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Il Farmaco 58 (2003) 101–106
IL FARMACO
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Preparation and in vitro evaluation of modified release ketoprofen microsponges

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Received 21 January 2002; accepted 12 October 2002

Abstract

Microsponges containing ketoprofen and Eudragit RS 100 were prepared by quasi-emulsion solvent diffusion method. The effects of different mixing speeds, drug–polymer ratios, solvent–polymer ratios on the physical characteristics of the microsponges as well as the in vitro release rate of the drug from the microsponges were investigated. All the factors studied had an influence on the physical characteristics of the microsponges. In vitro dissolution results showed that the release rate of ketoprofen was modified in all formulations.

Keywords: Microsponges; Ketoprofen; Modified release; Quasi-emulsion solvent diffusion method

1. Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug usually used for the treatment of arthritis and it is known that it has some side effects in gastrointestinal system [1–3]. It is probable that a modified release dosage form would reduce the severity of these side effects [4,5].

Commercial pharmaceutical forms of acrylic resins are good candidates for the preparation of modified release dosage forms because of their inertness, solubility in non-toxic solvents (alcohol) and availability of this polymer with widely different properties [6,7].

This study concerns the use of this polymer; Eudragit® RS 100 to prepare modified release of microsponges. Ketoprofen was used as a model drug.

2. Experimental

2.1. Preparation of microsponges

All microsponges were prepared by quasi-emulsion solvent diffusion method [8–14] using an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72 000. The internal phase was consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC) which was added at an amount of 20% of the polymer in order to facilitate the plasticity.

At first, the internal phase was prepared at 60 °C and added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 h. Then the mixture was filtered to separate the microsponges. The product was washed and dried by vacuum oven at 40 °C for 24 h.

2.2. Variation of formulation and process factors

In each formulation, the amounts of polymer and TEC were kept constant at a concentration of 0.096 and 0.019 g/ml, respectively. The solvent amount was 10 ml.

2.2.1. Determination of the effect of drug–polymer ratio

Seven different ratios of drug to Eudragit RS 100 (1:1, 3:1, 5:1, 7:1, 9:1, 10:1 and 11:1) were employed to determine the effects of drug–polymer ratio on physical characteristics and dissolution properties of microsponges (Table 1). In each formulation, the amount of polymer was kept constant at 0.096 g/ml, the amount of TEC was 0.019 g/ml and the solvent amount was 10 ml.

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0014-827X/03/$ - see front matter
PII: S0014-827X(02)00007-1

Table 1
Effect of drug to polymer ratio on drug loading capacity, production yield and particle size of ketoprofen microsponges

Formulation code	Drug–polymer ratio	Ketoprofen amount (g/ml)	Drug loading capacity (%±SD)	Production yield (%±SD)	Mean particle size (μm) [b]
MS1	1:1 [a]	0.096			
MS2	3:1	0.288	91.55±0.2	16.45±0.3	691.73±0.1
MS3	5:1	0.480	94.09±0.1	42.82±0.1	674.12±0.2
MS4	7:1	0.672	94.09±0.2	47.25±0.3	656.37±0.2
MS5	9:1	0.864	96.63±0.1	94.12±0.2	626.94±0.3
MS6	10:1	0.960	96.63±0.2	96.84±0.1	578.39±0.2
MS7	11:1	1.056	96.63±0.1	99.71±0.3	410.88±0.1

***, Microsponges were produced with a mixing speed of 350 rpm.
[a] Microsponge formation was not achieved at that ratio.
[b] Measuring range was 400–1750 μm.

Ketoprofen amount was regulated according to the drug–polymer ratio.

2.2.2. Determination of the effect of solvent–polymer ratio

The effect of solvent–polymer ratio was investigated by keeping the amount of polymer (0.96 g) and drug (10.56 g) constant and changing the amount of solvent. Three different solvent amounts were chosen and the formulations were coded as MS 7A, MS 7B and MS 7C (Table 2).

2.2.3. Determination of the effect of agitation speed

Different agitation speeds (300, 350 and 400 rpm) were employed to a chosen ratio of drug to polymer (11:1).

2.3. Particle size analysis

The particle size of the microsponges was determined with Sympatec HELOS (H0728) particle size analyzer. Each determination was carried out in triplicate. Some samples of ketoprofen microsponges which were containing ketoprofen in different concentrations were shown in Figs. 1 and 2.

Table 2
Different solvent amounts and related drug and polymer concentrations that applied to MS 7

Formulation	MS 7A	MS 7B	MS 7C
Inner phase			
Ketoprofen (g/ml)	3.520	2.112	1.509
Eudragit RS 100 (g/ml)	0.320	0.192	0.137
Ethanol (ml)	3	5	7
TEC (g/ml)	0.064	0.038	0.027
External phase			
Distilled water	200	200	200
PVA 72 000 (mg)	40	40	40

2.4. Assay procedures

2.4.1. Analytical method for the assay of ketoprofen

In order to determine the standard calibration curve of ketoprofen, a stock of 1 mg/ml in pH 7.4 phosphate buffer solution was prepared. Then, dilutions were made to prepare a series of solutions containing ketoprofen in different concentrations. In these solutions, absorbance values at 262 nm (λ_{max}) were determined UV spectrophotometrically. Plotting the concentration values (x) versus absorbance values (y) calibration curve of ketoprofen in pH 7.4 phosphate buffer was determined [15,16]. Analytical parameters for the assay of ketoprofen were calculated by using ANOVA test.

2.4.2. LOD and LOQ determination

The limit of detection (LOD) and the limit of quantitation (LOQ) were determined by using the following equations [17–20]:

$$\mathrm{LOD} = 3\mathrm{SD}/m \qquad \mathrm{LOQ} = 10\mathrm{SD}/m$$

where SD is the standard deviation of the absorbance values ($n = 6$) of the second smallest concentration, m is the slope of the calibration curve.

2.4.3. Recovery studies

To study the accuracy, reproducibility, precision and to check the interference from excipients used in the formulation of the above method, recovery experiments were carried out. In order know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the microsponges containing the known amount of ketoprofen. Mixtures were analyzed by spectrophotometrically. Percentage recovery was calculated after three experiments.

2.4.4. Drug loading capacity and production yield values

Drug loading capacity of the microsponges was determined by dissolving accurately weighed portions for each batch in 25 ml of ethanol and 25 ml of distilled water and observing the spectrophotometric absorbance

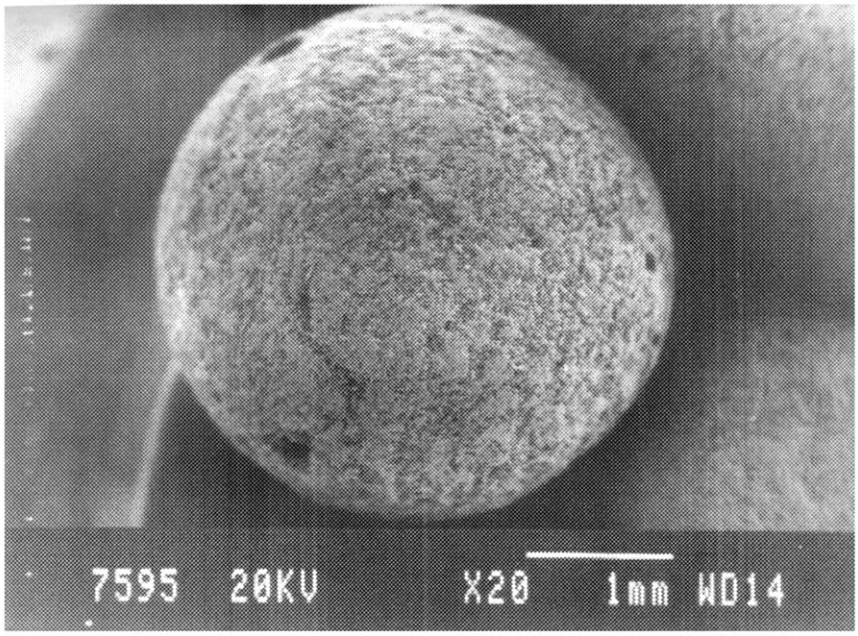

Fig. 1. Ketoprofen microsponges containing the polymer and ketoprofen at the concentrations of 0.320 and 3.520 g/ml, respectively, and solvent amount is 3 ml (MS 7A).

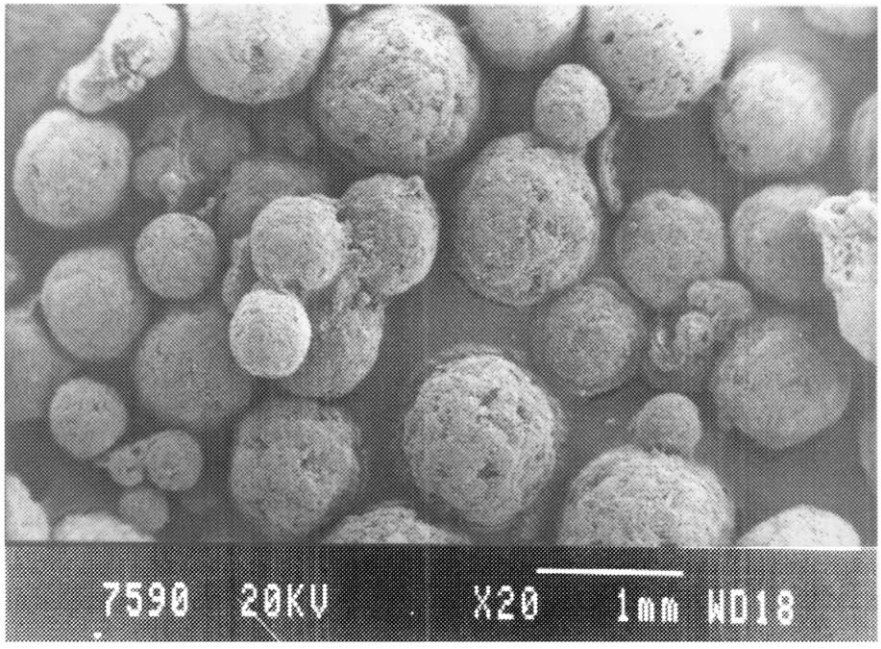

Fig. 2. Ketoprofen microsponges containing the polymer and drug at the concentrations of 0.096 and 1.056 g/ml, respectively, and solvent amount is 10 ml (MS 7).

at 262 nm. Triplicate samples were assayed and the mean values reported.

Production yield of the microsponges was determined by calculating accurately the initial weight of raw materials and the last weight of the microsponges obtained. Triplicate data were calculated.

2.5. In vitro dissolution studies

In vitro release rate studies were carried out by paddle method specified in USP XXIII. Accurately weighed samples of microsponges were used which were calculated to contain 200 mg of ketoprofen. They were placed

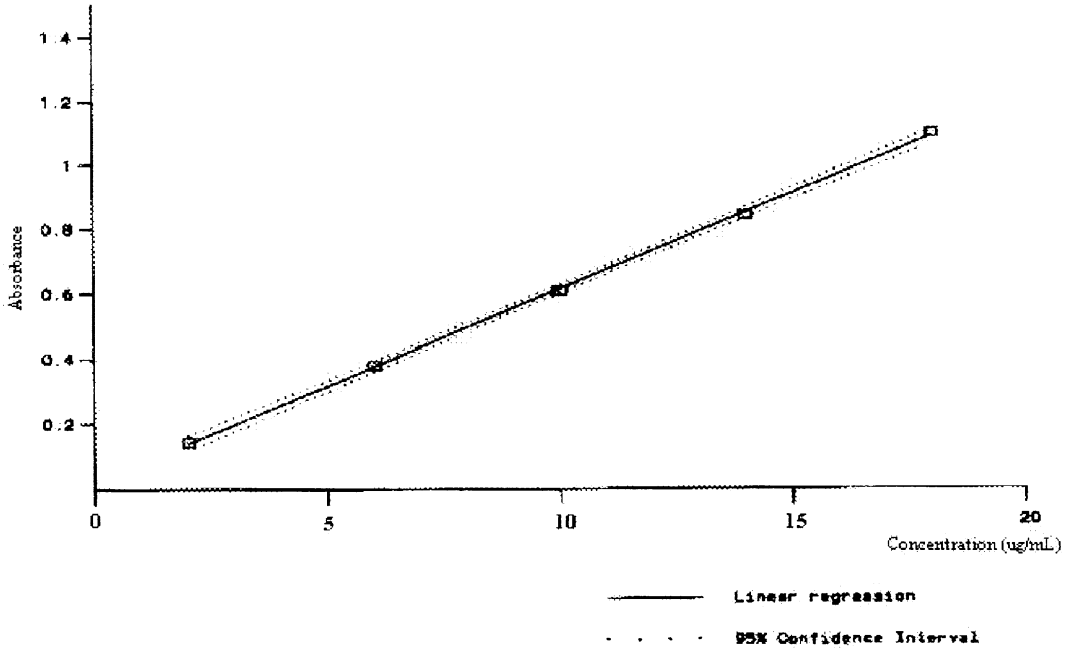

Fig. 3. Calibration curve of ketoprofen.

in pH 7.4 phosphate buffer solution at 37±1 °C and rotated at 100 rpm. Five ml aliquots were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, and 120th min and then hourly intervals up to 12 h and a last aliquot was withdrawn at 24 h. The samples were assayed at 262 nm. Each determination was carried out in triplicate.

3. Results and discussion

3.1. Effect of formulation variables on physical properties of microsponges

3.1.1. Effect of drug to polymer ratio

When the amount of polymer was kept constant but the ratio of drug to polymer was varied as it is reported in Table 1, the drug loading capacity was not much affected by drug to polymer ratio but production yield was enormously changed from minimum ratio to maximum. Another parameter which was affected from drug–polymer ratio change was particle size. It was observed that when drug amount increased, particle size of the microsponges increased.

3.1.2. Effect of solvent–polymer ratio

When the amount of solvent increases, polymer and drug concentration decrease (Table 2). As a result of the decrease in the polymer concentration, microsponge particle size increases as shown in Table 1, Figs. 1 and 2.

3.2. Effect of process variables on physical properties of microsponges

3.2.1. Effect of mixing speed

Three different agitation speeds were selected and it was observed that particle size of the microsponges decreased with the increasing of the mixing speed from 300 to 350 rpm, but at 400 rpm because of the turbulence of the external phase, the polymer stuck around the paddle of the mixer and a great loss of the polymer was indicated. Therefore, as a mixing speed of 350 rpm for the preparation of the ketoprofen microsponges was thought suitable.

Table 3
Analytical parameters for the assay of ketoprofen by UV spectrophotometric method

Parameter	Result	Confidence limits	
		Lower 95%	Upper 95%
Linearity range (μg/ml)	0.4–1.0		
Slope	0.059	0.570	0.062
Intercept	0.021	−0.006	0.048
RSD of slope (%)	0.81		
RSD of intercept (%)	8.23		
Determination coefficient (r^2)	0.9995		
Standard error of slope	0.00074		
Standard error of intercept	0.009		
LOD (μg/ml)	0.045		
LOQ (μg/ml)	0.151		

Table 4
Recovery study results for ketoprofen microsponges

Theoretical value (mg)	Practical value (mg)	Recovery (%)	Mean recovery	RSD (%) [a]
220	216.27	98.30		
220	214.42	97.46		
220	217.71	98.95	98.24	0.76

[a] Relative standard deviation (%).

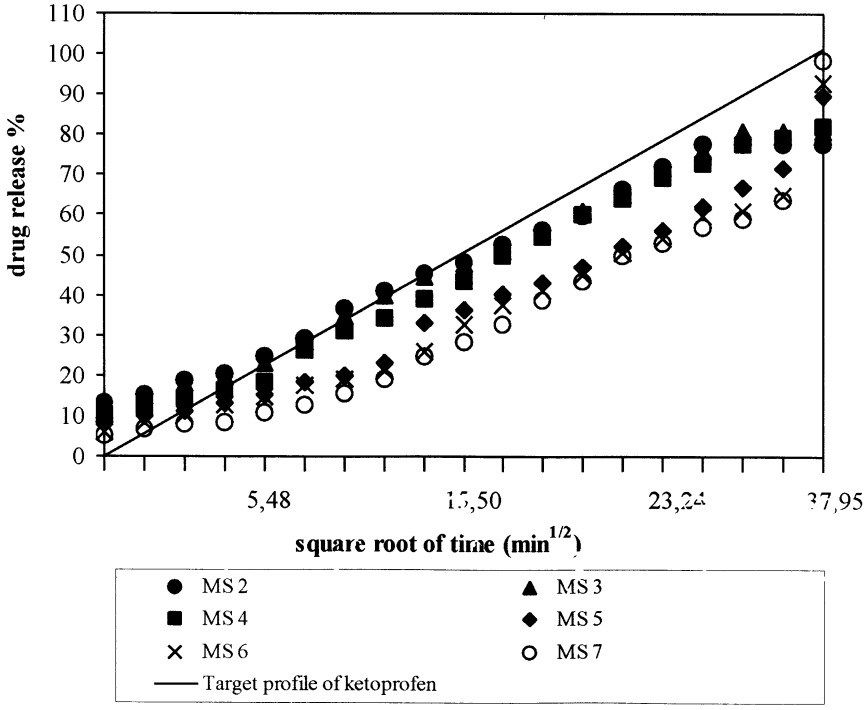

Fig. 4. Release profiles of ketoprofen from microsponges in pH 7.4 buffer solution at 37±1 °C.

3.3. Results of assay procedures

3.3.1. Results of assay of ketoprofen

Calibration of ketoprofen was performed by using the method which was explained in Section 2.4.1, and calibration curve was shown in Fig. 3. Analytical parameters for the determination of ketoprofen by UV spectrophotometric method were given in Table 3.

3.3.2. Results of recovery studies

Recovery study results of ketoprofen microsponges were given in Table 4. Each dose contains 200 mg of ketoprofen.

As it can be seen from Table 4 high percentage recovery results show that the method is free from the interferences of the excipients used in the formulation.

3.3.3. Results of drug loading capacity, mean particle size and production yield value

Data about drug loading capacity, mean particle size and production yield values were given in Table 1.

Production yield and drug loading capacity of MS 7 shows us that ketoprofen can be loaded in form of microsponges for oral use in very high percentages and this is supported by mean particle size value. The particle size that is given in literature is 5–300 μm [21].

3.4. Results of release rate studies

Drug release of microsponges can be explained by Higuchi matrix model [14]. All formulations of ketoprofen microsponges modified the release of ketoprofen when compared drug itself. Among all the formulations of microsponges, it can be said that MS 7 is the best formulation when it is evaluated with all physical parameters and in vitro release profiles which can be seen in Fig. 4.

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