DESIGN AND DEVELOPMENT OF PRESS COATED PULSATILE RELEASE OF KETOPROFEN TABLETS

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Submitted by

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CERTIFICATE

This is to certify that the dissertation entitled "**DESIGN AND DEVELOPMENT OF PRESS COATED PULSATILE RELEASE OF KETOPROFEN TABLETS"** is a bonafide and genuine research work carried out by **M.Sindhu Chowdary B.Pharm** during the year 2018-2019 under the supervision of Prof. **Dr.K.Senthil kumaran M.Pharm. Ph.D.,Professor & Head Department of Pharmaceutics, K.K.College of Pharmacy**,Chennai-600128. This dissertation is submitted for partial fulfillment of the requirement for the award of degree of Master of Pharmacy (Pharmaceutics), by the Tamil Nadu Dr.M.G.R Medical University, Chennai – 32.

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M.Sindhu chowdary

DEDICATED

TO MY

BELOVED PARENTS, TEACHERS

AND

MY

DEAREST FRIENDS

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LIST OF ABBREVIATIONS

S.No	Abbreviation	Full Form
1.	Abs	Absorbance
2.	Avg	Average
3.	NcE	New Chemical Entity
4.	IV infusion	Intravenous infusion
5.	FDA	Food and Drug Administration
6.	CAS	Chemical Abstracts Service
7.	grm	Gram
8.	cm	Centimeter
9.	GI	Gastro intestinal
10.	PDDS	Pulsatile drug delivery System
11.	RA	Rheumatoid Arthritis
12.	NSAIDS	Non Steroidal Antiinflammatory drugs
13.	DMARDS	Disease modifying Anti rheumatic drugs
14.	COX	Cyclooxygenase
15.	FTIR	Fourier Transform Infra-red Spectrophotometer
16.	MCCP	Microcrystalline Cellulose
17.	SSG	Sodium Starch Glycolate
18.	IPA	Isopropyl Alcohol
19.	g/mol	Gram/Mole
20.	hr	Hour(s)
21.	HPMC	Hydroxy propyl Methyl Cellulose
22.	HCl	Hydrochloric acid
23.	KBr	Potassium Bromide
24.	M	Mass
25.	Mg	Milligram (s)
26.	min	minutes
27.	ml	Milliliters
28.	BCS	Biopharmaceutical Classification system

29.	nm	Nanometer
30.	UV Spectroscopy	Ultra Violet Spectroscopy
31.	V	Volume
32.	Q.S	Quality Sufficient
33.	°C	Degree Centigrade
34.	%	Percentage
35.	NLT	Not less than
36.	mm	millimeter

1. INTRODUCTION

In pharmaceutical field day by day technologies are developing and leading to most efficacious dosage form. In that for oral route of administration has been most popular and successfully used route of administration.

- Convenience and ease of administration
- Greater flexibility in dosage form design
- Ease of production and low cost of such a system

In regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized. Modified release oral dosage forms have brought new lease of life into drugs that have lost market potential due to the requirement of frequent dosing, dose related toxic effects and gastrointestinal disturbances.

The term modified release drug product is used to describe products that alter the timing and /or the rate of release of the drug substance. A modified release dosage form is defined is defined "as one for which the drug –release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms as presently recognized"

Several types of modified release drug products are recognized:

- Extended Release drug products
- Delayed release drug products
- Targeted release drug products
- Conventional drug delivery system

By this above controlled and sustained release drug delivery system having draw back in treating the diseases like Peptic Ulcer, Asthma, Cardiovascular, Arthritis, Diabetes, Hypercholesterolemia because these occurs depending on the biological rhythms.

To introduce the concept of chronotherapeutics, it is important to define the following concepts.[1] "chronopharmaceutics" consists of two words chronobiology and pharmaceutics. chronobiology is a science concerned with the biological mechanism of the diseases according to a time structure. 'chrono' pertains to time and 'biology' pertains to the study, or science of life.[1] Pharmaceutics is the discipline of pharmacy that deals with the process of turning a new chemical entity (NcE) into a medication to be used safely and effectively by patients. It is also called the science of dosage form design and deals with the formulation of a pure drug substance into a dosage form.[1]

Chronopharmaceutics: It is a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Chronopharmaceutics may be considered as a bridge to fill up the gap between the existing concepts of chronobiology, chronopharmacology, chronopharmacokinetics, chronotherapeutics and chronotoxicology[3]

Chronobiology is the study of biological rhythms. These rhythms are described by different terms according to the duration of the rhythmic cycle.[3]

Types of biological rhythms:

- **Ultradian rhythms**, shorter than a day . Eg: thousandths of a second (like the pulses in neurons) seconds (like the heartbeat)

Circadian rhythms, which last about one day. •Circadian rhythms are self-sustaining and endogenous oscillations that occur with a periodicity of about 24 Hours. Eg: the sleep-waking rhythm, the body temperature, sensitivity to pain or alcohol, reaction time, levels of hormones in the blood etc.

Infradian rhythms, longer than a day.[5]

Eg: monthly rhythm - menstrual cycle Yearly rhythm – bird migration

Tidal rhythms, commonly observed in marine life, which follow the roughly 12-hour transition from high to low tide and back.

Pharmaceutics deals with the design and evaluation of pharmaceutical dosage forms or drug delivery systems to assure their safety, effectiveness, quality and reliability. The

combination of all these areas defined above has led to the development of chronopharmaceutics, which deals with development of pharmaceutical formulations that release the drug according to the biological rhythm of the disease.[3]

Pulsatile drug delivery system

Drug Delivery system that is designed to delayed release. The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time.[7]

Such systems are also called time-controlled released is independent of the environment. It has been reported Pulsatile drug delivery systems are gaining a lot of interest and attention these days

Pulsatile systems will- deliver the drug at the right site of action, at the right time and in the right amount -- increasing patient compliance.

The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired.

Various Dosage form in Pulsatile Drug Delivery System::

ORAL DOSAGE FORM:

TABLETS:

Multi Layered Tablets

Press Coated Tablets

Core And Cup Tablets

MICROPARTICLES/MICROBEADS:

Multiparticulate Systems

CAPSULES:

Pulsincap system

Multilayered capsules.

IV INFUSION:

Infusion pumps

Multilayered tablets:

Multilayer tablets (2 or 3) are prepared by repeated compression of powders are made primarily to separate incompatible drugs from each other. And it consists of several different granulations compressed on top of each other to form a single tablet.

Press coated Tablet:

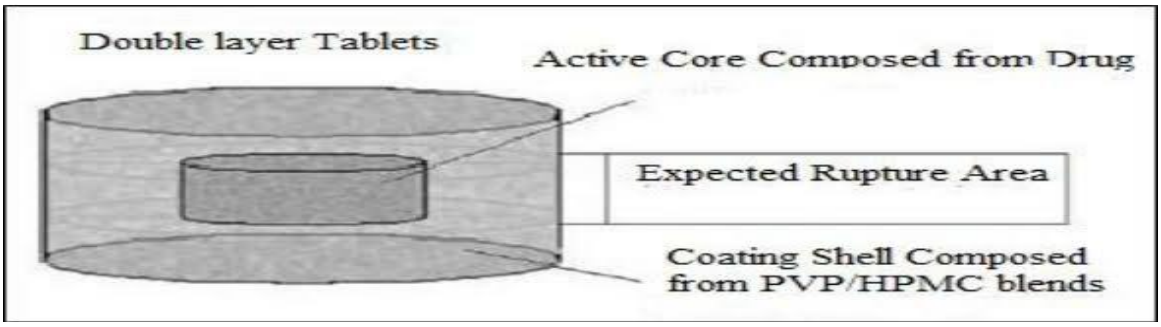


Fig:1.1 Press coated pulsatile tablet

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tablet machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it allows the drug release at the point in circadian cycle when clinical signs develop and increase.

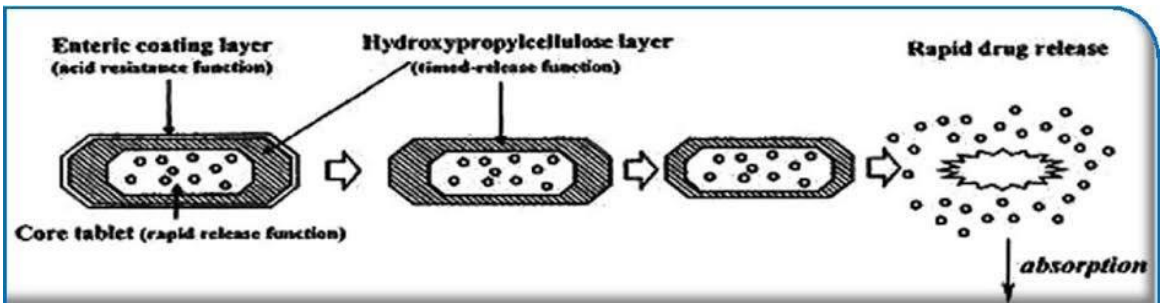


Fig:1.2 Release of Press coated pulsatile tablet

Core and Cup Tablets

It is a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three different parts, a core tablet, containing active ingredient, an impermeable outer shell and a top cover layer- barrier of a soluble polymer. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increases when quantity of top layer increases, whereas drug release decreases.

Multiparticulate Systems:

These systems have been developed on the basis of various approaches of designing pulsatile drug delivery system discussed later (like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems).these can be developed in various types of dosage forms like: Pellets, Granules, Microspheres, Beads, Nanoparticles. In recent pharmaceutical applications involving pulsatile drug delivery, multiparticulate dosage forms are gaining much favour over single unit dosage forms. A no. of multiparticulate pulsatile drug delivery systems has been developed for chronotherapy. For instance, colonic delivery of microspheres and coated pellets for nocturnal asthma, formulation of pellets and microspheres for chronotherapy of rheumatoid arthritis and floating beads of alginates encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract. Numerous advanced technologies have been developed in designing of pulsatile release multiparticulate dosage forms and many of them are FDA approved and being marketed.

Pulsincap system:

As well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and

predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released. To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles

Multilayered capsules:

The pulsatile capsule is designed for two drug doses. First is placed into the capsule cap while the second dose is released from an insoluble capsule body.lag time is determined by an osmotic system which presses an insoluble plug out of the capsule body These are time controlled rupturable pulsatile drug delivery systems either in form of hard gelatin capsules tablets. The capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating. Upon water ingress the swelling layer swells to attain a threshold hydrodynamic pressure required to rupture the outer coating and allowing the release of contents in surrounding medium. The time required by swelling layer to rupture outer coating surves the purpose of desired lag time required in chrono therapy of disease. The tablets are manufactured and coated on the same principle as that of double coated gelatin capsules.

Infusion pumps:

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. The portable pumps are usually characterized by a light weight (300-500 grm) for easy portability and precision in drug delivery. For example portable programmable multi-channel pumps allowed demonstration of the clinical relevance of the chronotherapy principle in a sufficiently large patient population. Specifically, a clinical phase III trial involving several patients with metastatic gastrointestinal malignancies compared a flat versus the chronomodulated three-drug

regimen, and demonstrated large, simultaneous improvements in both tolerability and response rates in patients with metastatic colorectal cancer receiving chronotherapy. In case of insulin therapy, implantable infusion pumps containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by the intraperitoneal route. Their advantages include the fact that the peritoneum provides a large, well-vascularized surface area, and absorption is faster by this route than after subcutaneous injection (better insulin gradient), improved glycemic control and a reduction in the frequency of hypoglycemic episodes. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion. Catheter blockade which can reduce insulin delivery, are the most common problems with implantable pumps. However, these pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes. Controlled-release microchip: An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology. A solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form.

ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM:

1. Increases absorption and bioavailability than conventional immediate release or sustained release drug.

2. Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in GI tract environment.

3. Reduces dose of drug without decrease in therapeutic effects, improved tolerability[2]

4. No risk of dose dumping and side effects [2].

5. Less inter- and Intra- subject variability. [2].

6. Pulse release allows multiple dosing in a single dosage form.

7. The System can be utilized for many solid dosage forms like granules, microspheres, micro particles, tablets, capsules, and pellets

8. Improves patient comfort and compliance, Extends patent protection, globalizes the product, and overcomes competition. [2]

9. Ease of combining pellets with different compositions or release patterns. [2]

10. Predictable, reproducible, and short gastric residence time.[2]

11. Limited risk of local irritation.

12. Improved Stability. [2]

13. Achieves a unique release pattern [2]

LIMITATIONS OF PULSATILE DRUG DELIVERY SYSTEMS:

1. Multiple manufacturing steps and large number of process variables, Lack of manufacturing reproducibility and efficacy.[2]

2. Homogeneity of the coated barrier in mandatory to assure the predictability of the lag time.

3. Rupture time cannot be always adequately manipulated as it depends on the physicochemical properties of the polymer.

4. Higher cost of production.

5. Raw material is not easily available.

6. Proportionally higher need for excipients.[2]

7. Low drug loading.[2]

8. Multiple formulation steps.[2]

9. Dosage form design requires highly skilled / trained professionals.

10. Technologies employed and the equipments used are complicated.

Diseases targeted for pulsatile technology[3]:

Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- compared to the conventional drug administration approach [3]. They include: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. hypertension and acute myocardial infarction) and colonic delivery [3].

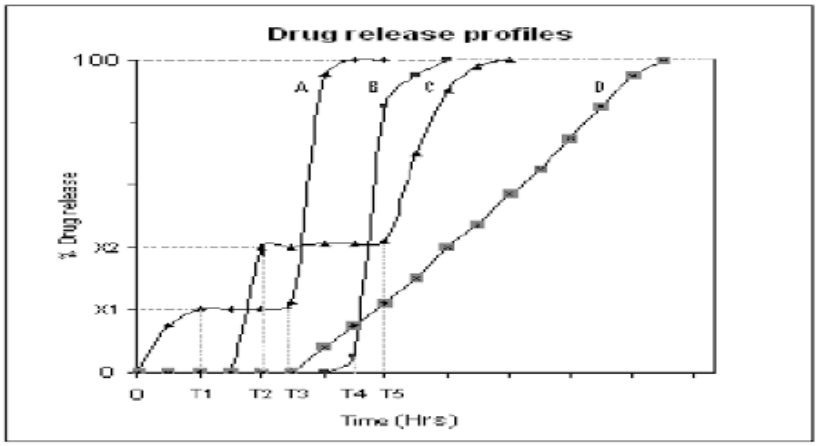


Fig:1.3 Drug release profile of pulsatile drug delivery System

Table:1.1 Disorders depending on circadian rhythms are:

Chronological behavior	Drugs Used	Diseases
Acid Secretion is high in the afternoon and at night	H2 blockers	Peptic Ulcer
Precipitation of attacks during night or at early morning	β2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, Calcium Channel blocker, ACE inhibitors	Cardiovascular
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in the blood sugar mellitus level after meal	Sulfonylurea, Insulin	Diabetes
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia

Arthritis:[4]

The chronobiologies of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 in patients with rheumatoid arthritis. Increasingly, the arthritis have shown statistically quantifiable rhythmic parameters. Included in the latter group are joint pain and joint size. In addition, a number of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects based on the time of day of administration Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day.

Chronic untreated inflammation may lead to joint erosions and joint destruction

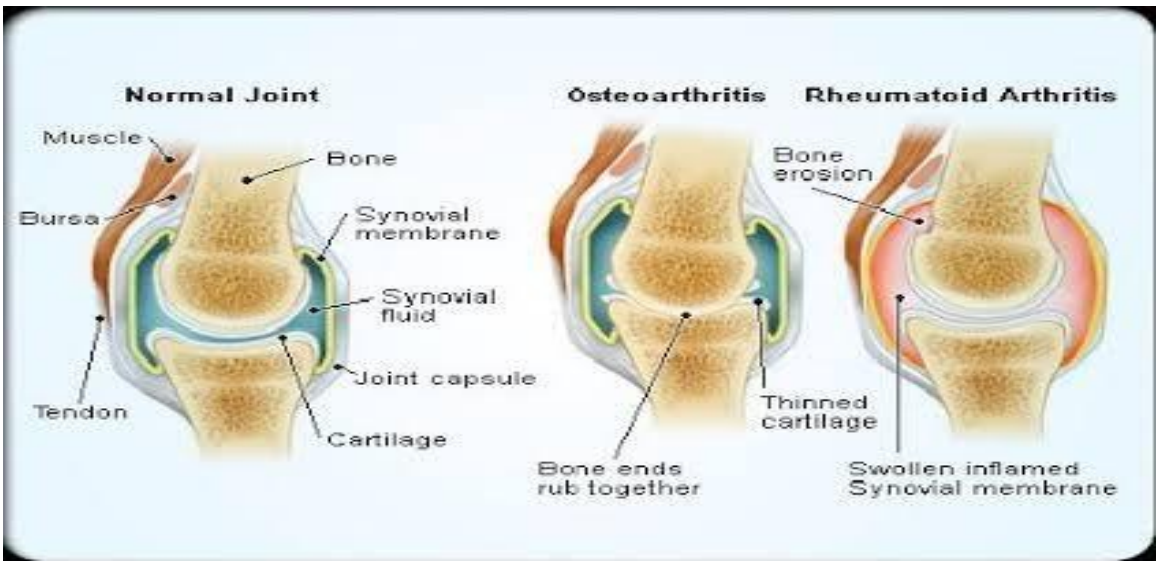


Fig:1.4: Difference between Normal joint and Rheumatoid Arthritis

Main symptoms:

Painful and swollen joints, especially on hands, wrists, elbow, knees and feet, fatigue muscular pain, loss of appetite and joint stiffness has been seen mainly in the morning or after long resting periods.

It may affects 0.5-1% of the population world wide with a peak prevalence between the ages of 30 and 50 years

Causes of Rheumatoid Arthritis:

The exact cause of Rheumatoid Arthritis is unknown.

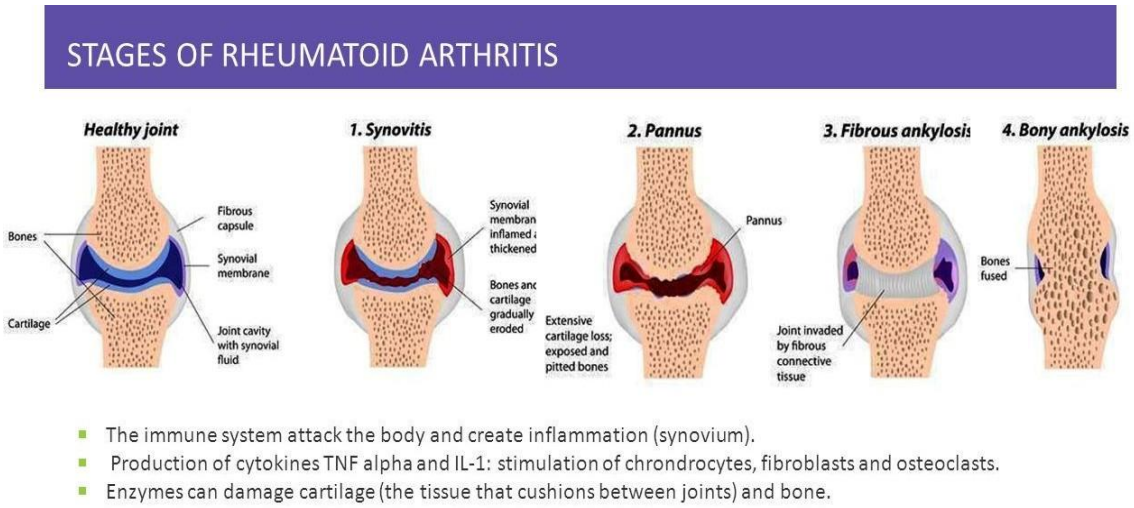


Fig:1.5: Stages of Rheumatoid Arthritis

Treatment for Arthritis:

The treatment of RA revolved around the use of high dose aspirin, Other Non steroidal Anti inflammatory drugs(NSAIDs), Corticosteroids and subsequently, disease modifying anti rheumatic drugs (DMARDs).

2. REVIEW OF LITERATURE

1. **Vineela. P* (2014)** published about Overview on Chronopharmaceutical Drug Delivery System,chronological behavior and how chronopharmaceutical drug delivery can be used in case of chronopharmacotherapy of diseases which shows circadian rhythm in their patho physiology which can tackle the problems as it is modulated to release the drug according to the biological clock. Various methodologies in development of drug delivery system.

2. **Rohit Bisht** (**2011)** published that Chronomodulated drug delivery system: A comprehensive review on the recent advances in a new sub-discipline of 'chronopharmaceutics' how pulsatile drug delivery system gained popularity. And recent technologies developed in the pulsatile drug delivery system.There considerations, coupled with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this would extend well into the future and result in the betterment of the quality of life.

3. **Sundeep Chaurasia*, et.al., (2011)** discussed on CHRONOPHARMACEUTICS: CONCEPT AND TECHNOLOGIES increasing research interest surrounding ChrDDS may lead to the creation of a new sub-discipline in pharmaceutics known as chronopharmaceutics. This review introduces the concept of chronopharmaceutics, addresses theoretical/formal approaches to this sub-discipline, underscores potential disease-targets, revisits existing technologies and examples of ChrDDS. Future development in chronopharmaceutics may be made at the interface of other emerging disciplines such as system biology and nanomedicine.

4. **B.Senthilnathan: et.al., (2012)** discussed on Design And Development Of Pulsatile Drug Delivery Of Glibenclamide Using Pulsincap Technology. The main objective is to formulate and evaluate the pulsincap for anti diabetic drug Glibenclamide to control the increased blood glucose level after food consumption in diabetic patient by allowing the drug to release immediately after a lag time (after meals). Microsponges of different concentrations were prepared and selected the best formulation for the development of pulsincap and the optimized microsponges were subjected to scanning electron microscopy, FT-IR, and In vitro studies. Invitro release studies were carried out for formulated pulsincaps. The release studies indicates that all the dosage forms released their first pulse within two hours and then release their second pulse after the swelling of hydrogel plug. The results showed that pulsincap dosage form of Glibenclamide could be effectively control the blood glucose levels after breakfast and lunch in respect to release of two pulses (i.e. first pulse after breakfast and second pulse after lunch). Hence it is found to be suitable for the diabetic patient to manage the blood glucose levels which are high after food consumption.

5. **Veena S Belgamwar: et.al,.(2008)** discussed on Pulsatile drug delivery system. Pulsatile drug delivery system is the most interesting time- and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Various systems like capsular systems, osmotic systems, pulsatile system based on the use of soluble or erodible polymer coating, use of rupturable membranes and pulsatile system based on membrane permeability are summarized in this article. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in gastrointestinal tract.

6. **Anamika Singhet.al,. (2012)** discussed on Pulsatile Drug Delivery System: an Approach of Medication according to Circadian Rhythm. Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease display it's most morbid and mortal state within a circadian cycle (24 hrs.). The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach. The potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in market. These systems are beneficial for diseases showing chronopharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also improve patient compliance by decreasing dosing frequency.

7. **Hetal patel et al,. (2015):** discussed on Pulsatile Release Of Ketoprofen From Compression Coated Tablets Using Eudragit® Polymers. The objective of the present research work is to develop compression coated tablet of ketoprofen as a pulsatile release system for treatment of rheumatoid arthritis. Methods: Core tablets of ketoprofen were prepared using the wet granulation method and evaluated for appearance, hardness, friability, weight variation, thickness, disintegration time and % drug release. Core tablets were coated with Eudragit S100 and Eudragit L100 by compression coating method to achieve desired lag time.

8. **Dr. S.S. Khadabadi et al,. (2013):**discussed on formulation and evaluation of press coated tablet of ketoprofen – A chronotherapeutic approach. Objective: The aim of present investigation was to develop press coated tablet for pulsatile drug delivery of Ketoprofen used for chronotherapy of rheumatoid arthritis. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. Methodology: The press coated tablets containing Ketoprofen in the inner core were formulated by direct compression method with an outer coating of different amounts of HPMC K4M. Results: The release profile of press coated tablet exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 32 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 7.1.4 software. The optimized batch F6 gave a lag time of 6 hr and drug release of 95.74% which consisted of 40% HPMC K4M and 2% SSG.

9. **Rewar S et al. (2014):** discussed on pulsatile drug delivery system: an overview. Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. A Pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Advantages of the Pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more. Now in market varies technologies of pulsatile drug delivery system like Pulsincap, Diffucaps etc. are launched by pharmaceutical companies.

10. **Patel S.R et al. (2012);** discussed on Floating pulsatile drug delivery system for chronotherapy.In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified shape systems, high-density systems and other delayed gastric emptying devices. Recent trends indicate that drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain desirable release patterns with less inter- and intra-subject

variability. A blend of floating and pulsatile principles of drug delivery system seems to present the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. Floating pulsatile drug delivery system (FPDDS) concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Diseases wherein FPDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children. To overcome limitations of various approaches for imparting, buoyancy and lag controlling were prepared by floating pulsatile delivery systems, for which time controlling system like swelling and rupturable membranes, soluble or erodible coating, capsule shaped system, and multiparticulate system are primarily involved in the control of release.

11. **Sanjay J Kshirsagar et al,. (2019).** discussed on Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. The purpose of this work was to develop hollow calcium alginate beads for floating pulsatile release of valsartan intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. Materials and Methods: To overcome the limitations of various approaches for imparting buoyancy, hollow/porous beads were prepared by simple process of acid-base reaction during ionotropic crosslinking by low viscosity sodium alginate and calcium chloride as a crosslinking agent. In this study, investigation of the functionality of the sodium alginate to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM). RSM was employed for designing of the experiment, generation of mathematical models and optimization study. The chosen independent variables, i.e. sodium alginate and potassium bicarbonate were optimized with a 32full factorial design. Floating time and cumulative percentage drug release in 6 h were selected as responses. Results: Results revealed that both the independent variables are significant factors affecting drug release profile. A second-order polynomial equation fitted to the data was used to predict the responses in the optimal region. The optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. The floating beads obtained were porous (21-28% porosity), hollow with bulk density <1 and had Ft70 of 2–11 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. Conclusion: The proposed mathematical model is found to be robust and accurate for optimization of time-lagged formulations for programmable pulsatile release of valsartan.

12. **NS Dey et al,. (2008);** discussed on Multiparticulate Drug Delivery Systems for Controlled Release. Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimising side effects. Recent trends

indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

13. **Wang H et al, (2017);** discussed on A time-adjustable pulsatile release system for ketoprofen: In vitro and in vivo investigation in a pharmacokinetic study and an IVIVC evaluation. A time-adjustable pulsatile release system (TAPS) containing ketoprofen (KF) as an active pharmaceutical agent was developed having been designed for bedtime dosing and releasing drug in the early morning to control the symptoms of rheumatoid arthritis (RA). The formulation involved a tablet core (KF) and a control-release layer, and the coating membrane was composed of EC and Eudragit L100. A single-factor study, a central composite design and a response surface method were selected to optimize the formula and the optimum prescription was as follows: tablet core (KF 50mg, MCC 70mg, lactose 40mg, L-HPC 38mg), and film (EC 7.8g, Eudragit L100 4.2g, PEG 6000 1.8g in 95% alcohol each 200ml). The in vivo release behavior of the tablets was evaluated in Beagle dogs after a parallel oral administration of KF TAPS tablets and commercial KF capsules, when it was found that the KF TAPS tablets released the drug after a lag-time of 3.458h and the T was 5.833h. The relative bioavailability was 85.01%, and the two formulations were bioequivalent in terms of C and AUC and the in vitro- in vivo correlations indicated that test formulation had a good in vivo-in vitro correlation (r=0.9703). These results show that the novel drug delivery system (TAPS) has the potential to be used as a KF preparation with chronophamacokinetics characteristics.

14. **Rawat s.* et al, (2013).** discussed on pulsatile drug delivery “a programmed polymeric device”. Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place, at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. The use of pulsatile release of the drugs is desirable where constant drug release is not desired. These systems are designed according to the circadian rhythm of the body. According to Latin literature circa means about and Diem means day. This could be advantageous for many drugs or therapies including asthma, peptic ulcer & arthritis etc. To correlate with our biological needs, “precisely timed drug delivery,” which could be accomplished with “programmable dosage forms,” is desirable. Precisely timed drug delivery may maximize therapeutic efficacy, minimize dose frequency, and may reduce toxicity. This paper outlines the concepts that have been proposed to release drugs in a pulsed manner from pharmaceutical device.

15. **Patel Vipul P et al, (2012):** discussed on Pulsatile drug delivery system for treatment of various Inflammatory Disorders: A Review. Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. These systems are designed according to the biological rhythm of the body. Here drug delivery is facilitated according to disease rhythm. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. These systems are beneficial for the drugs having chronopharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis like inflammatory disorders. Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, evaluations, advantages, limitation, and future aspects of pulsatile drug delivery system.

3.1. AIM AND OBJECTIVES

Ketoprofen, which is active pharmaceutical ingredient, belongs to Non steroidal anti-inflammatory drug used to treat inflammation and Rheumatoid arthritis disease. As sustained and controlled release drug delivery system is not suitable for rheumatoid arthritis because it occurs depending on the biological rhythms mainly in early morning and night.
The main aim of the work is to design and development of press coated pulsatile release of Ketoprofen tablet. Hence that drug delivery will be at right time by avoiding first pass metabolism.

The present study is planned with the following objectives:

- To formulate pulsatile drug release tablet using Press coated method by using polymers.
- To study the effect of polymers for their retarding efficiency of the drug.
- To characterize the polymers to various physicochemical and drug release parameters in certain lag time.
- To evaluate the formulated press coated pulsatile tablet for drug content uniformity, *in-vitro* dissolution studies & stability studies.

3.2 PLAN OF WORK

The work is planned according to the following steps:

I. Literature review.

II. Procurement of raw materials.

III. Preformulation studies

1. Organoleptic Properties.
2. Solubility study
3. Determination of Lamda max.
4. Construction of Calibration curve.
5. Compatibility studies of drug with the excipients by using FT-IR.
6. Assay of purity for ketoprofen

IV. Formulation of Ketoprofen core tablet

1. Blending of materials
2. Angle of repose
3. Bulk density
4. Tapped density
5. Hausners ratio
6. Compressibility index

V. Evaluation of ketoprofen core tablet.

1. Thickness
2. Diameter
3. Hardness
4. Weight variation
5. Content Uniformity

6. Friability.

VI. Compression of Ketoprofen coat tablet.

VII. Evaluation of Ketoprofen coat tablet.

1. Thickness
2. Diameter
3. Hardness
4. Weight variation
5. Content Uniformity
6. Friability.
7. *In vitro* release studies.

VIII. Selection of better formulation based on *in-vitro* dissolution.

IX. Stability Studies (Accelerated stability studies)

4. 1 LIST OF CHEMICALS

Table: 4.1 : List of chemicals

S.NO	DRUG/POLMER/SOLVENT	COMPANY
1	Ketoprofen	Infinity Pharmaceuticals
2	Lactose Monohydrate	Biocon
3	Microcrystalline Cellulose	Sigachi industries
4	Sodium Starch Glycolate	Maruthi chemicals
5	PVP K 30	Boai NKY pharmaceuticals
6	Isopropyl Alcohol	Rankem
7	Purified Talc	Gangotri inorganics
8	Magnesium Stearate	Amishi Drugs and Chemicals
9	HPMC E5	Jianxin Cellulose
10	HPMC E15	Jianxin Cellulose
11	Xanthan Gum	Shandong Fufeng Fermentation

4.2 LIST OF EQUIPMENTS:

Table :4.2: List of equipments used

S.NO	NAME OF THE EQUIPMENT	MANUFACTURED COMPANY
1	Electronic Balance	Citizen
2	UV-Vis spectrophotometer	Shimadzu
3	Hardness tester	Monsento hardness tester
4	Vernier calipers	Digimatic caliper
5	Friability Tester	Roche Fribilator
6	Dissolution Apparatus	Lab India

4.3 DRUG AND EXCIPIENTS PROFILE:

Ketoprofen:

Synonyms : 2-(3-Benzoylphenyl)propionic acid, 3-Benzoyl-alpha-methylbenzeneacetic acid, 3-Benzoyl-α-methylbenzeneacetic acid, 3-Benzoylhydratropic acid, Ketoprofeno, L'acide (benzoyl-3-phenyl)-2-propionique,m-Benzoylhydratropic acid

IUPAC name : 2-(3-benzoylphenyl)propanoic acid

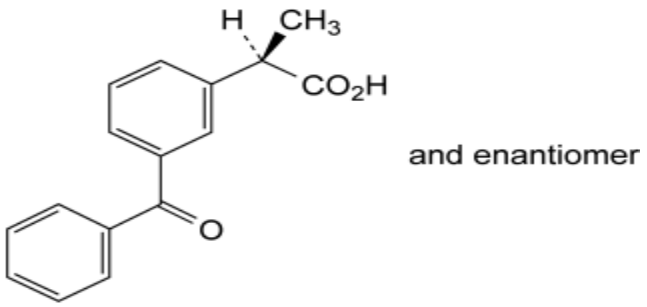
Chemical formula : $C_{16}H_{14}O_3$

Molecular mass : Average: 254.2806

Monoisotopic: 254.094294314

Route of adminstration : Oral, external

Structure :



MECHANISM OF ACTION:

The anti-inflammatory effects of ketoprofen are believed to be due to inhibition cylooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway. This results in decreased levels of prostaglandins that mediate pain, fever and inflammation. Ketoprofen is a non-specific cyclooxygenase inhibitor and inhibition of COX-1 is thought to confer some of its side effects, such as GI upset and ulceration. Ketoprofen is thought to have anti-bradykinin activity, as well as lysosomal membrane-stabilizing action. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation.

INDICATION:

For symptomatic treatment of acute and chronic rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, primary dysmenorrhea and mild to moderate pain associated with musculotendinous trauma (sprains and strains), postoperative (including dental surgery) or postpartum pain.

PHARMACODYNAMICS:

Ketoprofen is a nonsteroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. Ketoprofen has pharmacologic actions similar to those of other prototypical NSAIDs, which inhibit prostaglandin synthesis. Ketoprofen is used to treat rheumatoid arthritis, osteoarthritis, dysmenorrhea, and alleviate moderate pain.

PHARMACOKINETIC DATA:

Absorption: Ketoprofen is rapidly and well-absorbed orally, with peak plasma levels occurring within 0.5 to 2 hours.

Volume of distribution: Not Available

Protein binding:99% bound, primarily to albumin

Metabolism: Rapidly and extensively metabolized in the liver, primarily via conjugation to glucuronic acid. No active metabolites have been identified.

Route of elimination: In a 24 hour period, approximately 80% of an administered dose of ketoprofen is excreted in the urine, primarily as the glucuronide metabolite.

Half life: Conventional capsules: 1.1-4 hours

Extended release capsules: 5.4 hours due to delayed absorption (intrinsic clearance is same as conventional capsules)

Symptoms of overdose: include drowsiness, vomiting and abdominal pain.

Side effects are usually mild and mainly involved the GI tract. Most common adverse GI effect is dyspepsia (11% of patients). May cause nausea, diarrhea, abdominal pain, constipation and flatulence in greater than 3% of patients.

Lactose Monohydrate:

Synonym: CapsuLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

Chemical names: O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate

Chemical Formula : $C_{12}H_{22}O_{11}$

CAS Registry number:64044-51-5

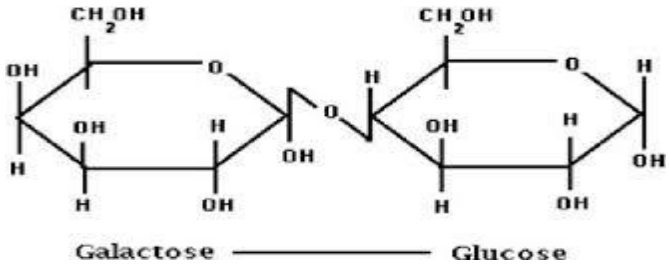
Appearance: Lactose occurs as white to off-white crystalline particles or powder, It is odorless and slightly sweet –tasting.

Molecular weight: 342.3 g/mol

Density: 1.52g/cm^3

Solubility: Chloroform Practically insoluble, Ethanol Practically insoluble, Ether Practically insoluble Water

Structure:



Functional category: Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Applications in pharmaceutical formulation or technology:

Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry-powder inhalation, Inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle is often dependent on the type of encapsulating

machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently. , where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately1:3) to prepare sugar- .It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation. Other directly compressible lactoses are spray-dried lactose and anhydrous lactose; see Lactose, Spray-Dried and Lactose, Anhydrous.

Microcrystalline cellulose:

Synonym: Cellulose gel

Chemical names: Cellulose gel, Celllulose, Microcrystalline cellulose

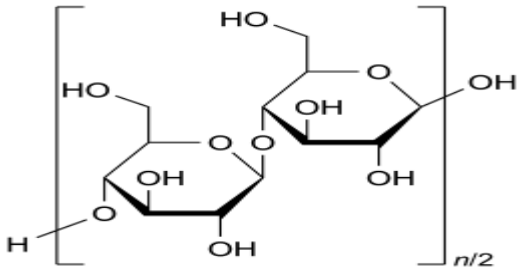
CAS Registry number: 9004-34-6

Chemical formula: $(C6H_{10}O_5)_n$

Description: White or almost white, fine or granular, slightly hygroscopic Powder

Solubility: Practically insoluble in water, in acetone, in anhydrous ethanol, in toluene, in dilute acids and in a 50 g/L solution of sodium hydroxide

Structure:



Functional category: thickener, Stabilizer or emulsifiers, abrasive, absorbent, Anticaking agent, binder, bulking agent emulsion stabilizer

Applications in pharmaceutical formulation or technology:

Used as a texturizer, an anti caking agent, a fat substitute, an emulsifier, an extender, and bulking agent in food production. The most common form is used in vitamin supplements or tablets. It is also used in plaque assays for counting viruses. Used as Slip modifier and texturizer this can be found in various hair and skin care products as well makeup.

The MCC is a valuable additive in pharmaceutical, food cosmetic and other industries. Different properties of MCC are measured to qualify its suitability to such utilization, namely particle size, density, compressibility index, angle of repose, powder porosity, hydration swelling capacity, Moisture content, crystallinity index, crystallite size, and mechanical properties such as hardness and tensile strength.

Sodium starch glycolate:

Synonym: Carboxymethyl starch, sodium salt; carboxymethylamylum natricum;Explosol;Explotab;Glycolys;Primojel;starchcarboxymethyl ether, sodium salt

Chemical names: Sodium carboxymethyl starch

Molecular formula: $C_2H_3NaO_3$

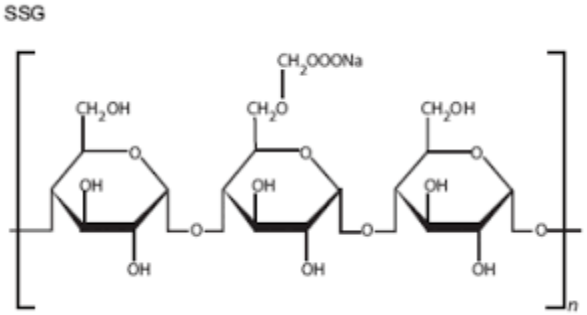
Molecular Weight: 98.033g/mol

CAS Registry number: 9063-38-1

Description: Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The granules show considerable swelling in contact with water.

Solubility: Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Structure:



Functional category: Tablet and capsule disintegrant.

Applications in pharmaceutical formulation or technology: SSG is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. SSG has also been investigated for use as a suspending vehicle.

PVP K30:

Synonym: Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm;c1vinyl-2-pyrrolidinone polymer.

Chemical names: 1-Ethenyl-2-pyrrolidinone homopolymer

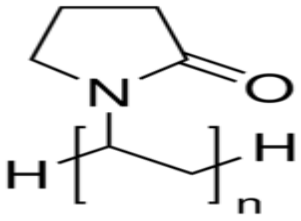
CAS Registry number: 9003-39-8

Molecular formula: $(C_6H_9NO)_n$

Description: Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Solubility: Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Structure:



Functional category: Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Applications in pharmaceutical formulation or technology: Intableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Isopropyl Alcohol:

Synonym: Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol.

Chemical names: Propan-2-ol

CAS Registry number: 67-63-0

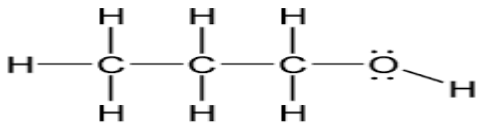
Molecular formula: C_3H_80

Molecular weight: 60.1g/mol

Appearance: IPA is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Solubility: Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

Structure:



Functional category: Disinfectant; solvent.

Applications in pharmaceutical formulation or technology: IPA (propan-2-ol) is used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. Although it is used in lotions, the marked degreasing properties of IPA may limit its usefulness in preparations used repeatedly. IPA is also used as a solvent both for tablet film-coating and for tablet granulation, where the IPA is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide from carbomer 934. IPA has some antimicrobial activity and a70%v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

Hydroxypropyl methyl cellulose :

Synonym: Cellulose, hydroxypropyl ether; E463; hydroxypropylcellulosum; hyprolose; Klucel; Nisso HPC; oxypropylated cellulose.

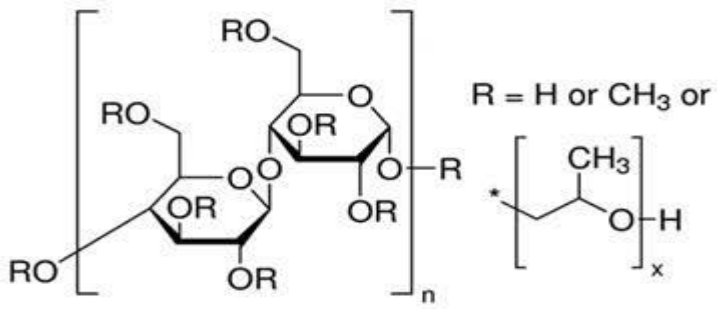
Chemical names: Cellulose, 2-hydroxypropyl ether

CAS Registry number: 9004-64-2

Description: Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder

Solubility: Soluble in cold water, in ethanol (96 per cent) and in propylene glycol giving colloidal solutions, practically insoluble in hot water.

Structure:



Functional category: Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in pharmaceutical formulation or technology: Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release-matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/wmaybeusedasabinderineitherwet-granulationordry,directcompression tableting processes. Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Blends of hydroxypropyl cellulose and other cellulosic polymers have been used to improve wet granulation characteristics and tableting characteristics, as

well as to achieve better control and manipulation of the rate of drug release. As an alternative technology to wet granulation, dry granulation and direct compression of hydroxypropyl cellulose formulations have been reported to exhibit acceptable tableting and flow characteristics for application in extended-release matrix tablets. Typically,a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose together with an amount of methyl cellulose or ethanolic solutions have been used. Stearic acid or palmitic acid may be added to ethanolic hydroxypropyl cellulose solutions as plasticizers. Environmental concerns have limited the use of ethanol in film coating solutions. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant; Hydroxypropyl Cellulose, Low-substituted. Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. In topical formulations, hydroxypropyl cellulose is used in transdermal patches and ophthalmic preparations. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Xanthan gum:

Synonym: Corn sugargum; E415; Grindsted;Keldent;Keltrol;polysaccharide B-1459; Rhodicare S; Rhodigel; Vanzan NF; xanthani gummi; Xantural.

Chemical names: Xanthan Gum

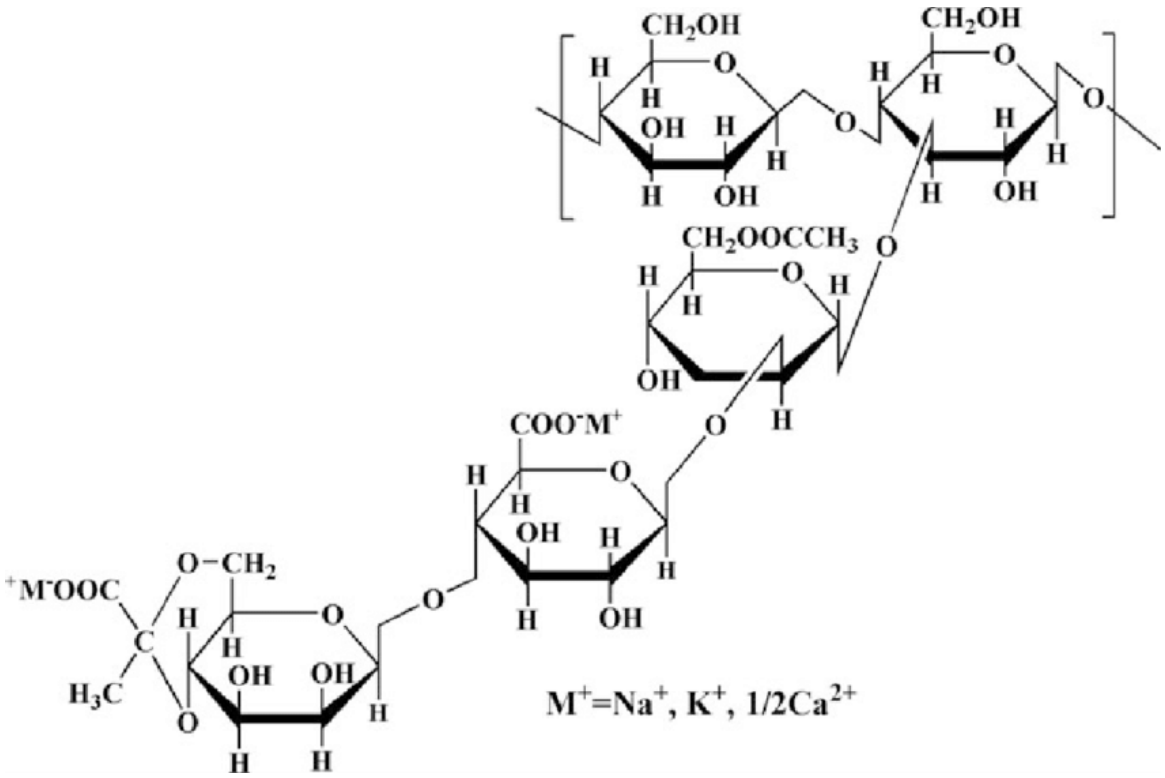
CAS Registry number: 11138-66-2

Molecular Formula: $C_{35}H_{49}O_{29}$

Description: Xanthan gum occurs as a cream- or white-colored, odorless, freeflowing, fine powder.

Solubility: Practically insoluble in ethanol and ether; soluble in cold or warm water.

Structure:



Functional category: Gelling agent; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent.

Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly proportional to the she arrate. The viscosity returns to normal immediately on release of shear stress. Xanthan gum has been used as a suspending agent for conventional, dry and sustained-release suspensions. When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur.Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Xanthan gum has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation. It has also been used in combination with chitosan, guar gum, galactomannan, and sodium alginate to prepare sustained-release matrix tablets. Xanthan gum has also been used with guar gum for the development of a floating drug delivery system. It has also has derivatized to sodium carboxymethyl xanthan gum and crosslinked with aluminum ions to prepare microparticles, as a carrier for protein delivery. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area. When added to liquid ophthalmics, xanthan gum delays the release of active substances, increasing the therapeutic activity of the pharmaceutical formulations. Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations. Xanthan gum alone or with carbopol 974P has been used as a mucoadhesive controlled-release excipient for buccal drug delivery. Xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results. It has been successfully used alone or in combination with agar for microbial culture media. Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo. Polyphosphate with xanthum gum in soft drinks is suggested to be effective at reducing erosion of enamel.

4.4. METHODS

I. Preformulation Studies:

1. Organoleptic properties:

The color, odor, taste and nature of the drug were recorded using descriptive terminology.

2. Solubility study:

Ketoprofen is the drug containing BCS Class II with weak acid property and high solubility. Sample was taken and tested for solubility by using water, Acetone, Menthol, Ethanol, 0.1N HCL and 6.8 pH Phosphate buffer.

3. Determination of lamda max of drug:

Ketoprofen 100mg sample was taken and dissolved in 100ml of 0.1N Hcl (1000µg/ml), 1 ml of the sample was withdrawn from the concentrated solution and check the lamda max of the drug. And sample procedure has been followed for 6.8 pH phosphate buffer and also with methanol.

4. Construction of calibration curve:

100mg of accurately weighed drug was taken into 100ml volumetric flask and made primary stock by make upping with 0.5N Hcl (1000mg/ml).From that solution serial dilutions (1,2,3,4,5) are made and scanned under UV at λ max 260nm. And same procedure was followed to 6.8 pH phosphate buffer solution and scanned under UV at λ max 262nm.and in menthol scanned under UV at λ max 257nm

5. Compatibility studies:

FTIR Study:

Compatibility studies are done by using FTIR. KBR was used to make the pellet. It is done in the 10:1 ratio. Empty drug was analyzed and along with that in combinations (1:1) of drugs are also analyzed(1. Ketoprofen 2. Ketoprofen+Lactose+ MCCP+ SSG+ PVP +talc+ Mg stearate 3.Ketoprofen + HPMC E5, 4. Ketoprefen + HPMC E15 5. Ketoprofen + Xanthan gum) . And structural elucidation was performed.

6. Assay for pure drug:

1. Spectroscopic method:

100mg of accurately weighed drug was taken into 100ml volumetric flask and made primary stock by make upping with 6.8 pH phosphate buffer (1000mg/ml).From that solution 1 ml of the sample was withdrawn followed by dilution in 100ml volumetric flask and scanned under UV at λ max 262nm.And this sample was compared with the standard sample.

II. Preparation of Ketoprofen core tablet:

1. **Core Tablet:**

The powder of Ketoprofen, Lactose, MCCP pH 102, Sodium Starch Glycolate was passed through a 210µm sieve to obtain a well- dispersed mixture and further mixed thoroughly with a pestle and mortar. A PVP K 30 alcoholic solution should be added to the mixture dropwise with continuous mixing. The resultant powdered mixtures should be compacted after lubrication. Granules was dried at 60ºC for 6 hrs using a convention oven. After adding Talc and Magnesium stearate as a lubricant, resulting dried and granules with size 25-60 mesh was directly compressed into tablets using a conventional single punch press.

Table:4.4.1 Design of preparation of Core tablet:

Materials	**Each tablet (mg)**	**1000 tablets (grms)**
Ketoprofen	75.00	75.00
Lactose	18.00	18.00
MCCP PH 102	55.73	55.73
Sodium Starch Glycolate	18.00	18.00
PVP solution	Q.s	Q.s
Talc	1.00	1.00
Magnesium Stearate	1.00	1.00

PRECOMPRESSION STUDIES:

2. **Angle of repose:**

A funnel was filled to the brim and the prepared granules was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, height(h)of the pile was also measured.

Angle of repose = $\tan^{-1}$ (h/r)

3. **Bulk Density**

A quantity of accurately weighed 20g granules was introduced into a 50ml of measuring cylinder. After the initial volume was observed and Calculated.

Bulk density= M/V_0

4. **Tapped density**

The measuring cylinder containing the granules was tapped for a 100 times

The minimum volume (Vt) occupied in the cylinder was observed and calculated.

Tapped density= M/Vt

5. **Hausner's ratio:**

Hanusers ratio was calculated by using Bulk density and tapped density.

Hausner's ratio: Tapped density- Bulk density

6. **Compressability Index or Carr's index:**

Compressability index was measured/Calculated by using the bulk density and tapped density.

CI = (TD-BD)/TD x 100

Preparation of Ketoprofen pulsatile drug delivery tablet (coat tablet):

Punched tablets was taken as cores, respectively, and 400mg of polymer (HPMC E5,HPMC E15, Xanthan Gum) and in combination (HPMC E5 and xanthan gum (1:1 and 3:1),HPMC E5and HPMC E15(1:1), HPMC E15 and Xanthan gum (1:1, 2:1and 3:1)).Polymer was used with two steps: the first 200mg coating polymer should be filled into the die, followed by cores in the center of die, and slightly pressed to fix the coatings around and under the core, and then the rest of the coatings were filled and compressed.

Table: 4.4.2 Design of formulation:

Materials	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ketoprofen	75mg	75mg	75mg	75mg	75mg	75mg	75mg	75mg	75mg
Lactose	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg
MCCP PH 102	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg	55.73mg
SSG	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg	18mg
PVP solution	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Talc	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
Magnisium Stearate	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
HPMC E5	400mg	-	-	200mg	-	200mg	-	-	300mg
HPMC E15	-	400mg	-	-	200mg	200mg	250mg	300mg	-
Xanthan gum	-	-	400mg	200 mg	200mg	-	150mg	100mg	100mg

Post compression Studies: (for Cores and Coated tablets)

1. **Thickness :**

Ten tablets was picked from each formulation randomly and thickness was measured individually by using determined using a vernier caliper . Standard deviation was also calculated.

2. **Diameter :**

Ten tablets was picked from each formulation randomly and Diameter was measured individually by using determined using a vernier caliper . Standard deviation was also calculated.

3. **Hardness:**

The hardness of the tablets was determined using Monsanto hardness tester. Five tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation value was calculated.

4. **Weight Variation Test:**

Ten tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weight of the individual tablets was compared with the average weight to determine weight variation.

5. **Friability Test:**

The friability of tablets was determined using Friabilator. Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The % friability was then calculated.

% Friability of tablets less than 1% are considered acceptable.

Content Uniformity:

Ten tablets was picked from the core tablet and powdered in the motar and pestle and weighed equivalent to 100mg of powder and dissolved in the 6.8 pH phosphate buffer and diluted to 100ml by withdrawing 1 ml of sample and measured at 262 nm.

***In-vitro* studies:**

Drug Release of Ketoprofen from the prepared pulsatile tablets was studied in 0.1N HCl for 2 hrs and in phosphate buffer pH 6.8 (900ml)for 4 hrs using an eight station dissolution rate testing apparatus with a rotating paddle at 50 rpm and 25cm depth. A sample of 5 ml was withdrawn at different time intervals and diluted using pH 6.8 phosphate buffer. Throughout the dissolution the temperature was maintained at 37.5ºC. And samples are withdrawn at 1 hr frequency. Drawn samples are measured at 260nm, 262 using UV- visible spectrophotometer against a blank.

Stability Studies:

Best formulation was choosen as formulation 8 and accelerated stability studies was carried out for only F8 under 40°C ± 2°C & 75% ± 5% RH and tested for dissolution and content uniformity for a period of 2 months.

5.1. RESULTS

5.1 Organoleptic properties:

Table: 5.1 Organoleptic properties of Ketoprofen

S. NO	CHACRECTERISTIS	RESULTS
1	Colour	White
2	Odour	Odourless
3	Taste	Tasteless
4	Nature	Amorphous

5.2 Solubility studies:

Table: 5.2 Solubility of Ketoprofen

SOLVENT	SOLUBILITY
Water	Practically insoluble
Acetone	Soluble
Methanol	Slightly soluble
Ethanol	Soluble
o.1N Hcl	Sparingly soluble
pH 6.8 phosphate buffer	Soluble

5.3 Determination of lamda max:

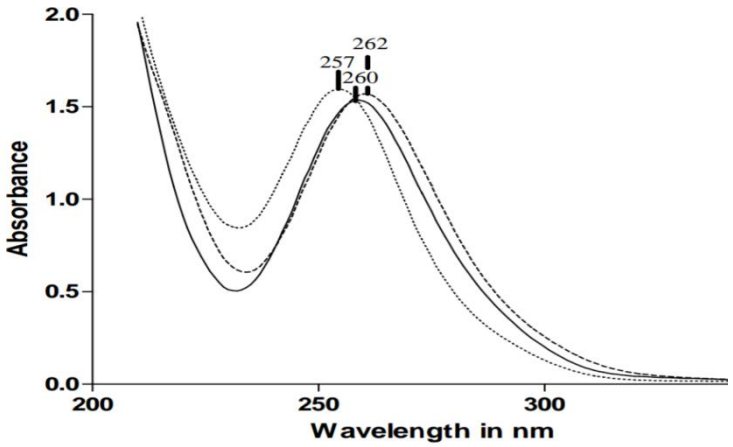


Fig: 5.1Determination of lamda max of Ketoprofen Drug

Construction of calibration curve:

Table: 5.3 Construction of Calibration curve of Ketoprofen

S.no	Concentration	Absorbance in 0.1N Hcl	Absorbance in 6.8 pH Phosphate buffer
1	10	0.098	0.113
2	20	0.191	0.240
3	30	0.293	0.352
4	40	0.398	0.456
5	50	0.487	0.545

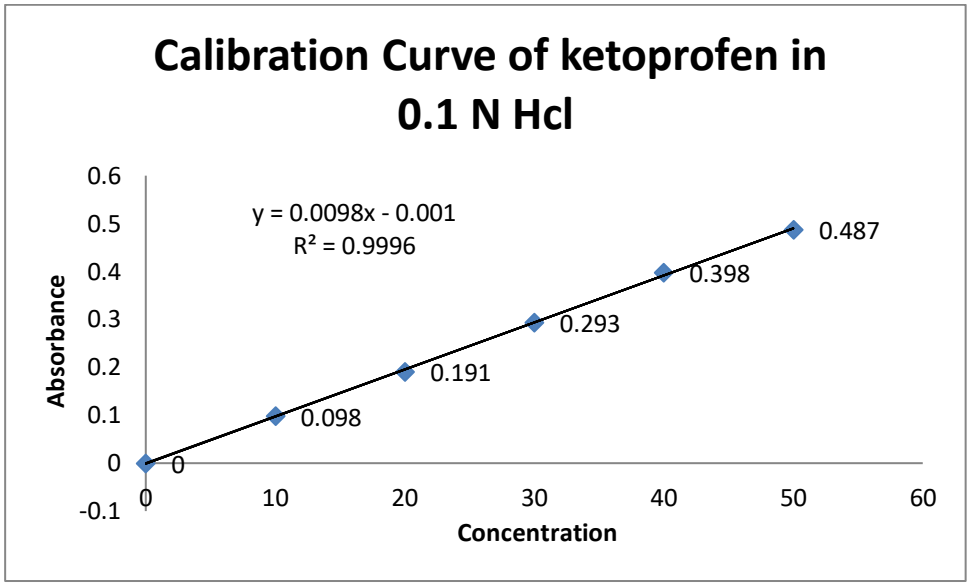


Fig:5.2 Calibration curve of Ketoprofen in 0.1N Hcl

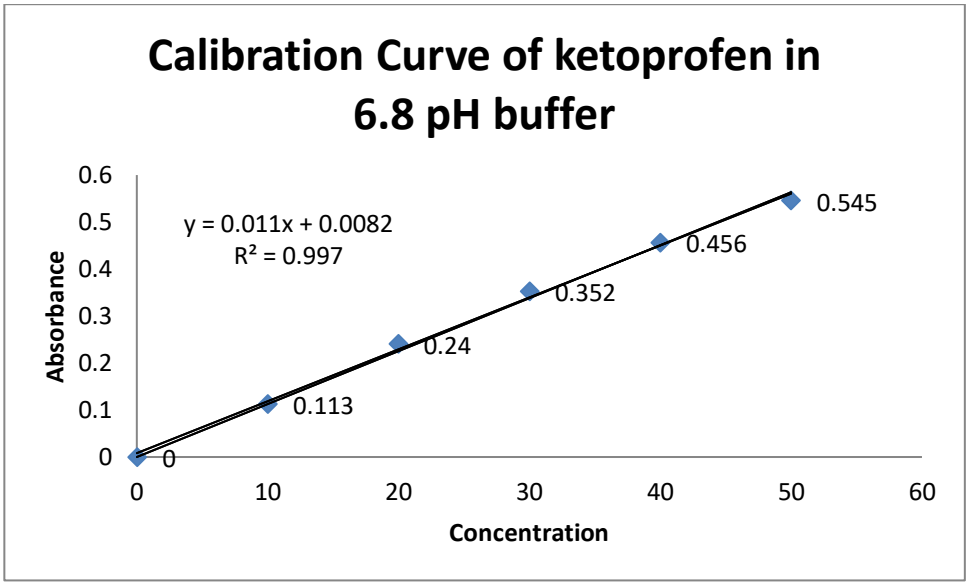
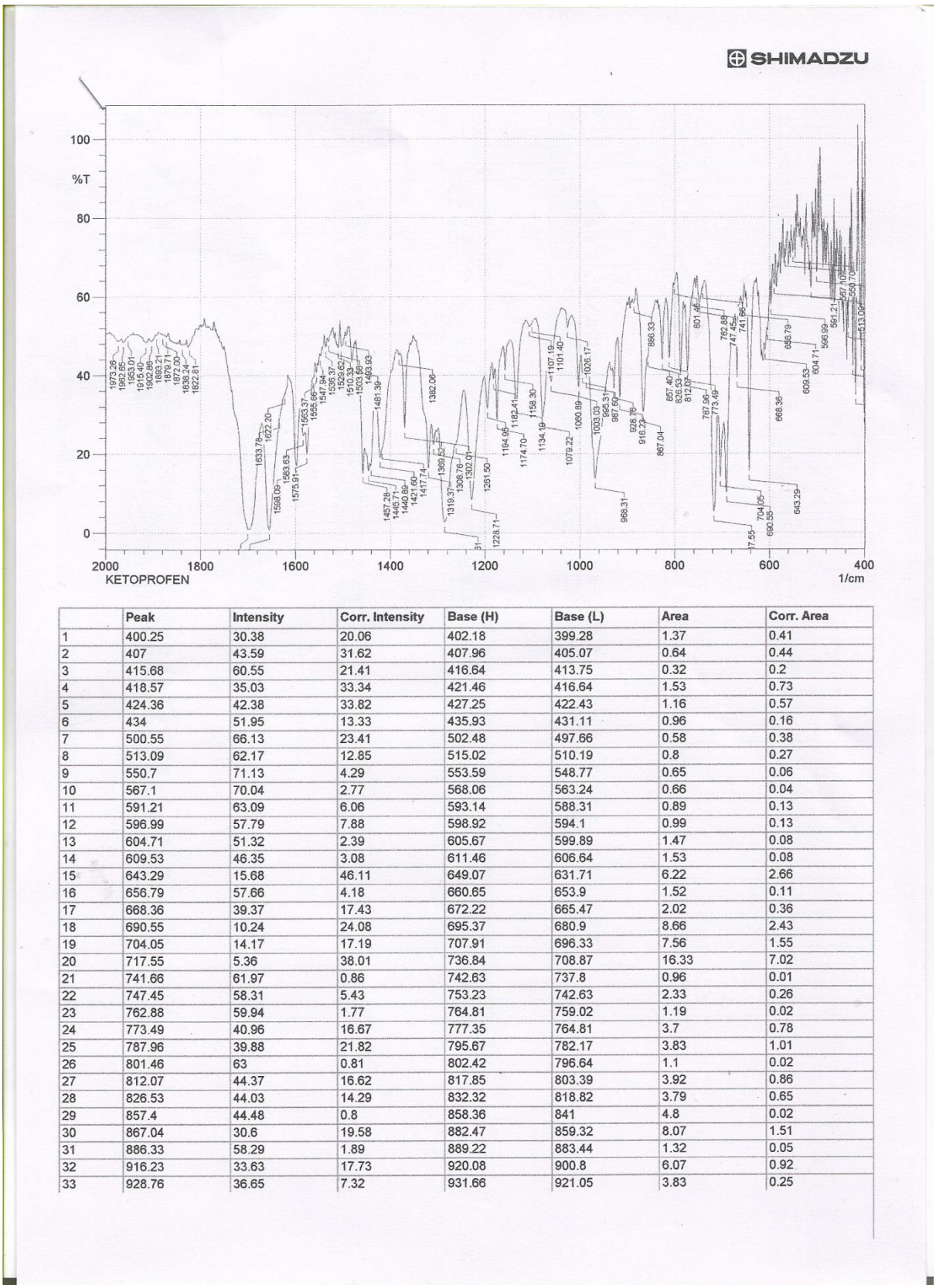


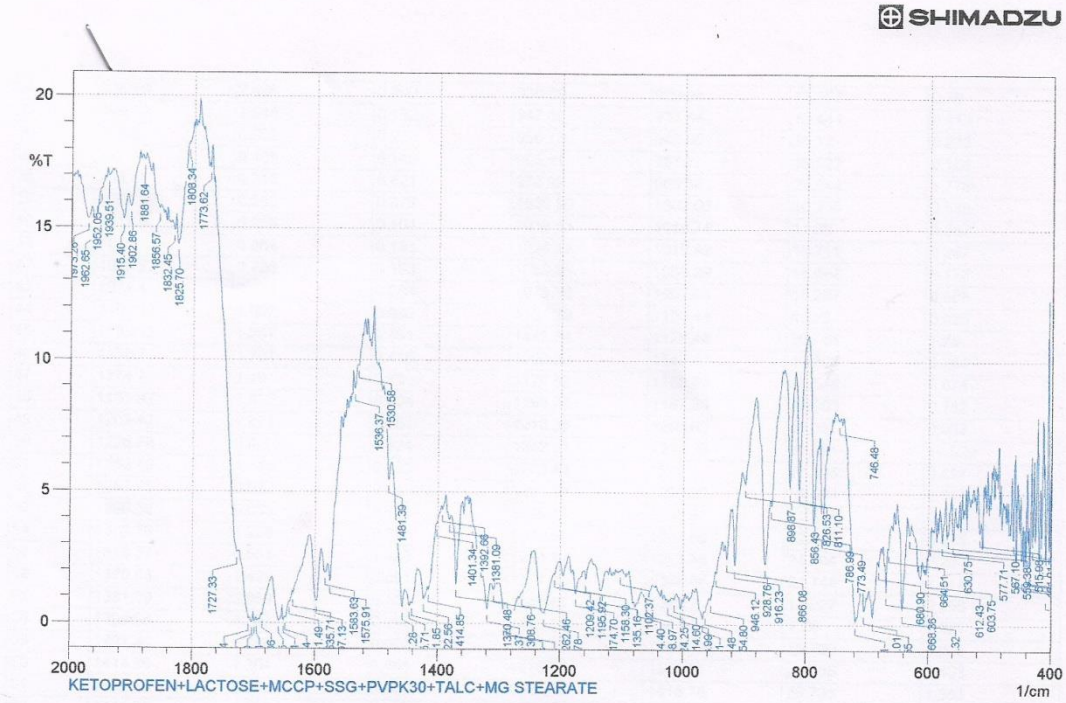
Fig: 5.3 Calibration curve of Ketoprofen in 6.8 pH Phosphate buffer

Compatibility studies:



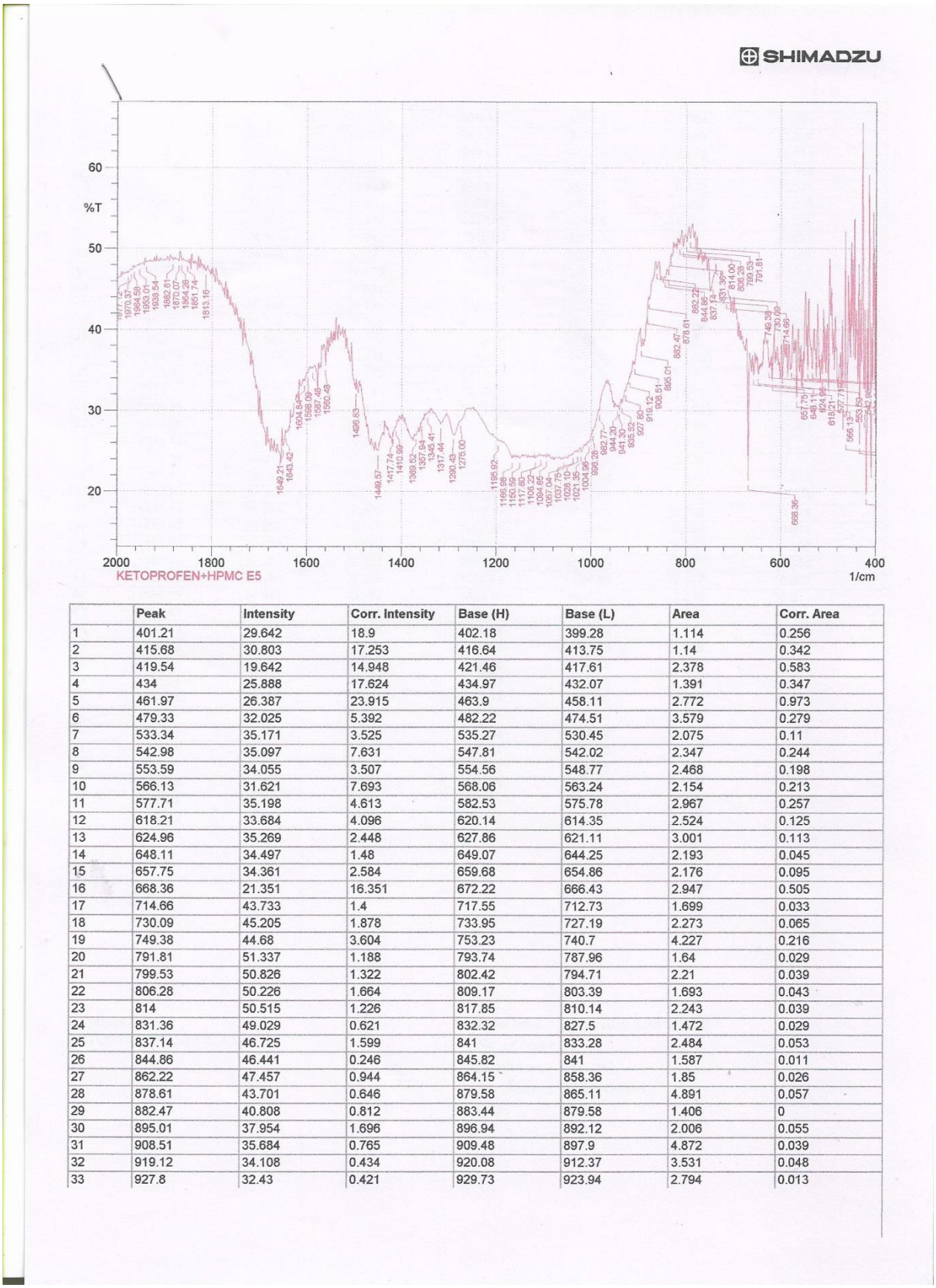
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	400.25	30.38	20.06	402.18	399.28	1.37	0.41
2	407	43.59	31.62	407.96	405.07	0.64	0.44
3	415.68	60.55	21.41	416.64	413.75	0.32	0.2
4	418.57	35.03	33.34	421.46	416.64	1.53	0.73
5	424.36	42.38	33.82	427.25	422.43	1.16	0.57
6	434	51.95	13.33	435.93	431.11	0.96	0.16
7	500.55	66.13	23.41	502.48	497.66	0.58	0.38
8	513.09	62.17	12.85	515.02	510.19	0.8	0.27
9	550.7	71.13	4.29	553.59	548.77	0.65	0.06
10	567.1	70.04	2.77	568.06	563.24	0.66	0.04
11	591.21	63.09	6.06	593.14	588.31	0.89	0.13
12	596.99	57.79	7.88	598.92	594.1	0.99	0.13
13	604.71	51.32	2.39	605.67	599.89	1.47	0.08
14	609.53	46.35	3.08	611.46	606.64	1.53	0.08
15	643.29	15.68	46.11	649.07	631.71	6.22	2.66
16	656.79	57.66	4.18	660.65	653.9	1.52	0.11
17	668.36	39.37	17.43	672.22	665.47	2.02	0.36
18	690.55	10.24	24.08	695.37	680.9	8.66	2.43
19	704.05	14.17	17.19	707.91	696.33	7.56	1.55
20	717.55	5.36	38.01	736.84	708.87	16.33	7.02
21	741.66	61.97	0.86	742.63	737.8	0.96	0.01
22	747.45	58.31	5.43	753.23	742.63	2.33	0.26
23	762.88	59.94	1.77	764.81	759.02	1.19	0.02
24	773.49	40.96	16.67	777.35	764.81	3.7	0.78
25	787.96	39.88	21.82	795.67	782.17	3.83	1.01
26	801.46	63	0.81	802.42	796.64	1.1	0.02
27	812.07	44.37	16.62	817.85	803.39	3.92	0.86
28	826.53	44.03	14.29	832.32	818.82	3.79	0.65
29	857.4	44.48	0.8	858.36	841	4.8	0.02
30	867.04	30.6	19.58	882.47	859.32	8.07	1.51
31	886.33	58.29	1.89	889.22	883.44	1.32	0.05
32	916.23	33.63	17.73	920.08	900.8	6.07	0.92
33	928.76	36.65	7.32	931.66	921.05	3.83	0.25

Fig: 5.4 FT-IR of Ketoprofen



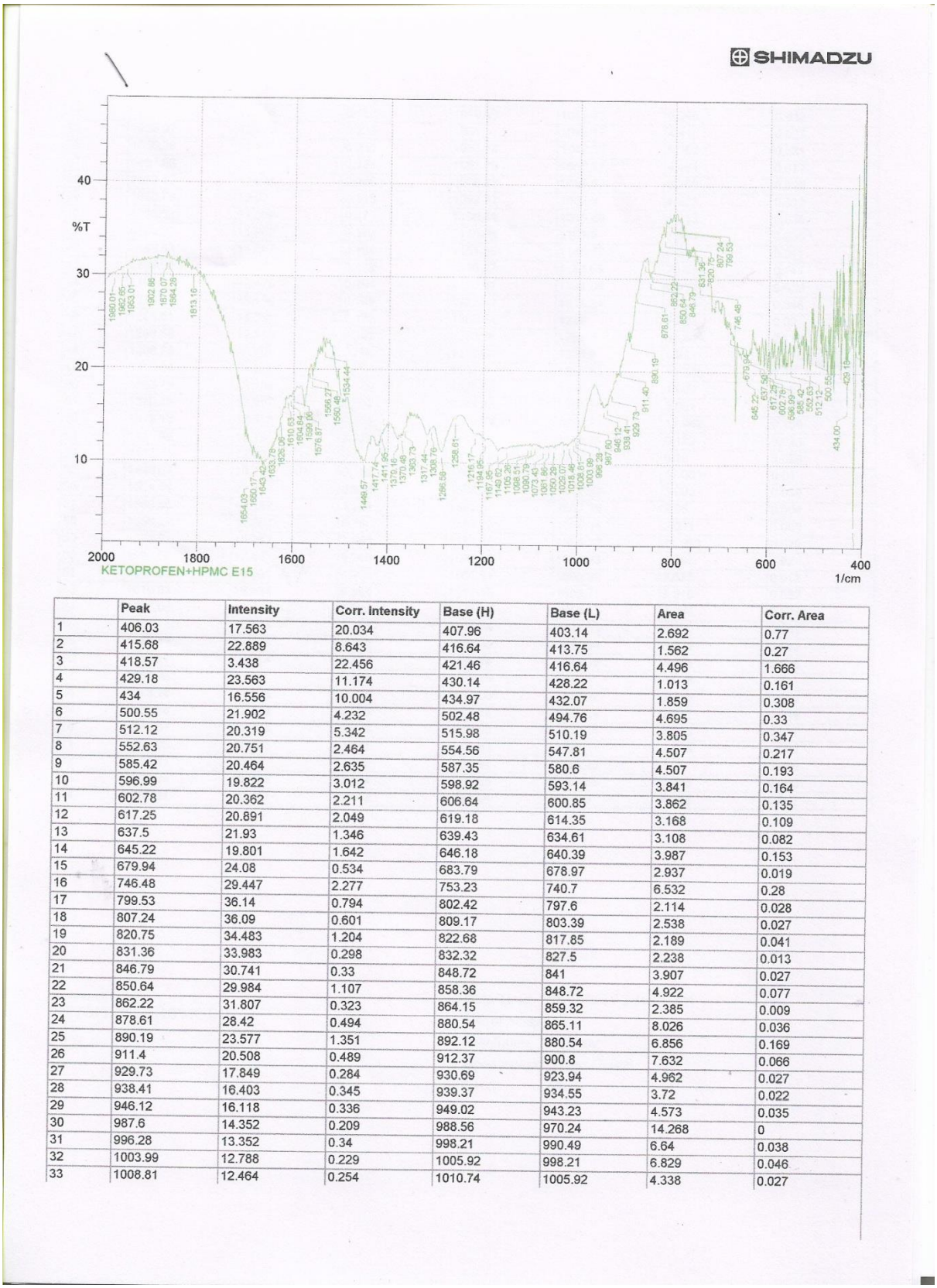
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	403.14	2.881	4.949	404.1	401.21	4.14	0.719
2	408.93	1.131	8.812	412.78	405.07	10.381	2.649
3	415.68	2.984	2.843	416.64	413.75	3.839	0.433
4	418.57	2.433	3.297	422.43	417.61	7.036	1.191
5	430.14	3.024	2.473	431.11	428.22	3.996	0.429
6	434.97	2.049	2.387	435.93	432.07	5.734	0.803
7	440.75	2.104	2.685	442.68	439.79	4.332	0.493
8	447.5	1.858	1.916	449.43	446.54	4.569	0.424
9	457.15	1.983	3.671	458.11	455.22	4.389	0.743
10	461.01	3.266	2.899	463.9	459.08	6.536	0.695
11	515.98	3.503	0.878	519.84	514.05	8.163	0.339
12	559.38	3.216	1.355	562.27	556.49	8.249	0.457
13	567.1	3.435	0.354	568.06	563.24	6.715	0.077
14	577.71	3.163	1.351	580.6	571.92	12.263	0.678
15	603.75	1.949	0.338	604.71	598.92	9.345	0.146
16	612.43	1.756	0.805	626.89	610.5	26.006	0.959
17	630.75	3.44	0.467	633.64	627.86	8.336	0.181
18	642.32	0.575	3.804	651	634.61	26.946	4.659
19	664.51	2.899	0.279	666.43	659.68	9.921	0.052
20	668.36	1.265	1.684	673.19	666.43	11.247	0.929
21	680.9	2.245	0.353	682.83	677.04	9.198	0.132
22	690.55	0.292	1.102	693.44	682.83	21.24	2.27
23	705.01	0.552	0.817	706.94	701.15	12.308	1.255
24	718.51	0.112	3.682	738.77	707.91	54.546	9.949
25	746.48	7.747	0.149	749.38	744.55	5.342	0.025
26	773.49	3.44	3.51	777.35	765.77	15.025	1.583
27	786.99	3.79	4.533	796.64	781.2	18.311	1.777
28	811.1	5.151	4.734	816.89	797.6	20.863	1.744
29	826.53	5.2	4.413	835.21	817.85	19.174	1.517
30	856.43	4.508	0.482	857.4	840.04	19.926	0.105
31	866.08	2.298	3.499	873.79	858.36	22.288	3.007
32	898.87	5.343	1.117	903.69	882.47	24.79	0.506
33	916.23	2.255	2.501	920.08	904.65	21.457	1.518

Fig: 5.5 FT-IR of Ketoprofen+ Lactose+ MCCP+SSG+PVP K 30+ Talc + Mg stearate



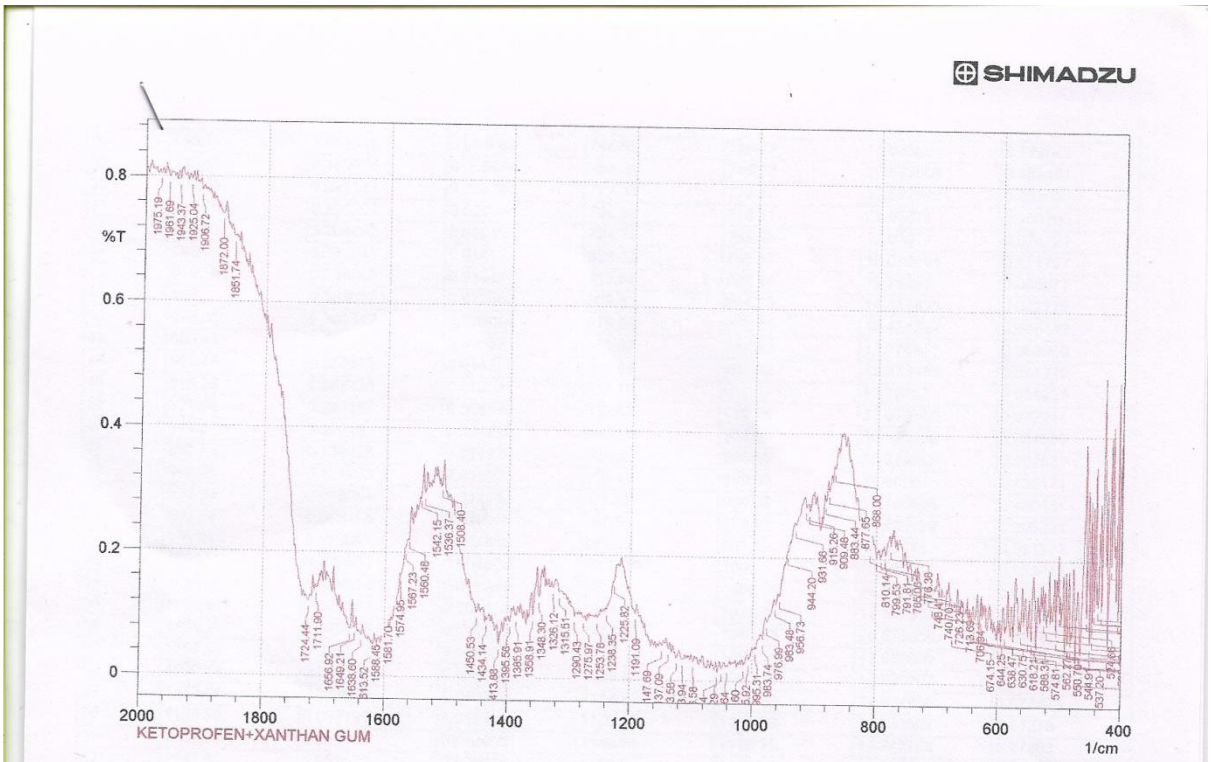
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	401.21	29.642	18.9	402.18	399.28	1.114	0.256
2	415.68	30.803	17.253	416.64	413.75	1.14	0.342
3	419.54	19.642	14.948	421.46	417.61	2.378	0.583
4	434	25.888	17.624	434.97	432.07	1.391	0.347
5	461.97	26.387	23.915	463.9	458.11	2.772	0.973
6	479.33	32.025	5.392	482.22	474.51	3.579	0.279
7	533.34	35.171	3.525	535.27	530.45	2.075	0.11
8	542.98	35.097	7.631	547.81	542.02	2.347	0.244
9	553.59	34.055	3.507	554.56	548.77	2.468	0.198
10	566.13	31.621	7.693	568.06	563.24	2.154	0.213
11	577.71	35.198	4.613	582.53	575.78	2.967	0.257
12	618.21	33.684	4.096	620.14	614.35	2.524	0.125
13	624.96	35.269	2.448	627.86	621.11	3.001	0.113
14	648.11	34.497	1.48	649.07	644.25	2.193	0.045
15	657.75	34.361	2.584	659.68	654.86	2.176	0.095
16	668.36	21.351	16.351	672.22	666.43	2.947	0.505
17	714.66	43.733	1.4	717.55	712.73	1.699	0.033
18	730.09	45.205	1.878	733.95	727.19	2.273	0.065
19	749.38	44.68	3.604	753.23	740.7	4.227	0.216
20	791.81	51.337	1.188	793.74	787.96	1.64	0.029
21	799.53	50.826	1.322	802.42	794.71	2.21	0.039
22	806.28	50.226	1.664	809.17	803.39	1.693	0.043
23	814	50.515	1.226	817.85	810.14	2.243	0.039
24	831.36	49.029	0.621	832.32	827.5	1.472	0.029
25	837.14	46.725	1.599	841	833.28	2.484	0.053
26	844.86	46.441	0.246	845.82	841	1.587	0.011
27	862.22	47.457	0.944	864.15	858.36	1.85	0.026
28	878.61	43.701	0.646	879.58	865.11	4.891	0.057
29	882.47	40.808	0.812	883.44	879.58	1.406	0
30	895.01	37.954	1.696	896.94	892.12	2.006	0.055
31	908.51	35.684	0.765	909.48	897.9	4.872	0.039
32	919.12	34.108	0.434	920.08	912.37	3.531	0.048
33	927.8	32.43	0.421	929.73	923.94	2.794	0.013

Fig: 5.6 FT-IR of Ketoprofen +HPMC E5



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	406.03	17.563	20.034	407.96	403.14	2.692	0.77
2	415.68	22.889	8.643	416.64	413.75	1.562	0.27
3	418.57	3.438	22.456	421.46	416.64	4.496	1.666
4	429.18	23.563	11.174	430.14	428.22	1.013	0.161
5	434	16.556	10.004	434.97	432.07	1.859	0.308
6	500.55	21.902	4.232	502.48	494.76	4.695	0.33
7	512.12	20.319	5.342	515.98	510.19	3.805	0.347
8	552.63	20.751	2.464	554.56	547.81	4.507	0.217
9	585.42	20.464	2.635	587.35	580.6	4.507	0.193
10	596.99	19.822	3.012	598.92	593.14	3.841	0.164
11	602.78	20.362	2.211	606.64	600.85	3.862	0.135
12	617.25	20.891	2.049	619.18	614.35	3.168	0.109
13	637.5	21.93	1.346	639.43	634.61	3.108	0.082
14	645.22	19.801	1.642	646.18	640.39	3.987	0.153
15	679.94	24.08	0.534	683.79	678.97	2.937	0.019
16	746.48	29.447	2.277	753.23	740.7	6.532	0.28
17	799.53	36.14	0.794	802.42	797.6	2.114	0.028
18	807.24	36.09	0.601	809.17	803.39	2.538	0.027
19	820.75	34.483	1.204	822.68	817.85	2.189	0.041
20	831.36	33.983	0.298	832.32	827.5	2.238	0.013
21	846.79	30.741	0.33	848.72	841	3.907	0.027
22	850.64	29.984	1.107	858.36	848.72	4.922	0.077
23	862.22	31.807	0.323	864.15	859.32	2.385	0.009
24	878.61	28.42	0.494	880.54	865.11	8.026	0.036
25	890.19	23.577	1.351	892.12	880.54	6.856	0.169
26	911.4	20.508	0.489	912.37	900.8	7.632	0.066
27	929.73	17.849	0.284	930.69	923.94	4.962	0.027
28	938.41	16.403	0.345	939.37	934.55	3.72	0.022
29	946.12	16.118	0.336	949.02	943.23	4.573	0.035
30	987.6	14.352	0.209	988.56	970.24	14.268	0
31	996.28	13.352	0.34	998.21	990.49	6.64	0.038
32	1003.99	12.788	0.229	1005.92	998.21	6.829	0.046
33	1008.81	12.464	0.254	1010.74	1005.92	4.338	0.027

Fig: 5.7 FT-IR of Ketoprofen +HPMC E15



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	401.21	0.290726	0.106035	402.18	399.28	7.043671	0.21082
2	404.1	0.106596	0.336365	405.07	402.18	7.912337	0.954997
3	415.68	0.193735	0.21213	416.64	413.75	7.313755	0.409219
4	421.46	0.048596	0.272119	422.43	417.61	13.744127	1.782948
5	431.11	0.11973	0.19078	432.07	428.22	10.107664	0.782196
6	436.9	0.127338	0.041432	437.86	433.04	13.079025	0.285248
7	442.68	0.120656	0.191672	444.61	441.72	7.921524	0.67047
8	446.54	0.080463	0.130448	448.47	445.58	8.339239	0.549158
9	450.4	0.066912	0.230178	452.33	448.47	10.959593	1.21027
10	455.22	0.11023	0.219153	457.15	453.29	10.620186	1.022779
11	465.83	0.050846	0.18052	469.69	458.11	33.150038	3.101934
12	473.54	0.021574	0.14381	476.44	470.65	17.644003	1.501442
13	482.22	0.063717	0.071523	484.15	480.3	11.748092	0.418354
14	487.05	0.066253	0.065634	488.01	485.12	8.820126	0.556941
15	490.9	0.051265	0.127971	492.83	488.98	11.702828	1.113093
16	499.58	0.116755	0.048998	501.51	498.62	8.329634	0.26442
17	505.37	0.078094	0.091777	507.3	504.41	8.467311	0.453035
18	520.8	0.09385	0.063132	522.73	516.94	16.945411	0.788175
19	524.66	0.105991	0.039472	526.59	523.7	8.385689	0.172908
20	537.2	0.05808	0.078753	539.13	535.27	11.820989	0.772277
21	544.91	0.071436	0.075774	547.81	542.98	14.355707	0.675618
22	550.7	0.076325	0.062763	554.56	548.77	17.25023	0.724047
23	562.27	0.086674	0.044572	564.2	560.35	11.444396	0.377143
24	574.81	0.070011	0.079224	577.71	571.92	17.059153	0.739841
25	588.31	0.083593	0.052907	591.21	584.46	20.174052	0.901777
26	618.21	0.084763	0.044713	621.11	614.35	20.107832	0.612919
27	630.75	0.089489	0.045698	633.64	628.82	14.352999	0.512651
28	638.47	0.088934	0.041608	640.39	634.61	17.170596	0.543607
29	644.25	0.091101	0.032919	646.18	641.36	14.314769	0.314789
30	674.15	0.081932	0.052042	676.08	671.26	14.289394	0.420797
31	706.94	0.128366	0.03038	708.87	703.08	16.516654	0.29113
32	713.69	0.144541	0.01152	715.62	709.83	16.295539	0.122001
33	726.23	0.156859	0.022097	729.12	722.37	18.805182	0.269173

Fig: 5.8 FT-IR of Ketoprofen + Xanthan gum

Assay:

Table 5.4: Study the purity of drug

Method	1	2	3	Avg
Spectrophotometric method	99.96%	100.1%	99.98%	100.01%

Limits: ≤ 99 % - ≥100.5%

Precompression Studies: Core tablet of Ketoprofen

1. **Core tablet of Ketoprofen**

Table .5.5: Angle of Repose, Bulk density, Tapped Density, Hausner's ratio, Compressibility Index

S.no	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Compressibility Index(%)
1	24.680 ± 0.47	0.432 ± 0.004	0.480 ± 0.005	1.112 ± 0.0119	10.067 ± 0.97

All the values are expressed as mean ± SD .n=3

Post compression Studies: For core tablet of ketoprofen

Table 5.6: Thickness, Diameter,Hardness, Friability,and weight variation of core tablet

S.no	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)
1	3.013 ± 0.009	8.005 ± 0.007	9.9 ± 0.316	0.01	0.185 ± 0.003

All the values are expressed as mean ± SD .n=10 For thickness ,diameter, and weight variation, Hence for hardness n=5,for friability n=1

Content Uniformity:

Table 5.7: Content Uniformity of Ketoprofen:

1	2	3	Avg
103.2%	102.99%	103.06%	103.08%

Post compression studies of coated tablet:

Table 5.8: Thickness, Diameter, Hardness, Friability, and weight variation after press Coat

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)
F1	3.79 ± 0.03	12.86 ± 0.008	16.9 ± 0.31	0.02	594.6 ± 2.10
F2	3.81± 0.006	12.32± 0.006	17.0 ±0.3	0.01	595.2 ± 1.469
F3	3.87 ± 0.006	12.867 ± 0.04	6.1 ± 0.3	0.04	595.2 ± 2.18
F4	3.748 ± 0.007	12.931 ± 0.005	16.9 ± 0.3	0.03	595.4 ± 1.624
F5	3.815 ± 0.006	12.983 ± 0.006	14.1 ± 0.3	0.04	594.6 ± 1.854
F6	3.893 ± 0.007	12.883 ± 0.06	15.9 ± 0.3	0.04	594.8 ±1.939
F7	3.847 ± 0.006	12.963 ± 0.004	16.9 ± 0.3	0.02	596.2 ± 1.66
F8	3.863 ± 0.004	12.863 ± 0.004	16.9 ± 0.3	0.01	597.4 ± 1.113
F9	3.851 ± 0.005	12.944 ± 0.004	17.0 ± 0.3	0.01	593.3 ± 1.676

All the values are expressed as mean ± SD .n=10 For thickness ,diameter, and weight variation, Hence for hardness n=5,for friability n=1

In vitro studies:

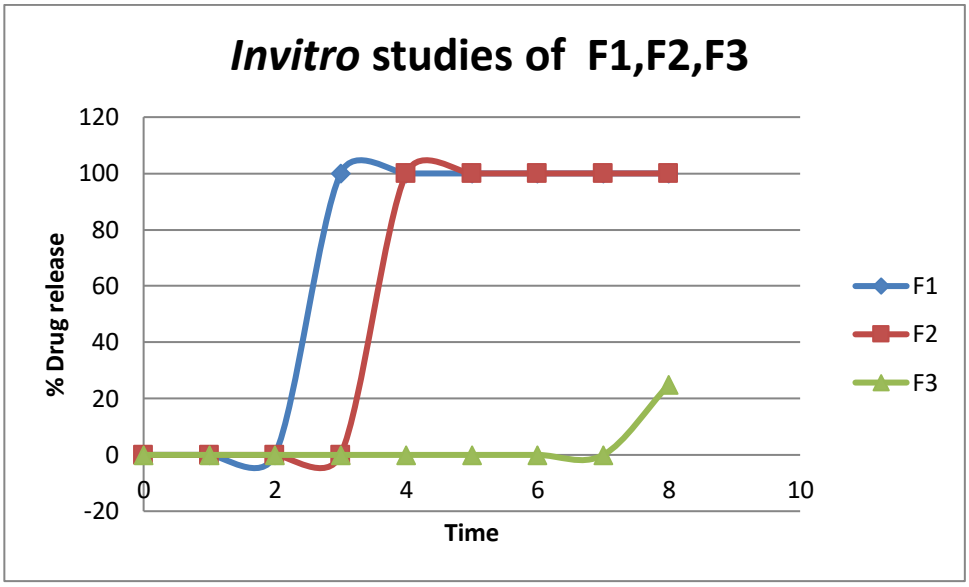


Fig: 5.9 :*Invitro* studies graph of F1,F2,F3

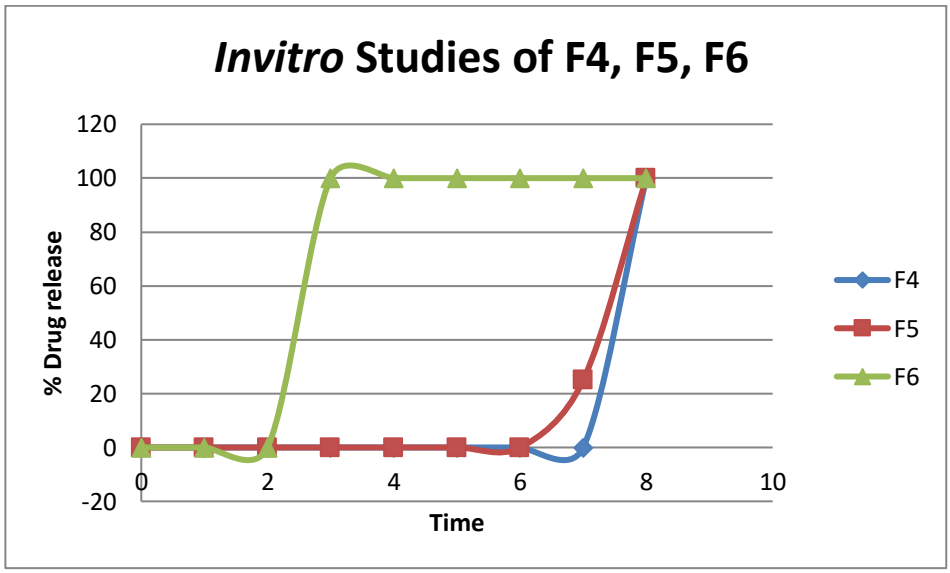


Fig: 5.10 :*Invitro* studies graph of F4 ,F5 ,F6

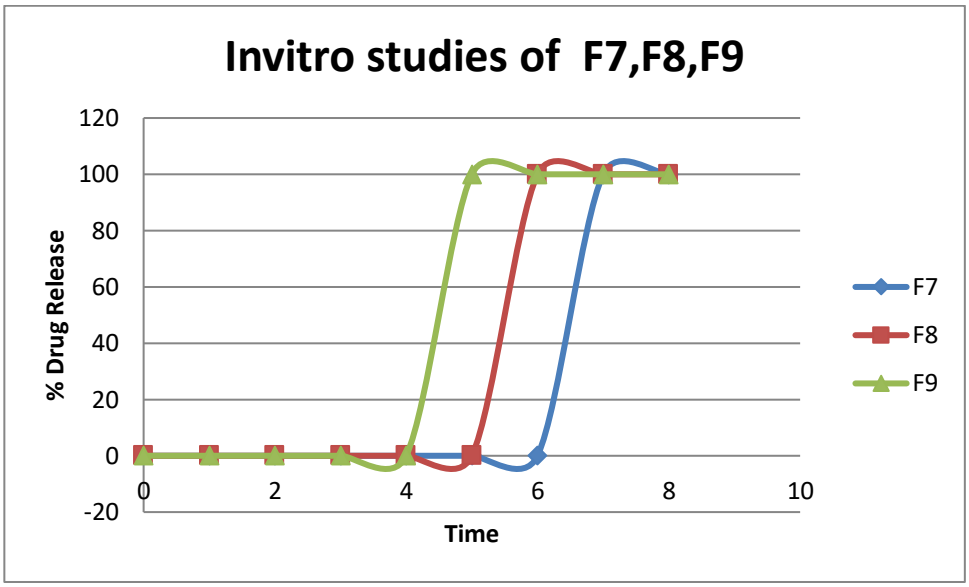


Fig: 5.11 :*Invitro* studies graph of F7 ,F8 ,F9

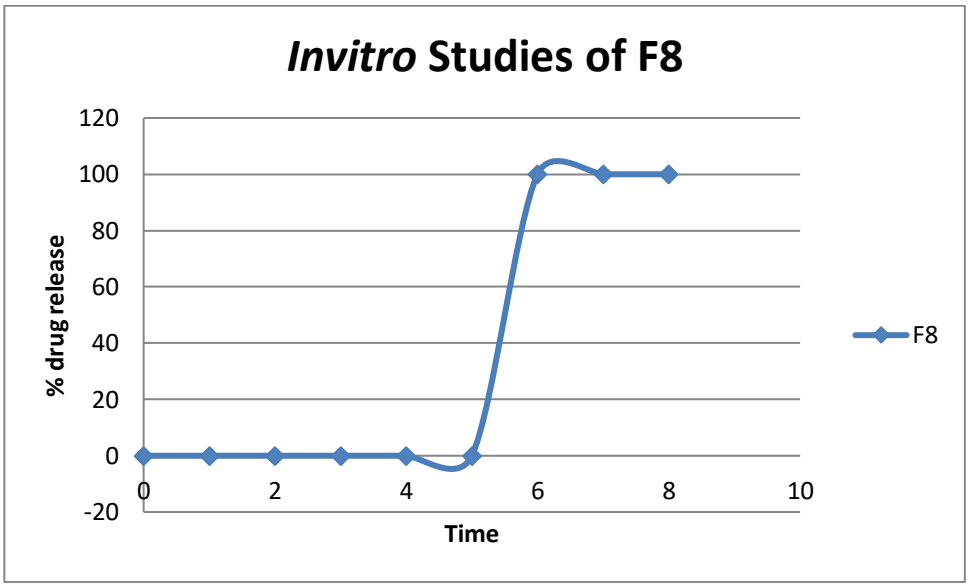


Fig:5.12 :*Invitro* studies of F8

Stability studies:

Accelerated studies: (40ºC ± 2ºC & 75%±5% RH)

Table 5.9: Stability studies data for the F8 formulation

S.no	Test parameters	F8	
		1 month	**2 months**
1	Appearance	Almost white colour	Almost white colour
2	Drug content	102.98%	102.91%
3	Dissolution	At the end of 6th hr released completely	At the end of 6th hr released completely

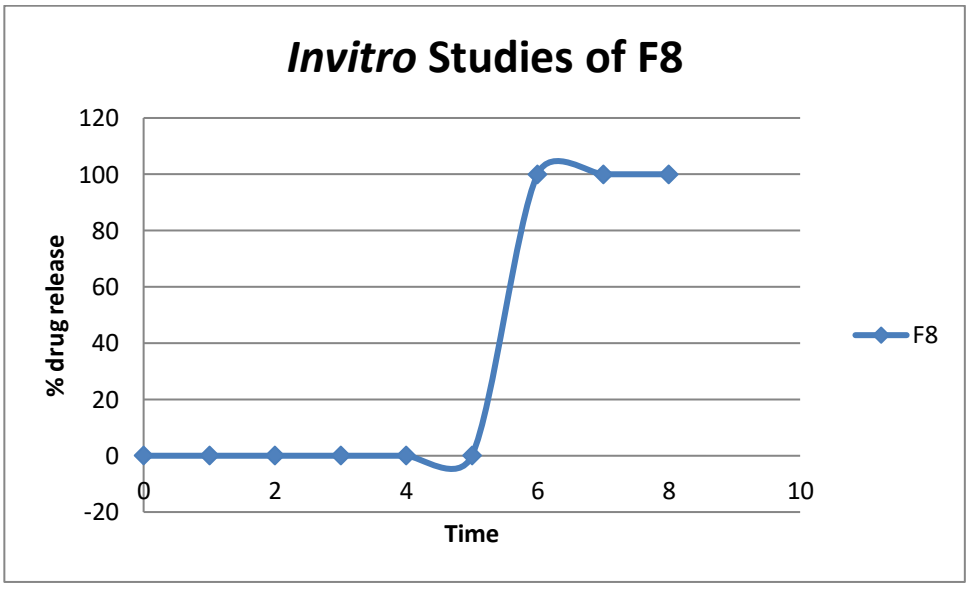


Fig: 5.13 :*Invitro* studies graph of F8 after stability studies.

5.2 DISCUSSION

The present study involves the Formulation and evaluation of Ketoprofen pulsatile tablets by using different polymers (HPMC E5, HPMC E15, Xanthan gum)and in combination of synthetic and natural polymers(HPMC E5 and xanthan gum (1:1 and 3:1),HPMC E5and HPMC E15(1:1), HPMC E15 and Xanthan gum (1:1, 2:1and 3:1)).

Organoleptic properties, Solubility was carried out and found to be satisfied. FTIR Study was performed for identification and compatibility study of drug and excipients, found no characteristic changes in drug-excipients powder mixture. Hence the excipients were selected for the formulation development are lactose, MCCP,SSG, PVP, Talc,Mg stearate and Polymers: HPMC E5, HPMC E15, Xanthan gum.

Powder blend were evaluated for the Pre formulation studies which include Angle of repose - 24.680 ± 0.47, Bulk density - 0.432 ±0.004, Tapped density - 0.480 ± 0.005,Compressability index - 10.067 ± 0.97, Hausner's ratio - 1.112 ±0.0119 were carried out before being punched as tablets. The angle of repose and compressibility index (Carr's index) for the formulation core tablet was found to be in the range, shown excellent flow property for compression.

Evaluations studies was performed for the core tablet include friability-0.01%, hardness- 9.9 ± 0.316 kg/cm^2, weight variation(mg) -0.185 ± 0.003 fall within 2%, Content uniformity is observed in the range of 103.08 % complies i.e NLT 90.0% to NMT 110.0% of label claim.

After evaluation studies of core tablet, by using coating material HPMC E5, HPMC E15, Xanthan gum again compressed as press coated tablet. Hence For Press coated tablet evaluation studies – friability, hardness, weight variation was performed and gave satisfactory results. *In vitro* dissolution studies were performed for the formulation F1 to F9 and the formulation 8 gave a Pulsatile drug release for 6 hrs. Here at once drug was released completely after predetermined time, and hence concluded that formulation was found to be satisfied. By *in vitro* release studies F8 was selected to do stability studies.

The Stability studied was carried out for the formulation 8 for two months as per ICH guidelines at 40° C ± 2° C /75 % RH ± 5% (Accelerated Stability Studies). Tablets were evaluated for assay and in vitro dissolution study and found no significant changes during the study period.

Drug release studies have been performed and concluded that the formulation 8 (F8) shows a pulsatile drug released in 6 hr which is (Synthetic polymer- HPMC E15 and natural polymer- xanthan Gum in the ratio of 3:1) conducted for 8hrs.And the F8 formulation found to be stable after 2 months of Accelerated studies.

6. SUMMARY

The present study involved the Formulation and evaluation of Ketoprofen pulsatile tablets by using different polymers and in combination of synthetic and natural polymers.

Organoleptic properties, Solubility, compatibility studies was carried out and found to be satisfied.

By preformulation studies of granules of core tablet, angle of repose and compressibility index was found to be in the range, shown excellent flow property for compression.

Evaluations studies was performed for the core tablet included friability, hardness, weight variation fall within SD±2%, Content uniformity was complies

Evaluation studies of coated tablet, friability, hardness, weight variation fall within SD±2%. *In vitro* dissolution studies were performed for the formulation F1 to F9 and the formulation 8 gave a Pulsatile drug release at the end of 6^{th} hrs. Here at once drug was released completely after predetermined time.

The Stability studied was carried out for the formulation 8 for two months as per ICH guidelines and found to be stable.

7. Conclusion

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis (In world mostly women are suffering with rheumatoid arthritis. Based upon the research F8 formulation was shown pulsatile release after completion of 6 hr i.e was suitable for the treatment of rheumatoid arthritis.

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