CHAPTER IV

LITERATURE ON DRUGS STUDIED

Lornoxicam

Lornoxicam is a nonsteroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. The mode of action of Lornoxicam is based on inhibition of prostaglandin synthesis (inhibition of the cyclooxygenase enzyme).

Lornoxicam is absorbed rapidly and almost completely from the gastric region of the gastrointestinal tract. Lornoxicam is very bitter in taste.

Lornoxicam is used in the treatment of rheumatoid arthritis, post-traumatic pain, musculoskeletal and joint disorders.

Chemistry:

The Chemical name is, \((\text{2-[2-(2,6 dichlorophenyl) aminophenyl] acetyl]oxyacetic acid})/ 6-chloro-4-hydroxy-2-methyl-\text{N-[2-pyridinyl]-2H-thieno[2,3-e]1,2-thiazine-3-carboxamide} \text{1,1-dioxide.}

Structure:

**Molecular Formula:** \(C_{13}H_{10}ClN_{3}O_{4}S_{2}\)

**Molecular Weight:** 371.82

**Therapeutic Category:** Anti-inflammatory and Analgesic agent.

**Physico Chemical Properties**

**Description:** Yellow, crystalline solid substance.
Melting Point: 225 - 230 °C

Partition Coefficient (Log P): 1.8

Solubility of Drug: Soluble in 0.05 N NaOH, slightly soluble in Chloroform. Soluble in methanol and in acetonitrile, insoluble in water.

Mechanism of Action: Lornoxicam inhibits prostaglandin biosynthesis by blocking the enzyme cycloxygenase leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. Lornoxicam inhibits both isoforms in the same concentration range, that is, the ratio of COX-1 inhibition to COX-2 inhibition is 1:1. It readily penetrates into the synovial fluid. The AUC ratio of synovial fluid to blood plasma is 0.5 after administration of 4 mg twice daily.

Pharmacokinetic Parameters:
Absorption: Lornoxicam is absorbed rapidly and almost completely from the gastric region of the gastrointestinal (g.i.) tract. Maximum plasma concentrations are achieved after approximately 1 to 2 hours. Food protracts the average time to maximum concentration from 1.5 to about 2.3 hours and can reduce the area under curve (AUC) by up to 20%.

Distribution: The absolute bioavailability of Lornoxicam is 90–100%. No first-pass effect was observed.
Metabolism:

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity. 

CYP2P9 has been shown to be the primary enzyme responsible for the biotransformation of the lornoxicam to its major metabolite, 5'-hydroxylornoxicam. 

Lornoxicam 5'-hydroxylation by the variants CYP2C9*3 and CYP2C9*13 is markedly reduced compared with wild type, both in vitro and in vivo. 

Excretion:

Approximately 1/2 to 2/3 is eliminated via the liver and 1/3 to 42% (data are inconsistent) via the kidneys as 5'-hydroxylornoxicam. 

Dosage and Administration:

4-16 mg daily through oral route.

Need for Sustained Release and Floating Tablets of Lornoxicam:

Lornoxicam has a short biological half-life of 3-5 h and is poorly soluble in acidic conditions, majorly absorbed from stomach. As such, it is an ideal drug candidate for formulation of sustained release floating tablets. 

Past Research Work on Lornoxicam Controlled Release Drug Delivery Systems:

Past Research Work on Lornoxicam Controlled Release Drug Delivery Systems is summarized in Table 4.1.
<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Type of floating/drug delivery system</th>
<th>Excipients/Polymers Used</th>
<th>Method</th>
<th>Reason/Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gastro-retentive floating sustained release matrix tablets</td>
<td>Hydroxypropyl methylcellulose K15M</td>
<td>Direct compression</td>
<td>Buoyancy lasted for up to 24 hrs was reported.</td>
</tr>
<tr>
<td>2</td>
<td>Lornoxicam loaded ethyl cellulose microspheres</td>
<td>Ethyl cellulose</td>
<td>Emulsion solvent evaporation</td>
<td>The result showed that the maximum yield of the microspheres was found to be 64.23 ± 0.25%, with particle size in the range of 64.24 ± 1.82 to 81.83 ± 3.43 μm and encapsulation efficiency was found to be in a range of 60.34 ± 1.63 to 3</td>
</tr>
</tbody>
</table>
It was concluded that Lornoxicam loaded ethyl cellulose microspheres formulation showed sustained effect over a period of 12 h.

Chronomodulated drug delivery system of lornoxicam Gelatin, NaCMC and Chitosan Emulsification, Suspension polymerisation and Emulsification solvent evaporation techniques. It was reported that a maximum of 95.75%, 87.68% and 68.40% drug entrapment efficiency was obtained in the Lornoxicam microspheres. The in vitro performance of Lornoxicam microspheres showed controlled release depending on the polymer concentration.

Bilayer tablets of Lornoxicam. HPMC K4M & HPMC K100M. Dry granulation method. Drug release of about 98% for 24 hr from sustained release layer was observed.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lornoxicam</td>
<td>Sustained Release Matrix Tablets</td>
<td>HPMC K4M, HPMC K15M, HPMC K100M</td>
<td>Direct compression, release followed zero order kinetics, best formulation quite stable, sustained release for prolonged periods of time as compared to other formulations, release followed zero order kinetics, best formulation found to be stable during stability studies for two months.</td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>Gastroretentive Floating Tablets</td>
<td>Okra Mucilage, HPMC K100M, Sodium alginate</td>
<td>Wet granulation, results showed incorporation of Okra mucilage into a floating tablet matrix positively affected swelling and buoyancy, swelling index increased to reach 221, 193, and 7</td>
</tr>
</tbody>
</table>
66.224% in comparison to 211, 182, and 208% respectively, the floating lag-time was shortened to be 0.23 minutes while the total floating duration was extended to exceed 12 hours. The drug release was retarded to be 85.3, and 75.7% in comparison to 97.7, and 93.4% respectively after 12 hr. It was concluded that the naturally occurring Okra mucilage is a promising additive to improve the floating and release properties of gastrotro retentive floating matrices.

Lornoxicam floating tablets. HPMC, Ethyl cellulose Melt granulation Sustained release of Lornoxicam over 10-12h in addition to good floating characteristics was observed.
Extended release matrix tablets HPMC K15M, Guar gum and Ethyl cellulose. Wet granulation. The influence of the ratio of HPMC K15M to Guar gum (hydrophilic polymers) and Ethyl cellulose (hydrophobic polymer) on Lornoxicam release from extended release matrix tablets was studied.

Sustained release tablets HPMC K100M and Eudragit RS 100. Wet granulation. It was observed that In vitro drug release profile for optimized formulation was at least 99% after 24 hours.
Respons surface graphs were presented to examine the effects of independent variables on the responses studied.

Sustained release microspheres were prepared using Ethyl cellulose as a polymer, Emulsion solvent and Emulsion disintegrant. The in-vivo study of microspheres demonstrated significant analgesic and anti-inflammatory activities of prepared microspheres for a longer period of time as compared to the standard drug. The microspheres showed minor changes (non-significant) in physical appearance, particle size with no appreciable change in drug content in different conditions of stability studies. Results also showed that no remarkable changes in the drug release from...
Results showed that the polymer concentration and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h) and its floating time (> 12 hr). The best results were obtained at the ratio of drug: HPMCK4M:HPMCK15 M (1:2:1.5). The developed floating microspheres of Lornoxicam used in clinic for prolonged drug release in stomach for at least 12 hrs., thereby improving the bioavailability, prevents degradation in stomach.
REFERENCES


Proprietary names:
Dilacor; Cardizem; Altiazem; Angize; Bruzen; Cardiem; Dilpral; Dilzem; Dilzene; Herbesser; Masdil; and Tildiem.

Chemical name:
(2S-cis)-3-(acetyloxy-5-[2-dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothiazepin-4(5H)-one monohydrochloride.

Molecular formula:
C_{22}H_{26}N_{2}O_{4}S·HCl

Molecular weight:
450.98 g/mole.

Therapeutic Use:
Anti-hypertensive

Dose:
30 mg 2 or 3 times a day

Bioavailability:
40 to 50%.

Half-life:
3–4.5 hrs

Volume of distribution:
3–8 l/kg

Clearance:
65 L/h

Protein binding:
80% in plasma.

Infra-red Spectrum:
Principal peaks at wave numbers 3056, 3035, 2966, 2837, 2393, 1743, 1679, 839, 781 cm^{-1}. 

Diltiazem is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has a short biological half-life of about 3.5 hours and is rapidly eliminated. It is favorably absorbed from the stomach, and the oral bioavailability is 40% in humans. 

Floating tablets of diltiazem were designed in the present study to enhance its bioavailability and to achieve sustained release over 12 hours for twice-daily administration.

Past Research on Floating Tablets of Diltiazem:

A few studies are reported on the formulation and evaluation of floating drug delivery systems of diltiazem. These are summarized in Table 4.2.

Table 4.2: Summary of Past Research Work on Floating Drug Delivery Systems of Diltiazem

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Type of floating drug delivery system</th>
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<th>Method</th>
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</tr>
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<tbody>
<tr>
<td>1</td>
<td>Sustained release gastroretentive floating tablets using effervescent drug form</td>
<td>Hydrophilic polymer like HPMC K4M, HPMC K15M and hydrophobic polymer</td>
<td>Direct compression</td>
<td>The extent of drug release was found to be around 99.81% at the desired time 12 hrs.</td>
</tr>
</tbody>
</table>
approach Ethyl cellulose. Controlled release floating tablets HPMC K100M, Starch acetate and Carbopol 934P. Melt granulation. Formulations exhibited floating over 44 to 48 h with a floating lag time of less than 36 sec. Also gave slow and controlled release of diltiazem over 24 h.

Bi-Layered Floating Tablets HPMCK100M, HPC, HEC and MC. Wet granulation. Rate of drug release from an immediate release layer was 99.9% were found at the end of 20 mins followed by sustained the drug release for 12hrs from sustained release layer.

Oral floating matrix tablet employing 2-factorial study. Hydroxypropylmethylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO. Direct compression. The results of factorial design indicated that a high level of both Methocel K100M CR (X₁) and Compritol 888 ATO (X₂) favors the preparation of floating controlled release of DTZ tablets. Comparable release
Alone or in combination and other standard excipients.

Profiles between the commercial product and the designed system were obtained.

Effervescent floating tablet using response surface methodology.

HPMC K100 M, Xanthan gum, Guar gum, alone or in combination

Direct compression The results of factorial design indicated that ratio of HPMC K100 M to Xanthan gum had dominant role on drug release from floating tablets.

All these formulations followed Korsmeyer and Peppas model.

Oral Sustained Release Gastro Retentive Floating tablets HPMC K4M, HPMC K100M, Carbopol 934, Ethyl cellulose, Xanthan gum Direct compression Optimum hardness, consistent weight uniformity and low friability and near-complete sustained release for Diltiazem HCl (90-100%) at the end of 24 h. A decrease in release kinetics of the drug was observed on increasing
polymer ratio.

Gastroretentive floating drug delivery tablets using Xanthan gum, kara ya gum, guar gum, and carrageenan. Formulations produced better sustained drug release (99.96%, 99.27% release in 24 h) and having good floating properties and showed better physical stability when stored at 40°C under 75% RH for 3 months.

Hydrodynamically balanced floating matrix controlled drug delivery system with HPMC K100LV, HPMC K4M, K15M, and carbopol. Direct compression formulation F containing equal ratio of HPMC K4M and K100LV showed optimum floating time and in vitro drug release of 82.19% at the end of 8 h.

Regioselctive floating tablets using HPMC K100M. Direct compression showed drug release at 6th hour was found to be 50.58±0.80, 45.68±0.59, 50.30±3.65, and 50.30±0.25 for F1, F2, F3, and F4.
The decrease in the release rate was observed with an increase in the polymeric system. Among the three viscosity grades of HPMC (K4M, K15M and K100M), HPMC K4M along with microcrystalline cellulose as diluent was found to be beneficial in improving the drug release rate and floating properties.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug Release Kinetics</th>
<th>Maximum Percentage of Drug Release</th>
<th>Prolonged Release Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4</td>
<td>Higuchi and Korsemeyer and Peppas' equation</td>
<td>99.87%</td>
<td>12 h</td>
</tr>
<tr>
<td>D4</td>
<td>Shows 99% drug release at the end</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wet granulation Drug release kinetics follow both Higuchi and Korsemeyer and Peppas' equation. The formulation A4 containing (HPMC K4M) shows maximum percentage of drug release (99.87%) and prolonged release for time period of about 12 h.
Tablets containing hydroxypropyl methylcellulose (HPMC) K4M, K15M, and K100M were used for floating tablets. In vitro drug release profile revealed an increase in drug:HPMC ratio resulted in retardation of drug release. Wet granulation Formulations produced better sustained drug release (99.96%, 99.27% release in 24 h) and had good floating properties. Kinetics of drug release from tablet followed the higuchi and korsmeyer.
Drug delivery system

Sodium alginate, Sodium carboxymethyl cellulose, polyox, methocel k100m in combination with methocel e6lv.

Abdominal x-ray imaging of formula f-6, loaded with barium sulfate, in eight healthy human volunteers revealed a mean gastric retention period of 5.50 ± 0.55 h.

Floating drug delivery system (tablet) HPMC K4M and HPMC K100M Wet granulation

Drug release (99.60%) and prolonged release of about 12 h was obtained. The release mechanism was found fickian type in most of the formulations.

Floating tablets Xanthan gum

Direct compression

The drug release data revealed that the formulation with low amount of xanthan gum (40% w/w) showed a low release rate compared to...
The formulations F2 and F5 (50% w/w) showed drug release of about 95.4 and 96.7%, respectively. Floating tablets polyvinyl alcohol and sodium carboxymethyl cellulose wet granulation. The floating lag time, time required to start floating, was found to be in between 124 to 206 seconds with a floating time of more than 24 h. In vitro drug release results were 43.56 to 59.42% in 8 h. Therefore, it is concluded that the GRDS can be exploited successfully for the delivery of diltiazem hydrochloride for the treatment of hypertension.
REFERENCES


