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DESIGN AND DEVELOPMENT OF CIPROFLOXACIN COLON SPECIFIC DRUG DELIVERY SYSTEM

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ABSTRACT:
The matrix tablets of antibacterial agent Ciprofloxacin for colon targeting were prepared by direct compression method using different natural gums like Sesbania gum, Locust bean gum, Pectin and Eudragit RS100 as enteric polymer. Prepared formulations were evaluated for angle of repose, tapped density, bulk density, compressibility index and hausner's ratios show good flow properties. The compressed matrix tablets were evaluated for hardness, uniformity weight, friability, drug content and *in vitro* dissolution studies. All the formulations showed good compliance with the Pharmacopoeial standards. In in vitro studies all the formulations showing greater than 12 hrs of drug release in 7.4 pH. The optimized formulation F2 dissolution studies was performed with Pectinase enzyme in 7.4 pH (Sesbania) have shown better release i.e 98.53 % in 36 hrs and following Zero order with drug release mechanism of Non-Fickian Diffusion (n=0.10).

Key words: Ciprofloxacin, Sesbania, Pectin and Pectinase enzyme

1. INTRODUCTION:

The colon drug delivery dosage forms are valuable in the treatment of disease of colon (ulcerative colitis, crohn's disease, carcinomas and infections). These drug deliveries ensures the direct treatment at diseased site with fewer systemic side effects, minimizes drugs first pass metabolism and prevents GI irritation which produced drug administration by oral route. The Colon specific formulation sould also be used to prolong the release of drug. Transit time in colon is more than stomach which improves bioavailability of poorly absorbed drugs.

Colonic delivery preferably suitable for drugs with polar, susceptible to enzymatic and chemical degradation in upper GIT, affected by hepatic metabolism highly, particularly for therapeutic proteins and peptides. Conventional dosage forms upon oral administration are normally dissolves in the stomach, intestinal fluid and absorb from GIT depending upon the physiologica land physicochemical properties of the drug, but others are by oral administration, not readily available which are incompatible with other properties and or demonstrate as poor uptake in the upper GIT. Due to the facility lack with digestive enzymes, colon is considered as good and suitable site for the absorption of various drugs. The simplest and easiest method for drugs targeting to the colon is to obtain slower or longer release periods by the preparation of thicker layers by conventional enteric coatings and extremely slow releasing matrices.

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2. MATERIALS AND METHOD

Active Pharmaceutical ingredients and Reagents: Ciprofloxacin was kindly supplied by Nihar trader, Hyderabad, India. Natural gums i.e Sesbania and locust bean gum obtained from lobacamia Pvt. Ltd. Pectin and Eudragit RS 100 from Qualikem fine chemicals Pvt. Ltd. Talc, starch, magnesium stearate and microcrystalline cellulose was obtained from Qualikem fine chemicals Pvt. Ltd. All the chemicals were used in this study were of LR grade. Pectinase was purchased from Kaypeeyes Biotech Pvt. Ltd.

Formulation design of colon targeted tablets containing Ciprofloxacin:

Preparation of Ciprofloxacin colon targeted matrix tablets: Accurately weighed drug (Ciprofloxacin), Pectin and gums such as Sesbania, locastbean gum with other excipients like Eudragit RS-100, microcrystalline cellulose, magnesium stearate, starch and talc were taken in a mortar and mixed properly then compressed by direct compression method using 11mm punch.

Evaluation of rheological characteristics of Ciprofloxacin blend:

All formulations powder blend was evaluated for Angle of repose, Bulk and density, Compressibility index and, Hausner's ratio.

i) Bulk density: 30 gms of blend was passed through sieve no. 25 to break up agglomerates then introduced into cleaned and dried 100mL cylinder. The powder was carefully levelled and the unsettled apparent volume read as v_0. The bulk density (grams per mL) calculated, using the formula.

$$M / V0$$

Where M = weight of sample

V0 = apparent volume of powder.

ii) Tapped density: Tapped density determines after carried out the procedure as given above in the bulk density measurement the cylinder containing powder sample was operated with mechanical tapped density apparatus which provides a fixed drop times of 14-2 mm at a nominal rate of 300 drop times per minute. The apparatus containing cylinder was tapped for 500 times initially, followed by an additional tap of 750 times until difference between succeeding trials was < 2% and then tapped volume vt was measured. The tapped density (g per cc) was calculated using below mentioned formula.

$$M / Vt$$

Where M = total weight of the powder blend

Vt = tapped weight of the powder

iii) Measures of powder compressibility: The compressibility index and hausner's ration are used to measure the powder property to be compressed. They two are measure to the relative importance of powder blend inter particulate interactions. Powder particle interactions are less significant in free-flowing powder, the bulk and tapped densities will be near in value. For poorer flowing powder materials, greater inter particle interactions and difference in the bulk and tapped densities will present. These

Table 1: Formulation of colon targeted matrix tablets of Ciprofloxacin

Code	Drug (mg)	Pectin (mg)	Sesbania (mg)	Locustbean gum (mg)	Eudragit RS 100 (mg)	MCC (mg)	Starch (mg)	Magnesium stearate (mg)	Talc (mg)
F1	250	250	-	-	-	5	5	5	5
F2	250	-	250	-	-	5	5	5	5
F3	250	-	-	250	-	5	5	5	5
F4	250	-	-	-	250	5	5	5	5

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differences would reflect in the hausner's ratio, and the compressibility index which are calculated using formulae

Compressibility index = v_t-v_0*100/v_t

Where V_t = Tapped density

V_0 = Bulk density

iv) Hausner's ratio: It is the ratio of bulk density to tapped density

V_0 / Vt

Where V_0 = Bulk density

V_t = Tapped density

Evaluation of compressional characteristics of Ciprofloxacin colon targeted matrix tablet

Weight variation: From each of formulation 20 tablets were selected and weighed individually with an electronic balance. The average weight determined and individual tablet weight was compared with average value then deviation was calculated using below formulae.

% deviation = (Individual weight-average weight)/ average weight ˣ100

Tablet thickness: The thickness of 20 tablets recorded by using screw guage. The core tablet average thickness is calculated and presented along with standard deviation. It is expressed in mm.

Tablet hardness: From each formulation 6 tablets utilized for the hardness by Monsanto hardness tester and its average is also calculated and presented with standard deviation

Friability test: Friability test measures mechanical strength and to assess the abrasion and shock effect that may often cause chip, cap or break to tablet.

In vitro release kinetics: The following conditions were used to study *in vitro* drug release to all the tablets by USP type-1dissolution rate apparatus.

Dissolution test parameters: Medium**:** 900mL of phosphate buffer (6.8, 7.4), 0.1 N HCl; Rotation speed**:** 50 rpm; Temperature**:** 37±0.5 ℃; Sampling volume**:** 5Ml.

5mL of samples were collected at predetermined time intervals and replaced with same volume of fresh medium. The content of drug in samples determined by UV-visible spectrophotometer at 271nm after filtered them through whatman paper.

Analytical method **used in the determination of Ciprofloxacin**

Standard stock solution:

5 mg of Ciprofloxacin used to prepare stock solution by dissolving it in 100 mL of phosphate buffer in volumetric flask for obtaining the 50µg/mL strength solution(stock 1). 10mL of this solution is added to 90mL distilled water to get a solution of 5µg/ml strength (stock 2). From this secondary stock 1,2,3,4 and 5ml were taken and added to make up to 10 mL with buffer, to produce 1,2,3,4 and 5 µg/mL strengths respectively. The absorbance of samples was measured using a UV-visible spectrophotometer. The standard graph of Ciprofloxacin in 0.1 N HCl, phosphate buffers of 6.8 and 7.4 were plotted.

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ii) Tapped density*:* Tapped density determines after carried out the procedure as given above in the bulk density measurement the cylinder containing powder sample was operated with mechanical tapped density apparatus which provides a fixed drop times of 14-2 mm at a nominal rate of 300 drop times per minute. The apparatus containing cylinder was tapped for 500 times initially, followed by an additional tap of 750 times until difference between succeeding trials was < 2% and then tapped volume vt was measured. The tapped density (g per cc) was calculated using below mentioned formula.

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Evaluation of compressional characteristics of Ciprofloxacin colon targeted matrix tablet

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value then deviation was calculated using below formulae.

% deviation = (Individual weight-average weight)/ average weight ×100

Tablet thickness: The thickness of 20 tablets recorded by using screw guage. The core tablet average thickness is calculated and presented along with standard deviation. It is expressed in mm.

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5mL of samples were collected at predetermined time intervals and replaced with same volume of fresh medium. The content of drug in samples determined by UV-visible spectrophotometer at 271nm after filtered them through whatman paper.

Analytical method used in the determination of Ciprofloxacin

Standard stock solution: 5 mg of Ciprofloxacin used to prepare stock solution by dissolving it in 100 mL of phosphate buffer in volumetric flask for obtaining the 50µg/mL strength solution(stock 1). 10mL of this solution is added to 90mL distilled water to get a solution of 5µg/ml strength (stock 2). From this secondary stock 1,2,3,4 and 5ml were taken and added to make up to 10 mL with buffer, to produce 1,2,3,4 and 5 µg/mL strengths respectively. The absorbance of samples was measured using a UV-visible spectrophotometer. The standard graph of Ciprofloxacin in 0.1 N HCl, phosphate buffers of 6.8 and 7.4 were plotted.

3. RESULTS AND DISCUSSION

Pectolytic enzyme (Pectinase) hydrolyses the pectin, which is a component of cell wall and catalyses the random hydrolysis of a –(1-4)-D-galactosiduronic linkages in pectin and other galacturonics. It produced from a selected strain of Asperagillus Niger. Pectinase mainly contains polygalacturonase, pectintransaminase and pectinesterase and small amounts of cellulose and hemicelluloses. Sesbania and locust bean gums were selected to the colon drug delivery since they are having the similar pH to the colon and these gums are having high viscosity. Due to the higher residence time in the colon, the drug absorption may increase.

The optimized formulation (F2) was evaluated using Pectinase enzyme in the dissolution medium, before the addition of enzyme the formulation done for dissolution and the drug release was found to be 99.61% for 48 hrs, the mechanism involved is Fickian diffusion. After the addition of Pectinase enzyme the linkages within the pectin was broke down. It undergoes erosion, follows the mechanism of Non-Fickian diffusion and the drug release was found to be 98.53% for 36 hrs.

4. CONCLUSION

Ciprofloxacin matrix tablets was successfully designed and evaluated. Optimized

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formulation F2 which include Sesbania has best control drug release for 36 hrs.
Further studies were required to confirm the results in vivo conditions.

by Brookfield viscometer	
Gums	**Viscosity (cPs)**
Pectin	1100
Sesbania	4100
Locust bean gum	3500

Table 2: Evaluation of rheological characteristics of Ciprofloxacin blend

Formulation code	Angle of repose	Bulk density (gm/cc)	Tapped density	Carr's index (%)	Hausner's ratio
F1	31.02±0.02	0.57±0.1	0.68±0.02	13.28±0.07	1.85±0.01
F2	33.8±0.07	0.53±0.05	0.61±0.02	13.37±0.03	1.86±0.06
F3	31.47±0.01	0.57±0.3	0.66±0.05	13.63±0.05	1.86±0.21
F4	35.32±0.03	0.56±0.07	0.65±0.01	15.31±0.2	1.84±0.16

Table 3: Evaluation of compression characteristics of Ciprofloxacin colon targeted matrix tablet

Formulation code	Weight variation(mg)	Hardness (kg/cm²)	Friability (% loss)	Thickness (mm)	Drug content(%)
F1	486.5±2.71	6.5±0.13	0.43±0.3	5.5±0.04	98%
F2	490.2±2.04	5.9±0.21	0.52±0.12	5.8±0.06	97%
F3	489.6±2.12	6.6±0.13	0.49±0.65	5.6±0.02	97%
F4	493.8±1.25	6.8±0.35	0.49±0.72	5.9±0.08	98%

Table 4: In-vitro drug release of Ciprofloxacin colon targeted matrix tablet in Phosphate buffer (7.4 pH)

Time (hrs)	**F1 (%)**	**F2 (%)**	**F3 (%)**	**F4 (%)**
0	0	**0**	0	0
1	12.13±1.09	**8.30±0.19**	4.15±1.42	6.31±0.23
3	13.80±0.86	**11.18±0.77**	5.53±1.40	7.53±0.52
5	15.47±0.78	**15.39±0.96**	6.86±1.39	11.07±0.64
9	16.98±0.92	**22.70±1.45**	9.13±2.01	15.95±0.73
12	19.82±0.21	**22.92±0.95**	14.73±1.54	19.93±1.21
24	70.27±1.72	**61.97±1.95**	18.38±2.71	41.31±0.59
36	88.48±1.59	**90.41±1.37**	20.82±0.98	60.81±0.47
48	95.55±1.02	**99.61±0.92**	42.75±1.74	97.86±1.57

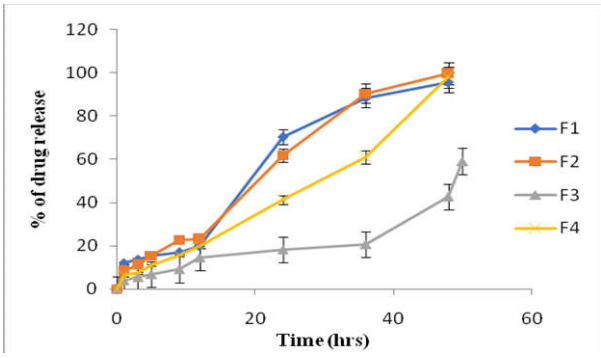

Fig 1 : Percentage drug release of colon targeted Ciprofloxacin F1-F4

Table 7: Viscosity studies of natural gums

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TABLE 5 : *In Vitro* Optimised Formulation With Pectinase		
Time (hrs)	**F2**	**Optimized formulation with Pectinase**
0	0	0
1	**8.30±0.19**	14.31±0.13
3	**11.18±0.77**	17.21±0.22
5	**15.39±0.96**	21.04±0.14
9	**22.70±1.45**	28.62±0.57
12	**22.92±0.95**	37.29±0.73
24	**61.97±1.95**	76.09±0.37
36	**90.41±1.37**	98.53±0.62
48	**99.61±0.92**	-

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Table 6: kinetics of drug release and mechanism of drug release from the dosage form of Ciprofloxacin colon targeted drug delivery

CODE	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMEYER PEPPAS	"n"
F1	0.83	0.81	0.94	0.99	0.17
F2	**0.97**	**0.90**	**0.92**	**0.99**	**0.50**
F3	0.97	0.86	0.92	0.44	0.09
F4	0.99	0.88	0.92	0.98	0.34

Table 8: kinetics of drug release and mechanism of drug release from the dosage form of Ciprofloxacin with Pectinase colon targeted drug delivery

Optimised Formulation with Pectinase	Zero order	First order	Higuchi	Korsmayer-peppas	'n'
F2	0.9956	0.9872	0.9632	0.9818	0.1036

6. CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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