from microspheres compressed with four different binders.

MATERIALS AND METHODS

Preparation of Microspheres

Microspheres with 60% w/w drug loading were prepared using cellulose acetate butyrate (CAB) with a m.w. of 65,000 (Eastman Chemical Products, Kingsport, TN) as the encapsulating polymer and micronized anhydrous theophylline (Knoll Fine Chemicals, New York, N.Y.) as the core material by the solvent-evaporation method as described previously (8).

Drug Content of Microspheres

Drug content of the microspheres was determined by grinding a known weight (25-30 mg) of the microspheres using a mortar and pestle. An accurately weighed sample (20 mg) of the ground material was placed in a 100 mL volumetric flask containing

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simulated intestinal fluid (SIF). The contents of the flask were then stirred for 8 hours at room temperature. An aliquot was withdrawn from the flask, filtered, and then spectrophotometrically analyzed for drug content at 271 nm.

Compression of Microspheres

Three different particle sizes (143 um, 215 um and 338 um) of microspheres were mixed with four different binders, namely: microcrystalline cellulose (FMC Corporation, Philadelphia, PA), glyceryl palmitostearate (Precirol ATO 5, Gattefosse Corporation, Elmsford, N.Y.), glyceryl stearate (Precirol WL 2155, Gattefosse Corporation, Elmsford, N.Y.) and glyceryl behenate (Compritol 888, Gattefosse Corporation, Elmsford, N.Y.). The mixtures were compressed on a Carver press (Fred C. Carver, Menomonee Falls, WI) at a pressure of 624 megapascals (MPa). The compression pressure was maintained for 10 seconds and then quickly released.

In Vitro Drug Release

In Vitro drug dissolution studies from the compressed microspheres were carried out in SIF using a rotating bottle apparatus (Van Kel Industries, Edison, N.J.) at 50 rpm. The temperature of the medium was maintained at 37°C. At predetermined time intervals, the dissolution medium was removed completely from the bottles and analyzed for drug content spectrophotometrically. The removed dissolution medium was replaced immediately with fresh SIF, thus maintaining sink condition.

RESULTS AND DISCUSSION

Figures 1 and 2 show the effect of varying concentrations of glyceryl behenate and glyceryl stearate respectively on the drug

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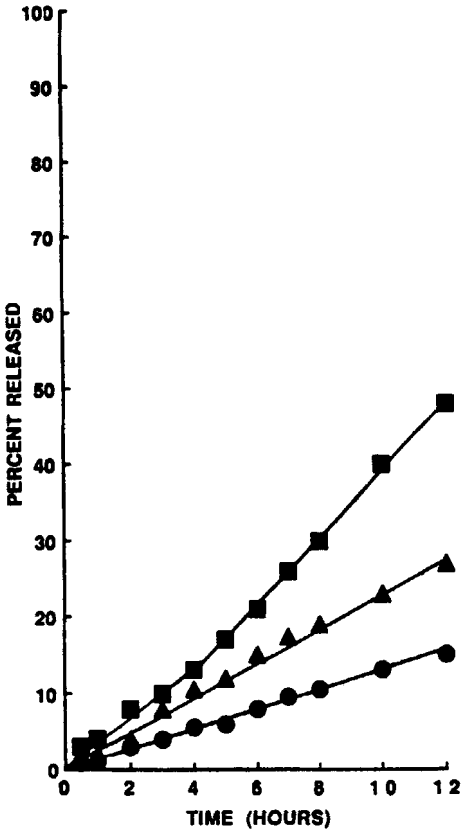

FIGURE 1: EFFECT OF VARYING CONCENTRATIONS OF GLYCERYL BEHENATE ON DRUG RELEASE FROM COMPRESSED MICROSPHERES

KEY: ● 38% W/W
▲ 30% W/W
■ 23% W/W

release characteristics from the compressed microspheres with 215 um diameter compressed at 624 MPa compression pressures. Decreasing the binder concentration from 38% w/w to 23% w/w significantly increased drug release from microspheres compressed with both the binders. Zero order release rates were observed after 3 hours for microspheres compressed with all the three

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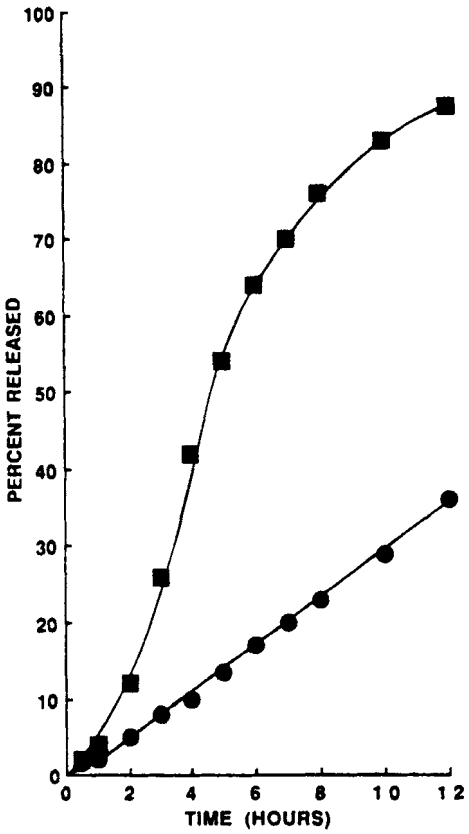

FIGURE 2: EFFECT OF VARYING CONCENTRATIONS OF GLYCERYL STEARATE ON DRUG RELEASE FROM COMPRESSED MICROSPHERES

KEY: ● 38% W/W
■ 23% W/W

concentrations of glyceryl behenate (Figure 1) and those compressed with 38% w/w of glyceryl stearate (Figure 2). Decreasing the concentration of glyceryl stearate to 23% w/w yielded a sigmoidal-shaped release profile (Figure 2). Since microspheres with less than 23% w/w binder did not yield satisfactory compressed matrices and since the drug release from the compressed matrices was too slow at higher binder

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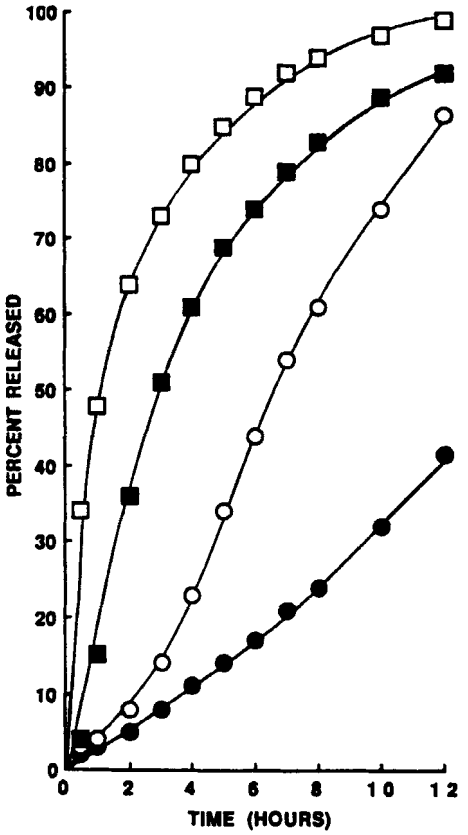

FIGURE 3: EFFECT OF BINDERS ON DRUG RELEASE FROM COMPRESSED MICROSPHERES OF 338 μm DIAMETER

KEY:
- ● GLYCERYL BEHENATE
- ○ GLYCERYL STEARATE
- ■ GLYCERYL PALMITOSTEARATE
- □ MICROCRYSTALLINE CELLULOSE

concentration, further studies were performed using 23% w/w binder concentration.

Comparison of drug release from three different particle sizes of microspheres compressed with the four binders at 23% w/w concentrations revealed that drug release was fastest from microspheres compressed with microcrystalline cellulose followed by those compressed with glyceryl palmitostearate, glyceryl stearate

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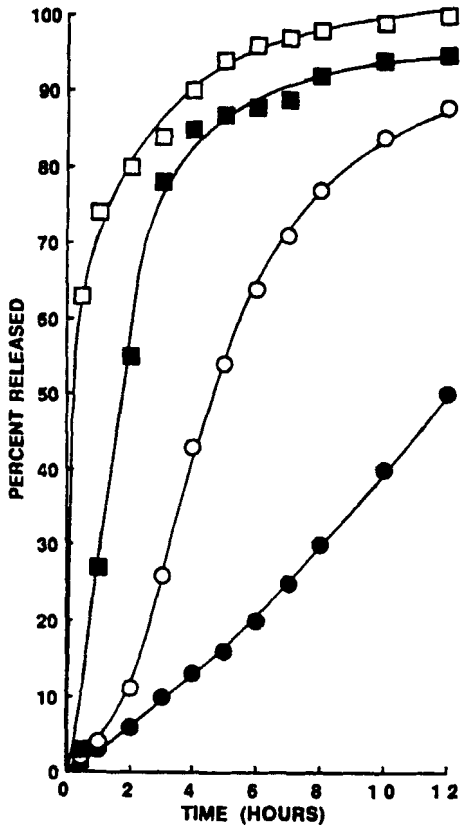

FIGURE 4: EFFECT OF BINDERS ON DRUG RELEASE FROM COMPRESSED MICROSPHERES OF 215 μm DIAMETER

KEY:
- ● GLYCERYL BEHENATE
- ○ GLYCERYL STEARATE
- ■ GLYCERYL PALMITOSTEARATE
- □ MICROCRYSTALLINE CELLULOSE

and glyceryl behenate (Figures 3 - 5). Dissolution studies were discontinued on 143 um microspheres compressed with glyceryl palmitostearate after 7 hours (Figure 5) because the compressed matrix started to disintegrate and some of the smaller microspheres were lost during the filtration process whilst changing the dissolution media in the bottles.

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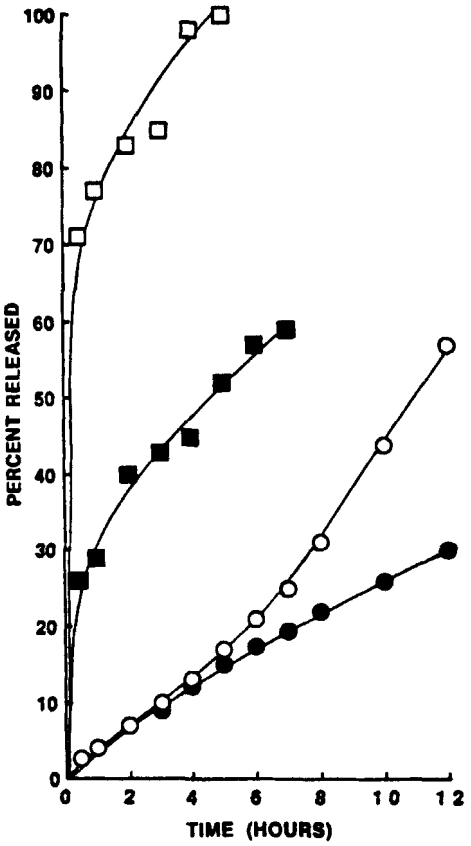

FIGURE 5: EFFECT OF BINDERS ON DRUG RELEASE FROM COMPRESSED MICROSPHERES OF 143 μm DIAMETER

KEY: ● GLYCERYL BEHENATE
○ GLYCERYL STEARATE
■ GLYCERYL PALMITOSTEARATE
□ MICROCRYSTALLINE CELLULOSE

Although microcrystalline cellulose has excellent tablet binding characteristics, rapid drug release from microspheres compressed with this binder would not be unexpected due to the hydrophilic nature of the cellulose derivative.

On the other hand, glyceryl esters of fatty acids are hydrophobic in nature. Hence they retard the rate of permeation of dissolution fluid into the compressed matrices, consequently

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Table I: T-50 Values in Hours for Three Different Particle Sizes of Microspheres Compressed With Four Different Binders

BINDERS	T-50 IN HOURS FOR THREE DIFFERENT MICROSPHERE PARTICLE SIZES		
	338 um	215 um	143 um
Microcrystalline Cellulose	1.2	0.4	0.3
Glyceryl Palmitostearate	3.2	1.8	4.8
Glyceryl Stearate	6.4	4.8	11.2
Glyceryl Behenate	14.5	12.2	21.0

retarding drug release from the compressed matrices. Drug release from compressed microspheres was correlated inversely with the melting points of the glyceride esters of fatty acids; i.e., fastest drug release was observed from microspheres compressed with glyceryl palmitostearate having the lowest melting point (55° - 58°C) followed by those compressed with glyceryl stearate with a melting point of 64°C and glyceryl behenate with a melting point of 70°C (Figures 3 - 5). This phenoemnon could be due to greater loss of structure or weakening of bonds between particles at 37°C in the compressed matrices prepared from glyceride esters of fatty acids with lower melting point compared to those prepared from higher melting points.

Table I shows the T-50 values (time required for 50% of the drug to be released) for microspheres compressed with all the four binders. It is evident from the table that decreasing the particle size of the microspheres increased the drug release when

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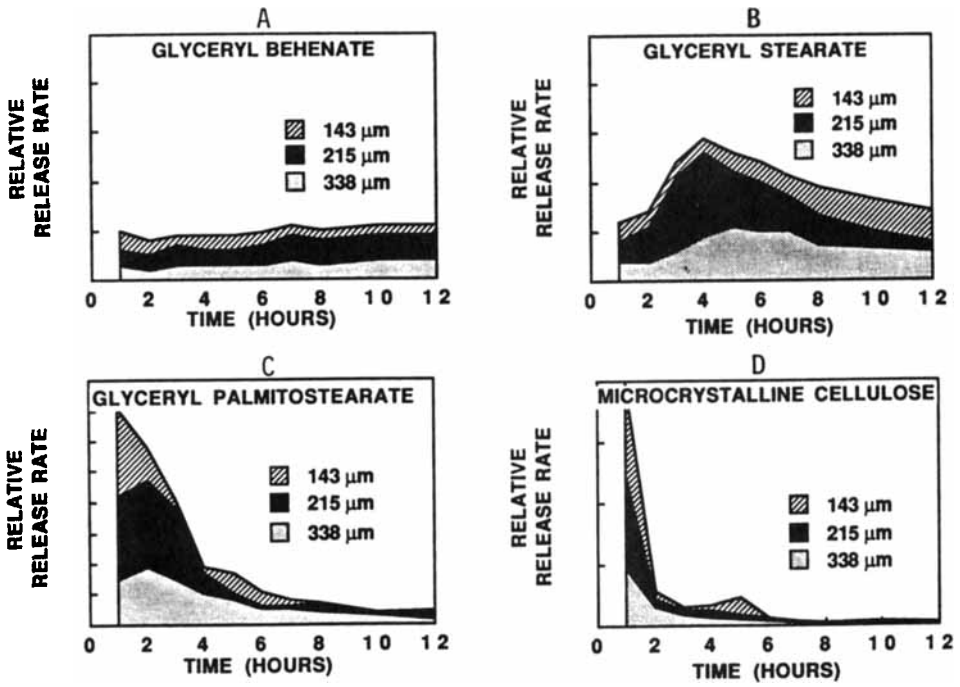

FIGURES 6A-D: AREA PLOTS SHOWING RELATIVE RELEASE RATE OF DRUG AT VARYING TIME INTERVALS

microcrystalline cellulose was used as a binder. However, T-50 values decreased slightly for all the three glyceryl esters of fatty acids when the particle size of the microspheres decreased from 338 um to 215 um, but then increased sharply with further decrease in particle size of the microspheres to 143 um. This phenomenon could be due to increased bonding between particles with increased contact surface area between particles as the size of the microspheres decreased. Moreover, the hydrophobic and waxy nature of the relatively low melting glyceryl esters of fatty acids may have contributed to better bonding between particles of

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smaller diameter, probably by partial melting and fusion during the compression process.

Figures 6 A-D are surface area plots depicting the relative drug release rates (calculated by dividing percentage of drug released by time) at every hour. The importance of these plots is to show how the rate of drug release varies every hour and also when the maximum drug release occurs from a dosage form. For example, Figure 6A shows zero order release rates from tablets compressed with all the three concentrations of glyceryl behenate. Figure 6B shows that maximum drug release occurred approximately between 3-5 hours from microspheres compressed with glyceryl stearate; while the maximum drug release occurred in the first two hours for microspheres compressed with glyceryl palmitostearate and microcrystalline cellulose as shown in Figures 6C and 6D respectively.

CONCLUSION

This study showed that is possible to use the solvent evaporation process of microencapsulation as a granulation process, since it is possible to prepare spherical free flowing coated drug particles or granules. If necessary, these coated microspheres or granules can be directly compressed using an appropriate binder in order to achieve sustained release. The study also indicated that low melting hydrophobic waxy materials could be appropriately used as efficient binders for compressing microspheres.

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REFERENCES

(1) I. Jalsenjak, C.F. Nicolaidou and J.R. Nixon, J. Pharm. Pharmacol., 29, 169-172 (1977).

(2) J.R. Nixon, I. Jalsenjak, C.F. Nicolaidou and M. Harris, Drug Dev. Ind. Pharm., 4, 117-119 (1978).

(3) I. Jalsenjak, J.R. Nixon, R. Senjkovic and I. Stivic, J. Pharm. Pharmacol., 32, 678-680 (1980).

(4) J.R. Nixon and M. Hassan, J. Pharm. Pharmacol., 32, 857-858 (1980).

(5) H.O. Alpar and V. Walters, J. Pharm. Pharmacol., 33, 419-422 (1981).

(6) A.A. El-Sayed, A.A. Badawi and A.M. Fouli, Pharm. Acta Helv., 57, 61-64 (1982).

(7) S. Borodkin and D.P. Sundberg, J. Pharm. Sci., 60, 1523-1527 (1971).

(8) J. Singh and D.H. Robinson, Drug Dev. Ind. Pharm., 14(4), 545-560 (1988).

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