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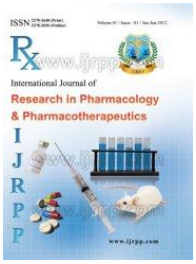

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Research article ***Open Access***

Development, optimization and evaluation of colon targeted drug delivery system utilizing 2^2 factorial design using ibuprofen as model drug

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ABSTRACT

Colon-specific drug delivery systems (CDDS) are not only desirable for the treatment of a range of local diseases such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer but also systemic delivery of proteins and peptides this is because of less diversity and intensity of digestive enzymes and less proteolytic activity of colon mucosa than that observed in the small intestine. The purpose of the present investigation was to prepare matrix tablets using polymers such as guar gum and pectin and the tablets were further coated with different concentrations of Eudragit S-100, a pH-sensitive polymer, by dip immerse method. *In vitro* drug release investigations of tablets were done in various dissolution media, i.e., 0.1 N HCl (pH 1.2), phosphate buffers pH 7.4, with or without rat cecal content. The swelling studies of all formulations were carried out. The physicochemical parameters of the formulations were seen as in consistence with the pharmacopoeial standards for pre and post compression evaluations. The stability studies for all formulations were executed according to ICH guideline and the result showed less degradation during accelerated and room temperature storage conditions for 6 months. The result of drug release study demonstrated that the tablets coated with Eudragit S-100 (30% w/v) showed a sustained release of 93.4% for 13 h, while the uncoated tablets released the drug within 5 h. With regard to release kinetics, the data were best fitted with the Hixson Crowell model. Thus the enteric-coated Eudragit S-100 coated matrix tablets of ibuprofen showed promising site-specific drug delivery in the colon region.

Keywords: CDDS, Ibuprofen, Colon delivery, Hixson Crowell model, Eudragit S-100

INTRODUCTION

Targeted drug delivery into the colon is exceptionally attractive for local treatment of different types of bowel diseases, for example ulcerative colitis, Crohn's disease, amitosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.

The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon [1-4].

Oral route is the most advantageous and favored route yet other routes for CDDS might be utilized. Rectal administration offers the shortest route for targeting drugs to the colon. Nonetheless, arriving the proximal part of colon by means of rectal administration is troublesome. Rectal administration can also be awkward for patients and compliance may be less than ideal. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. Focal points of CDDS over conventional drug delivery in chronic colitis, particular in the ulcerative colitis and Crohn's ailment are now treated with glucocorticoids and other anti-inflammatory agents.

Different drug delivery system approaches have been produced for colon-specific medication delivery, which incorporate pH-sensitive system, time-dependent system, pro medications, and micro flora-initiated delivery to deliver anti-inflammatory to the destinations of inflammations and henceforth systemic drug absorption ought to be decreased as this prompts undesirable systemic side effects. This aim our attempt was made to deliver the drug at colon site with model drug as ibuprofen, the enteric coated time release matrix tablets using Eudragit S-100 as a pH dependent polymer [5].

MATERIALS AND METHODS

Materials

Ibuprofen was obtained as a gift sample from Micro labs, Bangalore, India. Eudragit S-100 was obtained as gift samples from Evonik Laboratory, Mumbai, India. All other chemicals and reagents used in study were of analytical grade.

Methods

Standard calibration curve of Ibuprofen

Calibration curve of ibuprofen was constructed by dissolving pure drug of ibuprofen (100 mg) in phosphate buffer pH 7.4 to get 1000µg/mL concentration and designed as stock solution1. From the stock solution 1, 10mL drawn and diluted 100mL to get 100 µg/mL concentration and designed as stock solution 2. From the stock Solution2 serial dilution was made by 1, 2, 3, 4, 5, 6 ml were pipette out and diluted to 50 ml with pH 7.4 phosphate buffer solution for obtain 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml and 12 µg/ml concentration solutions. and absorbance was measured at 264 nm by using UV visible spectrophotometer[2], the linearity was observed for ibuprofen in phosphate buffer pH 7.4, while the regression was 0.980. The absorbance of relative concentration can observe in Table 1, the linear curve was represented in Figure 1.

Table1. Calibration of standard cure of ibuprofen

Sl.no	Concentration (µg/ml)	Absorbance @ 264
1	2.0	0.0618
2	4.0	0.1290
3	6.0	0.1987
4	8.0	0.2636
5	10.0	0.3341
6	12.0	0.4194

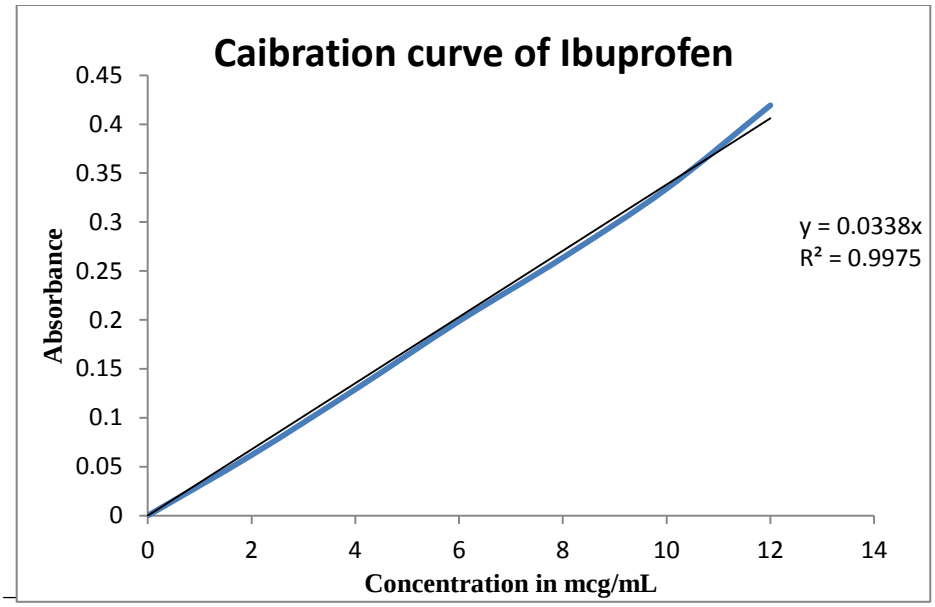

Figure 1. Shows calibration of Ibuprofen

FTIR STUDY

The Fourier transform infrared (FTIR) spectra of pure drug, physical mixture of drug–polymers were recorded using a FTIR spectrophotometer (Perkin Elmer Spectrum 400, England) according to the KBr disk technique. The smoothing of the spectra and the baseline correlation procedures were applied. The FTIR measurements were performed in the scanning range of 4000-400 cm^{-1} at ambient temperature and presented in Figure 2& 3.

Factorial design

Matrix tablets containing ibuprofen were dry blended with appropriate quantity of polymers direct compression technique by using MCC as a diluent to achieve 500mg of total weight of each tablet as given in Table 4. Blend of powder and magnesium stearate (2:1) was used as lubricant. Guar gum and gelatin were incorporated into different extents. All compositions are sieved separately and blended by spatulation technique in mortar and pastel as given in Table 5.7 and compressed to tablet utilizing 8 mm concave punches on 8 station tablet compression machine (Karnavati Rimek, Mini press-II, Mumbai).

Table 2.2^2 factorial design represents two variables at two levels

Level	Factor A	Factor B
High	+	+
Low	-	-

Table 3 Concentration of polymers variables

Level	Factor A	Factor B
High	200	150
Low	50	50

Preparation of the matrix tablets

Table 4.Shows formulation composition of matrix tablet

Ingredient	IBC-A	IBC-B	IBC-C	IBC-D	ICB-E
Ibuprofen	100	100	100	100	100
Guar gum	50	200	50	200	125
Pectin	50	50	150	150	75
Microcrystalline cellulose	335	185	185	35	185
Magnesium stearate	5	5	5	5	5
Talc	10	10	10	10	10
Total	500	500	500	500	500

Table 5.Guar gum and Pectin ratio in Batch A, B, C & D

Batch	Guar Gum (Factor A)	Pectin (Factor B)
IBC-A	10% (Minimum)	10% (Minimum)
IBC- B	40% (Maximum)	10% (Minimum)
IBC – C	10% (Minimum)	25% (Maximum)
IBC– D	40% (Maximum)	25% (Maximum)
IBD-E	25% (Minimum)	15% (Minimum)

Enteric coating of the matrix tablets

Ibuprofen matrix tablets were further coated with pH-dependent polymer Eudragit S-100 using dip immerses method[5] using factorial design. A different concentration (i.e., 20, 30, and 35 %) of coating solution of Eudragit S-100 was prepared in a mixture of isopropyl alcohol (IPA) and acetone as presented in table 6 and 8. The coated tablets were dried at room temperature for 24 hrs and kept in vacuum desiccators.

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Table6. Experimental design for coating of core matrix tablet

Factor	Level			Responses
	(-1)	(0)	(+1)	
Amount of polymer (%) (X1)	25	30	35	Drug release after lag time (Y1)
Core to coating ratio (X2)	1:1	1:2	1:3	Lag time of 5 h (Y2)

Table 7. Composition of Experimental coating Formulations

Run	X1 Eudragit S 100 (%)	X2 Coating Level (%)
CIT1	25	1:1
CIT2	25	1:2
CIT3	25	1:3
CIT4	30	1:1
CIT5	30	1:2
CIT6	30	1:3
CIT7	35	1:1
CIT8	35	1:2
CIT9	35	1:3

PRECOMPRESSION EVALUATION OF GRANULES

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$\tan\theta = h/r$,

Where θ = angle of repose, h = height, and r = radius.

Bulk density

Bulk density is defined as ratio of total mass of powder to the bulk volume of powder. Bulk volume is the volume occupied by a certain mass of powder when gently poured into a measuring cylinder. It was measured by pouring initially weighed powder into a measuring cylinder and the volume (bulk volume) was noted. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$D_b = M/V_b$,

Where M is the mass of powder and V_b is the bulk volume of the powder.

Tapped density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 100 times and then the tapped volume was noted. It is expressed in g/ml and is given by

$D_t = M/V_t$,

Where M is the mass of powder and V_t is the tapped volume of the powder.

PHYSICOCHEMICAL EVALUATION OF IBUPROFEN MATRIX TABLETS

Weight variation

For estimating weight variation, 20 tablets of each formulation were weighed using an electronic balance (Shimadzu BL220H) and the test was performed according to the official test.

Thickness

The thickness of the tablet was measured using a Digital Vernier Calliper (Mitutoya Digimatic Calliper, Kanagawa Japan).

Hardness

The crushing strength of ten tablets was measured using Monsanto tablet hardness tester (Interlabs, Ambala, India). A tablet hardness of about 5-7 kg/cm^2 is considered adequate for mechanical stability.

Friability

The friability of the tablets was determined in Roche Friabilator. Six tablets were weighed accurately from each batch of tablets and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. Tablets were taken and again weighed. The percentage loss was determined by using the formula:

Drug content

Tablets were finely powdered and quantity of the powder equivalent to 100 mg was accurately weighed and transferred to a volumetric flask containing 50 ml of phosphate buffer, pH 7.4. The flask was shaken to soluble and the volume was made up to 100 ml with phosphate buffer 7.4. The solution was filtered through a membrane filter (0.22 µm) and analyzed for drug content using UV/Visible spectrophotometer (Systronics, Mumbai, India) at 264 nm.

Swelling studies

The swelling studies were carried out of optimized formulations. The swelling index of the tablet was estimated by means of 1% agar gel plate. The initial weight of the matrix tablet was deliberate (W1). The matrix tablet from each formulation was located on gel surface in a Petridis incubator at 37 ± 5°C. The tablets were detached at dissimilar time intervals (1, 2, 3, 4, 5 and 6 h) and wiped with filter paper and weighed again (W2). The % swelling index was calculated using the following formula:

S.I = [(W2-W1)/ W1] X 100

Where S.I= Swelling Index

In vitro drug release studies

The in vitro dissolution studies were performed for the ibuprofen matrix tablet using USP II

dissolution apparatus (Lab India, DS 8000, Mumbai, India) in 900 ml dissolution medium at 100 rpm, 37°C ± 0.5°C. The dissolution media with pH 1.2 and phosphate buffer pH 7.4 were used in order to simulate the pH change along the GIT.

The in vitro drug release experiments were performed at pH 1.2 for 2 h. Then a pH 1.2 buffer was replaced with pH 6.8 phosphate buffer dissolution media for 3 h. After performing the experiments for 3 h with pH 6.8 phosphate buffer, the dissolution media were replaced finally with phosphate buffer pH 7.4 for the next 19 h. At regular time intervals, samples were withdrawn from the dissolution media and filtered with Whatmann filter paper (0.22 µm). The absorbance was measured using UV/Visible spectrophotometer (Systronics) at 264 nm. The graph was plotted against cumulative percentage drug release versus time. The experiment was done in triplicate and data were expressed in mean ± SD [6].

Preparation of rat-cecal content for dissolution studies

The drug release studies were carried out using USP dissolution rate test apparatus in 900 ml dissolution medium at 100 rpm, 37°C ± 0.5°C, with slight modification, as previously discussed by Mundargi [7]. After completing the dissolution studies in pH 1.2 phosphate buffers for 2 h, the matrix tablet was transferred to pH 6.8 phosphate buffers for 3 h. After placing matrix tablet in pH 6.8 phosphate buffer, it was transferred to 200 ml phosphate buffer pH 7.4 diluted with 4% (w/v) rat cecal medium for 19 h. As cecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers. At regular time intervals, 2 ml of the dissolution samples was withdrawn and replaced with 2 ml of 4% (w/v) rat cecal medium. The absorbance was measured using UV/Visible spectrophotometer (Systronics) at 264 nm.

Kinetic analysis of dissolution data

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. The dissolution data were also fitted to the well-known exponential equation (Korsmeyer – Peppas equation), which is often used to describe the drug release behavior from polymeric systems:

$\text{Log } Mt/M_\infty = \log k + n \log t$,

Where M_t is the amount of drug released at time t, $M \infty$ is the amount of drug released after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the mechanism of drug release.

To determine the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch. A value of $n = 0.45$ indicates > 0.45 Fickian (case I) release, <0.89 indicates non-Fickian (anomalous) release, and n > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.

Stability Study

The stability study was conducted according to ICH guidelines. All the formulations were stored in aluminum packaging laminated with polyethylene (cellophane packets) and kept in humidity chamber at 30°C ± 2°C/65% ±5% RH (room temperature studies) and 40°C ± 2°C/75% ±5% RH for 6 months. The tablets were analyzed after 0 day, 1 month, 2 months, 3 months, and 6 months. At the end of the study period, the tablets were observed for any changes in physical appearance, color, and drug content.

RESULT AND DISCUSSION

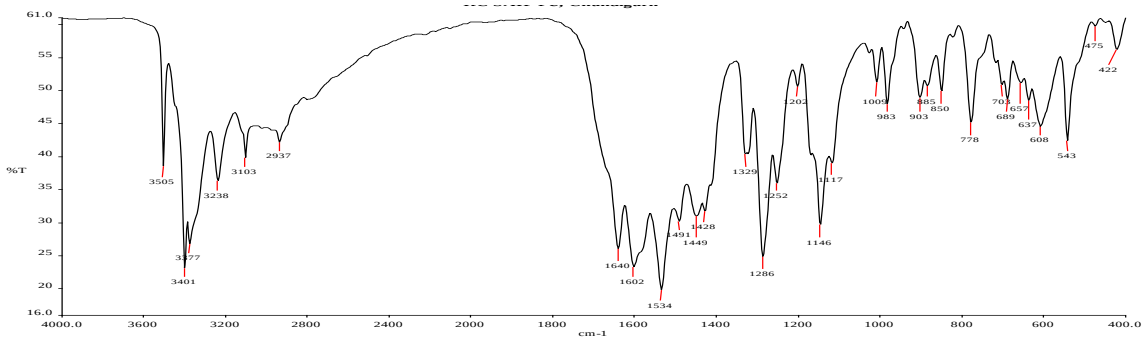

Figure 2 shows FTIR Spectra of pure Ibuprofen

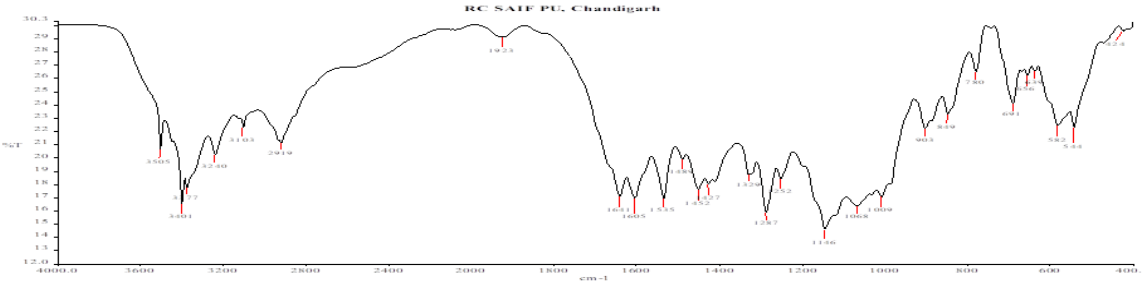

Figure 3 depicts FTIR spectrum of formulation

FTIR ANALYSIS

The FTIR spectrum of ibuprofen[8] and formulation was shown in Fig.2&3. FTIR spectrum of ibuprofen shows the peak at 2937cm^{-1}for C-H stretching of alkane which is observed in the formulation at 2919cm^{-1}. Peaks for C=O stretching for carboxylic acid shows peak at1640cm^{-1} which can be observed in the formulation at 1641cm^{-1}. C-C stretching in the aromatic ring is observed for pure ibuprofen at 1428. cm^{-1} which is observed in the formulation at 1427 cm^{-1}. C-O stretching for carboxylic acid shows peak at 1183.03 cm-1which is also present in the formulation at 1146cm^{-1}. O-H bending for carboxylic acid is observed at 983cm^{-1}which can be seen in the formulation at 1009 cm^{-1}.The characteristic peaks appeared in the FTIR spectrum of ibuprofen is observed in the formulation without any significant shifting of peaks which indicates the absence of any chemical or physical interaction during and after preparation.

PRECOMPRESSION EVALUATION

The granules for ibuprofen matrix tablets were prepared by direct compression method according to the formula shown in Table 1. The granules were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The parameters for evaluation of granules are depicted in Table 8. The angle of repose of different formulation batches was found to be from 32.8° ± 0.22 to 48.4° ± 0.1. The angle of repose was between 41-45° for all the formulation batches of granules, indicating passable of flow property. However, aid is required to increase flow ability. Similarly, The Carr's index of all formulation batches was in the acceptable range from 7.6 to 32.9. The Hausner ratio of all formulation batches was found to be from 1.08 ± 0.3 to 1.49 ± 0.21 were also depicting essential of aid to improve the flow properties. The bulk density and tap density of all the formulation batches were found to be from 0.350 ± 0.1 to 0.44 ± 0.22 g/ml and from 0.46 ± 0.3 to 0.57 ± 0.03 g/ml. depicting good compressibility of the granules.

Table 8 Pre-compression Evaluation of prepared matrix granules

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Angle of Repose (θ)	Hausner's ratio	Carr's index
IBC-A	0.350±0.12	0.522±0.09	32.8± 0.22	1.49±0.21	32.95± 0.21
IBC-B	0.388±0.01	0.552±0.02	36.8±0.12	1.42±0.11	29.71±0.11
IBC-C	0.410±0.02	0.570±0.03	40.0±0.22	1.39±0.22	28.07±0.22
IBC-D	0.440±0.22	0.504±0.04	48.4±0.11	1.14±0.22	12.69±0.25
IBC-E	0.425±0.01	0.460±0.03	45.2±0.12	1.08±0.01	7.6±0.02

POST-COMPRESSION EVALUATION

The tablets of different formulations without coating were subjected to various evaluation tests of weight variation, thickness, hardness, friability, and drug content. In Table 9 is presented the results of physicochemical evaluation of all batches of ibuprofen matrix tablets. The weight variation of all formulated batches, i.e., from IBC-A to IBC-E, was found to be from 496 ± 3.11 to 506.3 ± 2.2 mg. The weight variation of all formulation batches was less than 4% which was in acceptable range. The thickness of formulations was found to be between 3.99 ± 0.12 and 4.23± 0.14 mm. The hardness of formulations was found to be from 2.8 to 8.20kg/cm^2.

The friability of all tablets in formulation was in acceptable range of less than 1%, ranging from 0.07% ±0.02% to 0.62% ±0.1%. The drug content of all formulation batches was found to be between 98.13% ±3.0% and 103.00% ±0.42%.

Table 9 Post-compression evaluation of Ibuprofen matrix tablets

Formulation	Hardness (Kg-cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Weight variation (mg)
IBC-A	2.8-3.2	0.62± 0.10	4.01± 0.21	98.10 ±3.02	499 ± 5.01
IBC-B	4.0-5.2	0.27± 0.03	4.11± 0.11	99.13 ±2.02	496 ± 3.11
IBC –C	5.1-6.6	0.129± 0.04	4.21± 0.31	101.13±1.02	502 ± 4.02
IBC –D	6.4-8.2	0.07± 0.02	4.23± 0.14	103.00±0.42	506 ± 2.21
IBC- E	5.2-6.0	0.14± 0.01	3.99± 0.12	100.10±0.12	499 ± 7.01

Table 10.Swelling study of various formulations

Time (hr)	IBC-B	IBC-C	IBC-D	IBC-E
0	0	0	0	0
1	0.392	0.0935	0.011	0.092
2	1.00	0.1872	0.023	0.190
3	1.311	0.4496	0.148	0.326
4	1.490	0.6918	0.485	0.790
5	1.879	0.9765	0.693	1.206
6	2.291	1.1726	0.877	1.510
7	2.43	1.3067	1.001	1.699
8	2.502	1.4060	1.067	2.186

Swelling study

The swelling study carried out for all formulations IBC-A to IBC-E. The swelling study of formulation IBC-A was completely disintegrated and IBC-B was more swelling properties than all three formulations might due to in this formulation higher concentration of anionic guar gum more uptake of water and hydrated to swelling.

Invitro release study

The in vitro drug release of formulations IBC-B and IBC-C was found to be 51 ±0.95% and

30.1±0.82%, respectively, within 5 h in pH 7.4 phosphate buffer [Figure 4]. Among the all formulations batch E was found to be better formulation with respect to formulation and compression characteristics. The release pattern of the batch E was also satisfactory and it can be defined as the optimized formula of overall formulation design. Moreover attempt was made to retarding the release of the drug for IBC-E, for the reason that its drug release further increase in the lag time and delay in release of drug to reaches to colon region consequently chose this formulation for to coat with different concentration of Eudragit S100 polymer. The coating of the tablet using different coating concentrations.

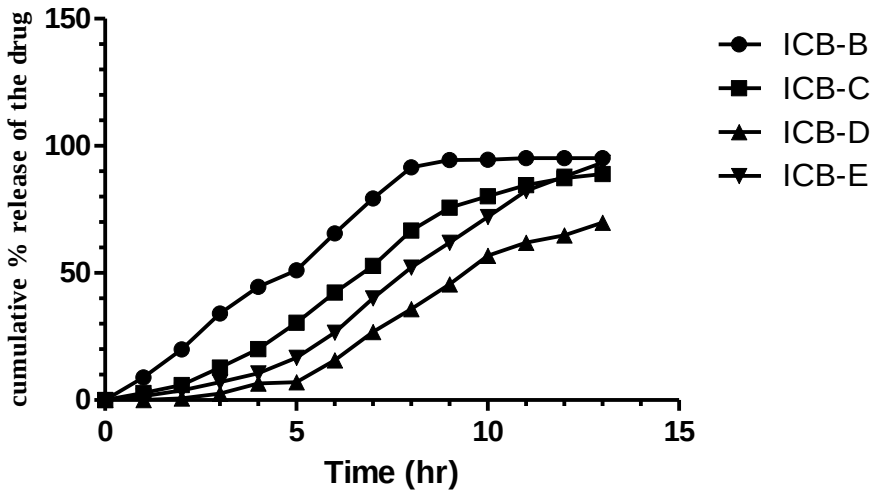

Figure 4. In vitro cumulative percentage release of ibuprofen of all formulations

Coated ibuprofen tablets of CIT1, CIT2 containing 25% polymer in conjunction with 1:1 and 1:2 cores to coating proportion displayed release of drug occurring before reaching to colon. This impact could be credited to little quantify of coating material which neglected to control drug release in stomach and small intestine. Formulation CIT4 and CIT5 containing 30% polymer with 1:1, 1:2 core to coating ratio despite the fact that displayed 98.98% and 100.19% drug release up to 12 h, nonetheless, these details likewise released drug in upper part of GI tract. CIT7 and CIT8 released 96.28% and 92.31% drug up to 12 h, however releasing small amount of drug in stomach and additionally small intestine (Figure 6.28).

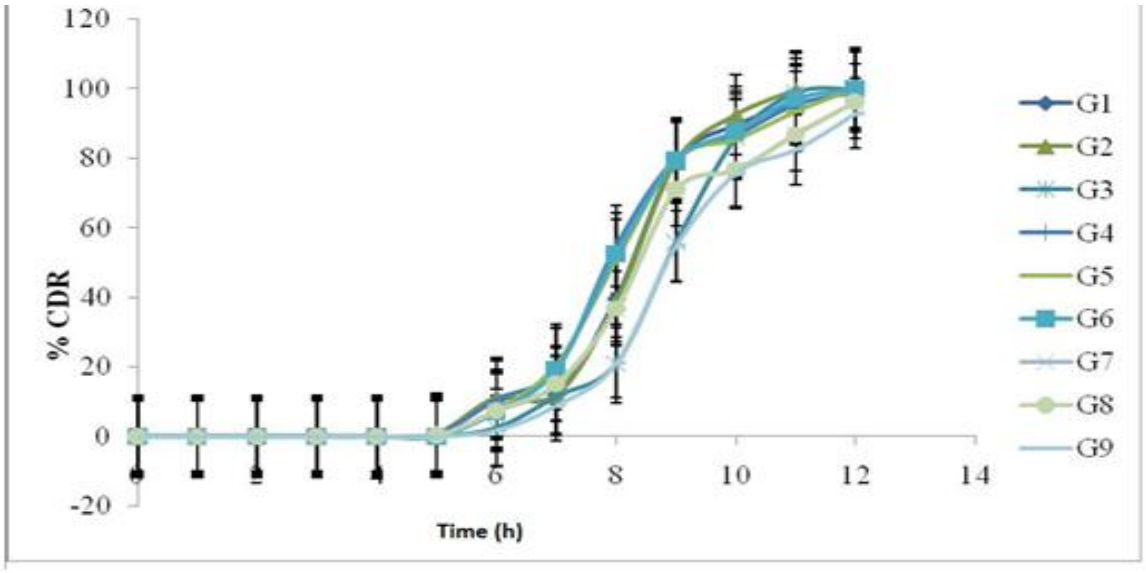

Figure 5 In vitro drug release study of enteric coated tablets (CIT1-CIT9)

Formulation CIT3, CIT6, CIT9 on other hand, did not allow drug to be released in upper part of GI tract and on reaching colonic region these formulations exhibited drug release sustained for 12 h. In vitro drug release data was then put up in Design expert software for regression analysis.

Table 11.Concentration polymer for optimized Batch

S. No.	Amount of polymer	Coating ratio	Drug release (%)	lag time (min)	Desirability
1	25%	1:3	99.76	330	0.993

Release pattern

Table 12.Regression coefficient (r^2) values of drug release data obtained from various kinetic models and "*n*" value (diffusional exponent) according to Korsmeyer–Peppas model.

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Hixson - crowell(r^2)	Korsmeyer peppas	
					r^2	n
IBC-B	0.997±0.02	0.986±0.06	0.988±0.21	0.860±0.06	0.990±0.22	0.94
IBC-C	0.998±0.01	0.997±0.20	0.990±0.11	0.998±0.22	0.989±0.12	1.4
IBC-D	0.995±0.04	0.995±0.23	0.989±0.22	0.998±0.13	0.987±0.12	1.0
IBC-E	0.993±0.01	0.991±0.13	0.990±0.16	0.993±0.11	0.987±0.22	1.7

The release kinetic of cumulative % of drug release against time represents that drug release of ibuprofen from the matrix is perfectly following Higuchi drug release model as the drug release profile is very closest to trend line or regression line and there is highest value of coefficient of correlation (r^2=0.988) and interpret that the prime mechanism of drug release is diffusion controlled release mechanism[9]. Also, the model Korsmeyer-Peppas power law equation states the type of diffusion, which was evaluated by value, n (Release exponent) which is higher than 0.89 which implies that the drug release from the system follow Super case II transport.

Stability studies

The stability studies of formulation of IBC-A for targeting ibuprofen to the colon was carried out at 30°C ± 2°C/65% ±5% RH (room temperature studies) and at 40°C ± 2°C/75% ±5% RH

(accelerated temperature studies) for 6 months as per ICH guidelines. After storage for 0 day, 1 month, 2 months and 3 months, the tablets was observed for physical appearance and were subjected to drug content and drug release study. No significant change in the physical appearance, drug content and release after storage, when compared to the tablets of the same batch before storage indicated that formulation (IBC-A) is stable and considered to be optimized which could provide a good shelf life for 3 months [10].

Table 13. Drug content for stability study

S. No.	Day 0	Day 30	Day 60	Day 90
Drug content	99.14±0.11	98.87±0.21	100.09±0.22	99.89±0.12
Drug release	99.76± 1.19	98.96 ± 1.40	98.02 ± 1.65	97.25 ± 1.87

The coating of the tablet using different coating concentrations of Eudragit S-100, pH-dependent meth acrylic acid copolymer, increased the lag time and provided entire coat that allowed the tablet to pass intact through the stomach and small intestine to target in the colon.

CONCLUSION

It is concluded from the present study that of a pH-dependent polymer (Eudragit S-100) coated prepared core formulation was suitable for adequately sustained drug release and to protect ibuprofen from being released in the upper region of the GI system. The in vitro drug release studies indicate that the optimized formulation was a promising system targeting ibuprofen to the colon. The drug release pattern from all formulations was best fitted with Higuchi release model and that the drug release from the system follow Super case II transport.

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