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Research Article

Formulation and evaluation of colon-specific microbially dissolvable matrix aceclofenac tablets

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Abstract

The aim of the present work was to formulate and evaluate colon specific sustained release matrix tablet of aceclofenac using different concentrations of microbial-dissolvable polysaccharides like xanthan gum, guar gum, pectin, katira gum and sterculia gum. These colon targeted matrix tablets were prepared by wet granulation technique. All combinations of matrix formulation sprepared within the official limits showed the desired physicochemical properties. All the batches of matrix tablets (F1 to F15) were subjected for *in vitro* dissolution studies in various simulated gastric fluids to target colon-specific drug delivery system. The drug release study results showed good sustained release dissolution profile for formulation F15.

Keywords: Colon-targeted, natural polysaccharides, aceclofenac, microbial dissolvable.

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1. Introduction

A perusal of literature indicates that tailoring colon-targeted drugs is of significant research interests in the drug industry. In the colon region drugs are delivered either specifically or systemically [1,2]. A local factor of drug delivery to colon could allow topical treatment of inflammatory bowel diseases like ulcerative colitis or Crohn's disease [3,4,5]. Such inflammatory conditions are usually treated with glucocorticoids [6] and sulfasalazine. The treatment will be effective if the drugs are targeted precisely to the site of disease in the colon. Site-specific drug delivery could also allow oral administration of peptide and protein drugs that otherwise are inactivated in the upper regions of gastrointestinal tract [7]. The orally administered drugs acton the colon targeted sites based on the pH-dependent polymers used and the carriers involved in their formulation [8, 9]. These drugs are assumed to remain within the physiological environment of stomach and small intestine that later undergo dissolution in the colonic regions as a result of action by colon bacteria. Various polysaccharides such as guar gum, inulin, pectin, cellulose, chondroit in sulphite and chitosan are employed for colon-specific targeted drug delivery [10,11,12]. Aceclofenac [13], non-steroidal anti-inflammatory drugs (NSAID) that are usually administered successfully for various painful indications like other NSAIDs with lower indications of gastro-intestinal adverse effects; and thereby has greater compliance with treatment. Aceclofenac, 2-[2-[2-[(2,6-dichlorophenyl) amino] phenyl]acetyl]oxy]-acetic acid, are available in oral formulations for the management of colitis, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

2. Materials and methods

Aceclofenac was ea gift sample from INTAS Pharmaceuticals, Ahmedabad, Gujarat. Xanthan gum and Sterculia gum were purchased from H.B. Gum Industries, Kalol. Guar gum was purchased from Swastik Gum Industries, Ahmedabad. Pectin was purchased from Nikunj Chemicals; Baroda. PVPK30 was purchased from S.D Fines Chemicals,

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Mumbai. All other chemicals used in this study were of analytical grade.

Fourier transform infrared spectroscopy (FTIR):

FTIR spectroscopy was used to study the structural changes and possible interactions between the drug and the natural gums. The gum samples were scanned over the frequency range of 4000–400 cm^{-1}. The resultant spectra were compared with the spectrum of the drug for spectral differences.

Formulation of colon-targeted matrix tablets:

100 mg of aceclofenac matrix tablets were prepared by wet granulation technique using different types of polymers (gum). All powder materials were blended and granulated with PVP K30 using IPA as the solvent. The wet mass was passed through a mesh (1000 µm) sieve and the granules were dried at 50 °C for 2-3 h. The dried granules were sieved (650 µm), lubricated with magnesium stearate and talc mixture; and compressed on multi-rotary tablet punch machine having 12 mm round concave punches. The combinations of the tested colon matrix tablet formulations are tabulated in Table1.

Evaluation of tablets:

Precompression parameters:

Bulk density:

Accurately weighed 25 g of aceclofenac drug that was previously passed through 20 mesh sieve, was transferred to 100 ml graduated cylinders. The powder was leveled without compacting and the unsettled apparent volume (Vo) was read using which the apparent bulk density in g/ml adopting the formula given below was calculated [14].

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Tapped density:

After measuring the bulk volume, the same measuring cylinder was used and tapped manually for 500 times The volume was noted as (Va) and again tapped for 750 times to note the volume (Vb). If the difference between Va and Vb was not greater than 2% then Vb was considered as final tapped volume [15]. The tapped density was calculated using formula:

$$\text{Tapped Density } \left(\frac{\text{grams}}{\text{ml}}\right) = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Carr's index:

Compressibility index (C.I.) was an important measure that can be obtained from the bulk and tapped densities [16]. Carr's index of a material having values of less than 20% is defined as the free flowing material that can be calculated as per the given formula:

$$\text{Compressibility index} = 100 \times \frac{Vt - Vb}{Vt}$$

Where, Vb = Bulk volume and Vt = Tapped volume

Hausner's ratio:

Hausner's ratio is an important character to determine the flow property of powder and granules that can be calculated using the formula [17]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose:

The angle of repose of API granules was determined by the funnel method. The powder blend was accurately weighed and was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel touched the surface of the powder blend layers. The powder blend was allowed to flow through the funnel freely on to the surface [18]. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

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

where, θ= angle of repose, h= height of the pile and r = average radius of the powder cone

Post compression parameters:

Hardness:

Hardness of the tablet was determined against Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to measure the force [19].

Friability:
Friability is measured by Roche friability tester. 10 tablets were kept in the friability tester and were rotated at 25 rpm for 4 minutes [20]. The initial and the final weights were recorded and the friability was calculated using the formula:

$$\% F=[1-(Wt/W)]*100$$

W - Initial weight of tablet
Wt- Weight of tablet after revolution.

% Friability of tablets less than 1% was considered acceptable.

Weight variation test:
Weight variation test was performed as per the Indian Pharmacopoeia. 20 tablets were weighed individually and the weight variation was calculated using standard deviation [21].

Drug Content:
The amount of drug present in one tablet was calculated using UV-visible spectrophotometer at absorbance 322 nm. Ten tablets were weighed and average weight was calculated. All the weighed 10 tablets were crushed in a mortar and the powder equivalent to 10 mg was accurately weighed, dissolved in 0.1 N HCl and made up to 100ml volume. The volumetric flask was shook for approximately 20 minutes. The solution was filtered and 1 ml of the filtrate was diluted to 10ml using 0.1 N HCl that was used for drug content measurementagainst0.1 N HCl as blank [20-21].

***In vitro* drug release studies:**
In vitro drug release studies were performed using USP dissolution test apparatus (Type 1) in the presence of rat caecal material. The dissolution studies were performed in 900ml of dissolution medium which was stirred at 50 rpm at 37±0.5°C following a pH progression method, - i.e. pH 1.2using 0.1 N HCl for first 2hours, pH 6.8 phosphate buffer for the next 3hours and pH 7.4 phosphate buffer for rest of the studies in the presence of rat faecal material. Aliquots were withdrawn periodically and replaced with fresh medium; aliquots were analyzed using UV-visible spectrophotometer at 322 nm [22].

Collection of rat caecal material:
Two Wistar rats of body weight (150-200g) with no prior drug treatment were used for all the present *ex vivo* studies. These rats were maintained on normal diet and administered 1ml of 2% pectin dispersed in water continuously for 7 days, following which the enzyme that specifically acts on natural gums could be included 30 minutes prior the abdomen of the rat was dissected to collect the caecal material. The caecum was traced, legated at both the ends, dissected and was immediately transferred into phosphate buffer saline (PBS) of pH 6.8 that was previously bubbled with CO_2. The caecal bag was then opened and the contents were weighed, homogenized and suspended in simulated colonic fluid of pH 7.4 to attain the desired concentration of 2%. The experiment was carried out with continuous supply of CO_2 into the dissolution media. Drug release observations for the first 5 hrs were performed adopting the method of *in vitro* drug release studies in simulated gastrointestinal fluid. After 5 hrs the drug release observations were carried out in simulated colonic fluid containing rat caecal material. Aliquots of samples were withdrawn periodically and replaced with appropriate freshly prepared buffer bubbled with CO_2. The samples were filtered through Whatmann filter paper and the drug content in the filtrate was determined spectrophotometrically.

Release kinetics:
Dissolution data of the optimized colon-specific aceclofenac matrix tablet (F15) was fitted in various release kinetics model like zero order, first order, Higuchi, Hixone-Crowell and Peppas model for the determination of r^2 and rate constant value.

3. Results and discussion

Fourier transform infrared spectroscopy (FTIR):
The samples were read over wave number range of 4000-400 cm^{-1} in IR. The resultant spectrums were compared against the standard spectrum of the pure drug dispersed in the same solution. From the variations observed between the spectra of pure drug and drug-polymer combinations, this was clear that the characteristic bands of the drug remain unaffected indicating that the polymers were inert. This, in other words suggests the absence of chemical interactions between the drug and polymers. (Figure 1-6)

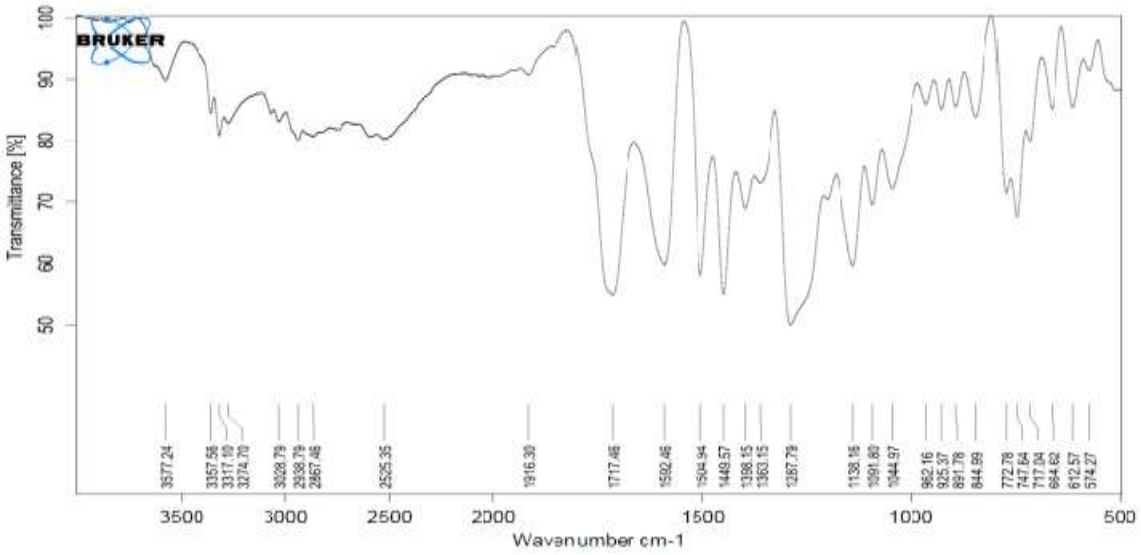

Figure 1: FTIR Spectroscopy of aceclofenac

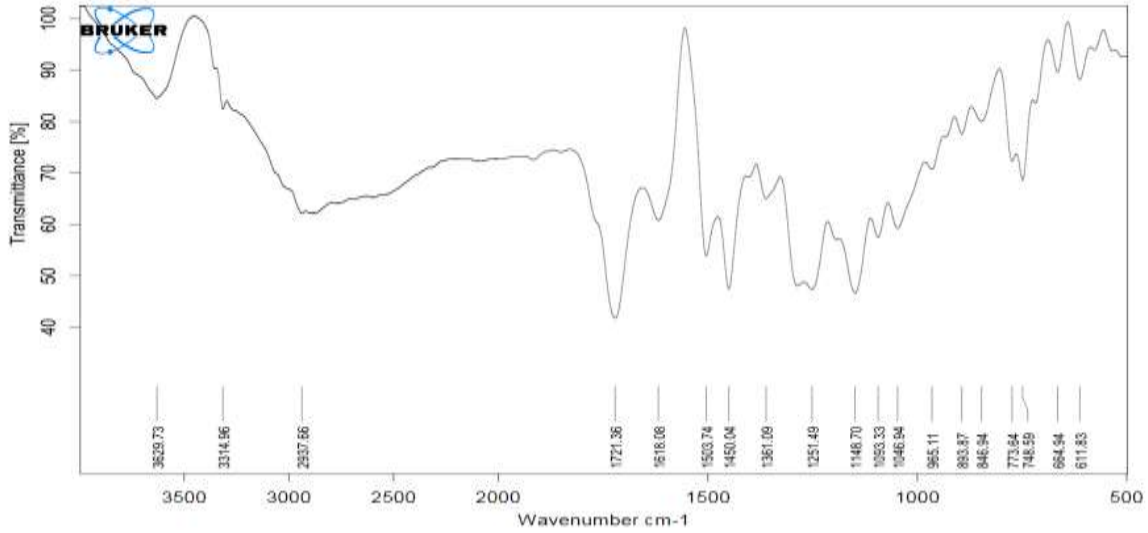

Figure 2: FTIR Spectroscopy of aceclofenac +xanthan gum

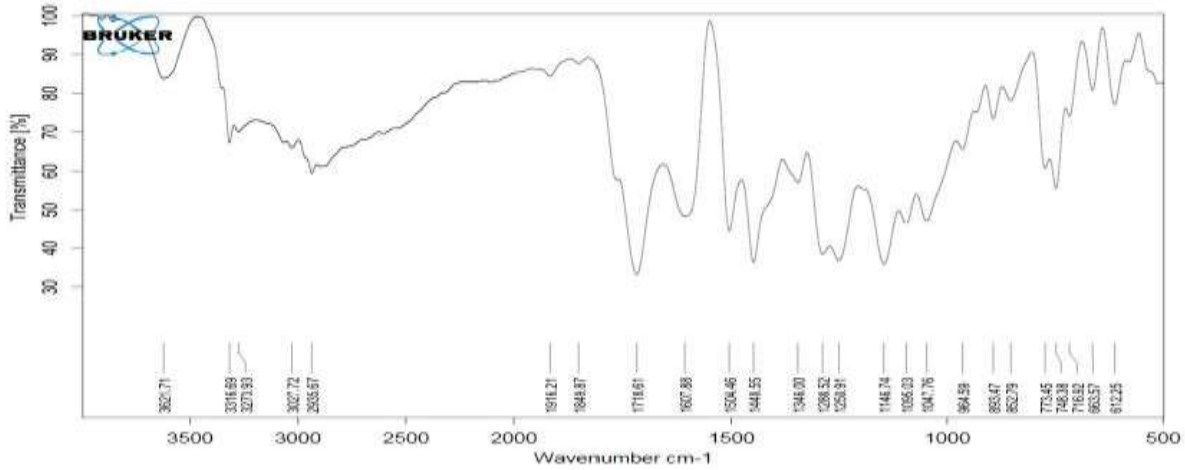

Figure 3: FTIR spectroscopy of aceclofenac+guar gum

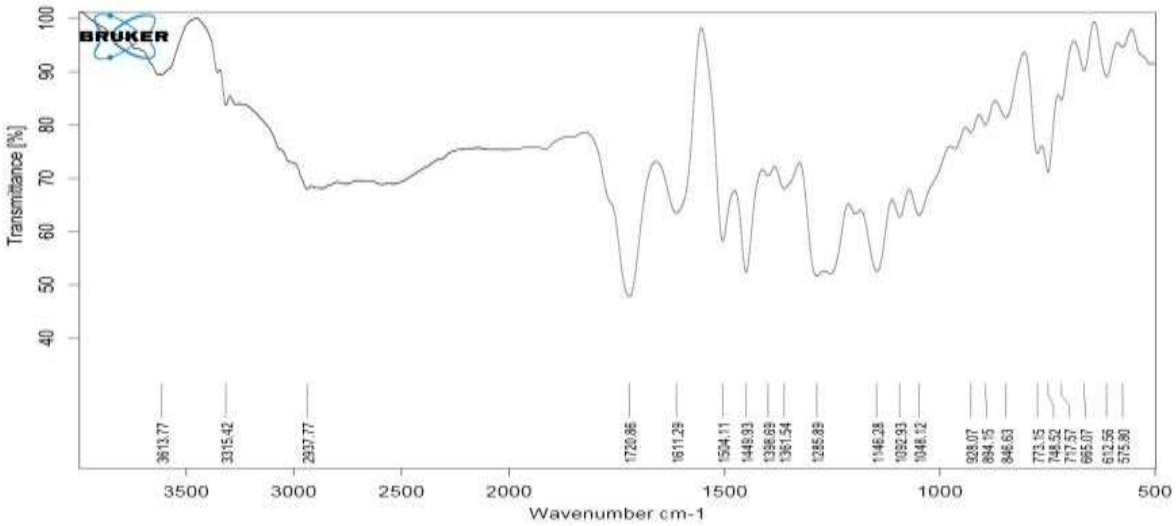

Figure 4: FTIR spectroscopy of aceclofenac+pectin

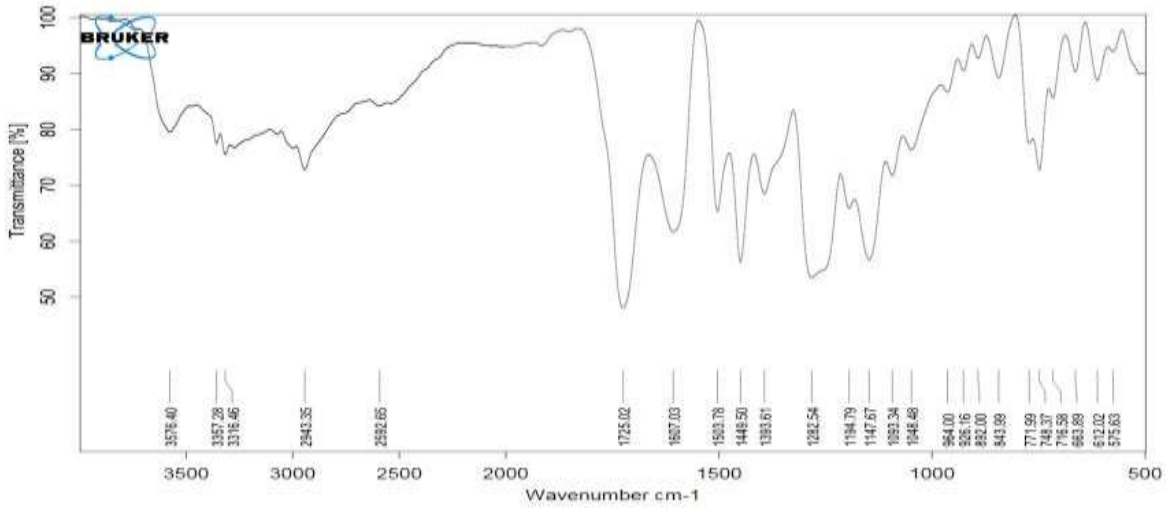

Figure 5: FTIR spectroscopy of aceclofenac+katiragum

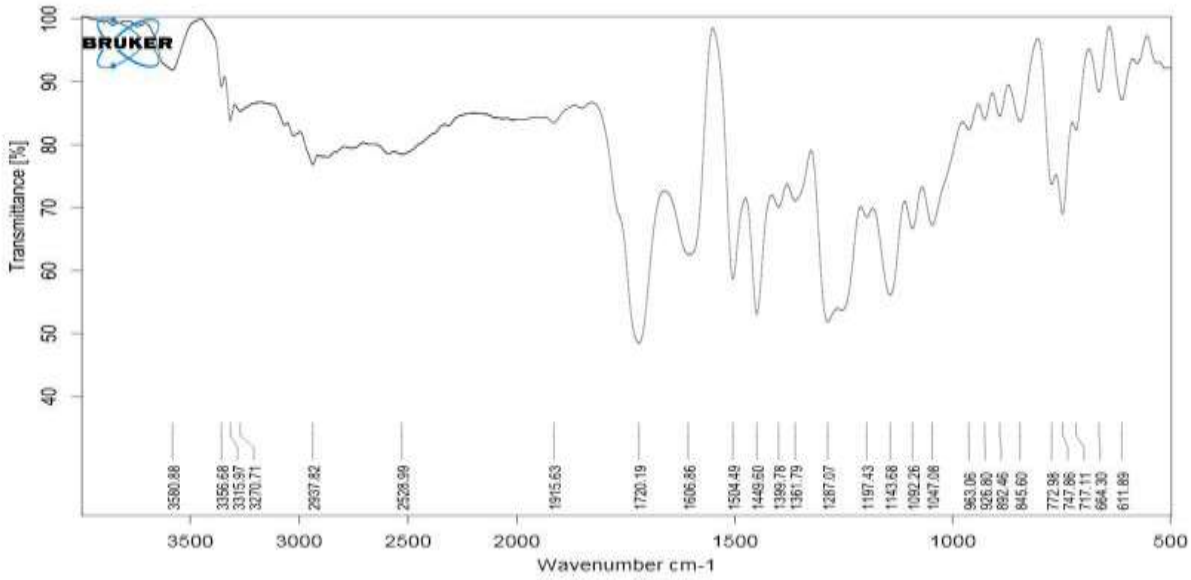

Figure 6: FTIR Spectroscopy of aceclofenac + sterculiagum

Precompression parameters:
Precompression parameters were evaluated and the results were within standard limits as shown in Table No. 2.

Postcompression parameters:
All the formulations were evaluated for their physical properties like hardness, friability, weight variation and drug content (Table no. 3) and were within the standard limits.

***In vitro* dissolution study:**
All the formulations were subjected for dissolution tests in 0.1N HCl for 2 hrs, phosphate buffer of pH 6.8 for 3 hrs and phosphate buffer of pH 7.4 for12 hrs (Figure no: 7 to 11). The natural gums showed better release at pH 7.4. Amongst all the matrix tablet combinations, the formulation containing Sterculia gum showed 97.88% sustained drug release for a period of 12 hrs.

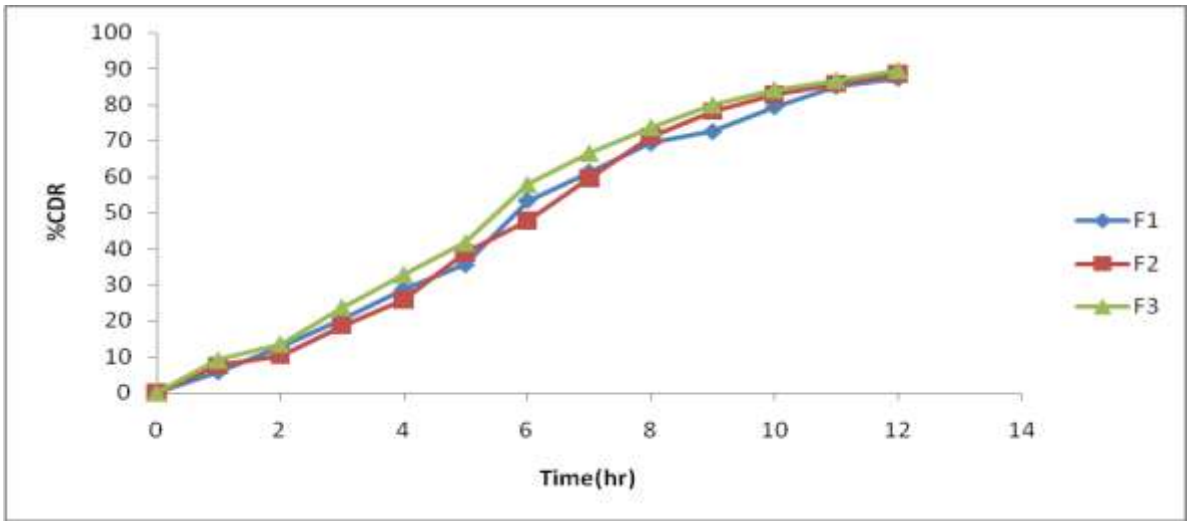

Figure 7: *In vitro* dissolution study of colon matrix tablets of F1 to F3

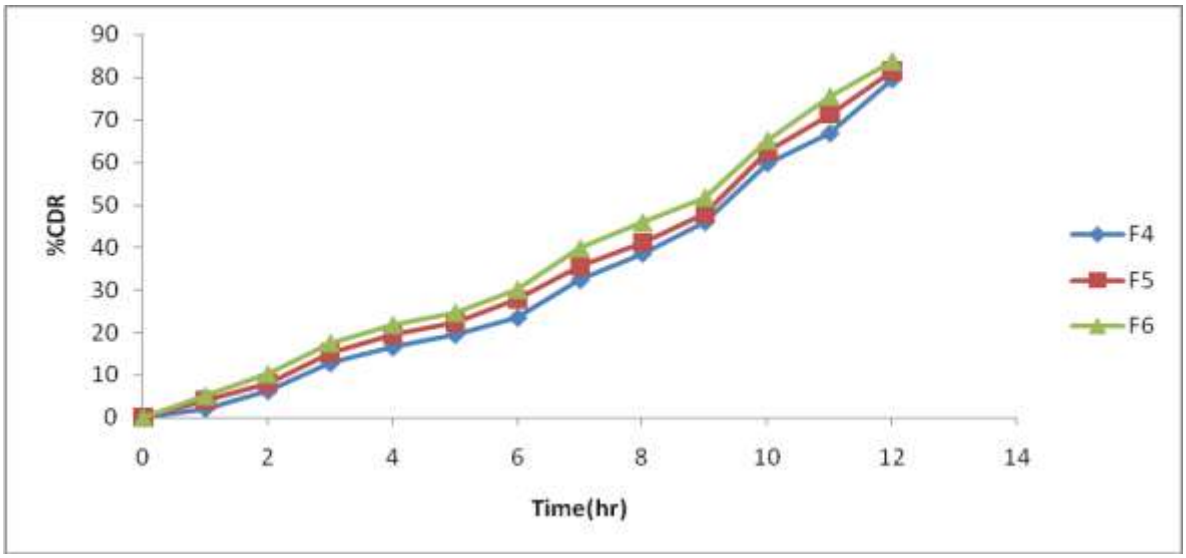

Figure 8: *In vitro* dissolution study of colon matrix tablets of F4 to F6

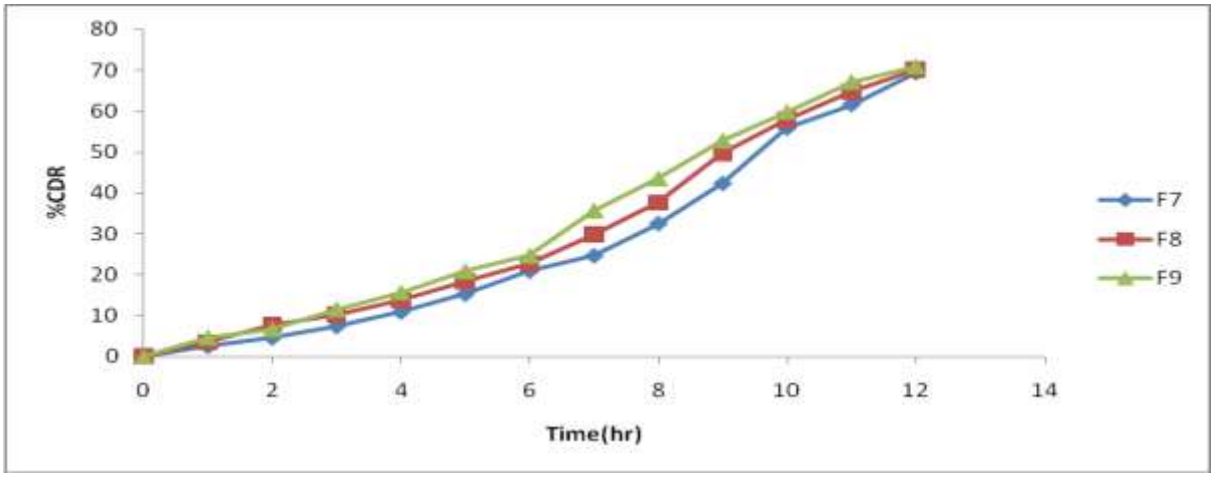

Figure 9: *In vitro* dissolution Study of colon matrix tablets of F7 to F9

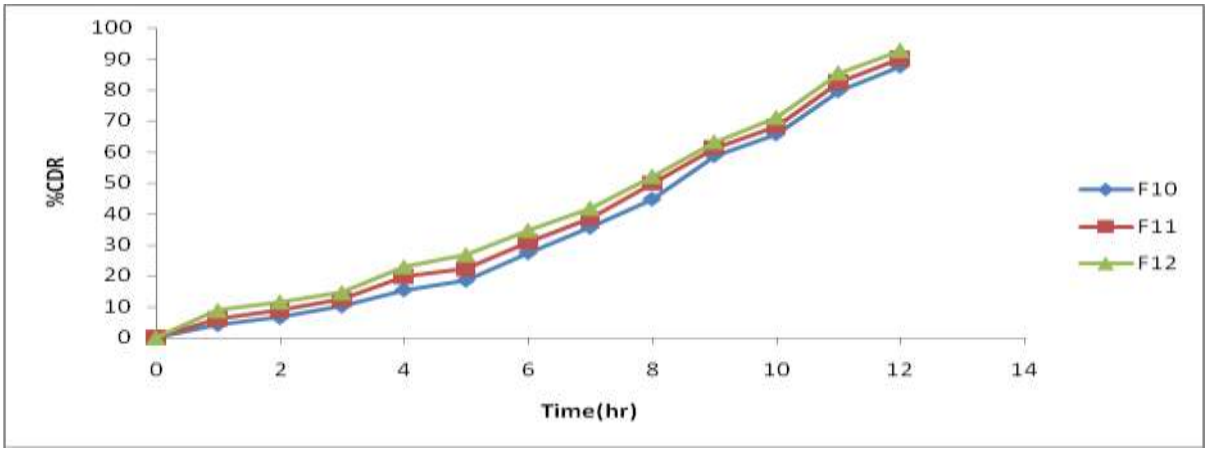

Figure 10: *In vitro* dissolution study of colon matrix tablets of F10 to F12

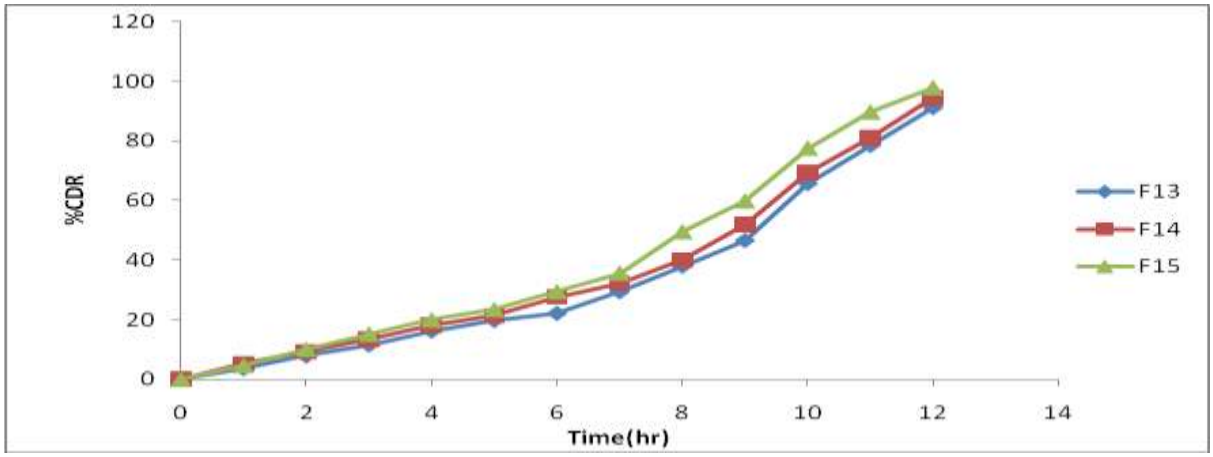

Figure 11: *In vitro* dissolution study of colon matrix tablets of F13 to F15

Table no.1: Composition of colon targeted matrix tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Aceclofenac	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Xanthan gum	30	60	90	-	-	-	-	-	-	-	-	-	-	-	-
Guar gum	-	-	-	30	60	90	-	-	-	-	-	-	-	-	-
Pectin	-	-	-	-	-	-	30	60	90	-	-	-	-	-	-
Katira gum	-	-	-	-	-	-	-	-	-	30	60	90	-	-	-
Sterculia gum	-	-	-	-	-	-	-	-	-	-	-	-	60	90	120
MCC	145	115	85	145	115	85	145	115	85	145	115	85	130	100	70
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mg,Stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
PVP K 30(%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
TOTAL(mg)	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300

Table 2: Precompression parameters of colon targeted matrix tablet

Batch	Bulk Density (g/cm^3) n=3	Tapped Density (g/cm^3) n=3	Hausner's ratio	Angle of repose (θ) n=3	Compressibility index (%)
F1	0.58±0.032	0.67±0.035	1.10±0.036	28.55±0.045	13.43±0.035
F2	0.48±0.025	0.56±0.024	1.08±0.025	26.25±0.035	14.28±0.055
F3	0.52±0.035	0.59±0.022	1.11±0.045	29.44±0.038	11.86±0.045
F4	0.47±0.060	0.53±0.030	1.17±0.035	30.35±0.041	11.32±0.022
F5	0.43±0.035	0.50±0.037	1.39±0.040	24.30±0.035	14.00±0.052
F6	0.39±0.055	0.46±0.032	1.09±0.055	27.34±0.061	15.21±0.036
F7	0.49±0.030	0.60±0.047	1.19±0.025	25.52±0.058	18.33±0.033
F8	0.53±0.041	0.58±0.043	1.25±0.041	31.43±0.049	8.62±0.029
F9	0.57±0.063	0.65±0.051	1.28±0.032	24.40±0.053	12.30±0.038
F10	0.42±0.049	0.50±0.032	1.18±0.028	28.50±0.046	16.00±.0053
F11	0.46±0.036	0.52±0.061	1.21±0.034	31.65±0.032	11.53±0.044
F12	0.63±0.042	0.68±0.045	1.15±0.029	25.48±0.030	7.35±0.035
F13	0.49±0.023	0.53±0.051	1.24±0.065	30.69±0.026	7.54±0.051
F14	0.61±0.034	0.68±0.049	1.34±0.044	24.18±0.048	10.29±0.047
F15	0.59±0.044	0.67±0.063	1.20±0.030	28.65±0.054	11.94±0.038

Table 3: Postcompression parameters of colon targeted matrix tablet

Batch	Hardness ($kg\ cm^2$+ %S.D) n=6	Friability (%)	Weight variation Avg weight (mg) (%S.D < 10%)	% Drug Content
F1	5.72± 0.30	0.32	1.22	96.51± 0.58
F2	5.24±0.32	0.45	2.13	99.26± 0.32
F3	7.12± 0.36	0.52	1.98	98.25± 0.3
F4	6.53± 0.26	0.56	2.45	99.52± 0.62
F5	5.55± 0.35	0.49	2.19	100.65 ±0.33
F6	7.23±0.38	0.66	2.36	98.29± 0.45
F7	5.06±0.38	0.42	2.76	96.43± 0.36
F8	5.52±0.33	0.59	2.79	98.69± 0.25
F9	6.59±0.30	0.65	2.74	101.36± 0.51
F10	6.53±0.42	0.43	1.98	97.89± 0.62
F11	7.23±0.33	0.36	2.15	98.44 ±0.31
F12	6.29±0.42	0.66	1.98	99.85 ±0.25
F13	5.12±0.38	0.83	2.74	97.45± 0.38
F14	6.52±0.42	0.42	2.15	96.99± 0.56
F15	5.59±0.38	0.49	1.22	97.53± 0.52

Table 4: Release kinetics of colon targeted matrix tablet

Formulation	Zero order		1st order		Higuchi		Hixone Crowell model		Peppas	
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K
F15	0.947	8.61	0.957	0.110	0.867	38.05	0.991	0.259	0.975	1.22

Release kinetics:

Dissolution data was fitted in various release kinetics model to find that the optimized matrix formulation (F 15) followed Hixon-Crowell model**.**The results of release kinetics is shown in Figure no. 4.

Conclusion

Over the past two decades research has turned focus on the importance of circadian rhythms of GIT physiology and disease stressing on the significance of the time-of-day of drug administration and the resultant pharmacodynamic and pharmacokinetic parameters. In the present study colon-targeted tablets that are microbially triggered for activation on administration was designed and characterized. Based on the FTIR spectra, the drug and the excipient were confirmed to be authentic and chemically compatible. Matrix formulations initially characterized by precompression studies were found to possess good flow characteristics. The tablets passed different physical evaluation tests and *in vitro* drug release study. Batch F15 with Sterculia gum was observed to have better results for in *vitro* sustained drug release tests. The drug release profile was evaluated in simulated gastro-intestinal fluid and simulated colonic fluid. The sterculia gum polysaccharides was degraded by enzymes liberated from the colonic microflora and was found to be suitable for targeting the drug, aceclofenac, for specific action on diseased colon sites.

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