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Original Research Article

Formulation and Evaluation of Bilayer Tablets of Lornoxicam for the Management of Pain

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Abstract:

The aim of present study was to formulate and evaluation of bilayer tablet for management of Pain Contacting Lornoxicam.

The Immediate release layer prepared by dry granulation method using sodium starch glycolate, cross povidone, aerosil, magnesium stearate, lake, microcrystalline cellulose and dicalcium phosphate are used. The sustained release layer prepared by wet granulation method using HPMC E50, PVPK30, eudragit, microcrystalline cellulose, talc, magnesium stearate and isopropyle alcohol. Both the layer was separately optimized and were prepared.

Optimized formulation F6 Over 42 % of levfloxacin s was released within the first 1 hour of dissolution study. This initial high amount of Lornoxicam can be attributed to the fast release layer of the formulation. Further release of Lornoxicam was studied for 12 hours. So it can be concluded that bilayer tablet of Lornoxicam which reduces pain incorporated in Immediate and sustain Layer.

Keywords: Bilayer tablet, HPMC, Lornoxicam, Dry granulation method, Sustained release.

Introduction

The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. During the past few decades, numerous oral drug delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a specific period of time at a predetermined and controlled rate. Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, superporous hydrogels and magnetic systems. The current review addresses briefly about the FDDS that is one of the most leading methodologies in gastroretentive drug formulations [1].

Floating drug Delivery System

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach fora longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the

gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [2]. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents, that delay gastric emptying. [3,4,5,6], Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [7]. Gastric emptying occurs during fasting as well as fed states.

The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours [5]. This is called the interdigestive myloelectriccycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington [8].

- Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regularcontractions for short period.It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycle

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (toless than 1 mm), which are propelled toward

the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate [9].

Table No.1: Salient Features, Of Upper Gastrointestinal Tract

Section	Length	Transit	pH	Microbial	Absorbing surface	Absorption
Stomach	.2	Variable	1-4	<103	.1	P, C, A
Small	6-10	3-10	5-7.5	103-1010	120-200	P, C, A, F, I, E

A – Active transport C – Aqueous channel transport F – Facilitated transport P – Passive diffusion E – Entero-or pinocytosis I– Ion-pair transport, CM – Carrier mediated transport

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single-and multiple-unit systems [10].

Single-Unit Dosage Forms

In Low-density [11] approach the globular shells apparently having lower density than that ofgastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells [12] popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid-filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber [13] into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid entersto dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug emains therein. The fluid present could be air, under partial vacuum or any other suitable gas, iquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

a. **Effervescent Systems (Gas-generating Systems)**

These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in thestomach.

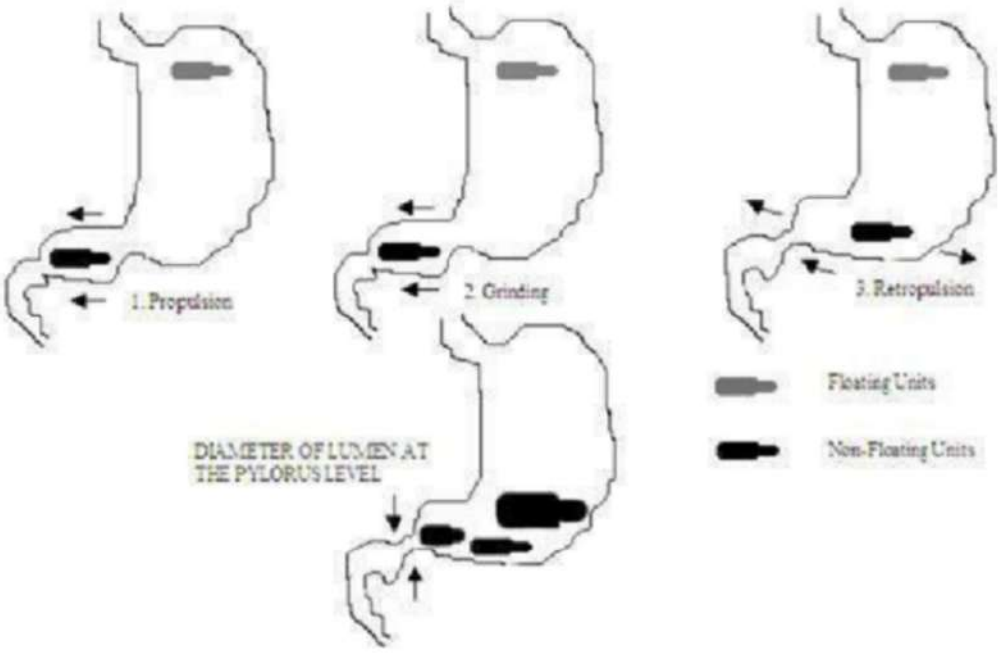

Figure 1: Intragastric residence positions of floating and nonfloating unit.

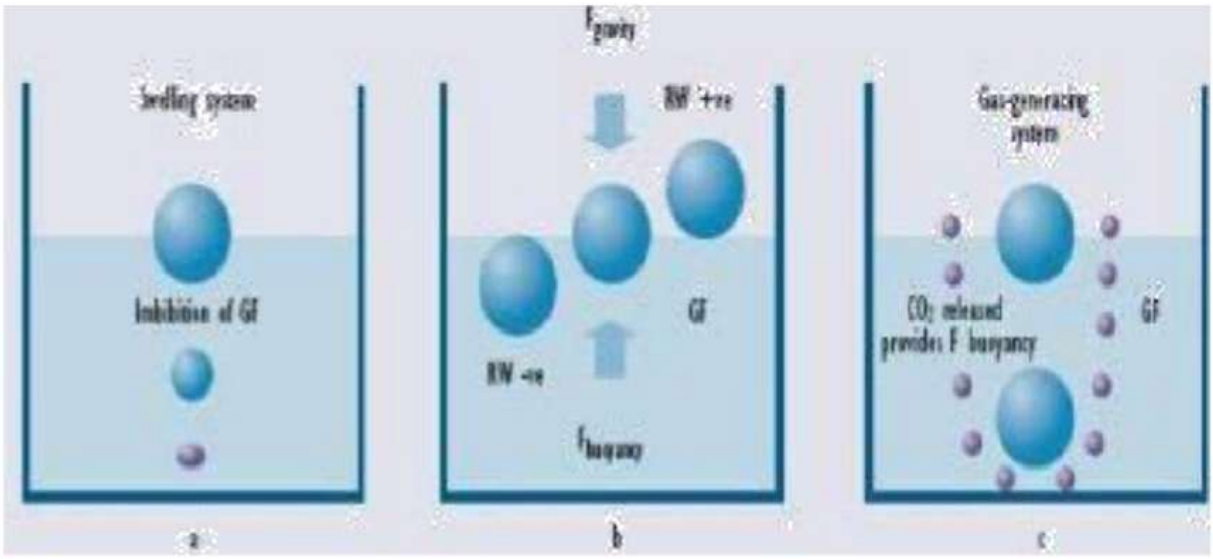

Fig No.2: Concept of Effervescent Tablet b. Non-effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.Examples of this type of FDDS include colloidal gel barrier, microporous compartment system, alginate beads, and hollow microspheres.

Hydrodynamically balanced systems (HBS)

These are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1. It should stay in the stomach, maintain its structural integrity,and release drug constantly from the dosage form. The success of HBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. HBS can either be formulated as a floating tablet or capsule. Many polymers and polymer combinations with wet granulation as a manufacturing technique have been explored to yield floatable tablets.

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose. Self- correcting floatable asymmetric

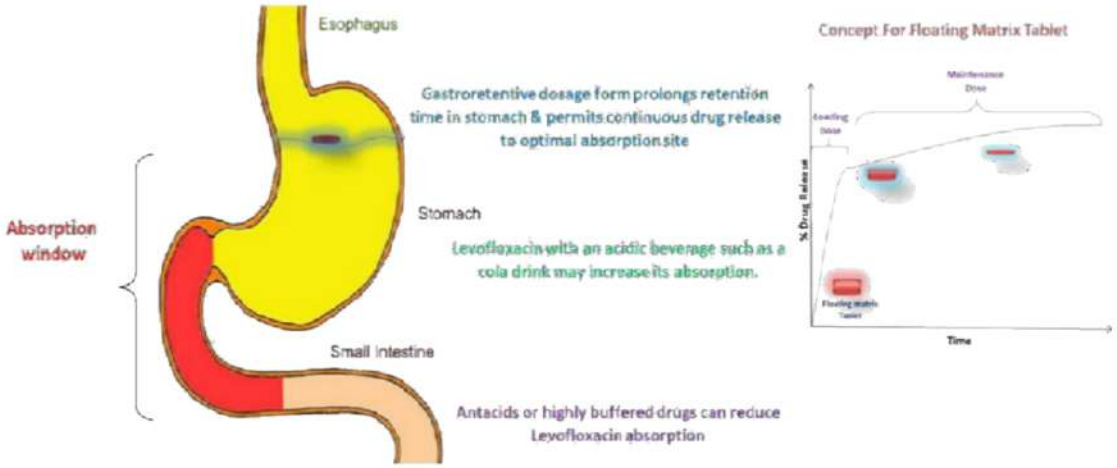

Fig No.3: Concept of floating matrix tablet

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the abovementioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges, also referred to as “microballoons,” have been prepared [12]. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability [13]. In Carbon dioxide– generating multiple- unit oral formulations, several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.[2]

Factors Affecting Floating Drug Delivery System

Density: Density of the dosage form should be less than the gastric contents(1.004gm/ml).

Size and Shape: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises

with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have betterGIT for 90 to 100 % retention at 24 hours compared with other shapes.

Fed or Unfed State: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of the meal: Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

Caloric Content: GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats. [1]

Advantages of FDDS [14, 15]

The Floating systems are advantageous for drugs meant for local action in the stomach. E.g.antacids.

Acidic substances like aspirin cause irritation on the stomach wall when come in contact withit. Hence FDDS may be useful for the administration of aspirin and other similar drugs.

The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferroussalts, antacids.

Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be availablefor absorption in the small intestine after emptying of the stomach contents.

It is therefore expected that a drug will be fully absorbed from floating dosage forms if itremains in the solution form even at the alkaline pH of the intestine.

Table No.2: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

Tablets	Chlorpheniramine maleate Theophylline Furosemide Ciprofolxacin Pentoxyfillin Captopril Acetylsalicylic acid Nimodipine Amoxycillin trihydrate Verapamil HCl Isosorbide dinitrate Sotalol Atenolol Isosorbide mononitrate Acetaminophen Ampicillin Cinnarazine Diltiazem Florouracil
Capsules	Nicardipine L-Dopaandbenserazide Chlordiazepoxide HCl Furosemide Misoprostal Diazepam Propranlol
	Urodeoxycholic acid
Microspheres	Verapamil Aspirin, griseofulvin, and p- nitroaniline Ketoprofen Tranilast Iboprufen Terfenadine
Granules	Indomathacin Diclofenac sodium
Films	Cinnarizine
Powders	Several basic drugs

Layer Tablet

Layer tablets are composed of two or three layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained-release preparations with the immediate- release quantity in one layer and the slow -release portion in the second. A third layer with an intermediate release might be added. The weight of each layer can be accurately controlled. Two-layer tablets require fewer materials than compression-coated tablets. Monograms and other distinctive markings may be impressed in the surfaces of the multilayer tablets. Colouring the separate layers provides many possibilities for unique tablet identity. Analytical work may be simplified by a separation of the layers prior to assay.[16]

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast-releasing layer and may contain bi- or triple layers to sustain the drug release [17]. Oral sustained release gastroprotective dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by narrow absorption window. The purpose of study was to formulate and develop a new gastroprotective floating sustained release delivery system of bilayer tablets of drug which show narrow absorption window [18].

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended-release manner. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layeris immediate release as initial dose and second layer is maintenance dose.

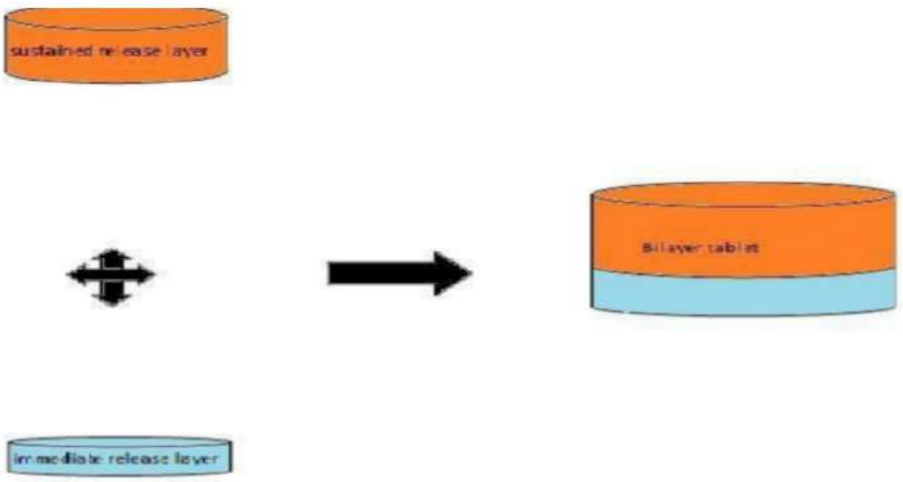

Fig No.4: Preparation of bilayer tablet

It is well known that modified release dosage forms may offer one or more advantages over immediate release formulation of the same drug. There are many ways to design modified release dosage form for oral administration, from film coated pellets, tablets or capsule to more sophisticated and complicated delivery system such as osmotically driven system, system controlled by ion exchange mechanism, system using three-dimensional printing technology and system using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and

continuousdelivery of drug over the entire dosing interval whilst also providing greater patient complianceand convenience.

The most common controlled delivery system has been the matrix type such as tablet and granules where the drugs is uniformly dissolved or disperse throughout the polymer because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period. Hydrophilic polymer are becoming more popular in formulating oral control release tablet, dissolution curve of drug release from hydrophilic matrix so a typical time dependent profile. Multilayer coated tablet is a drug delivery device, which comprise a matrix core containing an active solute and one or more barriers in corporate during tableting process. The barrier delays the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate.

Advantages of Floating Bilayer Tablet [17, 18]

Bilayer tablet can be manufactured in such a way that one layer provides sustained release and second later provides immediate release of the medicament. This approach is beneficial for providing initial loading dose and then maintenance dose within therapeutic window so it avoids frequent dosing of the drug.

Bilayer tablet can be formulated as buoyant dosage form (floating bilayer tablet) which is helpful to increase residence time in the stomach that is a need for a drug whose absorption occurs from stomach and also to enhance the therapeutic effect.

- Fast onset of action.
- Reduction in drug plasma level fluctuation.
- Simple and cheap manufacturing.
- Improve patient compliances.

Table No.3: Marketed Preparations of Gastro retentive technologies available in the international market

S. N	Product	Active ingredient	Type
1	Glumetza	Metformin	Polymer Based
2	proQuin XR	Ciprofloxacin	Polymer Based
3	Cifran OD	Cifrofloaxacin (1 g)	Gas generating Floating Form
4	GabapentinGR	Gabapentin (In Phase-III clinical trials)	Polymer Based
5	Baclofen GRS	Baclofen	Coated multi-layer floating & swelling system
7	Madopar	Levodopa and benserzide	Floating, CR Capsule
8	Valrelease	Diazepam	Floating Capsule
9	Topalkan	Aluminum magnesium antacid	Floating Liquid Alginate
10	Almagate flatcoat	Antacid	Floating Liquid form
11	Liquid gavison	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation
12	Cytotec	Misoprostol (100mcg/200mcg)	Bilayer Floating Capsule
13	Conviron	Ferrous Sulphate	Colloidal gel forming FDDS

Inflammation:

Since antiquity, the defining clinical features of inflammation have been known in Latin as rubor (redness), calor (warmth), tumor (swelling) and dolor (pain) **(Bastard et al., 2000)**. These hallmarks of inflammation were first described by Celsus -- Aulus (Aurelius) Cornelius, a Roman physician and medical writer, who lived from about 30 B.C. to 45 A.D.

Inflammation is a response of a tissue to injury, often injury caused by invading parasites. It is characterized by

1. Increased blood flow to the tissue causing
2. Increased temperature
3. Redness
4. Swelling
5. Pain
6. Loss of function (Ross and Wilson, 2005)

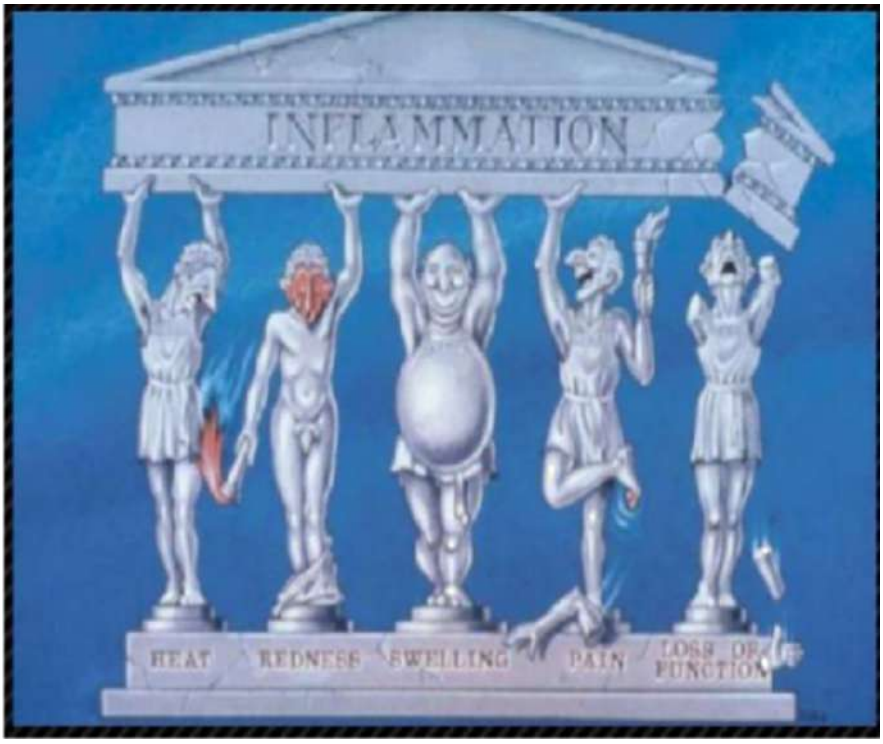

Fig. 5: Steps involved in inflammation

Types of inflammation:

Depending upon the defense capacity of the host and duration of response, Inflammation can be classified as acute and chronic inflammation.

1. **Acute Inflammation:**

Acute inflammation is of short duration (e.g. Days to few weeks) and may range frommild to very severe.

The inflammation response is described as

- Vascular events.
- Cellular events.

2. **Chronic inflammation:**

The processes involved are very similar to those of acute inflammation but, because the process is of longer duration, considerably more tissue is likely to be destroyed. **(Ross and Wilson, 2005)**

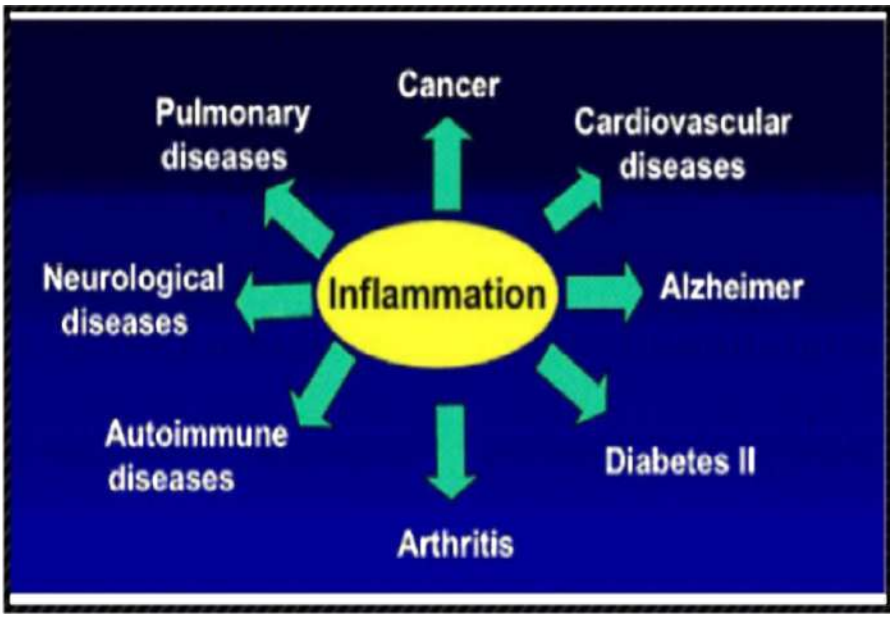

Fig. 6: inflammation plays a role in development of various diseases

Causes of inflammation:

1. Physical agents – Heat, cold, radiation, mechanical trauma
2. Chemical agents – Organic and inorganic poisons
3. Infective agents – Bacteria, viruses and their toxins
4. Immunological agents – Cell mediated and antigen-antibody reactions. (Ferrero etal., 2007)

Regulation or treatment of Inflammation:

1. **NonSteroidal Anti-Inflammatory Drugs (NSAIDs):**

The NSAIDs achieve their effects by blocking the activity of cyclooxygenase. In addition to reducing the fever and pain of inflammation, NSAIDs also inhibit clotting.

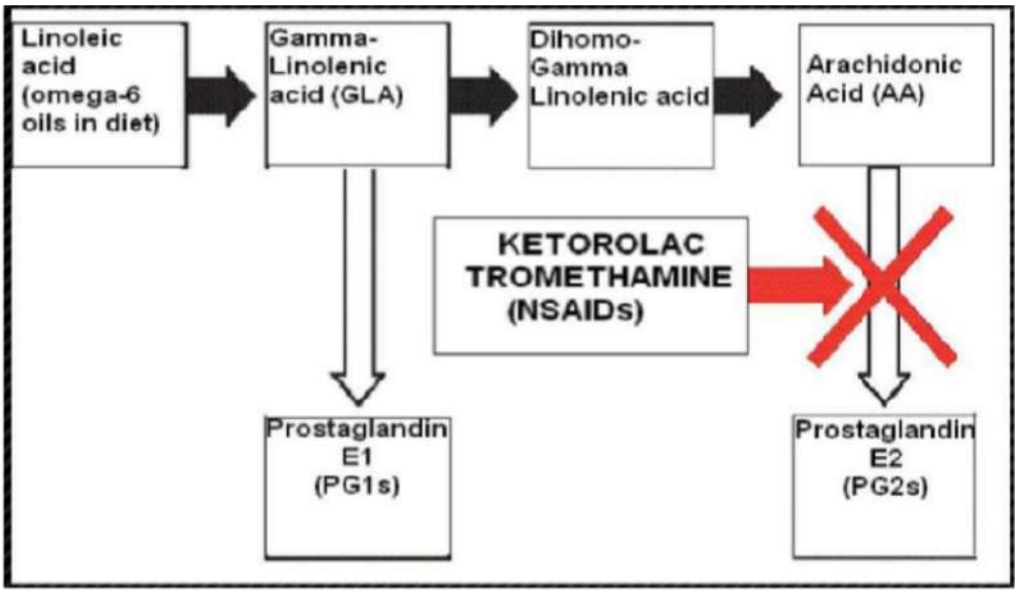

Fig. 7: Inhibition of inflammation by NSAID

Chemical Mediators of Inflammation:

The substances acting as chemical mediators of inflammation may be released from the cells, the plasma, or damaged tissue itself. They are broadly classified in to two groups.

1. Mediators released by cells and
2. Mediators originating from plasma. **(Giorgi et al., 1994)**

It involved in causing increased vascular permeability and edema of tissues.

Cell-derived Mediators:

1. **Vasoactive amines:**
    1. **Histamine**
    2. **5-hydroxytrypptamine (5-HT or serotonin)**

Histamine: it is stored in the granules of mast cells, basophils and platelets. Histamine is released from these cells under following conditions: Heat, cold, irradiation, trauma,irritant chemicals and immunological reactions. The main actions of histamine are: vasodilatation, increased vascular permeability, itching and pain.

Serotonin: it is present in tissues like chromaffin cells of GIT, spleen, nervous tissue, mast cells and platelets. The actions of 5-HT are similar to histamine but it is a less potent than histamine.

2. **Arachidonic acid metabolites (eicosanoids):** Arachidonic acid is a fatty acid, eicosatetraenoic acid, and its two main sources are: From diet directly, and Conversion of essential fatty acid, linoleic acid to, and arachidonic acid. So asto form arachidonic acid metabolites by two pathways: Metabolites via cyclo-oxygenase and lipo-oxygenase pathway (prostaglandins, thromboxane A2, prostacyclin). Prostaglandin and related compounds, called autocoids.

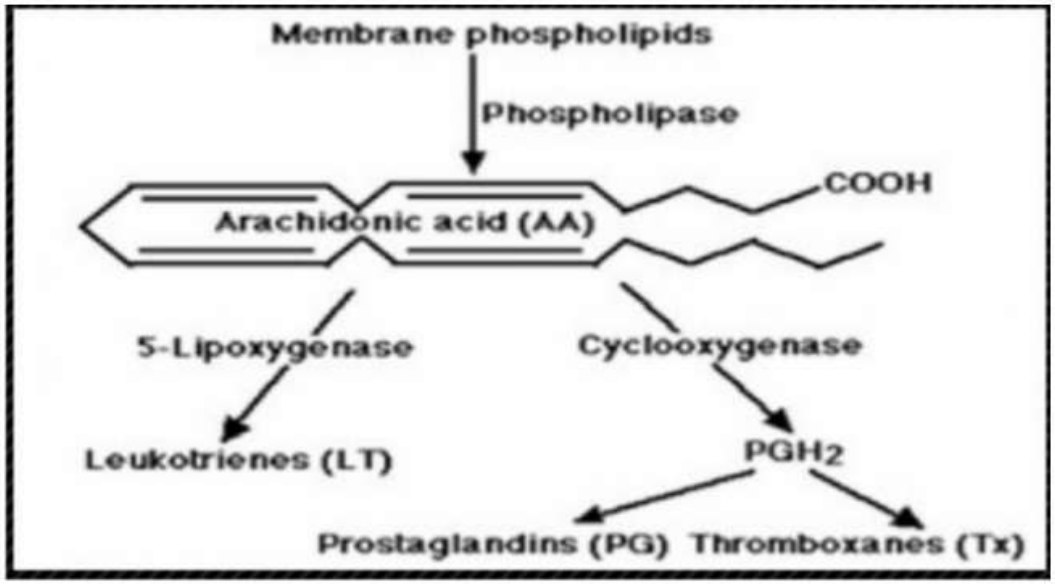

Fig. 8: Arachidonic Acid Pathway

1. **Lysosomal Components:** The Inflammatory cells- neutrophils and monocytes, contain lysosomal granules.
2. **Platelet activating factor:** It is released from IgE sensitized basophils or mast cells, other leucocytes, endothelium and platelets.

The actions of PAF as mediators of inflammation are:

Increased vascular permeability, Bronchoconstriction, and adhesion of leucocytes to endothelium

3. Cytokines: Cytokines are polypeptide substances produced by activated lymphocytes (lymphokines) and activated monocytes (monokines). Main cytokines acting as mediators' inflammation are: interleukin (IL-1), tumour necrosis factor (TNF) -a and b, interferon (IF) -g and chemokines (IL-8, PF4).
4. Nitric oxide and oxygen metabolites: Nitric oxide (NO) was originally described as vascular relaxation factor produced by endothelial cells. Nitric oxide plays the role in inflammation like Vasodilatation and Anti-platelet activating agent

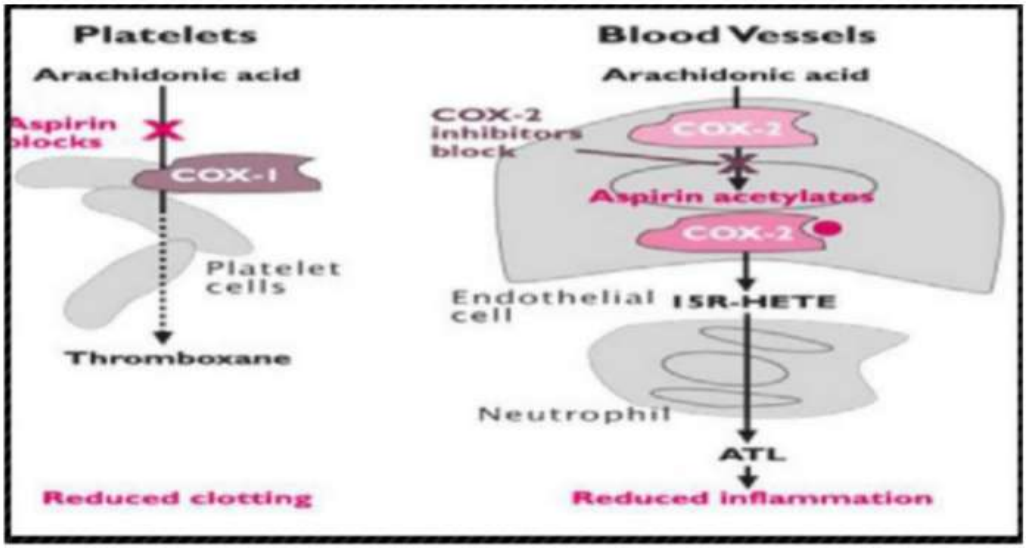

Fig. 9: Mechanism of action of Arachidonic Acid

1. **Plasma-derived mediators (plasma proteases):** These include the various products derived from activation and interaction of four interlinked systems: kinin, clotting, fibrinolytic and complement. (Harshmohan, 2005)

Pain

Pain is a more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings. It is and unpleasant sensory and emotional experienceassociated with actual or potential tissue damage or described in terms of such damage.

The purpose of pain

Pain is mainly a protective mechanism for the body; it occurs whenever any tissues are being damaged and it causes the individual to react to remove the pain stimulus.

Types of pain and their qualities- Fast pain and slow pain

Pain has been classified into two major types: fast pain and slow pain. Fast pain is felt within about 0.1 second after a pain stimulus is applied, whereas slow pain begins only after 1 second or more and then increases slowly over many seconds and sometimes even minutes.

Fast pain is also described by many alternative names, such as sharp pain, pricking pain, acutepain and electric pain. This type of pain is felt when a needle is stuck into the skin, when the skin is cut with a knife or when the skin is acutely burned. It is also felt when the skin is subjected to electric shock. Fast, sharp pain is not felt in most of the deeper tissues of the body.

Slow pain also goes by multiple additional names, such as slow burning pain, aching pain, throbbing pain, nauseous pain and chronic pain. This type of pain is usually associated with tissue destruction. It can lead to prolonged,

unbearable suffering. It can occur both in skin andin almost any deep tissue or organ.

Pain receptors and their stimulation

All pain receptors are free nerve endings. The pain receptors in the skin and other tissues are all free nerve endings. They are widespread in the superficial layers of skin as well as in certain internal tissues, such as the periosteum, the arterial walls, the joint surfaces and the falx and tentorium of the cranial vault. Most other deep tissues are not extensively supplied with pain endings but are sparsely supplied; nevertheless, any widespread tissue damage can still summate to cause the slow-chronic-aching type of pain in these areas.

These types of stimuli excite pain receptors-Mechanical, thermal and chemical. Pain can be elicited by multiple types of stimuli. They are classified as mechanical, thermal and chemical stimuli. In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.

Some of the chemicals that excite the chemical type of pain include bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine and proteolytic enzymes. In addition, prostaglandins and substance P enhance the sensitivity of pain endings but do not directly excite them. The chemical substances are especially important in stimulating the slow, suffering type of pain that occurs after tissue injury.

Nonadapting nature of pain receptors. In contrast to most other sensory receptors of the body, the pain receptors adapt very little and sometimes not at all. In fact, under some conditions, the excitation of the pain fibers becomes progressively greater, especially so for theslow aching nauseous pain, as the pain stimulus continues. This increase in sensitivity of the pain receptors is called hyperalgesia.

Rate of tissue damage as cause of pain

The average person first begins to perceive pain when the skin is heated above 45 ºC. This is also a temperature at which the tissues begin to be damaged by heat; indeed, the tissues are eventually destroyed if the temperature remains above this level indefinitely. Therefore, it is immediately apparent that pain resulting from heat is closely correlated with the ability of heat to damage the tissues.

Furthermore, the intensity of pain has also been closely correlated with the rate of tissue damage from causes other than heat- bacterial infection, tissue ischemia, tissue contrusion and so forth.

Special importance of chemical pain stimuli during tissue damage. Extracts from damaged tissues cause intense pain when injected beneath the normal skin. All the chemicals listed above that excite the chemical pain receptors are found in these extracts. One chemical that seems to be more painful than others is bradykinin. Many research workers have suggested that bradykinin might be the single agent most responsible for causing the tissue damage type of pain. Also, the intensity of pain felt correlates with the local increase in potassium ion concentration. It should be remembered, too, that proteolytic enzymes can directly attack the nerve endings and excite pain by making their membranes more permeable to ions.

Tissue ischemia as a cause of pain. When blood flow to a tissue is blocked, the tissue becomes very painful within a few minutes. The greater rate of metabolism of the tissue, the more rapidly the pain appears. For instance, if a blood pressure cuff is placed around the upper arm and inflated until the arterial blood flow ceases, exercise of the forearm muscles sometimes can cause severe muscle pain within 10 to 20 seconds. In the absence of muscle exercise, the pain may not appear for 3 to 4 minutes.

One of the suggested causes of pain during ischemia is accumulation of large amounts of lactic acid in the tissues, formed as a consequence of the anaerobic metabolism (metabolism without oxygen) that occurs during ischemia. It is also possible that other chemical agents, such as bradykinin and proteolytic enzymes are formed in the tissues because of cell

damage and that these, rather than lactic acid, stimulate the pain nerve endings.

Muscle spasm as a cause of pain. Muscle spasm is also a common cause of pain and it is the basis of many clinical pain syndromes. This pain probably results partially from the direct effect of muscle spasm in stimulating mechanosensitive pain receptors. It possibly results also from the indirect effect of muscle spasm to compress the blood vessels and cause ischemia. Also, the spasm increases the rate of metabolism in the muscle tissue at the same time, thus making the relative ischemia even greater, creating ideal conditions for release of chemical pain-stimulating substances.

Dual transmission of pain signals into the central nervous system

Even though all pain receptors are free nerve endings, these endings use two separate pathways for transmitting pain signals into the central nervous system. The two pathways at least partially correspond to the two types of pain, a fast-sharp pain pathway and a slow-chronic pain pathway.

Peripheral pain fibers- "Fast" and "slow" fibers. The fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli; they are transmitted in the peripheral nerves to the spinal cord by small type Aδ fibers at velocities of between 6 and 30 m/sec. on the other hand, the slow–chronic type of pain is specifically elicited by the chemical types of pain stimuli but also at times by persisting mechanical or thermal stimuli; this slow-chronic pain is transmitted by type C fibers at velocities of between 0.5 and 2 m/sec.

Because of this double system of pain innervations, a sudden onset of painful stimulus often gives a "double" pain sensation: a fast-sharp pain that is transmitted to the brain by the Aδ fiber pathway followed a second or later by a slow pain that is transmitted by C fiber pathway. The sharp pain apprises the person rapidly of a damaging influence and therefore plays an important role in making the person react immediately to remove him or herself from the stimulus. On the other hand, the slow pain tends to become more and more painful over a period of time. This sensation eventually gives one the intolerable suffering of long- continued pain.

On entering the spinal cord from the dorsal spinal roots, the pain fibers terminate on neurons in the dorsal horns. Here again, there are two systems for processing the pain signals on their way to the brain, as shown in figure no. 10 and 11.

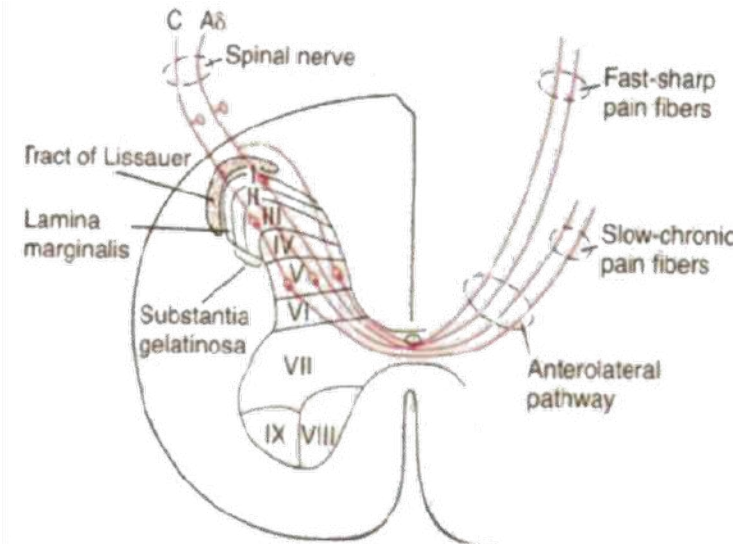

Figure No. 10: Transmission of both acute-sharp and slow-chronic pain signals into andthrough the spinal cord on the way to the brain stem.

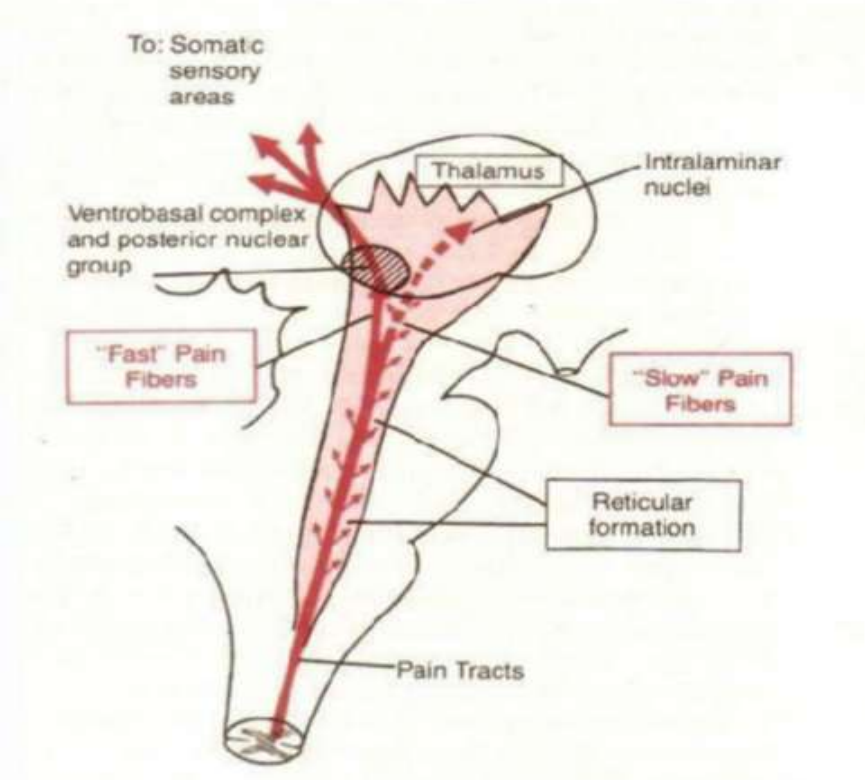

Figure No. 11: Transmission of pain signals into the hindbrain, thalamus and cortex by way of fast pricking pain pathway and the slow burning pain pathway.

Drug Profile

Lornoxicam is a non-steroidal anti-inflammatory drug of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parenteral formulations. Lornoxicam differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that particularly explains the pronounced efficacy of the drug. Lornoxicam is used for the treatment of various types of pain, especially resulting from inflammatory diseases of the joints, osteoarthritis, surgery, sciatica, and other inflammations.

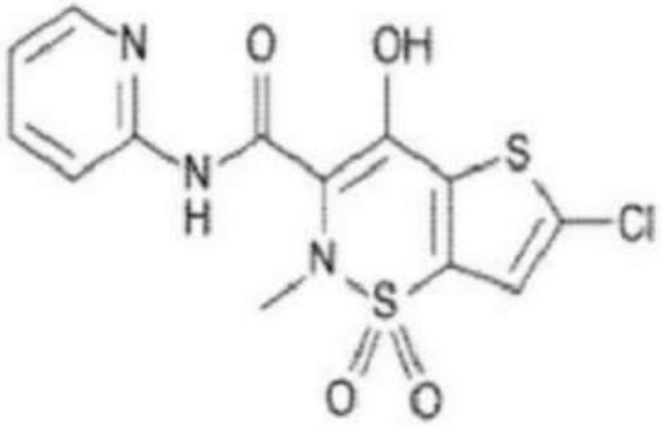

Figure 12: Structure of Lornoxicam

IUPAC name: (3E)-6-chloro-3-[hydroxy(pyridin-2-ylamino) methylene]-2-methyl-2,3-dihydro-4Hthieno[2,3-e][1,2] thiazin-4-one 1,1-dioxide

Molecular formula: C13H10ClN3O4S2

Molecular mass: 371.8192 g/mol

Half-life: 3 – 4 hrs

Therapeutic category: Non-steroidal anti-inflammatory drug (NSAID)

Route: Oral, Parenteral

Solubility: Poorly soluble in water, Soluble in 0.1N NaOH solution

Mechanism of action:

Lornoxicam'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. However, the exact mechanism of lornoxicam, like that of the other non-steroidal anti-inflammatory drugs (NSAIDs), has not been fully determined.

Dosage: The adult dosage of Lornoxicam for pain relief is 8-16mg daily and maximum of 24mg/day. The daily dosage for Osteoarthritis is 12 mg daily in 2-3 divided doses, up to 16 mg daily.

Adverse effects:

The most common side effects reported with the regular use of the tablet form of Lornoxicaminclude dizziness, headache, stomach pain, upset stomach, diarrhea, nausea, vomiting and indigestion. As an injection, users most commonly report headache, flushing, insomnia and redness and irritation at the injection spot.

The market available formulations, dosage form and manufacture details ofLornoxicam are shown in table.

Table 4: List of Brand names of Lornoxicam

S.NO	Brand name	Available form	Dose	Manufacturer
1	Camri	Tablet	4mg	Zydus
2	Lornoxi	Tablet	4mg	Hetero
3	Lornofan	Tablet	4mg	Emar
4	Lorasid	Injection (Vial)	8mg	Piramal
5	Xilor	Tablet	8mg	Sanify(syntonic)
6	Zelorn	Tablet	4mg	Anthus

2. Literature Review

Patil et al., (2011) developed floating tablets of ofloxacin which were designed to prolong the gastric residence time after oral administration. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC K100M.

Veeraredyy et al., (2011) developed and evaluated gastroretentive drug delivery tablets (GRDDTs) of ofloxacin using different polymers such as HPMC K4M, HPMC K15M, Xanthan Gum. The study showed increase in the gastric residence time for the effective localized action of the ofloxacin in the treatment of Helicobacter pylori causedpeptic ulcer.

Arunachalm et al., (2010) developed a floatable drug delivery system of Lornoxicam for sustained drug delivery, using hydroxy propyl methyl cellulose (HPMCK100M) and sodium bicarbonate. Thus, the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in prolonged absorption.

Barhate et al., (2010) were reported that the bilayer floating tablets of famotidine were prepared by using HPMC K100LV, HPMC K4MCR, sodium bicarbonate, sodium starch glycolate, croscarmellose, crospovidone and lactose. The polymers HPMC K100LV, HPMC K4MCR showed better control over drug release.

Kumar et al., (2010) prepared a bilayer gastro retentive tablet of ranitidine andoptimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. HPMC-K-100, HPMC-K-4M, HPMC-E-15, CARBOPOL- 934 was used as gel forming agents either alone or in combination.

Naeem et al., (2010) were developed and characterize bilayer tablet formulations of tramadol HCl and acetaminophen microparticles. Coacervation via temperature change was the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of as the polymer for extending drug release.

Shinde et al., (2010) were prepared a gastroretentive floating drug delivery system (GFDDS) of cephalexin (CFL), using hydroxy propyl methyl cellulose (HPMC), sodium bicarbonate and citric acid. The drug release from the tablets was sufficiently sustained followed the Korsmeyer and Peppas model-controlled mechanism of cephalexin tablet.

Karthikeyini C. et al., (2009). designed formulation and evaluation of Aceclofenac sodium bilayer sustained release tablets using,Sodium starch glycolate for the fast release layer and water immiscible polymers such as Eudragit RL 100 for the sustaining layer. Optimized formulation releases the drug upto 24 hours and fulfilled manyrequirements such as easy to fabricate, cost effective and high patient compliance.

Kulkarni et al., (2008). developed and evaluate bilayer floating tablets of atenolol and lovastatin for to give immediate release of lovastatin and sustained release of atenolol The immediate release layer comprised sodium starch glycollate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers.

Martinez et al., (2008). studied, in vitro sustained release of captopril from Metolose SH 4000 SR/sodium bicarbonate floating tablets by varying the proportions of Metolose and bicarbonate. The increase of the matrix polymer proportion increases the maximal hydration volume as well as the time to attain this maximum. The matrices hydration volume increases with the inclusion of sodium bicarbonate in the formulation.

Parikh et al., (2008). described the methodologies used for in vitro and in vivo evaluations of gastro- retentive drug delivery sytems (GRDDS). They proposed critical parameters for floating and swelling types of GRDDS are discussed.

Rao et al., (2008). Developed sustained release tablets by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), crospovidone, sodium starch glycolate, croscarmelose sodium and sodium bicarbonate. There combination of HPMC K100M, crospovidone, and sodium carbonate shows the good swelling, drug release, and floating characters than the CIFRAN OD®.

Thakkar et al., (2008) developed floating Lornoxicam tablets and to understand the kinetics of drug release by applying mathematical and model-dependent approaches. Zero- order, first- order, Higuchi, Hixson-Crowell, and Korsmeyer et al. models were used to estimate the kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness-of-fit test and lowest sum of squaresresidual.

Chinam et al., (2007) Studied bilayer tablet of propranolol hydrochloride using sodium starch glycolate for the fast release layer and water immiscible polymers such as Eudragit for the sustaining layer. Bilayer tablets showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 12 h,

indicatinga promising potential of the propranolol hydrochloride bilayer tablet as an alternative to the conventional dosage form.

Putheti et al., (2007) reviewed on development of floating and swellable sustaineddrug delivery systems. These systems mainly consist of swelling and expanding systems, floating and inflating systems and bioadhesive systems. These systems are also useful for drugs, which are poorly soluble or unstable in intestinal fluids.

Janardhan et al., (2007) prepared a gastroretentive drug delivery system of Ofloxacin. It is highly soluble in acidic media and precipitates in alkaline media thereby losing its solubility. Hence, a gastroretentive system was developed using hydroxy propyl methyl cellulose, sodium bicarbonate and citric acid to enhance the bioavailability by retaining it in the acidic environment of the stomach.

Rahman et al., (2006) developed a bilayer-floating tablet (BFT) for captopril using HPMC-K15M grade, citric acid and sodium bicarbonate. Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

Wagenlehner et al., (2006). Studied antimicrobial treatment of both uncomplicatedand complicated urinary tract infections UTIs:(i) rapid and effective response to therapy and prevention of recurrence of the individual patient treated; (ii) prevention of emergence of resistance to antimicrobial chemotherapy in the microbial environment.

Sasa et al (2000). developed floating matrix tablets, which after oral administration are designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of irritating drugs. With the incorporation of a gas- generating agent together with microcrystalline cellulose, besides optimum floating, the drug content was also increased.

Kristl et al., (1999). worked on optimization of floating matrix tablets and evaluation of their gastric residence time. In the current work a matrix floating tablet containing HPMC K4M, Avicel®PH 101, gas-generating agent and high dose of freelysoluble active substance is described.

Tanaka et al., (1993). Studied that mechanisms of reduction in absorption of Lornoxicam (LVFX) by coadministration of aluminum hydroxide. The partition coefficient between chloroform and phosphate buffer (pH 5.0) was reduced by 60 to 70% with the addition of metal ions such as Cu2+, A13+, and Fe2+,which suggest that quinolones precispitated in the small intestine would play an important role in the reduced bioavailability .Very few analytical methods have been reported previously for the estimation of Lornoxicam in bulk, pharmaceutical dosage forms and biological samples using different analytical techniques. The summary results of the previously reported methods were discussed below.

Aher et al [3] developed a simple, rapid, and precise method for quantitative analysis of Lornoxicam in pharmaceutical dosage forms. Chromatographic separation of Lornoxicam was achieved on a C18 analytical column with potassium dihydrogen phosphate buffer: acetonitrile, 70:30 (v/v), as mobile phase at ambient temperature. The flow rate was 1.0 ml/min and detection were carried out by absorption at 291 nm using a photodiode-array detector. The number of theoretical plates and tailing factor for Lornoxicam were 6,577 and 1.03, respectively. The linearity of the method was excellent over the range 10–100 µg/ ml Lornoxicam. The correlation coefficient was 0.9999. Relative standard deviations of peak areas from six measurements were always less than 2%. The proposed method was found to be suitable and accurate for quantitative analysis of Lornoxicam.

Mahesh Attimarad et al [4] developed a simple RP-HPLC method for the simultaneous determination of paracetamol and lornoxicam without prior separation. In this method,

Kromasil C8 (250 mm, 4.6 mm, 5 µm) column was used. The mobile phase used was methanol:phosphate buffer (60:40, v/v, pH 6.4), at flow rate of 1 ml min -1. UV detection was monitored at 302 nm. Calibration graphs were established in the range of 1-150 µg ml -1 and 0.5-100 µg ml -1 for paracetamol and lornoxicam, respectively. The average retention time for paracetamol and lornoxicam was found tobe 3.15 ± 0.03 min and 5.25 ± 0.06 min, respectively. The detection limit and quantification limit for paracetamol were 0.19 µg ml -1 and 0.59 µg ml -1 and for lornoxicam 0.10 µg ml -1 and 0.31 µg ml -1, respectively. The intraday and interday precisions expressed as percent relative standard deviation were below 2%. The mean recovery of paracetamol and lornoxicam was found to be in the range of 99.03-101.2%.

B.S. Kuchekar et al [5] developed a simple, selective, rapid, and precise RPHPLC-PDA method for the simultaneous estimation of Lornoxicam (LOR) and Thiocolchicoside (THIO) in pharmaceutical dosage form by reverse phase liquid chromatography using Waters Symmetry C18 (250 mm × 4.6 mm, 5.0 µ) column. The63 mobile phase consisting of methanol: THF: acetate buffer (60: 10: 30 v/v); pH adjusted to 5.5 with glacial acetic acid at a flow rate of 0.75 ml min-1and column was maintained at 500C with detection at 382 nm. The retention time of Thiocolchicoside and Lornoxicam was 3.36 and 4.08 minutes, respectively. The method was validated according to the ICH guidelines with respect to specificity, linearity, accuracy, precision and robustness, limit of detection and limit of quantification. Linearity of Lornoxicam and Thiocolchicoside were in the range of 0.2 to 80 µg/ml and 0.1 to 40 µg/ml, respectively and its percentage recovery were found to be 100.37 % and 100.51 %, respectively. The proposed method was suitable for simultaneous determination of Lornoxicam and Thiocolchicoside in pharmaceutical dosage form Method was successfully applied for dissolution study of tablet formulation.

Patel et al [6] developed and subsequently validated a simple reverse phase liquid chromatographic method for simultaneous determination of paracetamol and lornoxicam in combination. The separation was carried out using a mobile phase consisting of potassium dihydrogen phosphate, pH adjusted to 7.3 with triethyl amine and acetonitrile 70:30(%v/v). The column was used phenomex C18, 5 µm, (250x 4.61. with flow rate 1.5ml/min using UV detection was at 257nm. The described method was linear over concentration range 20 to 60 µg/ml & 0.2 to1.8µg/ml for assay of paracetamol & lornoxicam respectively. The retention time of paracetamol & lornoxicam were found to be 2.33 & 7.61 min, respectively. Result of analysis was validated statistically. The method show good reproducibility & recovery with % less than 1, all the tests of above-mentioned studies were found to be in acceptance criteria.The method was found to be rapid, specific, precise & accurate and can be successfully applied for routine analysis of paracetamol & lornoxicam in bulk & combined dosage forms.

G.devala rao et al [7] described two simple and sensitive visible spectrophotometric methods (A & B) for the determination of lornoxicam (loc) in bulk and pharmaceutical dosage forms. Method-A, was based on oxidation of drug with ferric chloride and subsequent complexation of Fe (II) with 2, 2' bipyridine toform a blood red colored species (λmax:520nm). Method-B, was based on oxidation of lornoxicam with ferric chloride and chelation of Fe (II) with bathophenanthroline to produce a blue colored chromogen (λmax:610 nm). These methods were extended to the analysis of pharmaceutical formulations and results were compared with the reference method.

3. Research Envisaged

Now days most of the pharmaceutical industries are involved in developing an ideal drug delivery system with an objective of not only curing the disease but also to achieve patient compliance. Approximately 50% of the all-drug delivery systems available in market are oral drug delivery system. Oral drug delivery system

is most convenient and easy route as compared to other systems. Conventional oral dosage form provides a specific drug concentration in systemic circulation without offering any control over drug delivery. Over the past decades, the exploration of devices designed to exert prolonged action like gastro retentive system, multilayered tablets.

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast-releasing layer and may contain bilayer or three layers to sustain the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer. Bilayer tablets provide dual advantage, in the same dosage form provides immediate as well as sustain action. This delivery system via constant release maintains plasma drug concentration for whole day which is much more as compared to available conventional dosage forms. It will help in the reduction of dose as well as dosing frequency with increase in patient compliance.

Rationale for Selecting Floating Bilayer Tablet:

1. Floating Bilayer tablet is beneficial for providing initial loading dose and then maintenance dose within therapeutic window so it avoids frequent dosing of the drug.
2. Reduction in drug plasma level fluctuation.
3. Fast onset of action.
4. Simple and cheap manufacturing.
5. Prevention of conversion to zwitter ion in intestine.
6. Improve patient compliance.

Bilayer tablet can be formulated as buoyant dosage form (floating bilayer tablet) whichis helpful to increase residence time in the stomach

4. **Plan of Work**

The project work was done under the following characters:

1. **Preformulation study**
   - Physical appearance
   - Melting point
   - FTIR spectroscopy
   - Solubility studies.
   - Partition coefficient
   - Determination of absorption maxima and preparation of standardcurve
   - Determination of absorption maxima in 0.1 N HCl (pH 1.2)
   - Preparation of standard curve in 0.1 N HCl (pH 1.2)
   - Preparation of standard curve in distilled water.
   - Preparation of standard curve in phosphate buffer pH6.8
   - Drug-Excipient interaction study
   - ıFourier transform infra-red spectroscopy (FTIR)
2. **Preparation of Fast release layer**
3. **Preparation of Bilayer tablets**
   - ıPreparation of bilayer tablets consisting of Eudragit RL100.
   - Preparation of bilayer tablets consisting of HPMC.
4. **Optimization of process variables**
   - Effect of ratio of polymer
   - Effect of ratio of superdisintegrant
5. **Evaluation parameters**
   - Weight variation
   - Thickness
   - Diameter
   - Hardness
   - Friability
   - Disintegration time
5. **Experimental Work**

Preformulation Study:

Before preparation and characterization of pharmaceutical dosage form containing therapeutic moiety, preformulation studies was done to characterize the physicochemical properties of the drug that could affect the

development of efficacious dosage form. (Lachman et al.,1991)

The preformulation studies were carried out in terms of tests for identification (Physical appearance, melting point, and IR spectra), solubility profile and determination of partition coefficient and quantitative estimation of drug.

Test for identification:

(a) **Physical appearance**

The sample of Lornoxicam was identified and characterized out by visual inspection.

(b) **Melting Point**

The Melting point was determined by the capillary method using Melting point apparatus. The pure drug was filled in a pre-sealed capillary tube then the tube was placed into the slot behind the eye-piece in the Melting point apparatus. Make sure the unit was plugged in and set to zero, and then turned on. Temperature at which drug was melted or decomposed was observed. (B.P.,2002)

Solubility:

The extent to which the solute dissolved in solvent was referred as its solubility, which is chemically and physically homogenous mixture of two or more substance. The solubility of drug will be tested in various common solvents. A definite quantity of drug was dissolved in each investigated solvents at room temperature. The solubility was observed by the UV method.

Excess amount of drug was dispersed in the 10 ml of solvent and placed on orbital shaker for 48 hours. After shaking solution was filtered, suitably diluted and amount of Lornoxicam wasdetermined by measuring the absorbance using UV spectrophotometer.

Table No. 5. Specifications of solubility (I.P.)

Descriptive terms	**pproximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Insoluble or practically insoluble	More than 10000

Partition Coefficient:

The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phase at equilibrium. The partition coefficient (P) therefore is the quotient of two concentrations and is usually given in the form of its logarithm to base 10 (log P). Octanol is chosen as the solvent for the oil phase as it has similar properties to biological membranes.

Po/w = (Coil / Cwater) equilibriumlog p = log po/w

Partition coefficient is a measure of drug lipophilicity and an indication of its ability to cross the biological membrane. The partition coefficient of Lornoxicam s was determined inn-octanol: water system. Lornoxicam s was accurately weight (10 mg) and added to 10 ml each of n-octanol and aqueous phase. The mixture was shaken using mechanical shaker for 24 hours until equilibrium will reach. Phases were separated by separating funnel and aqueous phase was analyze for amount of drug after appropriate dilution by using UV spectrophotometer.

Determination of absorption maxima and preparation of standard curves:

Determination of absorption maxima (λmax)

Absorption maximum was determined by using solution of Lornoxicam in different solvents like 0.1 N HCl (pH 1.2), and distilled water. These solutions were scanned in the range of 200-400 nm in the Shimadzu-1700 UV/Visible Spectrophotometer.

Preparation of 0.1 N HCl (pH 1.2)

8.64 ml concentrated hydrochloric acid was taken and volume was made up to 1 liter with distilled water. The pH was adjusted to 1.2 with water prior to quantitative estimation.

Preparation of standard curve in 0.1 N HCl (pH 1.2)

10 mg Lornoxicam was dissolved in 100ml of o.1NHCL. From this stock solution different dilutions were prepared in the concentration range of 2.0, 4.0, 6.0, 8.0, and 10 µg/ml in 10 mlvolumetric flask and absorbance was taken at 293 nm.

Drug Excipient Interaction Studies:

Fourier Transform Infrared Spectroscopy (FTIR) studies

The spectrum of Lornoxicam hemiydrate was determined by infrared absorption spectrophotometry. The drug was directly place on the stub and determined by FT-IR which shows the characteristic absorption of various functional groups of drugs in FT-IRspectra. The

pure drug and physical mixtures were subjected for FTIR analysis. Spectra were analyzed for drug polymer interactions.

Design and optimization of Formula:

The experiment was designed using 2x22 factorial design having two variables namely disintegrant and polymer and 2 levels were selected. The variable disintegrant affectsdirectly to the disintegration time of the immediate layer of tablet and the polymer will affect the drug release, floating lag time and floating time of sustained layer of drug.

The different factors chosen were:

- Optimization of immediate release layer
  - Disintegration time of immediate layer
  - By varying disintegrating agents and concentration
  - Optimization of sustained release layer

1. Floating lag time and floating time
2. Drug release

By varying polymer concentration and gas forming agent ratio.

No. of Batches = level ^{factor}

$=2x2^2$ i.e. total 8 batches

Table 6. Variable Value of $2x2^2$ factorial Design for Preparation of Lornoxicam bilayer tablet

S.No	Variable	Levels	
		High	Low
1	Crosspovidone	+1	- 1
2	Sodium Starch Glycolate	+1	-1
3	HPMC k 100m	+1	-1

Dose and Calculation:

The dose in formulation for fast release was 100 mg and the maintenance or sustain dose150 mg of Lornoxicam was calculated as per pharmacokinetic parameters as follows.

Fast release dose= Css× Vd/F

Where, Css= steady state plasma concentrationVd=Volume of distribution F=Bioavailability

Total dose

Dt=Dose(1+0.693×t/T1/2)

Where, Dt= Total dose,

Dose=dose of fast release part
T=duration(hours) of sustained release desired
T1/2=Half life

Preparation of granules: By wet granulation method

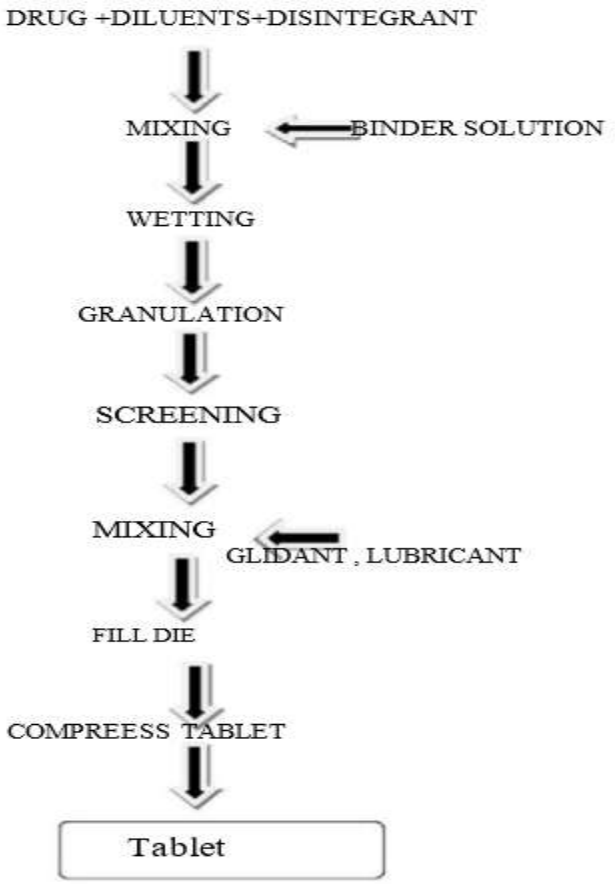

Fig No.13. manufacturing of tablet by wet granulation method

Precompression Studies:

Physical properties such as bulk density, tapped density, compressibility index, Hausner ratio,and the angle of repose of final blend were determined.

Loose Bulk density:

It is the ratio of total mass of powder to bulk volume of powder. It was measured by pouring the weigh powder in to a measuring cylinder and the volume was noted. It is expressed in gm/ml is given by

LBD= M/Vo

Where,

M=The mass of powder

Vo= the bulk volume of powder

Tapped Bulk Density:

It is the ratio of total mass of powder of the tapped volume of powder. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the intial volume was observed, the cylinder allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at2sec. intervals. The tapping was continued

until no further change in volume was noted. TBDwas calculated using following formulas,

TBD=M/Vt

Where,

M= The mass of powder

Vt=The tapped volume of powder

Angle of Repose:

The frictional force in a loose powder can be measured by angle of repose. This is maximum angle responsible between surface of a pile of powder and the horizontal plane is used to determine the flow property of granules.

The angle of repose was determined by funnel method. The accurately weighed granule was taken in a funnel. The height of funnel was adjusted in such a way that the tip of funnel just touched the apex of the heap of granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using following equation

Tan ø = h/r ø

= tan-1 (h/r)

Where,

H= the height of pile of powder R= the radius of pile of powder

Table no. 7. Angle of Repose – Flow ability Correlation Data (USP)

S.NO	Angle of Repose	Flow ability
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair- aid not needed
4	41-45	Passable may hang up
5	46-55	Poor must not agitate, vibrate
6	56-65	Very poor
7	>66	Very,very poor

Carr s Index:

The compressibility index of the granule s was determined by Carr s compressibility index

Carr s Index (%) = [(TBD-LBD)100]/ TBD

Where,

TBD= tapped density of the powderLBD=bulk density of the powder

Table No. 7. Compressibility – Flowabilty Correlation Data (USP)

S.NO.	Carr s index (%)	Type of flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Fair to passable
4	23-35	Poor
5	35-38	Very poor
6	>40	Extremely poor

Hausner Ratio

This value was calculated by making use of LBD and TBD

Hausner s Ratio= TBD/LBD

Where,

TBD= tapped density of the powderLBD= bulk density of the powder

Table No. 8. Hausner s Ratio- Flow Correlation Data (USP)

S.NO	Hausner s Ratio	Flow ability
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-126	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very poor
7	1.60	Very, very poor

Formulation of floating bilayer tablet:

The bilayer tablets of Lornoxicam s were prepared by wet granulation method. All the components were screened and then thoroughly mixed for a period of 15 mins. The powder blend was granulated with isopropyl alcohol. The wet mass was passed through sieve # 16 and the granules were dried at 50°C for 5 min in a hot air oven. The dried granules were passed through sieve # 22 and lubricated with magnesium stearate and talc by further blending for 3 mins. The quantity of granules for the sustained release layer was compressed lightly using 16 station tablet compression machines (Rimek minipress) equipped with 12.7 mm round flat and plain punches. Over this compressed layer the required quantity of the fast release layer was placed and compressed to obtain required hardness to form bilayer matrix.

Table No.9.Formulation of Immediate release layer

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Lornoxicam	100	100	100	100	100	100	100	100
Sodium starch glycolate	6.5	9.3	6.5	9.3	-	-	-	-
Crosspovidone	-	-	-	-	6.5	6.5	1.5	1.5
Microcrystalline cellulose	43.5	40.7	43.5	40.7	43.5	43.5	48.5	48.5
Magnesium stearate	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2
Total	**155**	**155**	**155**	**155**	**155**	**155**	**155**	**155**

All the amounts are shown as milligrams (mg).

Table No 10. Formulation of sustained release layer

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Lornoxicam	150	150	150	150	150	150	150	150
HPMCK100M	88.5	88.5	59.5	59.5	88.5	59.5	88.5	59.5
Citric acid	15	15	15	15	15	15	15	15
Sodium bicarbonate	30	30	30	30	30	30	30	30
Magnesium stearate	5	5	15	5	15	15	5	15
Talc	5.5	5.5	15	2.5	15	15	5.5	15
Total	**295**	**295**	**295**	**295**	**295**	**295**	**295**	**295**

Evaluation of Formulated Floating Bilayer Tablet:

Hardnes: Hardnes is amount of strength of tablet to withstand mechanical shocks of handling in manufacture, packaging and shipping and tablet should be able to withstand reasonable abuse when in the hand of consumer. Hardness of tablet was evaluated by **Monsanto hardness tester or Pfizer tester.** Hardness was measured in kg/cm2 and for floating tablet it is above 4-6 kg/cm2.

Friability: This test is applicable to compressed tablets and is intended to determine thephysical strength of tablets. It was evaluated by Roche Friabilator with 100 revolutions rotating 25 per minute for 4 min by using 6 tablets. According to USP tablet should have limit < 1%. for acceptance

Following formula was used to calculate the friability.

%F=1- (loss in weight/initial weight)100

Weight variation: Weight variation was calculated as per method describe in USP.20tablets was weighed individually and the average wias calculated.The requirements are metif the weight of not more then 2 of tablets differ by more then percentage listed in the tabletand no tablets differ by in weight by more then double that percentage.

Table No.11. percentage weight variation of tablet (I.P)

S.No.	Avg. weight of individual tablet	Limits (%
1	≤ 130	10
2	130-324	7.5
3	≥ 324	5

Floating Lag Time and Floating Time:

The invitro buoyancy was determined by observing floating lag time and floating time. The tablets were placed in a 900 ml beaker containing 0.1N HCl. The time required for the tabletto rise to the surface and float will be considered as the floating lag time and the time or which drug floats on dissolution media will be noted.

Content of Active Ingredients:

Prepared tablets were accurately weighed and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to dose (250mg) of the prepared tablet was transferred in to a volumetric flask and the drug was dissolved in the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 293 nm.

In-vitro Dissolution studies of tablet using dissolution apparatus:

In-vitro release studies were carried out by using United States of Pharmacopoeia (USP) Dissolution Testing Apparatus II (VEEGO, VDA-6DR). The dissolution test was performed using 900 ml of 0.1NHCl (pH 1.2) at 37±0.5oC. 75 rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 12 hours and the same volume of the fresh medium was replaced. The absorbance of the withdrawn sample was measured spectrophotometrically at a wavelength of about 293 nm and cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Kinetic analysis of dissolution data:

Several mathematical models have been introduced to elucidate the water and drug transportprocesses and to predict the resulting drug release kinetics. Each model makes certain assumptions and due to these assumptions, the

applicability of the respective models is restricted to certain drug-polymer systems.

To analyze the in-vitro release data various kinetic models were used to describe the release kinetics. The rate and mechanism of release of Lornoxicam from the prepared bilayer tabletswere analyzed by fitting the dissolution data into various models.

The zero order rate equation describes the system where the drug release rate isindependent of its concentration.

$$C=k_ot$$

Where, C is the amount of drug released at time t and ko is the zero order releaserate constant.

The First order rate equation describes the release from system where release rate is concentration dependent.

$$\log C= \log C_o- kt/2.303$$

where, Co is the initial concentration of drug and k is the first order rate constant.

Higuchi described the release of drugs from insoluble matrix as a square root oftime dependent process based on fickian diffusion.

$$Q= kt^{1/3}$$

where, k is constant reflecting the design variables of the system.

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

$$Qo^{1/3} – Qt^{1/3} = Hkc\ t$$

where, Qt is the amount of drug released in time t, Qo is initial amount of drug in tabletand kHc is rate constant for Hixson-crowel rate equation.

Korsmeyer equation use to describe the drug release behavior from polymeric systems.

$$\log (M_t/M_\infty) = \log k + n \log t$$

where, Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release

6. Results And Discussion

Preformulation studies:

Identification of drug:

Physical appearance:

Table No.12, Physical appearance of Lornoxicam

S.NO	Parameters	Sample
1	Colour	Pale yellow colour powder
2	Odour	Odourles

Melting Point:

he melting point of Lornoxicam was found to be in the range of 225-227 ºc.

Solubiity profile of drug:

Table No. 13, Solubility profile of Lornoxicamin aqueous and non-aqueous solvents

S.NO	Solvent	Solubility
1	0.1 N HCL	Soluble
2	Distill water	Soluble
3	Methanol	Soluble

Partition coefficient:

The partition coefficient value of Lornoxicam was found to be -0.54.

Table No. 14, Partition coefficient of Lornoxicam

Charecterstic	Standard	Sample
LogP	-0.54	-0.65

The partition coefficient of Lornoxicam was determined using shake flask method in solvent which shows permeability of drug.

Selection of absorbance maxima:

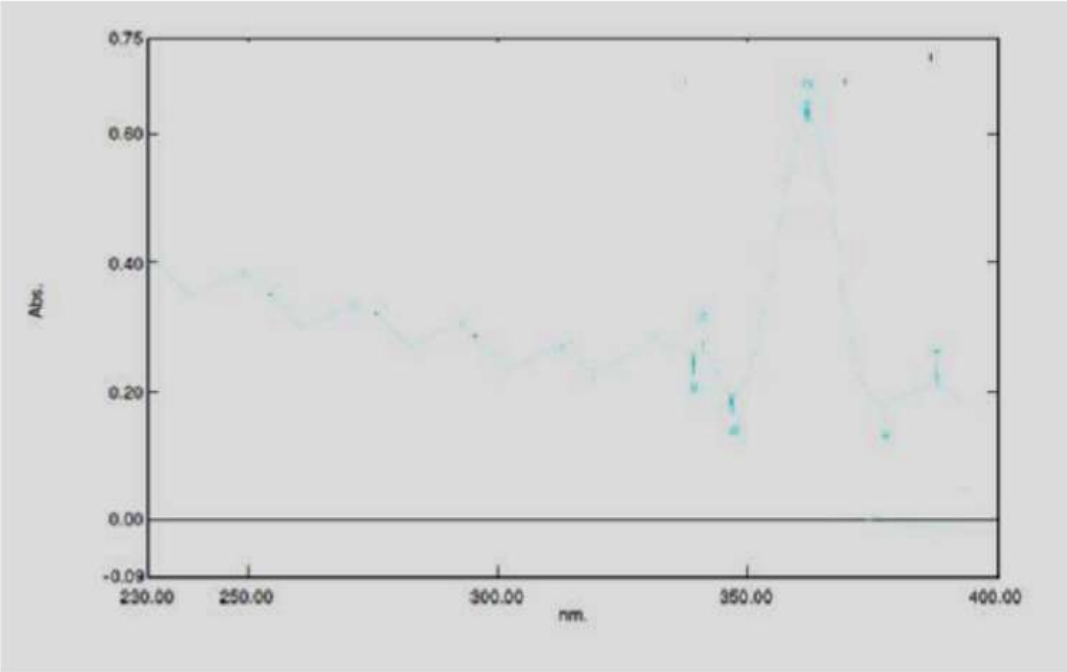

Fig. No. 14, Determination of absorption maxima in distilled water at 288nm

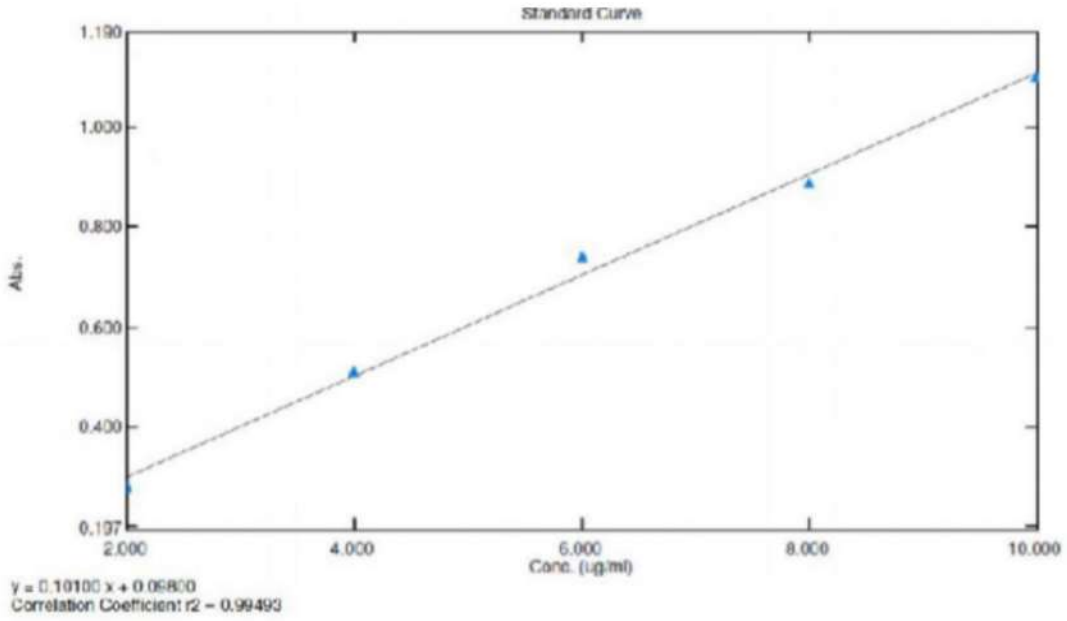

Fig No.15, Standard caliberation curve in 0.1 N HCL at 293 nm

Table No. 15, Sample value at WL293

S.No.	Conc.	WL374
1	0.000	0.000
2	2.000	0.280
3	4.000	0.510
4	6.000	0.740
5	8.000	0.890
6	10.000	1.100

Absorption maximum was determined by using solution of Lornoxicam in different solvents like 0.1N HCL (pH 1.2), distilled water and methanol. The observed maximum wavelength (λ max) was 293 in 0.1 N HCL (pH 1.2) and 288 in distilled water.

Table No. 16, Statistical parameters related to standard curve of Lornoxicam

S.No	Absorption media	Parameters	Values
1	Standard curve in 0.1 N HCL (pH 1.2)	Concentration range Regression coeffifient(r^2) Regressed line equation	2-10 ug/ml 0.994 Y=0.101
2	Standard curve in Distilled water	Concentration range Regression coeffifient(r^2) Regressed line equation	2-10 ug/ml 0.996 Y=0.103

Drug –Excipient interaction studies:

Fourier Transform Infrared Spectroscopy (FTIR) studies

The charaterstics peaks were determined by FTIR spectra, which show purity of drug. If sample does not contain characteristic peaks of compound d that shows the impurity of sample.

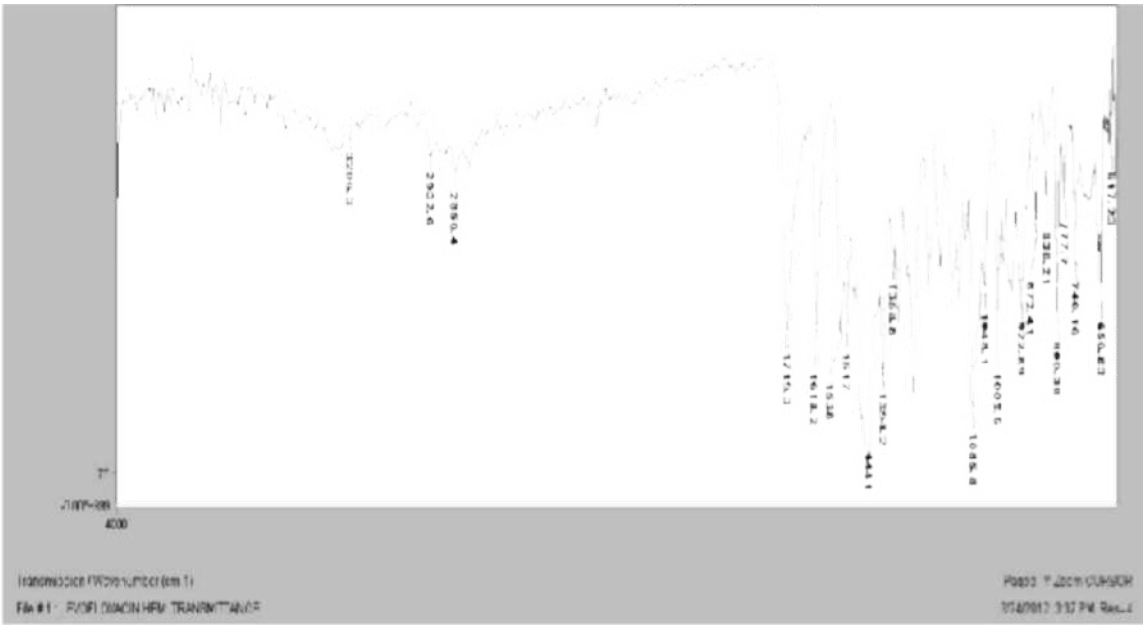

Fig. No.16, FTIR Spectra of Lornoxicam

Table No. 17, Characterstics Peak of FTIR Spectra of Lornoxicame

S.NO.	Functional Group	Standard Peaks (CM-1)	Sample Peaks (CM-1)
1	OH Stretching	**3264**	**3264.3**
2	C-H Stretching piperazine	**2786**	**2785.4**
3	C=0, (COOH) Stretching	**1714**	**1715**
4	C-F Stretching	**1057**	**1057.5**

FTIR show characteristic peaks of drug which was similar to that of standard. It was the test for identification of drug. This test confirms the presence of various groups in the sample and confirms that it was Lornoxicam.

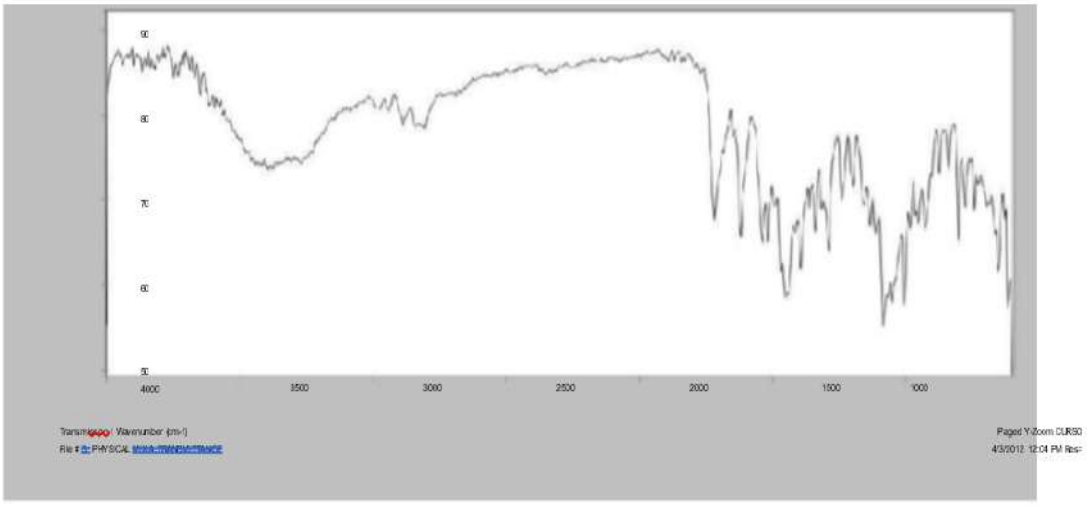

Fig. No. 17, FTIR spectra of physical mixture (Lornoxicam, HPMCK100M)

FTIR spectra of physical mixture show broad OH peak at 3320 cm-1, C-H stretching at 2800cm-1, C-O stretching at 1245 cm-1 which may be due to HPMCK100m and OH stretching at 3264cm-1, C=O stretching at 1715 cm-1, C-f stretching at 1057 cm-1for pure drug. The major peak of pure drug Lornoxicam was also present in the physical mixture, which indicates that there was no interaction between drug and the polymers, which confirms the stability of drug.

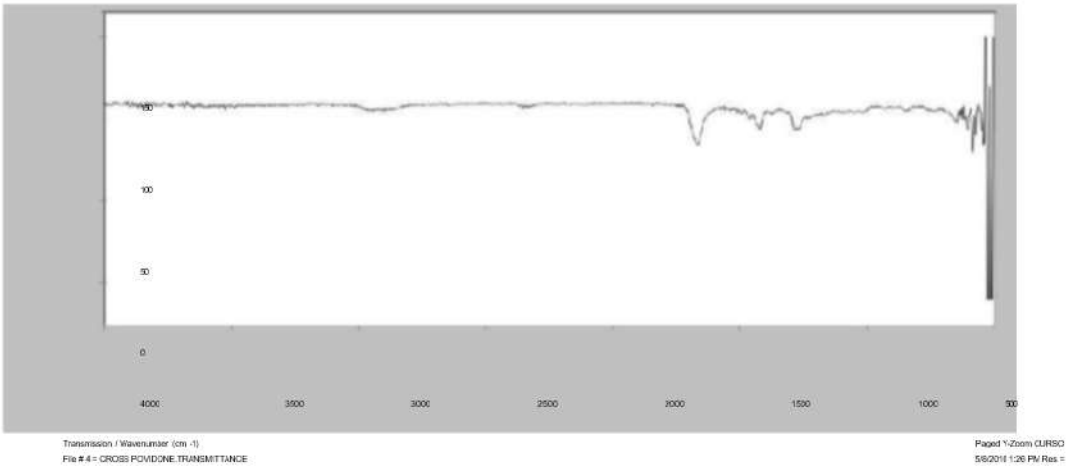

Fig. No. 18, FTIR spectra of crospovidone

FTIR spectra show characteristic peaks of crosspovidone which was similar to that of standard.

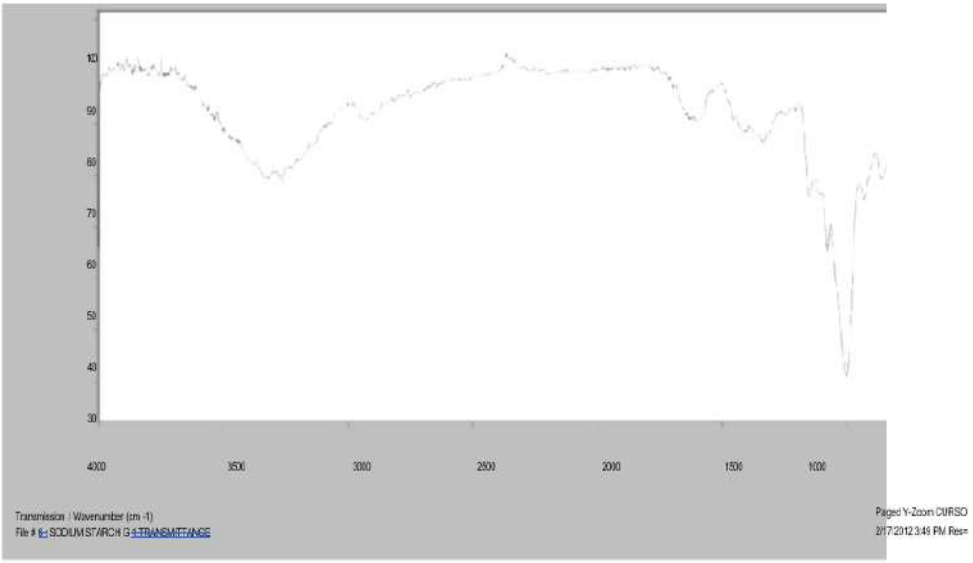

Fig.No.19, FTIR spectra of sodium starch glycolate

FTIR spectra show characteristic peaks of sodium starch glycolate which was similar to thatof standard.

Precompression studies:

Table No.18, Precompression studies of Sustained layer granules

Formulation Codes	Parameters				
	Bulk Density (g/ml)	**Tapped Density (g/ml)**	**Hausner's Ratio**	**Compressibility Index (%)**	**Angle of Repose (^{o})**
F1	0.341	0.375	1.12	10.81	26.12
	±0.025	±0.006	±0.003	±0.761	±0.657
F2	0.378	0.436	1.16	13.45	29.30
	±0.015	±0.012	±0.024	±0.423	±1.041
F3	0.259	0.304	1.20	16.07	29.04
	±0.012	±0.013	±0.012	±1.330	±0.653
F4	0.378	0.451	1.05	17.76	26.5
	±0.004	±0.002	±0.015	±1.221	±0.973
F5	0.376 ±0.013	0.487 ±0.005	1.07 ±0.010	12.79 ±0.361	27.6 ±1.096
F6	0.393 ±0.023	0.485 ±0.021	1.23 ±0.013	18.56 ±0.954	25.01 ±1.132
F7	0.379 ±0.034	0.463 ±0.014	1.13 ±0.006	17.42 ±1.086	29.2 ±0.431
F8	0.384 ±0.013	0.405 ±0.017	1.057 ±0.016	11.43 ±0.769	27.02 ±1.136

Table No. 19, Precompression studies of Immediate layer granules

Formulation Codes	Parameters				
	Bulk Density (g/cc)	Tapped Density (g/cc)	lausner's Ratio	Compressibilit y Index (%)	Angle of Repose (^{o}
F1	0.400	0.434	1.11	10.01	25.05
	±0.062	±0.056	±0.003	±0.631	±0.457
F2	0.480	0.515	1.13	11.92	29.74
	±0.031	±0.012	±0.024	±1.012	±0.752
F3	0.440	0.492	1.15	12.07	27.75
	±0.042	±0.023	±0.012	±0.630	±1.024
F4	0.432	0.490	1.13	11.83	29.78
	±0.004	±0.002	±0.045	±0.841	±1.126
F5	0.416	0.476	1.14	12.60	26.10
	±0.033	±0.045	±0.041	±0.912	±0.756
F6	0.409	0.473	1.15	13.53	28.95
	±0.043	±0.021	±0.093	±1.024	±0.952
F7	0.412	0.460	1.11	10.43	29.60
	±0.034	±0.054	±0.076	±1.086	±1.165
F8	0.420	0.466	1.10	9.87	25.02
	±0.033	±0.067	±0.069	±0.897	±1.136

Formulation of Floating Bilayer Tablets:

The bilayer tablets of Lornoxicam were prepared by wet granulation method. The drug and polymer for both fast and sustained release layer were passed through sieve no. 22.

Evalaution of Formulated Floating Bilayer Tablet:

Physical Tests of Bilayer Tablet:

Table No. 20, Physical Tests of Bilayer Tablet

Code	Thickness (mm)^n	Hardness (kg/cm^2)^n	Weight Variation*	Friabillty (%)	Floating lag time ^{n}	Floating time^n
F1	6.76±0.06	5.8	455±2.1	0.51	1.40 sec	>12 hr
F2	6.86±0.03	4.4	452±1.1	0.16	66 sec	>12 hr
F3	6..76±0.04	4.9	455±1.7	0.27	3.60 sec	>12 hr
F4	6.63±0.06	4.8	451±1.4	0.34	1.56 sec	>12 hr
F5	6.68±0.05	5.3	452±1.2	0.38	1.20 sec	>12 hr
F6	6.55±0.25	4.5	453±1.7	0.14	60 sec	>12 hr
F7	6.50±0.04	5.3	455±1.9	0.34	1.56 sec	>12 hr
F8	6.62±0.07	4.8	459±1.5	0.18	2.6 sec	>12 hr

n=mean of 3±s.d, *=mean of 20±s.d

All the batches of bilayer tablets were produced under similar conditions to avoid processing variables. Average weight of the bilayer tablets was in the range of 451 to 455mg. Hardness was in the range of 4.4 to 5.8 kg/cm2 and thickness was in range f6.50 to 6.86 mm. The percentage friability of all the formulations was in the range of 0.18 to 0.51 %. Values of hardness test and percentage friability indicate good wear and tear properties of bilayer tablet.

Drug Content of Active Ingredients:

Table No.21, Percentage Drug Content of Active Ingredients

Code	Drug content (%) [n]
F6	**97.91±1.5**

Values are expressed in Mean+ SD, n=3

The drug content of active ingredients was estimated by UV spectrophotometric method. The drug content in the optimized F6 bilayer tablets was found to be 97.9% which was shown in table no.8.0.

Drug Release profile of Bilayer Tablet:

Table No.22, Drug Release profile of Bilayer Tablet

Time (mnt)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10	**7.**9	15.1	12.8	20.5	14.6	28.3	6.05	8.6
20	10.1	19.4	14.5	25.8	17.3	33.3	11.4	10.2
30	11.4	22.8	17.8	27.2	18.4	34.6	14.9	13.3
40	15.6	25.2	19.9	28.4	19.8	38.2	16.8	15.6
50	18.4	27.2	22.1	30.9	21.3	39.4	17.1	16.8
60	21.7	28.5	23.5	32.1	22.7	41.9	20.3	18.1
120	24.8	30.2	25.8	33.9	25.3	53.8	23.5	20.3
180	27.4	32.9	29.4	38.3	28.8	58.2	24.3	24.2
240	30.2	35.6	32.6	41.4	31.9	59.4	28.5	27.2
300	32.7	38.3	37.5	43.2	37.3	63.1	31.4	30.8
360	33.9	40.5	42.7	45.7	43.1	64.7	33.4	35.6
420	35.8	43.8	46.9	49.3	47.3	66.8	36.3	39.9
480	35.9	46.4	49.2	53.6	49.2	68.2	36.7	43.7
540	36.6	49.3	53.4	58.1	52.4	71.5	38.2	49.2
600	37.3	52.4	55.2	63.2	54.6	74.8	39.2	53.8
660	38.2	56.7	57.2	67.2	59.8	78.4	39.9	56.9
720	41.7	60.3	62.1	75.5	69.2	89.9	42.3	65.8

Time in (minutes). Values are expressed in Mean±D, n=3

In vitro drug release of all formulations was carried out in 0.1 N HCL as per United States of Pharmacopeia and cumulative drug release was calculated at specific time interval. The result of in vitro drug release of Lornoxicam for different formulation are shown in Table no.24 The release of Lornoxicam from the prepared formulations was analyzed by plotting the cumulative percent drug release vs time as shown in Fig. Optimized formulation F6 Over 42% of levfloxacin s was released within the first 1 hour of dissolution study. This initial high amount of Lornoxicam can be attributed to the

fast release layer of the formulation. Further release of Lornoxicam was studied for 12 hours.

7. Summary And Conclusion

The aim of present study was to formulate and evaluation of bilayer tablet for management of Pain Contacting Lornoxicam.

The FTIR studies were carried out to check possible interaction between the drug and the excipient and the study confirmed that there was no interaction between the selected drug and excipient of both the drug.

The Immediate release layer prepared by dry granulation method using sodium starch glycolate, cross povidone, aerosil, magnesium stearate, lake, microcrystalline cellulose and dicalcium phosphate are used. The sustained release layer prepared by wet granulation method using HPMC E50, PVPK30, eudragit, microcrystalline cellulose, talc, magnesium stearate and isopropyle alcohol. Both the layer was separately optimized and were prepared. The granules of both the layer were evaluated for angle of repose, bulk density, tapped density, Hausners ratio and cars index. The angle of repose shows that powder for all batches had good flow ability and the compressed tablet were evaluated for its hardness, weight variation and friability.

In vitro drug release of all formulations was carried out in 0.1 N HCL as per United States of Pharmacopeia and cumulative drug release was calculated at specific time interval. The result of in vitro drug release of Lornoxicam for different formulation are shown in Table no.24 The release of Lornoxicam from the prepared formulations was analyzed by plotting the cumulative percent drug release vs time as shown in Fig. Optimized formulation F6 Over 42 % of levfloxacin s was released within the first 1 hour of dissolution study. This initial high amount of Lornoxicam can be attributed to the fast release layer of the formulation. Further release of Lornoxicam was studied for 12 hours.

Conclusion

From above experiment finding it can be concluded that bilayer tablet of Lornoxicam which reduces pain incorporated in Immediate and sustain Layer. It will give Fast onset of action due to immediate layer and longer duration of action due to sustain Layer. So, the bilayer tablet can be used as an alternative to conventional dosage form for the management of Pain.

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