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Formulation and evaluation of keterolac tromethamine colon specific drug delivery system

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ABSTRACT

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Natural polysaccharides are non-extensively used for the development of solid dosage forms for delivery of drugs to the colon. Various major approaches utilizing polysaccharides for colon specific delivery are fermentable coating of drug core. The preparation of the matrix tablets with guar gum and pectin containing keterolac was done by wet granulation method. The average weight was found to be within the prescribed limit. The hardness of the tablets was found to be in the range of 3.34±0.752 to 7.84 ±0.508 (kg/cm2). Thicknesses of the tablets were found to be in the range of 1.14±0.02 to 3.50±0.01 mm for tablets. The friability of the tablets was found to be less than 0.5 %. The invitro drug release profile of these tablets showed delayed release characteristics. Compatibility studies such as DSC and FTIR studies were carried out to understand the drug-polymer compatibility and revealed that there was no possible interaction between them.

Keywords: keterolac tromethamine

INTRODUCTION

Oral route is considered most natural, uncomplicated, convenient and safe in respect to Parentral route due to its ease of administration, patient acceptance, and cost effective manufacturing process. The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose'[1]. Enhancement of colonic absorption by these agents appears to be drug specific. For example mixed unicelles composed of either taurocholate (or) glycocholate with monolein. Olic and lauric acid enhanced the absorption of 5-fluoro uracil, heparin etc. Since many of these absorption enhancers are acidic in nature, local high concentration might alter luminal pH and have significant effects on the colonic microbial flora, which can result in epithelial pathologies. The agents also produce transport windows in colonic epithelia large enough for the passage for many bacterial toxins[2].

The present investigation is aimed to formulate and evaluate compressed coating tablets of keterolac tromethamine to target the colon. Formulations that release drug in to the colon rather than the upper intestinal tract are beneficial for a number of clinical situations. Local delivery of the drugs has distinct advantages that dosing level is less with minimal side effects and hepatic bypass could be avoided while the optimum therapeutic level is effectively produced and maintained[3].

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MATERIALS AND METHODS

Keterolac, Eudragit L&S 100, Pectin Guar gum received as a gift sample from Meenaxy labs, Hyderabad, India; Lactose anhydrous from FMC Bio Polymer, Magnesium Stearate from Loba Chemie.

Pre Compression Parameters[4,5]

Bulk Density (BD)

Bulk density = Weight of powder / Bulk volume

Tapped density (TD)

Tapped Density = Weight of powder / Tapped volume

Carr's Index

It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material and their standard values are given in table 1.

Hausner's Ratio = TD / BD

Table 1: Effect of Carr's Index and Hausner's Ratio and Angle of repose on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio	Angle of repose
Excellent	≤10	1.00-1.11	<20
Good	11-15	1.12-1.18	20-30
Fair	16-20	1.19-1.25	-----
Passable	21-25	1.26-1.34	30-34
Poor	26-31	1.35-1.45	-------
Very poor	32-27	1.46-1.59	>35
Very very poor	>38	>1.6	-------

Angle of repose

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone respectively.

Compatibility Studies

Physical observation was conducted at room temperature, 40^0 C/75% RH & 2-80C after 30 days were conducted.

Preparation of keterolac matrix tablets[6]

The preparation of the matrix tablets with guar gum and pectin containing keterolac was done by wet granulation method. The ingredients in the quantities mentioned were wet granulated using starch paste (10%). Granules of the above wet mass were prepared by passing through a sieve with a nominal aperture of 1 mm. The granules were dried for 6 h at a temperature of 50◦C. The dried granules were passed through a sieve with a nominal aperture of 1mm and mixed with talc (1.7%) and magnesium stearate (1.2%). Then after weighing the granules (90 mg) per sample, all the granules were punched in the 5mm die cavity punch with the help of KBr-pellet punch machine. Total nine batches were prepared with different proportions of the polymers.

Identification of drug

Infrared absorption spectrum

The infrared absorption spectrum of Keterolac was recorded with a KBr disc over the wave No. 4000 to 400 cm^{-1}.

Table 2: Composition table of keterolac matrix tablets

Ingredients	*(mg/tablet)*								
	Batch – A			**Batch – B**			**Batch –C**		
	1:0.5	**1:1**	**1:1.5**	**1:0.5**	**1:1**	**1:1.5**	**1:0.5**	**1:1**	**1:1.5**
API	10	10	10	10	10	10	10	10	10
Guar gum	5	10	15	-	-	-	-	-	-
Pectin	-	-	-	5	10	15	-	-	-
Guar gum & Pectin	-	-	-	-	-	-	5	10	15
Lactose	73.2	68.2	63.2	73.2	68.2	63.2	73.2	68.2	63.2
Talc	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Mg.stearate	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Total	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**	**90**

The coating of the matrix tablets was done by dip coating technique by using Eudragit L-100, S-100 and L-100+S-100. The formulated matrix tablets were coated with the coating solution, the tablets were dipped in the coating solution to get the required weight gain and the tablets were air dried.

Table 3: Coating of matrix tablets by using eudragit L-100, S-100 and L- 100+S100

Batch	Ratio	Coated with Eudragit		
		L- 100	**S- 100**	**L- 100+ S-100**
A	1:0.5	A1	A2	A3
	1:1	A4	A5	A6
	1:1.5	A7	A8	A9
B	1:0.5	B1	B2	B3
	1:1	B4	B5	B6
	1:1.5	B7	B8	B9
C	1:0.5	-	C1	-
	1:1	C2	C3	C4
	1:1.5	C5	-	-

Post-compressional Studies

Shape and appearance

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light[5].

Uniformity of thickness

Thickness and diameter of both core tablets and coated tablets were measured using a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated[7].

Weight variation test

To study weight variation 20 tablets of each pulse dose formulation were weighed separately using a Sartorius electronic balance and the test was performed according to the official method. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated[8].

Friability test

For each pulse dose tablet formulation, the friability of 6 tablets was determined using the Roche friabilator (17). Friability can be determined by following equation:

$$F = \left[\frac{Wt_{Initial} - Wt_{Final}}{Wt_{Initial}}\right] \times 100$$

***In vitro* dissolution studies**

Dissolution test was conducted in USP II apparatus at 50 rpm and at a temperature of 37° ± 0.5ºC. Initial drug release studies were conducted in 650 ml of 0.1N HCl for 3 hr with regular sampling at fixed time intervals, then 250 ml of 0.2M trisodium phosphate buffer was added to the dissolution media and the pH was adjusted to 6.8, with sampling at regular time intervals for a period of 9 hrs, after which to the above media 1ml of 1M NaOH was added to bring the pH of the solution to 7.2. After withdrawal of the samples of 10 ml aliquots same volume of same pH was replaced back to the jars to the dissolution volume constant[9]. The withdrawn samples were appropriately diluted and analyzed spectrophotometrically at a wavelength of 319 nm**.**

Fourier Transforms Infrared Spectroscopy (FT-IR)

The FT-IR spectrum of pure drug and formulation were determined. A FT-IR (Thermo nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm^{-1} and 4cm^{-1} resolutions. The reagents were the means of 6 determinations. A quality equivalent to 2mg of pure drug was used for the study.

Differential Scanning Calorimetry (DSC)[10]

Thermal properties of pure drug and the formulation were evaluated by Differential scanning Calorimetry using dimon DSC (Shimadzu, Japon). The analysis was performed at a rate 5^{0}C min^{-1} to 200^{0}C temperature range under nitrogen flow of 25ml min^{-1}.

Stability Studies

The stability studies for the formulation F015 - Eudragit EPO coated Ibuprofen MCC lactose tablet was conducted over 3 months of time.

RESULTS AND DISCUSSION

Identification of drug

Characterization of API (identification test by FTIR,) was performed and it was found that all are within the range specified in the pharmacopoeia.

Pre Compression Parameters

Preformulation is a group of studies that focus on the physicochemical properties of a drug candidate that could affect the drug performance and the development of a dosage form. This could afford imperative information for formulation design or sustenance the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been deliberate before development of pharmaceutical formulation. This property affords the framework for drugs combination with pharmaceutical components in the fabrication of dosage form.

Table 4: Evaluation of pre-compression parameters

B. No	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner' s Ratio	Angle of Repose
			Batch A (Guar gum)		
A1	0.560	0.608	8	1.08	33^0
A2	0.608	0.700	13	1.15	32^0
A3	0.630	0.700	9.09	1.10	29^0
A4	0.583	0.700	16.66	1.20	28^0
A5	0.625	0.681	8.33	1.09	27^0
A6	0.652	0.750	13.04	1.15	32^0
A7	0.638	0.714	10.63	1.11	25^0
A8	0.681	0.750	9.09	1.10	34^0
A9	0.714	0.789	9.50	1.10	30^0
			Batch B (Pectin)		
B1	0.66	0.508	9	1.08	33^0
B2	0.508	0.6	12	1.13	22^0
B3	0.62	0.6	9.09	1.1	29^0
B4	0.583	0.5	16.66	1.3	28^0
B5	0.625	0.681	9.33	1.09	27^0
B6	0.672	0.752	13.04	1.16	32^0
B7	0.648	0.614	12.63	1.11	25^0
B8	0.581	0.65	9.09	1.14	31^0

B9	0.614	0.789	11.5	1.1	30^0
		Batch C (Combination of Guar gum and Pectin)			
C1	0.526	0.612	32.1	1.16	$26^0.7`$
C2	0.782	0.869	28.28	1.2	$28^0.68$
C3	0.695	0.823	25	1.19	$24^0.6`$
C4	0.662	0.763	27.02	1.15	$27^0.5`$
C5	0.56	0.631	29.23	1.12	$24^0.6`$
C6	0.469	0.526	31.21	1.17	$25^0.46$
C7	0.578	0.636	30.76	1.18	$26^0.85$
C8	0.621	0.69	34.02	1.12	$24^0.2`$
C9	0.714	0.789	9.5	1.1	30^0

Compatibility Studies

Physical observation was mentioned in Table 5.

Table 5: Physical observation of compatibility study

rug and Excipients (Ratio 1:1)	***Observation***			**Results**
	Room Temp	**40^0 C/75% RH after 30 days**	**2-8^0C after 30 days**	
keterolac	White to off white powder	White to off white powder	White to off white powder	Compatible
Keterolac and Eudragit L & S 100	White to off white powder	White to off white powder	White to off white powder	Compatible
keterolac& Guar Gum	White to off white powder	White to off white powder	White to off white powder	Compatible
keterolac& Pectin	White to off white powder	White to off white powder	White to off white powder	Compatible
keterolac & Mg Stearate	White to off white powder	White to off white powder	White to off white powder	Compatible

Post-compressional Studies

The shape and size of the prepared tablets were found to be within the limit. The average weight was found to be within the prescribed limit. The hardness of the tablets was found to be in the range of 3.34±0.752 to 7.84 ±0.508 (kg/cm^2). Thicknesses of the tablets were found to be in the range of 1.14±0.02 to 3.50±0.01 mm for tablets. The friability of the tablets was found to be less than 0.5 %.

Table 6: Post-compressional Parameters

B. No	**Weight variation (%)**	**Hardness**	**Thickness**	**Friability (%)**	**Assay (mg /tablet)**
			Batch A		
A1	±2.19	7.84 ±0.508	1.14±0.02	0.01	8.91±0.10
A2	±2.66	7.37±0.6	1.19±0.08	0.08	8.55±0.12
A3	±2.04	7.17±0.6	1.26±0.05	0.03	8.82±0.19
A4	±2.05	7.42±0.5	1.34±0.08	0.04	8.79±0.25
A5	±2.07	7.02±0.681	1.42±0.04	0.03	8.12±0.01
A6	±2.22	7.15±0.752	1.68±0.07	0.01	8.18±0.15
A7	±2.31	7.22±0.614	1.85±0.25	0.08	8.59±0.11
A8	±2.18	7.62±0.65	1.69±0.12	0.09	8.65±0.22
A9	±1.89	7.52±0.789	1.89±0.03	0.02	8.73±0.34
			Batch B		

B1	±1.73	6.7±0.508	3.28±0.020.30	9.91±0.22
B2	±1.48	8.08±0.6	3.19±0.050.02	9.55±0.32
B3	±1.64	5.7±0.6	3.50±0.010.18	9.91±0.12
B4	±1.16	5.31±0.5	3.12±0.130.02	10.35±0.18
B5	±2.12	4.39±0.681	3.15±0.060.12	10.20±0.28
B6	±2.83	3.34±0.752	3.35±0.020.01	10.11±0.22
B7	±2.40	5.98±0.614	3.21±0.010.12	10.32±0.13
B8	±1.32	5.2±0.65	3.11±0.050.14	10.33±0.11
B9	±1.19	6.3±0.789	3.18±0.080.01	10.52±0.02
		Batch C		
C1	±1.32	7.89±0.508	2.18±0.220.02	10.31±0.02
C2	±2.21	7.42±0.6	2.59±0.140.04	10.44±0.52
C3	±1.64	7.05±0.6	2.33±0.40.06	10.89±0.22
C4	±2.07	5.87±0.5	2.89±0.110.09	10.82±0.43
C5	±1.89	7.42±0.681	2.61±0.330.18	10.67±0.11
C6	±1.32	7.32±0.752	2.50±0.220.12	10.23±0.14
C7	±2.30	6.2±0.614	2.81±0.160.11	10.68±0.45
C8	±1.22	5.20±0.65	2.85±0.110.13	10.53±0.02
C9	±1.78	5.9±0.789	2.64±0.110.18	10.78±0.22

***In vitro* dissolution studies**

The cumulative percentage released at various time intervals was calculated and tabulated in table 7 & 8. The cumulative percentage released was then plotted against time in Figure 1 to 3. A maximum release of 68.52%, 67.3%, 68.8%, 65.6%, 66.7%, 68%, 66.8%, 65.2%, and 67.7% were shown by batches A1, A2, A3 A4, A5, A6, A7, A8, and A9 respectively. A3 prepared using 1:0.5 drug polymer ratio showed better drug release when compared to other batches. The cumulative percentage released at various time intervals was calculated.

A maximum release of 80.6%, 82%, 83.7%, 79%, 84.42%, 80.24%, 77.9%, 78.8%, and 79.8% were shown by B1, B2, B3, B4, B5, B6, B7, B8 and B9 respectively. B5 using 1:1 drug polymer ratio showed better drug release when compared to other batches. A maximum release of 77.69%, 82.20%, 80.60%, 80.25% and 79.12% were shown by C1, C2, C3, C4 and C5 respectively. C2 1:1 drug polymer ratio showed better drug release when compared to other batches.

Table 7: *Invitro* Drug release studies of Batch A & B

Time	***Cumulative % release***																	
(hrs.)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	0.39	0.6	1.3	0.7	0.9	0.7	0.61	0.63	0.74	1.1	1.2	0.6	0.5	0.8	0.6	0.3	0.2	0.8
1	0.5	0.9	1.7	0.9	1.1	1	1.23	0.9	0.9	1.7	0.5	2.2	1.3	1.7	1.2	1	1.6	1.2
2	0.9	1.3	2.2	1.3	1.7	1.3	1.4	1.2	1.11	2.5	1.5	3.1	2	2.5	1.6	1.5	1.6	1.5
3	1.4	1.5	2.4	1.7	1.8	1.5	1.9	1.4	1.69	2.8	1.7	3.7	2.8	2.7	2	1.8	2.3	2.1
4	2.7	2.2	4.8	3.2	4	3.4	3.1	3.2	3.2	4.6	4.6	5	5	3.7	3.3	3.5	3.7	3.5
5	5.4	2.8	5.9	3.6	4.6	3.6	3.3	3.8	3.7	5.1	5	6	6	4.3	4.3	3.9	3.7	4
6	6.2	3.8	6.3	4.2	5.4	4.8	3.6	4.6	3.5	6	5.3	6.6	6.3	6.2	4.5	4.2	3.7	4.6
8	7.6	4.7	7.7	5.5	6.5	5.8	3.9	5.23	4.56	7	6.2	7.5	7.1	7.8	5.9	5.4	4.9	5
10	8.5	6.4	8.8	8.8	8.9	6.9	4.4	5.3	7.2	7.5	6.4	7.9	7.5	8.7	7.2	7.4	6	5.6
12	11.3	10.9	10.3	11.4	10.7	7.7	5.3	5.7	8.2	7.9	9.5	8.3	9.6	9.3	8.4	9.1	7.8	6.7
15	20.8	17.22	17.8	16	14.6	16.7	12.3	14.5	16.7	29.9	32.1	27.5	19.6	18.4	18.4	16.3	17.7	16.8
17	57.7	52.9	52.2	47.7	49.9	36.55	42.1	44.21	46.8	58.3	56.3	61.3	60.9	51.6	63.224	57.7	54.6	62.88
20	63.9	60.78	62.33	56.9	59.5	53.6	46.7	45.2	51.8	63.1	64.6	69	73	73.5	75.6	71.8	72.7	74.8
22	67.5	62.9	64.7	60.9	64.8	59.4	56.3	54.5	57.5	76.97	74.7	81.1	76.9	82.4	78.9	76.5	74.8	77.3
24	68.52	67.3	68.8	65.6	66.7	68	66.8	65.2	67.7	80.6	82	83.7	79	84.428	80.249	77.9	78.8	79.8

Table 8: *Invitro* Drug release studies of Batch C

Time (hrs.)	*Cumulative % release*				
	C1	C2	C3	C4	C5
0	0	0	0	0	0
0.5	0.59	0.70	0.87	0.94	0.63
1	1.02	1.27	1.01	1.30	1.47
2	1.39	1.84	1.27	1.40	1.76
3	1.74	2.25	1.90	2.09	1.84
4	3.65	3.25	2.97	3.16	2.64
5	3.16	3.55	3.40	3.97	3.65
6	3.53	4.27	3.86	5.10	3.84
8	3.72	4.77	4.80	5.24	4.14
10	4.27	5.27	5.67	5.50	4.53
12	5.17	7.72	8.22	7.17	6.35
15	16.47	17.24	16.93	17.85	16.72
17	50.64	60.35	59.30	62.40	57.74
20	70.32	71.70	73.21	71.23	69.65
22	74.35	77.67	76.94	77.60	76.27
24	77.69	82.20	80.60	80.25	79.12

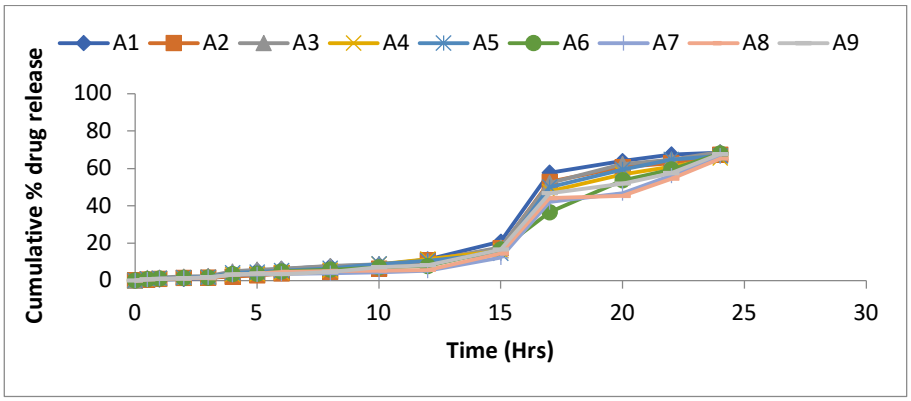

Fig 1: *Invitro* Drug release studies of Batch A

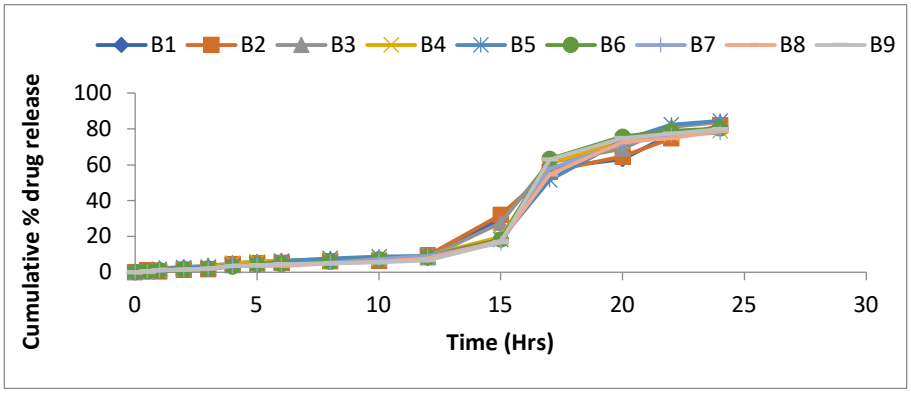

Fig 2: *Invitro* Drug release studies of Batch B

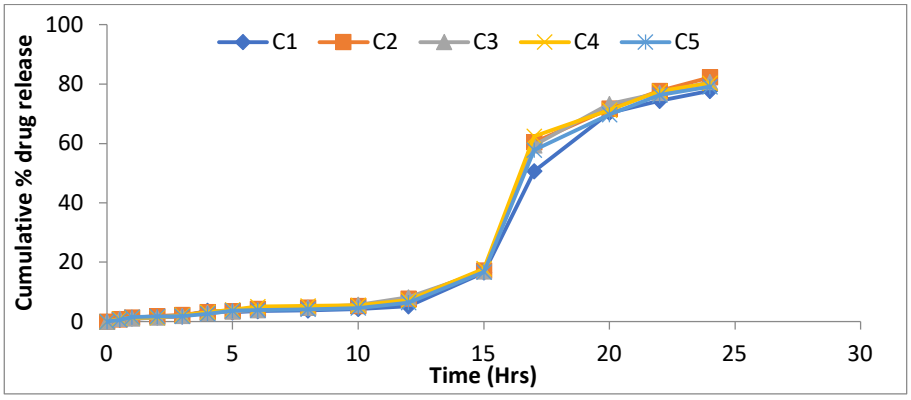

Fig 3: *Invitro* Drug release studies of Batch C

Fourier Transforms Infrared Measurements (FTIR)

FTIR spectra of the keterolac tromethamine, guar gum and pectin presented in Figure 4

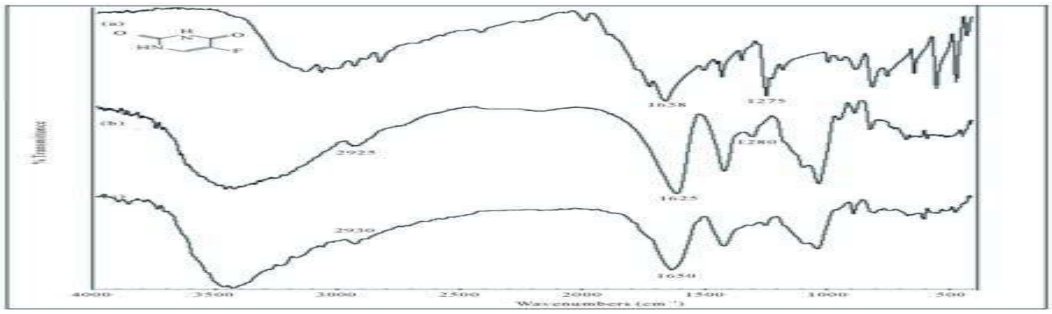

Fig 4: FTIR spectra of (a) pure drug ; (b) with guar gum; (c) with pectin

Differential Scanning Calorimetry (DSC)

The thermal analysis was carried out with DSC displayed Figure 5.

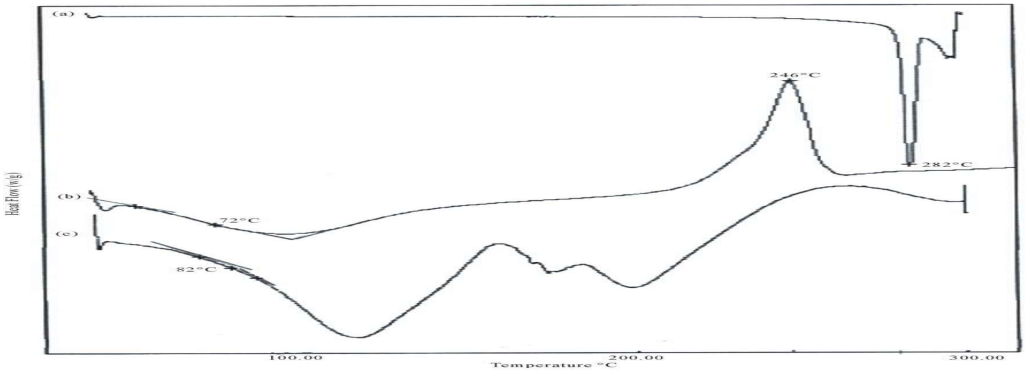

Fig 5: DSC thermogram of (a) pure drug ; (b) with guar gum; (c) with pectin

By the above compatibility studies such as DSC and FTIR studies were carried out to understand the drug-polymer compatibility and revealed that there was no possible interaction between them.

Stability Studies

The stability studies for the formulation B5 is done in order to access the stability of the drug along the period of time.

Table 9: Results of Stability studies

Parameters	Initial value	Value after 30 days
Thickness (mm)	4.48	4.45
Weight (mg)	500	498
Appearance	3.0	3.4

CONCLUSION

The main objective of this project is to develop a dosage form, which can be used to provide release of drugs for local action in the GIT for diseases like colo-rectal inflammation. Delivery systems such as matrix tablets were utilized for the colon specific drug delivery which is one of the seemingly interesting areas to target drugs to colon through oral route. This might be expected to localize the drug concentration and thus help in the efficient treatment of disorders associated with colon. So this matrix tablet was designed based on natural polymers such as guar gum, pectin and enteric coating employing pH sensitive polymers like Eudragit L/S, which remain undigested in the stomach and the small intestine and are degraded by only the vast anaerobic microflora of the colon to release the drug in lumen of large bowel. For targeting the drug in colonic region, the matrix tablets with different ratios of guar gum, pectin, and combination of guar gum and pectin (1:0.5, 1:1 and 1:1.5) were prepared by wet granulation method. These tablets consist of various proportions of drug and polymer. These tablets were coated with Eudragit L-100, S-100 & combination of both L-100 & S-100.The tablet showed good physico-chemical properties such as hardness, friability, weight variation and drug content. The *invitro* drug release profile of these tablets showed delayed release characteristics. The developed formulations were also evaluated for dissolution study by half dilution method in order to maintain the gastrointestinal transit conditions similar to human beings. All the developed systems showed a minimum release at pH 1.2 and maximum release at pH 6.8. The release of the drug from guar gum was delayed when compared to other batches such as pectin and some combination batches. Comparison of these formulations indicate that the release profile of pectin were better when compared to other batches of guar gum and combination batch of guar gum and pectin. From the results of *in vitro* evaluation of the different dosage forms, it was found that formulated drug delivery systems containing keterolac could be used for drug targeting to colon for the treatment of colonic inflammation.

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