Development and Evaluation of Sustained-Release Ibuprofen-Wax Microspheres. I. Effect of Formulation Variables on Physical Characteristics

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A congealable disperse phase encapsulation method was used to prepare sustained-release ibuprofen-wax microspheres. Microspheres prepared with paraffin wax, such as ceresine and microcrystalline waxes, using polyvinylpyrrolidone (PVP) as dispersant had a tendency to aggregate, but the addition of wax modifiers (stearyl alcohol and glyceryl monostearate) greatly reduced aggregation. Optimum modifier and dispersant concentrations were 20% (w/w) and 5% (w/v), respectively. The particle size distribution of the microspheres was log-normal. An increase in modifier, dispersant concentration, emulsification stirring speed, or temperature shifted the size distribution toward finer particles. Microcrystalline wax required a higher emulsification temperature and produced finer particles than ozokerite wax. The recovery of drug from the different microsphere formulations varied between 71 and 92%. Differential scanning calorimetry (DSC) of the single components and physical mixtures showed endothermic peaks at the respective melting-point ranges. The DSC of the ceresine and microcrystalline wax microspheres was similar to rescans of ternary mixtures of components of the microspheres with less prominent and lower melting temperatures than individual components or physical mixtures.

KEY WORDS: ibuprofen; waxes; microspheres; modifiers; size analysis; thermal analysis.

INTRODUCTION

Ibuprofen [±-2-(*p*-isobutylphenyl) propionic acid] is a nonsteroidal, antiinflammatory drug. It is used as an analgesic, an antipyretic, and an adjunct in steroid therapy (1) and for symptomatic relief of dysmenorrhea (2). Considerable work has been done on conventional dosage forms such as tablets (3), suppositories (4), ointments (5), powdered drug (6,7), and suspension (8,9). In contrast, relatively limited work has been reported on sustained-release forms of ibuprofen. Kawashima (10) investigated the preparation of sustained-release ibuprofen along with other drugs using a crystallization method. This report did not include details concerning the optimization of variables and methods.

Considering that the solubility of ibuprofen is in excess of 5% (w/v) in almost all organic solvents and relatively insoluble in water, spray congealing and hydrophobic congealable disperse phase encapsulation procedures become the methods of choice because these methods do not require the use of organic solvents. Kagadis and Choulis (11) prepared ibuprofen microcapsules from stearic acid wax using a congealable encapsulation method. The microspheres produced were relatively large (6–10, 10–16, and 16–20 mesh). Benita *et al.* (12) also utilized this method to prepare 5-fluorouracil microspheres and reported that the surfactant concentration used during preparation had no effect on particle size distribution, while increasing the emulsification stirring speed decreased the mean particle size of the microspheres. A spray congealing technique was used by Cusimano and Becker (13) and John and Becker (14) to produce sustained-release sulfaethyldiazole. The former authors varied wax, nozzle size, and surfactant concentration. They reported that the geometric mean and volume–surface diameters were affected by the wax chosen and nozzle sizes.

The aim of this investigation was to develop sustained-release microspheres of ibuprofen and determine the effect of waxes, dispersant, modifier concentration, and emulsification stirring speed on the formulation and physical characteristics of the microspheres. Information from microsphere studies would be useful for formulation of an oral suspension and other oral dosage forms.

MATERIALS AND METHODS

Materials

The materials used were ibuprofen,[4,5] beeswax,[6] ceresine wax 1530,[6] microcrystalline wax 1135/15W,[6] ozokerite 1556,[6] polyvinylpyrollidone (PVP),[7] glyceryl monostearate,[8] stearyl alcohol,[9] and cyclohexane.[10]

Methods

Preparation. Ibuprofen microspheres were prepared using a hydrophobic congealable disperse-phase encapsulation procedure. The drug was dissolved in the respective molten wax (1:4 drug-to-wax ratio) and a one-phase melt was formed. During the emulsion step of microsphere preparation, the temperature was maintained at about 10°C above the melting point of wax. A dispersant solution, previously heated to 5°C above the wax melting point, was added to the melt with constant stirring to form an O/W emulsion. Hardening of the oily internal phase (containing wax and drug) and formation of the microspheres were accomplished rapidly by pouring twice the emulsion volume of ice-cold water (4°C) into the beaker. Three times the volume of the cooled mixture was used for microsphere washing. Blank microspheres (without drug) were similarly prepared for each batch.

Three emulsification stirring speeds, 750, 980, and 1250

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[4] Upjohn Company, Kalamazoo, Michigan.

[5] Interchem Corporation, Paramus, New Jersey.

[6] Frank B. Ross Company, Jersey City, New Jersey.

[7] GAF Corporation, New York.

[8] Fisher Scientific Company, Fairlawn, New York.

[9] Matheson, Coleman & Bell, Norwood, Cincinnati, Ohio.

[10] J. T. Baker Chemical Company, Phillipsburg, New Jersey.

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rpm, were used to determine the effect of this variable on particle size distribution.

Assay of Drug Content of Ibuprofen-Wax Microspheres. To determine the yield of ibuprofen and the efficiency of the encapsulation process, the microspheres were assayed for drug content.

Microspheres containing approximately 25 mg of ibuprofen were accurately weighed in a volumetric flask, cyclohexane (25.0 ml) was added, and the microspheres were dissolved by shaking and slightly warming the solution to 30–32°C. This was then filtered and the absorbance was determined spectrophotometrically at a 261.7-nm wavelength against a blank prepared with microspheres containing no drug. Corresponding concentrations were calculated from a standard curve which was linear up to at least 400 μg/ml.

Particle Size Analysis of Ibuprofen-Wax Microspheres. Size analysis of the microspheres was accomplished by sieving. The respective microsphere batch was placed on a nest of six sieves, with the largest (710-μm size) at the top, and the sieves were mechanically shaken for 5 min. The microspheres retained on each sieve were lightly pressed using a spatula to separate further loosely aggregated particles. An optical microscope was used to follow the deaggregation process. Each sieved fraction was returned to the respective sieve and further shaken for 5 min and the arithmetic mean size of the preceding and retaining sieves was assigned to the fraction of microspheres on the retaining sieve.

Microscopic Evaluation of Microspheres. The formation of the microspheres during emulsification was monitored with an optical microscope. A scanning electron microscope (SEM) was used to observe the surface characteristics of the finished microspheres. The SEM microsphere samples were prepared by coating with a 40-nm layer of pure gold under vacuum.

Thermal Analysis. A differential scanning calorimeter (DSC)[11] was used to determine the crystalline state of the formulation components before and after formation of microspheres. The analysis was performed using microspheres, ibuprofen, waxes, stearyl alcohol, and the physical mixtures in amounts equivalent to the ratios present in the microspheres. The scanning was done in static air and at a heating rate of 20°C/min. All samples were scanned 40 to 200°C but illustrations are abbreviated to include only areas of observable heat flow change (all below 120°C).

RESULTS AND DISCUSSION

Formation of Ibuprofen-Wax Microspheres

Formulations prepared with waxes without modifiers had a tendency to agglomerate. This tendency varied with the waxes used and were ranked as follows: beeswax > ceresine > ozokerite > microcrystalline wax having melting points of 64, 73, 84, and 94°C, respectively. Ceresine and beeswax microspheres are shown in Figs. 1A and B, respectively.

Microspheres prepared with formulations of ceresine wax or microcrystalline wax and glyceryl monostearate (nonemulsifying) or stearyl alcohol showed little agglomeration tendency. However, a formulation prepared with 40% (w/w) glyceryl monostearate did not produce microspheres; instead a colloidal, gel-like mass was formed during emulsification. Glyceryl monostearate in sufficient quantity is known to form colloidal gels when heated with water. Microspheres were formed at a 40% concentration of stearyl alcohol. Stearyl alcohol has only one hydroxyl group while glyceryl monostearate has two; therefore, it is less hydrophilic and does not interact with water as strongly as glyceryl monostearate. The aggregation tendency of the microspheres containing stearyl alcohol decreased with increasing concentration of the modifier. Figures 1C and D represent microspheres prepared using stearyl alcohol and glyceryl monostearate, respectively.

Particle Size Analysis of Ibuprofen Microspheres

Effect of Stearyl Alcohol. Increasing the concentration of stearyl alcohol from 10 to 20% resulted in the shifting of the size distribution curve toward finer particles. A concentration of 40%, however, produced a lower frequency of 96- and 151-μm-size microspheres (Table I). The formulation containing 20% stearyl alcohol was chosen as optimum because the size fractions produced were suitable for future suspension formulation studies.

Effect of Dispersant (PVP) Concentration on Size Distribution of Microspheres Containing 20% Stearyl Alcohol as Modifier. PVP at 2.5, 5, and 10% was used to study the effect of dispersant concentration on particle size distribution. The 2.5% PVP concentration produced microspheres whose most prevalent particle size (modal size) approximated 151 μm. At higher PVP concentrations, the size distribution shifted toward finer particles; however, the size difference between 5 and 10% PVP concentration was not significant (Table I). A 5% PVP concentration was considered optimum because more of the 96 μm size microspheres were produced as compared to the 10% concentration.

Effect of Type of Wax on Particle Size Distribution. Different batches of microspheres were prepared with ceresine, ozokerite, and microcrystalline wax. Each batch was prepared with 20% stearyl alcohol and the modal sizes of the different batches are shown in Table I. Microcrystalline wax (melting point, 93°C) produced the finest particles, perhaps because of the higher melting and emulsification temperature. The most prevalent size was 96 μm. It has been reported that finer particles are produced as the temperature increases using this method of encapsulation (14). Although it has a higher melting temperature, Ozokerite wax (melting point, 84°C) is more viscous when melted than ceresine wax (melting point, 74°C). Consequently, ozokerite wax formed relatively larger particles compared to ceresine and microcrystalline waxes. Scanning electron micrographs showing the differences between ceresine and microcrystalline wax microspheres at low and high magnification are shown in Figs. 2A–D. The morphology of ozokerite microsphere is similar to that of ceresine microspheres and is not shown.

Effect of Emulsification Speed on Particle Characteristics. Increasing the stirring speed during manufacture from 750 to 1200 rpm resulted in the formation of smaller particles. The particle size distribution was log-normal. At 750,

[11] Dupont Company Instrument System, Wilmington, Delaware.

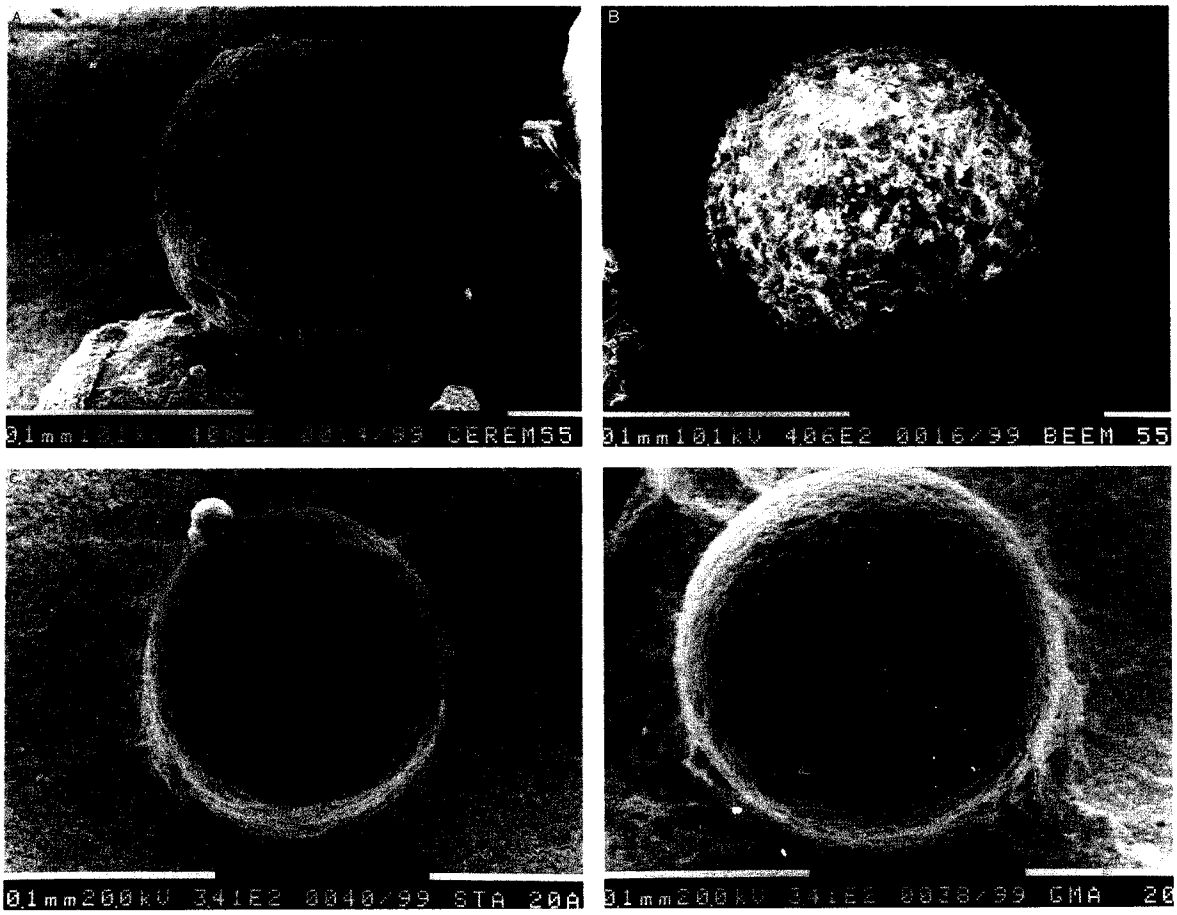

Fig. 1. Scanning electron micrographs of ibuprofen-wax microspheres containing different drug loadings and wax modifiers. (A) Ceresine wax microsphere and (B) beeswax microsphere containing 20% drug loading and no modifier. (C) Ceresine microsphere containing 17% drug loading and 20% stearyl alcohol as modifier. (D) Ceresine microsphere containing 17% drug loading and 20% glyceryl monostearate as modifier. (A, B) ×400 and (C, D) ×340; reduced 50% for reproduction.

980, and 1200 rpm, geometric mean diameters (dg) were 291, 200, and 141 μm, respectively. Other calculated size parameters are shown in Table II. The optimum speed required to produce particle size ranges suitable for subsequent testing was 980 rpm.

Effect of Formulation on Drug Yield. Other than with formulations containing 40% modifier or microcrystalline wax, there was no significant difference in percentage yield of drug in the 21 different formulations prepared (Table III). Table IV gives the typical percentage drug recovery from microcapsules of formulations selected for further study. The percentage yield was slightly higher in formulations that contained no wax modifier as in Formulation 2. The percentage recovery of drug was calculated, based on the recovery of the respective microsphere solids and their assayed drug content. The drug yield was lowest with the 40% concentration of stearyl alcohol partly because some of the finer particles produced with this concentration were washed away during recovery. The low yield obtained with the microcrystalline wax formulation can also be attributed partly to a loss of the fine particles.

Table I. Effect of Formulation Variables on Modal Sizes of Microspheres

Variable 1[a]		Variable 2[b]		Variable 3[c]	
PVP conc.	Modal size (μm)	% STALC[d] conc.	Modal size (μm)	Wax	Modal size (μm)
2.5	151	10	151	Ceresine	96
5	96	20	96	Ozokerite	303
10	96	40	151	MC[e]	96

[a] All with ceresine wax and 20% stearyl alcohol.
[b] All dispersed in 5% PVP.
[c] All with 20% stearyl alcohol and dispersed in 5% PVP.
[d] Stearyl alcohol.
[e] Microcrystalline wax.

Thermal Analysis

Single Components. Differential scanning calorimetric (DSC) analysis was performed to determine the melting behavior of the single components, and binary and ternary physical mixtures of the components, and microspheres of the ceresine–stearyl alcohol and microcrystalline wax-stearyl alcohol formulations. The DSCs of the single components (ceresine, microcrystalline waxes, stearyl alcohol,

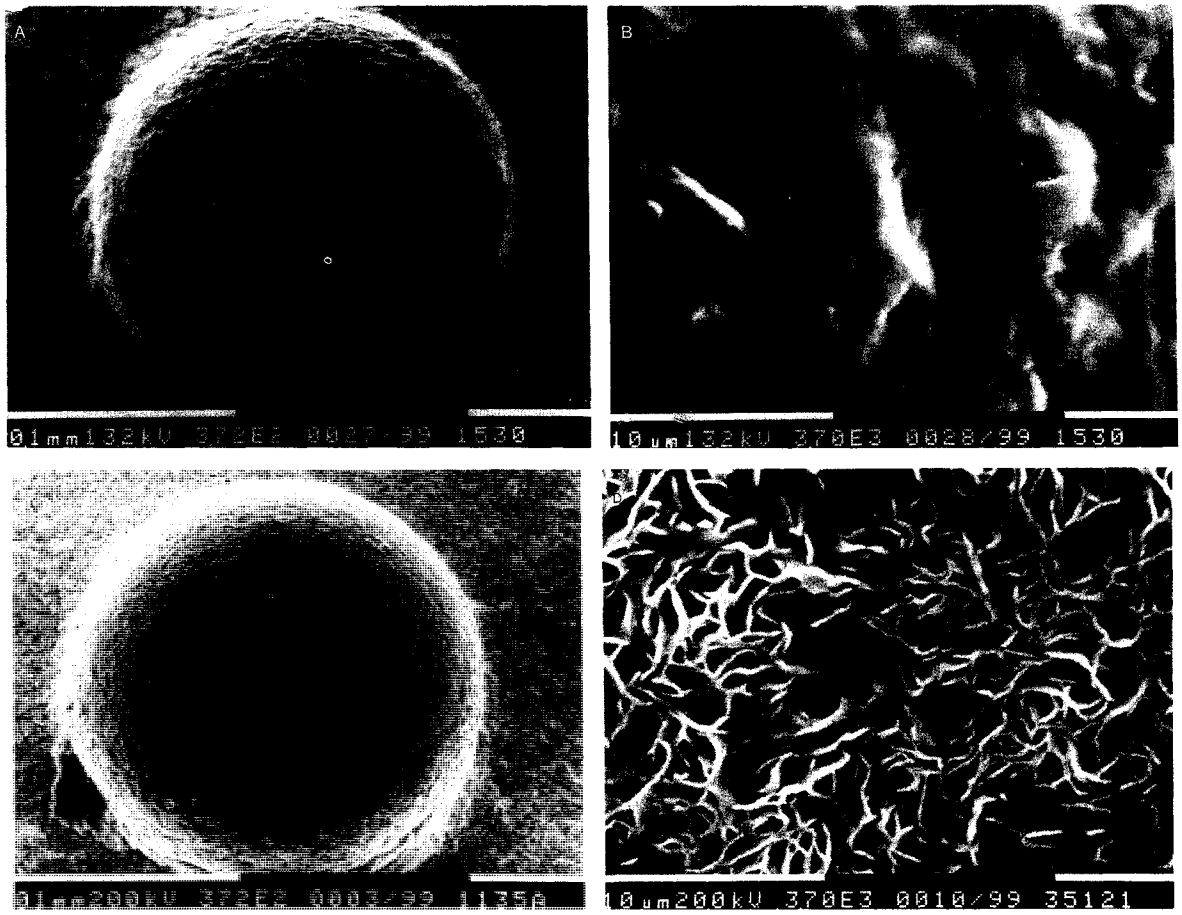

Fig. 2. Scanning electron micrographs of ceresine and microcrystalline wax microspheres. (A) Ceresine wax microsphere. (B) Ceresine wax microspheres. (C) Microcrystalline wax microsphere. (D) Microcrystalline wax microsphere. (A, C) ×370, (B, D) ×3700; reduced 50% for reproduction.

and ibuprofen) showed endothermic peaks, typical of melting of crystalline material (Figs. 3A–D).

Binary Physical Mixtures. The thermograms of five binary mixtures (ceresine wax/ibuprofen, ceresine/stearyl alcohol, ibuprofen/stearyl alcohol, ibuprofen/microcrystalline wax, and microcrystalline/stearyl alcohol) are shown in Figs. 4A–E, respectively. The solid lines represent the thermograms of the binary mixtures on first scan, while the dotted lines represent thermograms of the samples cooled to room temperature and rescanned. Generally, the peaks of the components on rescanning were observed at lower temperatures. In Fig. 4A, the endothermic peaks of the physical mixture of ceresine wax and ibuprofen overlapped because of dissolution of ibuprofen crystals in the melted wax and their similar melting point ranges. When the sample was cooled and rescanned, the ibuprofen peak was not observed, which implies that the ibuprofen was in solution in the solidified wax. A similar result was obtained with stearyl alcohol and ibuprofen except that the congealed solid melted at a lower temperature than either solid alone (Fig. 4B). The respective peaks of the components (62° and 76°C) are seen on the first scan, but on rescanning, only the stearyl alcohol peak is present. The microcrystalline wax/ibuprofen binary mixture thermograms (Fig. 4D) are somewhat different in

Table II. Particle Size Analysis Parameters of Microspheres Prepared Using Different Emulsification Stirring Speeds

Size parameter	Speed (rpm)		
	750	980	1200
Geometric mean diameter (dg), μm	291	200	141
Geometric standard deviation (∂g), μm	1.40	1.60	1.73
Modal size, μm	303	151	96
Particle surface diameter (d_{vs}), μm	273	179	121
Particle mean volume diameter (d_{vn}), μm	244	143	90
Specific surface area, (cm^2/cc)	2.20×10^{-2}	3.35×10^{-2}	4.96×10^{-2}

Table III. Microsphere Formulations

Formulation	Wax	Wax solids:[a] drug	PVP[b] (%, w/v)	STALC[c] (%, w/w)	GMS[d] (%, w/w)
1	Beeswax	4:1	5	—	—
2	Ceresine	4:1	5	—	—
3	Fully refined paraffin wax, 150/155	4:1	5	—	—
4	Microcrystalline, 1275/7	4:1	5	—	—
5	Ceresine	4:1	5	—	—
6	Ceresine	4:1	10	—	—
7	Ceresine	5:1	5	—	—
8	Ceresine	3:1	5	—	—
9	Ceresine	4.4:1	5	—	10
10	Ceresine	4.8:1	5	—	20
11	Ceresine	5.6:1	5	—	40
12	Ceresine	4.4:1	5	10	—
13	Ceresine	4.4:1	5	10	—
14	Ceresine	4.8:1	5	20	—
15	Ceresine	5.6:1	5	40	—
16	Ceresine	4.8:1	5	20	—
17	Ceresine	4.8:1	5	20	—
18	Ceresine	4.8:1	2.5	20	—
19	Ceresine	4.8:1	10	20	—
20	Ozokerite	4.8:1	5	20	—
21	Microcrystalline, 1135/15W	4.8:1	5	20	—

[a] Includes modifier when used.
[b] Polyvinylpyrrolidone.
[c] Stearyl alcohol.
[d] Glyceryl monostearate.

Table IV. Percentage Recovery of Ibuprofen in Typical Formulations

Formula No.	Wax	Stearyl alcohol conc. (%)	Theoretical drug content (%)	Assay drug content (%)	Solids recovery (%)	Drug recovery (%)[a]
2	Ceresine	0	20	19.6	94.2	92.3
13	Ceresine	10	18.5	17.0	96.0	90.1
14	Ceresine	20	17.2	16.5	95.7	91.8
15	Ceresine	40	15.2	12.6	91.0	75.7
20	Ceresine	20	17.2	16.0	96.7	90.0
21	Microcrystalline wax	20	17.2	14.6	89.6	76.0

[a] Drug recovery (%) = (assayed drug content/theoretical drug content) × % solids recovered.

that the ibuprofen melts before complete melting of the wax. A rescan of the congealed mix shows a reduced melting temperature typical of substances that remain molecularly homogeneous upon concealing. Figure 4E also shows melting temperature depression of microcrystalline wax/stearyl alcohol components on rescanning.

Ternary Physical Mixtures and Microspheres. The curves representing the stearyl alcohol/ibuprofen/ceresine wax and stearyl alcohol/ibuprofen/microcrystalline wax ternary physical mixtures are shown in Figs. 5A and B, respectively. In Fig. 5A, the respective peaks were shown at 60, 72, and 78°C, but on rescanning the peaks either disappeared or were shifted and less distinct. This result indicates a reduced tendency to recrystallize into pure fractions on cooling. Similarly, in Fig. 5B, the respective peaks of the ternary mixture

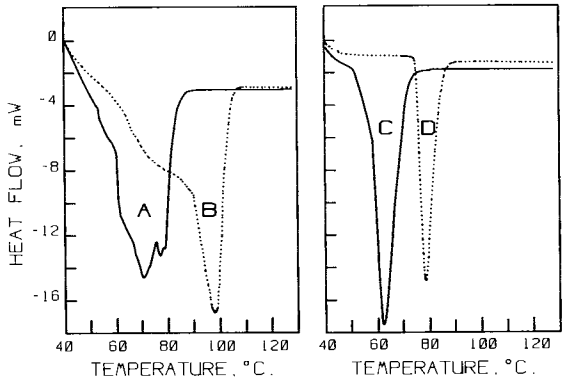

Fig. 3. Differential scanning thermograms of ceresine wax (A), microcrystalline wax (B), stearyl alcohol (C), and ibuprofen (D).

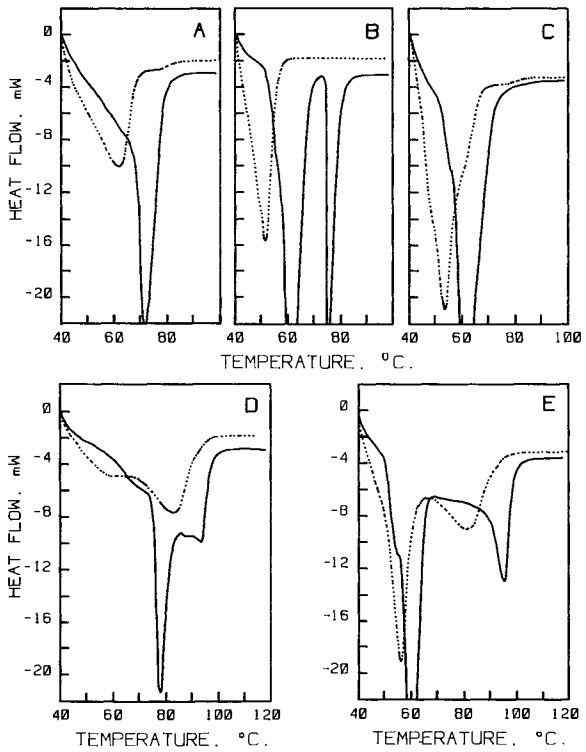

Fig. 4. Differential scanning thermograms of binary physical mixtures: ceresine/ibuprofen (A), ibuprofen/stearyl alcohol (B), ceresine/stearyl alcohol (C), microcrystalline/ibuprofen (D), and microcrystalline/stearyl alcohol (E). (· · · · ·) Rescanned samples.

shown at 60, 78, and 95°C were not observed in the rescanned sample.

The thermograms of the ceresine wax and microcrystalline wax formulations of microspheres are shown in Figs. 6A and B, respectively. The solid lines represent the microspheres containing the drug, while the dotted lines represent blank microspheres. The DSC scans of microspheres with drug are similar to rescans of ternary mixtures of the respective waxes, while blank microcapsules are similar to rescans of binary mixtures of the waxes with stearyl alcohol.

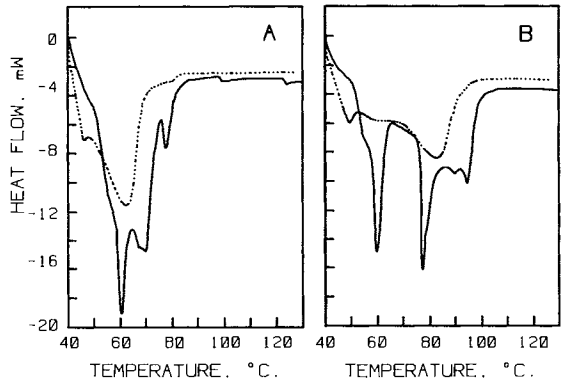

Fig. 5. Differential scanning thermograms of ternary physical mixtures: stearyl alcohol/ibuprofen/ceresine wax (A) and stearyl alcohol/ibuprofen/microcrystalline wax (B). (· · · · ·) Rescanned samples.

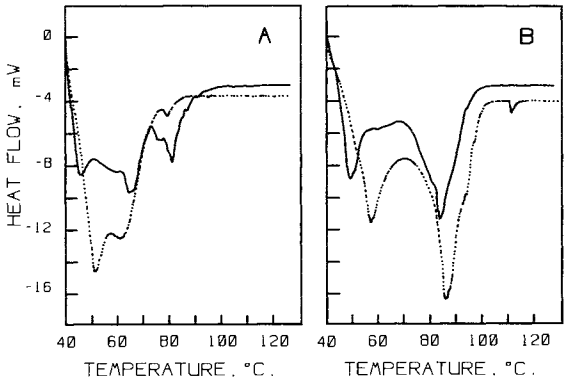

Fig. 6. Differential scanning thermograms of ceresine wax-ibuprofen microspheres (A) and microcrystalline wax-ibuprofen microspheres (B). (· · · · ·) Blank microspheres.

CONCLUSION

Ibuprofen-wax microspheres for sustained release have been developed using a congealable dispersion microencapsulation technique. Formulation variables such as wax modifiers, modifier concentration, emulsification dispersant concentration, and nature of the wax affected the particle size distribution, which was log-normal. Ibuprofen dissolves in the melted waxes and congeals to form microspheres in which much of the drug does not recrystallize as the pure drug but forms a homogenous solid with the waxes. The melt-dispersion method is a simple, viable method for the production of sustained-released microspheres of ibuprofen and other drugs with similar solubility and melting characteristics.

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