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DEVELOPMENT OF COLON TARGETED LORNOXICAM MATRIX TABLET

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The aim of the present research work was to develop sustained release matrix formulation of lornoxicam targeted to colon by using both hydrophilic and hydrophobic polymers and in-vitro drug release study. Matrix tablets were prepared by direct compression method using different concentration of Hydroxypropylmethylcellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation etc. Tablets were subjected to In-Vitro drug release in 0.1 N HCl (pH 1.2), phosphate buffer (pH 7.4) followed by phosphate buffer (pH 6.8). In-vitro drug release data were fitting to Higuchi and Pappas equation indicated that diffusion along with erosion could be the mechanism of drug release. It was observed that combination of both the polymers exhibited the best release profile and able to sustain the drug release for prolong period of time. The test batch comparison analysis was confirmed that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the sustained release colon targeted matrix tablets of lornoxicam.

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Key Words

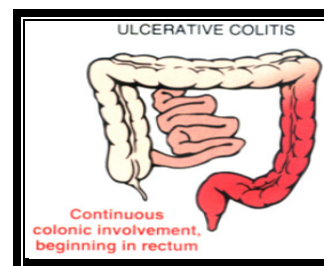
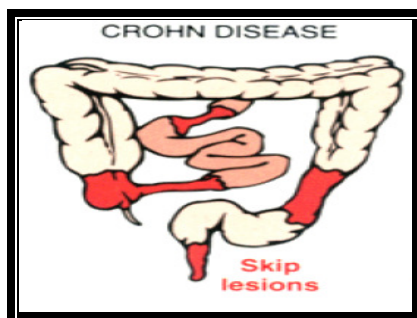
Lornoxicam, Diffusion, Erosion, inflammatory bowel disease, test batch study etc.

INTRODUCTION

An appropriately designed controlled release drug delivery system can be major advance towards solving problems concerning targeting drug to specific organ or tissue and controlling the rate of drug delivery to the target tissue. Matrix tablet are an interesting option when developing an oral controlled release formulation. The present study focuses on oral controlled release polymer dosage forms and type of various polymers used to formulate matrix tablets. Conventional dosage form release the drug instantaneously and showing large distribution to all organs but in certain disease or disorder there is need to have more drug concentration at specific site and the problem in conventional dosage form is drugs may distributed to all parts, least concentration reaches to required site along with some drug damage to unintentional organ or body tissue. So there is need to target the drug to specific site.

Colon targeted matrix tablet is one controlled release dosage form, which release the drug in continuous manner at colon. The release of drug by both dissolution controlled as well as diffusion controlled maintaining therapeutic blood or tissue levels at of the drug for extended period of time with minimized local or systemic adverse effects.

Colon are concerned with number of diseases like IBD, colon cancer etc. The term inflammatory bowel disease (IBD) covers a group of disorders in which the intestines become inflamed (red and swollen). Two major types of IBD are described: ulcerative colitis and Crohn's disease. As the name suggests, ulcerative colitis is limited to the colon (large intestine). Although Crohn's disease can involve any part of the gastrointestinal tract from the mouth to the anus, it most commonly affects the small intestine and/or the colon.



Both ulcerative colitis and Crohn's disease usually run a waxing and waning course in the intensity and severity illness. When there is severe inflammation, the disease is considered to be in an active stage, and the person experiences a flare-up of the condition.

It is very challenging task to prepare such dosage form which could be target the colon hence, one of active drug Lornoxicam a nonsteroidal antiinflatemy and antipyretic agent, has 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 hours 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. The objective of the present study was to develop controlled release matrix formulations of Lornoxicam and to examine the effects of both hydrophilic and hydrophobic polymers on in-vitro drug release. In the present study, Lornoxicam matrix formulations were prepared by using hydrophilic polymer, HPMC and hydrophobic polymer, EC alone and in combination to study the release kinetics and find out the effects of both the polymers and their combinations.

MATERIALS AND METHODS

Materials

Lornoxicam was a gift sample from alembic pharmaceutical Pvt. Ltd, Nasik. HPMC (USV pharmaceutical Pvt. Ltd, Nasik) Ethyl cellulose, Microcrystalline Cellulose, magnesium Stearate and talc other materials and solvents used were of analytical grade. *In vitro* analysis of the prepared tablets was

carried out as per the requirements of matrix tablets as specified in official pharmacopoeia.

Preparation of tablets

All the formulations were prepared by direct compression method. The drug (10 mg/tablet) and other excipients used in the formulations passed through a No. 60 sieve prior to compression. Powder blends were prepared using a cone mixer for 15 min.

Table no .01: Composition of colon targeted matrix tablet(100mg)

Then talc was added and mixed for another 5 min. The amount of polymers and others ingredients are given in Table 1. The required quantity of the ingredients for preparing the sustained release formulations were compressed using a rotator punch tablet machine equipped with 4.5 mm circular, flat and plain punches. The batch size of each formulation was 50 tablets.

FORMULATION TEST BATCH	LORNOXICAM (mg)	HPMC (mg)	EC (mg)	MCC (mg)	TALC (mg)
F1	10	20		65	5
F2	10	40		65	5
F3	10		20	65	5
F4	10		40	65	5
F5	10	20	20	45	5

EVALUATION / QUALITY CONTROL TEST :

The quality control tests for the matrix tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is placed between the anvils and the crushing strength, which causes the tablet to break, is recorded control limit is (4 to 5 kg/cm). Friability was determined by first weighing tablets equivalent to 6.5g after deducting and placing them in a Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation

was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated. Disintegration time was determined using the USP disintegration apparatus in phosphate buffer pH 6.8 maintaining the temperature at $37 \pm 2^\circ\text{C}$. Not a single tablet has disintegrated with two hours in 0.1N HCL, But not a single tablet has remain intact after one hours pH 6.4 phosphate buffer. Drug release profile was evaluated in vitro using a dissolution test apparatus .The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of lornoxicam .The dissolution for six tablets into phosphate buffer pH 6.8. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$ and a constant paddle rotation speed of 100 rpm. Samples (5

ml) were withdrawn at regular intervals and filtered. The samples were analyzed by UVspectrophotometer at wavelength 374 nm. The thickness of the tablets was determined using a digital screw gauge (Mitutoyo,

Table no.02 Evaluatory data of lornoxicam matrix tablet showing all parameter in comparative form

Japan).Five tablets from each batch were used, and average

Values were calculated (Table2). All values are mentioned in table no.2.

Test batch Formulations	Thickness* (mm)	Hardness** (kg/cm ²)	Friability (%)	Weight Variation(%)	% Drug Release
F1	3.24	4.1	0.5	3.51	94.13
F2	3.41	4.3	1.26	2.47	93.12
F3	3.16	3.5	0.6	1.92	92.46
F4	3.48	4.2	1.5	2.15	90.35
F5	3.20	4.6	0.9	1.25	99.00

Analysis of release profiles

The rate and mechanism of release of lornoxicam from the prepared matrix tablets were analyzed by kinetic model such as

Table no: 03 kinetic model describing equation and R² value

Kinetic model	Rigreation coefficient value and equation
Higuchi model	Y = 8.0923x-99.188 R ² = 0.9463
Hixson Crowell cube model	Y = 0.0099x + 7.3218 R ² = 0.8941
Pappas model	Y = 1.2231x – 1.3929 R ² = 0.9217

RESULT AND DISCUSSION:

Physical characterization of the tablets

All the formulations were prepared according to the formula given in Table 1. The prepared matrix tablets were evaluated for various physical properties as indicated in Table no (2, 3, 4, 5). All the batches were produced under similar conditions to avoid processing variables. All the formulations were evaluated for various physical Parameters such as weight variation, thickness, hardness, friability and drug content.

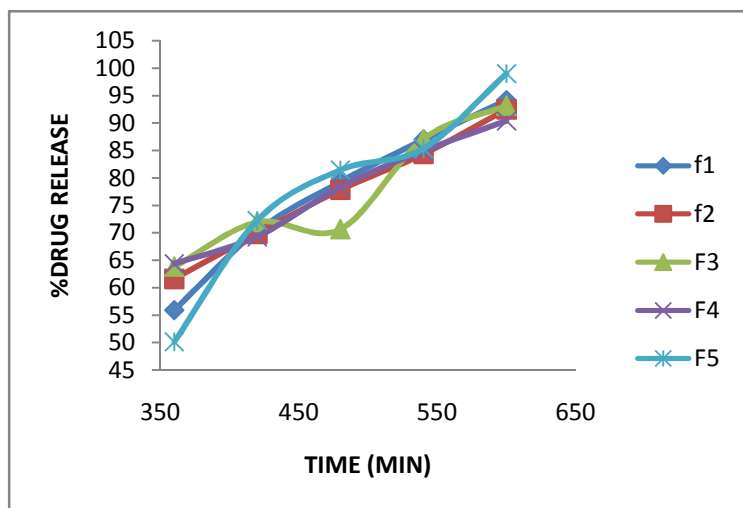
Hardness of tablets ranged from 3.7 to 5.2 kg/cm², thickness of tablets were found within the range of 3.16 to 3.45 mm. The percentage friability of all the formulations was in between 0.41 to 1.5 percent. The values of hardness test and percent friability indicates good handling property of prepared tablets. The drug content uniformity in the tablets was within the range from 90 to 99 percent.

In-vitro drug release studies

The in vitro drug release study was shown from different kinetic model. Result of kinetic model suggests that their significant difference among test result Obtained. It was observed that the drug release was slower from formulations containing hydrophobic polymer ethyl cellulose as compared to hydrophilic HPMC polymer. This may be due to hydrophobic nature of ethyl cellulose, which restrict the penetration of medium inside the matrix and also restrict the formation of gel layer around the matrix as compared to the hydrophilic HPMC.

When the polymer concentration was increase from 10 to 30% the drug release rate was found to decrease. This is due to the reason that the swelling degree is less because of higher concentration of polymers. But, further increase in concentration of the polymer did not significantly affect the drug release rate. Formulation F1 and F3 containing 10% HPMC and 10%EC individually were able to sustain the drug release for 4 and 8 hours respectively (94.13 for HPMC at 4 hours and 93.12 for EC at 8 hours at colon). In case of formulation F2, F4 containing 20% and 30% HPMC showed 92.46 and 90.35 drug released in 6 hours and 8 hours respectively This again, is due to the hydrophobic nature of ethyl cellulose which restricts the formation of gel layer around the matrix formulation and retarded drug release from the matrix.

Graph no.01 Percent Drug Release V/S Time

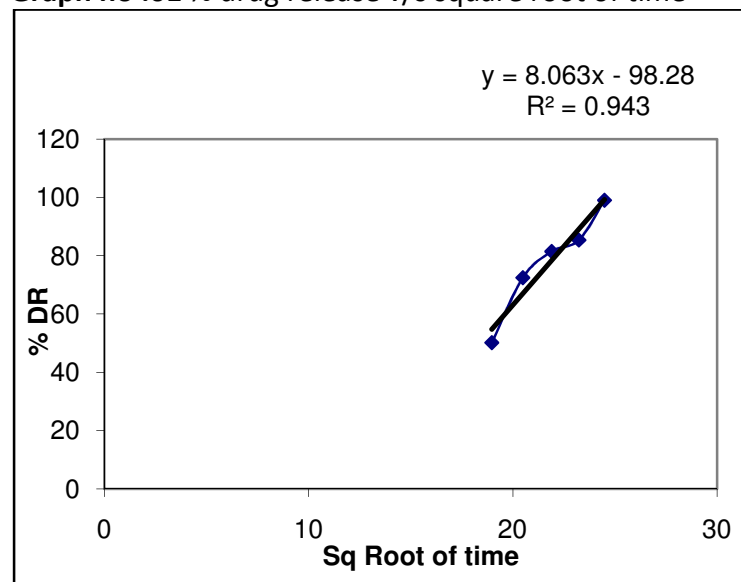


In case of formulation F5, where combination of both the hydrophilic and hydrophobic polymers were present at a low concentration (10% EC was incorporated with 10%HPMC), was able to drug release for 10 hours (99 % drug released in 10 hours). This may occur due to presence of both hydrophilic and hydrophobic polymer which allows little swelling but did not allow Rapid diffusion of the drug from the matrix.

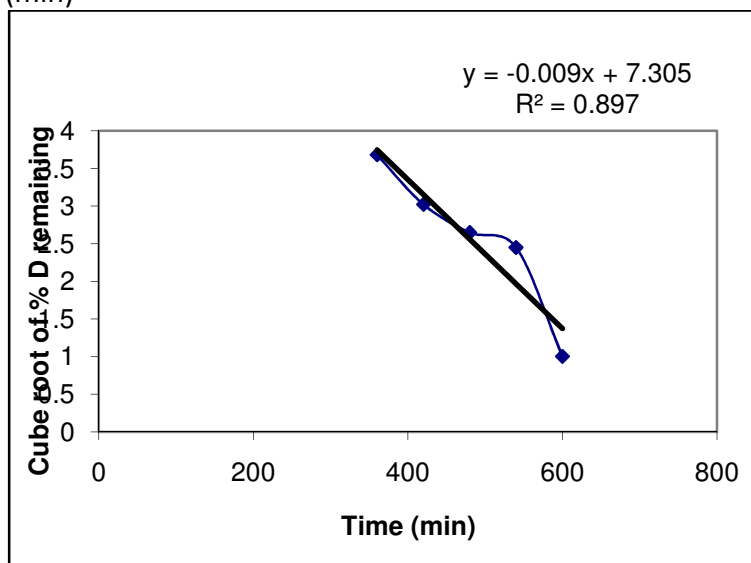
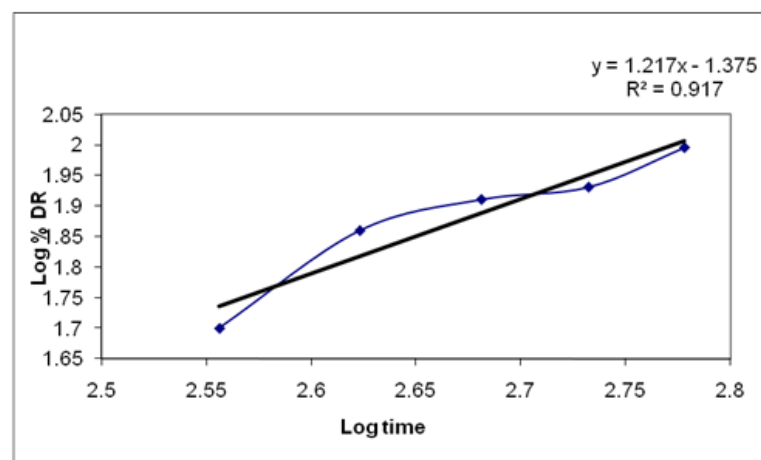
The release kinetic data for all the formulations is shown in Table no.3. The kinetic data of all the formulation showed good fit in Higuchi model equation which indicated the combined effect of diffusion and erosion mechanism for controlled drug release. The R^2 value of Higuchi model is nearer to 1. Hence test batch f5 produces desired release pattern which is responsible for maintaining concentration at colon.

Higuchi Model

Graph no :01 % drug release v/s square root of time



Hixson Crowell cube root model

Graph no: 02 cube root of % drug remaining v/s time (min)**Pappas model****Graph no: 03** log % drug release v/s log time**CONCLUSION**

Results of the present research work demonstrate that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the Controlled release matrix tablets of lornoxicam. It is observed that 10% of each the polymer in combination was able to produce desire formulation which release more than 90% drug in 10 hours. The mechanism of drug release was observed the combined effect of diffusion and erosion for controlled drug

release So, combination of both hydrophilic and hydrophobic polymer was suitable to produce the matrix tablet rather than the using a single type of polymer.

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