FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC TABLETS OF LORNOXICAM

A dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai 600032.

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

Reg. No. 26108309

under the guidance of
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COLLEGE OF PHARMACY

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Date:

This is to certify that the dissertation entitled **"Formulation and Evaluation of Controlled Porosity Osmotic Tablets of Lornoxicam"** submitted by the candidate bearing **Reg. No. 26108309** for **The Tamil Nadu Dr. M.G.R. Medical University** examinations.

Evaluated.

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CERTIFICATE

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Place: Chennai

Date:

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Prof. K. Elango, M.Pharm., (Ph.D.)

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Date:

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DEDICATED TO MY

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Table of Contents

LIST OF ABBREVATIONS

AE	Aerosil
BCS	Biopharmaceutical Classification System
CA	Cellulose Acetate
CPOP	Controlled Porosity Osmotic Pump
COX	Cyclo Oxygenase
DBP	Di Butyl Phthalate
EC	Ethyl Cellulose
EOP	Elementary Osmotic Pump
FTIR	Fourier Transformer Infra Red
GIT	Gastro Intestinal Tract
HPMC	Hydroxy Propyl Methyl Cellulose
LA	Lactose
LOX	Lornoxicam
ML	Mannitol
MOTS	Monolithic Osmotic Tablet System
MS	Magnesium Stearate
NC	No Change
NSAID	Non Steroidal Anti Inflammatory Drug
OA	Osteoarthritis
OPT	Osmotic Pump Tablet
PVP	Poly Vinyl Pyrrolidone
PEG	Poly Ethylene Glycol
PEO	Poly Ethylene Oxide
RA	Rheumatoid Arthritis

SEM	Scanning Electron Microscope
SLS	Sodium Lauryl Sulphate
SPM	Semi Permeable Membrane
SCMC	Sodium Carboxy Methyl Cellulose
SEOP	Swellable Elementary Osmotic Pump
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
TA	Talc
TR	Tromethamine
UV/VIS	Ultra Violet/ Visible
Cm	Centimetre
Kg	Kilogram
mg	Milligram
ml	Millilitre
mm	Millimetre
mcg	Microgram
nm	Nanometre

Introduction

INTRODUCTION

With increasing world population, the need for health care is increasing. For decades an acute disease or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, pills, creams, liquids, ointments, aerosols, injectables and suppositories. Presently these conventional dosage forms are primarily prescribed pharmaceutical products and available over-the-counter. To achieve and maintain the concentration of an administered drug within therapeutic effective range it is often necessary to take drug dosage several times and this result in a fluctuating drug levels in plasma. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms.

THREE BASIC MODELS OF DRUG DELIVERY

TARGETED DRUG DELIVERY

It refers to the systemic administration of a drug-carrier with the goal of delivering the drugs to specific cell types, tissues or organs.

A. MODULATED RELEASE SYSTEMS:

It implies the use of a drug delivery device that releases the drug at a variable rate controlled by environmental conditions, biofeedback, sensor input or an external control device.

B. CONTROLLED DRUG DELIVERY

It refers to the use of a delivery device with the objective of releasing the drug into the patient body at a predetermined rate, or at specific times or with specific release profiles.

Apparently, there has been an accelerating realization for the need of controlled drug delivery as evinced by the multitude of systems developed and under development. The drug therapeutic indices could be maximized while incidences of adverse reactions or side effects could be minimized by regulating the drug release in a well defined controlled manner. The latter eliminates or excludes haphazard and uncontrolled blood plasma profiles associated with

conventional dosage forms. With properly designed or customized systems the concentration of a drug substance in blood plasma pool and site of action follows an exquisite temporal pattern while extraneous sites receive minimal drug quantity resulting into an improve therapeutic performance. A variety of approaches and materials has been proposed, which could effectively be used in designing and construction of systems with potential to provide predictable, precise and reproducible pattern of controlled release or even site specific drug delivery. [1]

ORAL CONTROLLED DRUG DELIVERY

Oral route has been the commonly adopted and most convenient route for the drug delivery. By considering the conventional dosage form of a drug and the drug profile data, such as dose, absorption and elimination rate constants, metabolic properties, drug properties and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form. (Figure 1.1)

Controlled drug delivery is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. [2]

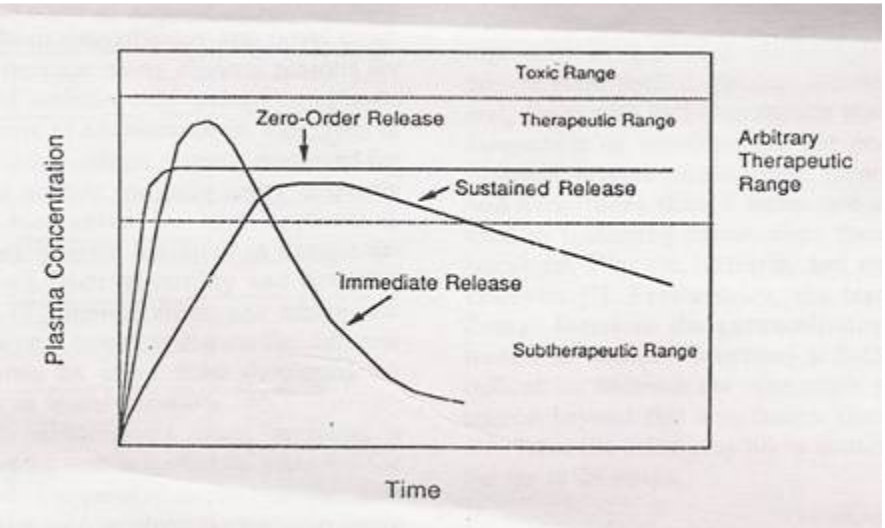


Fig. 1.1: Plasma drug concentration profile for Immediate, Sustained and Controlled release formulations

Advantages of controlled drug delivery[1]

- Controlled delivery of active agents at predetermined rate.
- Maintenance of optimal and effective drug level for prolonged duration.
- Reduction of untoward effects.
- Increase in patient compliance.
- Reduction in frequency of dosing.
- Delivery of drug in the vicinity of site of action.
- More efficient utilization of active agent.

Disadvantages of controlled drug delivery

- Dose dumping.
- Reduced potential for accurate dose adjustment.
- Need of additional patient education.
- Stability problem.

Classification of rate controlled drug delivery system[2-4]

Rate controlled drug delivery system

1. Activation modulated drug delivery system.
2. Feedback regulated drug delivery system.
3. Site specific drug delivery.

Activation modulated drug delivery system

In this group of Controlled drug delivery system the release of drug molecule from the drug delivery system is activated by some physical, chemical or biochemical processes.

CLASSIFICATION

1. Physical means

a. Osmotic pressure activated drug delivery system

b. Hydrodynamic pressure activated drug delivery system

c. Vapour pressure activated drug delivery system

d. Mechanically activated drug delivery system

e. Magnetically activated drug delivery system

f. Sonophoresis activated drug delivery system

g. Iontophoresis activated drug delivery system

h. Hydration activated drug delivery system

2. Chemical means

a. pH activated drug delivery system

b. Ion exchange drug delivery system

c. Hydrolysis activated drug delivery system

3. Biochemical means

a. Enzyme activated drug delivery system

b. Biochemical activated drug delivery system

OSMOTIC PRESSURE ACTIVATED DRUG DELIVERY SYSTEM

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semipermeable membrane. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent. Drug

delivery from these systems, to a large extent, is independent of the physiological factors of the GIT. These systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component, size of the delivery orifice and nature of the rate-controlling membrane. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate.

An osmotically dispersion formulation comprises of the following (Figure 1.2)

1. A water permeable membrane forming a part or all the walls of enclosure surrounding.

2. An activated agent.

3. An additive known as an osmotically attractant which together exhibit an osmotic pressure.

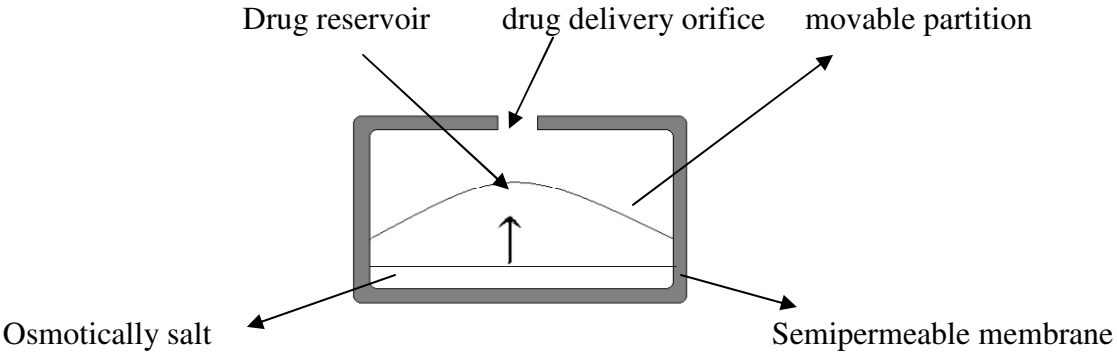


Fig. 1.2: Osmotic Drug Delivery System

When placed in aqueous environment water is osmotically drawn into the enclosure by the combined action of active component and movable partition which distend and swells and result in the release of drug from the orifice to the external environment. The rate of drug release is modulated by controlling the gradient of osmotic pressure. The intense rate of drug release **(Q/t)** is defined by equation (1)

$$\frac{Q/t = P_w A_m (p_s - p_c)}{h_m} \quad \text{---------- (1)}$$

Where:

P_w - Water permeability.

A_m - Effective surface area.

h_m - Thickness of the semipermeable housing.

(p_s - p_c) - Difference of osmotic pressure between the drug delivery system with osmotic pressure (p_s) and environment with osmotic pressure (p_c)

Historic back ground

The Rose Nelson pump

In 1955 two Australian Physiologist Rose and Nelson reported the first osmotic pump (Figure. 1.3). They were interested in delivery of drugs to the gut of sheep and cattle.

- A drug chamber with an orifice.
- A salt chamber with elastic diaphragm containing excess solid salt.
- A water chamber.

The drug and water chamber are separated by a rigid semipermeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into salt chamber. The volume of salt chamber increases because of this water flow, which distends the latex diaphragm separating salt and drug chamber there by pumping drug out of this device. The pumping rate of Rose-Nelson pump is given by the equation (2):

dm/dt = dv/dt*c ---------- (2)

Where:

dm/dt - Drug release rate.

dv/dt - Volume flow of water into salt chamber.

c - Concentration of drug into drug chamber.

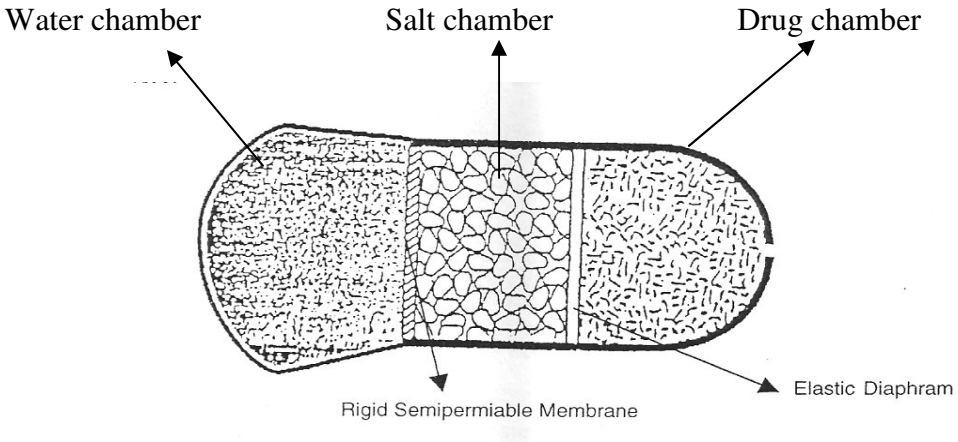


Fig. 1.3: Rose Nelson Pump

Higuchi Leeper pump

The design of Higuchi Leeper pump (Figure 1.4) represents the first simplified version of the Rose Nelson pump made by the Alza Corporation in the early 1970. The benefit of this pump over Rose Nelson pump is that it does not have water chamber and the device is activated by water imbibed from the surrounding environment.

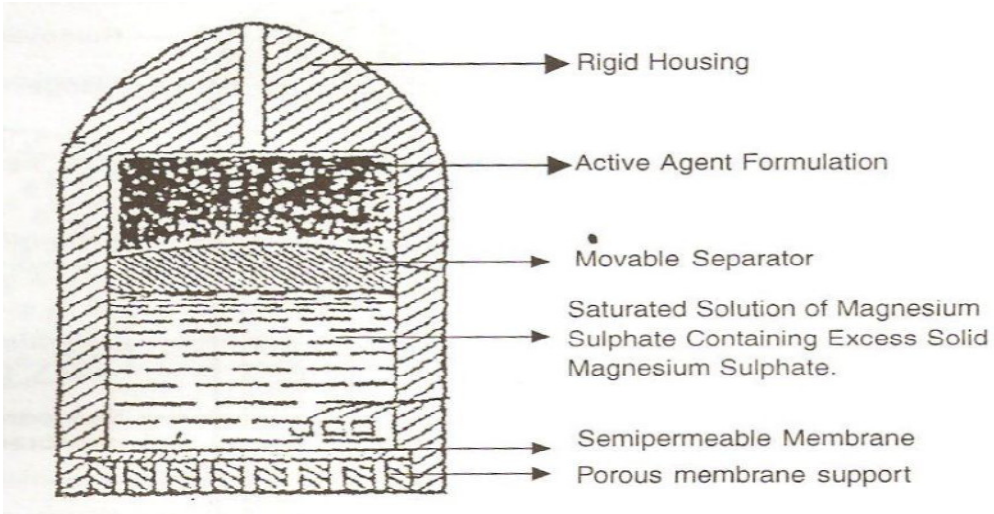


Fig. 1.4: Higuchi Leeper pump

Higuchi- Theeuwes pump

In the early 1970 Higuchi – Theeuwes developed a similar form of Rose Nelson pump (Figure1.5). The semi permeable wall itself act as a rigid outer casing of the pump .The device is loaded with drug prior to use. When the device is put in an aqueous environment the release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing.

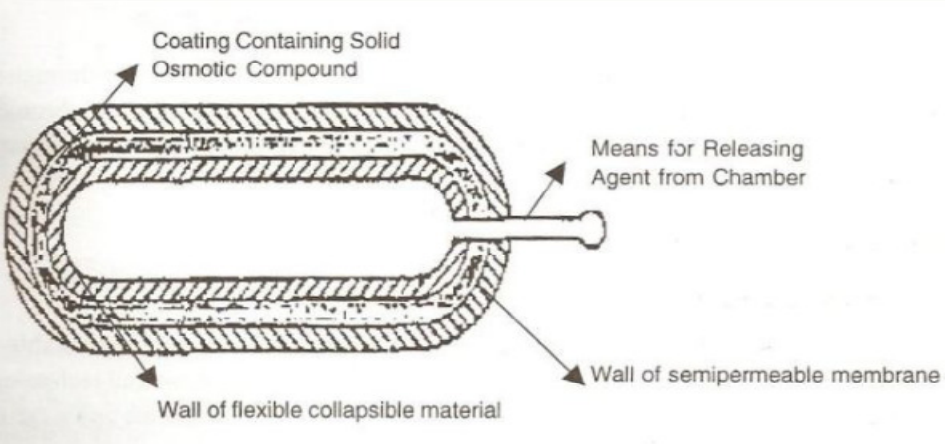
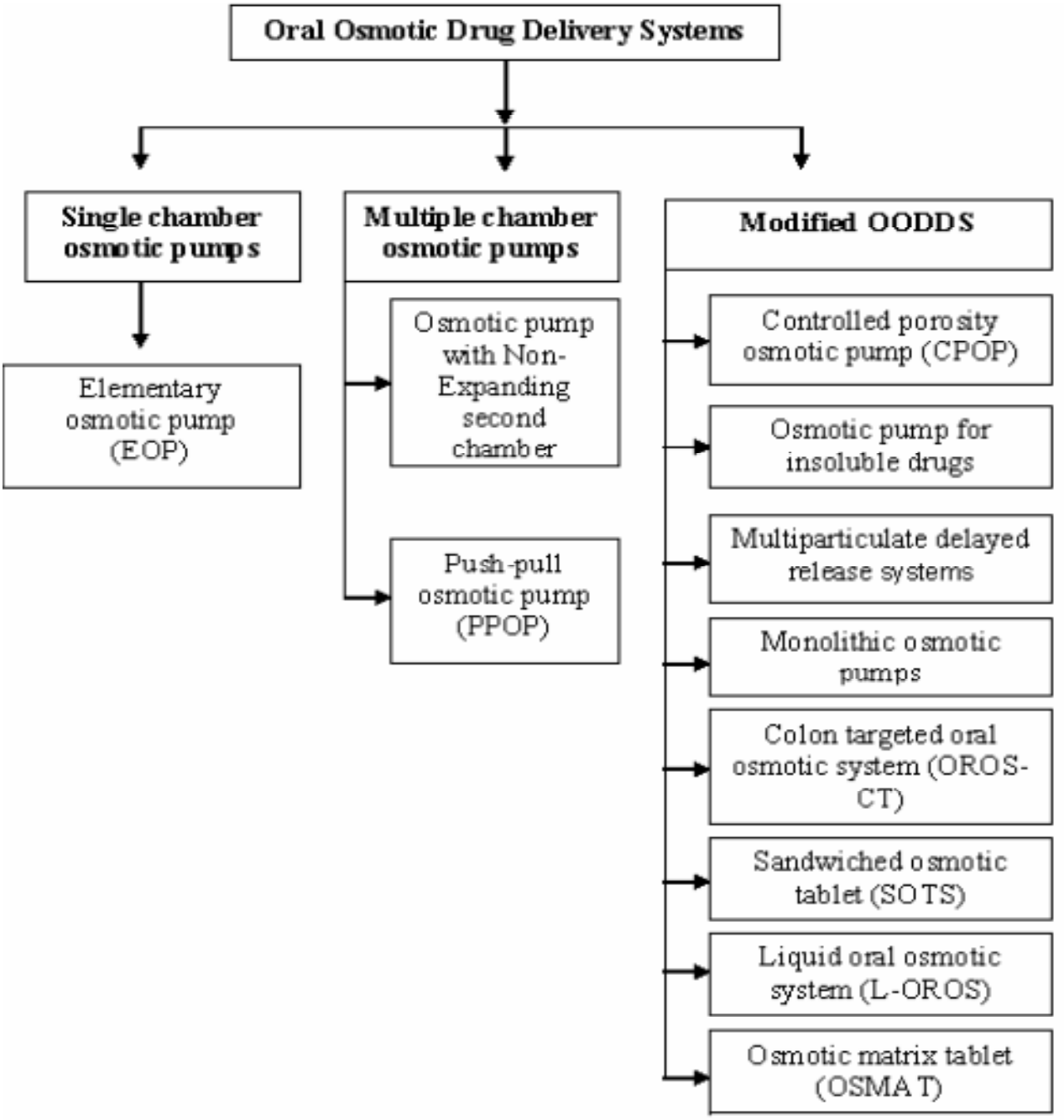


Fig. 1.5: Higuchi- Theeuwes pump

Classification of the Oral Osmotic Drug Delivery Systems

Oral osmotic drug delivery system can be classified as follows


Oral Osmotic Drug Delivery Systems
Single chamber osmotic pumps
Elementary osmotic pump (EOP)
Multiple chamber osmotic pumps
Osmotic pump with Non-Expanding second chamber
Push-pull osmotic pump (PPOP)
Modified OODDS
Controlled porosity osmotic pump (CPOP)
Osmotic pump for insoluble drugs
Multiparticulate delayed release systems
Monolithic osmotic pumps
Colon targeted oral osmotic system (OROS-CT)
Sandwiched osmotic tablet (SOTS)
Liquid oral osmotic system (L-OROS)
Osmotic matrix tablet (OSMAT)

TYPES OF OSMOTIC SYSTEMS AND THEIR MECHANISM

The design, mechanism and application of various types of osmotic system are shown in table 1.1.

Table 1.1: Different types of osmotic systems - Design, mechanism and uses

Osmotic System	Design of Dosage Form	Mechanism	Applications
Single chamber osmotic pumps			
Elementary Osmotic Pump (EOP)	**Core:** API ± osmogen. **Coat:** Semi permeable membrane with delivery orifice.	The water penetrates inside the dosage form. This results in formation of saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice present in the membrane.	**Moderately soluble** API 60- 80% constant release.
Controlled porosity osmotic pump (CPOP)	**Core:** API ± osmogen **Coat:** Semi permeable membrane containing water soluble additives	Delivery orifice is formed by the incorporation of a leachable component. Once the tablet comes in contact with aqueous environment, water-soluble additives dissolve and lead to the formation of a micro porous membrane. Water diffuses into the core through the	Poorly soluble drugs.

		micro porous membrane, creating an osmotic gradient. Thereby the release of drug is controlled	
Multi chamber osmotic pumps			
Sandwiched Osmotic tablets (SOTS)	**Core tablet:** 3 layers. Middle layer: push layer.2 attached layers of API **Coat:** Semi permeable membrane with two side delivery orifice	The middle push layer swells and drug is released from delivery orifices present on two sides of the tablet.	API release from two sides of tablets.
Push-pull osmotic pump (PPOP)	**Core Tablet:** Layer 1: API ± osmogent Layer 2: Polymeric osmotic agents **Coat:** Semi permeable membrane with delivery orifice.	After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer and thus releasing drug in the form of fine dispersion through the orifice.	For delivery of APIs having extremes of water solubility. Modifications can be done: - delayed push-pull - multi-layer push- pull - push-stick system

Controlled-Porosity Osmotic Pump (CPOP)

The CPOP is a spray-coated or coated tablet with a semi permeable membrane containing leachable pore forming agents. They do not have any aperture to release the drugs. Drug release is achieved through the pores, which are formed in the semi permeable wall *in situ* during the operation. In this system, the drug after dissolution inside the core is released from the osmotic

pump tablet by osmotic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane (Figure 1.6). The osmotic pressure is created either by an osmogen or by the drug itself or by a tablet component, after water is imbibed across the semi permeable membrane. This membrane after formation of pores becomes permeable for both water and solutes. A controlled-porosity osmotic wall can be described as having a sponge like appearance. The pores can be continuous that have micro porous lamina, interconnected through tortuous paths of regular and irregular shapes. Generally, materials (in a concentration range of 5% to 95%) producing pores with a pore size from 10 Å -100 µm can be used.

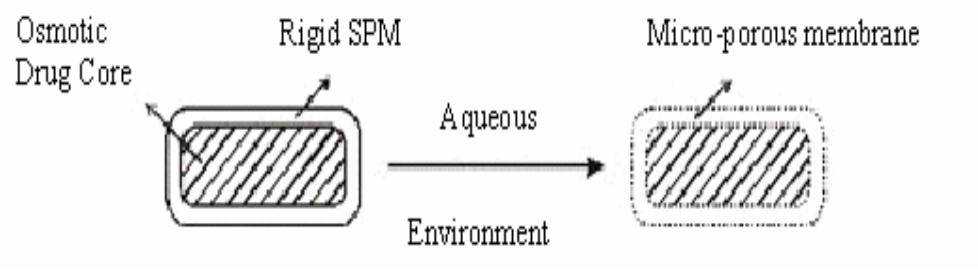


Fig. 1.6: CPOP tablet before and after dissolution studies

Basic components required for CPOP

a) Drug

b) Osmogen

c) Semi permeable membrane

d) Channeling agents or pore forming agent

Specifications for CPOP

The specification for developing CPOP is given in table 1.2.

Table 1.2: Specifications for controlled- porosity osmotic pump

S.No	Materials	Specifications
1	Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals).
2	Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients.
3	Core solubility	To get continuous uniform release of 90% or greater of the initially loaded core mass solubility S, to the core mass density, must be 0.1 or lower. Typically it occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.
4	Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material.
5	Surfactants	0 to 40, preferably 0.001to 40 parts per 100 parts of wall material.
6	Wall thickness	1 to 1000, preferably 20 to 500 µm
7	Micro porous nature Pore forming additives	5 to 95% pores between $10A^0$ to 100 µm diameter. 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer.

1. Criteria for selection of a drug:

i. Short biological Half-life (2- 6 hrs)
ii. High potency
iii. Required for prolonged treatment (Example: Nifedipine, Glipizide, Verapamil and Chlorpromazine hydrochloride)

2. Osmogen

Polymeric osmogen is mainly used in the fabrication of osmotically controlled drug delivery systems and other modified devices for controlled release of relatively insoluble drugs. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atmospheric pressure (atm) for sodium phosphate up to 500 atm for a lactose-fructose mixture (Table 1.3). These osmotic pressures can produce high water flows across semi permeable membrane.

Table 1.3: Osmotic Pressure of Saturated Solutions of Common Pharmaceutical Solutes

S.No	Compound or mixture	Osmotic Pressure(atm)
1	Lactose-fructose	500
2	Dextrose-fructose	450
3	Sucrose-fructose	430
4	Mannitol-fructose	415
5	Sodium chloride	356
6	Fructose	335
7	Lactose-sucrose	250
8	Potassium chloride	245
9	Lactose-dextrose	225
10	Mannitol	38

3. Semipermeable Membrane (SPM)

The membrane should be stable to both outside and inside environments of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogen is not lost by diffusion across the membrane. The membrane must be biocompatible. Some good examples for polymeric materials that form membranes are cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose and Eudragit.

Ideal properties of SPM

a) The material must possess sufficient wet strength (10^{-5} Psi) and wet modules so (10^{-5} Psi) as to retain its dimensional integrity during the operational lifetime of the device.
b) The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
c) The reflection coefficient or "leakiness" of the osmotic agents should approach the limiting value of unity.

4. Channeling agents/ leachable pore forming agents

These are water-soluble components which play an important role in the controlled drug delivery systems. When the dissolution medium comes into contact with the semi permeable membrane it dissolves the channeling agent and forms pores on the semi permeable barrier. Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis. Some examples of channeling agents are Polyethylene glycol (PEG) 1450, Mannitol, Bovine serum albumin (BSA), Diethyl phthalate, Dibutylphthalate (DBP) and sorbitol.

Advantages of oral controlled osmotic drug delivery system (OCODDS)

1. Provides Zero-order delivery rate.
2. Delayed or pulsed drug delivery is obtainable with osmotic system.
3. The delivery rate is significantly greater than that attainable with diffusion based systems of comparable size.
4. *In vitro* delivery rate can be accurately predicted using mathematical equations, which in turn, bears high degree of correlation with *in vivo* delivery rate.
5. Delivery rate is independent of pH variations in the environment, including those in the gastrointestinal tract (GIT).
6. Delivery rate is independent of agitation outside, including GI motility.
7. Release rate from osmotic system is highly predictable and programmable.
8. Delivery of drug takes place in the solution form ready for absorption, with osmotic pump simulating as a liquid dosage form prepared *in-situ*.
9. Delivery rate is almost independent of delivery orifice size within limits.
10. Drugs with widely varying solubility can be incorporated.
11. The device is relatively simple to fabricate using conventional pharmaceutical manufacturing equipment.
12. Drug release from the osmotically controlled oral drug delivery system exhibits significant *in vitro-in vivo* correlation [*IVIVC*] within specific limits.

Disadvantages

1. Drug release from the osmotic systems is affected to some extent by the presence of food.
2. Retrieval of therapy is not possible in case of unexpected adverse events.

Patents related to Controlled porosity osmotic pump

The Patents related to CPOP is given in table 1.4 and the commercially available osmotic systems are given in table 1.5.

Table1.4: Patents related to Controlled porosity osmotic pump

S.No.	U.S. Patent number	Type of osmotic system
1	4,968,507	Controlled porosity osmotic pump.
2	4,880,631	Controlled-porosity osmotic pump of Diltiazem L-maleate.
3	4,256,108	Micro porous semi permeable laminated osmotic system.
4	4,160,452	Osmotic system having laminated wall comprising of semi permeable lamina and micro porous lamina.
5	4,340,054	Semi permeable membrane consisting of impregnated micro porous membrane.
6	4,450,198	Semi permeable membrane consisting of a micro porous film impregnated with a hydrophilic polymer.
7	4,946,686	Controlled-porosity solubility modulated osmotic pump for delivering of drug having low water solubility.
8	4,994,273	Controlled-porosity solubility modulated osmotic pump for delivering of drug having low water solubility.

Table 1.5: Marketed products of different osmotic systems

Product Name	Active ingredient	Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Alpress LP	Prazosin	Push Pull	2.5-5mg
Cardura XL	Doxazosin	Push pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240mg
Ditropan XL	Oxybutynin chloride	Push Pull	5, 10 mg
Dynacirc CR	Isradipine	Push Pull	5, 10 mg
Efidac 24	Chlorpheniramine meleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push – Pull	5, 10 mg

Review Of Literature

REVIEW OF LITERATURE FOR OSMOTIC DRUG DELIVERY SYSTEMS

1. **Shahla Jamzad et al.**[5] developed a new monolithic matrix system to completely deliver Glipizide, a BCS Class II drug in a zero order manner over an extended time period. Two approaches were examined using drug in formulations that contain swellable Hydroxyl Propyl Methyl Cellulose (HPMC) or erodible Poly Ethylene Oxide (PEO). The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. As a result it was concluded that there was a linear release of Glipizide, similar to the profile of the commercial Glucotrol XL. The kinetics of drug release was shown to be in accordance with kinetics of hydration/swelling in HPMC-based formulation, while in PEO system erosion kinetics dominated the release operation.

2. **Mothilal et al.**[6] formulated Osmotic drug delivery system (ODDS) for Metoprolol Succinate using different concentrations of mannitol by wet granulation technique. The tablets were coated by dip coating with Cellulose acetate and stainless steel drill pins were used to make an orifice on the tablets and the orifice diameter was examined using scanning electron microscopy (SEM). As a result of *in vitro* release study it was concluded that rate of drug release were found to be increasing with increase in osmogen content and bore size and the optimum orifice diameter was identified to be 0.8 mm to give a zero order release.

3. **En-Xian Lu et al.**[7] designed a monolithic osmotic tablet system (MOTS) of Naproxen, a water insoluble drug with two orifices in both side surfaces. Gum Arabic was used as an osmotic, suspending and expanding agent. Cellulose acetate (CA) was used as semipermeable membrane with PEG-400 as a plasticizer. The influences of gum Arabic, PEG-400, membrane thickness and orifice size on the Naproxen release profiles were investigated and the optimal MOTS was evaluated in different environment media and stirring rates. As a result of this study, optimal MOTS was found to be able to deliver Naproxen at a rate of approximately zero order up to 12 h , independent on environment media and stirring rate and it was concluded that this MOTS can be used in oral drug- controlled delivery especially for water-insoluble drug.

4. Rashmin Thakor et al.[8] developed and evaluated an oral monolithic osmotically controlled delivery system for Nifedipine using asymmetric membrane technology. Asymmetric membrane is formed by dry process with phase inversion technology using CA as the coating material. Higher water influx of this membrane aids in delivery of Nifedipine, which is highly water insoluble with low osmotic pressure. The porous structure of the membrane was confirmed by SEM. *In vitro* release studies showed that as the concentration of osmotic agent increases, the drug release was also enhanced and independent of external agitation and pH of dissolution media.

5. Basani Gavaskar et al.[9] formulated elementary osmotic pump tablets (EOPT) of water soluble Tramadol HCl by wet granulation method, coated with CA solution containing varying amount of DBP and PEG-400. The optimized formulation of Tramadol EOPT was obtained by orthogonal designs based on the single factor influence test. It was evident from the result that the rate of drug release can be controlled through osmotic pressure of the core, the level of pore former and membrane weight with release to be fairly independent of pH and hydrodynamic conditions of the body.

6. Javad Shokri et al.[10] designed a new type of Swellable Elementary Osmotic Pump (SEOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs like Indomethacin. SEOP tablets were prepared by compressing the mixture of micronized drug and excipients into convex tablets. The results showed that the concentration of wetting agent in the core formulation was a very important parameter in release pattern of Indomethacin from SEOP system. Increasing the amount of wetting agent to an optimum level (60 mg) significantly increased the drug release and improved zero order release pattern of Indomethacin. Increasing concentration of castor oil (hydrophobic) in the Semipermeable Membrane of the device or hydrophilic plasticizer (glycerin) in coating formulation markedly increased the lag time and decreased the drug release.

7. Longxiao Liu et al.[11] developed a method for the preparation of Atenolol MOPT by coating the indented core tablet compressed by the punch with a needle. Formulation contains sodium chloride as osmotic agent, PEO as suspending agent and ethyl cellulose (EC) was employed as semipermeable membrane containing PEG 400 as plasticizer. The formulation was optimized by orthogonal design and evaluated by similarity factor (f2). It was evident from the result that the indentation size of core tablet hardly affected drug release in the range of (1.00–1.14) mm. The optimal osmotic tablet was found to be able to deliver Atenolol at an approximately constant rate up to 24 h, independent of both release media and agitation rate.

8. Jin Guan et al.[12] developed a novel Famotidine gastric resident osmotic pump tablet containing Pharmaceutical iron powder as gas formation and density increasing agent. Central composite design response surface methodology was used to investigate the influence of factors, like PEO (Mw 1,000,000) content, sodium chloride content, iron powder content and weight gain, on the responses including ultimate cumulative release and correlation coefficient of drug release profile. A second order polynomial equation was fitted to the data and actual response values are in good accordance with the predicted ones. The optimized formulation displayed a complete drug delivery and zero order release rate. Gamma scintigraphy was selected as the method to monitor *in vivo* gastric residence time of the 99mTc labeled system in Beagle dogs. It was observed that the system can retain in stomach for an extended period of 7 h after administration compared with conventional tablets.

REVIEW OF LITERATURE FOR CONTROLLED POROSITY OSMOTIC DRUG DELIVERY SYSTEMS

9. Gaylen M Zentner et al.[13] investigated the zero-order release of water soluble, Osmotically active agents from tablets coated with controlled porosity walls. The rate of drug release was a function of the wall thickness, level of leachable additives incorporated and permeability of the polymer component of the walls, the total solubility of the core tablet, the drug load and the osmotic pressure difference across the wall. Release was not affected by the pH and degree of agitation in the receptor media.

10. The release kinetics from controlled porosity osmotic pumps (CPOP) was manipulated by **Gaylen M Zentner et al.**[14] The solubility of Diltiazem Hydrochloride was reduced for an extended period of 12-14 hours through incorporation of sodium chloride into the core. Other Diltiazem Hydrochloride core tablet containing the positively charged anion-exchange resin (Poly (4-vinylpyridine)) was prepared. In both instances, *in vitro* Diltiazem Hydrochloride release profile was zero-order and pH-independent.

11. A cellulose acetate latex was modified for use as a microporous coating for osmotic devices by **Leah E Appel et al.**[15] Potassium chloride core tablets were coated with a CA latex formulation containing a plasticizer, Triacetin and a pore-former, Urea. The results indicated that the urea content was the most important variable factor, followed by Triacetin content and cure time. Cure temperature was not found to affect the results. The *in vitro* drug release and burst strength results agreed with those predicted by the model.

12. Russell U Nesbitt et al.[16] studied the release of water soluble substrates from Aquacoat coated pellets through water-filled channels. Each pellet worked like a mini osmotic pump. The energy was supplied by the osmotic pressure differences between the internal medium of the coated pellets and the external dissolution medium. The drug release was dependent on the substrate solubility and the osmotic pressure of the dissolution medium.

13. Kazuto Okimoto et al.[17] developed a CPOP tablet for poorly water soluble drug (Prednisolone) using a sulfobutyl ether-β-cyclodextrin, (SBE)7m- β -CD or Captisol, which acted both as a solubilizer and an osmogen. The results showed that the drug release tablet with (SBE) 7m- β -CD was complete. Hence Captisol modified the input rate of Prednisolone without affecting oral bioavailability.

14. Rajagopal Kumaravelrajan et al.[18] formulated a CPOP system to deliver Nifedipine (NP) and Metoprolol (MP) in a controlled manner up to 12h. It was prepared by incorporating drugs in the core and coated with various types Poly vinyl pyrrolidone (PVP), PEG-400 and HPMC and levels (30, 40 and 50% w/w of polymer) of pore former at a weight

gain of 8, 12 & 15%. This study suggested that drug release from these systems is controlled by osmotic pressure as the major mechanism; release pattern followed zero order kinetics and independent of environmental medium and the mobility of gastrointestinal tract and it was concluded that drug release was directly related to the level of pore former and inversely proportional to the membrane weight gain.

15. Sapna N Makhija et al.[19] described a CPOP of Pseudoephedrine (half life 5–8 hours) containing sodium bicarbonate as osmogen and CA as semi permeable membrane. Different channeling agents tried was dibutylsebacate, diethylphthalate, DBP and PEG 400. It was found that the rate increased with the amount of osmogen due to increased water uptake.

16. Rajan K Verma et al.[20] developed extended release Isosorbide Mononitrate tablets based on osmotic technology. Formulation variables like (PVP, PEG-4000, and HPMC) and level of pore former (0–55% w/w of polymer), percentage weight gain were found to affect the drug release. Release was dependent on membrane weight, level of pore former in the membrane, osmotic pressure of the dissolution media and independent of pH and agitational intensity.

17. Pritam Kanagale et al.[21] designed an osmotic pump tablet for controlled release of Oxybutynin for 24 hours. The osmotic pump contains water-soluble pore-former in the semipermeable membrane (CA) which dissolves after coming in contact with water, resulting in an *in situ* formation of a microporous structure. This osmotic pump was found to deliver Oxybutynin at a zero order rate for upto 20 hours.

18. Controlled porosity osmotic pump tablets of Glipizide were developed by **Mahalaxmi R et al.**[22] The effect of level of wicking agent, solubilizing agent, pore former and membrane weight gain on *in vitro* release rate were studied. Drug release was directly proportional to the pore former (sorbitol), inversely proportional to weight gain of the membrane, independent of pH and agitational intensity but dependent on osmotic pressure of the release media.

19. Anil Chaudhary et al.[23] developed microporous bilayer osmotic tablet bearing Dicyclomine Hydrochloride and Diclofenac Potassium using a new oral drug delivery system for colon targeting. The tablets were coated with micro-porous semipermeable membrane and enteric polymer. The colon-specific biodegradation of pectin could form *in situ* delivery pores for drug release. The effect of formulation variables like inclusion of osmogen, amount of HPMC and SCMC in core, amount of pore former in SPM was studied. *In vitro* dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h.

20. Prakash Rao B et al. [24] formulated a swellable controlled porosity osmotic pump tablet of Theophylline. The core tablets were spray coated with ethyl cellulose (EC) solution containing varying amounts of PEG 400 and plasdone. The results indicated that the release rate of Theophylline was directly proportional to the levels of osmotic agent, solubilizing agent and pore former in the tablet core and the membrane respectively. The preparation was facilitated by coating the core tablet with pore forming agent, thus eliminating the need for the more expensive laser drilling.

21. Ji-Eon Kim et al.[25] studied the effect of various pore formers on the controlled release of an antibacterial agent from a polymeric device. Cefadroxil was chosen as the model antibiotic and was incorporated into a polyurethane matrix by the solvent-casting method. PEG 1450 or D-mannitol, or bovine serum albumin (BSA) was used as a pore former. The morphological changes in the matrices before and after release studies were investigated by SEM. Changing the weight fraction and particle size of the pore formers/drug mixtures could control the release of Cefadroxil from the matrix. The release rate of Cefadroxil increased as the loading dose of the pore former increased (15<20<25%).

22. Rajan K Verma et al.[26] studied the formulation aspects in the development of osmotically controlled oral drug delivery systems. In this review, different types of oral osmotic systems, various factors governing drug release from these systems and critical formulation factors were discussed.

23. Sudeesh Edavalath et al.[27] designed a porous osmotic pump tablet of Diclofenac sodium using D-Optimal study design and numerical optimization method was used to find out the best formulation. Osmotic agent sodium chloride and pore former PEG-400 were considered as independent variables. The influence of pH and agitational intensity on drug release was studied. As a result of D-Optimal and ANOVA study it was concluded that osmotic agent and pore former have significant effect on the drug release upto 24hrs.

24. Hui Liu et al.[28] developed a microbially triggered colon-targeted osmotic pump of Budesonide based on both the gelable property at acid conditions and colon-specific biodegradation of chitosan. The effects of different formulation variables were studied to select the optimal formulation. From the study it was concluded that Budesonide release from the developed formulation was directly proportional to the initial level of pore former, but inversely related to level of pH modifier (citric acid) which affected the viscosity of chitosan solution, resulting in the change of osmotic pressure in the core tablets. The amount of chitosan in core formulation had a profound effect on the amount of drug release.

25. Farheen F et al.[29] developed a microbially triggered colon-targeted osmotic tablets of Prednisolone using different polymers like chitosan, xanthan gum and pectin by wet granulation method and coated with an inner semi permeable layer of EC with chitosan as pore forming agents and an outer enteric layer of Eudragit L 100-55. The *in vitro* dissolution study indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 18h. The release was influenced by the type and amount of polymer and the percentage of chitosan in SPM and it was concluded that among the different polymers used, chitosan was found to be more suitable for colon targeting.

REVIEW OF LITERATURE FOR USING SOLUBILITY ENHANCERS

26. Meiying Ning et al.[30] obtained a method for the preparation of Vinpocetine(VIN) elementary osmotic pump tablet by adding organic acid additives to increase VIN solubility. From the *in vitro* and *in vivo* release study it was concluded that the VIN dissolution was increased with increasing the amount of citric acid.

27. Deelip Derle et al.[31]developed numerous approaches for solubility enhancement of BCS class II drugs. Various particle engineering processes like super critical fluid technology, cryogenic technology, nanomilling, evaporative precipitation into aqueous solution, melt sono crystallization and cryo-vacuum etc., were developed based on the drug properties and requirement of nanoparticles characters. From the study it was concluded that the use of these processes has improved *in vitro* dissolution rates and *in vivo* bioavailability of many poorly water soluble drugs.

28. Kapoor Devesh et al.[32] used solubility enhancer SLS, HPMC and osmogen (mannitol) to enhance the solubility and osmotic pressure in CPOP of Valsartan. As a result of the study, the release of Valsartan increased with increasing the amount of SLS, HPMC and mannitol.

29. Kumar P et al.[33] investigated a method to increase the solubility of Naproxen(NS) in elementary osmotic pump by using different solubility enhancers. The findings of this study concluded that the rate and extent of NS release were found to be dependent on different osmogen, SLS, and sodium bicarbonate in the core formulation of Elementary Osmotic Pump and independent of agitational intensity of release medium.

30. Roger A Rajewski et al.[34] studied the membrane controlling factors responsible for drug release from a CPOP tablet that utilizes sulfobutyl ether cyclodextrin, $(SBE)_{7m}$ β -CD, both as solubilizing agent and osmogen. The release rate of Chlorpromazine from OPTs containing $(SBE)_{7m}$ β -CD increased with increasing amounts of micronized lactose and decreasing amounts of triethyl citrate. The effect of lactose particle size in the membrane on drug release was studied.

31. Roger A Rajewski et al.[35] investigated the application of CPOP tablet utilizing $(SBE)_{7m}$ β CD both as a solubilizer and an osmotic agent for drugs with varying physical properties. CPOP tablets utilizing $(SBE)_{7m}$ β CD were prepared for five poorly soluble drugs such as Prednisolone, Estradiol, Naproxen, Indomethacin and Chlorpromazine and for two highly water soluble drugs such as Diltiazem Hydrochloride and Salbutamol Sulfate.

It was found that for the soluble drugs (SBE) $_{7m}$ β -CD acts primarily as an osmotic and an OPT control agent. Significantly, (SBE) $_{7m}$ β CD not only enhances the delivery of poorly soluble drugs from OPTs but acts as a controlling excipient for soluble drugs such that the release rate, corrected for tablet surface area, of both poorly soluble and soluble drugs are similar.

32. Stella J et al.[36] developed CPOP system for poorly watersoluble drugs such as Testosterone using sulfobutyl ether -cyclodextrin (SBE)$_{7m}$β CD sodium salt, which can act as both a solublizing agent and an osmogen. The effect of (SBE) $_{7m}$β -CD as the solubilizing and osmotic pump agent was compared with Hydroxypropyl- β -cyclodextrin (HP-β CD), a neutral cyclodextrin, and a sugar mixture (osmogen only). Testosterone release from the device was significantly faster with (SBE) $_{7m}$ β CD than with HP β CD or the sugar mixture. It was concluded that (SBE) $_{7m}$ β CD provides novel properties for the development of CPOP tablet for poorly soluble drugs.

33. Gaylen M et al.[37] studied the application of either solubility or resin-modulated method to effectively manipulate drug release kinetics from CPOPs. These solubility-modulated devices administered to dogs release Diltiazem Hydrochloride with similar *in vivo / in vitro* kinetics. These approaches may be applicable to extend osmotic pump technology to drugs with intrinsic water solubility that is too high or low for conventional osmotic pump formulation.

34. Philip AK et al.[38] developed an asymmetric membrane capsular system, formed *in situ,* for poorly water soluble drug, Ketoprofen and evaluated it by both *in vitro* and *in vivo* methods for osmotic and controlled release of the drug. Membrane characterization by SEM showed an outer dense region with less pores and an inner porous region for the prepared asymmetric membrane.

35. Longxiao Liu et al.[39] developed a method for the preparation of monolithic osmotic pump tablet was obtained by modulating atenolol solubility with acid and employed

sodium chloride as osmotic agent and polyvinyl pyrrolidone as retardant agent. EC was employed as SPM containing PEG 400 as plasticizer. The formulation of Atenolol MOTS was optimized by orthogonal design and evaluated by similarity factor (f2). The influences of tartaric acid, PVP, sodium chloride and membrane thickness on drug release profile were investigated to determine significant associations of factors based on the L orthogonal design. From the study it was concluded that the optimal monolithic osmotic pump tablet was able to deliver Atenolol at the rate of approximate zero-order up to 24 h, independent of release media and agitation rate.

REVIEW OF LITERATURE FOR LORNOXICAM

36. Yassin El-Said Hamza et al.[40] formulated an extended release matrix tablets of Lornoxicam (LOX) using different grades of HPMC K4M, K15M, K100M as a matrix former. Matrix tablets were prepared by direct compression and the effect of two basic pH-modifiers, sodium bicarbonate and magnesium oxide, on the release characteristics of Lornoxicam from the prepared hydrophilic matrices was investigated. All the matrices prepared using different viscosity grades of HPMC employed at concentrations of 25% and 30% showed comparable release profiles. Results obtained demonstrated that tablets composed of 15% of HPMC K15M and 10% sodium bicarbonate, possessed acceptable physical properties and elicited the required *in vitro* release pattern.

37. Hariprasanna RC et al.[41] prepared bi-layer tablet of Lornoxicam (LOX) for the effective treatment of arthiritis. The tablets were formulated as immediate release layer and sustained release layer using hydrophilic matrix polymer sodium alginate by wet granulation method. It is evident from the results that a matrix tablet prepared with sodium alginate and binding agent (PVP 4% w/v) is a better system for twice -daily sustained release of a highly water-insoluble drug like LOX.

38. Ganesh N S et al.[42] formulated chronomodulated drug delivery system of Lornoxicam to prolong its duration of action and thus reduce the frequency of usage and to minimize its irritant effect on the stomach. Nine formulations of Microspheres of LOX were formulated at

various drug: polymer ratio by emulsification, suspension polymerization and emulsification solvent evaporation techniques by using polymers like Gelatin, SCMC and Chitosan respectively. From the *in vitro* release study it was concluded that natural polymers like Gelatin, SCMC and Chitosan can be successfully used for the chronomodulated drug delivery system of LOX for the effective treatment of arthritis, where morning stiffness is more prominent.

39. Metker Vishal et al.[43] prepared mouth dissolving tablets of Lornoxicam by wet granulation technique using KYRON T-314 as superdisintegrant and menthol as subliming agent. It can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets using KYRON T-314 disintegrate within few seconds without need of water; thereby enhancing the absorption leading to its increased bioavailability.

40. Phani Kumar et al.[44] formulated Lornoxicam matrix tablets by wet granulation method by using 10%, 20%, 30% and 40% Tamarind Seed Polysaccharide (TSP) as a natural binding agent and its optimized batch was compared with maximum ratio of various binders (HPMC K4M, SCMC, Guar Gum). After 24 hours release study tablets with 20% TSP binder showed maximum drug release (99.45%) and tablets with 40% TSP binder showed minimum drug release (62.55%). It was concluded that matrix tablet containing 20% TSP binder release the drug which follows Zero order kinetics via, swelling, diffusion and erosion.

41. Fawzia Habib et al.[45] formulated mucoadhesive buccal patches of Lornoxicam using different polymers including, Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), HPMC, chitosan, polyvinyl alcohol (PVA), gelatin, sodium alginate and SCMC. The *in vitro* release study and drug permeation study was conducted. It was concluded that Gelatin, Sodium alginate and SCMC patches showed the highest drug release rate of the drug *in vitro* and more drug permeation through rabbit buccal mucosa than other formulations.

42. Gülgün Yener et al.[46] prepared transdermal film formulations for Meloxicam (MX) and Lornoxicam using different polymers. From the study it was concluded that HPMC as a polymer and propylene glycol (PG) as a plasticizer provided best release profile. *In vivo* studies on rats employed for the assessment of anti-inflammatory effect indicated that MX and LOX transdermal patches gave satisfactory results regarding the edema inhibition. All those results were supported by *ex vivo* penetration study in that effects of log P, molecular weight, pKa and solubility constraint of the relevant drugs were considered.

43. Sheth SK et al.[47] developed a taste masked oral disintegrating tablet of poorly soluble Lornoxicam by direct compression technique with β cyclodextrin complexes using various super disintegrants. Results suggested that formulation containing complexing drug with BCD in 1:2 ratio, and with 7.5% of croscarmellose sodium masked bitter taste of drug and satisfy all the criteria of oral disintegrating tablet.

44. Kavitha K et al.[48] developed and evaluated matrix type transdermal patches of Lornoxicam using different polymers like HPMC and EC in different ratios by solvent evaporation technique. From the study it was concluded that formulation with combination of polymers (1:1) showed maximum release in 24 hours.

45. Vinod Dube et al.[49] developed sustained release matrix formulation of Lornoxicam targeted to colon using different concentration of HPMC and EC by direct compression method. From the study it was observed that 10% of each polymer in combination was able to produce desire formulation which releases more than 90% of drug in 10 hours.

46. Yassin El-Said Hamza et al.[50] developed new directly compressed, double-layer tablets (DLTs) of Lornoxicam. Each of the proposed DLTs is composed of a fast-release layer and a sustained release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect. An amorphous, freeze-dried inclusion complex of Lornoxicam with Hydroxypropyl-β-cyclodextrin, present in 1:2 (drug/cyclodextrin) molar ratio was employed in the

fast-release layer to enhance the dissolution of LOX in the stomach. Xanthan gum (XG), a hydrophilic matrix-forming agent, was integrated in the sustained-release layer. DLTs composed of sustained-release layer (40% XG) to fast-release layer in 2:1 weight ratio and those composed of sustained-release layer (50%XG) to fast-release layer in 1:1 weight ratio showed the desired release profile.

REVIEW OF LITERATURE FOR THE ANALYSIS OF LORNOXICAM

47. Bhupendra Singh et al.[51] developed a simple spectrophotometric method for the determination of Lornoxicam in pharmaceutical tablet dosage form. From these characteristics of the proposed method, it was found that LOX follow linearity within the concentration range of 1-20mcg and it was found that the percentage recovery values of pure drug from the analyzed solution of formulation were in between 95.01 to 124 which indicates that the proposed method is accurate and also reveals that the commonly use excipients and additives in the pharmaceutical formulation were not interfering in the proposed method. Hence, concluded that this method can be used for the routine determination of LOX in pure and pharmaceutical formulation.

48. Kondawar MS et al.[52] developed a new simple, accurate, precise and economic spectrophotometric methods in UV/VIS region for the determination of Paracetamol (PARA) and LOX in bulk and tablet formulations. The developed method was validated in terms of parameters like accuracy, precision, linearity, and limit of detection and limit of quantitation in this method, the overlain spectra of drugs showed the λmax of 235 nm and 376 nm for PARA and LOX respectively. The percent recoveries were found near to 100% for both the drugs showed the absence of interference indicating that the method is precise and reproducible. The method was found to be precise as % RSD for precision were < 2. Hence the method was found to be economic, simple and rapid, and can be employed for routine analysis in quality control laboratories.

49. Atul R Bendale et al.[53] developed a new spectrometric method for Lornoxicam estimation in tablet dosage form with good accuracy, simplicity and precision. From the study

it was concluded that Lornoxicam obeyed linearity in the concentration range of 5-30mcg and the proposed method was statistically validated.

50. Nilesh Jain et al.[54] developed a spectrometric method for simultaneous estimation of Lornoxicam and Paracetamol in tablet dosage form. The methods employed were Absorbance ratio method and simultaneous estimation method. These methods were developed based on the simultaneous estimation of drugs in a binary mixture without previous separation. From the study it was concluded that LOX and PARA obeys Beer's law in the concentration range of 8-40mcg/ml and 10-50mcg/ml respectively. Thus the proposed method was validated and successfully applied for simultaneous determination of LOX and PARA in tablet dosage form.

Aim & Plan Of The Work

AIM OF THE WORK

Lornoxicam (LOX) is a mainstay Non Steroidal Anti Inflammatory Drug (NSAID) for the treatment of inflammatory diseases like Rheumatoid Arthritis (RA) and Osteoarthritis (OA). But this drug has shorter half life (3-4 hours) and induces side effects when used for long term. The aim of the present study is

1. To formulate controlled porosity osmotic tablets of LOX using mannitol as osmogen.
2. To increase the solubility of LOX using tromethamine as solubility modifier and SLS as wicking agent.
3. To release LOX in a controlled manner osmotically with cellulose acetate coating along with sorbitol as a pore former.

The main objective of the study is to produce controlled release of LOX for the pain management of RA and OA and to improve the efficacy and patient compliance.

PLAN OF THE WORK

The present study was designed and planned as follows:

1. Preformulation studies
    - Physical compatibility studies.
    - Fourier Transform InfraRed Spectroscopy (FTIR) study- Identification and Compatibility of drug and excipients.

2. Standard curve for LOX.

3. Preformulation studies of drug, blends and granules.

4. Formulation and development.

    - Formulation of LOX core tablets using mannitol as Osmogen.
    - Controlled porosity osmotic coating of LOX using sorbitol as pore former.

5. Evaluation of Coated and Uncoated tablets.

- Physical characteristics
  - Description
  - Uniformity of weight
  - Diameter and thickness
  - Hardness
- Friability
- Drug content
- Uniformity of content
- *In vitro* release study of tablets
- Evaluation of optimized formulation
  - Effect of agitation speed on drug release
  - Effect of osmotic pressure on drug release
  - Effect of pH on drug release
- Evaluation of release kinetics of optimized formulation
- Stability of optimized formulation as per ICH guidelines

Rationale of Study

RATIONALE OF THE STUDY

Arthritis is a form of joint disorder that involves inflammation of one or more joints. There are over 100 different forms of arthritis. The most common form, Osteoarthritis (degenerative joint disease) is a result of trauma to the joint, infection of the joint or age. Other arthritis forms are Rheumatoid Arthritis, Psoriatic Arthritis and related. The major complaint by individuals who have arthritis is joint pain. Pain is often constant and may be localized to the joint affected. The pain from arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff, painful joints and fatigue.[55, 56]

RATIONALE FOR SELECTION OF THE DRUG

NSAIDs are a large class of medications used to treat arthritis, pain and inflammation. There are three categories of NSAIDs: Salicylates (aspirin), the traditional NSAIDs and Cyclo Oxygenase enzyme (COX-2) selective inhibitors.

LOX is a member of the oxicam group of NSAIDs. Oxicam have potent anti inflammatory and analgesic effects, but their use is associated with a high risk of GI adverse effects. LOX combines the high therapeutic potency of oxicam with an improved GI toxicity profile as compared to Naproxen. The clinical trials published so far clearly documents the efficacy of LOX as a potent analgesic with excellent anti inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and RA.[57]

But LOX has shorter half life, which makes the development of controlled release formulations extremely advantageous. However, due to its weak acidic nature, its release from extended release delivery system is limited to the lower GIT which consequently leads to a delayed onset of its analgesic action. This affects the therapeutic efficacy of drug. Therefore it is preferable to incorporate solublizing agents and develop a method to deliver the drug in a controlled manner. So that the frequency of dosing and dose size can be minimized.[40]

RATIONALE FOR THE SELECTION OF DOSAGE FORM [4]

The aim of the study is to formulate controlled porosity osmotic tablets. Basic pH modifier (solubility modifier) Tromethamine, wicking agent SLS were incorporated into the core tablet to create basic environmental pH inside the tablets, which provides complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continue in the intestine to maintain protracted analgesic effect.

The core tablet is coated with cellulose acetate, a semi permeable membrane with sorbitol as pore forming agent. In this controlled porosity system, the drug, after dissolution inside the core, is released from the osmotic tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane (Figure 4.1). This membrane after formation of pores becomes permeable for both water and solutes. [2, 3]

A controlled porosity osmotic wall formed will release the drug in a controlled manner for a period of 24 hours and thus the dosing frequency is reduced.

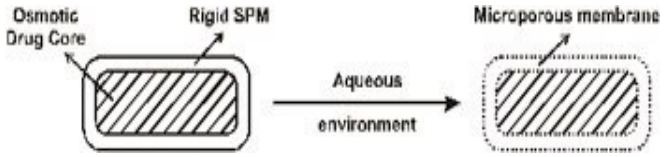


Fig. 4.1: Controlled porosity osmotic tablet

Disease Profile

INFLAMMATION [58-63]

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants. Inflammation is a process by which the body's white blood cells and chemicals protect us from infection and foreign substances such as bacteria and viruses.

Diseases Associated With Inflammation

Some but not all types of arthritis are the results of misdirected inflammation. Arthritis is a general term that describes inflammation in joints. Some types of arthritis associated with inflammation include:

- ❖ Rheumatoid arthritis (RA)
- ❖ Shoulder tendinitis or bursitis
- ❖ Gouty arthritis
- ❖ Polymyalgia rheumatica

Other painful conditions of the joints and musculoskeletal system that are not associated with inflammation include osteoarthritis, fibromyalgia, muscular low back pain and muscular neck pain.

Arthritis

Arthritis is a chronic degenerative disease that affects the joints of the body.

Arthritis Types

- Childhood Arthritis
- Fibromyalgia
- Gout
- Osteoarthritis (OA)
- Rheumatoid Arthritis
- Systemic lupus erythematosus (SLE or lupus)

A. RHEUMATOID ARTHRITIS

RA is a chronic (long-standing) joint disease that damages the joints of the body. The damage is caused by inflammation of the joint lining tissue. Inflammation is normally a response by the body's immune system to "assaults" such as infections, wounds and foreign objects. In RA, the inflammation is misdirected to attack the joints.

Background

RA is a chronic inflammatory polyarthritis.

The natural history of RA varies considerably with at least three possible disease courses.

1. **Monocyclic**: Have one episode which ends within 2-5 years of initial diagnosis and did not reoccur. This may result from early diagnosis and aggressive treatment.
2. **Polycyclic**: The levels of disease activity fluctuate over the course of condition
3. **Progressive**: RA continues to increase in severity and is unremitting.

Pathophysiology

Cells that play major role in the pathophysiology of the disease are CD4 T cells, fibroblasts, mononuclear phagocytes and osteoclasts. On the other hand, other cells like B lymphocytes give rise to auto antibodies like rheumatoid factors. The pathophysiology of rheumatoid arthritis is mediated by an inter-related network of cytokines, proteolytic enzymes and prostanoids. IL-1, TNF-alpha, etc. are proinflammatory cytokines and are the central mediators in the disease.

The pathogenesis of RA is a complex phenomenon and includes synovial cell proliferation, fibrosis, pannus formation and bone and cartilage erosion.

RA patients show abnormal production of certain inflammatory mediators like cytokines and chemokines of numerous types, tumor necrosis factor alpha (TNF-alpha), interleukin-1 (IL-1), IL-6, IL-8, transforming growth factor beta (TGF-beta), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF).

Stages of Development in Rheumatoid Arthritis

Stage I: - Synovial Membrane becomes hyperemic and edematous with foci of infiltrating small lymphocytes. (Synovitis)

- Effussions of joint with high cell count (5,000 to 60,000 per mm^3).
- X-rays show no destructive changes, but soft tissue swelling or osteoporosis.

Stage II: - Proliferation of inflammed synovial tissue and its growth into joint cavity

- Narrowing of joint due to loss of articular cartilage;

Stage III: - Pannus of Synovium;

- X-rays show extensive cartilage loss, erosions around the margins of joint.

Stage IV: - End stage of disease

- Subsiding of inflammatory process.
- Fibrous or bony ankylosing of joint will end its functional life;
- Subcutaneous Nodules associated with severe disease.

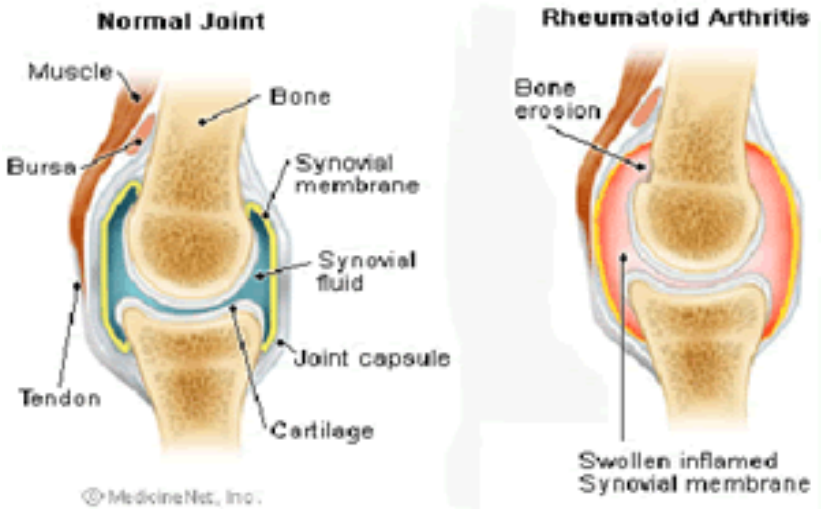


Fig. 5.1: Normal Joint and Rheumatoid Arthritis Joint

Incidence and Prevalence

Approximately 2.1 million people in the United States and about 1 to 2% of the world's population is affected by RA. About 75% of RA patients are women. Typically disease onset occurs between 30 and 60 years of age

Etiology

The exact cause of rheumatoid arthritis is still unknown. It is believed that it results from genetic as well as environmental triggers. The most significant inflammatory agents are tumor necrosis factor and interleukin-1. These are believed to be the triggers for the process of joint destruction in RA. Therefore treatment for the disease involves blocking of cytokines to reduce inflammation and joint damage.

Risk Factors

1. Non Modifiable Risk Factors

A. Socio-demographics

The incidence of RA is typically two to three times higher in women than men. In both women and men the onset is highest among in the age of sixty.

B. Genetics

There is longstanding evidence that specific HLA class II genotypes are associated with increase risk.

2. Modifiable Risk Factors

A.Smoking

Among the risk factors, the strongest and most consistent evidence is smoking. A history of smoking is associated with a modest to moderate (1.3 to 2.4 times) risk of RA onset and is strongest among people with ACPA-positive (anti-citrullinated protein/peptide antibodies), a marker of auto-immune activity.

B. Reproductive and breastfeeding history

Hormones related to reproduction have been studied extensively as potential risk factors for RA:

1. Oral contraceptives: Studies found that women who had ever used OCs had a modest to moderate decrease in risk of RA.
2. Hormone replacement therapy: There is mixed evidence of an association between HRT and RA onset.
3. Live birth history: Studies have found that women who have never had a live birth have a slight to moderately increased risk of RA.
4. Breastfeeding: Recent studies found that RA is less common among women who breastfeed.
5. Menstrual history: Studies have observed that women with irregular menses or a truncated menstrual history have an increased risk of RA.

Signs and Symptoms

Stiffness, Inflammation, Swelling, Nodules, Pain, Malaise, Fever, Fatigue, Loss of appetite, Weight loss, Myalgia, Weakness.

TREATMENT

Nondrug approaches

- Physical therapy helps in increasing the muscle strength and reducing pain.
- Hydrotherapy involves exercising or relaxing in warm water. .
- Relaxation therapy teaches techniques for releasing muscle tension, which helps relieve pain.
- Both heat and cold treatments can relieve pain and reduce inflammation. Heat can be applied by ultrasound, microwaves, warm wax, or moist compresses.
- Prosorba column is a medical device that filters antibodies linked to rheumatoid arthritis out of the blood. This is used only for severe RA.

Drug approaches.

Rheumatoid arthritis was treated with a stepwise approach starting with NSAIDs and progressing through more potent drugs such as glucocorticoids, disease-modifying anti rheumatic drugs (DMARDs) and biologic response modifiers.

NSAIDs

- COX-2 inhibitors: These agents block only the COX-2 enzyme and are referred to as selective NSAIDs. They have fewer side effects than the other NSAIDs. Example: Celecoxib
- Nonselective NSAIDs: These drugs block both COX-1 and COX-2 enzyme. Example: Ibuprofen, Ketoprofen , Naproxen, Lornoxicam and Diclofenac.

B. OSTEOARTHRITIS

Osteoarthritis is a disease characterized by degeneration of cartilage and its underlying bone within a joint as well as bony overgrowth. The breakdown of these tissues eventually leads to pain and joint stiffness. The joints most commonly affected are the knees, hips and those in the hands and spine.

Background

- Also known as degenerative joint disease.
- Most common form of arthritis.
- Classified as: Idiopathic (localized or generalized) or Secondary (traumatic, congenital, metabolic/endocrine/neuropathic and other medical causes).
- Characterized by focal and progressive loss of hyaline cartilage of joints, underlying bony changes.

Stages of Osteoarthritis

There are several stages of osteoarthritis:

- Cartilage loses elasticity and is more easily damaged by injury or use.
- Wear of cartilage causes changes to underlying bone. The bone thickens and cysts may occur under the cartilage. Bony growths, called spurs or osteophytes develop near the end of the bone at the affected joint.
- Bits of bone or cartilage float loosely in the joint space.
- The joint lining or the Synovium becomes inflamed due to cartilage breakdown producing cytokines and enzymes that further damage the cartilage.

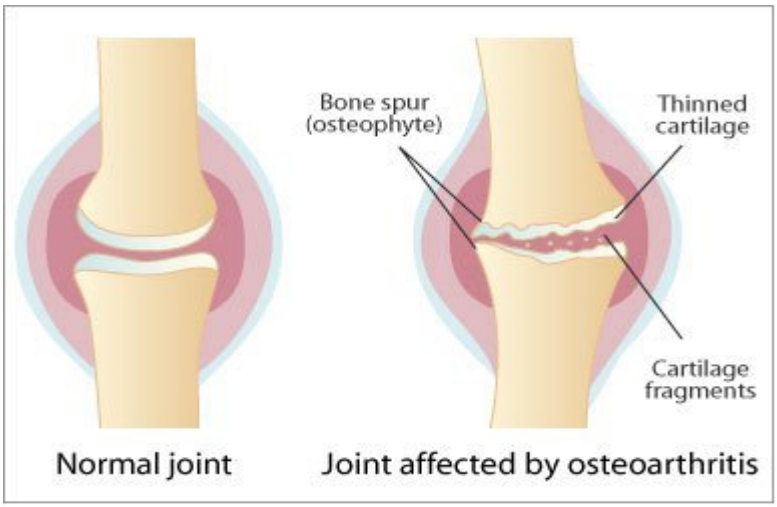


Fig. 5.2: Normal and Osteoarthritis Joint

Pathophysiology

- Cytokines and growth factors play an important role in the pathophysiology of OA
- Proinflammatory cytokines like TNF- α and IL-1 are believed to play a pivotal role in the initiation and development of the disease process
- Anti inflammatory cytokines like IL-4, IL-10, IL-13 are found in increased levels in OA synovial fluid.

Prevalence

OA affects 13.9% of adults aged 25 and older and 33.6% of those aged 65+

Incidence

Incidence rates increased with age.

Women had higher rates than men, especially after age 50.

- Men have 45% lower incident risk of knee OA and 36% reduced risk of hip OA than women.
- Prevalent knee OA but not hip or hand OA is significantly more severe in women compared to men.

Causes

Endocrine: People with diabetes may prone to OA. Other endocrine problems include acromegaly, hypothyroidism, hyperparathyroidism and obesity.

Post traumatic: Traumatic causes can be divided into macrotrauma or microtrauma. Macrotrauma is an injury to the joint such as a bone break causing the bones to line up improperly, lose stability, or damage cartilage. Microtrauma may occur over time like repetitive movements or the overuse noted in several occupations.

Inflammatory joint diseases: This includes infected joints, chronic gouty arthritis and rheumatoid disease.

Metabolic: Diseases causing errors of metabolism like Paget's disease and Wilson disease may cause osteoarthritis.

Congenital or developmental: Abnormal anatomy such as unequal leg length may be a cause of osteoarthritis.

Genetic: A genetic defect may promote breakdown of the protective architecture of cartilage. Examples include collagen disturbances such as Ehlers-Danlos syndrome.

Risk Factors

- **Modifiable risk factors**
  - Excess body mass.
  - Joint injury.
  - Occupation (due to excessive mechanical stress: hard labor, heavy lifting, knee bending, repetitive motion).
  - Structural malalignment, muscle weakness.

- **Non-modifiable risk Factors**
  - Gender (women higher risk).
  - Age (increases with age and levels around age 75).
  - Race (some Asian populations have lower risk).
  - Genetic predisposition.

- **Other possible risk factors**
  - Estrogen deficiency.
  - Osteoporosis.
  - Vitamins C, E and D – equivocal reports.
  - C-reactive protein (increased risk with higher levels).

Signs and symptoms

Pain, inflammation and swelling in the joint, joint stiffness especially upon waking, gradual loss of flexibility in the joint, appearance of small bumps in the affected joint.

TREATMENT

Non Medication: Self-Care at Home

Lifestyle changes may delay or limit osteoarthritis symptoms.

- Diet: Antioxidant vitamins C and E may provide some protection. Vitamin D and calcium are recommended for strong bones. The recommended daily dose of calcium is 1000-1200 mg and for vitamin D is 400 IU per day.
- Heat: Application of Hot soaks and warm wax (paraffin) may relieve pain.
- Orthoses: These assistive devices are used to improve function of moveable parts of the body or to support, align, prevent, or correct deformities. Splints or braces help with joint alignment and weight redistribution. Other examples include walkers, crutches or canes, and orthopedic footwear.
- Weight loss and Exercise

Medications

Initially, simple over-the-counter pain relievers such as acetaminophen are recommended followed by NSAIDs. A new generation of prescription NSAIDs are the COX-2 inhibitors.

Nonselective NSAIDs: These drugs block both COX-1 and COX-2. They include Ibuprofen, Ketoprofen , Naproxen, Lornoxicam and Diclofenac.

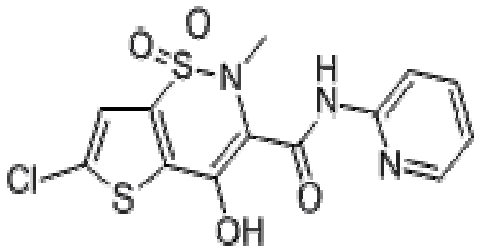
Drug Profile

LORNOXICAM [55-60]

Lornoxicam (chlortenoxicam) is a potent inhibitor of both COX-1 and COX-2 enzymes. It is a new NSAID of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug.

PHYSIOCHEMICAL PROPERTIES

Structure



Molecular Formula : $C_{13}H_{10}ClN_3O_4S_2$

Molecular weight : 371.819

Chemical name: :2H-Thieno[2,3-e]-1,2-thiazine-3-carboxamide,6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-, 1,1-dioxide

CAS Number : 70374-39-9

Category : Analgesic, antipyretic and anti-inflammatory agent

Description : A yellow crystalline powder

Solubility : Slightly soluble in chloroform and 0.1mol/L NaOH and very slightly soluble in methanol and acetonitrile and hardly soluble in water.

Storage : Store at room temperature (15°-23°C).

Melting point : 225° -230°C

PHARMACOKINETICS

Absorption

LOX is absorbed rapidly and completely from the GI tract. Peak plasma concentration is obtained within 1-2 hours after oral administration and 25 min after Intramuscular injection.

Distribution

Lornoxicam has 99% plasma protein binding. LOX and its metabolites bind extensively to plasma albumin and it readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies.

Metabolism

LOX is metabolized completely by Cytochrome P2C9 with the principal metabolite being 5'-hydroxy-lornoxicam and only negligible amounts of intact lornoxicam are excreted unchanged in the urine.

Excretion

Excreted in the faeces (as metabolites) and urine (as unchanged drug). Approximately 2/3 of the drug is eliminated via the liver and 1/3 via the kidneys in the active form. Mean elimination half life of 3-4 hours.

PHARMACODYNAMICS

LOX is a potent inhibitor of the COX enzymes, which are responsible for catalyzing the formation of prostaglandins and thromboxane from arachidonic acid. Unlike some NSAIDS, lornoxicam's inhibition of COX does not lead to an increase in leukotriene formation and the arachidonic acid is not moved to the 5-lipoxygenase cascade, resulting in the minimization of the risk of adverse effects.

MECHANISM OF ACTION

LOX's anti-inflammatory and analgesic activity is related to its inhibitory action on prostaglandin and thromboxane synthesis through the inhibition of both COX-1 and COX-2. This leads to the reduction of inflammation, pain, fever and swelling, which are mediated by prostaglandins.

INDICATION AND USAGE

LOX is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica and other inflammations of the joints caused by certain types of rheumatic diseases.

DOSAGE

Post Operative Pain management: 8-16 mg/day. Max: 24 mg/day.

Osteoarthritis and Rheumatoid arthritis: 12mg/day in 2 -3 divided doses, up to 16mg/day.

SIDE EFFECTS

LOX has more common side effects like GI disorders (nausea and diarrhea) and headache. Severe but seldom side effects include bleeding and bronchospasms.

CONTRAINDICATIONS

Patients with peptic ulceration, severe renal impairment, pregnancy and lactation.

INTERACTIONS

Enhanced effects of anticoagulants, Sulfonylurea, Methotrexate, Cyclosporin, Digoxin and decreased effects of diuretics and ACE inhibitors when administered along with LOX.

ADVERSE REACTIONS

Abdominal pain, diarrhoea, dizziness, dyspepsia, nausea, vomiting, headache, haematologic disorders.

AVAILABLE MARKETED PRODUCTS

Camri tabs	- Cadila
Flexilor inj,tab	- Glenmark
Fulactive inj, fulactive 4P, 8P tab	- Ranbaxy
Lanagesic tab	- Wockhardt
Lofecam tab	- Sun Pharma
Lorcheck P	- Indoco
Lornasafe tab	- Mankind

Excipient Profile

EXCIPIENT PROFILE

MANNITOL[70]

1. Nonproprietary Names

BP: Mannitol, JP: D-Mannitol, PhEur: Mannitol, USP: Mannitol.

2. Synonym

Cordycepic acid, Emprove, Manna sugar, D-mannite, Mannite, Mannitolum, Mannogem, Pearlitol.

3. Empirical Formula

$C_6H_{14}O_6$

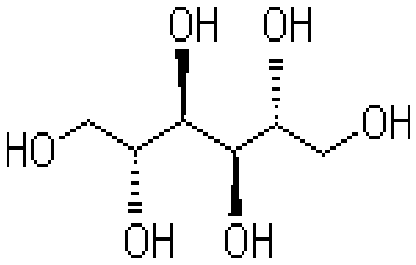
4. Molecular Weight

182.17

5. Chemical Name

D-Mannitol

6. Structural Formula



7. Functional Category

Diluent, plasticizer, sweetening agent, tablet and capsule diluents, therapeutic and tonicity agent.

8. Description

Mannitol occurs as a white, odourless, crystalline powder or free flowing granules. It has a sweet taste and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

9. Solubility

Soluble in water, very slightly soluble in ethanol, practically insoluble in ether.

10. Incompatibilities

Mannitol solutions (20% w/v or stronger) may be salted out by potassium chloride or sodium chloride. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper and iron.

11. Applications

Used as an osmogen in osmotic pumps which aids in releasing the drug. Mannitol is widely used in Pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as an excipient (10–90% w/w) in tablet formulations. It is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness and 'mouth feel'.

TROMETHAMINE[70]

1. Nonproprietary Names

Tris buffer.

2. Synonym

Tris (Hydroxymethyl) aminomethane, addex-tham, Tromethanmin, Tromethane, Tris(hydroxymethyl)methylamine, Tromethamine, Addex-Tham.

3. Empirical Formula

$C_4H_{11}NO_3$.

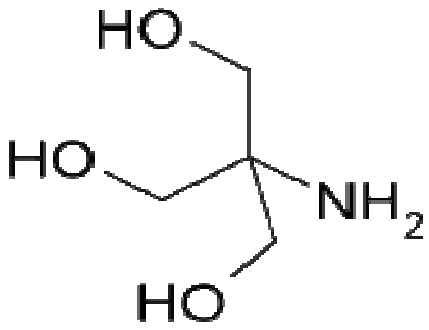
4. Molecular Weight

121.14

5. Chemical Name

2-Amino-2-Hydroxymethyl-m 1,3-Propanediol.

6. Structural Formula



7. Functional Category

Buffer solution or alkalizer for the correction of metabolic acidosis.

8. Description

White, Crystalline powder, Slight characteristic odour, faint sweet soapy taste.

9.Solubility

Easily soluble in cold water, hot water. Partially soluble in methanol, acetone.

10. Incompatibilities

Incompatible with metals such as copper, brass and aluminum. Incompatible with aldehydes.

11. Application

It is used in the synthesis of surface-active agents and as an emulsifying agent for cosmetic creams and lotions, mineral oil and paraffin wax emulsions, as a biological buffer and used as an alkalizer.

SODIUM LAURYL SULPHATE[70]

1. Nonproprietary Names

BP: Sodium lauryl sulfate, JP: Sodium lauryl sulfate, PhEur: Natrii laurilsulfas USPNF: Sodium lauryl sulfate.

2. Synonyms

Dodecyl sodium sulfate, Elfan *240*, sodium dodecyl sulfate, sodium laurilsulfate, sodium monododecyl sulfate, sodium monolauryl sulfate.

3. Empirical Formula

$C_{12}H_{25}NaO_4S$

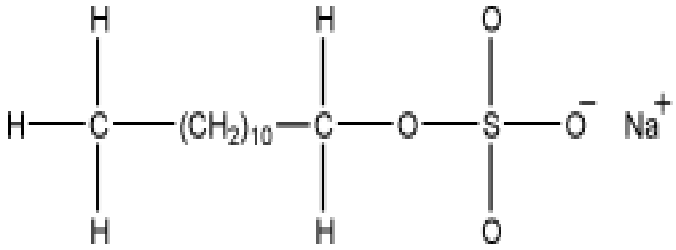
4. Molecular Weight

288.38.

5. Chemical Name

Sulfuric acid monododecyl ester sodium salt

6. Structural Formula



7. Functional Category

Anionic surfactant, detergent, emulsifying agent, skin penetrant, tablet and capsule lubricant, wetting agent.

8. Description

Sodium lauryl sulfate consists of white or cream to pale yellow-coloured crystals, flakes, or powder having a smooth feel, a soapy, bitter taste and a faint odour of fatty substances.

9. Solubility

Freely soluble in water, giving an opalescent solution, practically insoluble in chloroform and ether.

10. Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants causing loss of activity even in concentrations too low to cause precipitation. It is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

11. Application

Used as a Solubilizer in concentrations greater than critical micelle concentration. anionic emulsifier, skin cleanser in topical applications, tablet lubricant and wetting agent in dentrifices.

LACTOSE[70]

1. Nonproprietary Names

BP: Lactose, PhEur: Lactose Monohydrate, JP: Lactose Hydrate, USP-NF: Lactose Monohydrate.

2. Synonyms

CapsuLac, GranuLac, Lactochem, Lactosum monohydricum, Monohydrate.

3. Empirical Formula

$C_{12}H_{22}O_{11}$ H_2O

4. Molecular Weight

360.31.

5. Chemical Name

Lactose

6. Functional Category

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

7. Description

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting.

8. Solubility

Freely but slowly soluble in water, Practically insoluble in alcohol.

9. Incompatibilities

A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown or yellow-brown-coloured products. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

10. Application

Lactose is widely used as a filler and diluent in tablets, capsules and dry-powder Inhalation.

TALC[70]

1. Nonproprietary Names

BP: Purified Talc, JP: Talc, PhEur: Talc, USP: Talc.

2. Synonyms

Magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star.

3. Empirical Formula

$Mg_6(Si_2O_5)_4(OH)_4$.

4. Chemical Name

Talc.

5. Functional Category

Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

6. Description

Talc is a very fine, white to grayish-white, odourless, impalpable, unctuous, crystalline powder.

7. Solubility

Practically insoluble in dilute acids and alkalis, organic solvents and water.

8. Incompatibilities

Incompatible with quaternary ammonium compounds.

9. Application

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. It is widely used as a dissolution retardant in the development of controlled-release products. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

COLLOIDAL SILICON DIOXIDE[70]

1. Nonproprietary Names

BP: Colloidal Anhydrous Silica, JP: Light Anhydrous Silicic Acid, PhEur: Silica, Colloidal Anhydrous, USP-NF: Colloidal Silicon Dioxide.

2. Synonyms

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, fumed silicon dioxide.

3. Empirical Formula

SiO_2

4. Molecular Weight

60.08

5. Chemical Name

Silica

6. Functional Category

Adsorbent, anti caking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

7. Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-coloured, odourless, tasteless, amorphous powder.

8. Solubility

Practically insoluble in organic solvents, water and acids. soluble in hot solutions of alkali hydroxide.

9. Incompatibilities

Incompatible with diethylstilbestrol preparations.

10. Applications

Colloidal silicon dioxide is widely used in pharmaceuticals,cosmetics and food products. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations

MAGNESIUM STEARATE[70]

1. Nonproprietary Names

BP: Magnesium stearate, JP: Magnesium stearate, PhEur: Magnesii stearas. USP NF: Magnesium stearate.

2. Synonyms

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid.

3. Chemical Name

Octadecanoic acid magnesium salt.

4. Empirical Formula

$C_{36}H_{70}MgO_4$

5. Molecular Weight

591.34

6. Functional Category

Tablet and capsule lubricant.

7. Description

Magnesium stearate is a very fine, light white, precipitated or milled, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

8. Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

9. Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

10. Applications

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0% w/w. It is also used in barrier creams.

CELLULOSE ACETATE[70]

1. Nonproprietary Names

BP: Cellulose Acetate, PhEur: Cellulose Acetate, USP-NF: Cellulose Acetate

2. Synonyms

Acetic acid, cellulose ester. acetyl cellulose, cellulose diacetate.

3. Chemical Name

Cellulose acetate.

4. Empirical Formula

$C_6H_7O_2(OH)_3$

5. Molecular Weight

38000

6. Functional Category

Coating agent, extended release agent, tablet and capsule diluents.

7. Description

Cellulose acetate occurs as a white to off-white powder, free-flowing pellets, or flakes. It is tasteless and odourless, or may have a slight odour of acetic acid.

8. Solubility:

Practically insoluble in water, soluble in acetone, in formic acid and in a mixture of equal volumes of methanol and methylene chloride, practically insoluble in alcohol.

9. Incompatibilities

Incompatible with strongly acidic or alkaline substances. Cellulose acetate is compatible with plasticizers like diethyl phthalate, triacetin and triethyl citrate.

10. Applications

Cellulose acetate is used as a semipermeable coating on tablets, especially on osmotic pump type tablets and implants. Cellulose acetate and other cellulose esters have also been used to form drug-loaded microparticles with controlled-release characteristics. Cellulose acetate films are used in transdermal drug delivery systems and also as film coatings on tablets or granules for taste masking.

SORBITOL[70]

1. Nonproprietary Names

BP: Sorbitol, JP: D-Sorbitol, PhEur: Sorbitolum, USPNF: Sorbitol.

2. Synonyms

PharmSorbidex E420, 1,2,3,4,5,6-hexanehexol, Liponic 70-NC, Liponic 76-NC.

3. Chemical Name

D-Glucitol

4. Empirical Formula

$C_6H_{14}O_6$

5. Molecular Weight

182.17

6. Functional Category

Humectant, plasticizer, sweetening agent, tablet and capsule diluents.

7. Description

Sorbitol occurs as an odourless, white or almost colourless, crystalline, hygroscopic powder.

8. Solubility

Very soluble in water, slightly soluble in ethanol.

9. Incompatibilities

Sorbitol will form water-soluble chelates with many divalent and trivalent metal ions in strongly acidic and alkaline conditions.

10. Applications

Sorbitol is used as a diluent in tablet formulations prepared by either wet granulation or direct compression. It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation. In capsule formulations it is used as a plasticizer for gelatin. It has been used as a plasticizer in film formulations. In liquid preparations sorbitol is used as a vehicle in sugar-free formulations and as a stabilizer for drug, vitamin, and antacid suspensions. Sorbitol is additionally used in injectable and topical preparations and therapeutically as an osmotic laxative.

POVIDONE[70]

1. Nonproprietary Name

Povidone

2. Synonyms

E1201, Kollidon, Plasdone, Poly[1-(2-oxo-1-pyrrolidinyl)ethylene], Polyvidon.

3. Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer.

4. Empirical Formula

$(C_6H_9NO)_n$

5. Molecular Weight

2500–3,000,000

6. Functional Category

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

7. Description

Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder.

8. Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water. Practically insoluble in ether, hydrocarbons and mineral oil.

9. Incompatibility

It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin.

10. Applications

Povidone is used in a variety of Pharmaceutical formulations primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. It is also used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

POLYETHYLENE GLYCOL 400[70]

1. Nonproprietary Names

BP: Macrogols, JP: Macrogol 400, PhEur: Macrogola, USPNF: Polyethylene glycol.

2. Synonyms

Carbowax, Lipoxol, Lutrol E, PEG, Pluriol , Polyoxyethylene glycol.

3. Chemical Name

Hydro-hydroxy poly(oxy-1,2-ethanediyl).

4. Empirical Formula

$HOCH_2(CH_2OCH_2)mCH_2OH$ where *m* represents the average number of oxyethylene groups.

5. Molecular Weight

380–420

6. Functional category

Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

7. Description

Liquid grades (PEG 200–600) occur as clear, colourless or slightly yellow-coloured, viscous liquids. They have a slight but characteristic odour and a bitter, slightly burning taste.

8. Solubility

Polyethylene glycol is soluble in water and miscible in all proportions.

9. Incompatibility

PEG can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

10. Applications

It is widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations. Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film.

ISOPROPYL ALCOHOL[70]

1. Nonproprietary Names

BP: Isopropyl alcohol, JP: Isopropanol, PhEur: Alcohol isopropylicus, USP: Isopropyl alcohol.

2. Synonyms

Dimethyl carbinol, IPA, Isopropanol, 2-propanol.

3. Chemical Name

Propan-2-ol

4. Empirical Formula

C_3H_8O

5. Molecular weight

60.1

6. Functional Category

Disinfectant, solvent.

7. Description

Isopropyl alcohol is a clear, colourless, mobile, volatile, flammable liquid with a characteristic, spirituous odour resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

8. Solubility

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin and water. Soluble in acetone, insoluble in salt solutions.

9. Incompatibility

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate and other salts, or by the addition of sodium hydroxide.

10. Application

Isopropyl alcohol (propan-2-ol) is used in cosmetics and Pharmaceutical formulations, primarily as a solvent in topical formulations. Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation.

METHANOL[71]

1. Synonyms

Methyl alcohol, wood alcohol, wood naphtha or wood spirits.

2. Chemical Name

Hydroxymethane.

3. Empirical Formula

CH_4O

4. Molecular weight

32.04

5. Functional Category

Common laboratory solvent.

6. Description

Clear, colourless, volatile, hygroscopic liquid.

7. Solubility

Miscible with water and methylene chloride.

8. Incompatibilities

Methanol is incompatible with Chloroform and a base explosive reaction.

9. Applications

Methanol is used as a solvent and as an anti freeze in pipeline and windshield washer fluid.

WATER[70]

1. Nonproprietary Names

BP: Purified water, JP: Purified water, PhEur: Aqua purificata, USP: Purified water.

2. Synonyms

Aqua; Hydrogen oxide.

3. Chemical Name

Water

4. Empirical Formula

H_2O

5. Molecular Weight

18.02

6. Functional Category

Solvent

7. Description

Water is a clear, colourless, odourless and tasteless liquid.

8. Solubility

Miscible with most polar solvents.

9. Incompatibilities

In Pharmaceutical formulations, water can react with drugs and other excipients that are susceptible to hydrolysis at ambient and elevated temperatures. Water can react violently with alkali metals and rapidly with alkaline metals and their oxides, such as calcium oxide and magnesium oxide. Water also reacts with anhydrous salts to form hydrates of various compositions and with certain organic materials and calcium carbide.

10. Applications

Water is widely used as a raw material, ingredient and solvent in the processing, formulation and manufacture of pharmaceutical products, active pharmaceutical ingredients (API) and intermediates and analytical reagents.

DICHLOROMETHANE[70]

1. Nonproprietary Names

Methylene dichloride, Solmethine, Narkotil, Solaesthin, Di-clo, Freon 30, R-30, DCM, UN 1593, MDC.

2. Synonym

Methylene chloride

3. Empirical Formula

CH_2Cl_2

4. Molecular Weight

84.93

5. Chemical Name

Dichloromethane

6. Functional Category

Solvent

7. Description

Colourless, volatile liquid with a moderately sweet aroma.

8. Solubility

It is not miscible with water, it is miscible with many organic solvents.

9. Incompatibilities

Incompatible with Diethylstilbestrol preparations.

10. Applications

It is used to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes. It is widely used as a paint stripper and a degreaser. It is used as an aerosol spray propellant and as a blowing agent for polyurethane foams.

Materials & Methods

MATERIALS AND METHODS

The list of drug and excipients, their manufacturer and use in the present study are shown in table 6.1

Table 6.1: List of Materials Used

S.No.	Drug/Excipient	Manufacturer	Use in Formulation
1	Lornoxicam	Glenmark	Active Ingredient
2	Mannitol	S.D.Fine Chemicals, Mumbai.	Osmogen
3	Tromethamine	S.D.Fine Chemicals, Mumbai.	Alkaliser
4	Sodium lauryl sulphate	S.D.Fine Chemicals, Mumbai.	Solubilizer
5	Lactose	D.M.V International.	Diluent
6	Poly vinyl pyrrolidone	S.D.Fine Chemicals, Mumbai.	Binder
7	Talc	S.D.Fine Chemicals, Mumbai.	Glidant
8	Magnesium Stearate	Mudha enterprises	Lubricant
9	Aerosil	Cabor Sanmar Ltd	Glidant
10	Cellulose acetate	S.D.Fine Chemicals, Mumbai.	Semipermeable membrane
11	PEG 400	Qualigens Fine Chemicals, Mumbai	Plasticizer
12	Sorbitol	S.D.Fine Chemicals, Mumbai.	Poore former
13	Iron oxide yellow	Colorcon Asia Limited	Colouring agent
14	Methanol	Qualigens Fine Chemicals, Mumbai	Solvent
15	Dichloromethane	Qualigens Fine Chemicals, Mumbai	Solvent

The list of instruments/ equipments used in the present study and their manufacturer are shown in table 6.2.

Table 6.2: List of Instruments / Equipments

S.No.	Instruments/ Equipments	Manufacturer
1	Electronic Weighing balance	Shimadzu, Japan.
2	Tray dryer	Chitra, Ahmedabad.
3	Hot air oven	Industrial Heaters, Chennai.
4	27 station rotary compression machine	Cadmach, Ahmedabad.
5	Coating Machine	Cadmach, Ahmedabad.
6	Vernier Caliper	Mitutoyo, Japan.
7	Monsanto Harness Tester	Erweka, Mumbai.
8	Friabilator	Electrolab, India
9	pH meter	Synchrony India
10	Sonicator	Toshniwal, Ajmeer
11	Dissolution Test Apparatus	Electrolab, India
12	UV-Visible Spectrophotometer	Shimadzu, Japan
13	Fourier Transform Infra Red Spectrophotometer	Nicolet
15	Stability chamber	Technico, India
16	SEM Analyzer	Hitachi, Japan.

PHYSICAL COMPATIBILITY STUDY [72]

The physical admixture of the drug and excipients so as to reflect those expected to be present in the final product were taken in 2 ml glass vials and sealed. These glass vials were kept at room temperature and at 40° ± 2°C / 75% ± 5% RH for 1 month. At the end of 10 days, the samples were withdrawn and analyzed for colour change.

FTIR STUDY- IDENTIFICATION AND COMPATIBILITY OF DRUG AND POLYMER [73]

Infrared Spectroscopy was conducted using FTIR spectrophotometer and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing the sample (drug alone, mixture of drug and excipients and the optimized formulation) in KBr and compressed into discs by applying a pressure of 5 Tons for 5minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.

STANDARD CURVE FOR LORNOXICAM[51]

Standard curve in 0.1 N Hydrochloric Acid Buffer pH 1.2

50 mg of lornoxicam was weighed, transferred to 50 ml standard flask and dissolved in equal proportions of methanol(25ml) and 0.1N Hydrochloric Acid buffer pH 1.2 (25ml) to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with 0.1N Hydrochloric Acid buffer pH 1.2 to get a concentration of 100mcg/ml. The above solution was further diluted with to get a concentrations of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solution was measured at 376nm using UV-Visible Spectrophotometer taking 0.1N Hydrochloric acid acid buffer pH1.2 as blank.

Standard curve in Acetate Buffer pH 4.5

50 mg of lornoxicam was weighed, transferred to 50ml standard flask and dissolved in equal proportions of methanol(25ml) and Acetate buffer pH 4.5 (25ml) to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with Acetate buffer pH 4.5 to get a concentration of 100mcg/ml. The above solution was further diluted to get a

concentrations of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solution was measured at 376nm using UV-Visible Spectrophotometer taking Acetate buffer pH 4.5 as blank.

Standard curve in Phosphate Buffer, pH 6.8

50 mg of lornoxicam was weighed, transferred to 50ml standard flask and dissolved in equal proportions of methanol (25ml) and Phosphate buffer pH 6.8 (25ml) to get a concentration of 1mg/ml. From the stock solution 10ml was taken and diluted to 100ml with Phosphate buffer pH 6.8 to get a concentration of 100mcg/ml. The above solution was further diluted to get a concentrations of 2, 4, 6,8,10 mcg/ml. The absorbance of the resulting solution was measured at 376nm using UV-Visible Spectrophotometer taking Phosphate buffer pH 6.8 as blank.

PRECOMPRESSION STUDIES OF THE DRUG AND BLENDS

BULK DENSITY (ρ_b) [74]

Bulk Density (g/ml) is a term obtained by dividing weight of powder by bulk volume of powder. 25 g of the drug, powder blend and granules from each formula was introduced into a 100 ml measuring cylinder. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals for three times. Bulk Density is calculated using the following formula

$$\textbf{Bulk density, } \rho_b = W / V_b$$

Where, W = Weight of the powder in g

V_b = Bulk volume of the powder in ml

TAPPED DENSITY (ρ_t) [74]

Tapped Density (g/ml) is a term obtained by dividing weight of powder by tapped volume of powder. 25 g of the drug, powder blend and granules from each formula was introduced into a 100 ml measuring cylinder. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals for 500 times. Tapped Density is calculated using the following formula

Tapped Density, $\rho_t = W / V_t$

Where, W = Weight of the powder in g

V_t = Tapped volume of the powder in ml

COMPRESSIBILITY INDEX OR CARR'S INDEX (CI) [74]

It is an indirect measure of Bulk Density, size and shape, surface area, moisture content and cohesiveness. It is expressed in percentage and can be calculated by following equation

Carr's Index, $CI = (\rho_t - \rho_b) / \rho_t \times 100$

Where, ρ_b = Bulk Density in g/ml

ρ_t = Tapped Density in g/ml

HAUSNER'S RATIO (HR) [74]

It is measured by the ratio of tapped density to bulk density. Ideal range should be between 1.2 and 1.5. It is calculated by the following formula

Hausner's Ratio, $HR = \rho_t / \rho_b$

Where, ρ_b = Bulk Density in g/ml

ρ_t = Tapped Density in g/ml

ANGLE OF REPOSE (θ) [75]

The angle of repose of the drug, powder blend and granules from each formula was determined by the fixed funnel method which employs a funnel that is secured with its tip at 2 cm above graph paper that is placed on a flat horizontal surface. From the radius of base of conical pile, angle of repose can be determined using following equation,

Angle of Repose, $\theta = \tan^{-1} (h/r)$

Where, h = height of the pile of powder in cm.

r = radius of the pile of powder base in cm.

Table 6.3: Angle of Repose, Carr's Index and Hausner's Ratio [76]

Flow Property	Angle of repose (θ in degrees)	Carr's Index (CI in %)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

FORMULATION DEVELOPMENT

Preparation of lornoxicam granules and compaction into tablets:

The lornoxicam tablets were prepared with varying ratios of the osmogen (Mannitol). Drug and all the ingredients except lubricants were weighed and passed through sieve no. 20. The powders were mixed together. To the resultant powder mixture, PVP dissolved in isopropyl alcohol was added to form a coherent mass. Then the coherent mass was passed through 16 mesh screen to form granules. The wet granules were dried at 50^0C for 15 minutes. The dried granules were passed through sieve no. 20 to break the lumps and to get uniform particle size of granules. The lubricant was passed through sieve no. 40 and mixed with the dried granules.

The lubricated granules were compressed into tablets using 11/32 inches (8.0mm) standard concave punches on a 27 station rotary tablet punching machine. The composition of core tablet is listed in Table 6.4.

Table 6.4: COMPOSITION OF CORE TABLETS

S.No	Ingredients	F01(mg)	F02(mg)	F03(mg)	F04(mg)
1	Lornoxicam	8	8	8	8
2	SLS	12	12	12	12
3	Tromethamine	25	25	25	25
4	Mannitol	0	50	100	150
5	Lactose	187	137	87	37
6	Povidone K30	12	12	12	12
7	Isopropyl alcohol	q.s	q.s	q.s	q.s
8	Magnesium Stearate	2.5	2.5	2.5	2.5
9	Talc	2.5	2.5	2.5	2.5
10	Aerosil	1	1	1	1
Total Weight		**250 mg**			

COATING OF TABLETS

Controlled porosity Osmotic coating

Three coating solutions of cellulose acetate in a mixture of methanol and dichloromethane containing different levels (0%, 10% and 20% w/v) of pore-forming agent (sorbitol) were prepared for semi permeable membrane coating. The composition of coating solutions is given in Table 6.5. PEG 400 acted as a hydrophilic plasticizer and was added to enhance the physical and mechanical property of cellulose acetate membrane.

The coating conditions were as follows:

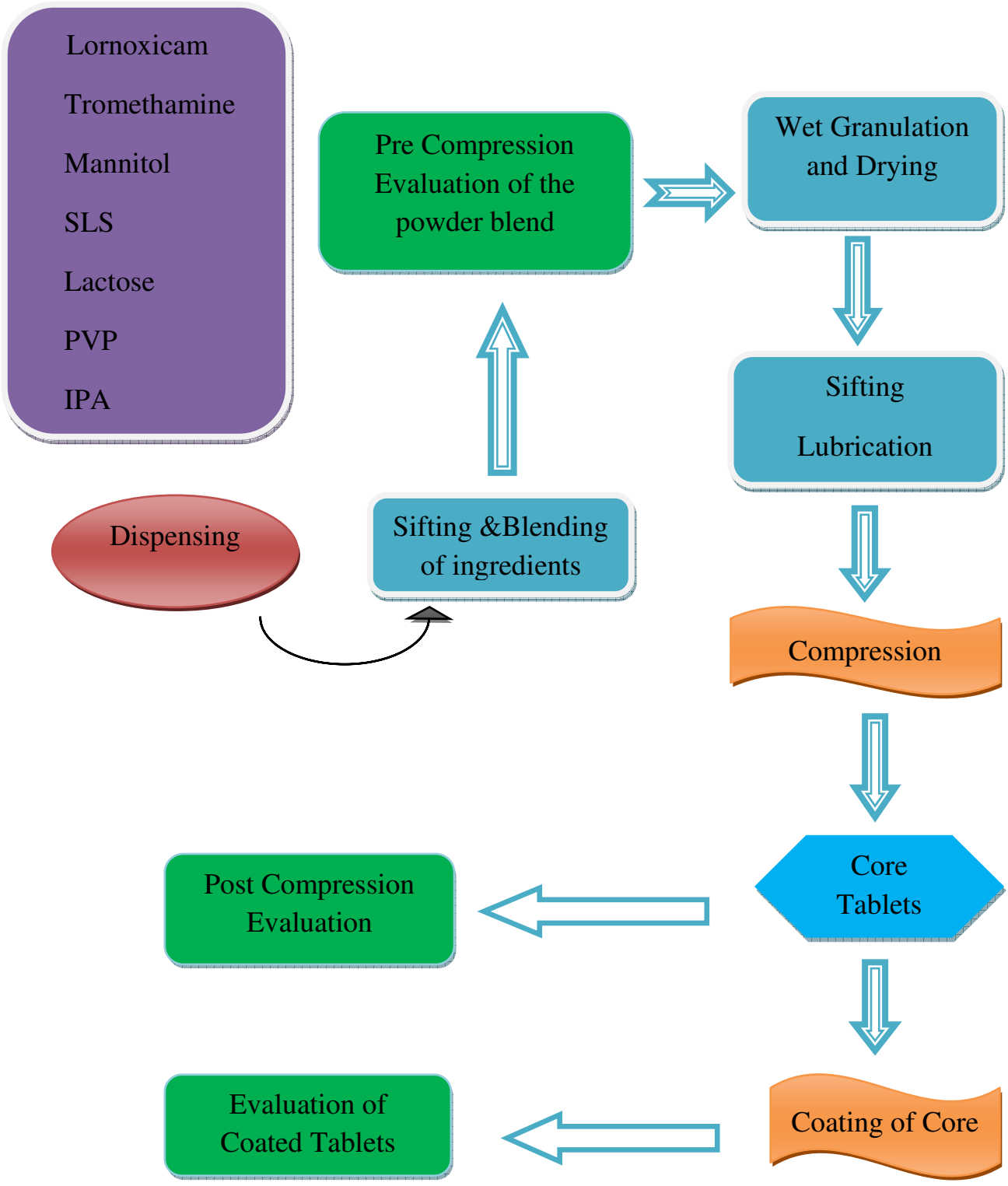
- Stainless steel pan with 200mm diameter
- Rotation rate of the pan - 40 rpm
- Nozzle diameter of spray gun - 1 mm
- Spray rate - 3 ml/min
- Drying temperature - 40^0C

After coating, the tablets were dried at 50^0C to remove residual solvent.

Table 6.5: COMPOSITION OF COATING SOLUTION

S.No	Ingredients	C1	C2	C3
1	Cellulose acetate	60g	60g	60g
2	Sorbitol	-	6g	12g
3	PEG 400	6g	6g	6g
4	Water	58ml	58ml	58ml
5	Dichloromethane	870ml	870ml	870ml
6	Methanol	580ml	580ml	580ml

Schematic representation of formulation development of controlled porosity osmotic tablets of Lornoxicam



EVALUATION OF TABLETS

Description

Ten tablets were placed in a petri dish. The tablets were observed from both sides for colour, shape and visual appearance of tablets.

Uniformity of Weight [77]

Twenty tablets were selected at random from each batch. The individual tablets were weighed. The average weight is determined. The individual weight of tablets was compared with the average weight.

Table 6.6: Uniformity of weight

S.No	Average Weight of tablet	%Deviation
1	80 mg or less	10
2	80-250 mg	7.5
3	More than 250 mg	5

Diameter and Thickness [78]

Five tablets from each formulation were selected. The diameter and thickness of the tablets was measured using Vernier calipers.

Hardness [78]

The resistance of tablets to chipping or breakage during storage, transportations and handling before usage depends on its hardness. Five tablets were selected randomly and the hardness was measured by Monsanto hardness tester in terms of Kg/cm^2.

Friability [77, 78]

Friability of tablets was measured using Roche friabilator. Twenty tablets were weighed and then placed in the chamber. The friabilator was set for 100 revolutions and the tablets were subjected to the combined effects of shock and abrasion because the plastic chamber

drops the tablets at a distance of six inches during every revolution. The tablets were dusted to remove the powder and reweighed. The friability is given by the formula:

$$F = (1- W / W_O) \times 100$$

Where

W_O is the weight of tablets before test.

W is the weight of tablet after test.

Drug Content [41]

Ten tablets were weighed and ground. The weight equivalent to 8mg of drug was taken and transferred to a 100ml standard flask. 25ml of methanol and 25ml of 6.8 pH phosphate buffer was added and sonicated for 10minutes and the volume was made up to 100ml with equal volume of methanol and 6.8 pH phosphate buffer. The above solution was filtered and 10ml of filtrate was taken and diluted to 100ml with 6.8 pH phosphate buffer. The absorbance of resulting solution was measured at 376nm and the content of LOX was calculated.

Uniformity of content [77]

Ten tablets were randomly selected and tested for their drug content.

***In vitro* release study of the tablets** [79]

Two step-dissolution conditions was used in USP Type II (paddle) dissolution apparatus to simulate the physiological conditions of GIT - 2 hours in 900 ml of simulated gastric fluid (SGF pH 1.2) and 22 hours in 900 ml of simulated intestinal fluid (SIF, pH 6.8). The stirring rate was 100 rpm and the temperature was maintained at 37 ± 0.5°C. Aliquots of dissolution medium were withdrawn at predetermined time intervals and the same volume of medium was replenished to maintain the consistent volume. The absorbance of the solutions was measured at 376nm and the release was calculated.

EVALUATION OF OPTIMIZED FORMULATION

Effect of Change in Agitation Speed on drug release [80]

In order to study the effect of agitational intensity on the optimized formulation, release studies were also performed in dissolution apparatus at various rotational speeds of 50, 100 and 150 rpm using two step-dissolution conditions 2 hours in 900 ml of SGF pH 1.2 and 22 hours in 900 ml of SIF pH 6.8 in USP Type II (paddle) dissolution apparatus. The temperature was maintained at 37±0.5°C. The release was studied at predetermined time intervals.

Effect of pH on drug release [81]

In order to study the effect of pH of release medium in the drug release of optimized formulation, the *in vitro* release study was carried out in buffers of different pH, viz pH 1.2 buffer, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer in USP type II dissolution apparatus. The temperature was maintained at 37° ± 0.5°C. The release was studied at predetermined time intervals.

Effect of Osmotic Pressure [27]

To confirm the major mechanism of drug release, release studies of the optimized formulation was conducted in release media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to 37° ± 1°C), mannitol (osmotically effective solute) was added to produce 1.5 atm, 3 atm and 4.5 atm respectively. The release was studied at predetermined time intervals.

MEMBRANE MORPHOLOGY OF POROUS OSMOTIC TABLET

Scanning Electron Microscopy[27]

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope. Membranes were dried at 45° C for 12 hours and stored between sheets of wax paper in a dessicator until examination. The membrane was coated under an argon atmosphere with gold-palladium and observed with a scanning electron microscope.

RELEASE KINETICS OF THE OPTIMIZED FORMULATION [82-84]

The *in vitro* release data for the optimized batch was fitted to various release kinetic models. The best fit was found out to describe the kinetics of drug release.

Zero order release model

Zero order models describe the systems where the drug release rate is independent of its concentration.

$$C = k_o t$$

Where, C -Cumulative percentage drug released

k_o **-**Zero-order constant

t -Time (Hours)

A plot of time on x-axis and cumulative percentage drug released on y-axis gives a straight line with slope (k_o) if it follows zero order kinetics.

First order release model

First order model describe the systems where the release rate is dependent on the concentration.

$$\text{Log } C = \log C_o - k t / 2.303$$

Where C - Cumulative percentage drug remaining

C_o - Initial concentration of drug

k **-** First order constant

A plot of time on x-axis and log cumulative percentage drug remaining on y-axis gives a straight line with slope (k / 2.303) if it follows first order kinetics.

Higuchi release model

The Higuchi model describes the release from where the solid drug is dispersed in an insoluble matrix and the rate of release is related to the rate of drug diffusion.

$$Q = k t^{1/2}$$

Where Q – Cumulative percentage drug released

k **–** Constant reflecting the design variables of the system

t – Time

A plot of square root of time on x-axis and cumulative percentage drug released on y-axis gives a straight line if it follows Higuchi kinetics.

Hixson-Crowell release model

The Hixson-Crowell cube root model describes the release from systems where there is a change in surface area and diameter of the tablets or particles.

$$Q_o^{1/3} - Q_t^{1/3} = K_{HC}\, t$$

Where Q_t - Cumulative percentage drug released in time t

Q_o - initial amount of the drug

K_{HC} - the rate constant for Hixson-Crowell rate equation

A plot of time on x-axis and cube root of cumulative percentage of drug remaining on y-axis gives a straight line if it follows Hixson-Crowell kinetics.

Korsmeyer and Peppas Model

Korsmeyer and Peppas model derive a simple relationship which describes the drug release from a polymeric system equation.

$$M_t / M_\infty = K\, t^n$$

Where M_t / M_∞ – fraction of drug released at time t

k - Release rate constant

n - Release exponent

A plot of log time on x-axis and log cumulative percentage of drug released on y-axis gives a straight line if it follows Korsmeyer and Peppas kinetics.

STABILITY STUDIES[85]

Optimized formulation tablets were packed in blister and stored in stability chambers maintained at 40°C±2°C and 75%±5% RH for three months. After every month tablet samples were analyzed for physical appearance, drug content and *in vitro* release.

Results & Discussion

PHYSICAL COMPATIBILITY STUDY

To obtain a stable and efficacious dosage form, the excipients must be carefully selected so that the incompatibility problems do not arise. The result is shown in table 7.1.

Table 7.1: Physical compatibility study of drug and excipients

S. No	Drug & Excipient	Description and Conditions						
		Initial	Room Temperature			$40^0 \pm 2^0$C / 75 ± 5% RH		
			10days	20days	30days	10days	20days	30days
1	LOX	Yellow coloured powder	NC	NC	NC	NC	NC	NC
2	TR	White coloured salt	NC	NC	NC	NC	NC	NC
3	SLS	White coloured powder	NC	NC	NC	NC	NC	NC
4	ML	White coloured powder	NC	NC	NC	NC	NC	NC
5	LA	White coloured powder	NC	NC	NC	NC	NC	NC
6	MS	White coloured powder	NC	NC	NC	NC	NC	NC
7	TA	White coloured powder	NC	NC	NC	NC	NC	NC
8	AE	White coloured powder	NC	NC	NC	NC	NC	NC
9	CA	Creamy white powder	NC	NC	NC	NC	NC	NC
10	LOX+TR	Yellow coloured powder	NC	NC	NC	NC	NC	NC
11	LOX+SLS	Yellow coloured powder	NC	NC	NC	NC	NC	NC
12	LOX+ML	Yellow coloured powder	NC	NC	NC	NC	NC	NC
13	LOX+LA	Yellow coloured powder	NC	NC	NC	NC	NC	NC
14	LOX+MS	Yellow coloured powder	NC	NC	NC	NC	NC	NC
15	LOX+TA	Yellow coloured powder	NC	NC	NC	NC	NC	NC
16	LOX+AE	Yellow coloured powder	NC	NC	NC	NC	NC	NC
17	LOX+CA	Yellow coloured powder	NC	NC	NC	NC	NC	NC

The physical compatibility study was performed visually. The results show that the drug and the excipients were physically compatible with each other.

FTIR STUDY – IDENTIFICATION AND COMPATIBILITY OF DRUG AND EXCIPIENTS

The identification of drug and the compatibility between the drug and the different excipients was carried out using FTIR. The FTIR spectrum of the pure drug, drug – excipients mixtures and final formulation were shown in figures 7.1 to 7.6 and tables 7.2 to 7.7.

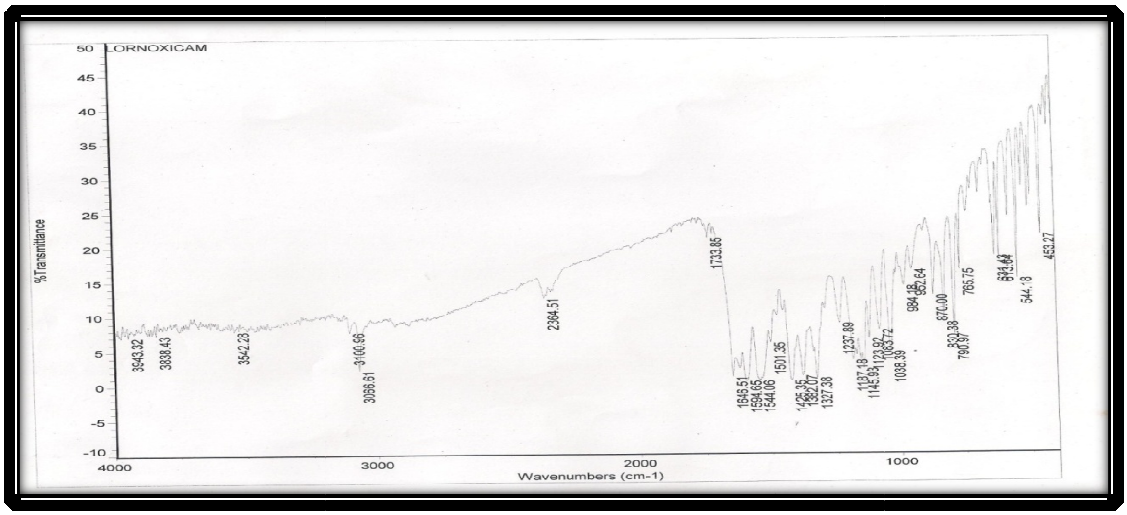


Fig. 7.1: FTIR Spectrum of Lornoxicam

Table 7.2: IR Interpretation of Lornoxicam

Wave Numbers (cm^{-1})	Interpretation
3066.61	Aromatic C-H Stretching
1425.35	C=C Stretching
1501.35	C=N Stretching
3100.96	N-H Stretching
3542.28	O-H Stretching
1646.51	C=O Stretching
1382.07	SO_2 Stretching
870	S-N Stretching
765.75	C-S Stretching

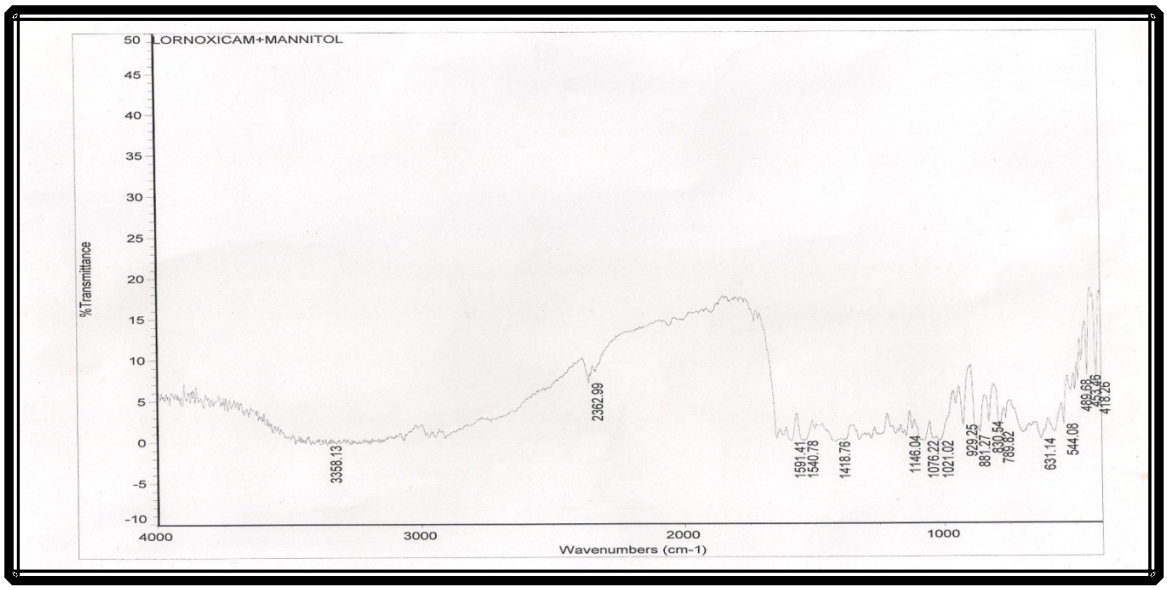


Fig. 7.2: FTIR Spectrum of Lornoxicam and Mannitol

Table 7.3: IR Interpretation of Lornoxicam and Mannitol

Wave Numbers (cm^{-1})	Interpretation
3066.00	Aromatic C-H Stretching
1418.76	C=C Stretching
1540.70	C=N Stretching
3100.00	N-H Stretching
3542.00	O-H Stretching
1591.41	C=O Stretching
1382.00	SO_2 Stretching
881.27	S-N Stretching
789.82	C-S Stretching

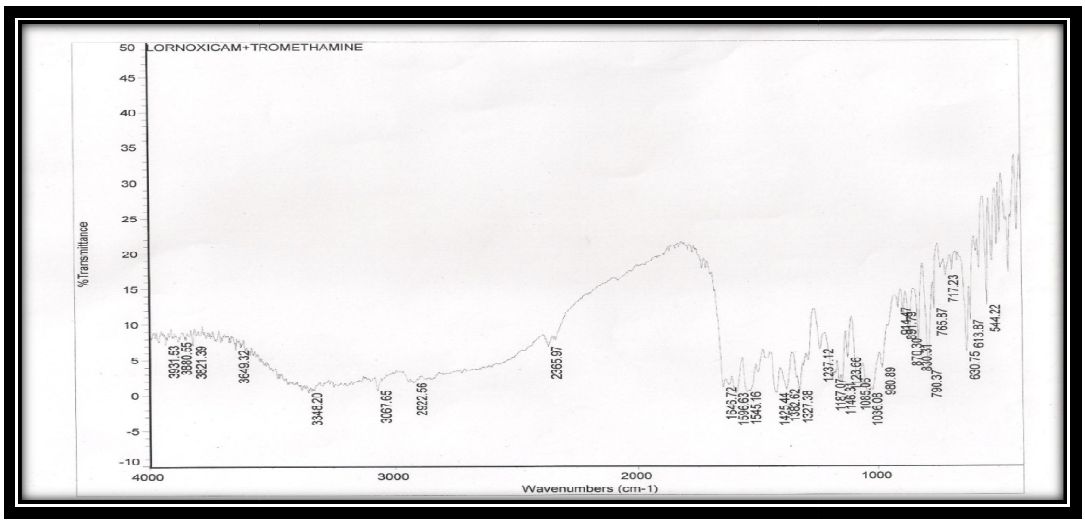


Fig. 7.3: FTIR Spectrum of Lornoxicam and Tromethamine

Table 7.4: IR Interpretation of Lornoxicam and Tromethamine

Wave Numbers (cm^{-1})	Interpretation
3067.65	Aromatic C-H Stretching
1425.44	C=C Stretching
1501.00	C=N Stretching
3067.65	N-H Stretching
3649.32	O-H Stretching
1646.72	C=O Stretching
1382.62	SO_2 Stretching
870.03	S-N Stretching
765.87	C-S Stretching

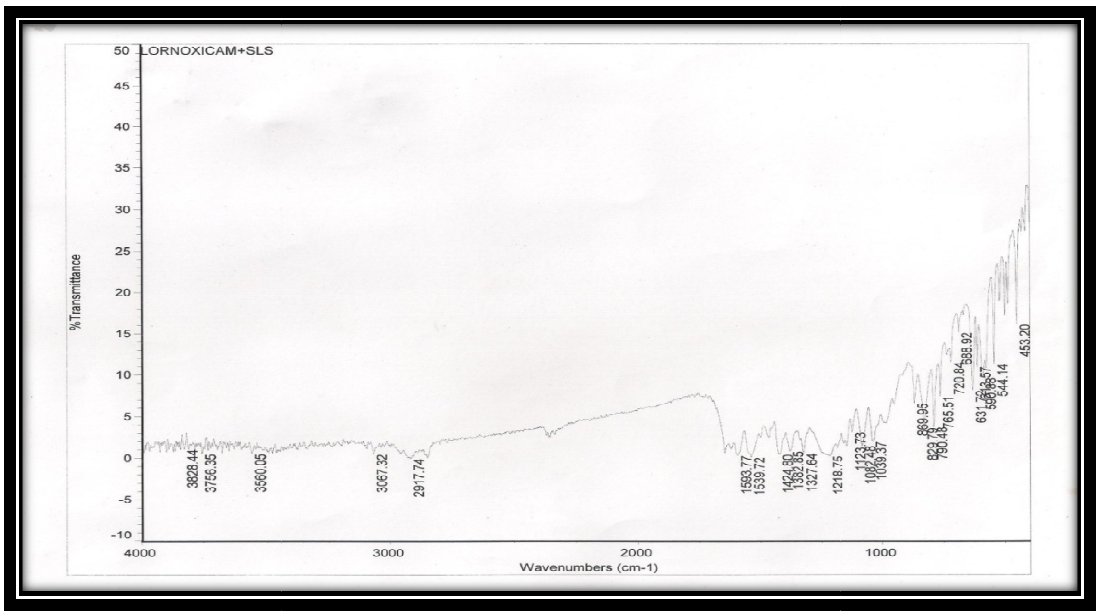


Fig. 7.4: FTIR Spectrum of Lornoxicam and SLS

Table 7.5: IR Interpretation of Lornoxicam and SLS

Wave Numbers (cm^{-1})	Interpretation
3067.32	Aromatic C-H Stretching
1424.50	C=C Stretching
1539.72	C=N Stretching
3100.00	N-H Stretching
3560.05	O-H Stretching
1646.00	C=O Stretching
1382.85	SO_2 Stretching
869.95	S-N Stretching
765.51	C-S Stretching

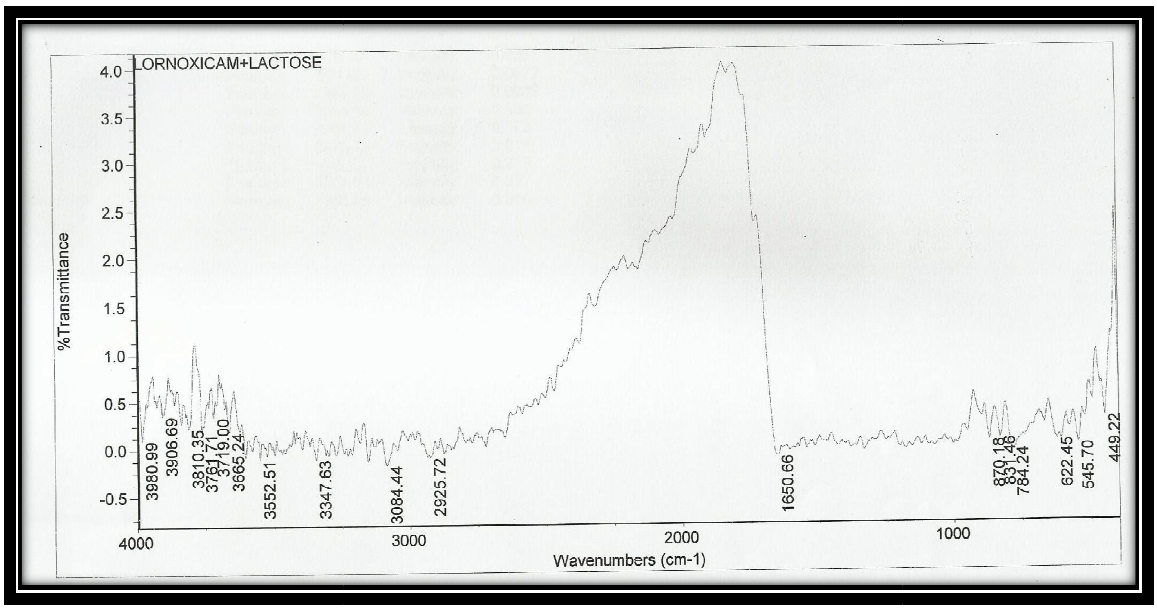


Fig. 7.5: FTIR Spectrum of Lornoxicam and Lactose

Table 7.6: IR Interpretation of Lornoxicam and Lactose

Wave Numbers (cm^{-1})	Interpretation
3067.32	Aromatic C-H Stretching
1427.00	C=C Stretching
1543.00	C=N Stretching
3093.00	N-H Stretching
3526.00	O-H Stretching
1643.00	C=O Stretching
1382.85	SO_2 Stretching
869.95	S-N Stretching
765.51	C-S Stretching

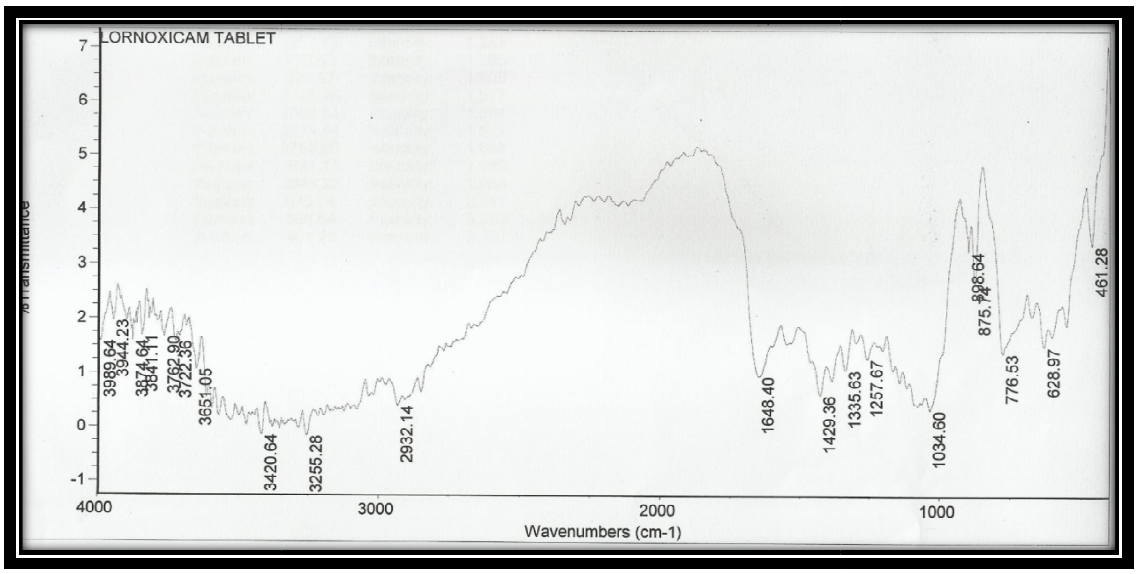


Fig. 7.6: FTIR Spectrum of Lornoxicam Tablet

Table 7.7: IR Interpretation of Lornoxicam Tablet

Wave Numbers (cm^{-1})	Interpretation
2932.14	Aromatic C-H Stretching
1429.36	C=C Stretching
1500	C=N Stretching
2932.14	N-H Stretching
3420.64	O-H Stretching
1648.40	C=O Stretching
875.74	SO_2 Stretching
1335.83	S-N Stretching
776.53	C-S Stretching

From the FTIR spectra, it is clearly evident that the physical mixtures of Lornoxicam with different excipients showed the presence of Lornoxicam characteristics bands at their same wave number. This indicated the absence of chemical interaction between the drug and the excipients.

STANDARD CURVE OF LORNOXICAM

The UV Spectrophotometric method was used to analyze LOX. The absorbance of the drug in various buffers: 0.1 N HCl buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8 was measured at a wavelength of 376 nm. The results are given in table 7.8 and Fig.7.7 to 7.9.

Table 7.8: Standard Curve of Lornoxicam

S. No.	Concentration (mcg/ml)	Absorbance at 376 nm		
		pH 1.2	pH 4.5	pH 6.8
1	2	0.0971	0.0874	0.0786
2	4	0.1861	0.1705	0.1477
3	6	0.2698	0.2536	0.2214
4	8	0.3490	0.3366	0.2950
5	10	0.4280	0.4095	0.3680

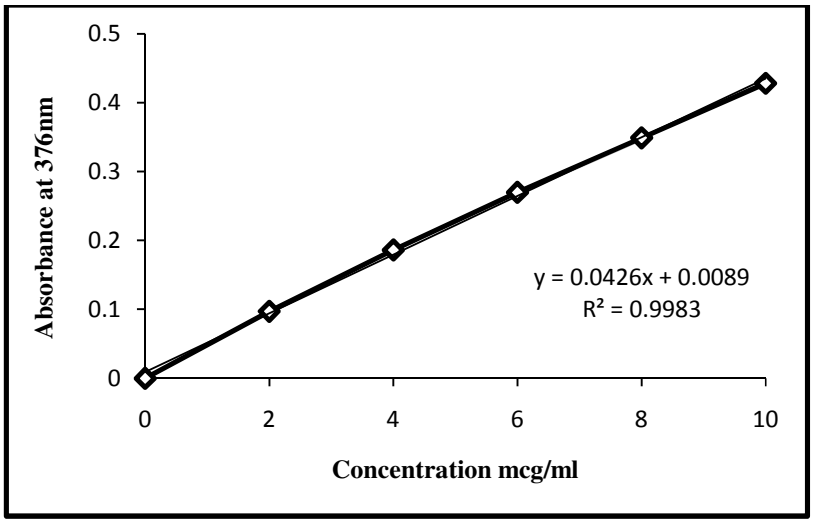


Fig. 7.7: Standard Curve of Lornoxicam in Acid buffer pH 1.2

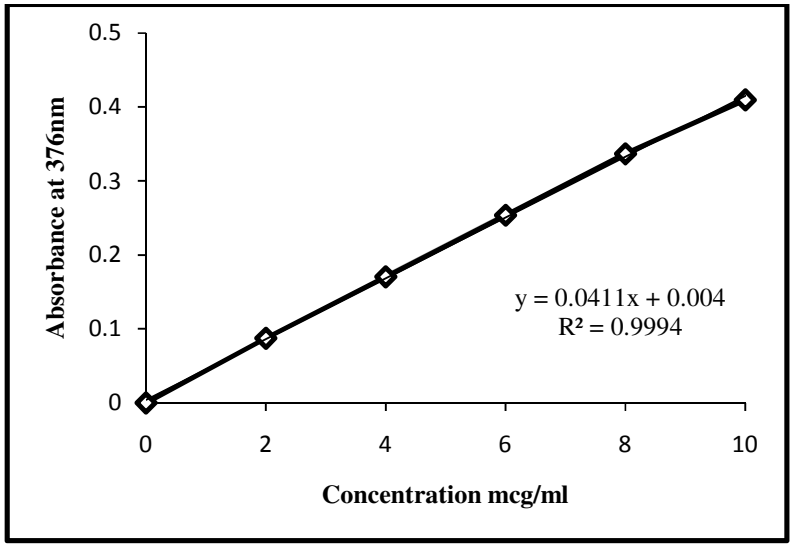


Fig. 7.8: Standard Curve of Lornoxicam in Acetate buffer pH 4.5

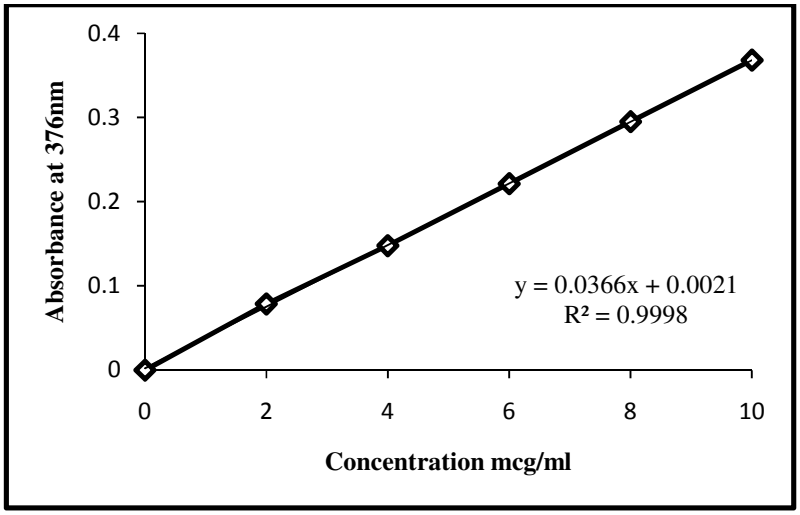


Fig. 7.9: Standard Curve of Lornoxicam in Phosphate buffer pH 6.8

The standard curve of lornoxicam in buffers pH 1.2, 4.5 and 6.8 are linear, starting from the origin. The curve obeys Beer Lambert law.[51]

PRECOMPRESSION STUDIES OF THE DRUG, BLENDS AND GRANULES

The result of precompression parameters for the drug and the formulated blends is given in table 7.9.

Table 7.9: Precompression Study of Drug and Formulated Blends

Drug & Formulation	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index*(%)	Hausner's Ratio*	Angle of Repose*(θ)
Drug	0.711±0.002	1.103±0.002	35.53±0.16	1.55±0.06	30.15±0.23
F01	0.663±0.007	0.768±0.008	13.67±0.10	1.15±0.08	31.32±0.23
F02	0.674±0.004	0.783±0.012	13.92±0.12	1.16±0.09	28.44±0.29
F03	0.622±0.005	0.730±0.009	14.79±0.14	1.17±0.12	35.44±0.28
F04	0.678±0.012	0.797±0.014	14.93±0.11	1.17±0.05	28.44±0.26

***Mean ± SD (n=5)**

The Angle of Repose of the blend ranged from 28.44^0 to 35.44^0. The Hausner's ratio of the formulated blends ranged from 1.15 to 1.17. The formulation blends showed poor – passable flow property.[76] Hence the wet granulation technique was used.

PRECOMPRESSION STUDIES OF DRUG AND GRANULES:

The result of pre compression studies of various formulations is given in table 7.10.

Table 7.10: Precompression Study of Drug and Granules

Drug & Formulation	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index*(%)	Hausner's Ratio*	Angle of Repose*(θ)
F01	0.510±0.004	0.585±0.007	12.82±0.21	1.14±0.03	19.44±0.16
F02	0.489±0.002	0.560±0.002	12.67±0.24	1.14±0.07	17.28±0.64
F03	0.479±0.003	0.534±0.006	10.29±0.28	1.11±0.05	19.43±0.17
F04	0.489±0.005	0.560±0.008	12.67±0.34	1.14±0.09	17.35±0.28

***Mean ± SD (n=5)**

The Angle of repose of the blend ranged from 17.28^0 to 19.44^0 .The Hausner's ratio of the formulated blends ranged from 1.11 to 1.14. The flow property of granules is excellent.[76]

EVALUATION OF LORNOXICAM CORE TABLETS

Uniformity of weight

Uniformity of weight of lornoxicam core tablets is given table 7.11.

Table 7.11: Uniformity of weight of Lornoxicam core tablets

Formulation	Average weight of tablet*(g)
F01	0.249±0.002
F02	0.249±0.001
F03	0.252±0.003
F04	0.249±0.001

***Mean ± SD (n=5)**

The core tablets were uniform in weight.[77]

Thickness

The thickness of core tablets is shown in table 7.12.

Table 7.12: Thickness of Lornoxicam Core Tablets

Formulation	Thickness*(mm)
F01	3.27±0.0
F02	3.27±0.0
F03	3.28±0.0
F04	3.27±0.0

***Mean ± SD (n=5)**

The thickness of core tablets is found to be 3.27mm and 3.28 mm. The tablets have uniform thickness.

Diameter

The diameter of core tablets is depicted in table 7.13.

Table 7.13: Diameter of Lornoxicam Core Tablets

Formulation	Diameter*(mm)
F01	8.76±0.0
F02	8.76±0.0
F03	8.77±0.0
F04	8.76±0.0

***Mean ± SD (n=5)**

The diameter of all the formulations was found to be 8.76mm and 8.77 mm. The tablets have uniform diameter.

Hardness

The hardness of core tablets is shown in table 7.14.

Table 7.14: Hardness of Lornoxicam core tablets

Formulation	Hardness* (kg/cm^2)
F01	3.0±0.0
F02	3.1±0.0
F03	3.0±0.0
F04	3.0±0.0

***Mean ± SD (n=5)**

The hardness of lornoxicam core tablets was found to be between 3 kg/cm^2 and 3.1 kg/cm^2. Hence the tablets have enough hardness to withstand stress during transport and handling.[29]

Friability

The percentage friability of various formulations is depicted below in table 7.15.

Table 7.15: Friability of Lornoxicam core tablets

Formulation	%Friability*
F01	0.16±0.023
F02	0.10±0.012
F03	0.12±0.025
F04	0.12±0.019

***Mean ± SD (n=5)**

The percentage friability of various formulations ranged from 0.10% to 0.16%. Hence the percentage friability complies with the official standard.[77]

EVALUATION OF LORNOXICAM COATED TABLETS

Uniformity of weight

Uniformity of weight of all the formulations is given in table 7.16.

Table 7.16: Uniformity of weight of Lornoxicam coated tablets

Formulations	Average weight of tablet*(g)
F01C1	0.278±0.003
F01C2	0.277±0.004
F01C3	0.277±0.002
F02C1	0.278±0.002
F02C2	0.277±0.003
F02C3	0.277±0.003
F03C1	0.277±0.002
F03C2	0.277±0.003
F03C3	0.276±0.002
F04C1	0.275±0.002
F04C2	0.276±0.002
F04C3	0.277±0.003

***Mean ± SD (n=5)**

The coated tablets were uniform in weight[77] and the weight ranged between 0.275g and 0.278 g.

Thickness

The thickness of all the coated formulations is given in table 7.17.

Table 7.17: Thickness of Lornoxicam coated tablets

Formulations	Thickness*(mm)
F01C1	3.542±0.014
F01C2	3.538±0.028
F01C3	3.568±0.019
F02C1	3.560±0.025
F02C2	3.546±0.016
F02C3	3.574±0.008
F03C1	3.542±0.034
F03C2	3.580±0.015
F03C3	3.568±0.013
F04C1	3.566±0.005
F04C2	3.570±0.033
F04C3	3.566±0.005

***Mean ± SD (n=5)**

The thickness of coated tablet was between 3.538mm and 3.580 mm. The table have uniform thickness.

Diameter

The diameter of all the formulations is given in table 7.18.

Table 7.18: Diameter of Lornoxicam coated tablets

Formulations	Diameter*(mm)
F01C1	8.966±0.020
F01C2	8.952±0.031
F01C3	8.956±0.020
F02C1	8.946±0.048
F02C2	8.912±0.042
F02C3	8.950±0.010
F03C1	8.954±0.023
F03C2	8.952±0.032
F03C3	8.960±0.010
F04C1	8.934±0.040
F04C2	8.966±0.015
F04C3	8.960±0.007

***Mean ± SD (n=5)**

The diameter of coated tablet was found to be 8.912mm to 8.966 mm. The tablets have uniform diameter.

Hardness

The hardness of all the coated formulations is given in table 7.19

Table 7.19: Hardness of Lornoxicam Coated Tablets

Formulation	Hardness* (kg/cm^2)
F01C1	5.7±0.273
F01C2	5.7±0.447
F01C3	5.6±0.418
F02C1	5.7±0.273
F02C2	5.5±0.353
F02C3	5.6±0.418
F03C1	5.5±0.353
F03C2	5.2±0.570
F03C3	5.9±0.273
F04C1	5.3±0.447
F04C2	5.8±0.570
F04C3	5.5±0.500

***Mean ± SD (n=5)**

The hardness of coated tablet ranged between 5.2 kg/cm^2 and 5.8 $kg/cm^{2.}$ Hence the tablets have enough hardness to withstand stress during transport and handling.[29]

Friability

The friability of all the formulations is given in table 7.20.

Table 7.20: Friability of Lornoxicam Coated Tablets

Formulations	Friability (%)
F01C1	0.10±0.023
F01C2	0.16±0.021
F01C3	0.15±0.019
F02C1	0.15±0.022
F02C2	0.14±0.026
F02C3	0.13±0.021
F03C1	0.12±0.028
F03C2	0.22±0.024
F03C3	0.18±0.021
F04C1	0.62±0.022
F04C2	0.71±0.027
F04C3	0.70±0.023

***Mean ± SD (n=5)**

The friability of osmotic tablet ranged between 0.10% and 0.71 %. Hence the tablets have enough hardness to withstand stress during transport and handling.[77]

Drug Content

The content of active ingredients of various formulations was analyzed using UV spectrophotometer at 376 nm. The results of drug content are depicted in table 7.21.

Table 7.21: Drug content

Formulations	Drug Content* (%w/w)
F01C1	100.84±1.403
F01C2	95.61±0.894
F01C3	97.33±0.976
F02C1	100.91±0.955
F02C2	99.08±1.110
F02C3	97.29±0.998
F03C1	95.26±0.987
F03C2	99.46±1.098
F03C3	97.15±1.143
F04C1	95.98±0.987
F04C2	98.33±1.056
F04C3	99.05±1.123

***Mean ± SD (n=5)**

The percentage of drug content of all the formulations ranged from 95.61% w/w to 100.91%w/w. All the formulations comply with the official standards.

Uniformity of content

The content of active ingredients of various formulations was analyzed using UV spectrophotometer at 376 nm. The results of drug content are depicted in table 7.22.

Table 7.22: Uniformity of content

Formulation	Drug Content* (%w/w)
F01C1	99.04±0.989
F01C2	97.23±0.709
F01C3	100.23±0.231
F02C1	99.87±0.897
F02C2	98.99±1.110
F02C3	95.90±0.289
F03C1	97.12±0.678
F03C2	99.98±0.092
F03C3	98.95±1.076
F04C1	98.98±0.678
F04C2	97.34±1.897
F04C3	100.23±1.021

***Mean ± SD (n=10)**

The drug content from all the formulations ranged from 95.90%w/w to 100.23%w/w. All the formulations comply with the test for uniformity of drug content[77].

***In vitro* release study of the tablets:**

The *in vitro* release of various formulations is shown in table 7.23 and figure 7.10.

Table 7.23: *In vitro* release of the tablets

Dissolution Medium	Time in Hours	Cumulative percentage drug release*											
		F01C1	F02C1	F03C1	F04C1	F01C2	F02C2	F03C2	F04C2	F01C3	F02C3	F03C3	F04C3
Acid Buffer pH 1.2	0	0	0	0	0	0	0	0	**0**	0	0	0	0
	1	0.17 ±0.04	0.50 ±0.40	3.50 ±0.4	3.76 ±0.48	0.20 ±0.02	2.76 ±0.02	5.90 ±0.08	**9.00 ±0.05**	0.23 ±0.03	3.29 ±0.56	10.70 ±0.16	12.09 ±0.91
	2	2.78 ±0.32	6.14 ±0.56	7.15 ±0.56	7.49 ±0.69	2.78 ±0.21	6.14 ±0.36	8.46 ±0.03	**11.50 ±0.49**	3.01 ±0.18	8.65 ±0.28	15.02 ±0.23	18.68 ±0.56
Phosphate Buffer pH 6.8	3	9.02 ±0.55	15.20 ±0.96	18.38 ±0.58	19.98 ±0.21	11.96 ±1.04	15.32 ±0.16	17.52 ±0.08	**21.63 ±0.26**	11.15 ±0.72	18.68 ±0.33	25.73 ±0.54	35.04 ±0.97
	4	11.73 ±0.45	18.19 ±0.23	22.78 ±0.53	23.77 ±0.98	16.61 ±0.29	19.32 ±0.15	28.73 ±0.04	**30.52 ±0.53**	16.02 ±0.04	24.04 ±0.52	34.96 ±0.05	43.31 ±0.69
	5	14.76 ±0.58	21.90 ±0.55	27.36 ±0.89	27.69 ±0.43	18.88 ±0.33	25.07 ±0.22	33.81 ±0.04	**39.60 ±0.59**	19.67 ±0.33	29.15 ±0.43	44.17 ±0.54	48.90 ±0.17
	6	18.33 ±0.55	26.82 ±0.50	33.08 ±0.21	32.82 ±0.55	24.76 ±0.24	31.29 ±0.02	37.82 ±0.08	**43.82 ±0.81**	27.53 ±0.21	35.13 ±0.07	51.30 ±0.05	55.37 ±1.62
	7	22.26 ±0.49	28.76 ±0.47	37.48 ±0.56	37.60 ±0.59	29.54 ±1.46	37.46 ±3.42	41.97 ±0.03	**47.76 ±0.89**	35.13 ±0.10	41.24 ±0.47	58.04 ±0.20	62.59 ±1.30
	8	26.42 ±0.87	33.28 ±0.45	41.35 ±0.53	41.29 ±0.59	32.29 ±0.71	41.95 ±0.20	47.30 ±0.30	**57.43 ±0.59**	39.91 ±0.01	48.71 ±0.40	62.45 ±0.89	68.06 ±0.15
	9	29.13 ±0.64	36.86 ±0.98	45.55 ±0.58	46.02 ±0.95	39.82 ±1.09	47.90 ±0.20	49.74 ±0.04	**61.49± 0.41**	44.05 ±0.77	56.70 ±0.40	65.64 ±0.51	74.72 ±0.51
	10	35.21 ±0.89	39.65 ±0.44	48.83 ±0.44	52.41 ±0.69	44.88 ±0.89	52.40 ±0.40	57.53 ±0.50	**68.45 ±0.23**	50.78 ±0.10	62.31 ±0.17	73.32 ±0.94	79.08 ±0.93
	24	45.81 ±0.66	49.38 ±0.85	55.98 ±0.48	59.94 ±0.65	52.89 ±0.16	63.59 ±0.30	86.18 ±0.02	**99.14 ±0.63**	58.04 ±0.20	76.39 ±0.45	97.43 ±0.11	99.01 ±1.00

***Mean ± SD (n=3)**

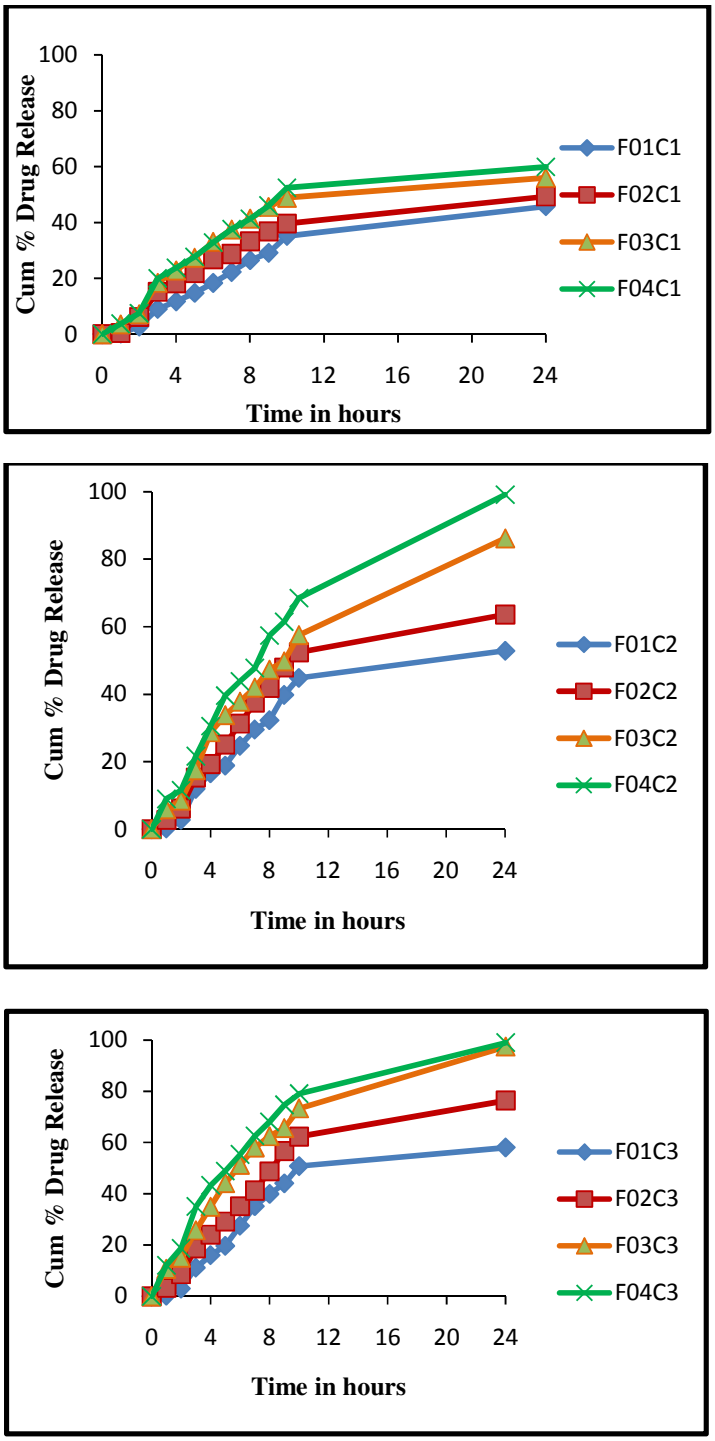


Fig. 7.10: *In vitro* release study of the tablets

***In vitro* Release Study of Optimized Formulation (F04C2)**

The *in vitro* release study of optimized formulation was shown in table 7.24 and figure 7.11.

Table 7.24: *In vitro* Release of Optimized Formulation (F04C2)

S. No	Time in hours	Cumulative percentage Drug Release*
1	0	0
2	1	9.22±0.026
3	2	15.89±0.067
4	3	21.11±0.078
5	4	27.21±0.038
6	5	33.90±0.067
7	6	38.75±0.087
8	7	45.21±0.028
9	8	52.03±0.078
10	9	55.90±0.065
11	10	62.01±0.042
12	12	68.89±0.067
13	14	74.23±0.029
14	16	83.89±0.098
15	24	99.13±0.023

***Mean ± SD (n=3)**

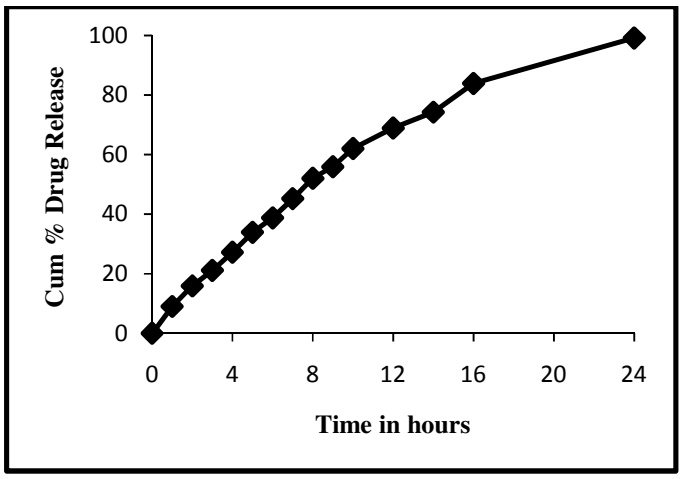


Fig. 7.11: Release study of optimized formulation (F04C2)

The formulatin F04C2 produced the drug release for 24 hours.

Effect of amount of osmogen on drug release:

The effect of amount of osmogen on drug release is shown in the figure 7.12

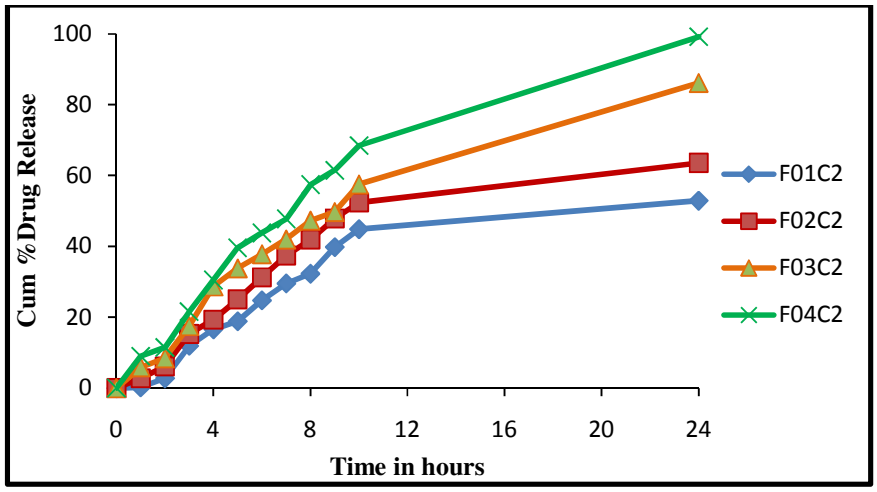


Fig. 7.12: Effect of osmogen concentration on drug release

Increase in concentration of mannitol increases the drug release. Higher the amount of osmogen, greater is the driving force to release the drug. This is because increase in osmogen concentration increases the osmotic pressure inside the tablet and thus the rate of drug release is increased.[29]

Effect of concentration of pore forming agents on drug release

To study the effect of concentration of pore forming agent(sorbitol), core tablet F04 with three different coatings C1, C2, C3 (Formulation F04C1, F04C2, F04C3) containing various concentration of sorbitol were selected.

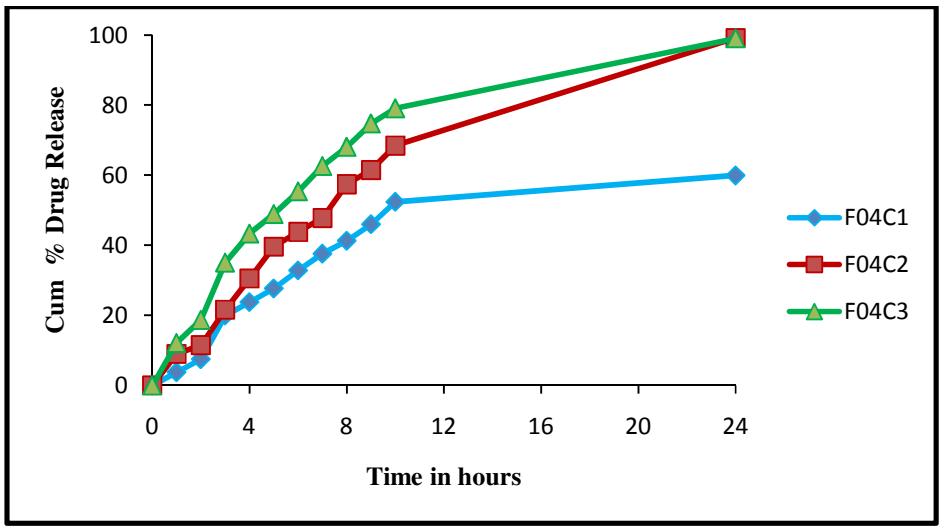


Fig. 7.13: Effect of concentration of pore forming agents on drug release

The formulation F04 with C1 coating showed only 52.41% of drug release at the end of 10 hours due to lack of pore forming agent (0% sorbitol). The formulation F04 with C2 coating(10% sorbitol) showed drug release of 68.45% at the end of 10 hours. The formulation F04 with C3 coating (20% sorbitol) showed faster drug release of 79.08% at the end of 10 hours. This shows that the level of pore former increases the membrane porosity resulting in faster drug release.[29](Figure 7.13)

EVALUATION OF OPTIMIZED FORMULATION

Effect of Agitation Speed on the drug release

Drug release under different agitation rates was conducted in order to investigate the influence of agitation rate on drug release and the results are shown in table 7.25 and figure 7.14.

Table 7.25: Effect of Agitation Speed on drug release

Dissolution Medium	Time in hours	Cumulative % drug release*		
		Speed of rotation of the paddle		
		50 rpm	100 rpm	150 rpm
Acid buffer pH 1.2	0	0	0	0
	1	9.29±0.56	8.45±0.55	10.45±0.78
	2	13.06±0.83	14.10±1.11	13.77±0.44
Phosphate buffer pH 6.8	3	21.33±0.88	21.05±1.63	21.48±1.41
	4	26.30±1.6	26.15±0.85	26.58±0.62
	5	31.54±0.50	31.33±1.11	31.86±0.14
	6	38.14±0.86	38.11±0.89	38.74±1.26
	7	45.35±0.64	43.73±0.87	48.50±0.40
	8	50.12±0.45	50.98±1.02	51.61±0.84
	9	57.91±1.09	57.40±0.60	57.44±0.90
	10	67.69±0.52	66.72±2.18	68.40±1.04
	24	99.10±0.13	99.32±0.49	99.50±0.28

***Mean ± SD (n=3)**

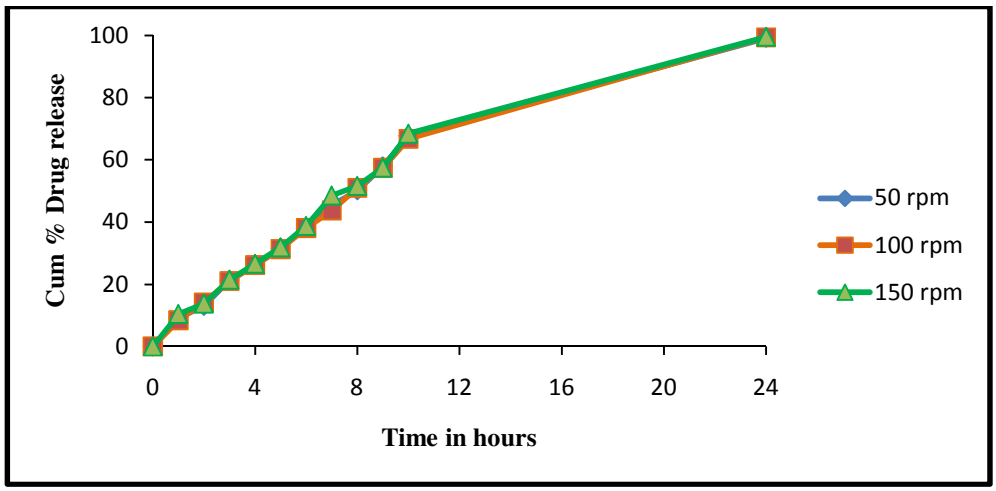


Fig. 7.14 : Effect of Agitation Speed on Drug release

The speed of rotation doesn't have much effect on drug release. Therefore the mobility of gastrointestinal tract might scarcely affect the drug release.[29]

Effect of Osmotic Pressure on drug release

Drug release under different osmotic pressure was conducted in order to investigate the influence of osmotic pressure of release medium on drug release and the results are shown in table 7.26 and figure 7.15.

Table 7.26: Effect of Osmotic Pressure on drug release

Dissolution Medium	Time in hours	Cumulative % drug release*		
		Osmotic Pressure of the medium		
		1.5 atm.	3 atm.	4.5 atm.
Acid buffer pH 1.2	0	0	0	0
	1	5.70±0.58	3.76±0.80	3.12±1.12
	2	7.87±0.36	8.72±0.51	6.93±0.41
Phosphate buffer pH 6.8	3	20.38±0.73	19.96±1.27	18.29±1.61
	4	24.11±0.89	22.11±1.10	23.20±1.01
	5	30.09±2.01	28.03±1.18	26.01±1.00
	6	38.02±1.07	35.98±0.25	33.81±0.19
	7	43.22±1.67	43.44±0.79	37.40±0.81
	8	53.45±0.77	48.08±0.95	42.66±0.55
	9	58.98±00.23	56.01±1.20	47.66±1.01
	10	67.94±0.27	61.44±1.46	49.81±2.18
	24	86.85±1.15	72.22±2.78	57.53±1.47

***Mean ± SD (n=3)**

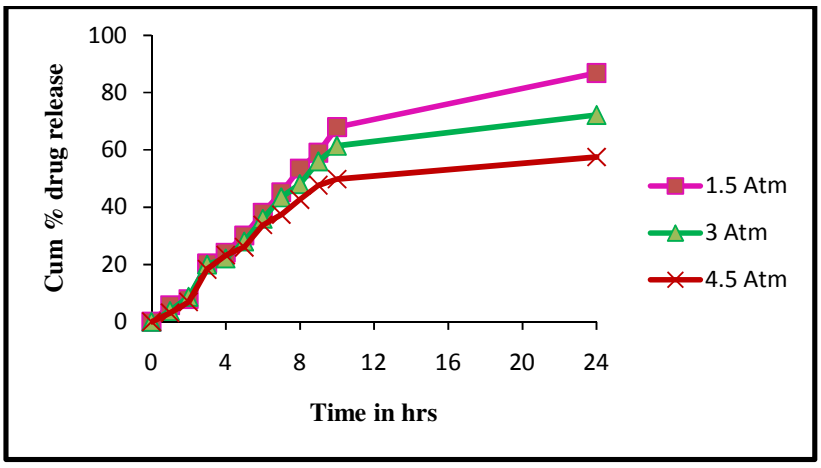


Fig. 7.15: Effect of Osmotic Pressure on drug release

The drug release from the formulation decreased with increase in osmotic pressure of the dissolution medium. This confirms that the mechanism of drug release is by osmotic pressure.[29]

Effect of pH on drug release

In order to study the effect of pH on drug release the optimized formulation (F04C2) was subjected to drug release study in different dissolution medium like acid buffer pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The results are depicted in table 7.27 and figure 7.16.

Table 7.27 : Effect of pH on drug release

Time in hours	Cumulative % drug release*		
	Acid Buffer pH 1.2	Acetate Buffer pH 4.5	Phosphate Buffer pH 6.8
0	0	0	0
1	9.93±1.07	9.46±1.53	10.16±2.82
2	14.80±1.40	14.86±0.35	14.92±0.42
3	21.29±0.61	21.10±1.90	23.73±2.26
4	28.47±0.83	29.06±1.17	29.01±1.11
5	33.09±1.41	35.01±1.37	36.21±1.78
6	38.2±4.20	38.69±0.54	42.35±0.86
7	44.84±0.00	44.42±1.47	47.73±1.05
8	52.63±0.63	51.34±0.78	54.47±0.86
9	58.73±0.07	58.40±0.83	59.06±2.17
10	67.61±0.20	65.33±1.79	65.55±1.45
24	99.45±0.45	99.13±0.63	99.21±0.36

***Mean ± SD (n=3)**

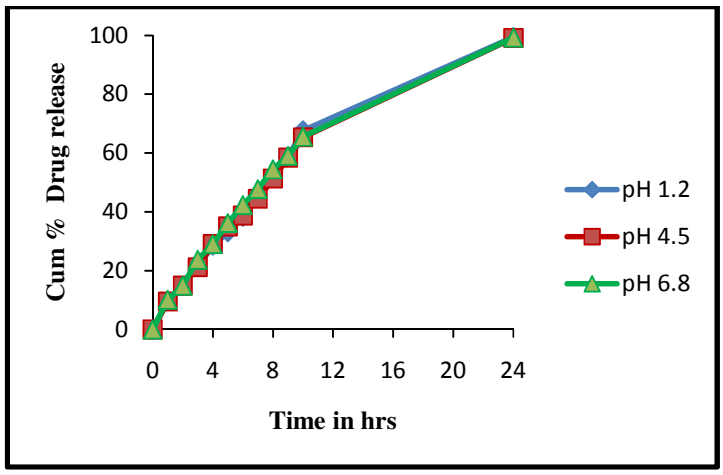


Fig 7.16 : Effect of pH on drug release

The pH of release medium does not have significant effect on drug release. Therefore the pH of gastrointestinal tract might scarcely affect the drug releaase.[22]

Membrane Morphology of porous Osmotic Tablets

Membranes obtained before and after dissolution was studied using scanning electron microscope. Membranes obtained before dissolution showed non porous region (Fig 7.17a, 7.18a). After 24 hours of dissolution the membrane showed pore formation owing to the dissoution of sorbitol from the membrane (Fig 7.17b, 7.18b) and thus the release of drug takes place. Coating solution C2 containing 10% sorbitol was coated on the formulation F04 produced less pores compared to formulation F04 coated with the coating solution C3 containing 20% sorbitol (Figure 7.17 a,b & 7.18 a,b).

a) Before Dissolution **b) After Dissolution**

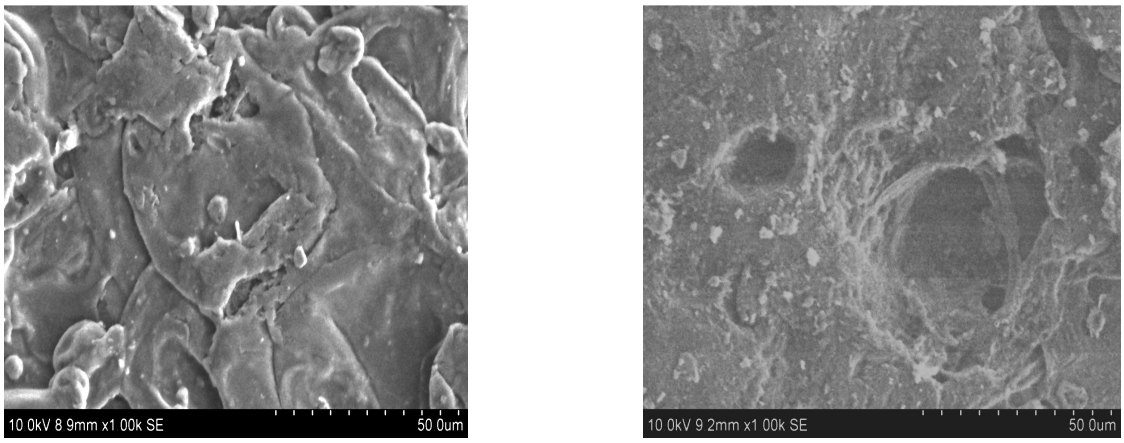


Fig. 7.17 : Membrane Morphology of Formultion F04C2 by Scanning Electron Microscope

a) Before Dissolution **b) After Dissolution**

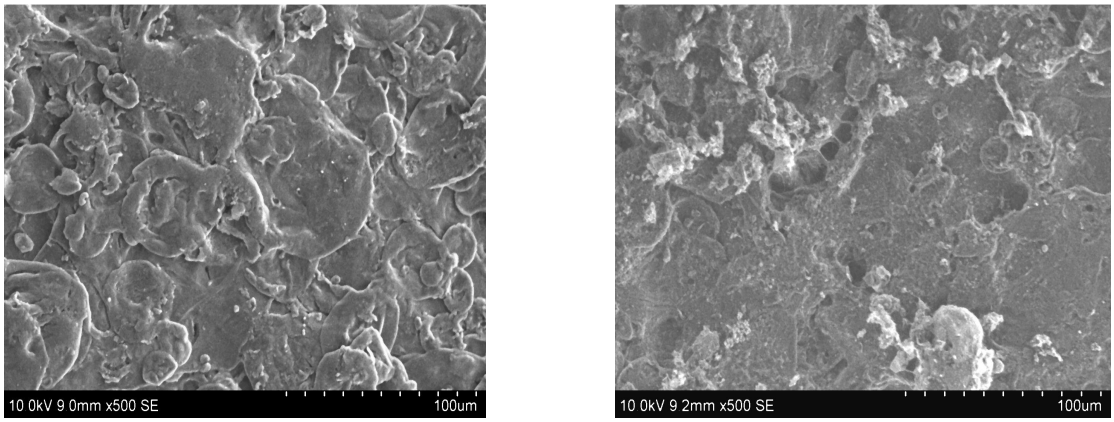


Fig. 7.18 : Membrane Morphology of Formultion F04C3 by Scanning Electron Microscope

Release Kinetics of the Optimized Formulation

The dissolution data of the optimized formulation was fitted to various kinetic models and the reults are tabulated in table 7.28 and figures 7.19 to 7.23.

Table 7.28 : Release Kinetics of the Optimized Formulation

Time (hours)	Log time (Hours)	Sq. root of time (hours)	Cum % drug release	Cum % Drug remaining	Log Cum % drug release	Log cum % drug remaining	Cube root of cum % drug remaining
0	-	0	0	100	-	2.00	4.64
1	0	1	9.22	90.78	0.96	1.96	4.49
2	0.30	1.14	15.89	84.11	1.20	1.92	4.38
3	0.48	1.73	21.11	78.89	1.32	1.89	4.29
4	0.60	2.00	27.21	72.79	1.43	1.86	4.18
5	0.70	2.24	33.90	66.10	1.53	1.82	4.04
6	0.77	2.44	38.75	61.25	1.59	1.79	3.94
7	0.85	2.65	45.21	54.79	1.66	1.74	3.80
8	0.90	2.83	52.03	47.97	1.72	1.68	3.63
9	0.95	3.00	55.90	44.10	1.75	1.64	3.53
10	1.00	3.16	62.01	37.99	1.79	1.60	3.36
12	1.07	3.46	68.89	31.11	1.84	1.49	3.15
14	1.15	3.74	74.23	25.77	1.87	1.41	2.95
16	1.20	4.00	83.89	16.11	1.92	1.20	2.53
24	1.38	4.90	99.13	0.87	1.99	-0.06	0.95

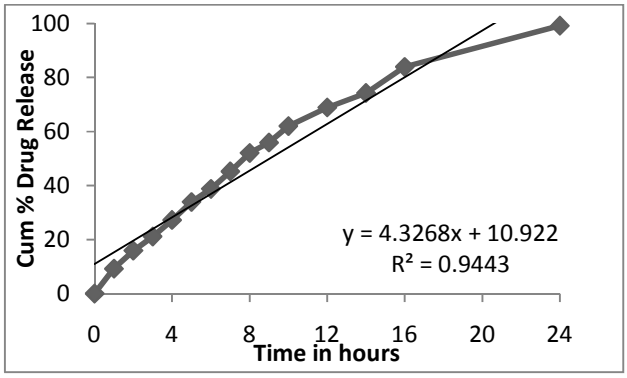


Fig. 7.19 : Plot of zero order kinetics

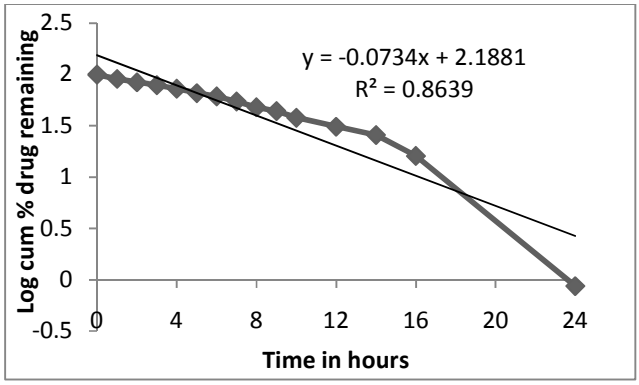


Fig. 7.20 : Plot of first order kinetics

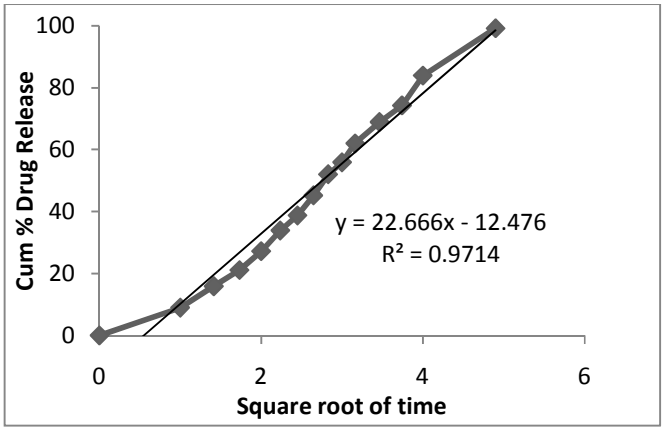


Fig. 7.21 : A Plot of Higuchi kinetics

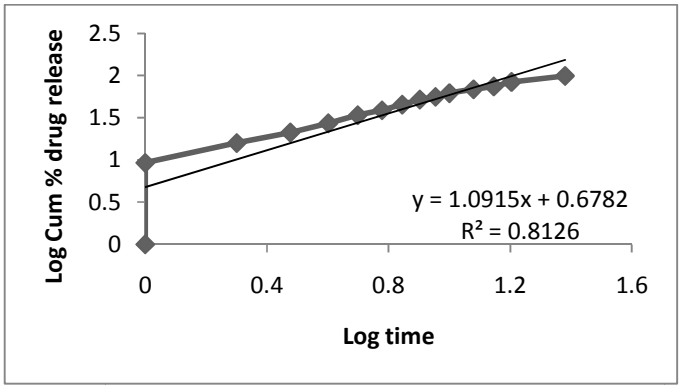


Fig. 7.22: Plot of Korsmeyer and Peppas Kinetics

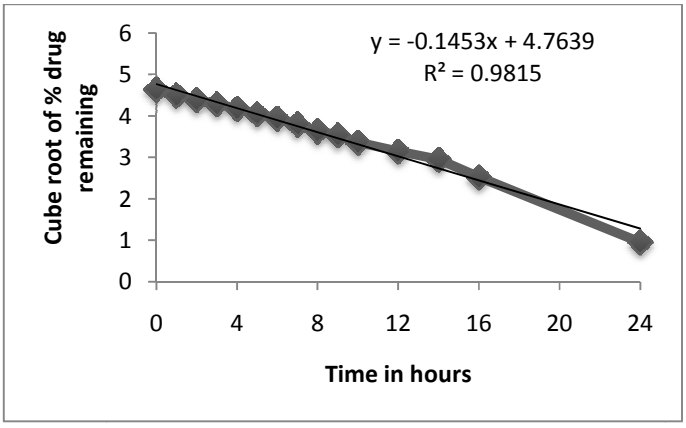


Fig. 7.23: Plot of Hixson-Crowell Kinetics

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2 values of various models are in table 7.29.

Table 7.29 : R^2 values of various kinetic models

Kinetic model	Coefficient of determination(R^2)
Zero order	0.9443
First order	0.8639
Higuchi	0.9714
Korsemeyer and Peppas	0.8126
Hixson Crowell	0.9815

The *in vitro* drug release of the optimized formulation F04C2 was best explained by Hixson Crowell as the plots showed the highest linearity (R^2=0.9815) followed by zero order (R^2=0.9443). The Hixson Crowell plot indicated a change in surface area and diameter of the tablets with progressive dissolution of the tablet as a function of time.[84]

STABILITY STUDY

After storage, the formulation F04C2 was subjected to evaluation of physical parameters, drug content and *in vitro* drug release. The results are tabulated in table 7.30 & 7.31.

Table 7.30 : Stability Studies

Parameter	Initial	1st Month	2nd Month	3rd Month
Description	Yellow round concave coated tablets	Yellow round concave coated tablets	Yellow round concave coated tablets	Yellow round concave coated tablets
Diameter* (mm)	8.966±0.0151	8.952±0.0311	8.978±0.0356	8.954±0.0309
Thickness*(mm)	3.570±0.0330	3.542±0.0148	3.574±0.0190	3.570±0.0178
Hardness* (kg/cm^2)	5.8±0.5700	5.7±0.2738	5.7±0.5734	5.8±0.3209
Drug content*(%w/w)	98.33±1.123	99.08±1.098	98.34±1.134	99.18±1.1290

***Mean ± SD (n=5)**

Table 7.31: *In vitro* release study before and during stability study

Dissolution Medium	Time in hours	Cumulative % drug release*			
		Initial	1st Month	2nd Month	3rd Month
Acid buffer pH 1.2	0	0	0	0	0
	1	09.00±0.05	8.37±0.75	7.75±0.46	7.34±0.50
	2	11.50±0.49	12.05±1.84	12.10±0.21	12.89±0.19
Phosphate Buffer pH 6.8	3	21.63±0.26	24.34±0.65	22.44±0.51	24.37±0.44
	4	30.52±0.53	30.02±1.10	29.83±0.68	29.71±0.39
	5	39.60±0.59	41.14±0.86	39.11±0.85	39.93±1.03
	6	43.82±0.81	43.75±1.06	44.07±0.12	44.77±0.51
	7	47.76±0.89	47.26±0.95	49.50±1.53	50.56±0.48
	8	57.43±0.59	56.21±1.79	56.40±0.42	57.41±0.42
	9	61.49±0.41	60.19±0.93	63.34±0.67	64.97±0.13
	10	68.45±0.23	69.71±0.31	69.82±0.57	69.79±0.70
	24	99.14±0.63	99.51±0.36	98.44±1.44	98.00±0.69

***Mean ± SD (n=3)**

When the osmotic tablets were stored at 40^0C±2ºC / 75±5% RH for 3 months there appeared no change either in physical appearance or in drug content. When the dissolution study was conducted in the simulated physiological environment of stomach (pH 1.2) and intestine (pH 6.8), not much difference was observed in the cumulative percentage release of Lornoxicam from F04C2.

Summary & Conclusion

The aim of the present study was to develop a controlled porosity osmotic tablet of LOX and to evaluate the *in vitro* release of the drug from the system. The osmotic tablet is developed such that it delivers 8 mg of LOX over a period of 24 hours.

- Drug – Excipient compatibility study was carried out using FTIR study. The results showed that there was no interaction between them.
- Calibration curves of LOX were constructed in three different pH; Acid buffer pH 1.2, Acetate buffer pH 4.5 and phosphate buffer pH 6.8.
- Wet granulation produced excellent flow and the granules were compressed on 9/32 concave punches into tablets. The tablets were then coated with a controlled porosity semipermeable membrane of CA with sorbitol as pore former.
- The post compression parameters namely uniformity of weight, thickness, diameter, hardness, drug content and uniformity of content were evaluated for the coated and uncoated tablets and were found to be within limits.
- The *in vitro* study was carried out for 2 hours in 0.1N HCl buffer pH 1.2 and for 22 hours in phosphate buffer pH 6.8.
- Among the different formulations, F04C2 gave satisfactory results by releasing 99.13% of LOX in 24 hours.
- The drug release was found to increase with increase in the osmogen content.
- Variation in the speed of rotation of the paddle did not alter the release to a greater extent. Increase in osmotic pressure of the medium decreased the drug release.
- The release study was conducted in different release medium like Acid buffer pH 1.2, Acetate buffer pH 4.5, and Phosphate buffer pH 6.8. Variation in pH does not affect the release to a greater extent.
- To describe the mechanism of drug release, the optimized formulation was fitted to various models. The drug release was found to follow zero order and Hixson Crowell release.
- The accelerated stability testing was carried out for 3 months and showed no change in the appearance, hardness, diameter, thickness, friability, drug content and *in vitro* release.

- Of the several formulations investigated, the formulation (F04C2) containing 60% mannitol in the core tablet as osmogen and 10% of sorbitol in the semipermeable membrane as pore former has come out successfully to comply with the requirements for controlled release formulations. The osmotic pressure exerted by the osmogen in the core tablet and the amount of pore former in the semipermeable membrane controlled the drug release.

Future Scope

- ✓ Gamma scintigraphy is required to be done to ensure that the release starts in the upper part of GIT.
- ✓ Stability studies – Short term and long term to be carried out.

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