Development and Evaluation of Sustained-Release Ibuprofen–Wax Microspheres. II. *In Vitro* Dissolution Studies

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Received July 18, 1993; accepted October 27, 1993

A modified USP paddle method using minibaskets was used to study the effects of various formulations on *in vitro* dissolution of ibuprofen microspheres. Formulations containing waxes such as paraffin or ceresine wax without modifiers exhibited very slow dissolution profiles and incomplete release, which did not improve with increased drug loading or the preparation of smaller microspheres. The addition of modifiers such as stearyl alcohol and glyceryl monostearate greatly increased the dissolution rate, with 20% (w/w) near the optimum for predictable dissolution. Higher drug loading and decreased microsphere size increased the dissolution rate from microspheres containing modifier. Optimum formulations contained ceresine wax or microcrystalline wax and stearyl alcohol as a modifier, with a drug content of 17%. An increase in the encapsulation dispersant concentration had little effect on the dissolution profiles. The dissolution data from narrow size fractions of microspheres indicated spherical matrix drug release kinetics; the 50% dissolution time decreased with the square of the microsphere diameter. With appropriate modifiers, wax microsphere formulations of drugs with solubility characteristics similar to those of ibuprofen can offer a starting basis for predictable sustained release dosage forms.

KEY WORDS: ibuprofen; microspheres; dissolution; matrix drug release.

INTRODUCTION

Ibuprofen, (±)-*p*-isobutyl hydratropic acid, is used as a nonsteroidal antiinflammatory drug. Its uses as an analgesic and antipyretic are also well established (1). Several studies have been reported on the development and dissolution testing of wax microspheres (2–4) and on ibuprofen sustained-release formulations (5–9). Kagadis and Choulis (8) produced ibuprofen microcapsules using a congealable dispersion method and reported that the microcapsules had a maximum 50% dissolution time of 3 hr and 15 min for formulations with a 1:5 drug:wax ratio and 2 hr for formulations with a 1:1.5 drug:wax ratio. These particles were relatively large and may not be suitable for formulations that require smaller particles (e.g., suspensions). Kawashima (9) produced microspheres whose 50% dissolution was 2.5 hr for a formulation having a 3:1 drug:polymer ratio, a time very similar to the biological half-life of the conventional ibuprofen dosage form. Adeyeye and Price (10) reported the development of ibuprofen microspheres and the effect of formulation variables on the physical characteristics of the microspheres. Further investigation of the release characteristics of wax microspheres is needed for developing sustained-release dosage forms. The dissolution characteristics of ibuprofen–wax microspheres prepared using various formulation parameters are compared in this paper.

MATERIALS AND METHODS

Materials

All materials except simulated intestinal and gastric fluids (USP) were reported earlier (10).

Methods

Assay for Drug Content of Ibuprofen-Wax Formulation Microspheres. Ibuprofen microspheres were assayed for drug content as previously reported (10).

Dissolution Studies. Pooled batches of each formulation type were assayed for drug content and used for dissolution studies with the USP Paddle Device.[4] The USP paddle dissolution method was modified because the microspheres had a tendency to float in the dissolution medium. Six 3 × 2-cm-diameter stainless-steel minibaskets with 100-mesh screens (Fig. 1) were constructed[5] to hold each sample in the six flasks. Time-staggered (3- to 4-min interval) dissolution testing was done for each sample to allow for transfer time. Simulated gastric and intestinal fluids USP (less enzyme but with 0.02% Tween 80) were used as dissolution media. The stirring speed was 100 ± 1 rpm and the temperature was maintained at 37 ± 0.1°C. Aliquots were withdrawn through polyethylene input filters at specific intervals and then filtered through a 0.45-μm membrane filter. The samples were analyzed at a 262.1-nm wavelength and each aliquot was returned to the dissolution flask after analysis. Results are reported as means of the data from at least two replicates of six dissolutions.

The formulation and optimization parameters investigated in the dissolution studies were retardants (waxes), encapsulation dispersant concentration, wax modifier type and concentration, drug loading, and microsphere size.

RESULTS AND DISCUSSION

Drug Content

The percentages drug contents of pooled batches of microspheres are shown in Table I. These values ranged from 89.5 to 96.0% of the theoretical formulation amount.

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[4] Prolabo Dissolutest dissolution apparatus and filtering unit, generously provided by the Prolabo Company, 12 Rue Peleo, 75011 Paris.

[5] Stainless-steel mini baskets, Machine Shop, University of Georgia, Athens, GA 30602.

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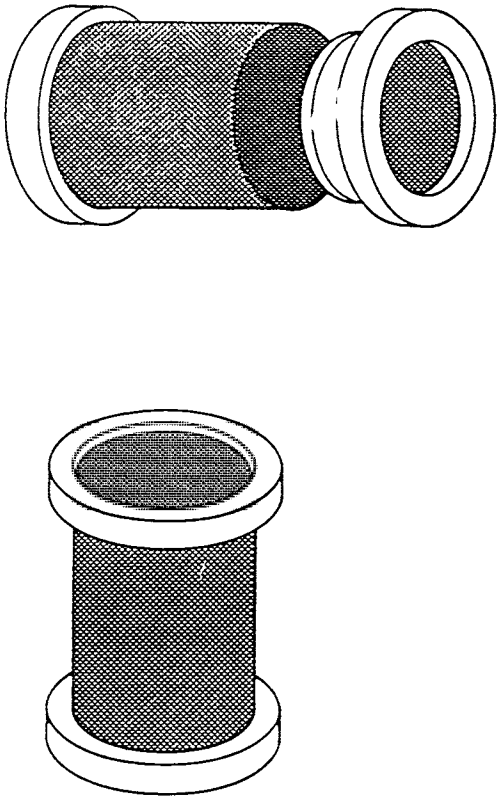

Fig. 1. Diagrams of minibasket for dissolution testing of microspheres.

Effect of Dissolution Medium pH on Dissolution Rate

The dissolution of ceresine microspheres was examined in simulated gastric fluid (pH 1.1). A sink condition throughout the dissolution was not obtained at this pH because the concentration from the dissolution sample reached 172 μg/mL ibuprofen (10% of the saturation solubility is 110 μg/mL). A sink condition was achieved with simulated intestinal fluid (pH 7.2), where the saturation solubility of ibuprofen is 27.1 mg/mL at 37°C. All subsequent dissolution studies were done with simulated intestinal fluid.

Effect of Waxes Without Modifier on Dissolution Rate

After an initial surge, microspheres with a 20% drug loading and made with different paraffin waxes (ceresine, microcrystalline, and fully refined paraffin wax) exhibited

Table I. Drug Content of Pooled Microspheres[a]

	Particle size			
	96 μm		151 μm	
Pooled batch	Assay DC (%)	% of th. DC	Assay DC (%)	% of th. DC
I	15.5	90.1	15.4	89.5
II	15.8	91.9	16.2	94.4
III	15.9	92.4	16.5	95.9
IV	16.5	96.0	15.8	91.9

[a] DC, drug content; th. DC, theoretical drug content = 17.2% in all batches.

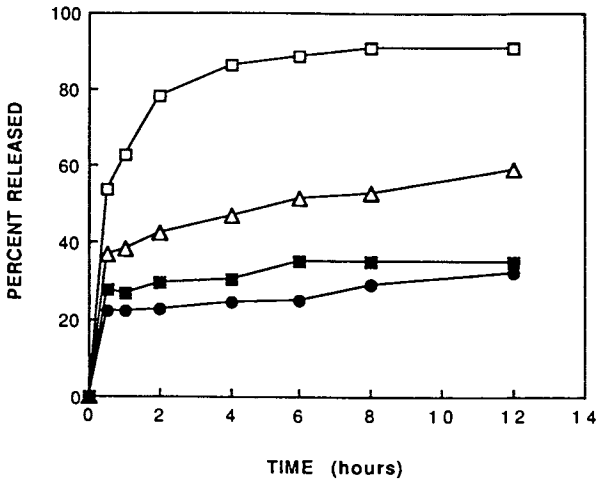

Fig. 2. Effect of waxes on the dissolution profiles of ibuprofen microspheres (213 μm) with 20% drug loading (no modifier). (●) Microcrystalline wax; (△) ceresine wax; (■) refined paraffin wax; (□) beeswax.

very slow dissolution profiles, with a maximum drug release of only 58% after 12 hr. In contrast, more than 82% of the drug was released in 1 hr from microspheres made with beeswax (Fig. 2). The significantly different dissolution profiles can be attributed to the physical and chemical properties of the respective waxes. Paraffin waxes are made up exclusively of hydrocarbons that have little affinity for the dissolution medium, whereas beeswax has hydroxyl and hydroxy acid groups, which make it more susceptible to hydration in the dissolution medium (Table II). Ceresine wax without modifier was subsequently used for studying the effect of dispersant (PVP) concentration during preparation (10), drug loading, and microsphere size on dissolution rate. However, all of these formulations had poor dissolution profiles, with no greater than 63% of the drug released after 12 hr in any of the batches.

Effect of Modifier Substances on Dissolution of Ibuprofen from Ceresine Microspheres

To enhance the dissolution of ibuprofen from the micro-

Table II. Composition of Waxes

Component	Percentage
Ceresine = 1:1 (ozokerite:paraffin)[a]	
Normal paraffin	28.1
Branched paraffin	7.9
Branched & cyclic paraffin	34.4
Cyclic	11.1
Cyclic and dicyclic	5.7
Dicyclic	12.8
Beeswax	
Hydrocarbons	16
Monohydric alcohols	31
Diols	3
Acids	31
Hydroxy acids	13
Others	6

[a] Source: Ref. 13.

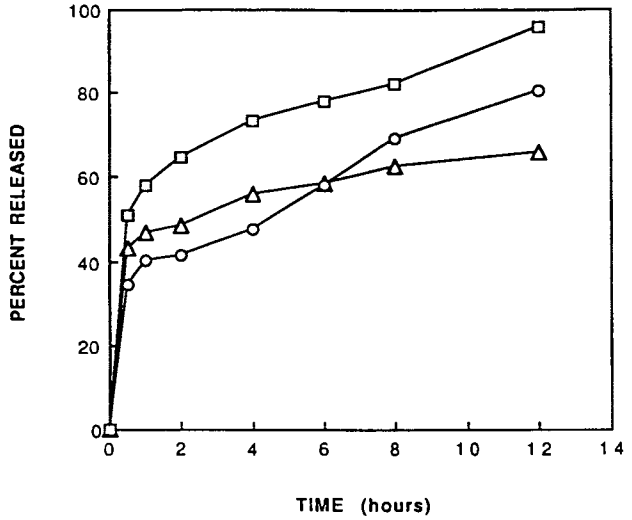

Fig. 3. Effect of glyceryl monostearate (GMS) on dissolution profiles of ceresine–ibuprofen microspheres (151 μm, 17% drug loading, no modifier): (△) 0% GMS; (○) 10% GMS; (□) 20% GMS.

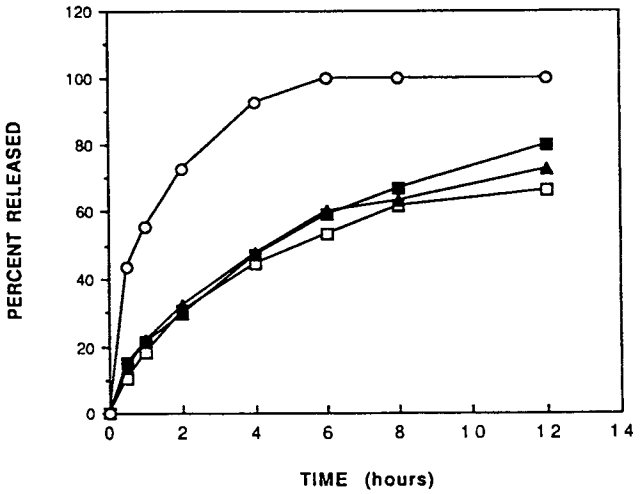

Fig. 5. Effect of drug loading on dissolution profiles of ceresine–ibuprofen microspheres containing 20% stearyl alcohol (151 μm): (□) 9% drug; (▲) 15% drug; (■) 17% drug; (○) 22% drug.

spheres, glyceryl monostearate (nonemulsifying) or stearyl alcohol was added to different batches of microspheres to introduce hydrophilic properties to the formulation. The dissolution was faster and more complete in these formulations than from the wax without modifiers.

Twenty percent glyceryl monostearate (GMS) gave a dissolution profile with a 50% release time of less than 1 hr and over 90% drug release after 12 hr (Fig. 3). Microspheres made with 10% GMS had a 50% release time of about 2 hr. It was not possible to make microspheres with 40% glyceryl monostearate because of the formation of a gel (3).

Results with stearyl alcohol modifier are shown in Fig. 4. The use of 20% stearyl alcohol and 151-μm microspheres with a 17% drug loading resulted in a dissolution profile with a 50% release time of 4.5 hr and about 81% drug release after 12 hr. There was little difference in the dissolution profiles of formulations containing ceresine with 10, 20, and 40% stearyl alcohol (17% drug). The 50% release time was 4–4.5 hr with a cumulative release of about 80% after 12 hr. Particles containing only 5% stearyl alcohol could not be successfully sized into fractions for dissolution testing because the particles tended to cluster together during processing, and the clusters could not be broken up for size separation. These results generally showed a great improvement in dissolution profiles compared to formulations without modifiers, which had a rapid initial release, a 50% release time of about 8 hr, and a cumulative release of only 66% after 12 hr. Subsequent dissolution studies were done using formulations containing ceresine as the wax, 20% stearyl alcohol as the wax modifier, and a 17% drug loading unless stated otherwise.

The modifiers, which have hydroxy groups, provide a hydrophilic pathway for water molecules to access the drug and increase the rate of dissolution. The unmodified wax microspheres and the microspheres containing GMS appar-

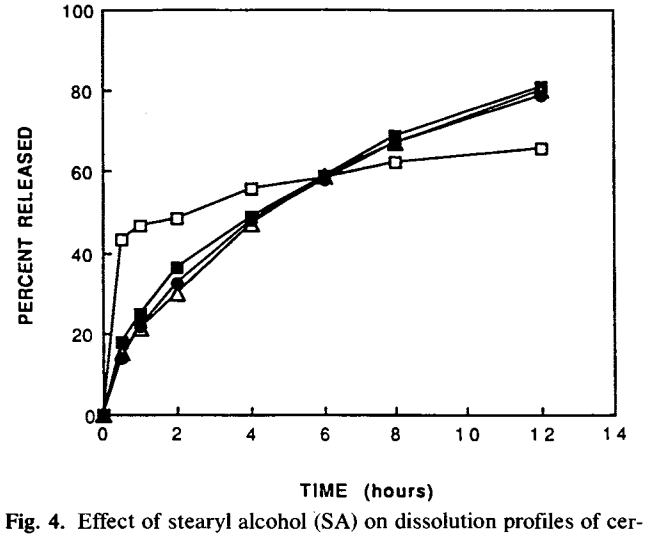

Fig. 4. Effect of stearyl alcohol (SA) on dissolution profiles of ceresine–ibuprofen microspheres (151 μm, 17% drug loading): (□) % SA; (△) 10% SA; (●) 20% SA; (■) 40% SA.

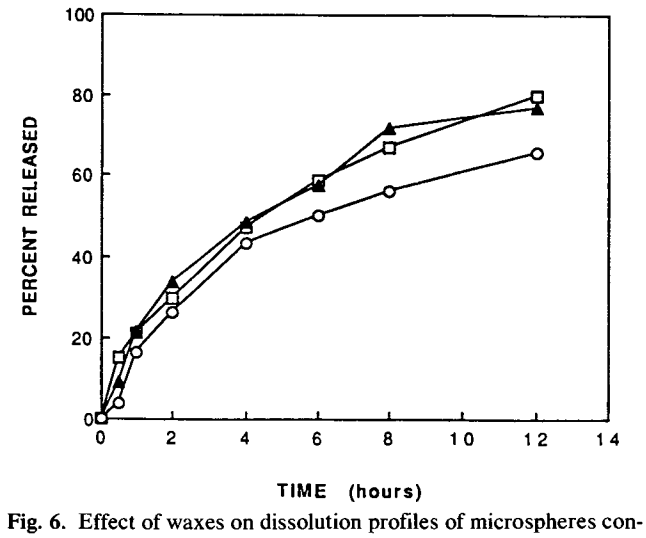

Fig. 6. Effect of waxes on dissolution profiles of microspheres containing 20% stearyl alcohol (151 μm, 17% drug loading). (□) Ceresine wax; (▲) ozokerite wax; (○) microcrystalline wax.

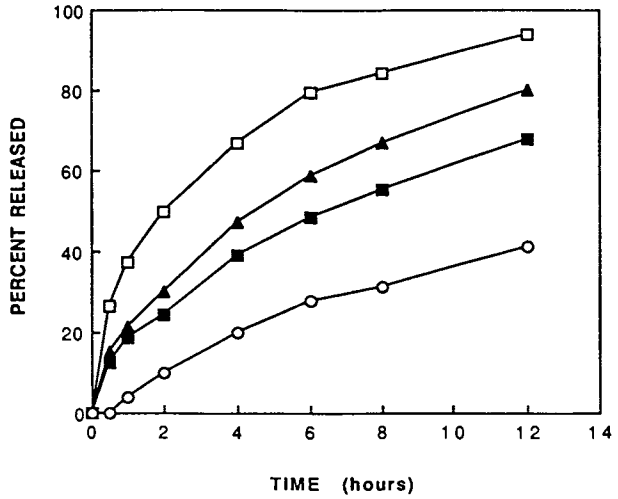

Fig. 7. Effect of microsphere size on dissolution profiles of ceresine–ibuprofen microspheres containing 20% stearyl alcohol (17% drug loading): (□) 96 μm; (▲) 151 μm; (■) 213 μm; (○) 303 μm.

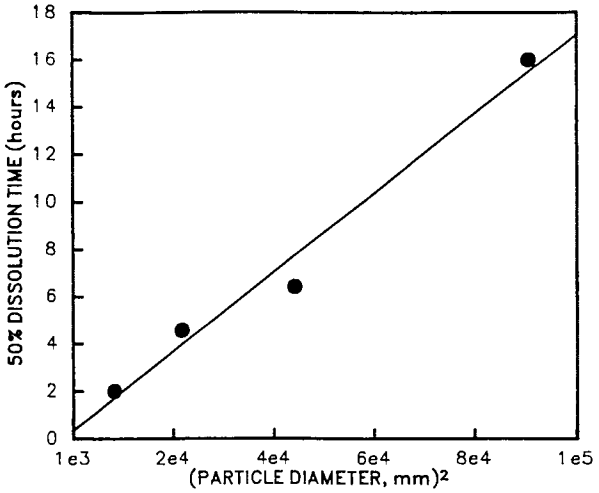

Fig. 8. Relationship of 50% dissolution time to square of microsphere diameter.

ently tend to form with some drug concentrated at the surface of the microsphere and give dissolution profiles that have a high initial dissolution rate followed by a much slower rate. Stearyl alcohol-modified microspheres, however, appear to be homogeneous matrices that do not release the drug in an initial surge. The reason for the difference in matrix behavior of the GMS-modified microspheres and the stearyl alcohol-modified microspheres is probably the greater than optimum hydrophilicity of the GMS.

Effect of Drug Loading on Dissolution of Ibuprofen from Ceresine Wax–Stearyl Alcohol Microspheres

A change in drug loading from 9 to 17% had only a small effect on the dissolution profiles of 151-μm microspheres. The 50% dissolution times for 9, 15, and 17% drug loading were 5.5, 5, and 4.5 hr, while the percentages released after 12 hr were 66.7, 72.9, and 80.0%, respectively. However, a further increase in drug content from 17 to 22% caused a significant change in the release profile; the 50% dissolution time for the 22% drug content was 1 hr, and all of the drug was released within about 6 hr (Fig. 5). This result can be explained by drug crystal formation outside the microspheres. The formulation with 17% drug was optimum because of the desirable dissolution characteristics with a reasonably high drug loading.

Effect of Wax Type on Dissolution from Wax–Stearyl Alcohol–Ibuprofen Microspheres

Ceresine, ozokerite, and microcrystalline wax microspheres showed only slight differences in their 50% dissolution times. The 50% dissolution time for ceresine and ozokerite was about 4.3 hr, while for microcrystalline wax it was 4.5 hr (Fig. 6). There were some differences, however, in the total amount released after 12 hr for the three waxes: 80 and 77% for ceresine and ozokerite microspheres, respectively, and 66% for microcrystalline wax microspheres. The amount released after 12 hr showed some correlation with the melting points of the three waxes, which are 74, 84, and 93°C, respectively. The higher the melting point, the less the cumulative amount released after 12 hr.

Effect of Microsphere Size on Dissolution of Ceresine–Stearyl Alcohol–Ibuprofen Formulations

Dissolution rate decreased with increasing particle size (Fig. 7). The 50% dissolution times for the different sizes (96, 151, 213, and 303 μm) were 2, 4.35, 6.33, and 12 hr. The specific surface areas calculated from these diameters were

Table III. Calculated Slopes, Intercepts, and Statistical Parameters of Dissolution Data for Different Sizes of Microspheres[a]

Microsphere size (μm)	Slope ± SD	Intercept ± SD	Corr. coeff. (r)	r^2
96	0.0571 ± .0016	0.000 ± .006	0.9972	0.9954
151	0.0286 ± .0011	0.009 ± .004	0.9955	0.9910
213	0.0177 ± .0006	−0.005 ± .002	0.9968	0.9937
303	0.0051 ± .0003	−0.003 ± .001	0.9878	0.9757
303 (after 1-hr lag)	0.0054 ± .0003	0.000 ± .001	0.9928	0.9856

[a] Higuchi spherical matrix model ($1 + 2F' - 3F'^{2/3} = KT$). F', fraction of drug remaining; K, a combined constant; T, time.

Table IV. Interbatch Reproducibility of Dissolution Data for Pooled Microspheres[a]

Dissolution time (hr)	96-μm particles: Mean % released ± SD	96-μm particles: % RSD	151-μm particles: Mean % released ± SD	151-μm particles: % RSD
0.5	22.3 ± 3.4	15.2	11.8 ± 4.0	33.0
1	33.4 ± 3.5	10.5	19.9 ± 2.9	14.7
2	47.0 ± 3.0	6.5	30.6 ± 2.0	6.6
4	64.6 ± 3.2	5.0	47.5 ± 1.2	2.6
6	77.2 ± 2.6	3.4	59.1 ± 2.0	3.4
8	84.7 ± 2.8	3.3	68.2 ± 2.3	3.4
12	93.3 ± 2.4	2.5	81.4 ± 2.6	3.2

[a] Mean of dissolution data from four pools. Each pool contained at least four batches of the same formulation.

6.25×10^{-2}, 3.97×10^{-2}, 2.82×10^{-2}, and 1.98×10^{-2} cm^2/cm^3, respectively. The 50% dissolution time increased with an increase in particle size because of the decreased relative surface area and the increased diffusion path length.

Drug Release Kinetics

The dissolution data for different microsphere sizes (formulations containing 20% stearyl alcohol) gave correlation coefficients of 0.99 between the dimensionless values ($1 + 2F - 3F'^{2/3}$) of the Higuchi spherical matrix model (5) and the dissolution times. Intercepts for 96-, 151-, 213-, and 303-μm particle sizes were negligible (Table III). From the Higuchi equation it can be shown that the 50% dissolution time decreases with the square of the diameter of the particles. The correlation coefficient between the 50% dissolution time and the square of the microsphere diameter was 0.9977 (Fig. 8).

Interbatch Reproducibility of Dissolution Data of Pooled Microspheres

The dissolution data of pooled microspheres (at least four batches of each formulation per pooled batch) used for the formulation of suspensions (for a later study) and the respective standard deviations and percentage relative standard deviations are given in Table IV. The relative standard deviations for 151-μm microsphere data was high in the first hour of dissolution, 33% at 30 min and 14.7% at 1 hr. However, the percentage relative standard deviations after 1 hr until the termination of dissolution testing was less than 10%, results which are within acceptable margins. For the 96-μm microsphere data, the percentage relative standard deviation was 15% at 30 min and 10.5% at 1 hr. After 1 hr the deviation was less than 10%. In general, the interbatch reproducibility was reasonable for the small-scale batches produced for the study.

CONCLUSIONS

With appropriate modifiers, wax microsphere formulations of drugs with solubility characteristics similar to those of ibuprofen can offer a starting basis for predictable sustained-release dosage forms. The microspheres with optimum characteristics in this study contained an average of 172 mg ibuprofen/g of microspheres; suspensions of 100- to 150-μm spheres can be readily formulated to contain 50% solids with good flow characteristics, therefore a teaspoonful (5 mL) could easily contain up to 430 mg ibuprofen. This is well within a practical dosage range, and higher drug concentrations may be possible with development. Other drugs with similar solubility characteristics but lower dosage requirements may be even better candidates for this type of dosage form.

ACKNOWLEDGMENT

The authors wish to thank Prolabo Company of Paris for donating the dissolution apparatus used in the study.

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