WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 21, 566-618. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF KETOPROFEN

Mohammed Hasan Faqera*, Venkatesh, Nagendra R., K. Hanumanthachar Joshi

Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru-570004.

Article Received on
06 Oct. 2023,

Revised on 27 Oct. 2023,
Accepted on 17 Nov. 2023

DOI: 10. 20959/wjpr202321-30358

***Corresponding Author**
Mohammed Hasan Faqera
Sarada Vilas College of Pharmacy, Mysuru-570004.

ABSTRACT

The main aim of present work was to formulate and evaluate sustain release matrix tablets of ketoprofen, "an anti-inflammation". Sustain release formulation are those which delivers the drug locally or systemically at a predetermined rate for a fixed period of time. The matrix tablet was prepared by direct compression method using by various concentration of HPMC and TRAGACANTH with combination of various release retardant polymer. The powder mixtures were subjected to various pre-compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, in-vitro dissolution and stability studies. In-vitro dissolution studies were carried out for 24 hours using 0.1 N HCL for first 2 hours and pH 6.8 phosphate buffer for 24 hours and the result showed that formulations F4 and F7 showed good dissolution profile to control the drug release respectively. Formulation containing higher concentration of HPMC and TRAGACANTH along with polymers sustained the drug release for the period of 24 hours. The compatibility of the drug, polymers and other excipients were determined by FT-IR Spectroscopy. Results showed that the drug was compatible with polymers and other excipients. The release data was fitted to various mathematical models such as Zero-order, First- order, Higuchi equation and Korsmeyer-Peppas model to evaluate the kinetics and the drug release. The drug release followed first order and the mechanism was found to be non-Fickian. The stability studies were carried out for 3 months and result indicates that the selected formulations (F4 and F7) were stable.

KEYWORDS

1) Oral administration
2) Sustained Release 3)Controlled release
4) Receptor targeting
5) NSAID (Non-steroidal anti-inflammatory drugs)
6) KETOPROFEN
7) Polymers
8) FTIR

1. INTRODUCTION

For both new and old medications, oral administration is one of the most popular routes and formulations. It could be because of how simple it is to administer, and most importantly, patient compliance. It has been common practice for many years to administer medications to patients in a variety of pharmaceutical dosage forms, such as tablets, capsules, pills, suppositories, and liquids. As drug carriers, lotions, ointments, liquids, aerosols, and injectable. It is well recognized that this kind of drug delivery system offers a rapid release of medication or an immediate release product. These immediate release medicines cause the drug to be absorbed and the commencement of any attendant pharmacodynamics effects to happen relatively quickly. Eventually, therapeutic effectiveness is lost when plasma drug concentrations drop below the minimal effective plasma concentration (MEC). If a persistent therapeutic impact is sought, another dose is typically administered before this time.

Due to the high cost of new drug research after the 20th century, it has been continued. Because of this, pharmaceutical companies and academic research facilities have concentrated on creating novel drug delivery systems or modified release dosage forms rather than researching and developing new medications.

The main goal of a sustained pharmaceutical delivery system consists of maximize a drug's biopharmaceutics, pharmacokinetic, and pharmacodynamics properties in order to minimize side effects and cure or control a condition in the shortest amount of time while using the least amount of drug and administering it via the most effective route.

Using a dosage form that provides sustained drug release and, as a result, maintain plasma drug concentrations above what is generally observed using rapidly releasing dosage forms is an alternative to giving a second dose. Various changes to drug release timing or modified

release have been made in recent years. However, plasma drug concentrations decrease in accordance with the drug's pharmacokinetics profile once drug absorption from the dose form is complete.

By mixing the drug with a release-retardant material to create a matrix core or by covering the core drug with a release-modifying film coat, modified oral release drug delivery systems have been developed to prolong the drug release for several hours. The MR system allows for less frequent dosing. Low occurrence of adverse effects, improved treatment outcome, and increased bioavailability.[1]

Any drug delivery system's goal is to maintain the desired concentration of the drug by delivering the drug in a therapeutic dose to the body's appropriate site of action. The most practical method of administering the dose form is orally. Tablets are a practical dosage form that both patients and doctors can use. A bilayer tablet is appropriate for the sequential release of two medications, one of which is released immediately and the other of which is released over time.[2]

The term "Drug Delivery" refers to a wide variety of methods used to introduce medicinal substances into the body of an individual. A is used to give medications. Primary goal of patient illness treatment. Drugs are never provided in their pure form; instead, a suitable formulation is created so that the onset, intensity, and overall duration of the action can be monitored. The most popular method of drug delivery among all the available ones is the oral route. However, the traditional dosage form has a few drawbacks that could be fixed by altering the current dosage form.[3]

Drug delivery systems have been improved, such as targeted drug delivery systems where the drug only acts in the specific area of the body to which it is targeted and sustained release formulations where the drug is released from the product over time in a controlled manner at predetermined intervals.

The class of medications known as nonsteroidal anti-inflammatory medicines (NSAIDs) includes ketoprofen. It is a derivative of propionic acid and is used to treat rheumatoid arthritis. The substance's chemical name is (2-benzoyl-3-phenyl propionic acid.). Similar to other NSAIDs, clinics utilize ketoprofen as an anti-inflammatory and analgesic medication to treat osteoarthritis and rheumatoid arthritis. Ketoprofen offers advantages over other NSAIDs

because it has little to no risk for addiction and has no sedative or respiration-depressing effects. Ketoprofen and other NSAIDs have a poor tolerance profile and certain side effects.[4]

Among all the ways that have been investigated for the systemic distribution of pharmaceuticals via diverse pharmaceutical products of varied dose forms, oral drug delivery has long been recognized as the most popular route of administration. The majority of pharmaceutical experts nowadays are working to create the ultimate DDS. This perfect setup should deliver the medication directly to the intended site and offer the benefit of a single dose for the length of the treatment. Scientists have succeeded in creating a system that comes close to being ideal, and this inspires them to create controlled release systems.

1.1 Sustained Release

The primary goal of the design of an oral sustained drug delivery system (DDS) should be to increase predictability and repeatability to control the release of the drug. By regulating a drug's release into the body with a lower and less frequently dose, its concentration in the target tissue is increased, and its therapeutic action is optimized. Regular administration of a therapeutic agent that has been prepared to maintain its stability, activity, and bioavailability is a common component of conventional pharmacological therapy. The majority of medications can be successfully formulated using traditional procedures. However, certain medications are poisonous, unstable, and have a limited therapeutic range. They may also have severe solubility issues, need to be localized to a specific area of the body, or require long-term use or rigorous adherence. By focusing on the medicine's site of action, lowering the dosage needed, or ensuring uniform drug delivery, sustained or sustained delivery systems aim to decrease the frequency of dosing or increase the drug's effectiveness. So, sustained release dosage form is a dose form that delivers one or more medications either centrally or to a specific target organ continuously in a predetermined sequence for a set amount of time. Extended release dosage forms offer more consistent distribution, reduced dosing frequency, less side effects, and improved control of plasma drug levels.

The interest in continuous release drug delivery systems has increased significantly during the past 20 years. The prohibitive cost involved in creating new drug entities, the expiration of current international patents, the discovery of new polymeric substances suitable for delaying the release of the drug, and the enhancements in therapeutic efficacy and safety attained by these delivery systems are just a few of the factors that have contributed to this. Today,

veterinary products are also using the technology of long-term release. These systems also offer a slow drug release over a longer duration of time and have the ability to control drug release in the body, either spatially or temporally or both. In other words, this system is effective at preserving unchanged drug levels in the intended tissue or cells.

A sustained release dosage form is one that permits a reduction in dosing frequency from that required by a traditional dosage form, such as a solution or an immediate release dosage form, according to the U.S. Food and Drug Administration (FDA).

In contrast to conventional forms that may need to be taken three or four times daily to have the same therapeutic impact, sustained release tablets and capsules are often taken just once or twice daily. Sustained release medicines often offer an instant drug release that quickly produces the intended therapeutic impact, followed by a steady release of further amount of drug to maintain that effect for a predefined duration of time (Fig 1). There is typically no need for nighttime dosage thanks to the maintained plasma medication levels provided by sustained release medicines, which is advantageous for both patients and healthcare providers.

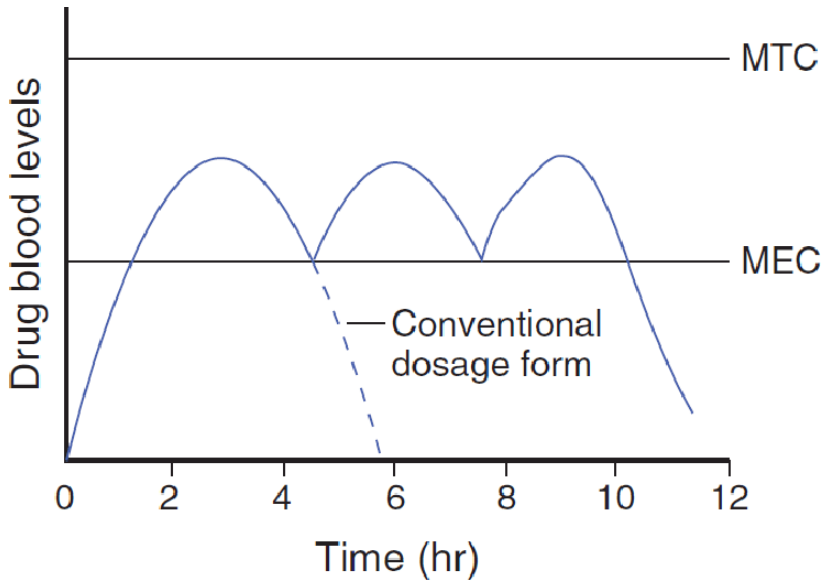


Fig.1: Hypothetical drug blood level – time coverage for a conventional solid dosage form and a multiple action product.

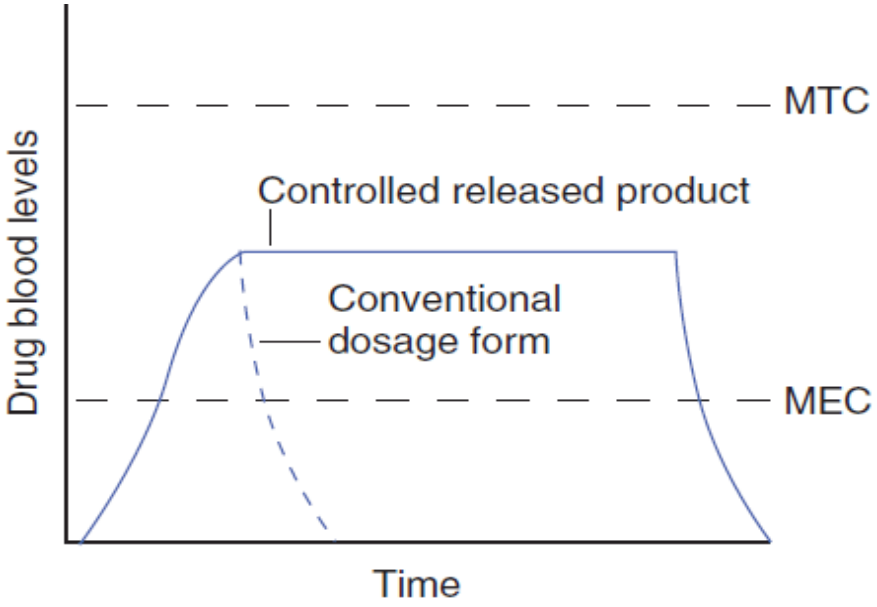


Fig.2: Hypothetical Drug Blood Level – Time Coverage For A Conventional Solid Dosage Form And A Controlled Release Product Terminology.

Pharmacokinetic Simulation of Sustained Release Products

Many sustained release medicines have plasma drug concentration patterns that are consistent with an oral single compartment model assuming the first-order absorption and disposal. Due to the prolonged release product's delayed absorption compared to an instant release product, it often exhibits a lower absorption rate constant. The time for peak concentration (tmax) is usually longer(fig3) and the peak drug concentration (Cmax) is reduced. Area under the plasma concentration of the drug curve should be the same if the drug is appropriately prepared. Parameters like Cmax, tmax, and AUC easily demonstrate how well the sustained release product operates in vivo. For instance, if a product's intended shelf life is 12 hours, a tmax of 3 hours might not be ideal. Similar to this, an abnormally high Cmax indicates dosage dumping as a result of poor formulation. Regulatory organizations have used the pharmacokinetics analysis of plasma data from single and repeated doses to assess a variety of sustained release products. Even though the medication cannot be released in a first order fashion, many products may be matched to this model, making the study useful. This sort of investigation has the drawback that the absorption rate constant might not match the rate at which the medication dissolves in vivo.

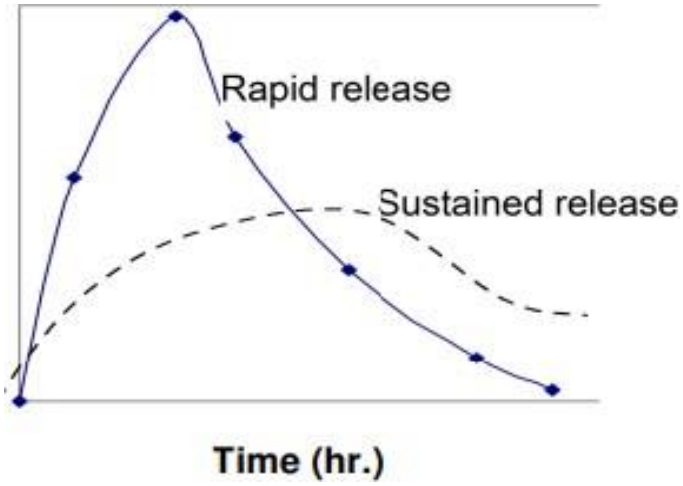


Fig. 3: Plasma drug concentration of a SR and a regular release product.

Other models have also been employed to predict prolonged release product plasma drug levels (Wellin, 1983). Equation can be used to simulate the plasma drug levels from a zero-order, sustained release drug product.

Where, is:

Ds = maintenance dose or rate of drug release (mg/ml), Cp = plasma drug concentration

K = overall elimination constant, VD = volume of distribution

In absence of loading dose, the drug level in the body rises slowly to a plateau with minimum fluctuations.

This simulation assumes that

1) Rapid drug release occurs without delay,
2) Perfect zero-order release and absorption of the drug takes place,
3) The drug is given exactly every 12 hours.

In practice, the above assumptions are not precise, and fluctuations in drug level do occur

When a sustained release drug product with a loading dose (rapid release) and a zero-order maintenance dose is given, the resulting plasma drug concentrations are described by:

$$C_p = \frac{D_i\, Ka}{V_D\ (Ka-K)}\ (e^{-Kt} - e^{-Kat}) + \frac{D_S}{V_D\, K}\ (1\text{-}e^{-Kt}) \quad \text{--------(2)}$$

Where, is:

Di = immediate – release (loading dose) and Ds = maintenance dose (zero-order).

This expression is the sum of the oral absorption equation (first part) and the I.V infusion equation (second part).

An example of a zero-order release product with loading dose is shown in fig-4 the contribution due to the loading and maintenance dose is shown by the dashed lines, the inclusion of a built-in loading dose in the extended release product has only limited use.

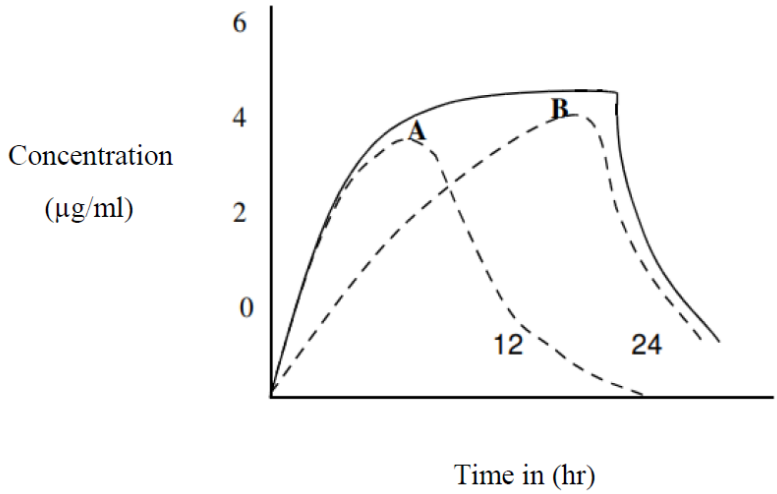


Fig.4: Simulated plasma drug level of a SR product with a fast release component (A) and a maintenance component (B). The solid line represents total plasma drug level due to the two components.

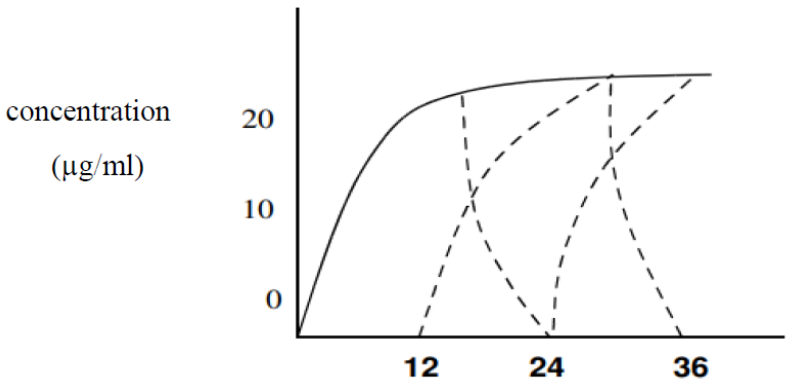


Fig. 5: Simulated plasma drug level of a SR product administered every 12 hrs. The plasma level shows a smooth rise to steady state level with no fluctuations.

With the majority of sustained release medications, the patient receives multiple doses, and future doses don't require a loading dose. In circumstances when a loading dose is required, the rapid- release product is used to adjust a loading drug that will raise the plasma drug concentration to therapeutic level. This prevents administering a loading dose to the body that is greater than necessary due to the topping effect.

There is also a pharmacokinetic model that proposes first-order absorbing of the loading and maintenance dose. This model forecasts spiking peaks caused by the loading dose when the medication is constantly delivered. (Fig.6).

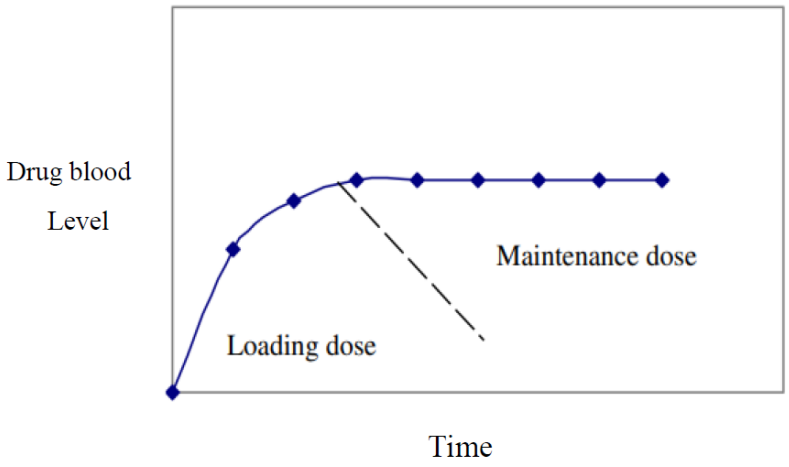


Fig. 6: A hypothetical plasma concentration time profile from sustained drug delivery formulation.

1.2 Terminology and Sustained Release Concept

Manufacturers have used a variety of terminology (and abbreviations) over the years to characterize different product kinds and attributes, including sustained release (SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA). These phrases are used to describe drug delivery systems that continually release medication over a protracted period of time after administration of a single dose in order to activate a prolonged therapeutic effect. This time frame can range from days to months when using an injectable dosing form. Although these terms are frequently used interchangeably, specific items bearing these characteristics may differ in performance and design, necessitating a closer look to identify their unique attributes.

Sustains release

- Controlled Release
- Extended Release

1) Controlled release

Any delivery system for drugs that achieves a gradual release of the drug over a longer period of time is included in these systems. The release profiles of controlled release (CR) systems are primarily governed by the unique technological design and construction of the system

itself, and they deliver drug release in an amount sufficient to sustain the medication's therapeutic level over an extended period of time. Therefore, it is preferable if the release of the active ingredient is unaffected by external influences.

A controlled release formulations called an extended release is intended to deliver an even and reliable release of the active ingredient. Extended release (ER) dosage forms are those that, as a result of unique preparation technique, quickly sustain therapeutic drug levels for 8–12 hours following a single dose administration.

2) Extended Release

Pharmaceutical dosage forms which distribute the medicine at a predetermined pace but in a slower than usual way must double the dosing frequency.[5]

3) Prolonged action

Prolonged or long-acting products are dose forms containing medicinal compounds that have been chemically altered to extend biological half-life. These terms are explained in following(Fig.7)

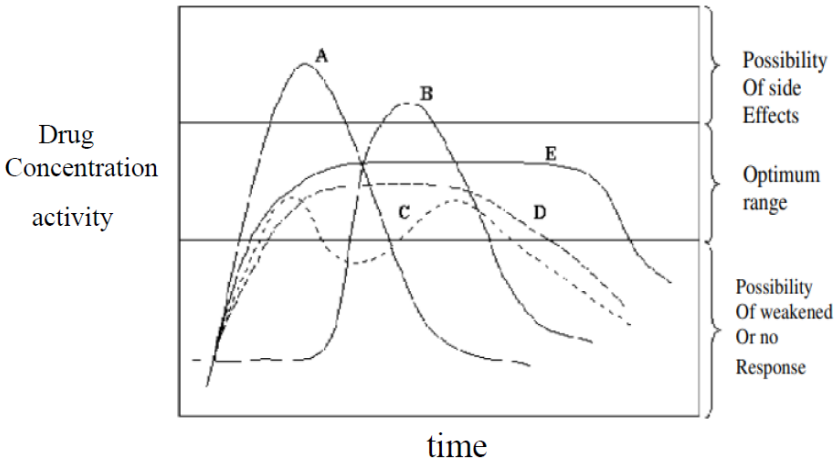


Fig. 7.

A -Immediate release

B -Delayed action

C - Repeat action

D - Prolonged release

E - Controlled, sustained release

An extended period of therapeutic drug levels in the blood or tissues is the major objective of sustained-release dose forms. Typically, this is done by aiming for zero-order release from the dose form.

Zero-order release is the consistent release rate of a drug from the dosage form that is unaffected by the quantity of the drug in the delivery system. In most cases, sustained release systems are unable to achieve this form of release and instead attempt to imitate zero-order release by slowly releasing the drug in a first-order manner (i.e., concentration-dependent). Systematic approaches to achieving sustained-release distribution can also be seen as prolonged release systems. Repeat- action tablets are an alternate sustained release approach in which a dosage form contains many doses of a medicine, each of which is given at regular intervals. Contrarily, delayed-release systems may not be sustaining because their primary purpose is frequently to keep the medicine contained in the body

1.3 ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY

The improvement in drug delivery is represented by several potential advantages as below:

1. It improves patient compliance.
2. It employs lesser quantity of the drug.
3. It may improve the pathophysiology of the diseases.

(a). It minimizes or eliminates local side effects.
(b). It minimizes or eliminates systemic side effects.
(c). It obtains less potentiation or reduction in drug activity with chronic use.
(d). It minimizes drug accumulation with chronic dosing.

4. It improves the efficiency in treatment.

(a) It cures or controls the condition more promptly.
(b) It improves the control of condition i.e. reduces fluctuation in the drug level.
(c) It improves bioavailability of some drugs.
(d) Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

5. Economy

(a) In comparison with conventional dosage forms the average cost of treatment over an extended period may be less.
(b) Economy also may result from a decrease in nursing time and hospitalization. Also

- ❖ Reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- ❖ Reduce amount of drug administration
- ❖ Maximizing availability with a minimum dose.
- ❖ Control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced.
- ❖ Safety margin of high potency drugs can be increased.
- ❖ Increased reliability of therapy

6. Improved therapy

a) Sustained blood level.

The dose form ensures consistent blood levels of the medication levels in contrast to the peak and valley pattern produced by sporadic treatment.

b) Attenuation of adverse effects.

Reduced peak medication concentrations from the usage of standard dose forms result in less often occurring and less severe adverse side effects.

c) It is seldom that a dose is missed because of non-compliance by the patient.

1.4 Inflammation

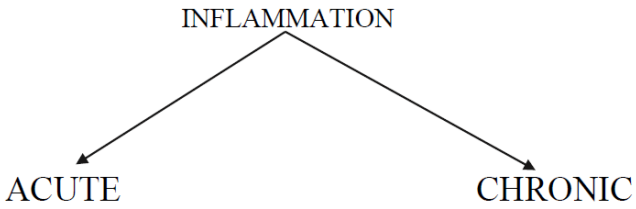
Inflammation involving both the adaptive and innate immune systems is a typical reaction to infection. However, Inflammation can lead to auto-immunity or auto-inflammatory disorders, cancer, neurological diseases, or other conditions if left untreated. Aspirin as well as other nonsteroidal anti-inflammatories are only a few of the safe and efficient anti-inflammatory medications that are readily available; numerous other medications are also being developed. In particular, "biologicals" like anti-cytokine treatments and small compounds that inhibit the activity of kinases are part of the new generation of anti-inflammatory drugs.[6]

What is inflammation

Your immune system is triggered when your body is exposed to a pathogen (such as viruses, bacteria, or toxic substances) or sustains damage. Inflammatory cells and cytokines, molecules that induce the production of more inflammatory cells, are the first immune system defenses that be deployed.

Inflammatory cells are released when your immune system is activated by your body. These cells fight bacteria or repair tissue injury. You may have chronic inflammation if your body

releases inflammatory cells even when you are healthy or uninjured. Numerous chronic disorders, including arthritis and Alzheimer's disease, exhibit inflammation as a symptom.



- **Acute inflammation**

The reaction to an immediate physical injury, like cutting your finger. Your body sends inflammation-producing cells to the wound to speed up healing. These cells initiate the process of healing.

Symptoms

- ✓ Flushed skin at the site of the injury.
- ✓ Pain or tenderness.
- ✓ Swelling.
- ✓ Heat
- ✓ Loos of function

- **Chronic inflammation**

Even when there is no threat from the outside, your body keeps releasing inflammatory cells. For instance, in rheumatoid arthritis, inflammatory cells and chemicals attack the joint tissues, causing an intermittent inflammation that can seriously harm joints and result in pain and deformity.

Symptoms

- ✓ Abdominal pain.
- ✓ Chest pain.
- ✓ Fever. (example: tuberculosis)
- ✓ Joint pain or stiffness. (example: rheumatoid arthritis)
- ✓ Mouth sores. (example: HIV infection)
- ✓ Skin rash. (example: psoriasis

1.5 Most common causes of inflammation

The most common reason of chronic inflammation:-

- Autoimmune disorders: such as lupus, where your body attacks healthy tissue.
- Exposure to toxins: like pollution or industrial chemicals.
- Untreated acute inflammation: such as from an infection or injury

❖ Inflammation in the human body is also influenced by certain lifestyle variables. Chronic inflammation may be more probable to occur if you:

- ✓ Drink alcohol in excess.
- ✓ Have a high body mass index (BMI) that falls within the ranges for obesity, unless that is a result of being very muscular.
- ✓ Exercise at your maximum intensity too frequently, or you don't exercise enough.
- ✓ Experience chronic stress.
- ✓ Smoke.

Treatment

Treatment is not usually necessary for inflammation. Rest, ice, and proper wound care can frequently reduce the pain associated with acute inflammation in a few of days.

❖ If you have chronic inflammation, your healthcare provider may recommend:

1) Supplements

Zinc supplements and some vitamins (vitamins A, C, and D) may help to promote healing and reduce inflammation. For instance, your doctor might advise taking vitamin(s) or a fish oil supplement. Alternately, you might add spices like turmeric, ginger, or garlic that have anti-inflammatory qualities.

2) Nonsteroidal anti-inflammatory drugs (NSAID)

These over-the-counter medicines lower inflammation. Your healthcare provider may recommend ibuprofen (Advil®), aspirin (Bayer®) or naproxen (Aleve®)

3) Steroid injection

Shots of corticosteroids reduce inflammation in a particular joint or muscle. For instance, if your back is affected by rheumatoid arthritis, your doctor can inject a steroid into your spine. The same body part shouldn't have more than three to four injections of steroids per year.

Prevention of inflammation

You may decrease your risk of chronic inflammation by developing healthy lifestyle habits.

Some of these habits include

- ✓ Achieving and maintaining a healthy weight.
- ✓ Avoiding or quitting smoking.
- ✓ Exercising three to five times per week at least (daily exercise is best).
- ✓ Limiting your alcohol intake (maximum 2 ounces per day).
- ✓ Managing stress with healthy tools such as meditation or journaling.

Table 1: Acute/Chronic Inflammation.

	ACUTE	**CHRONIC**
Cause	Harmful pathogens or tissue injury.	Pathogens that the body cannot break down, including some types of viruses, foreign bodies that remain in the system, or overactive immune responses.
Onset	Rapid.	Slow
Duration	A few days	From months to years.
Outcomes	Inflammation improves, or an abscess develops or becomes chronic.	Tissue death, thickening, and scarring of connective tissue.

1.6 DRUG USED FOR ANTI-INFLAMMATORY AGENT

- ❖ IBUPROFEN: such as (NUROFEN)
- ❖ NAPROXEN: such as (NAPROSYN)
- ❖ DICLOFENAC: such as (VOLTAREN)
- ❖ INDOMETHACIN

&

- ❖ KETOPROFEN

1.7 Polymers

Large molecules, often known as macromolecules, or polymers, are essentially collections of several components. The Greek word for "polymer" is "many parts." From the strand of DNA, a naturally occurring biopolymer, to polypropylene, a biopolymer that is utilized in the production of plastic all over the world, polymers are present everywhere.

Natural and synthetic polymers are both generated by humans and can be found in both plants and animals. Due to their various distinctive physical and chemical characteristics, several

polymers are used in daily life.

Polymers cannot be classified under one category because of their complex structures, different behaviors and vast applications. We can, therefore, classify polymers based on the following norms.

❖ **Natural polymers**

Biologically derived polymers, such as those from plants and animals. They are present in all living things and support the metabolic processes in both plants and animals. In both kingdoms, natural polymers serve as building blocks for upkeep and bodybuilding. They can be found everywhere and are omnipresent. As an illustration, cellulose, rubber, etc. DNA and RNA are two further examples of natural polymers. These two polymers are crucial to every phase of life in all living things. Peptides, proteins, and enzymes can only be produced by this messenger RNA in a living organism.

Example of natural polymers

✓ Proteins and Polypeptides
✓ Collagen
✓ Latex
✓ Cellulose
✓ Starch

❖ **Semi-synthetic polymers**

These were produced using cellulose. Natural polymers are the primary source of semi-synthetic polymers. However, they are altered through a synthetic chemical process to either increase or decrease specific features. A specific natural polymer is now more capable to perform in the particular role it was intended for thanks to this human intervention

Example of semi-synthetic polymers

✓ Cellulose acetate
✓ Rayon
✓ Nitrocellulose

❖ Synthetic Polymers

Synthetic polymers are those that are produced through chemical reactions and are utilized in daily life. They come from petrochemical resources like oil and petroleum. They go through

treatment to develop desirable qualities like durability and flexibility, just like semi-synthetic polymers. They therefore display a variety of appealing qualities.

Example of synthetic polymers

(Vulcanized rubber - Nylon -Teflon - Polyethylene)

2.1 AIM OF WORK

There are various methods for administering medications to patients in the practice of pharmacy. If the medication is taken according to the recommended dosing schedule, it must be taken more than once to have the desired therapeutic impact. Because of this frequent dosing, drug level fluctuations in the plasma happen. When the concentration falls below the minimal therapeutic level, the noticeable fluctuation caused by conventional drug administration is likely to produce a period of therapeutic benefits. Sustained release methods can be used to regulate drug concentration within the constrained therapeutic range, reducing the severity of adverse effects.

2.2 PLAN OF WORK

1) Drug selection
2) Literature Survey
3) Preformulation study: Compatibility evaluation was carried out between drug and polymers in physical observation and by using FT- IR spectral study
4) Drug excipients interaction study
5) Formulation of ketoprofen
6) The following evaluation parameter was studied to prepare sustained release tablets:

2.3 Evaluation of granules

1. Angle of repose
2. Apparent bulk density
3. Tapped bulk density
4. Percent compressibility
5. Hausenr ratio

2.4 Evaluation of the tablet

1. Tablets description
2. Tablets thickness and diameter
3. Hardness

4. Friability
5. Weight variation
6. Content uniformity of active ingredients
7. FT-IR
8. DSC
9. In vitro dissolution study

7) Evaluation of stability studies as per ICH guideline.

1. **Andrade LN, de Sousa DP et al., (2018):** Faced with the need to find new anti-inflammatory agents, great effort has been expended on the development of drugs for the treatment of inflammation. This disorder reduces the quality of life and overall average productivity, causing huge financial losses. In this review the anti-inflammatory activity of 32 bioactive monoterpenes found in essential oils is discussed. The data demonstrate the pharmacological potential of this group of natural chemicals to act as anti-inflammatory drugs Inflammation is a complex biological response of vascular tissues against aggressive agents such as pathogens, irritants, or damaged cells. It can be classified as either acute or chronic, and involves a cascade of biochemical events comprising the local vascular system, the immune system, and different cell types found in the injured tissue. Acute inflammation is the initial response and is characterized by the increased movement of plasma and innate immune system cells, such as neutrophils and macrophages, from the blood into the injured tissues. Chronic inflammation concerns a progressive change in the type of cells present at the site of the inflammatory reaction and is characterized by simultaneous destruction and healing of the injured tissue.[8]
2. **Hasler P, Stanga Z et al., (2021):** Various nutritional therapies have been proposed in rheumatoid arthritis, particularly diets rich in ω-3 fatty acids, which may lead to eicosanoid reduction. Our aim was to investigate the effect of potentially anti-inflammatory diets (Mediterranean, vegetarian, vegan, ketogenic) on pain. The primary outcome was pain on a 10 cm visual analogue scale. Secondary outcomes were C-reactive protein levels, erythrocyte sedimentation rate, health assessment questionnaire, disease activity score 28, tender/swollen joint counts, weight, and body mass index. We searched MEDLINE (OVID), Embase (Elsevier), and CINAHL for studies published from database inception to 12 November 2021. Two authors independently assessed studies for inclusion, extracted study data, and assessed the risk of bias. We performed a meta-analysis with all eligible randomized controlled trials using RevMan 5. We used mean

differences or standardized mean differences and the inverse variance method of pooling using a random-effects model. The search retrieved 564 unique publications, of which we included 12 in the systematic review and 7 in the meta-analysis. All studies had a high risk of bias and the evidence was very low. The main conclusion is that 6 | P a g e anti-inflammatory diets resulted in significantly lower pain than ordinary diets (−9.22 mm; 95% CI −14.15 to −4.29; p = 0.0002; 7 RCTs, 326 participants).[9]

3. **Tan L, Song X et al., (2021):** Cordycepin is the major bioactive component extracted from Cordyceps militaris. In recent years, cordycepin has received increasing attention owing to its multiple pharmacological activities. This study reviews recent researches on the anti- inflammatory effects and the related activities of cordycepin. The results from our review indicate that cordycepin exerts protective effects against inflammatory injury for many diseases including acute lung injury (ALI), asthma, rheumatoid arthritis, Parkinson's disease (PD), hepatitis, atherosclerosis, and atopic dermatitis. Cordycepin regulates the NF-κB, RIP2/Caspase-1, Akt/GSK-3β/p70S6K, TGF-β/Smads, and Nrf2/HO-1 signaling pathways among others. Several studies focusing on cordycepin derivatives were reviewed and found to down metabolic velocity of cordycepin and increase its bioavailability. Moreover, cordycepin enhanced immunity, inhibited the proliferation of viral RNA, and suppressed cytokine storms, thereby suggesting its potential to treat COVID-19 and other viral infections. From the collected and reviewed information, this article provides the theoretical basis for the clinical applications of cordycepin and discusses the path for future studies focusing on expanding the medicinal use of cordycepin. Taken together, cordycepin and its analogs show great potential as the next new class of anti-inflammatory agents.[10]
4. **Luo C, Zou L et al., (2020):** Inflammatory diseases are caused by abnormal immune responses and are characterized by an imbalance of inflammatory mediators and cells. In recent years, the anti-inflammatory activity of natural products has attracted wide attention. Rosmarinic acid (ROSA) is a water-soluble phenolic compound that is an ester of caffeic acid and 3, 4- dihydroxyphenyl lactic acid. It is discovered in many plants, like those of the Boraginaceous and Lamiaceae families. ROSA has a wide range of pharmacological effects, including anti-oxidative, anti-apoptotic, anti-tumorigenic, and anti-inflammatory effects. The anti-inflammatory effects of ROSA have been revealed through in vitro and in vivo studies of various inflammatory diseases like arthritis, colitis, and atopic dermatitis. This article mainly describes the preclinical research of ROSA on inflammatory diseases and depicts a small amount of clinical research data. The purpose of

this review is to discuss the anti-inflammatory effects of ROSA in inflammatory diseases and its underlying mechanism.[11]

5. **Abbas S, Abbas Z. et al., (2022):** Ketoprofen has recently been proven to offer therapeutic potential in preventing cancers such as colorectal and lung tumors, as well as in treating neurological illnesses. The goal of this review is to show the methods that have been used for determining ketoprofen in pharmaceutical formulations. Precision product quality control is crucial to confirm the composition of the drugs in pharmaceutical use. Several analytical techniques, including chromatographic and spectroscopic methods, have been used for determining ketoprofen in different sample forms such as a tablet, capsule, ampoule, gel, and human plasma. The limit of detection of ketoprofen was 0.1 ng/ ml using liquid chromatography with tandem mass spectrometry, while it was 0.01-0.30 µg/ ml using high performance liquid chromatography and 0.00004 - 0.436 µg/ ml, 0.82 µg/ ml, 1.0 µg/ ml, 10 µg/ ml and 208.5 - 237.6 µg/ml using flow injection, electro kinetic chromatography, capillary electrophoresis, gas chromatography-flame ionization detection and derivative infrared spectroscopy respectively.[12]
6. **Chawla G, Ranjan C, et al., (2016):** Ketoprofen, a potent anti-inflammatory, analgesic and anti-pyretic drug belonging to the propionic acid class was synthesized in 1968. Rapid absorption, simple metabolism, faster blood brain barrier crossing and high antinociceptive activity are the features responsible for its high use. But, free acidic moiety present in its structure is the major factor that declines its popularity by causing various gastric side effects. Many researchers have chemically modified this drug with the aim to discover an improved and safe NSAID candidate or a new drug with altered activity. We thoroughly searched the literature and found that during the period 2004-2016, more than fifty reports are available on chemical modification of ketoprofen. Along with this, many patents involving chemical modification of ketoprofen have also been reported. However, it was very surprising to note that there are only a few review articles available covering only its pharmacological and clinical properties. There is no review article available covering the chemistry part of ketoprofen. This motivated us to compile the information available on ketoprofen and its derivatives. The purpose of this article is to present an updated review about this topic.[13]
7. **Carbone C, Rende P, et al., (2013):** Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID), which acts by blocking cyclooxygenase (COX 1 and 2), an enzyme involved in the production of prostaglandins, messengers in the development of inflammation. All NSAIDs reduce signs of inflammation by blocking this enzyme and therefore

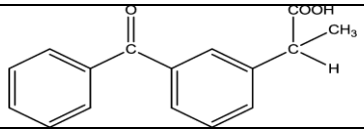
prostaglandin production. In Calabria, 3.69% of adverse drug reactions (ADRs) reported in the National Network of Pharmacovigilance concerns the use of ketoprofen; only in one case in which the patient was under the age of 12 years, hospitalization was required for severe episode of pancreatitis. In Italy, Ketoprofen is the 6th drug for ADRs incidence (560 ADRs in the year 2012, of which, 31% are severe). Despite the high rate of spontaneous reporting, it must be considered that ketoprofen is one of the most used NSAIDs; therefore, as it happens for other commonly used drugs (e.g., amoxicillin), the total number of ADRs should be related to the therapeutic use. However, it remains the problem of fragile patients (e.g., children) and the safety of the drug in different ages. This paper presents a retrospective study on 2012 ADRs reviewing literature on the safety of ketoprofen in the elderly, children, and during pregnancy.[14]

8. **Hemmati K, Masoumi A, et al., (2016):** A highly selective magnetic molecularly imprinted polymer (MMIP) with core–shell structure has been synthesized by a sol–gel process composed of Tragacanth Gum (TG) cross linker, Fe3O4/SiO2 nanoparticles, and Nvinyl imidazole(VI) functional monomer in the presence of template Quercetin (QC). Different techniques including scanning electron microscopy (SEM), SEM–energy dispersive spectroscopy (SEM–EDS), vibrating sample magnetometer (VSM), and transmission electron microscopy (TEM) were used to verify the successful synthesis of MIP on the surface of Fe3O4/SiO2 nanoparticles. The swelling behavior of MMIP, its recognition and selectivity for QC and structural analog, Catechu (CT), were tested and compared with magnetic non imprinted polymer (MNIP). MMIP adsorbs the template drug quickly and equilibrium could be reached in 2 h. The mechanism for adsorption was found to follow the Langmuir model with the maximum capacity of 175.43 mg g−1. The MMIP indicated excellent recognition and binding affinity toward QC, selectivity factor (ε) relative to CT was 2.16. 9 | P a g e 6.3 Finally, the MMIP was evaluated as a drug delivery device by performing in vitro release studies in PBS.[15]
9. **Singh B, Sharma V. et al., (2014):** The present article deals with design of tragacanth gum-based pH responsive hydrogel drug delivery systems. The characterization of hydrogels has been carried out by SEMs, EDAX, FTIR, 13C NMR, XRD, TGA/DTA/DTG and swelling studies. The correlation between reaction conditions and structural parameters of polymer networks such as polymer volume fraction in the swollen state (ϕ), Flory–Huggins interaction parameter (χ), molecular weight of the polymer chain between two neighboring cross links ($\bar{M}c$), crosslink density (ρ) and mesh size (ξ) has been determined. The different kinetic models such as zero order, first order, Higuchi

square root law, Korsmeyer–Peppas model and Hixson–Crowell cube root model were applied and it has been observed that release profile of amoxicillin best followed the first order model for the release of drug from the polymer matrix. The swelling of the hydrogels and release of drug from the drug loaded hydrogels occurred through non-Fickian diffusion mechanism in pH 7.4 solution.[16]

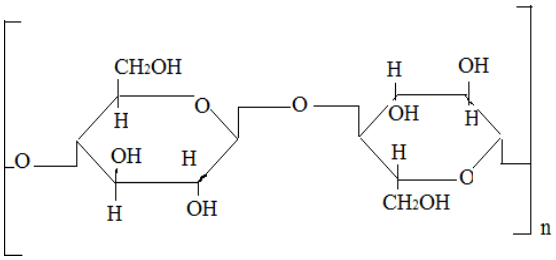
3.1 DRUG PROFILE

3.2 KETOPROFEN

STRUCTURAL FORMULA	
MOLECULAR FORMULA	$C_{16}H_{14}O_3$
CHIMICAL NAME	2-(3-bezoylphenyl) propionic acid
MOLECULAR WEIGHT	Average: 254.2806 Monoisotopic: 254.094294314
CATEGORY	NSAID
TYPE	Small Molecule
GENERIC NAME	Ketoprofen
SYNONYME	1). 2-(3-Benzoylphenyl) propionic acid 2). 3-Benzoyl-alpha-methylbenzeneacetic acid 3). 3-Benzoyl-α-methylbenzene acetic acid 4). 3-Benzoylhydratropic acid 5). Ketoprofen 6). Ketoprofeno

3.3 POLYMER AND EXCIPIENT PROFILE

HYDROXYPROPYL METHYLCELLULOSE



Nonproprietary Name: Hydroxymethylcellulose

Synonyms: Hydroxypropyl methyl ether, methyl hydroxypropyl cellulose, methylcellulose, methocel.

Chemical name: Cellulose, 2-hydroxypropyl methylcellulose

Application: Pharmaceutical formulations for use topically and orally frequently use Hypromellose. Hypromellose is utilized as a film coating, tablet matrix, and tablet binder. In

either wet or dry granulation procedures, a binder may be utilized at concentrations of 2% to 5% w/w.

Hypromellose is also utilized in topical formulations, notably ophthalmic treatments, as a thickening and suspending ingredient. Hypromellose is also used as a wetting agent for hard contact lenses and as an adhesive in plastic bandages.

Solubility: Chloroform, ethanol, and ether are essentially insoluble in this substance. It is soluble in cold water and forms a thick colloidal solution. However, it is soluble in alcohol and water mixes as well as methanol and dichloromethane mixtures.

Description: Hypromellose is a tasteless, odourless powder that can be white, creamy, or granular. pH: 1% w/w solution 5-8

Viscosity: There is a large selection of HPMC viscosities. 50 mPas HPMC E50 Viscosity.

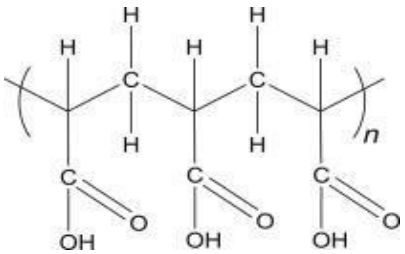
Storage: Hypromellose is a stable powder that becomes hygroscopic after drying. Solutions are stable between pH 3 and 11, and their viscosity decreased as temperature increases. Since Hypromellose is relatively resistant to enzymes, its aqueous solutions offer good viscosity stability during long-term storage. It could become spoiled by microorganisms; benzalkonium chloride is a typical preservative.

Incompatibilities: Some oxidizing agents are incompatible with Hypromellose.[17]

Carbopal 974p

Is a polymer used as a lacrimal substitute to treat symptoms associated with dry eyes.

Structural formula



Generic name: Carbopol 974P

Type: Small Molecule

Synonyms

- Carbomer 974 (p)
- Carbomer holypolymer type (B)
- Carbopol polymer

- Acrylic Acid Resin
- 2-Propenic Acid Homopolymer

Molecular weight: 3×106D

Functional category

Viscosity-increasing, tablet-binding, emulsifying, suspending, and release-modifying agents are all types of adhesives.

Application in Pharmaceutical formulation or technology

Pharmaceutical formulations that are liquid or semisolid typically contain carbopal 940 as a suspending or viscosity-increasing ingredient. Creams, jellies, and ointments are included in the formulation for topical and ophthalmic treatments. Carbomers are employed in tablet formulations as a dry or wet binder as well as a rate-regulating excipient.

Additionally, the development of sustained release matrix beads, peptide-containing dosage forms, bioadhesive patches for cervical patches and intranasally administered microspears, magnetic granules for site-specific drug delivery to the oesophagus, and oral mucoadhesive controlled drug delivery systems have all been investigated.

Stability and storage condition

Due to its stability, carbopol should be kept in tight containers.

Incompatibility

Resorcinol causes carbomer to turn discoloured, and phenol, cationic polymers, strong acids, and high levels of electrolyte are incompatible.

Safety

Generally speaking, it is thought to be a harmless and nonirritating substance.

Indication

Investigated for use/treatment in contraception and HIV prevention Associated condation:

- Dry eye
- Inflammation caused corticosteroid dermatoses

Background

Carbopol 974P is a highly carboxylated polymer composed of lightly cross-linked polyacrylic

acid with a broad-spectrum mechanism based on acidification of pathogens.

Storage

Keep container tightly closed. Keep container in a cool, well-ventilated area.

Tragacanth Gum

Tragacanth is a natural gum obtained from the dried sap of several of middle eastern legumes of the genus astragalus

Chemical name: tragacanth gum

Weight: Tragacanth gum has an approximate molecular weight of 840 000.

Synonyms

- Gum Benjamin;
- Gum dragon;
- Gum tragacanth;
- Persian tragacanth;

Functional Category: Suspending agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used. Tragacanth gum is also used similarly in cosmetics and food products, and has been used as a diluent in tablet formulations.

Description

Tragacanth gum occurs as flattened, lamellated, frequently curved fragments, or as straight or spirally twisted linear pieces from 0.5–2.5 mm in thickness; it may also be obtained in a powdered form. White to yellowish in color, tragacanth is a translucent, odorless substance, with an insipid mucilaginous taste.

Stability and Storage Conditions

Both the flaked and powdered forms of tragacanth are stable. Tragacanth gels are liable to exhibit microbial contamination with enterobacterial species, and stock solutions should therefore contain suitable antimicrobial preservatives. In emulsions, glycerin or propylene

glycol are used as preservatives; in gel formulations, tragacanth is usually preserved with either 0.1% w/v benzoic acid or sodium benzoate. A combination of 0.17% effective preservative for tragacanth gels;(1) see also Section 12. Gels may be sterilized by autoclaving. Sterilization by gamma irradiation causes a marked reduction in the viscosity of tragacanth dispersions. (2) Tragacanth dispersions are most stable at pH 4–8, although stability is satisfactory at higher pH or as low as pH 2. The bulk material should be stored in an airtight container in a cool, dry place.[18]

Microcrystalline cellulose

Storage Temperature: 20°C to 25°C

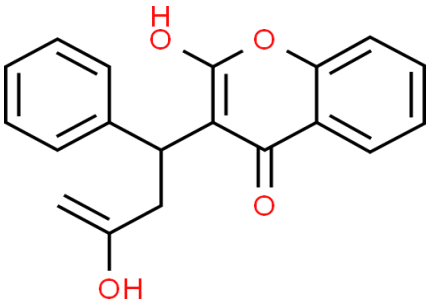
Functional category: It is a type of cellulose that has undergone a controlled partial depolymerization process, resulting in small, fine particles or crystals of cellulose.

Chemical Name: It is composed of glucose units linked together by β-1,4 glycosidic bonds

Description: Microcrystalline cellulose (MCC) is a refined wood pulp derived from the cellulose found in plants.

Solubility: Microcrystalline cellulose is not soluble in water, it can absorb water and swell, which is beneficial for its role as a binder in wet granulation process.

Structural formula



Stability and storage conditions: The stability of microcrystalline cellulose is generally good under appropriate storage conditions. The ideal temperature range for storage is typically between 15°C to 30°C.

Applications: MCC has binding, bulking, disintegrating, and stabilizing capabilities, making it a valuable additive in different industries. It is extensively used as a filler and binder in the formulation of tablets and capsules. As a texturizer, stabilizer, and anti-caking agent. It improves the texture of processed foods, enhances mouthfeel, and prevents clumping in powdered products. MCC is commonly found in baked goods, dairy products, sauces, and

dressings.[19]

Starch

BP: Maize starch Potato starch Rice starch Wheat starch

PhEur: Maydis amylum (maize starch) Solani amylum (potato starch) Oryzae amylum (rice starch) Tritici amylum (wheat starch

USPNF: Corn starch

Potato starch

Tapioca Wheat starch

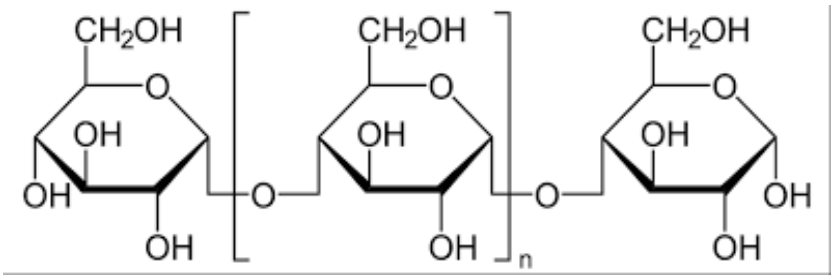
Synonyms: Amido; amidon; amilo; amylum; Aytex

Chemical name: STARCH

Empirical formula: (C6H10O5) n

Molecular weight: 50000–160000

Structural formula



Functional Category

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation or Technology

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant. As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations.

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Description

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.[20]

4.1 Materials Used in study

Table 2: Material Used.

Sr.no	Materials used	Company name
01	Ketoprofen	Yarrow Chem Product
02	Tragacanth Gum	Karnataka Fine Chem
03	Hydroxypropylmethylcellulose	Loba Chemie Pvt.Ltd
04	Carbopal 974p	Loba Chemie Pvt.Ltd
05	Starch	Karnataka Fine Chem
06	Crystalline Cellulose	Spectrum Reagentsand Chemicals
09	Magnesium Stearate	Loba Chemie Pvt.Ltd
10	Talc	Nice Chemicals

4.2 List of instrument

Table 3: Equipment.

Sl.no	Equipment	Source
01	Tablet Compression Machine	Rimek, Minipress, Uk
02	Electronic Balance	Shimadzu, Ahmedabad
03	Hot Air Oven For Drying	Hicon, New Delhi.
04	Ph Meter	Techno Scientific Products
05	Bulk Density Apparatus	Veego, Mumbai
06	Dissolution Apparatus	Labindia, Mumba
07	Friabilator	Ef - 2 Electrolab, Mumbai
08	Hardness Testing Apparatus	Tablet Hardness Tester, Monsanto
09	Melting Point Apparatus	Techno Scientific Products
10	Ft infrared Spectroscopy	Cary630,Agilant, New Delhi
11	Uv-spectrophotometer	Uv-2450, Shimadzu, Mumbai

Preparation of buffer solution

Preparation of phosphate buffer (pH 7.4): 6.8 gm of potassium di-hydrogen phosphate (KH_2PO_4) dissolved in 1000 ml distilled water. To maintain the pH 7.4 sodium hydroxide solution was used.

Preparation of standard curve for ketoprofen

10 mg of ketoprofen was taken in a 100 ml volumetric flask and makes up the volume with

phosphate buffer (pH 7.4) and named it stock solution, its concentration was 0.1 mg/ml. From the above solution 0.1, 0.2, 0.4, 0.6, 0.8 and 1 ml was taken in 10 ml volumetric flask and makes up the volume. Its concentration was 1, 2, 4, 6, 8, 10 µg/ml. The average values of absorbance values were plotted against respective drug concentration and thus standard curve of ketoprofen was produced.

4.3 Formulation of ketoprofen

Tale 4: Formulation of Ketoprofen.

FORMULA CODE	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Ketoprofen	129	129	129	129	129	129	129
Tragacanth gum	100	---	---	---	50	---	---
Hydroxyl propyl methyl cellulose	---	100	---	---	50	50	---
Carbopal 974p	---	---	100	---	---	50	50
Crystalline cellulose	---	---	---	100	---	---	50
Starch	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3
Total	250	250	250	250	250	250	250

4.4 Pre-Formulation Studies

Pre-formulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.

IDINTIFICATION OF THE DRUG

- ✓ The identification of drug was done by FT-IR Spectroscopy.

Analytical Method used in the Determination of ketoprofen

The UV spectrophotometric method was developed for the analysis of the drug using Shimadzu 1800 spectrophotometer.

Determination of λmax

1% w/v ketoprofen was prepared in 0.1 N NaOH and scanned for maximum absorbance in UV double beam spectrophotometer (Shimandzu-1800) in the range from 200 to 400 nm, using 0.1 N as blank. The λmax of the drug was found to be 254 nm.

Compatibility study using FT-IR[21]

Careful selection of the excipients that are included to make administration easier, enhance the constant release and bioavailability of the medication, and safeguard it against degradation is essential for the formulation of a stable and effective solid dosage form.

A Thermo Nicolet FTIR was used for the infrared spectroscopy, and the spectrum was collected between 4000 and 400 cm-1. By looking for any changes in drug peak locations in the spectrum of the physical mixture of the drug, the interaction between the excipients and the drug was discovered by IR spectral investigations.

Procedure

Weighed amount of drug (3 mg) was mixed with 100mg of potassium bromide (dried at 40-50oC). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer. Similar procedure is followed for all relevant excipients used.

Drug-Excipient Compatibility Study

In order to choose suitable chemically compatible excipients, compatibility studies were carried out to evaluate and forecast the physicochemical interaction between drug ingredient and excipients.

Table 5: Physical Observation of Compatibility Study.

Drug & Excipient Ratio (1:1)	Observation			RESULT
	Initial	30oC±2/65% ±5 RH after 30 days	40oC±2/75%±5 RH after 30 days	
KETOPROFEN + TRAGACANTH GUM	White to off White powder	White to off White powder	White to off White powder	Compatible
KETOPROFEN+ HPMC K4m	White to off White powder	White to off White powder	White to off White powder	Compatible
KETOPROFEN+ CARBOPAL 974p	White to off White powder	White to off White powder	White to off White powder	Compatible
KETOPROFEN+ STARCH	White to off White powder	White to off White powder	White to off White powder	Compatible
KETOPROFEN+ CRYSTALLINE CELLULOSE	White to off White powder	White to off White powder	White to off White powder	Compatible

4.5 EVALUATION OF PRE-FORMULATION PARAMETERS

Melting point

Melting point of drug was determined by capillary method in triplicate.

Determination of Angle of Repose[22],[23]

The frictional forces that have been excited between granules particles are shown by the angle of repose.

It is the greatest angle that can be formed between the granule pile's surface and the horizontal plane:

$$\text{Tan } \theta = h/r$$

Where, θ = the angle of repose,

h = height of the heap of the powder r = radius of the heap of the powder

Table 6: Angle of Repose.

SL.NO	ANGLE OF REPOSE(θ)	TYPE OF FLOW
01	< 20	Excellent
02	20-30	Good
03	30-40	Passable
04	>40	Very poor

Procedure

Weighed quantities of powder (mix blend) were poured through the funnel from the fixed height onto the graph paper. The height of the heap was measured. The circumference of the heap was marked by pencil. The area of the circle formed was calculated on the basis of large squares and small squares present inside the circle and angle of repose was then calculated on the parameter "r" which was found out from the area of circle.

Determination of Bulk Density and Tapped Density[23],[24]

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

: The bulk density, and tapped density were calculated using the following formulae.

Bulk density = W / VO

Tapped density = W / VF

Where,

W = weight of the powder mixture,

VO = initial volume of the powder mixture and VF = final volume of the powder mixture.

Carr's compressibility Index (CI)[25],[26]

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% has good flow property

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Table 7: Compressibility Index (ci).

SL NO	% COMPRESSIBILITY INDEX	PROPERTIES
01	5-12	Free flowing
02	12-16	Good
03	18-21	Fair
04	23-35	Poor
05	33-38	Very poor
06	>40	Extremely poor

Hausner's Ratio[26]

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausener's Ratio = Tapped density/Bulk density

Table 8: Hausner's Ratio.

Sl.no	Hausner's Ratio	Property
01	0-1.2	Free flowing
02	1.2-1.6	Cohesive flowing

4.6 POST-COMPRESSION EVALUATION PARAMETERS

Tablets were subjected to various evaluation parameters including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Weight variation[26],[27]

To guarantee that a tablet contains the right amount of medication, the weight of the tablets being manufactured was frequently determined. In order to perform the USP weight variation

test, 20 tablets are individually weighed, the average weight is calculated, and then the individual weights are compared to the average. The tablets complied with the USP requirement that no tablet may differ by more than twice the percentage restriction and that no tablet may differ by more than 2 times the percentage limit on any given day. The USP's official tablet percentage deviation limitations are displayed in the

Table 9: Weight Variation Limit.

Sl. No.	Average weight of tablet (mg)	Maximum % difference allowed
01	130 or less	10
02	130-324	7.5
03	324<	5

Tablet hardness[26]

The hardness of tablets determines how resistant they are to shattering during storage, transportation, and handling prior to use. Each batch of tablets had its hardness tested using a Monsanto hardness tester. The hardness was expressed in kg/cm2 units. Five tablets were chosen at random, and their hardness was assessed.

Five determinations' average hardness was noted.

Friability[27]

Friability is the term used to describe the weight loss of tablets in their containers as a result of the removal of particles from their surface. Friability typically indicates inadequate ingredient cohesiveness in tablets.

Method: 20 tablets were weighed, their initial weight was noted, they were put in the Roche friabilator, and it rotated for 100 revolutions at a speed of 25 rpm. The tablets were then taken out of the friabilator, sprinkled with particles, and weighed once again.52 percent friability was determined by applying the following formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \text{ X } 100$$

Tablet thickness[26]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Callipers. It was determined by checking the thickness of ten tablets of each formulation batch.

Drug content uniformity[28]

10 tablets were weighed from each batch and average weight is calculated. All tablets were crushed and powder equivalent to 80 mg drug was dissolved in phosphate buffer 6.8 and the volume was made up to 100 ml with pH 6.8 phosphate buffer. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 6.8 phosphate buffers. Solution was filtered and absorbance was measured spectrophotometrically at 249 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

In-vitro dissolution studies[29],[30]

The USP-II (Paddle) dissolution device was used for the in-vitro dissolution investigations at a speed of 50 rpm. The temperature was kept at 37°C and the dissolution medium, phosphate buffer pH 6.8, was used for the remaining 2 hours. At predetermined intervals, 5 ml were removed and replaced with the same volume of new medium. The samples that had been withheld were diluted with pH 6.8, filtered, and then subjected to UV spectrophotometer analysis at 249 nm with pH 6.8 serving as a blank. Calculated was the cumulative drug release percentage.

Table 10: Details Data of Dissolution Test.

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of media	900 ml
Volume withdrawn	5 ml
Medium used	6.8 phosphate buffer
Temperature	37±0.5ºC

Mathematical modelling of drug release profile[31],[32]

By examining the release data with zero order, first order kinetics, and the Higuchi equation, the drug release from the ketoprofen sustain release matrix tablets was investigated. By using Korsmeyer Peppas' model to suit the data, the release process was comprehended.

a) Zero order kinetics

The data follows zero-order release kinetics with a slope equal to K0 when the data is shown as cumulative% drug release vs time.

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

$$At = A0 - K0t$$

Where,

At= Drug release at time(t). A0= Initial drug concentration.

K0=Zero-order rate constant (hr^{-1}).

b) First order Kinetics

A straight line results from plotting the data as log cumulative% medication remaining vs time, showing that the release follows the first-order kinetics. You may get the constant "K" by multiplying 2.303 by the slope values.

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

$$Log\ C = log\ C0 - Kt / 2.303$$

Where,

C = Amount of drug remained at time(t).

C0 = Initial concentration of drug.

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

c) Higuchi's model

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

Drug release from the formulation by diffusion has been described by following Higuchi"s classical diffusion equation:

$$Q = [D\varepsilon / \varepsilon (2A - \varepsilon CS)\ CSt]^{1/2}$$

Where,

Q = Amount of drug released at time(t).

D = Diffusion co-efficient of the drug in the matrix. A = Total amount of drug in unit volume of matrix. CS = Solubility of the drug in the matrix.

ε = Porosity of the matrix. t = Tortuosity.

d) Korsmeyer equation/ Peppa's model

A straight line with a slope equal to "n" results from plotting the data as the log of drug release vs time, and the "K" value may be calculated from the y-intercept. The release data were also fitted to the well-known exponential equation (Korsmeyer equation/Peppa's law

equation), which is frequently used to describe the drug release behavior from polymeric systems, in order to explore the mechanism of drug release.

$$M_t / M_a = Kt^n$$

Where,

M_t / M_a = the fraction of drug released at time(t).

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

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

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

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

For Fickian release (n) = 0.5 while for anomalous (non- Fickian) transport (n) ranges between 0.5 and 1.0.

Table 11: Mechanism of Drug Release As Per Korsmeyer Equation/ Peppa's Model.

SL. No	'n' value	Drug release mechanism	Rate as a function of time
01	0.45	Fickian release	$t^{-0.5}$
02	0.45 <n = 0.89	Non- Fickian transport	t^{n-1}
03	0.89	Class II transport	Zero order release
04	Higher than 0.89	Super case II transport	t^{n-1}

Stability studies[33]

Stability of a drug has been defined as (the ability of a particular formulation in a specific condition, to remain within its physical, chemical, therapeutical and toxicological specifications). The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence of various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage condition, re-test periods and shelf- life of the drug can be established.

Stability studies are important for the following reasons

Stability studies are important for the following reasons. 1. This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life.2. The drug control administration insists on manufacturers on conducting the stability studies, identity, strength, purity and quality of the drug for an extended period of time in the conditions of normal storage.3. Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product.

Purpose of stability studies

Stability studies are done to understand how to design a product and its packaging, such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used.

Storage conditions

The selected formulations were subjected for three-month stability study as per ICH guidelines. The selected formulations were placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations.

5. RESULTS AND DISCUSSION

Determination of λ max of KETOPROFEN

The maximum absorption wavelength was determined to be λ = 254 nm for a ketoprofen alcoholic standard solution of 1.4 µg/mL.

Calibration curve of KETOPROFEN

The absorbance of ketoprofen was measured in a UV spectrophotometer at 254 nm against 0.1 N NaOH as blank. The absorbance so obtained was tabulated and graph was obtained by plotting absorbance Vs concentration.

Table 12: Spectrophotometric Data For The Estimation of Valsartan In 0.1 N Naoh.

SL. No.	Concentration (µg/ml)	Absorbance at 254 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	0	0	0	0	0	0
2	5	0.0125	0.0153	0.0153	0.00952	0.00306
3	10	0.0222	0.022	0.0219	0.0189	0.0088
4	15	0.0259	0.0258	0.0258	0.0258	0.00077
5	20	0.0320	0.0331	0.0329	0.0360	0.00351
6	25	0.0369	0.0376	0.0378	0.04174	0.00422
7	30	0.0432	0.0433	0.0434	0.0533	0.00412

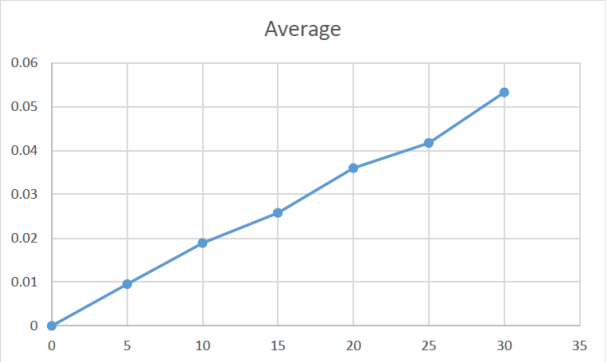


Fig.8: Calibration Curve of ketoprofen in 0.1 N NaOH.

Compatibility studies using FT-IR

Infra-red spectrum of drug, polymers and mixture of both were determined by KBr disks method. Samples were prepared in KBr disks by means of a hydrostatic press at 5 tons' pressure for 5 min and obtained spectra were shown in the no ------

All the characteristic peaks of Valsartan were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Ketoprofen were found to be unaltered in the drug- polymer physical mixtures, indicating that they were compatible chemically. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

Table 13: Interpretations of Ir-Spectrum.

Ingredients	Functional groups with wave number (cm-1)				
	N-H(s)	N-O (b)	C-H(b)	C-O(s)	O-H (b)
Ketoprofen	1651.12	1558.54	1427.37	1280.78	840.99
Ketoprofen+tragacanth gum	---	1550.82	1388.79	1273.06	895.00
Ketoprofen+carbopal	1643.41	1550.82	1396.56	1273.06	856.42
Ketoprofen+crystalline celluloss	---	1550.82	1396.51	1273.06	856.42
Ketoprofen +starch	1705	1550.82	1388.79	1273.06	864.14

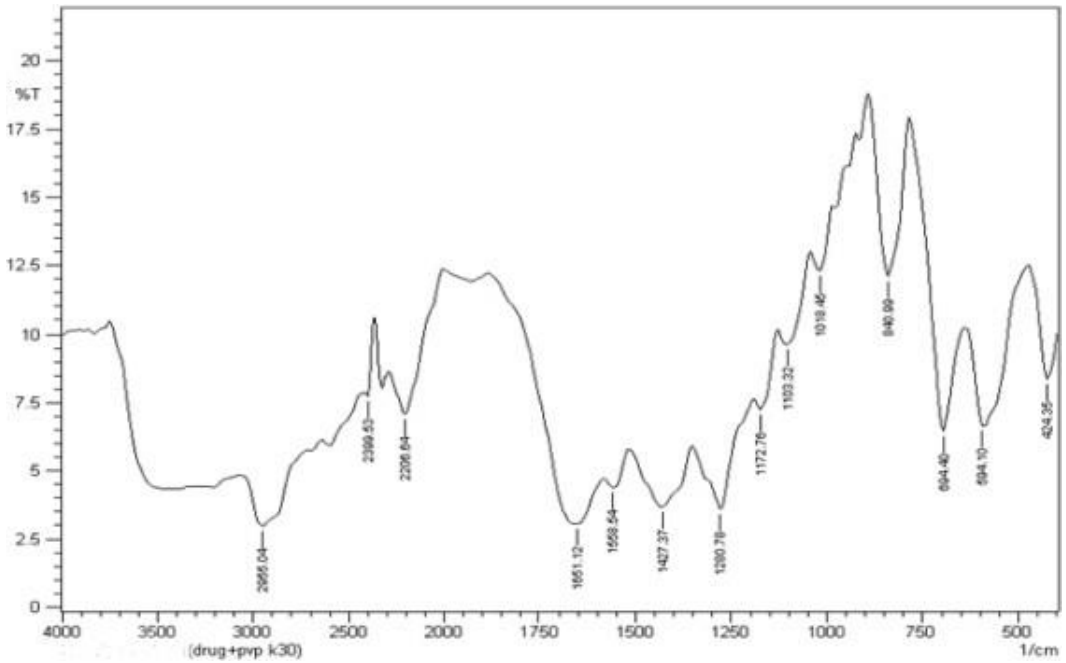


Fig.9: IR Spectrum of Pure Drug KETOPROFEN.

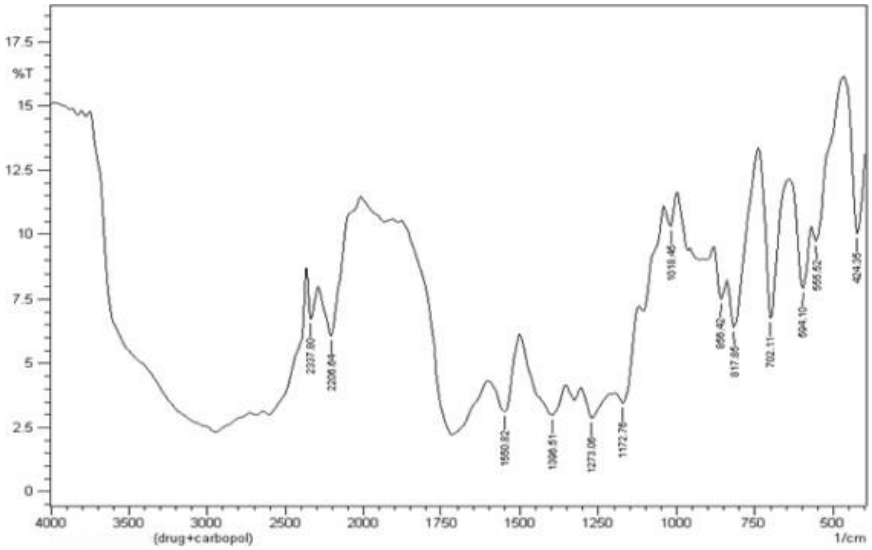


Fig.10: IR Spectrum of Carbopal.

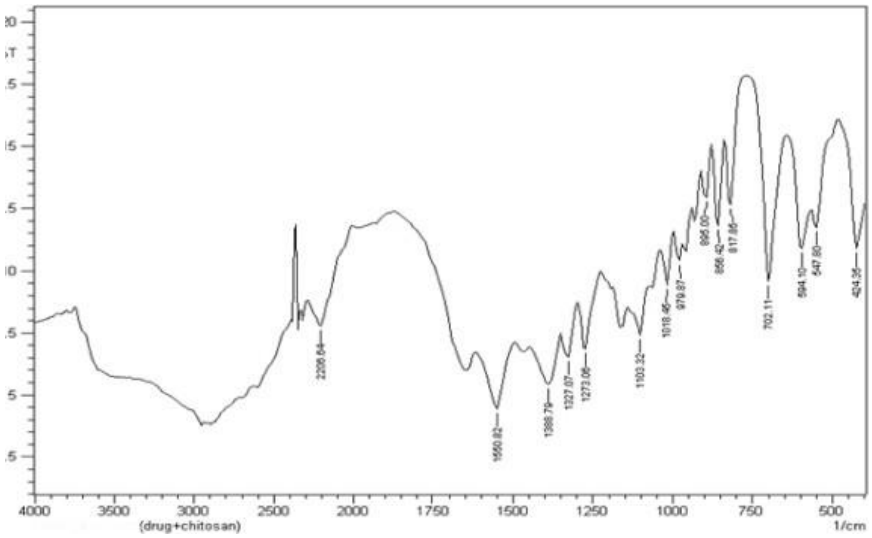


Fig.11: IR Spectrum of Tragacanth.

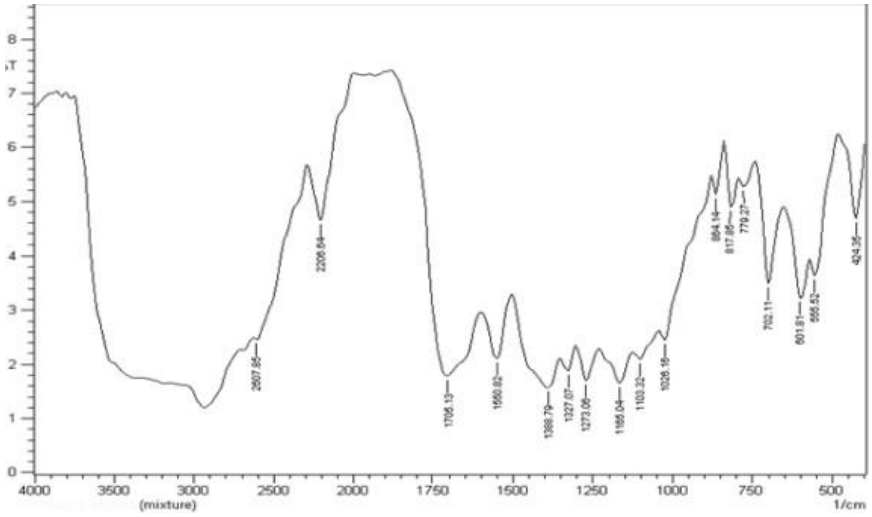


Fig.12: IR Spectrum of Starch.

FORMULATION DESIGN

The main aim of present study was to formulate sustain release matrix tablets of ketoprofen using chitosan in order to improve its therapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency.

In this case nine formulations of sustain released matrix tablets were prepared by using different polymers such as Tragacanth gum, crystalline cellulose, HPMC, Carbapol, in different ratios. The detailed composition of each formulation is given in the table. The powder mixture was subjected to pre-compression and post-compression evaluation before and after compression.

Evaluation Parameters

Evaluation of powder blended characteristics of matrix tablet formulation of ketoprofen

For each type of formulation, blends of ketoprofen and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr‟s compressibility index, Hausner‟s ratio and angle of repose. Bulk density was found in the range of 0.355-0.3850 g/cm3 and the tapped density between 0.4101- 0.4880g/cm3 indicating both parameters were found to be within the limits. Using the above two density data, Carr‟s compressibility index were calculated. The compressibility index and Hausner‟s ratio was found in the range of 7.27-18.42 % and 1.053-1.24 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.33-31.43°. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in table.

Table 14: Evaluation Parameters of Pre-Formulation Characteristics Of Powder Blend.

Formulation number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3716±0.0011	0.4101±0.0025	7.27±0.659	1.177±0.0076	29.73 0.41
F2	0.3803±0.0005	0.4120±0.0026	7.58±0.514	1.053± 0.0060	25.33 0.63
F3	0.3843±0.0015	0.4120±0.005	7.43±0.760	1.059±0.0088	28.44 0.35
F4	0.376±0.0020	0.4270±0.0037	13.78±0.386	1.073±0.0053	27.48 0.52
F5	0.355±0.0017	0.4600±0.0024	17.31±0.794	1.224±0.011	31.34 0.13
F6	0.3810±0.0045	0.4880±0.0065	18.42±0.120	1.24±0.0020	28.26 0.43
F7	0.3850±0.0081	0.4384±0.133	10.88±0.030	1.123±0.0021	27.27±0.42

Physical evaluation of tablets

After compression various quality control tests were carried out, which demonstrated following organoleptic properties viz. colour, odour and shape. All formulations (F1 to F8) were found to be white in colour, odourless and concave round flat with break-line on one side.

Table 15: Organoleptic Properties of Prepared Tablets.

Formulation code	Color	Odour	Shape
F1	White color	odourless	Concave, round and flat with break-line on one side
F2	White color	odourless	Concave, round and flat with break-line on one side
F3	White color	odourless	Concave, round and flat with break-line on one side
F4	White color	odourless	Concave, round and flat with break-line on one side
F5	White color	odourless	Concave, round and flat with break-line on one side

F6	White color	odourless	Concave, round and flat with break-line on one side
F7	White color	odourless	Concave, round and flat with break-line on one side

Table 16: Post-Compression Parameters Result.

Formulation	Diameter (mm)± SD	Thickness (mm)±SD	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	7.82±0.012	3.9±0.09	250.89±0.12	7.3±0.04	0.61±0.007	98.25±0.044
F2	7.80±0.002	4.0±0.02	253.88±0.60	7.8±0.03	0.52±0.005	100.31±0.037
F3	7.85±0.007	4.2±0.01	251.12±0.52	8.0±0.07	0.58±0.031	98.54±0.07
F4	7.84±0.022	3.9±0.07	249.81±0.13	6.5±0.04	0.72±0.016	99.67±0.087
F5	8.0±0.015	4.0±0.04	250.80±0.32	6.8±0.08	0.665±0.09	99.37±0.058
F6	67.94±0.010	3.8±0.09	248.92±0.44	7.1±0.03	0.714±0.01	98.97±0.073
F7	7.97±0.016	4.1±0.01	252.61±0.60	6.0±0.05	0.447±0.00	101.61±0.08

Discussion about the physical parameters such as

A. Thickness of tablets
B. Hardness
C. Friability
D. Weight Variation
E. Drug content

A. Thickness of tablets

All the formulations were evaluated for their thickness using "Vernier callipers" as per procedure in methodology section 4 and the results are shown in table no 16. The average thickness for all the formulations was found in the range of 3.8-4.2 mm which is within the allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the tablet formulation was in the range of 8.0-7.8 mm.

B. Hardness

Tablet hardness is one of the critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. All the controlled release matrix tablet formulations of ketoprofen were evaluated for their hardness as per procedure in methodology section 4 and the results were dissipated in table no 16. Hardness test was performed by "Monsanto hardness tester". All the formulations have an average hardness in between 6.0 to 8.0 kg/cm2 This ensures good handling characteristics of all formulation batches.

C. Friability

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing,

handling and transporting. Friability of prepared tablets was determined by using "Roche friabilator". The entire controlled release matrix tablet formulations were evaluated for their percentage friability and the results are shown in table no 16. The average percentage friability for all the formulations was found in between 0.447% to 0.72%, which is found within the pharmacopoeia limit (i.e. less than 1%).

So the maximum friability was 0.72% observed for F4 and the minimum friability 0.447% observed for F7.

D. Weight variation test

As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 249.92 to 253.88 mg and results were dissipated in table no 16. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

E. Drug content

The percentage of the drug content for formulation F1 to F7 was found to be between 98.25%w/w and 101.61%w/w. It complies with official specifications. The results were shown in table no 16.

In-vitro drug release study

In this study carbopal was chosen as polymer and it was combined with tragacanth and hydroxyl propyl methyl cellulose to explore their sustain release capability. The in-vitro release data for tragacanth-carbopal and hydroxyl propyl methyl cellulose -carbopal based ketoprofen sustain released matrix tablets are represented in table 17 and illustrated in figure 10. The in-vitro release of ketoprofen, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of hydroxyl propyl methyl cellulose, concentration of tragacanth and concentration of polymers. The in-vitro release of ketoprofen form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The in-vitro release study was performed in 0.1 N HCL for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hours. The in-vitro release of ketoprofen was higher in first 6-7 hours in all formulations. After 1 hour, approximately 10.29%- 18.34% of

ketoprofen from hydroxyl propyl methyl cellulose-carbopal tablets, 16.90%- 21.91% from tragacanth-carbopal, 25.12% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. Formulation F1 do not contains any crosslinking agent, so almost all drugs were released at the end of 12 hrs. Formulation F2, F3, F5, and F7 containing lower concentration of hydroxyl propyl methyl cellulose and tragacanth showed almost all drug release within 16 hrs, 20 hrs, 16 hrs and 18 hrs respectively. Thus these formulations were not considered as good formulation as the maximum amount of drug was released before desire period of time i.e. 24 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation F4 and F7 containing highest concentration of hydroxyl propyl methyl cellulose and tragacanth respectively along with carbopal gum respectively prolong the release of ketoprofen to 24 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of cross linking agent-polymer based system. Swelling study also showed that formulation which contains higher concentration of cross linking agent showed higher swelling capacity and prolonged the drug release to 24 hrs.

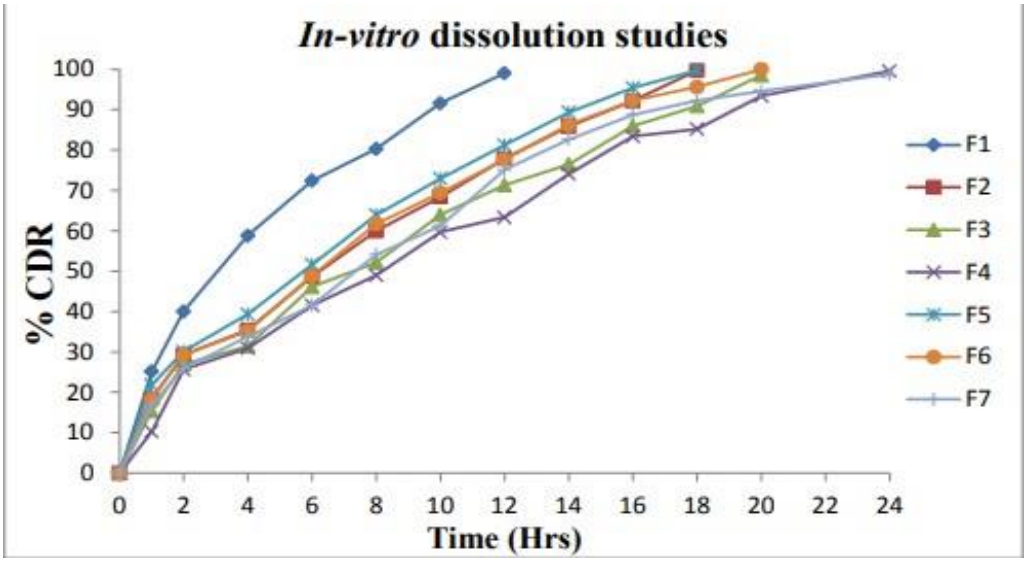


Fig.13: In-vitro dissolution studies

Table 17: Comparative Dissolution Profile of The Formulations F1 To F7.

Time (Hrs)	Cumulative Percentage Drug Release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	25.12±0.09	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85

2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.14	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.2	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.38	63.93±0.65	61.73±0.85	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	------	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.45	86.24±0.76	82.67±0.48
16	------	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	92.28±0.87	88.75±0.48
18	------	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	------	------	98.54±0.43	93.39±0.14	------	99.99±0.61	94.54±0.48
24	------	------	------	99.54±0.11	------	------	98.78±0.48

Release kinetic studies

The in-vitro drug release data of all formulations were analyzed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics and Higuchi model. The highest correlation coefficient (r2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient „r" indicated that the drug release followed first order release kinetics. It was found that the value of „r" for first order ranged from 0.981-0.992, which is near to 1 when compared to Higuchi square root ranged from 0.892-0.958 and zero order ranged from 0.895-0.969. So, it was understood to be following first order release pattern followed by all formulations. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer Peppas exponential model Mt / Ma = Ktn. Where Mt / Ma is the fraction of drug released after time 't' and 'k' is kinetic constant and 'n' release exponent which characterizes the drug transport mechanism. The release exponent (n) ranges in between 0.483-0.7911. For all the formulations F1 to F9 the values for 'n' ranged above 0.89 which indicates that all the formulations followed non-fickian release mechanism. The relative complexity of the prepared formulations may indicate that the drug release mechanism was possibly controlled by the combination of diffusion and erosion.

Table 18: Kinetic Studies.

Formula	Zero order	First order	Higuchi's plots	Orsmeyer-Peppas plots		Best fit Model	Drug release mechanism
	R^2	R^2	R^2	R^2	N		
F1	0.9293	0.982	0.9116	0.912	0.597	First order	Non-Fickian
F2	0.969	0.974	0.8944	0.915	0.594	First order	Non-Fickian
F3	0.916	0.984	0.9217	0.899	0.6077	First order	Non-Fickian
F4	0.946	0.978	0.8926	0.892	0.577	First order	Non-Fickian
F5	0.944	0.992	0.9581	0.902	0.488	First order	Non-Fickian
F6	0.895	0.958	0.9022	0.929	0.7911	First order	Non-Fickian
F7	0.896	0.981	0.9258	0.938	0.4838	First order	Non-Fickian

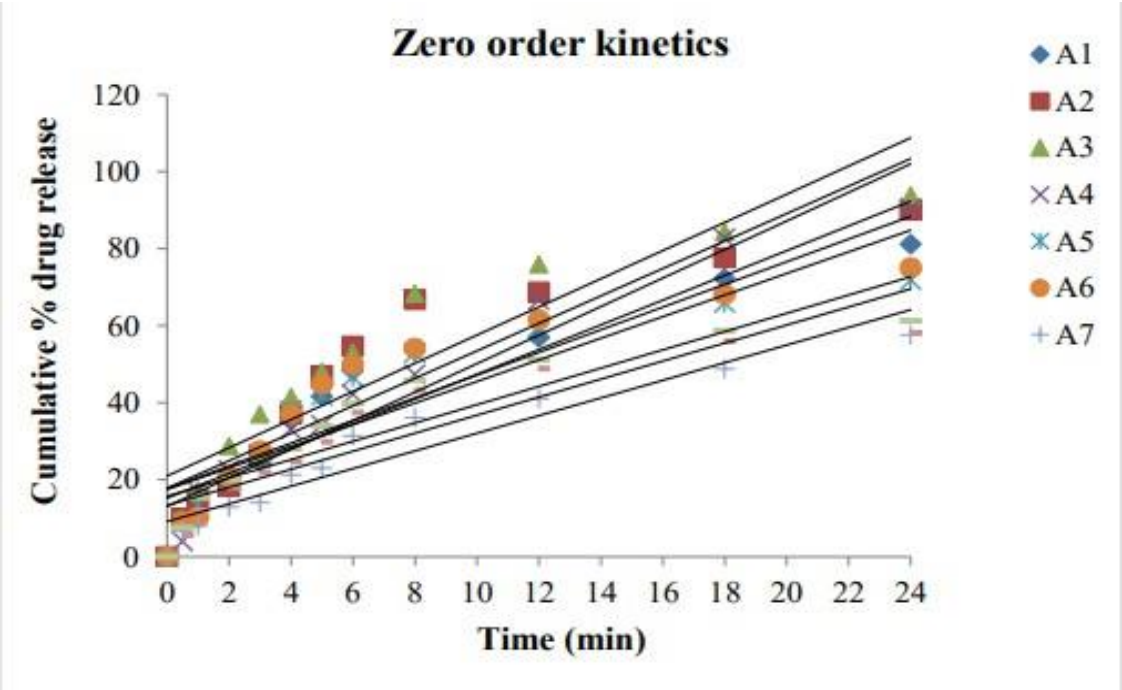


Fig. 14: Comparative Zero Order release profile of formulations F1 to F7.

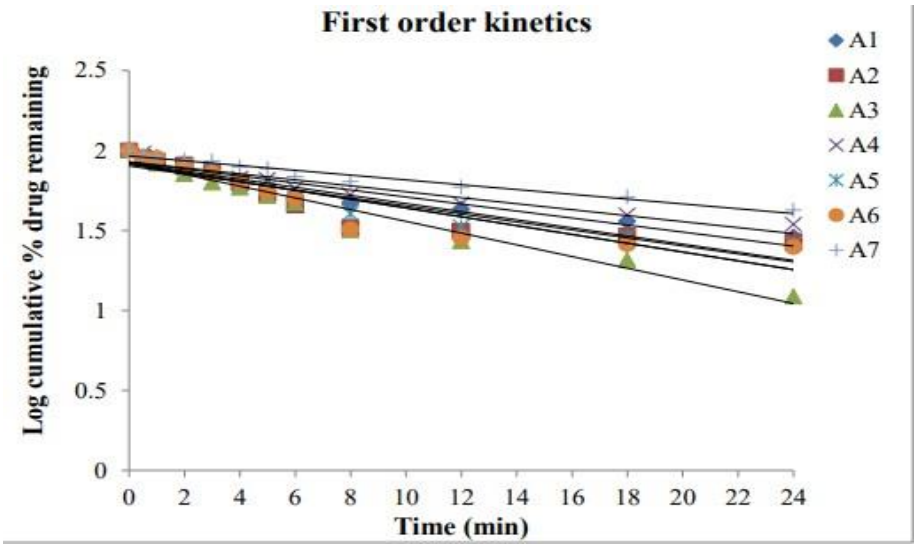


Fig. 15: Comparative First Order release profile of formulations F1 to F7.

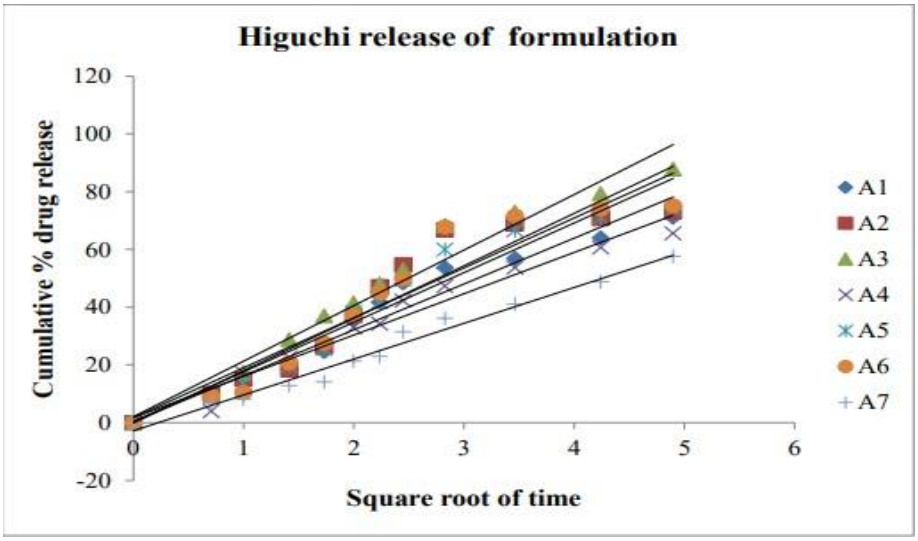


Fig.16: Comparative Higuchi release profile of formulations F1 to F7.

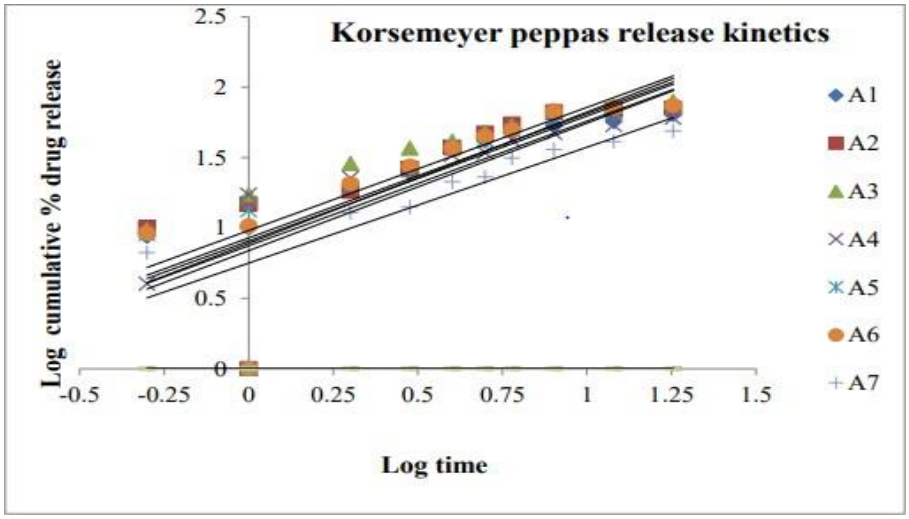


Fig.17: Comparative Korsemeyer peppas release profile of formulations F1 to F7.

Stability studies

Stability studies: Based on the results of in-vitro drug release two best formulations F4 and F7 were selected for three-month stability studies at 25ºC/60% RH and at 45ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content and in- vitro drug release. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies was tabulated in table no 19.

Table 19: Results of Stability Studies For Formulation F4 Stored AT 25ºC/60% AND 45ºC/75% RH.

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F4				Formulation F4			
	Hardness Kg/cm2	% friability	% Drug content	% CDR	Hardness Kg/cm2	% friability	% Drug content	% CDR
Initial	8.0±0.07	0.58±0.1	99.67±0.3	99.5±0.4	98.0±0.4	0.58±0.2	99.6±0.3	99.5±0.2
After 1 month	7.9±0.12	0.60±0.3	98.84±0.1	99.2±0.4	7.7±0.098	0.61±0.1	98.7±0.2	99.0±0.3
After 2 month	7.8±0.46	0.65±0.2	97.97±0.2	98.6±0.4	7.5±0.07	0.64±0.3	97.4±0.3	98.3±0.2
After 3 month	7.6±0.13	0.62±0.1	97.76±0.3	98.0±0.4	7.4±0.07	0.66±0.1	97.1±0.3	97.8±0.2

Table 20: Results of stability studies for formulation F7 stored at 25ºC/60% and 45ºC/75% RH.

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F7				Formulation F7			
	Hardness Kg/cm2	% friability	% Drug content	% CDR	Hardness Kg/cm2	% friability	Drug content	% CDR
Initial	6.6±0.06	0.54±0.2	101.6±0.3	98.6±0.5	6.6±0.09	0.54±0.3	96.8±0.3	98.7±0.5
After 1 month	6.5±0.16	0.57±0.3	99.6±0.1	98.5±0.5	6.4±0.11	0.55±0.1	96.5±0.3	98.5±0.5
After 2 month	6.3±0.21	0.60±0.4	99.4±0.2	98.1±0.5	6.2±0.21	0.59±0.1	96.2±0.3	97.8±0.2
After 3 month	6.2±0.15	0.62±0.3	98.3±0.6	97.6±0.5	6.0±0.23	0.61±0.3	96.0±0.3	97.4±0.3

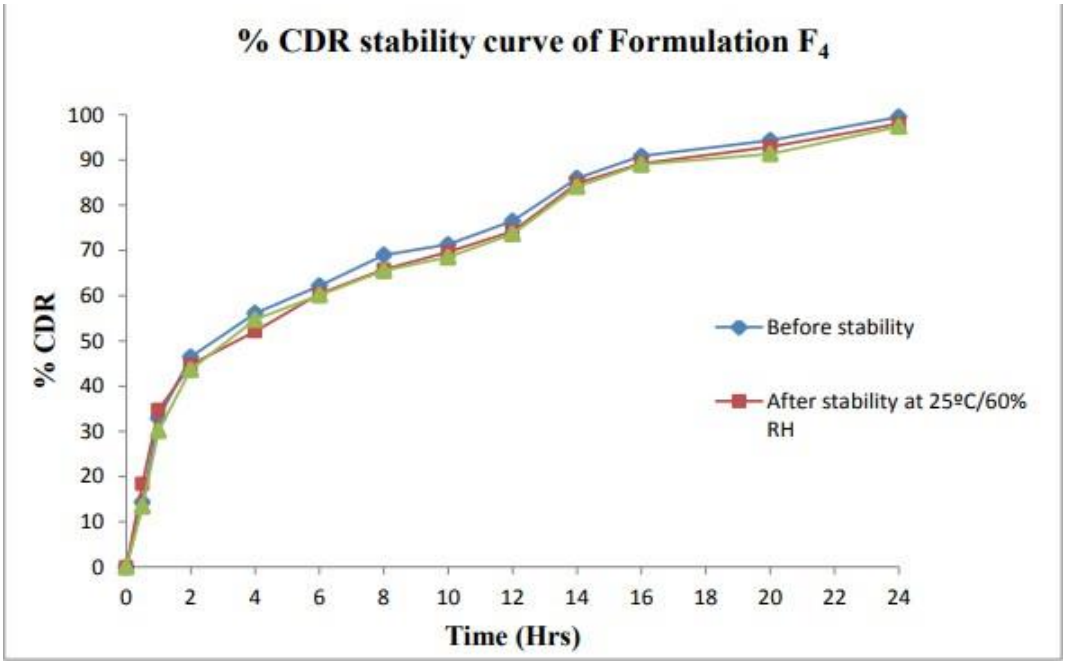


Fig.18: Dissolution rate profile of formulation F4 before and after stability.

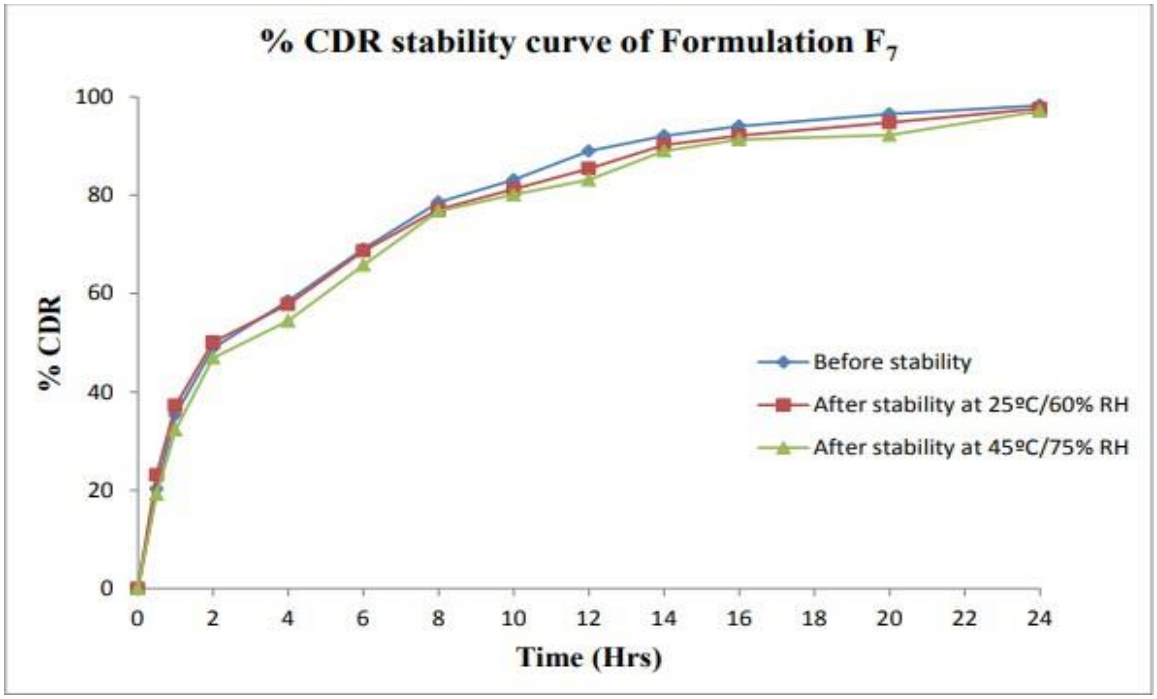


Fig.19: Dissolution rate profile of formulation F7 before and after stability.

6. CONCLUSION

Ketoprofen, a strong, a nonsteroidal anti-inflammatory drug (NSAID) taken orally, reducing pain and treating inflammation. The goal of the current study was to look into the potential to maintain the release of ketoprofen from matrix tablets made with various concentration of polymers and cross-linking agents.

The following conclusions can be drawn from the result obtained

- The pre-formulation studies like angle of repose, bulk density, tapped density Haunser's ratio and Carr's index of all formulations were found to be within the standard limits.
- FTIR studies revealed that there was no chemical interaction between drug and other excipients.
- The powder mixtures were compressed into tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, friability and drug content. All the formulation batches showed acceptable results.
- The in-vitro drug release was studied with USP Type-II dissolution apparatus in both simulated gastric fluid and intestine fluid for a period of 24 hours. Results showed that formulations containing higher concentration of HPMC i.e. F4 (99.54%) and Tragacanth i.e. F7 (98.78%) sustained the drug release over a period of 24 hours.
- The in-vitro drug release follows first order and indicated that non-Fickian could be the

mechanism of drug release.

- Stability studies showed that the tablets formulations were stable throughout the stability period.
- It was concluded that the polymer and cross linking agents plays a major role in the formulation of sustain release matrix tablets of KETOPROFEN. Finally, the study revealed that the release of drug was low when the matrix tablet contained higher concentration of cross linking agents and polymers also showed similar diffusion and erosion kinetics.

7. SUMMARY

KETOPROFEN, which acts by reducing pain and swelling and stiffness, which in turn results in reduced the pain. It is also used to treat join pain, and to reduce death for people with inflammation. Due to its shorter has a half-life in most animals of less than 2 hours, but it has a duration of action for up to 24 hours and frequent administration, ketoprofen was selected as candidate for developing sustain released matrix tablets.

The most common method for administering medication is orally. Patients and doctors alike favour tablets, which are the most widely used oral forms on the market. It has been shown that sustain release dosage forms increase therapeutic efficacy by maintaining a constant medication plasma concentration for two to three times.

The creation of pharmaceutical dosage forms now heavily relies on the usage of polymers to maintain the release of pharmaceuticals. The use of carbopol 934P in conjunction with cross-linking agents, starch, and HPMC as direct compressible agents, as well as talc and magnesium stearate as glidants and lubricants, respectively, might result in sustain release.

Drug and excipients were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and excipients.

All the formulations were subjected for various pre-compression studies such as angle of repose, bulk density, tapped density, Carr's index, Haunser's ratio and results revealed that the powder mixtures showed good to acceptable flow and compressibility properties.

All the formulations were subjected for various post-compression studies such as weight variation, hardness, thickness, friability, drug content and in-vitro dissolution studies. The hardness and thickness of prepared tablets were found in the range of 6.0 to 8.0 kg/cm2 and 7.8.0-8.0 mm and all other parameters were within the standard official specifications.

The results of in-vitro dissolution study indicated that the drug release from formulation F4 and F7 showed 99.54% and 98.78% respectively at the end of 24 hours in sustain manner.

To analyze the mechanism of drug release from the matrices, the in-vitro drug release data were fitted to Zero order, First order, Higuchi and Korsmeyer's-Peppas model. It was observed that the release of drug followed first order and the mechanism was found to be non-Fickian.

The best formulations F4 and F7 were subjected to 3 months stability studies and results showed there was no significant change in the hardness, friability, drug content and invitro drug release. Thus it was found that prepared tablets were physico-chemically stable throughout stability period.

Thus it can be summarized that the stable matrix tablet dosage form of ketoprofen has been developed for sustain release in the treatment of INFLAMMATION.

8. REFRENCESE

1. Shashank tiwari and navneet batra. oral drug delivery system: a review. american journal of life science researches.
2. Mr. shaikh arbaz hussain, mr.t.a. gaikwad. formulation and evaluation of bilayer tablet containing diclofenac sodium as sustained release international journal of research publication and reviews, June. 2022; 3(6): 1080-1086.
3. Gaurav agarwal, shilpi agarwal, pk karar and shagun goyal. oral sustained release tablets, american journal of advanced drug delivery.
4. Syed umer jan, gul majid khan, release pattern of three new polymers in ketoprofen controlled- release tablets, african journal of pharmacy and pharmacology, 8 march, 2012; 6(9): 601-607.
5. K.p. sampath kumar*, debjit bhowmik, shweta srivastava. sustained release drug delivery system potential the pharma innovation.
6. Charles a. dinarello. anti-inflammatory agents.
7. Sanjoy kumar das, jasmina khanam, arunabha nanda. optimization of preparation method for ketoprofen-loaded microspheres consisting polymeric blends using simplex lattice mixture design. materials science and engineering, 2016; c69: 598–608.
8. De cássia da silveira e sá r, andrade ln, de sousa dp. a review on anti-inflammatory activity of monoterpenes. Molecules, Jan. 18, 2013; 18(1): 1227-54.

9. Schönenberger ka, schüpfer ac, gloy vl, hasler p, stanga z, kaegi-braun n, reber e. effect of anti- inflammatory diets on pain in rheumatoid arthritis: a systematic review and meta-analysis. Nutrients, Nov. 24, 2021; 13(12): 4221.
10. Tan l, song x, ren y, wang m, guo c, guo d, gu y, li y, cao z, deng y. anti- inflammatory effects of cordycepin: a review. phytotherapy research, Mar, 2021; 35(3): 1284-97.
11. Luo c, zou l, sun h, peng j, gao c, bao l, ji r, jin y, sun s. a review of the antiinflammatory effects of rosmarinic acid on inflammatory diseases. frontiers in pharmacology, Feb 28, 2020; 11: 153. 2018.
12. Abbas s, abbas z. analytical methods for determination of ketoprofen drug: a review. ibn al- haitham journal for pure and applied sciences, Jul. 20, 2022; 35(3): 76-82.
13. Chawla g, ranjan c, kumar j, a siddiqui a. chemical modifications of ketoprofen (nsaid) in search of better lead compounds: a review of literature from 2004-2016. anti-inflammatory & anti-allergy agents in medicinal chemistry (formerly current medicinal chemistry-anti-inflammatory and anti- allergy agents), Dec. 1, 2016; 15(3): 154-77.
14. Carbone c, rende p, comberiati p, carnovale d, mammì m, de sarro g. the safety of ketoprofen in different ages. journal of pharmacology and pharmacotherapeutics, Dec, 2013; 4(1): s99-103.
15. hemmati k, masoumi a, ghaemy m. tragacanth gum-based nanogel as a superparamagnetic molecularly imprinted polymer for quercetin recognition and controlled release. carbohydrate polymers, Jan 20, 2016; 136: 630-40.
16. Singh b, sharma v. influence of polymer network parameters of tragacanth gum-based ph responsive hydrogels on drug delivery. carbohydrate polymers, Jan. 30, 2014; 101: 928-40.
17. Rowe RC, Sheskey PJ SC. Handbook of pharmaceutical excipient fifth Edition.
18. Rowe RC, Sheskey PJ SC. Handbook of pharmaceutical excipient fifth Edition.
19. "Hindi, S. S. Z. Microcrystalline cellulose: Its specifications and pharmaceutical processing. Biocrystals Journal, 2016; 1(1): 26-38". BioCrystals. Retrieved 2016-04-22.
20. Rowe RC, Sheskey PJ SC. Handbook of pharmaceutical excipient fifth Edition
21. 21-. R Sharma. Elementary organic spectroscopy, principles and chemical application. 1st ed. S. chand publication, 2001; 81-82.
22. Liberman H, Lachman L. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Verghese Publication House, 1991; 171-193.
23. Martin A, Micromeretics. In: Martin A, ed. Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins, 2001; 423-454.

24. Alfred Martin, Physical Pharmacy-physiochemical principles in the pharmaceutical sciences. 4th ed. New Delhi. B.I Waverly Pvt. Ltd., 1996; 313-316. 25-54. http://en.wikipedia.org/wiki/carbopol.
25. Martin A, Micromeretics. In: Martin A, ed. Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins, 2001; 423-454.
26. D. Bhowmik, B. Chiranjib, Krishnakanth, Pankaj, R. Margret Chandira, Fast Dissolving Tablet: An Overview. Journal of Chemical and Pharmaceutical Research., 2009; 1(1): 163-77.
27. Hansiya Sultana H, GB Kiran Kumar, Acharya A, Ahmed MG. Development and evaluation of chitosan based oral controlled release matrix tablets of Pregabalin. World J Pharm Pharma Sci., 2015; 4(6): 1306-19.
28. Uddin M. Development of sustained release tablet of Valsartan. World J Pharm Pharma Sci., 2015; 3(5): 1196-05.
29. Hansiya Sultana H, GB Kiran Kumar, Acharya A, Ahmed MG. Development and evaluation of chitosan based oral controlled release matrix tablets of Pregabalin. World J Pharm Pharma Sci., 2015; 4(6): 1306-19.
30. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci., 2001; 13: 123-33.
31. Ahmed MG, Choudhari R, Acharya A. Formulation and evaluation of in situ gel of Atorvastatin for the treatment of periodontitis, 2015; RGUHS J Pharm Sci., 5(2): 53-60.
32. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products. [Online]. [Cited 2008 Nov 10]; Available from: