

FORMULATION AND *IN VITRO* EVALUATION OF ILEO-CLONIC TARGETED TABLET OF FLURBIPROFEN USING NATURAL AND SEMI SYNTHETIC POLYMERS FOR ULCERATIVE COLITIS

Abstract: In this present research work, the aim was to develop ileo-colonic targeted matrix tablets of flurbiprofen for chronotherapeutic treatment of ulcerative colitis. So Matrix tablets of flurbiprofen were formulated using microsomal enzyme dependent and pH-sensitive polymers by direct compression method. The compatibility was assessed using FTIR and DSC studies for pure drug, polymers and their physical mixtures. The formulated batches were subjected to physicochemical studies, drug content estimation, *in vitro* drug release and stability studies. When FTIR and DSC studies were performed, it was found that there was no interaction between flurbiprofen and polymers used. The physicochemical properties of all the prepared matrix tablets batches were found to be in limits. The drug content percentage in the optimized formulation C5 was found to be $98 \pm 0.10\%$. This formulation was also found to be stable as per the guide-lines of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use. Six formulations are prepared. Friability of all developed formulations was less than 1%, which shows the tablets had good mechanical resistance. The tablet thickness was found to be 4.41 to 4.50 mm. Acceptable weight variation and content uniformity. For the protection of drug from the environment of the stomach pH dependent polymers Eudragit S100 was used for its enteric coating.

Keywords: Eudragit, colon targeted tablets, polymers, ileo-clonic, matrix.

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(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 while several topical advantages such treatment of IBS can be achieved(3). Different diseases such as angina pectoris(4) and asthma can be treated by sustain release of drug in colon⁵, and this route can also be used for the drugs which are 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 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) material mostly used in delay release dosage form(17). Among different approaches Enteric-coated system is most commonly used(2), while the difference of pH difference between the small intestine and colon leads to poor specificity(18). The difference of enzyme gradient activity depends on the microbial flora of GIT (19). In humans, the concentration of microbial flora raises from ilium to colon(20) i.e. 1,011–1,012 CFU/mL.Hence, the delivery of drug to colon is best achieved by enzymatic controlled drug delivery system (21).Flurbiprofen (FLB) is a nonsteroidal anti-inflammatory drug used to treat inflammation and pain related to colon(22) . The frequent intake of FLB leads to gastric ulceration, bleeding, and other gastric complications (23). Thus the development of colonic delivery of FLB is appropriate to reduce its side effects and achieve high local drug concentrations in the colon (23). Some of the recent research examples for FLB colon targeted systems are flurbiprofen microsponges (22) ,flurbiprofen pulstate tablets and flurbiprofen controlled release tablets (24).

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

EXPERIMENTAL

Materials

Flurbiprofen, Lactose Anhydrous, Avicel PH 102, Magnesium stearate, Guar gum, Hydroxypropyl Methyl Cellulose(HPMC k100) & Eudragit S100 were provided as a gift sample by Ameer Adnan Pharmaceuticals (Pvt.) Ltd., Lahore, Pakistan. All the chemicals used for this research study were of Analytical grade.

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 k100) were sieved through mesh no. 30 to achieve uniform 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 k100 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.

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Table 1 Composition of the formulations of ileo clonic matrix tablet

Formulation	Flurbiprofen	HPMC k100	Guar Gum	Mg.Stearate	Lactose	Avecil 102	Total weight
C1	100 mg	60mg	-	10mg	10mg	20mg	210mg
C2	100mg	50mg	20mg	10mg	10mg	20mg	210mg
C3	100mg	40mg	30mg	10mg	10mg	20mg	210mg
C4	100mg	30mg	40mg	10mg	10mg	20mg	210mg
C5	100mg	20mg	50mg	10mg	10mg	20mg	210mg
C6	100mg	-	60mg	10mg	10mg	20mg	210mg

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84 **Enteric coating**

85 The compressed tablets obtained than coated with enteric coating polymer by a method
86 known as dip coating. Magnetic stirrer was used for dissolving the recommended quantity of
87 Eudragit S100 in isopropyl alcohol 70%. Anti-adherent material such as Talc was added and
88 stirring carried out for further 15 minutes. Then these tablets, which were weighed previously,
89 were 3-5 times dipped in the prepared solution.

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Table 2 Composition of enteric coating material

Ingredients (mg)	Enteric coating					
	E1	E2	E3	E4	E5	E6
Eudragit S100	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	

RESULTS AND DISCUSSION

Evaluation of Physical Parameters (25)

The prepared tablets were evaluated for weight variation, hardness, friability, and drug content. To estimate the weight variation, 20 tablets from each formulation were weighed using an electronic weighing balance (Shimadzu, Japan) and calculated the average weight and deviation. The hardness of six tablets was determined using Monsanto tablet hardness tester. Friability was measured on ten tablets in a Roche friabilator. To estimate the drug content, ten tablets were crushed and powder equivalent to 100 mg of FLB was weighed accurately, prepared the solution, and analyzed for FLB using the spectrophotometer at wavelength of 254 nm.

Study of interaction by FTIR (6)

The interaction between drug and its polymer, polymer with polymer were studied with FTIR

DSC studies

The above FTIR studies observation was further confirmed by DSC studies.

The DSC thermograms of pure drug flurbiprofen and their physical mixtures with microsomal enzyme and pH sensitive polymers are shown in Fig. 7 and 8. The DSC thermogram of pure drug flurbiprofen, corresponding to its melting point gives a sharp exothermic peak at 116.08°C. However, the DSC thermograms for physical mixtures of flurbiprofen, guar gum, HPMC k100, flurbiprofen and Eudragit S100 have not shown any significant shift in their exothermic peaks i.e. their peaks were found at 50.75°C, 83.30°C and 115.22°C, respectively. Thus, the results of DSC thermo-grams also confirmed that the physical mixtures of drug and polymers used in the formulation batches were free from any chemical interaction

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/cm². 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.

Uniformity of contents (27, 28)

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

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°C in distilled water. The time for the disintegration of the tablet was measured.

Study of *In vitro* Swelling of drug (29)

Different solutions were used for calculating the swelling index of prepared tablet i.e. HCl

buffer pH 1.2, PBS pH 6.8 and 7.4. After determining the initial weight of the tablet it was placed in 10mL Hcl buffer pH 1.2 for 2 hours and then 10mL of PBS of pH 6.8 for 3 hours and then at last in 10mL of PBS of pH 7.4 up to 24 hours. At different intervals tablets were removed and reweighed (W2). Formula for the calculation of swelling index given by:

$$\text{Swelling index} = 100 (W2 - W1) / W1$$

Where; W1 = initial weight of the tablet.

W2 = final weight of the tablet.

Drug Release Studies *In vitro* (27, 29)

Dissolution test apparatus-2 was used for studying dissolution of these coated tablets using USP XXIII at a speed of 50rpm at 37.0±0.5°C. The study was performed using 250mL Hcl buffer 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.

Short term stability studies (30)

Short term stability study was performed at a temperature of 40 ± 20°C over a period of 3 months (90 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 3 months. Samples were taken at each month interval for evaluation of drug content and in vitro drug release study.

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 regression coefficient 'r²' values.

Zero order kinetic models (31)

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

First order kinetic (32)

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

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.

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.

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.

Effect of microsomal enzyme dependent polymers

Effect of microsomal enzyme dependent polymers (Guar gum) From the *in vitro* dissolution profile, it was found that as the guar gum polymer concentration was increasing and release rate of flurbiprofen also increased. This is due to the reason that guar gum polymer, because of its microsomal enzyme dependent characteristics has retarded the release of flurbiprofen in acidic and intestinal pH buffers and increased the release in colonic buffer. But when guar gum and HPMC k100 were used as combination polymers, it was found that the flurbiprofen release rate was good while compared to batches formulated with guar gum alone. This is due to the reason that HPMC k100 retarded release in intestinal buffer

Effect of pH dependent polymers (Eudragit S100)

From the *in-vitro* dissolution profile, it was found that as the coating with Eudragit S100 polymer on matrix-mini-tablets were increasing the lag time and release rate of flurbiprofen was decreased. This is due to the reason that Eudragit S100 polymer because of their pH dependent solubility characteristics have retarded the release of flurbiprofen in acidic pH buffers and increased the release in ileo-colonic buffer. This is due to the reason that the Eudragit S100 polymer because of its good solubility in 6.5 and 6.8 pH.

Table 4: Blend flow properties of powder

Sr. no.	Formulation trial no.	Angle of repose(°)	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

Table 5: Evaluation parameters of tablets

Formulation	Thickness (mm)	Hardness (kg/cm ²)	Weight variation (mg)	Friability (%)
C1	4.410.02	6.21 0.02	210.53 0.02	0.41 0.01
C2	4.55 0.02	6.55 0.02	210.55 0.02	0.55 0.01
C3	4.50 0.02	6.83 0.02	210.50 0.02	0.50 0.01
C4	4.43 0.02	6.21 0.02	210.13 0.02	0.43 0.01
C5	4.52 0.02	6.35 0.02	210.45 0.02	0.51 0.01
C6	4.50 0.02	6.80 0.02	210.50 0.02	0.50 0.01

Table 6 Regression 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

246 **Table 7 Standard curve of Flurbiprofen in phosphate buffer pH (7.4) at 254 nm**
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Sr. No.	Concentration (μ /mL)	Absorbance			Average Absorbance
		1	2	3	
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
5	25	0.544	0.544	0.543	0.544
6	30	0.699	0.697	0.695	0.697
7	35	0.760	0.762	0.761	0.761
8	40	0.890	0.891	0.891	0.891

248 Correlation Coefficient = 0.997
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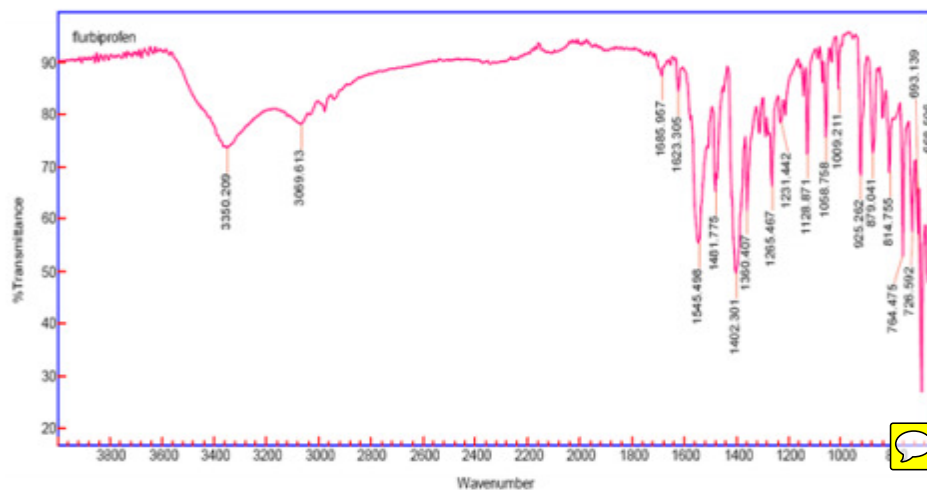


Figure 1 FTIR of flurbiprofen

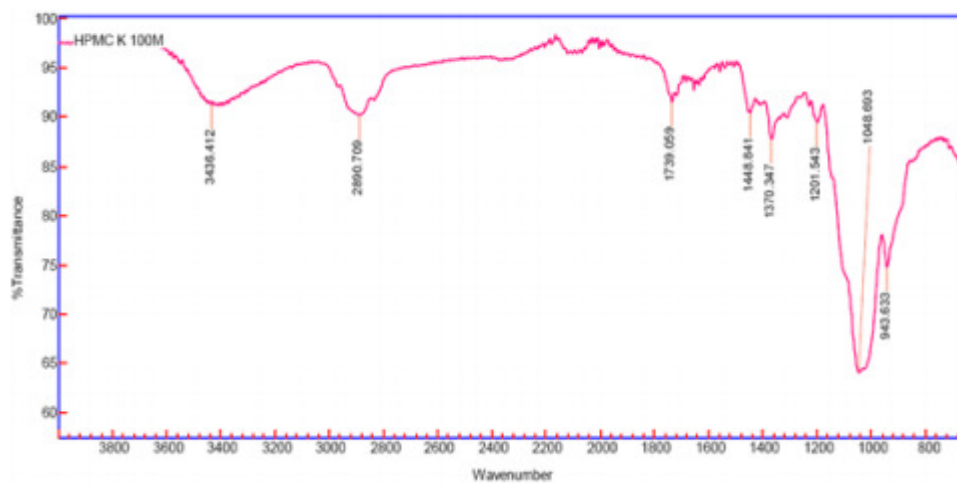


Figure 2 FTIR of HPMC k100 material

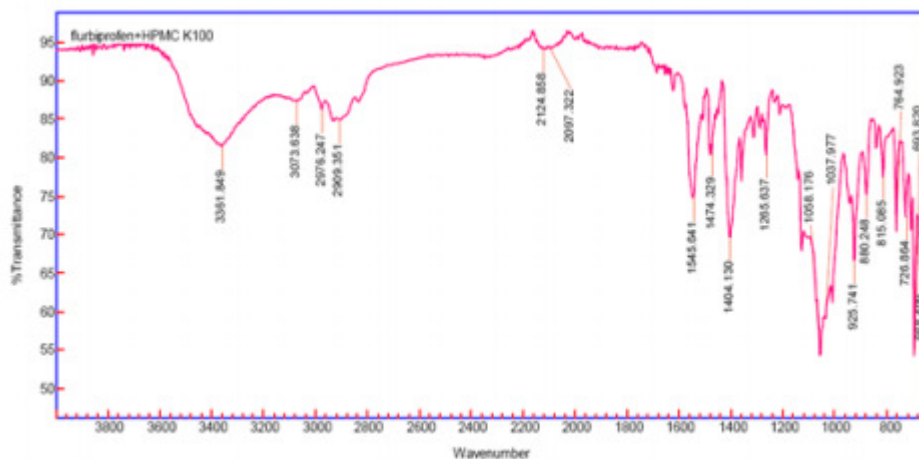
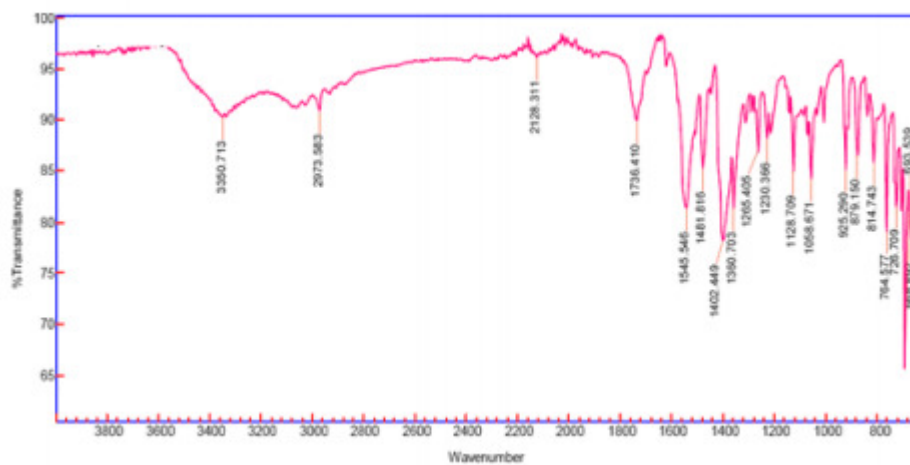


Figure 3 FTIR of flurbiprofen and HPMC k100

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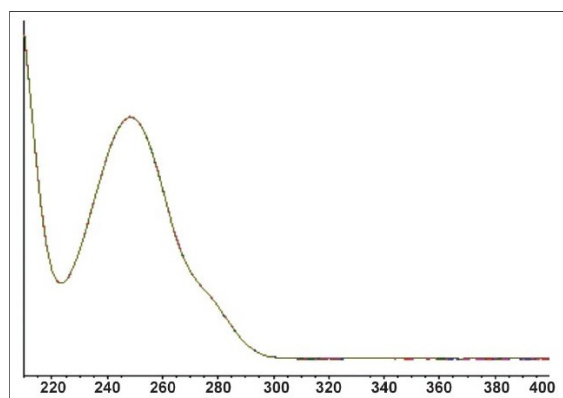
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Figure 4 FTIR of blend



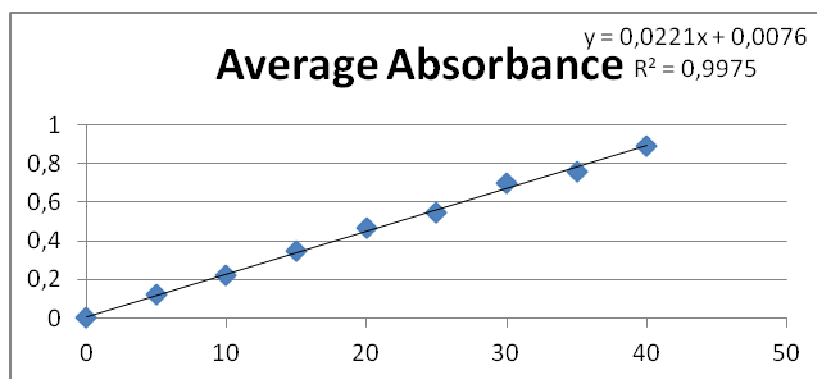
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Figure 5 UV/VIS spectra of Flurbiprofen



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Figure 6 calibration curve of flurbiprofen raw material

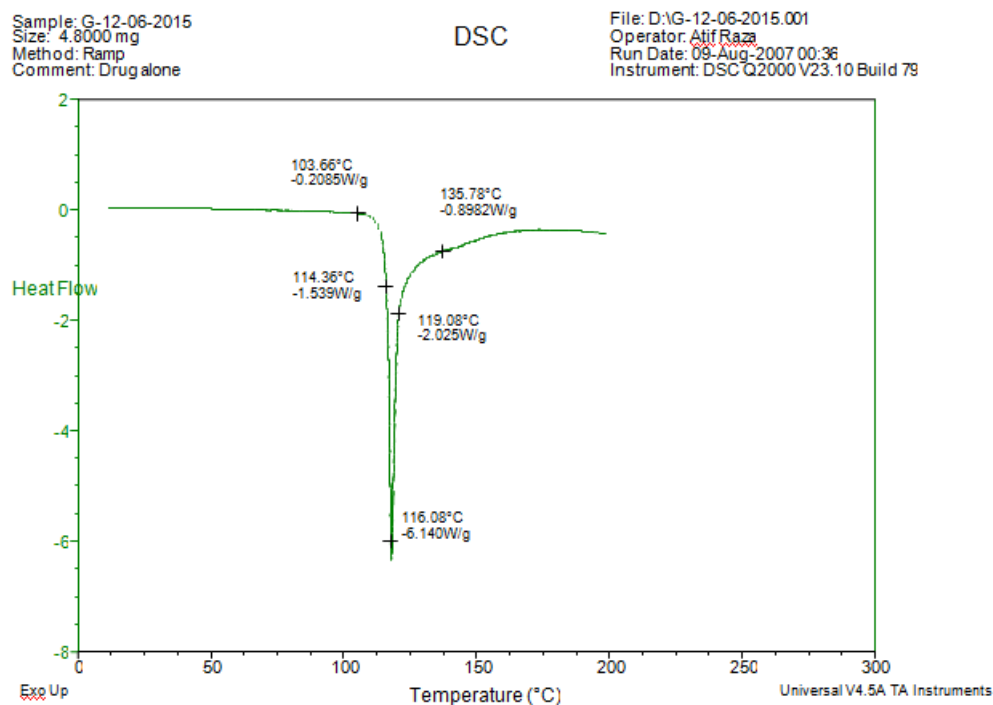


Figure 7 DSC of flurbiprofen alone

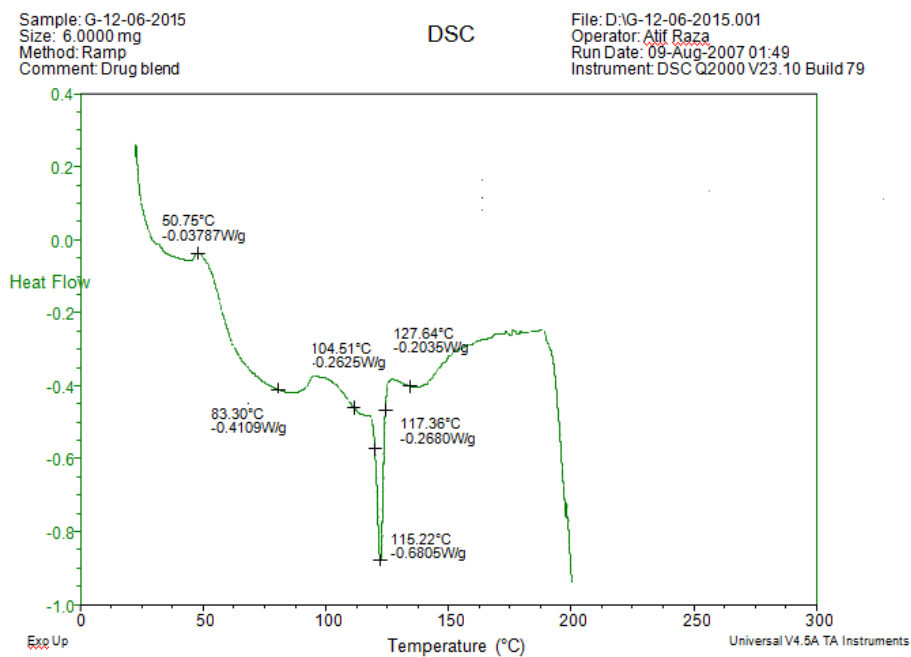


Figure 8 DSC of flurbiprofen blend

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				

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 k100 in low concentration and Guar gum in high concentration. Reason: Being more viscous in nature, HPMC k100 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 k100 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.

Stability Studies

In consideration of the potential utility of the formulation, stability studies were carried out at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for six months to assess their stability. After storage for six months, the tablets were subjected to drug assay and *in vitro* dissolution studies, and from the statistical analysis there was no significant difference between before and after storage ($p < 0.05$).he similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 97%.

Conclusion

The ileo-colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. ileo-colon specificity is more likely to be achieved with

systems that utilize natural materials that are degraded by colonic bacterial enzymes. 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 k100 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 k100, the release of flurbiprofen was good in ileo-clonic 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.

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