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Research Article

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DESIGN AND DEVELOPMENT OF INDOMETHACIN MATRIX TABLET WITH pH MODULATED RELEASE KINETICS

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ABSTRACT

Controlled release preparations have been reported to reduce the gastro irritant and ulcerogenic effects of Non-steroidal Anti-inflammatory drugs. In the present study, an attempt was made to develop matrix tablet-based controlled release formulations of Indomethacin, using ethyl cellulose as the rate-controlling polymer. In order to prevent initial release of the drug in the acidic environment of the stomach, cellulose acetate phthalate was incorporated in the matrix in varying amounts. It was found that with increasing the proportion of ethyl cellulose in the matrix, the drug release initial release of the drug in the first 2-3 h followed by enhanced release rate in alkaline medium owing to the high solubility of cellulose acetate phthalate at basic pH which led to creation of a porous matrix. It was concluded that combination of cellulose acetate phthalate with ethyl cellulose in the matrix base can be an effective means of developing a controlled release formulation of indomethacin with very low initial release followed with controlled release up to 14-16 h.

Keywords: Indomethacin, ethyl cellulose, matrix tablet, cellulose acetate phthalate, controlled release.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are highly effective in the treatment of rheumatoid and osteoarthritis[1], but their long term use results in gastrointestinal (GI) toxicity in a large number of cases like ulceration and stricture formation in esophagus, stomach and duodenum leading to severe bleeding, perforation and obstruction. Indomethacin, like other drugs of this group, also has a wide spectrum of gastrointestinal side effects ranging from mild dyspepsia to gastric bleeding. Due to its short plasma half-life (1-3 h) and GI toxicity parole, Indomethacin is an ideal candidate for preparing extended or controlled release drug products that can potentially avoid drug release in upper position of the GI tract[1]. Several matrixes based controlled release products of Indomethacin have been reported based on the use of either hydrophilic (HPMC or Carbopol) and/or hydrophobic polymers (EC).[2] The reported controlled release formulations of Indomethacin did not involve any attempt to prevent drug release in the upper GI tract. Cellulose acetate phthalate (CAP) is a commonly employed enteric coating polymer in pharmaceutical industry in combination with cellulose acetate butyrate. CAP has been employed for preparing enteric matrix microspheres by emulsiosolvent evaporation technique.[3] In the present study, it was envisaged to design controlled release formulation of Indomethacin with pH dependent release profile so as to minimize initial drug release in stomach that will reduce the possible gastro irritant and ulcerogenic effects of the drug. At the same time, there would be no compromise on the biopharmaceutical profile of the drug as Indomethacin is reported to be well absorbed throughout the GI tract.[1,3]

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MATERIALS AND METHODS

Chemicals

Indomethacin and cellulose acetate phthalate were obtained as gift samples from Themis pharmaceutical Limited, Mumbai and Colorcon India, Mumbai, India respectively. Ethyl cellulose was obtained as gift samples from Research lab, Mumbai, India. All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Analytical method

Indomethacin in pure form and designed formulation was analyzed using in-house developed and validated UV spectrophotometric method using Shimadzu1700 UV/Vis spectrophotometer. The method involved analysis of the drug at 320 nm in 7.4 pH phosphate buffer using 1 cm matched quartz cells.[4, 5]

Preparation of matrix tablets

Different matrix embedded formulations of Indomethacin were prepared by wet granulation technique using varying proportion of polymers (Table **1**). Accurately weighed quantities of pre-sieved drug and polymer(s) were mixed thoroughly and granulated with ethyl alcohol. The wet granules were sieved through 20 sieves and the final granules were blended with 1% talc and 0.5%magnesium stearate and compressed using 8 mm punches on single station tablet press (Cadmach, Ahmadabad, India).[6-8]

Table 1. Formulation Chart of Indomethacin matrix tablets

Batch/ Ingredients (mg)	Drug	Ethyl cellulose	Cellulose acetate phthalate	Lactose	Mg stearate	Talc	Total Weight
F1	75	3.75	-	118.25	1	2	200
F2	75	7.5	-	114.5	1	2	200
F3	75	11.25	-	110.75	1	2	200
F4	75	3.75	9.375	108.875	1	2	200
F5	75	3.75	18.75	99.5	1	2	200
F6	75	7.5	18.75	95.75	1	2	200
F7	75	7.5	28.125	86.375	1	2	200
F8	75	11.25	28.125	82.625	1	2	200
F9	75	11.25	37.5	73.25	1	2	200

Physicochemical characterization of tablets

The designed formulations were studied for their physicochemical properties such as weight variation, hardness, friability, and assay[9]. For estimation of drug content 10 tablets were crushed and powdered. The aliquot of powder equivalent to 10 mg of drug was weighed and dissolved in methanol: phosphate buffer pH 7.4 (1:10) mixture. The resultant solution was filtered and suitably diluted with phosphate buffer (pH 7.4) and analyzed using the UV method discussed earlier. From the absorbance value, drug content was calculated on average weight basis (Table **2**).

Table 2. Standard Physical Tests for Matrix Tablets

Formulation	Hardness (kg/cm2)	Percent friability	Thickness (mm)	Content uniformity (%)	Weight variation
F1	5.8±0.2	0.61±0.02	3.37±0.03	99.23%	Passes
F2	6.2±0.3	0.55±0.03	3.28±0.06	100.16%	Passes
F3	6.1±0.3	0.54±0.01	3.29±0.02	99.41%	Passes
F4	6.2±0.4	0.52±0.03	3.27±0.01	99.37%	Passes
F5	6.3±0.2	0.51±0.03	3.26±0.03	100.13%	Passes
F6	65±0.1	0.48±0.04	3.23±.03	99.74%	Passes
F7	6.5±0.2	0.52±0.05	3.22±0.01	100.26%	Passes
F8	6.3±0.3	0.51±0.02	3.25±0.04	99.63%	Passes
F9	6.4.±0.2	0.49±0.03	3.23±0.02	99.85%	Passes

All the values represent mean ± Standard deviation (n=3)

In-vitro release studies, *In-vitro* dissolution studies were carried out using USP Type II (paddle) apparatus (Electro lab TDT-08L, Mumbai, India) at 75 rpm.[6-10] The dissolution was carried out for the first 2 h in distilled water (500 ml). Then, 200 ml of phosphate buffer concentrate (4.75 g of KH_2PO_4 and 1.07 g of NaOH in distilled water was added to raise the total media volume to 700 ml and pH to 7.4 for the remaining period. At predetermined time intervals, a 10ml sample was withdrawn and replaced with fresh dissolution media. The samples were filtered, suitably diluted, and analyzed using the UV method discussed earlier. The release studies were conducted in duplicate and the mean values along with the SD were plotted against time (Table **3** & **4;** Figure **1**, **2**, **3**, **4** & **5**).

Table 3. *In-vitro* Dissolution Data of F1, F2, F3, F4 and F5

Time in Hours	% Cumulative drug release				
	Batch code				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	6.31±0.403	5.42±0.41	4.91±0.376	5.74±0.363	4.54±0.282
2	11.09±0.451	10.34±0.349	9.17±0.312	10.13±0.401	8.71±0.253
3	15.27±0.424	13.61±0.423	12.21±0.434	17.27±0.422	15.34±0.361
4	18.64±0.489	17.73±0.471	15.48±0.348	21.85±0.503	19.57±0.444
5	24.86±0.439	22.77±0.398	21.71±0.46	28.84±0.481	26.12±0.56
6	31.25±0.513	29.89±0.557	27.46±0.462	37.24±0.542	36.59±0.457
7	37.83±0.449	35.11±0.465	34.69±0.511	43.67±0.481	45.32±0.453
8	43.97±0.536	41.57±0.42	38.33±0.381	50.54±0.441	53.41±0.523
9	48.31±0.534	45.34±0.522	43.84±0.335	54.68±0.554	60.29±0.412
10	52.27±0.421	48.12±0.376	47.39±0.522	59.41±0.574	66.14±0.524
11	55.07±0.563	53.61±0.494	50.41±0.501	66.97±0.514	71.89±0.605
12	59.85±0.419	56.02±0.389	56.11±0.455	71.3±0.609	76.47±0.519
13	62.19±0.407	60.84±0.445	58.82±0.407	75.43±0.536	80.53±0.407
14	66.48±0.429	65.19±0.459	63.55±0.475	78.13±0.649	84.69±0.421

All the values represent mean ± Standard deviation (n=3)

Table 4. *In-vitro* Dissolution Data of F6, F7, F8, and F9

Time in Hours	% Cumulative drug release			
	Batch code			
	F6	F7	F8	F9
0	0	0	0	0
1	3.57±0.384	2.85±0.233	2.26±0.212	1.69±0.147
2	7.64±0.351	6.51±0.211	5.41±0.223	4.17±0.207
3	14.37±0.423	13.29±0.302	11.69±0.343	10.84±0.271
4	19.88±0.381	19.18±0.473	16.28±0.414	16.44±0.329
5	25.49±0.436	26.36±0.419	23.19±0.419	23.58±0.417
6	34.77±0.501	35.84±0.517	29.41±0.397	31.79±0.354
7	44.61±0.495	45.56±0.573	38.69±0.388	42.08±0.507
8	51.54±0.612	52.79±0.488	47.55±0.571	51.26±0.561
9	57.79±0.703	60.34±0.587	55.31±0.413	60.73±0.532
10	61.38±0.527	67.21±0.591	62.44±0.515	67.91±0.479
11	65.86±0.428	73.29±0.611	69.41±0.55	75.16±0.44
12	72.59±0.686	78.46±0.587	75.11±0.549	82.37±0.361
13	78.41±0.594	83.25±0.616	80.88±0.483	88.34±0.399
14	82.27±0.499	87.13±0.523	85.06±0.491	93.22±0.416

Figure 1. *In-vitro* Dissolution Profile of Formulation F1, F2 and F3

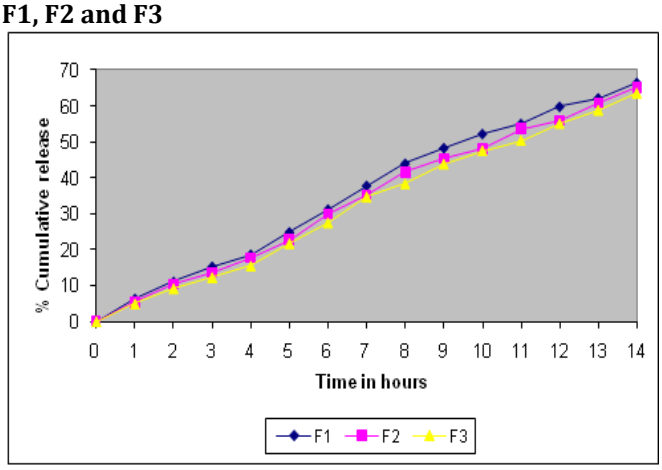


Figure 2. *In-vitro* Dissolution Profile of Formulation F1, F4 and F5

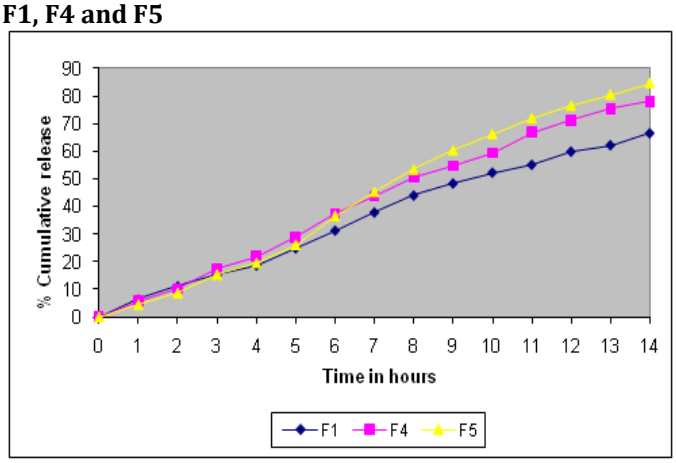
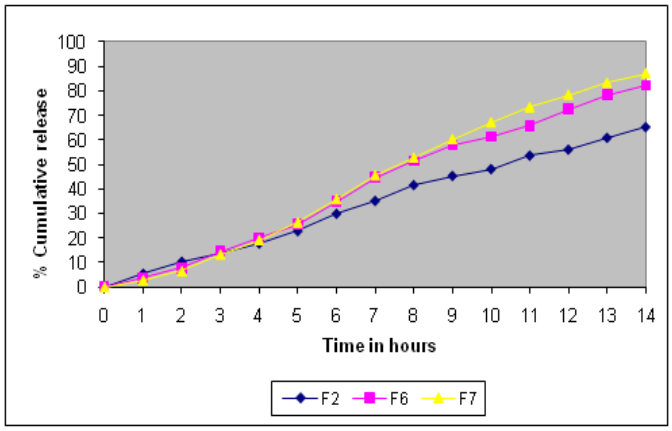


Figure 3. *In-vitro* Dissolution Profile of Formulation F2, F6 and F7



Effect of simulated GI fluid pH (without enzymes) on release

The release profile was also studied in a medium of changing pH without enzymes (Table **5**)[1, 6-8]. The initial condition was 350 ml of 0.1N HCl (pH 1.2) for 0–2 h. At the end of second hour, the pH of the media was raised to 4.5 and the total dissolution media volume to 600ml. At the end of fourth hour, pH was raised to 7.4 by adding 300 ml phosphate buffer concentrate (2.18 g of KH_2PO_4 and1.46 g of NaOH in distilled water). The study was further continued till the end in 900 ml volume. At predetermined time intervals, a 5ml sample was withdrawn and replaced with fresh dissolution media. After appropriate dilutions, the samples were analyzed by the UV method discussed earlier. The corresponding release profiles are presented in Table **5**.

Table 5. Effect of GI Simulated Conditions on Release Profile of F9

Time in Hours	% Cumulative drug release
	Batch code
	F9
0	0
1	0.95±0.101
2	2.21±0.207
3	6.19±0.256
4	10.88±0.311
5	17.47±0.356
6	26.11±0.403
7	36.69±0.481
8	47.35±0.429
9	56.17±0.505
10	63.58±0.491
11	70.22±0.477
12	76.08±0.423
13	82.19±0.441
14	87.31±0.488

All the values represent mean ± Standard deviation (n=3)

Figure 4. *In-vitro* Dissolution Profile of Formulation F3, F8 and F9

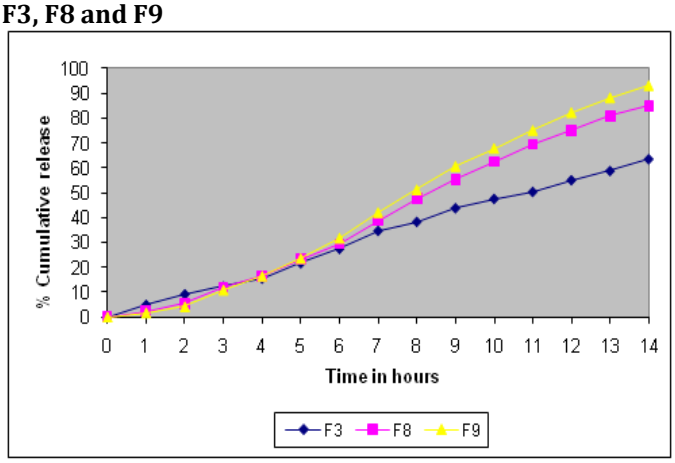
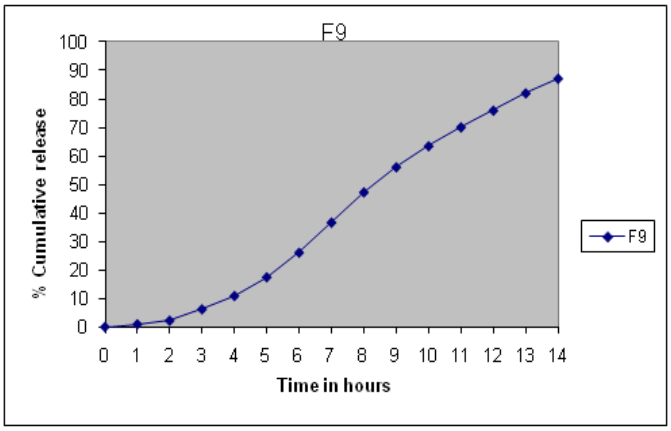


Figure 5. *In-vitro* Dissolution Profile of Formulation F9



Model Fitting

The model fitting for % cumulative release was done using Microsoft excel 2003 to find the best fits kinetic equation for the dissolution profile

Kinetics of Drug Release

In order to understand the mechanism and kinetics of drug release.[11-13] The results of the *in-vitro* dissolution study of the batches were fitted with various kinetic equations like

i) Zero order (% release =K t)
ii) First order (log %Unreleased =Kt)
iii) Higuchi's model (%Release =Kt0.5)
iv) Peppas Korsmeyer Equation (% Release=Ktn)
v) Empirical equation (Power law expression) of

$$Mt / M\infty = K t$$

Where,

Mt = am

If n = 0.45; indicates Fickian diffusion mechanism (Higuchi matrix)

n = 0.45 to 0.89; indicates Anomalous Transport or Non Fickian transport.

Amount of drug release at time t

$M\infty$ = amount of drug release at infinite time

K = constant characteristics, and

n = Diffusion exponent

n = 0.89; indicates Case II Transport

n > 0.89; indicates Super case –II transport

Coefficient of correlation (r^2) values were calculated for the linear curves obtained by regression analysis of the above plots (Table **6**, **7**, **8** & **9**).

Batch reproducibility and stability on storage

Three batches of each formulation were prepared and their respective dissolution rates were evaluated under the same conditions.[14] The best formulation of each

type was studied after 6 months and 1 year for the effect of storage in ambient conditions on the stability and release profiles of drug from the different formulations respectively. The tablets were sealed in airtight cellophane packets and were stored in ambient conditions. (Temp 25°C and RH 65%). The *In-vitro* release profile for each was studied as per the specification enlisted in previous sections and compared with its initial release profile.

Table 6. Kinetic Data of Indomethacin Matrix Tablets

Formulation Code	Zero Order (R2)	First order (R2)	Matrix Model (R2)	Korsemeyer-peppas model (R2)
F1	0.9915	0.991	0.9368	0.8722
F2	0.995	0.9876	0.9302	0.883
F3	0.996	0.9858	0.9206	0.9087
F4	0.9943	0.9775	0.9309	0.9022
F5	0.9903	0.9617	0.9088	0.9345
F6	0.9923	0.9616	0.9109	0.9489
F7	0.9911	0.9491	0.9003	0.9658
F8	0.9904	0.9331	0.8788	0.9802
F9	0.9881	0.8879	0.8712	0.989

Table 7. Estimated Values of n and k by Regression of log (M_t / M_∞) of log (t)

Batch No.	N	K	r2	Model Fitting
F1	1.197	3.427	0.9915	Zero order
F2	1.201	3.235	0.995	Zero order
F3	1.233	2.864	0.996	Zero order
F4	1.3	3.133	0.9943	Zero order
F5	1.396	2.642	0.9903	Zero order
F6	1.426	2.371	0.9923	Zero order
F7	1.512	2.055	0.9911	Zero order
F8	1.547	1.741	0.9904	Zero order
F9	1.662	1.452	0.9890	Peppas

Table 8. Kinetic Data of Indomethacin Matrix Tablets in GI Simulated Conditions

Formulation Code	Zero Order (R2)	First order (R2)	Matrix Model (R2)	Korsemeyer-peppas model (R2)
F9	0.9771	0.9147	0.8445	0.9909

Table 9. Estimated Values of n and k by Regression of log (M_t / M_∞) on log (t) of F9 in GI Simulated Conditions

Batch No.	N	K	r2	Model Fitting
F9	1.815	1.109	0.9909	Peppas

RESULTS AND DISCUSSION

Physical appearance, hardness, friability, weight variation and drug content uniformity of different tablet formulations were found to be satisfactory. The manufactured tablets showed low weight variation and high degree of drug content uniformity. Indomethacin, a weak indole acetic acid derivative with a pKa of 4.5 is practically insoluble in simulated gastric fluid. Therefore, dissolution studies were carried out in distilled water for the first two hours followed by phosphate buffer pH (7.4) for the remaining period of study. This medium was considered as most suitable as the drug was freely soluble at this pH and it also mimics the alkaline environment of small intestine. The selection of wet granulation technique for matrix tablet preparation was based on previously reported study which suggested that wet granulation results in harder tablets with lower matrix porosity that give very low release rates when compared to direct compression .In our study, the use of ethyl alcohol as granulating agent was based on the partial solubility of EC in this granulating solvent which resulted in providing the necessary adhesion between the various matrix components and precluded the use of a separate binder. All the formulations were subjected to *in-vitro* dissolution studies and results are shown in table and figure no. The results revealed release profiles of matrix tablets of Indomethacin containing varying proportion of ethyl cellulose (5%, 10%, 15% w/w of drug) i.e. F1, F2 and F3 showed 66.48, 65.19 and 63.55 % of drug release in 14 hours . This showed that as concentration of ethyl cellulose as matrix former increases the rate of drug release decreases on account of formation of strong matrix with reduced porosity. As the presence of only ethyl cellulose in the matrix would not give the desired release profile of low initial drug release followed by increased release rate, CAP was included in the matrix. It was expected that presence of these pH dependent polymers would provide pH modulated release characteristic with very low drug release in acidic environment of upper GIT (Stomach and initial Duodenum) followed by higher release rate in alkaline pH of small intestine on account of formation of a porous matrix due to dissolution of Cellulose acetate phthalate. The release profile of F4and F5 containing fixed proportion of ethyl cellulose (5% w/w of drug) with Cellulose acetate phthalate 12.5% and 25% respectively showed 78.13, 85.69% respectively. The F4 and F5 show more release then F1 which may be due to increased erosion of matrix as the polymer concentration increases. Similarly the release profile of F6 and F7 containing fixed proportion of ethyl cellulose 10% w/w of drug with Cellulose acetate phthalate at 25% and 37.5% w/w of drug respectively showed 81.37, 88.13, % respectively in 14 hours. There is increase in the drug release in comparison to only ethyl cellulose (10% w/w of drug) based matrix tablets which may be due to increased erosion of Cellulose acetate phthalate based formulation. Formulation F8, F9, contains fixed proportion ethyl cellulose (15 % w/w of drug) with varying proportion of Cellulose acetate phthalate. (37.5% w/w of drug and 50% w/w/ of drug) showed 88% and 94%, respectively in 14 hours.

The increased release with increase in concentration of pH dependent polymers in comparison to tablet containing ethyl cellulose alone may be attributed to increase erosion of Cellulose acetate phthalate containing tablets at pH 7.4. The results showed that formulation F9 showed very low initial drug released in first two hours in compared to other formulation while in 14 hours they release the drug almost completely. Hence these formulations were selected for further studies till simulated GI conditions of changing pH. The results shown in table & figure revealed that the formulations when subjected to GI simulated condition release about 2.21% of drug during first 2 hours in 0.1N HCl or 1.2 pH. For the next 2 hours the release slightly increases in both the formulation due to slightly acidic condition of the medium simulated duodenal pH of 4.5. The released after 4 hours is 10.88% respectively after words when the pH of the medium is raised to pH 7.4 the release of the drug from both the formulations increases quite rapidly due to increased erosion of Cellulose acetate phthalate in the alkaline conditions of small intestine. The data obtained from *in vitro* dissolution studies and dissolution studies in GI simulated conditions were fitted in different models like zero order, First order, higuchi model and korsemeyer peppas model. The zero order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release from these matrix tablets the data was fitted according to korsemeyer empirical equation of Mt / M∝ =

Ktn Regression values r^2 were found 0.8722 to 0.9909 for different formulations. The mean diffusional exponent values (n) was found to be ranged from 1.197 to 1.983 indicated all the formulation follows super case II transport i.e. swelling and erosion simultaneously occur during the release. Since both swelling and erosion occur simultaneously, zero order release is achieved from these matrices. This behavior is responsible for maintaining zero order release in which the increase in diffusion path length due to swelling is balanced with the decrease in diffusion path length due to matrix erosion. Overall a constant diffusion path length is maintained. Thus it was found that drug release from indomethacin matrix tablet follows zero order models. No significant difference was observed in the release profile of different batches of each matrix formulation, indicating that the manufacturing process employed was reliable and reproducible. Also, the release kinetics remained unaltered up to one year of storage and there were no changes in the tablet characteristics, suggesting that ibuprofen was stable in EC matrices. In conclusion, matrix embedding technique using EC as the retardant has successfully extended the release of ibuprofen from its tablet formulations. In the present case, we found that the incorporation of CAP in the matrix not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time. The manufacturing method employed is simple and easily adaptable in the conventional tablet-manufacturing units.

CONCLUSION

In the above view of findings it can be concluded that the combination of hydrophobic polymer and pH dependent polymer are better suited for site specific drug delivery system than hydrophobic polymer alone. A matrix design of this kind can serve as an alternative strategy to enteric film coating techniques commonly employed for the design of delayed release systems.

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