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Formulation and *In-vitro* Evaluation of Ileo-Colonic Targeted Tablet of Flurbiprofen Using Natural and Semi Synthetic Polymers for Ulcerative Colitis

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Authors' contributions

This work was carried out in collaboration among all authors. Author YM designed the study, performed research work and wrote the protocol. Authors SA and HY managed the materials. Authors AT and LS collected all data and performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

In present research work, we have developed ileo-colonic targeted matrix tablets of flurbiprofen for chronotherapeutic treatment of ulcerative colitis. Direct compression technique was used to formulate matrix tablets of flurbiprofen using microsomal enzyme dependent and pH-sensitive polymers. FTIR and DSC studies were conducted to access the compatibility for flurbiprofen, polymers and physical mixtures. In this research we have used two types of polymer one is synthetic and other is natural, and both polymers have achieving colon targeted drug A physicochemical study was evaluated of all formulated batches. Estimation of drug content, *in vitro* release of drug and stability studies was also performed. No interaction was observed between drug

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and the polymers in FTIR and DSC studies. However when the formulated matrix tablets were subject to physicochemical properties then all the readings were within limits. The percentage of flurbiprofen in the optimized formulation C5 was found to be 98±0.10%. According to the guide-lines of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use the formulation was found to be stable. Six formulations were prepared and evaluate. For the protection of drug from the environment of the stomach pH dependent polymers Eudragit S100 was used for its enteric coating.

Keywords: Eudragit S100; colon targeted tablets; polymers; ileo-colonic; matrix.

1. INTRODUCTION

Different diseases such as ulcerative colitis, colon cancer and diarrhea can be treated by using delivery of drug through colon, and by this route different drugs of different nature and molecular weight can be administered effectively [1]. This method is good for poorly absorbed drugs because colon provides long retention time and shows good absorption [2]. Local and systemic delivery of drugs can be used by this method. Several therapeutic advantages can be achieved by targeting of the drug to the colon [3]. Different diseases such as angina pectoris [4] and asthma can be treated by sustain release of drug in colon [5], and this route can also be used for the drugs which are destroyed or metabolized by the stomach enzymes. More effective treatment can be obtained by direct delivering the small amount of drug to colon [6]. This route is attracting to the researcher for its improved bioavailability [7]. Targeting of drug to colon depends on different approaches which are:

1. Delivery to colon of pH sensitive polymer coated drug [8].
2. Delayed release drug delivery [9].
3. Microbial triggered drug delivery [10].
4. Pressure controlled drug-delivery systems [3].
5. Novel colon targeted delivery system [11].
6. Osmotic controlled drug delivery system [2].

Researchers have developed various colon targeted drugs using different polymers such as metronidazole [12], imidazole [13], ornidazole [14] Prednisolone [15] and flurbiprofen [16]. Hydroxy Propyl Methyl Cellulose (HPMC. polymer mostly used in sustain release dosage form [17]. Among different approaches Enteric-coated system is most commonly used [2]. The difference of enzyme gradient activity depends on the microbial flora of GIT [18]. In humans, the concentration of microbial flora raises from ilium to colon [19] i.e. 1,011–1,012 CFU/mL. Hence, the delivery of drug to colon is best achieved by enzymatic controlled drug delivery system [20]. Flurbiprofen (FLB) is a nonsteroidal anti-inflammatory drug and it is used to treat various colon infections [21]. However the long term use of FLB may leads to various side effects like gastric bleeding, peptic or gastric ulcer etc [22]. So these side effects may be prevented by the technique of direct delivery of FLB in the colon as high concentration in the colon may also be achieved in this way [22]. Some recent researches were performed also in development of colon targeting for FLB. However in their cases colon targeted systems are flurbiprofen microsponges [21], FLB pulstate tablets and controlled release tablets [23].

Present study was conducted to produce the colon targeted formulation using different materials and microbial flora dependent polymers. Direct compression process used for prepared the tablets. Then after wards the enteric coating was carried out on these formulations.

2. EXPERIMENTAL

2.1 Materials

Flurbiprofen (sigma Aldrich), Lactose Anhydrous (sigma Aldrich), Avicel PH 102, Magnesium stearate (Merck chemicals), Guar gum, Hydroxypropyl Methyl Cellulose (HPMC k 100) (sigma Aldrich) & Eudragit S 100 (sigma Aldrich). All the chemicals used for this research study were of Analytical grade.

2.1.1 Preparation of ileo-colonic targeted matrix tablets

Ileo-colonic targeted matrix tablets of flurbiprofen were made using the direct compression technique. Flurbiprofen, Lactose Anhydrous, Avicel PH 102 Magnesium stearate and polymers (Guar gum and HPMC k 100) were sieved through mesh no. 30 to achieve uniform

Table 1. Composition of the formulations of ileo-colonic matrix tablet

Formulation	Flurbiprofen	HPMC k 100	Guar Gum	Mg. stearate	Lactose	Avecil 102	Total weight
C1	100 mg	60 mg	-	10 mg	10 mg	20 mg	200 mg
C2	100 mg	50 mg	20 mg	10 mg	10 mg	20 mg	200 mg
C3	100 mg	40 mg	30 mg	10 mg	10 mg	20 mg	200 mg
C4	100 mg	30 mg	40 mg	10 mg	10 mg	20 mg	200 mg
C5	100 mg	20 mg	50 mg	10 mg	10 mg	20 mg	200 mg
C6	100 mg	-	60 mg	10 mg	10 mg	20 mg	200 mg

Table 2. Composition of enteric coating material

Ingredients (mg.)	Enteric coating					
	E1	E2	E3	E4	E5	E6
Eudragit S 100	10	20	30	40	50	60
Color	2	2	2	2	2	2
Titanium dioxide	20	20	20	20	20	20
Talc	30	30	30	30	30	30
IPA 70%	600 mL	600 mL	600 mL	600 mL	600 mL	600 mL

Table 3. Resistance of enteric coated tablets in 1.2 Hcl medium

Time/Min	C1	C2	C3	C4	C5	C6	
0	0	0	0	0	0	0	E1
120	15	15	15	15	15	15	
0	0	0	0	0	0	0	E2
120	30	30	30	30	30	30	
0	0	0	0	0	0	0	E3
120	50	50	50	50	50	50	
0	0	0	0	0	0	0	E4
120	90	90	90	90	90	90	
0	0	0	0	0	0	0	E5
120	125	125	125	125	125	125	
0	0	0	0	0	0	0	E6
120	140	140	140	140	140	140	

particle size. All the sieved materials were mixed together geometrically for 15 minutes. The blended mixture was compressed into tablets using 10.5 mm round biconvex dies & punches using ZP-9 compression machine. Polymers with different ratios of Guar gum & HPMC k 100 was used to prepare the matrix tablets.

Table 1 shows the formulations of different batches with varying %age concentration of excipients with the active pharmaceutical ingredient (API). All the tablets of formulations were stored in an air tight container till further use.

2.1.2 Enteric coating

The compressed tablets obtained than coated with enteric coating polymer by a method known as dip coating. Magnetic stirrer was used for dissolving the recommended quantity of Eudragit S 100 in isopropyl alcohol 70%. Anti-adherent material such as Talc was added and stirring carried out for further 15 minutes. Then these tablets, which were weighed previously, were 3-5 times dipped in the prepared solution.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Physical Parameters [24]

The prepared tablets were then evaluated for different quality control testing. Variation in the weight, friability, hardness and drug content were estimated. For weight variation, 20 tablets were selected randomly from each formulation and these were weighed on electronic weighing balance (Shimadzu, Japan). Average value and deviation were then calculated. Monsanto tablet hardness tester was used to determine tablet hardness of six tablets. Roche friabilator was used to determine friability of ten tablets. For the

estimation of drug content, ten tablets were selected randomly and these were then crushed. Crushed tablets were then weighed equivalent to 100 mg of FLB. Solution was then prepared and analyzed for FLB using the spectrophotometer at wavelength of 254 nm.

3.2 Study of Interaction by Fourier Transform Infrared Spectrometry (FTIR) [6]

The interaction between drug and its polymer, polymer with polymer were studied with FTIR (Perkin elmer Model 12. 1954).

3.3 Differential Scanning Calorimetry (DSC. Studies)

Perkin elmer DSC 8500 was used to confirm the observations obtained by FTIR studies.

Figs. 7 and 8 shows the DSC thermograms of pure flurbiprofen and their physical mixture. At 116.08℃ a sharp exothermic peak of FLB was obtained as shown by the DSC thermogram. However, the peaks of physical mixtures of flurbiprofen, guar gum, HPMC k 100, flurbiprofen and Eudragit S100 were found at 50.75 ℃, 83.30℃ and 115.22℃, respectively. Hence it was confirmed from the results of DSC thermo-grams that the physical mixtures of drug and polymers used in the formulation batches does not show any chemical interaction.

3.4 Construction of Standard Calibration Curve

Flurbiprofen can be estimated spectrophotometrically at 254 nm as it obeys Beer-Lambert's law. From Stock solution, dilutions are done finally giving the concentration of each solution ranging from 5-840 µg/ml. Absorbance of each solution was measured at 254 nm against 7.4 phosphate buffers as a blank. A plot of concentrations of drug versus absorbance was plotted. The analysis was done on absorbance data points and given in Table 7 and Fig. 6.

3.5 Flow Properties of Powder [25]

3.5.1 Bulk density

It was calculated by pouring pre sieved powder into a graduate cylinder through a funnel. The volume and weight of powder was calculated

Bulk density = weight of powder/ Bulk volume of powder.

3.5.2 Tapped density

Tapped density was estimated using a graduated cylinder containing an identified mass of powder blend and placing it on a mechanical tapper which taps the powder until a minimum volume of powder blend is reached

Tapped density = weight of powder/Tapped volume of powder

3.5.2.1 Angle of repose

It was estimated by pouring the powder blend via a conical funnel by raising it vertically until a cone shape heap is achieved. Measuring height and diameter of the heap it is determined by following way;

$\text{Tan}\Theta = h/r$

$\Theta = \tan^{-1} h/r.$

Where h is the height of heap, r is radius and Θ is the angle of repose .The flow of powder blend is excellent if the value of angle of repose is less than 20. If the value is in range of 25 to 30, flow of powder is considered good. Flow of powder is satisfactory if the value is 30 to 40. If the value is more than 40 it means powder flow is very poor.

3.5.3 Hausner's ratio

It denotes the flow properties of the powder and is the ratio of tapped density to the bulk density of the powder. It was established that this ratio is related to inter-particle resistance.

Hausner's Ratio = Tapped density/Bulk density

According to IP, flow of the powder is considered excellent if the value is 1 to 1.1 and if the value is 1.1 to 1.18 the flow is good. Ratio is consider fair if the value is 1.19 to 1.25 and if value is 1.26 to 1.34 flow is consider as passable. If the value is more than 1.35 than powder flow is consider poor.

3.6 Evaluation of Tablets for Post Compression Parameter (Hardness, Thickness and Weight Variation [26]

For handling different amount of pressure during manufacturing and handling tablets, require

different amount of strength & resistance to friability. Monsanto Hardness tester was used for the determination of hardness of these tablets and is indicated by Kg/cm^2. Standard deviation and thickness was calculated by randomly taking the 6 tablets from the formulation. Thickness was calculated using screw gauge. Test for the weight variation of randomly selected 20 tablets were also carried out according to the procedure by electronic balance.

3.7 Uniformity of Contents [27,28]

Core tablet was powdered and transferred to 100 mL volumetric flask. The complete solubility of drug was obtained by adding 50 mL methanol and allowed to stand for 6 hours with occasional shaking. 100 mL volume was made up with methanol. Then 1 mL of the prepared solution was taken diluted, filtered and analyzed at 254 nm taking methanol as blank solution. The contents of the drug were calculated.

3.8 Study of *In-vitro* Disintegration of Internal Core Tablet [3]

Disintegration apparatus was used for studying *in-vitro* disintegration profile of tablets according to specification. Basket of the apparatus was filled with one tablet each and places the disc in each tube over the tablet and then on adding 900mL solution of pH7.4 runs the apparatus. The cycles were adjusted at 30 cycles/min at 37℃ in distilled water. The time for the disintegration of the tablet was measured.

3.9 Drug Release Studies *In-vitro* [27,29]

Dissolution test USP apparatus II was used for studying dissolution of these coated tablets at a speed of 50 rpm at 37.0±0.5℃. The study was performed using 250 mL 0.1 N Hcl of pH 1.2 for 2 hours, followed by 250 mL PBS of pH 6.8 for 3 h, and finally 250 mL PBS pH 7.4 for 24 hours. After every hour, 1 mL solution is withdrawn and equal amount of solution added. Then the solution was filter by 0.45 µm filter and analyzed by spectrophotometer (shomadzo).

3.10 Short Term Stability Studies [30]

Short term stability study was performed at a temperature of 40±2 ℃ over a period of six months (180 days). on the promising flurbiprofen colon targeted tablets. Sufficient numbers of tablets (10) were individually wrapped using aluminium foil and packed in amber color screw cap bottle and kept in stability chamber for six months. Samples were taken at each month interval for evaluation of drug content and in vitro drug release study.

3.11 Data Analysis

Regression analysis was performed by using Microsoft excel on the *in-vitro* release data to best fit into various kinetic models like zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell model according to the coefficient of determination.

3.11.1 Zero order kinetic models [31]

This kinetic model is constant rate process which usually does not depend on the drug concentration.

3.11.2 First order kinetic [32]

This process follows the linear kinetic which means that process having direct proportional relationship with drug concentration involved.

3.11.3 Higuchi model [31,33]

This is a mathematical model that intended to give explanation about drug release from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

3.11.4 Korsmeyer-peppas model [34]

Korsmeyer-Peppas model describes a simple relationship of drug release from a polymeric system equation and give explanation about fraction of drug release in time and drug release mechanism.

3.11.5 Hixson-crowell model [35]

Equation derived from Hixson-Crowell mode describes the drug release from systems where there is a change in surface area and diameter of particles or tablets.

3.12 Effect of Microsomal Enzyme Dependent Polymers (Guar Gum)

The *in-vitro* dissolution profile showed that the release rate of flurbiprofen was increased with the increased concentration of guar gum polymer. It was because of the reason that guar gum polymer hinders the release of flurbiprofen in acidic and intestinal pH buffers and increased the release in colonic buffer as it possess the microsomal enzyme dependent characteristics. But FLB release rate was good when guar gum in combination with HPMC k 100 was used as

compared to guar gum alone. Actually HPMC k 100 hinders the release of drug in intestinal buffer.

3.13 Effect of pH Dependent Polymers (Eudragit S100)

The *in-vitro* dissolution profile showed that with the use of Eudragit S100 polymer coating on matrix-mini-tablets, release rate of FLB was decreased while lag time was increased. It was because of the reason that Eudragit S 100 polymer hinders the drug release in low pH buffers while in ileo-colonic buffer the release rate was increased. The reason behind this is that the Eudragit S100 polymer possesses good solubility in 6.5 and 6.8 pH.

3.14 FT-IR Study and Interpretation of Flurbiprofen with Polymers and Excipients

We studied FT-IR of flurbiprofen raw material and HPLC k 15 for its identification and found according to specifications, secondly we checked compatibly of flurbiprofen with polymer and other excipients. We observe no extra peak in our blend and it means there is no interaction in flurbiprofen and polymer.

3.15 Thermal Analysis Interpretation

The DSC analysis of flurbiprofen given in Fig. 7 and 8 shows that material was stable. Differential scanning calorimetry is the thermal analysis method practiced to evaluate the temperatures and heat flow linked with shifts as a function of time and temperature. Transi-tion related to absorption or emission of heat created alteration heat flow. At 116.08℃ a sharp exothermic peak of FLB was obtained as shown by the DSC thermogram. However, the peaks of physical mixtures of flurbiprofen, guar gum, HPMC k 100, flurbiprofen and Eudragit S 100 were found at 50.75℃, 83.30℃ and 115.22℃, respectively. Difference in energy is recorded as a peak. The area under the peak is directly related to enthalpy changes, and the direction of peak designates the thermal episode as endothermic exothermic.

Table 4. Blend flow properties of powder

Sr. no.	Formulation trial no.	Angle of repose(č)	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio
1	C1	28.72	0.618	0.761	18.75	1.23
2	C2	26.35	0.649	0.769	15.63	1.19
3	C3	27.12	0.610	0.697	12.50	1.14
4	C4	25.24	0.721	0.781	7.69	1.08
5	C5	29.36	0.636	0.749	15.15	1.18
6	C6	29.64	0.668	0.713	6.25	1.07

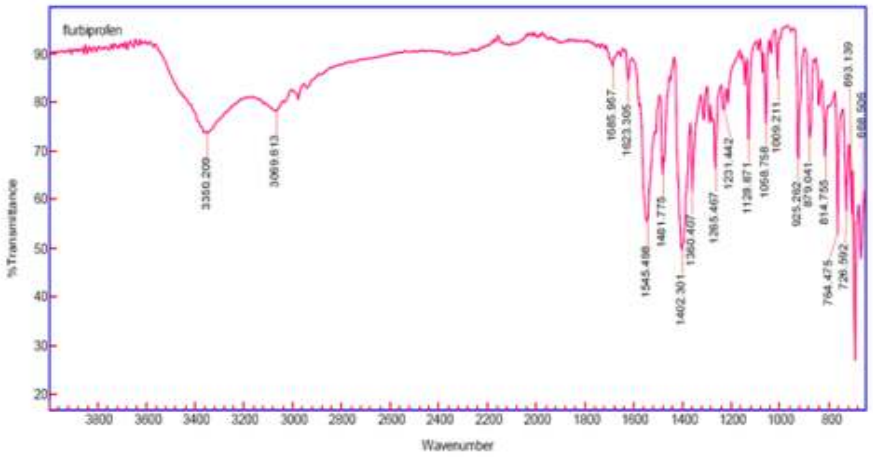

Fig. 1. FTIR of flurbiprofen

Table 5. Evaluation parameters of tablets

Formulation	Thickness (mm)		Hardness (kg/cm^2)		Weight variation (mg)		Friability (%)	
C1	4.41	0.02	6.21	0.02	200.53	0.02	0.41	0.01
C2	4.55	0.02	6.55	0.02	200.55	0.02	0.55	0.01
C3	4.50	0.02	6.83	0.02	200.50	0.02	0.50	0.01
C4	4.43	0.02	6.21	0.02	200.13	0.02	0.43	0.01
C5	4.52	0.02	6.35	0.02	200.45	0.02	0.51	0.01
C6	4.50	0.02	6.80	0.02	200.50	0.02	0.50	0.01

Table 6. Analysis of the *in-vitro* release data according to various release kinetic models

Formulation code	Zero order	First order	Higuchi	Hixson-crowell	Korsmeyer-peppas	
	r^2	r^2	r^2	r^2	r^2	r^2
C1	0.8477	0.9530	0.8880	0.9240	1.7286	0.8447
C2	0.8059	0.9470	0.8628	0.9185	1.2346	0.7628
C3	0.9858	0.8713	0.9770	0.9307	1.3320	0.9714
C4	0.8471	0.9530	0.8881	0.9245	1.7281	0.8497
C5	0.8052	0.9470	0.8625	0.9185	1.2346	0.7625
C6	0.9853	0.8711	0.9770	0.9306	1.3322	0.9716

Table 7. Standard curve of flurbiprofen in phosphate buffer pH (7.4. at 254 nm)

Sr. No.	Concentration (µ/mL)	Absorbance 1	2	3	Average Absorbance
1	0	0	0	0	0
2	5	0.120	0.122	0.121	0.121
3	10	0.222	0.220	0.221	0.221
4	15	0.350	0.346	0.348	0.348
5	20	0.467	0.465	0.463	0.465
6	25	0.544	0.544	0.543	0.544
7	30	0.699	0.697	0.695	0.697
8	35	0.760	0.762	0.761	0.761
9	40	0.890	0.891	0.891	0.891

Correlation coefficient = 0.997

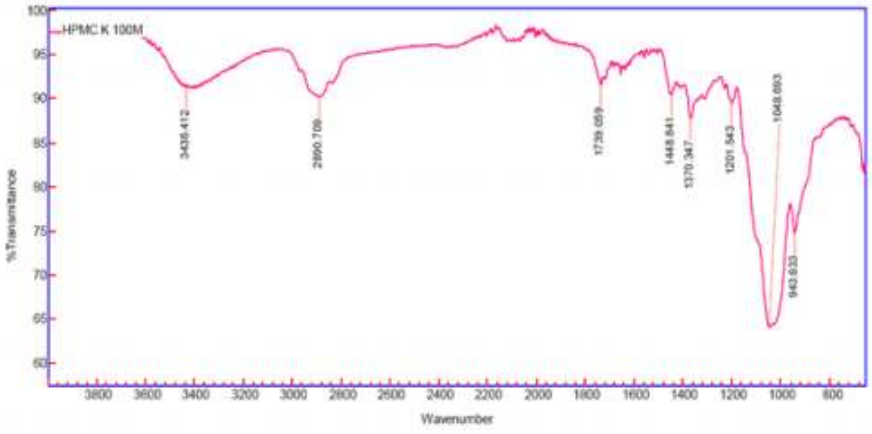

Fig. 2. FTIR of HPMC k 100 material

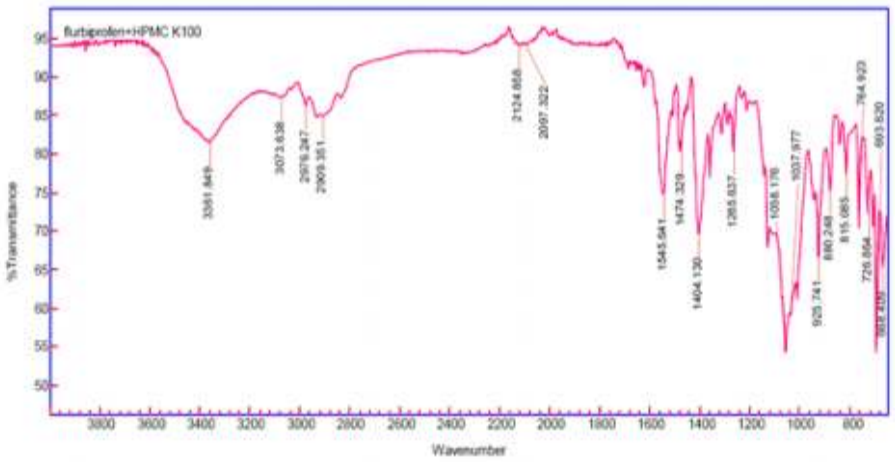

Fig. 3. FTIR of flurbiprofen and HPMC k 100

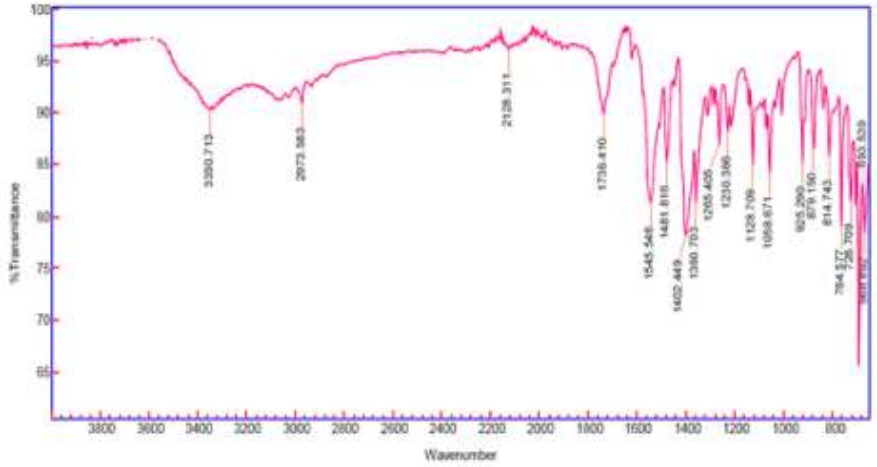

Fig. 4. FTIR of blend

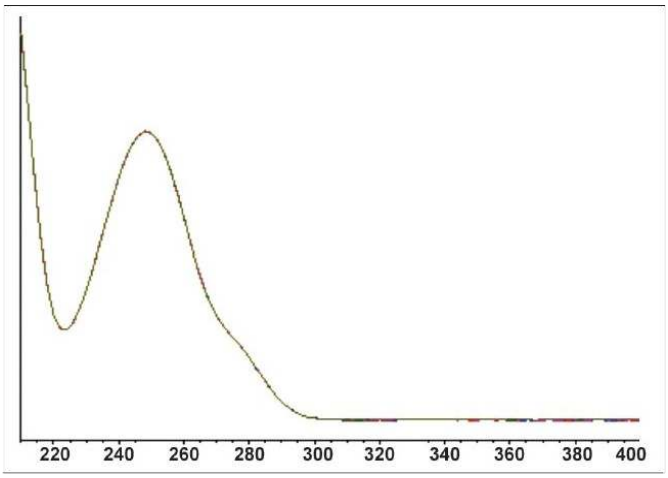

Fig. 5. UV/VIS spectra of flurbiprofen

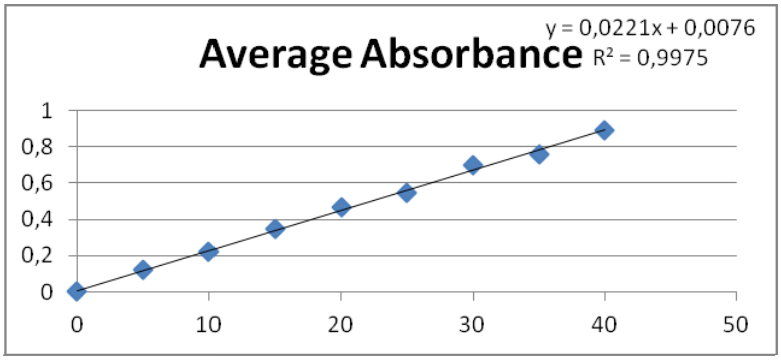

Fig. 6. Calibration curve of flurbiprofen raw material

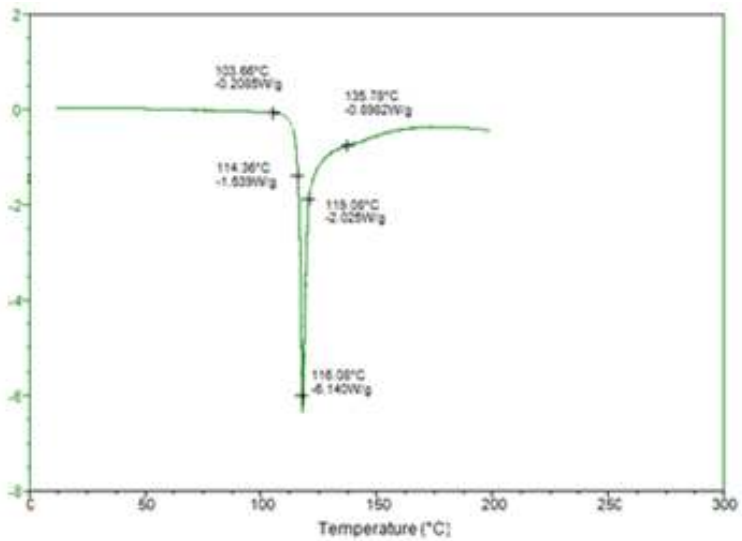

Fig. 7. DSC of flurbiprofen alone

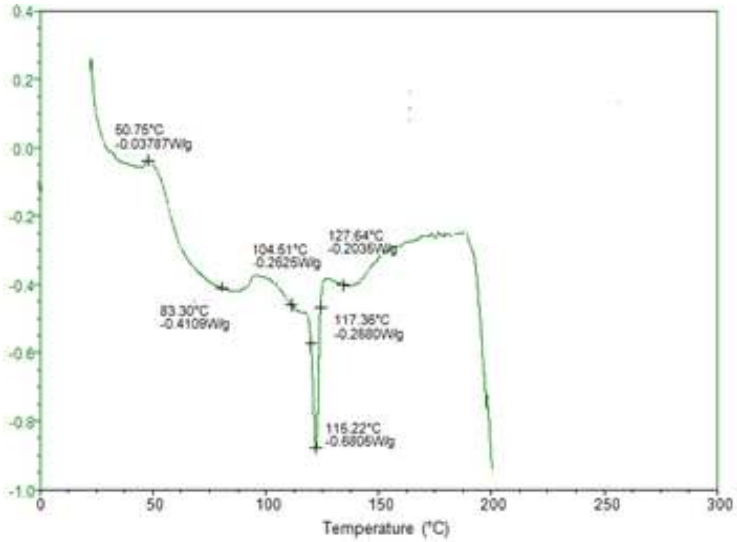

Fig. 8. DSC of flurbiprofen blend

Table 8. Flurbiprofen release profiles in colonic microbial media with phosphate buffer solution

Time	C1	C2	C3	C4	C5	C6
0	0	0	0	0	0	0
1	28	45	35	31	22	56
2	30	54	43	39	29	76
3	38	64	65	48	37	86
4	41	69	79	61	50	98
6	48	75	89	79	79	
8	51	79	94	96	98	
10	65	80	98			
12	70	89				

3.16 Effect of Polymer Type and Concentration on Drug Release Behavior

From the observation of *in vitro* dissolution studies, it was clear that drug release depends upon the concentration of polymer and type of polymer. Drug release was found to be higher in case of formulations based on HPMC k 100 in low concentration and Guar gum in high concentration. Reason: Being more viscous in nature, HPMC k 100 reduces the seepage of dissolution media into tablet core, hence sustain the release of drug. Delay in drug release was also owing to the enormous swelling potential of HPMC k 100 which led to increase in diffusion path length. But Guar gum is microbial flora dependent polymer so when high concentration of Gaur gum used it produce increase release rate in colon which is destination and in this research we want to deliver flurbiprofen in colon and there it have to give maximum release.

3.17 Stability Studies

Stability studies of developed formulation were performed at 40±2 ℃ and 75±5% RH for six months. Assay of drug and *in vitro* dissolution studies were performed after six months. No significant difference was observed before, between and after storage (P < 0.05). 97% similarity index of optimized formulation was found before and after storage.

4. CONCLUSION

The ileo-colonic region of the GIT has become an important site for drug targeting and drug absorption. Colon drug delivery system provide local and systemic treatment to the patients suffering from colon infections and colon diseases. However more commonly; systems that use natural materials that degraded by colonic bacterial enzymes are used now a days for ileo-colon specificity. Different diseases such as ulcerative colitis, colon cancer, and diarrhea can be treated by using delivery of drug through colon method and by this route different drugs of different nature and molecular weight can be administered effectively This method is good for poorly absorbed drugs because colon provides long retention time and shows good absorption. By comparing the dissolution data of test formulations and standard %age drug release was predicted. It was observed that release of drug in solution pH 1.2 was minimum and it was also observed that release of drug in microbial media with phosphate buffer pH 6.8 was slow for those formulations which have more HPMC k 100 concentration and less Guar gum concentration. As the concentration of HPMC in formulation C1 was maximum and which gives less release in colonic media. But when we gradually increased with concentration of natural polymer Guar Gum and decrease the concentration of HPMC k 100, the release of flurbiprofen was good in ileo-colonic fluid.

From the above outcome we can conclude that flurbiprofen formulations prepared with HPMC k100 and Guar gum showed acceptable properties like friability, weight variation, hardness etc and *in vitro* drug release which remained unchanged upon storage for 3 months. However, HPMC k100 and Guar gum based flurbiprofen tablets with the formulation code C5 proved to be the formula of choice, since it showed the highest drug release and lag time. So, flurbiprofen tablets with polymers combination synthetic and natural can be used in targeted drug delivery in treatment of ulcerative colitis so as to reduce the side effects of drug in stomach and also to reduce the dosing frequency of the drug.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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