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Fabrication and Characterization of Lornoxicam Loaded Microsponge Tablets for Colon Delivery

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ABSTRACT

In present investigation first attempt was made to developed lornoxicam (LXM) loaded microsponges prepared by quasi emulsion solvent diffusion technique, by using ethyl cellulose in different concentrations. Microsponges were evaluated for percentage yield, encapsulation efficiency, drug content, surface morphology. Optimized batch of microsponges was further formulated as tablet for colon delivery. In-Vitro dissolution study of tablets was performed under sink condition with and without caecal contents. Microsponge tablet showed drug release after 8th hour corresponding to the arrival time in proximal colon and drug release of 81.28% up to 24 hrs. From this study, it can be concluded that, microsponges is an advance combined approach of both the triggering mechanism of microflora-activation and avoiding release in the small intestine.

Keywords: Lornoxicam; Microsponge; Quasi emulsion solvent diffusion; Microsponge tablet

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INTRODUCTION

A colon-targeted drug delivery system should avoid drug release in the upper GI tract and influence a sudden beginning of drug release after going into the colon [1]. Colon as a site for drug delivery offers a few advantages like a close neutral pH, longer transit time, lessened stomach related enzymatic action and a considerably more prominent responsiveness to absorption enhance [2-4]. Colon targeted drug delivery systems increasing interest due to the importance of this area of the gastrointestinal tract, not only for local but also for systemic therapy. Additionally, colonic delivery of drugs may be extremely useful when a delay in drug absorption is needed from a therapeutic standpoint, e.g. in case of diurnal asthma, angina pectoris and arthritis [5,6]. Lornoxicam is a non-steroidal anti-inflammatory drug (Figure 1) utilized in rheumatoid arthritis 9. It shows different pH dependent solubility, it is very poor soluble in acidic conditions present in the stomach thus it remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration. Half-life of LXM is 3 to 5 hours which increases dosing frequency of the drug and it leads to side effects. Colon is attracting site to deliver lornoxicam systemically to attain good therapeutic effect [7,8]. To avoid such problems we focus on a novel approach to design a microsponge based colon specific tablet formulation. Microsponges are porous microspheres which have small sponge like spherical shape that consist of a numerous interconnecting spaces within a non-collapsible structure with a large porous surface. The proposed study involves preparation and characterization of lornoxicam loaded microsponges by quasi emulsion solvent diffusion technique with ethyl cellulose as a pore forming sustained release polymer and study the effect of drug: polymer ratio, effect of inner phase solvent amount, effect of stirring time and stirring speed on microsponges, finally the optimized microsponge formulation was compressed in to core tablet, then compressed these core tablets with coating of guar gum and HPMC for formulation of

mechanically strong colon specific tablet. *In-Vitro* dissolution studies were performed with and without addition of caecal content in dissolution media.

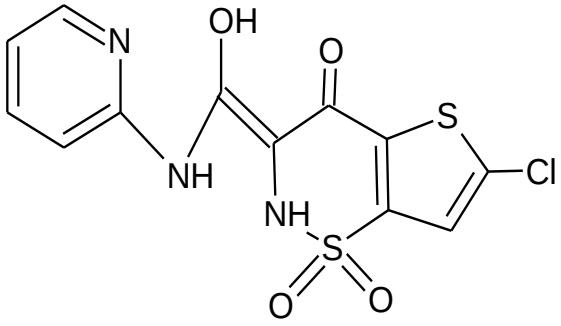

Figure 1: Structure of Lornoxicam

METHODOLOGY

Lornoxicam (LXM) was generously gifted by F&D, Glenmark Pharmaceuticals Ltd, Satpur, Nasik. Ethyl Cellulose, Guar Gum, Starch were purchased from Loba Chemie, Mumbai, Methocel®K4MCR Premium EP, Poly vinyl alcohol was purchased from RFCL Limited, New Delhi, Microcrystalline cellulose, sodium starch glycolate were purchased from Merck specialties Pvt. Ltd, Mumbai, India.

Preparation of Microsponges

Lornoxicam loaded microsponges were prepared by quasi emulsion solvent diffusion technique. In this method, Outer phase was prepared by dissolving polyvinyl alcohol in warm distilled water with continuous stirring at 200 rpm and inner phase was prepared by dissolving ethyl cellulose and drug in solvents like dichloromethane and methanol (4:1 ratio), with constant stirring, Then added 0.1% of dibutyl Phthalate as plasticizer to produce plasticity in microsponges. Composition of microsponges are given in Table 1. Then inner phase was incorporated drop wise into outer phase with constant stirring at 500-1000 rpm for 12 hours to remove and diffuse dichloromethane and methanol completely from reaction vessel, the mixture was centrifuged at 3000 rpm for 30 min and separated microsponges were dried in oven at 40°C for 12 hours [9-11].

Table 1: Formulation of microsponges

Ingredients	CL1	CL2	CL3	CL4	CL5	CL6	CL7
Lornoxicam (mg)	300	400	500	600	900	1000	1100
Ethyl cellulose (mg)*	100	100	100	100	100	100	100
Dichloromethane (ml)*	3	3	3	3	3	3	3
Methanol(ml)*	2	2	2	2	2	2	2
Di-butyl Phthalate(ml)*	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Polyvinyl Chloride (mg)*	50	50	50	50	50	50	50
Distilled water(ml)*	200	200	200	200	200	200	200

*Values were kept constant.

Optimization of Formulation and Process Variables of Microsponges Preparation

Effect of drug: polymer ratio

The different drug to polymer ratios (LXM:Ethyl cellulose) 3:1, 4:1, 5:1, 6:1, 9:1, 10:1 and 11:1 were taken for the fabrication of different microsponge formulations, during study other parameters like amount of polymer, PVA, Dibutyl phthalate, inner phase solvent etc. were kept constant [12]

Effect of inner phase solvent amount

The inner phase solvent dichloromethane and methanol was selected on the basis of maximum solubility of drug and polymer. LXM was partially soluble in methanol so that, we selected the ratios of dichloromethane and methanol to make it soluble under stirring at 200 rpm, during preparation all other parameters were kept constant [13].

Effect of stirring speed

The effect of stirring speed on the particle size and production yield of microsponges were studied at stirring speed 500 and 1000 rpm. All other parameters were kept constant [13].

Characterization of Microsponges

Fourier Transforms Infrared (FTIR) analysis

Infrared spectra of Drug, Polymer and formulation CL1, CL2, CL3 were taken by using FT-IR spectrophotometer (IR Infinity, Shimadzu). IR spectrum was measured in the solid state as potassium bromide disk pellet method. The spectra were measured over the range of 4000-400 cm^{-1} with an instrument resolution of $4cm^{-1}$ [14].

Morphology and Particle Size Studies

Particle size analysis of LXM loaded microsponges were performed by using Malvern Mastersizer (Malvern Instruments, Mastersizer 2000, and UK). The values (d50) were expressed for all formulations as mean size range. LXM microsponges were coated with gold–palladium under argon atmosphere at room temperature and studied the morphology and surface characteristics by using scanning electron microscopy (SEM, JEOL JXA 840A, USA) [15].

Actual Drug Content and Encapsulation Efficiency

The Weighed amount of LXM loaded Microsponges (10 mg) were dissolved in 10 ml 0.1 N NaOH with continuous stirring for 24 hours at 30°C. The samples were filtered by using 0.2 membrane filter and analyzed at 376 nm against blank using UV-spectrophotometer. The actual drug content and encapsulation efficiency were calculated by using the following formulas. All analyses were carried out in triplicate [16].

$$\text{Actual drug content (\%)} = \frac{M\,\text{act}}{M\text{ms}} \times 100`$$

$$\text{Encapsulation efficiency (\%)} = \frac{M\,\text{act}}{M\,\text{the}} \times 100$$

Where,

Mact is the actual lornoxicam content in weighed quantity of Microsponge,

Mms is the weighed quantity of powder of Microsponge,

Mthe is the theoretical amount of lornoxicam in Microsponge calculated from the quantity added in the process.

***In vitro* Drug Release of Microsponges**

The *In-Vitro* drug release of lornoxicam loaded microsponge batches (CL1-CL7) were carried out using USP type II dissolution test apparatus-TDT-06T (Electrolab, Mumbai, India) at 100 rpm. The dissolution study was conducted in 900 ml of 0.1N HCl having pH 1.2 for 2 hours followed by phosphate buffer pH 6.8 for 14 hours at 37°C+0.5°C. A 5 ml aliquot of dissolution medium was withdrawn at 0-1hour with a pipette and filter through 0.45 µm Whatman filter and then analyzed lornoxicam content in triplicate by spectrophotometrically (UV/Vis Spectrophotometer, Shimadzu-1800) at λ max 376 nm. Fresh medium (5 ml), which was pre warmed at 37°C, was replaced immediately into the dissolution medium after each sampling to maintain its constant volume during the test [17].

Rheological Properties of Microsponges

The flowability of the prepared microsponges was determined by measuring their angle of repose, hausner's ratio and Compressibility index [18].

Preparation of Microsponge Core Tablet

The core tablets containing LXM loaded microsponges (Equivalent to 8 mg LXM), sodium starch glycolate, microcrystalline cellulose, talc and magnesium stearate were prepared by direct compression method. The composition of core tablets are given in Table 2. All tablet ingredients were accurately weighed and mixed properly, after mixing tablets were compressed by using 12 station multi-punch tooling, Mini Press-II Tablet Machine (Karnawati, Ahemedabad) [12].

Table 2: Formulation of Core Tablet

Ingredient	microsponge formulation (equivalent to 8 mg lornoxicam)			Sodium starch Glycolate	MCC	Talc	Mg. stearate
Core tablet formulation	CL1	CL2	CL3				
CLC1	10	-	-	5	84.02	0.5	0.5
CLC2	-	9.79	-	5	84.21	0.5	0.5
CLC3	-	-	10	5	83.88	0.5	0.5

CLC1, CLC2 and CLC3 indicate core tablets containing CL1, CL2 and CL3 microsponge formulations respectively**.**

Coating of Colon Targeted Tablets

The optimized LXM Microsponge core tablets were coated by taking different ratios of Guar Gum and HPMC. The composition of coat of tablets are given in Table 3. The coating mixture used was 200 mg. Fifty percent, that is 100 mg coating material was placed in the die cavity and the core tablet was placed in center, then added remaining mixture of coat in the die cavity and compressed at high pressure using round concave punches (12.6 mm) on electric, semi-automatic, 12 station multi-punch tooling, Mini Press-II Tablet Machine (Karnawati, Ahemedabad) [16].

Table 3: Composition of Coat of Tablets

Ingredients	Coated Formulation		
	CT60	CT70	CT80
Guar gum	60	70	80
HPMC K4M	40	30	20
Starch paste	10	10	10

Evaluation of Coated and Uncoated Tablets

The LXM loaded microsponges coated and uncoated tablets were evaluated for their friability (By Roche friabilator), hardness (By Monsanto hardness tester), thickness (By vernier calipers), weight variations and drug content [19].

Determination of *In-Vitro* transit time

In-Vitro transit time were determined by placing tablets (n=6) in tablet disintegration test apparatus USP and subjected to regular up and down movement in a series of gastrointestinal fluids at 30 ± 2 cpm. The sequence followed was exposure to simulated gastric fluid (SGF, pH 1.2) for initial 2 hours followed by simulated intestinal fluid (SIF, pH 7.4) for the next 6 hours at 37 ± 0.5°C. The tablets were visually observed for any damage and disintegration.

Preparation of caecal contents for *In-Vitro* drug release studies

The susceptibility of guar gum coats to the enzymatic action of colonic bacteria which shows microbial triggered release mechanism followed by microflora-activation for caecal contents were prepared by

administered 1ml of 2% w/v aqueous dispersion of guar gum in male albino rats pretreatment for 7 days. Make a plan before 1hour drug release studies to isolate caecal content by killing six albino rat by spinal traction. The cecal bag were isolated after opening abdomen of rat, then transferred individually weighed caecal content give a final concentration 4% w/v. as caecum is naturally anaerobic in to previously bubbled with CO_2 pH 6.8 phosphate buffer solution and all this operation were carried out under continuous bubbled with CO_2 [20-22].

***In-Vitro* Drug Release Studies**

The *In-Vitro* drug release study of compressed LXM loaded Microsponge core coated tablet formulations was carried out by USP type II (paddle) apparatus (TDT-06T, Electrolab, Mumbai, India. at 100 rpm at 37°C ± 0.5°C) in different dissolution media. The drug release studies were carried out for 24 hours and samples were withdrawn periodically and sink conditions were maintained by replacing with equal amount of fresh pre-warmed dissolution medium. The dissolution study was performed using 900 ml 0.1 N HCl having pH 1.2 for 2 hours, followed by pH 7.4 Sorensen's Phosphate buffer (900 ml) for 3 hours. Drug release was continued for 24 hours in Sorensen's Phosphate buffer containing 4% w/v rat caecal matter under anaerobic condition. After 24 hours, samples were analyzed by spectrophotometrically (UV/Vis Spectrophotometer, Shimadzu-1800) at λ max 376 nm [23,24].

RESULTS AND DISCUSSIONS

Optimization of Formulation and Process Variables of Microsponges Preparation

The formulation parameters were optimized on the basis of surface morphology, particle size, actual drug content, encapsulation efficiency and drug release of Microsponges. The optimized parameters are given in Table 5. It was observed as drug to polymer ratio increased from 3:1 to 5:1 there was decreased particle size from 109 to 88 µm. The production yield, actual drug content, encapsulation efficiency of microsponge formulations were 93.75 to76.75%, 82.41 to 75.34% and 96.66 to 84.66% respectively, as given in Table 4. After complete drying of prepared microsponges, It was subjected to weighing, the weight of microsponges after 3 hours stirring was more than 6 hours and 8 hours. This indicated that there was presence of organic solvent in the microsponges prepared at 3 hours and 6 hours, as a result 8 hours stirring time was investigated as optimized stirring time. If stirring speed decreased the fibrous and course particles are prepared. It was observed that as concentration of plasticizer increases, drying rate of microsponges were also increases. Optimized formulation parameters of lornoxicam loaded Microsponges are given in Table 4.

Table 4: Production yield, encapsulation efficiency, mean particle size, actual drug content of formulation.

Formulation code	LXM:EC Ratio	Production yield (%)	Theoretical drug content (%)	Actual drug Content (%)	Encapsulation Efficiency (%)	Mean particle size (µm)
CL1	03:01	93.75	95.27	82.41	96.66	109
CL2	04:01	91.66	90.21	77.33	90.63	98
CL3	05:01	76.75	88.23	75.34	84.66	88

Table 5: Optimized formulation Parameter of Microsponge

Specification	Optimum values
Lornoxicam : ethyl cellulose ratio	3:1, 4:1 and 5:1
Amount of emulsifying agent (mg)	PVA 50 mg
Inner phase solvent (ml)	Dichloromethane,Methanol.
Plasticizer	Dibutyl phthalate
Amount of plasticizer	0.01 ml

Amount of inner phase solvent (ml)	5 ml
Amount of water in the outer phase (ml)	200 ml
Stirring rate (rpm)	5000
Stirring time (Hours)	8

PVA: Polyvinyl Chloride (Emulsifying agent).

***In-Vitro* Drug Release of Microsponges**

The drug release profiles obtained from formulations CL1 to CL7 are depicted in Figure 2. The release showed a bi phasic pattern with an initial burst effect. The formulations CL1, CL2 and CL3 showed more control release action than CL4, CL5, CL6 and CL7. At the end of 8 hours, the percent drug release shown by formulations CL1, CL2, CL3 was 85.80%, 92.41% and 96% respectively and for formulations CL4 to CL7 showed 100% release in 5-7 hours respectively.

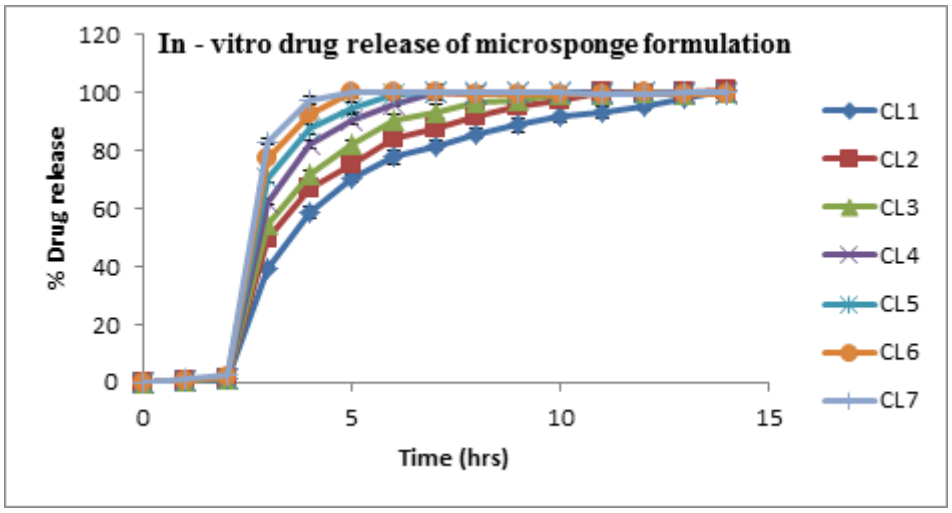

Figure 2: *In-Vitro* Drug release of Microsponge formulation (data represent mean ± standard deviation, *n*=3)

Characterization of Microsponges

Pre-compression Parameters

Pre-compression Parameters of microsponges such as angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index were studied. The Hausner's ratio and compressibility index were found to be 1.16 ± 0.02 to 1.25 ± 0.01 and 14.1 ± 1.7 to 20.5 ± 0.9. The bulk density and tapped density were found in the range of 0.53 to 0.56 and 0.60 to 0.71. The angle of repose was found in the range of 19.66 ± 0.57 to 28.33 ± 1.52 it indicates that microsponges have good flow property. The results are represented in Table 6.

Table 6: Pre-compression Parameter of Microsponges

Formulation Code	Parameter				
	Angle of Repose(θ)	Bulk Density (gm/cm)	Tapped Density (gm/cm^3)	Hausner's Ratio (HR)	Compressibility Index (%)
CL1	19.66 ± 0.57	0.53	0.6	1.16 ± 0.02	14.1 ± 1.7
CL2	21 ± 0.57	0.54	0.62	1.24 ± 0.01	19.4 ± 0.7
CL3	21.33 ± 0.55	0.55	0.63	1.25 ± 0.01	20.5 ± 0.9

CL4	23.33 ± 0.577	0.55	0.66	1.17 ± 0.009	15.1 ± 0.6
CL5	25 ± 1	0.56	0.67	1.17 ± 0.02	14.8 ± 1.6
CL6	25.66 ± 1.52	0.56	0.69	1.21 ± 0.03	17.8 ± 2.1
CL7	28.33 ± 1.52	0.54	0.71	1.17 ± 0.04	14.4 ± 2.9

Morphology

The morphology and structure of LXM loaded microsponge samples were examined using a scanning electron microscope. The representative SEM images of the microsponges are shown in Figures 3 and 4 and 5 respectively. Microsponges presented in SEM images are porous but not spherical.

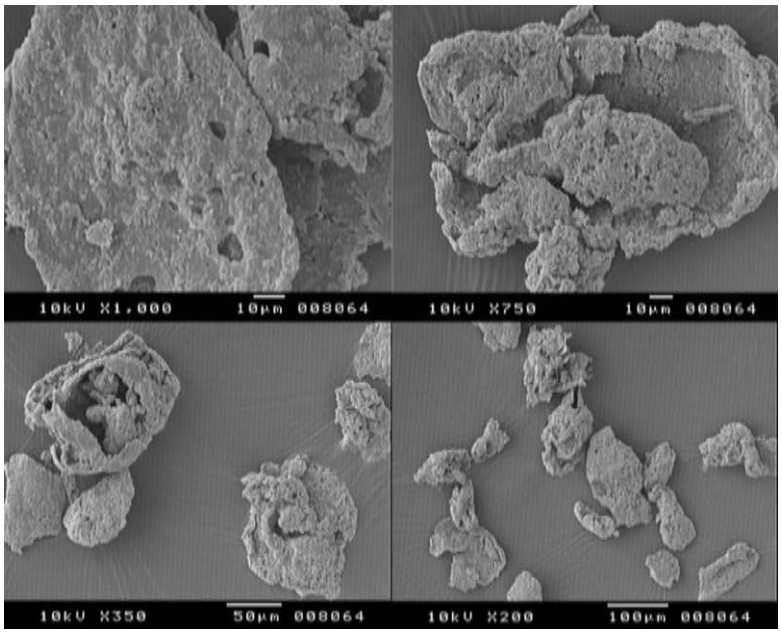

Figure 3: SEM of CL1

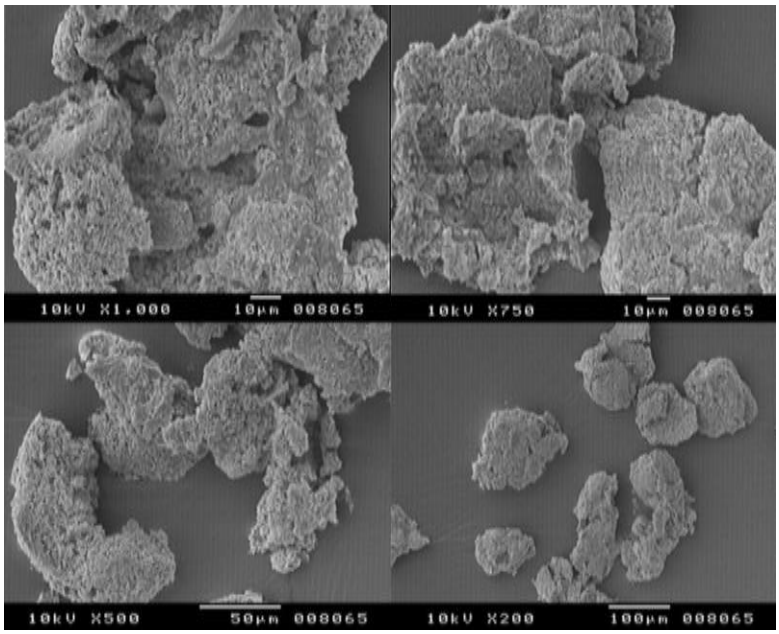

Figure 4: SEM of CL2

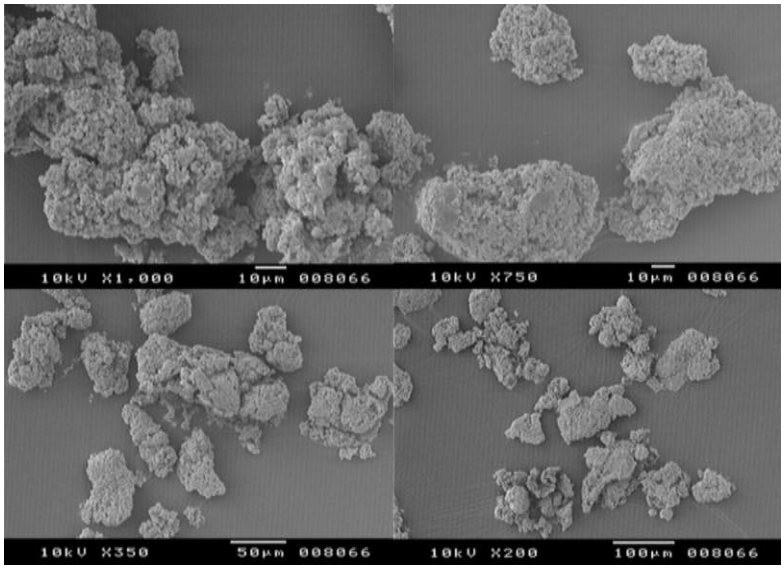

Figure 5: SEM of CL3

Fourier Transforms Infrared (FT-IR) Analysis

Figure 6 represents FTIR spectra of lornoxicam, ethyl cellulose, and formulation batches (from CL1 to CL2). The FT-IR spectrum of lornoxicam showed a characteristic peak at 3090 cm^{-1} corresponding to –NH stretching vibration. Intense absorption peak was found at 1642 cm^{-1} due to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1597 and 1559 cm^{-1} which were assigned to bending vibrations of the N–H group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1157, 1387, and 1336 cm^{-1}. Other prominent peaks appeared at 827.94 cm^{-1} corresponding to –CH aromatic ring bending and hetero aromatics and others appeared at 766.8 cm^{-1} due to the C–Cl bending vibration. The spectrum of ethyl cellulose shows characteristic absorption bands for –C–O–C– stretching vibration at 1052 cm^{-1} and C–H stretching bands at 2880 cm^{-1} and 2970 cm^{-1}. The absorption at 1369 cm^{-1} corresponds to C–H bending. The characteristic peak of drug was found in formulations of microsponges, so it indicates that there is no chemical interaction of drug and polymer.

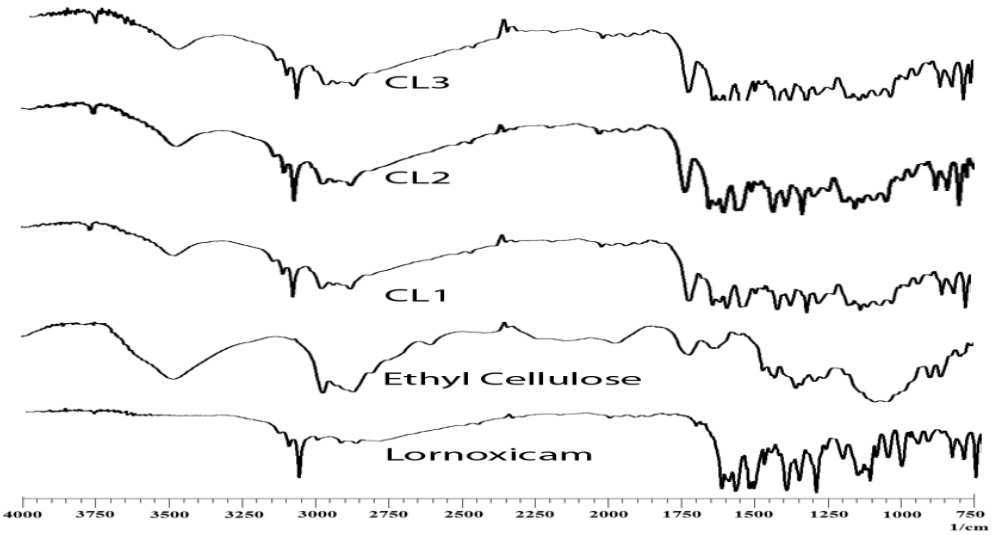

Figure 6: FT-IR of Drug, ethyl cellulose and formulation

Evaluation Parameters of Core and Coated Tablets

The core tablets of microsponges containing Lornoxicam (8 mg), sodium starch glycolate, MCC, talc and magnesium stearate were prepared by direct compression method. The core tablets were evaluated for the drug content, friability, thickness and hardness. The mean drug content of core tablet was found to be 95-98%. The hardness of tablets was found in range between 3.5-4.1 kg/cm^2. Thickness of tablets were found to be 3.5-3.75 mm (diameter 6.33mm). The friability was found in range of 0.31 To 0.51. The results are given in Table 7.

The compression coated tablet was prepared by taking different concentrations of guar gum and HPMC K4M. The composition of coat is given in Table 3. The batches of microsponges (CL1, CL2 and CL3 containing 3:1, 4:1 and 5:1 drug to polymer ratio respectively) were compressed with gaur gum and HPMC K4M using high compression force, having hardness of 4 to 5 kg/cm^2. Thickness was found to be 4.34 mm (diameter 10.34mm) (Table 8). The difference in the core and coated tablet was 6 mm. This indicated that, the 3.00 mm guar gum coat was applied over the core of the tablet. The friability was found in range of 0.31-0.54 which indicating satisfactory mechanical strength. The results are shown in Table 8.

Table 7: Post compression parameters of core tablets

Formulation code	Hardness	Friability	Thickness	Drug content
CLC1	3.5 kg/cm^2	0.34	3.5	95
CLC2	4.1 kg/cm^2	0.31	3.75	97
CLC3	4.0kg/cm^2	0.51	3.75	98

Table 8: Post compression parameter of coated tablet formulation

Formulation code	Hardness	Friability	Thickness
CT60,3	4 kg/cm^2	0.34	4.34
CT60,4	4 kg/cm^2	0.31	4.34
CT60,5	5 kg/cm^2	0.51	4.34
CT70,3	4 kg/cm^2	0.48	4.34
CT70,4	4kg/cm^2	0.54	4.34
CT70,5	5kg/cm^2	0.53	4.34
CT80,3	5kg/cm^2	0.43	4.34
CT80,4	4kg/cm^2	0.45	4.34
CT80,5	4kg/cm^2	0.52	4.34

***In vitro* Gastric Transit Time**

Tablets were evaluated for in vitro gastric transit time, all tablets were subjected to the disintegration

apparatus. Each tablet showed resistance to disintegration during it's passage from stomach to intestine .

***In vitro* Release of Compression Coated Tablet**

The developed formulations CT 60, CT 70, CT 80 were subjected to in vitro dissolution study. It was observed that drug was not released in first 5 hour of dissolution study. This indicated that compression coating of guar gum formulation avoids drug release in the physiological pH of stomach and Small intestine. The dissolution studies of three formulation coating mixtures were carried out in simulated stomach fluid having pH 1.2 followed by simulated intestinal fluid having pH 7.4 Sorensen's Phosphate buffer, after 5 hours lag period dissolution media changed with 4% rat caecal content. The percent drug release of formulation batches CT 60, CT 70, CT 80 (having 3:1 drug to polymer ratio) was found to be 66.94, 58.50 & 48.94%, The percent drug release of formulated batches CT 60, CT 70, CT 80 (having 4:1 drug to polymer ratio) was found to be 78.1953, 64.13 & 57.38 %, and percent drug release of formulation batches CT 60, CT 70, CT 80 (having 5:1 drug to polymer ratio) was found to be 81.28, 70.31 & 59.91% respectively. The results are depicted in Figure 7. Comparative study of all formulation showed that, as guar gum coat concentration increased with decreased drug release of formulations. The percent drug release (without caecal content) for formulated CT80 batches (having drug to polymer ratio 3:1, 4:1, 5:1) was found to be 48.94%, 57.36% and 59.91%. The percent drug release for formulated CT70 batches (having drug to polymer ratio 3:1, 4:1, 5:1) was found to be 58.50%, 64.13% and 70.31%. The percent drug release for formulated CT60 batches (having drug to polymer ratio 3:1, 4:1, 5:1) was found to be 66.94%, 78.1953% and 81.28%. The results are illustrated in Figure 8. From the result compression coated formulation CT 60 shows drug release above 60% using minimum concentration of guar gum in 24 hours study. The *In-Vitro* dissolution study of formulations CT 60, CT 70 and CT 80 (having drug to polymer ratio 5:1, 4:1 & 3:1) were performed without rat caecal content. From this study it was observed that, the drug release increased in the presence of 4% rat caecal content.

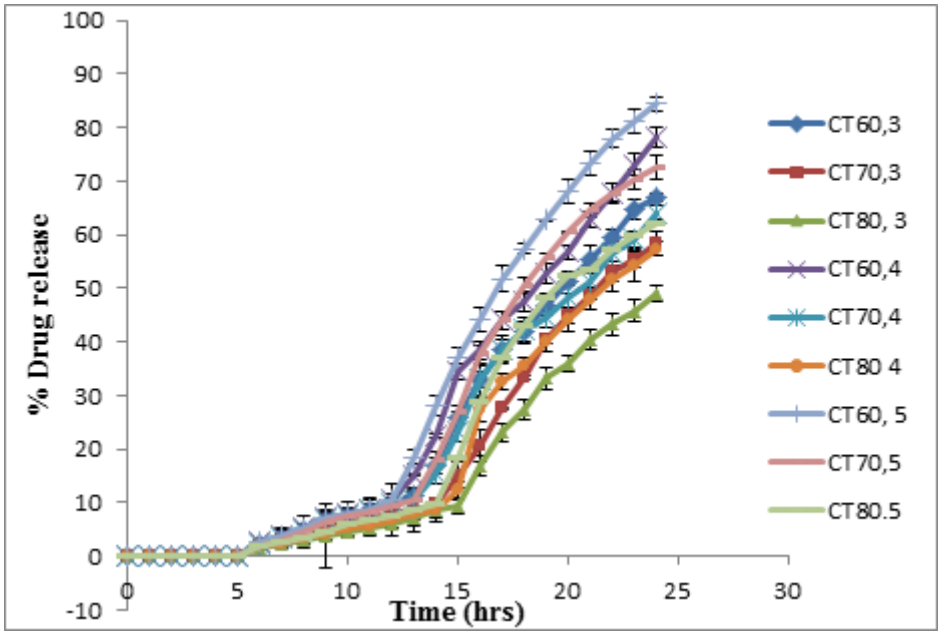

Figure 7: Comparative study of 3:1, 4:1 and 5:1 (i.e CL1,CL2 and CL3 microsponge batches) compression coated tablets with rat caecal content (data represent mean ± standard deviation, *n*=3)

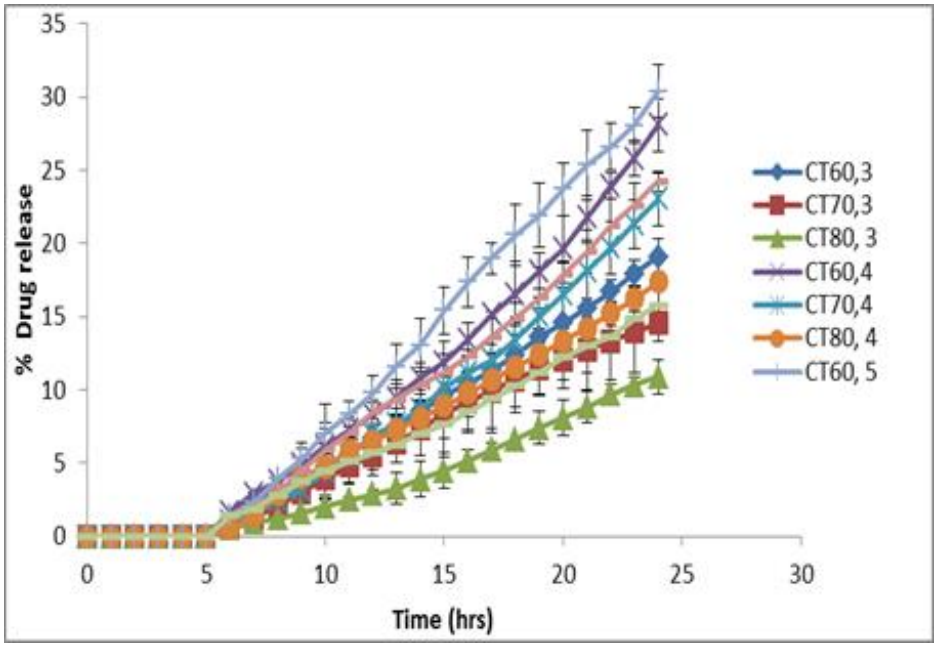

Figure 8: Drug release of the compression coated formulation without rat caecal content (data represent mean ± standard deviation, *n*=3)

CONCLUSIONS

Lornoxicam loaded microsponges were prepared by quasi emulsion solvent diffusion technique, further colon targeted tablets were prepared by direct compression method and coating was done using different concentrations of gaur gum and HPMCK4M. All the colon specific tablets were evaluated for drug content, *In-Vitro* dissolution study, friability, thickness, hardness were found to be within pharmacopoeal limits. The susceptibility of the prepared tablets to the enzymatic action of colonic bacteria was examined by performing the drug release in medium containing rat caecal material (4%). From the *In-Vitro* dissolution studies it was found to be that formulation CT60,5 with 60:40 ratio of guar gum and HPMCK4M coating material was observed to be the best because, it shows the best appearance, friability, hardness and extreme percentage drug release of 81.28% with rat caecal content at the end of 24 hours in *In-Vitro* dissolution studies. In the present work, the colon targeted tablet formulation containing guar gum and HPMCK4M 60:40 as a coating is most likely to target drug to colon.

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