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# FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF LORNOXICAM USING NATURAL AND SYNTHETIC POLYMERS

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## ABSTRACT

The objective of the present work is to design of sustained release matrix tablets of Lornoxicam influence of natural and synthetic polymers on the release rate and *in vitro* evaluation.Lornoxicam is widely used member of non-steroidal anti inflammatory and analgesic drug with short biological half- life.Lornoxicam is practically insoluble in water because of this reason it is suitable to develop sustained release matrix tablet using hydrophilic polymers. The natural polymers like Aloe barbadensis miller leaf mucilage, Hibiscus rosa-sinensis leaves mucilage, Ghatti gum, Isabgol husk mucilage and synthetic polymers. Lactose were utilized in the formulation of matrix tablets containing Lornoxicam by wet granulation technique and evaluated for its *in-vitro* drug release. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, thickness, friability, drug content and weight variations), *in vitro* drug release and stability studies.

**KEYWORDS:** Lornoxicam, SRDF, Controlled Release, Diffussion, Polymers.

## INTRODUCTION

The goal of any drug delivery system is to provide therapeutic amount of drug at the targeted site in the body. Its aim is to achieve and maintain the desired drug concentration within the body for required period of time. Matrix tablet is one of the sustained drug delivery system which is widely used for conditions where prolonged drug concentration in the blood is desired.[1,2]

The steady state drug concentration in blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.[3]

Because of increased complication and expense involved in marketing of new drug entities, this has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.[4]

Sustained drug delivery systems have acquired a centre stage in the field of pharmaceutical research and development sector. Such systems offer temporal and /or spatial control over the release of drug and grant a new life to a drug molecule.

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. Approximately 50% of the drug products available in the market are administered orally and historically, oral drug administration has been the predominant route for drug delivery. Tablets are the most commonly and widely used dosage form. This type of drug delivery system is called conventional drug delivery system and is known to provide an immediate release of drug. Such immediate release (IR) products results in relatively rapid drug absorption and onset of accompanying pharmaco dynamic effects. However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached

another dose is usually given if a sustained therapeutic effect is desired.[5]

Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

**The modified release oral delivery system classification[7]**

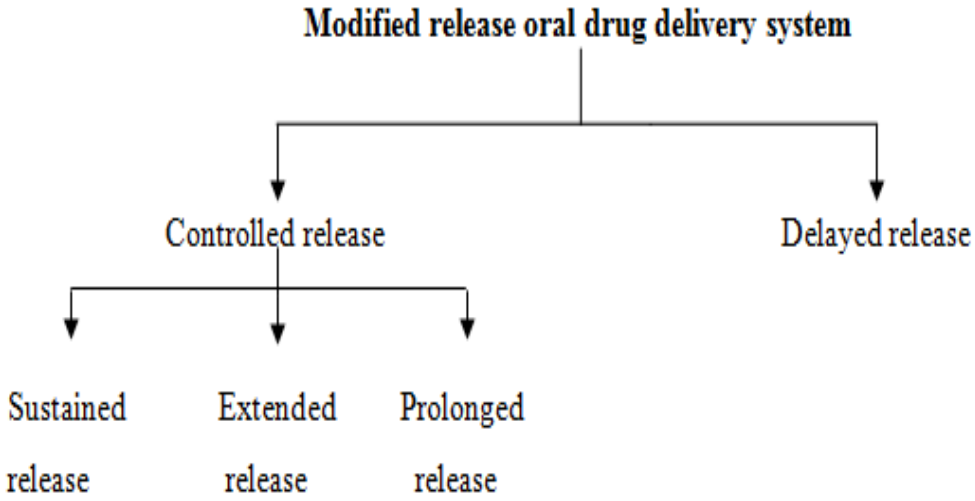


**Figure 1: Classification of Modified Release Drug Delivery System[7]**

The IR (immediate release) drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.(Figure 2) shows the relation between plasma concentration verses time.[7]

**1.2 Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form.[7]**

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

Matrix tablet is one of the most widely used approaches to sustain the drug action. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". Matrix drug delivery systems release the drug in continuous manner.[6]

**1.1 METHODS FOR TABLET PREPARATION[6]**

1. Granulation method
a. Wet granulation
b. Dry granulation
2. Direct compression method

- Medication or over medication in narrow therapeutic index drug.

**1.3 Limitation of oral conventional dosage form.[7]**

Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

- The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible.

**1.4 SUSTAIN RELEASE DOSAGE FORMS[8]**

The term "Controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. But, there is some confusion in terminology between "Controlled release" & "Sustained release" which is given below.[5]

**Sustained Release**

The term sustained release has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed &/or prolonged & its plasma profile is sustained in duration.

**Controlled Release**

This term on the other hand, has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability & reproducibility in the drug release kinetics, which means that the release of drug ingredient from a controlled delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

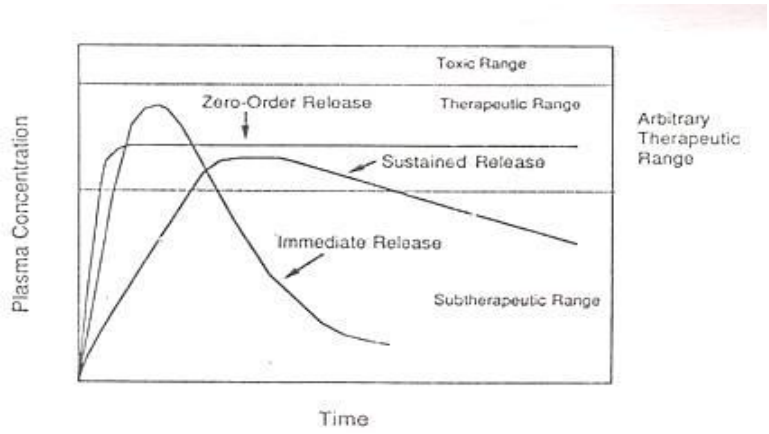


**Figure 2: Plasma Drug concentration verses time profile showing differences between zero order, controlled releases, first order extended release and release from conventional tablet(IR).**

**Advantages of SR Matrix DDS[9]**

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus: Maximizing availability with minimum dose. Minimize or eliminate local side effects Minimize or eliminate systemic side effects. Minimize drug accumulation with chronic dosing.
- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment, Cure or control condition more promptly Improve control of condition. Improve bioavailability of some drugs, make use of special effects; eg : sustain release aspirin for morning relief of arthritis by dosing before bed-time.

**Disadvantages of SR matrix DDS[9]**

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor in vitro and in vivo correlations.
- Dose dumping, toxicity can occur if system fails.

**1.5 GENERAL PRINCIPLE OF CONTROLLED – RELEASE SYSTEMS**

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

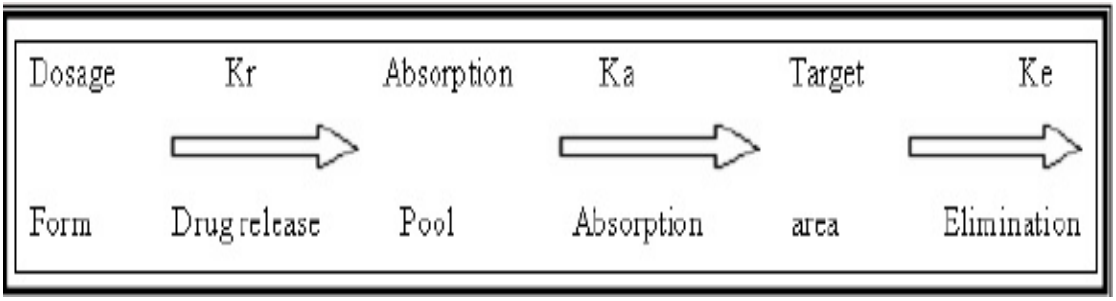


**Figure 3: Kinetic scheme of conventional dosage form.**

The absorption pool represents a solution of the drug at the site of absorption and the term Kr, Ka and Ke are first order rate-constant for drug release absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka.

Alternatively speaking the absorption of drug across a biological membrane is the rate limiting step. For non-immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This causes the above Kinetic scheme to reduce the following.

Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release delivery system must be directed primarily at altering the release rate.

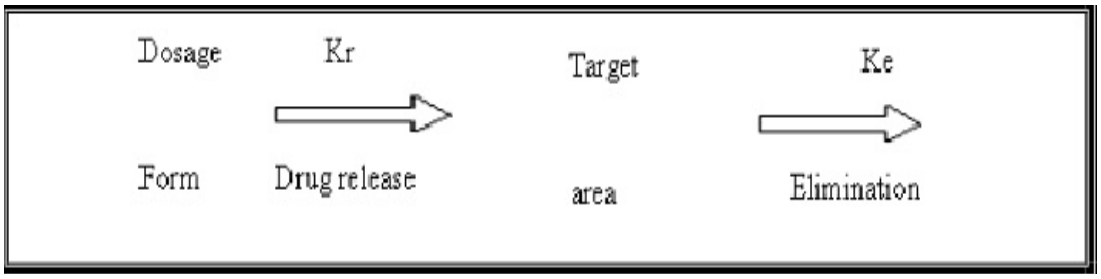


**Figure 4: Kinetic scheme of non-conventional dosage form.**

The main objective in designing an extended release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follows zero-order kinetics, as shown by the following equation.

**$K_r$ ° = Rate in = Rate out = Ke $C_d V_d$**

**$K_r$°**: Zero-order rate constant for drug release- Amount/time
**$K_e$:** First-order rate constant for overall drug elimination- time-1
**$C_d$:** Desired drug level in the body - Amount/volume
**$V_d$:** Volume space in which the drug is distributed- Liters

The value of Ke, $C_d$ and $V_d$ are obtained from appropriately designed single dose pharmacokinetic study.

The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theoretically, non-zero-order release may be equivalent clinically to constant release in many cases.

Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered as a controlled-release system.[9]

### 1.6 Classification of SR Formulation[10]

The most common methods used to achieve sustained release of orally administered drugs are as follows.

**Diffusion systems**

Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of

diffusional systems are recognized reservoir devices and matrix devices.

**a) Reservoir Devices**

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. It is also possible to use polymer coatings to achieve sustained release. For this purpose the polymer itself should not dissolve, but rather should allow the drug to diffusion through the polymer membrane to the outside, in the case of oral drug delivery, into the gastrointestinal tract.

**b) Matrix Devices**

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion ate of dissolved drug leaving the matrix.

**Diffusion Type Reservoir System.**

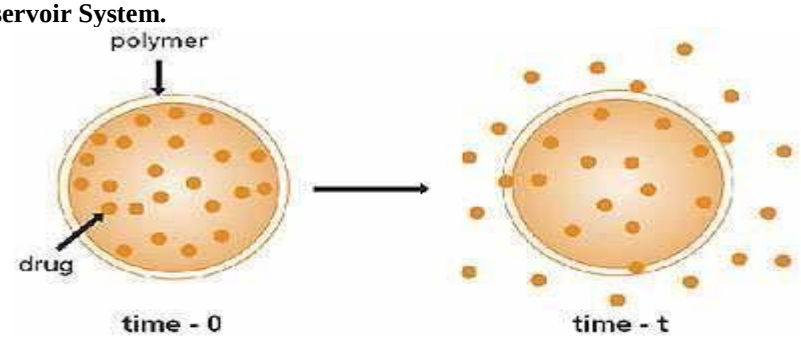


**Figure5: Schematic Representation of Diffusion Type Reservoir System.**

**Diffusion Type Matrix System**

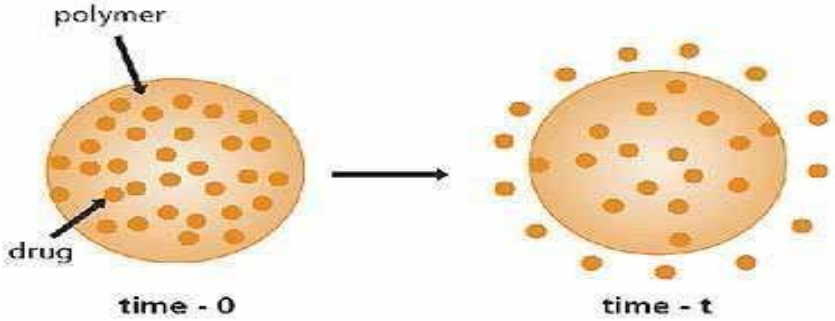


**Figure 6: Schematic Representation of Diffusion Type Matrix System.**

**Dissolution systems**

It seems inherently obvious that a drug with a slow dissolution rate will demonstrate sustaining properties, since the release of drug will be limited by the rate of dissolution. This being true, sustained-release preparation of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

a) Osmotic system.
b) Ion-exchange resins.
c) Swelling and expansion systems.
d) Floating systems.
e) Bioadhesive or Mucoadhesive systems.

**1.7 Matrix Systems**

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant materials and additives to form a tablet in which drug is embedded in matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression.

**Types of Matrix**

**Hydrophobic Matrices**

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

**Lipid Matrices**

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

**Hydrophilic Matrices**

A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

**a. Cellulose derivatives:** HPMC 400 and 4000cPs,HPMC 25, 100, 4000 Sodium carboxy methyl cellulose.

**b. Non cellulose natural or semi synthetic polymers:** Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, chitosan and modified starches.

**Biodegradable Matrices**

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non enzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

**Mineral Matrices**

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

**On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types**

**Macro porous systems**: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

**Micro porous system:** Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

**Non-porous system:** Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.[10]

**1.8 MATRIX TECHNOLOGY[11]**

Matrix technologies are popularly used because of the simplicity of the manufacturing processes required, level of reproducibility, stability of the raw materials and dosage form as well as ease of scale up operation, validation and favourable *in-vitro in-vivo* correlation (IVIVC). Classically, simple matrix delivery systems exhibit first order or square root of time release kinetics.

These systems improve patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, a controlled-release formulation maintains therapeutic blood level of a drug for a specific period of time. A number of oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects. In order to overcome all those problem mentioned above, the matrix tablets has additional advantage like, matrix tablets are resistant to dose dumping. They are simple in nature of the formulations and due to robustness they are unaffected by variations in ingredients.

Matrix tablets containing hydrophilic polymers are a common and commercially successful means of prolonging oral drug delivery. A common problem observed with hydrophilic matrix systems containing water soluble drugs is an initial burst effect of the drug release.

**Process of Manufacturing Matrix Tablets**

One of the commonly employed processes for the manufacture of extended release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which the drug is embedded in the matrix core of retardant. Alternately, the Retardant-drug blends can be granulated prior to compression.

**Matrix devices are of two types**

- Matrix dissolution controlled drug delivery devices.
- Matrix diffusion controlled drug delivery devices.

**Matrix Diffusion Controlled Drug Delivery Devices**

Matrix diffusion devices are prepared by dispersing a solid drug in an insoluble polymer matrix carrier system, i.e. a drug reservoir is formed by homogenous dispersion

of solid drug particles throughout a lipophilic or hydrophilic polymer matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. The equation describing drug from this system T. Hugichi has derived this system.

$$Q = [D/ (2 A - Cs) Cst]^{1}/2$$

Where

Q = Weight in grams of drugs in the unit surface area.

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix.

τ = Tortuosity of the matrix.

Cs = Solubility of the drug in release medium.

A = Concentration of drug in the tablet expressed as g/ml.

The following assumptions were made in deriving the above equation:

- A pseudo-steady state is maintained during release.
- A>>Cs i.e. excess solute is present.
- C = 0 in solution at all times (perfect sink condition)
- Drug particles are much smaller than those in the matrix.
- The diffusion coefficient remains constant.
- No interactions between the drug and the matrix occur.
- One many control drug release from a homogenous matrix by varying the following parameters.
- Initial concentration of drug in the matrix.
- Drug solubility.
- Porosity.
- Tortuosity.
- Leaching solvent composition.
- Polymer system making up matrix.

**Matrix Dissolution Controlled Drug Delivery Devices**

Matrix dissolution devices can also be formulated by compressing the drug by slowly dissolving the polymer carrier into a tablet form. There are two general methods of preparing drug-wax particles: congealing method and aqueous dispersion method. In congealing method the drug is mixed with wax material and either sprays congealed or congealed and screened. In the aqueous dispersion method, the drug-wax mixture is sprayed or placed in water and the resultant particles are collected.

Matrix tablets are made by direct compression of mixture of drug, polymer and excipients. The rate limiting step in controlling release from these formulations is liquid penetration into the matrix. Some channelling agents (wetting agents) can be incorporated with the blend of mixture to promote permeation of polymer matrix by water, which allows drug dissolution and diffusion from the channels created in the matrix. Formulations should be designed, so that pore diffusion becomes the rate-controlling step.

Drug bioavailability, which is critically dependent on the drug: polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in low-milligram potency formulations.

The polymer selected for formulation as well as the drug polymer ratio controls the extent to which diffusion or erosion which controls release of the drug from the formulation.

**1.9 POLYMERS[12,13]**

An excipients help in the manufacturing of dosage form and it also improves physicochemical parameters of the dosage form. Polymers play an important role as excipients in any dosage form. They influence drug release and should be compatible, non-toxic, stable, economic etc.[12]

**They are broadly classified as**

- Natural polymers
- Synthetic polymers

Many researchers have explored the usefulness of plant-based materials as pharmaceutical excipients.The plant based polymers have been studied for their application in different pharmaceutical dosage forms like matrix controlled system, film coating agents, buccal films, microspheres, nano particles, viscous liquid formulations like ophthalmic solutions, suspensions, implants and their applicability and efficacy has been proven . These have also been utilized as viscosity enhancers, stabilisers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives, binders in the above mentioned dosage.

Natural polymer became a thrust area in majority of investigations in drug delivery systems. Natural gums can also be modified to meet the requirements of drug delivery systems and thus can compete with the synthetic excipients available in the market.[13]

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)**

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis). A number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory actions, and thus have utility in the treatment of fever. Most of these drugs express their therapeutic actions by inhibition of prostaglandin biosynthesis as described in the sections that follow. Some of the primary indications for NSAID therapy include

- Rheumatoid Arthritis (RA): No one NSAID has demonstrated a clear advantage for the treatment of RA. Individual patients have demonstrated variability in response to certain NSAIDs. Anti-inflammatory activity is shown by reduced joint swelling, reduced pain, reduced duration of morning stiffness and disease activity, increased mobility, and by enhanced functional capacity (demonstrated by an increase in grip strength, delay in time-to-on set of fatigue, and a decrease in time to walk 50 feet).

- Osteoarthritis (OA): Improvement is demonstrated by increased range of motion and a reduction in the following: Tenderness with pressure, pain in motion and at rest, night pain, stiffness and swelling, overall disease activity, and by increased range of motion. There are no data to suggest superiority of one NSAID over another as therapy for OA in terms of efficacy and toxicity. NSAIDs for OA are to be used intermittently if possible during painful episodes and prescribed at the minimum effective dose to reduce the potential of renal and GItoxicity. Indomethacin should not be used chronically because of its greater toxicity profileand its potential for accelerating progression of OA.
- Acute gouty arthritis, ankylosing spondylitis: Relief of pain; reduced fever, swelling, redness and tenderness; and increased range of motion have occurred with treatment of NSAIDs.
- Dysmenorrhea: Excess prostaglandins may produce uterine hyperactivity. These agents reduce elevated prostaglandin levels in menstrual fluid and reduce resting and active intrauterine pressure, as well as frequency of uterine contractions. Probable mechanism of action is to inhibit prostaglandin synthesis rather than provide analgesia.

**NSAID Mechanism of Action**

The major mechanism by which the NSAIDs elicit their therapeutic effects (antipyretic, analgesic, and anti-inflammatory activities) is inhibition of prostaglandin (PG) synthesis. Specifically NSAIDs competitively (for the most part) inhibit cyclooxygenases (COXs), the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins. Two COX isoenzymes have been identified: COX-1 and COX-2. COX-1, expressed constitutively, is synthesized continuously and is present in all tissues and cell types, most notably in platelets, endothelial cells, the GI tract, renal microvasculature, glomerulus, and collecting ducts. Thus COX-1 is important for the production of prostaglandins of homeo static maintenance, such as platelet aggregation, the regulation of blood flow in the kidney and stomach, and the regulation of gastric acid secretion. Inhibition of COX-1 activity is considered a major contributor to NSAID GI toxicity. COX-2 is considered an inducible isoenzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, neoplasias, and GI tract. The COX-2 isoenzyme plays an important role in pain and inflammatory processes. Inhibition of COX by NSAIDs Generally, the NSAIDs inhibit both COX-1 and COX-2. Most NSAIDs are mainly COX-1selective (eg, aspirin, ketoprofen, indomethacin, piroxicam, sulindac). Others are considered slightly selective for COX-1 (eg, ibuprofen, naproxen, diclofenac) and others may be considered slightly selective for COX-2 (eg, etodolac, nabumetone, and meloxicam). The mechanism of action of celecoxib and rofecoxib is primarily selective inhibition of COX-2; at therapeutic concentrations, the COX-1 isoenzyme is not inhibited thus GI toxicity may be decreased. Other mechanisms that may contribute to NSAID anti-inflammatory activity include the reduction of superoxide radicals, induction of apoptosis, inhibition of adhesion molecule expression, decrease of nitric oxide synthesis, decrease of pro inflammatory cytokine levels (tumornecrosis factor-a, interleukin-1), modification of lymphocyte activity, and alteration of cellular membrane functions. Central analgesic activity has been demonstrated in animal pain models by some NSAIDs such asdiclofenac, ibuprofen, indomethacin, and ketoprofen. This may be because of the interference of prostaglandin (PGE1, F2 and F2a) mediated pain formation or with transmitters or modulators in the nociceptive system. Other proposals include the central action mediated by opioid peptides, inhibition of serotonin release, or inhibition of excitatory amino acids or N-methyl-D-aspartate receptors. NSAIDs are mainly effective against the type of pain in which PGs sensitize pain receptors (inflammation and tissues) including the pain of arthritis, bursitis, pain of muscular and vascula origin and dysmenorrhea. The effectiveness of these agents against headache may result from their ability to inhibit PG-mediated cerebral vascular vasodilation. Antipyretic activity of NSAIDs results from inhibition of prostaglandin E2 (PGE2) synthesis in circum ventricular organs in and near the preoptic hypothalamic area. Infections, tissue damage, inflammation, graft rejection, malignancies, and other disease states enhance the formation of cytokines that increase PGE2 production. PGE2 triggers the hypothalamus to promote increases in heat generation and decreases in heat loss.

**Other Actions of the NSAIDs**

The NSAIDs also express a variety of other actions in addition to their anti-inflammatory, analgesic and antipyretic activities as outlined below.

- GI Tract (N/V, ulceration and hemorrhage). In the gastric mucosa, prostaglandins play acytoprotective role inhibiting the proton pump and thereby decreasing gastric acid synthesis, stimulating the production of glutathione that scavenges superoxides, promoting the generation of a protective barrier of mucous and bicarbonate, and promoting adequate blood flow to the gastric mucosal cells. Since NSAIDs block PG biosynthesis in the GI tract, they block these cyto protective processes. The primary toxicity seen with the NSAIDs is GIirritation which may lead to the production of ulcers when used in large doses over a long period of time. This occurs quite frequently in patients with RA and it may become so severe that the drug must be discontinued. There have been a number of attempts to eliminate this side effect and some success has been achieved but since most of the compounds suppress the production of PGs involved in limiting the secretion of gastric acid and since this a consequence of their mechanism of action it has been difficult to completely eliminate this side effect. In additional to inhibition of PG

biosynthesis, NSAID gastric irritation may also be due to a direct irritation of the gut by these acidic compounds.

- CNS: High NSAID doses cause CNS stimulation (confusion, dizziness, etc), tinnitus, etc.PGE2 may also cause fever via interactions within the hypothalamus.
- Respiratory: Direct and indirect (increased CO2 production) stimulation of respiratory centres, stimulation of O2 consumption in muscle (increased CO2); respiratory alkalosis. AlsoPGI2 and the PGEs cause bonchodilation while PGF2a, PGGs, PGH2, PGD2 and TxA2 are bronchoconstrictors (asthma)
- Acid-Base: Initial respiratory alkalosis. This is generally somewhat unique to the salicylates and is only seen with large doses.
- Cardiovascular: PGH2 and PGH2 cause transient vasoconstriction, but these intermediates are converted to PGI2 and other PGS (PGD2 PGF2a) which are vasconstrictors. At high doses NSAIDs cause vasodilation and depression of the vasomotor centre.
- Uterus: PGF2a and PGE2 (in low concentrations) promoateuteral contraction while PGI2and PGE2 in high concentrations promote uteral relaxation. NSAIDs decrease contractility and prolong gestation
- Blood clotting: PGS I2 (vascular endothelium), E2 and D2 inhibit platelet aggregation whileTXA2 (platelets) promotes aggregation. NSAIDs may significantly increase clotting times and can be used for prophylaxis of thrombo embolism and MI. However, patients with liver damage, vitamin K deficiency, hypoprothrombinemia or hemophilia should avoid aspirin therapy.
- Renal: The inhibition of PGE2 and PGI2 both of which produce vasodilation in the kidney results in a decrease blood flow to the kidneys due to constriction of afferent arterioles which is mediated by norepinephrine and Angiotensin II. NSAIDs may decrease sodium and fluid elimination resulting in edema.
- Reye's syndrome: This is seen in children who take an NSAID such as aspirin while recovering from mild viral infection. Although it occurs rarely there is a 20-30% mortality seen with this type of side effect.[14]

**Properties of NSAIDs**

- mildly analgesic
- antipyretic
- anti-inflammatory
- act on sub-cortical sites such as thalamus and hypothalamus
- no affinity for morphine receptors
- In addition, tolerance and drug dependence do not develop to these drugs in patients.

**Oxicams (Enolic Acids)**

- **Structure and Chemistry:** Oxicams (Piroxicam Lornoxicam and Meloxicam) are characterized by the 4-hydroxybenzothiazineheterocycle. The acidity of the oxicams is attributed to the 4-OH with the enolate anion being stabilized by intra molecular H-bonding to the amide N-H group. Also, the presence of the carboxamide substituent at the 3-position of the benzothiazine ring contributes toward acidity by stabilizing the negative charge formed during ionization(resonance stabilization). Although these compounds are acidic (pKa = 6.3), they are some what less acidic than carboxylic acids NSAIDs. Yet the oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity.
- Oxicam Absorption and Distribution: The oxicams are well but slowly absorbed after oral administration (Tp = 3-5 hours). The long plasma half-life of these compounds (20-50 hours)allows for once a day dosing. The long half-life of this agent is due in part to the lack of acarboxylic acid functionality which can be readily glucuronidated and excreted.[15]

**AIM OF THE WORK**

The aim of this research work was to design of sustained release matrix tablets of Lornoxicam: influence of natural & synthetic polymers, on the release rate and *in vitro* evaluation, in view to sustain the drug release, reduce the frequency of drug administration, improved patient compliance and therapeutic action. The specific objective of this research includes.

1. To prepare sustained release matrix tablet of Lornoxicam by using natural & synthetic polymers
2. Evaluation of the tablets for their hardness, friability, drug content and *in vitro* dissolution study.
3. Treatment of dissolution data with various mathematical models to know the release mechanisms.
4. To carry out compatibility studies by FT-IR.
5. To carry out SEM studies for optimized formulation.

The best formulation is to be selected on the basis of evaluation characteristics.

**The scope of the present work is**

- To provide a drug delivery system for continuous release of drug at controlled rate of maintain the therapeutic blood plasma concentration for a required period of time.
- Finally to provide the drug delivery system which increases the patient compliance, effectiveness of therapy and reduces the chances of adverse effect and hypersensitivity of reaction by maintaining the plasma drug concentration at the same level within therapeutic range for the required period of time.

**PLAN OF WORK**

The present work was carried out to formulate sustained release matrix tablets of Lornoxicam. The sustained release matrix tablets were prepared by wet granulation method by using various natural & synthetic polymers. Keeping in view the objectives described above the following plan of work was adopted.

**THE SCHEME OF THE ENTIRE WORK IS LISTED AS FOLLOWS**

1. Standardization of the method and construction of calibration curve for the estimation of Lornoxicam.
2. Pre-formulation studies of drug and polymer by FT – IR spectral studies.
   - Formulation of granules for Lornoxicam sustained – release matrix tablets by using natural & synthetic polymers namely Aloe barbadensis, miller leaves mucilage, Hibiscus rosa-sinensis leaves mucilage, Ghatti gum, Isphagula husk mucilage, Ethyl cellulose, HPMC.

3. Evaluation of blend characteristics of granulated mixture of drug, polymers and excipients:
   - Angle of repose.
   - Determination of bulk density.
   - Determination of tapped density.
   - Compressibility index.
   - Drug Content uniformity test etc.

4. Formulation of Lornoxicam sustained – release matrix tablets by using rotary tablet punching machine.

5. Evaluation of physical parameters of Lornoxicam sustained – release matrix tablets.
   - Hardness**.**
   - Friability.
   - Weight variation.
   - Drug Content uniformity test.
   - Thickness.
6. Evaluation of *in vitro* release characteristics of all formulations by using USP dissolution apparatus 2 (Paddle).
7. To study the mechanism of drug release by applying kinetic parameters.
8. To carry out compatibility studies by FT-IR.
9. To carry out SEM studies for the optimized formulation.
10. To carry out short term stability studies on the most satisfactory formula.

**REVIEW OF LITERATURE**

Syed Namath U *et al*, Lornoxicam, a potent non-steroidal anti-inflammatory drug which has short half-life, makes the development of sustained release (SR) forms extremely advantageous. However, due to its weak acidic nature, its release from SR delivery systems is limited to the lower gastrointestinal tract which consequently leads to a delayed onset of its analgesic action. Therefore, the present investigation of this study was to develop Lornoxicam SR matrix tablets that provide complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continues in the intestine to maintain analgesic effect. Lornoxicam showed maximum absorption at wavelength 373 nm I 0.1N HCl and 379 nm in pH 6.8. Drug-polymer compatibility studies by FTIR gave confirmation about their purity and showed no interaction between drug and selected polymers. Various formulations were developed by using release rate controlling and gel forming polymers like HPMC (K4M, K15M, K100M) by direct compression method. From among all the developed formulations, F1 formulation sustained the drug release for longer period of time as compared to other formulations. So, F1 was selected as the best formulation. It was concluded that the release followed zero order kinetics, as the correlation coefficient (R2 value) was higher for zero order release, so the drug release mechanism is controlled release. The best formulation was found to be stable during stability studies for two months. Thus, best formulation satisfied physicochemical parameters and *in vitro* drug release profile requirements for a sustained drug deliverysystem.[16]

Patidar Deepak *et al.*, Formulation and evaluation of pioglitazone hydrochloride matrix tablet by using *aloe barbadensis* miller , di-basic calcium phosphate , poly vinyl pyrrolidone And magnesium stearate. They found that the pre-compressional parameters angle of repose, % compressibility and Hausner's ratio are in the range of given in official standard, indicated that granules prepared by wet granulation method were free flowing. The post-compression parameters of matrix tablets (hardness, friability, weight variation, thickness and drug content) were within the acceptable official limits. They concluded that dried *aloe barbadensis* miller leaves mucilage in combination with poly vinyl pyrolidone forms a good matrix for sustained release of drug from the tablets. The release of the drug form matrix tablets containing 1.25, 2.5, 3.75, 5, & 6.25 % of polymer was release drug 98.59, 94.52, 91.81, 89.05, & 83.65 % cumulative release within 12 hrs. The F5 batch tablets formulation were selected for the Stability studies were carried out according to ICH guidelines at 30$^{o}$C & 65% RH and 40°C & 75% RH for three months indicated that the pure drug was stable in layered tablets.[17]

Hindustan AA *et al.*, The present research work was aimed to develop matrix tablets of Glimepiride with *Aloe barbadensis miller* leaves mucilage and Povidone and to study its functionality as a matrix forming agent for sustained release tablet formulations. Physicochemical properties of dried powdered mucilage of *Aloe barbadensis miller* mucilage and Povidone tablet blend were studied. Various formulations of Glimepiride *Aloe barbadensis miller* mucilage and Povidone were prepared. They found to have better satisfactory physicochemical properties with low SD values. The swelling behavior and release rate characteristics were studied. The dissolution study proved that the dried *Aloe barbadensis miller* mucilage and Povidone combination can be used as a matrix forming material for making Sustained release matrixtablets.[18]

Majmudar H*et al*., in the present study of Pharmaceutical Applications of Isabgol Husk: Mucilage, the Natural carbohydrates have been popularly used as a material for centuries in all kinds of pharmaceutical applications. It is the world's most abundant renewable and biodegradable

polymer. They were concluded that Isabgol has high potential in developing an unconventional source as an 'excipient' and very high potential in developing new formulations and in design of dosage forms.[19]

Moin A *et al.,* Formulation of sustained release diltiazem matrix tablets by using microcrystalline cellulose, hydroxy propyl methyl cellulose, locust bean gum and karaya gum. Matrix tablets of diltiazem were prepared at different ratios of drug: gum (1:1, 1:2 and 1:4) and of the gum blends (karaya gum, karaya gum/locust bean gum, karaya gum/hydroxy propyl methyl cellulose and karaya gum/locust bean gum/hydroxyl propyl methyl cellulose) by direct compression. The matrix tablets were evaluated for hardness, friability, in vitro release and drug content. They concluded that locust bean gum alone cannot efficiently control drug release, a suitable combination of the two natural gums (karaya and locust bean gum) may be successfully employed for formulating sustained release matrix tablets of diltiazem.[20]

PunnaRoa Devi *et al.,* Oral controlled release matrix tablets of lamivudine were prepared by using hydroxy propyl methyl cellulose as the retardant polymer. Matrix tablets containing 60% hydroxy propyl methyl cellulose 4000 cps were found to show good initial release (26% in first hour) and extended the release up to 16 hours. Matrix tablets containing 80% hydroxy propyl methyl cellulose 4000 cps and 60% hydroxy propyl methyl cellulose 15000 cps showed a first-hour release up to 22% but extended the release up to 20 hours. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release. No incompatibility was observed between the drug and excipients used in the formulation of matrix tablets.[21]

Streubel A *et al.,* Formulation and evaluation of verapamil sustained release matrix tablets by using two different polymers as matrix formers, the water insoluble and almost non-swellable ethyl cellulose (EC) and the water soluble and highly swellable hydroxy propyl methyl cellulose (HPMC). The pH independent system was achieved by the addition of organic acids such as fumaric, succinic or adipic acid to the drug-polymer system. The addition of organic acids to both matrix formers was found to maintain low pH values within the tablets during drug release in phosphate buffer (pH 6.8 or 7.4). Thus, the micro-environmental conditions for the dissolution and diffusion of the weakly basic drug were almost kept constant. The release of verapamil hydrochloride from tablets composed of EC or HPMC and organic acids was found to be pH independent.[22]

Marina Levina *et al.,* The influence of excipients on drug release from hydroxy propyl methyl cellulose matrices by using spray-dried lactose (SDL), microcrystalline cellulose (MCC) and Starch 1500. They found that addition of 20 to 49.25% w/w Starch 1500 resulted in a significant reduction in drug release rates compared to when MCC or SDL was used. The study showed that using lactose or microcrystalline cellulose in the formulations resulted in faster drug release profiles. Partially pregelatinized maize starch contributed to retardation of both soluble and slightly soluble drugs. This effect may be imparted through synergistic interactions between starch 1500 and HPMC and the filler actively forming an integral part within the HPMC gel structure.[23]

## DRUG PROFILE[38-39]

### LORNOXICAM

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses > or = 8 mg to control pain after oral surgery.

Lornoxicam combines the high therapeutic potency of oxicams with aniproved gastrointestinal toxicity profile as compared to naproxen, which is probably due to the short half-life of Lornoxicam as compared to the other oxicams. Clinical investigations have established it as a potent analgesic with excellent anti- inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain.

**Chemistry**

6-Chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1- dioxide.

**Proprietary names** Lornoxi, Lorna, Lornex, Lornox, Losnasafe, Lorsid, LRN, Nyox, Telos, Xefo, Xefocam, Zeficam.

**Empirical formula –$C_{13}H_{10}ClN_3O_4S_2$**
**Molecular weight – 371.82**
**Ionization constant – pKa of 4.7**
**Melting point -225-230$^{o}$c**

**Structural formula**

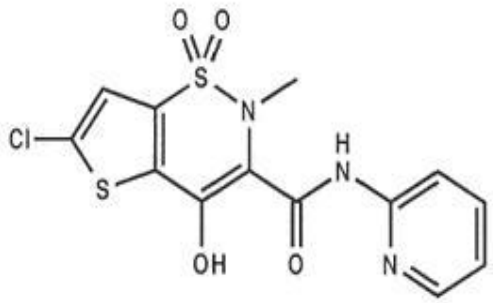


**Figure 7: Structure of Lornoxicam.**

**Appearance**
Lornoxicam is an orange to yellow crystalline powder.

**Mechanism of action**
Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and it belongs to the class of oxicams. Lornoxicam is a potent inhibitor of both COX-1 and COX-2 enzymes. The mechanism of the analgesic action is related to the inhibition of cyclo oxygenase, which suppresses the production of prostaglandins and thromboxanes thereby reducing pain and inflammation. The analgesic activity is related to balanced inhibition of COX-1 and COX-2 and release endogenous dynorphin and b-endorphin with reported central analgesic activity. The unlike some NSAIDs, the inhibition of cyclo oxygenase by lornoxicam does not result in an increase in leukotriene formation, and the shunting of arachidonic acid to the 5- lipoxygenase cascade is therefore not expected, which minimizes the risk of some adverse events, for example, allergic reactions.

**Pharmacokinetics**
Lornoxicam is absorbed from gastrointestinal tract and is characterized by a rapid rate. The peak blood concentration is reached after approximately 1–2 hrs. The absolute bioavailability (calculated as AUC) of XEFO film-coated tablets is 90–100%. Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity. Lornoxicam is metabolized completely, and approximately 2/3 is eliminated via the liver and 1/ 3 via the kidney as inactive substance. 5- Hydroxylation is the main metabolic pathway, which accounts for up to 95% of total intrinsic lornoxicam clearance, and cytochrome P450 2C9 has been proven to be the primary enzyme involved in the formation of 5-hydroxy lornoxicam in vitro. When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data showed no evidence of accumulation of lornoxicam after repeated administrations, when given according to a recommended dosage. This finding was supported by drug monitoring data from 1 year studies. Simultaneous intake of lornoxicam with meals reduced Cmax by approximately 30%. Tmax was increased from 1.5 to 2.3 hrs. The absorption of lornoxicam (calculated as AUC) can be reduced up to 20%. Simultaneous intake with antacids has no effect on the pharmacokinetics of lornoxicam. The bioavailability of lornoxicam after oral application is more than 90%. Maximum plasma concentrations are achieved after about 2 hrs. Lornoxicam is found in the plasma in unchanged form and as its hydroxylated form. The hydroxylated metabolite exhibits no pharmacological activity. Given normal liver and kidney function, the plasma half-life is about 4 hrs. It readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies. In elderly patients, the clearance of lornoxicam is reduced by about 30–40%; thus, the half-life is somewhat longer. Even in the presence of impaired kidney and liver function, no major differences in pharmacokinetics have been observed. On account of its short half-life, no accumulation is likely to occur even in cases of repeated administration. Like other oxicams and diclofenac, lornoxicam is metabolized via cytochrome P450 2C9. Due to a genetic polymorphism, some individuals may metabolize slowly and, therefore, have elevated level of lornoxicam. The maximum therapeutic blood level that elicit analgesic activity reported 1 mg/ml. After administration of lornoxicam 4 mg tablets to healthy volunteers, mean peak serum concentrations of 300–360 ng/ml were obtained after 1.6–3 hrs. There is no evidence of accumulation or elimination rate changes with repeated-dose administration.

**Uses and applications**
Lornoxicam, an oxicam derivative, is a non steroidal anti-inflammatory derivative. It is used in muscular skeletal and joint disorders such as osteoarthritis and rheumatoid arthritis. It is also used in the treatment of other painful conditions including postoperative pain. In the treatment of osteoarthritis and rheumatoid arthritis lornoxicam is given by mouth in a daily dose of 12 mg in two or three divided doses. Lornoxicam is given in doses of 8–16 mg daily by mouth for the treatment of pain. Doses above 8 mg should be given in divided doses. Similar doses may be given by intravenous or intramuscular injection, although in rare cases the maximum initial daily dose may be increased to 24 mg; treatment by injection should be limited to two days. Lornoxicam has demonstrated clinical efficacy in relieving chronic pain associated with osteoarthritis , rheumatoid arthritis, and ankylosing spondylitis. In the treatment of postoperative pain, lornoxicam has been shown to be as effective as morphine. An in vitro study suggested that lornoxicam is 100 times more potent than tenoxicam as a COX inhibitor and its analgesic potency is 12 and 10 times greater than that of piroxicam and tenoxicam, respectively. Lornoxicam analgesic potency of 16 mg (i.m.) is comparable with that of 20 mg morphine (i.m.) or 50 mg tramadol (i.v.).

**Anti-Inflammation**
In osteoarthritis, 8mg twice daily improves pain and functional disability. Other area where lornoxicam is found useful is ankylosing spondylitis and Rheumatoid arthritis. Anti-inflammatory and antipyretic effects of lornoxicam include prevention of the degenerative bone loss seen in chronic inflammation by inhibiting polymorphornuclear leucocyte migration (for this effect an additional dose of 0.1mg/kg is required). Antipyretic effect is observed at a dose 10 fold higher than that required for inflammation. Reduction of myocardial infarction volume activation of inflammation and enzyme cyclo oxygenase with formation of pro inflammatory prostaglandins is a key element of development of myocardial infarction in patients with acute coronary syndrome.

**Dosage and Route**

It is available in oral and parenteral formulations. Its oral dose is 4mg thrice daily or 8mg twice daily. Safety Pharmacology & Toxicological studies Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and in inhibiting gastric acid secretion. Thus the adverse effects of the acidic NSAIDs are mainly because of inhibition of prostaglandin production. The gastric side effects range from mild dyspepsia and heartburn to ulceration and haemorrhage. Lornoxicam does not increase the serum pepsinogen levels (a marker of morphological and functional state of gastric mucosa in contrast to other NSAIDs e.g. indomethacin, ibuprofen which increase the serum pepsinogen levels). Risk factors for NSAIDs induced gastropathy include smokers, old age, history of peptic ulcer and those receiving oral corticosteroids and oral anticoagulants.

**Drug Interaction**

Like other NSAIDs, it appears to interact with warfarin, sulphonyl ureas, digoxin and furosemide. It is not affected by the co-administration of ranitidine, aluminium, magnesium and calcium containing antacids. Cimetidinen co-administration inhibits elimination of Lornoxicam resulting in significant increase in steady state Cmax and AUC (area under curve) values and a reduction in apparent plasma clearance. Lornoxicam displaces glibenclamide from its protein binding site leading to enhanced glibenclamide effect.

**POLYMER PROFILE**

**Aloe vera (*Aloe barbadensis* miller leaf)[17,24,25,26,27]**

**Figure 13: Aloe barbadensis leaves.**

**Table 3: Details of Aloe barbadensis leaves.**

| | |
|---|---|
| Common name | Aloe vera |
| Botanical Name | Aloe barbadensis |
| Kingdom | Plantae |
| Family | Liliaceae |
| Genus | Aloe |
| Species | Barbadensis |

*Aloe vera*is well known for its marvelous medicinal properties. These plants are one of the richest sources of health for human beings coming from nature. It has been grown as an ornamental plant widely. The natural range of *A.vera* is unclear, as the species has been widely cultivated throughout the world. Products of the plant are used in the treatment of various ailments. Various parts of the plant have different effects on the body. The plant has been used in traditional and folk medicines for thousands of years to treat and cure a variety of diseases.

**Therapeutic uses:** It is a bitter herb with anti-inflammatory, Anti-diabetic activity,astringent, emollient, antifungal, antibacterial and antiviral properties, and is useful in the eradication of parasites and stimulating the uterus. It contains a host of compounds that are biologically active and includes anthraquinones, saccharides and prostaglandins as well as other constituents.

**Anthraquinones:** Aloin (barbaloin), Isobarloin, Anthranol, Aloetic acid, Anthracene, ester of Cinnamic acid, Aloe-emodin, Emodin, Chrysophanoic acid, Ethereal oil as well as Resistannol.

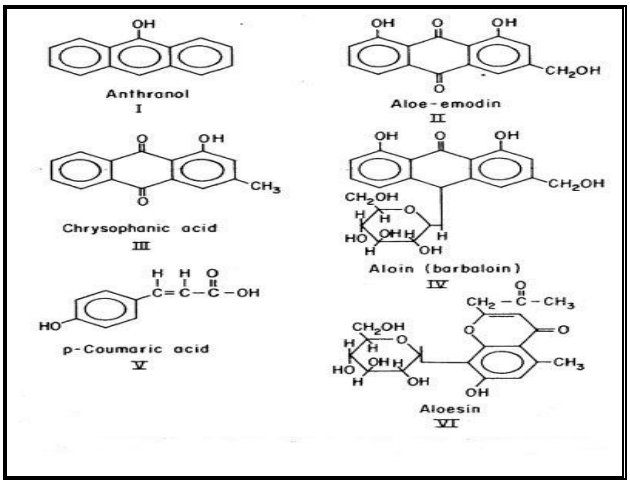


**Figure 14: Different chemical constituents of aloe vera.**

**Pharmaceutical use:** *Aloe barbadensis* miller leaves mucilage suitable for use as a release retardant in the manufacture of sustained release matrix tablets & tablet binder, suspending agent it is having good swelling, good flow and suitability for matrix formulations.

**ISABGOL[28,29]**

**Figure 17: Isabgol Seeds.**

**Table 5: Details of Isabgol.**

| | |
|---|---|
| Common name | Ispaghula, Isabgol |
| Botanical Name | *Plantagoovata* |
| Kingdom | Plantae |
| Family | Plantaginaceae |
| Genus | Plantago |
| Species | P. Ovata |

**Mechanism**[30]

Substance which absorbs water and due to its enhanced swelling properties, forms an emollient gel that facilitates the passage of intestinal contents and stimulates bowel movement. Because isabgol forms a bulk on swelling, it is classified as a bulk-laxative. It is usually effective within 8-12 hrs. Since isabgol is unaffected by the digestive enzymes and not absorbed into the system, it does not affect the absorption of other nutrients. It passes unchanged through the intestines. Therefore the action of isabgol is purely mechanical, as it relives constipation by mechanically stimulating bowel movement. This process closely approximates the body's own mechanism. The Jelly-like substance has, in addition, the triple-refined isabgol in nature care contains large quantities of a gelatinous remarkable capacity to absorb bacterial and other toxins in the intestines. In short, isabgol works partly by lubrication and partly by increasing the bulk of the intestinal contents, which stimulates bowel movement.

**Chemical Constituents**

Isabgol husk and seeds contain pentosan and aldobionic acid. Mucilage is also present in the epidermis seed. Some other important constituents are Fixed oil and proteins. Hydrolytic products are rhamnose, arabinose and galacturonic acid. Plantago seeds contain, Iridoids. The mucilage contains weakly acidic Arabinoxylans composed of a xylan backbone linked with Arabinose, Rhamnose, and Galacturonic acid units. Also 17.4% protein, 6.7% fat, 24.6% total dietary fibre, 19.6% insoluble fibre, 5.0% soluble fibre, and a combustion heat of 4.75 kcal/g. Osborne fractionation (based on solubility) yielded albumin 35.8%, globulin 23.9%, and Prolamin 11.7%. The oil from plantago seeds had a high percentage of Linoleic acid (40.6%) and oleic acid (39.1%) and a minor proportion of Linolenic acid (6.9%). In vitro protein digestibility of the plantago seed was 77.5%, suggesting a highly digestible protein. Lysine content was 6.82 g/100 g of protein.

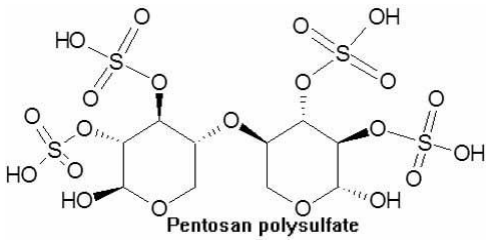


**Figure 18: Chemical structure of Isabgol.**

**Therapeutic uses:** Due to its bulk forming and emollient properties Isabgol is indicated in the following conditions.

1. In constipation.
2. Useful in piles and rectal disorders.
3. Irritable bowel syndrome.
4. Chronic diarrhoea and dysentery.
5. For preventing post-operative constipation.

**Pharmaceutical uses**[3]

Isabgol mucilage has several advantages on other super disintegrant as it is natural, compatible, non-irritant, cheap and easily available moreover its hydrophilic nature would not only decrease the disintegration time but also expected to enhance the dissolution rate. *Plantagoovata* mucilage, obtained from natural source could be used as a reliable alternative over the synthetic polymers used for sustained release formulations.

**ETHYL CELLULOSE**[32]

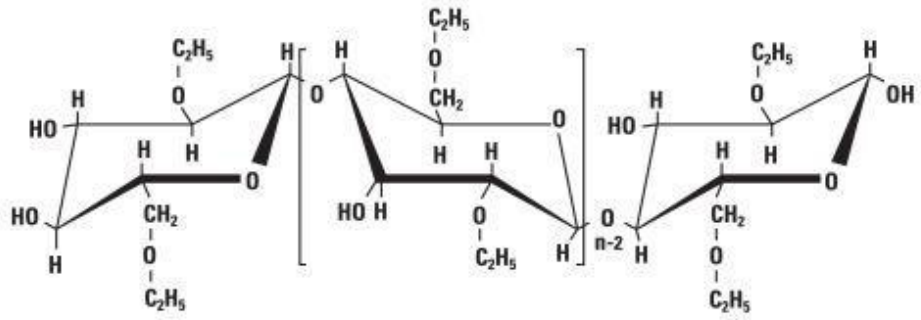

**Figure 19: Structure of Ethyl Cellulose.**

**1. Nonproprietary Names**

BP: Ethyl cellulose

USP: Ethyl cellulose

**2. Synonyms:** Aqua coat; E462; Ethocel; Surelease.

**3. Chemical Name**: Cellulose ethyl ether

**4. Empirical Formula Molecular Weight:** $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$

**5. Functional Category:** Coating agent; flavoring fixative tablet binder; tablet filler; Viscosity-increasing agent.

**6. Description**: Ethyl cellulose is a tasteless, free-flowing, white to light tan coloured powder.

**7. Typical Properties:**

Density (bulk): 0,4 g/cm3

Glass transition temperature: 129-133$^0$C

**8.Solubility**

Ethyl cellulose is practically insoluble in glycerine, propylene glycol, and Water, and Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetra hydro furan, and in mixtures of aromatic hydrocarbons with ethanol (95%).Ethyl cellulose that contains not less than46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

**9. Applications in Pharmaceutical Formulation**

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations; the main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug.

**10. Stability and Storage Conditions**

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions. It is however, more sensitive to acidic materials than cellulose esters. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures.

**11. Safety**

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. It is not metabolized following oral consumption and is therefore a non-caloric substance. It is generally regarded as a nontoxic, non-allergenic, and non irritating material. It is not metabolized and therefore is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

**HYDROXYPROPYL METHYLCELLULOSE (HPMC K 100)[33]**

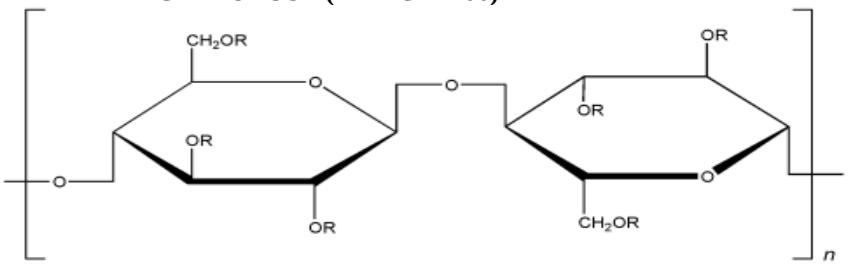


**Figure 20: Structure of HPMC.**

**1. Non proprietary Name:** BP: Hypromellose.
USP: Hypromellose.

**2. Synonyms:** hydroxyl propyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxyl propyl cellulose, Metolose.

**3. Chemical Name:** Cellulose hydroxyl propyl methyl ether

**4. Empirical Formula:** The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose.

**5. Molecular Weight:** Approximately10,000–1,500,000.

**6. Applications in Pharmaceutical Formulation or Technology**

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations.

- Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard. the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.
- Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25– 5.0%.

**7. Description:** Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

**8. Solubility:** Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane.

**9. Viscosity (dynamic):** A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared.

Typical viscosity values for 2% (w/v) aqueous solutions of methocel (Dow Chemical Co.) viscosities measured at 20ºC.

**Table 6: Different grades of methocel.**

| Methocelgrade | Viscosity(cps) |
|---|---|
| K4 M | 4,000 |
| K15M | 15,000 |
| K100M | 1,00000 |

**10. Stability and Storage Conditions:** Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

**11. Safety:** Hypromellose is generally regarded as a nontoxic and non-irritating material, although excessive oral consumption may have a laxative effect.

**DC-Lactose**[34]

Lactose has a long track history of use in pharmaceutical formulations. This can be explained by the high stability, low hygroscopicity, relatively low cost and the various functionalities of pharmaceutical lactose. For direct compression, spray-dried lactose, beta anhydrous lactose and alpha-monohydrate lactose crystals can be used.

The most important requirements for directly compressible lactose are good flow and high compaction of the lactose. A good flow ensures rapid and uniform die-filling during the tabletting process. The flow of lactose is influenced by the particle shape, particle size and particle size distribution. These parameters can be controlled by milling, classification and agglomeration. Alpha monohydrate lactose crystals have typically a tomahawk shape These crystals have a good flow and a brittle compaction behaviour. The brittleness is reduced when the particle size is reduced.[1] But small particles have poor flow. In a spray-drying process, the good aspects of small crystals are combined together with a good flow of the spherical spray dried particles.

A high compactability is required to obtain sufficient strength of the final tablets. The ability of a powder to compact into tablets dependents on a balance between the plastic deformation and brittle fracture properties of the powder particles. Brittle fracture is required to reduce sensitivity towards lubricants, and plasticity is necessary to reduce the distance between the particles. The various pharmaceutical lactose products have different deformation properties. Below 45-micron, alpha monohydrate lactose crystals behave ductile and above 45-micron, the crystals behave brittle.

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**POLYVINYL PYRROLIDONE**[35]

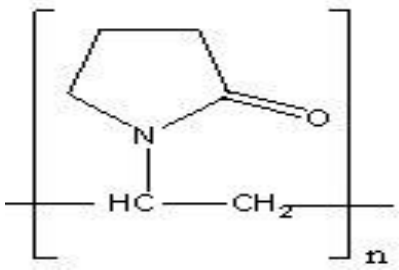



**Figure 14: Structure of Polyvinyl Pyrrolidone.**

**Nonproprietary Names**

1. BP: Povidone
2. PhEur: Povidone
3. USP: Povidone

**2. Synonyms:** Povidone, Poly [1-(2-oxo-1-pyrrolidinyl) ethylene], Polyvidone.

**3. Chemical name:** 1-ethenyl-2-pyrrolidinone homopolymer

**4. Functional category:** Suspending agent, tablet binder.

**5. Description:** Polyvinyl pyrrolidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

**6. Solubility:** Freely soluble in water, acids, chloroform, ethanol, ketones and methanol. Practically insoluble in ethers, hydrocarbons and mineral oil.

**7. Applications:** It is primaril used in solid dosage forms used as binders for tablet formulations. It is also used as coating agent. Polyvinyl pyrrolidone additionally used as suspending, stabilizing and viscosity increasing agent in a number of topical, oral suspensions and solutions.

**8. Storage:** Polyvinyl pyrrolidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container.

**9. Safety:** Polyvinyl pyrrolidone is used widely in pharmaceutical formulations and is generally regarded as nontoxic. However, it is moderately toxic by ingestion, producing gastric disturbances. It has no irritating or sensitizing effects on the skin.

**MAGNESIUM STEARATE**[35]

**1. Non-proprietary Names:**

BP: Magnesium stearate JP: Magnesium stearate.
PhEur: MagnesiistearasUSP: Magnesium stearate.

**2. Synonyms:** Magnesium octadecanote; stearic acid magnesium salt; Octadecanoic acid, magnesium salt.

**3. Chemical Name**: Octadecanoic acid, magnesium salt.

**4. Empirical Formula:** $C_{36}H_{70}MgO_{4.}$

**5. Structural Formula:** $[CH_3 (CH_2)_{16}COO]_2$ Mg.

**6. Functional Category:** Tablet and capsule lubricant.

**7. Description:** Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

**8. Typical Properties.**

Density (bulk): 0.159 g/cm$^3$
Density (tapped): 0.286 g/cm$^3$
Density (true): 1.092 g/cm$^3$

**9. Solubility**

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

**10. Applications in Pharmaceutical Formulation**

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 – 5.0%. It is also used in barrier creams.

**11. Stability and Storage Conditions**

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

1. **Safety:** Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However oral consumption of large quantities may result in some laxative effect or mucosal irritation.

**TALC**[35]

**1. Non-proprietary Names**

BP: Purified Talc JP: Talc

PhEur: Talc USP: Talc

**2. Synonyms:** Hydrous magnesium calcium silicate, hydrous magnesium silicate, magnesium hydrogen metasilicate, MagsilOsmanthus, Magsil Star powdered talc, purified French chalk, Purtalc, soapstone; steatite, Superiore, talcum.

**3. Chemical Name**: Talc

**4. Structural Formula:** $Mg_3(Si_4O_{10})(OH_2)$

**5. Molecular Weight:** 379.26

**6. Functional Category:**

Anticaking agent, Glidant, Tablet and Capsule diluents, Tablet and Capsule lubricant.

**7. Description:** Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

**8. Typical Properties:**

- Acidity/alkalinity: - pH = 7 – 10 for a 20% w/v aqueous dispersion.
- Hardness (Mohs):- 1.0 – 1.5
- Moisture content: - Talc absorbs insignificant amounts of water at 258°C and relative humidities up to about 90%.
- Refractive index :- 1.54 – 1.59
- Solubility: - Insoluble in dilute acids and alkalis, organic solvents, and water.
- Specific gravity:- 2.7 – 2.8
- Specific surface area: - 2.41 – 2.42 $m^2$/ g.

**9. Applications in Pharmaceutical Formulation**

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

**10. Stability and Storage Conditions:** Talc is a stable material. It may also be sterilized by heating at 160°C for not less than one hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

**11. Incompatibility:** Incompatible with quaternary ammonium compounds.

## METHODOLOGY

The following excipients, chemicals and instruments were used for the formulation. and evaluation studies.

**Table 2: Materials used in present work.**

| SL.NO. | INGREDIENTS AND REAGENTS | INGREDIENTS AND REAGENTS |
|---|---|---|
| **1** | Lornoxicam | Yarrowchem Products,Mumbai |
| **2** | Aloe barbadensis miller leaf | SD Fine chemicals Ltd. Mumbai |
| **3** | Isabgol husk seeds | Local market |
| **4** | Lactose | SD Fine chemicals Ltd. Mumbai |
| **5** | PVP K 30 | SD Fine chemicals Ltd. Mumbai |
| **6** | Magnesium Stearate | Loba Chemie Pvt. Ltd. Mumbai |
| **7** | Talc | SD Fine Chem. Limited, Mumbai |

**INSTRUMENTS USED IN PRESENT WORK.**

**Table 3: Instruments used in present work.**

| SL.NO. | NAME OF THE INSTRUMENT | MANUFACTURING COMPANY |
|---|---|---|
| **1.** | Digital Balance | Essae Teraoka Limited |
| **2.** | Tablet hardness tester | Monsanto tablet hardness tester |
| **3.** | Friability tester | Riche Rich Pharma tablet friability test apparatus |
| **4.** | Vernier Calliper | ABSOLUTE Coolant proof IP-61 |
| **5.** | Dissolution apparatus USP | Electrolab TD T08Ltablet dissolution apparatus |
| **6.** | Double beam UV Spectrophotometer | Labindia-25UV/VIS spectrometer, Mumbai |
| **7.** | 10 Station mini rotary tableting machine | Shakti Pharmatech Pvt. Ltd, Ahmedabad |
| **8.** | pH meter | Hanna Instruments, Japan |
| **9.** | FT-IR Spectrophotometer | Agilent Technologies, Cary 630 FTIR |
| **10.** | Stability Chamber | Labtop, India |
| **11.** | Hot air oven | Vijay Enterprises, Bangalore |
| **12.** | Bulk density apparatus | Ketan digital, Bangalore |

**PREFORMULATION STUDY**

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre formulation studies are to develop and to provide information about the drug substance, so that this information useful to develop formulation. Pre-formulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the tests performed for the pre-formulation study.

**ORGANOLEPTIC CHARACTERISTICS:**

The colour, odour and taste of the drug were characterized and recorded using descriptive terminology.

**Table 4: Organoleptic characteristic of Lornoxicam.**

| PROPERTY | RESULT |
|---|---|
| Description | Amorphous |
| Taste | Bitter |
| Odour | Odour less |
| Colour | Yellow crystalline powder |
| Solubility | 0.1 N NaoH& DMSO |

**DEVELOPMENT OF ANALYTICAL METHOD OF DRUG**

**Calibration curve for Lornoxicam in 0.1N Hcl& phosphate buffer pH 6.8**

- **Preparation of Hydrochloric acid (0.1N) solution**

8.6ml concentrated hydrochloric acid was added in 1000ml of volumetric flask the volume was made up to the mark with distilled water.

- **Preparation of phosphate buffer pH 6.8 solution**
- **Solution A: 0.2 M potassium dihydrogen phosphate solution:** 27.218 g of potassium dihydrogen phosphate was dissolved in water and diluted it with water to make the volume 1000 ml.
- **Solution B: 0.2N NaOH solution:**8 g of NaOH was dissolved in 1000 ml of water.

From **solution A** take 250ml and **solution B** take 112ml then make up volume up to 1000ml this gives the 1000ml of 6.8 phosphate buffer.

**Scanning Lornoxicamin 0.1 N HCL**

The solution containing 4µg/ml of Lornoxicam in 0.1 N HCl (pH 1.2) solution were prepared and scanned over wavelength range 400-200nm against 0.1N HCl as blank using Double beam UV/Visible Spectrophotometer. Then the plot of Absorbance v/s Wavelength was recorded using UV/Visible Spectrophotometer.

**Scanning Lornoxicam in pH 6.8 phosphate buffer solution**

The solution containing 4µg/ml of Lornoxicamin pH 7.4 phosphate buffer solution were prepared and scanned over wavelength range 400-200nm against pH 6.8 phosphate buffer as blank using Double beam UV/Visible Spectrophotometer. Then the plot of Absorbance v/s Wavelength was recorded using UV/Visible Spectrophotometer.

**Calibration Curves of Lornoxicamin 0.1 N HCL**

An accurately weighed quantity of Lornoxicam (100 mg) was dissolved in 100 ml of 0.1NHCl in volumetric flask to generate primary stock solution of 1000µg/ml or 1 mg/ml concentration, from this primary solution, 5 ml was pipetted and diluted up to 50 ml with 0.1 N HCl (Second Stock: 100µg/ml or 0.1mg/ml). The different volumes ofsecond stock (2-18mcg) were pipetted in 10 ml volumetric flask and diluted up to 10 ml to produce standard aliquots solution of concentration of 2-18µg/ml. The absorbance of solution was measured at 376 nm using UV/Visible double beam spectrophotometer against 0.1N HCl as blank. Then the plot of Absorbance vs. Concentration (µg/ml) was plotted.

**Calibration Curves of Lornoxicam in pH 6.8 Phosphate buffer**

An accurately weighed quantity of Lornoxicam (100 mg) was dissolved in 100 ml of pH 6.8 Phosphate buffer in volumetric flask to generate primary stock solution of1000µg/ml or 1 mg/ml concentration, from this primary solution, 5 ml was pipette and diluted up to 50 ml with pH 6.8 Phosphate buffer (Second Stock: 100µg/ml or0.1mg/ml). The different volumes of second stock (2-18mcg) were pipetted in 10ml volumetric flask and diluted up to 10 ml to produce standard aliquots solution of concentration of 2-18µg/ml. The absorbance of solution was measured at 376 nm using UV/Visible double beam spectrophotometer against 6.8 Phosphate buffer as blank. Then the plot of Absorbance vs. Concentration (µg/ml)was plotted.

**COMPATIBILITY STUDIES (FT-IR Spectroscopic studies)**

**Procedure**

Active pharmaceutical ingredient (API) and excipients were been thoroughly mixed in predetermined ratio and passed through the 40# sieve. The blend was to be filled in amber glass vials and were closed with gray coloured rubber stoppers and further sealed with aluminium seal and charged in to stress condition at room temperature,60°C. Similarly, API should also be kept at that condition as for the samples. Samples were withdrawn for analysis within two days of sampling date as per the compatibility study plan. The samples were tested for physical observation.

**Table 5: Protocol for drug-excipients compatibility.**

| SI. No | Combination of Materials | Ratio of Mixer | Initially physical Observation | Physical observation (after 1 month) |
|---|---|---|---|---|
| 1 | API alone | – | Yellow crystalline powder | No colour change & No lumps forming |
| 2. | API + Aloe barbadensis miller leaf mucilage | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 3. | API + Isabgol gum | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 4. | API + Ethyl Cellulose | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 5. | API + HPMC K100 | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 6. | API + Lactose | 1:1 | Yellow crystalline powder e | No colour change & No lumps forming |
| 7. | API + Mg stearate | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 8. | API + Talc | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |
| 9. | API + PVP K 30 | 1:1 | Yellow crystalline powder | No colour change & No lumps forming |

At the time of physical observation after the completion of study, there were no colour changes, lump formation or any significant visual changes observed as against the control or initial results.

**Table 7: Preliminary confirmatory tests for dried gums and mucilage[45,46]**

| Test | Observation | Inferences |
|---|---|---|
| Test for Carbohydrate :<br>Molisch's test:<br>dried mucilage powder + Molisch's reagent +conc. H2SO4 on the side of a test tube | Violet green colour observed at the<br>junction of the two layers | Carbohydrate present |
| Test for Mucilage:<br>Ruthenium test:<br>Take a small quantity of dried mucilage powder, mount it on a slide with ruthenium red solution, and observe it under microscope. | Pink colour develops | Mucilage present |
| Test for Polysaccharides:<br>Iodine test:<br>100mg dried mucilage powder + 1mL 0.2N iodine soln. | No colour observed in solution present | Polysaccharides present<br>(starch is absent) |
| Test for Tannins<br>Ferric chloride test:<br>Test solutions, a few drops of 5% ferric chloride solution were added | Bluish-black or greenish-black colour | Tannins present |
| Test for Alkaloids<br>Wagner's test:<br>The sample was treated with solution of iodine in potassium iodide (Wagner's reagent). | Brown precipitate | Alkaloids present |

**PREPARATION OF MATRIX TABLETS OF LORNOXICAM:**

Tablet formulations were prepared by wet granulation method Using (polyvinyl pyrrolidone K-30 and isopropyl alcohol). A non-aqueous granulation process was adopted to prepare Lornoxicam SR matrix tablets Proportion of excipients with drug was as given in Table no 8 and 9.

Granules were prepared as follows.

1. **Sifting:** The drug and all other ingredients were sifted through sieve # 60.
2. **Mixing:** The sifted ingredients were mixed thoroughly in a poly bag for 15min.
3. **Preparation of Granules:** Viscous solution of polyvinyl pyrrolidone K30 prepared by isopropyl alcohol, was added in well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve # 16.

4. **Drying:** The prepared granules were dried at $60^0$C for 1 hour in hot air oven, and then it was sifted through sieve # 20.
5. **Lubrication:** Magnesium stearate and Talc were sifted through sieve #60 and mixed with the prepared granules in a polybag for 5min.
6. **Compression:** Finally tablets were compressed at 300 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 9 mm spherical shaped punches.

**Table 8: Tablet composition of Lornoxicam sustained release matrix tablets prepared with different releases retardant natural matrices (F-1 to F-6).**

| FORMULATION CODE | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| DRUG | 16 | 16 | 16 | 16 | 16 | 16 |
| ISABGOL MUCILAGE | - | - | - | - | 150 | 225 |
| ALOE BARBADENSIS MUCILAGE | - | - | - | - | - | - |
| H P M C | - | - | - | - | - | - |
| ETHYL CELLULOSE | - | - | - | - | - | - |
| LACTOSE | 110 | 80 | 50 | 110 | 80 | 50 |
| MAGNESIUM STERATE | 6 | 6 | 6 | 6 | 6 | 6 |
| TALC | 3 | 3 | 3 | 3 | 3 | 3 |
| PVP K-30 | 15 | 15 | 15 | 15 | 15 | 15 |

**Table 9: Tablet composition of Lornoxicam sustained release matrix tablets prepared with different releases retardant natural matrices (F-7 to F-12).**

| FORMULATION CODE | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|
| DRUG | 16 | 16 | 16 | 16 | 16 | 16 |
| ISABGOL MUCILAGE | - | - | - | - | - | - |
| ALOE BARBADENSIS | - | - | 150 | 225 | - | - |
| H P M C | 150 | 180 | 210 | - | - | - |
| ORANGE PEEL PECTIN | - | - | - | 150 | 180 | 210 |
| LACTOSE | 110 | 80 | 50 | 110 | 80 | 50 |
| MAGNESIUM STERATE | 6 | 6 | 6 | 6 | 6 | 6 |
| TALC | 3 | 3 | 3 | 3 | 3 | 3 |
| PVP K-30 | 15 | 15 | 15 | 15 | 15 | 15 |

**Evaluation of Parameters**[36,37]

**Pre Compression Parameters**

**1. Bulk density (Db)**

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

**Db = M / Vo**

Where, Db = Bulk density (gm/cc)
M is the mass of powder (g)
Vo is the bulk volume of powder (cc)

**2. Tapped density (Dt)**

10 gms of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 Ts from a constant height and tapped volume were read. It is expressed in gm/cc and is given by,

**Dt = M / Vt**

where, Dt = Tapped density (gm/cc)
M is the mass of powder (g)
Vt is the tapped volume of powder (cc)

**3. Compressibility Index.**

The compressibility of the powder was determined by the Carr's compressibility index.

**Carr's index (%) = [(TBD – LBD) x 100]/TBD**

where, TPD is Tapped bulk density
LBD is Loose bulk density.

**4. Carr's index (%) type of flow.**

**Table 10: Relation between the Carr's index of granules and its flow characteristics.**

| CARR'S INDEX (%) | TYPE OF FLOW |
|---|---|
| 5-12 | Excellent |
| 12-15 | Good |
| 18-23 | Fair to possible |
| 23-35 | Poor |
| 35-38 | Very poor |
| > 40 | Extremely poor |

**5. Angle of repose (θ)**

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel until the apex of the

conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

**θ = tan-1(h/r)**

where, θ = angle of repose ,

h = height of pile, & r = radius of the base of the pile.

**Post Compression Parameters**

**1. Thickness and diameter**

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers (ABSOLUTE Coolant Proof IP-61). It is measured in mm.

**2. Hardness**

The Manosanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in $Kg/cm^2$.

**3. Friability (F)**

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were de-dusted. The percentage weight loss was calculated rewriting the tablets.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where, F = Percentage friability

W initial = Initial weight before friability test.

W final = Final weight after friability test.

**4. Weight variation**

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

$$PD = \frac{W_{avg} - W_{initial}}{W_{avg}} \times 100$$

Where, PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = individual weight of tablet.

**Table 11: IP standards of uniformity of weight**

| SL. No. | Average weight of tablet (mg) | Percentage of deviation allowed |
|---|---|---|
| 1. | ≤ 80 | 10 |
| 2. | > 80 to < 250 | 7.5 |
| 3. | ≥ 250 | 5 |

**5. Swelling Index**

Swelling index of the dosage form is conducted by using USP dissolution apparatus-II in 900 ml of pH 6.8 phosphate buffer which is maintained at 37±0.5°C, rotated at 50 rpm. At selected regular intervals, the tablet is withdrawn the excess water was blotted with tissue paper. This procedure was repeated until the tablet reaches constant weight. The swelling index was calculated by using following formula.

**% Swelling Index = {(Wt) – (Wo) / (Wt)} x 100**

where, Wt is the weight of the swollen tablet,

Wo is the initial weight of the tablet.

**6. Uniformity of drug content**

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Lornoxicam , transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCL. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the absorbance, of the resulting solution at the maxima at about 376nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation.

**Cu/Cs = Au/As * dilution factor**

Cu = Concentration of unknown sample, Cs = Concentration of Standard sample.

Au = Absorbance of unknown sample & As = Absorbance of standard sample.

***In-vitro* release study**

**Table 12: *In Vitro* Release Study Parameters.**

| Apparatus | USP Dissolution apparatus type II |
|---|---|
| Dissolution media | 0.1 N HCl for 1st 2 hours and pH 6.8 phosphate buffer after 2 hours |
| Temperature | 37± 0.5 $^0$C |
| RPM | 50 |
| Volume withdrawn and replaced | 5ml for every 1 hour |
| λ max | 376nm with 0.1N HCL |
| λ max | 376nm with Ph 6.8 phosphate buffer |
| Blank solution | 0.1 N HCl for 1st 2 hours and pH 7.4 phosphate buffer after 2 hours |
| Duration of study | 12 hours |
| Volume of dissolution media | 900 ml |

**In-vitro dissolution study**

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37±0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of (Lornoxicam) tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 6.8) and continue dissolution. Aliquots of 5 ml were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Lornoxicam was determined spectrophotometrically at a wavelength of 376nm for first 2 hr and then after take in 376nm. At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. The release studies were conducted and results were noted in respective tables.

**Kinetic analysis of in-vitro release rates of controlled release tablets of Lornoxicam[10,45]**

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

**1. Zero order kinetics**

Zero order release would be predicted by the following equation:-

$$\mathbf{At = A_0 - K_0 t}$$

Where, At = Drug release at time't'.

$A_0$ = Initial drug concentration

$K_0$ = Zero – order rate constant (hr-1).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to $K_0$.

**2. First Order Kinetics**

First – order release would be predicted by the following equation.

$$\mathbf{Log\ C = log\ C_0 - Kt / 2.303}$$

Where,

C = Amount of drug remained at time't'.

$C_0$ = Initial amount of drug.

K = First – order rate constant ($hr^{-1}$).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

**3. Higuchi's model**

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

Q = [D□□/ □(2 A - □Cs) $C_S$t]1/2

Where, Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

τ = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes.

$$\mathbf{Q = Kt^{1/2}}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963).

**4. Korsmeyer equation / Peppa's model**

To study the mechanism of drug release from the sustained – release matrix tablets of Ropinirole HCl the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{M_t / M_a = Kt^n}$$

Where, Mt / Ma = the fraction of drug released at time't'.

K = constsnt incorporating the structural and geometrical characteristics of the drug / polymer

N = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides, and we get

$$\mathbf{Log\ M_t / M_a = Log\ K + n\ Log\ t}$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept.

For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0. The result of *in vitro* drug release study of all the formulation as shown below.

**Table 13: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model.**

| n Value | Mechanism | $dm_{tt}/dt$ Dependence |
|---|---|---|
| n < 0.5 | Quasi-Fickian diffusion | $t^{0.5}$ |
| 0.5 | Fickian diffusion | $t^{0.5}$ |
| 0.5 < n< 1.0 | Anomalous (non-Fickian) diffusion | $t^{n-1}$ |
| 1 | Non-Fickian case II | Zero order |
| N > 1.0 | Non-Fickian super case II | $t^{n-1}$ |

The diffusional exponent is based on Korsmeyer-peppas equation. Mt/Mt = Ktn

**SCANNING ELECTRON MICROSCOPHY:**

SEM has been used to determine the surface topography, texture and to examine the morphology of fractured or sectioned surface. The examination of the surface of polymeric drug delivery system can provide important information about the porosity and micro structure of device**.** The optimized formulation was selected for scanning electron microscopy (SEM) by using JEOL-JSM-840A, Japan. The tablet surface morphology was studied at $2^{nd}$, $6^{th}$ and $12^{th}$ hours.

**COMPATABILITY STUDIES OF DRUG WITH EXCIPIENTS:**

**FTIR study of Lornoxicam:** FTIR spectra of the selected (Optimized) formulations were taken and compared with the spectrum of the pure drug. The characteristic peaks of drug were checked in the formulation spectra.

**Stability studies**

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

**Method**

Selected formulations were stored at different storage conditions at elevated temperatures such as $25^{o}C\pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}C$ / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes.

**RESULTS**

**Selection of Excipients**

**Table 14: Compatibility studies of Lornoxicam with excipients at 1:1 ratio.**

| Sl. No | EXCIPIENTS | Drug: Excipient Ratio | Initial physical Observation | 30°C±2°C/60%±5%RH | | |
|---|---|---|---|---|---|---|
| | | | | 1Week IR Study | 2WeekIR Study | 3 Week IR Study |
| 1 | API alone | - | Yellow Crystalline powder | * | * | * |
| 2 | API + Aloe Barbadensis Mucilage | 1:1 | Yellow Crystalline powder | * | * | * |
| 3 | API + Isabgol Mucilage | 1:1 | Yellow Crystalline powder | * | * | * |
| 4 | API + H P M C | 1:1 | Yellow Crystalline powder | * | * | * |
| 5 | API + Ethyl Cellulose | 1:1 | Yellow Crystalline powder | * | * | * |
| 6 | API + Lactose | 1:1 | Yellow Crystalline powder | * | * | * |
| 7 | API + Magnesium stearate | 1:1 | Yellow Crystalline powder | * | * | * |
| 8 | API +TALC | 1:1 | Yellow Crystalline powder | * | * | * |
| 9 | API + PVP K 30 | 1:1 | Yellow Crystalline powder | * | * | * |

* Indicates no incompatibility.

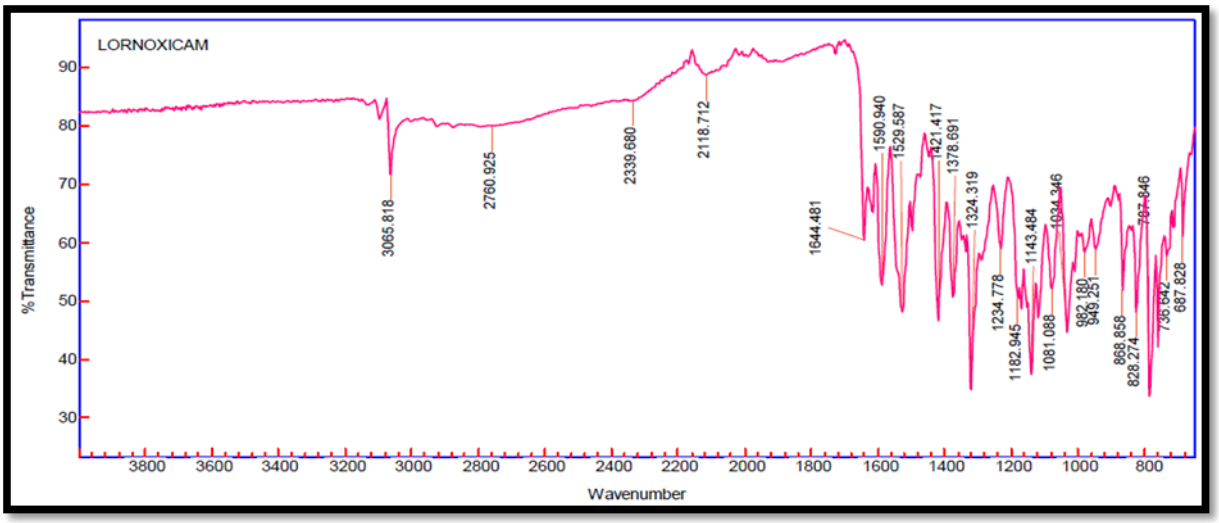



**Figure 17: FT-IR of Lornoxicam.**

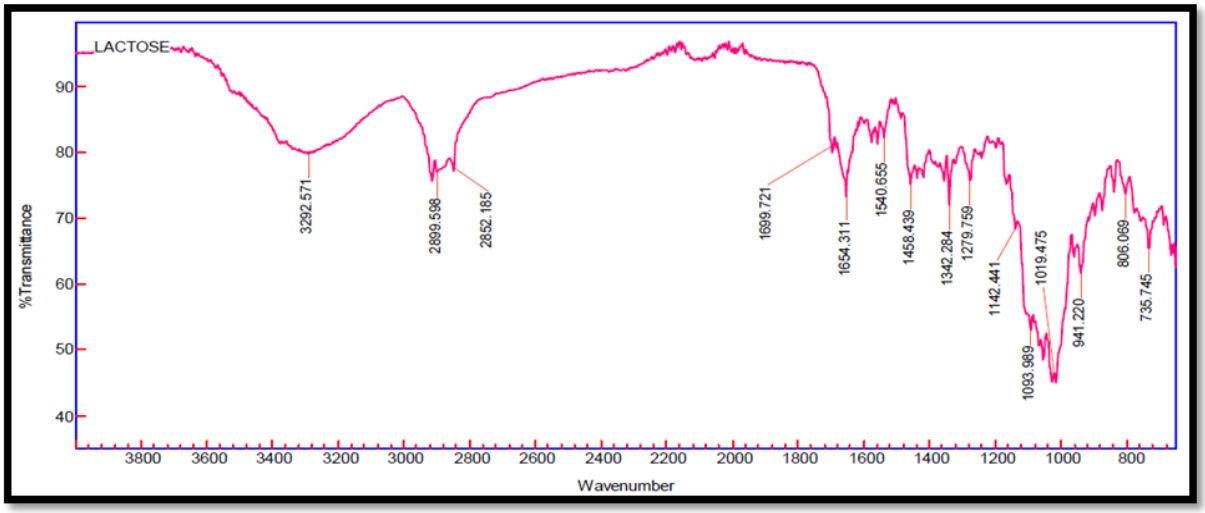



**Figure 26: FT-IR of Lactose.**

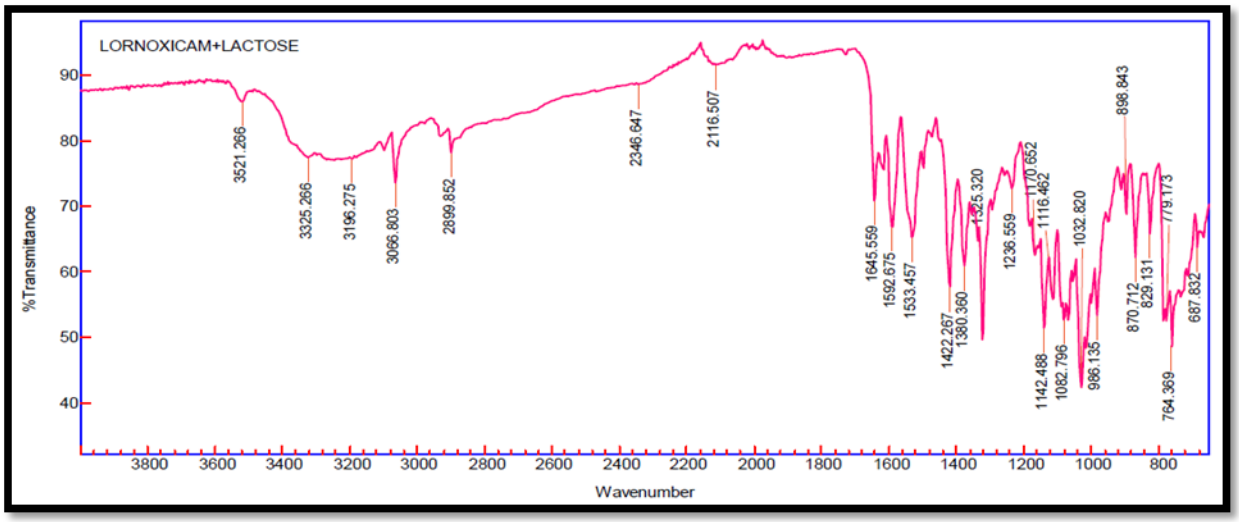



**Figure 27: FT-IR of Lornoxicam+ Lactose.**

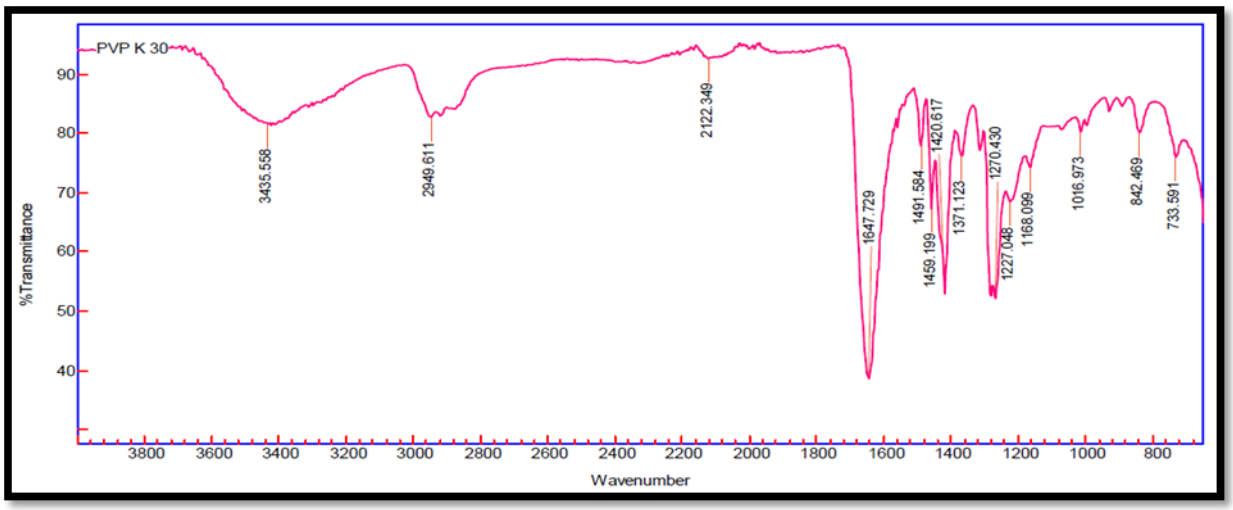



**Figure 28: FT-IR of PVP K30.**

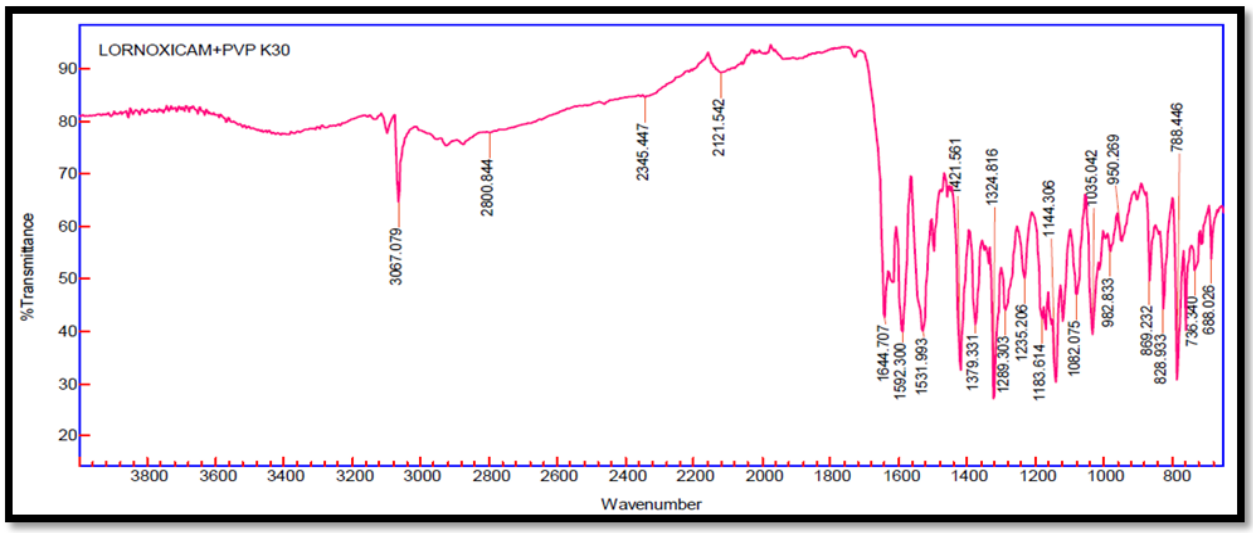



**Figure29: FT-IR of Lornoxicam+ PVP K30.**

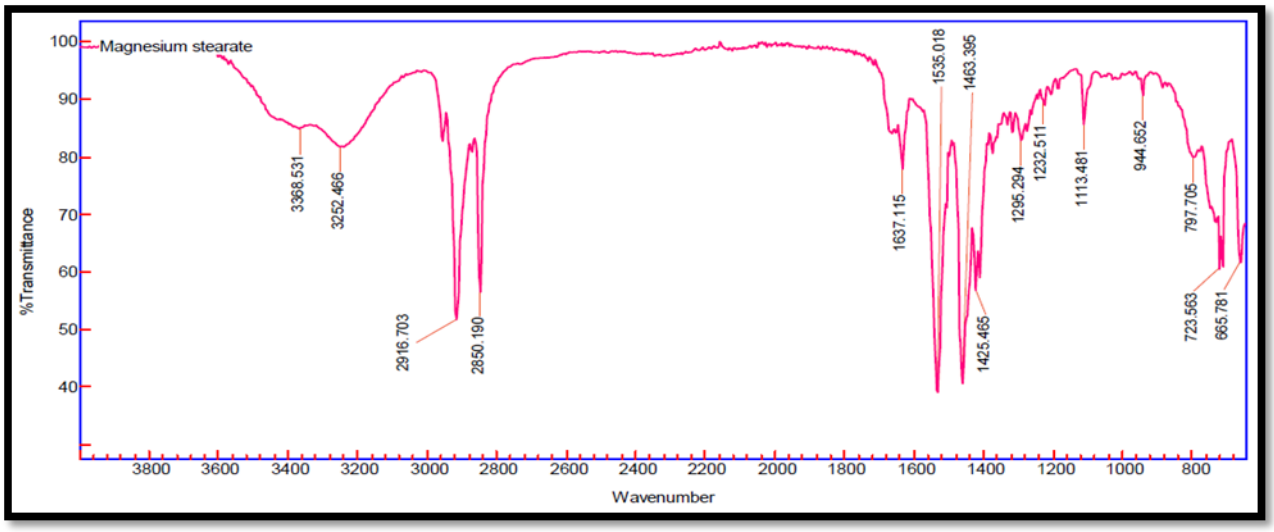



**Figure 30: FT-IR of Mg. Stearate.**

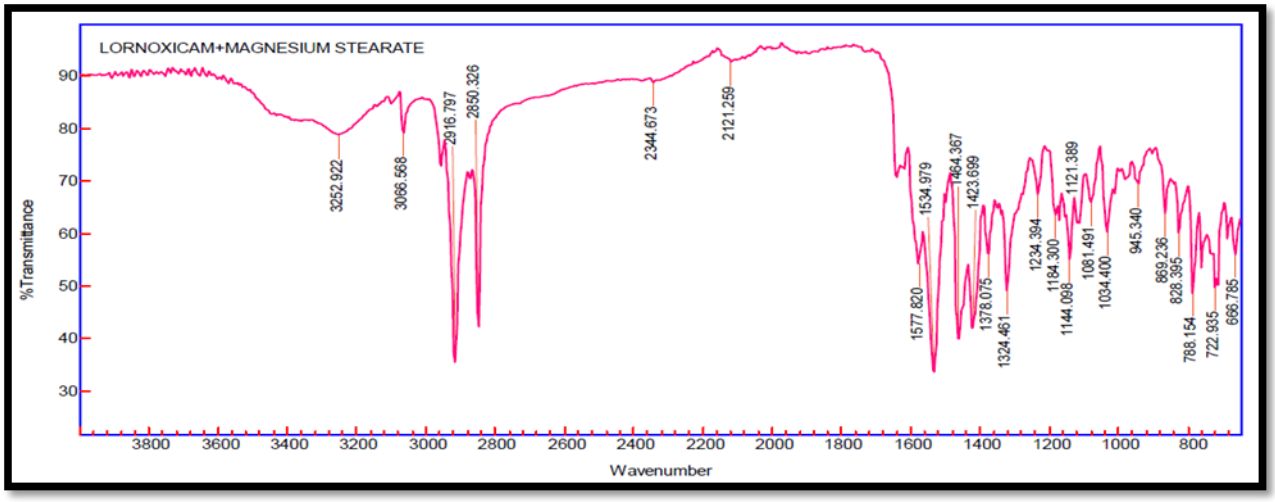



**Figure 31: FT-IR of Lornoxicam + Mg. Stearate.**

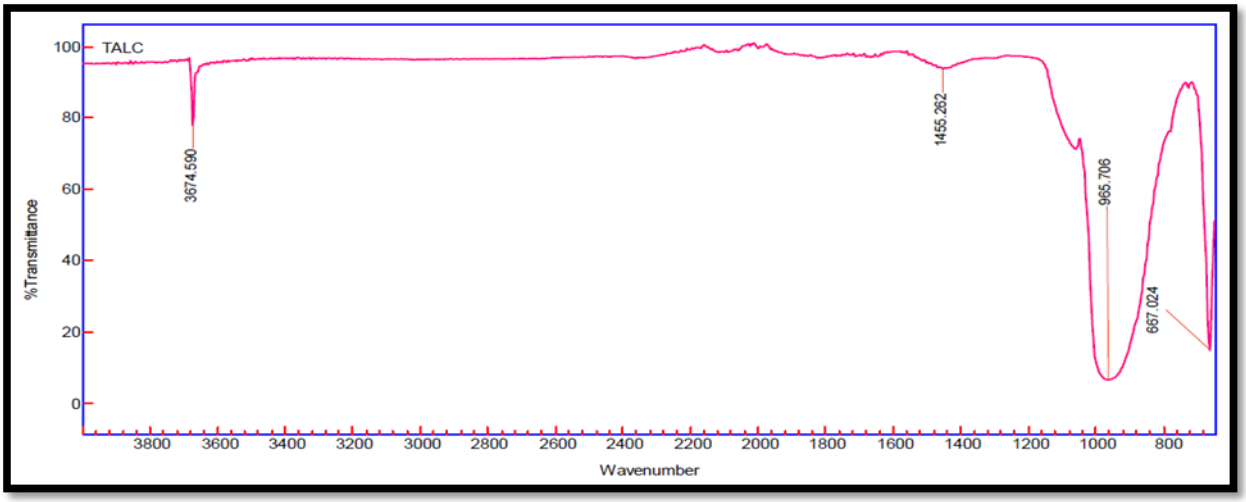



**Figure 32: FT-IR of Talc.**

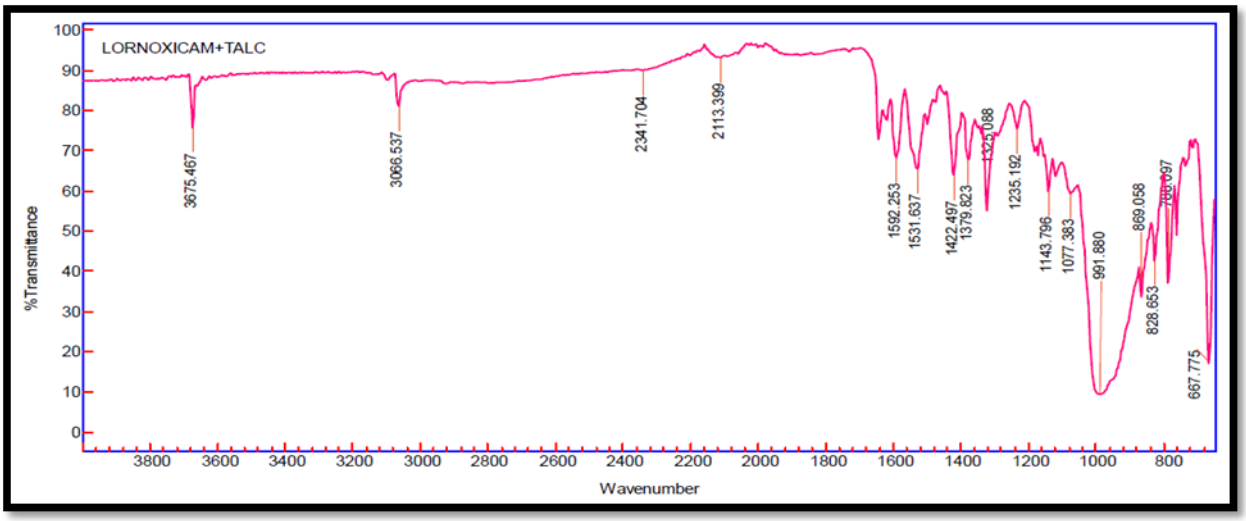



**Figure 33: FT-IR of Lornoxicam + Talc.**

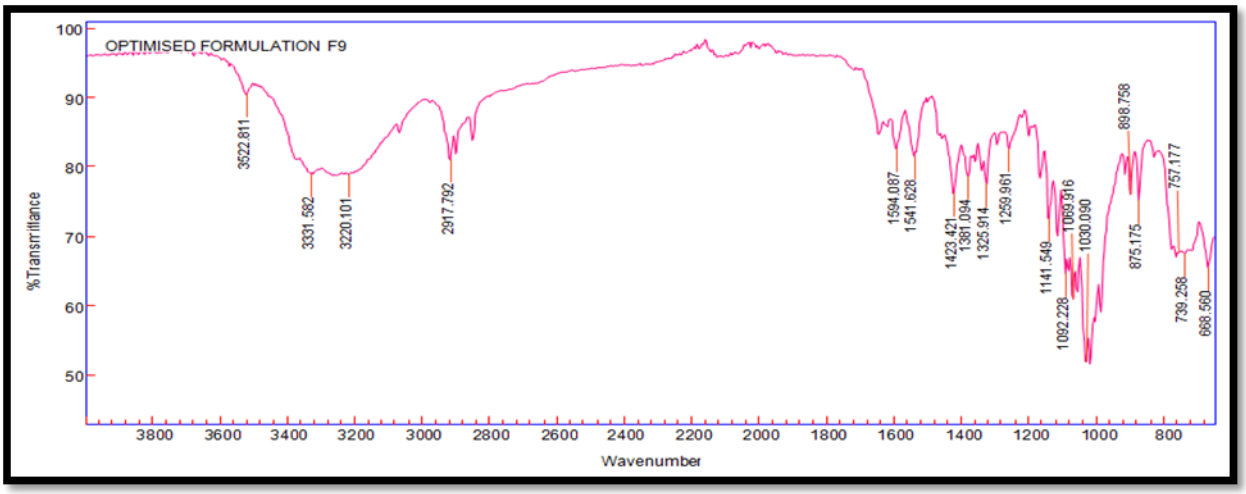



**Figure 34: FT-IR of Optimised Formulation F-9.**

**DISCUSSION ON FT-IR**

**Table no 15: Interpretation of FT-IR.**

| Functional group vibrations | Lornoxicam (RS) ($Cm^{-1}$) | Optimised formulation F-9 ( $Cm^{-1}$) |
|---|---|---|
| N-H stretching | 3065.818 | - |
| C=C, C=N ring stretching | 1529.587 | 1541.628 |
| Asymmetric $SO_2$ stretching | 1324.319 | 1325.914 |
| Symmetric SO2 stretching | 1143.484 | 1141.549 |
| Aromatic –C-H bending | 868.858 | 875.175 |
| C-Cl bending | 687.828 | 668.566 |
| C-S stretching | 767.846 | 757.177 |

Overly IR spectrum of Lornoxicam(RS) matches and optimised formulation F-9 was found to be similar. Importantly, finger print region of both tested compounds was found to be matching. Indicates no signs of drug-excipients in incompatility.

**Scanning electron microscopy (SEM) of the optimized formulation**

The Scanning Electron Microscopic (SEM) analysis was conducted using a JOEL (Model - JSM 840A) Scanning Microscope for the optimized formulations in three states involving dry tablet surface, Tablet after swelling for 2 hours 6 hours and 12hours, so as to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surfaces.

As with SEM high vacuum is required for image formation and samples must be thoroughly desiccated before entering the vacuum chamber, therefore samples were thoroughly dried after swelling for analysis. The dried samples were mounted on sample holder using double sided adhesive carbon tape. The SEM was operated at 15 KV. The condenser lens position was maintained at a constant level. SEM study further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet(F-9). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix. SEM photomicrographs with graphs of tablet surface at different time intervals also showed that erosion of matrix increased respect to time indicated by the photomicrographs at $2^{nd}$, $6^{th}$, and $12^{th}$hrs revealing pores with increasing diameter.

These photomicrographs also revealed formation of gelling structure indicating, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Lornoxicam from formulated matrix tablets. As shown in (Figure 35 a,b,c).

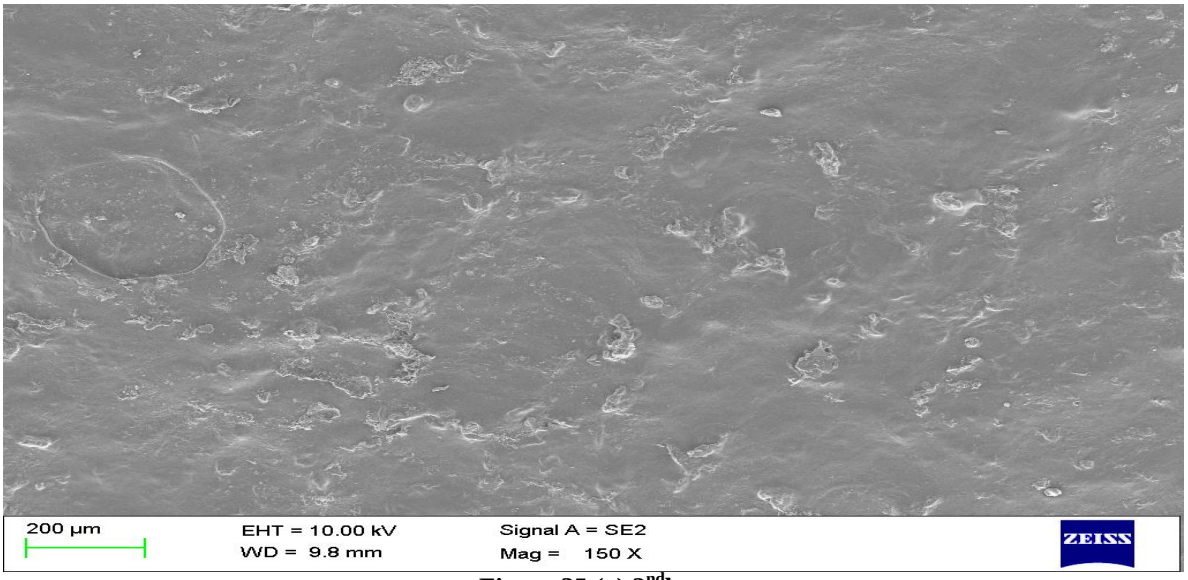



**Figure 35 (a) $2^{nd}$hrs.**

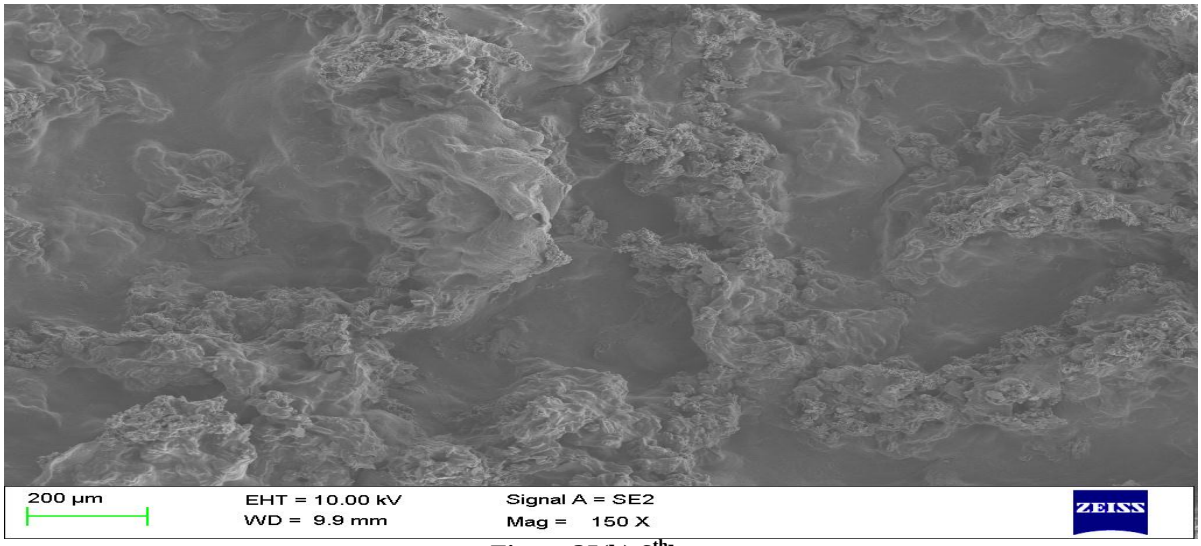



**Figure 35(b) 6$^{th}$hrs.**

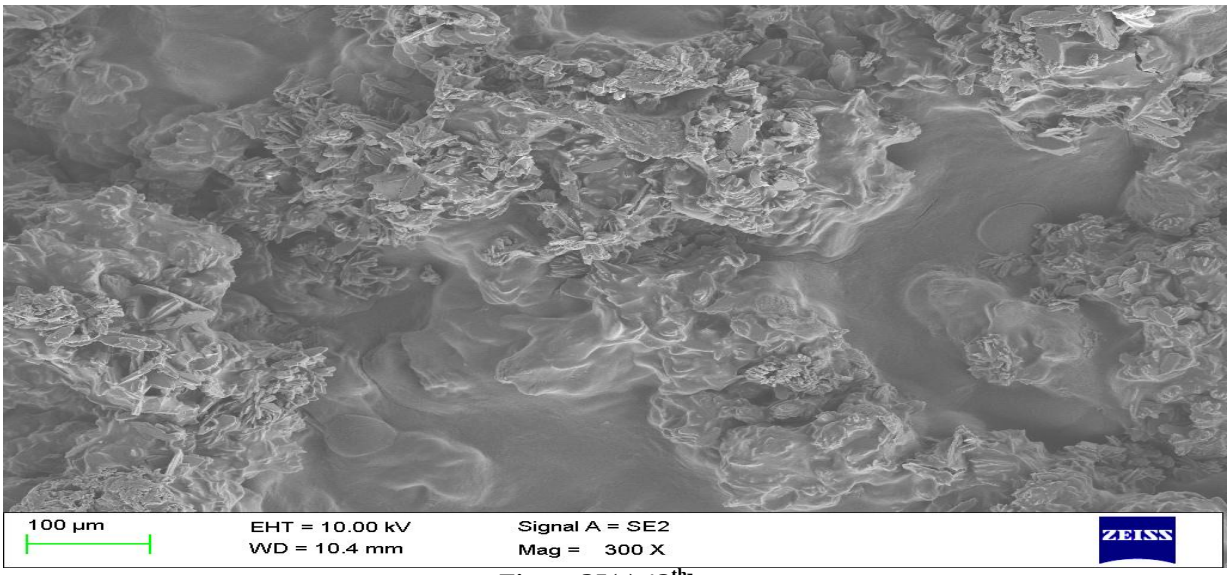



**Figure 35(c) 12$^{th}$hrs.**

**Figure 35 (a, b, c): SEM studies of optimised formulation.**

**Preliminary confirmatory tests for dried gums and mucilage**

Preliminary phytochemical tests of the four below mentioned extracts carried out shows the presence of Carbohydrate, Mucilage, Polysaccharides, Alkaloids and Tanninsin table below.

**Table 16: Preliminary confirmatory tests for dried gums and mucilage.**

| Sl.No. | CHEMICAL TEST | Okragum |
|---|---|---|
| 1. | **Test for Carbohydrate**Molisch's test: | + |
| 2. | **Test for Mucilage** Ruthenium test: | + |
| 3. | **Test for Polysaccharides** Iodine test: | + |
| 4. | **Test for Tannins** Ferric chloride test | _ |
| 5. | **Test for Alkaloids** Wagner's test | + |

**DETERMINATION OF λ max OF LORNOXICAM**

**UV –Spectrum of Lornoxicam in 0.1 N HCL**

UV –Spectrum of Lornoxicamin 0.1 N HCL (Figure 36) shows that the drug had λ max of 376nm.

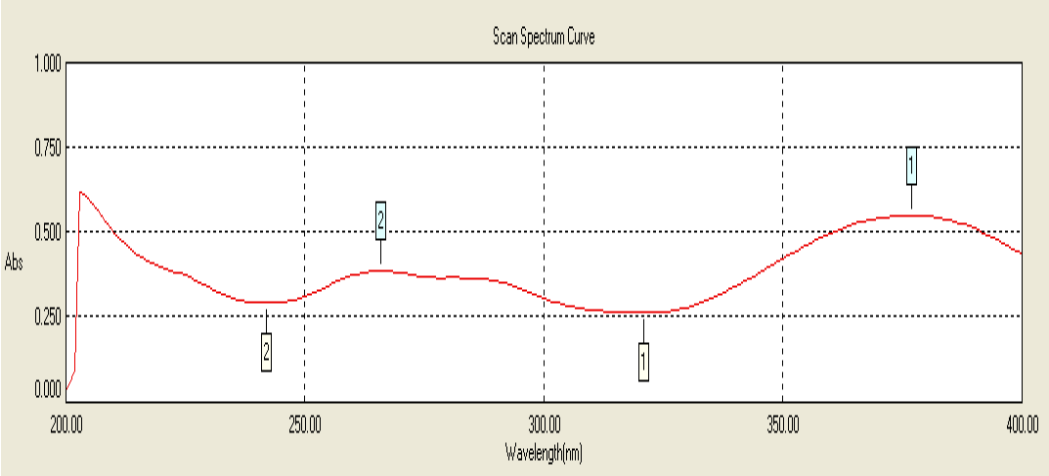



**Figure 36: UV –Spectrum of Lornoxicamin 0.1 N HCL.**

UV –Spectrum of Lornoxicamin pH 6.8 phosphate buffer
UV –Spectrum of Lornoxicam in pH 6.8 phosphate buffer**(**Figure 37) shows that the drug had λ max of 376nm.

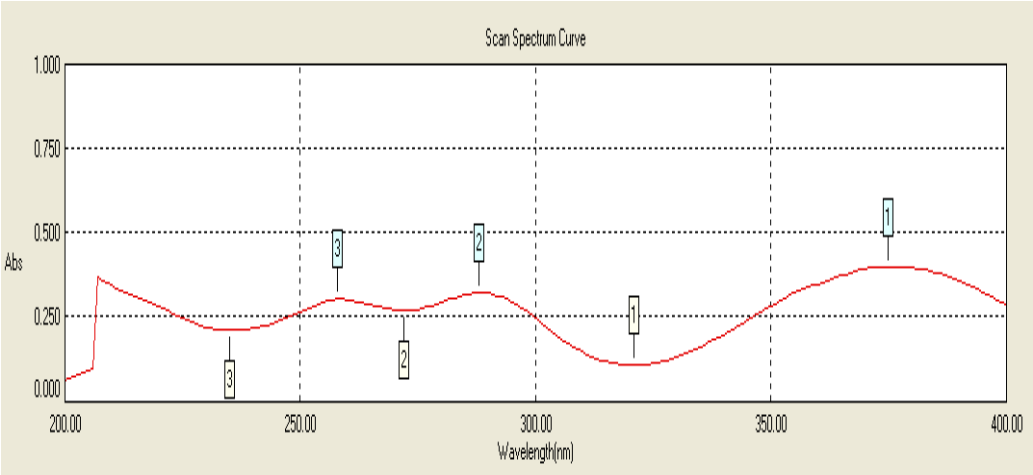



**Figure 37: UV –Spectrum of Lornoxicamin pH 6.8 phosphate buffer.**

**Standard plot of Lornoxicamin 0.1N HCL**
The standard plot of Lornoxicam is as shown in (Figure 38). The data of absorbance is shown in table 17. The correlation coefficient obtained was0.9988 and equation of regression line was y =0.0133x.

**Table 17: Standard plot of Lornoxicamin 0.1 N HCL.**

| a | Concentration (µg/ml) | Absorbance at 376nm |
|---|---|---|
| 1 | 2 | 0.028 |
| 2 | 4 | 0.055 |
| 3 | 6 | 0.079 |
| 4 | 8 | 0.109 |
| 5 | 10 | 0.139 |
| 6 | 12 | 0.16 |
| 7 | 14 | 0.185 |
| 8 | 16 | 0.215 |

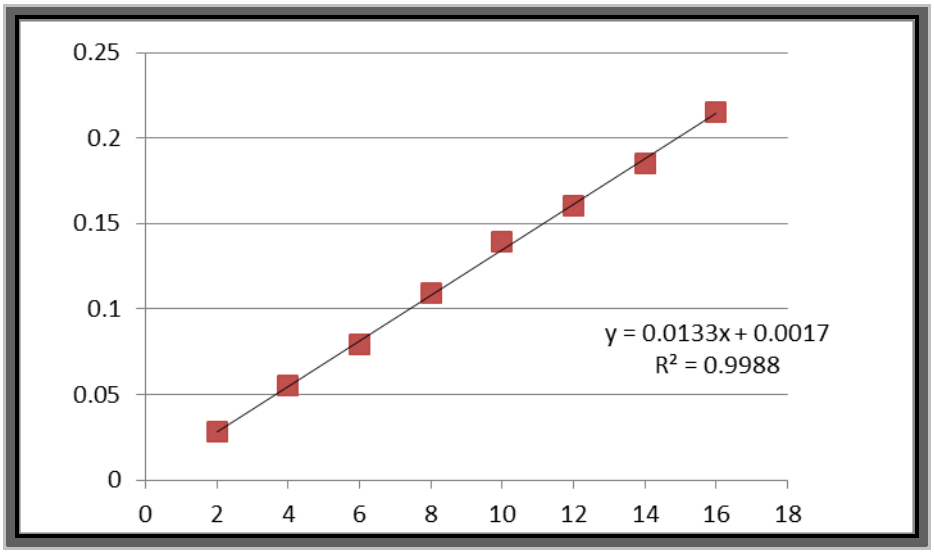



**Figure 38: Standard plot of Lornoxicamin 0.1 N HCL.**

**Standard plot of Lornoxicamin ph 6.8 Phosphate buffer**

The standard plot of Lornoxicam is as shown in (Figure 39). The data of absorbance is shown in table 18. The correlation coefficient obtained was0.9991 and equation of regression line was y =0.0296x.

**Table 18: Standard plot of Lornoxicam in ph 6.8 Phosphate buffer.**

| Sl. No | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 2 | 0.086 |
| 2 | 4 | 0.152 |
| 3 | 6 | 0.212 |
| 4 | 8 | 0.275 |
| 5 | 10 | 0.333 |
| 6 | 12 | 0.393 |
| 7 | 14 | 0.445 |
| 8 | 16 | 0.502 |

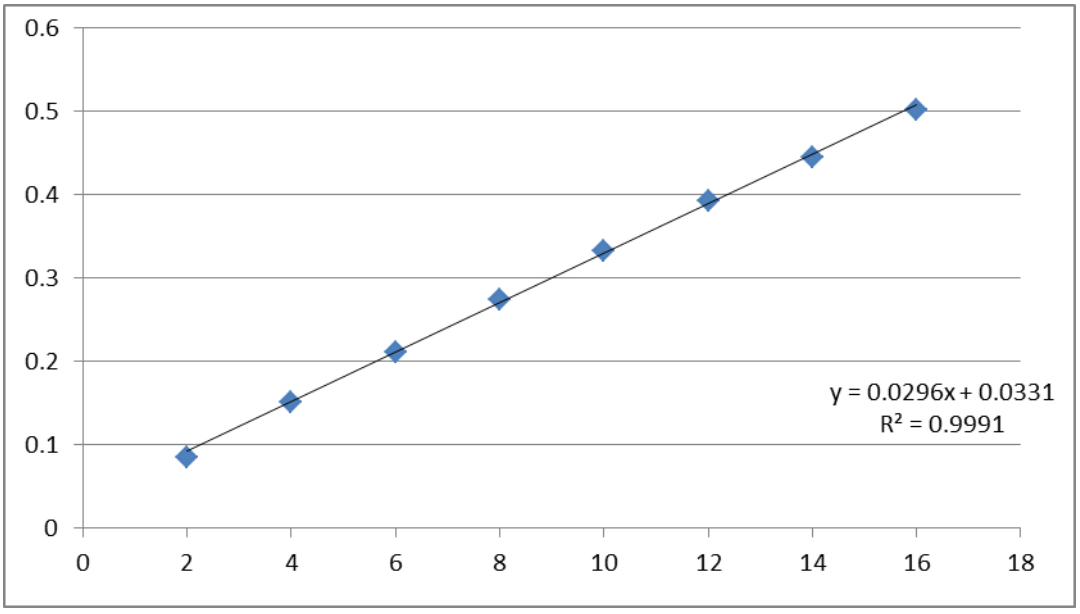



**Figure 39: Standard plot of Lornoxicamin pH 6.8 Phosphate buffer.**

**Evaluation of Lornoxicam Tablets**

**Pre Compression Parameters**

**Table 19: Data for blend evaluation of formulation (F-1 to F-6).**

| Formulations | Bulk Density* (g/ml) | Tapped bulk* density (g/ml) | Carr's index (%) | Angle of repose* |
|---|---|---|---|---|
| **F1** | 0.289 ± 0.002 | 0.295±0.019 | 11.34±1.41 | 27.66±1.42 |
| **F2** | 0.284 ±0.005 | 0.311 ± 0.012 | 11.18±0.78 | 26.62±1.25 |
| **F3** | 0.299 ± 0.006 | 0.289 ± 0.014 | 9.71±1.32 | 27.12±1.12 |
| **F4** | 0.291 ±0.008 | 0.329 ± 0.014 | 10.46±1.31 | 26.58±1.32 |
| **F5** | 0.286 ± 0.006 | 0.316 ± 0.015 | 9.49±1.41 | 28.03±1.86 |
| **F6** | 0.296 ±0.004 | 0.328 ±0.016 | 11.5±1.39 | 27.17±1.61 |

**Table 20: Data for blend evaluation of formulation (F-7 to F-12)**

| Formulations | Bulk Density* (g/ml) | Tapped bulk* density (g/ml) | Carr's index (%) | Angle of repose* |
|---|---|---|---|---|
| **F7** | 0.302 ± 0.001 | 0.325 ± 0.016 | 8.54±0.75 | 27.33±1.74 |
| **F8** | 0.266 ± 0.006 | 0.294 ±0.011 | 10.20±1.44 | 26.71±1.14 |
| **F9** | 0.292 ± 0.003 | 0.326 ± 0.013 | 10.42±1.36 | 26.22±1.78 |
| **F10** | 0.286±0.004 | 0.310±0.016 | 11.63±1.63 | 27.20±1.18 |
| **F11** | 0.251 ± 0.005 | 0.277 ± 0.010 | 9.38±1.32 | 26.12±1.42 |
| **F12** | 0.282 ±0.004 | 0.322 ± 0.017 | 12.42±1.43 | 28.37±1.44 |

*The values represent mean ± SD, n=3.

**POST COMPRESSION PARAMETERS:**

**Table 21: Physical properties of tablet formulation (F-1 to F- 6) of Lornoxicam sustained release matrix tablets.**

| Parameters | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| **Thickness* (mm)** | 3.55±0.08 | 3.52±0.12 | 3.52±0.12 | 3.58±0.02 | 3.56±0.08 | 3.57±0.13 |
| **Hardness* (kg/cm$^2$)** | 6.2±0.09 | 6.3±0.1 | 6.6±0.06 | 5.9±0.18 | 6.2±0.20 | 6.4±0.06 |
| **Friability* (%)** | 0.26±0.09 | 0.26±0.22 | 0.29±0.10 | 0.31±0.16 | 0.30±0.13 | 0.27±0.116 |
| **Drug content(%)** | 98.99±0.14 | 99.21±0.16 | 99.64±0.12 | 98.23±0.14 | 99.15±0.29 | 98.99±0.14 |

*The values represent mean ± SD, n=3.

**Table 22: Physical properties of tablet formulation (F-7 toF- 12) of Lornoxicam sustained release matrix tablets.**

| Parameters | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** |
| **Thickness* (mm)** | 3.56±0.05 | 3.65±0.04 | 3.62±0.07 | 3.58±0.04 | 3.65±0.05 | 3.55±0.02 |
| **Hardness* (kg/cm$^2$)** | 6.7±0.11 | 6.3±0.08 | 6.6±0.06 | 6.1±0.15 | 6.2±0.20 | 6.1±0.08 |
| **Friability* (%)** | 0.33±0.19 | 0.25±0.24 | 0.31±0.10 | 0.35±0.31 | 0.30±0.12 | 0.27±0.12 |
| **Drug content (%)** | 98.92±0.23 | 98.29±0.13 | 99.09±0.13 | 98.58±0.24 | 99.15±0.19 | 99.02±0.16 |

*The values represent mean ± SD, n=3.

**Table 23: Weight variation of formulations F1 to F6 of Lornoxicam sustained release tablets.**

| SI. NO | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| **1** | 300.1 | 299 | 300.2 | 299.8 | 301.2 | 301.1 |
| **2** | 300.0 | 300.7 | 300.4 | 300.9 | 301.2 | 299.8 |
| **3** | 300.3 | 299.1 | 300.3 | 298.8 | 300.8 | 298.8 |
| **4** | 298.9 | 301.5 | 298.7 | 301 | 300.5 | 301.3 |
| **5** | 301.0 | 301.4 | 299.2 | 301.4 | 299.2 | 300.1 |
| **6** | 300.5 | 300.5 | 301.1 | 300.8 | 300.1 | 300.6 |
| **7** | 300.7 | 299.7 | 300 | 299.5 | 299.3 | 299.0 |
| **8** | 299.3 | 299.6 | 300.1 | 300.3 | 300.9 | 300.1 |
| **9** | 300.2 | 300.4 | 299.5 | 299.9 | 301 | 300.5 |
| **10** | 300.1 | 301.0 | 300.8 | 300.3 | 300.1 | 300.2 |
| **Average wt of 10 tablets** | 300.11 | 300.29 | 300.03 | 300.3 | 300.4 | 300.15 |

**Table 24: Weight variation of formulations F7 to F12 of Lornoxicam sustained release tablets.**

| SI. NO | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | F7 | F8 | F9 | F10 | F11 | F12 |
| 1 | 300 | 301.9 | 301.2 | 300.1 | 299.5 | 300.3 |
| 2 | 300.1 | 299.2 | 301.1 | 300.0 | 299.8 | 299.9 |
| 3 | 300 | 300.2 | 300 | 300.2 | 300.2 | 299.4 |
| 4 | 299.9 | 300.3 | 300.1 | 300 | 300 | 300.1 |
| 5 | 300 | 302.2 | 300.5 | 299.8 | 301.2 | 300.2 |
| 6 | 300.3 | 299.8 | 300.2 | 299.9 | 300.5 | 300.1 |
| 7 | 300 | 299.7 | 299.8 | 300.2 | 300.1 | 300 |
| 8 | 299.9 | 301.2 | 299.7 | 300.1 | 300.3 | 300 |
| 9 | 300.1 | 300.8 | 300.3 | 300.5 | 300 | 300.3 |
| 10 | 300.1 | 300.3 | 300.4 | 300.3 | 300 | 300.2 |
| Average wt of 10 tablets | 300.04 | 300.5 | 300.3 | 300.11 | 300.16 | 300.05 |

***IN VITRO* DISSOLUTION STUDIES**

Dissolution tests were performed in a USPXXII dissolution apparatus type II (Electro lab, Mumbai, India)at 37 ±0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of (Lornoxicam) tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2hrs. For the next 10 hrs the dissolution were conducted in ph 6.8 phosphate buffer. 5 ml sample were withdrawn every hour for 12 hours and the same volume of fresh medium was replaced every time. Sample were filtered through 0.45 µm filter paper and the content of Lornoxicam was determined spectrophotometrically at a wavelength of 376nm for first 2 hr and then after take in 376nm. The release studies were conducted and results were noted in respective tables.

**Table 25: Percentage drug release of formulations F1 to F6.**

| TIME IN (Hrs) | FORMULATIONS | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| 1 | 13.75 | 9.56 | 10.67 | 8.40 | 10.55 | 13.14 |
| 2 | 19.16 | 17.72 | 21.28 | 15.38 | 14.40 | 19.23 |
| 3 | 28.80 | 32.46 | 35.16 | 21.24 | 25.55 | 26.19 |
| 4 | 37.80 | 44.56 | 42.65 | 34.16 | 36.46 | 33.15 |
| 5 | 49.50 | 53.74 | 53.12 | 42.15 | 47.52 | 41.72 |
| 6 | 58.66 | 65.15 | 61.37 | 53.40 | 58.65 | 53.43 |
| 7 | 66.56 | 74.25 | 72.30 | 66.48 | 69.46 | 66.72 |
| 8 | 78.67 | 86.36 | 87.20 | 78.59 | 84.85 | 78.35 |
| 9 | 89.70 | 97.45 | 96.61 | 84.98 | 97.89 | 87.19 |
| 10 | 98.80 | - | - | 91.45 | - | 98.76 |
| 11 | - | - | - | 97.86 | - | |
| 12 | - | - | - | - | - | |

**Table 26: Percentage drug release of formulationsF-7to F-12.**

| TIME IN Hrs | FORMULATIONS | | | | | |
|---|---|---|---|---|---|---|
| | F7 | F8 | F9 | F10 | F11 | F12 |
| 1 | 11.81 | 15.63 | 9.15 | 12.26 | 10.26 | 11.41 |
| 2 | 23.74 | 23.75 | 16.24 | 23.29 | 21.59 | 20.30 |
| 3 | 29.42 | 31.52 | 23.28 | 37.97 | 29.18 | 28.45 |
| 4 | 35.81 | 40.96 | 32.43 | 48.23 | 41.87 | 37.14 |
| 5 | 43.42 | 47.17 | 41.52 | 59.27 | 53.89 | 49.70 |
| 6 | 52.63 | 54.56 | 48.36 | 72.89 | 66.14 | 58.10 |
| 7 | 59.23 | 60.59 | 56.68 | 86.67 | 75.02 | 67.33 |
| 8 | 66.25 | 67.28 | 64.52 | 98.23 | 84.50 | 79.98 |
| 9 | 72.63 | 75.59 | 72.23 | - | 97.06 | 86.28 |
| 10 | 78.62 | 83.73 | 81.60 | - | - | 98.12 |
| 11 | 85.75 | 87.65 | 89.72 | - | - | - |
| 12 | 92.83 | 95.82 | 98.89 | - | - | - |

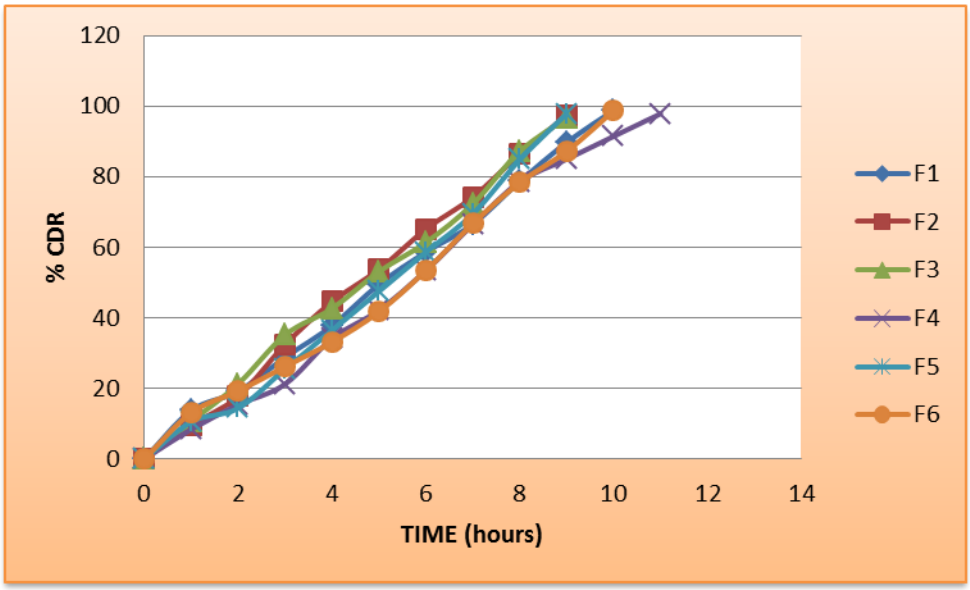



**Figure 40: *In Vitro* Dissolution Profile of F-1 to F-6 Formulations.**

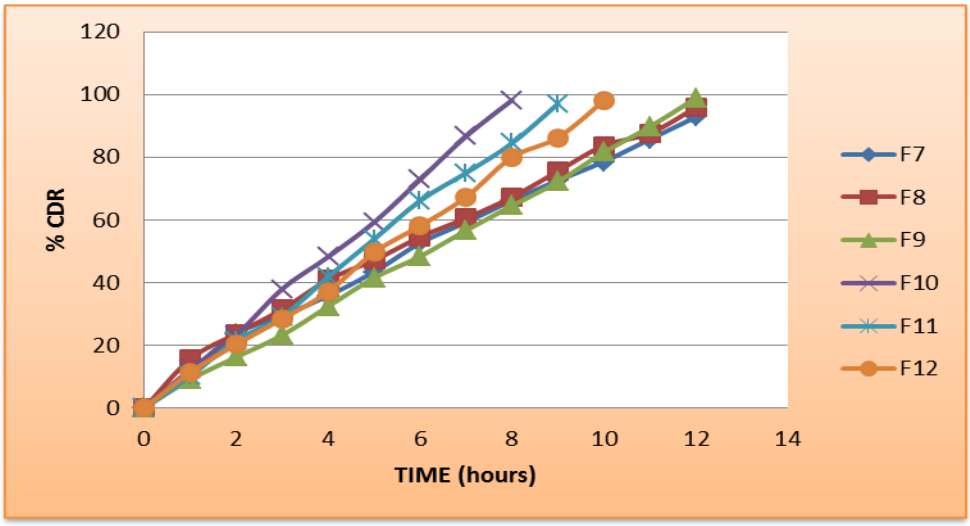



**Figure 41:*In Vitro* Dissolution Profile of F-7 to F-12 Formulations.**

**RELEASE KINETICS**

**Table 27: Correlation coefficients of different mathematical models for formulations F-1 to F-6.**

| Formulation Code | Zero Order $R^2$ | First Order $R^2$ | Higuchi $R^2$ | Peppas- model | |
|---|---|---|---|---|---|
| | | | | $R^2$ | Slope n |
| F1 | 0.9969 | 0.8889 | 0.961 | 0.9818 | 0.8897 |
| F2 | 0.9983 | 0.7993 | 0.9816 | 0.989 | 1.3569 |
| F3 | 0.9962 | 0.81 | 0.974 | 0.994 | 0.9732 |
| F4 | 0.9925 | 0.8449 | 0.9683 | 0.9918 | 1.1491 |
| F5 | 0.9899 | 0.7329 | 0.9624 | 0.9769 | 1.0726 |
| F6 | 0.9848 | 0.8986 | 0.9238 | 0.9666 | 0.8647 |

**Table 28: Correlation coefficients of different mathematical models for formulations F-7 to F-12.**

| Formulation Code | Zero Order $R^2$ | First Order $R^2$ | Higuchi $R^2$ | Peppas- model | |
|---|---|---|---|---|---|
| | | | | $R^2$ | Slope n |
| F7 | 0.9936 | 0.9092 | 0.9853 | 0.9962 | 0.8098 |
| F8 | 0.9913 | 0.8684 | 0.9845 | 0.9966 | 0.7417 |
| F9 | 0.9995 | 0.8951 | 0.7147 | 0.9979 | 0.9735 |
| F10 | 0.9991 | 0.9189 | 0.9769 | 0.9987 | 1.0051 |
| F11 | 0.9986 | 0.9119 | 0.9766 | 0.998 | 1.0231 |
| F12 | 0.9981 | 0.9119 | 0.9714 | 0.996 | 0.9408 |

**Table 29: Kinetic Model Fitting For Optimised Formulation (F9)**

| Time in Hours | % CDR | Log of % drug unreleased | Log time | SQRT | Log % CDR |
|---|---|---|---|---|---|
| **0** | 0 | 2 | 0 | 0 | 0 |
| **1** | 9.15 | 1.958325 | 0 | 1 | 0.961421 |
| **2** | 16.24 | 1.923037 | 0.30103 | 1.414214 | 1.210586 |
| **3** | 23.28 | 1.884909 | 0.477121 | 1.732051 | 1.366983 |
| **4** | 32.43 | 1.829754 | 0.60206 | 2 | 1.510947 |
| **5** | 41.52 | 1.767007 | 0.69897 | 2.236068 | 1.618257 |
| **6** | 48.36 | 1.712986 | 0.778151 | 2.44949 | 1.684486 |
| **7** | 56.68 | 1.636688 | 0.845098 | 2.645751 | 1.75343 |
| **8** | 64.52 | 1.549984 | 0.90309 | 2.828427 | 1.809694 |
| **9** | 72.23 | 1.443576 | 0.954243 | 3 | 1.858718 |
| **10** | 81.6 | 1.264818 | 1 | 3.162278 | 1.91169 |
| **11** | 89.72 | 1.011993 | 1.041393 | 3.316625 | 1.952889 |
| **12** | 98.89 | 0.045323 | 1.079181 | 3.464102 | 1.995152 |

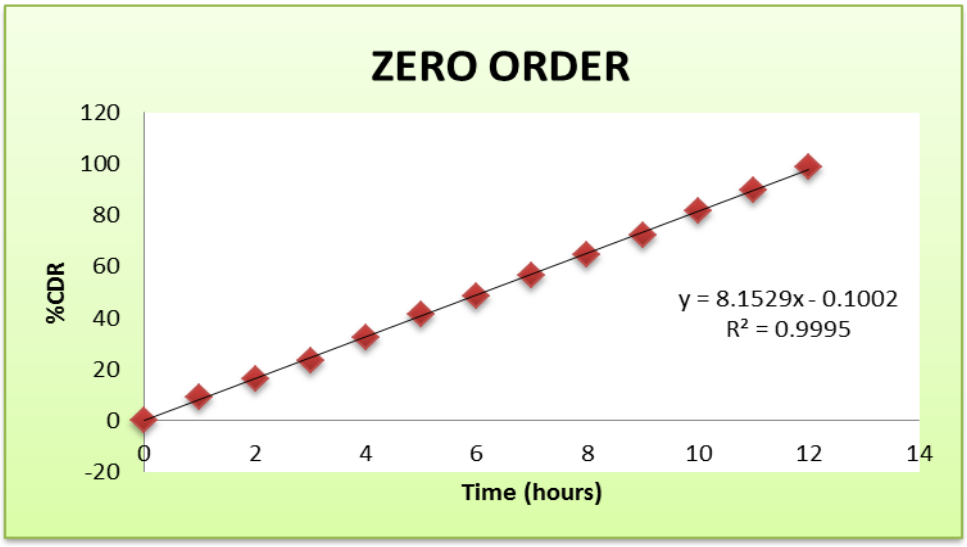
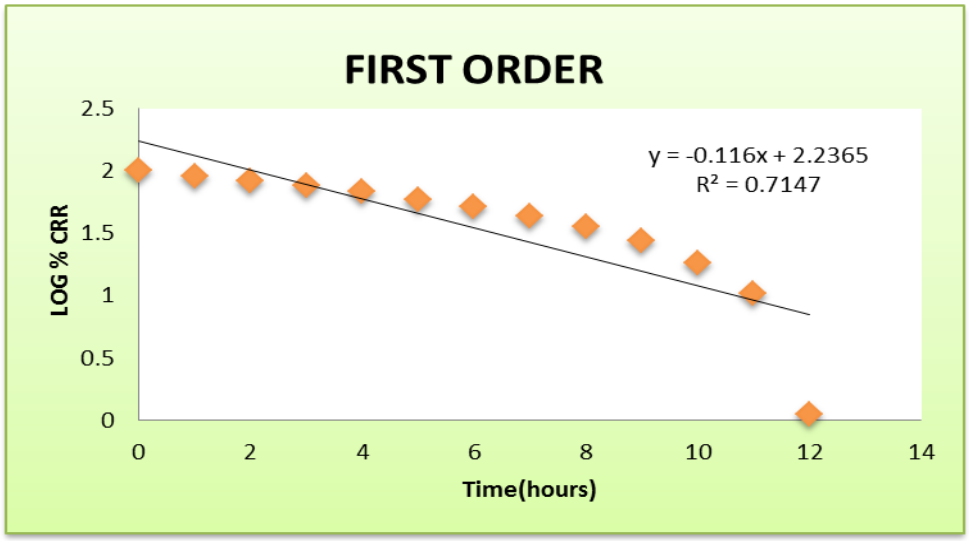
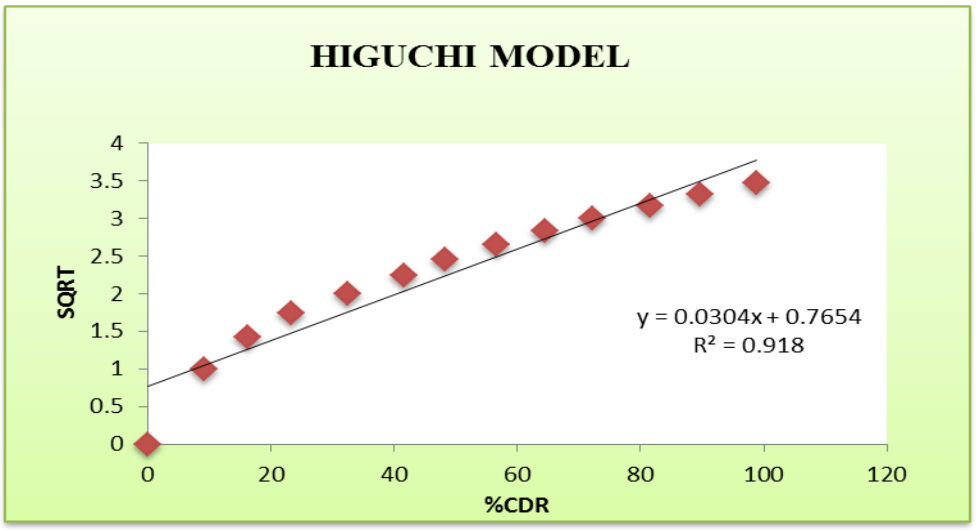



**Figure 42: Kinetic Model Fitting For Optimised Formulation F-9.**

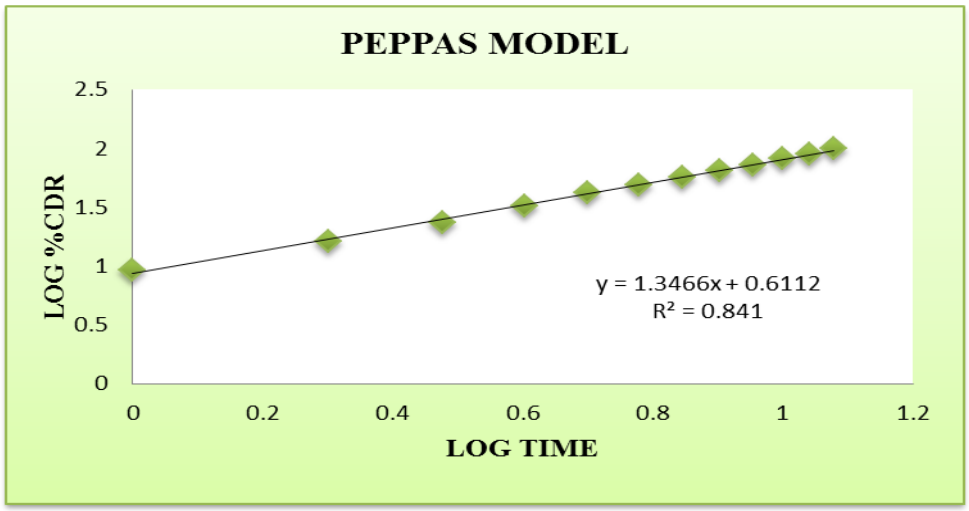
**Zero order plot of formulation F-9**




**First order plot of formulation F-9.**




**Higuchi plot of formulation F-9.**




**Peppas model of formulation F -9.**

**STABILITY STUDIES**

**Table 30: Physical appearance of optimized formulation after stability studies.**

| TEMPERATURE AND RELATIVE HUMIDITY | FORMULATION F-9 | | | | | | | | PARAMETERS |
|---|---|---|---|---|---|---|---|---|---|
| | Days | | | | | | | | |
| | 0 | 15 | 30 | 45 | 60 | 75 | 90 | 105 | |
| $25^0C \pm 2^0C$ / 60% ± 5% RH | No change | | | | | | | | Physical appearance |
| $35^0C \pm 2^0C$ / 60% ± 5% RH | | | | | | | | | |
| $40^0C \pm 2^0C$ / 60% ± 5% RH | | | | | | | | | |

**Table 31: Friability and Hardness of optimized formulation after stability studies.**

| No. of Days | Formulation F-9 | | | | | |
|---|---|---|---|---|---|---|
| | Friability (%) | | | Hardness ($Kg/cm^2$) | | |
| | $25^0C$ /60% RH | $30^0C$ /65% RH | $40^0C$ /75% RH | $25^0C$ / 60% RH | $30^0C$ /65% RH | $40^0C$ /75% RH |
| 0 | 0.28 | 0.38 | 0.41 | 6.7 | 6.6 | 6.4 |
| 15 | 0.31 | 0.44 | 0.48 | 6.7 | 6.5 | 6.4 |
| 30 | 0.37 | 0.50 | 0.56 | 6.6 | 6.4 | 6.3 |
| 45 | 0.42 | 0.53 | 0.62 | 6.4 | 6.3 | 6.2 |
| 60 | 0.47 | 0.60 | 0.65 | 6.3 | 6.1 | 6.0 |
| 75 | 0.53 | 0.69 | 0.71 | 6.2 | 6.2 | 6.0 |
| 90 | 0.61 | 0.72 | 0.74 | 6.0 | 5.8 | 5.7 |

**Table 32: % Drug release and Drug content of optimized formulation after stability studies**

| No. of Days | Formulation F-9 | | | | | |
|---|---|---|---|---|---|---|
| | % Drug release | | | Drug content (%) | | |
| | $25^0C$ /60% RH | $30^0C$ /65% RH | $40^0C$ /75% RH | $25^0C$ / 60% RH | $30^0C$ /65% RH | $40^0C$ /75% RH |
| 0 | 98.54 | 98.34 | 98.28 | 99.26 | 99.26 | 99.26 |
| 15 | 98.19 | 98.10 | 98.04 | 99.16 | 99.10 | 99.04 |
| 30 | 98.10 | 98.0 | 98.0 | 99.06 | 98.96 | 98.86 |
| 45 | 98.0 | 97.98 | 97.94 | 98.86 | 98.88 | 98.74 |
| 60 | 98.0 | 97.89 | 98.87 | 98.80 | 98.66 | 98.63 |
| 75 | 98.81 | 98.78 | 98.72 | 98.69 | 98.52 | 98.48 |
| 90 | 98.80 | 98.76 | 98.69 | 98.50 | 98.34 | 98.28 |

## CHAPTER - 6
## DISCUSSION

The present study was carried out to develop sustained release matrix tablets of Lornoxicam by wet granulation method. Hence it was necessary to find suitable excipients with good compatibility.

Oral route of administration is the most widely accepted route of delivery due to the ease of administration, avoidance of pain and other risks of parenteral administration and has good patient compliance. The main advantage of the oral sustained release dosage form is that it maintains the therapeutic concentration over an extended period of time. Several new technologies have been developed to overcome the physicochemical and pharmacokinetic characteristic of drugs, while improving the patient compliance. One of these technologies is the matrix type of dosage forms.

**Drug Selection**

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic properties and it belongs to the class of oxicams. Lornoxicam is a potent inhibitor of both COX-1 and COX-2 enzymes. The analgesic action is related to the inhibition of cyclooxygenase, which suppresses the production of prostaglandins and thromboxanes thereby reducing pain and inflammation. The analgesic activity is related to balanced inhibition of COX-1 and COX-2. unlike some NSAIDs, the inhibition of cyclooxygenase by lornoxicam does not result in an increase in leukotriene formation, and the shunting of arachidonic acid to the 5-lipoxygenase cascade is therefore not expected, which minimizes the risk of some adverse events, for example, allergic reactions. The half-life of Lornoxicam is 3-4 hours. The absolute bioavailability (calculated as AUC) of XEFO film-coated tablets is 90–100%. Lornoxicam is metabolized completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidney as inactive substance. All these criteria responsible for selection of drug.

**Dosage Form Selection**

Oral route of administration of the dosage form is one of the most convenient ways for administration of medicaments because of its safety and simplicity. Matrix technologies have often proven popular because of the simplicity of the manufacturing processes required, level of reproducibility, stability of the raw materials and

dosage form as well as ease of scale up operation, validation and favourable *in-vitro in-vivo* correlation (*IVIVC*). Classically simple matrix delivery systems exhibit first order or square root of time release kinetics. Matrix tablets are resistant to dose dumping. Due to the simple nature of the formulation and being robust they are unaffected by variations in ingredients. Matrix tablets containing acrylic polymers are common and commercially successful means of prolonging oral drug delivery and hence patient compliance.

**Matrix Tablets**

Aloe barbadensis miller leaf mucilage, Hibisus rosa-sinensis leaves mucilage, Ghatti gum, Isabgol husk mucilage and synthetic polymers. PVP K-30 as suspending agent. Magnesium stearate, Talc, Lactose were chosen as excipients for the formulations of sustained release matrix tablets. So they were used to sustain the release of the drug according to specification given in USP.

**Melting Point Determination**

Melting point was found to be 226°Cand it is within the range specified in the official limits.

**Compatibility study**

Compatibility study is important to understand the interaction between the drug and polymers. It saves costs and it makes easier to choose a few excipients from the long list of excipients for a better formula. Drug–excipients compatibility studies were carried out at an accelerating condition of $30^0C \pm 2^0C$ / 60% ± 5% RH.

A small quantity of each mixture was evaluated by FTIR with the control i.e. the pure Lornoxicam and the excipients were studied. It was found that all peaks corresponding to different functional groups of pure drug were present in the drug-excipient mixture. This shows the absence of interaction between the drug and excipients listed in Table 14.

**Flow Properties**

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility values of the powders were below 15% and hence they exhibit good flow characteristics. Values of angle of repose are rarely $20^0$ and values up to $40^0$ indicate reasonable flow properties. Above $50^0$ however the powder flows only with great difficulties. Dynamic angle of repose measurements can be replicated with relative standard deviations of approximately 2%. They are particularly sensitive to changes in particle size distribution and to the moisture content, and they provide a rapid means of monitoring significant batch to batch differences in these respects.

The Carr's Index (Compressibility) of the powders was in the range of 8.54 ± 1.39 to12.42±1.43. The angles of repose of the powders were in the range of $26.12\pm1.42^0$to$28.37\pm1.90^0$flow, which indicate a good flow property of the powders. Here the angle of repose was found to be below $40^0$ this shows that the reasonable flow property of powders.

**Evaluation of Tablets**

**Physical Parameters (Shape, Size, Hardness & Friability)**

The punches used to compress the tablets were 9 mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 5.9±0.18 to $6.7\pm0.11 Kg/cm^2$.

It was within the range of monograph specification. Thicknesses of the tablets were found to be in the range of 3.52±0.02 to 3.65±0.05mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

**Weight Variation and Drug Content**

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations twenty tablets were randomly selected and weighed. The results are given in table 23 & 24. The average weights of the tablets were found to be within the prescribed official limits (IP). Drug content for each of the formulations were estimated. The drug content for all the batches were found to be in the range of 98.23 % to 99.64%. The results are given in table 21 & 22.

***In-Vitro* Release Study**

*In vitro* release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing rotating paddle at 50rpm using 900ml of pH 1.2 Hcl medium for 2 hours and phosphate buffer of pH 6.8 as dissolution medium up to remaining 10 hours. (The results were evaluated for 12hrs).

The tablets of different formulations were evaluated for thickness, uniformity of weight, drug content, hardness, friability and *in vitro* dissolution. All the formulations showed uniform thickness. In a weight variation test the pharmacopeial limit for the percent deviation for tablets of more than 250 mg is ± 5%.

The percentage deviation of all tablet formulations found to be within the above limit and hence all the formulations passed test for uniformity weight as per official requirements. Good uniformity in drug content was found among different batches of tablets and the percentage of drug content is more than 99%.

From formulation F-1 to F-3 decrease in drug release was observed with higher concentration of polymer like Isabgol husk mucilage. Rate drug release was faster in F-1 and slower in F-3, as the concentration of polymer

increases the drug release decreased. The highest release of drug from formulation F1 Shows 98.8% drug release after 10 hours, and F-2 & F-3 shows 97.45%, 96.61% drug release after 9 hrs respectively.

Formulation F-4 to F-6, the release rate increase with increases in polymer concentration of polymer like Ghatti gum. The rate of drug release in F4 it shows 97.86% of drug release up to 11hrs and also in F5 formulation the drug release shows 97.89% at 9 hrs and in F6 formulation shows at 98.76% drug release at 10hrs respectively.

Matrix tablet of formulation F-7 to F-9,were containing Aloe mucilage gum as polymer. Among these formulations, the release rate was increased. This result has shown that as the proportion of Aloe mucilage gum increased, the overall time of release of the drug from the matrix tablet was also increased. For F-7 (92.83%)up to 12 hrs, F-8(95.82%) up to 12 hrs, F-9 (98.89%) in 12 hrs. respectively, the rate of drug release was optimized in formulation F-9 (i.e. 98.89%) up to 12 hrs and slower in F-7 formulation (i.e. 92.83%). This result shown that as the proportion polymer concentration increased, the overall time of release of the drug from the matrix tablet was also increased(release retarding).Appears to be suitable for use as a release retardant in the formulating sustained release matrix tablets because of its compatibility, good swelling, good flow properties and drug release characteristics.

The addition of polymer like Isabgol + aloe mucilage gum in formulation of F-10 to F-12,it shows the release rate of drug is increased as the polymer concentration increased but the overall time of the drug release is reduced in F10 formulation 98.23% at 8 hrs , F11 formulation 97.06% and F12 formulation shows that 98.12% drug release at 10 hrs.

**Kinetics**

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F- 12 could be best expressed by zero order equation as the plots showed highest linearity ($R^2$ : 0.9848 to0.9995 ), than first order release kinetics ($R^2$: 0.7993to0.9119). The n values obtained from Korsmeyer Peppas plots range from (0.7417to1.3569) indicate that mechanism of release of formulations F-1 to F-12 was Anomalous (non- Fickian) diffusion.

**FT-IR SPECTROSCOPY**

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected formulations This confirms that no interaction between drug and excipients.

**SCANNING ELECTRON MICROSCOPHY (SEM) STUDIES**

SEM study further established both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet (F-9). SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact, pores had formed throughout the matrix and also found formation of gelling structure.

**STABILITY STUDY**

Stability studies were carried out on selected formulation F-9 as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability and drug release (table 30-32 ) for the selected formulation F- 9 after 90 days at $25^0C\pm 2^0C$ / 60% ± 5% RH, $30^0C \pm 2^0C$ / 65% ±5% RH and $40^0C \pm 2^0$ / 75% ± 5% RH.

Therefore the main objective of the study to formulate and evaluate the matrix tablets of a Lornoxicam by using Aloe barbadensis miller leaf mucilage, Hibiscus rosa-sinensis leaves mucilage, Ghatti gum, Isabgol husk mucilage and synthetic polymers., and Ethyl cellulose as a retardant were achieved.

**CONCLUSION**

Matrix tablet of Lornoxicam can be prepared successfully by using wet granulation method, using Aloe barbadensis miller leaf mucilage, Hibiscus rosa-sinensis leaves mucilage, Ghatti gum, Isabgol husk mucilage and synthetic polymers. Polymers as retardant and. Lactose is used as a diluents and Magnesium stearate and Talc is used as a Lubricants PVP-K30 is used as a binding agent. From the above observations it was concluded that slow and controlled release of Lornoxicam over a period of 12 hours was obtained from matrix tablets F-9. It was found that increase in the polymeric concentration in polymeric ratio increase the drug release.

All the tablet formulations showed acceptable quality control properties like hardness, friability, thickness, weight variation, drug content uniformity etc. and complied with in the specifications for tested parameters. Formulation F-9 having drug –polymer ratio (Drug: Xanthan gum) gave better drug release rate over a period of 12 hours. Thus, formulation F-9 was found to be the most promising formulation on the basis of acceptable tablet properties and *in vitro* drug release rate of 98.89%.

The kinetic treatment of selected optimized formulation shows that the regression coefficient for zero-order kinetics were found to be higher when compared with those of the first-order kinetics, indicating that drug release from all the formulations followed zero-order kinetics and the n value lies between 0.7417to1.3569 (Korsmeyer-Peppas model) demonstrating that the

mechanism controlling the drug release was Anomalous (non-Fickian)diffusion.

Therefore, the results of the kinetic study obtained permit us to conclude that an orally sustained Lornoxicam matrix tablet delivers the drug through a complex mixture of diffusion, swelling and erosion.

Based on the FT-IR studies, there appears to be no possibility of interaction between Lornoxicam and polymers/ other excipients used in the tablets. SEM studies revealed that the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Lornoxicam from formulated matrix tablets.

Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of90 days which revealed that the formulations were stable. The results suggest that the developed sustained-release tablets of Lornoxicam could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance.

**SUMMARY**

About 12 different formulations were prepared by wet granulation method using different polymers Aloe barbadensis miller leaf mucilage, Isabgol husk mucilage and synthetic polymers.. Lactose is used as a diluent and Magnesium Stearate & Talc were used as lubricants and PVP K-30 is used as a binding agent.

Characterization of the drug was done by performing the melting point, UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all the excipients used in the study. The results showed that there was no drug-excipient interaction.

The melting point was found to be $226^0$C and from the UV spectral analysis of the drug solution indicated that λ max value as 376 nm in 0.1 N HCL and 6.8 pH phosphate buffer. Pre compression parameters and Carr‘s index of the pure drug indicated that the drug had good flow property, even the formulations were found to be within the range. Post compression studies, for tablets like thickness, hardness, friability, drug content uniformity was done.

The thickness depends on the size of the die cavity compression force, and tablet weight. The thickness of the formulations was in the range of 3.55±0.12 to3.65±0.10mmand the hardness was in the range of 5.9±0.18 to 6.7±0.11Kg/$cm^2$, indicated good mechanical strength of the tablets. Friability and drug content uniformity was found to be within official limits for all the formulations.

The dissolution studies were carried out for 12 hours. As per the result of dissolution study formulation F-9 showed good drug release profile of 98.89%, It showed excellent matrix integrity during the period of study, when compared to other formulations.

Based on all these results, formulation F-9 was selected as the optimized formulations with 98.89% drug release.

The release kinetics was fitted to different mathematical models like Zero order, First order, Higuchi‘s and Peppa‘s plot. The optimized Formulation F-9 follows Korsmeyer-Peppa‘s equation and the mechanism of drug release was found to be anomalous (non-Fickian) diffusion.

The drug polymer interaction was evaluated by FT-IR. Spectrum of pure drug was compared with that of the polymers and optimized formulation. All peaks corresponding to the different functional groups of pure drug were present in the formulations which indicate the absence of interaction between the drug and excipients.

The optimized formulation was checked for compatibility of drug with the other excipients used in optimized formulation F-9. This indicates that there is no interaction between drug and matrix materials. The optimised formulation F-9 was subjected to SEM studies.

SEM photomicrographs of tablet surface at different time intervals, indicates the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Lornoxicam from formulated matrix tablets.

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