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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE IBUPROFEN TABLETS WITH ACRYLIC POLYMERS (EUDRAGIT) AND HPMC

RANJIT PRASAD SWAIN*, T. RATNA KUMARI, SATYAJIT PANDA

Maharajah's College of Pharmacy, Phool Bagh, Vizianagaram 535002, Andhra Pradesh, India
Email: ranjit.prasad797@gmail.com

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ABSTRACT

Objective: An attempt was made to develop sustained release matrix tablets of ibuprofen using HPMC (K4M, K15M & K100M) and eudragit (RS 100 & RL 100) as release retardant polymers.

Methods: The ibuprofen matrix tablets were prepared by direct compression method using lactose as a diluent. Nineteen formulations of different polymer percentages were formulated, (F1-F19 with 7.5%, 10%, 15%, 20%, 25%, 30% w/w).

Results: The formulations were optimized on the basis of acceptable weight variation, thickness, hardness, % friability, % drug content and *in vitro* drug release. The *in vitro* release studies were performed using USP type II apparatus using 7.2 pH phosphate buffer as a dissolution medium, showed that optimized formulation F8 consisting of eudragit RL with 20% of the polymer was found to sustain the release of ibuprofen over a period of 12 h. The formulation exhibited highest correlation (R) value in case of Hixson-Crowell model and the release kinetic study proved that the formulation showed erosion process, and shown to follow zero order kinetics.

Conclusion: It was concluded that eudragit RL can be used for the preparation of sustained release tablet of ibuprofen.

Keywords: Ibuprofen, Eudragit, HPMC, Sustained release.

INTRODUCTION

Over the past few decades, significant medical advances have been made in the area of drug delivery with the development of controlled release dosage forms. The primary benefit of a sustained release dosage form in comparison with conventional dosage form, maintains uniform drug plasma concentration over an extended period of time and hence the uniform therapeutic effect is achieved. To get a successfully sustained release product, the drug must be released from the dosage form at a predetermined rate and dissolve in the gastrointestinal fluids [1-4].

Ibuprofen (fig. 1) is a nonsteroidal anti-inflammatory agent used extensively in the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, and low back pain [2, 5]. Ibuprofen is belong to the group of propionic acid derivatives; it has a plasmatic half-life of 1.8-2.0 h; as a result, it has to be administered 3-6 times a day, making this drug a suitable candidate for a controlled or sustained release drug products that can potentially avoid drug release in upper position of the GI tract [6, 7].

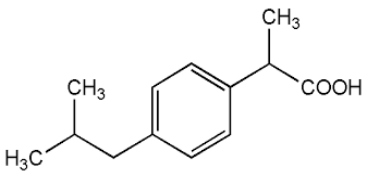

Fig. 1: Structure of ibuprofen

The drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations [8]. Because of low costs and ease of fabrication, one of the most common approaches to get controlled release is to embed a drug in a hydrophobic matrix such as ethyl cellulose or hydrophilic matrix such as hydroxypropyl methyl cellulose (HPMC), eudragit, sodium carboxymethyl cellulose and sclero glucan [9]. Hydrophilic polymer matrix is widely used for formulating sustained release dosage form. HPMC is widely used hydrophilic polymer to prolong drug release due to its rapid hydration, good compression and gelling characteristics along with its ease of use, availability, and very low toxicity. It regulates the release of drug by controlling the swelling and cross-linking [8]. Poly acrylates and polymethacrylate, the glassy substances, are commonly referred to by the trade name eudragit. The commonly used eudragit for the preparation of controlled release formulations are eudragit L, eudragit RL, eudragit RS, eudragit RLPO and eudragit RSPO. Eudragit RL and eudragit RS, are ammonio methacrylate copolymers. The ammonium groups are present as salts and are mainly responsible for independent pH permeability of the polymers [1]. Abbaspour *et al.* (2008) used eudragit RS 30D & RL 30D with triethyl citrate to prepare SR pellets of ibuprofen and Ofokansi *et al.* 2013 formulated colon targetted ibuprofen tablets based on eudragit RL 100-chitosan inter polyelectrolyte complexes. However, to the best of our knowledge, there is no reported study on sustained release ibuprofen tablets with acrylic polymers (eudragit) and HPMC.

Thus, this study was designed to investigate the formulation of sustained release tablets of ibuprofen and tested for controlled delivery of drug using hydrophilic matrix polymer such as HPMC K 4M, HPMC K 100M, HPMC K 15M and polyacrylate polymers such as eudragit RL100 and eudragit RS100 to produce additive an inflammatory activity, results to reduce in frequency of dose of administration and to improve patient compliance.

MATERIALS AND METHODS

Materials

Ibuprofen was procured from Yarrow chem. Products; Mumbai (India). Eudragit (RS 100, RL 100) and HPMC (K4M, K15M and K100M) were also procured from Yarrow chem. Products; Mumbai (India), lactose monohydrate, was procured from Finer Chemicals Ltd., Mumbai (India), talc was purchased from Loba chemei Pvt. Ltd., Mumbai (India). And magnesium stearate was purchased from Moly chem. Mumbai (India).

Methods

Method for preparation of sustained release ibuprofen SR tablets

Different tablet batch formulations (F1-F19) were prepared by direct compression method. Pure drug (ibuprofen) and polymers (eudragit RS 100 & RL 100 and HPMC K4M, K15M & K100M) were passed individually through #40 sieves and mixed well for 10 min in a mortar and pestle. To this blend, lactose (diluent) was added after passing through #40 sieves and mixed thoroughly for 5 min.

This powder blend was lubricated with sufficient amounts of magnesium stearate and talc after passing through #60 sieves and then directly compressed into tablets using a single punch rotary tablet machine (Rimek tablet mini press, Ahmadabad) using 10 mm flat punches. Tablet hardness was kept within the range of 6-8 kg/cm^2.

Table 1: Formulation trails of 100 mg ibuprofen SR tablets

Ingredients per tablet (mg) →		Ibuprofen	Eudragit RS 100	Eudragit RL 100	HPMC K 15 M	HPMC K 4 M	HPMC K 100 M	Lactose monohydrate	Talc	Mg. stearate	Total tablet weight (mg)
Formulation codes	F 1	100	18.75	_	_	_	_	128.25	2	1	250
	F2	100	25	_	_	_	_	122	2	1	250
	F3	100	37.5	_	_	_	_	109.5	2	1	250
	F4	100	50	_	_	_	_	97	2	1	250
	F5	100	_	18.75	_	_	_	128.25	2	1	250
	F6	100	_	25	_	_	_	122	2	1	250
	F7	100	_	37.5	_	_	_	109.5	2	1	250
	F8	100	_	50	_	_	_	97	2	1	250
	F9	100	_	62.5	_	_	_	84.5	2	1	250
	F10	100	_	75	_	_	_	72	2	1	250
	F11	100	_	_	18.75	_	_	128.25	2	1	250
	F12	100	_	_	25	_	_	122	2	1	250
	F13	100	_	_	37.5	_	_	109.5	2	1	250
	F14	100	_	_	_	18.75	_	128.25	2	1	250
	F15	100	_	_	_	25	_	122	2	1	250
	F16	100	_	_	_	37.5	_	109.5	2	1	250
	F17	100	_	_	_	_	18.75	128.25	2	1	250
	F18	100	_	_	_	_	25	122	2	1	250
	F19	100	_	_	_	_	37.5	109.5	2	1	250

Each batch contains 50 tablets.

Micromeritic properties of formulation blends

Angle of repose

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of powder. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of the orifice was 11 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of the sample had been built, the height of the powder forming the cone (h) and the radius (r) of the base were measured [10]. The angle of repose (θ) was calculated as follows:

$$\mathrm{Tan}\,\theta = \frac{h}{r}$$

$$\theta = \mathrm{Tan}^{-1}\frac{h}{r} \qquad \text{---------- (1)}$$

Bulk density

Apparent bulk density (ρ_0) was determined by weighing accurately 25 g of powder (M), which was previously passed through #40 sieves and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0) [11]. Calculate the apparent bulk density in g/ml by the following formula:

$$\text{Bulk density}\ (\rho_0) = \frac{M}{V_0} \qquad \text{---------- (2)}$$

Tapped density

Weigh accurately 25 g of powder (M), which was previously passed through #40 sieves and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_f) [11]. Calculate the tapped density in g/ml by the following formula:

$$\text{Tapped density} = \frac{M}{V_f} \text{---------- (3)}$$

Compressibility index or Carr's index (CI)

Compressibility index or Carr's index is measured using the values of bulk density and tapped density [12]. The following equation is used to find the Carr's index:

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100\text{-------- (4)}$$

Table 2: Range of Carr's index and Hausner's ratio and flow character according to I. P

Carr's index	Flow character	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Hausner's ratio

It indicates the flow properties of the powder and the ratio of tapped density to the bulk density of the powder or granules [12]. It can be measured as:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \qquad \text{---------- (5)}$$

Evaluation of compressed tablets

Thickness

The thickness of the matrix tablets was determined using vernier caliper (Mitutoyo, New Delhi, India) and the results were expressed as mean values of 3 determinations, with standard deviations.

Weight uniformity test

Twenty tablets from each batch were weighed using an electronic balance (Infra instruments Pvt. Ltd, Chennai; Model-IN 201 L EC) together and individually, and the mean weight and % deviations were calculated according to USP [13].

Hardness measurement

For each formulation, the hardness of 5 tablets (according to IP) [14] was determined using an electronic hardness tester (Monsanto type, Dolphin). The mean crushing strength (hardness) was determined, and the data are presented in the table 4.

Friability [12, 16]

Ten tablets (according to IP) [14] were randomly selected from each batch and weighed. The tablets were set to rotate at 25 rpm for 4 min in a friabilitor (Roche Friabilator, DBK instruments). Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight. The friability was calculated according to the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad \text{---------- (6)}$$

Drug content

Accurately weighed the quantity of the tablet powder equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of buffer solution of pH-7.2 was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through 0.45 µm membrane (Nunc, New Delhi, India) 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under U. V Spectrophotometer (Agilent Technologies, Germany; Model-Cary 60 UV-Vis) at 220 nm.

***In vitro* release studies**

In vitro release of ibuprofen from the tablets was studied using USP Type II dissolution apparatus (Disso 2000, Labindia) in pH 7.2 phosphate buffer at 37±1 °C. The volume of the dissolution medium was 900 ml, and the stirring speed was set at 50 rpm. At predetermined time intervals, 5 ml of sample was withdrawn and replaced with fresh pre-heated (maintained 37±1 °C) dissolution media. Samples were filtered through 0.45-µ membrane (Nunc, New Delhi, India) and analyzed after suitable dilution. All dissolution studies were carried out in triplicate, and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results.

RESULTS AND DISCUSSION

Ibuprofen is a non-steroidal anti-inflammatory agent belonging to the group of propanoic acid derivatives. It shows a plasmatic half-life of 1.8-2.0 h; as a result it has to be administered 3 to 6 times a day, making this drug a suitable candidate for a controlled/sustained release formulation [6]. In this present study hydrophilic polyacrylate polymer such as eudragit (RS 100 & RL 100) and the hydrophilic polymer of HPMC in different grades like HPMC K4M, K100M & K15M have been employed to formulate sustained release tablets of ibuprofen in different batches.

The sustained release tablets of ibuprofen were prepared (19 batches) by direct compression method according to the formulae given in table 1. Direct compression is one of the techniques which require the incorporation of directly compressible diluents into the formulation. It does not require the use of water or heat the formula and is the ideal method for moisture and heat liable medications. This is a process of compressing mixed powders into tablets without the need of intermediate granulating step. This technique involves conventional equipment, commonly available excipients and a limited number of processing steps. High doses can also be accommodated, and the final weight of tablet can easily exceed than that of other methods. The pre-compression powder blends of different batches were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio & the values are in table 3. The formulations F3, F9, F11, F16, F18 and F19 showed good flow property (26.12-29.0), but other formulations (F1, F2, F4, F5, F6, F7, F8, F10, F12, F13, F14, F15, F17) showed excellent flow property (21.02-25.68). The compressibility index ranged from 8.47 to 14.97. Bulk densities of powder blend contain HPMC polymer (F11-F19) was found to be quite higher than those of other powders. This may be due to the presence of more fines in the blend. In addition, the density may influence compressibility, dissolution, and other properties [15-17]. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and Hausner's ratio.

Table 3: Micromeritic properties of formulation blends*

Formulation code	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
F1	21.02±1.08	0.367±1.04	0.401±1.10	8.47±1.11	1.09±1.14
F2	24.52±1.05	0.283±1.1	0.325±1.11	12.92±1.04	1.14±1.13
F3	27.64±1.18	0.354±1.03	0.402±1.09	11.94±1.08	1.13±1.23
F4	23.69±1.11	0.345±1.04	0.412±1.08	14.07±1.11	1.13±1.19
F5	22.89±1.05	0.298±1.05	0.348±1.14	12.86±1.14	1.16±1.21
F6	25.64±1.20	0.289±1.02	0.325±1.20	11.07±1.07	1.12±1.11
F7	23.98±1.31	0.393±1.09	0.454±1.09	13.43±1.11	1.15±1.12
F8	23.54±1.25	0.391±1.04	0.451±1.23	13.30±1.09	1.15±1.32
F9	28.12±1.24	0.386±1.16	0.454±1.26	14.97±1.11	1.17±1.05
F10	21.58±1.18	0.352±1.32	0.419±1.21	12.90±1.15	1.14±1.32
F11	26.94±1.05	0.464±1.21	0.524±1.10	11.45±1.09	1.12±1.21
F12	23.84±1.07	0.394±1.22	0.454±1.08	13.21±1.08	1.15±1.49
F13	22.58±1.06	0.382±1.05	0.435±1.06	12.18±1.06	1.13±1.20
F14	23.94±1.03	0.389±1.07	0.439±1.14	11.38±1.11	1.12±1.12
F15	25.68±1.11	0.512±1.04	0.582±1.09	12.02±1.23	1.13±1.41
F16	26.12±1.06	0.499±1.08	0.569±1.07	12.30±1.25	1.14±1.56
F17	23.02±1.22	0.502±1.10	0.581±1.15	13.59±1.36	1.15±1.63
F18	29.00±1.18	0.359±1.04	0.410±1.09	12.43±1.28	1.14±1.72
F19	28.48±1.18	0.444±1.22	0.512±1.18	13.28±1.31	1.15±1.35

*All values are expressed as mean±SD, n=3

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness and friability values in table 4 and *in vitro* dissolution test (fig. 2, fig. 3). The thickness of tablets ranged from 5.3 to 5.6 mm. Tablet thickness is consistent batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working order. Tablet thickness should be controlled within a±5% variation of a standard value; thickness must be controlled to facilitate packaging. The average weight of 20 tablets from each formula was ranged from 245.11 to 255.09 mg. The pharmacopeial limit for the percentage deviation for tablets of more than 250 mg is ± 5%. The average percentage deviation of all tablet formulations was to be within the above limit, and hence, all formulations passed the test for uniformity of weight as per official requirements [14]. Drug content was found to be uniform among different batches of the tablets and ranged from 95.60 to 101%. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 95%. The hardness and friability of the tablets of all batches ranged from 6-8 kg/cm^2 and 0.54 to 0.88 % respectively. The formulations containing HPMC showed comparatively high hardness values of 7-8 kg/cm^2. This could be due to the presence of more fines in powder blend. Tablet hardness is not an absolute indicator of strength [18]. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered as acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits [17]. All the formulations showed acceptable pharmacopeial properties for weight variation, drug content, hardness, and friability.

Table 4: Evaluation of compressed tablets

Formulation code	Thickness [a] (mm)	Weight variation [b] (mg)	Hardness [c] (kg/cm^2)	Friability [d] (%)	Drug Content [e] (%)
F1	5.5±2.15	251.08±2.65	6.5±2.12	0.75±2.12	98.20±2.12
F2	5.4±2.12	245.11±2.23	7.5±2.23	0.88±2.02	100.96±2.12
F3	5.6±2.08	249.23±2.12	6.5±2.04	0.85±2.02	98.37±2.03
F4	5.4±2.14	253.18±2.22	6±2.03	0.76±2.05	98.92±2.12
F5	5.4±2.62	254.28±2.06	6.5±2.15	0.72±2.11	101.55±2.12
F6	5.6±2.32	255.07±2.30	7±2.15	0.73±2.12	99.54±2.13
F7	5.3±2.02	252.12±2.65	6.5±2.08	0.68±2.54	98.36±2.13
F8	5.4±2.16	250.06±2.92	7±2.06	0.61±2.45	99.96±2.12
F9	5.3±2.09	252.15±2.68	7.5±2.12	0.88±2.16	98.03±2.26
F10	5.5±2.28	253.22±2.34	8±2.11	0.62±2.28	98.54±2.16
F11	5.4±2.23	252.26±2.08	7.5±2.09	0.65±2.12	100.99±2.12
F12	5.6±2.18	248.19±2.16	7±2.12	0.75±2.11	99.01±2.12
F13	5.5±2.15	251.24±2.34	8±2.07	0.73±2.04	100.64±2.15
F14	5.4±2.15	255.09±2.35	7.5±2.16	0.64±2.12	99.32±2.15
F15	5.3±2.17	247.29±2.18	7±2.32	0.58±2.32	99.54±2.13
F16	5.4±2.13	254.08±2.63	8±2.24	0.69±2.41	99.69±2.12
F17	5.6±2.16	252.09±2.02	7.5±2.26	0.73±2.15	98.06±2.12
F18	5.3±2.19	248.24±2.32	7±2.54	0.65±2.02	99.10±2.15
F19	5.5±2.36	250.05±2.12	7.5±2.02	0.72±2.68	98.89±2.11

a: mean±SD, n=3; b: mean±% deviation, n=20; c: mean±SD, n=5; d: Tablets equivalent to 6.5g; e: mean±SD, n=3

The *in vitro* drug release characteristics were studied in phosphate buffer (pH 7.2) for a period of 12 h using USP type II dissolution apparatus (Disso 2000, Labindia). The formulation F1 to F4 composed of eudragit RS 100 with 7.5%, 10%, 15%, 20% w/w. As the concentration of eudragit RS 100 increased the release was sustained. The formulation F3 & F4 showed drug release within 8 h & 9 h completely respectively.

These formulations were further modified by using similar polymer category of another grade with same concentrations of eudragit RL 100 (7.5%. 10%, 15%, 20% w/w). Formulation F5 released 90% drug at the end of 3 h. Formulation F6 and F7 completely drug release within 4 h and 6 h. The formulation F8 releases the drug slowly and complete up to the end of 12 h. We tried higher polymer concentration (25%, 30% w/w) indicated F9 and F10 to find out the drug release profile of ibuprofen, as the concentration was increased there was no release retardant for 12 h.

The targeted release profiles parameters for tablet formulations were calculated as per Robinson and Erikson equation: after 1h, 30-35% of the drug is released; after 6h, 60-65% of the drug is released; and finally, after 12 h; the remaining drug is released [19]. From the *in vitro* release profiles of formulation F8, it is evident that the prepared tablet exhibited release profile that fulfilled the above-mentioned release requirement.

Further, the formulae were modified by using another polymer which is hydrophilic i.e. HPMC with various grades like HPMC K15M, K4M and K100M with same concentrations (7.5%, 10% and 15%). The formulation F11, F14, F16, F17, F18 showed more than 90% drug release within 1 h because burst release of ibuprofen, but formulation F12 showed 100% drug release within 5h and F13 showed within 7 h, due to its hydrophilic nature of the polymer. The formulation F19 showed 75% drug release in 1 h but showed complete drug release within 7 h. So all the formulations from F11 to F19 containing different grades of HPMC with various concentrations not showed the sustained drug release pattern.

Among all the formulations containing eudragit (F1-F10) and HPMC (F11-F19), formula F8 (eudragit RL 100 with 20% w/w) showed better-sustained release pattern. Because eudragit RL has more ammonium groups are present as salts and make the polymers permeable. Eudragit reduced the drug release due to a reduction in the penetration of solvent molecule into the system. The rate of release was controlled by the permeability of matrix structure [20].

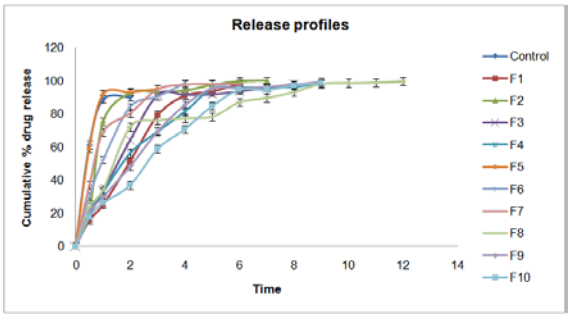

Fig. 2: *In vitro* dissolution profile of ibuprofen sustained release tablets with various concentrations of eudragit polymer (formula F1 to F10)

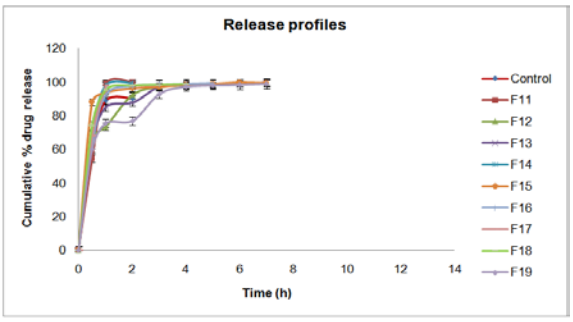

Fig. 3: *In vitro* dissolution profiles of ibuprofen sustained release tablets with various concentrations of HPMC polymer (formula F11 to F19)

Characterization of drug releases kinetics

In order to understand the kinetics and mechanism of drug release, the results of the *in vitro* drug release study were fitted into various kinetic models like zero order (cumulative percent drug released verses time), first order (log cumulative percentage drug retained verses time), Higuchi (cumulative percent released verses √T), and Peppas (log of cumulative percent released verses log time). The kinetic model that best fits the dissolution data was evaluated by comparing the coefficient of determination (r^2) values obtained in various models [21]. The best formulation (F8) among all was fitted into different kinetic models. The formulation exhibited the highest correlation (R) value in case of Hixson-Crowell model, and the release kinetic study proved that the formulation showed erosion process (fig. 4).

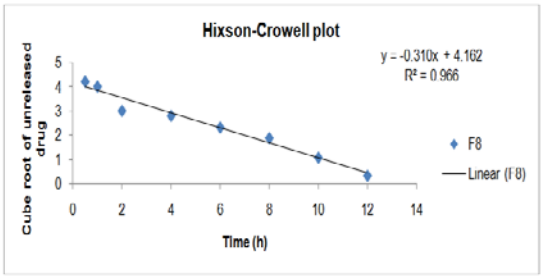

Fig. 4: Best fit kinetic release data of F8 formulation (optimized batch)

CONCLUSION

The hydrophilic matrix tablets of HPMC could not control the ibuprofen release effectively for 12 h. The matrix tablets containing eudragit RL 100 with 20% where found to be significantly effective in sustaining the drug release up to 12 h, is mainly due to the erosion process. It was concluded that eudragit RL can be used for the preparation of sustained release tablet of ibuprofen. It is evident from the results that a matrix tablet of ibuprofen is a better system for twice daily sustained release dosage regimen.

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CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Tapan KG, Amit A, Hemanth B. A novel and alternative approach to controlled release drug delivery system are based on solid dispersion technique. Bull Fac Pharm 2012;50:147-59.
2. Girish B, Ismail P, Gowda D. Formulation and evaluation of sustained release matrix tablets of flurbiprofen using guar gum. Int J Pharm Pharm Sci 2012;4 Suppl 5:120-3.
3. Oluwatoyin A, Okunlola A, Lamprecht A. Formulation and *in vitro* evaluation of natural gum based micro beads for delivery of ibuprofen. Trop J Pharm Res 2014;13:1577-83.
4. Hind Z, Khalil S, Fars K. Designing an extended release waxy matrix tablet containing nicardipine-hydroxy propyl ß cyclodextrin complex. Saudi Pharm J 2011;19:245-53.
5. Tripathi KD. Essentials of medical pharmacology. 6th ed. Jaypee Publishers, New Delhi; 1985. p. 173-210.
6. Ofokansi KC, Kenechukwu FC. Formulation development and evaluation of drug release kinetics from colon–targeted ibuprofen tablets based on eudragit RL 100-chitosan inter polyelectrolyte complexes. ISRN Pharm 2013;10:1-10.
7. Chandran S, Laila F, Asghar A, Neelima M. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. Indian J Pharm Sci 2003;20:596-602.
8. Rohini D, Alexandar S, Sekar C. Preparation and *in vitro* evaluation of sustained release tablet formulations of metformin HCl. Asian J Pharm Clin Res 2012;5:45-8.
9. Rahman A, Gamal M, Mahmoud E. Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 2009;17:283-8.
10. Shah RB, Tawakkul MA, Khan MS. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech 2008;9:251-60.
11. Arunachalam A, Mazumde A. The outcome of formulation and *in vitro* release studies of levothyroxine sodium tablets. Asian J Pharm Sci Tech 2011;1:33-9.
12. Sarker A, Pathan A, Shrestha D, Kibria G, Jalil R. Investigation of *in vitro* release kinetics of carbamazepine from eudragit ® RS PO and RL PO matrix tablets. Trop J Pharm Res 2009;8:145-52.
13. United state pharmacopeia. The council of experts. Asian ed. The board of trustees publications, US pharmacopeia national formulary; 2004. p. 305.
14. Indian pharmacopoeia. Ministry of health and family welfare. 4th ed. Controller of publications, Govt. of India. New Delhi; 1996. p. 735.
15. Aulton EM. Pharmaceutics: Controlled release systems. The science of dosage form design. 2nd ed. living stone, Elsevier; 2007. p. 101-25.
16. Martin physical pharmacy and pharmaceutical sciences. (Sinko PJ eds). Physical-chemical and biopharmaceutical principles in the pharmaceutical sciences. 6th ed. Wolter Publishers, New Delhi; 2011. p. 138-50.
17. Raghuram K, Srinivas M, Srinivas R. Once-daily sustained release matrix tablets of Nicorandil: formulation and *in vitro* evaluation. AAPS PharmSciTech 2003;4:1-9.
18. Vyas SP, Paliwal SR, Paliwal R. The theory and practice of industrial pharmacy. (Lachman HA, Lieberman L, eds). Targeted drug delivery systems. 4th ed. CBS Publishers, New Delhi; 2013. p. 936-8.
19. Sanjay D, Bhaskar M, Sankha C, Das MK, Samarendu S, Ganguly S, *et al*. Polymers derived from xanthomonas competencies and retardant materials for the formulation of sustained release floating matrix tablet of atenolol. Int J Biol Macromol 2014;651:345-56.
20. Chithirra A, Mohamed S, Pillai k, Abirami A, Aruna A. Formulation and evaluation of controlled release frusemide tablets by bilayer technology. J Drug Delivery Res 2013;3:37-44.
21. Chime SA, Onunkwo GC, Onyishi II. Kinetics and mechanisms of drug release from swellable and nonswellable matrices: a review. Res J Pharm Biol Chem Sci 2013;4:97-104.