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Preparation and evaluation of ketoprofen floating oral delivery system [1]

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Abstract

A sustained release system for ketoprofen designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating microparticles. The drug retained in the floating microparticles decreased with increase in ERL content. All floating microparticle formulations showed good flow properties and packability. Scanning electron microscopy and particle size analysis revealed differences between the formulations as to their appearance and size distribution. X-ray and DSC examination showed the amorphous nature of the drug. Release rates were generally low in 0.1 N HCl especially in presence of high content of ES while in phosphate buffer pH 6.8, high amounts of ES tended to give a higher release rate. Floating ability in 0.1 N HCl, 0.1 N HCl containing 0.02% Tween 20 and simulated gastric fluid without pepsin was also tested. The formulation containing ES:ERL1:1 (FIII) exhibited high percentage of floating particles in all examined media.

Keywords: Ketoprofen; Floating microparticles; Eudragit; Emulsion solvent diffusion; Sustained release

1. Introduction

The gastrointestinal transit time is one of several physiological limitations that must be controlled in the development of peroral sustained release dosage forms (Porter and Ghebre-Sellassie, 1994). Various attempts have been made to prolong the retention time of the dosage form in the stomach. One such method is the preparation of a device that remains buoyant in the stomach contents due to its lower density than that of the gastric fluids (Desai and Bolton, 1993; Deshpande et al., 1996; Kawashima et al., 1992; Oth et al., 1992; Whitehead et al., 1998).On the other hand, a floating system made of multiple unit forms has relative merits compared to a single unit preparation (Iannuccelli et al., 1998). Indeed, the gastric emptying of a multiparticulate floating system would occur in a consistent manner with small

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individual variations. On each subsequent gastric emptying, sunk particles will spread out more uniformly over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way (Acikgoz et al., 1995). Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced (Iannuccelli et al., 1998).

The concept of floating microparticles can also be utilized to minimize the irritant effect of weakly acidic drugs on the stomach by avoiding direct contact with the mucosa and providing a mean of getting low dosage for prolonged periods (Thanoo et al., 1993). Ketoprofen is a well known nonsteroidal anti-inflammatory agent requiring a high dosage for efficacy in arthritis. Being a weak acid, $pK_a \sim 4.55$ (Dollery, 1999), the drug is well absorbed from the upper portion of the duodenum. Therefore, a floating multiparticulate system is expected to produce a prolonged release of the drug without irritant particles lodging in the mucosa.

In the present study, the floating microparticle technique was adopted to achieve the floating multiunit system for ketoprofen using ES100 alone or in a mixture with the permeable Eudragit RL. Eudragit polymers were selected to form the floating microparticles since they have been approved by FDA and are widely used in the pharmaceutical industry.

2. Experimental

2.1. Materials

Ketoprofen (courtesy of Amriya Pharm. Ind Alexandria, Egypt), Eudragit S100 (ES100) and RL (ERL) (Rohm Pharma, Darmstadt, Germany), ethanol and sodium lauryl sulfate (El-Nasr Pharmaceutical Chemical), dichloromethane (Cambrian Chemicals) were used. All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of floating microparticles

Floating microparticles containing ketoprofen were prepared using the emulsion-solvent diffusion technique (Kawashima et al., 1992) with some modifications. The drug polymer ratio used to prepare the different formulations was 1:1. The polymer content was a mixture of ES:ERL 1.5:0.5 (FI), 0.5:1.5 (FII), 1:1(FIII) and 2:0 (FIV). The drug polymer mixture dissolved in a mixture of ethanol and dichloromethane (1:1) was dropped into 0.2% sodium lauryl sulfate solution. The solution was stirred with a propeller-type agitator at room temperature for 1 h at 150 rpm. The formed floating microparticles were filtered, washed with water and dried at room temperature in a desiccator. The floating microparticles were sieved and fractions corresponding to particle size range 100–1250 μm were collected.

2.2.2. Determination of drug retained and yield of floating microparticles

Ten milligrams of floating microparticles were dissolved in 10 ml ethanol. The samples were assayed for drug content by UV-spectrophotometry (Pharmacia LKB-Ultrospec) at 260 nm after suitable dilution. No interference was found due to the other floating microparticle components at 260 nm. The percentage drug retained and yield were calculated as follows:

$$\% \text{ Drug retained} = (\text{Calculated drug conc.}/\text{Theoretical drug conc.}) \times 100$$

$$\% \text{ Yield} = (\text{Total weight of floating microparticles}/\text{Total weight of drug and polymer}) \times 100$$

2.2.3. Scanning electron microscopy

The floating microparticles were coated uniformly with gold after fixing the samples in individual stubs. All samples were examined for surface morphology using scanning electron microscope (Jeol, SEM model JSM-25SII, Tokyo, Japan).

2.2.4. Particle size analysis

Size distribution was determined by sieving the floating microparticles in standard test sieves (Martin, 1993).

2.2.5. Measurement of flow properties

Angle of repose of different formulations was determined by a fixed funnel method (Ritschel et al., 1980).

Bulk density was measured by tapping method (Martin, 1993).

Packing properties of floating microparticles were measured also by tapping method (Martin, 1993). The packing rate (b, k) was calculated from the following equations:

$$n/c = (1/ab) + (n/a) \text{ (Kawakita, 1964)}, \quad (1)$$

where $c = (v_o - v_n)/v_o$, n is the tap number, and v_o and v_n are the powder bed volumes at initial and tapped state, respectively.

$$\rho_f - \rho_n = (\rho_{f-} \rho_o) \exp(-k_n) \text{ (Kuno, 1979)}, \quad (2)$$

where ρ_f, ρ_n and ρ_o are the apparent densities at equilibrium, nth tapped state and initial state, respectively.

The packing factor was also calculated as the ratio of bulk density after tapping to bulk density before tapping (Ritschel et al., 1980).

Compressibility was computed according to the following equation:

$$\text{Compressibility (\%)} = (\rho_t - \rho_b/\rho_t) \times 100 \text{ (Lin and Kao, 1989)}, \quad (3)$$

where ρ_t is the tapped bulk density and ρ_b is the initial bulk density.

2.2.6. X-ray diffraction

X-ray diffraction analysis for pure drug, polymers and floating microparticles was done by Siemens D-500 X-ray powder diffractometry (Germany). The X-ray diffraction patterns were recorded automatically using rate-meter with time constant 400 pulse/s and scanning speed of 2° 2θ/min and chart speed 1 cm/min.

2.2.7. Differential scanning calorimetry

Thermograms of the drug, polymers (ES100 and ERL) and floating microparticles were obtained using Perkin-Elmer 17 series thermal analysis system. Heating rate was 5°C/min.

2.2.8. Measurement of drug release rate from floating microparticles

The drug release rate from floating microparticles was carried out using USP dissolution apparatus I. A weight of floating microparticles corresponding to 200 mg drug was filled into a capsule and placed in the basket. Dissolution media were 900 ml of either 0.1 N HCl or phosphate buffer pH 6.8 maintained at 37 ± 0.1°C and stirred at 100 rpm. Samples were withdrawn at suitable time intervals and assayed spectrophotometrically at 260 and 259 nm in case of pH 6.8 and in 0.1 N HCl, respectively.

2.2.9. In vitro evaluation of floating ability

Fifty milligrams of the floating microparticles were placed in 50 ml beakers. Twenty milliliters of 0.1 N HCl or 0.1 N HCl containing 0.02% Tween 20 or simulated gastric fluid without pepsin (USP, 1995) were added. The beakers were shaken horizontally in a water bath at 37 ± 0.1°C. Floated particles were collected at 1, 2, 4 and 6 h and dried in a desiccator till constant weight. The percentage of floating microparticles was calculated by the following equation:

$$\%\text{Floating microparticles} = (\text{weight of floating microparticles}/\text{initial weight of floating microparticles}) \times 100$$

All the previous experiments were done in triplicate.

3. Results and discussion

3.1. Percentage yield of floating microparticles and drug retained

The percentage yield of floating microparticles determined by weighing after drying was 67, 63, 63 and 60% for FI, FII, FIII and FIV, respectively. On the other hand, the drug retained decreased with the increase in ERL content of floating microparticles (Fig. 1). This could be due to the permeation characteristics of this polymer that could facilitate the diffusion of a part of entrapped drug to the surrounding medium during preparation of floating microparticles.

Physicochemical properties of the prepared floating microparticles;
micromeretic properties;
shape, surface topography and size distribution of floating microparticles

The sphericity and size distribution of the floating microparticles were also influenced by the content and type of Eudragit used and its ratio in the formulations.

Scanning electron microscopic photographs of floating microparticles are shown in Fig. 2. The shape and surface topography were different among the formulations. While floating microparticles of FIV formed entirely of ES100 were observed to be fairly spherical with nearly regular surface, FII floating microparticles containing the highest ratio of ERL to ERS gave floating microparticles with somewhat folded and invaginated surface. Sphericity was improved when the content of ERL decreased (Fig. 2). The size distribution varied somewhat among the formulations (Table 1). Formula III showed the highest population of small and lowest population of big size floating microparticles (61.9 and 11.1%, respectively). Formula IV showed a relatively high percentage of the big size fraction (21.4% of particles > 500 μm).

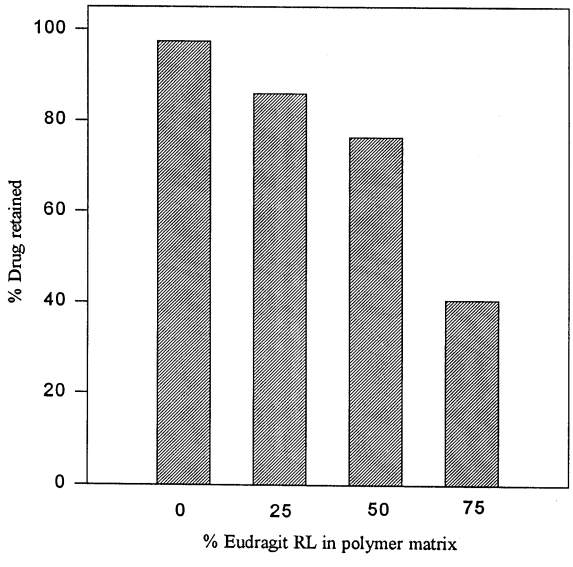

Fig. 1. Effect of polymer matrix composition on percent ketoprofen retained in floating microparticles.

3.2. Flow properties and packability of floating microparticles

All formulations showed excellent flowability as represented in terms of angle of repose ($< 40°$) (Lin and Kao, 1989) except for FII (40.4°), probably due to its high content of ERL (ES:ERL 0.5:1.5). However, percentage compressibility values were all less than 20 suggesting also excellent flowability of floating microparticles (Lin and Kao, 1989). Nevertheless, the larger value of parameter '*b*' (packing velocity index) in the equation of Kawakita (1964), '*k*' in Kuno's equation (Kuno, 1979) and packing factor (Ritschel et al., 1980) for FIII indicated that the rate of its floating microparticles packing process was much higher compared to that of other formulations (Table 2).

3.3. X-ray diffractometry and differential scanning calorimetry

In order to determine the physical state of the drug whether amorphous or crystalline before and after floating microparticle formulation, X-ray and DSC examinations were conducted for the pure drug, the polymers and the different formulations (Figs. 3 and 4). From X-ray patterns it is obvious that the pure drug exhibited crystalline characteristics, while polymers and all formulations showed amorphous pattern, peak of drug being absent or nearly so in case of the formulations. Moreover, the endothermic peak due to fusion of drug crystals at 99.8°C disappeared in the floating microparticle thermograms.

3.3.1. Dissolution rate study

The release of ketoprofen in 0.1 N HCl was generally low compared to that in buffer pH 6.8 for all formulation ratios studied. This is due to the fact that the drug is a weak acid (pK_a 4.55) and therefore it will be unionized and of lower solubility at lower pH values. In the absence of ERL, the release rate was very low (Fig. 5). It was found that the greater the content of ERL, the greater is the rate of drug release. ES 100 polymer, which is present in all formulations, is of low permeability and insoluble in acid medium. It is

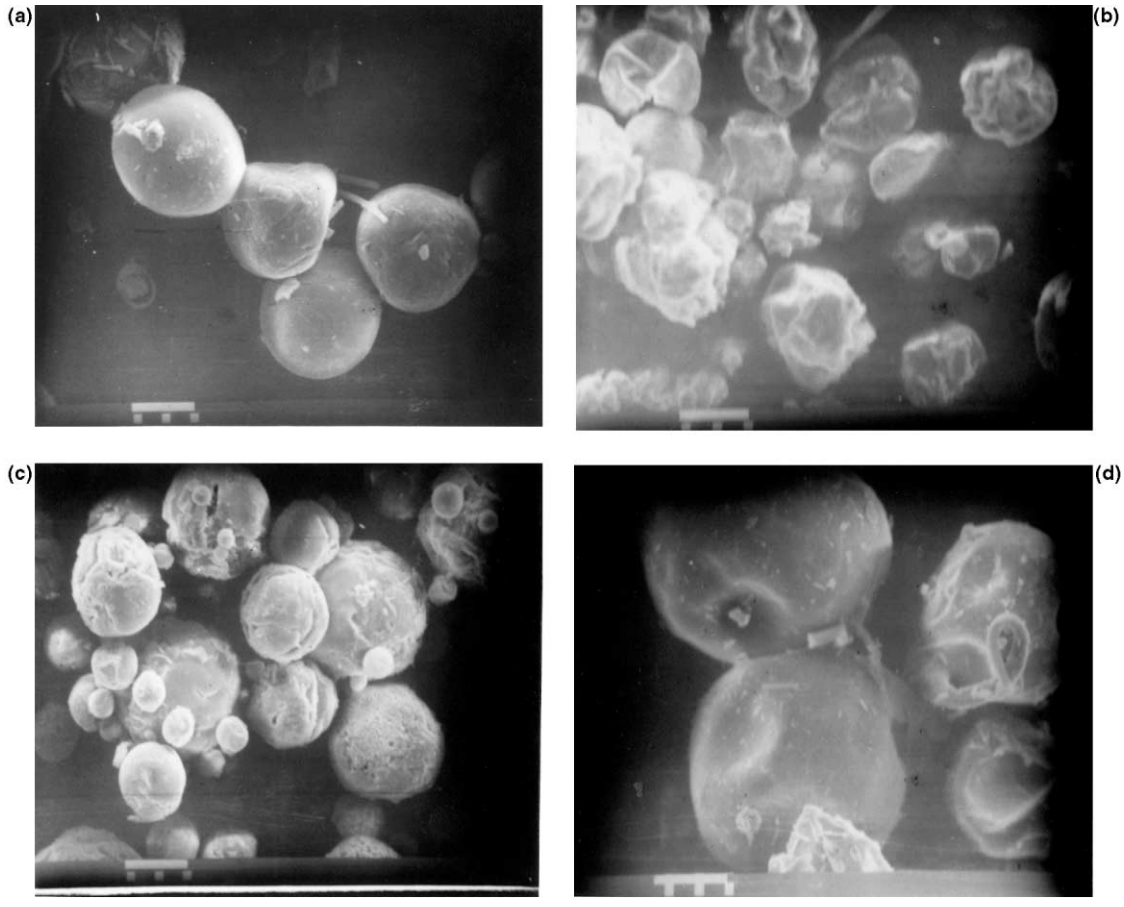

Fig. 2. Scanning electron microphotographs of different formulations of ketoprofen floating microparticles. (a) FI; (b) FII; (c) FIII; and (d) FIV.

an anionic copolymer of methacrylic acid and methyl methacrylate containing free carboxylic and ester groups. Its very low permeability results from high intermolecular attraction between its molecules. Hydrogen bonding between the hydroxyl groups of the carboxylic moiety and the carbonyl oxygen of ester groups increases the degree of compactness of the polymer and decreases its porosity and permeability. On the other hand, ERL is a copolymer of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups (Röhm Pharma, 2001). The ammonium groups present as salts give rise to permeability and act, after their dissolution, as channeling agents for the entrance of the dissolution medium through the floating microparticle wall causing its swelling. This gives an opportunity for the dissolved drug to diffuse out to the bulk medium.

Table 1
Particle size analysis of floating microparticles

Formula (ES:ERL)	Percentage particles weight		
	<250 μm	250–500 μm	>500 μm
FI (1.5:0.5)	47.48	39.92	12.57
FII (0.5:1.5)	52.07	26.05	20.24
FIII (1:1)	61.91	29.11	11.05
FIV (2:0)	38.01	39.33	21.48

Table 2
Micromeretic properties of different formulations of floating microparticles

Micromeretic properties	FI	FII	FIII	FIV
Angle of repose (°)	33.5	40.4	34.7	31.5
Bulk density (g/cm^3)				
Before tapping	0.33	0.34	0.28	0.42
After tapping	0.39	0.41	0.34	0.47
Packing factor	1.2	1.18	1.20	1.13
Compressibility (%)	16.8	16.0	17.8	11.4
b[a]	0.011	0.006	0.013	0.004
k[b]	0.24	0.21	0.26	0.21

[a] b is the constant of Kawakita's equation (Kawakita, 1964).
[b] k is the constant of Kuno (1979).

Based on the dissolution efficiency (Khan, 1975) as a parameter for comparison (Table 3), the results obtained at pH 6.8 showed a different trend. While the formulation formed of ES100 only, showed the least amount released in 0.1 N HCl, it gave an appreciable release in buffer pH 6.8. ES100 is an enteric coating material. So, it will start to dissolve at pH 6.8 due to ionization of carboxylic acid groups, thus allowing penetration of solvent and liberation of the drug. Moreover, formulation made of this Eudragit polymer only, left no residue at the end of the dissolution experiment as observed visually. In addition, the order of dissolution efficiency did not parallel neither the ES 100 nor ERL content of the floating microparticles (Table 3). Formulation containing 1:1 ES:ERL gave the lowest dissolution rate while that containing 0.5:1.5 ES:ERL gave the highest one (Fig. 6), suggesting a mixed effect due to the presence of two different types of Eudragit. Both the high degree of hydration of ERL leading to formation of hydrated channels, associated with the dissolution of ES100, determined the release of drug at pH 6.8.

The mode of drug release from floating microparticles was evaluated using the semi-empirical equation $M_t/M_\alpha = Kt^n$ (Peppas, 1985).The value of n (Table 3) fell within the range of 0.2–0.5, and of 0.7–0.93 in 0.1 N HCl and buffer pH 6.8, respectively, suggesting that drug release mechanism changed with change of the pH of the medium and ratio between SE100 and ERL. A value of n around 0.5 indicates Fickian release while values of n near to one indicate non Fickian release in which the rate of dissolution medium uptake into the polymer is largely determined by

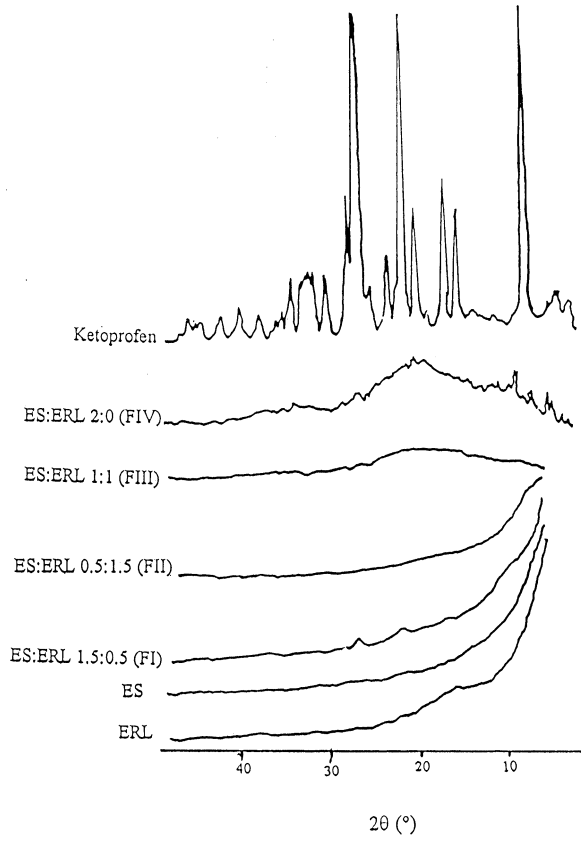

Fig. 3. X-ray diffraction patterns of ketoprofen, Eudragit polymers and different floating microparticle formulations.

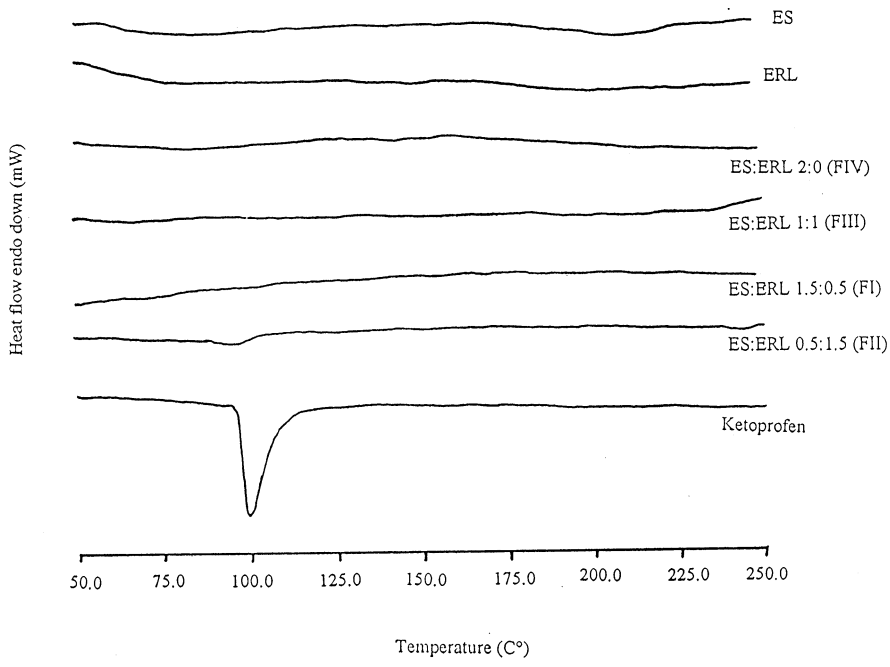

Fig. 4. DSC thermograms of ketoprofen, Eudragit polymers and different floating microparticle formulations.

relaxation of the polymer chains. In the presence of ERL, accessibility of the drug depends on the number of fluid filled channels after dissolution of the quaternary ammonium groups and its diffusion through the formed pores. On the other hand, ES100, at pH 6.8 undergoes gradual dissolution, thus allowing for escape of the drug. From the release study, it could be concluded that by changing the ratio between ES100 and ERL, the rate of release of ketoprofen could be controlled.

3.3.2. Floating ability

The floating ability pattern differed according to the formulation tested and the medium used suggesting interplay between various factors. FIII composed of ES100:ERL, 1:1, gave the best floating ability in all media, as evidenced by the percentage of particles floated at different time intervals (Table 4). This can be mainly due to its low bulk density value obtained before and after tapping, respectively, (Table 2). Moreover, its high packing velocity (b and k values) plus its high packing factor (Table 2) mean that the inter-void spaces is relatively low. In addition, the high population of small size floating microparticles and low population of big ones (Table 1), allow for a more complete and effective filling of avail-

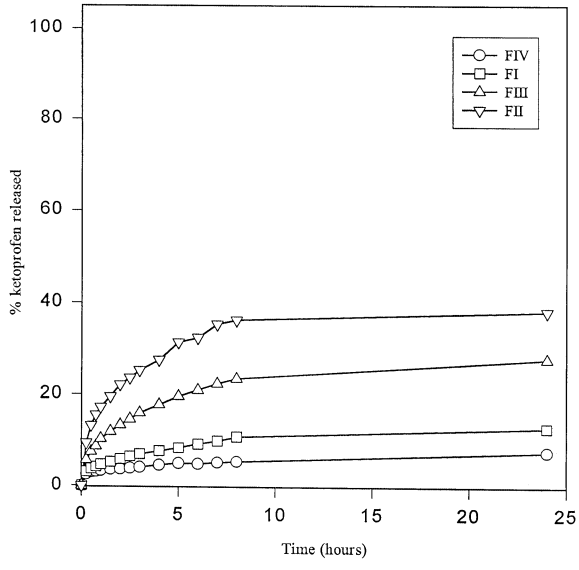

Fig. 5. Dissolution profiles of ketoprofen from different floating microparticle formulations in 0.1 N HCl.

Table 3
Dissolution efficiency (DE) and n values for the prepared floating microparticles in 0.1 N HCl and at pH 6.8

Formula (ES100:ERL)	DE[a] (%)		n[b]	
	0.1 N HCl	pH 6.8	0.1 N HCl	pH 6.8
FI (1.5:0.5)	7.40	64.10	0.34	0.70
FII (0.5:1.5)	26.60	74.80	0.50	0.93
FIII (1:1)	16.70	57.90	0.44	0.70
FIV (2:0)	4.30	66.90	0.20	0.90

[a] DE, dissolution efficiency (Khan, 1975).
[b] n: $M_t/M_\alpha = Kt^n$ (Peppas, 1985).

able liquid surface. The best medium tested was 0.1 N HCl containing Tween 20 followed by 0.1 N HCl and then by simulated gastric fluid. Tween 20, by lowering surface tension counteracts the downward pulling at the liquid surface, while the relatively high surface tension of simulated gastric fluid causes the highest decrease of area at the air fluid interface. Although the formulation contains a percentage of the permeable ERL, yet the surface of floating microparticles is regular. This would decrease points of contact and therefore the opportunity of aggregate formation upon hydration.

Compared to FIII, the formulation without ERL content (FIV) exhibited a lower ability of floating. This can be attributed to its high bulk density before and after tapping (Table 2). Moreover, it possesses high population of big size floating microparticles that would not fill effectively the available liquid surface (Table 1). On the other hand, FII showed the least percent weight of floating microparticles in all media, in particular 0.1 N HCl containing Tween 20, while simulated gastric fluid was the best medium for floating. Tween 20 would increase wetting and therefore hydration of the permeable ERL with subsequent replacement of air inside the floating microparticles by liquid. Moreover, the floating microparticle surface exhibited invaginations creating points of contact and increasing the possibility of aggregation and sinking with time. However, sodium chloride content of simulated gastric fluid would act to decrease hydration of ERL (Bonferoni et al., 1995). A similar trend was exhibited by FI regarding the effect of medium but the floating ability was of higher magnitude than in case of FII. This may be due to the lower bulk density (Table 2) and ERL content of FI (ES100:ERL, 1.5:0.5), in addition to its higher packing rate (b and k values, Table 2).

In conclusion, the floating microparticles of ketoprofen prepared with a suitable ratio of ES 100 to ERL, may provide a convenient dosage form for achieving best performance regarding flow, release and floating properties.

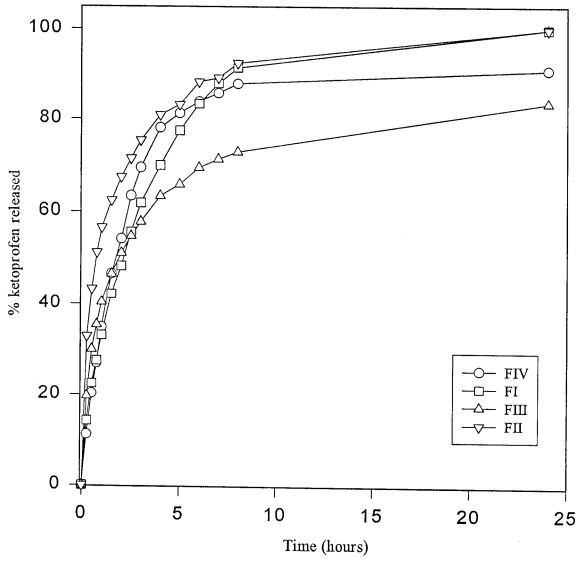

Fig. 6. Dissolution profiles of ketoprofen from different floating microparticle formulations in buffer pH 6.8.

Table 4
Percentage floating of different formulations of floating microparticles in different media

Formula	Percentage microparticles floated											
	0.1 N HCl				0.02% Tween 20 in 0.1 N HCl				Simulated gastric fluid			
	1 h	2 h	4 h	6 h	1 h	2 h	4 h	6 h	1 h	2 h	4 h	6 h
FI (1.5:0.5)	56	44	28	24	48	32	32	22	64	64	50	40
FII (0.5:1.5)	20	18	16	14	18	18	14	10	30	26	20	18
FIII (1:1)	86	82	80	64	90	86	86	74	78	74	60	58
FIV (2:0)	58	56	42	32	48	48	40	20	56	34	26	22

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