Development of Sustained-Release Ibuprofen Microspheres Using Solvent Evaporation Technique

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Summary

The emulsion-solvent evaporation method was used for the preparation of ibuprofen microspheres using cellulose acetate polymer. Polyethylene glycol was used as a surfactant to improve the release properties of ibuprofen at a drug to polymer to PEG ratio of 1:2:1. The microspheres were prepared at three different speeds (800, 1200, 1600 rpm), and were characterized with regard to their surface morphology, percentage yield, average drug content, particle size distribution, and release properties in phosphate buffer pH 6.9 at 37 °C. The particles decreased with increasing stirrer speed. The formed ibuprofen microspheres were subjected to accelerated stability studies for 3 months, and the effect of the storage time on the different characteristics was studied. The physical properties and release profiles of ibuprofen microspheres did not change after storage under accelerated stability conditions for 3 months.

Introduction

Ibuprofen is a well-known hydrophobic nonsteroidal anti-inflammatory drug (NSAID) that can be used orally for the treatment of acute and chronic rheumatoid arthritis and osteoarthritis [8]. Ibuprofen has adverse effects, in common with those for most NSAIDs, such as diarrhea, nausea, vomiting, ulcers, abdominal pain, and gastric irritation [10]. From a medical standpoint, prolonged dissolution characteristics of a drug have many desirable advantages, e.g. the compliance of the patient can be improved (frequency of drug administration is reduced, making its use more convenient), the blood level fluctuation is reduced, maximizing availability with a minimum dose (total amount of drug administered can be reduced), better control of drug absorption can be attained, and safety margin of high-potency drugs can be increased [6]. Due to its short biological half-life and the hazards of gastric irritation, ibuprofen is a potential candidate for preparing prolonged or controlled release drug products [3]. A reduced incidence of undesirable side effects would then be expected. Ibuprofen dose is initially 1.2–1.8 g daily in 3–4 divided doses preferably after food and increased if necessary to a maximum of 2.4 g daily; maintenance dose of 0.6–1.2 g daily may be adequate. In children the dose is 20 mg/kg daily in divided doses, and in juvenile arthritis, the dose may be up to 40 mg/kg daily. However, ibuprofen is not recommended for children under 7 kg [2].

The emulsion-solvent evaporation technique has been widely used for the formulation of different encapsulated drugs [1,5,9]. Polyethylene glycol has been used as a channeling agent to enhance the release rate of several drugs including those from microcapsules [7].

The purpose of this study is to prepare ibuprofen microspheres using the emulsion-solvent evaporation method, and to study the effect of different formulation parameters on the characteristics of the produced microspheres. Accelerated stability studies were also established on the produced microspheres for 3 months.

Results and Discussion

Several preliminary trials have been performed, using the solvent evaporation technique, using different polymers like cellulose propionate (CP), ethyl cellulose, and carboxymethyl cellulose polymers. All experiments made to formulate ibuprofen microspheres were unsuccessful in producing suitable product. Many problems have been faced concerning choice of a suitable solvent that dissolves the polymer but does not dissolve ibuprofen; also visual examination of the microspheres formed showed them to have inappropriate morphological characteristics. However, acceptable morphological ibuprofen microspheres were obtained using cellulose acetate polymer at drug-to-polymer ratio of 1:2 and 1:3. The microspheres were spherical and well formed. It was also noted the higher loading dose of ibuprofen (1:2 ratio) produced more regular and spherical microspheres. This might be due to the fact that ibuprofen is insoluble and uniformly dispersed in the matrix of the polymer, and the

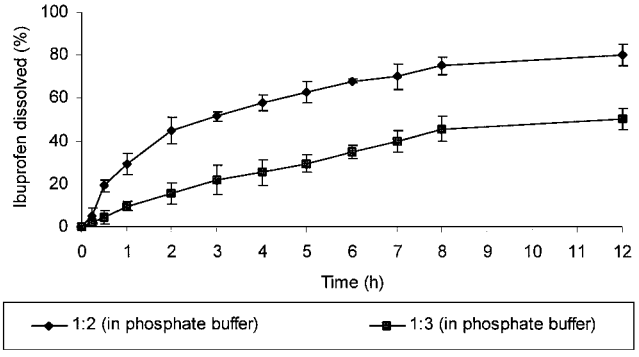

Figure 1. Effect of drug to polymer ratio on the dissolution rate profiles of ibuprofen microspheres.

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release shows zero-order kinetics. Figure 1 shows that the release profiles were better upon using a drug-to-polymer ratio of 1:2. It was also noted that decreasing the ratio to 1:3 leads to 40% plateau compared to 80% at the higher ratio of 1:2. This is mostly due to the increase in the thickness of the polymer which will hinder the release of the drug, hence increasing the ratio to 1:2 will lead to an increase in the release and thus better and higher release rate and higher plateau. This strong hindrance can be further proved by the fact that the drug is not completely released even after 12 h exposure to the dissolution media. Moreover, this would suggest that the dissolution process follows a matrix controlled process. PEG 1000 was incorporated in a 25% (w/w) of the total formula. Ibuprofen microspheres with satisfactory results in respect to morphology and drug release were obtained using the following final formula:

Ibuprofen: Cellulose acetate: Polyethylene glycol 1000
1:2:1

The effect of paddle stirring speed on the particle size distribution of the ibuprofen microspheres as determined by sieve analysis can be seen in Table 1. The results indicate that increased stirrer speed leads to smaller produced particles, in agreement with findings of Kawashima et al. [4] in his work on ibuprofen and acrylic polymers.

The effect of stirring speed on the percentage yield and drug content can be seen in Table 2. The percentage yield was calculated by dividing the total weight of the dried ibuprofen microspheres by the total weight in the formulation, multiplied by 100%. Drug content was measured using a spectrophotometer. The ideal speed of the paddle stirrer was 1600 rpm.

Table 1. Effect of stirring speed on particle size distribution of the final formula of ibuprofen microspheres.

Screen opening (μm)	Mean screen opening (μm)	Weight retained (%) at rotational speed (rpm) 800	1200	1600
1400 – 1250	1325	13.7	0.0	0.0
1250 – 1000	1125	59.5	32.8	0.0
1000 – 800	900	26.8	55.1	5.3
800 – 500	650	0.0	12.1	91.5
500 – 315	407.5	0.0	0.0	3.2

Table 2. Effect of stirring speed on percentage yield and drug recovery of ibuprofen microspheres in the final formula (n = 3, mean ± S.D.).

	Rotational speed (rpm) 800	1200	1600
Yield (%)	74.6 ± 5.4	93.4 ± 2.1	91.1 ± 3.1
Drug recovery (%)	82.7 ± 6.5	87.5 ± 5.5	95.5 ± 4.2

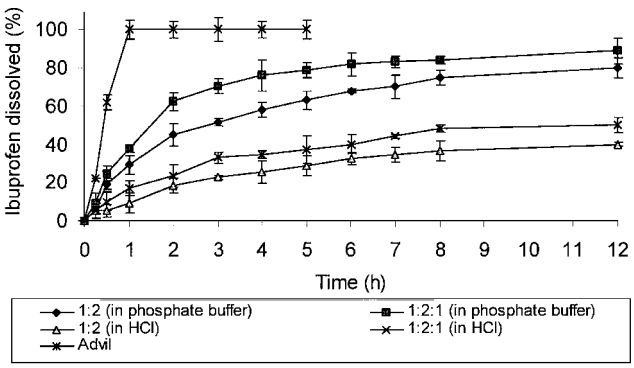

Figure 2. Effect of PEG on the dissolution rate profiles of ibuprofen microspheres prepared at 1:2 and 1:2:1, drug: polymer and drug: polymer: PEG, in either phosphate buffer or 0.1 N HCl.

Figure 2 shows the effect of dissolution media on the release of ibuprofen microspheres under sink conditions, as well as the effect of adding PEG to the formulation. Incorporation of PEG improves the rate of ibuprofen release significantly. Nokhodchi and Farid [7] have shown that PEG enhances the release of acetyl salicylic acid from cellulose acetate phthalate microspheres. However, it can be concluded from Figure 2 that the release of ibuprofen from the formulation is pH dependent. The release rate over an extended period of time and the better release of the drug in the alkaline media indicates the suitability of this technique in producing ibuprofen sustained-release microspheres and minimizes the release in the acidic media (HCl), which may reduce the possibility of irritating the stomach and other unwanted effects. Figure 3 shows the effect of stirring speed on the release rate profiles of ibuprofen using the final formulation. Increasing the speed of the paddle stirrer is seen to enhance the release. This is mainly because the specific surface area of the microspheres will increase as the stirrer speed increases, leading to a higher dissolution rate.

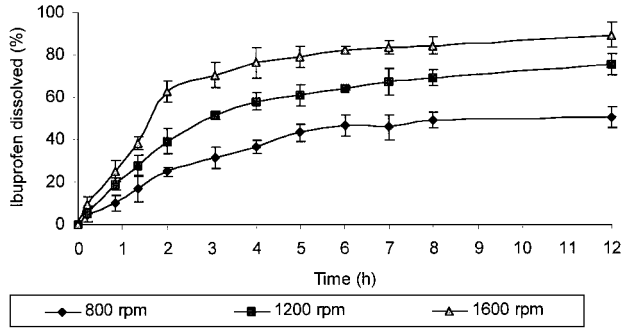

Figure 3. Dissolution rate profiles for ibuprofen microspheres (final formula) prepared at different stirring speed.

A stability study has been performed on ibuprofen microspheres in hard gelatin capsules for three months. Visual examination of the capsules showed no change to occur in the physical appearance of the capsules. Microspheres were free flowing inside he hard gelatin capsules. This indicates the good physical characteristics and the stability of the ibuprofen microspheres after storage. Table 3 shows the average drug content at zero time and after 1, 2, and 3 months at 40 °C/30% and 40 °C/80% R.H. The data show that the

Table 3. Percentage of average drug content of ibuprofen microspheres (final formula) prepared at 1600 rpm. calculated relative to zero time (prestorage), (n = 3, mean ± S.D.).

Storage conditions	Average ibuprofen content (%) after storage time (months)			
	0	1	2	3
40 °C/30% R.H.	100.0	99.6 ± 1.0	100.2 ± 1.2	99.5 ± 1.2
40 °C/80% R.H.	100.0	100.3 ± 1.1	100.6 ± 2.1	101.3 ± 0.1
Room temp.	100.0	100.1 ± 1.0	101.3 ± 0.1	100.1 ± 0.1

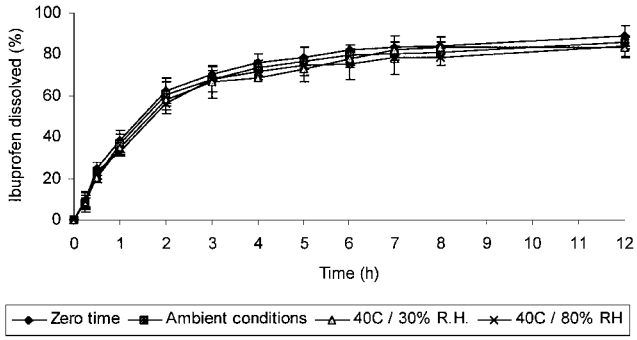

Figure 4. Dissolution rate profiles of ibuprofen microspheres before and after storage for three months under different conditions.

average drug content did not change after 3 months of storage, reflecting the good chemical stability. Figure 4 indicates that there is no change in ibuprofen release from these batches compared with data of pre-storage batch.

Conclusion

A survey of the market to find sustained release ibuprofen capsules. To the knowledge of the authors no such product is available. A novel dosage form was therefore suggested and compared to a commercial product of ibuprofen (Advil tablets). The commercial tablets showed 100% drug release, compared to about 80% drug release in the final formulation described this study. The delay of release is most probably to the polymer used in the formula. Stable sustained release ibuprofen-loaded microspheres can be prepared using cellulose acetate polymer in a 1:2 drug to polymer ratio. The desired release characteristics can be attained by including PEG in the formulation, and by controlling the particle size of the microspheres, and the type of the polymer.

Experimental

Materials

Racemic ibuprofen was kindly provided by Arab Pharmaceutical Manufacture (Sult, Jordan), cellulose acetate (Acros, New Jersey, USA), acetone, hydrochloric acid, and ethanol 96% (Gainland Chemical Company, UK), Span 80 and polyethylene glycol (PEG) 1000, 4000, 8000 (Sigma, St. Louis, USA), liquid paraffin (Bufa, Uitgeest, Holland), Na-dihydrogen-orthophosphate (Pharmacos, UK).

Preparation of Microspheres

The emulsion-solvent evaporation technique was used to prepare the ibuprofen-loaded microspheres. Ibuprofen was dispersed in an acetonic solution containing cellulose acetate polymer and PEG at different drug-to-polymer ratios. The dispersion of ibuprofen, cellulose acetate, acetone and PEG was used as the emulsion internal phase. This was added slowly to liquid paraffin, the external phase of the emulsion, containing 1.0% Span 80 and was emulsified using a paddle mixer (Type RW20, Janke and Kunkel GmbH and Co. KG, Staufen, Germany). Stirring was continued at room temperature until the acetone was evaporated. Agitation was continued for another 2 h to ensure the removal of acetone. The resulting microspheres were filtered, washed with ethanol, and dried under reduced pressure.

The average particle size and size distribution for batches produced at different speeds were determined using sieve analysis under ambient conditions (20 °C, 30% R.H.). The amplitude of vibration in the sieve shaker was 3 mm and was calibrated to vibrate 40 times a second.

An accurate amount of the microspheres corresponding to about 50 mg ibuprofen was extracted with 50 ml ethanol 96%. After filtration and appropriate dilution with distilled water, the concentration of ibuprofen was measured spectrophotometrically at 224 nm. The assay was carried out in triplicate and the average drug content was determined.

The release rate of microspheres were performed using tablet dissolution machine (Hanson Research Corporation, Chats Worth, California USA). An accurate amount of the microspheres corresponding to about 50 mg ibuprofen, were filled in hard gelatine capsules. The test was carried out according to the USP XXIII dissolution procedure (Apparatus II), using 500 ml phosphate buffer, pH 6.9 with 0.02% Tween 80, equilibrated at 37 °C ± 0.5. Paddles were rotated at 100 rpm, 5 ml samples were taken from the dissolution bath at certain time intervals, and dissolution media were compensated each time with 5 ml phosphate buffer. Release studies were done under sink conditions.

0 size Hard gelatin capsules filled with an amount of microspheres equivalent to 150 mg ibuprofen were packed in amber colored glass containers with the mouth covered with aluminum foil followed by a plastic cap. Containers were placed in closed desiccators containing saturated salt solutions to give rise to relative humidity of 30% and 80% when kept in incubators adjusted and maintained at 40 °C, also some hard gelatin capsules were stored under ambient conditions (20 °C, 30%R.H.) as a control. Results for average drug content and dissolution rate were compared with the prestorage data.

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