FORMULATION DEVELOPMENT AND EVALUATION OF COLON TARGETED DOSAGE FORM OF IBUPROFEN

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ABSTRACT

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome but also for the potential it holds for the systemic delivery of proteins and therapeutic peptides. The aim of the study was to develop colon targeted film coated tablets of Ibuprofen using HPMC K4M, Eudragit L100, and Ethyl cellulose as carriers. All the formulations (F1 to F6) were evaluated for the physicochemical parameters and were subjected to in vitro drug release studies. The amount of Ibuprofen released from tablets at different time intervals was estimated by UV spectrophotometer. The formulation F6 released 98.34 % of Ibuprofen. The results of the study showed that formulation F6 is most likely to provide targeting of Ibuprofen for local action in the colon owing to its minimal release of the drug in the first 5 h. The results of the present study have demonstrated that the film coated tablet system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of Ibuprofen for the treatment of disease of colon region.

Key Words: Colon specific, Ibuprofen, Physiochemical parameters, Eudragit L 100.

INTRODUCTION

In recent years, colon targeted delivery systems have been the focus point of formulation laboratories because the colon[1] is considered as a suitable site for delivery of both conventional and labile molecules, and it is also a site for some specific diseases, such as, ulcerative colitis, Crohn's disease, bowel cancer, some infections[2], and constipation, which require local delivery of the drug. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine. In order to develop a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal (GI) tract needs to be understood very well[3,4]. The transit of perorally administered formulation through the GI tract is highly variable and depends on various factors. For example factors like disease state of the lumen (diarrhea, diabetes, peptic ulcer etc)[5], concomitant administration of other drugs (domperidone, cisapride, metoclopromide etc), body posture (vertical or supine) and food type (fat and protein content) can influence the gastric emptying rate. Gastric transit time of single-unit non-disintegrating dosage forms has been reported to vary from 15 min to more than 3 h.[6,7] At the same time, the small intestinal residence time is fairly constant and varies between 3-4 h. The maximum mean colonic transit time in humans is reported to be as high as 33 h in men and 47 h in women. Due to the distal location of the colon in the GI tract, a colon specific drug delivery system[8] should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Such a system can be formulated utilizing some specific conditions existing in the colon in comparison to other parts of the GI tract[9]. Overall, the physiological changes along the GI tract can be generally characterized as a continuum, with decrease in enzymatic activity, motility and fluid content and an increase in pH as we move from esophageal end to the rectum. Another challenge in developing therapeutically effective products for the treatment of colonic pathologies is the impact of disease on the delivery system. The aim of this study was to explore the feasibility of the colonic microorganism to develop CDDS by using ibuprofen as model drug.

ADVANTAGES OF COLON DRUG DELIVERY SYSTEM

- pH dependent system : formulation is well protected in the stomach. It has minimum side effect.
- Unnecessary systemic absorption does not occur.
- Colon specific formulation could be used to prolong drug delivery.
- Enhance the absorption of poorly absorbed drug.
- By this poorly absorbed drug molecule may have improved bioavailability.
- It helps in efficient vaccine delivery.

MATERIAL AND METHODS

Ibuprofen was obtained as a gift sample from Shreya Pharmaceutical, Aurangabad. Hydroxy Propyl Methyl Cellulose K4M was obtained from Colorcon Asia pvt. Ltd, Verna. Eudragit L 100 was gifted by Noveon, Mumbai. Ethyl cellulose, Lactose, Magnesium Stearate, Talc, Polyethylene glycol (PEG-400), and Isopropyl alcohol were purchased from Karnataka fine chem. Ltd. Bangalore.

DRUG POLYMER COMPATIBILITY STUDIES

- Drug polymer compatibility studies were carried out using FTIR.
- The study was carried out on individual pure drug and its physical mixture with the selected polymers under study.

PREPARATION OF COLON TARGETED IBUPROFEN TABLETS

Ibuprofen, HPMCK4M/Eudragit L 100, Ethyl cellulose and Lactose were taken in required quantities mixed and passed through #60 sieves, lubricated with magnesium stearate and talc then was compressed into tablets by rotary tablet punching machine. Then film coating is done by 6% w/v solution of eudragit L 100 in isopropyl alcohol using 2% PEG-400 as plasticizer in coating pan. The weight of tablet was kept constant for all formulations. A minimum of 100 tablets were prepared for each batch.

EVALUATION OF COLON TARGETED TABLETS OF IBUPROFEN

Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

PRECOMPRESSION PARAMETERS

ANGLE OF REPOSE[10]:

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$\text{Tan } \varphi = h/r$

Therefore, $\varphi = \text{Tan}^{-1} h/r$

Where, φ = angle of repose, h = height of the cone

r = radius of the cone base

Where φ- Angle of repose, h- height and r- radius

The relationship between angle of repose and powder flow is as follows in given table 1.

BULK DENSITY

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 10 g of powder from each formulation was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to tap. The tapping was continued until no further change in volume was noted. Bulk density is calculated by using formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

CARR'S INDEX

The carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD -LBD) × 100]/TBD

Where, LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing

POST COMPRESSION PARAMETERS

TABLET THICKNESS

Thickness and was measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

HARDNESS

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

FRIABILITY

Roche friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

WEIGHT VARIATION

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. Deviation should not exceed the values given in table

DRUG CONTENT[11]

Ten tablets were weighed and powdered and 250 mg equivalent weight of ibuprofen was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with phosphate buffer pH 6.8. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 223 nm using UV-Visible spectrophotometer (Shimadzu UV-1601). The drug content of each sample was estimated from standard curve of ibuprofen using phosphate buffer pH 6.8.

***IN –VITRO* DISSOLUTION STUDIES[12]**

The release rate of Ibuprofen from tablets were determined using USP dissolution testing apparatus I (basket type). The test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 100 rpm for first 2 h. then replaced with 6.8 pH phosphate buffer and continued for 24 h. Aliquot volume of 5 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

RESULT AND DISCUSSION

MICROMERITIC PROPERTIES

ANGLE OF REPOSE

The results of angle of repose were ranged between 25.49 ± 2.02 to 27.15 ± 1.09, which indicates good flow properties of powder.

CARR'S INDEX

The carr's index values were found to be in the range of 14.84 ± 2.11 % to 16.53 ± 0.72%. These findings indicated that the powder mixture of all batches of formulation exhibited good flow properties.

EVALUATION OF PHYSICOCHEMICAL PARAMETERS

TABLET THICKNESS

Thickness of the developed formulations F1 to F6 varied from 5.20 ± 0.012 mm to 5.42 ± 0.042 mm.

TABLET HARDNESS

Hardness of the developed formulations F1 to F6 varied from 7.4 ± 0.31 kg/cm2 to 9.5 ± 0.39 kg/cm2.

FRIABILITY

Friability of the developed formulations varied from 0.24 ± 0.41 % to 0.45 ± 0.030 % loss which was less than 1% as per official requirement of IP.

WEIGHT VARIATION BEFORE COATING

The average weight of twenty tablets was calculated for each formulation which varied from 449.92 ± 0.37 mg to 450.59 ± 0.32 mg that complied the official requirement as per IP.

WEIGHT VARIATION AFTER COATING

The average weight of twenty tablets was calculated for each formulation which varied from 456 ± 0.82 mg to 458 ± 0.33 mg.

UNIFORMITY OF DRUG CONTENT

The drug content varied from 99.09 ± 0.92 % to 100.00 ± 0.72 % which was within the required limits.

***IN VITRO* DRUG RELEASE STUDIES**

The release of Ibuprofen from colon targeted tablets varied according to the types and proportion of matrix forming polymers.

HPMC K4M AND ETHYL CELLULOSE BASED FORMULATIONS

The progressive decrease in the amount of drug release from formulations F1 to F3 attributed to gradual increase in HPMC K4M and Ethyl cellulose contents. The duration of drug release was slower with formulation F3 which was about only 97.92 % in 20 h from among the formulations F1 to F3.

EUDRAGIT L100 AND ETHYL CELLULOSE BASED FORMULATIONS

The progressive decrease in the amount of drug release from formulations F4 to F6 attributed to gradual increase in Eudragit L100 and Ethyl cellulose contents. The duration of drug release was slower with formulation F6 which was about only 98.34 % in 24 h from among the formulations F4 to F6.

CONCLUTION

- The present investigation was concerned with the development of the colon targeted tablets, which after oral administration were designed to prevent the drug release in stomach and small intestine. It improves the bioavailability of the drug as well as its half life.
- Various formulations were developed by using release rate controlling polymers like HPMC K4M, Eudragit L100, Ethyl cellulose by direct compression method.
- Developed film coated colon targeted tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content.
- Drug release studies shows that F6 shows good release behavior in colon and restricts release in stomach and intestine as compare to F1–F6.
- Therefore, it was concluded that the most satisfactory formulation is (F6).

ACKNOWLEDGEMENT

The authors are expressing their sincere thanks to Respected Chairman and G.M. sir, IIMT College of Medical sciences, Meerut for providing all the facilities for this research work.

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TABLES

Standard value of powder flow property test

S. No.	Angle of repose	Powder flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Standard value of powder Carr's index test

S.No.	Carr's index	Type of Flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Satisfactory
4	23-35	Poor
5	>40	Very poor
6		Extremely poor

Standard limit value in weight variation test

Average weight of a tablet	Percentage Deviation
80 mg or less	±10
>80 and <250mg	±7.5
250mg or more	±5

FORMULATION CHART OF DEVELOPED COLON TARGETED TABLETS

Ingredients(mgs)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Ibuprofen	250	250	250	250	250	250
HPMC K4M	40	60	80			
Eudragit L100				40	60	80
Ethyl cellulose	40	50	60	40	50	60
Lactose	110	80	50	110	80	50
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total weight	450	450	450	450	450	450

EVALUATION OF PREFORMULATION PARAMETERS
Micromeritic of Ibuprofen colon targete tablets

Formula code	**Angle of repose (0)**	**Bulk density gm/ml**	**Tapped density gm/ml**	**Carr's index %**
F_1	26.37± 1.51	0.4517± 0.019	0.5432± 0.029	16.31± 0.78
F_2	26.96± 1.72	0.4631± 0.036	0.5333± 0.079	15.21± 0.99
F_3	27.15± 1.09	0.4505± 0.018	0.5465± 0.019	15.82± 1.21
F_4	26.01± 1.15	0.4674± 0.061	0.5569± 0.048	16.53± 0.72
F_5	25.98± 1.91	0.4609± 0.012	0.5418± 0.037	15.42± 0.34
F_6	25.49± 2.02	0.4589± 0.013	0.5501± 0.040	14.84± 2.11

All values are mean of 3 readings ± standard deviation

EVALUATION OF PHYSICOCHEMICAL PARAMETERS OF DEVELOPED COLON TARGETED TABLETS
Physicochemical parameters of developed colon targeted tablets of Ibuprofen

Formula code	**Hardness Kg/cm^2**	**Friability % loss**	**Weight variation Before coating mgs**	**Weight variation After coating mgs**	**Drug content %**	**Thickness mm**
F_1	7.4± 0.31	0.45± 0.030	450.42± 0.27	457± 0.65	100±0.72	5.42±0.042
F_2	7.6± 0.45	0.38± 0.065	449.92± 0.37	457± 0.27	99.81± 0.22	5.20±0.012
F_3	7.9± 0.37	0.32± 0.028	450.31± 0.92	458± 0.33	99.27± 0.38	5.39± 0.010
F_4	8.6± 0.62	0.34± 0.070	450.56± 0.75	456± 0.82	99.35± 0.32	5.27± 0.039
F_5	8.9± 0.41	0.32± 0.035	450.24± 0.61	457± 0.18	99.91± 0.67	5.23± 0.016
F_6	9.5± 0.39	0.24± 0.041	450.59± 0.32	457± 0.67	99.09± 0.92	5.41± 0.028

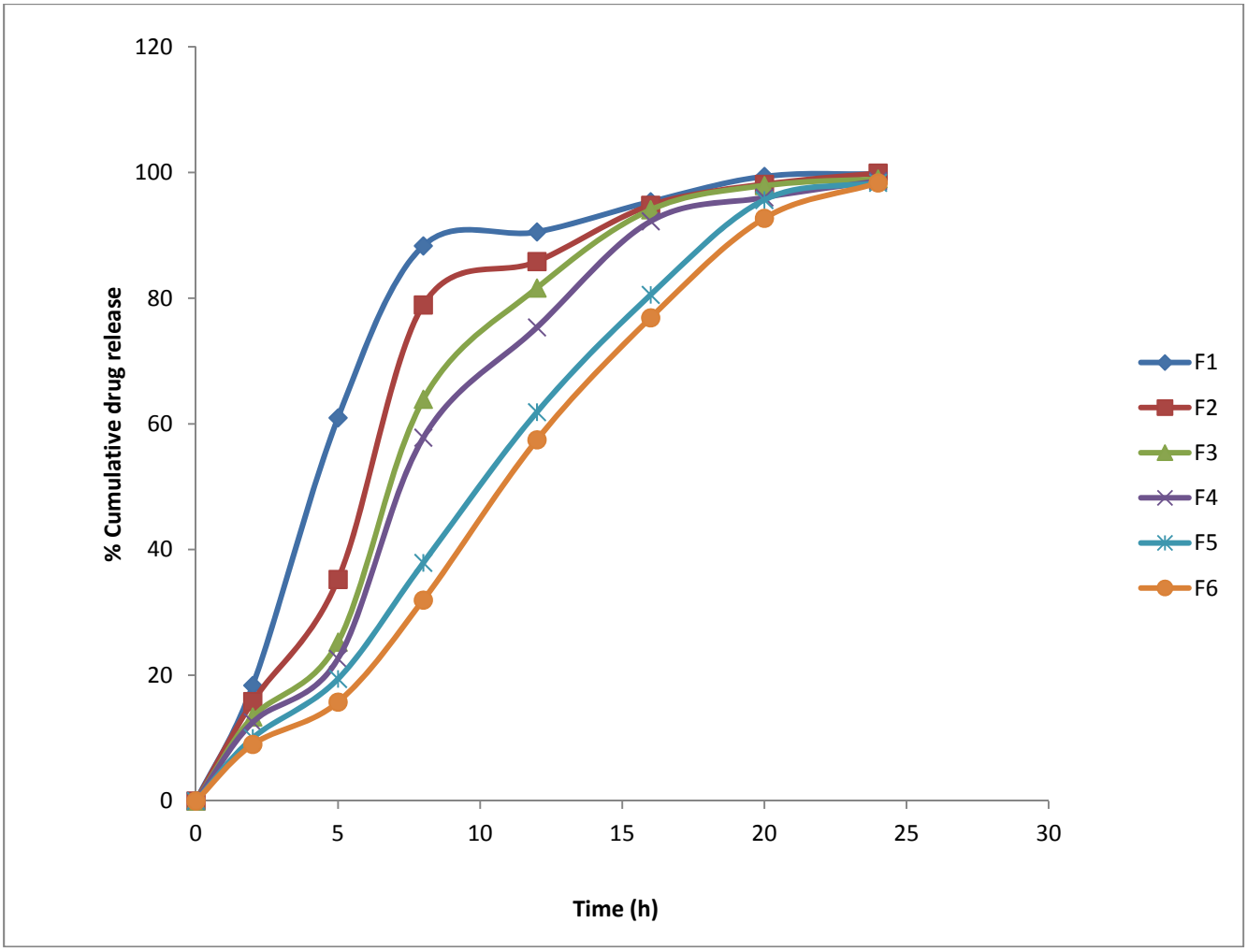
All values are mean of 3 readings ± standard deviation

IN VITRO DRUG RELEASE STUDY

Drug release profile (%CDR) of various formulations of developed colon targeted tablets

		Formulation code					
Dissolution Media	**Time (Hrs)**	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Simulated gastric fluid	2	18.39	15.82	13.37	12.53	10.03	9
Simulated intestinal fluid	5	60.97	35.25	25.28	22.62	19.42	15.73
Simulated colonic fluid	8	88.32	78.92	63.91	57.81	37.89	31.96
Simulated colonic fluid	12	90.54	85.82	81.62	75.53	61.87	57.46
Simulated colonic fluid	16	95.35	94.78	94.08	92.24	80.53	76.87
Simulated colonic fluid	20	99.37	98.12	97.92	96.02	95.63	92.71
Simulated colonic fluid	24	99.76	99.89	98.71	98.66	98.37	98.34

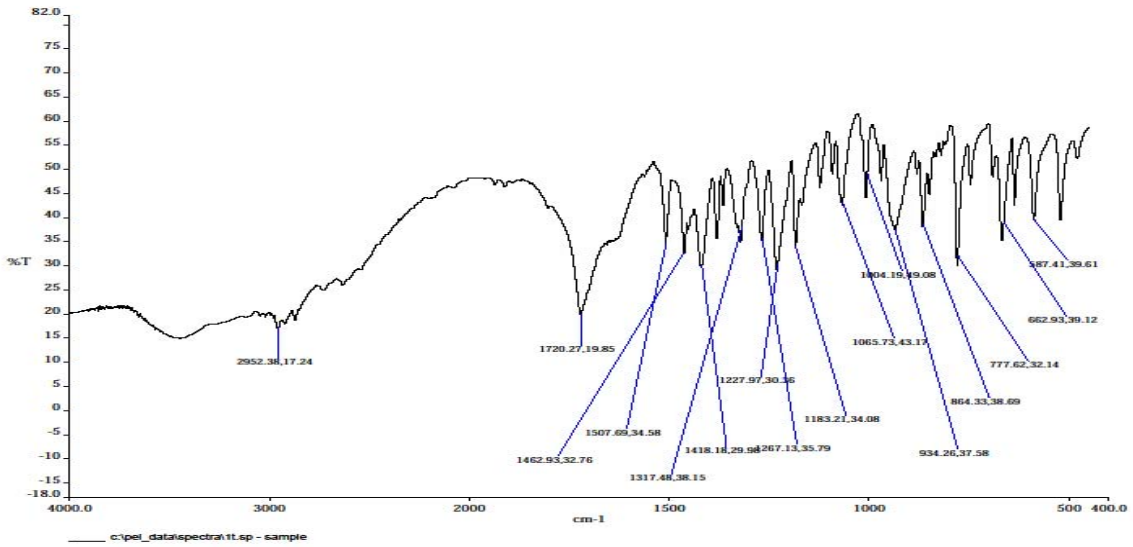
Figures of % drug release are mean of triplicate study.



% Drug release pattern of different batches of colon targeted tablets of Ibuprofen.

DRUG POLYMER COMPATIBILITY STUDIES BY FTIR

Pure drug



Pure drug along with excipients