Innovation And Preparation of Ketoprofen

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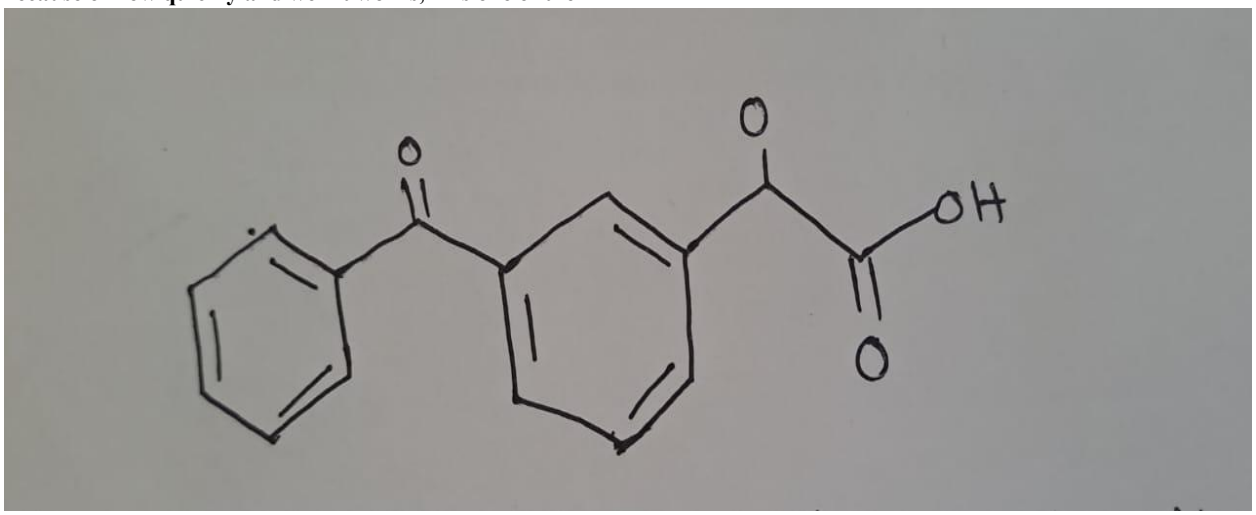
***Abstract*—The pharmacokinetic profile of ketoprofen changed as a result of formulation variations brought forth by the study, most notably the addition of different dissolving or extended-release agents. When poloxamer-188 was used as a release modifier, the pharmacokinetic parameters Cmax and AUC of ketoprofen increased the most. Consequently, the pharmacokinetic profile of the medication may be significantly impacted by the use of release modification drugs.Microsponges are drug delivery systems made of porous polymeric microspheres. They improve stability, lessen systemic side effects, and provide a regulated release of medications.**

There are numerous preparations and formulations of ketoprofen that are frequently utilized. Solubilizing and prolonging release agents can be used to create different formulations. This investigation sought to ascertain how variations in formulation affected the pharmacokinetic profile of ketoprofen in rats. A literature review was the focus of this study. Between 2011 and 2020, articles were obtained from the ScienceDirect and PubMed databases. As a member of the nonsteroidal anti-inflammatory medication (NSAID) family, ketoprofen (K) exhibits analgesic, anti-inflammatory, and antipyretic effects. Because of how quickly and well it works, K is one of the most widely utilized NSAIDs. Although K is now utilized to alleviate pain and rheumatic disease symptoms, numerous researchers are searching for further applications for this nutrient.

***Index Terms*—Microsponges, Ketoprofen, NSAD, Formulation, pharmacokinetics**

I. INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory inhibition drug (NSAID) derived from propionic acid derivatives, which have anti-inflammatory, analgesic, and antipyretic properties in acute and chronic rheumatoid arthritis therapy and for the treatment of osteoarthritis (Kuczynska and Nieradko-Iwanicka, 2022; Mariniello et al., 2022; Sarzi-Puttini et al., 2010 According to the Biopharmaceutical Classification System, ketoprofen is a class II medication because of its high permeability and poor solubility. Due to its relatively fast half-hour onset and six-hour duration of action, oral ketoprofen is particularly effective.



2-(3- benzoyl phenyl) propanoic acid

In 1968, ketoprofen (K) was created. [1]. It works by non-specifically inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) to prevent prostaglandin formation. The production of prostaglandins with physiological roles is carried out by COX 1, while the production of pro-inflammatory prostaglandins at the site of inflammation is carried out by COX 2. Only the S-enantiomer of the chiral compound K exhibits COX-inhibiting action [4]. After being broken down in the liver, it is mostly eliminated in the urine and, to a lesser degree, in the feces. It doesn't build up. K can be absorbed by injection (intramuscular, intravenous), transdermal application, and oral and rectal administration.

K can be purchased as an over-the-counter medication in 50 mg capsules and as a prescription medication in a number of pharmaceutical formulations, including injectable solution (50 mg/ml), tablets, suppositories (100 mg), gels (25 mg/g), and capsules (100 mg, 150 mg, and 200 mg) [5]. K's effects on COX are linked to its side effects [6]. Chronic use side effects include headache and fatigue, depression, anxiety, nightmares, drowsiness, cardiovascular responses (peripheral edema), and dermatological issues such as skin sensitivity and photosensitization following topical treatment. K results in increased liver enzyme activity, platelet dysfunction, ulcers, bleeding, and gastrointestinal issues include diarrhea, vomiting, and irritation of the stomach and duodenum. K side effects include decreased renal blood flow, which can result in electrolyte imbalance, hypertension, and renal impairment.

However, because to its quick and efficient action, K is one of the most widely used nonsteroidal anti-inflammatory medicines (NSAIDs).It is extensively utilized in the treatment of fever, pain, and inflammatory and musculoskeletal disorders (such as rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis). According to the product's properties, the drug's indications for administration include the reduction of certain pain syndromes and the symptomatic treatment of inflammatory and degenerative rheumatic illnesses of the skeletal system. Rheumatoid arthritis, osteoarthritis, and moderate pain are among the conditions for which intramuscular injection is indicated.Uses of ketoprofen pain alleviation

II. MATERIAL AND METHODS

1 Apparatus -

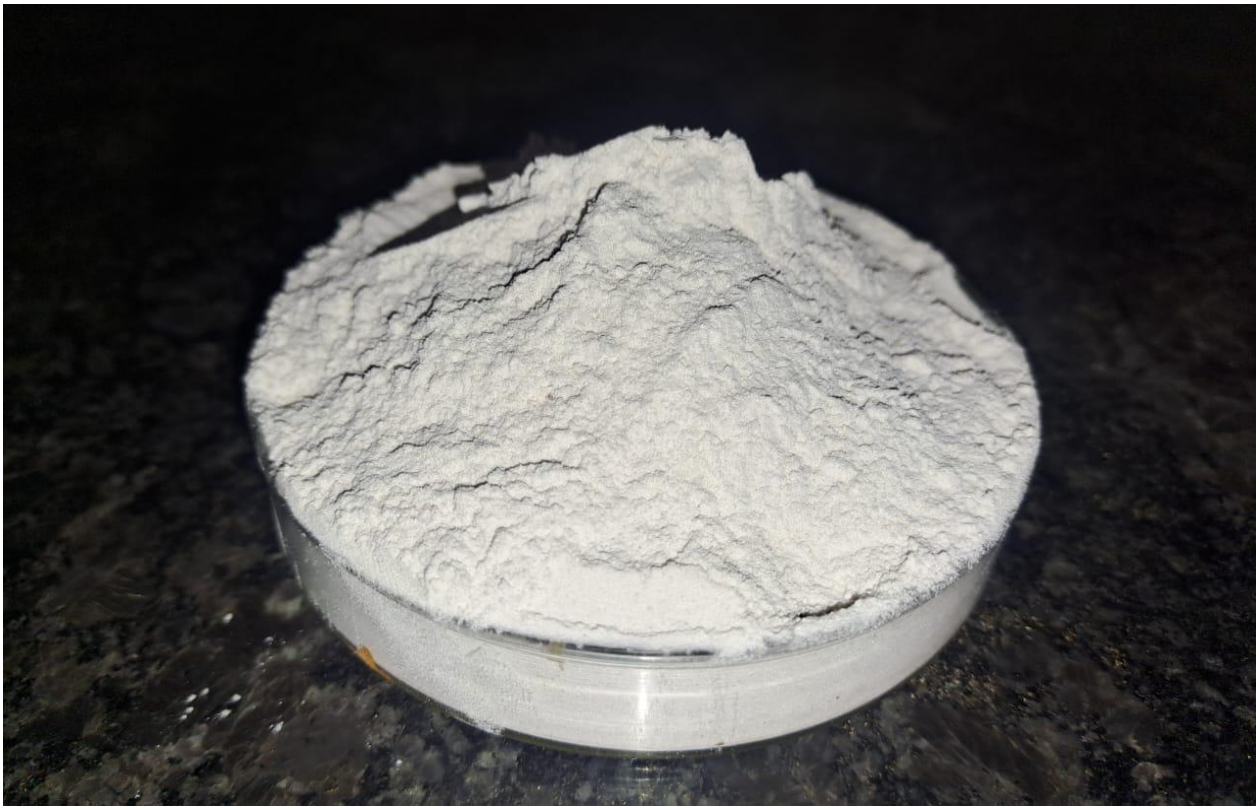
The compatibility of the drug with the formulation components was established by Fourier Transform Infrared Spectra (IRAffinity-1S)and thermogravimetric analysis (Mettler TG50). The morphology of the microsponges prepared was investigated using scanning electronic microspcopy(JEOL 7200) and optical microscop (Oxion).

2 Reagents -

ketoprofen (KP) is a gift sample from a national company. Ethyl cellulose (EC), Polyvinyl alcohol

(PVA) and Dichloromethane were purchased from SIGMA-ALDRICH. ,
3. Qualitative drug analysis

A validated UV spectroscopy using a SHIMADZU UV-1800spectrophotometer was adopted to quantify ketoprofen content in the microsponges at a maximum Formulation and characterization of controlled release ... JNTM(2019)



Ketoprofen uses

- Pain relief
- it reilves pain and inflammation
- Rheumatoid arthritis
- Muscles pain
- Low back pain and toothache

Side effect of ketoprofen

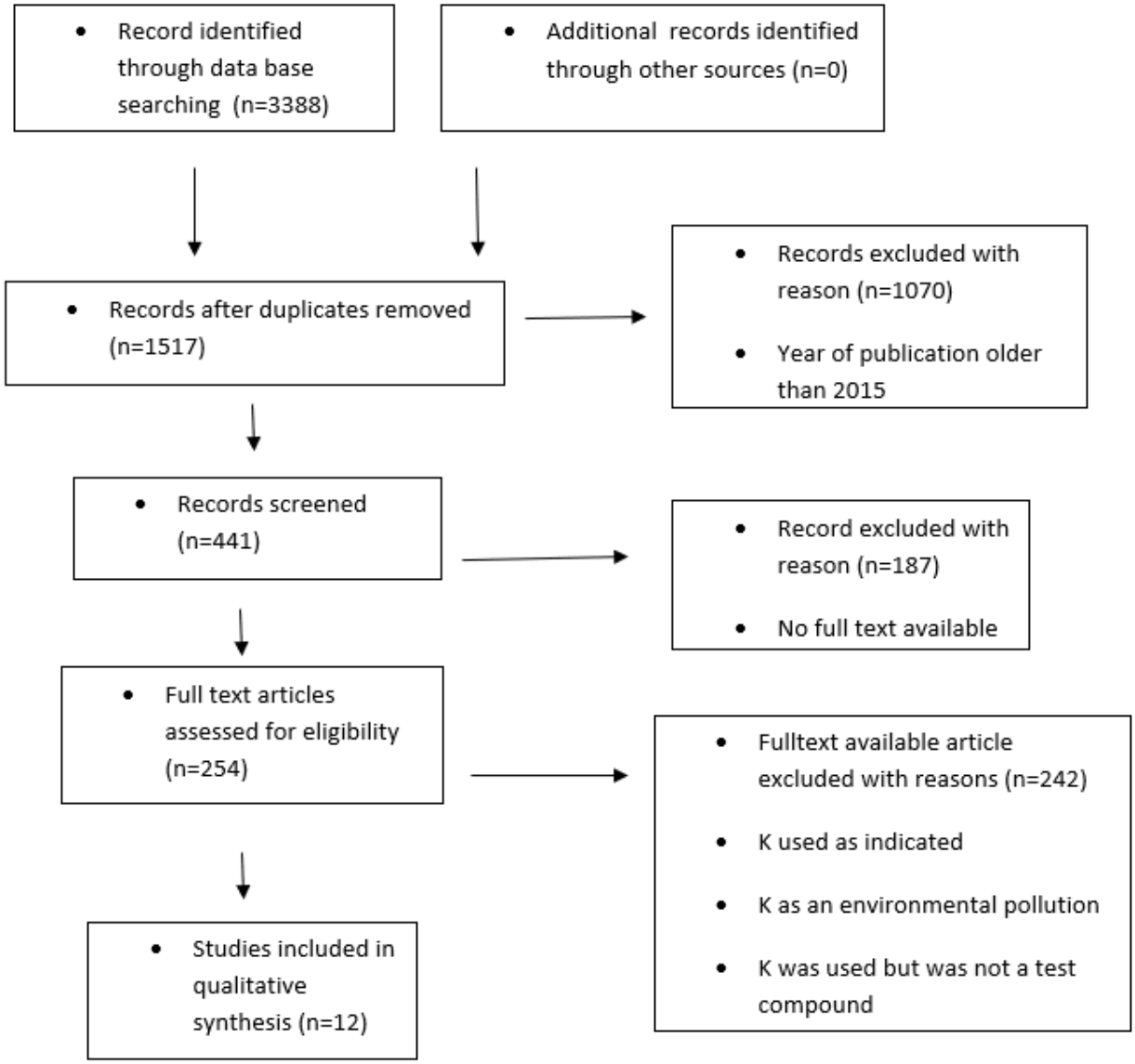
- Vomiting
- Nausea
- Abdominal pain
- Constipation
- diarrhoea
- Headache
- Dizziness
- Ringing in ear
- Visual disturbance
- Rash
- Edema
- Decreased appetite

How ketoprofen functions

Non-steroidal anti-inflammatory medicines (NSAIDs) like ketoprofen function by preventing the release of certain molecules that cause inflammation and fever pain.

III. METHODOLOGY

The literature data was reviewed using the most recent, standard criteria. A lookup for English-language publications in Google Scholar, PubMed, Medline Complete, and
database was used. In February 2021, the terms "ketoprofen,""ketoprofen and treatment," and "ketoprofen and effects" were used to audit the Scholar databases.



I. Oral Drug Delivery Systems (To Reduce Gastric Irritation & Sustain Release)

Common oral tablets/capsules can be the cause of direct irritation of gastric mucosa. To address this issue, scientists have developed various formulations such as those that delay release, control release rate, or increase the drug's solubility.

1. Sustained and Controlled Release Systems

The aim is to extend the drug's therapeutic effect and lower the dosing frequency.

Matrix Tablets:

The drug is homogeneously mixed in a polymer matrix (usually hydrophilic polymers like Hydroxypropyl Methylcellulose (HPMC) or natural gums such as Hibiscus rosa-sinensis mucilage or Neem Gum are used).

The drug release is limited by the erosion and/or swelling and diffusion of the polymer matrix, thus giving release up to 24 hours.

Delayed Release (DR) Pellets:

These are small spherical units (pellets) coated with a pH-sensitive polymer (e.g., Acrycoat L30D, or polymers that do not dissolve in stomach acid).

The enteric layer does not allow drug release in the acid stomach and dissolves only when the pellets arrive at the small intestine with a higher pH, thus the drug release occurs in the intestine, and gastric irritation is avoided.

2. Gastroretentive Systems (To Increase Residence Time)

Such systems are the ones which remain in the stomach for a prolonged period and thus improve the

drug absorption of drugs that are absorbed in the upper GI tract.

Floating Drug Delivery Systems (FDDS) / Floating Microparticles:

The products (such as microspheres or in-situ gels) are made to have a bulk density lower than gastric fluid, so they can float.

As the formulation stays in the stomach (transit is delayed), it slowly releases the drug, thus absorption is prolonged and bioavailability is increased.

In-Situ Gels:

This is a liquid preparation which, after being administered to the stomach, turns into gel due to the change in pH, temperature, or the presence of ions (e.g., Gellan Gum or Sodium Alginate may be used for cation-driven gelation). In this way, the drug residence time is prolonged.

II. Topical & Transdermal Drug Delivery Systems (To Bypass Systemic Side Effects)

Topical delivery (drug application directly to the skin) is an ideal mode of administration for Ketoprofen as it brings the drug directly to the site of pain or inflammation, thereby achieving high local concentration with minimum systemic exposure and side effects (such as GI bleeding) resulting from systemic administration.

1. Enhanced Conventional Topical Formulations

Gels and Emulgels:

Gels are typically semisolid (usually with a gelling agent like Carbopol) and are easy to spread on the skin, thus they are well accepted by patients.

Emulgels contain a gel base and an emulsion (oil-in-water or water-in-oil), thus they are a biphasic system that can more efficiently deliver hydrophobic drugs such as Ketoprofen. Moreover, these products usually have diffusion enhancers (e.g., Mentha oil, Clove oil) to facilitate the penetration of drugs through the skin.

Transdermal Patches:

These are drug-containing adhesive patches that are temporarily fixed to the skin and from which drugs are released at a controlled rate into the blood vessels or tissues around the application site.

2. Advanced Nanocarrier Systems (Novel Delivery)

These innovative systems employ nanotechnology to improve the solubility, stability, and penetration of drugs through the skin.

Nanoparticulate Gels (Nanogel):

Ketoprofen nanoemulsion (extremely small oil and water droplets stabilized by surfactants) is applied to the skin along with a gel base (commonly Chitosan).

By this way, the minuscule particles of the drug can easily penetrate the tough outer layer of the skin (stratum corneum).

Transethosomes:

They are advanced energetic vesicular carriers that consist of the drug, phospholipids, and a very large amount of ethanol.

The high concentration of ethanol in the vesicles makes them extremely flexible and hence they can pass through tiny pores or channels in the skin, thus the drug delivery is not only increased but the drug can also reach the deeper layers of the tissue.

Microemulsions/Nanoemulsions:

They are clear, thermodynamically stable mixtures of oil, water, and surfactants/co-surfactants (e.g., Oleic acid, Tween 80).

Being these excellent solubilizers they solubilize Ketoprofen effectively and are excellent carriers for skin penetration.

Pharmacosomes:

A drug-delivery system of vesicles, in which the drug is complexed with a phospholipid (like phosphatidylcholine). It makes the drug more water-soluble and gives high bioavailability along with sustained-release profile.

Drug-in-Cyclodextrin-in-Nanostructured Lipid Carriers (NLC):

An intricate, multi-layered system whereby the drug is first bound to a Cyclodextrin (Cd) to enhance its solubility and stability.

This drug-Cd complex is then inserted into Nanostructured Lipid Carriers (NLC) (composed of a mixture of solid and liquid lipids) for the dual purpose of extended release and increased percutaneous absorption..

Safety Profile of Ketoprofen (Without References)

Ketoprofen is a strong and non-selective non-steroidal anti-inflammatory drug (NSAID), the safety issues of which, are mainly due to its primary mechanism of action: the inhibition of cyclooxygenase (COX) enzymes. This inhibition interferes with the body's essential protective processes, which are mainly in the digestive, cardiovascular, and renal systems.

1. Gastrointestinal (GI) Toxicity (The Most Frequent Side Effect)

The foremost and most severe side effect of oral Ketoprofen that has been recognized is the injuring of the stomach and intestinal lining, which may feature a mild upset or, in contrast, may develop to severe bleeding and ulceration.

Mechanism of Harm:

Systemic Prostaglandin Depletion: Ketoprofen blocks the COX-1 as well as COX-2 enzymes non-selectively. COX-1 is a "housekeeping" enzyme responsible for producing protective prostaglandins (PGE 2 and PGI 2).

Loss of Defense: These prostaglandins are the main ones which guarantee the gastric mucosa integrity by:

Encouraging the production of protective mucus.

Supporting the release of bicarbonate (to neutralize acid).

Ensuring that blood supply to the stomach lining is enough.

Acid Attack: Inhibiting COX-1 by Ketoprofen, therefore, takes away this protective barrier which makes the acid of the stomach able to injure the stomach lining that results in ulcers, perforations, and haemorrhage.

Mitigation Strategies:

Topical/Transdermal Delivery: The use of drugs through gels or patches gives relief to the local area and also minimizes systemic exposure and thus the risk of gastritis apart from completely bypassing the digestive tract.

Prodrugs/Salts: Products such as Ketoprofen Lysine Salt (KLS) are made to enhance solubility and quicken absorption, thus the concentration of the acidic drug that directly causes the irritation of the stomach wall may be lowered.

Enteric Coating: Making the tablets that break down only at the higher \text{pH} of the intestine also lessens the direct contact of the stomach with the drug.

2. Cardiovascular (CV) Thrombotic Risk

As with almost all other traditional NSAIDs, Ketoprofen elevates the possibility of having serious thrombotic events such as heart attack (Myocardial Infarction) and stroke.

Mechanism of Harm (Pro-Thrombotic State):

Imbalance of Prostaglandins: The source of the risk is in the interference with the fragile equilibrium between the two opposing compounds:

Thromboxane : One of the major sources of platelets via is a strong vasoconstrictor and supports platelet aggregation (clotting) by attracting more platelets and initiating the releasing of granules.

Prostacyclin Most of the comes from the inner lining of the blood vessels through is a vasodilator and thus helps to widen blood vessels. It also blocks platelet aggregation, thus preventing the formation of clots.

The Change: Through inhibiting by Ketoprofen, the production of decreases. While production is affected only to a small extent. Therefore, the balance is now tipped towards the pro-clotting and vasoconstrictive effects of which leads to thrombosis, consequently MI or stroke may be the results.

3. Renal (Kidney) Impairment

Ketoprofen has the potential to impair kidney function, particularly in at-risk patients.

Mechanism of Harm:

Blood flow compromised: Prostaglandins and are very important in maintaining good blood flow to the kidney in situations where the kidney's blood supply is already limited (for example, in heart failure, dehydration, or kidney disease of any origin).

Vasoconstriction: By blocking the production of these physiologically very important prostaglandins by Ketoprofen, the blood vessels that carry blood to the kidney get narrowed and as a result, fluid retention, swelling, high blood pressure, and, if it is a severe case, acute kidney injury will occur.

4. Other Side Effects

Dermatological/Photosensitivity: The local application of Ketoprofen is specifically related to the risk of photosensitivity, i.e. the treated skin may react with an extreme damage when exposed to the sun.

Hypersensitivity: The appearance of hypersensitivity symptoms is rare, but if it happens, it includes just as well severe skin disorders.

IV. CONCLUSION

The NSAID ketoprofen was used as a model for the direct compression method of creating fast-dissolving tablets. Different superdisintegrant concentrations were added to create fast-dissolving tablets, and various ketoprofen FDT formulas were created using various excipients. Masking the harshness of Ketoprofen's flavor has been done to reduce pill formulation compliance. Weight variation, thickness uniformity, friability, hardness, wetting time, water absorption time, dispersion time, disintegration time, and dissolution time were all assessed for each

manufactured FDT. Infrared spectroscopy has been used to identify ketoprofen as a pure medicine and to determine whether ketoprofen and any excipients interact (are compatible).

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