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Original Research Article

Development and *In vitro* Evaluation of Flurbiprofen Microcapsules Prepared by Modified Solvent Evaporation Technique

Muhammad Farhan Sohail[1], Pervaiz Akhtar Shah[2], Imran Tariq[2]*, Syed Saeed-ul-Hassan[2], Umair Amin[2], Syed Atif Raza[2], Tariq Saeed[2], Misbah Sultana[2] and Najam ul Hassan Jawa[2]

[1]Riphah Institute of Pharmaceutical Sciences, Riphah international University, Islamabad, Pakistan -54000; [2]University College of Pharmacy, University of the Punjab, Lahore, Pakistan 54000

For correspondence: **Email: imran_1982@hotmail.com; **Tel:** 0092-322-4218583, 42-36156006*

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Abstract

Purpose: *To develop modified release microcapsules of flurbiprofen for sustained release and reduced gastrointestinal side effects.*
Method: *A co-polymer containing Eudragit RS 100 and hydroxypropyl methylcellulose (HPMC) in different drug/co-polymer ratios was used for microencapsulation of flurbiprofen by modified emulsion solvent evaporation (MESE) technique. The microcapsules were evaluated by x-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infra-red spectroscopy (FTIR) and scanning electron microscopy (SEM). Dissolution study was conducted in 0.1 M HCl for 2 h and phosphate buffer (pH 7.4) for 8 h, and the resulting data were analyzed by various pharmacokinetic models.*
Results: *The data obtained from pre-formulation confirmed the purity of flurbiprofen. Particle size, flow rate and angle of repose showed good flow properties. FTIR and DSC confirmed the absence of incompatibilities among the drug and polymers. XRD of flurbiprofen showed characteristic sharp peaks confirming the crystalline nature of the drug which, however, decreased slightly in the formulation. SEM revealed that microencapsules of spherical shape and rough surface were produced at lower drug to co-polymer ratio in contrast to the higher ratio which produced irregular microcapsules. Encapsulation efficiency was 65 - 85 % while regression coefficient (R2) values from kinetic analysis showed that release followed Korsmeyer-Peppas model with "n" > 1 indicating release mechanism followed super case II transport.*
Conclusion: *MESE technique using Eudragit RS 100/HPMC polymer blend is a suitable approach to development of modified release flurbiprofen microcapsules.*

Keywords: *Microcapsules, Eudragit RS-100, Hydroxypropyl methylcellulose, Emulsion solvent evaporation, Flurbiprofen, Sustained drug release*

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INTRODUCTION

A well designed modified drug delivery system can overcome many of the problems of conventional dosage forms and enhance the therapeutic efficacy of the administered drug [1]. Microencapsulation is one of such techniques by which solid, liquid or even gas molecules can be coated with a very thin wall material converting them to free flowing particles [2].

Eudragit RS 100 is a polymethacrylate, with a chemical names such as poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), having low amount of quaternary ammonium attached which gives pH-independent permeability and renders the film form by RS 100 less permeable to water [3]. It is a versatile polymer with a wide range of applications in development of transdermal delivery system, modified release dosage forms, ocular formulations, oral delivery system and Nano particles formulation [4]. HPMC is a white, colourless, odorless powder which is available in various forms and grades [3]. It is a multi-purpose material having wide pH stability and used as binder, coating agent, suspending agent, emulsifying agent, release retardant and thickening agent in different formulations depending on the grade and concentration used [3,5].

Flurbiprofen, a, 2-(2-flurobiphenyl-4yl) propionic acid belongs to a group of non-steroidal anti-inflammatory drugs used for the treatment of mild to moderate pain [6]. They impart their action by inhibiting the synthesis of prostaglandins involved in pain and inflammation [7]. There are many methods for microencapsulation and selection of method depends on hydrophilicity or hydrophobicity of the drug [8].

The present work was aimed to study the development and evaluation of microencapsulated flurbiprofen by modified solvent evaporation technique using varying polymer ratios, for modified release of the drug.

EXPERIMENTAL

Materials

Eudragit RS 100 and HPMC 4000 cps were gifts by Surge Laboratories Pvt. Ltd. Lahore, Pakistan. Flurbiprofen was a gift from Schazoo Laboratories Pvt. Ltd. Lahore Pakistan. Acetone, n-hexane, petroleum ether 40 – 60 ^{o}C (research grade, Merck), liquid paraffin (commercial grade, UCP Laboratories, Lahore, Pakistan), Span 20 (Pdh Pharmaceuticals, Lahore Pakistan), and magnesium stearate (commercial grade, purchased from a local store, Lahore, Pakistan) were also used in this study.

Formulation of microcapsules

A total of twelve formulations with varying polymer ratios were prepared as stated in Table 1. For this purpose the weighed amount of polymer was dissolved in 25 ml acetone; by stirring the mixture at 600 rpm for 15 min, using magnetic stirrer. The weighed amount of flurbiprofen was dispersed in liquid paraffin already containing 1 % w/w span 20 and magnesium stearate while stirring at 800 rpm for 15 min. The polymer solution was then added slowly to this dispersion using burette. After 10 – 15 % of polymer addition, n-hexane was added to the liquid paraffin mixture. The mixture was stirred at 800 rpm at room temperature (25 ± 2 °C) for 4 h until the acetone and n-hexane were completely evaporated. Liquid paraffin was decanted off, the microcapsules collected, washed with n-hexane thrice to remove any remaining oil phase, and then dried at room temperature for at least 12 h. The formulations were stored in an air-tight glass container and placed in a desiccator containing silica beads. The same procedure was done for all the formulations.

In vitro characterization

Percentage yield, actual drug loading, encapsulation efficiency were determined as previously described [8].

Scanning electron microscopy (SEM)

Surface morphology was performed by using JEOL JSM 6480, Japan, with image analysis system. The sample was prepared by fixing the prepared microcapsules to double sided conducting tape, which was fixed to a brass specimen stub coated with gold. The samples were run at accelerating voltage of 15 kV at high vacuum mode.

Fourier transformed infrared (FTIR) spectroscopy

The compatibility of flurbiprofen and polymers was studied through FTIR analysis. The FTIR study was performed using Nicolet FTIR 6700 with zinc selenide optics, Thermoscientific, USA. For analysis, very small quantity of sample was placed on the lens of equipment directly with the help of spatula and pressure was applied through screwed up to the specified mark. The spectrum was recorded between 4000 - 500 cm^{-1}.

Differential scanning calorimetry (DSC)

Thermal analysis was performed with DSC Q 2000, TA instruments, USA. The weighed amount (10 mg) of sample was sealed in aluminum pan. The analysis was performed at nitrogen flow of 40 ml/min and scanning was done at the heating rate of 10 ^{o}C/min from 25 ^{o}C

Table 1: Composition of microcapsule formulations

Formulation code	Polymer ratio	Drug : polymer	Drug (mg)	HPMC (mg)	Eudragit RS-100 (mg)
A1	75 % HPMC	1 : 0.5	2000	750	250
A2	25 % Eudragit	1 : 1	2000	1000	1000
A3		1 : 1.5	2000	2250	750
B1	75 % HPMC	1 : 0.5	2000	750	250
B2	25 % Eudragit	1 : 1	2000	1000	1000
B3		1 : 1.5	2000	2250	750
C1	75 % HPMC	1 : 0.5	2000	750	250
C2	25 % Eudragit	1 : 1	2000	1000	1000
C3		1 : 1.5	2000	2250	750
F1	100 % HPMC	1 : 1	2000	2000	0
F2	100% Eudragit	1 : 1	2000	2000	0
F3	Reference drug	0	100	0	0

to 200 ^{o}C using empty aluminum pan as reference.

Powder x-ray diffraction (PX-RD)

Powder XRD was performed to check the effect of different formulation on crystallinity of the drug.

***In vitro* dissolution studies**

The *in vitro* release of flurbiprofen was determined using USP dissolution apparatus type I with basket assembly. The weighed amount of microsphere equivalent to 100 mg of flurbiprofen was filled in inert hard gelatin capsule and placed in basket of dissolution apparatus. For the first two hours the microspheres were run in acidic media using 900 ml of 0.1 M HCl. The temperature was maintained at 37 + 0.5 ^{o}C and the apparatus was set at 100 rpm. Samples were collected at predefined intervals, i.e., 15, 30 min, 1 h and 2 h. 10 ml of sample was collected using a syringe and the sample was filtered using 0.45 µm filter paper and was replaced with same amount of fresh acidic solution pre-warmed at 37 ^{o}C. After 2 h, the dissolution media was replaced with 900 ml of phosphate buffer pH 7.4 to perform further dissolution studies. Samples were collected at hourly intervals up to 12 h and then after 24 h. All samples were diluted with phosphate buffer and analyzed at a wavelength of 247 nm spectrophotometrically (model UV 2550, Shimadzu, Japan).

Release kinetics

Dissolution data was analyzed using various kinetic models: zero order, first order, Higuchi's model, Hixon-Crowell and Korsmeyer-Peppas to determine the release kinetics of the formulations.

Determination of similarity factor (f2)

For comparison of the *in vitro* dissolution profiles of the standard reference drug (flurbiprofen, Ansaid® tablet) and the test drug formulations, similarity factor (f2) was determined. Its value ranges from 50 - 100. Values > 50 show dissimilarity while < 50 indicate similarity in in vitro release drug profile [10].

$f_2 = 50 + \log \{[1+ (1/n)? t=1 * n (Rt-Tt)2]-0.5 *100\}...(1)$

where Rt and Tt are the cumulative percentage dissolved at each of the selected 'n' time points of the reference and test product, respectively.

Statistical analysis

For statistical analysis, one-way ANOVA was performed to check the release profile using SPSS version 12.0. The level of significance was set at $p < 0.05$.

RESULTS

Drug loading and encapsulation efficiency

Drug loading percentage showed maximum in formulation A3 (52.9 %) and least with C3 (25.79 %). As with an increase in drug polymer ratio drug loading decreased. Maximum encapsulation is also shown by A3 (85 %) and minimum by C3 (65 %). As Eudragit proportion increased in the co-polymer blend, drug loading decreased (Table 2).

Yield

The yield of the formulations was maximum for C2 (98 %) and minimum for C3 (81 %) (Table 2).

Table 2: Yield, drug loading and encapsulation efficiency of formulations

Formulation	Yield (%)	% Drug loading (%)	Encapsulation efficiency (%)
A1	86.000	52.935	84.696
A2	88.567	38.141	76.280
A3	91.967	28.647	71.613
B1	84.775	45.340	72.544
B2	92.325	33.473	66.950
B3	86.250	28.014	70.038
C1	85.000	42.967	68.744
C2	97.600	32.761	65.520
C3	80.860	25.799	64.500
F1	88.100	33.552	67.100
F2	86.975	30.783	61.570

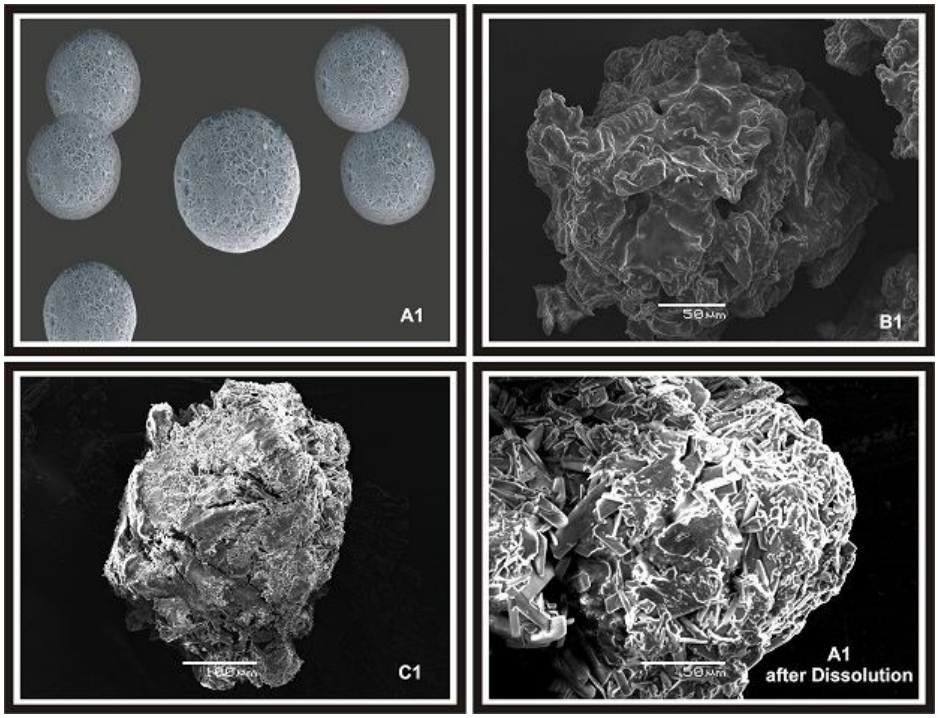

Figure 1: SEM of formulations A1, B1, C1 and A1 after dissolution

Scanning electron microscopy (SEM)

SEM revealed that the particle size of microcapsules ranged from 10 to 50 µm. The microcapsules formed were of irregular in shape except for A1 which was spherical in shape with slightly rough surface It is observed that with an increase in polymer ratio, the surface became rough and irregular in shape. SEM analysis of microencapsules after 10 h dissolution showed surface erosion and diffusion mechanism as presence of channels on surface (Figure 1).

Infrared spectra

FTIR spectrum of flurbiprofen gives characteristic sharp peak at 1694.9 representing the presence of (C=O) carbonyl compound, peak at 1215.6 represents stretching of (C-F) and a characteristic broad peak of flurbiprofen in the range of 2,500 – 3,300 cm^{-1} due to hydrogen bonding. Spectra of formulation A1 showed the same absorbance pattern as the combination of drug and polymers (Figure 2).

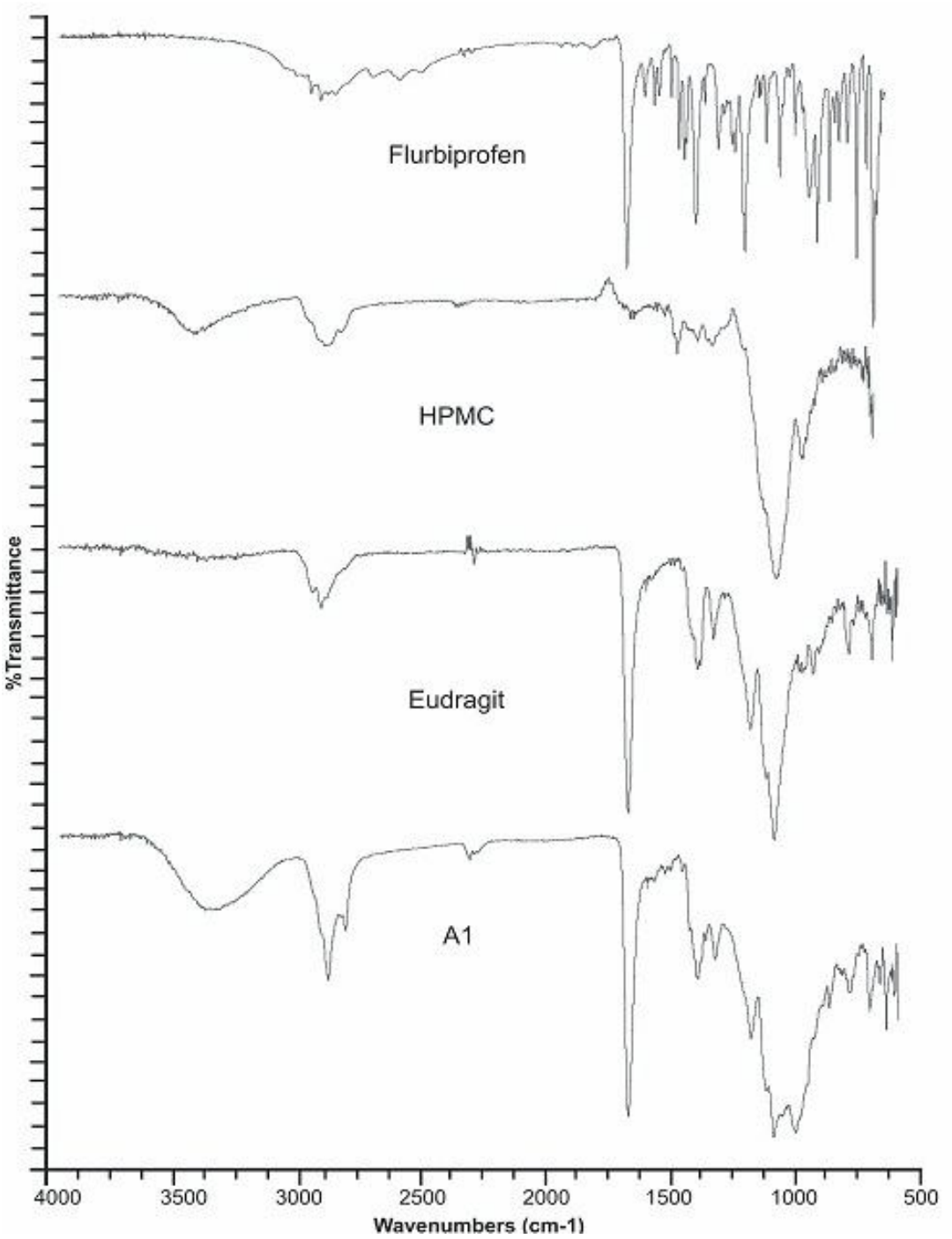

Figure 2: FT-IR spectrum of flurbiprofen, HPMC, Eudragit and formulation A1

Thermal properties

Thermal analysis was performed to check the stability and compatibility of the drug with polymers. Thermogram of pure flurbiprofen given in the figure above gives a sharp endothermic peak at 119.86 ^{o}C. The thermograms of HPMC and Eudragit RS 100 as well as formulation A1 (Fig 3) showed that there is a decrease in the sharpness of the peak as clearly visible from the thermograms.

Powder x-ray diffraction (PX-RD)

The XRD pattern of flurbiprofen showed the characteristic peaks of 2θ at 30.256^{o} and 34.182^{o}. XRD pattern of formulation A1 showed the characteristic peak in the same region with slight depression in the sharpness from 30.256^{o} to 29.014^{o} and 34.182^{o} to 33.453^{o} showed a little reduction in crystallinity of flurbiprofen (Figure 4).

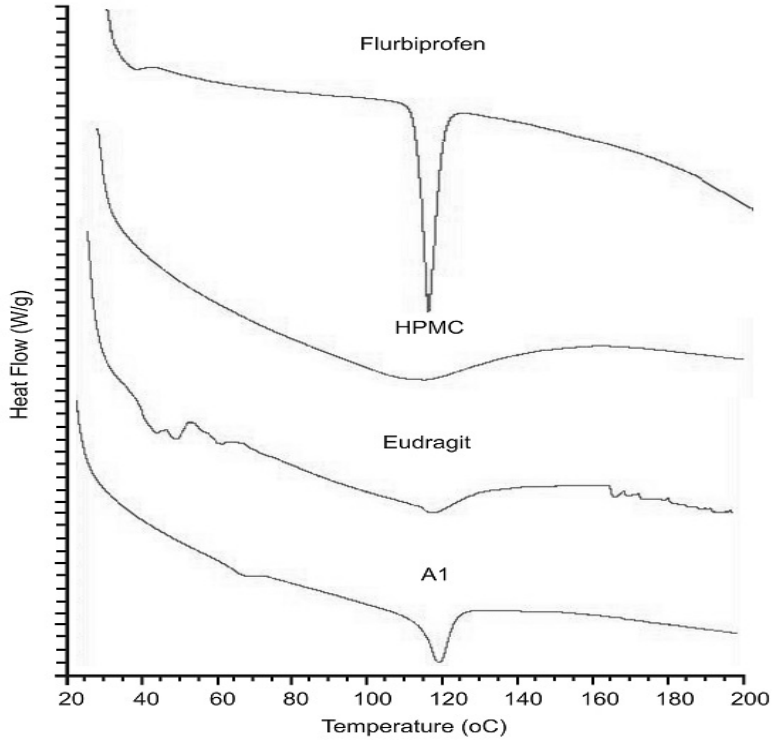

Figure 3: Thermograms of flurbiprofen, HPMC, Eudragit and formulation A1

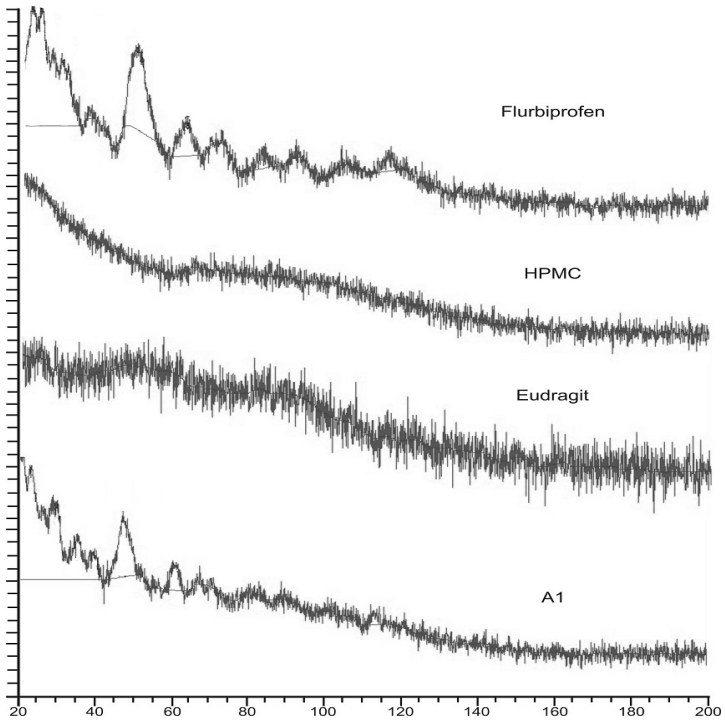

Figure 4: Powder XRD studies of Flurbiprofen, HPMC, Eudragit and Formulation A1

In vitro dissolution

The cumulative release (Figure 4) revealed that with an increase in drug polymer ratio, release of the formulations were decreased. It was also observed that as Eudragit RS 100 concentration increased, drug release was decreased accordingly. The formulation A1 having least Eudragit concentration gave 85.04 % release whereas C3 having highest ratio gave least release of 45.77 % (Fig 5).

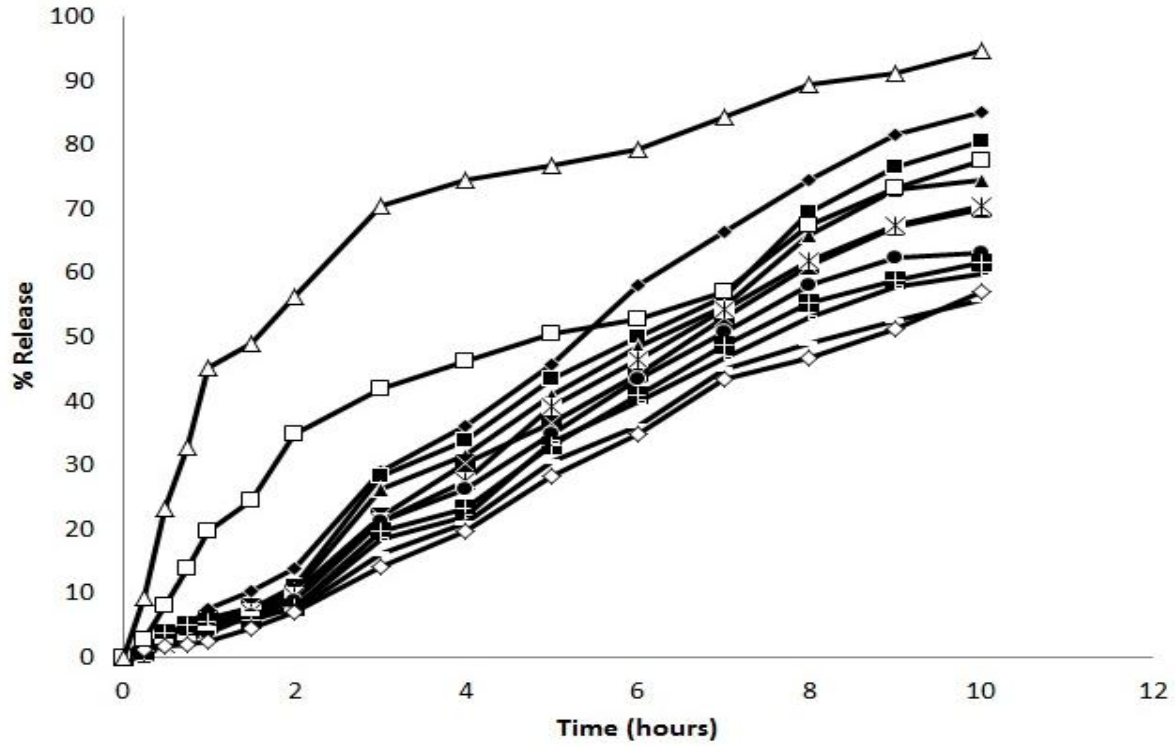

Figure 5: Cumulative drug release profiles of the formulations

Key: A1 A2 A3 B1 B2 B3 C1 C2 C3 F1 F2 F3

Table 5: Drug release kinetic data

	Zero order		First order		Higuchi		Hixon-Crowell		Korsmeyer-Peppas	
Formulations	R^2	k_0	R^2	$k1$	R^2	kH	R^2	kHC	R^2	n
A1	0.9930	9.054	0.9561	0.142	0.8519	22.685	0.9760	0.041	0.9930	1.001
A2	0.9912	8.319	0.9544	0.124	0.8376	20.757	0.9720	0.036	0.9919	1.045
A3	0.9897	7.879	0.9594	0.114	0.8350	19.645	0.9747	0.034	0.9903	1.045
B1	0.9938	7.328	0.9674	0.103	0.8423	18.304	0.9806	0.031	0.9943	1.039
B2	0.9902	7.411	0.9615	0.105	0.8308	18.454	0.9757	0.031	0.9914	1.062
B3	0.9865	6.837	0.9668	0.094	0.8316	17.043	0.9776	0.028	0.9871	1.043
C1	0.9882	6.516	0.9673	0.088	0.8335	16.260	0.9779	0.027	0.9890	1.052
C2	0.9891	6.328	0.9698	0.084	0.8336	15.783	0.9796	0.026	0.9899	1.053
C3	0.9891	5.860	0.9725	0.076	0.8319	14.607	0.9809	0.023	0.9901	1.058
F1	0.9861	5.688	0.9612	0.073	0.8056	14.062	0.9717	0.022	0.9924	1.152
F2	0.8701	8.750	0.9678	0.148	0.9687	22.977	0.9483	0.042	0.9831	0.605
F3	0.4537	12.147	0.9495	0.384	0.9372	33.128	0.8920	0.106	0.9658	0.395

Release kinetic data

When cumulative release was subjected to kinetic modeling, all the formulations followed Korsmeyer-Peppas equation with super case II transport mechanism except F2 which followed non-Fickian transport.

Similarity factor

The similarity factor (f2) for A1, A2, A3, B1, B2 and B3 was 32, 31, 30, 30, 29 and 29 respectively, while for formulations C1, C2, C3, F1 and F2, it was 29, 29, 28, 28 and 41, respectively. So, the release profiles of the test formulations were different from that of the reference standard (F3).

DISCUSSION

The results of the proposed study, presented in Table 2 showed that "F2" (Eudragit alone) produced larger particles as compared with particles of "F1" (HPMC alone). Higher concentration of Eudragit RS 100 resulted in increased viscosity of the system thus increasing the particle size [9,10]. FTIR spectrum of flurbiprofen showed the presence of (C=O) carbonyl compound. Absorbance below 1700 cm^{-1} gives an idea of conjugation with another carbonyl group or aromatic ring [11,12]. FTIR spectrum of physical mixture showed little change in the position and sharpness of the peaks [12,13]. This alteration could be due to variations in the resonance structure, stretching and bending, rotation of a part of molecule or certain bonds or minor distortion of bond angle during formulation development [14]. Thermogram of pure flurbiprofen gave a sharp endothermic peak which represented the melting point of pure flurbiprofen and confirmed the crystalline structure [15]. Thermogram of HPMC and Eudragit RS 100 represented the amorphous nature of the substances. Formulation "A1" presenting a decrease in sharpness of the peak along with slight shift in temperature showing decrease in crystallinity of the substance [12]. XRD pattern of formulation A1 presented the characteristic peak in the same region with slight depression in the sharpness showed a little reduction in crystallinity of flurbiprofen. All the formulations showed a good sustained release profile. Kinetic model showing highest value of coefficient was selected as best fit model for release kinetics. All the formulations followed Korsmeyer-Peppas model with super case II transport mechanism except F2 which followed non-Fickian transport [12].

CONCLUSION

Modified emulsion solvent evaporation technique has been successfully employed for flurbiprofen microencapsulation into Eudragit RS 100 and HPMC co-polymer coats. No physical or chemical interaction was observed among the drug and polymer used. It is possible to develop a modified release formulation of flurbiprofen with minimum dose related side effects and improved patient compliance.

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