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Original Article

ONCE DAILY IMMEDIATE-AND EXTENDED-RELEASE BILAYER TABLETS OF ETORICOXIB: A STUDY ON THE RELEASE KINETICS

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ABSTRACT

Objective: In the present work, the main objective was to develop bilayer extended release matrix tablets of etoricoxib by providing a loading dose followed by maintenance dose that expected to improve the therapeutic efficacy of the medication with less toxic effect.

Methods: Bilayer tablets of etoricoxib was developed successfully with the meticulous proportion of release controlling Hydroxy propyl methyl cellulose K100 (HPMC K100) and lactose. The tablets were prepared by wet granulation technique. Granules for immediate layer and extended layer for different formulations were prepared separately. The formulations were developed and evaluations were performed to examine the parameters that affect the in vitro performance of the tablets. The drug-excipient compatibility was ensured by Fourier transform infrared spectroscopy (FTIR) study.

Results: The values of physical parameters of all formulations were found within appreciable limit. Formulation containing HPMC K 100 and lactose in the proportion of 2:1 in the extended release layer was able to release 26.22% of drug in 15 min and shown a steady release of drug for an extended period of 12 h. The dissolution data was put in Korsemeyer–Peppas model in order to find out n value, which describes the drug release mechanism. The n-value of different formulations were found to be variable. The Fourier transform infrared spectroscopy (FTIR) study revealed absence of any other new peaks and also no differences in the positions of the absorption bands in the bilayer tablet F8 that indicate the lack of significant interactions between etoricoxib and other excipients.

Conclusion: It had been concluded that once daily immediate-and extended release bilayer tablet of etoricoxib can be formulated with profound physical characteristics and dissolution properties. This resulted in reducing the daily dose and thus minimise the cardiovascular toxicity of etoricoxib.

Keywords: Etoricoxib, Bilayer technology, Once daily tablet, Release kinetics

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INTRODUCTION

Etoricoxib; (5-chloro-2-[6-methyl pyridin-3-yl]-3-[4-methyl sulfonyl phenyl] pyridine) is a selective second generation cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug [1, 2]. However, the drug possesses a saturation solubility of 78.48±1.47 µg/ml. This leads to formulation problems and limit its therapeutic efficacy by delaying the rate of absorption and the onset of action [3].

The recommended dose for etoricoxib is between 60 and 120 mg/day. It has an estimated logP of 3.14 and pKa of 4.6. Pharmacokinetic studies reveal that despite of a potent drug for osteoarthritis, it suffers from severe cardiovascular toxicity issues. The cardiovascular risks of etoricoxib may increase with dose and duration of exposure. Therefore the possible lowest effective daily dose should be developed to combat this problem [4].

Recently, multilayer tablets have been gaining importance for enhancing the formulation efficacy and improving the patient compliance by reducing the dosing burden [5, 6]. Moreover, the release profiles can be modified using multiple compatible components in the multilayer tablet strategy [7, 8]. In bilayer tablet technology, one is for immediate-release layer and the other is for modified-release layer. The immediate-release layer will disintegrate rapidly and transiently after oral administration, thus providing enough drug for immediate onset of action while, on the other hand, the modified-release part will dissolve slowly in the gastrointestinal tract to maintain a steady drug release.

The rationality of the present study was to explore the feasibility of developing a bilayer tablet strategy, a once daily immediate-and extended-release formulation of etoricoxib. The fast release of drug from the immediate release layer achieve the quick onset and the extended release of drug capable of maintaining the therapeutic level. This resulted in reducing the daily dose and thus minimise the cardiovascular toxicity of etoricoxib. In this study the formulations were developed, and evaluations were performed to examine the parameters that affect the *in vitro* performance of the tablets.

A novel once daily immediate-and extended-release drug delivery system of etoricoxib was developed for the following reasons: 1) To synchronize drug delivery to achieve quick onset of action in severe pain; 2) To prolong therapeutic effect by continuously releasing the medication over an extended period of time after administration of a single dose; 3) To minimize the frequency of drug administration by developing a once daily therapy; 4) Improved therapy can be provided as the drug exerts its action at a time when it is needed most and dose related side effects could be minimized; 5) Patient convenience and compliance could be achieved.

MATERIALS AND METHODS

Materials

Drug etoricoxib was obtained as a gift sample from Hetero drugs, Baddi, India. HPMC K 100 M, HPMC E5 and croscarmellose sodium were procured from Colorcon Asia Pvt. Ltd., Goa, India. Microcrystalline Cellulose, Lactose, starch, Talc and magnesium stearate were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Poly Vinyl Pyrollidone was bought from SD Fine Chem Limited, Mumbai, India. The materials that were of AR/lR grade and were used as supplied by the manufacturer without further purification or investigation.

Methods

Preparation of bilayer tablet

The tablets were prepared by wet granulation technique. Granules for immediate layer and extended layer for different formulations were prepared separately. The composition of two layers of tablets are depicted in table 1 [9].

Extended release layer of etoricoxib

The granules of the extended release layer were prepared by the wet granulation method. After being grinded and sifted through sieve no 60, the drug was mixed thoroughly with other inactive ingredients excluding talc and subsequently passed through a 16-mesh screen to

blend the ingredients uniformly. The mixture was granulated using 3% (w/w) PVP in a 90% ethanol solution as binder and then pressed through a 20-mesh screen to prepare wet granulates. After drying at 45 °C for 1 h in an oven, the granules were sieved through an16-mesh screen and then mixed with talc for the following table ting process.

Immediate release layer of etoricoxib

The granules of the immediate release layer containing etoricoxib and other excipients (table 1) were fabricated by a similar procedure described above. The superdisintegrant and talc of specified amount were added after granulation.

Preparation of bilayer matrix tablets

The bilayer tablets were fabricated with a single-punch tablet machine (Cadmach-Ahmedabad) via a single compaction method. Briefly, the weighed granules were sequentially fed manually into the die cavity and then compressed into tablets under pressure between 3 and 15 kg/cm^2. Table 1 exhibits the detailed formula compositions for the bilayer tablets. The size batch was 100 tablets for each formulation.

Table 1 Formulation composition for bilayer tablet

Excipients	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Extended release layer										
Etoricoxib (mg)	60	60	60	60	60	60	60	60	60	60
HPMC K100 (mg)	60	60	60	60	45	45	60	60	30	30
Lactose (mg)	-	-	-	-	45	45	30	30	60	60
PVP (%)	3	3	3	3	3	3	3	3	3	3
Talc (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Immediate release layer										
Etoricoxib (mg)	30	30	30	30	30	30	30	30	30	30
HPMC E5	30	-	-	-	-	-	-	-	-	-
Lactose (mg)	-	-	30	-	30	30	30	30	30	30
MCC (mg)	-	30	-	-	-	-	-	-	-	-
Starch (mg)	-	-	-	30	-	-	-	-	-	-
Croscarmellose Sodium (%)	3	3	3	3	3	4	3	4	3	4
PVP (%)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

*PVP-poly vinyl pyrollidone; HPMC-Hydroxy propyl methyl cellulose; MCC-micro crystalline cellulose

Evaluation of etoricoxib bilayer tablet

Flow property of granules

The flow characteristics of the granules of both immediate and extended layer were examined through determining inter particle porosity, Hausner ratio and Carr's index [10, 11]. All the determinations were done in triplicate and the mean values were reported.

Physical parameters of bilayer tablets

Weight variation, thickness and diameter uniformity, hardness and friability of different batches of bilayer tablets were performed. Twenty tablets were selected randomly from the lot and weighed individually by using digital balance and the weight variation of individual tablet from its mean value was calculated. The thickness and diameter of the tablets in mm was measured by vernier calliper scale. The hardness of the tablets (kg/cm^2) was determined in triplicate using Monsanto Hardness Tester [12]. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (W_o) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The final weight of the tablet (W_t) was measured. The % friability was calculated by,

$$F = [1 - \frac{W_t}{W_0}] X100 \text{ ---------- (1)}$$

Content uniformity

Three tablets were selected randomly from each batch and triturate by mortar and pestle. The powder equivalent to 100 mg of etoricoxib was taken into three different 100 ml volumetric flasks. To each of it, 100 ml of ethanol was poured, sonicated for 10 min and kept for 24 h away from light. The solutions were filtered through whattman filter paper and the filtrate was analysed in UV-Visible spectrophotometer at 282 nm. The unknown concentration of the drug was determined using standard calibration curve.

***In vitro* drug release study**

The release of etoricoxib from different formulations was monitored using standard USP dissolution apparatus No. 2 (Paddle method). Three tablets from each formula were individually tested. The dissolution was performed in 900 ml of Phosphate buffer pH 7.4 for 12 hour. The stirring rate was 50 rpm±1 and the temperature was maintained at 37±0.5 °C. Aliquots of 5 ml were withdrawn manually at predetermined time points till 12 h and replaced with same quantity of fresh preheated (at 37 °C) dissolution medium. Samples were measured spectrophotometrically at λ= 282 nm. The amount released was calculated from the regression line of the standard calibration curve developed in the same medium [13, 14].

Kinetics of drug release

To analyze the drug release rate kinetics and mechanism of drug release from the bilayer tablets, the *in vitro* dissolution studies data was fitted into Zero order, First order, Higuchi, Hixon crowell and Korsmeyer Peppas models. Co-relation coefficient (R^2) value were the determinant for the best-fit of the model [11].

FTIR-ATR spectroscopy

FTIR spectra were recorded at room temperature in the mid-IR range (500–4000 cm^{-1}) on a Bruker Alfa FTIR spectrometer equipped with a Bruker ZnSe ATR accessory with a single reflection ZnSe crystal. Each spectrum was averaged over 24 scans with a resolution of 4 cm^{-1}. A background scan was recorded prior to the measurement and subtracted from the sample spectra. For each sample, the initial aqueous solution was placed directly on the ATR ZnSe and the spectrum recorded. The ATR correction to each spectrum was applied using the OPUS software. The spectra were normalized to the same area and compared to each other. To get some insights into the conformational differences of the investigated samples, some spectral ranges were analyzed.

RESULTS AND DISCUSSION

Evaluation of immediate and extended layer granules

Flow properties of immediate release layer granules and extended release layer granules

The immediate layer granules and extended layer granules of all formulations were determined and the results were depicted in table 2. The result of flow property study revealed that the granules

have good flowability against the flowability of drug that ensure the uniform flow of the granule from hopper to the die cavity as a result of reduced cohesiveness. Result of all the flow parameters were obtained within the permissible limit [15].

Table 2 Flow properties of immediate and extended release layer granules

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Inter particle porosity	Hausner's ratio	Carr's index (%)	Bulk density (g/ml)	Tapped density (g/ml)	Inter particle porosity	Hausner's ratio	Carr's index (%)
	Extended Release Layer (Limit)					Immediate release layer (Limit)				
	0-1	0-1	0-1.2	<1.2	<40	0-1	0-1	0-1.2	<1.2	<40
Drug	0.232	0.370	1.608	1.595	37.297	-	-	-	-	-
F1	0.469	0.518	0.202	1.104	9.459	0.453	0.519	0.281	1.146	12.717
F2	0.469	0.518	0.202	1.104	9.459	0.458	0.520	0.260	1.135	11.923
F3	0.469	0.518	0.202	1.104	9.459	0.576	0.611	0.099	1.061	5.728
F4	0.469	0.518	0.202	1.104	9.459	0.764	0.891	0.187	1.166	14.254
F5	0.972	1.137	0.149	1.170	14.512	0.627	0.683	0.131	1.089	8.199
F6	0.972	1.137	0.149	1.170	14.512	0.638	0.721	0.180	1.130	11.512
F7	0.472	0.507	0.146	1.074	6.903	0.627	0.683	0.131	1.089	8.199
F8	0.472	0.507	0.146	1.074	6.903	0.638	0.721	0.180	1.130	11.512
F9	0.732	0.807	0.127	1.102	9.294	0.627	0.683	0.131	1.089	8.199
F10	0.732	0.807	0.127	1.102	9.294	0.638	0.721	0.180	1.130	11.512

n= 3, All determinations were done in triplicate and the mean values are reported.

Evaluation of immediate and extended release bilayer tablets

The physical parameters for all the formulations is shown in table 3. All the tablets passed weight variation test as the average % weight variation were within the pharmacopoeia limits of ±7.5%. Tablet mean thickness (n=5) were almost uniform in all the formulations and values ranged from 3.5±0.03 to 4.5±0.06. Tablet mean diameter (n=5) were also found to be uniform all the ten formulations i.e. 7.9 mm. The standard deviation values indicated that all the formulations were within the range [9].

Table 3: Evaluation of bilayer tablet formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Average weight (mg)	182	180	182	182	252	258	253	261	254	259
Weight variation (%)	±1.56	±1.39	±2.07	±1.91	±2.30	±2.27	±2.01	±2.15	±2.03	±2.21
Thickness (mm)*	3.7	3.5	3.5	3.6	4.2	4.3	4.3	4.3	4.3	4.5
	±0.03	±0.06	±0.03	±0.06	±0.03	±0.06	±0.03	±0.06	±0.03	±0.03
Hardness (kg/cm^2)#	7.0	6.1	6.0	6.2	5.1	4.7	6.1	5.4	6.0	6.1
Friability (%)	0.187	0.243	0.142	0.174	0.183	0.119	0.324	0.286	0.232	0.327
Drug content (%)	98.86	99.45	100.05	99.39	100.01	99.78	98.97	99.93	99.65	99.09
	±1.84	±1.23	±1.39	±1.90	±1.09	±2.03	±1.53	±1.41	±1.19	±1.27

All the values are expressed as mean±SD, where *n=5and #n=3

The mean hardness values (n=3) were measured for all the formulations using a Monsanto hardness tester. The results are tabulated in table 3. The hardness values ranged from 4.7 to 7.0 kg/cm^2. The values of friability test were given in table 3. The percent friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. The results of friability test indicate that the tablets possess good mechanical strength [16].

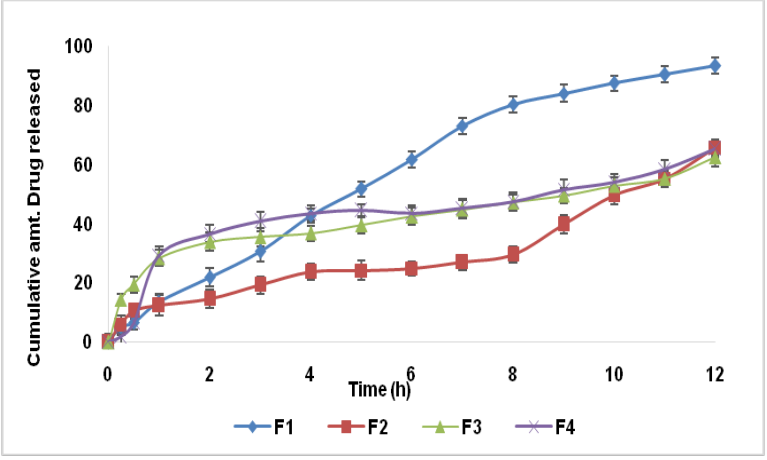

Fig. 1: Comparative n *in vitro* dissolution profile of F1, F2, F3 and F4

Content uniformity

The percent drug content value of etoricoxib was within 98.86±1.84 to 100.05±1.39. The results within range indicate uniformity of mixing.

***In vitro* drug release study**

The comparative dissolution profile of F1 to F4 and F5 to F10 are depicted in fig. 1 and fig. 2 respectively. In the formulation F1 to F4 it was observed that for the formulation containing lactose had shown a steady release rate profile as compared to formulation containing HPMC E5, Micro crystalline cellulose and starch. From formulation F1, F2 and F3 the drug was released in a slower rate not able to get a dissolution of 30% even in the first hour. It is due to the binding ability of HPMC E5, Micro crystalline cellulose and starch that retard the drug dissolution.

From F5 to F10 the extended layer contains HPMC K100 with different proportion of lactose whereas the immediate layer contains only lactose. Cross carmelose sodium was used as superdisintegrant in the immediate layer. It was observed from the dissolution profile that more than 30% of drug released in the first 15 min from F5, F6, F9 and F10. The drug release was successfully extended up to 5hr, 6hr, 8hr and 9hr for F9, F10, F6 and F5 respectively. F7 was able to release 22.59% of drug in 15 min and shown a steady release of drug for an extended period of 12 h. Similarly F8 was able to release 26.22% of drug in 15 min and shown a steady release of drug for an extended period of 12 h (fig. 1 and fig. 2). From the above observation we concluded that the drug release from all the formulations were extended for a longer period of time [17].

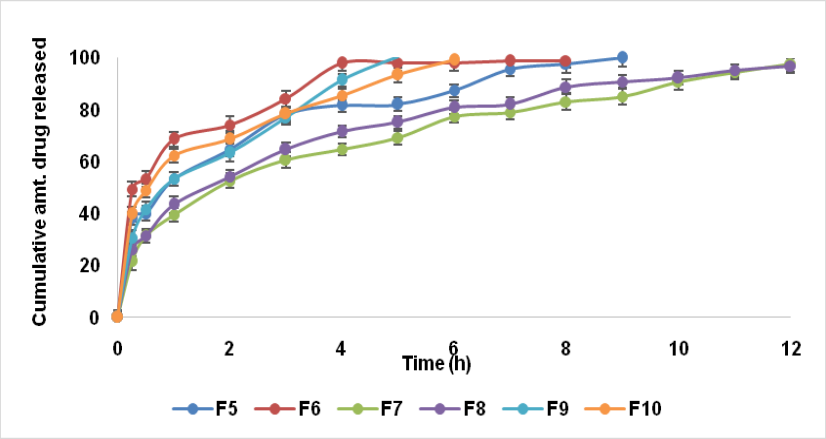

Fig. 2: Comparative *in vitro* dissolution profile of F5, F6, F7, F8, F9 and F10

From the dissolution profile of all formulation it had been observed that F7 and F8 are suitable for once daily immediate-and extended release bilayer tablet of etoricoxib. In all formulation the rate of release was different due to their differences in composition. The reason behind the variation in drug release kinetics were based upon the nature of ingredients used [10, 11].

HPMC K100 had faster drug diffusion from the polymeric matrix with increase in the water uptake. The high water uptake leads to considerable swelling of the polymer matrix that caused the drug to diffuse out from polymer matrix at a faster rate. HPMC K100 had uniform gelling and binding effect because it was easily gelled in presence of aqueous solvent. It plays a significant role in the design of a controlled release product thus it showed better sustained release. The drug diffusion patterns of all the formulations were also depended upon the viscosity of the polymer used. By increasing the viscosity of the system which increased the chances of availability of active binding sites in the polymeric chain [18].

In cross carmelose sodium, the cross-linking reduces water solubility while still allowing the material to swell (like a sponge) and absorb many times its weight in water. As a result, it provides superior drug dissolution and disintegration characteristics, subsequently bringing the active ingredients into better contact with bodily fluids.

Table 4: Various parameters of the model equations of the *in vitro* release kinetics

Formulation code	Zero order		First order		Higuchi model		Hixon crowell model		Korsmeyer-peppas model		
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	K_{HC}	r^2	K_P	n
F1	0.9692	8.0947	0.9776	0.0981	0.9812	29.861	0.8883	0.226	0.9921	7.4353	1.6299
F2	0.9176	4.2599	0.8441	0.0293	0.8275	14.831	0.9527	0.1503	0.9121	8.3483	1.0593
F3	0.9285	3.1586	0.9629	0.0231	0.9727	11.852	0.8474	0.0935	0.9754	4.0870	0.656
F4	0.7632	3.8296	0.855	0.0271	0.8749	15.033	0.5695	0.1422	0.8164	8.1433	1.4678
F5	0.9025	6.9481	0.803	0.2437	0.9776	25.747	0.8543	0.134	0.9854	1.8750	0.5797
F6	0.9045	6.837	0.958	0.232	0.9646	23.832	0.8837	0.1243	0.9561	1.6018	0.4523
F7	0.9323	5.7498	0.9113	0.1055	0.9874	24.104	0.8521	0.1227	0.9911	2.6062	0.7356
F8	0.8946	5.6064	0.9828	0.1072	0.9807	23.913	0.8232	0.1161	0.9949	2.3768	0.693
F9	0.9763	13.946	0.8606	0.3318	0.9909	38.746	0.9346	0.2828	0.9903	1.9165	0.7599
F10	0.9451	9.5277	0.8653	0.2604	0.9885	29.00	0.9011	0.1824	0.9916	1.7018	0.553

K_0, K_1, K_H, K_{HC} are the rate constants for Zero Order, First Order, Higuchi Model, Hixon crowell Model respectively, r^2 = correlation co-efficient

Taking different data's from the kinetic profiles, we got different kinetic models belonging to different equations. There was a comparison of all the R^2 value of Zero Order, First Order, Higuchi equation and Hixon Crowell equation of F1 to F10 depicted in table 4. From this table we got that in all the formulations the correlation coefficient values were variable. All the formulation followed

Higuchi model as the R^2 value found to be maximum except F2 and F8. The data obtained was also put in Korsemeyer–Peppas model in order to find out n value, which describes the drug release mechanism. The n-value of different formulations were found to be variable as depicted in and the drug release mechanism was predicted accordingly table 5.

Table 5: Release mechanism of drug from different formulation

Formulation	Diffusion exponent 'n'	Release mechanism
F1	1.63	Super case II transport
F2	1.06	Super case II transport
F3	0.66	Non-Fickian transport
F4	1.47	Super case II transport
F5	0.58	Non-Fickian transport
F6	0.45	Non-Fickian transport
F7	0.74	Non-Fickian transport
F8	0.69	Non-Fickian transport
F9	0.76	Non-Fickian transport
F10	0.55	Non-Fickian transport

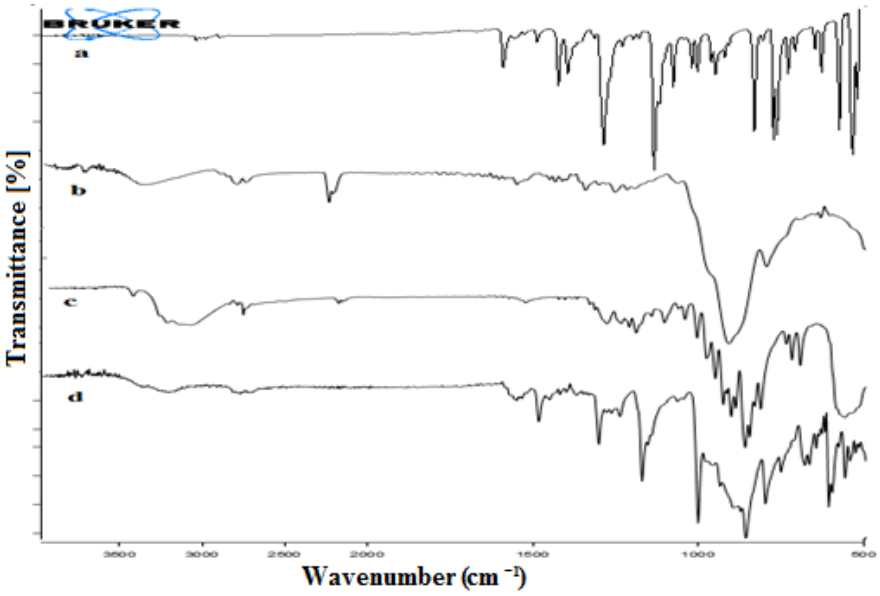

Fig. 3: FTIR study. a) Etoricoxib; b) HPMC K100; c) Lactose; d) F8

FTIR study

FT-IR studies were done to find out the possible intermolecular interactions between the etoricoxib and other ingredients. The characteristic peaks of etoricoxib, HPMC K100, lactose and F8 are depicted in fig. 3. Absence of any other new peaks and also no differences in the positions of the absorption bands in the bilayer tablet F8 indicate the lack of significant interactions between etoricoxib and other excipients [19].

CONCLUSION

Bilayer tablets of etoricoxib was developed successfully with meticulous proportion of release controlling HPMC K100 and lactoseThe n-value of different formulations obtained from Korsemeyer–Peppas model were found to be variable. The FTIR study revealed absence of new peaks and also no differences in the positions of the absorption bands in the bilayer tablet F8 that indicate the lack of significant interactions between etoricoxib and other excipients. Hence it had been concluded that F7 and F8 are suitable for once daily immediate-and extended release bilayer tablet of etoricoxib.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors have reported no potential conflict of interest in this work

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