INDUSTRIAL PREPARATION OF DRUG:KETOROLAC TROMETHAMINE USP., COMPARATIVE & RESEARCH STUDIES (INJECTABLE AND OPHTHALMIC)

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IN
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Submitted by
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DECLARATION

I here by declare that this dissertation entitled **"INDUSTRIAL PREPARATION OF DRUG:KETOROLAC TROMETHAMINE USP, COMPARATIVE & REARCH STUDIES (INJECTABLE AND OPHTHALMIC)"** is a bonafide genuine work carried out by **KRISHNAKUMAR.N(Reg.No:261710755)** in Partial fulfillment of the requirements for the award of degree in **Master of pharmacy in pharmaceutics** of The **Tamilnadu Dr.M.G.R.Medical University,Chennai.,Institutional Under the guidance Mr.T.AKELESH**, M.Pharm.,Ph.D.,Associate Professor, Department of Pharmaceutics, RVS College of Pharmaceutical Sciences and **Mr.BALAJI SRIKANTH REDDY (Industrial guide) Assistant Manager , Caplin Steriles Limited,Chennai** during the academic year of 2018-2019

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Mr. KRISHNA KUMAR, N.

Dedicated to our

Beloved Parents,

Teachers, Friends

& Almighty God

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1. INTRODUCTION

- The research study will outline formulation and the evaluation methds of injectable dosage form ophthalmic preparation their procedure in The various initial formulations of the developed and those are examined for drug release profile, bioavailability, and clinical effectiveness and for the pilot plant studies and production scale-up,Exhibit baches .
- The drug that we need should be most convenient and in proper form then only it reaches to the desired site of action. This is greatly influenced by which the type of dosage form of the drug. Since, injections include much variety of therapeutic agents. Injections are sterile, pyrogen limited, that is, bacterial endotoxin units limit, preparations intended to be administered parenterally.
- It is well recognized that the advantages of parenteral injections are immediate systemic drug availability and rapid onset of action
- The prime function of Research and Developments in pharmaceutical companies is to discover and to develop the new medicines. To achieve these objectives are not easy, in this a small percentage of the synthesized chemical compounds become medicines.
- A generic drug is the same as a brand name drug in its dosage, safety, strength, how it taken, how it performance, quality and intended use. The U.S FDA doesn't provide regulatory formal definition for excipients, and then also, according to guidance on nonclinical safety studies, new excipients are inactive ingredients that added intentionally to the therapeutic and diagnostic products.
- The desired product type must be determined as possible to establish the framework for product development, before formulating a drug substance into a dosage form.Before a medicinal agent is formulated into one or more dosage forms, the factors to considered are such therapeutic matters are the nature of illness, in which the manner it is treated (locally or systemic action), age and patient's anticipated condition.
- The drug that we need should be most convenient and in proper form then only it reaches to the desired site of action. This is greatly influenced by which the type of dosage form of the drug.

An ideal dosage form should be:- It should be safe and easy to administer.

- It should be easy to handle.
- It should be easy to produce and manufacture
- Provide high patient compliance.
- Should be physically and chemically stable.
- It should maintain its therapeutic activity throughout the shelf life.

The common parenteral routes are

- intramuscular (IM),
- subcutaneous (SC) and
- intravenous (IV)

Parentral [1-5]

- Development of parenteral products,based on the requirements of sterility of the finished product parenteral products manufacturing process considered the Production of parenterals .
- Filtration if the product is a solution, after its compounding, it should filter.
- Filtration process is employed to clarify a solution and removing particulate matter down to 0.2μm in size will eliminate the micro-organisms. It is accomplished by cold sterilization. Filters mainly functions by: Sieving or screening:
- The particles are retained on the surface of the filter by sieving Entrapment or impaction:
- If the particles smaller than the dimensions of the pore, they impact on the surface of the pore.

Electrostatic attraction

- Opposite charged particle to that of the surface of the filter pore to be adsorbed on the surface. Membrane filters are used for parenteral preparations because they have high effective in particle- retention, non-shedding property, non- reactivity and have disposable characteristics also. The most common membranes are made up of cellulose esters, nylon, polycarbonate, PVDF, and Teflon.

- Membrane filters are disposable type and can be discarded after use. It should clean thoroughly while using. Most pharmaceutical industries that preparing parenterals uses 0.2 μm membrane filter. Filling The solutions which sterilized through filtration are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill and by using media fills it is validated. A liquid is more easily exposed uniformly into the container having the narrow mouth than is used for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling.

- Liquid The filling of liquids into containers with high accuracy involves mainly three methods

    1. Volumetric filling
    2. Time/pressure filling
    3. Net weight filling

- Volumetric filling machines have pistons or peristaltic pumps. These are most common used method.
- Timepressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism. Time/pressure filling is preferable usually with the proteins that are sensitive to shear forces. Sealing The filled containers should be filled as soon as possible to prevent the contents being contaminated. It represents the final aseptic procedure.
- Ampoules Sealing of ampoules are done by melting of the portion of the glass neck. There are two types of sealing:-
- Pull –seals
- Tip-seals (bead –seals)

- Tip seals are employed by melting the glass at the tip of the ampoule neck to form a bead like and close the opening. This is performed in a high temperature gas oxygen flame. Pull-seals are performed by heat the ampoule neck below the tip. The ampoule to be seal is rotated in the flame from a single burner. The tip is grasped and then pulled quickly from the ampoule body, when the glass is softens.
- Pull sealing process is slower one, but the sealing done by this is more secure than that of tip-sealing. Vials and bottles By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly.
- This should be done by after filling with care, to prevent the contamination of the contents inside. Increased chances for contamination are the large opening in the vials than the ampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow.
- By using the aluminium caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole through the closure. Sterilization of parenteral products should be done after sealing it to the final container that is called as terminal sterilization.
- It should done within as short time as that possible after the filling and sealing are fully completed. This is accomplished usually by the thermal process.
- Radiation sterilization also will do to the parenteral finished products in sometimes.
- The care should be taken in the effect of the elevated temperature on the stability of the products. The elevated temperature that required for the sterilization by thermal process is adversely affects in many products like both pharmaceutical and biological. Non thermal methods are used for the heat-labile products.
- These non thermal methods include filtration through the bacteria retaining filters. Aseptic conditions should be strictly followed for all operations, and then only the contamination is not introduced into the filtrate.
- Dry-heat sterilization is performed for few dry solids that are not adversely affects by the high temperatures and that require long period of heating.
- For the sterilization of glassware and metal ware mostly performs the dry-heat sterilization process. After ,the sterilization process all the equipment will be sterile, dry and pyrogen-free. Autoclaving (saturated steam under pressure) is the most common

method used for sterilization process. It is the most effective sterilization method that used for the aqueous liquids or substances, since it can be reached or penetrated by the steam. Radiation sterilization is a terminal sterilization method with an ionizing radiation (gamma rays). There is an advantage for the applying on drugs in their final container, that also without any rise in temperature. One of the disadvantages is the possible formation of radiolytic products which leads to a change in the color and odor of the product.

- Packaging of parenterals Types of containers: A. Glass containers B. Plastic container
- Glass containers
- In most of the SVIs glass is used as the material choice for the containers. Principally glass containers are composed of silicon dioxide with varying amounts of

Table : 1 USP glass types

TYPES	GENERAL DESCRIPTION	GENERAL USE
TYPE 1	Highly resistant borosilicate glass	Buffered and unbuffered aqueous solutions All other uses.
TYPE 2	Treated soda- lime glass	Buffered aqueous solutions with pH below 7.0 Dry powders Oleaginous solutions.
TYPE 3	Soda- lime glass	Dry powders Oleaginous solutions
NP	General purpose soda-lime glass	Not for parenterals. For tablets, oral solutions, ointments, external liquids

- Plastic containers Sterile preparation like large-volume parenterals, ophthalmic solutions and mainly in small volume parenterals uses thermoplastic polymers as packaging materials.
- The principal advantage of plastic while comparing with glass, it is not breakable easily and reduction in weight also. In large-volume intravenous fluids currently uses the flexible bags of PVC (polyvinyl chloride) or select polyolefin.
- This having major advantage that there is no requirement of air interchange. Rubber Closures Rubber closures are made up of using milling machines by multiple ingredients plasticized and mixed together at an elevated temperature .
- The allergenic proteins from the natural rubber vial closures or stoppers that release into aqueous pharmaceuticals induce some allergic reactions in individuals with latex allergy receiving medications from such vials.

INJECTABLE SOLUTION [6-10]

Injections include much variety of therapeutic agents. In USP more than 400 injections products are listed. The dosage forms that conveying the drug by means of the injection through skin or the mucous membranes.

Some medicines cannot be given by oral due chemical action of enzymes. The most convenient and simplest form of an injectable product is an isotonic aqueous solution, which have the pH close to that of blood and the body tissues (pH 7.4).Injections that prepared in containers, antimicrobial agents also will add.

These are intended to suppress the growth of micro-organisms accidentally inoculated into the solution. Aqueous solutions which given through intramuscularly, the release of drug may be controlled by:

i. Increasing the vehicle viscosity by using MC, CMC, or PVP and thus decreasing the molecular diffusion and localizing the injected drug.
ii. Formation of complex with macromolecules like MC, CMC, or PVP from which the drug dissociates at controlled rate

Guiding principles for simple parenteral solutions Selection of injectable volume Pharmacopoeias classify the injection into types:-

Small-volume parenterals:

These are usually 100ml or less. Depends on the intended use these are packaged in different ways.

Large-volume parenterals:

- A single dose injection which intended for IV use and is packaged in containers, containing more than 100 ml. 13 SVPs are usually given rapidly in small volume are called as a bolus. In LVPs also they added like 5% dextrose and 0.9 %sodium chloride injection or infusion is administered through IV infusion.
- Based on the pharmacokinetics of the drug the bolus or infusions are selected. A bolus administration is preferred for intramuscular or subcutaneous injections. Subcutaneous route is used if the injection volume is less than 1- 1.5 mL and through intramuscular route usually no more than 2 mL.
- In the formulation of a solution product, the main step is to select the administration volume and concentration. 14 pH and Tonicity requirements pH considerations The generation of pH/stability and pH/ solubility profiles is the main step in the selection of pH in a formulation.
- For the maximum physiological acceptability, the target pH is approximately pH 7.4.
- When the dosing through IV route, a wide pH range can be tolerated and a rapid dilution wit blood also can be achieve.
- pH value ranging from 2 to 12 can be tolerated in these situations when intramuscular administration is uses the dilution rate is slower and it is further decreases when the subcutaneous route is administered.

Tolerability of a formulation depends on its buffering capacity.

Buffers used in the approved parenteral products Buffer pH Range

- Acetate 3.8 -5.8
- Ammonium 8.25 – 10.25
- Ascorbate 3.0 -5.0
- Benzoate 6.0 – 7.0
- Bicarbonate 4.0 – 11.0
- Citrate 2.1 – 6.2
- Diethanolamine 8.0 – 10.0

Tromethamine (TRIS, THAM) Tonicity consideration All parenteral products should be isotonic, especially osmolarities should target between 280 and 290 mOsm/L during a formulation.

For LVPs isotonicity is very essential. Either the rapid dilution with blood that will occur after injection or prior to administration the product itself diluted with an LVP, a wider range of osmolarities can be tolerated in SVPs. For hypotonic solutions hypertonic solutions are preferred since the risk of haemolysis associated with the hypotonic solution. By the use of excipients the hypotonic solutions are avoided, since the sodium chloride to raise the osmolality.

To avoid the tissue damage parenteral formulations should be isotonic with human plasma.Choice of excipients In pharmaceutical products the formulations should developed by using excipients. In parenteral products the quality, particularly in microbial terms of excipients should be considered necessarily.

The injectable grades are usually used for parenteral excipients which have strict bio burden and endotoxin limits. The excipients have pharmacopoeial grade also acceptable. But this is usually to apply In-House microbiological specification limits. The integral part of pharmaceutical products development is excipients, to achieve the desired product profile (stability and efficacy).

Excipients are important to assure safety (antimicrobial preservatives), to minimize pain and irritation on injection, and to control or prolonged drug delivery. General guidance for developing formulations of parenteral drugs The following factors should follow, when a drug is given through parenterally rather than orally:

i. The onset of action of drug is mostly more rapid but the duration is short.

ii. Since the drug potency tends not to alter immediately by the liver or stomach, so the dosage form is often smaller.

iii. The cost for the therapy is higher. Pharmacokinetics of the drug: The absorption rate for routes of administration other than intravenous or intra-arterial, distribution, metabolism and excretion of drugs have effect on route of administration that selected, based on the type of formulation.

For example: a drug having a rapid pharmacokinetic profile, there is need of development of modified release dosage formulations. Pharmacokinetics also affects the drug dose and the dosage regimen.

Drug solubility: The formulation must contain a co-solvent or a solute which sufficiently increases and maintains the drug in solution, if the drug is insufficiently soluble in the water at the dosage required. Solubility is the major factor that gives the concentration in the dosage form.

A dispersed system dosage form developed, when simple formulation additives do not result in the solution.

Drug stability: If the drug possesses significant degradation problems in the solution, then freeze dried or sterile solid dosage form should be developed. Sometimes drug concentration affects the stability in turn, affect size and the packaging system used also. Stability determines the storage conditions since it indicates the drug expiration date.

Advantages of parenteral products:

These are useful in :-

- Unconscious patients
- Uncooperative and unreliable patients
- Onset of action of drugs is faster; hence it is suitable for emergency. Patients with vomiting and diarrhea. These are suitable for irritant drugs and drugs with high first pass metabolism. Drugs are not absorbed orally. Drugs destroyed by digestive juices.

Disadvantages

Parenteral preparations should be sterile and expensive. They require aseptic conditions. Cost They can't easily self- administrated. Causes local tissue injury to nerves, vessels, etc. Parenteral product formulation depends upon the understanding of several factors that dictate the choice of formulation and dosage form.

OPHTHALMIC

Definition

- Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids.
- The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The addition of colouring agents is not recommended.
- Unless the active ingredient itself has antimicrobial activity, ophthalmic preparations supplied as multidose preparations may include a suitable antimicrobial agent. The antimicrobial activity should remain effective throughout the entire period of use. The different categories of ophthalmic preparations include drops consisting of emulsions, solutions or suspensions, and ointments.

Manufacture

- The manufacturing processes should meet the requirements of Good Manufacturing Practices, especially with regard to crosscontamination.
- The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important.
- Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls.
- These should be designed to guarantee the effectiveness of each stage of production. In-process controls during production of ophthalmic preparations should include monitoring

environmental conditions (especially with respect to particulate and microbial contamination), pyrogens (use of a limulus amoebocyte lysate (LAL) test may be advantageous), pH and clarity of solution, and integrity of container (absence of leakage, etc.). Appropriate limits should be set for the particle size of the active ingredient(s). It is essential that ophthalmic preparations are sterile. An aseptic manufacturing process is usually employed when the dosage form does not allow routine sterilization methods to be used.

Methods of sterilization

Packaging must be adequate to protect ophthalmic preparations from light, moisture, microbial contamination, and damage due to handling and transportation.

Visual inspection

Inspect the ointments, aqueous or oily solution, suspensions, or emulsions. Evidence of physical and/or chemical instability is demonstrated by noticeable changes in colour and odour. Sterility Ophthalmic preparations comply with Qc results.

Test for sterility.

- Particle size Ophthalmic preparations containing dispersed solid particles comply with the following test. Take a quantity of the preparation (shake the container gently if necessary) corresponding to at least 10µg of solid active ingredient and place in a counting cell or spread in a thin layer on a slide. Firmly apply a cover-glass and scan the whole area of the sample under a microscope. For practical reasons, the whole sample is first scanned at low magnification (e.g. × 50) and particles >25µm are identified.
- The larger particles can then be measured at a higher magnification (e.g. ×200-×500). For each 10µg of solid active substance not more than 20 particles should have a maximum dimension greater than 25µm and not more than two of these particles should have a maximum dimension greater than 50µm.
- None of the particles should have a maximum dimension greater than 90µm. Containers The materials for containers and closures should not adversely affect the quality of the preparation or allow diffusion of any kind into or across the material of the container into

the preparation. The container should be fitted with a closure that minimizes microbial contamination and a device that reveals whether the container has ever been opened.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established by Good Manufacturing Practices.Ophthalmic preparations The label should include:

1. The name of the pharmaceutical product;
2. The name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible;
3. The concentration(s) of the active ingredient(s) and the amount or the volume of preparation in the container;
4. The batch (lot) number assigned by the manufacturer;
5. The expiry date, the utilization period, and, when required, the date of manufacture;
6. Any special storage conditions or handling precautions that may be necessary;
7. If applicable, the period of use after opening the container;
8. Directions for use, warnings and precautions that may be necessary;
9. The name and address of the manufacturer or the person responsible for placing the product on the market;
10. If applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and
11. The statement "This preparation is sterile". Storage Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Special storage recommendations or limitations are indicated in individual monographs.

REQUIREMENT S:

- Requirements for specific types of ophthalmic preparations Ophthalmic drops Definition Ophthalmic drops (eye drops) are sterile aqueous or oily solutions, suspensions, or emulsions intended for instillation into the conjunctival sac.
- Ophthalmic drops should be clear and practically free from particles when examined under suitable conditions of visibility. "Water for injections" should be used in the manufacture of aqueous ophthalmic drops.
- The preparation of aqueous ophthalmic drops requires careful consideration of the need for isotonicity, a certain buffering capacity, the desired pH, the addition of antimicrobial agents and/or antioxidants, the use of viscosity-increasing agents, and the choice of appropriate packaging.
- Ophthalmic drops are considered isotonic when the tonicity is equal to that of a 0.9% solution of sodium chloride. The eye can usually tolerate solutions equivalent to 0.5-1.8% of sodium chloride. Ideally, the pH of ophthalmic drops should be equivalent to that of tear fluid, which is 7.4.
- However, the decision to add a buffering agent should be based on stability considerations. The pH selected should be the optimum for both stability of the active pharmaceutical ingredient and physiological tolerance. If a buffer system is used, it must not cause precipitation or deterioration of the active ingredient. The influence on the lachrymal flow should also be taken into account.
- Visual inspection Evidence of physical instability is demonstrated by the cloudiness of aqueous solutions, due to the formation of a precipitate.
- Containers Ophthalmic drops are normally supplied in suitable multidose containers that allow successive drops of the preparation to be administered. The container should be fitted with a tamper-evident device. The maximum volume of the preparation in such a container should be no more than 10 mL, unless otherwise specified and authorized.
- Multidose ophthalmic drop preparations may be used for up to 4 weeks after the container is initially opened. Droppers supplied separately should also comply with Test for sterility.

EVALUATION

pH

pH is the measure of concentration of protons (H+) in a solution that is the potential of hydrogen. It is the identification of a substance how it is acidic or alkaline by using a scale of acidity from 0 to 14. More the acidic solutions having lower pH, and more alkaline solutions having higher pH values. pH value less than 7 are acids and pH of greater than 7 are alkaline.

The neutral solutions that are the substances which are not acidic or alkaline have a pH value of 724 Particulate matter In injections and parenteral infusions particulate matter are considered as, the mobile undissolved particles, other than the gas bubbles, unintentionally that present in the solutions. There are two procedures involved in the determination of particulate matter. Sub-visible particles various oxides such as potassium, sodium, calcium, magnesium, aluminum, boron, and iron. Silicon oxide tetrahedron forms the basic structural network of glass. Boric oxide will enter into the basic structural network and the other oxides do not enter into this structure

- Method 1 (light obscuration particle count test)
- Method 2 (microscopic particle count test)
    - ❖ Injections and parenteral infusions are examined for subvisible particles usually method 1 is preferred mostly.
    - ❖ Then also some preparations by light obscuration particle count test that followed by microscopic particle count test is necessary to test.
    - ❖ No all parenterals are examined by method 1such as preparations that reduced clarity or increased viscosity, since these tests are carried out according to method 2.

For example: colloids, emulsions. Particulate matter contamination is still having a potential cause to the harm patients.

Sterility

Sterility testing is to identify the presence or absence of viable micro-organisms in the sample. . Immersion (Direct inoculation) It requires the test article to be inoculated directly into test media

Membrane Filtration

- It requires the test article to pass through a size exclusion membrane which capable of retaining microorganisms. Filter should be rinsed.
- Then the membrane is transferred to the test medium

Media types:

- Mostly used Soya-bean casein digest (SCD) and Fluid thioglycollate media (FTM). 28-29 Incubation period: all test containers should incubated at temperatures as specified in the pharmacopoeial method , that is for each test media at least 14 days, depends on whether filtration or direct inoculation test is used.

Stability

- Defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period.
- The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications.
- Stability testing also gives information about drug vulnerability to degrade by oxidation, hydrolysis, isomerisation, polymerization, decarboxylation, moisture, heat and light. Stability study is performed for specific time at specific environmental condition according to ICH guideline.

2 . REVIEW OF LITERATURE

INJECTION

Ronald J.**et .al.** ,Ketorolac tromethamine is a new injectable/oral nonsteroidal anti-inflammatory analgesic with no apparent opiate receptor activity that has been administered alone and in combination with other opiate analgesics for the treatment of post-operative pain. The drug has shown promise in analgesic comparisons with morphine sulfate; it lacks the effects of respiratory depression and nausea and vomiting usually associated with narcotic agents. Intramuscular ketorolac may be particularly useful with those patients who have respiratory disease and patients being dismissed following short ambulatory or private-office anesthetic procedures.(1)

VR Sinha. **.et .al,**Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug that belongs to the class of heteroaryl acetic acid derivatives. It is a non-selective cyclooxygenase (COX) inhibitor, being marketed in the racemate form. Most of its analgesic and COX inhibitory activity is retained in the S-isomer. Ketorolac is administered as its tromethamine salt orally, intramuscularly, intravenously and as a topical ophthalmic solution. The frequent occurrence of gastrointestinal disturbances including gastrointestinal bleeding, perforation and peptic ulceration along with the short mean plasma half-life ($t_{1/2} \sim 5.5$ h) has prompted for the development of various formulation strategies for the appropriate delivery of KT. The article gives an overview of the main concepts used thus far to design various pharmaceutical dosage forms for the therapeutically effective delivery of the drug candidate through various routes. At present, a great deal of emphasis is being placed on the development of sustained release forms for the drug as this would aid in achieving the required therapeutic efficacy and better tolerance with fewer gastrointestinal side effects.(2)

Vadivelu N. **.et .al**,Opioids have long been used for analgesic purposes for a wide range of procedures. However, the binding of these drugs to opiate receptors has created various challenges to the clinician due to unfavorable side effect profiles and the potential for tolerance and abuse. In 1989, ketorolac became an approved nonsteroidal inflammatory drug (NSAID) for injectable use as an analgesic. Over the last 20 years, numerous studies have been conducted involving ketorolac. These studies have provided additional information about various routes of administration and their effect on the efficacy and the side effect profile of ketorolac.

Moreover, ketorolac has been compared with several widely used analgesics. This review evaluates both the potential benefits and potential drawbacks of ketorolac generally, and specifically discusses routes of administration, including their advantages and disadvantages when compared to several traditional analgesics in both inpatient and outpatient settings.(3)

Redden RJ. **.et .al**,Ketorolac tromethamine is a new injectable/oral nonsteroidal anti-inflammatory analgesic with no apparent opiate receptor activity that has been administered alone and in combination with other opiate analgesics for the treatment of postoperative pain. The drug has shown promise in analgesic comparisons with morphine sulfate; it lacks the effects of respiratory depression and nausea and vomiting usually associated with narcotic agents. Intramuscular ketorolac may be particularly useful with those patients who have respiratory disease and patients being dismissed following short ambulatory or private-office anesthetic procedures.(4)

Litvak KM. .et .al,Clinical studies of the injectable nonsteroidal anti-inflammatory agent (NSAIA) ketorolac tromethamine are reviewed, and the chemistry, pharmacology, pharmacokinetics, drug interactions, and adverse effects of ketorolac are described. Ketorolac exhibits anti-inflammatory, analgesic, and antipyretic activity. Although the exact mechanisms of action have not been determined, its effects appear to be associated principally with the inhibition of prostaglandin synthesis. After oral, i.m., or i.v. administration, ketorolac and its metabolites are excreted mainly in urine. Ketorolac tromethamine has been used for the symptomatic relief of moderate to severe postoperative pain, including that associated with abdominal, gynecologic, oral, orthopedic, or urologic surgery. Ketorolac has also been used for the relief of acute renal colic, pain associated with trauma, and visceral pain associated with cancer. When administered i.m., ketorolac produced analgesia comparable to that of i.m. doses of meperidine, pentazocine, or morphine. The most common adverse effects associated with short-term administration are nervous system and gastrointestinal effects; these are usually mild and occur in about 39% of patients. Unlike opiate analgesics, ketorolac does not appear to cause tolerance or physical dependence in patients receiving long-term therapy. Ketorolac tromethamine has been administered concomitantly with morphine or meperidine without apparent adverse interaction. For short-term pain management, an initial i.m. ketorolac

tromethamine loading dose of 30 or 60 mg is recommended. Ketorolac tromethamine appears to be as effective as morphine or meperidine for short-term management of moderate to severe postoperative pain. It lacks the respiratory depressant effects of opiate analgesics but shares the toxic potentials of other NSAIAs.(5)

DeAndrade JR. **.et .al**,Ketorolac tromethamine (Toradol) is a nonsteroidal antiinflammatory drug (NSAID) available in intramuscular (IM) and oral formulations for the management of acute pain. Intramuscular ketorolac is the only parenteral NSAID available for analgesic use in the US. The clinical profile is reviewed, and clinical studies most applicable to a postoperative patient are discussed in detail. The results of a clinical study performed at Emory University School of Medicine are presented. In this single-dose study, 176 patients received either 10 mg of oral ketorolac, 5 mg or 10 mg of IM morphine, or placebo after orthopedic surgery. The analgesic efficacy of ketorolac was comparable to both doses of morphine and significantly superior to placebo. Ketorolac, when administered intramuscularly or orally, is a safe and effective analgesic agent for the short-term management of acute postoperative pain and can be used as an alternative to opioid therapy.(6)

Brown CR., **.et .al .,**A multicenter, randomized, double-blind, parallel study in 542 patients with moderate or severe postoperative pain compared the analgesic efficacy and safety of intramuscular ketorolac 30 mg (324 patients), morphine 6 mg (110 patients), and morphine 12 mg (108 patients) administered as needed as often as every 2 hours for a maximum of 20 doses or 5 days. The efficacy of ketorolac 30 mg was comparable to that of morphine 12 mg on every efficacy measure (average pain intensity, average pain relief, mean overall medication rating, and percentage of patients withdrawing because of inadequate relief). Ketorolac was statistically superior to morphine 6 mg for average pain intensity and mean overall rating. Ketorolac-treated patients had fewer adverse events than those who received either morphine dose.(7)

Stanski DR. .et .al, Ketorolac tromethamine, a potent nonnarcotic prostaglandin synthetase-inhibiting analgesic, was compared with meperidine for relief of moderate to severe postoperative pain. In a double-blind, randomized study, 125 patients received single intramuscular doses of ketorolac 30 or 90 mg or meperidine 50 or 100 mg. The degree of pain and pain relief were quantified verbally and with visual analog scales at baseline and 30 minutes, then hourly for 6 hours. Ketorolac 30 and 90 mg were significantly superior to meperidine 50 mg

in six of nine efficacy measures. The onset of and peak analgesic effect of both doses of ketorolac and of meperidine were equivalent. Compared with both doses of meperidine, the two doses of ketorolac exhibited significantly longer duration of analgesic effect, as measured by the percentage of patients who terminated the study because of inadequate pain relief. The frequency of side effects was not significantly different between the drugs. The prolonged efficacy of intramuscular ketorolac combined with the reduced risk of respiratory depression suggest an important use of this drug for the relief of postoperative pain.[8]

Chellman GJ. .et .al,The local tolerance of ketorolac tromethamine (Toradol, Syntex) was compared with that of four other injectable nonsteroidal anti-inflammatory drugs (NSAIDs) (diclofenac sodium, piroxicam, ketoprofen, and metamizol magnesium) in the rat paw-lick/muscle irritation assay as described previously. All drugs were tested at concentrations approved for clinical use. After subplantar (footpad) injection, ketorolac produced virtually no pain-on-injection as assessed by the number of paw-lick/lift responses during a 15 min observation period. The other NSAIDs produced slight to moderate paw-lick/lift responses. Redness and swelling at the injection site were less severe for ketorolac than for the other NSAIDs. After intramuscular (i.m.) injection, all of the NSAIDs produced some degree of muscle damage, as assessed histopathologically 24 h after injection. The lesions, consisting primarily of muscle degeneration, were less severe for ketorolac than for the other NSAIDs. Ketorolac and metamizol produced the smallest elevations in serum creatine kinase, as measured 2 h after i.m. dosing, not significantly different from isotonic saline. Overall, ketorolac was better tolerated in the assay than the other injectable NSAIDs, thereby suggesting the possibility of improved local tolerance on clinical use.[9]

OPHTHALMIC

Helga P Sandoval. .et .al.,,The non-steroidal anti-inflammatory drug (NSAID) ketorolac tromethamine 0.4% ophthalmic solution, a recent reformulation containing 20% less active ingredient that the original formulation, is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery. Clinical studies have shown ketorolac tromethamine 0.4% to be as effective as ketorolac tromethamine 0.5% to control inflammation after cataract surgery including prevention of cystoid macular edema (CME). Its efficacy to inhibit miosis during cataract surgery as well as its role in the treatment of dry eye has been reported. The purpose of this paper is to review the use of ketorolac tromethamine 0.4% in the treatment of post-surgical inflammation following cataract and refractive surgery.(1)

Perry HD .et .al .,Ketorolac tromethamine 0.4% ophthalmic solution, a recent reformulation of the original ketorolac tromethamine 0.5% solution, is indicated for the reduction of ocular pain and burning/stinging following cataract and refractive surgery. Studies have demonstrated that ketorolac tromethamine 0.4% has equivalent efficacy to ketorolac tromethamine 0.5% in reducing postsurgical inflammation and controlling pain. Several studies have demonstrated that, as well as reducing pain and ocular inflammation, ketorolac tromethamine 0.4% effectively treats cystoid macular oedema, inhibits miosis and may prevent cystoid macular oedema when used both pre- and postoperatively. Ketorolac tromethamine 0.4% is a versatile agent and is effective when used as either monotherapy or as an adjunct therapy to steroids.(2)

Price MO .et .al .,This was a single-center, double-masked, randomized, fellow-eye placebo-controlled clinical study of 25 patients (mean age 72 years; 76% female) requiring bilateral cataract surgery. Patients received either ketorolac tromethamine 0.4% ophthalmic solution (Acular LS*) or placebo, 1 drop QID for 3 days prior to and 1 day following phacoemulsification and intraocular lens implantation on their first eye, and the other treatment for surgery on the second, fellow eye 1 week–4 weeks later. The physician rated patient cooperation and ocular pain or discomfort during surgery, and patients rated ocular pain or discomfort immediately and 24 h

after surgery. he reduction in pain associated with cataract surgery afforded by ophthalmic ketorolac 0.4%, together with its favorable safety profile, make it an important tool to help surgeons meet the high expectations of today's cataract and refractive surgery patients.(3)

Rajpal RK .et .al .,The analgesic efficacy and safety of topical ketorolac tromethamine 0.5% ophthalmic solution (Acular) in photorefractive keratectomy was compared to its vehicle.Double-masked, multicenter, study of 200 patients dosed with 1 drop of study medication (ketorolac or vehicle) in the operated eye immediately after surgery (eye patched), with fourtimes daily dosing for the next 3 days starting 3 hours after surgery. Mepergan Fortis was available as an escape pain medication.Patients (102) in the ketorolac group reported significantly greater pain relief and less pain intensity than the vehicle group (98) at several time points (P =£ .039). Time to first use of escape medication was significantly longer in the ketorolac than the vehicle group (mean, 16.0 vs 5.5 hr; P=.001). Time to complete pain relief was significantly shorter in the ketorolac than the vehicle group (mean, 41.3 vs 50.3 hr; P=.022). Significantly fewer patients in the ketorolac group reported sleep difficulties, ocular discomfort, or other difficulties. Few adverse events were reported with ketorolac treatment (less than with vehicle), and there were no clinically significant changes in any of the safety variables monitored. Ketorolac tromethamine 0.5% ophthalmic solution (Acular) is safe and significantly more effective than vehicle in alleviating pain following photorefractive keratectomy.(4)

Sandoval HP ,et .al .,compare the effectiveness and patient tolerance of 0.4% ketorolac tromethamine ophthalmic solution and 0.5% ketorolac tromethamine ophthalmic solution after routine phacoemulsification and lens implantation.The setting for this study was the Storm Eye Institute and Magill Research Center for Vision Correction, Medical University of South Carolina (Charleston, SC).This work was a prospective, double-masked study that included 40 eyes of 40 patients randomly assigned to receive topical treatment with 0.4% ketorolac or 0.5% ketorolac, starting 15 min prior to routine phacoemulsification and foldable posterior chamber intraocular lens implantation. Following the procedure, patients were instructed to use the assigned treatment agent 4 times a day after surgery for 1 week and twice a day for 3 weeks, when drops were discontinued. Slit-lamp examination, intraocular pressure (IOP), laser cell and flare measurements, and subjective patient tolerance were evaluated postoperatively at 1, 7, and 30 d. Comparisons between the 2 groups were made at each visit, as well as comparisons to

baseline. A P = value less than .05 was considered statistically significant.At day 1, a higher percentage of patients (70% vs. 40%) reported symptoms (mainly foreign body sensation and stinging/burning) in the 0.5% ketorolac group, compared to the 0.4% ketorolac group. No significant differences were found between the 2 groups over time regarding best-corrected visual acuity (BCVA), IOP, slit-lamp assessment of cells, and cell and flare measured using the laser cell/flare meter. Treatment with 0.4% ketorolac tromethamine ophthalmic solution is as effective as 0.5% ketorolac tromethamine ophthalmic solution in reducing inflammation after routine cataract surgery. Patients reported less discomfort using 0.4% ketorolac.[5]

Solomon KD .,et .al,compare the efficacy and safety of ketorolac 0.5% ophthalmic solution with its vehicle in the treatment of ocular inflammation after cataract surgery and intraocular lens implantation One hundred four patients were prospectively randomized, 52 patients in treatment group, 52 patients in control group.Patients received either ketorolac or vehicle four times daily in the operated eye for 14 days starting the day after surgery in a prospective, double-masked, randomized, parallel group study. Only patients with moderate or greater postoperative inflammation the day after surgery were enrolled.The main outcome measures include inflammation (cell, flare, ciliary flush), intraocular pressure and visual acuity.Ketorolac was significantly more effective than vehicle in reducing the manifestations of postoperative ocular inflammation, including: anterior chamber cells (P = 0.002) and flare (P = 0.009), conjunctival erythema (P = 0.010), ciliary flush (P = 0.022), photophobia (P = 0.027), and pain (P = 0.043). Five times as many patients were dropped from the study for lack of efficacy from the vehicle group (22/52) than from the ketorolac group (4/52; P = 0.001). Ketorolac was found to be equally as safe as vehicle in terms of adverse events, changes in visual acuity, intraocular pressure, and biomicroscopic and ophthalmoscopic variables.Ketorolac tromethamine 0.5% ophthalmic solution was significantly more effective than vehicle in the treatment of moderate or greater ocular inflammation following routine cataract surgery, while being as safe as vehicle.[6]

Solomon KD .,et .al .,To compare the efficacy of a topical nonsteroidal anti-inflammatory agent (ketorolac tromethamine 0.5%) with that of a topical steroid (rimexolone 1%) to control inflammation after cataract surgery. Thirty-six patients were prospectively and randomly assigned to receive topical treatment with either ketorolac tromethamine 0.5% or rimexolone 1% starting the day after routine cataract extraction. Treatment was masked to both patient and

investigator. Each patient had uneventful small incision phacoemulsification with placement of a foldable posterior chamber intraocular lens. Patients used 1 of the 2 antiinflammatory agents 4 times each day starting 24 hours after surgery. No antiinflammatory medications were used preoperatively, intraoperatively, or for 24 hours postoperatively. Signs and symptoms of inflammation, intraocular pressure (IOP), and Kowa cell and flare measurements were evaluated 1, 4, 7, and 30 days postoperatively. There was no statistically significant difference in any measurement of postoperative inflammation between the 2 groups. There was no difference in objective or subjective cell and flare measurements. In addition, there was no difference in IOP measurements between groups.[7]

Solomon KD., et .al., To evaluate the safety and analgesic efficacy of ketorolac tromethamine 0.4% ophthalmic solution in postoperative photorefractive keratectomy (PRK) patients. This pooled analysis of 2 multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies comprised 313 patients having unilateral PRK. After surgery, patients were treated with 1 drop of ketorolac tromethamine 0.4% ophthalmic solution (Acular® LS) (n = 156) or vehicle (n = 157) 4 times daily for up to 4 days. Pain intensity, pain relief, use of escape medication, and severity of ocular symptoms were assessed. Adverse events, epithelial healing, and visual acuity were recorded. There was significantly less pain intensity experienced by patients in the ketorolac group (P<.001). During the first 12 hours post PRK, 50% fewer patients in the ketorolac group than in the vehicle group had severe to intolerable pain (41.6% [64/154] and 84.5% [131/155], respectively). The median time to no pain was 30 hours in the ketorolac group and 54 hours in the vehicle group (P<.001, survival analysis). Ketorolac patients reported significantly greater pain relief than vehicle patients throughout the study (P<.001). Ketorolac patients used significantly less escape medication than vehicle patients for 48 hours post PRK (P≤.008). Treatment-related adverse events occurred in 2.6% (4/156) of ketorolac patients and 6.4% (10/157) of vehicle patients.[8]

Simone JN .,et .al .,To compare the anti-inflammatory and analgesic efficacy and safety of ketorolac tromethamine 0.5% ophthalmic solution with those of prednisolone acetate 1% in patients having cataract surgery. This double-blind, randomized, single-site study comprised 59 healthy men and women with a clinical diagnosis of routine ocular cataract requiring surgical removal. All patients had extracapsular cataract extraction and posterior chamber intraocular lens

implantation. After surgery, patients were randomized to receive ketorolac tromethamine 0.5% or prednisolone acetate 1%, self-instilled in the treated eye, according to the following schedule: 1 to 2 drops 4 times daily (week 1); 3 times daily (week 2); 2 times daily (week 3); once daily (week 4). Patients were examined postoperatively on days 1, 7, and 28. Intraocular anti-inflammatory efficacy was assessed by lid edema, lid injection, conjunctival injection, corneal edema, ciliary flush, and anterior chamber cells. Analgesic efficacy was assessed by patient self-rated pain severity, pain frequency, total symptom sum, and overall global improvement.[9]

Yaylali V ., et .al .,To compare the therapeutic effects of two ophthalmic solutions (0.1% olopatadine hydrochloride and 0.5% ketorolac tromethamine) with different pharmacological mechanisms on the clinical signs and Symptoms of seasonal allergic conjunctivitis (SAC). days. mins and at 2, 7 and 15 Forty patients with the signs and symptoms of SAC (i.e. hyperaemia, itching, mucus discharge, tearing) were included in this placebo-controlled, randomized, parallel group, single centre study. In group 1 (20 patients) one eye of each patient was treated with olopatadine and the other with placebo. In group 2 (20 patients) one eye of each patient was treated with ketorolac solution and the other with placebo. The principal signs and symptoms of SAC (hyperaemia and itching) were evaluated at 30. Both olopatadine and ketorolac ophthalmic solutions were found to be effective in alleviating the clinical signs and symptoms of SAC compared to placebo. However, olopatadine reduces ocular itching significantly more than ketorolac.[10]

Yee RW .,et .al .,To compare the analgesic efficacy and safety of nonpreserved ketorolac tromethamine 0.5% with those of its vehicle in the treatment of postsurgical ocular pain following radial keratotomy. This study employed a multicenter, double-masked, randomized, parallel-group design. Radial keratotomy patients were treated with either nonpreserved ketorolac tromethamine 0.5% or its vehicle four times daily for up to 3 days following surgery. Patients were provided with an escape medication (acetaminophen) for use only as needed for intolerable pain. Nonpreserved ketorolac tromethamine 0.5% ophthalmic solution was significantly more effective than, and as safe as, vehicle in the treatment of postoperative pain associated with radial keratotomy. Therefore, topical ketorolac may be a valuable treatment option for the maintenance of patient comfort following refractive surgery.[11]

3.AIM AND OBJECTIVE

Comparision between the two liquid preparation like injectable solution and ophthalmic solution. In Pharmaceutical industrially and they method of preparation ,Different concentration some same Pharmaceutical ingredients effective,they are procedure to preparae the drug based upon the dose and dosage ,concentration and by aseptic procedure .

PLAN OF WORK

- Literature Survey
- Selection and procurement of drug/API and excipients
- Method of preparation injectable and ophthalmic solution follow the USFDA guidelines
- pH
- Solubilty
- Dissociation constant,specific gravity
- Compatabilty studies - Tonicity and surfactants ,some prepared exhibit batch results
- Formulation and evaluation of solid in liquid . (parentral)
- Stability studies of optimized they are storage condition
- Results and Discussion

4 . DRUG PROFILE

DRUG SUBSTANCE

- **Proper Name**: Ketorolac tromethamine

- **Chemical IUPAC Name**: (±)-5-Benzoyl-2, 3-dihydro-lH-pyrrolizine-l-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-l, 3-propanediol (1:1).

- **Brand name** Toradol, Acular
- **Synonyms** Ketorolac tris salt, KetorolacTrometamol.
- **Chemical Structure:**

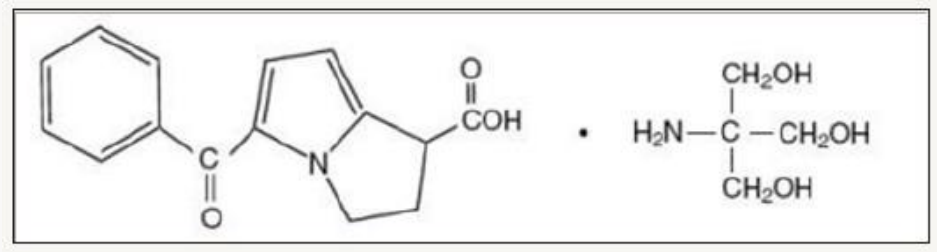


Figure :1

- **Molecular Formula**: C15H13NO3 . C4H11NO3
- **Molecular Weight**: 376.41 g/mol
- **Physiochemical Properties**: Ketorolac tromethamine (pKa = 4.47) is a white to off-white crystalline powder that melts at about 162°-170°C with decomposition.
- It is freely soluble in water and methanol, slightly soluble in ethanol and practically insoluble in acetone, methylene chloride and toluene.

  The pH of a 1% (w/v) solution in distilled water is 5.7-6.7.
- **Solubility:**

  It is freely soluble in water and methanol; slightly soluble in alcohol, in dehydrated alcohol, in tetrahydrofuran; and practically insoluble in acetone, in dichloromethane, in toluene, in

ethylacetate, in dioxane, in hexane, in butyl alcohol and in acetonitrile. pKa and pH: The pKa is 3.46 and the pH of a 1% (w/v) solution in carbon dioxide free, purified water is 5.7 - 6.7.

Melting Point: Melts at about 162 °C with decomposition.

Mechanism of Action

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic activity mediated by peripheral effects. The mechanism of action of ketorolac, like that of other NSAIDS, is not completely understood, but is believed to be related to prostaglandin synthetase inhibition.

Pharmacokinetics

- The pharmacokinetics are linear following single and multiple dosing. Steady state plasma levels are attained after one day of Q.I.D. dosing. Following intramuscular administration, peak plasma concentrations of 2.2 to 3.0 mcg/mL occur at an average of 50 minutes after a single 30 mg dose. The terminal plasma half-life ranges between 3.5 and 9.2 hours in young adults and between 4.7 and 8.6 hours in elderly subjects (mean age = 72 years). In renally impaired patients, there is a reduction in clearance and an increase in the terminal halflife of ketorolac tromethamine
- The parenteral administration of ketorolac tromethamine has not been demonstrated to affect the hemodynamics of anesthetized patients. A series of studies were carried out in mice, rats, rabbits, monkeys and humans to characterize the pharmacokinetic profile of the free acid of ketorolac and ketorolac tromethamine.
- The salt form of the compound was later selected for development due to its more rapid and complete absorption.

Absorption:

- Ketorolac tromethamine was rapidly (Tmax ranged from 0.25-1.5 hr) and completely absorbed after oral and IM doses in animals (>87%) and humans (>99%).

Melting point

Melts at about 160-165°C with decomposition.

Distribution:

- The volume of distribution of ketorolac was estimated following intravenous dosing and ranged from 0.09 L/kg in mice to 0.38 L/kg in rats; in humans, it averaged 0.15 L/kg. Ketorolac was highly protein bound in human (99.2%), monkey (98.3%) and rabbit (98.2%) plasma; moderately bound in rat plasma (92.1%); and poorly bound in mouse plasma (72.0%). Binding was concentration independent in all species studied.
- The tissue distribution of ketorolac-associated radioactivity was studied in male mice. The highest levels were found in the kidney which was the only organ which exceeded plasma levels at all time points (by about 50%).
- The lowest levels were present in the brain. However, all tissues eliminated ketorolac-associated radioactivity rapidly with a tissue half-life of A moderate first pass metabolism (about 20%) was observed in humans, while rabbits exhibited more extensive first pass metabolism (about 50%) following oral doses. The metabolism and excretion patterns of ketorolac and its metabolites were similar following PO, IV and IM dosing in the species studied. Ketorolac accounted for most of the radioactivity circulating in the plasma ranging from 79% in rabbits to 99% in mice and averaged 96% in humans. Conjugates of ketorolac were not detected in plasma in appreciable amounts in any species.
- However, the p-hydroxy metabolite (which is essentially inactive when compared to ketorolac) was detected in the plasma of rats, rabbits and humans. Ketorolac and its metabolites were excreted predominantly in the urine of all species, ranging from 69% in rats to essentially 100% in the cynomolgus monkey and averaged 92% in humans. The most comparable species with respect to man, metabolically, was the mouse.

Dissociation Constant $pK_{a3.49}$

- Solubility It is freely soluble in water and methanol, slightly soluble in alcohol, indehydrated alcohol, in tetrahydrofuran, and practically insoluble in acetone, indichloromethane, in toluene, in ethylacetate, in dioxane, in hexane, in butyl alcoholand in acetonitrile.
- ***Pharmacokinetic Data***
- Bioavailability 80-100%
- Protein binding 99%
- Metabolism Hepatic
- ***Volume of distribution 0.15 to 0.33 L/kg***
- Half–life 3 to 6 h
- t_{max} 2 to 3 h
- Excretion Renal:91.4% (mean); Biliary:6.1% (mean)

Elimination/Excretion:

- The primary route of excretion of ketorolac tromethamine and its metabolites (conjugates and the ρ-hydroxy metabolite) is in the urine (91.4%) with the remainder (6.1%) being excreted in the feces. Special Populations and Conditions Geriatrics (≥65 years of age): The terminal plasma half-life of ketorolac is prolonged compared to young healthy volunteers to an average of 7 hours (ranging from 4.3 to 8.6 hours).
- The total plasma clearance may be reduced compared to young healthy volunteers, on average to 0.019 L/h/kg.

Hepatic Insufficiency:

- Patients with impaired hepatic function do not have any clinically important changes in ketorolac pharmacokinetics, although there is a statistically significant prolongation of Tmax and terminal phase half-life compared to young healthy volunteers.

Renal Insufficiency:

- Elimination of ketorolac is decreased in patients with renal impairment as reflected by a prolonged plasma half-life and reduced total plasma clearance when compared to young healthy subjects. The rate of elimination is reduced roughly in proportion to the degree of renal impairment except for patients who are severely renally impaired, in whom there is higher plasma clearance of ketorolac than estimated from the degree of renal impairment alone.

STORAGE AND STABILITY

- Store between 20°C and 25°C. Protect from light and freezing. Discard unused portion. dosage forms, composition and packaging
- Ketorolac Tromethamine Injection USP, 15 mg/mL, is a clear and slightly yellow sterile solution. Each mL contains: ketorolac tromethamine 15mg, ethyl alcohol 10% (w/v), sodium chloride for tonicity, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection. Ketorolac Tromethamine Injection USP, 15 mg/mL, is available in 1 mL single-use vials.

PHARMACOLOGY

- Animal Pharmacology Analgesic Properties Ketorolac is a potent orally active analgesic agent in tests utilizing an underlying inflammatory state. In mice, given oral or subcutaneous doses ranging from 0.05-2.25 mg/kg, the compound was 250-350 times more potent than ASA in inhibiting phenylquinone-induced writhing.

- Using a similar test in rats which received 0.03-1.0 mg/kg PO, ketorolac was 180 times as potent as aspirin in inhibiting the writhing response. In rats having adjuvant-induced arthritis, ketorolac PO was 400-800 times more potent than aspirin and twice as potent as naproxen in alleviating pain.
- The compound also significantly increased the pain threshold in yeast-inflamed paws of rats which were compressed at a constant rate of pressure (Randall-Selitto Test), its potency being 3 to 10 times that of naproxen.
- The fact that ketorolac does not increase the pain threshold of the non-inflamed paw and does not exhibit analgesic activity in the mouse hot plate test indicates that it is not a morphine like compound. Anti-inflammatory Properties Ketorolac displayed anti-inflammatory properties when tested in classical rat models to test intrinsic anti-inflammatory actions.
- The free acid form of the compound had approximately 36 times the anti-inflammatory potency of phenylbutazone, while the tromethamine salt was 118 times as active as phenylbutazone in inhibiting carrageenan-induced paw inflammation when administered orally.
- This difference in potency is due to the compound. Ketorolac was weakly effective in inhibiting the development of ultraviolet-induced erythema when applied topically at a dose of 1 mg to guinea pigs.
- In the rat, however, topical application at dose levels of 0.01 and 0.1 mg/rat, was very effective in suppressing the heat induced local inflammatory reaction.
- When administered to rats at a dose of 2 mg/kg/day PO, for 6 days, ketorolac did not produce thymic involution. This indicates that the anti-inflammatory activity is not due to intrinsic corticosteroid activity in the molecule nor due to the stimulation of endogenous corticosteroid production.
- These findings were further confirmed by the dose-related anti-inflammatory activity in adrenalectomized rats.
- Antipyretic Properties When administered orally to yeast-infected rats in doses ranging from 0.1-2.7 mg/kg, ketorolac had 20 times the antipyretic potency of aspirin.

- Prostaglandin Inhibition There is substantial evidence in the literature to suggest that the anti-inflammatory, analgesic, and antipyretic activities of nonsteroidal anti-inflammatory drugs (NSAIDs) are due to their ability to inhibit prostaglandin biosynthesis.
- Ketorolac, like other NSAIDs, inhibited the prostaglandin synthetase activity in bovine seminal vesicle microsomes, rabbit renal medullary microsomes, and human platelet microsomes, having substantially greater potency (1.0 to 5.3 times) than indomethacin. Platelet Effects In in vitro studies, ketorolac was 37 times as active as aspirin in inhibiting aggregation of human platelets induced by collagen and 28 times more potent than aspirin in inhibiting arachidonic acidinduced platelet aggregation.
- However, ketorolac did not inhibit the primary phase of adenosine diphosphate-induced aggregation nor the aggregation elicited by thromboxane A2.
- Central Nervous System Effects The acute intraperitoneal administration of ketorolac to mice had minimal behavioural effects at doses up to 300 mg/kg. Above this dose level, depression of normal behaviour was seen. No appreciable central nervous system (CNS) activity was produced by ketorolac. It did not possess anticonvulsant activity in mice in the maximal electroshock test nor did it inhibit pentylenetetrazol-induced seizures in mice or rats.
- In mice, hexobarbital-induced sleep time was unaltered by ketorolac suggesting that the compound was not a CNS depressant. The gross behaviour and sleep patterns of cats dosed at up to 10 mg/kg IV were unchanged.
- Cardiovascular Effects Sequential administration of 1, 3 and 10 mg/kg IV of ketorolac to anesthetised cats, produced minimal cardiovascular or autonomic responses. In anesthetised dogs, doses of 1 to 30 mg/kg IV produced inconsistent and variable changes in the cardiac contractile force, heart rate and blood pressure.
- The cardiovascular responses to adrenaline, nor-adrenaline, tyramine, phenylephrine and bilateral carotid artery occlusion were inhibited by ketorolac, suggesting that the compound may possess mild alpha-adrenoceptor blocking activity.
- Bronchial Effects Ketorolac, when administered intravenously to guinea pigs in doses of 0.01-10 mg/kg, failed to block histamine- or methacholine-induced bronchoconstriction.
- In the rat, the compound blocked methacholine-induced airway constriction (ED50 = 0.5 mg/kg). Gastric Effects Doses of ketorolac at 0.1 and 1.0 mg/kg PO in rats did not alter

significantly either the gastric juice volume or the total mEq of hydrogen ions secreted in response to histamine stimulation. Moreover, in common with other NSAIDs, both the acid and the tromethamine salt of ketorolac had a similar propensity to cause gastrointestinal erosions in rats independent of the route of administration.

TOXICOLOGY

Acute Toxicity Studies Animal Strain Sex Route

LD50 (mg/kg) Mouse HLA-SW/ICR F
Oral approx. 400 Mouse HLA-SW/ICR M/F Oral + 529 (281-1540)

* Rat COX-SD F Oral 112(68-191)

* Rat COX-SD M/F Oral + 100-400 Mouse HLA-SW/ICR F IP > 400 Mouse HLA-SW/ICR M/F IP + 473 (315-771)* Rat COX-SD F IP 158 (101-248)

* Rat COX-SD M/F IP + 100-400

Note: * 95% confidence interval + studies with ketorolac tromethamine; all others with ketorolac free acid. All doses were administered in solution form.

Administration of the free acid of ketorolac at a dose of 200 mg/kg PO in 1 male and 1 female cynomolgus monkey caused both monkeys to vomit after dosing.

Other changes seen in the female included diarrhea and anorexia starting 5 days after dosing. The male monkey gained weight while the female had weight loss.

Both animals had decreased hemoglobin and hematocrit and survived the 2 week post-dose period. In another study, the identical dose of ketorolac tromethamine salt caused vomiting in the female. No other clinical signs were recorded for this animal.

- Ketorolac tromethamine (KT), a nonsteroidal anti-inflammatory drug (NSAID), is indicated for the short-term management of severe acute pain that requires analgesia at the opioid level.

- It is one of the commonly used drugs for the treatment of pain that is inexpensive, safe, and well tolerated.1 Ketorolac (free acid) is sparingly soluble in water and, therefore, it is marketed in the form of tromethamine salt, which increases its solubility in water.
- Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks when administered as a conventional oral dosage form. The major side effect is gastrointestinal (GI) complications including peptic ulcers, and GI bleeding or perforations. KT is available for oral, intravenous (IV), or intramuscular (IM) administration. The half-life of ketorolac tromethamine is around 6 hours.
- The recommended daily dose of KT injection is 120 mg in divided doses. Frequent dosing of the drug may reduce patient compliance. Moreover, the majority of adverse reactions to KT are dose related, and it is strictly advised not to exceed this limit. Hence the need to have a controlled drug delivery system for KT is necessary. A trend in NSAID development has been to improve therapeutic efficacy and reduce the severity of upper GI side effects through altering dosage forms of NSAIDs by modifying release of the formulations to optimize drug delivery.
- These formulations are designed to increase patient compliance through a prolonged effect and to reduce adverse effects through lowered peak plasma concentrations. Many controlled-release dosage forms are designed to release the drug at a predetermined rate, thus maintaining relatively constant drug levels in the plasma for an extended period of time.
- Several benefits may result from the use of such formulations. Reduction of frequency of dosing, lowered adverse effects, and improved patient compliance are considered the primary advantages of controlled-release dosage forms. One such formulation uses polymeric microspheres as carriers of drugs. Many authors have reported that nanoparticles and microparticles have a tendency to accumulate in the inflamed areas of the body. It has been reported that microspheres of NSAIDs reduce the GI toxic effects and exhibit sustained action, thus increasing patient and therapeutic compliance.
- The use of biodegradable polymeric microparticulate systems is an interesting application in the control of drug release and targeting. The yield, drug content, and particle size distribution depend on different factors such as the nature of the polymer, and the formulative and preparative methods. Albumin microspheres are biodegradable particles

that can be produced in a size range of 1 to 200 μm in diameter, by either physical or chemical solidification of an albumin emulsion in an organic phase. Bovine serum albumin (BSA) is widely used for microsphere preparation because it is nonantigenic, biodegradable, free from toxicity, able to control the physicochemical characteristics of the microspheres produced, and readily available.. Drug release from the microspheres can be controlled by the extent and nature of cross-linking, size, and drug incorporation level in the microspheres. In the present study, preparation and characterization of KT-loaded albumin microspheres was performed. Many process variables can influence the characteristics of the resultant albumin microspheres. It is difficult to assess the effect of the variables individually or in combination.

The effects of 3 variables, namely:

- (1) drug:albumin ratio,
- (2) amount of glutaraldehyde, and
- (3) duration of cross-linking, on the encapsulation efficiency of albumin microspheres were studied using a factorial design. The objective of the study was to prepare KT-loaded albumin microspheres using a factorial design and to characterize the microspheres for encapsulation efficiency, release mechanism, particle size, and surface morphology.
- A technique of 33 factorial design taking 3 prime selected variables at 3 different levels affecting the entrapment efficiency was used to design the experimental batches for the preparation of KT-loaded albumin microspheres by chemical cross-linking method.
- A factorial design evaluating 3 factors at all combinations for each factor would result in a fullfactorial design consisting of 33 = 27 runs. The addition of center points allows for detection of nonlinearity in the responses.
- The total number of runs becomes 27 + 5 runs = 32 runs. The center points were run 6 times to get an estimate of experimental or pure error. F test was used to compare the variance among the treatment means with the variance of individuals within the specific treatment

EXCIPIENTS PROFILE

1. Polyethylene Glycol 400[30-33]

Nonproprietary Names

BP Macrogols

PhEur Macrogols

USP-NF Polyethylene Glycol

Synonyms

Carbowax; macrogola; PEG; polyoxyethylene glycol.

Chemical Name α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

Molecular Formula $H(OCH_{2}CH_{2})_{n}OH$

Molecular Weight 380-420 g/mol

Functional Category

Ointment base; plasticizer; solvent; suppository base;
tablet andcapsule lubricant.

Description

Clear, colorless or slightly yellow- colored, viscous liquid. It have a slight but characteristicodor and a bitter, slightly burning taste.

Typical Properties

Density 1.11–1.14 g/cm^3 at 25^{0}C

Freezing point 4–8^{0}C

Moisture content

Very hygroscopic, although hygroscopicity decreaseswith increasingmolecular weight.

Solubility

Soluble in water, acetone, alcohols, benzene, glycerin, andglycols.

Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution,although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth,and they do not become rancid. Polyethylene glycols should be stored in well- closed containers ina cool, dry place. Stainless steel, aluminum, glass, or lined steelcontainers are preferred for the storage of liquid grades.

Incompatibilities All grades can exhibit some oxidizing activity, incompatible with some coloringagents. The antibacterial activity of certainantibiotics is reduced in PEG bases. Plastics, suchas polyethylene, phenolformaldehyde, polyvinyl chloride, andcellulose-ester membranes (in filters) may be softened or dissolvedby PEGs.

Safety

Generally, theyare regarded as nontoxic and non irritantmaterials.PEGs administered topically may cause stinging, hypersensitivityreactions includingurticaria anddelayed allergic reactions. The most seriousadverse effects

associated with PEGs are hyperosmolarity, metabolic acidosis, andrenal failure. The WHO has set an estimated acceptabledaily intake of polyethylene glycols at up to 10mg/kg body-weight.

Applications

Attractive ingredient in cosmetics such as creams, jellies and lotions. Inconcentrations up to 30% v/vPEG400 have been used as the vehiclefor parenteraldosage forms.Other uses are assolid dispersions; lubricant in tyre manufacturing; plasticiser forsponges and synthetic leather; paper softner; anticurl agent; flux for soldering; intermediate in resinmanufacturing.PEG 400 also find uses intoothpaste to remove dirt on the teeth and incosmetics soaps as a wetting agentpreventing thesoap from cracking.

2.Ethanol[34-36]

Synonyms Ethyl alcohol; ethyl hydroxide; grain alcohol; methylcarbinol.

Molecular Formula C_2H_6O

Molecular weight 46.07 g/mol

Structural Formula C_2H_5OH

Functional Category Antimicrobial preservative; disinfectant; skin penetrant; solvent.

Description

Alcohol is clear, colorless, mobile and volatile liquid with a slight, characteristic odor and burningtaste.

TypicalPropertis

Boiling point 78^0C

Density 0.789 g/cm^3

Melting point 114^0C

Solubility

Miscible with chloroform, ether, glycerin and water (with rise of temperature and contraction of temperature and contraction of volume).

Stability and Storage Conditions

- Aqueous ethanol solutions may be sterilized by autoclaving or by filtration and should be stored in airtight containers, in a cool place.
- Incompatibilities In acidic conditions, ethanol solutions may react vigorously with oxidizing materials. Mixtures with alkali may darken in color due to a reaction withresidual amounts of aldehyde. Ethanol solutionsare also incompatible with aluminum containersand may interact with some drugs.
- Safety Ethanol is rapidly absorbed from the GIT and the vapor may be absorbed through the lungs; it is metabolized, mainly in the liver, to acetaldehyde, which is further oxidized to acetate.
- Applications Ethanol is primarily used as a solvent; it is also employed in solutions as an antimicrobial preservative. Topical ethanol solutions are also used as penetration enhancers and as disinfectants.

3.Lecithin[37-38]

The word lecithin was originally coined in 1847 by French chemist and pharmacist Theodore Gobley to designate pure phosphatidylcholine. Gobley originally isolated lecithin from egg yolk(lekithos) is egg yolk in ancient Greekand established the complete chemical formula of phosphatidyl choline in 1874; in-between he had demonstrated the presence of lecithin in a variety of biological matters including venous blood, bile, human brain tissue, fish eggs, fish roe, chicken and sheep brain.

Nonproprietary Names

USP-NF Lecithin

Synonyms

Lipoid, Egg lecithin; mixed soybean j phosphatides; ovolecithin; soybean lecithin; soybean phospholipids; vegetable lecithin.

Chemical Name 1, 2-diacyl-sn-glycero-3- phosphocholine

Molecular Formula $C_{46H89NO8P}^{+}$

Molecular Weight 815.17 g/mol

Functional Category Emollient; emulsifying agent; solubilizing agent.

Description

Lecithins vary greatly in their physical form, from viscoussemi liquids to powders, depending upon the free fatty acid content. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity. Lecithins have practicallyno odor. Those derived from vegetablesources have a bland or nutlike taste, similar to that of soybean oil.

TypicalProperties

Density 0.97 g/cm^3 for liquid lecithin; 0.5 g/cm^3 for powdered lecithin

Iodine number 95–100 for liquid lecithin; 82–88 for powdered lecithin

Saponification value 196

Solubility

Lecithins are soluble in aliphatic and aromatic hydrocarbons,halogenated hydrocarbons, mineral oil, and fatty acids.They are practically insoluble in cold vegetable and animal oils,polar solvents, and

water. When mixed with water, however, lecithins hydrate to form emulsions.

Stability and Storage Conditions

Lecithins decompose at extreme pH. They are also hygroscopic andsubject to microbial degradation. When heated, lecithins oxidize, darken, and decompose. Temperatures of 160–180^{0}C will causedegradation within 24 hours. Purified solid lecithins should be stored in tightly closed containers at subfreezing temperatures.

Incompatibilities

Incompatible with esterases owing to hydrolysis.

Safety

Lecithin is a component of cell membranes and is thereforeconsumed as a normal part of the diet. Although excessiveconsumption may be harmful, it is highly biocompatible and oraldoses of up to 80 g daily have been used therapeutically in the treatment of tardive dyskinesia. When used in topical formulations,lecithin is generally regarded as a nonirritant and nonsensitizingmaterial.

Applications

Mainly used inpharmaceutical products as dispersing, emulsifying, and stabilizing agents, and areincluded inintramuscular and intravenous injections, parenteral nutritionformulations, and topical products such as creams and ointments. Lecithins are also used in suppository bases. Lecithin can protect against alcohol cirrhosis of the liver, lowerserum cholesterol levels, and improve mental and physicalperformance.

4. **Propylene Glycol[39]**

Nonproprietary Names

BP Propylene Glycol

PhEur Propylene Glycol

USP Propylene Glycol

Synonyms

1, 2-Dihydroxypropane; 2-hydroxypropanol; methylethylene glycol; methyl glycol; propane-1, 2-diol.

Chemical Name 1, 2-Propanediol

Molecular Formula $C_3H_8O_2$

Molecular Weight 76.09 g/mol

Structural Formula $CH_3CHOHCH_2OH$

Functional Category Antimicrobial preservative disinfectant; humectant;plasticizer; solvent; stabilizer for vitamins; water-miscible cosolvent.

Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling glycerin.

Typical Properties

Boiling point 188^0C

Density 1.038 g/cm^3 at 20^{0}C

Melting point 59^{0}C

Solubility

Miscible with acetone, chloroform, ethanol (95%), glycerin and water; soluble 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Stabilityand Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%),glycerin, or water; aqueous solutions may besterilized by autoclaving.

Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such aspotassium permanganate.

Safety : Generallyregarded as a relatively ontoxic material.Propylene glycol is rapidly absorbed from theGIT; there is also evidence that it is absorbed topically when applied to the damaged skin. Intopical preparations, propylene glycol is regardedas a minimally irritant, although it is more irritantthan glycerine.

Applications

Propylene glycol has become widely sed as a solvent, extractant and preservative in a variety of parenteral an nonparenteral pharmaceutical formul- ations. It is a better general solvent than glycerin and dissolves a wide variety of materials. Used as humectant ~ 15 (%), solvent or cosolvent 5-80 (%) in topicals.

5 . MATERIAL AND METHODS

INJECTABLE (VIAL) Ketorolac Tromethamine injection USP,15mg/ml-1 ml

Table : 2 RAW MATERIAL INFORMATION:

S. No	Ingredients	Functional Category
1	Ketorolac Tromethamine USP	Active Pharmaceutical ingredient
2	Sodium chloride USP	Tonicity agent
3	Alcohol USP	Preservative
4	Sodium Hydroxide USP – NF	pH adjusting agent
5	Hydrochloric acid USP-NF	pH adjusting agent
6	Water for Injection USP/BP	Vehicle
7	Nitrogen BP	Processing aid

PRODUCT SPECIFIC INSTRUCTIONS:

- Ensure that all the ingredients /materials used ,carry “APPROVED” label and are within the retesting /use before date.
- While manufacturing care should be taken to avoid the cross contamination and generation of particles .

- Stainless steal container of grade SS316L/316 should be used for batch manufacturing and storage.
- Take adequate precaution steps to ensure that no microbial contamination of the bulk solution occurs during compounding process and storage .
- Only sterilized and shortest possible thermoplastic elastomer ,(Pharmapure)tubing from Saint –Gobain should be used for connections in filling operation.
- The bulk solution must be aseptically filtered immediately after manufacturing and stored in an aseptic area ata temperature not exceeding 22˚c $\pm$ 2˚c.
- Check the filter integrity test of product filters before and after filteration.
- Filling should be done aseptically.

All manufacturing operations and controls must be carried out under the proper procedure.

LABEL CLAIM:

Each ml contains 15mg of ketorolac tromethamine USP,

Example :Ketorolac Tromethamine injection USP,15mg/ml-1 ml

Table :3 UNIT FORMULA:

S. No.	Ingredients	Quantity/mL	Quantity/30.0 L***
1	Ketorolac Tromethamine USP	15.0 mg	450.0 g*
2	Sodium chloride USP	6.68 mg	200.4 g
3	Alcohol USP	10 % w/v	3.0 g
4	Sodium Hydroxide USP – NF	q.s to adjust pH	40.0 g#
5	Hydrochloric acid USP-NF	q.s to adjust pH	101.15 g##
6	Water for Injection USP/BP	q.s to 1 mL	q.s to 30.0 L
7	Nitrogen BP	NA	NA

#: To prepare 1 L solution of 1 N Sodium hydroxide.

##: To prepare 1 L solution of 1 N Hydrochloric acid.

Formula for calculation of standard quantity for Ketorolac Tromethamine USP:

$$\text{Qty/Batch (g)} = \text{Label Claim} \times \text{Batch Size (L)} \times \frac{100 \times 100}{\%\ \text{Assay on dried basis} \times (100 - \%\text{LOD})}$$

Formula for calculation of standard quantity for Benzalkonium chloride USPNF:

$$\text{Qty/Batch (g)} = \frac{\text{Label Claim} \times \text{Batch Size (L)} \times 100}{\text{Assay on as is basis (or) 50\% whichever is lesser}}$$

STORAGE CONDITION:

Store at 20° to 25°C (68° to 77°F) Excursion permitted to 15˚ – 30˚ (59 ˚ – 86˚ F).

NOTE: Light protection steps to be considered while manufacturing.

PRODUCT SPECIFIC REQUIREMENTS:

- Stainless steel container of grade SS316L should be used for batch manufacturing and storage.
- Use 0.22 µm filtered Nitrogen gas during filtration.
- Throughout the manufacturing process (compounding, filtration, filling) maintain controlled Room temperature.
- Static contact time with the tubing should not exceed 24 Hrs; the bulk solution which is in static contact with tube above 24 Hrs shall be discarded.
- Static contact time with the filter should not exceed 24 Hrs; the bulk solution which is in static contact with the filter above 24 Hrs shall be discarded.
- Total processing time is 84 Hrs (This is the time starting from the start of addition of API addition to end of Sealing). Processing time for various stages is defined below.

Table : 4 DETAILS OF PROCEDURE FOR HOLD TIME :

Stage		**Recommended time**
Total Bulk Solution Compounding time (from API addition)	:	NMT 12 Hrs
End of bulk solution compounding to end of the filtration	:	NMT 18 Hrs
Start of the filling to completion of filling and sealing	:	NMT 24 Hrs

- Use 0.2 µm PES capsule filters from Millipure for filtration. Filter areas/sizes and volume of solution to be discarded (Flush volume) are recommended in table below.

TABLE :5 FILTER DETAILS

Filter Details	
Batch Size	**Filter area recommended (m^2)**
≤50L	0.35
≤125 L	0.69

- Check for filter integrity test of product filters before and after filtration.
  - Pre-integrity: Bubble point Test value with water ≥ 3200 mbar (≥46.41 psi)
  - Post-integrity: Bubble point Test value with Product ≥ 1900 mbar (≥ 27.55 psi)
- Maintain a minimum stirring speed of 250 ± 50 rpm in order to dissolve the raw materials during compounding process.

KEY PROCESSING EQUIPMENT

- Weighing balance
- Dispensing booth
- Vial washing machine
- HPHV Steam sterilizer
- Tunnel sterilizer
- pH meter
- vial filling,bunging and sealing machine

- Inspection machine/table
- Labeling machine
- Filter integrity tester
- Class 100 laminar air flow
- Stainless steel grade 316L compounding reactor vessel of suitable capacity
- Stainless steel grade 316L filling tanks of suitable capacity
- Stainless steel grade 316 L pressure vessel (makeup vessel) of suitable capacity.

UTILITIES :

- Purified water
- Sterile compressed air filtere with online 0.22µ Filter
- Sterile nitrogen (99.97%) supply with online 0.22µ Filter
- Water for injection

BRIEF MANUFACTURING PROCESS:

- **PREPARATION OF 1N SODIUM HYDROXIDE SOLUTION:** Add 40.0 g of Sodium Hydroxide in approximately 800 mL of Water for Injection (20°C - 30°C) and stir until a clear, colorless solution observed. Cool the solution to 20°C - 30°C. Make up the volume to 1000 mL with Water for Injection (20°C - 30°C), mix well.
- **PREPARATION OF 1N HYDROCHLORIC ACID SOLUTION:** Add 101.15 g (85.0 mL) of Hydrochloric Acid in approximately 800 mL of Water for Injection (20°C - 30°C) and mix until a clear solution observed. Cool the solution to 20°C - 30°C. Make up the volume to 1000 mL with Water for Injection (cool the solution to 20°C - 30°C), mix well.

Bulk solution preparation

1. Collect the water for injection at temperature not less than 80°C, which is approximately 100% of the total batch size (Weight equivalent to 100% batch size based on density of 0.997 g/mL) in SS316L reactor of suitable capacity. Bring down the temperature of the water for Injection in the Compounding vessel to 25°C ± 5°C by circulating chilled water in the reactor jacket. Check the pH of the water for injection (Limit 5.0 to 7.0). The compounding lessthan 2 ppm by Nitrogen bubbling.
2. Transfer Approximately 30% of water for injection (Weight equivalent to 30% of batch size based on density of 0.997 g/mL) to a suitable stainless steel vessel required for rinsing and final volume make up.
3. Add weighed quantity of Sodium Chloride USP to the compounding vessel and stir for not less than 10 minutes or until a clear solution is observed.
4. Add weighed quantity of Ketorolac Tromethamine USP to the compounding vessel and rinse the bag with 3 times with approx 100 mL water for injection and add the rinse to the compounding vessel. Continue stir for not less than 15 minutes or till solution becomes clear.
5. To step 4 ,Add calculated and weighed quantity of Alcohol USP and stir for not less than 10 mins or until a clear solution observed.
6. Check and adjust the pH of the step 5 solution to target 7.4 ± 0.2 (Limit: pH 6.9 to 7.9) with 1N Sodium Hydroxide solution/1N Hydrochloric Acid solution and record the quantity used. Continue the stirring for not less than 10 minutes.
7. Check the pH of the step 8 solution [limit 7.2 to 7.6]; if required adjust the pH with 1N Sodium Hydroxide solution/1N Hydrochloric Acid solution to pH 7.4 ± 0.2 and record the quantity used. Continue the stirring for not less than 10 minutes.

8. Makeup the volume of step 9 to 95% of total batch size (based on wt/mL = 0.99 g/mL) with water for injection collected in step 2 stir for Not less than 10 minutes. Collect the sample and send the samples to AD /QC for pH and wt/mL.
9. Makeup the volume of step 10 to 100% of total batch size (based on result obtained from step 10) with water for injection collected in step 2 and stir for Not less than 20 minutes
10. Check the clarity and final pH of step 11 solution.

TABLE : 6 BULK SOLUTION ACCEPTANCE CRITERIA

Clarity	Should be clear
Ph	Between 6.9 and 7.9
Color	Slightly yellow in color solution

ASEPTIC FILTRATION

- After receiving AD / QC approval, filter the drug solution from step11 (from step 3 bulk solution preparation).
- Slowly pressurize the reactor to pass solution to filter. Once the product filled in the filter, hold the process for 10 min, 20 min and 30 min points. Each time points collect 50 mL sample for analysis.
- After 30 minutes hold slowly filter the solution through the filter of about 250 mL (as flush volume) in a sterile container. Submit the collected filter flush solution for analysis.
- Filter the remaining bulk through sterilized PES 0.2 µm, capsule filter from millipore using 1.0 to 2.0 kg/sq.cm pressure of 0.22 µm filtered nitrogen through filter and collect in to SS 316 L holding vessel.
- After filtration, perform post bubble point test with product for 0.2 µ filters as per SOP.

ASEPTIC FILLING

- Ensure that all laminar air flows are running within the specified limits.
- Transfer the sterilized machine parts to filling room and assemble the parts as per sop.
- Transfer the sterilized bulk solution collected in filling room as per sop.
- Set required fill volume of 1.15 ml (Limit :1.10 ml to 1.20 ml) set the nitrogen pressure for filling at 0.25 to 1 bar .
- Start the filling operation as per filling and sealing machne SOP's.

NOTE:System flush (System should be flushed with the bulk solution about 400 ml,this solution will be used for fill volume adjustment).

TABLE : 7 Calculation for Recommended fill volume:

Fill volume (mL)	USP Limit (mL)	Lower Limit (mL)	Set Limit (mL)	Upper Limit (mL)
1.15	0.20	1.10	1.15	1.20

Note: system flush to be established during production batch.

Next process:

- **STOPPERING OPERATIONS**

  Perform stoppering operations as per SOP.

- **SEALING OPERATIONS**

  Perform sealing operations as per SOP.

  Leak testing operation is carried out as per the leak testing operation sop

- **TERMINAL STERILIZATION**

Terminal sterilization of filled vials is carried out at 121 ˚c for 15 mins as per validated pattern based perform.

- **SAMPLING FOR ANALYSIS**

  Based upon product some requirement studies have that QC/MICROLABOREATORY

- **RECONCILATION**

  Each stages after completion of the process activity record the qty of vial,losses of solutions,etc..

- **YIELD CALCULATION**

  Losses on various stages of the process including manufacturing ,filtration ,filling ,inspection and inprocess checking will be finalized based on the process evaqluation batches.

- **FINISHED PRODUCT FOR ANALYSIS**

Send the samples for analysis to AD/QC as per Drug product Release specification.

- **VISUAL INSPECTION**

Carry out the visual inspection as per current approved plant SOP.

- **LABELING AND PACKING**

Label the product and pack the VIALS as per the current packing specifications/instructions.

OPHTHALMIC FILLING

Ketorolac Tromethamine Ophthalmic Solution 0.5% (5 mg/mL) (5 mL fill)

TABLE : 8 RAW MATERIAL INFORMATION:

S. No	Ingredients	Functional Category
1	Ketorolac Tromethamine USP	Active Pharmaceutical ingredient
2	Benzalkonium chloride (50% aqueous solution) USP – NF	Preservative
3	Disodium Edetate - USP/BP/EP	Chelating agent
4	Sodium chloride USP	Tonicity agent
5	Octoxynol 40 (70 % solution) (TRITON X-405 SOLUTION)	Surfactant
6	Sodium Hydroxide USP – NF	pH adjusting agent
7	Hydrochloric acid USP-NF	pH adjusting agent
8	Water for Injection USP/BP	Vehicle
9	Nitrogen USP-NF/BP^	Pharmaceutical aid

^: Used as process aid during bulk solution transferring.

PRODUCT SPECIFIC INSTRUCTIONS:

LABEL CLAIM:

Ketorolac Tromethamine USP……..… 0.5% (5 mg/mL)

Benzalkonium Chloride USP-NF …….. 0.01% (0.1 mg/mL)

TABLE : 9 **UNIT FORMULA:**

S. No.	Ingredients	Quantity/mL	Quantity/30.0 L***
1	Ketorolac Tromethamine USP	5.0 mg	150.0 g*
2	Benzalkonium chloride (50% aqueous solution) USP - NF	0.1 mg (0.2 mg)$	6.0 g$
3	Disodium Edetate - USP/BP/EP	1.0 mg	30.0 g
4	Sodium chloride USP	7.9 mg	237.0 g
5	Octoxynol 40 (70 % solution) (TRITON X-405 SOLUTION)	0.1 mg	3.0 g
6	Sodium Hydroxide USP – NF	q.s to adjust pH	40.0 g#
7	Hydrochloric acid USP-NF	q.s to adjust pH	101.15 g## (85.0 mL##)
8	Water for Injection USP/BP	q.s to 1 mL	q.s to 30.0 L
9	Nitrogen USP-NF/BP^	q.s	q.s

$ - Label claim of Benzalkonium chloride is 0.01% (0.1 mg/mL), For batches we use Benzalkonium chloride 50% aqueous solution 0.02% (0.2 mg/mL). Potency correction to be done at the time of dispensing.

#: To prepare 1 L solution of 1 N Sodium hydroxide.

##: To prepare 1 L solution of 1 N Hydrochloric acid.

Formula for calculation of standard quantity for Ketorolac Tromethamine USP:

$$\text{Qty/Batch (g)} = \text{Label Claim X Batch Size (L) X } \frac{100 \text{ X } 100}{\text{\% Assay on dried basis X (100-\%LOD)}}$$

Formula for calculation of standard quantity for Benzalkonium chloride USPNF:

$$\text{Qty/Batch (g)} = \frac{\text{Label Claim X Batch Size (L) X 100}}{\text{Assay on as is basis (or) 50\% whichever is lesser}}$$

STORAGE CONDITION:

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use.

PRODUCT SPECIFIC REQUIREMENTS:

- Stainless steel container of grade SS316L should be used for batch manufacturing and storage.
- Use 0.22 µm filtered Nitrogen gas during filtration.
- Throughout the manufacturing process (compounding, filtration, filling, nozzling and capping) maintain temperature 25˚C ± 5˚C.
- Use Sanipure BDF tubing from Saint-Gobain for filtration and filling operation.
- Static contact time with the tubing should not exceed 12 Hrs; the bulk solution which is in static contact with tube above 12 Hrs shall be discarded.
- Static contact time with the filter should not exceed 24 Hrs; the bulk solution which is in static contact with the filter above 24 Hrs shall be discarded.
- Product is light sensitive, protect from light.
- Sodium monochromatic light (yellow) shall be used during API dispensing, manufacturing, filtration, filling & packing of product.
- Total processing time is 48 Hrs (This is the time starting from the start of addition of API addition to end of Capping). Processing time for various stages is defined below.

TABLE : 10 PROCEDURE FOR HOLD TIME:

Stage		Recommended time
Total Bulk Solution Compounding time (from API addition)	:	NMT 12 Hrs
End of bulk solution compounding to end of the filtration	:	NMT 12 Hrs
Start of the filling to completion of filling and capping	:	NMT 24 Hrs

- Use 0.2 µm PES capsule filters from Sartorius for filtration. Filter areas/sizes and volume of solution to be discarded (Flush volume) are recommended in table below.

TABLE :11 DETAILS ABOUT FILTER

Filter Details		
Batch Size	Filter area recommended (m2)	Recommended Flush volume (L)
≤10L	0.01	0.07
≤30 L	0.03	0.23
≤80 L	0.10	0.77
≤200 L	0.20	1.53
≤250L	0.45	3.46

Note: The above filter size recommendation is not binding. The production team may change the size/surface area of the filter for a particular batch size at their discretion, however the total filter contact time should not exceed 24 Hr.

- Check for filter integrity test of product filters before and after filtration.
    - Pre-integrity: Bubble point Test value with water ≥ 3200 mbar (≥46.41 psi)
    - Post-integrity: Bubble point Test value with Product ≥ 1900 mbar (≥ 27.55 psi)
- Maintain a minimum stirring speed of 250 ± 50 rpm in order to dissolve the raw materials during compounding process.

KEY PROCESSING EQUIPMENT

- Weighing balance
- Dispensing booth
- Steam sterilizer
- pH meter
- Container filling, nozzling and capping machine
- Inspection machine/table
- Labeling machine
- Filter integrity tester
- Class 100 laminar air flow
- Stainless steel grade 316L compounding reactor vessel of suitable capacity
- Stainless steel grade 316L filling tanks of suitable capacity

- Stainless steel grade 316 L pressure vessel (makeup vessel) of suitable capacity

ENVIRONMENTAL CONDITIONS

- As per Plant SOP

BRIEF MANUFACTURING PROCESS:

❖ PREPARATION OF 1N SODIUM HYDROXIDE SOLUTION:

Add, 40.0 g of Sodium Hydroxide in approximately 800 mL of Water for Injection (20°C - 30°C) and stir until a clear, colorless solution observed. Cool the solution to 20°C - 30°C. Make up the volume to 1000 mL with Water for Injection (20°C - 30°C), mix well.

❖ PREPARATION OF 1N HYDROCHLORIC ACID SOLUTION:

Add, 101.15 g (85.0 mL) of Hydrochloric Acid in approximately 800 mL of Water for Injection (20°C - 30°C) and mix until a clear solution observed. Cool the solution to 20°C - 30°C. Make up the volume to 1000 mL with Water for Injection (cool the solution to 20°C - 30°C), mix well.

Bulk solution preparation

1. Collect the water for injection at temperature not less than 80°C, which is approximately 110% of the total batch size (Weight equivalent to 110% batch size based on density of 0.997 g/mL) in SS316L reactor of suitable capacity. Bring down the temperature of the water for Injection in the Compounding vessel to 25°C ± 5°C by circulating chilled water in the reactor jacket. Check the pH of the water for injection (Limit 5.0 to 7.0).
2. Transfer Approximately 30% of water for injection (Weight equivalent to 30% of batch size based on density of 0.997 g/mL) to a suitable stainless steel vessel required for rinsing and final volume make up.
3. Add weighed quantity of Disodium Edetate Dihydrate USP to Water for Injection in the compounding vessel collected at step 1 and mix for not less than 15 minutes or till solution becomes clear.
4. To step 3, add weighed quantity of Octoxynol 40 (70% solution). Rinse the bottle with 3 times with approx 100 mL water for injection from step 2 and add the rinse to the compounding vessel and stir for not less than 15 minutes or till solution becomes clear.
5. Add weighed quantity of Sodium Chloride USP to the compounding vessel of step 4 and stir for not less than 10 minutes or until a clear solution is observed.

6. Add weighed quantity of Benzalkonium Chloride USPNF to the compounding vessel of step 5. Rinse the bottle with 3 times with approx 100 mL water for injection from
7. step 2 and add the rinse to the compounding vessel and stir for not less than 15 minutes or until a clear solution is observed.
8. Check and adjust the pH of the step 6 solution to target pH 9.6 (Limit: 9.6 ± 0.2) with 1N Sodium Hydroxide solution/1N Hydrochloric Acid solution and record the quantity used. Continue the stirring for not less than 10 minutes.
9. Add weighed quantity of Ketorolac Tromethamine USP to the compounding vessel of step 7 and rinse the bag with 3 times with approx 100 mL water for injection from step 2 and add the rinse to the compounding vessel. Continue stir for not less than 15 minutes or till solution becomes clear.
10. Check the pH of the step 8 solution [limit 7.2 to 7.6]; if required adjust the pH with 1N Sodium Hydroxide solution/1N Hydrochloric Acid solution to pH 7.4 ± 0.2 and record the quantity used. Continue the stirring for not less than 10 minutes.
11. Makeup the volume of step 9 to 95% of total batch size (based on wt/mL = 0.99 g/mL) with water for injection collected in step 2 stir for Not less than 10 minutes. Collect the sample and send the samples to AD /QC for pH and wt/mL.
12. Makeup the volume of step 10 to 100% of total batch size (based on result obtained from step 10) with water for injection collected in step 2 and stir for Not less than 20 minutes

TABLE : 12 ACCEPTANCE CRITERIA

Check the clarity and final pH of step 11 solution.

Clarity	Should be clear
Ph	Between 7.2 and 7.6

ASEPTIC FILTRATION

- After receiving AD / QC approval, filter the drug solution from 6.3.11 (from 6.3 bulk solution preparation).
- Slowly pressurize the reactor to pass solution to filter. Once the product filled in the filter, hold the process for 10 min, 20 min and 30 min points. Each time points collect 50 mL sample for analysis.
- After 30 minutes hold slowly filter the solution through the filter of about 250 mL (as flush volume) in a sterile container. Submit the collected filter flush solution for analysis.
- Filter the remaining bulk through sterilized PES 0.2 µm, capsule filter from Sartorius using 1.0 to 2.0 kg/sq.cm pressure of 0.22 µm filtered nitrogen through filter and collect in to SS 316 L holding vessel.
- After filtration, perform post bubble point test with product for 0.2 µ filters as per SOP.

ASEPTIC FILLING

- Slowly pressurize the holding vessel to pass solution to filter in filling line. Once the product filled in the filter, hold the process for 10 min, 20 min and 30 min points. Each time points collect 50 mL sample for analysis.
- After 30 minutes hold slowly filter the solution through the filter of about 250 mL (as flush volume) in a sterile container. Submit the collected filter flush solution for analysis.
- Set the required fill volume of 5.35 mL [Limit: 5.3 mL to 5.4 mL], and fill the remaining bulk solution from holding vessel in 10 mL 3 piece sterile containers.

TABLE : 13 Calculation for Recommended fill volume:

Fill volume (mL)	USP Limit (mL)	Standard fill volume (mL)	Filling pump accuracy (mL)	Lower Limit (mL)	Set Limit (mL)	Upper Limit (mL)
5.0	0.30	5.30	0.05	5.30	5.35	5.40

Note: system flush to be established during production batch.

NOZZLING AND CAPPING OPERATIONS

Perform nozzling and capping operations as per SOP.

FINISHED PRODUCT FOR ANALYSIS

Send the samples for analysis to AD/QC as per Drug product Release specification.

VISUAL INSPECTION

Carry out the visual inspection as per current approved plant SOP.

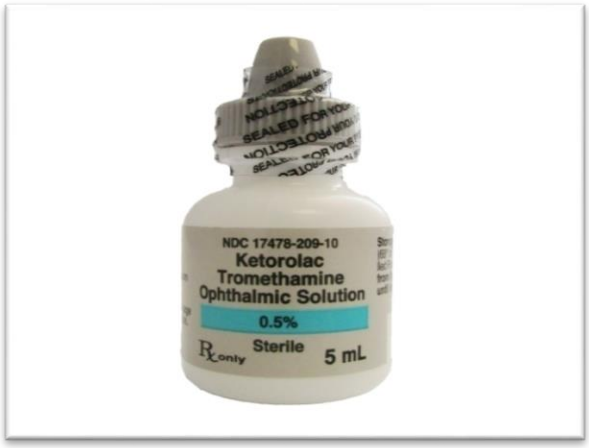
LABELING AND PACKING

Label the product and pack the bottles as per the current packing specifications/instructions.

INGREDIENTS OF INJECTION VS OPHTHALMIC

TABLE : 14 RAW MATERIALS

s.no	Injectable	Ophthalmic
1.	Ketorolac Tromethamine USP	Ketorolac Tromethamine USP
2.	Sodium chloride USP	Benzalkonium chloride (50% aqueous solution) USP – NF
3.	Alcohol USP	Disodium Edetate - USP/BP/EP
4.	Sodium Hydroxide USP – NF	Sodium chloride USP
5.	Hydrochloric acid USP-NF	Octoxynol 40 (70 % solution) (TRITON X-405 SOLUTION)
6.	Water for Injection USP/BP	Sodium Hydroxide USP – NF
7.	Nitrogen BP	Hydrochloric acid USP-NF
8.		Water for Injection USP/BP
9.		Nitrogen USP-NF/BP^
	Ex: **Toradol IV /IM**	Ex:**ACULAR ®**



VIAL **DROPPER**

ketorolac systemic:

Brand names: **Toradol, Toradol IM, Sprix, Toradol IV/IM**

Drug class(es): **Nonsteroidal anti-inflammatory drugs**

Ketorolac systemic is used in the treatment of:**Pain**,**Postoperative Pain**

ketorolac ophthalmic:

Brand names: **Acular, Acuvail, Acular LS, Acular PF**

Drug class(es): **ophthalmic anti-inflammatory agents**

Ketorolac ophthalmic is used in the treatment of:

Corneal Refractive Surgery

Postoperative Ocular Inflammation

Seasonal Allergic Conjunctivitis:cyclopentolate/ketorolac/phenylephrine/tropicamide ophthalmic

Dexamethasone/ketorolac/moxifloxacin systemic

Drug class(es): quinolones

ketorolac/phenylephrine ophthalmic Brand names: **Omidria**

Drug class(es): **ophthalmic surgical agents**

Ketorolac/phenylephrine ophthalmic is used in the treatment of:

Ophthalmic Surgery,**Postoperative Ocular Inflammation**

Drug	Ketorolac Tromethamine USP

ketorolac/phenylephrine/proparacaine/tropicamide

Sodium chloride USP	Tonicity agent	Preservative	Benzalkonium chloride (50% aqueous solution) USP – NF
Alcohol USP	Preservative	Chelating agent	Disodium Edetate - USP/BP/EP
Sodium Hydroxide USP – NF	pH adjusting agent	Tonicity agent	Sodium chloride USP
Hydrochloric acid USP-NF	pH adjusting agent	Surfactant	Octoxynol 40 (70 % solution) (TRITON X-405 SOLUTION)
Water for Injection USP/BP	Vehicle	pH adjusting agent	Sodium Hydroxide USP – NF
Nitrogen BP	Processing aid	pH adjusting agent	Hydrochloric acid USP-NF
Ketorolac Tromethamine USP	Active Pharmaceutical ingredient	Vehicle	Water for Injection USP/BP
		Pharmaceutical aid	Nitrogen USP-NF/BP
INJECTION SOLUTION		OPHTHALMIC SOLUTION	

6. Comparative anlaysis trial batches with R&D trial with admixture:

This both comparative studies depends upon the pharmaceutical ingredients like Chealting agent and tonicity to create or formulate the another form of preparation .The injectable formulation have same like ophthalmic preparation but ophthaqlmic formulation have some additional pharmaceutical ingredients to improve effective of drug and surface contact for particular drug.

The admixture study was performed to evaluate the compatibility of **Ketorolac Tromethamine injection USP,15mg/ml-1 ml** filled in 1 mL vial with the diluent 5% Dextrose injection.

- US **Reference Standard (RS) vs Exhibit batch results**

TABLE : 15 **Excipient studies**

S.NO	EXCIPIENTS	RATIO	DESCRIPTION	
			INITIAL	FINAL
1	API-**Polyethylene Glycol**	1:1	Clear, colorless or slightly yellow-colored, viscous liquid	Clear, colorless or slightly yellow-colored, viscous liquid
2	API-Ethanol	1:1	Alcohol is clear, colorless, mobile and volatile liquid with a slight, characteristic odor and burningtaste	Alcohol is clear, colorless, mobile and volatile liquid with a slight, characteristic odor and burningtaste
3	API –Lechitin	1:1	color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity.	color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity.
4	API- Propylene glycol	1:1	Propylene glycol is a clear, colorless, viscous, practically odorless liquid	Propylene glycol is a clear, colorless, viscous, practically odorless liquid

DISCUSSION :Preliminary studies were carried between drug and excipients.

The result shows no change.This confirms there is no physical interactionbetween drug and excipients.

Ketorolac Tromethamine injection USP,15mg/ml- 1 ml vial, BATCH NO: E0010119

TABLE : 16 SOLUTION 1 AND SOLUTION 2

S.No	Parameter	Acceptance criteria	Results obtained			
			SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag)		SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag)	
Analytical Reference Number			**QC/ST/19/0996**			
Time point			**Initial**		**Initial**	
			0 Hour	**24 Hours**	**0 Hour**	**24 Hours**
1.	Description	clearSlightly yellow in color solution, free from visible particles.	clearSlightly yellow in color solution, free from visible particles.	clearSlightly yellow in color solution, free from visible particles.	clearSlightly yellow in color solution, free from visible particles.	clearSlightly yellow in color solution, free from visible particles..
2.	Ph	Between 6.9 and 7.9	7.24	7.27	7.57	7.51
3.	Assay by HPLC	90.0% to 110.0%	94.4%	95.2%	97.2%	97.1%
4.	Related substances by HPLC	a) Ferrocyanide Not more than 0.04%	Not Detected	Not Detected	Not Detected	Not Detected
		b)Any unspecifiedImpurity Not morethan 0.2%	Not Detected	Not Detected	Not Detected	Not Detected
		c)Total impurities Not morethan 1.0%	Not Detected	Not Detected	Not Detected	Not Detected

Ketorolac Tromethamine injection USP,15mg/ml-1 ml vial,

TABLE : 17 BATCH NO: E0020119 IN SOLUTION 1 AND SOLUTION 2

S.No.	Parameter	Acceptance criteria	Results obtained			
			SOLUTION 1 (1 Vial in 250 mL 5% Dextrose infusion bag)		SOLUTION 2 (1 Vial in 1000mL 5% Dextrose infusion bag)	
Analytical Reference Number			QC/ST/19/0997			
Time point			Initial		Initial	
			0 Hour	24 Hours	0 Hour	24 Hours
1.	Description	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles..	Clear Slightly yellow in color solution, free from visible particles.
2.	Ph	Between 6.9 and 7.9	7.35	7.24	7.56	7.54
3.	Assay by HPLC	90.0% to 110.0%	99.5%	97.1%	100.9%	100.8%
4.	Related substances by HPLC	Ferrocyanide Not more than 0.04%	Not Detected	Not Detected	Not Detected	Not Detected
		Any unspecified Impurity Not more than 0.2%	Not Detected	Not Detected	Not Detected	Not Detected
		Total impuri Not more than 1.0%ties	Not Detected	Not Detected	Not Detected	Not Detected

COMPARISION OF TRIAL STUDY RESULTS OF RS VS GENERIC DRUG

TABLE: 18 PRODUCT EXHIBIT BATCHES IN SOLUTION 1

S.NO	Parameter	Acceptance criteria		Results obtained					
				Generic product Exhibit batches				RS- sample	
Batch Number				B.No: E0010119		B.No: E0020119		390108F (ketorolac)	
AR.Number				QC/ST/19/0996		QC/ST/19/0997		QC/ST/19/0999	
				0 Hour	24 Hours	0 Hour	24 Hours	0 Hour	24 Hours
1.	Description	Clear ,Slightly yellow in color solution, free from visible particles.		Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles..	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles.	Clear Slightly yellow in color solution, free from visible particles..
2.	Ph	Between 6.9 and 7.9		7.24	7.27	7.35	7.24	7.56	7.61
3.	Assay by HPLC	90.0% to 110.0%		94.4%	95.2%	99.5%	97.1%	103.9%	104.1%
4.	Related substances by HPLC	Ferrocyanide	Not more than 0.04%	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
		Any unspecified impurity	Not more than 0.2%	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

TABLE :19 Finished Product test results:

TEST	SPECIFICATION	E0010119	E0020119
Description	A Clear Slightly yellow in color solution, free from visible particles	A Clear Slightly yellow in color solution, free from visible particles	A Clear Slightly yellow in color solution, free from visible particles
i) By HPLC DAD/UV	The Retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay	The Retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay	The Retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the Assay
ii) By HPLC DAD	The UV spectrum of the ketorolac tromethamine peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay	The UV spectrum of the ketorolac tromethamine peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay	The UV spectrum of the ketorolac tromethamine peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay
Each 1mL contains ketorolac tromethaminein mg % Labelled Amount	12.5 to 18.5 mg/1mL 93.0 to 107.0%	15.112mg/1mL (99.2%)	15.514mg/2mL (99.0%)
Ph	6.9 to 7.9	7.32	7.30
Bacterial Endotoxins Test (USP Endotoxin Units/mg of ketorolac tromethamine)	Not more than 8.3 Eu/mg	Less than 1.038 Eu/mg	Less than 1.038 Eu/mg
Sterility	Should be Sterile	Sterile	Sterile

7. RESULT

TABLE :20 TRIAL 1 & TRIAL 2

Ingredient	Actual	Observation	
		T0011118	T0021118
Ph	6.9 to 7.9	6.95	7.12
Conductivity	NMT 1.3	0.81	0.76
TOC	550 ppb	33	37.8
pH of WFI after purging with carbon – dioxide gas	4.00	4.03	4.04

Discussion:

Initially taken trial its not achieved the pH,conductivity, Because alcohol and Hydrochloride,API addition stirring time also less .

EXHIBIT BATCHES EXECUTION AND ANALYSIS REPORT

TABLE :21 BULK COMPOUNDING PROCESS

Ingredient	Actual	Observation	
		E0010119	E0020119
pH	6.9 to 7.9	7.35	7.37
Conductivity	NMT 1.3	0.88	0.91
TOC	550 ppb	33	37.8
pH of WFI after purging with carbon – dioxide gas	4.00	4.03	4.04

TABLE :22 Inprocess Bulk solution test results:

Test	spec limit	Observation	
		E0010119	E0020119
Ph	6.9 to 7.9	7.25	7.31
Weight/mL	0.9971-1.0376	1.002 g/Ml	0.9987 g/mL
Assay (%w/w)	95.0 to 105.0	99.1%	98.4%

Discussion: Inprocess Bulk solution test results of all the 2 batches meets the acceptance criteria.

Bulk Solution Test Results

TABLE :23

Test	Specification		E0010119			E0020119	
			TOP	BOTTOM		TOP	BOTTOM
10 minutes Sample							
Description	A Clear, Slightly yellow in color solution, free from visible particles..	NA	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles.	NA	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles
pH	Between 6.9 and 7.9		7.24	7.24		7.35	7.35
Assay	90.0 to 110.0 12.5 to 18.5 mg/1mL		94.4%	94.4%		99.5%	99.5%
wt/Ml	Report the resulted value		1.002 gm/Ml	1.001 gm/mL		1.007 gm/mL	1.007 gm/mL

NA: Not applicable

Filtration:

Solution was filtered aseptically using sterilized 0.2 µ filter connected under the laminar flow in filtration room using Carbon – dioxide as a processing gas.

TABLE :24 Filtration pressure limit and observation are provided below

Batch No	Filtration pressure Limit	Observation
E0010119	1.0 to 2.0 Kg/ sq. cm	1.0 kg/sq.cm
E0020119	1.0 to 2.0 Kg/ sq. cm	1.0 kg/sq.cm

Bulk solution testing after passing through 0.2µ filter before final filtration:

Sample for analysis was collected at end of 1st filtration. The results of the analysis samples are presented below. **TABLE :25**

TEST	Specification	Batch Numbers	
		E0010119	E0020119
Bioburden	Not more than 10 cfu/100 mL	Nill cfu/100 mL	Nill cfu/100 mL
Bacterial Endotoxins Test (USP Endotoxin Units/mg of ketorolac tromethamine)	Not more than 8.3 EU/mg	Less than 1.038 EU/mg	Less than 1.038 EU/mg

Filling and Sealing:

The items required for filling have been washed & sterilized as per the Filling BMR and respective SOPs.

The parameters for washing, sterilization of vials were set as per the Filling BMR and respective SOPs.

System Flush Study:

System flush study was performed to clear and condition the tubing, and filling line components.

System Flush Study Results

TABLE :26 System Flush Samples of 1, 2, 3 & 4 strokes 32 vials samples

Test	Specification	E0010119	E0020119
Description	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles
Ph	Between 6.9 and 7.9	7.28	7.32
Assay Each 1mL contains ketorlolac tromethamine in mg % Labeled amount	93.0 to 107.0 % 12.5 to 15.5 mg/mL	98.2% 14.62 mg/mL	98.1% 14.47 mg/mL

TABLE :27 System Flush Samples of 5, 6, 7 & 8 strokes 32 vials sample

Test	Specification	E0010119	E0020119
Description	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles
Ph	Between 6.9 and 7.9	7.27	7.34
Assay Each 1mL contains ketorolac tromethamine in mg % Labeled amount	93.0 to 107.0 % 12.5 to 15.5 mg/mL	98.2% 14.72 mg/mL	98.1% 14.57 mg/mL

TABLE :28 **9, 10, 11 & 12 strokes 32 vials samples**

Test	Specification	E0010119	E0020119
Description	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles	A Clear, Slightly yellow in color solution, free from visible particles
pH	Between 6.9 and 7.9	7.275	7.33
Assay Each 1mL contains ketorolac tromethamine in mg % Labeled Amount	93.0 to 107.0 % 12.5 to 15.5 mg/mL	98.2% 14.67 mg/mL	98.1% 14.52 mg/mL

Remarks: Results obtained on collected system flush samples were in line with the set In process specification, indicating that the flush volume of solution required to condition the filling line components after production line set up volume of approximately 120 mL is sufficient to condition the system to be within the specified limits.

Product uniformity at the beginning, middle and end of filling:

During the filling (Batch No. E0010119, E0020119) samples were collected at beginning, middle and end of filling to evaluate the product uniformity throughout the filling process. Product uniformity test results at the beginning, middle and end of filling.

VISUAL INSPECTION AFTER SEALING:

After completion of sealing submission batches samples (Batch No. E0010119, E0020119) were subjected to 100% manual Visual inspection and inspected good quantities were again subjected to AQL as described in the Packing Batch Production and Control Record (BMR) and found within the acceptance criteria.

Details of the visual inspection are presented

TABLE :29 Details of Visual Inspection

Description	E0010119	E0020119
Total units taken for Visual inspection	83,798	84,018
Rejects during Visual inspection	1215	1658
Good qty. transferred to Packing	82,583	82,360

TABLE :30 Product Yield at various stages

S. No.	Description	E0010119	E0020119
1	%Yield after compounding	96.22 %	95.22 %
2	% Yield after Filtration	97.22 %	97.22 %
3	Batch yield	96.37 %	96.62%
4	Packing yield	94.97%	94.71%

Finished Product Sampling

- After completion of filling and sealing vials are collected for microbial testing
- chemical testing as per finished product specification

8. DISCUSSION

- Pharmaceutical manufacturing occurs in two general steps. First,firms convert raw materials into APIs. Then, firms create final formulations by mixing APIs and excipients (other non-active ingredients),pressing the mixture into tablets, or filling capsules or preparing solutions, and then packaging the product for the consumer market.
- For the purposes of this project, final formulations will refer to the second stage of pharmaceutical manufacturing and not the entire process.
- Active Pharmaceutical Ingredients (API) of good quality are core to the manufacturing of effective and safe essential drugs. The price of APIs is the main cost driver for manufacturing.And , Discussed drug profile of Ketorolac tromethamine and it industrial method of preparation and evaluation and storage **,(LIQUID: INJECTION VS OPHTHALMIC)**
- Injection are sterile solution or suspensions of drugs in aqueous or oily vehicle meant for introduction into the body by means of an injectable needle under or through one or more layers of skin or mucous membrane.
- And ,Addition of pharmaceutical ingredients it can change the formulation and administration of drug .
- Injections should be sterile ,isotonic and free from foreign particles,much as dust ,fibres
- Tonicity is a measure of effective osmolarity in cell biology. Osmolarity and osmolarity are properties of a particular solution, independent of any membrane. Osmolarity is a concentration scale to express the total concentration of solute particles and is directly related to any of the four colligative properties.
- It is derived from molality by factoring in the dissociation of electrolytic solutes. Tonicity is a property of a solution in reference to a particular membrane, and is equal to the sum of the concentrations of the solutes which have the capacity to exert an osmotic force across the membrane. Tonicity depends on solute permeability. The permeable solutes do not affect tonicity.

- Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids.
- This both comparative studies depends upon the pharmaceutical ingredients like Chealting agent and tonicity to create or formulate the another form of preparation .The injectable formulation have same like ophthalmic preparation but ophthaqlmic formulation have some additional pharmaceutical ingredients to improve effective of drug and surface contact for particular drug.
- Discussion of the manufacturing methods and master formula record instruction and they preparation,procedures,Activity how to handle the equipment ,Dispensing,Compounding,sterilization,Filling ,Terminal sterilization,Visual Inspection ,Packing,Product and percentage yield .

9.CONCLUSION

- This Project of comparative studies of injectable and ophthalmic industrial based preparation Drug:Ketorolac tromethamine. And they are procedure of dispensing ,compounding,sterilization,filling,storage ,labelling .
- Even though, these results have to be additionally brand drug toradol vs acular evaluate and compare the both brands method of preparation,dose,dosage ,different from general of preparation.
- And ,Addition of pharmaceutical ingredients can changes the formulation and administration of drug through the body.
- This studies not performed till any research reveal its role in further research they will reduce the side effect,and easily they will know the method of preparation ketorolac tromethamine in industrial preparation. which help,it opens up new research areas. Also, explore the Drug responsible for these therapeutic effects, study the mechanism of its action.

RS(REFERENCE STANDARD) and EXHIBIT BATCH

- study was performed by exhibit batch samples of **Ketorolac Tromethamine injection USP,15mg/ml-1 ml vial** and RS Ketorolac samples with 5% w/v Dextrose injection diluents present in 250 mL and 1000 mL infusion bags, accordingly physical and chemical test parameters were evaluated.

- Initial time point Admixed samples in 5% w/v Dextrose injection 250 mL and 1000 mL infusion bag, are analysed at 0 hrs and 24 hrs after dilution for the test parameter Description, pH, Assay and Related Substances and the results are found within the acceptance criteria of specification.

- Based on the obtained results, it is confirmed that the admixed generic product is stable for 24 hours, after admixing with 5% Dextrose injection in 250 mL infusion bag and 1000 mL

infusion bag.

- The results obtained for admixture study of RS -Ketorolac injection batch Number: 890108F were compared with the results as obtained for Trial study of generic product exhibit batches for **Ketorolac Tromethamine injection USP,15mg/ml-1 ml vial**, Batch Numbers E0010119, E0020119 and were found to be comparable.

BATCH

- All in - process samples such as fill volume and quality assurance checks (sealing & visual inspection) met the in-process specifications. Submission batches were tested according to the current version of the specifications.
- Samples were collected throughout the manufacturing process and physical, chemical & microbiological parameters were analyzed as per Submission batch Record and Submissio batch Sampling plan.
- **Bulk Solution testing:** Top, bottom and Pooled bulk solution samples (Batch No. E0010119, E0020119) were taken after batch volume make up (and subsequent 10 & 15 minutes mixing) and subjected to analyses. All evaluated parameters were in compliance with the bulk solution specification.
- **Filter Integrity:** During the manufacturing of submission batches (Batch No. E0010119, E0020119) pre-filtration (using WFI) and post-filtration (using product solution) integrity of the filters were tested. In submission batches results of pre and post-filtration filter integrity testing complied with the set limits of NLT 46.4 PSI for Water bubble point and NLT 46.4 PSI for product solution bubble point pressure test, demonstrating the integrity of the 0.2 µm PES capsule filter .

- **System flush study (Stroke Samples):**

  System flush study was performed and established in submission batch (Batch No E0010119, E0020119).Results obtained on collected system flush samples were in line wit the specification limits.

- **Product uniformity at the beginning, middle and end of filling:**

  During the manufacturing of submission batches (Batch No. E0010119, E0020119) samples were collected at beginning, middle and end of filling to evaluate the product uniformity throughout the filling process. Results obtained were complied with finished

product release specification, proving the uniformity of the product throughout the filling process.

- Concluded with some Batches yield and they are results.

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