"FORMULATION, DEVELOPMENT AND EVALUATION OF KETOROLAC TROMETHAMINE FILM COATED TABLETS"

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DHARMAPURI, TAMILNADU

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CERTIFICATE

This is to certify that the dissertation entitled

"**FORMULATION, DEVELOPMENT AND EVALUATION OF KETOROLAC TROMETHAMINE FILM COATED TABLETS"**

Constitutes the original work carried out by

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Under my guidance and supervision

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I.INTRODUCTION[2-8]

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency.[1] Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs. Greater flexibility in dosage form design, ease of production and low cost.

Drugs are administered by the oral route in a variety of pharmaceutical dosage forms. The most popular are tablets, capsules, suspensions, various pharmaceutical solutions. [2, 3] Among the drugs that are administered orally, solid dosage form represent the preferred class of product. They are versatile, flexible in dosage strength, relatively stable, present lesser problem in formulation and packaging and it is convenient to manufactured store handle and use. Solid dosage form provides best protection to the drug against light, temperature, humidity, oxygen, and stress during transportation. Of the two oral dosages form i.e. tablets & capsules. Tablets are in wide use.

1.1 TABLETS: [4]

Tablets may be defined as solid pharmaceutical dosage forms containing medicament or medicaments with or without suitable excipients & prepared either by compression or moulding.

Advantages of tablets:

- They are the lightest and the most compact of all oral dosage form.
- Tablets are easy to packaging and transportation.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- Their cost is lowest of all oral dosage forms.
- Tablets are the unit dose form having greatest capabilities of all oral dosage form for the dose precision and least content variability.
- Tablets are better suited to large-scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical, microbiological stability of all oral forms.

Disadvantages of tablets:

- Drugs with poor wetting slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT, or any combination of these features difficult to formulate.
- Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low-density character.

- Bitter tasting drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression. [4]

1.1.2 Classification of tablets: [5]

Based on the route administration or the function the tablets are classified as follows.

1. **Tablets ingested orally:**
    a) Compressed tablets.
    b) Multiple compressed tablet.
        i. Layered tablet
        ii. Compression coated tablet
    a) Repeat action tablet.
    b) Delayed action and enteric coated tablet.
    c) Sugar and chocolate coated tablet.
    d) Film coated tablet.
    e) Chewable tablet.
2. **Tablets used in the oral cavity**:
    a) Buccal tablet.
    b) Sublingual tablet.
    c) Troches and lozenges.
    d) Dental cones.
3. **Tablets administered by other routes:**
    a) Implantation tablet.
    b) Vaginal tablets.

4. **Tablets used to prepare solution:**
    a) Effervescent tablet.
    b) Dispensing tablet.
    c) Hypodermic tablet.
    d) Tablets triturate.

1.2. FORMULATION OF TABLETS: [6,7,8]

1. Diluents:

Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet filler include lactose, starch, dibasic calcium phosphate and microcrystalline cellulose, chewable tablets often contain sucrose, mannital, sorbitol as a filter, where the amount of active ingredients is small the overall tableting properties are in large measure determined by the filler. Because of problems encountered with bio availability of hydrophobic drug of low water solubility water soluble are used as fillers for these tablets.

2. Binders:

It gives adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They added to the cohesive strength already available in the diluents while binders may be added dry. They are more effective when added out of solution, common binders include acacia, gelatin, sucrose, povidone, methyl cellulose, CMC, hydrolyzed stated pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

3. Disintegrating agent:

It serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegration agent is starch, chemically modified starch and cellulose, aliginic acid, microcrystalline cellulose and cross linked povidone, are also used for tablet purposed effervescent mixtures are used in soluble tablet system as disintegrating agents. The concentration of the disintegrating agents, methods of addition and degree of compaction play a role of effectiveness. [5]

4. Lubricants:

They reduce friction during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies & punches. Metallic stearates, stearic acid, hydrogenised vegetable oils, and talc are used as lubricants because of the nature of this friction, most lubricant are hydrophobic and such tend to reduce and rates of tablet disintegrator and dissolution. Consequently, excessive concentration of lubricant should be avoided. SLS salts have been used as soluble lubricants but such agents generally do not posses optimal lubricating properties and comparatively high concentrations are usually required.

5. Glidants:

It is used to improve powder fluidity and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silica.

6. Colorants:

Colorants are often added to tablet formulation for esthetic value or for product identification. Most dyes are photosensitive and they fade when

exposed to light. The federal food & drug administration regulates colorants employed in drugs.

7. Flavouring agents:

These substances are added to impart flavour to lozenges tablets, chewable tablets, etc. flavouring agents are general nature, therefore they must be sprayed over the granulation, compression, e.g. fruit flavours and volatile oils.

8. Sweetening agents:

These substances are added to formulation to improve the and make them sweet. These agents are used in lozenges tablets, etc. some of the common sweetening agents like sucrose and lactose, [5] etc.

1.2.1 Tablet manufacturing methods: [7,8]

Tablets are manufactured by direct compression method. Dry granulation and wet granulation method.

1. The direct compression method.

A compressible vehicle is blended with the medicinal agent, and if necessary, with a lubricant and a disintegrant, and then the blend is compressed. Substances that are commonly used as directly compressible vehicles are: anhydrous lactose, dicalcium phosphate, granulated mannitol, microcrystalline cellulose, compressible sugar, starch, hydrolyzed starch, and a blend of sugar, invert sugar, starch and magnesium stearate.

2. The dry granulation method (slugging method).

The ingredients in the formulation are mixed and precompressed on heavy duty tablet machines. The slug which is formed is ground to a uniform size and compressed into the finished tablet.

3. The wet granulation method.

This method has more operational manipulations, and is more time-consuming than the other methods. The wet granulation method is not suitable for drugs which are thermolabile or hydrolyzable by the presence of water in the liquid binder.

Table no -1.

Processing steps commonly required in the various tablet granulation preparation technique.

S.No	Processing Step	Wet Granulation	Dry Granulation	Direct Compression
1.	Raw materials	X	X	X
2.	Weight	X	X	X
3.	Screen	X	X	X
4.	Mix	X	X	
5.	Compress (slug)		X	
6.	Wet mass	X		
7.	Mill	X		
8.	Dry	X		
9.	Mill	X	X	
10.	Mix	X	X	
11.	Compress	X	X	X

COMPRESSION AND COMPACTION:

The uniaxial compaction of pharmaceutical powder results in an anisotropic and heterogeneous tablet with variations in such properties as density, porosity and mechanical strength throughout the tablet . The tablet porosity of most materials is about 5 to to 30%. This means that even at relatively high compaction pressures, tablets will rarely be non-porous.

1.3. TABLET COATING: [6,7,8]

Tablet coating is done for the fulfillment of the following objective:

Objectives:

1. Protecting the drug from its surrounding environment with a view to improving stability.
2. To mask the taste, odor or color of the drug.
3. To control the release of the drug from the tablet.
4. To protect the drug from the gastric environment of the stomach with an acid resistance enteric coating.
5. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
6. To improve the pharmaceutical elegance by uses of special colors and contrasting printing. [7]

Types of tablet coating:

1. Sugar coating.
2. Film coating.

1.3.1. Sugar coating:

Sugar coating is regarded as the oldest method for tablet coating and involves the deposition from aqueous solution of coating based predominantly sucrose as a raw material.

The sugar coating process can be subdivided into six mains steps:

1. Sealing:

To prevent moisture penetration into the tablet core, a seal coat is applied.

2. Sub coating:

Is applied to round the edges and build up the tablet size.

3. Smoothing:

Smoothing usually can be accomplished by the application of sample syrup solution.

4. Color coating:

Involves the multiple application of syrup solution containing the requisite coloring matter.

5. Polishing:

Is achieved by applying mixtures of waxes to the tablets in a polishing pan.

6. Printing:

To identify sugar coated tablets often it is necessary to print them either before or after polishing.

1.3.2. Film coating:

Film coating technique reduces process time. Offer greater control over coating parameter and provide more opportunity for innovation.

History: [11]

Film coating was introduced in the year of 1950s to combat the short comings of the then predominant sugar coating process. Film coating has proved successful as a result of the many advantages.

Film coatings are an integral part of the dosage form development process. The process of film coating involves the application of a thin polymeric film onto the surface of a solid substrate. Though new uses of coatings are being continually developed. The following categories cover most current uses.

Advantages:

- Protection of drugs in the substrate from environmental factors such as light, moisture, and air, in order to improve chemical and physical stability.
- Modification of product appearance to enhance marketability and product identify or hide undesirable color changes of the substrate.
- Masking of unpleasant taste, texture or odor.
- Enhancement of swallowability.
- A mechanical barrier to the interaction of incompatible ingredients by coating one more of the individual ingredients.
- Improved handling during packaging operations by reducing dust formation.
- Controlled or modified release of drugs.
- Increased process efficiency and output.
- Increase flexibility in formation.
- Improved resistance to chipping of the coating.

Composition of film-coating formulations: [12]

A typical film-coating formulation includes a film-coating polymer, insoluble fillers such as pigments and opacifiers, soluble, insoluble fillers add color and protect from light. Pigments are usually aluminum lakes titanium dioxide. Soluble fillers are used to alter the permeability characteristics of the film-coating in order to modify taste or control release.

Film-coating solutions may be nonaqueous or aqueous, the nonaqueous solutions contain the following types of materials to provide the desired coating to the tablets.

- **A film former** capable of producing smooth, thin films reproducible under conventional coating conditions and applicable to variety of tablets shapes.
- **An alloying substances** providing water solubility or permeability to the film to ensure penetration by body fluids and therapeutic availability of the drugs.
- **A plasticizer** to produce flexibility and elasticity of the coating and thus provide durability.
- **A surfactant** to enhance spreadability of the film during application.
- **Opaquants and colorants** to make the appearance of the coated tablets handsome and distinctive.
- **Sweeteners, flavours, and aromas** to enhance the acceptability of the tablet to the patient.
- **A glossant** to provide luster to the tablets without a separates polishing operation.
- **A volatile solvent** to allow the spread of the other components over the tablets while allowing rapid evaporation to permits an effective yet speedy operation.

Equipments use in film coating: [13]

1) **G**ans-coata system.
2) Hi-coater system.
3) Dry coater system.
4) Standard coating pan.
5) Pellegrini pan.
6) Fluidized bed coater.
7) Automated coating system.

2.1 LITERATURE SURVEY. [49,50]

Bailey r..,(1997) et.al. Ketorolac tromethamine is a Non Steroidal Anti Inflammatory agent.A prospective, randomized, double-blind study was designed to evaluate the bleeding risk of ketorlac using adult tonsillectomy patients as the model. Patients were randomized into two groups receiving Meperidine (MP) (controls) or ketorolac tromethamine for the first postoperative day. Posttonsillectomy bleeding rates of 7% (3/43) in the MP group and 18.9% (7/37) in the ketorolac tromethamine group were demonstrated, but this difference was not statistically significant. This study and other reports in the literature support the manufacturer's warning that the use of ketorolac tromethamine is contraindicated in major surgery. Laryngoscope, Page.No. 166-9. [14]

Alex Macario., (2001)[37] et.al., The recent introduction of oral COX-2 selective NSAIDs with potential for perioperative use, and the ongoing development of intravenous formulations, stimulated a systemic review of efficacy, side effects, and regulatory issues related to ketorolac for management of postoperative analgesia.To examine the opioid dose sparing effect of ketorolac, we compiled published, randomized controlled trials of ketorolac versus placebo, with opioids given for breakthrough pain, published in English-language journals from 1986–2001. Odds ratios were computed to assess whether the use of ketorolac reduced the incidence of opioid side effects or improved the quality of analgesia. Ketorolac should be administered at the lowest dose necessary. Analgesics that provide effective

analgesia with minimal adverse effects are needed. Pain Med. Page No. 336-51. [15]

Ohmori shinji., (2004) et.al., The purpose of this study was to develop and evaluate the thin-layer sugarless coated tablets containing Vitamin C, Vitamin E, Vitamin B_2, calcium pantothenate, and L-cysteine. As a result of the formulation study, three coating layers, 2% Under Coating (UC), 38% Build-up Coating (BC), and 5% Syrup Coating (SC) were necessary for sufficient impact toughness, elegant appearance, and improvement of appearance stability after storage at 25°C/75% RH for 6 months under open conditions. International Journal Pharm. 2004, Page No. 459-69. [16]

Fiona McLeod., (2005**) et.al.,** Continuous subcutaneous infusion is a method frequently used in palliative care to manage patient symptoms. To deliver the dose required, and prevent subcutaneous sites from becoming inflamed and painful, the drug is often diluted in a solution, most commonly sterile water for injection or sodium chloride. The use of sterile water for injection has been recommended for cyclizine yet beyond this example there appears to be limited clinical direction regarding diluent selection. Inconsistency or lack of guidelines can be problematic if a diluent that may enhance the effectiveness of a drug compared with an alternate is not used because of lack of knowledge or guidance.National journal of polliative nursing. Page No.54-60. [17]

M.Cecilia Madamba.,(2007)et.al., Laser-Induced Breakdown Spectroscopy (LIBS) was evaluated as an early phase process analytical technology (PAT) tool for the rapid characterization of pharmaceutical tablet coatings. Model formulation tablets were coated with varying amounts (2%-4% w/ws) of red and yellow Opadry II, and a pulsed laser was used to sample at multiple sites across the tablet face. LIBS was able to successfully detect the emissions of Fe and Ti in the coated samples, and a proportional increase in signal with coating thickness was observed.Increasing photostability was observed with increasing levels of ferric oxide, providing a new understanding of the photoprotection mechanism in the coated formulation. Determination of levels of ferric oxide and coating thickness by LIBS demonstrated its utility as a good PAT tool for the determination of photoprotection of the drug, thereby enabling facile optimization of the coating process.AAPS PharmSciTech.2007.Article.No.103. [18]

Yang JH., **(2008) et.al.,** This study examined the effects of ketorolac tromethamine (KT) and baicalein (BE) on the levels of inflammatory factors in human synoviocytes. The fibroblast-like synoviocytes (FLS) cells were used to determine the possible regulatory effects of KT and BE (KTBE) on the levels of inflammatory factors in FLS cells. In addition, the levels of TNF-alpha, IL-6, and IL-1beta mRNA expression in FLS cells induced by a TNF-alpha and IL-1beta co-treatment were largely inhibited by a KTBE treatment. The level of FLS cells proliferation was increased by IL-1beta and TNF-alpha, and strongly inhibited by KTBE treatment. The production of oxygen species (ROS) was inhibited by KTBE in FLS cells. KTBE

appears to regulate the levels of mRNA that are important for regulating RA progression. Arch Pharm Res. Page No.1517-23. [19]

Nagarsenker MS., (2008) et.al., The objective of this investigation was to evaluate the effect of delivery strategies such as cyclodextrin complexation and liposomes on the topical delivery of ketorolac acid (KTRA) and ketorolac tromethamine. Ketorolac acid-hydroxypropyl-beta-cyclodextrin solid dispersions were prepared by kneading method. The study concluded that anti-inflammatory activity of the topically applied KTRA-CD gel was similar to that of the orally administered KTRM. Thus, cyclodextrin complexation enabled effective transdermal delivery of the ketorolac. AAPS PharmSciTech. Page No.1165-70. [20]

Moodie JE., **(2008) et.al.,** This study evaluated the safety and efficacy of multiple doses of intranasal ketorolac tromethamine (ketorolac) for postoperative pain. This was a double-blind, placebo-controlled study in patients undergoing major surgery who were randomized to receive intranasal ketorolac, 10 mg or 30 mg, or placebo every 8 h for 40 h. Among 127 patients enrolled, morphine use during the first 24 h was significantly less in patients receiving 30 mg of ketorolac (37.8 mg) than in the placebo group (56.5 mg) and in the 10-mg ketorolac group (54.3 mg. Other adverse events were reported with similar frequency in all treatment groups and most were considered unrelated to treatment. Anesth Analg. Page.No.2025-31. [21]

Chelladurai S., (2008) et.al., The present study was aimed at developing safe and effective bioadhesive gelling systems of ketorolac tromethamine, a potent non-narcotic analgesic with moderate anti-inflammatory activity for nasal systemic delivery. The anti-inflammatory activity and mucosal

irritancy of selected gels were also evaluated in rats and these results were compared with per oral, intraperitoneal and nasal solution administration of ketorolac tromethamine. All the prepared formulations gelled immediately at the nasal mucosal pH and showed longer contact time. Addition of hydroxypropyl methylcellulose (HPMC) in both chitosan and pectin based gelling systems increased the viscosity and gel strength. In vitro release characteristics were observed before and after accelerated studies. The developed gelling systems produced only mild to negligible irritant effect to nasal mucosae as compared to control group. Chem Pharm Bull (Tokyo).Page No.1596-1599. [22]

Hamilton SM., (2008) et.al., Myonecrosis due to group a streptococci (GAS) often develops at sites of nonpenetrating muscle injury, and Non Steroidal Anti-Inflammatory Drugs (NSAIDs) may increase the severity of these cryptic infections. We have previously shown that GAS bind to vimentin on injured skeletal muscles in vitro. The present study investigated whether vimentin up-regulation in injured muscles in vivo is associated with homing of circulating GAS to the injured site and whether NSAIDs facilitate this process. J Infect Dis. Page.No.1692-1698. [23]

Genç L., **(2008) et.al.,** Controlled release matrix tablets of ketorolac tromethamine (KT) were prepared by direct compression technique using cellulose derivatives as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), and carboxymethyl cellulose (CMC) in different concentrations (10-20%). The effect of polymer type and concentration was investigated on drug release by 2 or 3 factorial designs. Dissolution profiles of the formulations were plotted and evaluated kinetically. An increase in polymer content resulted with a slow release rate

of drug as was expected. According to the dissolution results, tablets prepared with HPMC + HEC + CMC (F1 and F8) were found to be the most suitable formulation for ketorolac. About 99.27% KT was released from F8 in 7 h.Drug Dev Ind Pharm. Page No.903-910. [24]

Alsarra IA., (2008) et.al., Ketorolac tromethamine a Non-Steroidal Anti-Inflammatory Drug, was formulated in buccoadhesive film to overcome the limitations in the currently available routes of administration which in sequence will increase patients' compliance. The film was formulated using aqueous solvents by means of two bioadhesive polymers namely: Hydroxyl Propyl Methyl Cellulose (HPMC) and Carbopol 934. The prepared film was subjected to investigations for its physical and mechanical properties, swelling behavior, in vitro bioadhesion, and in vitro, in situ and in vivo release. Results indicate that the concentration of KT in the oral cavity was maintained above 4.0 µg/ml for a period of at least 6 h. It is concluded from this clinical evaluation that ketorolac formulated into a buccoadhesive film is effective as a potent analgesic in dental and postoperative oral surgery in a single dose of 30 mg with minimal GI side effects. Pharmazie , Page.No.773-8. [25]

Schechter BA., (2008) et.al. Objective this manuscript will review the off-label application of this topical NSAID medication as a treatment for allergic conjunctivitis. Methods: An extensive medline search was undertaken to evaluate data on the use of ketorolac for allergic conjunctivitis. Data on both human and animal data were reviewed. Result of this study have demonstrated that ketorolac 0.4% has equivalent efficacy to ketorolac 0.5%. Several studies have demonstrated that ketorolac effectively treats allergic conjunctivitis. Ketorolac 0.4% is effective when used as either monotherapy

or as adjunct therapy to steroids. Expert Opin Drug Metab Toxicol. Page No.507-11.[26]

Ohmori S,.,et.al., The purpose of this study was to develop and evaluate the thin-layer sugarless coated tablets containing Vitamin C, Vitamin E, Vitamin B2, calcium pantothenate, and L-cysteine. As a result of the formulation study, three coating layers, 2% Under Csoating (UC), 38% Build-up Coating (BC), and 5% Syrup Coating (SC) were necessary for sufficient impact toughness, elegant appearance, and improvement of appearance stability after storage at 25 degrees C/75% RH for 6 months under open conditions. **:** Int J Pharm., Page.No. 459-69. [27]

López-Bojórquez E (2008) et.al. Ketorolac tromethamine is a potent nonsteroidal anti-inflammatory drug that is widely used in the treatment of moderate to severe pain. A new method was developed and validated for quantifying ketorolac (the free acid of the tromethamine salt) in human plasma by high-performance thin-layer chromatography. The stationary phase was silica gel 60, and the composition of the mobile phase was n-butanol-chloroform-acetic acid-ammonium hydroxide-water (9:3:5:1:2, v/v). The densitometric analysis of ketorolac was performed at 323 nm. Average recovery was 73.67%. The method proved to be accurate, precise, and sensitive for the ketorolac tromethamine quantification. J AOAC Int. 2008, Page No. 1191-95. [28]

Kim SJ., (2008) et.al. To evaluate the effects of topical ketorolac in patients undergoing vitreoretinal surgery. One hundred nine patients undergoing vitrectomies were randomized to receive either topical ketorolac tromethamine, 0.4%, or placebo. Patients were instructed to begin taking the study medication 3 days preoperatively (4 times daily) and to continue

taking it 4 weeks postoperatively. Arch Ophthalmol. 2008, Page. No. 1203-1208. [29]

Bucci FA Jr.,et.al. To compare aqueous drug concentrations and prostaglandin E(2) levels in patients treated with ketorolac 0.4% and bromfenac 0.09% at trough dosing. This single-center randomized investigator-masked clinical study comprised 56 patients having cataract surgery. Patients received 1 drop of ketorolac 0.4% or bromfenac 0.09% 6 hours and 12 hours preoperatively consistent with on-label dosing schedules. Aqueous humor was collected at the start of surgery and analyzed for concentrations of ketorolac and bromfenac using a reverse-phase high-performance liquid chromatography-mass spectroscopy system and for prostaglandin E(2) levels by competitive enzyme immunoassay. These findings suggest that ketorolac 0.4% administered 4 times a day may provide better control of prostaglandin-mediated inflammation than bromfenac 0.09% administered twice a day. Page.No.1509-1512.[30]

3.1 AIM OF WORK

Ketorolac tromithamine is a member of the pyrrolopyrrole group of Non-Steroidal Anti-Inflammatory Drug (NSAID) that exhibits analgesic, anti-inflammatory and antipyretic activity. It inhibits the cyclo-oxygenase enzyme system and hence prostaglandin synthesis. It has more pronounced analgesic activity than most NSAIDs. The aim of this work was to prepare and evaluate the Ketorolac tromithamine tablets with higher dissolution rates. Direct compression method was adopted for preparation of tablet using different excipients namely microcrystalline cellulose, spray dried lactose and starch 1500. The effect of excipients on the drug release from prepared tablets was also studied.

- To improve the higher dissolution rate.
- To achieve the short term treatment of the post operative pain relief.

3.2. PLAN OF WORK

1. Preformulation studies.
    1) IR Spectrum Studies.
    2) Drug exicipients compatibility studies.
2. Formulation of Tablets.
3. Evaluation of Tablets.
    1) Description.
    2) Identification.
    3) Uniformity of weight.
    4) Thickness.
    5) Hardness.
    6) Average weight.
    7) Friability test.
    8) Rate of disintegration.
    9) Dissolution.
    10) Percentage of medicament.
4. Stability studies.

4.1. RAW MATERIALS USED.

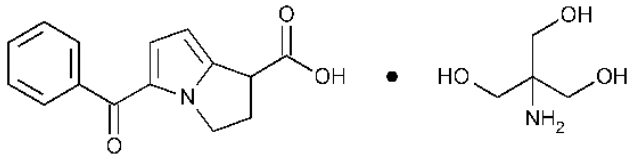
S.No.	RAW MATERIALS USED	SOURCE
1.	Ketorolac tromithamine.	Dr.reddy lab, hyd.
2.	Maize starch B.P.	Universal starchemallied Ltd.
3.	Lactose B.P.	Hollandse melkescuti fubricate Ltd.
4.	Microcrystalline cellulose	Vikash chemicals Pvt.Ltd.
5.	Sodium starch glygolate.	Vasa pharma chem. Pvt.Ltd
6.	Magnesium streate.	Vislak pharma Ltd.
7.	Colloidal anhydrous silicon dioxide.	Cabot sanmar Pvt.Ltd.
8.	Hydroxy propyl methyl cellulose	Feicheng ruitaitineCo.Ltd.
9.	Isopropyl alcohol.	Leechang yung chemicals Ltd
10.	Propylene glycol	Vislak pharma Ltd.
11.	Dichloromethane	Leechang yung chemicals Ltd
12.	Titanium dioxide.	Travancore titepam products Ltd.
13.	Olive green	Neelicon food dyes, chemicals.Ltd

4.2. HANDLING OF EQUIPMENTS

1. Electronical balance.
2. Moisture balance.
3. Mesh different sizes.
4. 16 station rotatatry tablet compression machine.
5. Vernior calipers
6. Tablet coating pan.
7. Tap density meter.
8. pH meter.
9. Tablet disintegration test machine.
10. Friabilator.
11. Tablet dissolution tester.
12. HPLC chromatogram.
13. Ultraviolet spectrometer.
14. Thermo lab stability chamber.
15. Fourier Transform Infra Red spectroscopy.
16. Hot air oven.
17. Microscope.

4.3.1. Ketorolac tromithamine[31, 32, 37]

1. Structure:



2. Molecular formula: $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$

3. Molecular weight: 376.40g/mol

4 IUPAC: 1*H*-Pyrrolizine-1-carboxylic acid,5-benzoyl-2,3-dihydro, (±)-,compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid,compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

5. Description: ketorolac tromithamine white to off-white to pale yellow crystalline powder and free from visible extraneous matter.

6. Solubility: Freely soluble in water and methanol. Slightly soluble in alcohol, dehydrated alcohol, tetrahydrofuran, toulene, ethyl acetate and acetonitrile.

7. Pka: 7.9

8. Category: pharmacology stubs, pyrrole pyrrole group of non steroidal anti inflammatory drug.

9. Melting point: 255℃

10. Mechanism of actions:

A highly potent member of a new class of compounds of Non Steroidal Anti-Inflammatory Drug (NSAID) available in Intramuscular (IM) and oral formulations for the management of acute pain. The compound shows potent prostaglandin cyclooxygenase inhibitory activity. The agent elicited mild CNS and cardiovascular activity only at doses far in excess of those required for analgesic and anti-inflammatory activity. A single 10 mg tablet given orally to human volunteers

following surgery provided pain relief Equivalent to that provided by 10 mg of morphine given intramuscularly.

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

11. Pharmacokinetics:

1. Absorption:

Ketorolac is 100% absorbed after oral administration. Oral administration of Ketorolac after a high-fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

2. Distribution:

The mean apparent volume (Vβ) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single-dose data. The ketorolac tromethamine racemate has been shown to be highly protein bound (99%). Nevertheless, plasma concentrations as high as 10 μg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

Ketorolac tromethamine is excreted in human milk.

3. Metabolism:

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the

parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

4. Elimination:

The route of elimination of ketorolac and its metabolites is renal. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. Approximately 6% of a dose is excreted in the feces. A single-dose study with 10 mg Ketorolac (n=9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans. The clearance of the racemate in normal subjects, elderly individuals and in hepatically and renally impaired patients is outlined.

12. Therapeutics:

Non Steroidal Anti-Inflammatory Drug (NSAID) available in intramuscular (IM) and oral formulations for the management of acute pain. The compound shows potent prostaglandin cyclooxygenase inhibitory activity . The agent elicited mild CNS and cardiovascular activity only at doses far in excess of those required for analgesic and anti-inflammatory activity. A single 10 mg tablet given orally to human volunteers following surgery provided pain relief equivalent to that provided by 10 mg of morphine given intramuscularly. [37]

13. Adverse effects:

Anorexia, nausea, vomiting, abdominal pain, intestinal perforation, stomatitis.

14. Contraindications:

- In children (or) adolescents in the growth phase.
- During pregnancy (or) in breast feeding women.

15. Storage: Stored in a room temparature

16. Dosage: 10-20mg per daily.

4.4.1. MICROCRYSTALLINE CELLULOSE [33]

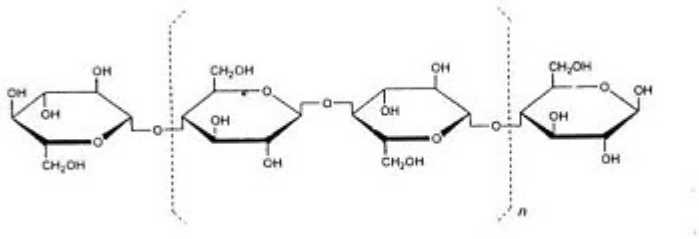
1. Synonym: Avicel PH. Celex, cellulose gel, E 460, celphere, emcocel.

2. Chemical name: Cellulose.

3. Empirical formula: $(C_6H_{10}O_5)_n$

4. Molecular weight: ≈ 36,000

5. Structural formula:



6. Functional category: Adsorbent, suspending agent, diluent, disintegrant,

7. Description: White, odorless, tasteless, crystalline powder composed of porous Particles.

8. Typical Properties:

1. Bulk density -- 0.337g/cm3
2. Tapped density – 0.478g/cm3
3. Melting point – 260-270℃
4. Moisture content – less than 5% w/w
5. PH -- 5.0 – 7.0

9. Solubility: Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids.

10. Stability and storage conditions: Its stable though hygroscopic material. Stored in well-closed container in a cool, dry place.

11. Incompatibilities: It is incompatible with strong oxidizing agents.

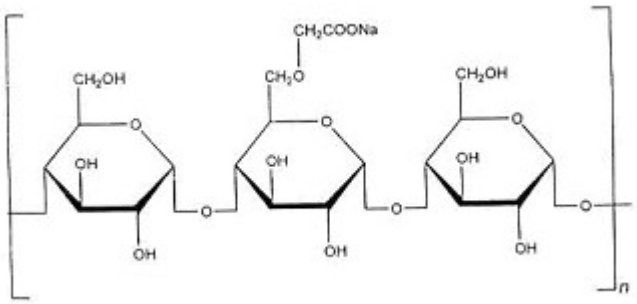
12. Safety: Nontoxic and nonirritant, large quantities of cellulose have a laxative effect.

4.4.2. SODIUM STARCH GLYCOLATE[33]

1. Synonym: Carboxy methyl starch, sodium salt.

2. Chemical name: Sodium carboxy methyl starch.

3. Structural formula:



4. Functional category: Disintegrant.

5. Description: White to off-white, odorless, tasteless, free flowing powder, oval or spherical granules.

6. Typical Properties:

1. Bulk density -- 0.756 g/cm
2. Tapped density – 0.945 g/cm
3. True density – 1.443 g/cm
4. Melting point – 200℃
5. Moisture content – less than 10% w/w
6. PH -- 5.5 – 7.5

7. Solubility: Sparingly soluble in ethanol, practically insoluble in water.

8. Stability and storage conditions: It's stable. Stored in well-closed container, protected from light, in a cool, dry place.

9. Incompatibilities: Incompatible with ascorbic acid.

10. Safety: Nontoxic and nonirritant.

4.4.3. ISOPROPYL ALCOHOL [33]

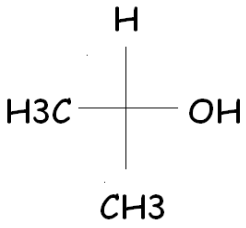
1. Synonym: Dimethyl carbinol, IPA, isopropanol, 2- propanol

2. Chemical name: Propan –2- ol.

3. Empirical formula: C_3H_8O

4. Molecular weight: 60.1

5. Structural formula:



6. Functional category: Disinfectant, solvent.

7. Description: Characteristic odour and a warm, bitter taste.

8. Typical Properties:

1. Boiling point – 82.4℃
2. Melting point – 88.5℃3.
3. Moisture content – 0.1 – 13 % w/w.

9. Solubility: Clear, colorless, volatile, flammable liquid, slightly bitter taste.

10. Stability and storage conditions: Stored in well-closed container, protected from light, in a cool, dry place.

11. Incompatibilities: Incompatible with oxidizing agents such as hydrogen peroxide, nitric acid, which cause decomposition.

12. Safety: Nontoxic and local irritant.

4.4.4. MAGNESIUM STEARATE [33, 34]

1. Synonym: Octadecanoic acid, magnesium salt, stearic acid.

2. Chemical name: Octadecanoic acid magnesium salt.

3. Empirical formula: $C_{36}H_{70}MgO_4$.

4. Molecular weight: 591.34

5. Structural formula: $(CH_3 (CH_2)_{16}COO)$ Mg.

6. Functional category: Lubricant.

7. Description: Fine, white, precipitated, faint odour, characteristic taste.

8. Typical Properties:

1. Bulk density -- 0.159 g/cm
2. Tapped density – 0.286 g/cm
3. True density – 1.092 g/cm
4. Melting point – 126 to 130℃

9. Solubility: Soluble in ethanol, water, insoluble in miner oil, vegetable oil.

10. Stability and storage conditions: It's stable. Stored in well-closed container, protected from light, in a cool, dry place.

11. Incompatibilities: Incompatible with strong acids, alkalis, iron salts, avoid mixing with strong oxidizing materials.

12. Safety: Nontoxic and mucosal irritant.

4.4.5. COLLOIDAL SILICON DIOXIDE [34, 36]

1. Synonym: Aerosil, cab-o-sil, colloidal silica, fumed silica.

2. Chemical name: Silica

3. Empirical formula: SIO_2

4. Molecular weight: 60.08

5. Functional category: Adsorbent, emulsifying agent, suspending agent, Anticaking agent, glidant, disintegrant.

6. Description: Light, loose, bluish-white colored, odourless, tasteless,

7. Typical Properties:

1. Bulk density -- 0.29 to 0.042 g/cm
2. Tapped density – 0.04 to 0.05 g/cm
3. PH -- 3.4 – 4.4

8. Solubility: Practically insoluble in organic solvents, water, acids, soluble in hot solutions of alkali hydroxide.

9. Stability and storage conditions: It's hygroscopic but absorbs large quantities of water without liquefying. Stored in well-closed container, protected from light, in a cool, dry place.

10. Incompatibilities: Incompatible with diethylstilbestrol preparations.

11. Safety: Nontoxic and nonirritant.

4.4.6. HYDROXY PROPYLMETHYL CELLULOSE [35, 36]

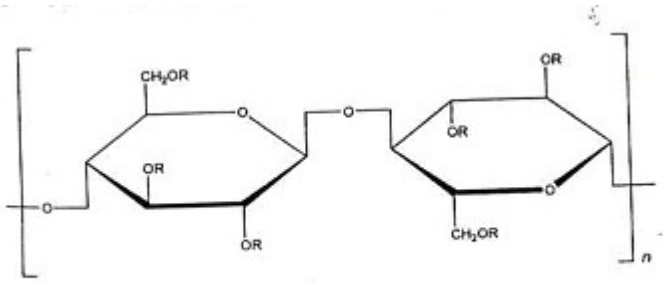
1. Synonym: Cellulose, E464, HPMC, methocel.

2. Chemical name: Cellulose, 2-hydroxy propyl methyl ether.

3. Empirical formula: $(OCH_2CH\ (OH)\ CH_3)$

4. Molecular weight: 1, 00, 00 to 1, 50, 00

5.Structuralformula:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6. Functional category: Coating agent, film former, stabilizing agent, suspending agent, binding agent.

7. Description: Odorless, tasteless, white or creamy white fibrous.

8. Typical Properties:

1. Bulk density -- 0.341 g/cm
2. Tapped density – 0.557 g/cm
3. True density – 1.326 g/cm
4. Melting point – 190 to 200℃
5. PH -- 5.5 – 8.0

9. Solubility: Soluble in cold water, practically insoluble in ethanol, ether.

10. Stability and storage conditions: Its stable material, it's hygroscopic after drying. Stored in well-closed container, protected from light, in a cool, dry place.

11. Incompatibilities: Incompatible with some oxidizing agents.

12. **Safety:** Nontoxic and nonirritant.

4.4.7. TITANIUM DIOXIDE [36]

1. Synonym: Titanic anhydride, tronox, tioxide, tipure.

2. Chemical name: Titanius oxide.

3. Empirical formula: TIO_2

4. Molecular weight: 79.88

5. Functional category: Coating agent, opacifier, and pigment.

6. Description: White, amorphous, odorless, tasteless, nonhygroscopic powder.

7. Typical Properties:

1. Bulk density -- 0.4 to 0.62 g/cm
2. Tapped density – 0.625 to 0.830 g/cm
3. True density – 3.8 to 4.1 g/cm
4. Melting point – 1855℃

8. Solubility: Practically insoluble in dilute sulphuric acid, nitric acid.

9. Stability and storage conditions: It's extremely stable at high temperatures, stored in well-closed container, protected from light, in a cool, Dry place.

10. Incompatibilities: Incompatible with certain active substances, and also unsaturated lipids.

11. Safety: Nontoxic and nonirritant.

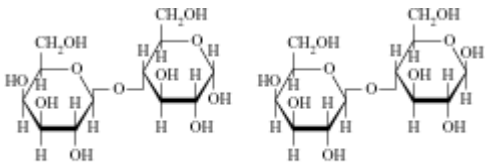
4.4.8. LACTOSE[35, 36]

1. Synonym: *Fast-Flo*; 4-(b-D-galactosido)-D-glucose; *Lactochem*; *Microtose*; milk sugar; *Pharmatose*; saccharum lactis; *Tablettose*; *Zeparox*.

2. Chemical name:

D-Galactopyranosyl-(1,4)-D-glucopyranose anhydrous.

D-Galactopyranosyl-(1, 4)-D-glucopyranose monohydrate.



α - lactose β - lactose

3. Empirical formula: $C_{12}H_{22}O_{11}$

4. Molecular weight: 342.30

5. Functional category: Tablet and capsule diluent.

6. Description: White to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 15% as sweet as sucrose, while b-lactose is sweeter than the a-form of lactose.

7. Typical Properties:

1. Bulk density -- 1.589 for anhydrous b-lactose
2. Melting point - 223°C for anhydrous a-lactose;

252.2°C for anhydrous b-lactose

8. Solubility: Practically insoluble in dilute sulphuric acid, nitric acid.

9. Stability and storage conditions: chlorafrom, ethanol, ether and water.

10. Incompatibilities: Lactose is incompatible with amino acids, aminophylline, and amphetamines.

11. Safety: Nontoxic and nonirritant.

4.4.9. MAIZE STARCH[36]

1. Synonym: *Bio-sorb*; double-dressed, white maize starch; Keoflo ADP, *Fluidamid R444P*; modified starch dusting powder; *Pure-Dent B851*; starch-derivative dusting powder; sterilizable corn starch

2. Chemical name: Sterilizable maize starch

3. Empirical formula: $(C_6H_{10}O_5)_n$

4. Molecular weight: Where n = 300-1000.

Sterilizable maize starch is a modified corn (maize) starch that may also contain up to 2.0% of magnesium oxide.

5. Functional category: Lubricant for surgeons' and examination gloves; vehicle for medicated dusting powders.

6. Description: Sterilizable maize starch occurs as an odorless, white-colored, free-flowing powder. Particles may be rounded or polyhedral in shape.

7. Typical Properties:

pH = 9.5-10.8 for a 10% w/v suspension at 25°C.

Density: 1.48 g/cm^3

Density (bulk): 0.47-0.59 g/cm^3

Density (tapped): 0.64-0.83 g/cm^3

Flowability: 24-30% (Carr compressibility index)

Moisture content: 10-15%

Particle size distribution: 6-25 µm; median diameter is 16 µm.

9. Solubility: very slightly soluble in chloroform and ethanol (95%); practically insoluble in water.

10. Stability and storage conditions: Sterilizable maize starch may be sterilized by autoclaving at 121°C for 20 minutes, by ethylene oxide or by irradiation.Sterilizable maize starch should be stored in a well-closed container in a cool, dry, place.

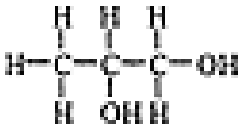
11. Safety: Nontoxic and nonirritant.

4.4.10. PROPYLENE GLYCOL[36]

1. Synonym: 1, 2-Dihydroxypropane; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol.

2. Chemical name:

1,2-Propanediol



3. Empirical formula: $C_3H_8O_2$

4. Molecular weight: 76.1

5. Functional category: Antimicrobial preservative, disinfectant, humectant, plasticizer, solvent, stabilizer for vitamins, water-miscible cosolvent.

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

7. Typical Properties:

Density: 1.038 g/cm^3 at 20°C

Flammability: upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point: 99°C (open cup)

Heat of combustion: 1803.3 kJ/mol (431.0 kcal/mol)

Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.

Melting point: 59°C

8. Solubility: Practically insoluble in dilute sulphuric acid, nitric acid.

9. Stability and storage conditions: chlorafrom, ethanol, ether and water.

10. Incompatibilities: Lactose is incompatible with amino acids, aminophylline and amphetamines.

11. Safety: Nontoxic and nonirritant.

4.5.1 **PREFORMULATION STUDY**

Preformulation testing is an investigation of physical properties of a drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.

4.5.2. Identification of drug:

The identification of drug was done by IR spectroscopy. The FTIR spectrum of pure drug **ketorolac** is shown in

Figure no: 1

Method:

Triturate 1-2 mg of the substance to be examined with 300-400 mg, unless otherwise specified, of finely powdered and dried potassium bromide R or pottasium chloride R. These quantities are usually sufficient to give a disc of 10-15 mm diameter and a spectrum of suitable intensity. Infrared spectrophotometers are used for recording spectra in the region of 4000 – 650 cm^{-1}.

FTIR Spectrum of ketorolac.

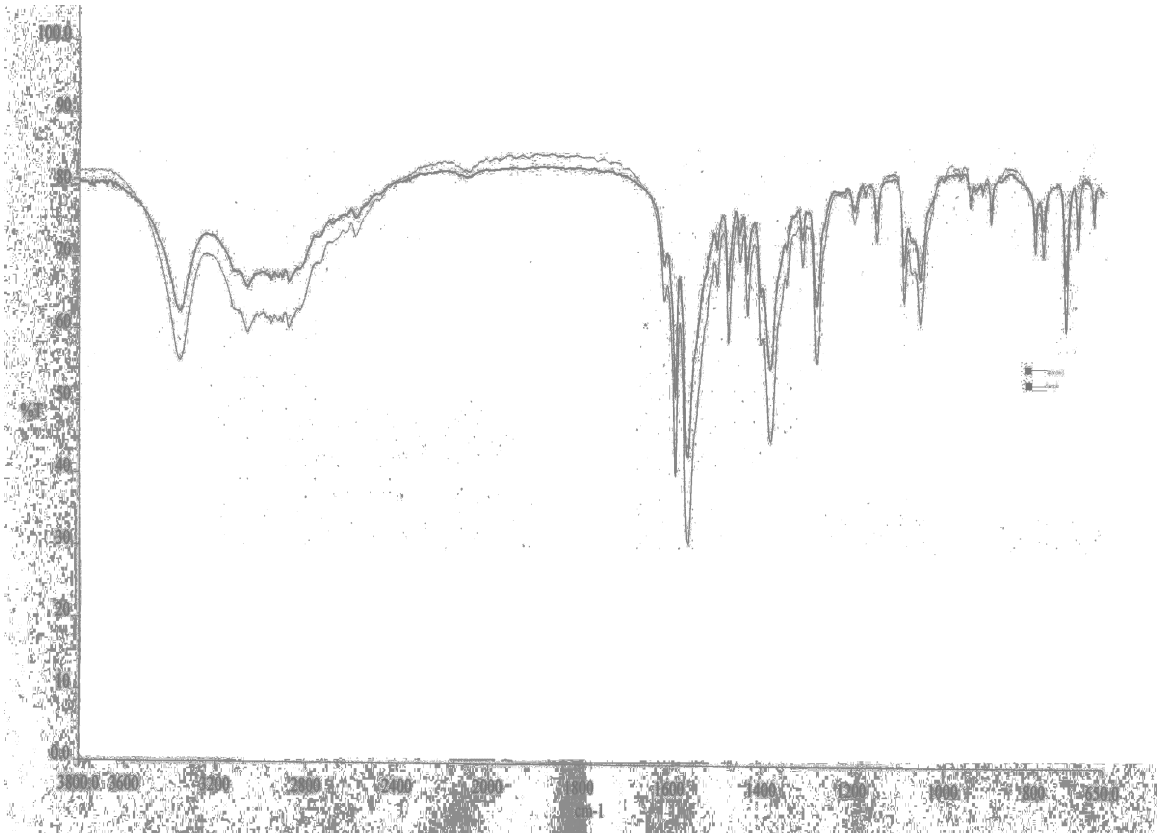


Figure No.1

5.4. Drugs – Excipients compatibility study: [39, 40]

Drug was mixed with excipients in difficult ratio. These mixtures were kept in a 2 ml glass vial and exposed to 40ºC, 60ºC, for 1 month. At the end of 30 days.

Table no. 2. ketorolac + Excipients Compatibility Studies.

S.No	Ingredients	Initial colour	Storage Conditions	
			40℃/75% RH	60℃/80% RH
			At the end of 30 days	At the end of 30 days
1.	Drug (D).	PW	PW	PW
2.	D+ Lactose.	W	W	W
3.	D+Microcrystalline cellulose.	W	W	W
4.	D+Maize starch.	W	W	W
5.	D+Sodium starch glycolate.	W	W	W
6.	HPMC	W	W	W
7.	D+propylene glycol.	W	W	W
8.	D+Isopropyl alcohol.	W	W	W
9.	D+Magnesium stearate.	W	W	W
10.	D+Colloidal silicon dioxide.	W	W	W
11.	D+Talc.	W	W	W
12.	D+Olive green.	O	O	O

W- white: PY- pale yellow: PW- pale white: O- orange:

Table .no.3.

Physical characteristics of ketorolac tromithamine.

S.No	Parameter	Observation
		ketorolac
1.	Loss on drying.	Less than 0.07%
2.	Bulk density.	0.471 -- 0.478 g/cc
3.	Tapped density.	0.661 -- 0.668 g/cc
4.	Compressibility index.	28.74 -- 29.52%
5.	Hausner ratio.	1.403 -- 1.408

4.6.1. FORMULATION OF TABLET[39-43]

The key process in the formulation development of ketorolac tromithamine tablets including direct compression method to be adopted using different excipients and before weighing active ingredient. The dispensing area maintained temperature below 25ºC and humidity below 30 % RH.

Dry Blending and Preparation of Tablets by Direct Compression Technique:

All of the mentioned materials except lubricant and glidant of respective formulation were taken into a bowl by passing through 40 mesh screen (if necessary) and mixed manually for five minutes. Then this mixture was mixed in a tumbling mixer Patterson-kelly Twin shell blender for about fifteen minutes. The effiency of mixing was verified by determination of drug content. Magnesium stearate, colloidal silicon dioxide

I. PREMIXING:

1. Drugs+diluent+disintegration+lubricant. All the products through 40 mesh, for 30 minutes.

↓

2. Binding agents.

↓

3. 1 and 2 step-1 material and mix well till uniformity is obtained.

II. LUBRICATION:

1. Charged the blender with material

2. Sifted drug+glidant+disintegrant. Through 30 mesh in a mechanical sifter.

3. Added above sieved materials to the blender and mixed for 15 minutes.

4. Sieved lubricant through 40 mesh.

5. Added to the blended materials and mixed for 5 minutes.

6. Stored the lubricated material in a airtight container and keep in a cool place at temperature between 25°C to 30°C.

7. Compression carried out only after getting in process approval for material from quality control department.

8. Set the 16 station rotary compression machine using punches and dies.

9. Compression carried out only with air conditioned and dehumidified atmosphere. Maintained the temperature and relative humidity of compression section at not more then 32°C and 65% respectively.

↓

10. Loaded material into the hopper of rotary compression machine and adjusted the machine for compression weight, hardness, thickness, disintegration time and friability as per the specification on parameters in IP.

Table. No.4, Design and development of formulation.

4.6.2. Preparation of coating solutions

Table.no.5.

S.No	Ingredients	mg/tablet
1.	**HPMC**	2 mg
2.	**Isopropyl alcohol**	0.25 ml
3.	**Propylene glycol**	0.5 mg
4.	**Dichloro methane**	2 mg
5.	**Olive Green**	0.90mg

Procedure:

Pass all the materials from the sieve no 200# and then mix the Dichloromethane and propylene glycol, in a coating solution tank. Then add HPMC with isopropyl alcohol in small quantity while stirring continuously till it forms a smooth suspension.

Add the olive green with the remaining quantity of the isopropyl alcohol. Mill the above preparation dispersion in colloidal mill with recirculation for 5min. transfer to the agitator tank while filtering through 200# nylon cloth.

4.7. IN PROCESS EVALUATION[39,40]

4.7.1. Determination of bulk density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder was closed with lid. Set into the density determination apparatus (bulk density apparatus. Electro lab, Mumbai.)

The bulk densities were calculated using the following formula:

Bulk density = W/V0

Where,

W = Weight of powder.

V0 = Initial volume.

The results are presented in the table no: 6

4.7.2. Determination of tapped density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder was closed with lid. The density apparatus (tapped density apparatus. Electro lab, Mumbai.). Was set 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal.

The tapped densities were calculated using the following formula:

Tapped density = W/Vf

Where,

W = Weight of powder.

Vf = Final volume.

The results are presented in the table no: 6

4.7.3. Compressibility index: [43]

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20 to 30 % is defined as the free flowing material.

The compressibility indexes were calculated using the following formula:

$$C1 = \frac{100\ (V0 - Vf)}{V0}$$

The results are presented in the table no: 9

4.7.4. Hausner ratio: [43]

Hausner ratio is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable.

The hausner ratios were calculated using the following formula:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

The results are presented in the table no: 6

4.7.5. Loss on drying: [43]

Determinations of loss on drying of material are important. Drying time during material was optimized depending on the LOD value. LOD of each batches were tested at 63ºC and 105ºC temperature by using "Moisture balance" electronic LOD apparatus.

% LOD = [lost wt X 100]/wt of sample

The results are presented in the table no: 6

4.7.6. Sieve analysis: [40, 43]

The main aim of sieve analysis is to determine the difficult size of drug particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (large sieve number) towards the bottom.

Procedure:

A series of sieves were arranged in the order of their decreasing pore diameter. (increasing in sieve number) i.e. sieve number #20, #40, #60, #80, and #100 passed. 100 gms of drugs were weighed accurately and transferred to sieve #20, which was kept on top. The sieves were shaken for about 5-10 minutes. Then the drug retained on each sieve were taken, weighed separately and expressed in terms of percentage. The results are presented in the table no: 7

Table. No.6.

Physical characteristics of blend material (formulation 1-9)

S.No	Formulation No	% Loss on drying	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner ratio
1.	F-1	2.420	0.5241	0.6823	23.16	1.304
2.	F-2	2.287	0.5678	0.6834	25.76	1.347
3.	F-3	2.346	0.5352	0.7191	25.59	1.343
4.	F-4	2.336	0.5704	0.7540	24.40	1.322
5.	F-5	2.289	0.5502	0.7319	24.76	1.329
6.	F-6	2.341	0.5843	0.7624	23.35	1.304
7.	F-7	2.287	0.5432	0.7465	24.89	1.327
8.	F-8	2.298	0.5673	0.6834	23.15	1.342
9.	F-9	2.316	0.5732	0.673	25.13	1.302

Table.no.7.

Sieve Analysis of blend material,Formulation: (1 – 9)

S.No.	Seive.No.	% weight of blend material retained								
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1.	# 20	8.00	6.00	6.00	0.00	2.00	0.00	0.00	0.00	0.00
2.	# 30	3.13	2.03	0.19	0.00	0.15	21.02	37.67	49.35	19.02
3.	# 40	39.72	40.82	10.19	13.73	23.77	22.00	17.15	20.00	21.15
4	# 60	17.52	14.25	18.62	11.72	14.05	8.41	10.63	17.25	7.32
5	# 100	4.62	3.65	8.54	1.25	10.32	6.58	4.61	4.56	7.51
6	># 100	29.21	30.20	64.25	58.20	56.80	12.56	14.64	11.24	13.02

6.1. DISSOLUTION[42,44]

Tablet dissolution was assessed using standard USP 24 apparatus II in 900 ml of water. The stirring speed was 50 rpm. (Revolution per minutes). Total 6 tablets were taken for test. Temperature was maintained 37ºC ± 0.5ºC through out the experiment. Dissolution study was carried out for 45 minutes. Sampling interval were 5 min, 10 min, 15min, 20 min, 30 min. After collection of sample in each interval, dissolution medium was replenished with the same volume of respective medium. Samples were withdrawn at regular intervals and diluted to 25 ml with corresponding medium and analyzed for drug content by U.V. [61]

Dissolution parameters:

1. Medium : purified water (degassed).
2. Quantity : 900 ml.
3. Apparatus : USP Type II (paddle).
4. Rotational Speed : 50 rpm
5. Time : 5, 10, 15, 20, 30min or required intervals.
6. Temperature : 37ºC ± 0.5ºC.
7. Wavelength : 322nm.

Standard solution Preparation:

Weigh accurately about 42mg working standard into a 100ml volumetric flask. Dissolve and dilute to volume with water and mix. Transfer 2ml of this solution to a200 ml volumetric flask and dilute to volume with water and mix.

Preparation of sample solution:

Put 6 tablets in the six dissolution flask containing 900ml of water that has been equilibrated to 37ºC ± 0.5ºC. Start the apparatus immediately. Collect the sample after 45min. withdraw the sample from the zone mid way between the surface of the medium and top of the rotating blade and not less than 1cm from the vessel wall and filter through 0.45 micron membrane filter and discard the first 5 ml and transfer 5ml of filtrate into a 20ml volumetric flask and dilute to volume with water and mix.

Procedure:

Check the absorbance of both standard and the sample preparation using U.V spectroscopy at 322nm using water as blank.

Calculations: (for Ketorolac tromethamine):

% W/W of Assay =

$$\frac{ATA}{ASA} \times \frac{SW}{100} \times \frac{2}{200} \times \frac{600}{LC} \times \frac{20}{5} \times P$$

Where,

ATA = Average peak area counts for test solution.

ASA = Average peak area counts for standard solution.

SW = Weight of standard solution taken. In mg

P = Purity of working standard. In mg

Table.no.11. Dissolution Profile of Formulation – 1

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	12.20
3	10	27.30
4	15	42.30
5	20	68.42
6	30	76.52

Figure no- 2.

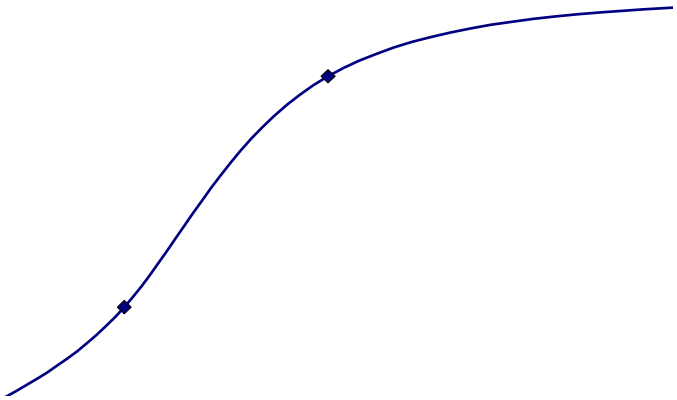


Table.no.12. Dissolution Profile of Formulation – 2

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	23.22
3	10	36.82
4	15	56.62
5	20	72.30
6	30	79.12

Figure no- 3.

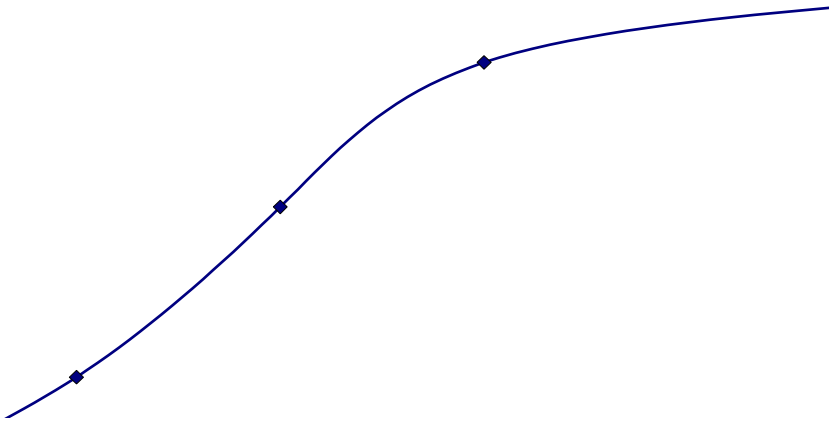


Table.no.13. Dissolution Profile of Formulation – 3

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	24.71
3	10	37.19
4	15	60.12
5	20	76.27
6	30	82.48

Figure no- 4.

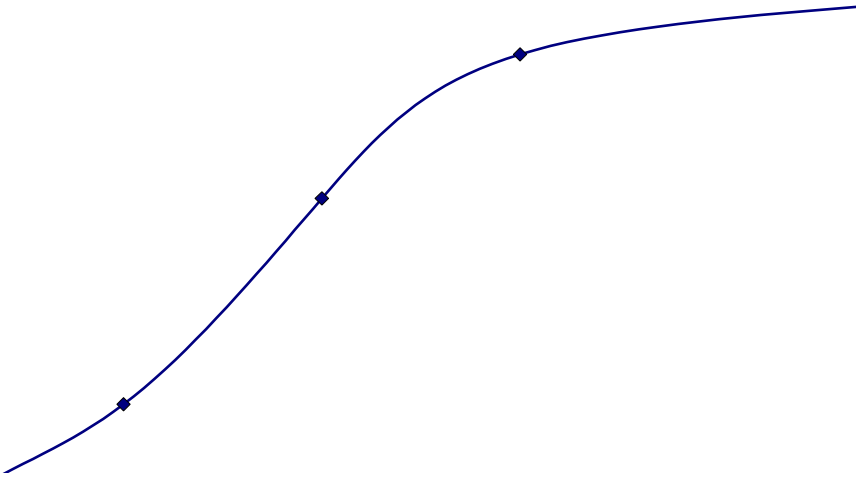


Table.no.14. Dissolution Profile of Formulation – 4

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	24.35
3	10	39.40
4	15	63.83
5	20	78.25
6	30	89.40

Figure no- 5.

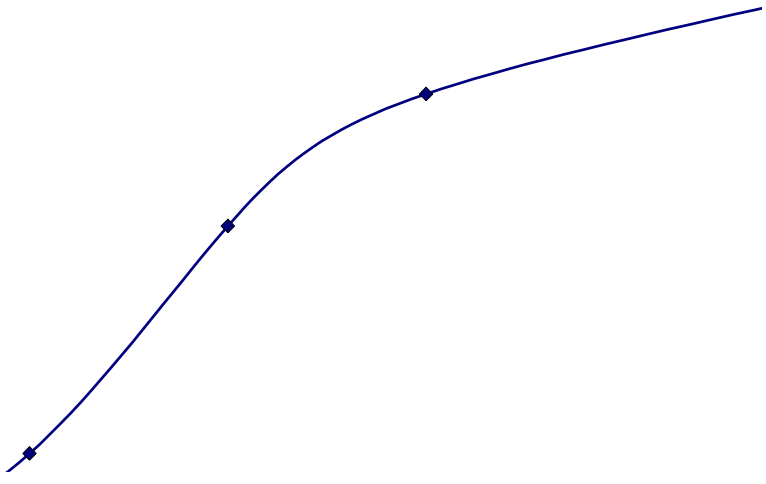


Table.no.15. Dissolution Profile of Formulation – 5

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	23.45
3	10	40.63
4	15	64.10
5	20	82.18
6	30	91.20

Figure no- 6.

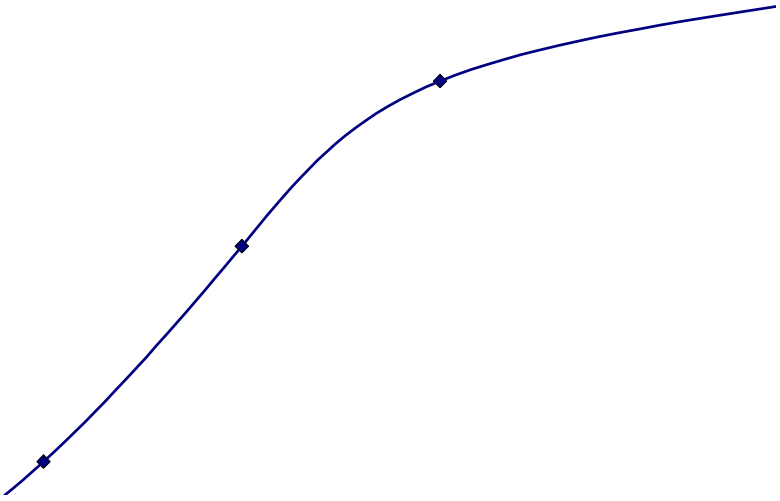


Table.no.16. Dissolution Profile of Formulation – 6

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	24.72
3	10	38.92
4	15	63.73
5	20	85.10
6	30	94.52

Figure no- 7.

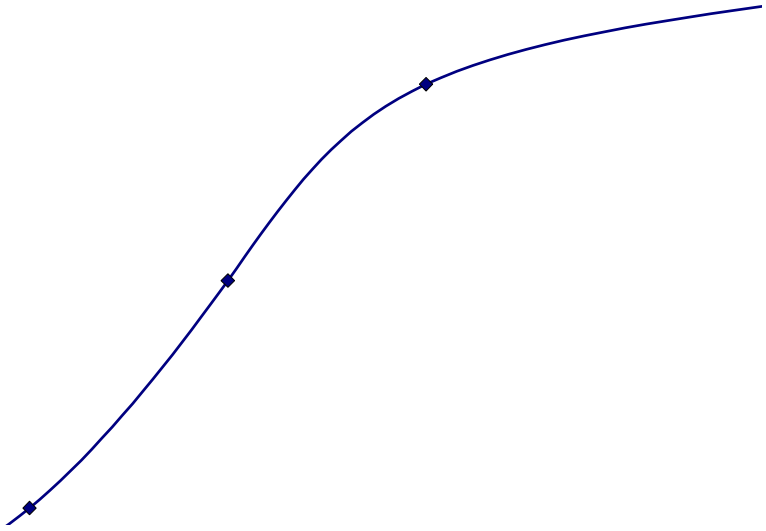


Table.no.17. Dissolution Profile of Formulation – 7

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	26.40
3	10	41.50
4	15	64.12
5	20	84.34
6	30	93.26

Figure no- 8.

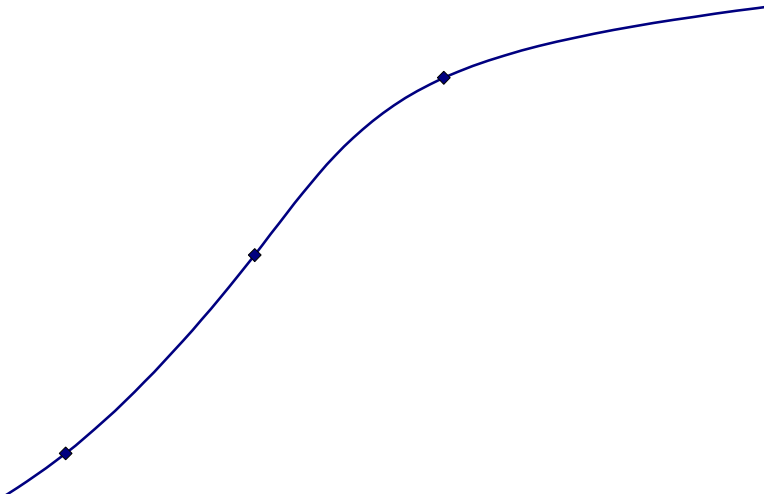


Table.no.18. Dissolution Profile of Formulation – 8

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	27.62
3	10	48.32
4	15	68.43
5	20	82.84
6	30	99.62

Figure no-9

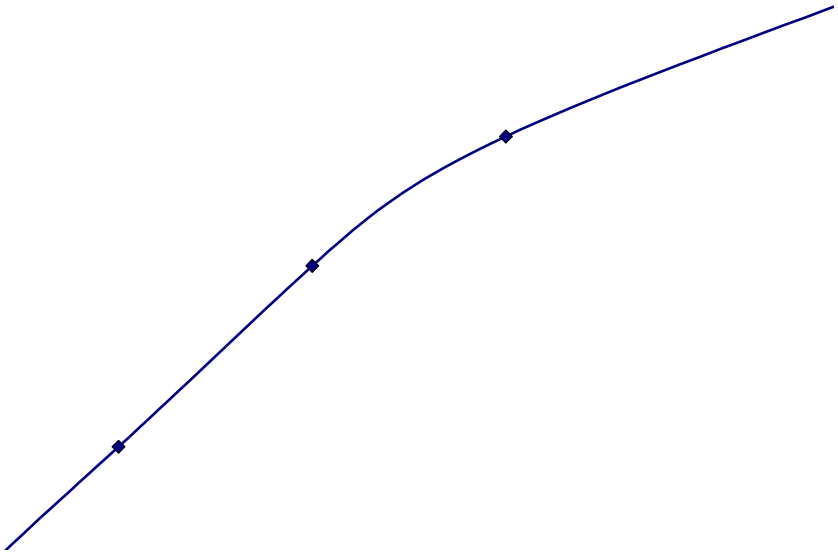


Table.no.19. Dissolution Profile of Formulation – 9

S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	23.12
3	10	36.72
4	15	62.14
5	20	87.26
6	30	98.47

Figure no-10

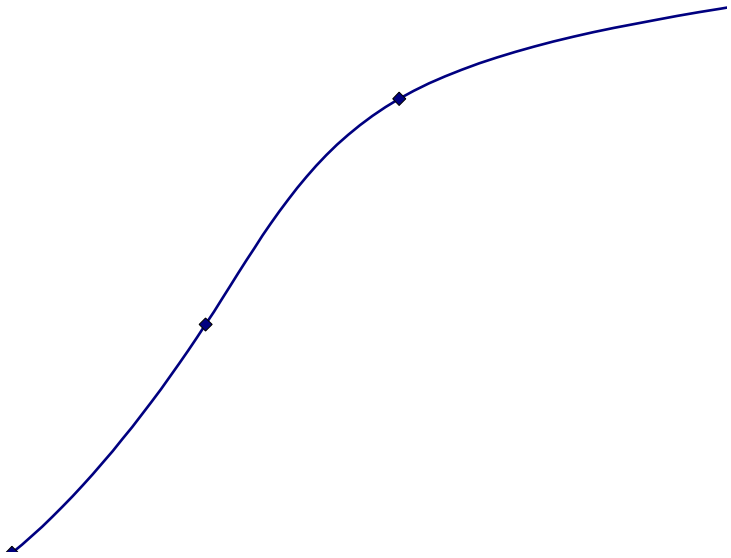


Table. No-20.

Dissolution Profile of Ketorolac tromethamine in (F1-F9).

S.No.	Time (min)	cumulative % drug release								
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1.	0	0	0	0	0	0	0	0	0	0
2.	5	12.20	23.22	24.71	24.35	23.45	24.72	26.40	27.62	23.12
3.	10	27.30	36.82	37.19	39.40	40.63	38.92	41.50	48.32	36.72
4	15	42.30	56.62	60.12	63.83	64.10	63.73	64.12	68.43	62.14
5	20	68.42	72.30	76.27	78.25	82.18	85.10	84.34	82.84	87.26
6	30	76.52	79.12	82.48	89.40	91.20	94.52	93.26	99.62	98.47

Figure no-11.

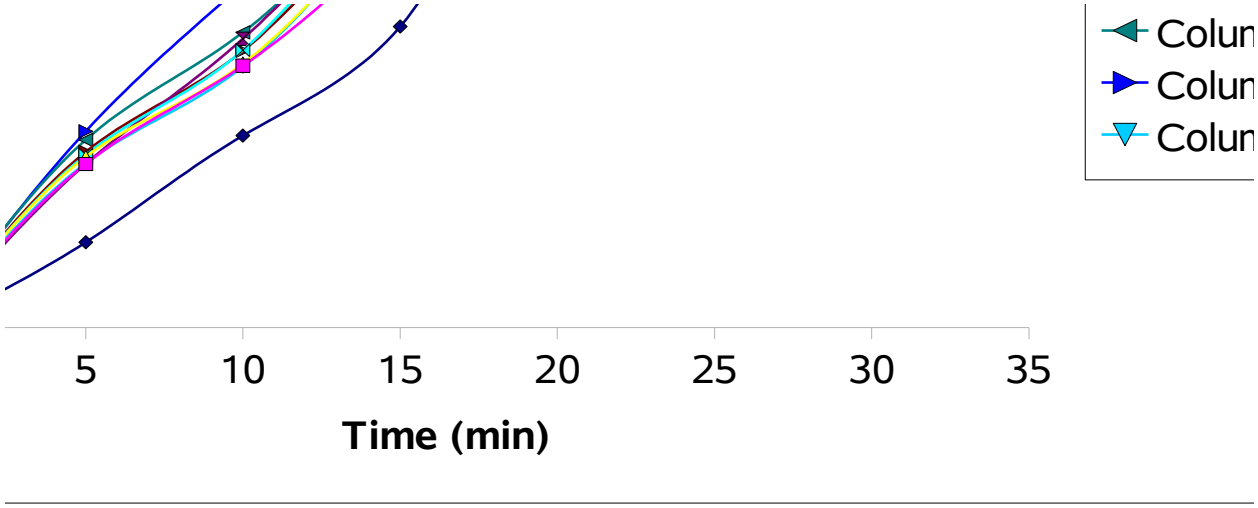
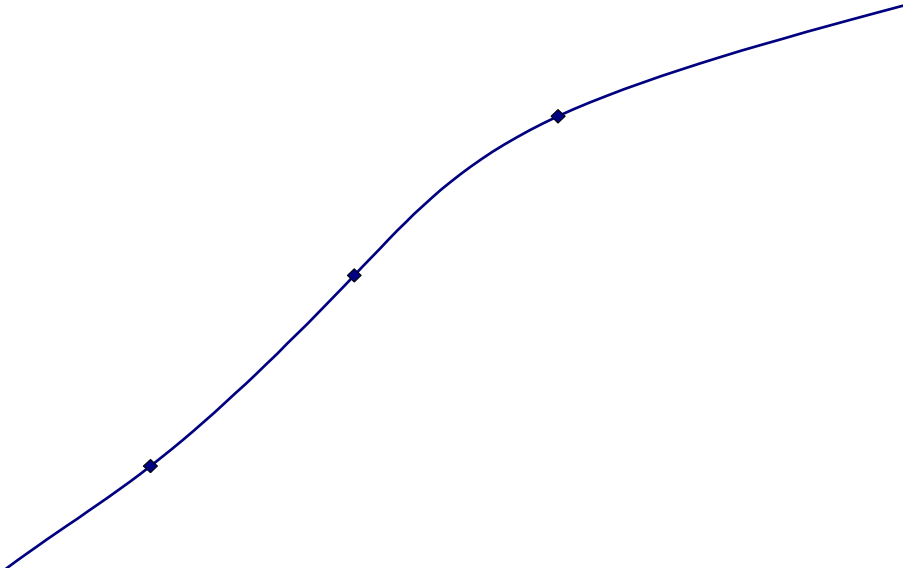


Table.no.21. Dissolution Profile of Marketed Product:

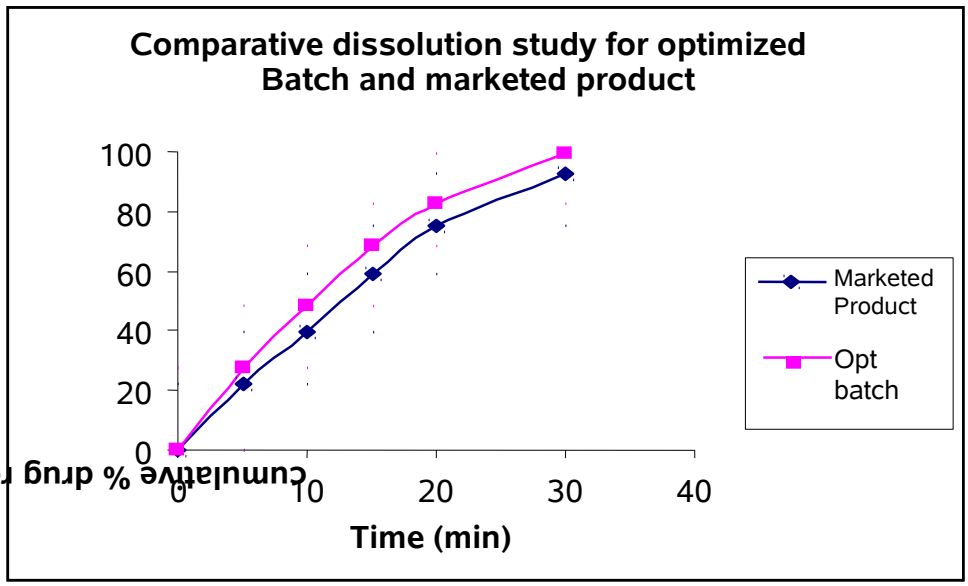
S.no	Time in minutes	cumulative % drug release
1	00	0
2	5	26.31
3	10	43.27
4	15	64.51
5	20	82.36
6	30	96.52

Figure no- 12.



Comparative Dissolution Profile of optimized batch and Marketed Product:

Figure No. 13.



5.1. EVALUATION OF TABLETS[42,43]

5.1. THICKNESS OF TABLET: [43]

The thickness of the tablets was measured by using Digital Vernier Caliper thickness tester in mm. twenty tablets from each batch were randomly selected and thickness were measured. The thickness of IP limits is 3.40 ±0.2mm.

The mean of measured thickness of tablets of each batch are shown in table no: 9

5.2. HARDNESS OF TABLET: [43]

Hardness of the tablets was determined by using Digital Hardness Tester. Twenty tablets from each batch were randomly selected. The force required to break the tablet is recorded. The unit is Newton. The hardness of IP limits is NLT 5-8 kg/cm2.

The mean of measured hardness of tablets of each batch are shown in table no: 9

5.3. FRIABILITY OF TABLET: [43]

Friability of the tablets was tested using a Friabilator (Friability testing apparatus, Electro lab). A loss of less than 1& in weight was acceptable. The weight of 10 tablets was noted initially (W1) and placed in the friabilitor for 4 minutes/25 rpm. (Revolution per minutes).The tablets were reweighed and noted as (W2).

The difference in the weight is noted and expressed as percentage.

$$\text{Percentage friability (\%F)} = \frac{(W1 - W2)\ 100}{W1}$$

Where,

%F = Friability in percentage.

W1 = Initial weight of tablet.

W2 = Weight of tablets after revolution.

The mean of measured friability of tablets of each batch are shown in table no: 9

5.4. WEIGHT VARIATION TEST: [42]

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in table, and none deviate by more than twice the percentage shown.

Table. no - 8.

Weight variation tolerance for tablet (USP)

5.5. DISINTEGRATION OF TABLET:

Method:

The tablets were taken in a rigid basket rack assembly supporting six cylindrical glass tubes. The glass tubes are of 77.5 ± 2.5 mm long. 21.5 mm in internal diameters and with a wall thickness of about 2mm. the assembly was suspended in the liquid medium in a 1000 ml beaker. The volume of liquid was such that, wire mesh at its lower point was at 25 mm below the surface of the liquid and its lower point was at 25 mm above the bottom of the beaker. A temperature was maintained at 37º± 2º. Five tablets are placed in each tube and the motor is switched on. Guided disc over the tablets does not allow them to float and imparts a slight pressure on the tablets. The tubes are then allowed 30 up and down movements till all the tablets disintegrate and particles remain above the wire mesh. Finally the average disintegration time was recorded. The disintegration of USP limits is NMT 10minutes.

Observation: the value of the disintegration time of all the batches given in the table no: 9

Table.no.9. Pysical Characteristic of Finished products.

5.6. AVERAGE DRUG CONTENT

5.6.1. Assay (By HPLC): [42]

Reagents:

1. Hydrochloric acid.
2. Sodium lauryl sulphate: HPLC grade.
3. Acetonitrile: HPLC grade.
4. Glacial acetic acid: HPLC grade.
5. HPLC grade water: Millie Q or equivalent.

Preparation of mono basic ammonium phosphate Buffer Solution:

Dissolve the 5.75g ammonium phosphate in 1000ml of HPLC grade water in suitable container; dissolve it and then make up to the volume with water and adjust the pH of 3.0.

Preparation of mobile phase:

Prepare a filtered and degassed mixer of buffer and tertrahydrofuran in the ratio of 70:30 v/v.

Note: make adjustment if necessary to achieve a retention time for ketorolac of about 8-12 min.

Blank: use mobile phase as blank.

Chromatographic parameters:

Use suitable high performance liquid chromatograph equipped with following:

1. Column : 4.6mm X 25cm
2. Column temperature : 40ºC
3. Sample compartment : 10ºC
4. Flow rate : 1.5 ml/mins
5. Wavelength : 313 nm

6. Injection volume : 10 µl
7. Run time : about 15 minutes.
8. Diluent : HPLC grade water.

Preparation of standard stock for ketorolac:

Weigh and transfer accurately about 40 mg of ketorolac in to 100 ml of volumetric flask. And dissolve and dilute with to volume with solvent mixture and mix. Sonicate (use ice chilled water in the sonicator to avoid heating of sample)

Test preparation:

Weigh and crush not less than 20 tablets. Weigh and transfer equivalent to one tablet into 50 ml volumetric flask, dissolve and dilute to volume with solvent mixture.

Procedure:

Separately inject equal volume of blank. Standard preparation and test preparation in to the chromatograph and measure the peak area counts for ketorolac tromithamine.

Evaluation of system suitability:

1. The RSD for the peak area counts of ketorolac tromithamine from 4 injections of standard solution should not be more than 2.0 %
2. The tailing factor for ketorolac tromithamine should not be more than 2.0.

Calculations: (for ketorolac tromithamine):

$$\% \text{ W/W of Assay} = \frac{ATA}{A} \times \frac{TW}{50} \times \frac{50}{SW} \times \frac{PS}{100} \times AW \times 1000$$

Where,

ATA = Average peak area counts for test solution.

ASA = Average peak area counts for standard solution.

TW = Weight of test solution taken. In mg

SW = Weight of standard solution taken. In mg

PS = Purity of working standard. In mg

AW = Average weight of tablet. In mg.

Table.no.10. Average Drug Content.

S.No.	Formulation no	Cumulative % drug Release
1.	F-1	80.32
2.	F-2	82.21
3.	F-3	93.20
4.	F-4	94.51
5.	F-5	97.60
6.	F-6	98.93
7.	F-7	98.20
8.	F-8	99.62
9.	F-9	98.93

8.1. RESULTS AND DISSCUSSION

8.1.1. Preformulation studies:

The procured sample of ketorolac tromethamine was tested by Dr.Reddy's laboratories. The manufactured also confirmed quality and purity of sample.

The drug-excipients compatibility was done at 40ºC/ 75 % RH. 60ºC/ 80 % RH. Open and closed vial methods were used. The result did not show any physical change to the mixture after interval at the end of 30 days. This fact concluded that the drug and excipients are compatible with each other.

8.1.2. Physiochemical parameters and drug release pattern:

The tablets of ketorolac tromethamine were prepared by direct compression and were evaluated for weight variation, drug content, friability, hardness, thickness and drug release pattern for all the formulation 1 to 9.

Deals with results of all formulations 1 to 9 and experiments and their discussions.

Formulation - 1:

Hardness, weight variation, defective in dies and punches occurs due to excessive fine powder were observed during compression. So, in the next batch, add with sodium starch glycolate and decreases the concentration of the maize starch.

Formulation - 2:

There was a flow problem and capping problems occurs. So, in the next batch add sodium starch glycolate and increased quantity.

Formulation - 3:

Colloidal silicon dioxide produced black dots in the tablets and excessive increasing in the disintegration time. So, in the next batch we decreases the concentration of maize starch and colloidal silicon dioxide

Formulation - 4:

Due to excessive fines the formulation is occurs capping and insufficient lubricant picking and sticking occurs. So in the next batch increase the concentration of maize starch.

Formulation - 5:

The first point of dissolution is slow release. Later, in the third point of dissolution again there is fast release. So, in the next batch, added maize starch (0.85mg) and sodium starch glycolate 5%.

Formulation - 6:

The release is increased as compare to the last batch. So, in the next batch removed the colloidal silicon dioxide

Formulation - 7:

The release is decreased as compare to the last batch.

Formulation - 8:

In this batch, the release of ketorolac tromethamine was better compare to the last batch. This formula passes the every aspect of specifications

Formulation - 9:

In this batch, the release is decreased as compare to the last batch.

For stability:

Optimized batch were taken and subjected for stability, we observed on stability data, optimized batch passes the tests.

9.1. CONCLUSION

The Study was undertaken with an aim to formulate, develop and evaluate ketorolac romethamine different excipients. Preformualtion study was done initially and results directed for the further course of formulation. Based on preformulaion studies different batches of ketorolac were prepared using selected excipients. Blend evaluated for tests loss on drying, bulk density, tapped density, compressibility index, Hausner ratio before ring punched as tablet. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables.

From the above results and discussion it is concluded that formulation ketorolac tromethamine containing 50% of micro crystalline cellulose, disintegrating agent Colloid silicon dioxide in Batch-VIII can be taken as an ideal or optimized formulation, it fulfills the requirements for short term release tablet and our study encourages for the further clinical trials and long term stability study on this formulation

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