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FORMULATION AND EVALUATION OF CIPROFLOXACIN COLON TARGETED TABLETS BY COMPRESSION COATING TECHNIQUE

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ABSTRACT

The aim of the present study is to develop colon targeted drug delivery system for ciprofloxacin using various proportions of guargum and HPMC K4M to treat the crohn's disease. The compression coated tablets of ciprofloxacin were prepared and were evaluated for hardness, thickness, friability, diameter, drug content, weight variation and *invitro* drug release studies. The amount of ciprofloxacin released from tablets at different time intervals was estimated by UV visible spectroscopy. From these evaluations it is observed that release of the drug was comparatively less in gastric and intestinal fluids and increased in colonic fluids. When the dissolution study was continued in simulated colonic fluids, the compression coated tablets with 175 mg of HPMC K4M coat released 96.07% (F8) and 99.02% (F9) of ciprofloxacin after degradation by colonic bacteria at the end of 24 h of the dissolution study. The compression coated tablets with 175mg of guar gum: HPMC K4M coat released about 98.09% (F14) of ciprofloxacin, respectively, in simulated colonic fluids indicating the susceptibility of the guar gum formulations to the rat caecal contents. The mean percentage of ciprofloxacin released at various time intervals was calculated and plotted against time. The mechanism of drug release with the formulations F8 and F9 was dominantly case-2 transport diffusion and followed zero order kinetics, where as the formulation F14 followed Korsemeyerpeppas equation.ciprofloxacin compression coated tablets showed no change either in physical appearance, drug content or in dissolution pattern. Based on the R^2 values obtained F9 is considered as the best formulation.

KEYWORDS: Ciprofloxacin, Guar gum, HPMC, Crospovidone, Colon targeted drug delivery, Compression coating tech.

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach or intestinal fluid and absorb from the regions of the GIT depends upon the physicochemical properties of the drug [1]. It is a serious drawback in conditions where localized drug delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of the upper GIT [2]. Dosage forms that deliver into the colon rather than upper GIT proffers number of advantages.[1]

The challenge in the development of colon-specific drug delivery system is to establish an appropriate dissolution method in designing in-vitro system. Due to the rationale after a colon delivery system is quite diverse. As, a site for delivery offers a near neutral pH, reduced digestive enzymes activity, a long transit time, and increased responsiveness to absorption enhancers, hence targeting is complicated, with reliability and delivery efficiency.

Pharmaceutical products designed for oral delivery are mostly the immediate release type, which are designed for the immediate release of drug for rapid absorption. Because for their clinical advantages over immediate release pharmaceutical products containing same drug, sustained release pharmaceutical products have gained medical assistance and popularity.

COLON

Colon was considered as BLACK BOX as most of the drugs were absorbed from upper part of GI tract.[2]

It has also been suggested that colonic delivery of orally administered protein and peptide drugs might be possible, because enzyme activity is low in the colon. Besides these low hostile environment, the colonic transit time is long (20-30 hours) and the colonic tissue is highly responsive to the action of absorbtion enhancers Analgesic peptides, oral vaccines, growth hormone and insulin are candidates for use of the colon as a site for absorption.

Anatomy of colon

It is a 6-foot long muscular tube that connects the small intestine to the rectum. The large intestine is made up of the ceacum, the ascending (right) colon, the transverse (across) colon, the descending (left) colon, and the sigmoid colon, which connects to the rectum. It is about 1.5m long, the transverse colon being the largest and most mobile part, and has an average diameter of about 6.5cm, although it varies in diameter from approximately 9cm in the ceacum to 2cm in the sigmoid colon. The appendix is a small tube attached to the ceacum. The large intestine is a highly specialized organ that is responsible for processing waste so that emptying the bowels is easy and convenient.[5]

pH of GI tract in healthy human subjects.

Location		pH
Oral cavity		6.2-7.4
Stomach	Fasting Fed	1.5-2.0 3.0-5.0
Small intestine	Jejunum Ileum	5.0-6.5 6.0-7.5
Large intestine	Right colon Mid colon and left colon	6.4 6.0-7.0

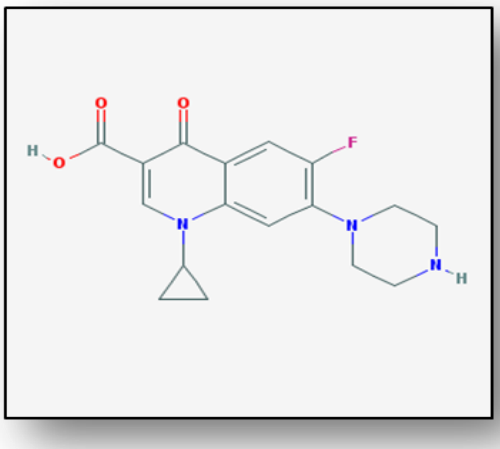
The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time.

Drug Profile

Name : Ciprofloxacin

In the present study, ciprofloxacin is formulated in to the compressed coated tablet. This drug is selected because, Ciprofloxacin is one of the most popular drug used in the treatment of Crohn's disease and Inflammatory Bowel Disease (IBD) but also for the potential holds for the systemic delivery of proteins and therapeutic peptides.

Structure



Structure of Ciprofloxacin

Description

Ciprofloxacin is a pale yellow to white crystalline powder which is soluble in dilute (0.1 N) hydrochloric acid and is practically insoluble in water and ethanol. Decomposition occurs between 261°C - 265°C.

pH of ciprofloxacin is 7.6 at 0.1 g/L water at 20°C.

It has a pKa of 6.5 and 8.9 determined using a 3 x 10^{-4}M solution at 25°C.

PHARMACOLOGY

Absorption: Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations are attained after 12 hours. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

Distribution: The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate when the steady-state volume of distribution is 2-3 L/kg. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism: Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Excretion: The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After the urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several folds higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is

recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

MATERIALS AND METHODS

Materials Used

List of materials used in the formulation.

Ingredient	Category	Supplier
Ciprofloxacin	Drug	Granules India Ltd, Hyderabad, India.
Guar gum	Polymer	Nutriroma, India
HPMC different grade: K4M,	Polymer	Colorcon Asia Pvt. Ltd, India.
Microcrystalline cellulose	Diluent	S. D. Fine Chemicals Ltd., India.
Crospovidone	Disintegrant	Savvy spechemspvt Ltd, Hyderabad.
Magnesium stearate	Lubricant	S. D. Fine Chemicals Ltd., India.
Talc	Glidant	S. D. Fine Chemicals Ltd., India.

***List of Equipments Used*.**

Equipment	Company
Weighing balance	Shimadzu, AX200, Japan.
Tablet compression machine	Cadmach.
Friabilator	Roche ltd.
Hardness tester	Pfizer
UV-Spectrophotometer	Beckman and Coulter (DU 520series) spectrophotometer.
Dissolution apparatus	Erweka DT 700
Fourier transform infrared radiation spectrophotometer	Shimadzu, Japan.

Preformulation Parameters

The drug was evaluated for bulk density tapped density, compressibility index, hausners ratio and angle of repose.

Angle of Repose

Angle of repose was determined by funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated by using the formula:

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

Bulk density

Apparent bulk density (ρb**)** was measured by pouring the pre-weight (M) blend into a graduated cylinder. The bulk volume (Vb) of the blend was determined. Then the bulk density was calculated by using the formula: ρb = M/ Vb.

Tapped density

The measuring cylinder containing a known mass (M) of blend was tapped for a fixed time, and the minimum volume (Vt) occupied in the cylinder was measured. The tapped density (ρt**)** was calculated by using the following formula:

$$\rho t = M / Vt$$

Preparation of Ciprofloxacin tablets

Preparation of ciprofloxacin core tablets

Each core tablet (average weight of 150mg) for *invitro* drug release studies consisted of Ciprofloxacin (100mg), Micro crystalline cellulose (38mg), Crospovidone (6mg), Talc (3mg), Magnesium stearate (3mg). The materials were weighed, mixed and passed through a mesh(200μm) to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 6mm round, flat and plain punches on a 16 station tablet punching machine (Cadmach, India).

Formula for the preparation of Ciprofloxacin core tablets.

SNo	Ingredients	Quantity for one tablet (in mg)
1	Ciprofloxacin	100
2	Cross povidone	38
3	Talc	6
4	Magnesium stearate	3
5	Microcrystalline cellulose	3

{Total weight = 150mg}

Compression coating of Ciprofloxacin core tablets

The ciprofloxacin core tablets were compression coated with different quantities of coating material (guar gum, HPMC K4M) containing different concentration. Since the coating system alone gave very soft coats. Microcrystalline cellulose was included in the coat formulations to impart enough hardness. Half the quantity of coating material was placed in the die cavity, the core was carefully positioned in the center of the die cavity and was filled with other half of the coating material. The coating material was compressed around the core using 9mm round,flat and plain punches.

Composition of guar gum (200 mg coat weight) coats used to cover ciprofloxacin core tablets.

Ingredients	Quantity (mg) present in the coat formulation				
Guar gum	**F1**	**F2**	**F3**	**F4**	**F5**
	180	170	160	150	140
Microcrystalline cellulose	15	25	35	45	55
Talc	3	3	3	3	3
Magnesium stearate	2	2	2	2	2
Total Weight	200	200	200	200	200

Composition of guar gum (175 mg coat weight) coats used to cover ciprofloxacin core tablets.

Ingredients	Quantity (mg) present in the coat formulation				
Guar gum	**F6**	**F7**	**F8**	**F9**	**F10**
	130	120	110	100	90
Microcrystalline cellulose	40	50	60	70	80
Talc	3	3	3	3	3
Magnesium stearate	2	2	2	2	2
Total Weight	175	175	175	175	175

Composition of combination of guar gum and HPMC (175mg coat weight) coats used to cover ciprofloxacin core tablets.

Ingredients	Quantity (mg) present in the coat formulation				
Guar gum	**F11**	**F12**	**F13**	**F14**	**F15**
	75	80	85	90	95
Hydroxypropylmethyl cellulose (HPMC K4M)	25	20	15	10	5
Microcrystalline cellulose	70	70	70	70	70
Talc	3	3	3	3	3
Magnesium stearate	2	2	2	2	2
Total Weight	175	175	175	175	175

*****The compression coating method is selected as the best method when compared to other approaches beacuse both the drug ciprofloxacin and the method were heat labile. And the other parameters like environmental degradation, difficulty in standardization,time consuming are not observed during formulation.

Characterization of Ciprofloxacin core tablets

Hardness test

The prepared five tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in Kg/cm². The results are placed in the table 4.6.

Friability test

The friability of the tablets was determined in Roche Friabilator and expressed in %. 10 tablets from each batch were weighed accurately and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. Tablets were taken and reweighed. The percentage weight loss was determined by using formula given below. The experiment was repeated for three times and average was noted. The results are placed in the table 4.6.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

Formula for Friability

Weight variation test

Twenty tablets (of 175mg, 200mg) were selected randomly and weighed individually. Average weight was calculated standard deviation and percent coefficient of variance was computed. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none more than 10%.

Ranges of Weight variation test.

Average Weight of a tablet	Percentage Deviation
130mg or less	± 10
>130mg and <324mg	± 7.5
324mg or more	± 5.0

Drug content

The prepared ciprofloxacin tablets were tested for their drug content. Five tablets of each formulation were weighed and finely powdered. About 0.1gm equivalent of ciprofloxacin was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. 1ml of the filterate was further diluted to 100ml with pH 6.8 buffer. Absorbance of the resulting solution was measured by UV- Visible spectrophotometer at 271nm.The method was followed triplicate. The results are placed in the table 4.6.

Characterization of Ciprofloxacin compression coated tablets

The characterization tests like Hardness, Friability, Uniformity of drug content and Thickness were performed for the formulated compressed coated tablets of 15 batches (F1-F15) following the above mentioned procedure.

Invitro Drug Release Study

Dissolution parameters

Apparatus : USP type II
Speed : 100rpm
Temperature : 37±0.5˚C
Stirrer type : Paddle
Volume of medium : 900ml
Time points : 0,1,2,3,4,5,8,12,16,20 and 24hrs
Volume of media withdrawn : 5ml
Medium used : 1.2pH for 2hrs followed by 7.4pH phosphate buffer for 3hrs and finally in 6.8pH phosphate buffer for 19hrs.

The *invitro* dissolution study must be conducted in the dissolution medium which simulate the *invivo* condition (that is actual physiologic condition).The *invitro* drug release studies for the prepared formulations were conducted for a period of 24hours using USP dissolution apparatus type I set at 100rpm[54] and the temperature of 37±0.5˚C.Formulation was placed in 900ml of respective dissolution media.

The drug release studies were conducted in 1.2pH buffer for 2hrs followed by 7.4pH buffer for 3hrs and finally to mimic the conditions of colon 6.8pH phosphate buffer is used as a dissolution media for 19hrs.at specified intervals 5ml samples were withdrawn from dissolution media and replaced with fresh media to keep the volume constant. The concentration of drug was estimated using UV Visible spectrophotometer (1.2pH -269nm, 7.4pH-277nm and 6.8pH-271nm). The experiment was conducted in triplicate.

Dissolution studies using rat caecal content

Colonic conditions of the rat caecal contents are used to mimic the bacterial enzymes in the media. Five Wister rats, weighing 200-300gms were intubulated with Teflon tubing for 7days before the release experiments were initiated. Each day 1ml of 2% w/v of polymer dispersion (i.e., Guargum / HPMC K4M) was directly administered to the rat's stomach through the Teflon tubing. This process provides the best conditions for *invitro* evaluation 30min before the commencement of drug release studies, five rats were killed by spinal traction. The abdomen were opened, the caecai were isolated, ligated at both ends, deselected and immediately transferred in to pH 6.8 phosphate buffer previously bubbled with CO_2.

The caecal bags were opened and their contents were individually weighed, pooled, suspended in PBS, to give a final caecal dilution of 4% w/v. As the caecum is naturally anaerobic, all these operations were carried out under CO_2. The experiment was conducted in triplicate.

Release kinetics

Data obtained from the *invitro* release studies of compression coated tablet of ciprofloxacin formulations (F5, F7, F8, F9, and F14) were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer - pappas model.

RESULTS AND DISCUSSION

Preparation of standard graphs

Standard graph for the Ciprofloxacin was done in 1.2, 6.8 and 7.4 pH phosphate buffers. Table shows the concentrations of the ciprofloxacin in different buffers and the respective absorbances. The figures show the calibration curves of ciprofloxacin in respective buffers.

Calibration curve of Ciprofloxacin in 0.1N HCL.

S.NO	Concentration in mcg/ml	Absorbance (nm)
0	0	0.000
1	5	0.071 ± 0.24
2	10	0.162 ± 0.07
3	15	0.264 ± 0.09
4	20	0.334 ± 0.16
5	25	0.421 ± 0.14
6	30	0.512 ± 0.21
7	35	0.596 ± 0.42
8	40	0.689 ± 0.14
9	45	0.787 ± 0.35
10	50	0.863 ± 0.24
11	55	0.959 ± 0.16

(n=3±SD)

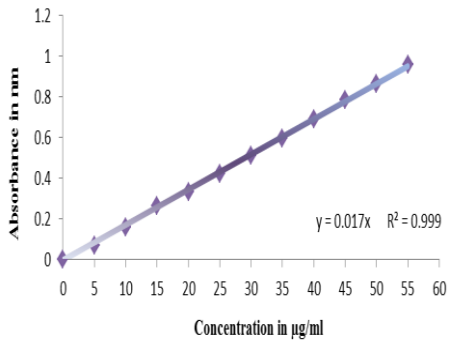


Fig 4.1: Calibration curve of Ciprofloxacin in 0.1N HCL

Calibration curve of Ciprofloxacin in 6.8 pH.

S.NO.	Concentration (mcg/ml)	Absorbance (nm) (n=3)
0	0	0.000
1	5	0.082 ± 0.02
2	10	0.176 ± 0.06
3	15	0.283 ± 0.14
4	20	0.376 ± 0.02
5	25	0.484 ± 0.12
6	30	0.587 ± 0.07
7	35	0.664 ± 0.04
8	40	0.758 ± 0.21
9	45	0.873 ± 0.14
10	50	0.969 ± 0.32

(n=3±SD)

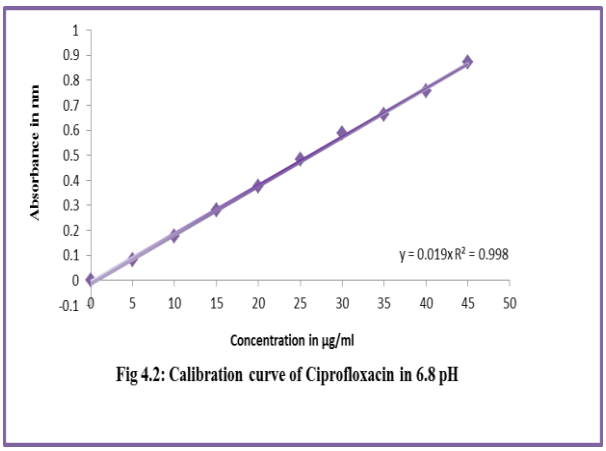


Fig 4.2: Calibration curve of Ciprofloxacin in 6.8 pH

Calibration curve of Ciprofloxacin in 7.4 pH.

S.NO.	Concentration in mcg/ml	Absorbance in nm
0	0	0.000
1	5	0.086 ± 0.42
2	10	0.172 ± 0.32
3	15	0.264 ± 0.05
4	20	0.362 ± 0.08
5	25	0.446 ± 0.26
6	30	0.534 ± 0.28
7	35	0.644 ± 0.42
8	40	0.724 ± 0.17
9	45	0.834 ± 0.14
10	50	0.952 ± 0.06

(n=3±SD)

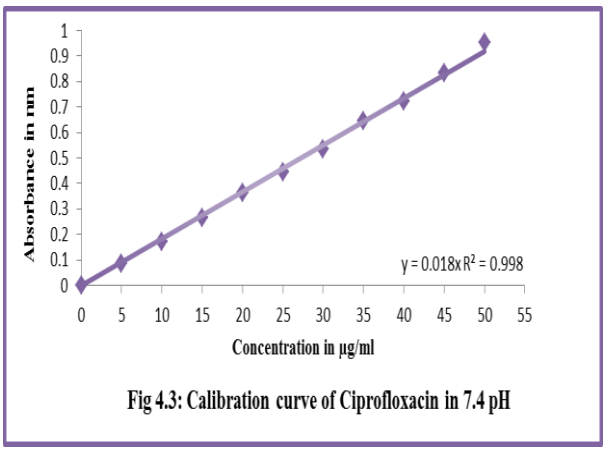


Fig 4.3: Calibration curve of Ciprofloxacin in 7.4 pH

Drug Polymer Interaction Study by FTIR Spectrophotometer

Drug-Excipient compatibility studies

An FT infrared (FT-IR) spectroscopy study was carried out to check the compatibility between the drug, crushed tablet and the physical mixtures used for the formulation. The spectra obtained from FT infrared spectroscopy studies at wave length from 4000cm^{-1} to 400 cm^{-1}.

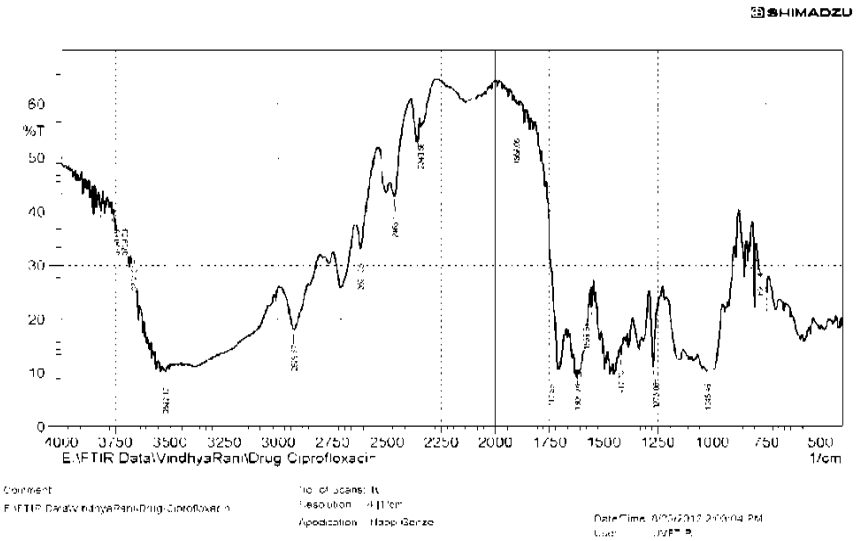


Fig 4.4: IR Spectrum of Ciprofloxacin.

IR interpretation of drug, crushed tablet and physical mixtures of drug-polymer.

Functional group	IR band of pure drug in cm^{-1}	IR band of drug-Guar gum	IR band of drug-HPMC K4M	IR band of drug-Crospovidone	IR band of drug-MCC	IR band of crushed tablet
C=O	1712.85	1734.06	1734.06	1734.06	1749.49	1747.57
N-H	1606.76	1610.61	1608.69	1635.12	1606.76	1608.69
C-O	1417.73	1417.73	1417.73	1419.66	1429.30	1419.66
O-H	1273.06	1273.06	1273.06	1273.06	1273.06	1273.06
C-F	1045.45	1024.24	1026.16	1024.24	1031.95	1031.95

Inference

The IR spectrum of ciprofloxacin drug was compared with the IR spectrum of ciprofloxacin physical mixtures and crushed tablet. The presence of all characteristic peaks of ciprofloxacin in the IR spectra was obtained with drug and other mixtures.

The above studies confirm that the drug and other excipients in the formulation were compatible with each other.

Data of *invitro* drug release studies without rat caecal contents

Cumulative percent drug release of F1-F5 formulations containing guar gum (200 mg coat weight).

Time (h)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	0.88 ± 0.95	0.95 ± 1.56	1.02 ± 1.02	1.16 ± 1.45	0.82 ± 2.54
2	1.64 ± 2.86	1.55 ± 1.02	1.58 ± 1.65	1.48 ± 2.86	1.028 ± 1.02
3	3.18 ± 0.95	3.10 ± 1.02	2.73 ± 2.54	3.48 ± 1.02	3.02 ± 1.02
4	3.67 ± 1.02	3.59 ± 1.02	3.18 ± 2.55	4.47 ± 0.95	4.72 ± 1.65
5	4.03 ± 1.02	4.33 ± 2.86	4.09 ± 1.02	5.21 ± 0.95	5.29 ± 2.86
8	5.54 ± 1.02	5.86 ± 0.95	5.83 ± 1.02	7.10 ± 2.55	7.92 ± 1.02
12	6.38 ± 2.86	6.59 ± 2.86	6.72 ± 2.54	8.08 ± 1.45	11.94 ± 2.86
16	6.98 ± 0.95	7.32 ± 0.95	7.83 ± 1.65	9.05 ± 2.55	12.66 ± 0.95
20	8.54 ± 2.54	9.62 ± 1.65	8.95 ± 2.54	10.39 ± 1.02	13.97 ± 1.65
24	9.98 ± 1.02	11.32 ± 1.02	12.96 ± 1.02	13.43 ± 2.86	15.07 ± 2.54

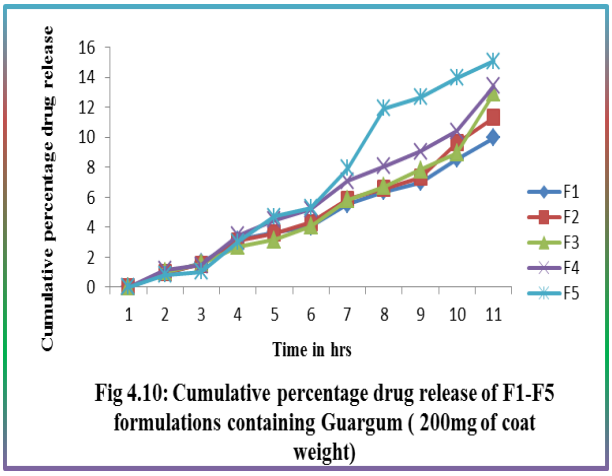


Fig 4.10: Cumulative percentage drug release of F1-F5 formulations containing Guargum (200mg of coat weight)

CONCLUSION

An anti infective ciprofloxacin was selected as the suitable drug to target the colon for the treatment of crohn's disease among other infectives because of its fewer side effects when compared to other. It is a fluoroquinoline and is susceptible to the sun heat.

The selected drug when subjected to preformulation studies the obtained bulk density results are with in the range of o.33 to 0.37 gm/cm^3.

The results of tapped density are with in the range of 0.42 to 0.48 gm/cm^3.

The results of compressibility index are with in the range of 19.04 to 22.22%.

The hausner's ratio values obtained with in the range of 1.23 to 1.43.

The angles of repose are in the range of 34 to 42.

Based on the above results the ciprofloxacin is considered as the suitable drug with all the parameters in the range.

The selected drug was subjected to the calibration studies at three different pH. The absorbance values obtained are 269 nm in 1.2 pH, 271nm in 6.8 pH, and 277nm in 7.4 pH.

The formulated core tablets were subjected to physic chemical tests and the mean values were calculated individually.

The value of hardness of core tablets was found to be 4.24 ± 0.05.

Weight variation of core tablets was found to be 149.01 ± 0.012 which shows ± 7.5% deviation.

Drug content was found to be 98.5 ± 0.4 % with in the limits of 98- 102%.

Friability was less than 1 in all cases.

Based on the above results, it was stated that the formulated core tablets can be subjected to coating.

The formulated coated tablets were again subjected to physico chemical tests and the mean values were calculated individually for 15 different batches.

The hardness of coated tablets was found to be with in the range of 4.76 to 5.06kg/cm^3.

The drug content and friability results were with in the limits for all the 15 different batches.

The *invitro* percentage drug release studies was performed for all the 15 batches at different time periods in 0.1N Hcl for 2hrs, 7.4pH phosphate buffer for 3hrs and followed by 6.8pH buffer for the remaining 19hrs.At the end of the study a slight swelling of the coat was observed due to the water sorption.

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