FORMULATION AND EVALUATION OF FLOATING TABLETS OF CEFIXIME TRIHYDRATE USING CHITOSAN

Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment

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MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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APRIL 2012

DECLARATION BY CANDIDATE

It gives me great pleasure and satisfaction to declare that the dissertation entitled **"FORMULATION AND EVALUATION OF FLOATING TABLETS OF CEFIXIME TRIHYDRATE USING CHITOSAN"** *is a bonafide genuine research work carried out by me in the Formulation and Development department of Uni-**Sankyo Ltd, Hyderabad,** under the guidance **of Mr.T.Akelesh** (Institutional Guide), Asst. Professor, Dept. of Pharmaceutics, **R.V.S College of Pharmaceutical Sciences,** Sulur, Coimbatore and **Mr. Deelip N. Muchlambe** (Industrial Guide), Deputy Manager, Formulation and Development department of **Uni-sankyo Ltd**, Hyderabad.*

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SUBHOJIT SAMANTA

LIST OF ABBREVIATIONS USED

CMC……. .....Carboxy methyl cellulose

ºC.....Degree centigrade

CGPS..... …….Controlled gas powered systems

DSC……...Differential scanning colorimetry

% .....Percent/ percentage

FTIR .....Fourier-transform infrared

GRDDS.....Gastric retentive drug delivery system.

GRT .....Gastric retention time.

GIT …….....Gastro intestinal tract

G.....Gram

HPMC .....Hydroxypropyl methyl cellulose

HEC…….....Hydroxy ethyl cellulose

hrs.....Hours

mcg (∝g).....Microgram

mg .....Milligram

min .....Minute

n.....Release exponent

$NaHCO_3$..... .....Sodium bicarbonate

nm .....Nanometer

r .....Correlation coefficient

rpm .....Revolutions per minute

SD .....Standard deviation

sec .....Second

$T_{50\%}$ .....Time for 50% of drug release

USP.....United States Pharmacopoeia

UV.....Ultraviolet

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1. INTRODUCTION

In a country like India because of ever increasing population, the demand for health care services is also increasing. With changing lifestyles and so-called "fast culture" good health is almost deprived. In this tremendous speed of life, the health, as defined by World Health Organization (WHO) is difficult to attain. With the up gradation of life style, the concepts and severity of illness, diseases and disorders are also changing. The major challenge faced by healthcare professionals in this view is that of gradation of the available drug delivery systems. The ultimate goal of any drug delivery system is effective disease/ disorder management, minimum side effects and greater patient compliance in the cost effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. This would eliminate the haphazard and uncontrolled blood plasma profiles of drugs usually associated with conventional dosage forms[1].

There are numbers of potential limitations associated with conventional per oral dosage forms[2], they are as follows:

1.The concentration of drug in plasma and hence at the site of action, fluctuates over successive dosing intervals even at the steady state condition .Therefore it is not possible to maintain constant therapeutic concentration of drug at the site of action.

2. The fluctuations of steady state concentration drug in plasma can subject the patient either to under medication or over medication. For drugs with short biological half-lives (<2 hrs), frequent doses would be required to maintain steady state plasma concentration.

These limitations, gives rise to the need for designing new drug delivery systems, which will eliminate or reduce the cyclical plasma concentrations seen after frequent administration of conventional drug delivery systems. The overall action of a drug molecule is dependent on its inherent therapeutic activity and the efficiency with which it is delivered to the site of action. An increasing appreciation of the latter has led to the evolution and development of novel drug delivery systems (NDDS), aimed at performance enhancement of potential drug molecules. A variety of approaches has been used to provide predictable, precise and reproducible pattern of controlled release or even site-specific delivery of drugs.

These approaches have provided a valuable tool to the pharmaceutical industry for enhancing the efficiency of delivery of a number of drug molecules. This in turn has offered enhanced commercial gains and extension of life cycle of products.

Various designations are used to describe the per oral NDD systems such as delayed release systems, repeat action, prolonged release, sustained release, extended release, controlled release, and modified release systems.

Per oral controlled release (CR) technology has following objectives:

- Reduction in frequency of administration and improved patient compliance
- Reduction in side-effect profiles of drug by maintaining blood levels within the therapeutic range.
- Increased safety and efficacy of drug due to reduced fluctuations in blood levels.
- Maintenance of therapeutic drug concentration even during the night

Among these the reduction in frequency of drug administration has been the most sought strategy in designing various per oral CR dosage forms. It is always advantageous to have good insight of biopharmaceutical characteristics of the drug molecule, and its interplay with various components of the biological system.

The ultimate goal of a drug delivery device, whether traditional or nove, should therefore be to attain and maintain drug concentrations within the therapeutic window or close to the average concentration, for the requisite duration, with minimum fluctuation. Some of the parameters likely to have an important forbearing on designing of oral CR formulations are given below:

Rational of controlled drug delivery system[8,9]

The basic rational for sustained/controlled drug delivery systems is to alter the pharmacokinetics and Pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and or physiological parameter inherent in a selected route of administration.

1. Reduction in fluctuation of drug blood levels about the mean.
2. Reduce the dosage frequency.
3. To improve patients compliance.
4. To ensure safety and improve efficacy of drugs.

5. More consistent and prolonged therapeutic effect.
6. Decreased incidence and intensity of adverse effects and toxicity.
7. Better drug utilization.

Basic gastrointestinal tract physiology

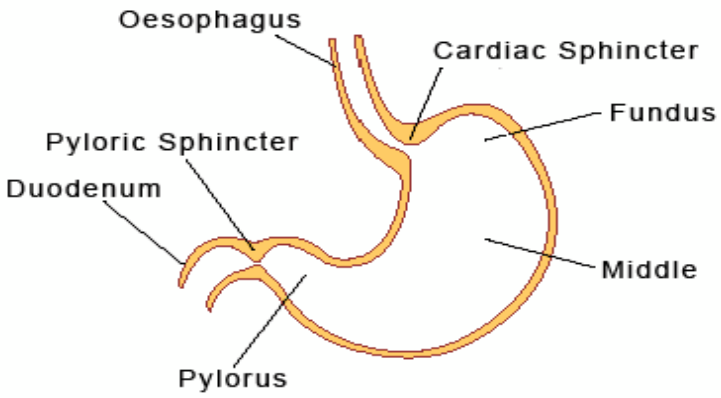


Fig-1 Anatomy of stomach

To comprehend the consideration taken in the design of the GRDDS and to evaluation their performance, the relevant anatomy (shown in above diagram) and physiology of the GI tract must be fully understood. The GI tract is essentially a tube about 9 m long that run from mouth to the anus and includes throat (pharynx), oesophagus, stomach, small intestine, and large intestine. The wall of GI tract has the same general structure through most of its length from the oesophagus to the anus, with some local variation for each region.

The stomach is a j-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac region of the abdominal cavity. Its size varies according to the amount distention: up to 1500 ml following a meal, after food has emptied, a `collapsed' state is obtained with a resting volume of only 25-50 ml. The stomach is composed of the following parts: fundus, above the opening of the oesophagus into the stomach; body, the central part; and antrum. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum. The fundus and body store food temporarily, secrete digestive juice and propels chime, a milky mixture of food with gastric juice to the antrum. The antrum grinds and triturates food particles and regulates the secretion of hydrochloric acid as well as emptying of food.

Fasting gastric pH is specially steady and approximate 2, but there are short periods of 7 ± 6 min characterized by higher values. Food buffers and neutralizes gastric acid, the pH rapidly falls back below 5 and then gradually decline to fasting state values over a period of few hrs.

The pyloric sphincter has a diameter of 12.8 ± 7 mm in humans. The duodenal pH is 6.1; and its transit time is relatively short, less than 1 min. The small intestine has a large surface area, which is comparable to the area of basketball, 463 m^2 The pH of the small intestine is 6-7 and its transit time is 3 ± 1 hrs, is relatively constant and is unaffected by food. The colon has some absorption properties of water and ions, certain drug and especially peptide molecule are also absorbed.

Physiological factors important for oral controlled drug delivery systems[5]

1. Gastric emptying

The process of gastric emptying occurs during both fasted stated and fed state however, the pattern of motility differs markedly in these two states. In the fasted state, it is characterized by an inter digestive series of electrical events, which propagate both through stomach as well as small intestine every 2-3 hrs. This activity is called as inter digestive myoelectric complex (MMC), and is often divided into four consecutive phases.

Phase I: It is a quiescent period lasting from 40-60 min. with rare contractions.

Phase II: It is a period of similar duration consisting of intermittent action potentials gradually increases an intensity and frequency as phase progresses.

Phase III: It is short period of intense, large regular contractions lasting from 4-6 min. as it serves to sweep undigested materials out of stomach and down in small intestine, it is termed as `**housekeeper waves**'. As the phase III of one cycle reaches the distal part of small intestine, the phase III of next cycle begins in duodenum.

Phase IV: It is brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to onset of gastric emptying.

Factors affecting gastric emptying time[6]

1. Volume: The resting volume of stomach is about 25-52ml. This volume is important for dissolution of dosage forms. As the volume is large, emptying is faster. Gastric emptying of small volumes like 100 ml or less is governed by Migrating Myoelectric Complex (MMC) cycle whereas large volumes of liquids like 200ml or more are emptied out immediately after administration. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids.

2. Hormonal effects: Stress conditions increases gastric emptying rate whereas depression slows down gastric emptying time. Generally females have slower gastric emptying rate than males. Age and obesity also affect gastric emptying.

3. Presence of food: Gastric emptying time differs in fasted state and in fed state. The calorific value of food affects the gastric emptying time.

4. Gastric secretions: Acids, pepsin, gastrin, mucus and other enzymes are the secretions of stomach. Normal adults produce a basal secretion up to 60ml with approximately 4mm mole of hydrogen ions every hrs.

Factors affecting gastric residence time of dosage forms are

Size and Shape of dosage forms

Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-Size tablets leave the stomach during the digestive phase while the large size tablets are emptied during the housekeeping waves.

Density

Dosage forms having a density lower than that of gastric fluid experience floating behaviour and hence gastric retention. A density of < 1.0gm/cm is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

Concomitant administration of drugs

Concomitant administration of anti-cholinergic drugs, prokinetic agents affects the gastric residence time of dosage forms.

Regional variability in intestinal absorption concept of absorption window[9,10]

The gastrointestinal tract (GIT) offers a varied environment capable of affecting the absorption of per orally administered drugs. These changes are contributed by anatomical features, physiological phenomenon, and nature of gastrointestinal milieu This can lead to the variations in intestinal permeability of drug molecules, resulting in the phenomenon of **'absorption window'** wherein the drug is preferentially absorbed only from a particular region of the GIT. Not all drugs candidates get uniformly absorbed throughout the GI tract. Drugs exhibiting absorption from only a particular region of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show 'absorption window' which signifies the region of GI tract from where absorption primarily occurs. The below diagram gives the various sites in GIT from where the drug absorption takes place.

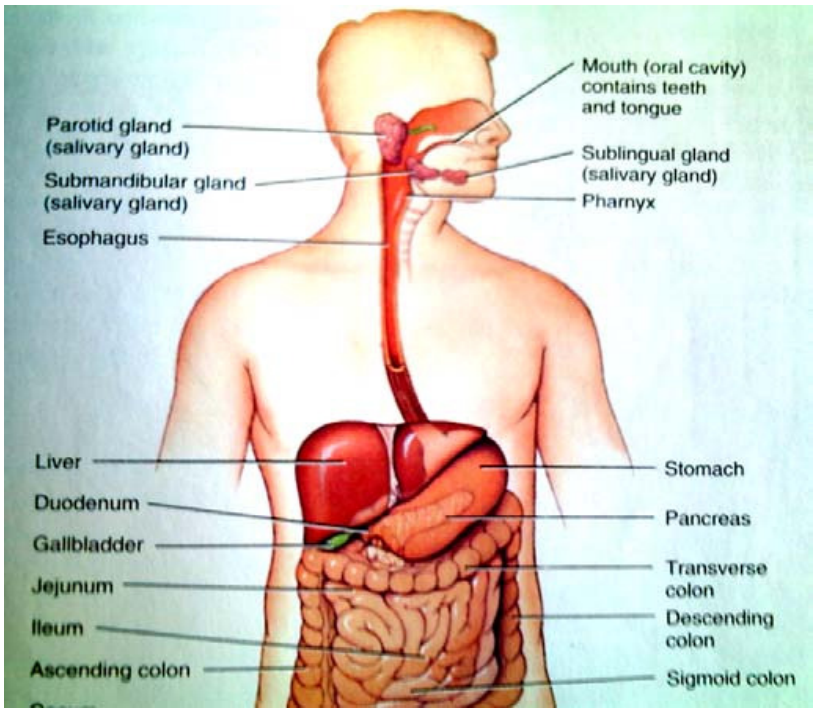


Fig-2 Sites in G.I tract for absorption of drug from conventional dosage from stomach, duodenum and jejunum.

This absorption window is observed due to following factors[6,9]

1. **Physicochemical factors**

a. pH dependent solubility

b. pH dependent stability

c. Degradation due to enzymes

2. **Physiological factors**

a. Mechanism of absorption

b. Degradation by intestinal micro flora

1. **Physico – chemical factors**

pH-dependent solubility and stability: A drug experience a pH range of 1-8 across the GIT, and needs to be in solubilised and stable form to successfully cross the biological membranes. Most of the drugs are passively absorbed; in their un-ionized form and the extent of ionization at different pH in different regions of GIT can significant alter the absorption profile. pH dependent solubility, stability and ionization by changing the physical properties of the drug in different portions of the GIT, can lead to regional variability in absorption of drugs.

2. **Physiological factors:**

An orally administered drug experiences certain physiological phenomenon which can contribute to absorption window.

Mechanism of absorption: Per orally administered drugs are absorbed both by passive diffusion as well as by non-passive means of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of GIT.

Metabolic enzymes: Presence of certain enzymes in a particular region of GIT can also lead to regional variability in absorption of drugs that are substrates to those enzymes intestinal metabolic enzymes (majorly, phase one metabolizers), like cytochrome p450 (eg, CYP3A), are abundantly present in the intestinal epithelium.

First-pass metabolism: Hepatic first-pass metabolism is another major contributory factor in reducing the bioavailability of orally administered drugs. A major portion of intestinally absorbed drugs is taken up by the portal veins to liver, a potential site of drug

metabolism. On the contrary, hepatic first-pass metabolism is of considerable interest in regard of drugs whose therapeutic actions is dependent on their hepatic metabolism. It is a well-accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances.

"The aim of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12hrs but to prolong the residence time in absorption region for desired period of time."

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT).Dosage forms with a It is evident from the recent scientific and patent literature that an prolonged GRT, i.e Gastro retentive dosage forms (GRDFs) will provide us with new and important therapeutic options. GRDF's extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance over the existing controlled release dosage forms.

Applications of GRDDDS[9,10]

1. Delivery of sparingly soluble and insoluble drugs

Especially effective in delivery of sparingly soluble and insoluble drugs, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, often several times per day.

2. Pharmacotherapy of the stomach

GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentrations at the gastric mucosa (eradication Helicobacter pylori from the sub mucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers gastritis and oesophagitis, reduce the risk gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3. Delivery of drugs with absorption window

GRDFs can be used as carriers for drugs with so-called absorption windows these substances, for example antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillin, cephalosporins, amino glycosides and tetracyclines, etc.) are taken up only form very specific sites of the GI mucosa. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms allow foe more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low-molecular-weight heparin, protease inhibitors and lutenising hormone-releasing hormone analogues.

Formulation Approaches for Gastric Retentive Drug Delivery Systems (GRDDS)[15,16]

Over last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, which include

- Floating systems (low density approach),
- Swelling and expanding systems,
- Bioadhesive systems,
- Modified shape systems,
- High density systems, and
- Delayed release gastric emptying devices
- Super porous hydro gel systems

A. Floating systems (gas powered controlled drug delivery systems)

These systems are also known as hydro dynamically balanced systems (HBS) or floating drug delivery systems (FDDDS). They have a bulk density lower than density of gastric fluid, i.e. their bulk density is less than 1. The specific gravity of gastric fluid is approximately 1.004-1.01g/cm, thus FDDS remains buoyant in stomach without affecting gastric emptying rate for prolonged period of time, releasing the drug slowly at desired rate. The improved controlled drug delivery system of the present invention is designed to deliver effectively a drug to a patient over a specific time period (temporal control) and from particular portion of the patients gastrointestinal tract (spatial control). The improved controlled drug delivery system avoids dose dumping and results in the most

therapeutic administration of a particular drug to a particular person with a particular ailment.

Effect of sodium bicarbonate on drug release

The use of gas generating agents in floating formulations has been tried. The gas generating component interacts with an acid source triggered by contact with water or simply with gastric fluid to generate carbon dioxide that gets entrapped within the hydrated get matrix of the swelling composition. The gas generating component such as carbonates and bicarbonates may be present in amounts from about 5% to about 50%, preferably from about 10% to about 30%, by weight of the composition. These salts may be used alone or in combination with an acid source as a couple. The acid source may be one or more of an edible organic acid, a salt of an edible organic acid or mixture thereof e.g., citric acid or its salt sodium citrate or calcium citrate; maleic acid, fumaric acid. Increasing the concentration of sodium bicarbonate decreases the floating lag time because of the faster and higher CO_2 generation. At higher concentration of effervescent agents the coating of the tablets becomes less stable due to increase in the internal pressure and thereby rupturing the polymer coating. This causes the sudden increase in the drug release.

For the floating system, the ideal dosage form should be coated. The ideal coating material should be highly impermeable for the dissolution medium the order to initiate CO_2 formation and should be highly permeable for generated CO_2 in the wet state to promote floating. Ichikawa M *et al*[17] reported that sodium bicarbonate not only increases the hydration in HPMC matrices, but also deviates drug release kinetics from matrix to zero order. In present study, in acidic media the sodium bicarbonate reacts to generate carbon dioxide. This might have contributed to the faster drug release in acidic media.

B. Swelling and expanding drug delivery system

To achieve gastro retention the most promising approach is that of creating a swelling and expanding system. Any system will need to expand to a size large enough to be retained in the (fasted) stomach, but to do so in a safe and reliable manner. It must not swell or expand in the esophagus or in the intestine; if it is emptied prematurely from the stomach (e.g. Problem could arise from the formation of an insoluble mass known to bezoars). The gastro retentive system will also need to display controlled release properties so that the drug is released at an appropriate rate for optimal absorption window. The systems

should have an ability to remain the stomach and withstand the mechanical force therein. Last but not least, it will need to decrease in size after it has performed its function and transit through the intestine in the normal way.

C .Bioadhesive Systems

These systems are used to localize a delivery device within the lumen and cavity of body to enhance the drug absorption process in site specific manner. Various bioadhesive polymers are used for achieving the effective bioadhesion. These polymers tend to form hydrogen and electrostatic bonds at the mucus membrane-polymers boundary. Rapid hydration contact with the mucoepithelial surface appears to favour adhesion.

D. Modified shape systems

These are non-disintegrating geometric shapes moulded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on the size, shape and flexural modulus of drug delivery system.

E. Mucoadhesive/bioadhesive drug delivery system

Bioadhesion is the phenomenon in which two materials, at least of which is biological are held together by means of interfacial, such as adhesion between a polymer and biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used.

Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance drug absorption in a site specific manner suitable polymers that can be used to form mucoadhesive microsphere include soluble and insoluble, non-biodegradable and biodegradable polymers.

F. Superporous hydro gel systems[3]

Although these are swellable systems, they differ sufficiently from the conventional; types to warrant separate classification. With pore size ranging between 10 nm and 10 μm, absorption of water by conventional hydro gel is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Super porous hydro gels, average pore size>100 μm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open

pores. Moreover, they swell to a large size (swelling ratio – 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

This is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium). In vivo studies with dogs showed that under fasting condition, the super porous hydro gel composite (i.e. containing Ac-Di-Sol) remained in the stomach for 2-3 hrs. This time increased to >24 hrs after feeding, even though the fed condition was maintained only for a few hours. After several hours (> 30 hrs), fragmentation occurred and the composite was rapidly cleared.

G. Delayed gastric emptying system

The use of passage-delaying excipients has been proposed as an attempt to develop a form that exerts some influence on its own transit. Preliminary in vivo result depicts a major problem related to the highly variable inter-subject reactions. Another analogue approaches consist of using passage delaying drug, for example propantheline, which is generally considered undesirable because of potential side effects.

Recent Developments in Floating Drug Delivery Systems (FDDS)[3,7]

The concept of FDDS was described in the literature as early as in 1968; the method was described for overcoming the difficulty of swallowing medicinal pills. The suggested method was providing the pills having a density less than 1.0g/ml so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating delivery system.

The various buoyant compositions include hollow microspheres (micro balloons), granules, powders, capsules, tablets (pills), and laminated films. Most of the floating systems include single unit systems, such as HBS and floating tablets. These systems are unreliable and irreproducible in prolonging residence time in stomach when orally administered, due to their `all or nothing' emptying process. On the other hand, multiple unit dosage forms appear to be effective in reducing inter-subject variability and lower the probability of dose dumping.

Based on mechanism of buoyancy, two distinctly types of systems have been utilized in the development of FDDS. They are non-effervescent and effervescent types of systems. The following figures demonstrate these various approaches.

1. Intragastric floating tablet employing hydrophilic swellable polymers

Fig-4 Pictorial diagram for the floating tablet of hydrophilic swellable polymers

2. Floating bilayer tablet containing hydrocolloids in the core

A bilayer tablet can also be prepared to contain one immediate release and other sustained release layer. Immediate release layer delivers the initial dose whereas sustained release layer absorbs gastric fluid and forms a colloidal get barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time.

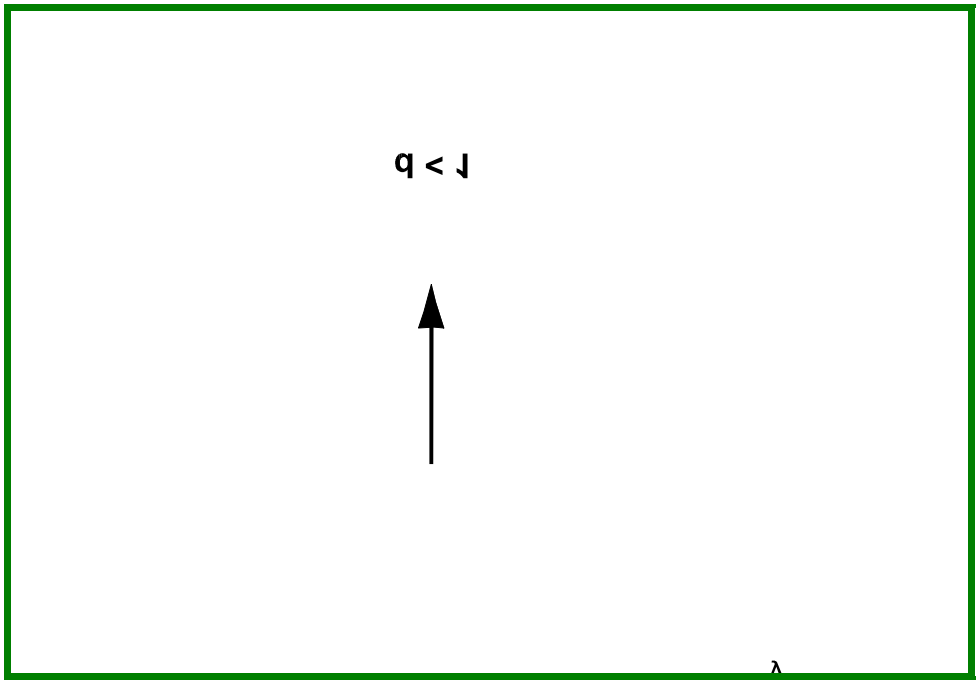


Fig-5 Pictorial diagram for the floating bilayer tablet of hydrocolloids

3. Intragastric floating drug delivery device containing micro porous membrane and floatation chamber

The technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct c contact of gastric mucosal surface with undissolved drug. In stomach, the floatation chamber containing entrapped air caused the delivery system to float over the gastric contents. Gastric fluid enters through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

4. Multiple-Unit oral floating dosage system

These buoyant delivery system uilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chime. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect. Multiple unit type of floating pills as show in below picture that generates CO_2, have also been developed. These kinds of systems float completed within 10 min and remain floating over an extended period of 5-6 hrs.

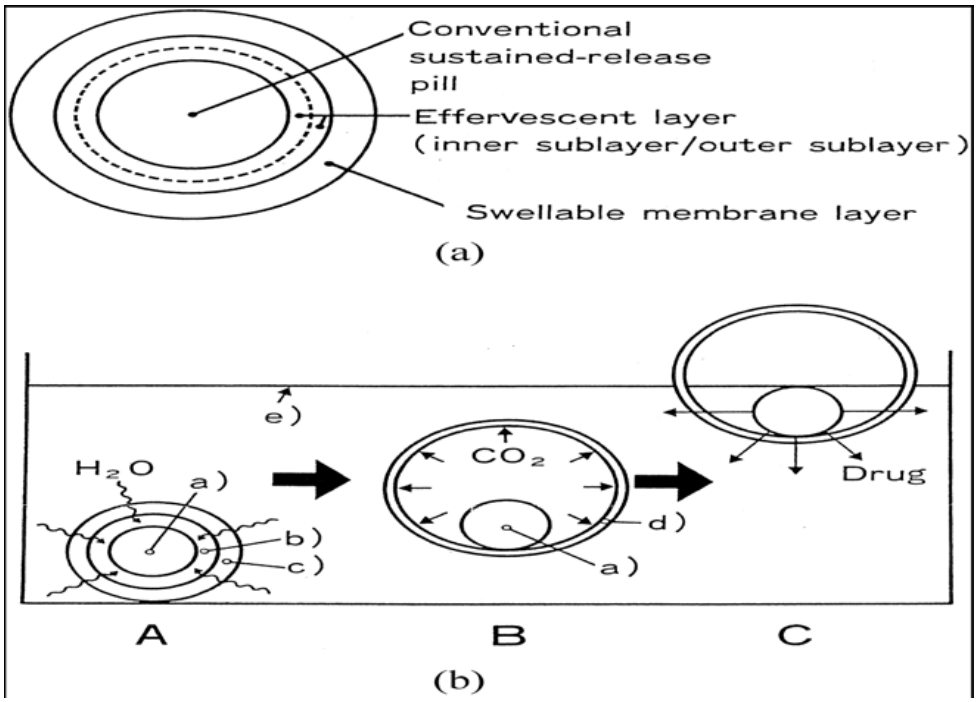


Fig-6 Pictorial diagram for multiple units of floating drug delivery system using gas generation technique

5. Intragastric osmosis controlled drug delivery system

Intragastric floating tablet that were hydrodynamically balanced in the stomach for an extended period of time until the entire drug-loading dose was released. Tables were comprised of an active ingredient, 0-80% by weight of inert material, and 20-75% by weight of one or more hydrocollids such as methylcellulose, hydroxyl ethyl cellulose, hydroxyl propyl methylcellulose, and sodium carboxy methylcellulose, which open contact with gastric fluid, provided a water impermeable colloid gel barrier on the surface of tablets.

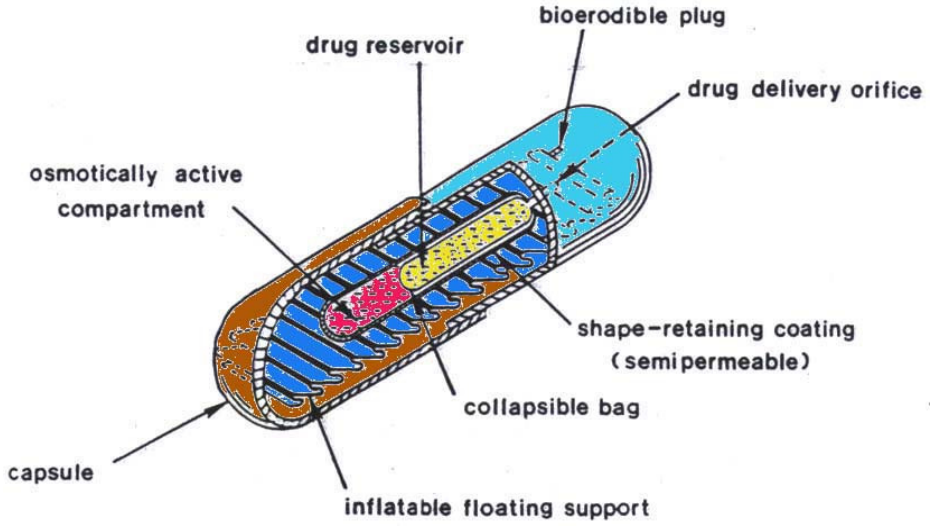


Fig-7 Pictorial diagram for the osmosis controlled gastric floating device

6. Gastro-inflatable drug delivery device

These devices are osmotically controlled floating system containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period.

A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid.

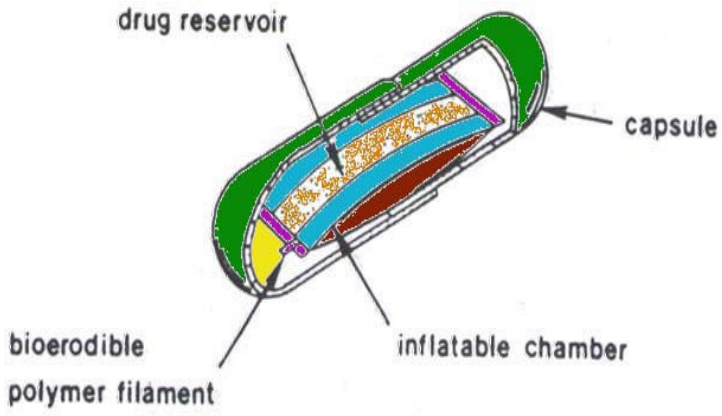


Fig-8 Pictorial diagram of gastro-inflatable drug delivery device

Advantages of FDDS[6,7]

1. **Sustained drug delivery**
2. **Site-specific drug delivery**
3. **Pharmacokinetic advantages**

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

Improvement of bioavailability of drugs having poor bioavailability, because of restricted absorption in upper GI tract. Minimization of fluctuations in the plasma levels of drugs due to variable gastric emptying. Improvement of the bioavailability of the drugs that show pH dependent solubility, such as Verapamil (solubility decreases with increase in pH).

Therapeutic applications

FDDS is effective in the treatment of *Helicobacter pylori*, causative organism for chronic gastritis and peptic ulcers. The eradication of which requires high concentrations of drug (antibiotics) maintained with the gastric mucosa for a long duration.

Sustained release drug delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Site-specific drug delivery

Floating drug delivery system is particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

Absorption enhancement

Drugs that have poor bioavailability because of sites specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery system, thereby maximizing their absorption. FDDS also serves as an excellent drug delivery system for the eradication of Helicobacter pylori, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted.

Limitations of FDDS

The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.[16]

The ability to float relies on the hydration state of the dosage form. In order to keep these tablets floating *in vivo,* intermittent administration of water (a tumbler full, every 2 hrs) is beneficial.

The ability of drug to remain in the stomach depends upon the subject being positioned upright.

FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid.

Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability.

Drugs that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms. One drawback of hydro dynamically balanced systems is that, this system being a matrix formulation consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa.

Marketed products of FDDS

The last three decades of intensive research work have resulted in the development of five commercial FDDS.

Table-1 Marketed products of floating drug delivery system

Product Name	**Use**
Madopar	Anti parkinsonism
Val release	Sedative, hypnotic
Liquid Gaviscon	Suppress gastrooeseophageal reflux & heart burn
Topalkan	Antacid, Antipeptic
Almagate Flotcoat	Antacid

Need for the study

The improved controlled drug delivery system of the present invention is designed to deliver effectively a drug to a patient over a specific time period (temporal control) and from particular portion of the patients gastrointestinal tract (spatial control).The improved controlled drug delivery system avoids dose dumping and results in the most therapeutic administration of a particular drug to a particular person with a particular ailment.

It is well known to those skilled in the art that for ailments requiring multiple doses of a particular drug, the blood levels of a drug need to be maintained above its minimum effective level and below its minimum toxic level in order to obtain the desired therapeutic effects, to avoid undesired toxic effects, and to minimize side effects .When the blood levels of a drug are in this range, the drug is eliminated from the body at a particular rate. A controlled drug delivery is usually designed to deliver the drug at this particular rate: safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug at this rate. Controlled drug delivery results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing doses forms are administered to a patient. Controlled drug delivery results in optimum therapy and not only reduces the frequency of dosing, but may also reduce the severity and frequency of side effects.

The above basic concepts of controlled drug delivery are well known to those skilled in the art. Considerable efforts have been made in the last decades to develop new pharmaceutically viable and therapeutically effective controlled drug delivery systems. Attention has been focused particularly on orally administered controlled drug delivery systems. Various pharmacokinetic advantages like, maintenance of constant therapeutic level over a prolonged period of time and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. For the present study cefixime is selected as drug candidate, it fulfills the following characteristics which indicate its suitability for fabrication into the floating drug delivery system. Cefixime is a very poorly soluble in water after its oral administration, it is slowly and incompletely absorbed from the gastrointestinal tract, which resulting into the poor bioavailability i.e., 40-50%.[2, 3, 4] So, in order to improve the therapeutic effect of the drug by increasing its bioavailability, we are planning to formulate Cefixime gas powered

systems for controlled release with increased gastric retention. The present development study of Cefixime in the form of tablet or capsule which provides a combination of spatial and temporal control of drug delivery to patients for effective therapeutic results.[18, 19]

1. Formulation of floating tablet containing Cefixime as a drug candidate which would remain in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site.
2. Cefixime having good absorption in GIT.
3. Cefixime having low pKa which remain unionized in stomach for better absorption.
4. For beta-lactum antibiotics the pharmacodynamic parameter that best correlates with eradication is more than above the MIC (minimum inhibitory concentration). It means that the drug should remain in the body above MIC for longer time.

2. OBJECTIVES

In the present research work, we are designing Cefixime gas powered systems for controlled release. It is an object of the present research topic to provide Pharmaceutical composition in the form of tablets, which constitute an oral controlled drug delivery system.

1. Generates and entraps a gas in a hydrated matrix upon contact with an aqueous medium or gastric fluids, and which retains a substantially monolithic form in the stomach.
2. Provides increased gastric residence and hence longer period of the drug delivery system in GI tract.
3. Delivers the drug at controlled rate such that the drug is delivered over period of time.
4. Shows increased absorption of drugs i.e. absorbed largely from the upper parts of the GI tract as compared to other oral controlled drug delivery system.
5. Safe and effective blood levels are maintained for a period as long as the system continues to the deliver the drug at this rate.
6. It not only reduces the frequency of dosing but may also reduce the severity and frequency of side effects

3. REVIEW OF LITERATURE

Talwar *et al*[15]developed a once daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34%sodiumalginate, 1.03% xanthan gum, 13.7% sodium bicarbonate and 12.1% cross linked polyvinyl pyrrolidone. The viscolyzing agents initially and the gel forming polymer later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach or upper part of the small intestine (spatial control). The hydrated gel matrix created a tortuous diffusion path for the drug, resulting in sustained release of the drug.

Baumgartner *et al*[44] (2001) developed floating tablets of ciprofloxacin Hydrochloride offer a new possibility of treating the stomach infected with *Helicobacter pylori*. The objective of this study was to select suitable materials such as polymers hydroxyl ethyl cellulose (HEC), hydroxyl-propylcellulose (HPC), HPMCK4M and obtained controlled drug release for more than 8hr from non disintegrated matrices plays an important role in prolonging gastric residence time.

H.Zou, *et al*[45] Developed a floating-pulsatile drug delivery system intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by burst release. To overcome limitations of various approaches for imparting buoyancy, they generate the system which consist of three different parts a core tablet containing the active ingredients, an erodible outer shell and a top cover buoyant layer. The buoyant layer, prepared with methocel K4M, Carbopol, 934P, and sodium bicarbonate, provides buoyancy to increase the tension of the oral dosage form in the stomach. Developed formulations were evaluated for their buoyancy, mass degree of swelling, weight variation, hardness, thickness, friability, dissolution, pharmacokinetic parameters.

Krogel *et al*[46]developed floating-pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. Preliminary studies identified important core and coating properties for the two systems. For the floating system, a polymer coating with a high elongation value and high water-and low CO_2 permeability's was selected (Eudragit® RL: acetyltributyl citrate 20%, w:w), while for the pulsatile DDS, a weak, semi permeable film, which ruptured after a certain lag time was best (ethyl cellulose : dibutylsebacate 20%, w:w). A polymer (cellulose acetate or hydroxyl propyl methyl cellulose) was added to the core to control the drug release. The time to flotation could be

controlled by the composition and hardness of the tablet core and the composition and thickness of the coating. For the pulsatile system, a quick releasing core was formulated in order to obtain a rapid drug releaseaftertheruptureofthepolymercoating.Thelagtimepriortotherapid drug release phase increased with increasing core hardness and coating level.

S.S.Badve *et al* [47] developed a hollow calcium pectinate bead by simple process of acid-base reaction during ionotropic cross linking. Invivo studies by gamma scintiography determined on rabbits showed gastro retention of beads up to5h.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. This approach suggested the use of hollow calcium pectinatemicroparticlesaspromisingfloating-pulsatiledrugdeliverysystem forsite and time-specific release of drugs acting as per chronotherapy of diseases.

B.S.Dave, *et al* [48] optimized a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum and hydroxyl propyl methyl cellulose were evaluated for gel-forming properties. Sodium bicarbonate was in corporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. Full factorial design was applied to systemically optimize the drug release profile. The results of the full factorial design indicated that allow amount of citric acid and a high amount of stearic acid favours sustained release of ranitidine hydrochloride from a gastro retentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. The similarity factor was applied between the factorial design batches and the theoretical dissolution profile. No significant difference was observed between the desired release profiles. These studies indicate that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile.

X. Xiaoqiang *et al* [49] studied three floating matrix formulations of phenoporlamine hydrochloride based on gas forming agent. Hydroxy propyl methylcellulose K4MandCarbopol971P NF was used in formulating the hydro gel drug delivery system. Incorporation sodium bicarbonate into matrix resulted in the tablet floating over simulated gastric fluid for more than 6 hr. The dissolution profiles of all tablets showed non-Fickian diffusion in simulated gastric fluid. Invivo evaluations of these formulations of phenoporlamine hydrochloride were conducted in six healthy male human volunteers to compare the sustained release tablets with immediate release tablets.

Yang *et al*[50] developed as well able asymmetric triple-layer tablet with Floating ability using hydroxyl propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. Tetracycline and metronidazole were in corporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The flotation was accomplished by incorporating gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2ratios) along with the polymers.

Nur *et al*[52] developed floating tablets of captoprilusing HPMC (4000and 15000cps) and carbopol934P. Invitro studies revealed that buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles and tablet porosity. A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24hrs controlled release from the dosage form of captopril was achieved.

Ozdemir *et al*[51]developed floating bilayer tablets with controlled release for furosemide. One layer contained the polymers HPMC 4000, HPMC 100 and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours.

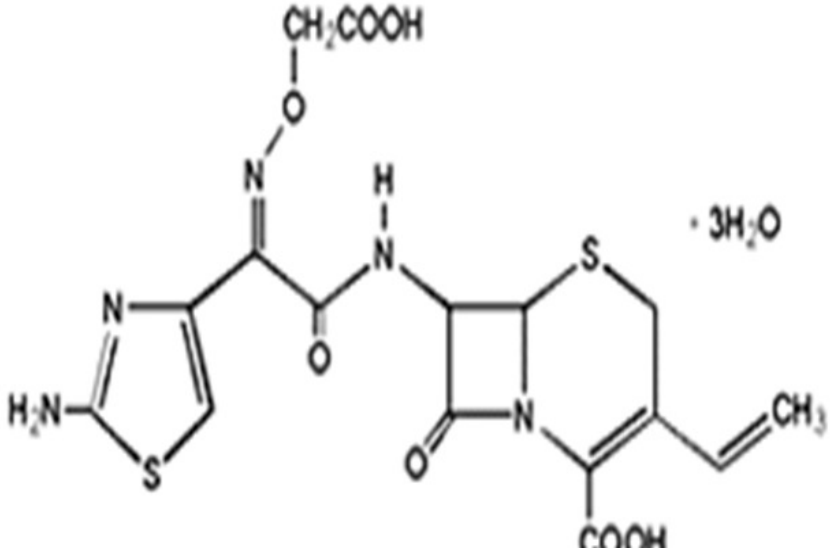
Nur *et al* [52] developed floating tablets of captopril using HPMC (4000 and 15000cps) and carbopol 934P. Invitro studies revealed that buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles and tablet porosity. A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24hrs controlled release from the dosage form of captopril was achieved.

Pentewar *et al* [68] developed a floating drug delivery system of cefixime trihydrate matrix tablet using polymer blends of different viscosity grades of HPMC. Gas producing agent used was sodium bicarbonate. The effect of citric acid on the drug release was also investigated by dissolution studies. Citric acid was found to be release rate enhancer

4. DRUG PROFILE

CEFIXIME TRIHYDRATE[18,26]

STRUCTURE



CHEMICAL NAME: (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2- (carboxymethoxy) imino] acetyl] amino] 3-ethenyl-8-oxo-5-yhia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylicacid trihydrates

CATEGORY: Antibacterial

MOLECULAR FORMULA: $C16H15N5O_7 S_2 .3H_2o$

MOLECULAR WEIGHT: 507.50

DESCRIPTION: Cefixime is a semisynthetic, cephalosporin antibiotic for oral administration. Cefixime is the first member of third generation orally active cephalosporin.

MELTING POINT: 240°-250° C with decomposition

P^{Ka}: PKa1-2.10 -COOH of the cephem group

P^{Ka}2-2.69 $-NH_2$ of the amino- thiazol group

P^{Ka}3-3.73 -COOH of the 7-side chain

ABSORPTION: Well absorbed in gastrointestinal tract

STORAGE: Store in well closed containers, in cool and dry place.

SOLUBILITY: soluble in methanol and propylene glycol, slightly soluble in alcohol in acetone and in glycerin

WATER CONTENT: 9% to 12%

IDENTIFICATION: IR absorption spectrum of test samples must comply with cefixime standard

PHARMACOKINETICS:

ABSORPTION: Well absorbed from the gastrointestinal tract

BIOAVAILABILITY: 40 – 50%

DISTRIBUTION: Protein binding approximately 65%

HALFLIFE: 3 – 4hrs may range up to 9 hrs

- Moderate renal impairment (creatinine clearance of 20ml/min to 40ml/min): Prolonged to 6.4 hours
- Severe renal impairment (creatinine clearance of 5ml/min to 20ml/min): Increases to 11.5 hours

EXCRETION: Excretion no biologically active metabolites of cefixime have been identified in plasma or urine in 24 hours. More than 10% of an administered dose is excreted via bile. The serum half life of cefixime in healthy subject is 3 – 4 hours.

MECHANISM OF ACTION: Cefixime is a Beta-lactum antibiotic. Its action is by binding to specific penicillin- binding protein (PBPS) located inside the bacterial cell wall; It inhibits the third and last stage of bacterial cell wall autolytic enzymes such as autolysins; It is possible that cefixime interferes with an autolysin inhibitor. As like other cephalosporin, bactericidal action of cefixime results from inhibition of cell-wall synthesis.

Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result many organisms resistant to penicillin's and some cephalosporin due to the presence of Beta-lactamase may be active against most strains.

INDICATIONS AND USAGE:

To reduce the development of drug resistant bacteria and maintain the effectiveness of Cefixime and other antibacterial drugs. Cefixime should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacterial

It is indicated in the treatment of the following infections, when caused by susceptible strains of the designed microorganisms:

- Un complicated UTI caused by *Escherchia coli* and *Proteus mirubillis*
- Otitis media caused by *Haemophilus influenza*(Beta-lactamase positive and negative strains), *Moraxella* (Branhamella), *Catarrhalis*, (Beta-lactamase positive) and *S.Pyrogenes*
- It is used to treat respiratory tract infections (Including Sinusitis, Otitis media, Pharyngitites, Tonsitities, Pnemonia), Skin and Soft tissue infections.

ADVERSE REACTIONS:

Gastrointestinal: Symptoms of pseudo-membranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Dyspepsia, Gastritis, and Abdominal pain have also occurred. As with sum Penicillins and sum other Cephalosporins transient hepatitis and Cholestatic, Jaundice have been reported rarely.

Hypersensitivity: Anaphylactic/ Anaphylactic reactions (including shock and fatalities), Skin rashes, Utricaria, Drug fever , Prurities, Angioedema, and Facial oedema, Erythema multiform, Stevens- Johnson syndrome and Serum sickness like reactions. A very serious allergic reaction to this drug is unlikely to occur.

HAEMIC AND LYMPATIC SYSTEM: Transient Thrombocytopenia, Leucopoenia, Neutropenia, and Eosinophilia, Prolongation in prothrombin time was seen rarely.

HEPATIC: Transient elevations in SGPT, SGOT, Alkaline phosphatase, Hepatitis, Jaundice.

CNS: Headache, Dizziness, Seizures.

RENAL: Transient elevations in BUN/ Creatinine, actual renal failure.

OTHERS: Genital prurities, Vaginitis, Candidacies, Toxicepidermalnecrolysis.

DRUG INTERACTIONS: Cefixime interactions with several other types of drugs like Probenecid, Warafin, Live bacterial vaccines and Carbamazepine. Its medication may decrease the effectiveness of combination type birth control pills. This can result in pregnancy. You may need to use an additional form of reliable birth control while using this medication. Cefixime medication may cause false positive results with certain diabetic urine testing products (cupric sulphate type). This drug may also affect the results of certain lab tests.

DOSAGE AND INDICATIONS:

Adult Dose:

1. *Gonorrhoea:* Uncomplicated, 400mg orally as one-time dose.
2. *Gonorrhoea:* Disseminated (after parenteral therapy), 400mg orally twice a day to complete at least one week of therapy.
3. *Active infective exacerbation of chronic obstructive pulmonary disease:* 400mg orally once a day or divided twice a day, depending on type and severity of infection.
4. *Bronchitis:* 400mg orally once a day or divided twice a day; depending on type and severity of infection.
5. *Otitis media:* 400mg orally once a day or divided twice a day, depending on type and severity of infection.
6. *Tonsilities:* 400mg orally once a day or divided twice a day; depending on type and severity of infection.
7. *URINARY TRACT INFECTIOUS DISEASE:* Uncomplicated: 400mg orally once a day or divided twice a day; depending on type and severity of infection.

Paediatric dose (over 50kgor over 12 years of age consider as a adult)

8. *Gonorrhoea:* Uncomplicated,(6 months to 12 years of age) 8mg/kg/day orally as one-time dose.
9. *Gonorrhoea:* Disseminated (after parenteraltherapy), (6 months to 12 years of age) 8mg/kg/day orally twice a day to complete atleast one week of therapy.
10. *Active infective exacerbation of chronic obstructive pulmonary disease:* (6 months to 12 years of age) 8mg/kg/day orally once a day or divided twice a day, depending on type and severity of infection.
11. *Bronchitis:* (6 months to 12 years of age) 8mg/kg/day orally once aday or divided twice a day; depending on type and severity of infection.
12. *Otitis media:* (6 months to 12 years of age) 8mg/kg/day orally once a day ar divided twice a day, depending on type and severity of infection.

13. *Tonsilities:* (6 months to 12 years of age) 8mg/kg/day orally once a day or divided twice a day; depending on type and severity of infection.
14. *Urinary tract infectious disease:* Uncomplicated :(6 months to 12 years of age) 8mg/kg/day orally once a day or divided twice a day; depending on type and severity of infection.
    - *Haemodialysis:* 75% of usual dose once a day
    - *Peritonealdialysis:* 50% of usual dose once a day

ADMINISTRATION:

Oral: May be given with or without food.

Oral: If suspension, shake well before measuring the dose

Overdose: Several Cephalosporins, shake well before measuring the dose in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. If seizures associated with drug therapy, the drug should

CONTRAINDICATIONS: Cefixime is contraindicated in patients with known allergy to cephalosporin group of antibiotics.

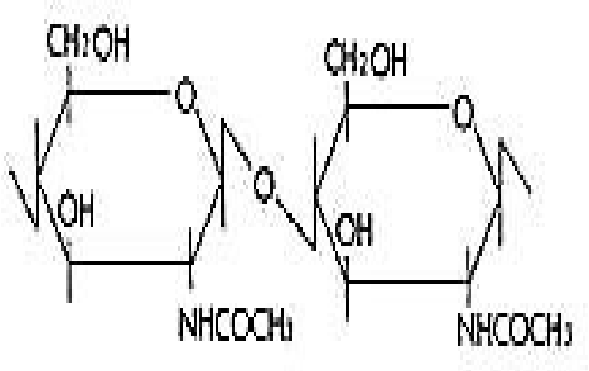
EXCIPIENTS PROFILE

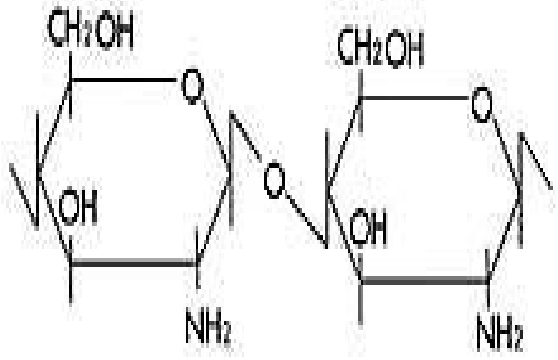
CHITOSAN[31,32]

SYNONYMS:

Chitosan Ascorbate; Deacetylated Chitosan, Enzymatic Polychitosamine Hydrolisat, HEP-30; Mono-Carboxymethylated Chitosan, N-Carboxybutyl Chitosan; N,O-Sulfated Chitosan; O-Sulfated N-Acetylchitosan; Quitosano, Sulfated N-Carboxymethylchitosan; Sulfated O-Carboxymethylchitosan, Trimethyl Chitosan Chloride.

STRUCTURE:





BIOLOGICAL SOURCE:

Chitosan is a sugar that is obtained from the hard outer skeleton of shellfish, including crab, lobster, and shrimp. Chitosan, the partially deacetylated polymer of N-acetyl-D-glucosamine, is water-soluble Chitin ("*chiton*", greek) is the primary structural component of the exoskeletons of crustaceans, molluscs, insects, some fungi and yeast. However, chitin is not present in higher plants and higher animals. The role played by chitin is similar to the roles played by cellulose in plants and collagen in higher animals. The annual biosynthesis of chitin has been estimated to 109 to 1011 tons. Chitin is widely distributed in nature, this is a

renewable bioresource. The shell of selected crustacean was reported by Knorr (1984) to consist of 30-40% protein, 30-50% calcium carbonate and calcium phosphate, and 20-30% chitin. The main commercial sources of chitin are the shellfish waste such as shrimps, lobster, crabs, squid pens, prawns and crawfish. Chitosan is found in nature, to a lesser extent than chitin, in the cell walls of fungi. Chitin is economically feasible and ecologically desirable because large amounts of shell wastes are available as a by-product of the seafood industry. Production of chitosan from these is inexpensive and easy. Commercially, chitosan is available in the form of dry flakes, solution and fine powder.

Crab/Shrimp shells

↓

Demineralization (dilute HCl)

↓

Deproteination (dilute NaOH)

↓

Decolourisation (dilute KMnO4)

↓

Chitin

↓

Deacetylation (concentrated NaOH)

↓

Chitosan

It is a linear ***polysaccharide*** composed of randomly distributed β-(1-4)-linked ***D-glucosamine*** (deacetylated unit) and ***N-acetyl-D-glucosamine***

CHEMISTRY

Chitin consists mainly of unbranched chains of beta-(1 → 4)-2-acetamido-2-deoxy-D-glucose (=N-acetyl-d-glucosamine). It is similar to cellulose, in which the C-2 hydroxyl groups are replaced by acetamido residue. Chitin is practically insoluble in water, dilute acids, and alcohol, with variation depending on product origin.

PHYSICO-CHEMICAL PROPERTIES

Chitosan is actually a denomination describing a series of polymers with different degree of deacetylation and molecular weight. These two factors are very important for the Physico-chemical properties of chitosan.

1. **Description**

Chitosan occurs as odourless. The pigment in the crustacean shells forms complexes with chitin. Then, chitosan is a quite flabby powder or flake and its color varies from yellow to white whereas spray-dried chitosan salts have smooth texture, fine powder and pale color.

2. **Degree of Deacetylation:**

The process of deacetylation involves the removal of acetyl groups from the molecular chain of chitin, leaving behind a compound (chitosan) with a high degree chemical reactive amino group (-NH2). This makes the degree of deacetylation (DD) an important property in chitosan production as it affects the physicochemical properties, hence determines its appropriate applications. Deacetylation also affects the biodegradability and immunological activity.

3. **Molecular Weight**

Molecular weight of native chitin is usually larger than one million Daltons while commercial chitosan products have the molecular weight range of 100,000 – 1,200,000 Daltons, depending on the process and grades of the product

4. **SOLUBILITY:**

Chitosan is a weak base with is also hydrophilic. The D-glucosamine
unit has a pKa value of 7.5 (Säkkinen 2003: 1-56). The basic nature of Chitosan depends on its degree of deacetylation an apparent pKa value for the polymer is 6.5. It is estimated that deacetylation must be at least 85% complete in order to achieve the desired solubility. Low-molecular weight Chitosan (MW <10 KDa) and chitosan salts may be more readily soluble, but high MW Chitosan were occured gel formation. Chitosan is soluble in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (including hydrochloric, lactic, glutamic and aspartic acids) that form water-soluble salts. Chitosan salts are soluble in water; the solubility depends on the degree of deacetylation and the pH of the solution

USES

There is some evidence of the effect of chitosan on lowering cholesterol and body weight, but the effect is unlikely to be of clinical importance. To some extent, chitosan is used in the

emergency setting to control bleeding. Chitosan has been used in various drug delivery systems. Antimicrobial and other effects are being evaluated for use in dentistry.

Pharmaceutical applications of Chitosan

- Chitosan in the pharmaceutical industry is used to mask bitter tastes in oral pharmaceuticals. Chitosan being employed in various types of drug delivery systems, including intranasal, transdermal, and site-specific delivery mechanisms, as well as in hydrogels, microspheres, liposomes, matrix forms, and conjugate forms.
- Diluent in direct compression of tablets
- Binder in wet granulation
- Slow-release of drugs from tablets and granules
- Drug carrier in micro particle systems
- Films controlling drug release
- Preparation of hydro gels, agent for increasing viscosity in solutions
- Wetting agent, and improvement of dissolution of poorly soluble drug substances
- Disintegrants
- Bioadhesive polymer
- Site-specific drug delivery(e.g. to the stomach or colon)
- Absorption enhancer(e.g. for nasal or oral drug delivery)
- Biodegradable polymer(implants, micro particles)
- Carrier in relation to vaccine delivery or gene therapy
- Being a bioadhesive polymer and having antibacterial activity, chitosan is a good candidate for oral cavity drug delivery. Also, because of its favourable biological properties, chitosan is using for the enhancement of drug absorption in buccal or sublingual delivery systems.
- Chitosan microspheres can remain longer in stomach and allow for stomach-specific drug delivery. This polymer could have promising application in colon-specific drug delivery. As a result of the physical, chemical and biological properties, chitosan has been using many different formulations for drug and gene delivery in the GI tract.

TOXICOLOGY

Chitosan's toxicity profile is relatively low.

Dietary chitosan reportedly affects calcium metabolism in animals

SIDE EFFECTS

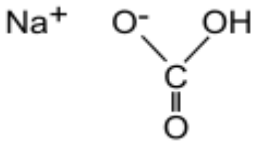
Side effects of chitosan following oral administration relate to its effects within the gastrointestinal tract. Consumption of several grams of chitosan daily by humans can result in constipation or diarrhoea, because chitosan entraps water and lipids in the intestine. The amounts of chitosan needed in pharmaceutical formulations are fairly low (less than 1000 mg/dose), and risks of side effects in the gastrointestinal tract are therefore also low.

INCOMPATIBILITIES:

Chitosan is clinically well tolerated, it has been suggested that it might not be desirable for administration to individuals allergic to crustaceans, in which consumption of crustaceans frequently results in allergic reactions, and serious adverse reactions are possible.

Sodium bicarbonate[31,32]

Structure:



Sodium bicarbonate natural mineral form is nahcolite. It is a component of the mineral natron and is found dissolved in many mineral springs. It is found in dissolved form in bile, where it serves to neutralize the acidity of the hydrochloric acid produced by the pancreas, and is excreted into the duodenum of the small intestine via the bile duct. It is also produced artificially..

IUPAC name: Sodium hydrogen carbonate

Other names Baking soda, bicarbonate of soda, nahcolite, sodium bicarbonate, E500,

Functional category: alkalizing agent, Therapeutic agent

Molecular formula: $NaHCO_3$

Molar mass	-	84.01 g mol^{-1}
Bulk density	-	0.869 g/ cm
Tapped density	-	1.369 1.369g/ cm
True Density	-	2.173 g/ cm
Melting point	-	50 °C, 323 K, 122 °F (decomposes)
Boiling point	-	851 °C, 1124 K, 1564 °F
Solubility	-	Insoluble in ethanol and ether, soluble in water - 9 g/100 mL, 69 g/L (0 °C), 96 g/l (20 °C), 165 g/l (60 °C), 236 g/L (100 °C)

Acidity (**pK_a**): 10.329- 6.351 (carbonic acid)

Refractive index : 1.3344

Routes of administration: Intravenous, oral

Description: Sodium bicarbonate is a white solid that is crystalline, odourless, but often appears as a fine powder. It has a slightly salty, alkaline taste resembling that of washing soda (sodium carbonate).

Chemistry: Sodium bicarbonate is an amphoteric compound. Aqueous solutions are mildly alkaline due to the formation of carbonic acid and hydroxide ion:

$$HCO3 + H_2O \rightarrow H_2CO_3 + OH^-$$

Sodium bicarbonate can be used as a wash to remove any acidic impurities from a "crude" liquid, producing a purer sample. Reaction of sodium bicarbonate and an acid produce a salt and carbonic acid, which readily decomposes to carbon dioxide and water:

$$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3$$

$$H_2CO_3 \rightarrow H_2O + CO_2\,(g)$$

Sodium bicarbonate reacts with acetic acid (found in vinegar), producing sodium acetate, water, and carbon dioxide:

$$NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2(g)$$

Sodium bicarbonate reacts with bases such as sodium hydroxide to form carbonates:

$$NaHCO_3 + NaOH \rightarrow Na_2CO_3 + H_2O$$

Sodium bicarbonate reacts with carboxyl groups in proteins to give a brisk effervescence from the formation of CO_2. This reaction is used to test for the presence of carboxylic groups in protein

Pharmaceutical applications:

It is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules it is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Recently, sodium bicarbonate has been used as a gas forming systems and in floating oral controlled release oral dosage forms of furosemide and cisapride.

Stability and storage conditions:

Sodium bicarbonate powder is stable below 76% relative humidity at 25 and below 48% relative humidity at 4°C. Aqueous solutions of Sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of Sodium bicarbonate by decarboxyation autoclaving, carbon dioxide is passed through the solution in its final container, which is than hermetically sealed and autoclaved aqueous solutions of sodium bicarbonate stored in glass containers may develop deposits of small glass particles. Sodium

bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well closed container in a cool, dry place.

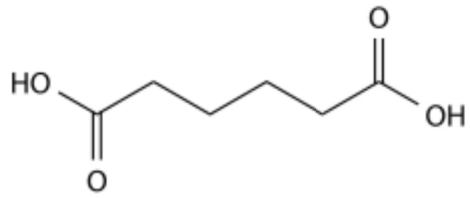
Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many salts, with the evolution of carbon dioxide.

Adipic acid[31]

IUPAC name: hexanedioic acid

Structure



Description:

Adipic acid is the organic compound. It is the most important dicarboxylic acid: About 2.5 billion kilograms of this white crystalline powder are produced annually, mainly as a precursor for the production of nylon. Adipic acid otherwise rarely occurs in nature.

Molecular formula $C_6H_{10}O_4$

Molar mass 146.14 g mol^{-1}

Density 1.36 g/cm^3

Melting point: 152.1 °C, 425 K, 306 °F

Boiling point: 337.5 °C, 611 K, 640 °F

Acidity (pK_a): 4.43, 5.41

LD_{50} : 3600 mg/kg (rat)

Pharmaceutical Applications of adipic acid:

By far the majority of the 2.5 billion kg of adipic acid produced annually is used as monomer for the production of nylon by a polycondensation reaction with hexa methylene diamine forming 6, 6-nylon. Other major applications also involve polymers: it is a monomer for production of Polyurethane and its esters are plasticizers, especially in PVC.

In medicine

Adipic acid has been incorporated into controlled-release formulation matrix tablets to obtain pH-independent release for both weakly basic and weakly acidic drugs. It has also been incorporated into the polymeric coating of hydrophilic monolithic systems to modulate the intra gel pH, resulting in zero-order release of a hydrophilic drug. The disintegration at intestinal pH of the enteric polymer shellac has been reported to improve when adipic acid

was used as a pore-forming agent without affecting release in the acidic media. Other controlled-release formulations have included adipic acid with the intention of obtaining a late-burst release profile

In foods

Small but significant amounts of adipic acid are used as a food ingredient as a flavorant and gelling aid. It is used in some calcium carbonate antacids to make them tart.

Safety: Adipic acid, like most carboxylic acids, is a mild skin irritant. It is mildly toxic, with an LD_{50} of 3600 mg/kg for oral ingestion by rats.

METHYLCRYSTALLINE CELLULOSE[31]

Non-proprietary names

BP: Microcrystalline cellulose

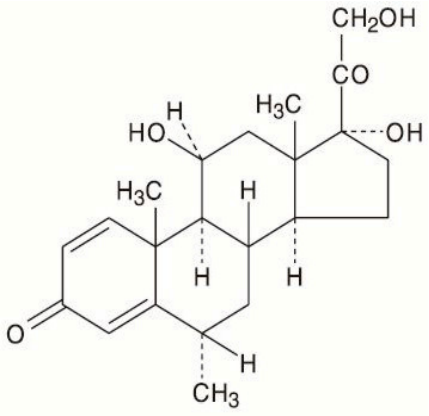
Ph. Eur. Cellulosum microcrystallinum

USPNF: Microcrystalline cellulose

Synonyms: Avicel; Cellulose gel; crystalline cellulose; E460; Emcocel, Fibrocel; Tables; Vivacel

Empirical formula: $C_6H_{10}O_5$

Structure of microcrystalline cellulose



Category: Tablet disintegrant (5 -15%), adsorbent, tablet and capsule diluents.

Description: The colour of the lactose is white to off-white crystalline particles or powder. MCC is odourless.

Properties:

Density: 1.540 to 1.589 g/cm3

Solubility: Practically insoluble in chloroform, Ethanol and 1 in 4.63 g of Water

Stability and Storage: Under humid conditions (80% and above) mould growth may occur. MCC may develop a brown coloration on storage, there action is accelerated by Warm and damp conditions. It should be sorted in a well closed container in a cool, dry place.

Safety: It is regarded as a non-toxic and non-irritant material. Adverse reactions may be seen in persons with deficiency of intestinal enzyme lactase.

LACTOSE[34]

Synonyms: Aero flow, fast flow, flow lac, milk sugar

Empirical formula **:** $C_{11}H_{22}O_{11}.H_2O$

Functional category **:** Tablet and capsule diluents and channeling agent

Applications in pharmaceutical technology:

Lactose is widely used as filter diluents in tablets, capsules and to a more limited in lyophilized products and infant-feed formulas.

Direct compression grades are generally composed of spray-dried lactose, which contains specially prepared pure lactose monohydrate along with a small amount of amorphous lactose.

Description: white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet taste.

Physical properties:

Bulk Density : 0.62 g/cm3

Tapped density: 0.94 g/cm3

True density: 1.522 g/cm^3

Specific rotation: + 52° to +52.6°

Solubility : highly soluble in water, practically insoluble in chloroform, ethanol, and ether.

Stability and storage conditions:

Lactose may develop a brown coloration on storage, the reaction being accelerated by warm dap conditions. Lactose should be stored in a well-closed container in a cool, dry place.

XANTHAN GUM[29,32]

Non-proprietary: USPNF: xanthan gum

Synonyms: Corn sugar gum; E415; Keltrol; Merezan; polysaccharide B-1459; Rhodigel; xanthan gum

Emperical formula: The USPNF XVII describes xanthan gum as a high molecular weight

polysaccharide gum. It contains D- glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

Molecular weight: 2 × 106

Functional category: stabilizing agent, suspending agent, viscosity-increasing agent.

Description: xanthan gum occurs as a cream or white-coloured, odorless, free flowing, and fine powder.

Typical properties:

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

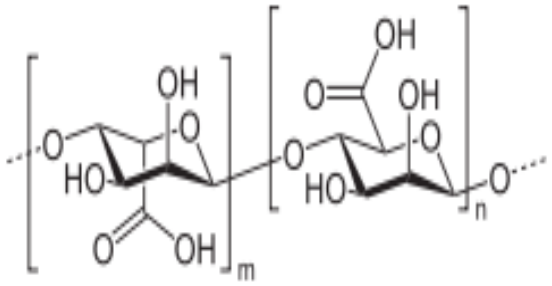
Viscosity: 1200 -1600 mPa s (1200 – 1600) for a 1% w/v aqueous solution at 25°C.

Stability and storage condition: Xanthan gum is a stable material. Aqueous solutions are Stable over a wide pH range (pH 3 – 12)

Safety: xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as non-irritant at the employed as pharmaceutical excipients.

SODIUM ALGINATE[32,33]

Structure:



It is a linear copolymer with homopolymeric blocks of (1-4)-linked β-D-mannuronate (M) and its C-5 epimer α-L-guluronate (G) residues, respectively, covalently linked together in different sequences or blocks

Molecular formula: $(C_6H_8O_6)_n$

Molar mass: 10,000 - 600,000

Density : 1.601 g/cm^3

'Acidity (pK_a): 1.5-3.5

Description: **Alginic acid**, also called **algin** or **alginate**, is an anionic polysaccharide. The chemical compound **sodium alginate** is the sodium salt of alginic acid, Its colour ranges from white to yellowish-brown. It is sold in filamentous, granular or powdered forms.

Viscosity: It distributed widely in the cell walls of brown algae, where it, through binding water, forms a viscous gum. In extracted form it absorbs water quickly; it is capable of absorbing 200-300 times its own weight in water.

Application in pharmaceutical formulation or technology:

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulation sodium alginate may be used as both binder and disintegrates it has been used as a diluents in capsule formulation.

Sodium alginate has also been used in preparations of sustained release oral formulations since it can delay the dissolutions of a drug from tablets capsules and aqueous suspensions.

In topical formulations sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.

TALC[33]

Talc is a mineral composed of hydrated magnesium silicate with the chemical formula $H_2Mg_3(SiO_3)_4$ or $Mg_3Si_4O_{10}(OH)_2$. Soapstone is a metamorphic rock composed predominantly of talc.

Synonym: Magsil Osmanthus, powder talc, purified French chalk, purtalc, oapstone; Steatite

Empirical formula: $Mg(Si2O5)_4(OH)_4$

Category Silicate mineral, anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

Description: talc is very fine, white to grayish- white coloured, odourless, crystalline powder. It adheres to the skin, is soft to the unch and free from grittiness.

Chemical formula $Mg_3Si_4O_{10}(OH)_2$

Crystal symmetry Either monoclinic 2mr triclinic

Identification:

Colour: Light to dark green, brown, white

Crystal habit: Foliated to fibrous masses, rare as platey to pyramidal crystals

PROPERITIES:

Density: 0.536 – 0.862 gm/cm^3

pH: 6.5 – 10 for a 20% w/w aqueous dispersion

Solubility: practically insoluble in dilute acids, alkalies, organic solvents and water.

Storage and Stability: Talc is stable material and may be sterilized by heating at 1600°C for not less than 1 hrs. It may also be sterilized by exposure to ethylene oxide or gamma irritation. Talc should be stored in a well-closed container in a cool, dry place.

Applications of talc:

- Talc is also used as food additive or in pharmaceutical products as a glidant. In medicine talc is used as a pleurodesis agent to prevent recurrent pleural effusion or pneumothorax.

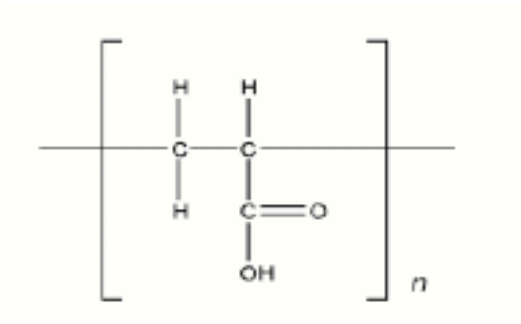
- Talc is used in many industries such as paper making, plastic, paint and coatings, rubber, food, electric cable, pharmaceuticals, cosmetics, ceramics, etc. A coarse grayish-green high-talc rock is soapstone or steatite and has been used for stoves, sinks, electrical switchboards, crayons, soap, etc.
- It is often used for surfaces of lab counter tops and electrical switchboards because of its resistance to heat, electricity and acids.
- Talc finds use as a cosmetic (talcum powder), as a lubricant, and as filler in paper manufacture. Talc is used in baby powder, an astringent powder used for preventing rashes on the area covered by a diaper (see diaper rash). It is also often used in basketball to keep a player's hands dry. Most tailor's chalk is talc, as is the chalk often used for welding or metalworking.
- Talc is widely used in the ceramics industry in both bodies and glazes. In low-fire art ware bodies it imparts whiteness and increases thermal expansion to resist crazing.

Safety

- Talc powder is a household item, sold globally for use in personal hygiene and cosmetics and used by many millions every year. Some suspicions have been raised about the possibility its use promotes certain types of diseases, mainly cancers of the ovaries and lungs.
- The studies reference, by subject: pulmonary issues, lung cancer, skin cancer and ovarian cancer. One of these, published in 1993, was a US National Toxicology Program report, which found that cosmetic grade talc containing no asbestos-like fibres was correlated with tumour formation in rats (animal testing) forced to inhale talc for 6 hours a day, five days a week over at least 113 weeks. A 1971 paper found particles of talc embedded in 75% of the ovarian tumors studied
- The US Food and Drug Administration (FDA) considers talc (magnesium silicate) to be generally recognized as safe (GRAS) for use as an anti-caking agent in table salt in concentrations smaller than 2%.

CARBOPOL[29,33]

Structure:



Carbopol-934, a synthetic high molecular weight, non-linear polymer of acrylic acid cross-linked with polyalkenyl polyether with average molecular weight 3×106 Daltons. It contains not less than 56% and not more than 68% of carboxylic acid (-COOH) groups.

Synonym: Acritamer, Acrylic acid polymer carboxyl vinyl polymer

Non proprietary names:

BP : carbomer,

USP: carbomer

Chemical name: carboxyl polymethylene

Empirical formula: (C_3HO) (-C H -Sucrose)

Category: Bioadhesive, Emulsifying, suspending & viscosity enhancing agent, tablet binder and release-modyfing agent

Description: white, fluffy, acidic, hygroscopic powder with a slight characteristic odour

Solubility: After neutralization with alkali hydroxides or amines, soluble in water, in ethanol (96%) and in glycerol.

$P^{H:}$ 2.5-3.0 (1% aqueous solution)

Glass transition temperature: 100-105°C

Melting point: Decomposition occurs within 30 min at 260°C

Specific gravity: 1.41

Viscosity: Carbomers disappears in water to form acidic colloidal solutions of low viscosity which when neutralized produce highly viscous gels. 29, 400 to 39,400 cps at 25°C (0.5% neutralized aqueous solution)

Stability and storage: Carbomers are stable, though hygroscopic materials and can be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency.

Applications: It is used as thickening, emulsifying and gelling agent. It is used as a tablet binder and matrix forming agent in sustained – release formulations affording zero- to near – zero – order release. It is used as the bioadhesive component in muco adhesive ointments, gels and tablets.

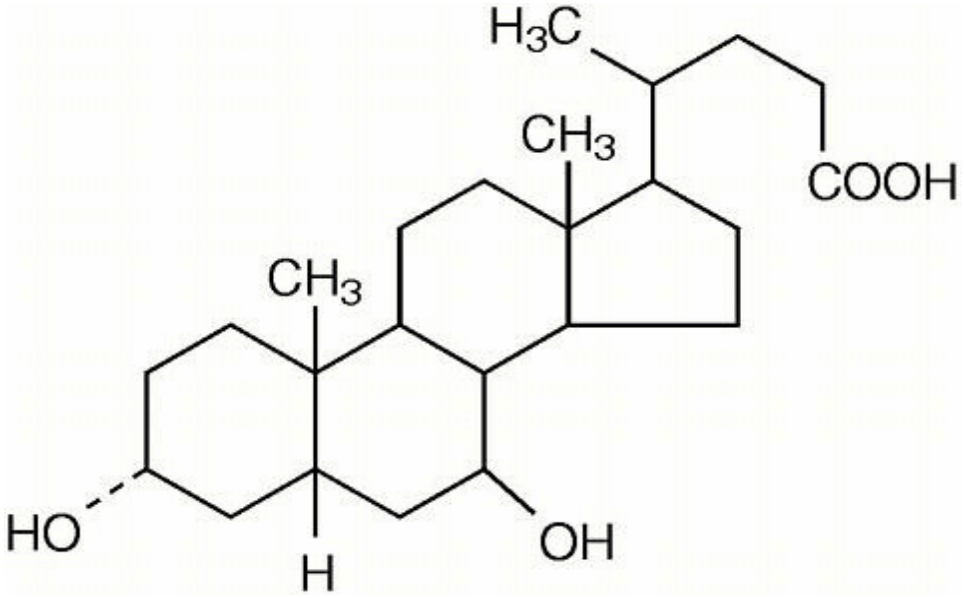
Safety: Carbomers are regarded as nontoxic and non irritant.

MAGNESIUM STERATE[33]

Synonyms: magnesium octadecanoate, stearic acid magnesium salt

Empirical formula: C_{36} H_{70} MgO_4

Structure:



Molar mass 591.34

'**Functional category**: Tablet and capsule lubricant

Description: Magnesium stearate is a fine; white precipitated or milled impalpable powder with low bulk density. The powder is greasy to touch and readily adhere to skin.

Bulk density: 0.159 gm/cm
Tapped density: 0.286 gm/ cm
True density: 1.092 gm/cm

Solubility: Slightly soluble in warm ethanol (95%); practically insoluble in ether, and water.
Melting range : 117-150
Applications in pharmaceutical formulation

It is widely used in cosmetics, foods and pharmaceutical formulations. Primary use is as a lubricant in capsule and tablet manufacturing at concentration between 0.25 – 5.0%

Storage conditions: Store in a well closed container in a cool & dry place
Incompatibility: Magnesium stearate is incompatible with strong acids, alkalis and iron salts. It cannot be used in products containing most alkaloidal salts. Aspirin, certain vitamins and most alkaloidal salts.

Safety: It is widely used as a pharmaceutical excipient and is regarded as non-toxic for oral administration. Oral consumption in large amount may result in laxative effect or mucosal irritation.

Handling precautions: Eye protection and hand gloves are recommended. Magnesium stearate should be handled in a well- ventilated environment, a respirator mask is recommended.

5. METHODOLOGY

All the material used was of pharmaceutical or analytical grade (PR/AR)

Table – 2 Chemical and Excipients used

Name of chemicals	Received from
Cefiximetrihydrate	Hyderabad
Chitosan	Hyderabad
Sodium alginate S.D. Fine chemicals,	Mumbai
Adipic acid S.D. Fine chemicals,	Mumbai
Crosscarmellose sodium Rajesh chemicals	Mumbai
Sodium bicarbonate S.D. Fine chemicals,	Mumbai
Talc S.D. Fine chemicals	Mumbai
Magnesium stearate S.D. Fine chemicals	Mumbai
Xantham gum	Mumbai
Carbopol934 Hi Media Chem. Pvt. Ltd	Mumbai

Table-3 List of instruments/equipments used

Name of instruments/ equipments	Source
Electronic Balance BT 220H	Shimadzu, Japan
UV visible spectrophotometer	Shimadzu1800
Compression machine	RimekMinipress II MT
FTIR	Perkin Elmer 1600 series
Dissolution test apparatus	EletrolabTDT-06
Friability Test Apparatus	020334 -Veego Digital
Hardness tester	Pfizer
Verniercaliper	Aerospace
Stability Chamber	Thermal Lab, Mumbai
Thickness tester	Screw Gauze

Analytical methods for the estimation of Cefixime:

Detection of *Absorption Maxima (max):* The samples of the standard solution were scanned between 200-400 nm regions on Schimadzu 1800 UV spectrophotometer. The absorption maximum for 0.1N HCL was found to be 288nm

Preparation of standard calibration curves:

The standard calibration curve for Cefixime was prepared by using Methanol and 0.1N HCL

Calibration curve for the estimation of Cefixime in methanol

In this method, the drug Cefixime was dissolved in little amount of methanol to get the clear solution, volume was adjusted with methanol. Then the maximum absorbance was measured at 288nm. Bear's law obeyed in the concentration range 3 to 15 mcg/ml

Standard solution:

Dissolve 50 mg of Cefixime in few ml of methanol in 50 ml volumetric flask. The volume was adjusted to 50 ml methanol

Stock solution

The resultant solution subsequently diluted with methanol to get concentration of 3, 6, 9, 12 and 15 mcg/ml. the absorbance of above said concentration solution was measured at 290 nm using methanol as blank. The concentration of Cefixime solution and corresponding absorbance

Calibration curve for the estimation of Cefixime in 0.1N HCl:

In this method the drug Cefixime was dissolved in little amount of 0.1N HCl to get a clear solution. Volume was adjusted with 0.1N HCl. Then maximum absorbance was measured at 288nm, bear's law obeyed in the concentration range3 to 15 mcg/ml.

Reagents: Cefixime, 0.1N HCl

Standard solution

Dissolve 50 mg of Cefixime in few ml of 0.1N HCL in 50 ml volumetric flask. The volume was adjusted to 50 ml with 0.1N HCL

Stock solution:

The resultant solution is filtered with Whatman filter paper subsequently diluted with 0.1N HCl get concentration of 3, 6, 9, 12 and 15 mcg/ml the absorbance of above said concentration solution was measured at 288nm using0.1N HCl as blank. The concentration of Cefixime solution and corresponding absorbance

Table-4 Standard calibration data of cefixime in methanol

Concentration (mcg/ml)	Absorbance
0	0
3	0.127
6	0.265
9	0.368
12	0.512
15	0.628
18	0.756

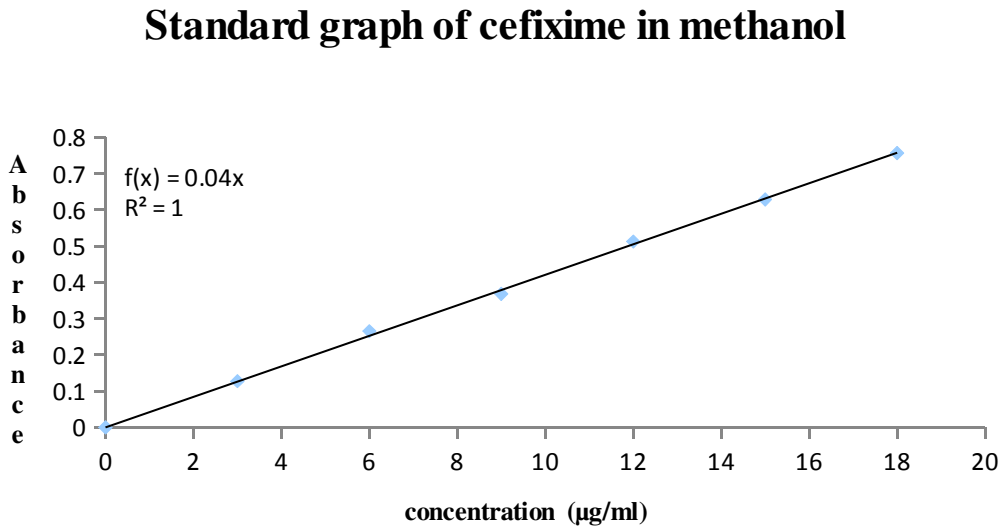


Fig-9 Standard calibration data of cefixime in 0.1 N HCL

Table-5 Absorbance values for standard Cefixime in Hcl

Concentration (mcg/ml)	Absorbance
0	0
3	0.138
6	0.265
9	0.378
12	0.512
15	0.656
18	0.834

Standard calibration data of cefixime in 0.1 N HCL

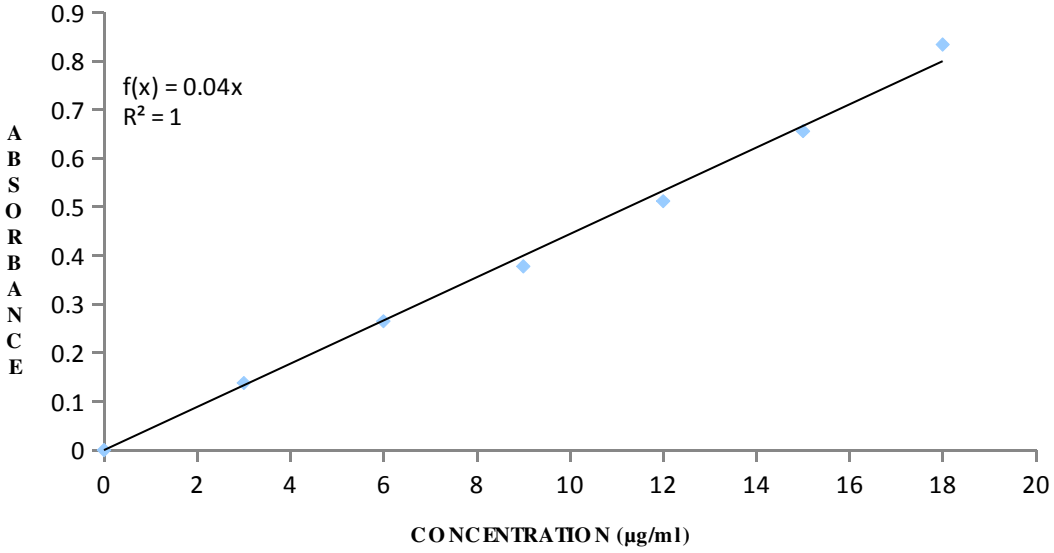


Fig-10 Standard calibration data of cefixime in 0.1 N HCL

Preformulation study:

Almost all the drugs which are active orally are marketed as tablets capsules or both. Prior to development of dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of the subsequent events and possible approaches in formulation development.

Preformulation study of Cefiximetrihydrate

Physiochemical properties of Cefiximetrihydrate

Official status official in USP and BP

Description: Cefixime is off-white to pale yellow powder

pH: pH measured by calibrated pH meter of a solution containing the drug equivalent of 0.7 mg per ml in water.

Identification tests

UV Spectrum: Cefixime in methanol shows maximum absorbance at 289.2 nm similar to reference spectrum

IR spectrum: The IR spectra is concordant with the reference spectrum of Cefixime

Melting point: The melting point of Cefixime was determined by capillary method

Preparation of 0.1N HCl: 0.1N HCl was prepared according to IP 1996. A quantity of 8.5 ml of HCl was diluted with fresh distilled water to produce 1000 ml.

Evaluation of dry mixed powder for precompressional parameters

Pure Cefixime and its physical mixture with different excipients as mixed in different formulas from F1 to F10 were evaluated for angle of repose, bulk density, tapped density, Hausner ratio, Carr's index, degree of homogeneity of blend.

Angle of repose

Angle of repose is the angle of inclination, formed to the flat surface by the bulk powder when it is allowed to flow under gravitational force from a fixed height. It is a characteristic of dry mixed powder flow properties.

The angle of repose of pure Cefixime and prepared mixture was determined by fixed funnel method

$$\Theta = \mathrm{Tan}^{-1} h/r$$

Θ = Angle of repose

h = Height of granules above the flat surface

r = Radius of the circle formed by the granule

Bulk density:

Bulk density is the ratio of mass to volume of material. Bulk density of pure Cefixime and prepared mixture was determined by pouring pre-weighed powder in to a graduated cylinder. Bulk density was determined by measuring poured volume of powder and mass of powder used.

$$P_b = M / V_b$$

Where,

P_b =Bulk density

V_b = Volume of bulk

b

M = Mass of powder.

Tapped density: Tapped density was determined by placing a known mass of mixed powder into the graduated cylinder and which is operated for fixed number of taps (100) until the powder bed volume has reached a minimum. Then by measuring the volume, tapped density was determined by using the formula.

$$Pt = M / Vt$$

Where,

Pt = Tapped density

Vt- Tapped volume

Hausner ratio

It is a simple index that can be determined on small quantity of powder and flow properties of powder may be interpreted. It was calculated by using

$$\text{Hausner ratio} = TBD / LBD \times 100$$

Carr's index:

It is a simple index that can be determined on small quantity of powder and flow properties of powder may be interpreted.

Carr's index = *TBD- LBD/ LBD×100*

Excipients Compatibility study

FTIR studies: The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of the excipients. Excipients are added to facilitate administration, promote the consistent release and bioavailability of drug. It's necessary to study the compatibility of excipients with drug. Here IR spectroscopy was used to investigate and predict any physicochemical interaction between components in a formulation and to the selection of suitable compatible Excipients selection of suitable compatible Excipients

FTIR studies were conducted and the spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1} . The procedure consisted of, dispersing a sample (drug alone, and mixture of drug and polymers in KBr and compressing into discs by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained.

Differential Scanning Colorimetry:

DSC scan of about 5mg, accurately weighed Cefixime and formulation F10 were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 50-300°C

METHOD OF PREPARATION

Preparation of Floating tablets of Cefixime[15, 18]

According to the present invention, the controlled gas powered system (CGPS) includes a swelling agent carbopol and a gel forming polymer. Together these agents form a hydrated gel matrix. The CGPS further contain sagas generating component such that a gas is

generated in a controlled manner and is entrapped in hydrate gel matrix.. The gas generated by sodium bicarbonate also causes matrix expansion. However, in the present invention, swelling of matrix is controlled by the viscolyzing agent (xanthangum), which acts both as swellability and release controlling agent. The gas generating component sodium bicarbonate interacts with an acid source citric acid by contact with gastric fluid to generate carbondioxide that gets entrapped within the hydrated gel matrix of the swelling composition. In the present invention, it has found that a xanthan gum helps in maintaining tablet integrity, when stirred in aqueous medium. The sodium alginate gel forming polymer cross-links with time to form a stable structure which entraps the generated gas. Thus, with the passage of time, the gel forming polymer results in hydrodynamically balanced system whereby the matrix system is retained in the stomach for extended period of time. Simultaneously, the viscolyzing agent and gel forming polymer provide a tortuous diffusion pathway for the drug there by resulting in controlled drug release. The hydrophilic polymers are useful in the present invention in modifying the rate of release of the drug from tablet. Various concentrations of Chitosan were reported to have duration of buoyancy of more than 8 hours in the simulated meal medium, as well as in distilled water.

In order to retain the dosage form in the stomach for a long period of time and to avoid erosion and dissolution, xanthan gum and Carbopol were used as a gelling agent in combination with Chitosan to retard the drug release. The hydrophilic polymers such as carbopol, chitosan are used in the present invention in modifying the rate of release of the drug from the tablets. Sodium bicarbonate ($NaHCO_3$) was incorporated in the formulation in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form. Lactose

was included in formulation as hydrophilic agent, with assumption that capillary action of lactose may facilitate higher drug release without affecting the matrix (floating ability), the incorporation of lactose showed appropriate release and floating time. In all the formulations designed weight of a single tablet was kept constant. The weight of a single tablet was 600 mg.

Table-6 METHOD OF PREPARATION-FORMULA

Preparation of Floating tablet of Cefiximetrihydrate

INGREDIENTS	**F_1 mg**	**F_2 mg**	**F_3 Mg**	**F_4 mg**	**F_5 Mg**	**F_6 mg**	**F_7 mg**	**F_8 mg**	**F_9 mg**	**F_{10} mg**
Cefixime	400	400	400	400	400	400	400	400	400	400

$NaHCO_3$	20	30	40	40	50	50	60	70	70	80
Na alginate	10	20	10	20	20	20	--	10	--	10
Chitosan	10	--	10	10	20	20	20	20	25	25
Carbopol	30	25	20	20	20	20	10	10	10	10
MCC	30	30	30	20	20	--	10	20	10	--
Xanthan gum	10	10	--	--	10	10	20	--	20	10
Lactose	40	35	30	30	20	20	20	20	15	15
Adipic Acid	10	10	10	10	10	10	10	10	10	10
Talc	10	20	10	20	-	20	20	10	10	10
Mg stearate	30	30	30	30	30	30	30	30	30	30

Evaluation of post-compressional parameters of tablets

Weight variation:

Twenty tablets were selected at random and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

Uniformity of weight:

Table-7 IP Standards for uniformity of weight

The values of average weight are given in above Table 7 and are in within limit

Sr. No	Average weight of tablet	Percentage of deviation
1	<80mg	10
2	80 – 250 mg	7.5
3	>250mg	5

Hardness: Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. A tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded in kg/cm.

Friability: Tablets require certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacturing, packaging, and shipping. A pre-weighed sample (20 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets and % friability was calculated using the formula

$$F = 1 - W_o / W \times 100$$

Where
W_o=Weight of tablet before test

W= Weight of tablet after test

Drugs content:

To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, 10 tablets were crushed using mortar pestle. Quantity equivalent to 100 mg of drug was dissolved in 100 ml Methanol, filtered and diluted up to 50µg/ml, and analyze spectrophotometrically at 290.00.nm. The concentration of drug was determined using standard calibration curve

Buoyancy determination:

The buoyancy test of tablet was studied by placing them in 200 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900ml 0.1N HCl, maintained at 37±0.5°C and agitated at 50 rpm. The floating onset time

(time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation

***In-vitro* dissolution study:**

The in vitro dissolution test was performed using USP type II dissolution test apparatus. The drug release study was carried out in 0.1 N HCl for 12 hrs in900 ml of dissolution media, maintained at 37±0.5°C and agitated at 100 rpm. Periodically 5 ml samples were withdrawn and filtered through Whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The concentration of Cefixime was measured spectrophotometrically at 288 nm. Percentage drug release was calculated using an equation obtained from a standard curve. Analysis of data was done by using 'PCP Disso V-3' software; India. The graphs of times vs. percentage release were plotted. To ascertain the order and mechanism of drug release the in vitro release data was subjected to various kinetic equations

Treatment of dissolution data with different kinetic equations

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into ***Zero order, First order, Higuchi matrix, Peppas release model***. Based on the r-value, the best-fit model was selected

Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$$Q_t = Q_o K_o t$$

Where

Q_t= amount of drug dissolved in time t

Q_o = initial amount of the drug in the solution and

K_0= zero order release constant

t = time in hours

It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

First order kinetics: To study the first order release rate kinetics, the release rate data were fitted to the following equation

$$\text{Log } Q_t = \log Q_o K_o t / 2.303$$

Where,

Q_t =the amount of drug released in time t

Q_o=the initial amount of drug in the solution

K_o is the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q = K_H t^{1/2}$$

Where

Q= cumulative amount of drug release at time "t"

K_H = Higuchi constant

t = time in hours

The Higuchi equation suggests that the drug release by diffusion.

Korsmeyer-peppas method:

Korsmeyer – peppas equation is

$$F = (M_t / M) = K_m t^n$$

Where

F = Fraction of drug released at time't'

M_t= Amount of drug released at time't'

M = Total amount of drug in dosage form

K_m= Kinetic constant

n = Diffusion or release exponent

t = Time in hours

'n' is estimated from linear regression of log (M_t/M) versus log t

If n = 0.45 indicates fickian diffusion

0.45<n<0.89 indicates anomalous diffusion or non-fickian diffusion.

Swelling characteristics (Water uptake study):

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37 ± 0.5°C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. (Table 6) Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation.

% WU = Weight of swollen tablet – initial wt of tablet/ initial wt of tablet × 100

Stability studies:

Short-term stability studies were performed at a temperature of 45°±1°C over a period of three weeks (21 days) on the promising CGPS tablet formulation F10 Sufficient number of tablets (10) were packed in amber coloured screw capped bottles and kept in hot air-oven maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *in vitro* floating studies were performed to determine the drug release profiles

6. RESULTS

Table-8 Precompressional data

Batch No	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (I_C)	Hausner ratio (H_R)	Angle of repose
F1	0.3432±0.04	0.4165±.05	21.35±0.07	1.21±0.03	24.92±0.08
F2	0.3648±0.06	0.4262±0.03	16.83±0.01	1.16±0.08	29.48±0.10
F3	0.3322±0.04	0.3950±0.04	16.94±0.07	1.18±0.05	25.24±0.17
F4	0.3655±0.05	0.4156±0.06	13.70±0.07	1.13±0.07	26.07±0.18
F5	0.3236±0.01	0.3946±0.01	21.94±0.06	1.21±0.09	22.14±0.14
F6	0.3938±0.06	0.4565±0.07	15.92±0.02	1.15±0.09	28.28±0.11
F7	0.3443±0.04	0.4166±0.04	20.99±0.09	1.20±0.09	30.14±0.13
F8	0.3258±0.06	0.3946±0.04	21.11±0.01	1.21±0.01	24.32±0.15
F9	0.3524±0.05	0.4214±0.08	19.58±0.002	1.19±0.05	21.09±0.12
F10	0.3364±0.06	0.3965±0.12	17.86±0.05	1.17±0.08	24.40±0.15

Preformulation study: Initially, procured raw materials were characterized for given specifications and comply with provided literature value. Physical mixture of cefixime and polymers were prepared and found to be compatible after evauation.

Melting point: Observed melting point of cefixime was found in the range of 240 - 242° C, which comply with given literature value.

Evaluations of dry mixed powder blend for precompressional parameters:

The granulation characteristics are the most important interest to formulation scientist and therefore most universally measured. These basic measurements of the granulation have been used to develop and monitor the manufacture of many successful pharmaceutical dosage forms. Table 4 depicts the powder blend properties of Cefixime floating tablets.

Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of powder blend was found to be between 0.3061 ± 0.04 to 0.3694 ± 0.04 g/cm3 (Table-8). This indicates good packing capacity of powder blend. Carr's index was evaluated. Interparticulate cohesive properties with angle of repose measurements and the effects of packing geometry of solids with bulk and tapped density were studied. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder consolidates. The degree of consolidation is unique to the powder and ratio of these densities is related to interparticulate friction. This ratio, percent compressibility, was used as an index of flow. Adhesive/cohesive forces of particles are related to flow behaviour. Values of Carr's index below 15% usually show good flow characteristics, but readings above 25 % indicate poor flow ability. Carr's index was found to be between 14.89 ± 0.03 to 21.06 ± 0.11. Hausner's ratio is simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed in Hausner's ratio that indicates good flowing ability. Many different types of angular properties have been employed to assess flowing ability. Angle of repose is suited for particles >150µm

Angle of repose of 30° generally indicate the free flowing material and angle of 40° suggest a poor flowing material. The angle of repose is indicative of the flowing ability of the material.

The angle of repose of all the formulations fell within the range of 19.09 ±0.017 to 29.24 ± 0.09 i.e. granules were of good flow properties.

Excipients compatibility study

DIFFERENTIAL SCANNING COLORIMETRY

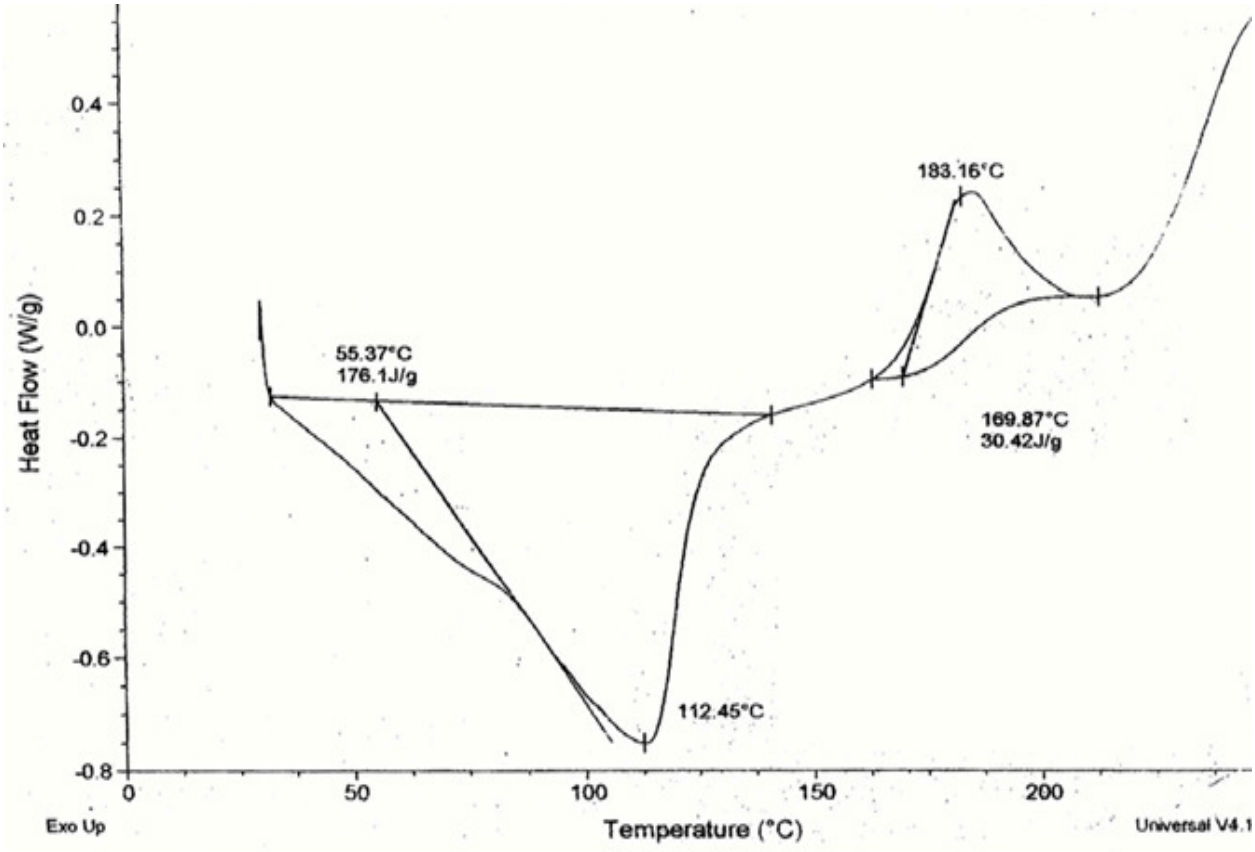


Fig-11 Differential scanning colorimetric study of pure drug cefixime

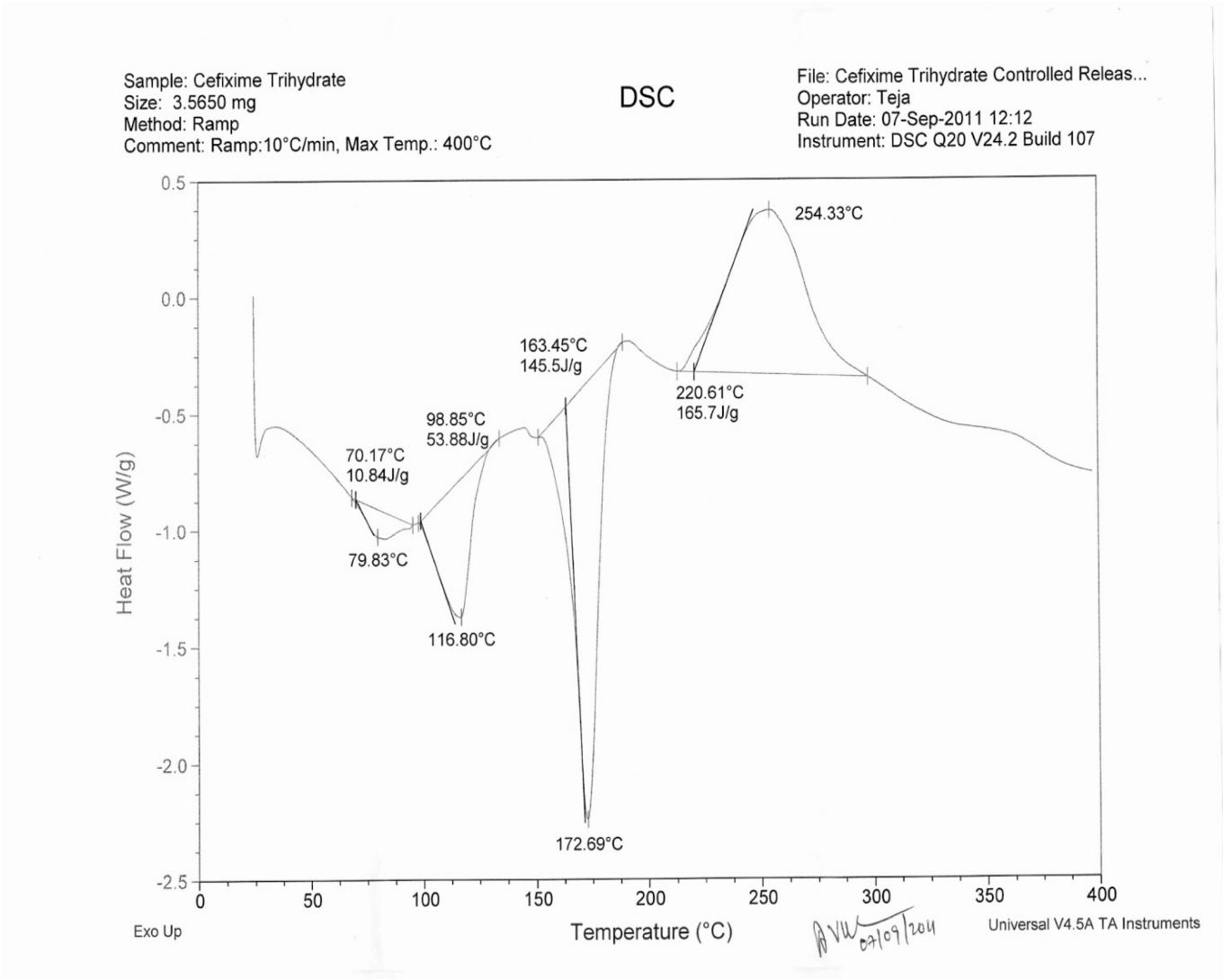


Fig-12 Differential scanning colorimetric study of F9

The floating tablet formulation prepared with Cefixime, chitosan, carbopol, sodium alginate were subjected for DSC studies, wherein formulation product F3 started melting at 85°C and completed at 164°C. This wide range of melting process suggests that formulation F9 is a product of physical mixture of all the constituents mentioned herein, if it is a reaction product which might have formed during the formulation, it would give rise to short range of melting process , which has not happened in this case. This confirms the drug used in the formulation is in the free state rather than in the chemically reacted form. Drug is freely available to the system whenever administered. Similar observation is made with the formulation F10. In this case also, the formulation started melting process, preceded up to185. One can draw the conclusion that, during the process of formulation in this case also, drug and constituents have not undergone any chemical reaction.

FTIR study

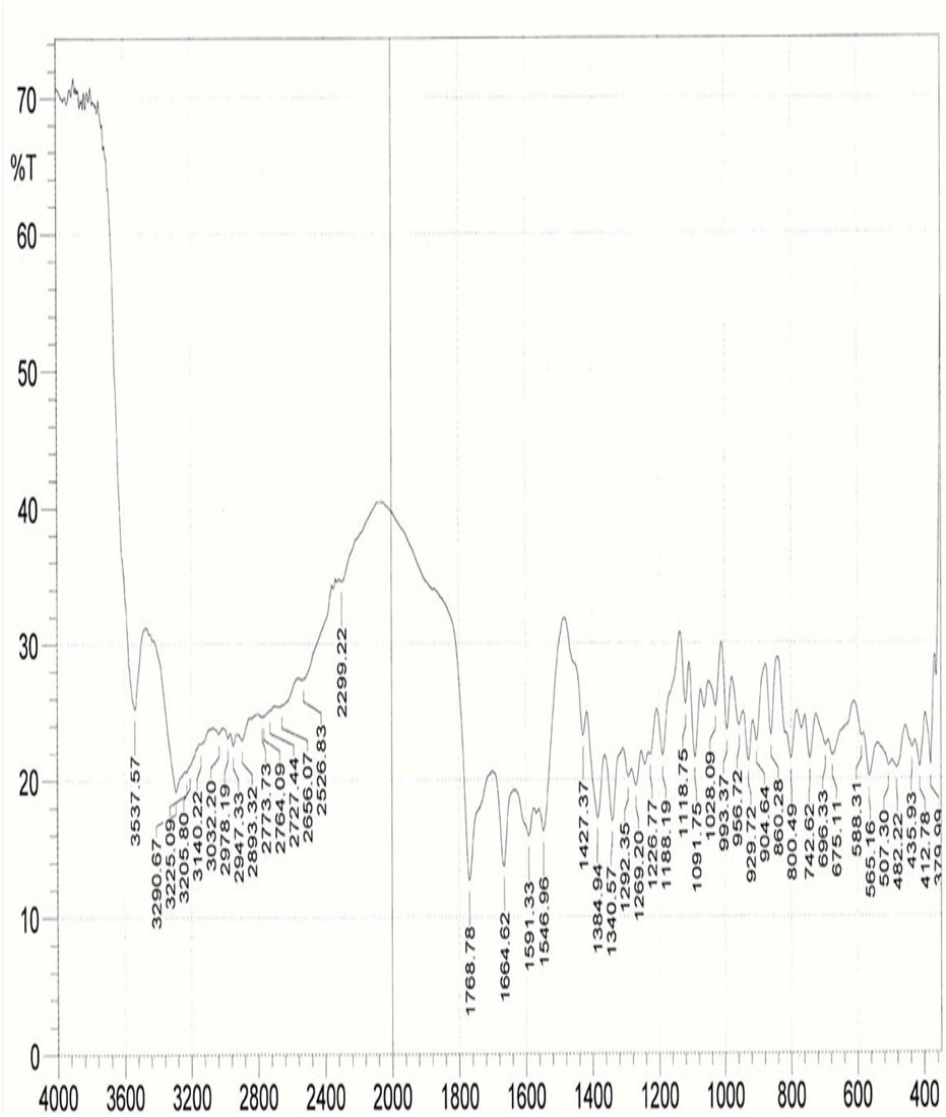


Fig -13 IR spectra of plain Cefixime Trihydrate

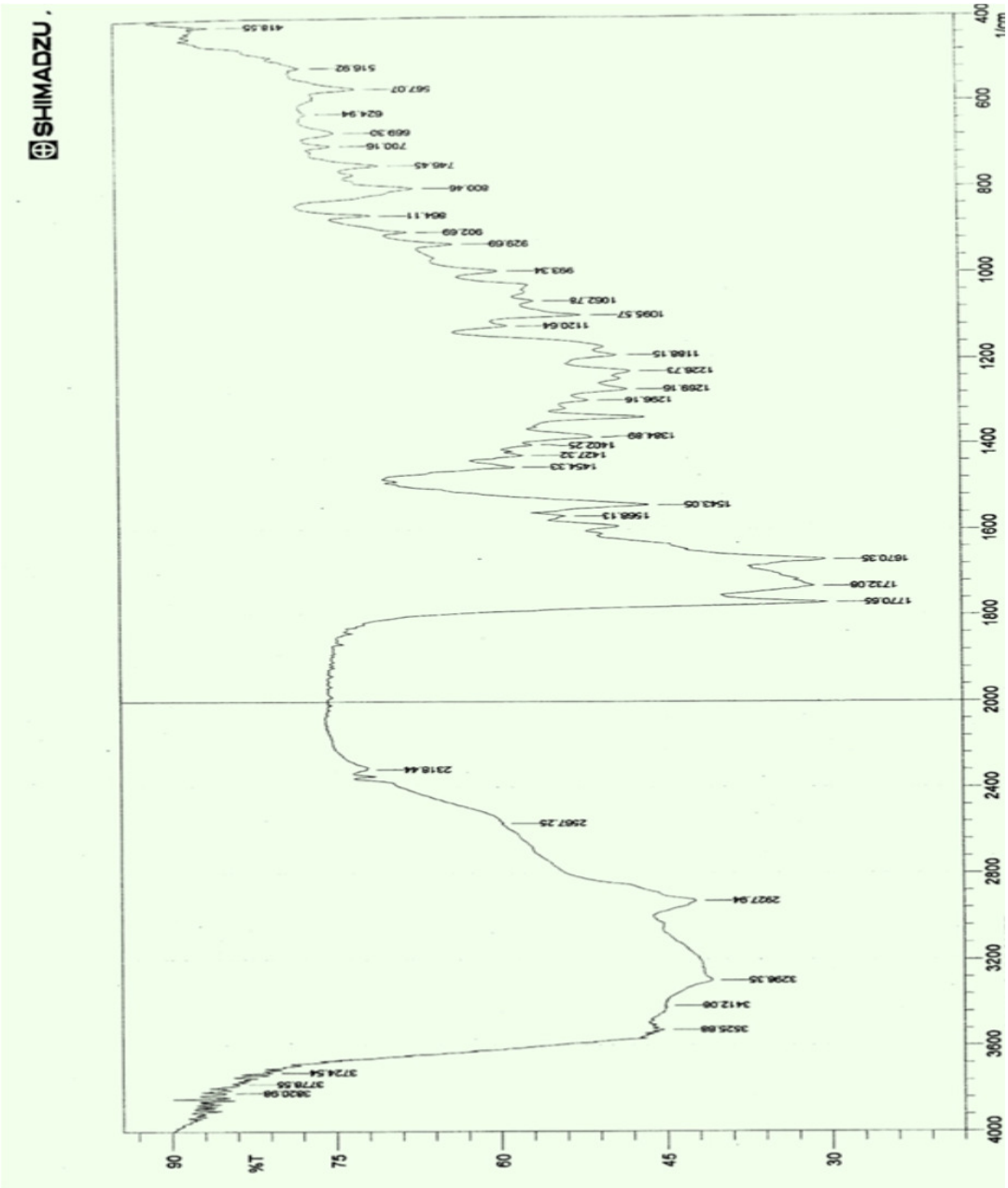


Fig-14 IR SPECTRA OF F8 FORMULATION

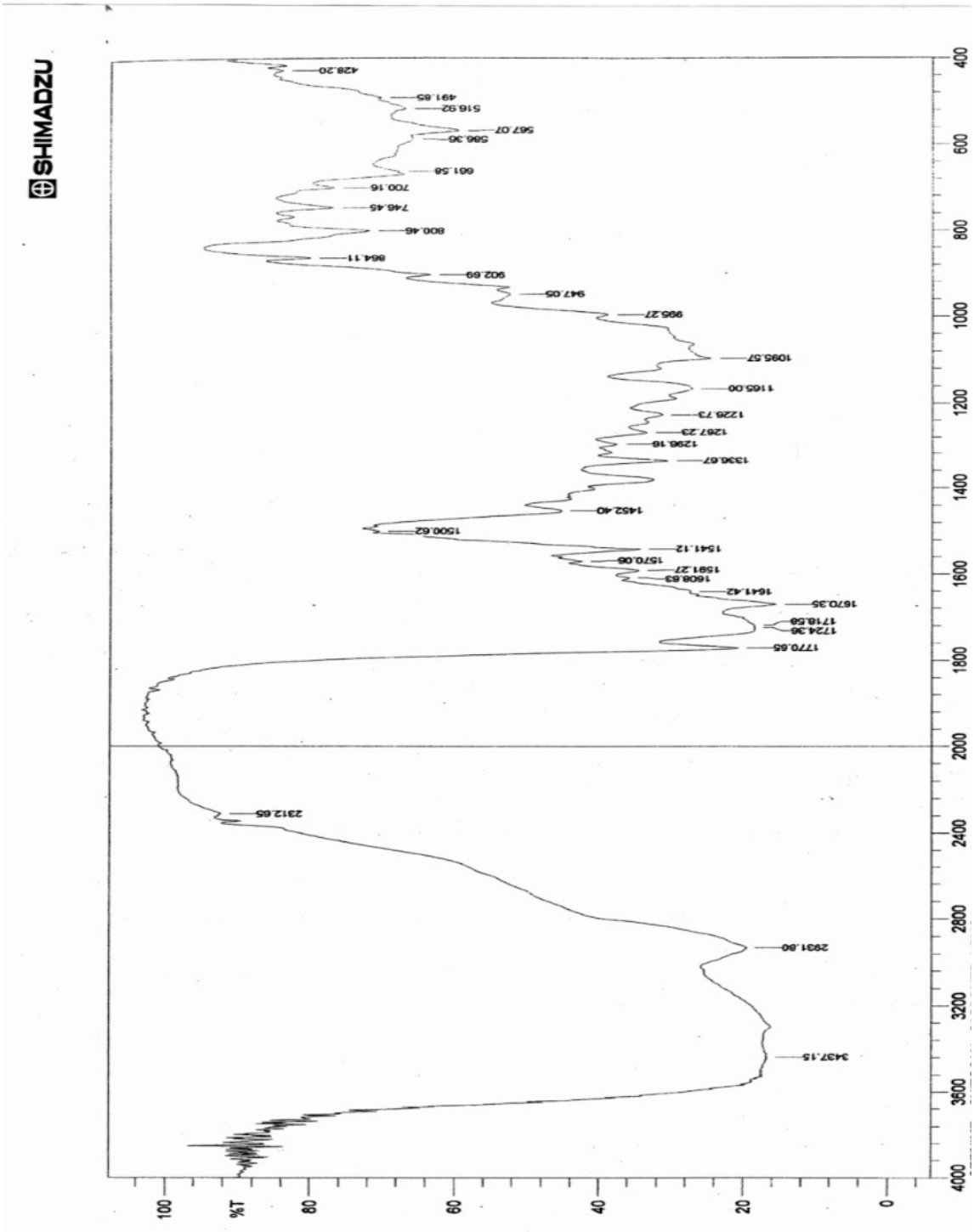


Fig-15 IR SPECTRA OF F9 FORMULATION

FTIR study

In the present study the drug Cefixime is taken for study. This molecule exhibited characteristic NH_3 absorption peak at 3290 cm which is a normal range of absorption of primary amines. The NH of the amide group has shown absorption range at 30 to 25 cm and corresponding the C-H of the aromatic as well as aliphatic functionalities are observed at 3140, 3032, 2978 and 2947 cm. The C=O absorption peak of the carboxylic acid have given rise to an overlapping absorption of two carboxylic acids functional groups. C=O of the amide both cyclic imides and amide are seen at 1664 cm these observations are in concurrence with the structure of the drug molecule. The formulation F9 is carried out with chitosan and the drug has given rise to absorption peaks at 3298 cm as a broad hump corresponding to NH, NH and OH functionalities present in the drug as well as polymer chitosan. Similarly broad peaks are observed at 1700, 1710 and 1600 cm corresponding to the C=O of the drug and polymer molecules. These data suggests that, the formulated product is a mixture of drug and the polymer chitosan but not the reaction product. is taken in which very broad hump is observed at 3420 cm corresponding to the NH the drug and polymer carbopol. Similar broad peaks are observed 1650 cm corresponding to the C=O of carboxylic acids and amide moieties present in the both the components. These observations support the idea that formulated product is a mixture of drug and the polymer but not the reaction product. Even in case of F8, expected broad humps are observed at 3398, 1700 cm corresponding to the NH, NH_2, OH functionalities and COOH, CO functional groups present in the drug suggesting that, this formulation is not a reaction product but it is a mixture of the drug and the polymer.

Evaluation of post compressional parameters of tablet characteristics

The floating tablets of Cefixime were prepared with direct compression technique. The tablets were evaluated for average weight, thickness, hardness, friability and drug content.

Tablet thickness, diameter and hardness

All the formulations were evaluated for various parameters, like thickness, diameter and hardness of all tablets from batch F1 to F10 are shown in table 9. As there was not much variation in thickness of tablets in each formulation, it shows that powder blends were consistent in particle size and uniform behaviour during compression process. Thickness and diameter of tablets of all batches was measured by vernier caliper and there will be no change in thickness and diameter of tablets respectively. Thickness was in range of

4.20±0.04 to 4.50± 0.04. The hardness of tablet was measured on monsanto hardness tester. The hardness was in range of 7 to 9 Kg/cm^2. Tablet hardness reflects differences in tablet density and porosity, which are supposed to result in difference release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet.

Friability of tablet:

The values of friability are given in table 9. The present study of tablets is within the limit and the slight variation in friability is because of the variation in compression force applied and its total weight. The friability of tablets also depends on type of filler and moisture content.

Table-9 Evaluation of post compressional parameters of tablet characteristics

Batch no	Average wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
F1	596	4.20±0.03	12.1±0.05	7.50±0.01	0.78±0.041
F2	600	4.35±0.04	12.08±0.02	8.40±.02	0.77±0.039
F3	597	4.20±0.02	12.05±0.03	9.0±0.04	0.75±0.044
F4	602	4.4±0.04	12.06±0.02	7.0±0.03	0.66±0.039
F5	600	4.30±0.03	12.01±0.01	7.6±0.05	0.76±0.054
F6	604	4.2±0.04	12.05±0.03	8.3±0.06	0.80±0.066
F7	602	4.23±0.03	12.06±0.04	8.1±0.07	0.72±0.042
F8	602	4.33±0.04	12.08±0.02	7.4±0.02	0.81±0.044
F9	601	4.45±0.04	12.07±0.01	7.0±0.03	0.70±0.065
F10	604	4.50±0.04	12.2±0.02	8.8±0.04	0.66±0.039

DRUG CONTENT AND SWELLING INDEX STUDY

Drug content was in range of 96.38 ± 0.12 to 106.44 ± 0.12 indicating good content uniformity in all formulations. That indicates drug was uniformly distributed throughout the tablet.

Swelling index:

Results of water uptake study showed that the order of swelling in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymer was achieved up to 12 hrs and then gradually decreased due to erosion.

The swelling of polymers used in this CGPS tablets (Chitosan, carbopol, sodium alginate) could be determined by water uptake of the tablets

Table-10 Drug Content and Swelling Index Study

The complete swelling was achieved by the end of 12 hrs. The % of swelling of F10 was higher due to increase in the concentration of carbopol which also gives the firm structure to the tablet form.

BATCH NO	Drug content (%)	Swelling index
F1	101.18±0.13	68.42±0.80
F2	108.63±0.12	96.56±0.56
F3	102.71±0.22	34.26±0.23
F4	104.91±0.15	51.68±0.14
F5	102.36±0.14	78.40±0.20
F6	104.73±0.13	46.36±0.20
F7	108.68±0.10	98.20±0.45
F8	109.88±0.21	76.40±0.63
F9	101.38±0.20	111.40±0.86
F10	98.68±0.20	86.23±0.23

IN VITRO BUOYANCY AND LAG TIME STUDY

From the results obtained , it was found that formulation F6 did not float. This was due to the lower percentage of gas generating agent and high concentrations of carbopol polymer. The formulation F2, F5, F6, F7 floated but the lag time was more and floating time is less. For the formulations F7, F8, F9 and F10 the duration of buoyancy was more than 12 hrs, the floating capacity increased in these formulations and floated with less lag time due to high concentration of gas generating agent. It was observed that paddle speed affected the floating properties of tablet. In the study with 200 ml 0.1N HCL without paddle it was found that the floating lag time decreased and the duration increased for the same formulations.

It was seen that as carbopol 934P concentration decreased, the floating capacity increased. F9 floated with less lag time due to high concentration of gas generating agent. It was observed that paddle speed affected the floating properties of tablet However, some results revealed that, as the concentration 0f chitosan increased, total floating time increased, this is because of increased gel strength of matrices, which prevents escape of evolved carbon dioxide from matrices, leading to decreased density of the formulations In the present invention, it has found that a xanthan gum helps in maintaining tablet integrity. As the

amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and at the same time floating lags time decreases.

Fig-16 *In vitro* Buoyancy Study

AFTER 1MIN **AFTER 1HOUR** **AFTER 12 HOURS**

Table-11 Floating ability of various CGPS cefixime tablet formulation

BATCH NO	Floating Lag time (min)	Floating duration (min) Integrity

F1	48	60
F2	60	60
F3	34	480
F4	12	180
F5	10	360
F6	Not floating	Not floating
F7	5	>720
F8	4	>720
F9	4	>720
F10	3	>720

***In-vitro* release study of CGPS floating tablets of Cefixime:**

In-vitro release data of all the formulations were given in table 8.at the end of 6hrs and 12 hrs. The releases of Cefixime from all the formulations were in the range of 38.48 ± 5.34 to 68.18 ± 1.34 at the end of 6 hr and 54.52 ± 0.69 to 97.35 ± 1.09 at the end of 12 hrs. The formulations F1, F2, F3 and F4 which are prepared by using 11% to 15% sodium bicarbonate, mcc 4% to 10%, xanthan gum 5% to 10%, sodium Alginate 5% to 15%, chitosan 5% to 10%, released the drug 66.85 at the end of 12 hrs respectively. The detailed in vitro data were plotted for percentage drug released Vs time The formulations F5, F6, F7, F8 and F9 which are prepared by using 10 to15% sodium bicarbonate, xanthan gum 5% to 10%, sodium alginate 5% to 15%, carbopol 2% to 10%, chitosan 10% to 15% and citric acid 5% released the drug 96.35 at the end of 12 hrs respectively. The detailed data were plotted for percentage drug released Vs time as shown in fig12.

From the dissolution study it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study is carried out up to 12 hrs. The percentage drug release from batch F1 to F10 vary from 54.52 to 97.35%. The results were revealed that as concentration of sodium bicarbonate increases from 50 - 80 mg/tab there is decrease in drug release but lag time decreases as increase in concentration of sodium bicarbonate and duration of floating has been increased with increase in concentration of sodium bicarbonate

Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release. Being water soluble polymers, they dissolve and form pores filled liquid in which drug can there after diffuse in dissolution medium. All the formulations were designed as dosage forms for 12 hrs. The results suggest that therapeutic levels of Cefixime can be delivered in the controlled manner. It may be concluded that, the

CGPS Cefixime tablet formulations F6, F8 and F9 show promising controlled drug release. In other studied the effect gas generating agent on ***In-vitro*** release of drug from floating formulation revealed that, as the concentration of sodium bicarbonate increases from 60 to 80 mg/tablet, drug release decrease, this might be because sodium bicarbonate creates an alkaline environment around the tablet. Formulation containing 60mg sodium bicarbonate showed maximum release when compared to formulation containing 70 mg and 80 mg of sodium bicarbonate shows less drug release at the end of 24 hrs.

Table-12 *In-vitro* % drug release data at the end of 12 hrs from CGPS

BATCH NO	1 hr	2hrs	4hrs	6hrs	8hrs	10hrs	12hrs
F1	7.8±0.6	13.5±0.91	21.88±1.6	35.5±0.8	42.64±0.9	50.93±1.2	62.43±0.23
F2	8.62±0.69	19.25±0.4	29.42±2	40.68±0.9	60.01±1.2	75.28±0.9	80.93±0.2
F3	6.48±0.3	12,26±0.4	25.68±0.5	37.48±3	47.67±2	52.68±4	68.45±0.4
F4	8.96±0.5	15.64±0.6	27.32±0.7	39.86±0.3	56.23±0.7	67.38±0.6	86.85±0.8
F5	7.36±0.2	18.78±0.5	32.68±0.53	43.64±0.6	59.42±0.7	70.42±0.8	83.46±0.6
F6	10.36±0.5	21.68±0.45	36.42±0.3	52.48±0.7	68.68±0.4	84.68±0.8	90.48±1
F7	9.46±0.4	19.88±0.3	31.62±0.2	46.48±0.5	62.32±0.2	79.78±0.6	88.64±0.7
F8	11.43±0.6	23.46±0.5	38.46±0.4	56.54±0.5	72.33±0.4	85.42±0.3	93.51±1
F9	10.48±0.5	28.48±0.6	42.38±0.4	62.26±0.6	83.46±0.7	94.64±0.8	96.35±0.9
F10	11.24±0.2	24.54±0.3	40.44±O.5	59.36±0.6	78.48±0.5	82.36±0.9	84.62±1.2

Fig -17 Percent Drug Released Vs Time Plots of formulations F 1 to F5

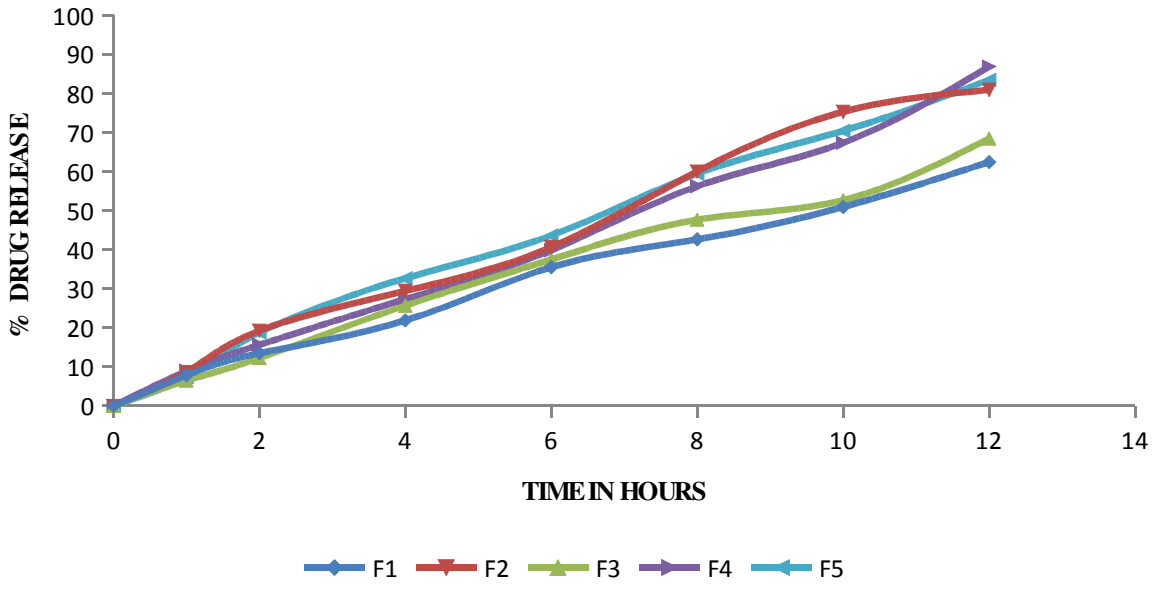
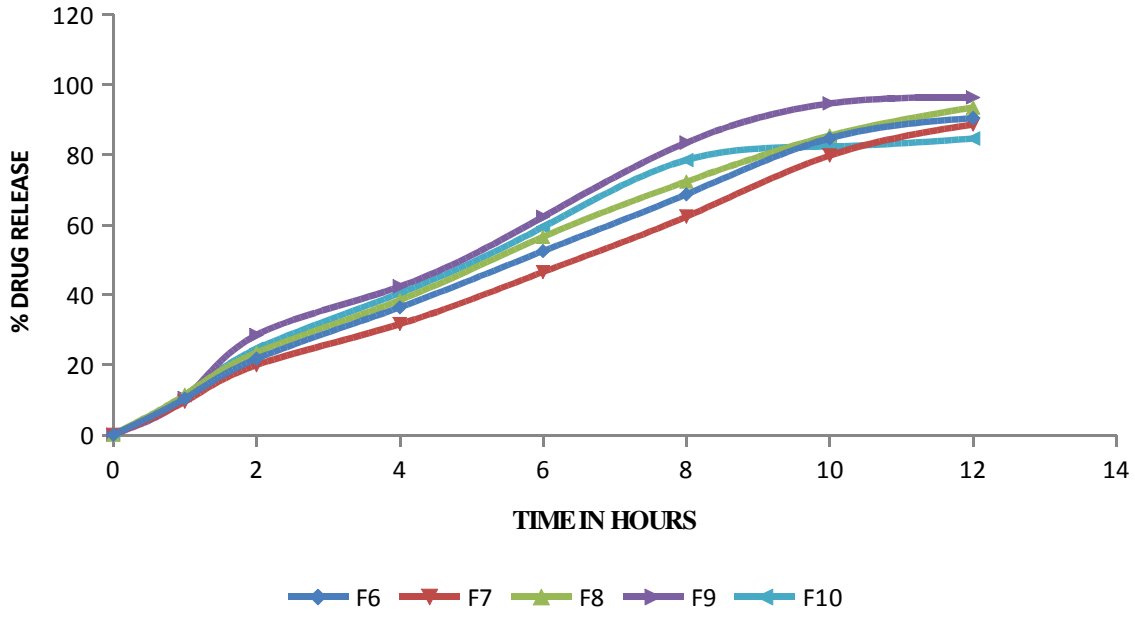


Fig-18 Percent Drug Released Vs Time Plots of formulations F5 to F10



Curve fitting analysis for different formulations

The kinetic data of CGPS Cefixime tablets

The correlation coefficient r values of zero order of all the formulations were in the range of 0.9357 to 0.9823 and first order r values were from 0.9397 to0.9816. Among the 10 formulations some formulations (F3, F5, F6,) release the drug by first order kinetics and some (F1, F2, F4, F7, F8, F9, F10,) release by zero order kinetics.

The results suggest that, the drug was released by mixed order kinetics to ascertain, the drug release mechanism the in-vitro release data were also subjected to Higuchi's diffusion plots and Peppas plots and the correlation coefficient values were in the range of 0.971 to 0.979 and 0.913 to 0.918 respectively. So it confirms that , the calculated r values for Higuchi plot and Peppas plots were nearer to one (1) in all the cases suggesting that drug released by diffusion mechanism

The mean diffusional exponent values (n) ranged from 0.55 to 0.66 indicating that all these formulations presented a dissolution behaviour controlled by Non Fickian Diffusion (When n tends towards< 0.5)

Table-13 Dissolution kinetics

Batch No	Zero order	First order	Higuchi's	Peppa's
F1	0.997	0.985	0.971	0.913
F2	0.994	0.983	0.965	0.908
F3	0.995	0.984	0.968	0.918
F4	0.997	0.972	0.954	0.900
F5	0.997	0.988	0.975	0.903
F6	0.994	0.991	0.969	0.907
F7	0.997	0.994	0.967	0.890
F8	0.992	0.994	0.980	0.871
F9	0.981	0.995	0.978	0.923
F10	0.972	0.995	0.979	0.875

Fig-19 Cumulative percent release Vs Time (Zero order) of Formulations F1, F2, F3, F4, and F5

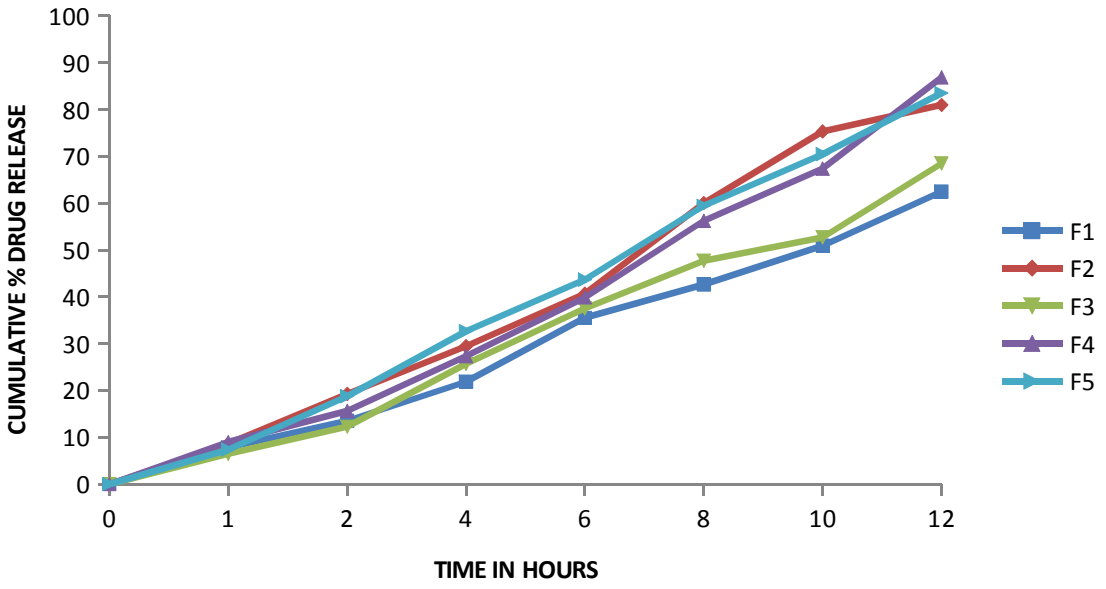


Fig-20 Cumulative percent release Vs Time (Zero order) of Formulations F6, F7, F8, F9 and F10

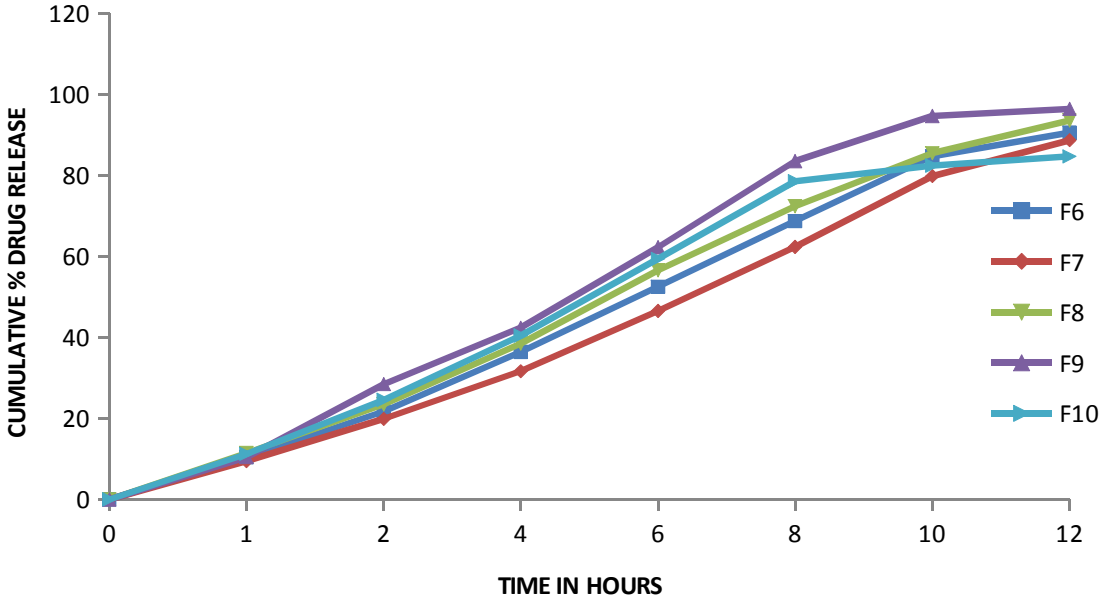


Fig-21 Cumulative percent release Vs Time (First order) of Formulations F1, F2, F3, F4

and F5

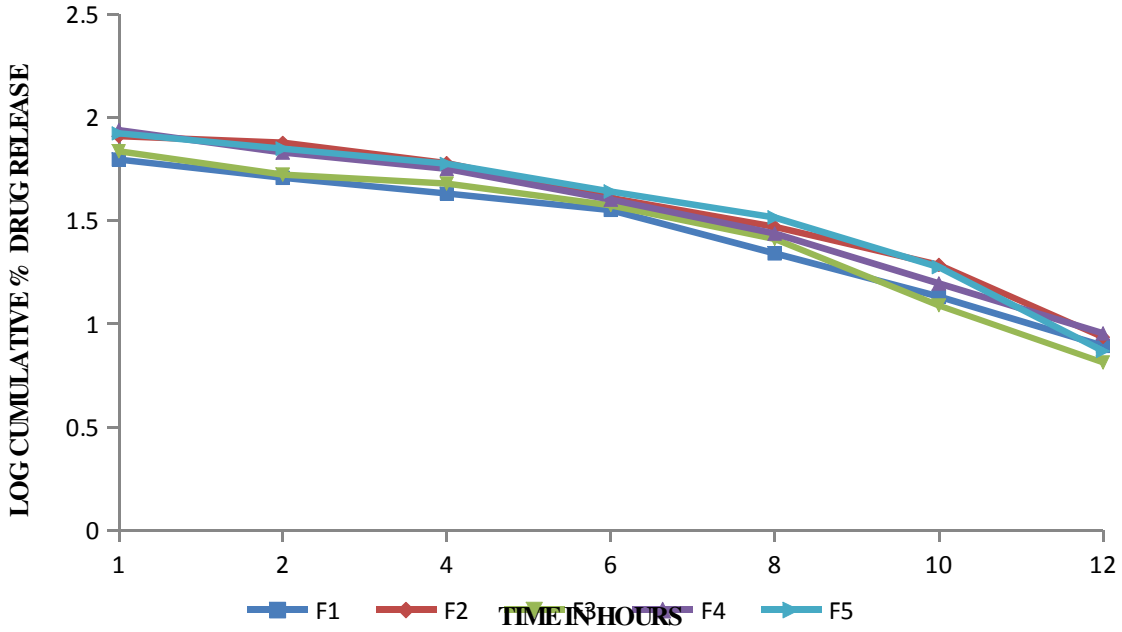


Fig-22 Cumulative percent release Vs Time (First order) of FormulationsF6, F7, F8, F9 and F10

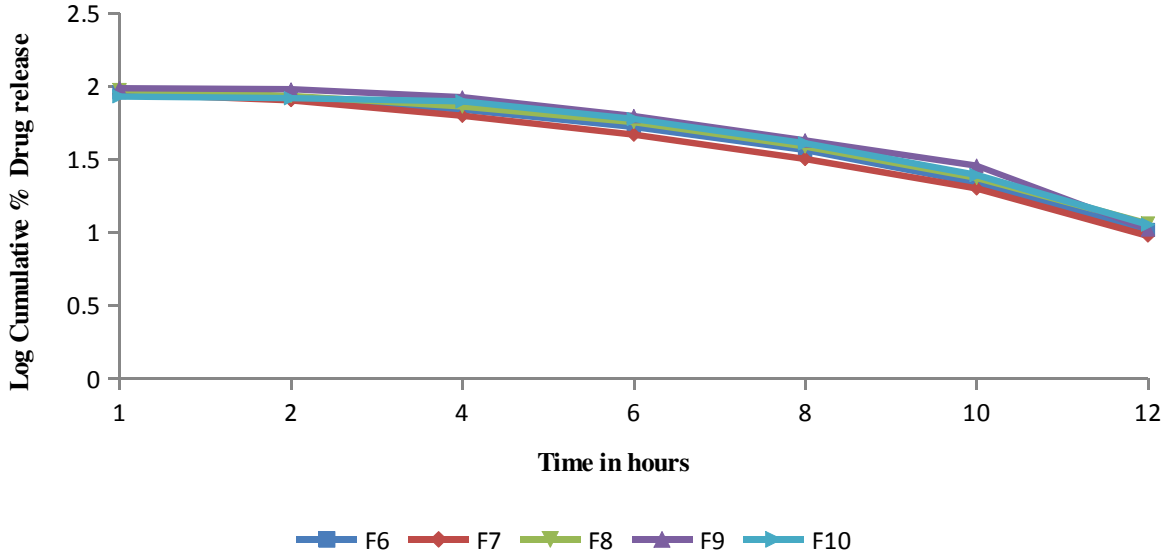


Fig-23 Cumulative percentage release Vs Square root of Time (Higuchi plot) of Formulations F1, F2, F3, F4, and F5

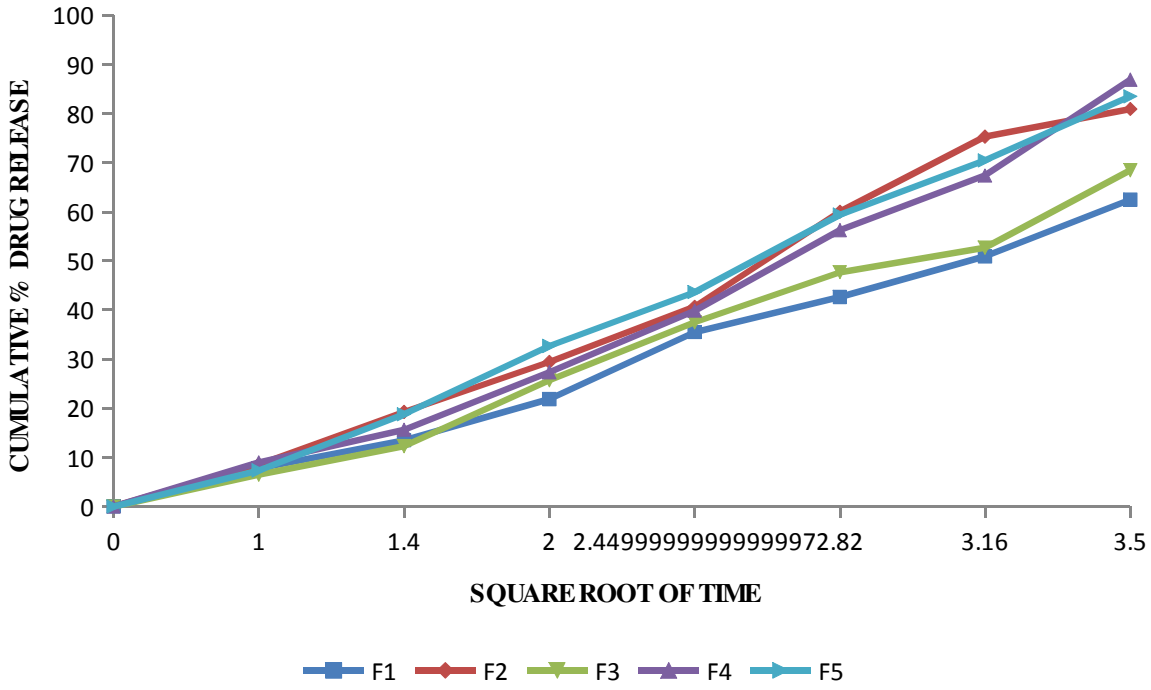


Fig-24 Cumulative percentage release Vs Square root of Time (Higuchi plot) of FormulationsF6, F7, F8, F9 and F10

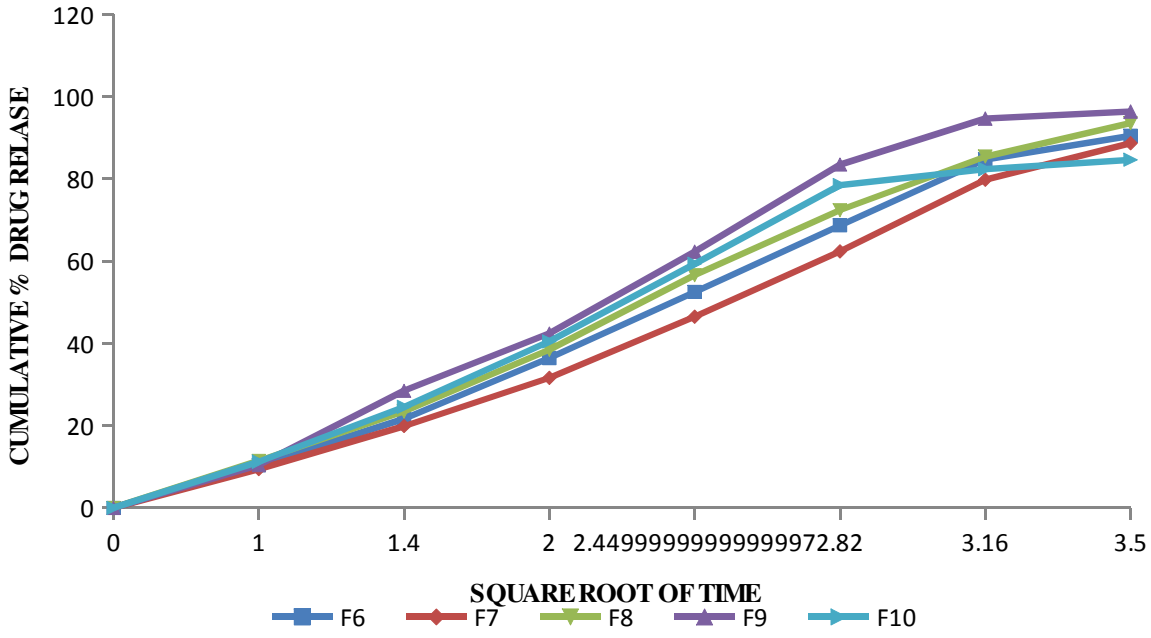


Fig-25 Log Cumulative percent release Vs Log Time (peppa's plot) of Formulations F1, F2, F3, F4 and F5

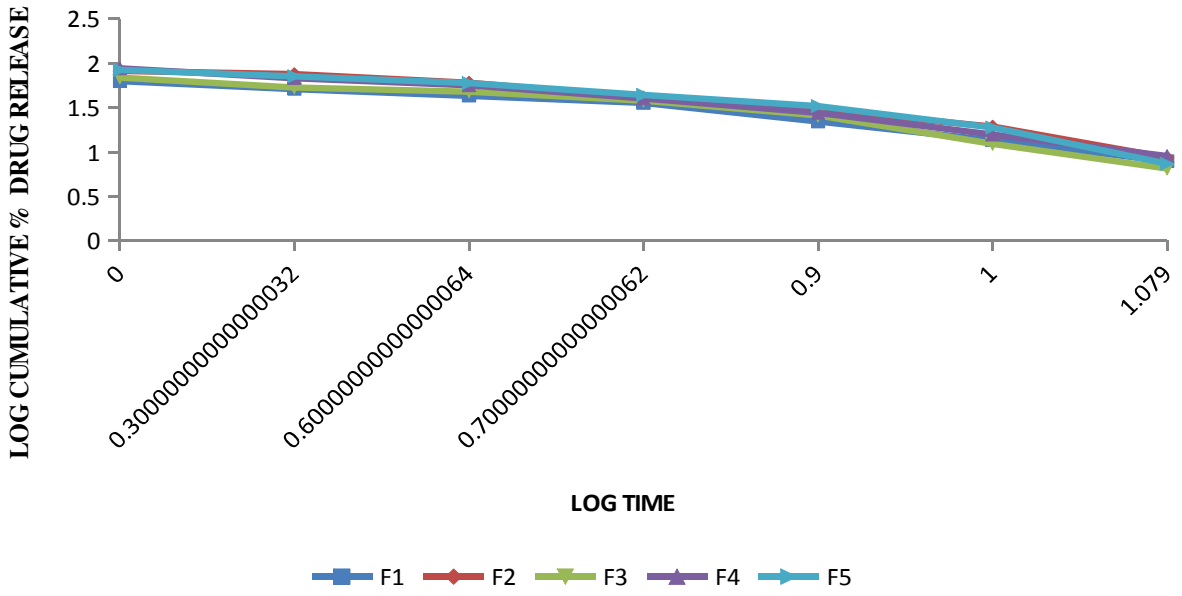


Fig-26 Log Cumulative percentage drug release Vs Log Time (peppa's plots) of FormulationsF6, F7, F8, F9 and F10

Stability studies

Short-term stability studies were performed at a temperature of 45° ± 1°C over a period of three weeks (21 days) on the promising CGPS tablet formulation F9. Sufficient number of tablets (15) were packed in amber coloured screw capped bottles and kept in hot air-oven maintained at 45° ± 1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and floating studies were performed to determine the drug release profiles, the estimation of drug contents and data of

SL.NO	TIME (hrs)	% cumulative drug release	
		1st Day	**21stDay**
1	1	10.48	9.41
2	2	28.48	26.98
3	3	36.54	35.13
4	4	42.38	40.48
5	5	58.21	57.27
6	6	62.26	61.39
7	7	72.56	73.46
8	8	83.46	82.87
9	9	89.23	88.73
10	10	94.64	92.78
11	11	95.81	94.21
12	12	96.35	95.60

Table-14 *In-vitro* release data of stability study of formulation F9

7. SUMMARY

According to the obtained results, the floating tablets of Cefixime include a swelling agent and a gel forming polymer. Together these agents form a hydrated gel matrix. The tablet further contains a gas generating component such that a gas is generated in a controlled manner and is entrapped in hydrated gel matrix. The swelling agent which belongs to class of super disintegrants absorbs large amount of fluid and causes matrix significantly. However, in the present invention, swelling of matrix is controlled by the viscolyzing agent (carbopol), which acts both as swellability and a release controlling agent. The gas generating component sodium bicarbonate interacts with an acid source citric acid by contact with gastric fluid to generate carbon dioxide. In the present invention, it has found that a carbopol helps in maintaining tablet integrity, when stirred in aqueous medium.

The floating tablet formulations are evaluated for different precompressional and post compressional parameters the results revealed that the all formulations shows good precompressional properties showing better flowability, hardness is maintained in the range of 5 to 7kg/cm^2 which provides good mechanical strength to the CGPS tablet. Other parameters like weight variation, friability, thickness, drug content are in the range of prescribed limits of IP.

The *in vitro* drug release results suggest that, the drug was released by mixed order kinetics. To ascertain, the drug release mechanism the in-vitro release data were also subjected to Higuchi's diffusion and Peppa' s plots by taking log percent versus log time. Results of these kinetic plots and n values, suggest that the drug was released by Non-Fickian control (Anomalous diffusion) with swelling. In the present study floating controlled drug delivery systems of Cefixime were successfully developed in the form of tablets to improve the local action and its bioavailability, which reduces the wastage of drug and ultimately improves the solubility for drugs that are less soluble in high pH environment.

CONCLUSION

From the above experimental results it can be concluded that, Formulated floating tablets gave satisfactory results for various post compressional parameters like hardness, friability, thickness, weight variation and content uniformity. Sodium bicarbonate has predominant effect on the buoyancy lag time, while Chitosan, has predominant effect on total floating time and drug release. Carbopol also shows significant effect on drug release. Sodium alginate and Xanthan gum has given extra adhesion property and helped to maintain the integrity of the tablet. Floating matrix tablet with good floating and a controlled release pattern. Swelling index has a significant effect on the drug release. The formulations F8 and F9 showed higher swelling index compared to others. In-vitro release rate studies showed that the maximum drug release was observed in F8 and F9 formulations up to 12 hrs. Formulations F9 found to be stable at 45^{o}C and 75% RH for a period of 21 days. FT-IR studies revealed that there was no interaction between Cefixime and the polymers used. From the study it is evident that a promising gas powered controlled release floating tablets of Cefixime can be developed to increase gastric residence time and thereby increasing its bioavailability. Further detailed investigations are required to establish efficacy of these formulations and fix the required dose.

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