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DESIGN, FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELUIVERY OF LORNOXICAM

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ABSTRACT

The aim of the present research work was to develop lornoxicam colon targeted tablets using polymers HPMC, Ethyl cellulose as carriers in various concentrations. Sustained Release tablets were prepared by direct compression method. Prepared formulations were subjected to various pharmacopoeial tests like hardness, friability, thickness, % drug content, weight variation, *In-vitro* drug release study etc. from the results conluded that all were with in pharmacopoeial limits. *In-vitro* studies revealed that tablets formulation with the high concentration of HPMC (300 mg) and low Concentration of Ethyl Cellulose (100mg) showed desired release of drug in colonic environment. Combination of retardants shows greater retarding of drug release. The compatibility of the drug and polymer were determined by FTIR spectroscopy. Results showed that the drug was compatible with all polymers.

KEYWORDS: Colon Targeting, Lornoxicam, HPMC, Ethyl cellulose, FTIR, Sustained Release.

INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. There are many reasons for this, not the least of which would include acceptance by the patient and ease of administration.[1-2] In case for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several

disadvantages. However, when administered orally, many therapeutic agents are subjected to extensive pre systemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites.

Conventional dosage form release the drug instantaneously and showing large distribution to all organs, least concentration reaches to required site but in disease or disorder there is need to have more drug concentration at specific site it is problem in conventional dosage form. So, there is need to target the drug to specific site. During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon.[3-4]

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 and constipation but also for the systemic delivery of proteins, therapeutic peptides, anti asthmatic drugs, antihypertensive drugs and antidiabetic agents. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded at either of the dissolution sites, but only released and absorbed once the drug reaches the colon.[5]

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic property and belongs to the class Oxicams. Lornoxicam inhibits synthesis of prostaglandins via inhibition of cyclo-oxygenase enzyme. It is used in the treatment of inflammatory bowel diseases and in colonic disorders. Lornoxicam undergoes extensive and highly variable hepatic first-pass metabolism following oral administration with a reported systemic bioavailability between 15% and 23%. Lornoxicam has half life of 3 to 5 hrs. So, patients are routinely asked to take Lornoxicam for several times in a day. Such frequent drug administration may reduce patient's compliance and therapeutic efficacy.[6-8]

Colon targeted formulation is needed for the Lornoxicam overcome the above mentioned problems and also to minimize the GI disturbances such as peptic ulcer with or without bleeding if present in larger concentration in GI tract. The aim of the present research work was to develop matrix tablets of Lornoxicam targeted to colon.

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Doxofylline was a gift sample from Chandra Labs, Hyderabad, India. HPMC, Ethyl cellulose were procured from Essel Fine Chemicals Ltd, Mumbai. Micro crystalline cellulose, Crospovidone, Croscaramellose, Sodium starch glycollate were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as magnesium stearate, Talc were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Lornoxicam Colon Targeted Tablets

Formulation involves Enteric Press coated Lornoxicam Tablets. The rapid release core tablet was formulated using using various superdisintegrants such as Crospovidone, Crosscaramellose sodium, Sodium starch glycolate at 3 levels. Totally nine formulations were developed using three superdisintegrants with 3,6,9 mg respectively. Among all nine formulations F_6 is considered as best formulation (from the dissolution parameters). It was subjected to enteric press coating with 400 mg of Polymer blend (Barrier Layer) with variable concentrations of HPMC, Ethyl Cellulose alone and in Combination. The prepared formulations were evaluated to find out the significance of combined effects of polymers to select the best combination and the concentration required to achieve the desired colon targeted release of drug from the dosage form.

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. powder mixtures of Lornoxicam, microcrystalline cellulose, cross-carmellose sodium Sodium starch glycollate, crospovidone, ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., Blend was subjected to compression by using 8 station rotary tablet punching machine (Minipress, RIMEK), Ahmedabad) using 8 mm circular punches and same hardness used for required number of tablets. (Core Tablet).

From the in-vitro dissolution studies of rapid release core it was concluded that the formulation F6 i.e, the formulation containing cros carmellose sodium is the best formulation.

Formulation of mixed blend for barrier layer

The various formulations containing Ethylcellulose and HPMC in different compositions were weighed dry blended at about 10 min and used as press-coating material to prepare press-coated tablets respectively by direct compression method.

Preparation of press-coated tablets

The core tablets were press-coated with 400mg of mixed blend/granules. 200mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the centre. The remaining 200mg of the barrier layer materiel was added into the die and compressed.

Preparation of enteric coating solution

Polymer solution was prepared with HPMC phthalate, myvacet and colour in ethanol as solvent. Formulation can be coated with p sensitive polymer which dissolves at the p of the colon .most of the enteric polymers dissolve in the terminal ileum. To target the drug specifically to colon, it is to be coated with either hydrophilic or hydrophobic polymer along with enteric polymers. For that reason press coated tablets coated with enteric solution.

Table 1: Formulae for Rapid Release Core Tablets.

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Lornoxicam	8	8	8	8	8	8	8	8	8
Microcrystalline Cellulose	137	134	131	137	134	131	137	134	131
Crospovidone	3	6	9	-	-	-	-	-	-
Croscaramellose sodium	-	-	-	3	6	9	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	3	6	9
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150	150	150

Table 2: Formulae for Press Coat.

Press Coat	Quantity of Ingredients per each Tablet (mg)				
	P_1F_6	P_2F_6	P_3F_6	P_4F_6	P_5F_6
HPMC	400	100	300	200	0
Ethyl Cellulose	0	300	100	200	400
Total Weight	400	400	400	400	400

Table 3: Composition for Enteric Coating Solution.

Name of the Ingredient	Quantity (mg)
HPMC Phthalate 55	17.17
Myvacet	1.72
Ferric oxide (red)	2.58
Ethanol	q.s

Evaluation of rapid release core (RRCT) and Enteric press-coated tablets of Lornoxicam Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.[9-10]

Friability

The friability of the tablets was measured in a roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.[9-10]

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.[9-10]

Assay

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg was dissolved in 100ml of phosphate buffer pH 6.8, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 378 nm using phosphate buffer pH 6.8 as blank.[6-8]

Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.[9-10]

***In-vitro* Dissolution Study**

The *In-vitro* dissolution study for the Doxofylline sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for first two hours followed by phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 378 nm using UV -Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).[9-10]

Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release.[11-14]

RESULTS AND DISCUSSION

All the prepared tablets (rapid release core tablets) were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness as per official methods The hardness of tablets was in the range of **5.1-5.8 Kg/cm^2.** Weight loss in the friability test was less than **0.54%**. Drug content of prepared tablets was within **acceptance range only**. Results for all Post-compression parameters were tabulated. *In-vitro* Dissolution studies were performed for rapid release core tablets using phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. results revealed that F_6 showed better results. Hence is further processed with barrier layer and finally prepared enteric press coated tablets.

In-vitro Dissolution studies were performed for prepared press coated tablets using 0.1 N HCl for first two hours followed by phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets were shown in Fig.1-2. Cumulative % drug release of factorial design formulations F_1-F_9 at 12Hr were found to be in the range of **75-98.4%**. From the result it reveals that the release rate was higher for formulations containing Low level of HPMC compared with other Formulations containing Higher level, due to High concentration of polymer drug may have entrapped within a polymer matrix causing a decrease in rate of drug release. variable concentrations of Ethyl cellulose produce modified release properties but high retardation of drug release also not

advisable. Therefore, required release of drug can be obtained by manipulating the composition of HPMC and ethyl cellulose.

CONCLUSION

The present research work envisages the applicability of Polymers such as HPMC and Ethyl cellulose in the design and development of colon targeted tablet formulations of Lornoxicam. From the results of *In vitro* dissolution studies it was clearly understand that as the retardant (HPMC) concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired targeted release of the drug for longer periods. On the basis of evaluation parameters, the optimized formulation **P_3F_6** may be used once a day administration in the management of IBW and other colonic disorders and to reduce the risk of Problems associated with them. This may improve the patient compliance by reducing the dosing frequency. Which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

Table 4: Post-Compression Parameters For Rapid Release Core Tablets.

S. No	Physical parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	**Avg Weight (mg)**	151	150	148	149	152	150	150	149	148
2	**Hardness (Kg/cm^2)**	5.1	5.3	5.6	5.1	5.2	5.3	5.4	5.7	5.8
	Thickness (mm)	3.51	3.48	3.51	3.5	3.5	3.47	3.49	3.52	3.61
4	**Friability %**	0.33	0.46	0.41	0.50	0.54	0.45	0.35	0.39	0.37
5	**Disintegration time**	2min 42sec	2min 52sec	2min 4sec	2min 21sec	1min 16sec	1min 08sec	2min 34sec	1min 48sec	2min 26sec

Table 5: *In Vitro* Dissolution Profile For Rapid Release Core Tablets (%Cumulative Drug Release).

Time (Min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
5	14.4	16.2	16.1	10.4	12.1	19.1	15.0	16.4	20.4
10	22.4	30.5	10.8	18.4	22.1	35.4	24.1	28.9	27.8
20	37.3	40.1	46.8	35.4	51.7	65.4	45.6	48.6	33.5
30	52.4	73.9	73.4	60.4	66.3	76.1	66.6	61.4	41.6
45	76.0	79.4	80.3	72.6	75.4	82.0	75.4	72.4	60.4
60	80.1	82.2	85.4	81.5	88.7	97.6	80.4	79.6	77.6

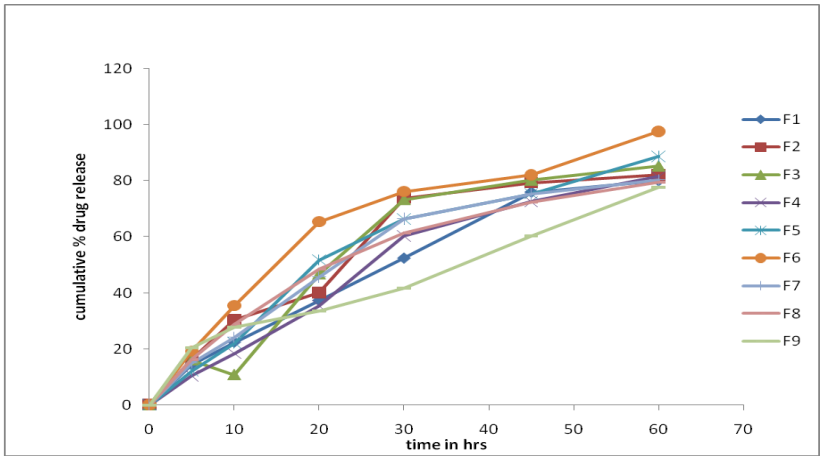

Fig.1 Comparative *In-vitro* dissolution Plots for F_1-F_9.

Table 6: Post-Compression Parameters For Enteric Press Coated Tablets.

S. No	Physical parameter	P1F6	P2F6	P3F6	P4F6	P5F6
1	Avg Weight (mg)	551	550	549	549	550
2	Hardness (Kg/cm^2)	7.4	7.0	7.7	7.4	7.5
	Thickness (mm)	2.45	2.49	2.5	2.51	2.5
4	Friability %	0.5	0.45	0.46	0.36	0.24

Table 7: *In Vitro* Dissolution Profile For Enteric Press Coated Tablets.

Time in hrs	P1F6	P2F6	P3 F6	P4 F6	P5 F6
	0.1N HCL				
1	0	0	0	0	0
2	0	0	0	0	0
	6.8 pH Phosphate buffer				
3	8	19	6	4	7
4	15	30	8.9	16	18
5	19	54	15.3	29	25
6	22	79	20.5	42	33
7	39	81	48.9	72	40
8	79	94	98.4	92	75

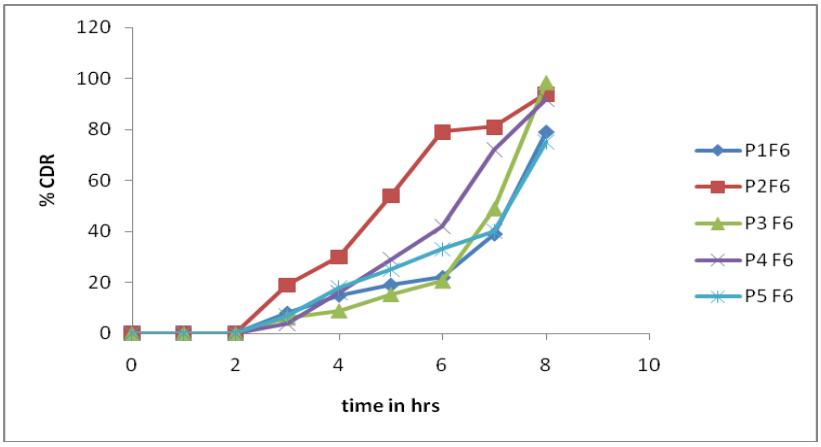

Fig.2 Comparative *In-vitro* dissolution Plots for P_1F_6-P_6F_6.

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