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Matrix-mini-tablets of lornoxicam for targeting early morning peak symptoms of rheumatoid arthritis

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ABSTRACT

Objective(s): The aim of present research was to develop matrix-mini-tablets of lornoxicam filled in capsule for targeting early morning peak symptoms of rheumatoid arthritis.
Materials and Methods: Matrix-mini-tablets of lornoxicam were prepared by direct compression method using microsomal enzyme dependent and pH-sensitive polymers which were further filled into an empty HPMC capsule. To assess the compatibility, FT-IR and DSC studies for pure drug, polymers and their physical mixture were performed. The formulated batches were subjected to physicochemical studies, estimation of drug content, *in vitro* drug release, drug release kinetics, and stability studies.
Results: When FTIR and DSC studies were performed it was found that there was no interaction between lornoxicam and polymers which used. All the physicochemical properties of prepared matrix-mini-tablets were found to be in normal limits. The percentage of drug content was found to be 99.60±0.07%. Our optimized matrix mini-tablets-filled-capsule formulation F30 released lornoxicam after a lag time of 5.02±0.92 hr, 95.48±0.65 % at the end of 8 hr and 99.90±0.83 % at the end of 12 hr. Stability was also found for this formulation as per the guidelines of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use.
Conclusion: A novel colon targeted delivery system of lornoxicam was successfully developed by filling matrix-mini-tablets into an empty HPMC capsule shell for targeting early morning peak symptoms of rheumatoid arthritis.

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Introduction

Rheumatoid arthritis is a chronic inflammatory syndrome which mainly causes the destruction of joints integrity. The patients with this disease have symptoms such as joint pain and functional disability which mainly persist in the early morning (1). These symptoms are mainly characterized due to the diurnal variations in the levels of circulating pro-inflammatory cytokines, tumor necrosis factor-α and/or interleukin-6 (2). Rheumatoid arthritis can be well treated by the concept of chronotherapy to maintain the highest concentration of drug in the bloodstream in the early morning, so that peak of the pain and stiffness of the disease can be overcome (3, 4). In this case, intentionally delayed absorption or colon targeting of drug can be advantageous in order to have a uniform therapeutic effect as the release of drug occurs after a lag time and can be delivered in higher concentration during the time of its greatest need. Thus, good therapeutic effectiveness and patient compliance can be achieved (5, 6).

A number of approaches can be used for targeting the drugs at the colonic junction which some of them are performed by using the enzyme and pH dependent approaches (7). In the former approach, polymers or carriers which are degraded by the enzymes produced by colonic bacteria were used. Because the colonic region is rich in micro flora and their energy is fulfilled by fermenting various types of substrates that have been left undigested in the small intestine such as disaccharide, trisaccharides, and polysaccharides. This fermentation takes place,

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by a vast number of enzymes such as arabinosidase, galactomannase, glucuronidase, galactosidase, xylosidase, azoreductase, nitroreductase, deaminase and ureadehydroxylase produced by microflora. As these enzymes are presented only in the colon, the use of enzyme degradable polymers such as natural polysaccharides originated from plant (eg. Guar gum) and algal (eg. Alginates) seems to be most interested for colon targeted drug delivery (8).

Mini-tablets are very small tablets having a diameter equal to or smaller than 3 mm which can be either filled into a capsule shell or placed in sachets for easy administration (10-13). Mini-tablets are having several advantages over single unit larger tablets, such as consistent drug release, uniform clinical performance, more flexibility during the formulation development and maximum stability on storage (12, 13). Moreover, mini-tablets are very easy to prepare using direct compression method, involving fewer steps using simpler equipments, saving the time and cost. Other benefits of mini-tablets include regular shapes and excellent size uniformity (10-15). In this research, the purpose of the designing matrix-mini-tablets-filled capsule dosage form is to develop a more reliable formulation which has all the advantages of a single unit larger tablet and yet devoid of the problems such as danger of dose dumping and alteration in drug release profile and formulation behavior due to unit to unit variation.

Lornoxicam possess potent analgesic and anti-inflammatory properties and comes under the class of NSAIDs **(**16). It is widely used for the symptomatic treatment of inflammation and pain in rheumatoid arthritis (17, 18). Lornoxicam mechanism of action is based on decreasing prostaglandin synthesis by inhibition of cyclo-oxygenase enzymes as similar to other NSAIDs (19).

The previous published works requires the usage of solvents, additional number of steps and highly specialized equipments which increases the time and the costs of the pharmaceutical industry (20-22).

By considering the above facts about treating the early morning peak symptoms of rheumatoid arthritis, colon targeted matrix-mini-tablets of lornoxicam filled in a capsule were developed.

Materials and Methods

Materials

Lornoxicam pure drug was received as a gift samples from Spectrum Pharma training and IPS institute, Hyderabad, A.P, India. Guar gum, sodium alginate, microcrystalline cellulose, Avicel PH 102 and Aerosil® were purchased from SD Fine Chemicals, Mumbai. Magnesium stearate was purchased from Himedia Chem Lab, Mumbai. pH sensitive methacrylic acid co-polymers (Eudragit® L-100 and S-100) were supplied as gifts samples by Degussa India Pvt. Ltd., Mumbai, India. Empty HPMC capsules (almost all sizes) were obtained as a gift sample from ACG Associated capsules Pvt. Ltd. Mumbai. All the remaining used materials were of analytical grade.

Pre-formulation studies

Identification of Absorption Maxima (λmax)

Lornoxicam pure drug was mixed in different pH range solutions (pH 1.2, 6.5, 6.8, 7.2 and 7.4) to the concentration of 10µg/ml. These prepared solutions were scanned between 200-400 nm regions on UV-Spectrophotometer in order to identify the absorption Maxima (λmax).

Fourier Transform Infrared (FTIR) spectral analysis

The pure drug lornoxicam, polymers and physical mixtures of drug and polymers used in this experimental condition were evaluated for compatibility by recording the spectra using FT-IR Spectrophotometer (Perkin Elmer, spectrum-100, Japan). The evaluation was performed by taking 5% of sample in potassium bromide (KBr) and the mixture was ground into a fine powder and then compressed into KBr pellets at a compaction pressure of 4000 Psi for 2 min. The range of scanning was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Diffraction scanning calorimetric (DSC) studies

DSC thermograms of pure drug lornoxicam and physical mixtures were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). The measurement was performed between 30 and 350^{0}C at heating rate 10^0 C/min.

Formulation methods

Preparation of matrix-mini-tablets of lornoxicam

The matrix-mini-tablets of lornoxicam were prepared by using a direct compression technique as shown in Table 1. At first, lornoxicam, polymer and microcrystalline cellulose Avicel PH 102 were passed through 60 mesh sieve, weighed as per the formulation tablet and mixed. Then magnesium stearate and aerosil were separately passed through the same sieve and after weighing were added to the above mixture and blended thoroughly. Then the prepared blend was compressed into matrix-mini-tablets by using 3mm flat round concave punches in a rotary tablet press (Model RSB-4, Rimek mini-press, Karnavathi engineering, Ahmadabad).

Preparation of matrix-mini-tablets-filled capsule formulations

For preparing the capsule formulation, 4 matrix-mini-tablets equivalent to 8 mg of lornoxicam were filled into size 4 HPMC capsule (as shown in Figure 1).

Table 1. Composition of matrix-mini-tablets formulations

F.C	Lornoxicam	Guar gum	Sodium alginate	Eudragit L-100	Eudragit S-100	Microcrystalline cellulose Avicel PH 102	Magnesium stearate	Aerosil
F1	2	2.5	--	--	--	20.25	0.125	0.125
F2	2	5	--	--	--	17.75	0.125	0.125
F3	2	7.5	--	--	--	15.25	0.125	0.125
F4	2	10	--	--	--	12.75	0.125	0.125
F5	2	12.5	--	--	--	10.25	0.125	0.125
F6	2	15	--	--	--	7.75	0.125	0.125
F7	2	2.5	2.5	--	--	17.75	0.125	0.125
F8	2	2.5	5	--	--	15.25	0.125	0.125
F9	2	2.5	7.5	--	--	12.75	0.125	0.125
F10	2	5	2.5	--	--	15.25	0.125	0.125
F11	2	5	5	--	--	12.75	0.125	0.125
F12	2	5	7.5	--	--	10.25	0.125	0.125
F13	2	7.5	2.5	--	--	12.75	0.125	0.125
F14	2	7.5	5	--	--	10.25	0.125	0.125
F15	2	7.5	7.5	--	--	7.75	0.125	0.125
F16	2	--	--	2.5	--	20.25	0.125	0.125
F17	2	--	--	5	--	17.75	0.125	0.125
F18	2	--	--	7.5	--	15.25	0.125	0.125
F19	2	--	--	10	--	12.75	0.125	0.125
F20	2	--	--	12.5	--	10.25	0.125	0.125
F21	2	--	--	15	--	7.75	0.125	0.125
F22	2	--	--	--	2.5	20.25	0.125	0.125
F23	2	--	--	--	5	17.75	0.125	0.125
F24	2	--	--	--	7.5	15.25	0.125	0.125
F25	2	--	--	--	10	12.75	0.125	0.125
F29	2	--	--	--	12.5	10.25	0.125	0.125
F27	2	--	--	--	15	7.75	0.125	0.125
F28	2	--	--	2.5	2.5	17.75	0.125	0.125
F29	2	--	--	2.5	5	15.25	0.125	0.125
F30	2	--	--	2.5	7.5	12.75	0.125	0.125
F31	2	--	--	5	2.5	15.25	0.125	0.125
F32	2	--	--	5	5	12.75	0.125	0.125
F33	2	--	--	5	7.5	10.25	0.125	0.125
F34	2	--	--	7.5	2.5	12.75	0.125	0.125
F35	2	--	--	7.5	5	10.25	0.125	0.125
F36	2	--	--	7.5	7.5	7.75	0.125	0.125

Note**:** 2.5=10 %; 5=20%; 7.5=30 %; 10=40%; 12.5=50 %; 15=60% as total weight of each mini-tablet was 25 mg

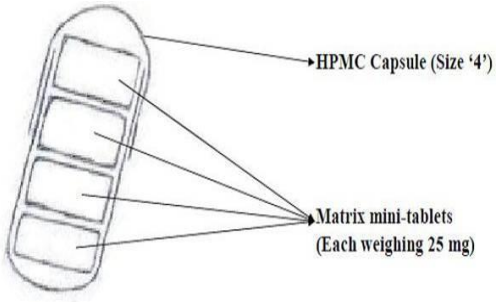

Figure 1. Matrix-mini-tablets-filled capsule formulation

Evaluation methods

Pre-compression parameters

The prepared powder blends ready for compression containing drug, polymers and various excipients were evaluated for pre-compression parameters to study their flow properties, and maintain uniformity of matrix-mini-tablets weight.

Angle of repose (θ)

The angle of repose for the prepared powder blend was determined by taking accurately weighed powder blend into the funnel. The height of the funnel was adjusted as the tip of the funnel touched the apex of the blend. Then the blend was allowed to flow through the funnel freely on to the surface. From the formed powder cone, height and radius was measured and the angle of the repose was calculated using the following equation, where, h and r are the height and radius of powder cone respectively (23, 24).

$$\tan \theta = h/r$$

Bulk density and tapped density

For the powder blends both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Two gram of powder blend from each batch, which previously was shaked to break any formed agglomerates, was introduced into 10 ml of measuring cylinder. Noting the initial volume, the cylinder was allowed to fall under its own weight over a hard surface from the height of 2.5 cm at 2 sec intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations (23, 24).

LBD= Weight of the Granules/Untapped Volume of the packing

TBD= Weight of the Granules/ Tapped Volume of the packing

Hausner's ratio: Hausner's ratio is considered as an indirect index of the ease of the powder flow. It is calculated by using the following equation (23, 24).

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_d}$$

Where, ρ_t is tapped density and ρ_d is bulk density.

Carr's compressibility index

The compressibility index of the powder blend was determined by Carr's compressibility index. Carr's Index (%) can be calculated by using the following equation (23, 24).

$$\text{Carr's Index (\%)} = \frac{\text{TBD-LBD}}{\text{TBD}} \text{ x } 100$$

Post-compression parameters

The prepared matrix-mini-tablets were evaluated for post-compression parameters to study their physicochemical properties.

Hardness test

The hardness of matrix-mini-tablets was determined using Pfizer hardness tester. From each formulation batch three matrix-mini-tablets were randomly taken and the values were calculated (23, 24).

Friability test

The test was performed by initially weighing ($W_{initial}$) twenty matrix-mini-tablets and then transferring into a Veego friabilator. The friabilator was operated at 25 rpm and run up to 100 revolutions. Then the mini-tablets were weighed again (W_{final}) (23, 24).
The % friability was then calculated by using the following equation.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

Weight variation test

From each formulation batch twenty mini-tablets were randomly taken and weighed individually to check the weight variation (23, 24).

Uniformity of thickness

From each formulation batch six matrix-mini-tablets were randomly taken and were measured for thickness using screw gauge (23, 24).

Drug content uniformity

Ten matrix-mini-tablets were chosen and crushed in a mortar then weighed powder containing equivalent to 8 mg of lornoicam was extracted in phosphate buffer of pH 6.8. The solution was filtered through a Millipore filter of 0.45 µm pore size and the drug content was determined spectrophotometrically at λ max of 375 nm after suitable dilution.

In vitro dissolution testing for matrix-mini-tablets-filled capsule formulations F1 to F15

Dissolution studies were carried out by using USP XXIII dissolution test apparatus using basket method. One HPMC capsule filled with 4 matrix mini-tablets were immersed completely at a time. To maintain the conditions of GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were used sequentially. These three media represents the stomach, the small intestine and the colon respectively. When performing studies, 750 ml of medium with pH 1.2 was first used for 2 hr, then continued with 900 ml of pH 7.4 phosphate buffers for 3 hr and was further continued with 900 ml of pH 6.8 dissolution medium containing 0.05 mg/ml of betagalactomannase enzyme for subsequent hours. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C. At predetermined time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hr), 5 ml of dissolution media were taken and replaced with fresh dissolution media. The withdrawn samples were analyzed at 376 nm, 377 nm and 375 nm respectively for pH 1.2, 7.4 and 6.8 buffers, respectively by UV absorption spectroscopy and the mean cumulative percentage drug release was calculated over the sampling times (25-27).

In vitro dissolution testing for matrix-mini-tablets-filled capsule formulations F16 to F36

Dissolution studies were carried out by using USP XXIII dissolution test apparatus using basket method. One HPMC capsule filled with 4 matrix mini-tablets were immersed completely at a time. To match the increased pH changes along the GI tract, four dissolution media with pH 1.2, 6.5, 6.8 and 7.2 were used sequentially. These four media represents the stomach, proximal and distal parts of the small intestine, and terminal ileum respectively. When performing studies, 750 ml of pH 1.2 medium was first used for 2 hr, followed by 900 ml of pH 6.5, 6.8 and 7.2 phosphate buffers for 1, 2 and subsequent hours respectively. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C. At predetermined time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hr), 5 ml of dissolution media were taken and replaced with fresh dissolution media. The withdrawn samples were analyzed at 376 nm for pH 1.2 buffer and 375 nm for pH 6.5 and 6.8 buffers, whereas 377 nm for 7.2 buffer by UV absorption

spectroscopy and the mean cumulative percentage drug release was calculated over the sampling times (28, 29).

Drug release kinetics

The *In vitro* dissolution data were fitted to mathematical models representing zero-order kinetics (Mean % cumulative drug release versus time), First-order kinetics (Log Mean % drug unreleased versus time), Higuchi's (Mean % cumulative drug release versus square root of time) and Korsemeyer-Peppas equation (Log mean % cumulative drug release versus Log time) in order to know the mechanism of release. The data was processed for regression coefficient analysis using Microsoft office Excel 2003 software (30).

Stability studies

These studies were performed both at room temperature and accelerated stability conditions. The conditions used for storing in room temperature were kept at 30±2°C and 65±5 % relative humidity and for accelerated stability were stored at 40±2°C and 75±5 % RH in a stability chamber. At regular intervals of 2, 3 and 6 months samples were withdrawn and tested for physical stability parameters such as Appearance, Weight variation, hardness, thickness, friability, drug content and *In vitro* release profile (31, 32).

Results

Evaluation of the prepared powder blend

The prepared powder blends of all the formulation batches were found to exhibit good flow properties as evident from the results.

Evaluation of prepared matrix-mini-tablets

The physicochemical properties of all the matrix-mini-tablets formulations were found to be within limits as evident from the results.

Table 2. Results of physical evaluation of Pre-compression Blend

Formulation code	Angle of repose (°) mean± SD, n=3	Bulk density (g/cc) mean± SD, n=3	Tapped density (g/cc) mean± SD, n=3	Carr's index (%) mean± SD, n=3	Hausner's ratio mean± SD, n=3
F1	22°.69'±0.14	0.534 ± 0.01	0.594 ± 0.01	10.10± 0.22	1.11±0.02
F2	23°.31'±0.17	0.561 ± 0.01	0.628 ± 0.01	10.66± 0.45	1.11±0.01
F3	23°.48'±0.12	0.565 ± 0.01	0.653± 0.01	13.47± 0.10	1.15±0.00
F4	23°.75'±0.18	0.572 ± 0.01	0.668 ± 0.01	14.37± 0.25	1.16±0.00
F5	24°.67'±0.20	0.586 ± 0.01	0.688 ± 0.01	14.82± 0.47	1.17±0.02
F6	24°.88'±0.14	0.590 ± 0.00	0.693 ± 0.01	14.86± 0.94	1.17±0.00
F7	23°.84'±0.10	0.561 ± 0.01	0.639 ± 0.02	12.20± 0.62	1.13±0.00
F8	24°.18'±0.16	0.570 ± 0.01	0.662± 0.01	13.89± 0.23	1.16±0.02
F9	24°.64'±0.18	0.572 ± 0.01	0.667 ± 0.01	14.24± 0.17	1.16±0.01
F10	23°.97'±0.16	0.566 ± 0.01	0.642 ± 0.01	11.83± 0.20	1.13±0.02
F11	24°.45'±0.10	0.573 ± 0.01	0.667± 0.01	14.09± 0.86	1.16±0.01
F12	24°.83'±0.08	0.578± 0.01	0.674 ± 0.01	14.24± 0.95	1.16±0.00
F13	24°.36'±0.10	0.576 ± 0.01	0.665 ± 0.01	13.38± 0.33	1.15±0.02
F14	24°.59'±0.19	0.579± 0.01	0.676 ± 0.01	14.34± 0.58	1.16±0.00
F15	24°.92'±0.12	0.589 ± 0.01	0.691 ± 0.01	14.76± 0.69	1.17±0.02
F16	22°.73'±0.10	0.506 ± 0.00	0.563 ± 0.01	10.12± 0.24	1.11±0.00
F17	22°.95'±0.16	0.526 ± 0.01	0.587 ± 0.02	10.39± 0.15	1.11±0.01
F18	23°.06'±0.20	0.531 ± 0.01	0.596± 0.01	10.90± 0.32	1.12±0.00
F19	23°.47'±0.12	0.541 ± 0.01	0.609± 0.01	11.16± 0.94	1.12±0.00
F20	23°.65'±0.17	0.547 ± 0.00	0.628 ± 0.01	12.89± 0.11	1.14±0.01
F21	24°.15'±0.12	0.551 ± 0.01	0.636 ± 0.01	13.36± 0.42	1.15±0.01
F22	21°.98'±0.16	0.510 ± 0.01	0.567 ± 0.01	10.05± 0.98	1.11±0.00
F23	22°.40'±0.18	0.533 ± 0.01	0.594 ± 0.01	10.42± 0.77	1.11±0.02
F24	22°.74'±0.11	0.538 ± 0.01	0.602± 0.01	10.63± 0.38	1.11±0.01
F25	23°.28'±0.17	0.544 ± 0.01	0.612 ± 0.01	11.11± 0.62	1.12±0.02
F26	24°.16'±0.10	0.552 ± 0.01	0.639 ± 0.01	13.61± 0.29	1.15±0.02
F27	24°.39'±0.16	0.556 ± 0.01	0.647 ± 0.01	14.06± 0.40	1.16±0.00
F28	22°.84'±0.12	0.530 ± 0.01	0.596 ± 0.01	11.07± 0.88	1.12±0.01
F29	22°.91'±0.18	0.535 ± 0.01	0.605± 0.01	11.57± 0.79	1.13±0.01
F30	23°.42'±0.16	0.542 ± 0.00	0.616 ± 0.01	12.01± 0.12	1.13±0.00
F31	21°.36'±0.19	0.537 ± 0.01	0.603± 0.01	10.94± 0.63	1.12±0.01
F32	23°.10'±0.14	0.540 ± 0.01	0.618 ± 0.01	12.62± 0.14	1.14±0.02
F33	23°.59'±0.15	0.555 ± 0.00	0.640 ± 0.01	13.28± 0.20	1.15±0.01
F34	22°.95'±0.10	0.546± 0.01	0.615 ± 0.01	11.21± 0.16	1.12±0.02
F35	24°.14'±0.12	0.558 ± 0.00	0.644 ± 0.01	13.35± 0.75	1.15±0.01
F36	24°.82'±0.16	0.557 ± 0.01	0.651 ± 0.01	14.43± 0.32	1.16±0.00

Table 3. Evaluation results of matrix-mini-tablets

Formulation code	Weight variation (mg) (mean±SD), n=20	Hardness (kg) (mean±SD), n=6	Thickness (mm) (mean±SD), n=6	Friability (%) (mean±SD), n=20	% Drug content (mean±SD), n=3
F1	26 ± 0.10	2.39 ± 0.05	2.05±0.01	0.43 ± 0.04	99.25± 0.04
F2	24 ± 0.14	2.41 ± 0.08	2.07±0.02	0.26 ± 0.06	99.48± 0.02
F3	26 ± 0.10	2.56 ± 0.04	2.16±0.02	0.28 ± 0.05	98.70± 0.07
F4	25 ± 0.07	2.58 ± 0.05	2.19±0.00	0.19 ± 0.04	99.37± 0.03
F5	27 ± 0.05	2.62 ± 0.04	2.20±0.01	0.21 ± 0.05	97.19± 0.02
F6	26 ± 0.12	2.60 ± 0.02	2.20±0.01	0.12 ± 0.06	98.90± 0.05
F7	25 ± 0.20	2.45 ± 0.00	2.10±0.02	0.41 ± 0.06	97.25± 0.07
F8	25 ± 0.06	2.48 ± 0.05	2.16±0.02	0.25 ± 0.04	99.86± 0.02
F9	27 ± 0.10	2.59 ± 0.04	2.18±0.01	0.20 ± 0.08	99.47± 0.08
F10	26 ± 0.12	2.50 ± 0.00	2.12±0.01	0.30 ± 0.07	99.72± 0.05
F11	25 ± 0.24	2.58 ± 0.01	2.18±0.00	0.25 ± 0.08	98.94± 0.04
F12	24 ± 0.18	2.62 ± 0.08	2.20±0.01	0.19 ± 0.10	98.83± 0.04
F13	26 ± 0.15	2.55 ± 0.04	2.16±0.02	0.34 ± 0.05	97.10± 0.06
F14	26 ± 0.10	2.60 ± 0.03	2.19±0.00	0.17 ± 0.05	98.44± 0.02
F15	25 ± 0.04	2.61 ± 0.09	2.20±0.00	0.10 ± 0.04	99.96± 0.08
F16	27 ± 0.23	2.38 ± 0.10	2.04±0.02	0.51 ± 0.07	97.39± 0.05
F17	25 ± 0.06	2.40 ± 0.05	2.04±0.00	0.46 ± 0.08	98.58± 0.03
F18	26 ± 0.22	2.42 ± 0.05	2.06±0.01	0.48 ± 0.05	99.05± 0.05
F19	24 ± 0.11	2.42 ± 0.07	2.08±0.02	0.37± 0.08	99.92± 0.06
F20	26 ± 0.10	2.48 ± 0.06	2.10±0.02	0.42 ± 0.02	97.51± 0.04
F21	25 ± 0.27	2.52 ± 0.05	2.14±0.01	0.35 ± 0.06	98.22± 0.02
F22	27 ± 0.16	2.40 ± 0.02	2.04±0.00	0.44 ± 0.05	99.16± 0.05
F23	24 ± 0.13	2.41 ± 0.06	2.06±0.01	0.53 ± 0.06	98.30± 0.01
F24	25 ± 0.05	2.43 ± 0.02	2.06±0.01	0.49 ± 0.09	97.86± 0.03
F25	25 ± 0.18	2.43 ± 0.00	2.10±0.00	0.34 ± 0.06	99.39± 0.06
F26	26 ± 0.12	2.56 ± 0.05	2.17±0.02	0.27 ± 0.05	99.90± 0.04
F27	24 ± 0.24	2.58 ± 0.05	2.18±0.01	0.31 ± 0.04	98.81± 0.05
F28	24 ± 0.04	2.54 ± 0.08	2.10±0.02	0.24 ± 0.08	99.27± 0.05
F29	26 ± 0.15	2.56 ± 0.02	2.12±0.02	0.55 ± 0.06	97.02± 0.03
F30	26 ± 0.10	2.43 ± 0.06	2.14±0.01	0.46 ± 0.09	99.60± 0.07
F31	25 ± 0.09	2.40 ± 0.00	2.06±0.00	0.52 ± 0.03	98.59± 0.01
F32	26 ± 0.14	2.45 ± 0.04	2.09±0.01	0.38 ± 0.05	99.87± 0.06
F33	24 ± 0.20	2.60 ± 0.02	2.16±0.02	0.51 ± 0.02	98.20± 0.05
F34	25 ± 0.02	2.54 ± 0.05	2.12±0.01	0.40 ± 0.06	99.18± 0.03
F35	27 ± 0.13	2.58 ± 0.10	2.18±0.00	0.34 ± 0.09	99.49± 0.02
F36	24 ± 0.18	2.62 ± 0.05	2.20±0.02	0.27 ± 0.08	98.80± 0.05

In vitro dissolution testing of matrix mini-tablets-filled capsule systems

From the dissolution testing of all these matrix mini-tablets-filled capsule formulations, it was found that formulation F30 prepared with 40% combined concentrations of Eudragit L100 and Eudragit S100 polymers in 1:3 ratio was able to release lornoxicam after a lag time of 5.02±0.92 hr. It was also found that this formulation rlease the drug more immediately at the ileo-colonic junction. Our aim in this dissolution testing was also to identify a suitable formulation which immediately releases lornoxicam after a lag time (less than 10 %) of minimum 5 hr or at colonic junction. Thus, it was considered to be the best formulation.

Drug Release kinetics

The mechanism of drug release kinetics was determined by fitting the *in vitro* dissolution data to Zero order, First order, Higuchi's plot and Korsemeyer-peppa's plot. The results suggest that none of the formulation have followed any of the mathematical models significantly because of the obtained low 'R^2' values from all of the four plots.

Stability studies

The results of physical stability revealed that the optimized formulation F30 was found to be stable for a period of 6 months based on ICH guidelines.

FT-IR studies

In order to check the compatibility between drug and polymers the spectra of pure drug, polymers and their physical mixtures were recorded. The spectra showed that all the peaks of pure drug and polymers were also visible in their physical mixtures. Absence of any peak was not noted, as they were found to be intact. Thus, it confirmed that combination of pure drug lornoxicam and the used polymers in matrix-mini-tablets can be suitable for designing a formulation intended for its desired therapeutic purpose.

DSC studies

The above observation of FT-IR studies was further confirmed by DSC studies. The DSC thermograms showed that the physical mixtures of drug and polymers did not show any significant shift in their endothermic peaks. Thus, the DSC thermograms results also confirmed that there is no chemical interaction between the physical mixtures of drug and polymers used in matrix mini-tablets.

Table 4. Results of *In vitro* drug release studies

Formulation code	Lag time in hours (i.e. time taken for less than 10 % of lornoxicam release)	Mean cumulative drug release at the end of 8 hr (%)	Mean cumulative drug release at the end of 12 hr (%)
F1	1.12±0.75	93.39±0.62	99.28±0.44
F2	2.08±0.91	91.80±0.95	99.16±0.77
F3	3.07±0.98	83.20±0.77	95.85±0.57
F4	3.53±0.83	78.66±0.69	94.99±0.42
F5	4.55±0.76	75.23±0.80	92.29±0.61
F6	5.28±0.84	67.74±0.96	86.40±0.79
F7	1.56±0.63	94.62±0.58	98.79±0.45
F8	3.54±0.71	91.06±0.43	99.77±0.74
F9	2.24±0.92	98.05±0.68	99.90±0.50
F10	3.15±0.64	95.35±0.83	99.36±0.54
F11	3.26±0.77	96.58±0.64	99.09±0.79
F12	2.50±0.89	91.18±0.70	97.69±0.55
F13	3.02±0.95	86.27±0.68	98.48±0.39
F14	3.58±0.72	79.15±0.44	92.29±0.56
F15	5.03±0.69	73.51±0.58	90.69±0.44
F16	2.03±0.54	99.11±0.33*	--
F17	2.04±0.28	99.02±0.22*	--
F18	2.06±0.85	99.28±0.66	--
F19	2.09±0.98	96.46±0.55	99.43±0.43+
F20	2.14±0.60	89.22±0.50	99.16±0.35
F21	2.28±0.85	86.15±0.88	99.33±0.26
F22	2.12±0.40	96.83±0.22	99.28±0.42
F23	2.20±0.73	92.41±0.53	99.21±0.40
F24	3.26±0.99	89.59±0.80	99.53±0.55
F25	5.14±0.61	84.19±0.69	99.38±0.48
F26	5.21±0.55	74.61±0.36	96.70±0.83
F27	5.32±0.78	68.48±0.84	94.62±0.67
F28	2.08±0.56	98.30±0.89	99.65±0.54
F29	3.16±0.47	96.21±0.34	98.67±0.60
F30	5.02±0.92	95.48±0.65	99.90±0.83
F31	2.32±0.96	97.81±0.98	99.65±0.78
F32	3.02±0.81	90.94±0.69	99.71±0.52
F33	5.03±0.76	76.21±0.51	98.42±0.69
F34	2.34±0.82	95.60±0.90	99.70±0.41
F35	4.40±0.75	78.17±0.75	98.79±0.84
F36	5.04±0.87	75.84±0.66	96.46±0.43

Note: *Mark indicates that the lornoxicam was released before 8 hr
+Mark indicates that lornoxicam was released before 12 hr

In vitro release profile of matrix-mini-tablets-filled capsule formulations

From the dissolution testing release profile results, it was found that as the concentrations of polymer or a combined polymer was increasing, the release rate of lornoxicam from matrix-mini-tablets formulations was decreasing. When guar gum in combination with sodium alginate or Eudragit S100 in combination with Eudragit L100 polymers was used, it was found that the release rate of lornoxicam was increased comparing with formulations prepared with individual polymers. It was also found that 10-50 % concentrations of guar gum polymer, all the concentrations of Eudragit L100 polymer and 10-30 % of Eudragit S100 polymer in matrix-mini-tablets were not suitable for targeting lornoxicam at the colonic junction. Whereas 60% concentration of guar gum polymer and 40-60 % of Eudragit S100 polymer were able to target lornoxicam at the colonic junction. When sodium alginate concentration was increased from 10 to 20 % along with 10 % concentration of guar gum polymer, the release rate of lornoxicam was decreased, but when it was further increased to 30 %, the release rate of lornoxicam was decreased. This similar effect was not seen in formulations when guar gum was also used in high concentration along with sodium alginate. In all the formulations, only the release from formulation F30 prepared with 40 % combine concentrations of Eudragit L100 and Eudragit S100 polymers in 1:3 ratio was found to be more immediate at the ileo-colonic junction and was also found to release lornoxicam after a lag time of 5 hr. Thus, it was considered as the best formulation.

Discussion

As mentioned above, the objective in this research was to develop matrix-mini-tablets of lornoxicam for treating early morning peak symptoms of rheumatoid arthritis. So, a pre-determined target release profile was set. Optimized formulation should release lornoxicam after a lag time (i.e less than 10 %) of minimum 5 hr and maximum till the end of 8 hr. This target release profile is based upon the assumption that if the patient takes our optimized formulation at night

Table 5. Curve fitting analysis results for different formulations

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi's (R^2)	Korsemeyer-Peppa's (R^2)
F1	0.9269	0.9191	0.8957	0.8652
F2	0.9228	0.9044	0.8540	0.9208
F3	0.9108	0.9107	0.7946	0.9518
F4	0.9016	0.881	0.7568	0.9341
F5	0.8926	0.8797	0.7314	0.9256
F6	0.8872	0.8784	0.7162	0.9011
F7	0.9078	0.9284	0.8660	0.8997
F8	0.8652	0.8490	0.7545	0.9134
F9	0.8816	0.9023	0.8396	0.9275
F10	0.8636	0.8949	0.7675	0.9349
F11	0.8528	0.8811	0.7481	0.9204
F12	0.8799	0.9064	0.7782	0.94408
F13	0.8934	0.8731	0.7652	0.9423
F14	0.8798	0.8850	0.7365	0.9251
F15	0.8791	0.8745	0.7156	0.9103
F16	0.9467	0.8481	0.8332	0.9065
F17	0.9574	0.7853	0.8281	0.9168
F18	0.9627	0.8059	0.8545	0.9257
F19	0.9409	0.8788	0.8668	0.9306
F20	0.9242	0.9181	0.8855	0.9298
F21	0.9401	0.8730	0.8638	0.9495
F22	0.8777	0.9431	0.8781	0.9022
F23	0.9173	0.9229	0.8715	0.9359
F24	0.8683	0.8463	0.7521	0.9420
F25	0.8530	0.8210	0.7118	0.9059
F26	0.8714	0.8069	0.6817	0.9179
F27	0.8668	0.8027	0.6685	0.8986
F28	0.8594	0.9400	0.8740	0.8862
F29	0.8354	0.8828	0.7371	0.9343
F30	0.8193	0.8402	0.6996	0.8965
F31	0.8690	0.8956	0.8065	0.9518
F32	0.8352	0.8217	0.7264	0.9320
F33	0.8918	0.8059	0.7244	0.9210
F34	0.8797	0.9003	0.8075	0.9486
F35	0.8951	0.8082	0.7336	0.9146
F36	0.8813	0.8494	0.7134	0.8943

10:00 AM (before going to bed) the drug starts releasing after 3:00 AM and be available in maximum concentration between 4:00 to 6:00 AM which is the time when the rheumatoid arthritis symptoms are worsened.

In this research, the designed formulations are based on microsomal enzyme and pH-sensitive dependent delivery system. The device was formulated into two steps: First, lornoxicam was prepared as matrix mini-tablets by using microsomal enzyme dependent or pH sensitive polymers with different combinations and concentrations. Second, these matrix-mini-tablets were filled into an empty HPMC capsule (Size '4').

Table 6. Results of physical stability studies for optimized formulation F30

Parameters	Storage conditions and time (months)				
	Initial results	Room temperature 30±2°C and 65±5% RH		Accelerated stability 40±2°C and 75±5% RH	
	0	3	6	3	6
Appearance	Yellow circular mini-tablets	No change in appearance	No change in appearance	No change in appearance	No change in appearance
Weight variation (mg) (mean±SD), n=20	26 ± 0.10	26 ± 0.13	25 ± 0.15	26 ± 0.16	26 ± 0.11
Hardness (kg) (mean±SD), n=6	2.43 ± 0.06	2.41 ± 0.03	2.40 ± 0.06	2.42 ± 0.05	2.42 ± 0.08
Thickness (mm) (mean±SD), n=6	2.14±0.01	2.13±0.01	2.12±0.01	2.14±0.01	2.13±0.00
Friability (%)(mean±SD), n=6	0.46 ± 0.09	0.51 ± 0.05	0.47 ± 0.07	0.45 ± 0.08	0.49 ± 0.10
% Drug content (mean±SD), n=3	99.60± 0.07	99.14± 0.12	99.05± 0.09	99.39± 0.05	99.22± 0.08
Lag time in hours (i.e. time taken for less than 10 % of lornoxicam release)	5.02±0.92	5.02±0.81	5.01±0.95	5.02±0.90	5.02±0.79
Mean cumulative drug release at the end of 8 hr (%)	95.48±0.65	95.17±0.80	94.94±0.39	95.27±0.74	95.02±0.59
Mean cumulative drug release at the end of 12 hr (%)	99.90±0.83	99.75±0.47	99.54±0.80	99.86±0.91	99.77±0.62

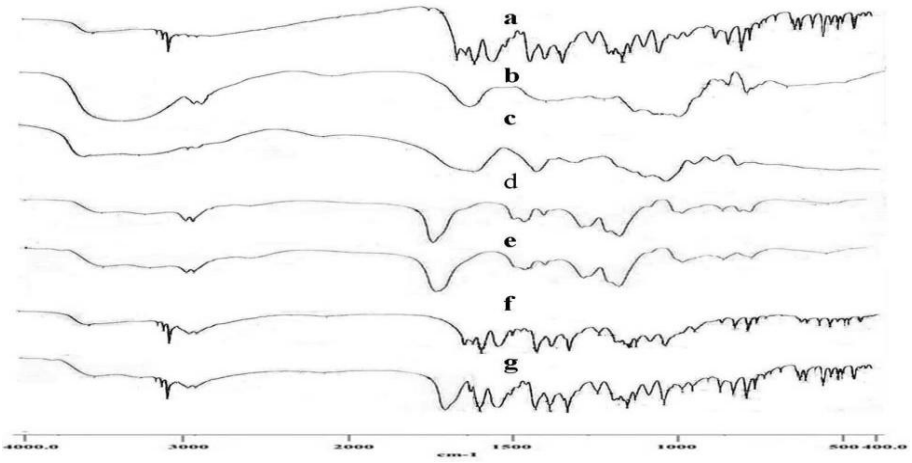

Figure 2. FTIR spectra of a) Pure drug lornoxicam b) Guar gum c) Sodium alginate d) Eudragit L100 e) Eudragit S100 f) Physical mixture of lornoxicam+ guar gum+ sodium alginate g) Physical mixture of lornoxicam+eudragit L100+eudragit S100

Identification of Absorption Maxima (λmax)

When lornoxicam pure drug was subjected to scanning in 200-400 nm regions on UV-Spectrophotometer, the λmax was found as 376 nm for pH 1.2 buffer and 375 nm for pH 6.5 and 6.8 buffers, whereas 377 nm for pH 7.2 and 7.4 buffers. Thus, these obtained results of λmax were used for calculating the *In vitro* release profile of lornoxicam.

FT-IR studies

In order to evaluate the compatibility between drug and polymers, the FT-IR spectra was recorded between 400-4000 cm^{-1} for pure drug lornoxicam, polymers and their physical mixtures in the formulations **(as shown in Figure 2)**. In present research, lornoxicam was taken as the model drug. It has shown -OH, -Ar-CH, -NH, -C=O, –CONH, SO_2N and CCl stretchings by the presence of characteristic peaks at 3512 cm^{-1}, 3100 cm^{-1}, 3066 cm^{-1}, 1647 cm^{-1}, 1594 cm^{-1}, 1327 cm^{-1} and 790 cm^{-1}, respectively. These are all the characteristic peaks of lornoxicam. The spectra of guar gum polymer shows -OH, -CH and -CO stretchings by the presence of characteristic peaks at 3382 cm^{-1}, 2938 cm^{-1} and 1241 cm^{-1}, respectively. Whereas, the spectra of sodium alginate polymer also shows similar -OH, -CH and -CO stretchings by the presence of characteristic peaks at 3567 cm^{-1}, 2943 cm^{-1} and 1302 cm^{-1}, respectively. The spectra of Eudragit L100 polymer shows –OH, $-OCH_3$, $-CH_3$ and -CO stretchings by the presence of characteristic peaks at 3258 cm^{-1}, 2997 cm^{-1}, 2952 cm^{-1} and 1731 cm^{-1}, respectively. Whereas, spectra of Eudragit S100 polymer also shows similar –OH, $-OCH_3$, $-CH_3$ and -CO stretchings by the presence of characteristic peaks at 3225 cm^{-1}, 2998 cm^{-1}, 2953 cm^{-1} and 1727 cm^{-1}, respectively.

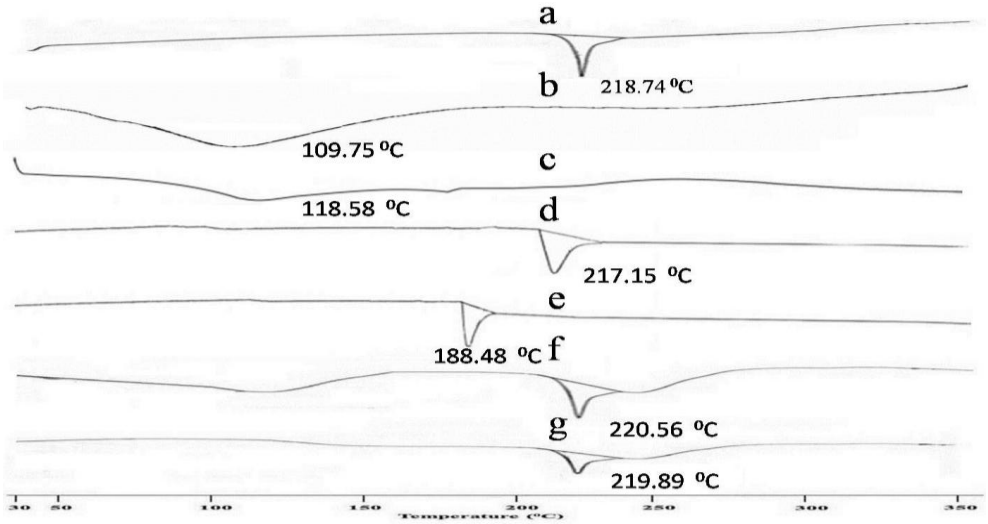

Figure 3. DSC spectra of a) Pure drug lornoxicam b) Guar gum c) Sodium alginate d) Eudragit L100 e) Eudragit S100 f) Physical mixture of lornoxicam+ guar gum+ sodium alginate g) Physical mixture of lornoxicam+eudragit L100+eudragit S100

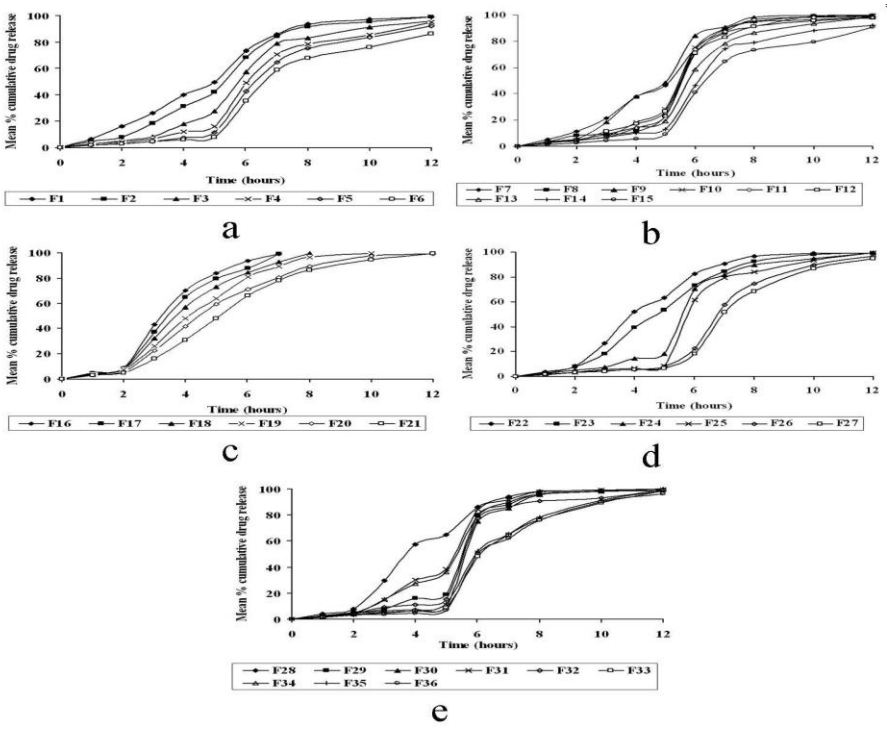

Figure 4. *In vitro* release profile of matrix-mini-tablets-filled capsule formulations prepared with a) Guar gum b) Combination of guar gum and sodium alginate c) Eudragit L100 d) Eudragit S100 e) Combination of Eudragit L100 and Eudragit S100

When the spectra of physical mixtures of lornoxicam, guar gum, sodium alginate and lornoxicam, Eudragit L100, Eudragit S100 were recorded, it was found that all the peaks corresponding to the three constituents were also visible in their respective higher spectra. No absence of any peak was noted, as they were found to be intact. Thus, it confirms that combination of pure drug and the above used polymers can be suitable for designing a formulation intended for its desired therapeutic purpose.

DSC studies

The above observation of FT-IR studies was further confirmed by DSC studies. The DSC thermograms of pure drug, polymers and their physical mixtures are shown in Figure 3. The DSC thermogram of pure drug lornoxicam, corresponding to its melting point gave a very sharp endothermic peak at 218.74°C. Whereas, the DSC thermograms of guar gum, Sodium alginate, Eudragit L100 and Eudragit S100 polymers showed the endothermic peaks at 109.75°C, 118.58°C, 217.15°C and 188.48°C, respectively. However, the DSC thermograms for the physical mixtures of lornoxicam, guar gum, sodium alginate and lornoxicam, Eudragit L100, Eudragit S100 did not show any significant shift in their endothermic peaks and. their peaks were found at 220.56°C and 219.89°C, respectively. Thus, the DSC thermograms results also confirmed that there is no chemical interaction between the physical mixtures of drug and polymers used in the formulation.

Evaluation of the prepared powder blend

The angle of repose values for the blend of matrix-mini-tablets was found to range between 21°.36'±0.19 to 24°.92'±0.12. The loose bulk density and tapped bulk density values were found to range between 0.506 ± 0.00 to 0.590 ± 0.00 and 0.563 ± 0.01 to 0.693 ± 0.01 g/ml respectively. The compressibility index values were found to range between 10.05± 0.98 to 14.86± 0.94%. The Hausner's ratio values were found to range between 1.11±0.01 to 1.17±0.02. As, angle of repose values were found to be less than 30°, compressibility values were found to be less than 15% and Hausner's ratio values were also found to be lesser than 1.25, it indicated better flow properties. Thus, the prepared powder blend was found to exhibit good flow properties as evident from the results shown in Table 2.

Evaluation of prepared matrix-mini-tablets

The weight variation values for the matrix-mini-tablets were found to range between 24 ± 0.11 to 27 ± 0.23 mg. The pharmacopoeial limit for % deviation of tablets of 130 mg or less is ±10 % and all the batches were found to pass as per the specifications given in Indian pharmacopoeia. The hardness values were found uniform and it was found to range between 2.39 ± 0.05 to 2.62 ± 0.08 kg. Friability values were found to range between 0.12 ± 0.06 to 0.55 ± 0.06 % and they also shown that matrix-mini-tablets have got sufficient strength. The thickness was found to range between 2.04±0.00 to 2.20±0.02 mm. Excellent uniformity in drug content was found

in the matrix-mini-tablets, and their values were found to range between 97.02± 0.03 to 99.90± 0.04 % which is more than 95%. Thus, all the physicochemical properties of matrix-mini-tablets were found to be satisfactory as shown in Table 3.

In vitro dissolution testing of matrix-mini-tablets-filled capsule systems

The prepared matrix-mini-tablets-filled capsule systems were subjected to *In vitro* dissolution testing. The main aim in this dissolution testing was to identify a suitable formulation which immediately releases lornoxicam after a lag time (less than 10%) of minimum 5 hr or at colonic junction.

During dissolution test, it was found that in all the formulations the HPMC capsule disintegrated and released the matrix mini-tablets within 9 min in 1.2 pH dissolution media.

In the first attempt we tried to target lornoxicam at the colonic junction based on microsomal enzyme dependent approach. So, we prepared initial six formulations of matrix-mini-tablets-filled capsule by using guar gum as a polymer at different concentrations (10, 20, 30, 40, 50 and 60%). From the results of dissolution testing, it was found that only formulation F6, prepared with 60% concentration of guar gum polymer was able to release lornoxicam after a lag time of 5.28±0.84 hr, but failed to give maximum release of lornoxicam at the end of 8 hr. As per our desired criteria, we need a formulation which could release lornoxicam after a lag time of minimum 5 hr and maximum at the end of 8 hr. So, we further prepared nine formulations by using the combination of guar gum and sodium alginate polymers. Based on the results of dissolution testing, it was found that only formulation F15, prepared with 60% combine concentration of guar gum and sodium alginate polymers in 1:1 ratio was able to release lornoxicam after a lag time of 5.03±0.69 hr. We also found that its release rate profile was little increased at the colonic junction while compared to formulation F6. But still it was found that this formulation also doesn't satisfy our desired criteria due to less release percentage at the end of 8 hr.

In the second attempt, we tried to target lornoxicam at the colonic junction based on pH dependent approach by using Eudragit L100 and Eudragit S100 polymers both alone and in combination. From the results of dissolution testing, it was found that the entire matrix-mini-tablets-filled capsule formulations prepared with Eudragit L100 alone could only prevent the lornoxicam release in pH 1.2 buffer but not prevent the release in pH 6.5, 6.8 and 7.2 buffers. Their lag times were found to be below three hours. Whereas for the matrix-mini-tablets-filled capsule formulations prepared with Eudragit S100 alone, it was found that only the formulations F25, F26 and F27 prepared with 40, 50 and 60% concentration of Eudragit S100 polymer were able to release lornoxicam after a lag time of 5.14±0.61, 5.21±0.55, and 5.32±0.78 hr respectively, but failed to give maximum release at the end of 8 hr. When matrix-mini-tablets-filled capsule formulations prepared with combine concentrations of Eudragit L100 and Eudragit S100 were evaluated for dissolution testing, it was found that only the formulations F30, F33 and F36 were able to release lornoxicam after a lag time of 5.02±0.92, 5.03±0.76, and 5.04±0.87 hr respectively. In these three formulations, only the release from formulation F30 prepared with 40% combine concentrations of Eudragit L100 and Eudragit S100 polymers in 1:3 ratio was found to befaster at the ileo-colonic junction. Thus, it was considered to be the best formulation. The *In vitro* dissolution testing results of all the matrix-mini-tablets-filled capsule formulations was shown in Table 4 and represented in Figure 4.

Effect of Guar gum and sodium alginate

During the dissolution testing, it was found that as the concentration of guar gum polymer was increasing, the release rate of lornoxicam from matrix-mini-tablets-filled capsule formulations was decreasing. This is due to the hydrophilic nature of guar gum polymer, and its rate of hydration has increased by the rise of its concentration, resulting in decreased dissolution rate. It was also found that 10-50% concentrations of guar gum polymer in matrix-mini-tablets-filled capsule were not suitable for targeting lornoxicam at the colonic junction, whereas 60% concentration prevented the lornoxicam release in pH 1.2, 6.5 and 6.8 buffers. Because of the enzyme dependent characteristics of polysachcharide polymers like guar gum, it remain insoluble in the stomach and small intestine and release the drug only in the presence of colonic enzymes because of their fermentation. This effect was better achieved when high concentration of guar gum polymer was used. But when guar gum polymer was used in combination with sodium alginate, it was found that the release rate of lornoxicam was increased comparing to formulations prepared with guar gum alone. I the quick water absorbing capacity of sodium alginate increase the permeation of lornoxicam from guar gum polymer. It was also observed that in formulations F7, F8 and F9 when sodium alginate concentration was increased from 10 to 20% along with 10% concentration of guar gum polymer, the release rate of lornoxicam was decreased. But when further sodium alginate concentration was increased to 30% in formulation F9 the release rate of lornoxicam was decreased. It is due to the reason that sodium alginate concentration was dominant in formulation F9 and it increased the permeation of lornoxicam from guar gum polymer. The similar effect was seen to a minimum extent in

formulations F10, F11 and F12, but not seen in formulations F13, F14 and F15 as guar gum was also used in high concentration along with sodium alginate. The only effect observed in these formulations was the decrease in the release rate of lornoxicam as the concentration of guar gum polymer increased.

Effect of Eudragit L100 and Eudragit S100

It was found that as the individual concentration of both polymers in matrix-mini-tablets-filled capsule formulations was increasing the release rate of lornoxicam was decreasing. It was also observed that the formulations prepared with Eudragit L100 alone, released maximum portion of lornoxicam in pH 6.5 buffer itself. This is because of their high solubility in pH 6.0 or above buffers. Whereas, formulations prepared with higher concentrations (40-60%) of Eudragit S100 alone were able to target lornoxicam at the ileo-colonic junction. This is because of their low solubility in pH 6.5 and 6.8 buffers and high solubility in pH 7.0 or above buffers. But when both the combination of Eudragit L100 and Eudragit S100 polymers were used, it was found that the release rate of lornoxicam was increased in comparison with formulations prepared with Eudragit S100 alone. It is due to the reason that the Eudragit L100 because of its good solubility in pH 6.5 and 6.8 buffers increased the permeation of lornoxicam from Eudragit S100 polymer which dissolves at pH 7.2 buffer.

It can be concluded that if combination of these two polymers are taken in different ratios and concentrations it can be possible to adjust the drug release in matrix-mini-tablets formulations. Also, this criteria of selection of polymers can be used if the drugs are be immediately targeted at the colonic junction after a lag time in stomach and small intestine and thus can be useful for targeting maximum concentration of drug in the early morning hours (i.e. between 4-6 AM).

Drug Release kinetics

The mechanism of drug release kinetics was determined by fitting the *In vitro* dissolution data to Zero order, First order, Higuchi's plot and Korsemeyer-peppa's plot (as shown in Table 5). The 'R^2' values obtained from zero order and first order plots of all the formulations was found to range between 0.8193 to 0.9627 and 0.8027 to 0.9431 respectively. Whereas the 'R^2' values obtained from Higuchi's plot and Korsmeyer-Peppa's plots was found to range between 0.6685 to 0.8957 and 0.8652 to 0.9518 respectively. These low 'R^2' values obtained from all the four plots suggested that none of the formulation had followed any of the mathematical models significantly. Thus, the results indicated that the above used polymers like guar gum and Eudragit S100, both alone and in combination with sodium alginate and Eudragit L100, in matrix-mini-tablets-filled capsule can be used for targeting lornoxicam at the colonic junction rather than controlling or sustaining the release. Because the release of lornoxicam is dependent upon the guar gum degradation by the enzymes which are secreted by microflora of the colon and for Eudragit S100 it is dependent upon its high solubility at the pH of colonic junction.

Stability studies

The obtained results of both room temperature and accelerated stability studies revealed that the optimized matrix-mini-tablets-filled capsule formulation did not show any significant change in physical stability parameters such as Appearance, weight variation, hardness, thickness, friability, drug content and *in vitro* release profile during the period of study (as shown in Table 6). Thus, stability was found for the optimized formulation as per ICH guidelines.

Conclusion

As the main aim of our study was to target early morning peak symptoms of rheumatoid arthritis, a novel colonic targeted delivery system of lornoxicam was developed by filling matrix-mini-tablets in an empty HPMC capsule. A total number of 36 formulations were prepared and formulation F30 was found to be the best formulation as it released lornoxicam after a lag time of 5.02±0.92 hr, 95.48±0.65 % at the end of 8 hr and 99.90±0.83 % at the end of 12 hr. Stability was also found for this formulation as per ICH guidelines. Thus, a formulation was designed which is very easy to prepare without any solvents and involves few steps using simple equipments during their manufacture in the pharmaceutical industry.

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