Lornoxicam gastro retentive floating matrix tablets: Design and *in vitro* evaluation

S. Sathiyaraj, Ramya D. Devi, Vedha B. N. Hari
Department of Pharmacy, SCBT, SASTRA University, Thanjavur, Tamil Nadu, India

**ABSTRACT**

The objective of this present investigation is to prolong the gastric residence time of Lornoxicam by fabricating it into a floating sustained release matrix tablets. Lornoxicam, a potent oxicam group of non-steroidal anti-inflammatory drugs, suffers from relatively short half life of 2 to 3 hrs showing maximal absorption in proximal gastro intestinal tract region necessitating its need to be formulated as a floating sustained release matrix tablets. In this current investigation, hydroxyl propyl methyl cellulose K15M, a high viscous grade polymer with apparent viscosity of 15,000 cps, was kept as a variable (10-50%) and calcium carbonate (13%) was used as a gas generator. The prepared blends were subjected for its pre-formulation characterization. The directly compressed tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content, *in-vitro* buoyancy with axial and radial enlargement measurement, swelling index. From the investigation it was observed that the buoyancy lasted for up to 24 hrs. Fourier transform infra-red spectroscopy peaks assured the compatibility of the drug with excipients and confirmed the presence of pure drug in the formulation. It was supported by *in-vitro* dissolution studies; and the dissolution data was subjected to various release kinetic models to understand the mechanism of drug release.

**Key words:** Buoyancy, hydroxyl propyl methyl cellulose (HPMC K15M), sustained release

**INTRODUCTION**

Floating drug delivery system (FDDS) exerts buoyancy in stomach for extended time period thereby offering extended gastric residence time for the dosage form ensuring optimal bioavailability (BA). The ideal drug candidate for FDDS are drugs that are acting locally in upper gastro intestinal tract (GIT) or drugs that are degrading in lower GIT or drugs that show poor intestinal absorption or drugs that are absorbed only in the initial part of small intestine (SI). Acid labile drugs and other drugs that are causing gastric lesions are unsuitable for such a formulations.[1] The residence time of the dosage form in the stomach depends upon various factors like pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states (hepatic failure, diabetes, chron’s disease).[2] Other techniques for gastro retentive dosage forms include swelling or expansion, inflation, mucoadhesion, sedimentation, microballoons[3,4] and low density systems, co-administration with drugs that are delaying gastric emptying. Out of all the available systems, the floating beads, floating tablets, floating granules, and floating microspheres have gained major importance in the formulation development more recently.

Oral sustained release dosage forms have been the field of focus for the past three decades attributed to the fact of overweighted benefits despite its limitations of unsuitability of drugs that are possessing narrow absorption window in upper part of GIT offering reduced BA. This limitation is tackled and overcome by gastro retentive dosage forms.[5] FDDS possess lower bulk density than the gastric fluid exerting buoyancy in the stomach leading to slow drug
release in an extended manner before it reaches absorption window. In this present formulation, dual benefits of buoyancy as well as sustained action is achieved with an intention to maintain the steady state of drug release. Hydrophilic matrix system is one of the easiest approach for developing modified and sustained release dosage forms. A polymer like hydroxypropyl methyl cellulose (HPMC) function as a pH independent gelling agent and drug release is elicited by swelling and erosion mechanism occurring simultaneously contributing to overall drug release. Less dense porous materials are being developed as a matrix formulation due to a stable uniform porous structure, modifiable pore size with narrow distribution, and higher surface area offering reproducible and predictable drug absorption.

Lornoxicam, belonging to the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs), is found to possess potent anti-inflammatory and analgesic activities. A commercially available form includes conventional immediate release tablets 4 mg/8 mg, rapid release 8 mg tablets, and parenteral formulations of 4 mg/ml for intravenous (i.v) and intramuscular (i.m) use. Lornoxicam is widely been recommended for the symptomatic treatment of pain and inflammation in patients with osteoarthritis and rheumatoid arthritis, pre-operative and post-operative pain associated with gynecological, orthopedic, abdominal and dental surgeries. As Lornoxicam shows half life of 3-5 hrs and poor solubility in acidic conditions, it is proven to be an ideal candidate for floating sustained release dosage forms.

Matrix system is the commonly used method for modulating the drug release. In terms of industrial feasibility, the production of matrix system is widely done by wet granulation and by direct compression technique. The manufacture of matrix tablets by direct compression is cheaper, simpler process, broad regulatory acceptance, and allows flexibility in obtaining desirable release profiles. In spite of the poor flow property of controlled release polymers, by admixture of directly compressible microcrystalline cellulose (MCC) and other excipients, excellent flow property is being achieved.

This investigation is restricted to floating tablets of Lornoxicam with sustained release by employing various concentrations of release retarding polymers, HPMC K15M, and gas generators.

**MATERIALS AND METHODS**

**Materials Used**

Lornoxicam, HPMC K15M, was obtained as gift sample from (Micro Labs, Hosur, India). Talc, magnesium stearate, microcrystalline cellulose, lactose monohydrate were procured from SD Fine chemicals, Mumbai, India, and calcium carbonate was procured from Paxmy speciality chemicals, Chennai, India. All the materials used were analytical grade, purchased from India.

**Methodology**

**Solubility studies**

Exactly weighed amounts of drug was repeatedly added to solubility bottles each containing fixed quantity of 0.1M HCl, 6.8 phosphate buffer, and distilled water until the solvent gets saturated. The suspension was agitated at 37 ± 0.5°C for 24 hrs. Aliquots were withdrawn from the suspensions and passed through millipore filter. The concentration of the drug in each solvent filtrate was analyzed using UV-Visible spectrophotometer (Perkin Elmer, Massachusetts, USA) at 380 nm. The solubility study for each solvent was carried out in triplicate.

**Formulation of floating matrix tablet**

Sustained release floating matrix tablets were prepared by direct compression method. All the ingredients were dispersed accurately, sifted through 40 mesh screen. Drug was geometrically mixed with diluents followed by addition of the polymer and gas generating agent. Dry mixing was done for 10 minutes and final sifting was carried through 22 mesh screen. Pre-lubrication and lubrication was done for 5 and 2 minutes, respectively. Pre-formulation parameters were evaluated for the blends and then compression was carried out by manual single punching machine (Model: KI-150, Khera Instruments Ltd, New Delhi, India) using 9 mm deep concave punches. The formulated tablets were stored in air tight container at room temperature for further evaluation of the tablet parameters. In all the formulations, polymers concentration was varied from 10 to 50% of the total weight. The composition of various formulations is shown in the Table 1.

**Evaluation of Granules**

**Angle of repose**

Fixed funnel method was used to measure the flow properties where the granules were poured from funnel walls to form conical heap in which its lower tip is 2-5 cm away from the hard surface. Static angle of repose was measured by using the formula:

\[
\theta = \arctan \left( \frac{h}{r} \right)
\]

where \(h\) is the height of the conical heap and \(r\) is its radius.

**Table 1: Various formulation parameters of Lornoxicam floating matrix tablets**

| Ingredients                | F1 | F2 | F3 | F4 | F5 |
|----------------------------|----|----|----|----|----|
| Lornoxicam                 | 8  | 8  | 8  | 8  | 8  |
| HPMC K15M                  | 15 | 30 | 45 | 60 | 75 |
| Calcium carbonate          | 20 | 20 | 20 | 20 | 20 |
| Microcrystalline cellulose | 41 | 34 | 27 | 20 | 13 |
| Lactose monohydrate        | 63 | 55 | 47 | 39 | 31 |
| Talc                       | 1.5| 1.5| 1.5| 1.5| 1.5|
| Magnesium stearate         | 1.5| 1.5| 1.5| 1.5| 1.5|
| Target weight              | 150| 150| 150| 150| 150|

HPMC - Hydroxyl propyl methyl cellulose
RESULTS AND DISCUSSION

Formulation of Floating Matrix Tablet

The pre-formulation studies were performed for the active pharmaceutical ingredient (API) to assess its formulation suitability. The solubility study data for the drug showed low solubility in acidic conditions (4.47 µg/ml) than water (43.85 µg/ml) and phosphate buffer pH 6.8 (77.95 µg/ml). The amount of Lornoxicam release in each sample was determined at wavelength of 380 nm using UV-Visible spectrophotometer (Perkin Elmer, Massachusetts, USA).

In-vitro buoyancy study

The in-vitro buoyancy was determined by observing the floating lag time and the total floating duration (floating capacity). For determining the floating lag time, 0.1 N HCl was taken as the media and three tablets were placed in it. The time required for the matrix tablet to rise from the bottom to the surface of the media for floating was determined. The time was observed visually and recorded using stop watch. For observing the total floating duration, three individual tablets from each formulation were put in a beaker containing 900 ml of 0.1N HCl media. Then the time taken for each tablet to constantly float on the media was measured. The sample mean and standard deviation were calculated for the observed data.[16,17]

Hydration response

The swelling properties of matrices containing drug were determined by placing the tablet in the dissolution test apparatus containing 900 ml of 0.1 N HCl and maintained at 37 ± 0.5°C. At periodic time intervals, the tablets were taken out of the medium and the weight gain in each tablet was checked using electronic weighing balance (Model: BL-220H, Shimadzu Corporation, Japan). The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation.[18]

\[
WU = \frac{\text{Weight of the swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100
\]

Fourier transform infra-red spectroscopy (FT-IR)

The powdered samples of the tablets were mixed thoroughly with previously dried potassium bromide (IR grade) so as to form transparent pellets. The spectral smoothening and baseline correlation procedure were done and then the samples are scanned from 4000 to 400 cm\(^{-1}\) at ambient temperature (Perkin Elmer, Massachusetts, USA).[16]

Mathematical models such as zero-order, first-order, Higuchi and Peppas kinetics were applied to the observed release profile data to analyze the rate, mechanism, and pattern of the drug release.
drug were prepared for Lornoxicam floating tablets by using HPMC K15M, calcium carbonate, magnesium stearate, aerosil, microcrystalline cellulose, and lactose monohydrate as shown in the formula [Table 1]. The formulations were optimized with the required quantity of excipients by various trials and the polymer concentration was variable (HPMC K15M at 10-50%).

**Granular Evaluation**

The bulk density and tap density of the formulation ranged from 0.3947-0.4166 g/ml, 0.4838-0.5 g/ml, respectively. The compressibility index and Hausner ratio ranged from 13.89-18.43 and 1.16-1.22, respectively, signifying satisfactory flow property which was further authenticated by the angle of repose values of 19.16°-22.13°. The average diameter of the particles ranged from 0.56-0.67 µm [Table 2].

**Tablet Characterization**

The average weight of the tablet ranges from 147 to 152 mg for all the formulations which complied with the monograph specification limit of ±7.5%. As a measure of mechanical strength, these formulations exhibited satisfactory hardness of 2 to 3 kg/cm² and the same fact was further supported by friability of less than 1%. Drug content of all the formulations ranged between 98.94 to 100.34 %, which was within the standard limits of 90.00 – 110.00 %. The average wetting time for the formulation F-1 to F-5 was in the range of 8-10 minutes and buoyancy lag time showed less than one minute, and the buoyancy duration showed more than 24 hrs [Table 3]. The tablets showed elegant appearance and excellent floating property [Figure 1]. The hydration and swelling index of all the formulations was evaluated and compared [Figures 2 and 3]. The FT-IR studies reveal that there is no interaction in between the drug and polymer [Figures 4 and 5].

**In-vitro Dissolution Studies**

As dictated by in-vitro dissolution data, the increase in the polymer concentration of HPMC K15M progressively retarded the drug [Table 4 and Figure 6]. The lowest polymer concentration (F-1) showed faster release 97.8% in 8 hrs and the highest polymer concentration (F-5) released only 55% drug after 8 hrs which falls within the pharmacopoeial limits. When the concentration of the hydrophilic polymer was increased, the time taken for its swelling and erosion in the media was increased due to high viscous gel strength. The pore distribution became less on the effective surface area of the tablet which is exposed to the dissolution media. Therefore, the diffusion of the water insoluble drug from the

![Figure 1: Optical microscope images of floating matrix tablets](image)

**Table 2: Granular characterization of Lornoxicam floating matrix tablets**

| Formulations | Bulk density (g/cm³) | Tapped density (g/cm³) | Hausner ratio | Carr’s index | Angle of repose (°) | Size (µm) |
|--------------|----------------------|------------------------|---------------|--------------|------------------|-----------|
| F1           | 0.416 ± 0.002        | 0.483 ± 0.002          | 1.161         | 13.890       | 22.13 ± 0.130    | 0.61      |
| F2           | 0.416 ± 0.003        | 0.501 ± 0.004          | 1.201         | 16.680       | 20.10 ± 0.075    | 0.67      |
| F3           | 0.405 ± 0.004        | 0.468 ± 0.001          | 1.156         | 15.311       | 19.49 ± 0.04     | 0.59      |
| F4           | 0.405 ± 0.002        | 0.483 ± 0.002          | 1.193         | 16.210       | 19.32 ± 0.06     | 0.66      |
| F5           | 0.394 ± 0.003        | 0.483 ± 0.002          | 1.225         | 18.430       | 19.16 ± 0.03     | 0.56      |

n = 3 with the mean ± SD

![Figure 2: The comparative swelling index for the formulations F1-F5](image)

![Figure 3: Hydration index comparison for the formulations F1-F5](image)
matrix was retarded to its maximum and the drug release was slowed down. The data obtained from the in-vitro dissolution study was fitted to different release kinetics model and found to be best suited with Higuchi and Peppas model [Table 5].
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CONCLUSION

Lornoxicam, available as conventional tablets in the market, can be successfully formulated as sustained release floating tablets which has the advantage to retain the dosage form in the effective site of absorption for a long period of time and release the drug in sustained manner, ultimately achieving desired steady state concentration level and increased bioavailability of the drug. The current investigation proved that a hydrophobic drug Lornoxicam can be designed as modified release dosage form with desired qualities, using a hydrophilic polymer HPMC K15M and calcium carbonate as a buoyancy initiator. Additionally, ease of manufacturing process by direct compression implies that it ensures the capability of commercial utility by large scale production with satisfactory industrial feasibility.

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