"FORMULATION AND EVALUATION OF CEFIXIME FLOATING MATRIX TABLETS"

Dissertation submitted to

THE TAMILNADUDr.M.G.R.MEDICAL UNIVERSITY, CHENNAI.

In partial fulfillment of requirement for the award of the degree of

MASTER OF PHARMACY

In

PHARMACEUTICS

Submitted by

Reg.No.261211001

Under the guidance of

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DEPARTMENT OF PHARMACEUTICS

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(Affiliated to the Tamilnadu Dr.M.G.R medical university, Chennai)

Approved by The Govt. of Tamilnadu, Chennai
All India Council for Technical Education, New Delhi
Recognized by pharmacy council of India, New Delhi

CERTIFICATE

This is to certify that the Dissertation entitled **"Formulation and Evaluation of Cefixime Floating Matrix Tablets"** submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **Reg No: 261211001** carried out in the department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore for the partial fulfillment for the degree of Master of Pharmacy under my guidance during the academic year 2013-2014.

This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

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EVALUATION CERTIFICATE

This is certify that the dissertation work entitled **"Formulation and Evaluation of Cefixime Floating Matrix Tablets"**submittedby **Reg. No: 26121101** to The Tamilnadu Dr. M.G.R medical university, Chennai, in the partial fulfillment for the degree of Master of Pharmacy in Pharmaceutics is a record of bonafide work carried out by the candidate at the department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore and was evaluated by us during the academic year 2013-2014.

Internal Examiner **External Examiner**

DECLARATION

The research work embodied in this work **"Formulation and Evaluation of Cefixime Floating Matrix Tablets"** was carried out by me in the department of Pharmaceutics, Cherraan's college of Pharmacy, Coimbatore under the direct supervision of **Mr. J. Karthikeyan,** M.Pharm, Asst. Professor, Cherraan's College of Pharmacy, Coimbatore-39.

The dissertation submitted to the Tamilnadu Dr.M.G.R Medical University, Chennai, for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year of 2013-2014.

Place: Coimbatore

Date: **Reg. No: 261211001**

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Place :

Date : ***Reg.No.261211001***

ABSTRACT

The present research work Cefixime Controlled Gas Powered System (CGPS) are retained for longer period oftime in the stomach. The bioavailability of cefixime is around 40-50 %. The gas powered tablets of Cefixime were prepared by direct compression method. The formulations were evaluated for quality control tests and all the physical parameters evaluated are within the acceptable limits. Drug compatibility with excipients was Checkedby FTIR studies and these results were revealed that, no interaction between drug with the excipients used. The results of *in-vitro* buoyancy time and lag time study revealed that as the concentration of sodium bicarbonate increases there is increase in total buoyancy time and decrease in lag time**.** In all the formulations buoyancy time ranges from 40-690 min and lag time ranges from 65-10 min. The formulation F3 shows the lag time of 10 min. and buoyancy time 600 min. The release of cefixime from all the formulations was in the range of 46.67- 58.93 % at the end of 6 hrs. and 64.43-98.49 % at the end of 24 hrs. The CGPS system using sodium carboxy methyl cellulose along with sodium bicarbonate and citric acid added significantly increased the drug release from the formulation. It is also evident that sodium bicarbonate levels had a considerable effect on the drug release profile. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. From this study, it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence, improve the therapeutic effect of the drug.

Keywords: Cefixime, Lactose, Hpmc, Carbopol, Eudragit, Sodium bicarbonate, Citric acid, Mg.sterate, Talc.

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LIST OF ABBREVATIONS

ABBREVATIONS	EXPANSION
API	Active pharmaceutrical ingredients
HPMC	Hydroxyl propyl methyl cellulose
MRT	Mean resident time
CRDDS	Controlled release drug delivery system
DDS	Drug delivery system
CDDS	Controlled drug delivery system
FIG.	Figure number
EX.	Example
ºC	Degree Celsius
Mm	Micrometer
Ml	Milliliter
ICH	International conference on hormonisation
RH	Relative humidity
µg	Microgram
Mg	Milligram
IP	Indian pharmacopeia
#	Mesh number
%	Percentage
Gm/cm	Gram per centimeter
A.D.M.E	Absorption,distribution,metabolisam,anddistribustion.
Lit	Litter
USP	United states pharmacopeia
BP	British pharmacopeia
SR	Sustain release
FTIR	Fourier transform infrared radiation
Hr	Hour
BCS	Biopharmaceutical classification system
HCl	Hydrogen chloride
Gm/c.c	Gram per cubic centimeter
W	weight

Gm/ml	**Gram per milliliter**
G	**Gram**
w/v	**Weight / volume**
w/w	**Weight / weight**
C.D.R	**Cumulative drug release**
C.R	**Cumulative release**
F	**Formulation**
FDA	**Food and drug administration**
s.no	**Serial number**
Nm	**Nano meter**
Mg/ml	**Milligram per milliliter**
SQRQ	**Square root time**
b/w	**Between**
Mg. steriate	**Magnesium steriate**

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process[1]. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed. Conventional oral controlled dosage forms suffer from mainly two adversities[2]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms.

Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the gastric residence time (GRT) using gastro retentive dosage forms (GRDFs*)* that offer a new and better option for drug therapy[3].

Dosage forms that can be retained in stomach are called **gastro retentive drug delivery systems** (**GRDDS).** GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability[2].

During the last decade many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric emptying

time (GET) The GET has been reported to be from 2 to 6 hours in humans in the fed state. Accordingly orally, sufficient bio availability and prolongation of the effective plasma level occasionally cannot be obtained.

Controlled release drug delivery systems that can be retained in stomach for a long time are important for drug that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. If the drugs are poorly soluble in intestine due to alkaline pH, gastric retention may increase solubility before they are emptied, resulting in improved gastrointestinal absorption of drugs with narrow absorption window as well as for controlling release of drugs having site-specific absorption limitation[4].

GASTRORETENTIVE DOSAGE FORMS AN OVERVIEW

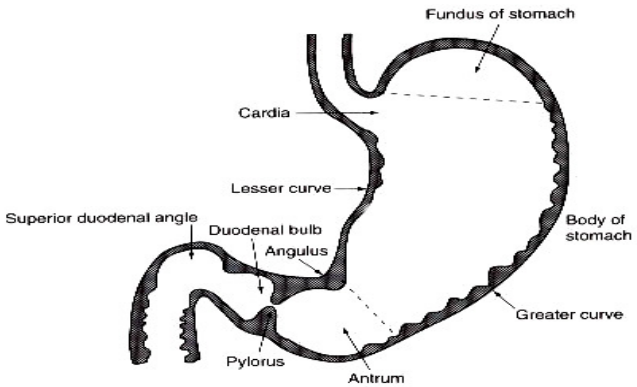
Gastroretentive Dosage Form (GRDF)

Dosage forms that can be retained in stomach are called gastro retentive drug deliverysystems (GRDDS).GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability

Physiological Considerations[3]

Stomach: The Site for Gastro Retention

Fig: 1



The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension, up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25-50 ml. The stomach is anatomically divided into 3 parts, fundus, body and antrum (or pylorus). The proximal stomach, made up of fundus and body regions serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying.

Gastrointestinal Motility & Emptying Of Food

The process of gastric emptying occurs both during fasting and fed states, however the pattern of motility differs markedly in the two states. Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. As a result the bioavailability of orally administered drugs will vary depending on the state of feeding.

In the fasted state, it is characterized by an interdigestive series of electrical event and cycle, both through the stomach and small intestine every 2-3 hrs. This activity is called the interdigestive myoelectric cycle or Migrating motor complex (MMC) is often divided into four consecutive phases: basal (Phase I) pre burst (Phase II), burst (Phase III), and Phase IV intervals.

PHASE I the quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretary, electrical and contractile activity. **PHASE II** , exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III. **PHASE III** is a short period of intense large regular contractions, termed “housekeeper waves” that sweep off undigested food and last 10-20 min. **PHASE IV** is the transition period of 0-5 mins between Phase III & I.

The motor activity in the fed state is induced 5-10 mins after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 h, and more typically, 3-4 h, with phasic contractions similar to Phase II of MMC.

When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in gastrointestinal tract.

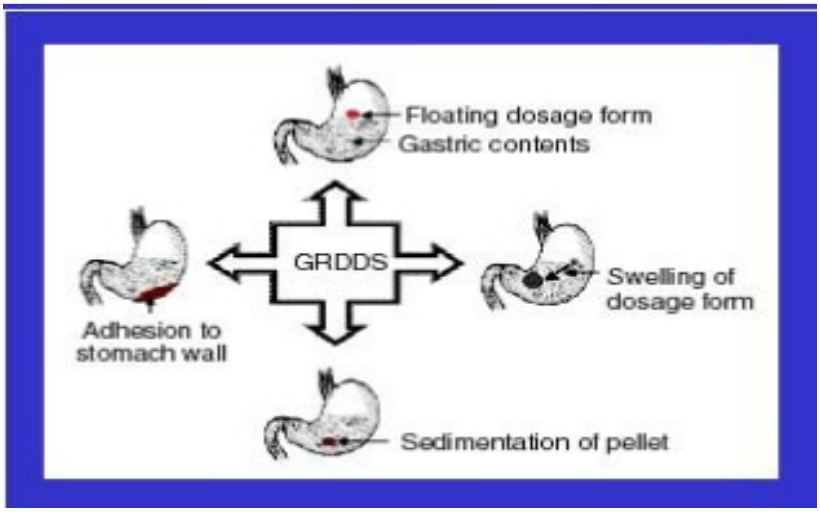
This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. On the other hand, in the fed stomach the gastric retention time (GRT) of non disintegrating dosage forms depends mostly on their size and composition and caloric value of food.

Requirements for Gastro Retention

From the discussion of the physiological factors in stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.

Approaches to Gastric Retention

Over the last 3 decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Bioadhesive systems, swelling and expanding systems, High density systems, Floating systems, Modified systems. **Fig: 1**



Incorporation of passage delaying food excipients, principally fatty acids, to decrease the gastric emptying rate.

Bio adhesive research based upon the adhesive capacity of some polymer with glycoprotein (Mucin) closely applied to the surface epithelium of the stomach and intestine.

The other approach is to alter the formulation's density by using either high or low-density pellets, so called altered density approach.

High density approach

Here, the density of the pellets must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a heavy core or mixed with heavy, inert materials such as barium sulfate, titanium dioxide, iron powder and oxide. The weighed pellet can then be covered with a diffusion controlled membrane.

Low-density approach

While the system is floating on the gastric contents the drug is slowly released from the low density pellets or floating drug delivery systems (FDDS) and are also called as hydro dynamically balanced systems (HBS). FDDS or HBS have a bulk density lower than gastric fluid, that is, bulk density of less than one. HBS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach.

Shells of polymer with lower density than that of the gastrointestinal fluid, (ex polystyrene) have been used for this purpose. Swelling type dosage forms are such that on swallowing these products swell to an extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred as 'plug type system' since they exhibit tendency to remain logged at the pyloric sphincter. Modified shape systems are no disintegrating geometric shapes molded from silstic elastomer or extruded from polyethylene blends which

extend the gastric retention time depending on size, shape and flexural modulus of the drug delivery system.

Unfortunately, most of these systems have many drawbacks. Floating system requires presence of food to delay their gastric emptying. They do not always release the drug at the intended sit. Bio-adhesive system adheres to the mucus. This adhesion is a result of electrostatic and H-bond formation at the mucus-polymer boundary. The bond formation is prevented by acidic environment and thick mucus present in the stomach.

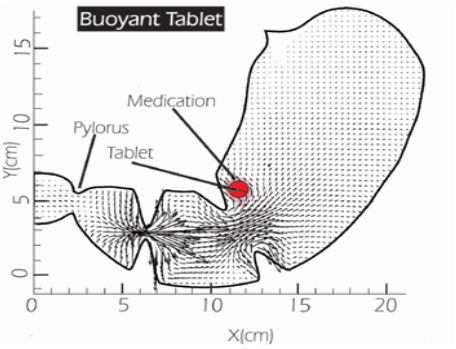
Different Techniques in Gastric Retention[6, 7.]

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include –

Buoyant/ Floating Systems:

Floating Drug Delivery Systems[8] (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system.

After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent system.



Graphic of Buoyant tablet, which is less dense than the stomach fluid therefore it remains in the fundus.

Bio/Muco-adhesive Systems[9, 10]

Bioadhesive drug delivery systems (BDDS) are used to localise a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. A microbalance-based system is reported for measuring the forces of interaction between the GI mucosa and the individual polymers, and the Cahn Dynamic Contact Angle Analyzer has been used to study the adherence.5 Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seems to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. Some investigators have tried out a synergistic approach between floating and bioadhesion systems. Other approaches reported include use of a novel adhesive material derived from the *fimbriae* (especially Type 1) of bacteria or synthetic analogues combined with a drug to provide for attachment to the gut, thereby prolonging the transit time, a composition comprising an active ingredient and a material that acts as a viscogenic agent (for example curdlan and/or a low-substituted hydroxypropylcellulose), etc.

Swelling and Expanding Systems[11]**:**

Theseare the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type system”, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

High Density Systems[8]:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Incorporation of Passage Delaying Food Agents[12]:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-$C_{14.}$

Ion Exchange Resin[13]:

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic Regulated Systems[2]:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio-erodible capsule. In the stomach the capsule quickly disintegrates to release the intra gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

Background for development of FDDS:

Many therapeutic agents ate metabolized in the upper GI tract into an active form. This active form is then through the wall intestine. The therapeutic agents ate metabolized by enzymes in the upper GI tract. If the therapeutic agent is present in large quantities, saturation of these enzymes can occur with the result that most of the therapeutic agent passes through the GI tract therefore limits the potency of the therapeutic agent.

Conventional controlled release dosage forms have a density greater than that of gastric contents, thus these dosage forms sink to the bottom of the stomach once ingested. The de novo design of oral controlled drug systems (DDS) is known in the art to achieve more predictable bioavailability of drugs. However, it is well known that conventional release DDS do not Overcome adversities such as gastric residence time (GST) and gastric empty time (GET). Gastric emptying is the process by the fasted stomach exhibits a cyclic activity called the inter-digestive migrating motor complex (IMMC). The purpose of this cycle is to migrate the contents of the stomach through the pyloric sphincter although ingestion of food interrupts the cycle.

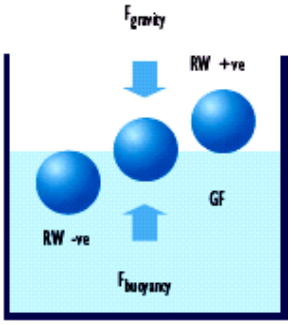
One approach to overcome the adversities of GRT and GET is the floating system also known as hydrodynamically balanced systems. These systems are expected to remain lastingly buoyant on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric fluids. The floating forms maintain their low density value while the polymer hydrates and forms a gel. The drug is progressively release from the swollen matrix in the case of conventional hydrophilic matrices.

Types of Floating Drug Delivery Systems (FDDS) [10]

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system.

After release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of the fluctuations in plasma drug concentration However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to

keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus (fig: 4) operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.



RW or **F** = F buoyancy - F gravity

= (Df- Ds) gV

Where

RW = total vertical force

Df= fluid density,

Ds= object density, V = volume;

Fig: 4. Diagrammatic representation of RW apparatus.

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are:

A. Effervescent System, and

B. Non- Effervescent System.

Effervescent System[12, 14.]

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

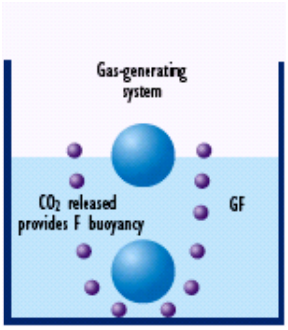
These effervescent systems further classified into two types.

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems.

Gas – Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System(HBS):

These are as shown in Fig. 5 and formulated by intimately mixing the CO_2 generating agents and the drug with in the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.



GF: Gastric Fluid

Fig: Intra Gastric Single Layer Floating systems.

Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig 6and containing two layer i.e.,

i. Immediate release layer and
ii. Sustained release layer.

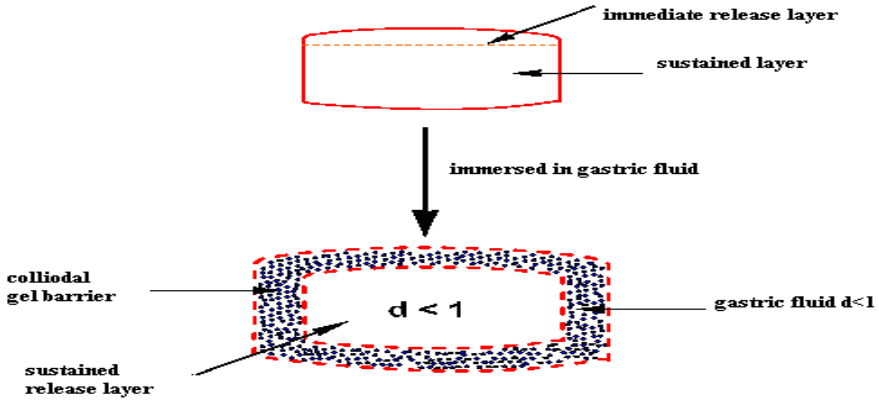


Fig: Intra Gastric Bilayer Buoyant Tablet.

Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers (fig: 7). The inner layers consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

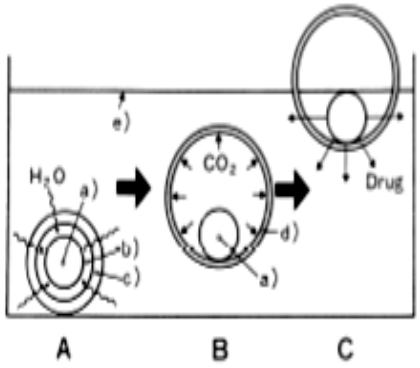


Fig: [15]**.**A multi-unit oral buoyant dosage system. Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

II. Volatile Liquid / Vacuum Containing Systems[16]:

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment, as shown in Fig.8

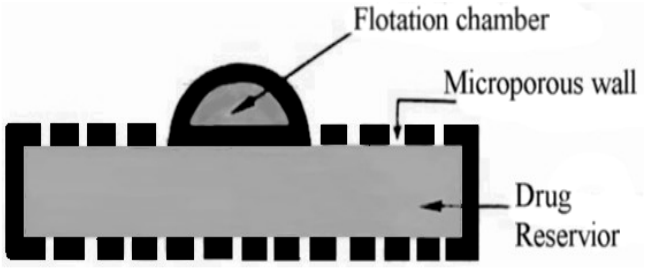


Fig: Intra Gastric Floating Gastrointestinal Drug Delivery Device

Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.

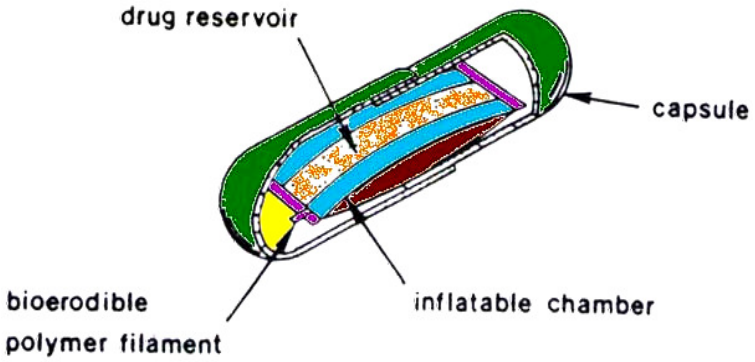


Fig no: Inflatable Gastrointestinal Delivery System

After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 9

IntragastricOsmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastircosmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig.10

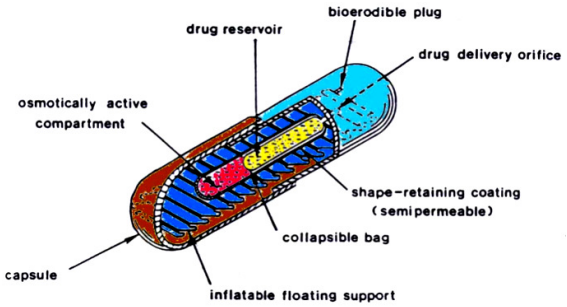


Fig: IntragastricOsmotically Controlled Drug Delivery System

Non-Effervescent Systems[17]

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Other approaches reported in the literature are hydro dynamically balanced (HBS) systems developed by Sheth and Tossounian, which contain a mixture of drug and hydrocolloids, sustained release capsules containing cellulose derivatives like starch and a higher fatty alcohol or fatty acid glyceride, bilayer compressed capsules, multilayered flexible sheet-like medicament devices, hollow microspheres of acrylic resins, polystyrene floatable shells, single and multiple unit devices with floatation chambers and microporous compartments and buoyant controlled release powder formulations, etc.

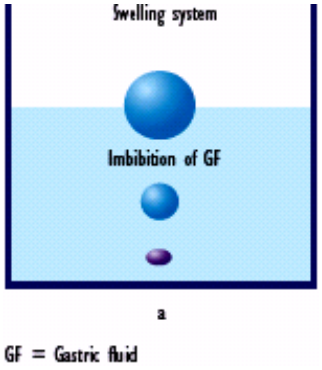


Fig: Swelling systems

Recent developments include use of superporous hydrogels that expand dramatically (hundreds of times their dehydrated form within a matter of seconds) when immersed in water. Oral drug delivery formulations made from the gels would swell rapidly in the stomach, causing medications to move more slowly from the stomach to the intestines and be absorbed more efficiently by the body.

Factors affecting gastric retention:

These factors include density, size and shape of dosage form, concomitant intake of food and drug such as anti-cholinergic agents (e.g. Atropine, propantheline), opiates (e.g. Codeine) and prokinetic agents (e.g. Metoclopramide) and biological factors such as gender, posture, age, body mass index and disease state. (e.g. Diabetes).

In order for a HBS dosage form to float in the stomach the density of the dosage form should be less than the gastric contents. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameters for describing its buoyancy.

These are better represented and monitored by resultant weight measurements and swelling experiments. This is because the magnitude of floating strength may vary as a function of time and usually decreases after immersion of the dosage form into fluid consequently to the evolution of its hydro-dynamical equilibrium.

The prolongation of gastric residence time (GRT) by food is expected to maximize drug absorption form FDDS due to increased dissolution of drug and longer residence at the most favorable sites of absorption. GRT of a dosage form in the fed state can also be influenced by its size.

Technological developments in FDDS (floating drug delivery system):

Most of the floating systems reported in the literature are single unit systems, such as floating tablets. These systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered owing to their fortuitous (all-or-nothing) emptying process. On the other hand, multiple unit dose forms appear to be better suited since they are claimed to reduce the inter subject variability in absorption and lower the probability of dose-dumping. It also eliminates the dependence of the drug effect on gastric emptying, the mini depots being sufficiently small to make possible their passage through pylorus even between its actual openings. As a result, the drug will reach the site of optimum absorption and a high local concentration will also be avoided.

MARKETED PRODUCTS OF FDDS[18]

Table:1

SL.NO	BRAND NAME	DRUG (DOSE)	COMPANY COUNTRY	TECHNOLOGY
1.	Modapar®	Levodopa(100mg), Benserazide(25mg)	Roche Products, USA	Floating CR capsule
2.	Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3.	Liquid Gavison®	Alhydroxide(95mg), Mg carbonate (358 mg)	GlaxoSmithKline, India	Effervescent floating liquid alginate Preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin(1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet
9	Glumetza™	Metformin HCl	Depomed,usa	Acuform™
10	ProQuin® XR	Ciprofloxacin hydrochloride	Depomed,usa	Acuform™

Drugs explored for various floating dosage forms

Table: 18

Dosage Forms	Drugs
Microspheres	Aspirin, Ibuprofen, Tranilast
Granules	Diclofenac sodium, Indomethacin, Prednisolone
Capsules	Diazepam, Furosemide, L-Dopa and Benserazide
Tablets / pills	AmoxycillinTrihydrate, Ampicillin, Diltiazem, *p* -Aminobenzoic acid, Riboflavin-5'-phosphate, Theophylline, Verapamil HCl

ADVANTAGES OF FDDS[2]:

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.

Other advantages are:

Sustained drug delivery:

As mentioned earlier, drug absorption from oral controlled release (CR) dosage forms is often limited by the short GRT available for absorption.

However, HBS type dosage forms can retain in the stomach for several hours and therefore, significantly prolong the GRT of numerous drugs. .

These special dosage forms are light, relatively large in size, and do not easily pass through pylorus, which has an opening of approx. 0.1– 1.9 cms.

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine.

The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

The eradication of Helicobacter pylorirequires the administration of various medicaments several times a day, which often results in poor patient compliance. More reliable therapy can be achieved by using GRDDS. Floating alginate beads have been used for the sustained release of Amoxycillintrihydrate. Thus, it can be expected that the topical delivery of antibiotic through a FDDS may result in complete removal of the organisms in the fundal area due to bactericidal drug levels being reached in this area, and might lead to better treatment of peptic ulcer.

Pharmacokinetic advantages

As sustained release systems, floating dosage forms offer various potential advantages. Drugs that have poor bioavailability because their absorption is limited to upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavalabilities.

Floating dosage forms with SR characteristics can also be expected to reduce the variability in transit performance. In addition, it might provide a beneficial strategy for gastric and duodenal cancer treatment.

The concept of FDDS has also been utilized in the development of various anti-reflux formulations. Floating systems are particularly useful for acid soluble drugs, drugs poorly soluble or unstable in intestinal fluids, and those which may undergo abrupt changes in their pH dependent solubility due to food, age and disease states.

LIMITATIONS

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.

2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.

3. The dosage form should be administered with a minimum of glass full of water (200-250 ml).

4. The drugs, which are absorbed throughout gastro-intestinal tract, which under gofirstpass metabolism (nifedipine, propranolol etc.),are not desirable candidate.

5. Some drugs present in the floating system causes irritation to gastric mucosa.

Antibiotics

The word "antibiotics" comes from the Greek anti ("against") and bios ("life").Antibiotics are drugs that either destroy bacteria or prevent their reproduction. Antibiotics that kill bacteria are called "bactericidal" and the ones that stop the growth of bacteria are called "bacteriostatic".

Since penicillin's introduction during the 1940s, scientists developed numerous other antibiotics. Today, over 100 different antibiotics are available. About 90% of antibiotics are made from living organisms search as bacteria, others produced synthetically, and either in whole or in park.

Antibiotics classification

Although there are several classification schemes for antibiotics, based on bacterial spectrum (broad, narrow) or administration (injectable, oral, topical), or type of activity (bactericidal, bacteriostatic). Most commonly used types of antibiotics are: Penicillin's, Fluoroquinolones, Cephalosporin's, Macrolides, and Tetracycline's.

Penicillins

The penicillin's are the oldest class of antibiotics. Penicillins have a common chemical structure which they share with the cephalosporins; penicillins are generally bactericidal, inhibiting formation of the cell wall.

There are four types of penicillins:

- The natural penicillins are based on the original penicillin-G structure.Penicillin-G types are effective against gram-positive strains of streptococci, staphylococci, and some gram-negative bacteria such as meningococcus.
- Penicillinase-resistant penicillins are active even in the presence of the bacterial enzyme that in actives most natural penicillins.
- Extended spectrum pencillins which are effective against a wider range of bacteria.
- Aminopenicillins such as ampicillin and amoxicillin have an extended spectrum of action compared with the natural penicillins.

Penicillins side effects

1. Penicillines are among the least toxic drugs known. The most common side effect of penicillin is diarrhea.Nausea, vomiting, and upset stomachs are also common. In rare cases penicillins can cause immediate and delayed allergic reaction – specifically, skin rashes, fever, and anaphylactic shock. Penicillins are classed as category B during pregnancy.

Cephalosporins:

Cephalosporins have a mechanism of action identical to that of the penicillins. However, the basic chemical structure of the penicillins and cephalosporins differs in order respects, resulting in some difference in the spectrum of antibacterial activity.

The first generation cephalosporins include: cephalothin, cefazolin, cefadroxil. Their spectrums of activity are quite similar. They possess generally excellent coverage against most gram-positive pathogens and variable to poor coverage against most gram negative pathogens.

The second generation cephalosporins include: cefaclor, ceforanide,cefuroxime. In addition to the gram-positive spectrum of the first generation cephalosporins, these agents have expanded gram-negative spectrum.

The third generation cephalosporins have much expanded gram-negative activity. However, some members of this group have decreased activity against gram-positive organism. The third generation cephalosporins include: cefdaloxime.

The fourth generation cephalosporins are extended-spectrum agents with similar activity against gram-positive organism as first-generation cephalosporins. Many fourth generation cephalosporins can cross blood brain barrier and are effective in meningitis. The fourth generation cephalosporin include: cefclidine, cefpirome, cefquinome.

Classification of Cephalosporins

Cephalosporins are grouped into "generation" based on their spectrum of antimicrobial activity. The first cephalosporins were designed first generation while later, more extended spectrum cephalosporins were classified as second generation cephalosporins. Each newer generation of cephalosporins has significantly greater gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against gram-positive organisms. Fourth generation cephalosporins, however, have true broad spectrum activity

First generation:

First generation cephalosoporins are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections and therefore are alternatives for skin and soft-issues infections, as well as for streptococcal pharyngitis

The first generation cephalosporins are:

- Cefadroxil
- Cephalexin
- Cephaloridine
- Cephalothin

Cefazolin is the most commonly used first generation cephalosporin. The other first generation cephalosporins have similar efficacy to cephalexin, but must be dosed more often, and are therefore not as commonly prescribed.

Second generation:

The second generation cephalosporins have a greater gram-negative spectrum while retaining some activity gram-positive bacteria. They are also more to beta-lactamase. They are useful agents for treating upper and lower respiratory tract infections. Cefoxitin is a second generation cephalosporin with anaerobic activity.

The second generation cephalosporins are:

- Cefaclor
- Cefprozil
- Cefuroxime

Third generation:

Third generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. Some members of this group have decreased activity against gram-positive organisms. The parenteral third generation cephalosporins have excellent activity against most strains of streptococcus pneumonia, including the vast majority of those with intermediate and high level resistance to penicillin.

The third generation cephalosporins are:

- Cefixime
- Cefpodoxime
- Ceftriaxone

Fourth generation:

Fourth generation cephalosporins are extended spectrum agents with similar activity against gram-positive organisms as first cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis.

The fourth generation cephalosporins are:

- Cefepime
- Cefozopran
- Cefquinome

Cephalosporin side effects:

Cephalosporin generally causes few side effects .common side effects associated these drugs include: diarrhoea, nausea, mild stomach cramps or upset. Cephalosporins antibiotics are contraindicated in people with a history of allergic reactions to penicillins or cephalosporins. Cephalosporins antibiotics are classed as pregnancy category B.

Administration

Oral antibiotics are simply ingested, while intravenous antibiotics are used in more serious cases, such as deep-seated systemic infections. Antibiotics may also sometimes be administered topically, as with eye drops or ointments.

Side effects

There are various side-effects that can be very serious depending on the antibiotics used and the microbial organisms targeted. The safety profiles of newer medications may not be as well established as those that have been in use for many years. Adverse effects can range from fever and nausea to major allergic reactions including photo dermatitis One of the more common side-effects is diarrhea is sometimes caused by anaerobic bacterium clostridium difficile. Such overgrowth of pathogenic bacteria may be alleviated by ingesting probiotics during a course of antibiotics. It has been hypothesized that interference of some antibiotics with the efficiency of birth control pills is thought occur in two ways. Modification of the internal flora may result in reduced Absorption of oestrogens. Second, induction of hepatic liver enzymes causing them metabolize the pill's active ingredients faster may affect the pill's usefulness. However, the majority of studies indicate that antibiotics do not interfere with contraception. Even though a small percentage of women may experience decreased effectiveness of birth control pills while taking antibiotic, the failure rate is comparable to the failure rate of those taking the pill.

Specific effects

Other effects of alcohol involve the activity of liver enzymes, which break down the antibiotics. In addition, serum levels of doxycycline and erythromycin in certain circumstances be significantly reduced by alcohol consumption. This is particularly important, since these drugs are bacteriostatic and require a sustained level of the drug in

the body to be effective: increased metabolism and clearance would result in diminished pharmacotherapeutic effect.

4.3 Antibiotic resistance

The emergence of antibiotic resistance is in evolutionary process that is based on selection for organisms that have enhanced ability to survive doses of antibiotics that would have previously been lethal. Antibiotics like penicillin and erythromycin, which used to be one-time miracle cures, are now less effective because bacteria have become more resistant. Antibiotics themself act as a selective pressure that allows the growth of resistant bacteria within a population and inhibits susceptible bacteria. Antibiotic selection of pre-existing antibiotic resistant mutants within bacterial populations was demonstrated in 1943 by the Luria-Delbruck experiment. Survival of bacteria often results from an inheritable resistance.

The bacterial chromosome may fail to encode a protein that the antibiotic targets. Acquired resistance results from a mutation in the bacterial chromosome or the acquisition of extra –chromosomal DNA. Antibiotic-producing bacteria have evolved resistance mechanisms that have been shown to be similar to, and may have been transferred to, antibiotic resistance strains. The spread of antibiotic resistance mechanisms occurs through vertical transmission of inherited mutations from previous generations and genetic recombination of DNA by horizontal genetic exchange. Antibiotic resistance is exchanged between different bacteria by plasmids that carry genes that encode antibiotic resistance that may result in co-resistance to multiple antibiotics. These plasmids can carry different genes with diverse resistance mechanisms to unrelated antibiotics but because they are located on the same plasmid multiple antibiotic resistances to the more than one antibiotic is transferred.

Antibiotic misuse

The poster from the U.S. centres for Disease control and prevention "get smart" campaign, intended for use in doctor's offices and other health care facilities, warns that antibiotics do not work for viral illnesses such as the common cold.

Inappropriate antibiotic treatment and overuse of antibiotics have been contributing factor the emergence of resistant bacteria. The problem is further exacerbated by self-

prescribing of antibiotics by individuals without be guide lines of a qualified clinician and non- therapeutics use of antibiotics as growth promoters in agriculture. Antibiotics are frequently prescribed for indications in which their use is not warranted, an incorrect or sub- optimal antibiotic is prescribed or in some cases for infections like to resolve without treatment.

Several organization concerned with antimicrobial resistance are lobbying to improve the regulatory climate. Approaches to tackling the issue of misuse and overuse of antibiotics by the establishment of the U.S. interagency Task Force on microbial resistance, are being organised and coordinated by the uscentres for disease control and prevention, the food and drug administration (FDA), and the national institutes of health (NIH), as well as federal agencies.

In agriculture, associated antibiotic resistance with the non-therapeutic use of antibiotics as growth promoters in animals resulted in their restricted use in the uk in the 1970(swnn report 1969).at the current time there is a EU wide ban on the non-therapeutic use of antibiotics as growth promoters. It is estimated that greater than 70% of the antibiotics used in us are given to feed animals (example: chickens, pigs, and cattle) in the absence of disease.

RESISTENCE-MODIFYING AGENTS

One solution to combat resistance currently being research is the development of pharmaceutical compounds that would revert multiple antibiotic resistances

PHAGE THERAPY

The therapy was in use during the 1920s and 1930s on humans in the US. The success of these therapies largely rigorous scientific studies in the form of clinical trials commonly used to evaluated the efficacy of new medications on the efficacy of phage therapy are limited the original publications in to phage therapies are also generally in accessible.

BACTERIOCINS

Different classes of bacteriocins have different potentials as therapeutic agents. Small molecule bacteriocins (microcins, for example, and antibiotics) may be similar to the classic antibiotics; colicin-like bacteriocins are more likely to be narrow spectrum, demanding new molecular diagnostics prior to therapie but also not raising the spectre of resistance to the same degree.one draw back to the large –molecule antibiotics is that they have relative difficulty crossing membranes and travelling systemically throughout the body. For this reason, they are most often proposed for applications topically are gastro intestinally.

4. LITERATURE REVIEW

Recent Reports on the Floating Drug Delivery System

Abubakr O. Nur*et al*[16] (**2000**) preparedCaptopril Floating and/or Bioadhesive Tablets by using two viscosity grades of hydroxypropylmethylcellulose (HPMC 4000 and 15000 cps) and Carbopol 934P. In- vitro dissolution was carried out in simulated gastric fluid (enzyme free) at 37°C ± 0.1°C using the USP apparatus 2 basket method.

Baumgartner*et al*[19] (**2000**) developed floating matrix tablets by using HPMC,drug and different additives which after oral administration are designed to prolong the gastric residence time, increase the drug bioavailability and diminish the side effects of irritating drugs. The importance of the composition optimization, the technological process development for the preparation of the floating tablets with a high dose of freely soluble drug and characterization of those tablets (crushing force, floating properties *in-vitro* and *in-vivo,* drug release) was examined. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release.

GuojieXu*et al*[20] (**2001**) formulated floating tablets containing sodium bicarbonate and HPMC in a cetyl alcohol matrix. When hydrated in an acid medium, this tablet consisted of a mixed solid with a viscous surface layer containing carbon dioxide bubbles through which the active ingredient (FITC-dextran) was released into the aqueous environment. However, it was observed that, above a critical molecular weight, the FITC-dextrn was only released into the medium by an erosion-type mechanism, whereas, below this value, both diffusion and erosion processes took place.

A.H El-Kamel*et al, (***2001**)[21] prepared ketoprofen-floating oral deliver system which was prepared by emulsion–solvent diffusion technique.four different ratios of Eudragit s100 with Eudragit RL were used for floating microparticles.

Shoufeng Li*et al* (**2003**)[22] investigated the effect of formulation variables on drug release and floating properties of floating delivery system of Calcium by using HPMC of different viscosity grades and Carbopol 934 P employing 2^3 full factorial designs. They observed that the decrease in release rate with an increase in viscosity of the polymeric system.

Brijesh S. Dave*et al*, (**2004**)[23] describedGastroretentive Drug Delivery System of Ranitidine Hydrochloride. InThis study discusses the preparation of gastroretentive tablets of Ranitidine HCl. The effervescent-based floating drug delivery was a promising approach to achieve in- vitro buoyancy. The addition of gel-forming polymer HPMC K_4 M and gas-generating agent sodium bicarbonate was essential to achieve in- vitro buoyancy.

Mahesh Chavanpatil*et al*(**2005**)[24] developed sustained release gastroretentive drug delivery system for ofloxacin. The design of the delivery system was done by, HPMC K_{100}M, crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 h. Various formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and in- vitro drug release profile. It was found that dimensional stability of the formulation increases with the increasing psyllium husk concentration. It was also found that in- vitro drug release rate increased with increasing amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release

XiaoqiangXu*et al* (**2006**)[25] developed a sustained release tablets of PhenoporlamineHCl by using HPMC K_4M and Carbopol 971 P. They observed that Carbopol was capable of sustaining delivery of the drug for longer period

Christian fernandes*et al. (2006)*[26]formulated the Lamivudine tablets using HPMC and EC polymers, and developed the dissolution test conditions and evaluated the results by using factorial design.

Viral F. Patel*et al* (**2006**)[27] developed intragastric drug delivery system for Cefuroxime Axetil and employed 3^2 factorial design to evaluate contribution of HPMC K_4M /K_{100} LV and SLS on drug release from HPMC matrix. They observed that as viscosity of polymers increases the release rate constant was decreased

ZiyaurRahman*et al* (**2006**)[28] developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer

contained Captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and in- vitro dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). °C/75% RH for three months.

Samuel B*et al, (***2006***)*[29] inpreparation and evaluation of gastro retentive delivery system of flurbiprofen. In this literature they prepared hallow microspheres by using emulsion- solvent diffusion method, which involved co-dissolution of drug and Eudragit RS 100 in various ratios in ethanol: dichlormethane mix. Which was finally dispersed in aqueous medium .the *in-vitro* testing revealed that the micro sponges floated continuously more than 12 hours.

C. Narendra*et al*(**2006**)[30] designed gastric floating drug delivery system containing metoprolol tartrate as a model drug. A 2^3 factorial design was employed in the formulating the GFDDS. With total polymer content to drug ratio (X1), polymer to polymer ratio (X2) and different viscosity grades of HPMC (X3) as independent variables. Four dependent variable considered: - % of drug release at 8 h, T50%, diffusion coefficient and floating time. The result indicates that X1 and X2 significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K_4M & K10M) was insignificant.

Ali, J., Hasan *et al* (**2006**)[31] in Formulation and development of Gastroretentive drug delivery system for ofloxacin, the hydrodynamically balanced capsules were prepared by physical mixing of various grades of HPMC and poly (ethylene oxide) (PEO) alone as well as in combinations. Cellulose acetate phthalate, liquid paraffin, and ethyl cellulose were used as release modifiers so as to maintain release of drug over a period of 12 h. various grades of Eudragit and PEO were used in combination for formulating floating microspheres using solvent diffusion technique for preparation of multiple unit system.

Sanjay S. Patel*et al*(**2006**)[32] formulated floating drug delivery system containing Clarithromycin for helicobacter Pylori different grades of HPMC (K_4M and K15M) .the study shows that tablets composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas generating agent together with polymer improved drug release. The drug release was sufficiently sustained and anomalous diffusion as well as zero order was confirmed.

Girish*et al* (**2007**)[33] developed bilayer and floating- bioadhesive tablets of Rosiglitazone maleate by using HPMC-K_{100}M. They observed that concentration of HPMC K_{100} M in release layer was the key factor governing drug release and in the bilayer drug release included the gelling agent forming a gelatinous barrier which controls the drug release without interference from gas bubbles generated in the floating layer.

V.F Patel*et al* (**2007**)[34] in statistical evaluation of influence of viscosity of polymer and type of fillers on Dipyridamole release from floating matrix tablets.This investigation describes the influence of HPMC and different type's fillers o dipyridamole release from floating matrix tablet using 3^2 factorial designs. Tablets were evaluated for *invitro* floating ability and drug release study using 0.1 N HCl. from the above study it was observed that as viscosity of polymers increases the release rate constant was decreased.

J.A. Raval*et al* (**2007**)[35] has developed ranitidine hydrochloride floating matrix tablets using hydrophilic matrix polymers HPMC K_4M, K15 M, K_{100} M, sodium alginate, psyllum, sesbania gum, guar gum, gum acacia with or without low density polymer. Tablets were physically characterized and evaluated for in- vitro characteristics for 8 h in 0.1 N HCL at 37^{o}C .the effect of addtion of low-density copolymers and the drug release pattern were also studied. They observed that the tablets eroded/ swelled upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablets erosion on the resulting release patterns varied significantly with the type of matrix forming polymer.

Basak SC*et al* (**2007**)[36] designed floatable gastroretentive tablet of metformin hydrochlorideformulated as a floating (buoyant) matrix tablet using a gas generating agent (sodium bicarbonate) and a gel forming hydrophilic polymer (hydroxypropyl methylcellulose). The formulation was optimized on the basis of floating ability and in-vitro drug release. In- vitro drug release tests of these tablets indicated controlled sustained release of metformin hydrochloride and 96-99% released at the end of 8 h.

Dasarath M. Patel*et al* (**2007**)[37] prepared Gastro retentive drug delivery system of Carbamazepine: formulation optimization using simplex lattice design .the tablets were prepared by using Beeswax, HPMC K_4M. Ethyl cellulose as a floating enhancer. The prepared tablets were evaluated for in- vitro drug release in simulated gastric fluid (pH 1.2). The release profile of promising formulation fitted best to zero-order model. The

factorial batches were subjected to short –term stability studies at 40^0 c and 75% relative humidity for 3 months.

Javed Ali*et al*(**2007**)[38] developed a hydrodynemically-balanced system of metformin as single unit floating capsule. Various grades of low-density polymer such as PEO and HPMC K_4M were used for formulating the system. The formulation was optimized on the basis of in-vitro buoyancy and in- vitro release in simulated fed state gastric fluid. They observed that the optimized HBS formulation of metformin could sustain the drug release in addition to remaining buoyant in the stomach as revealed by Gamma scintigraphic images.

Manoj N. Gambhire*et al* (**2007**)[39] developed floating drug delivery system of diltiazem HCL using HPMC $K_{100}M$ and compritol 888 ATO. They investigated the effect of sodium bicarbonate succinic acid on the drug release profile and floating properties. A 3^2 factorial design was applied to systematically optimize the drug release profile. The linear regression analysis and model fitting showed that all these formulation followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient. While the tablets hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Shivakumar HN*et al* (**2007**)[40] inOptimization of Gastroretentive System for Oral Controlled Delivery of Cinnarizine Using Response Surface Methodology.A controlled release effervescent floating system is proposed for gastroretentive delivery of cinnarizine. The effect of the formulation variables such as levels of HPMC K_4M (X1), sodium bicarbonate (X2) and citric acid (X3) on the tablet floating characteristics and drug release was studied.

Tejaspatel*et al* (**2008**)[41] formulated gastric floating drug delivery system for ranitidine HCL. HPMC of different viscosity grades and carbopol 934 P was used in formulating the GFDDS. Employing 2^3 full factorial designs. They observed that the HPMC, the presence of carbopol and their interaction had significant impact on the drug release and floating properties of the delivery system. The decrease in the release rate was observed with increase in the viscosity of the polymeric system.

Pravinchaudhri*et al*(**2008**)[42] developed bilayered floating tablets for Tizanidine HCL using HPMC- Gelucire 43/01, and HPMC- xanthan gum. They observed that the use

of high viscosity polymer can also decreased the floating lag time but this use of high viscosity polymer increase the matrix integrity and resultant weight.

Swamy P.V *et al* (**2008**)[43] designed gastro retentive drug delivery of Atenolol by using HPMC of different viscosity grades (K_4M and 50 cps) and sodium bicarbonate as a gas-generating agent to reduce the floating lag time. Six batches of preliminary trials formulations were designed and from the results of evaluation, the constraints for independent variables X1 (amount of HPMC 50 cps) and X2 (amount of sodium bicarbonate) have been fixed.

Ravikumar*et al* ***(2009)***[44]formulated and evalvuated effervescent floating tablet of famotidine by developing a floating delivery system using gas forming agents like,sodiumbicarbonate,citricacid,and hydrocolloids like HPMCandCarbopol 934P

3. AIM AND OBJECTIVES

Aim: Formulation and Evaluation of Cefixime Floating Matrix tablet Using (Controlled drug Release tablet) to treat Bacterial infections to improve the patient compliance.

Objectives:

- To improve the time bounded system of cefixime Matrix tablet.
- Develop a floating Matrix tablet of cefixime by direct compression method.
- To conduct Preformulation study of the drug with excipients.
- To study the effect of polymer concentration on drug release.
- To study the effect of fillers on drug release.
- To check for drug excipient compatibility.
- To conduct the different formulations.
- To evaluate the formulated floating Matrix tablet.
- To conduct the In-vitro drug release of the formulated floating Matrix tablet.

4.PLAN OF WORK

The main objective of the study i.e. Formulation and Evaluations of floating matrix tablet of cefixime (Controlled drug release tablet) can be achieved by following plan of work.

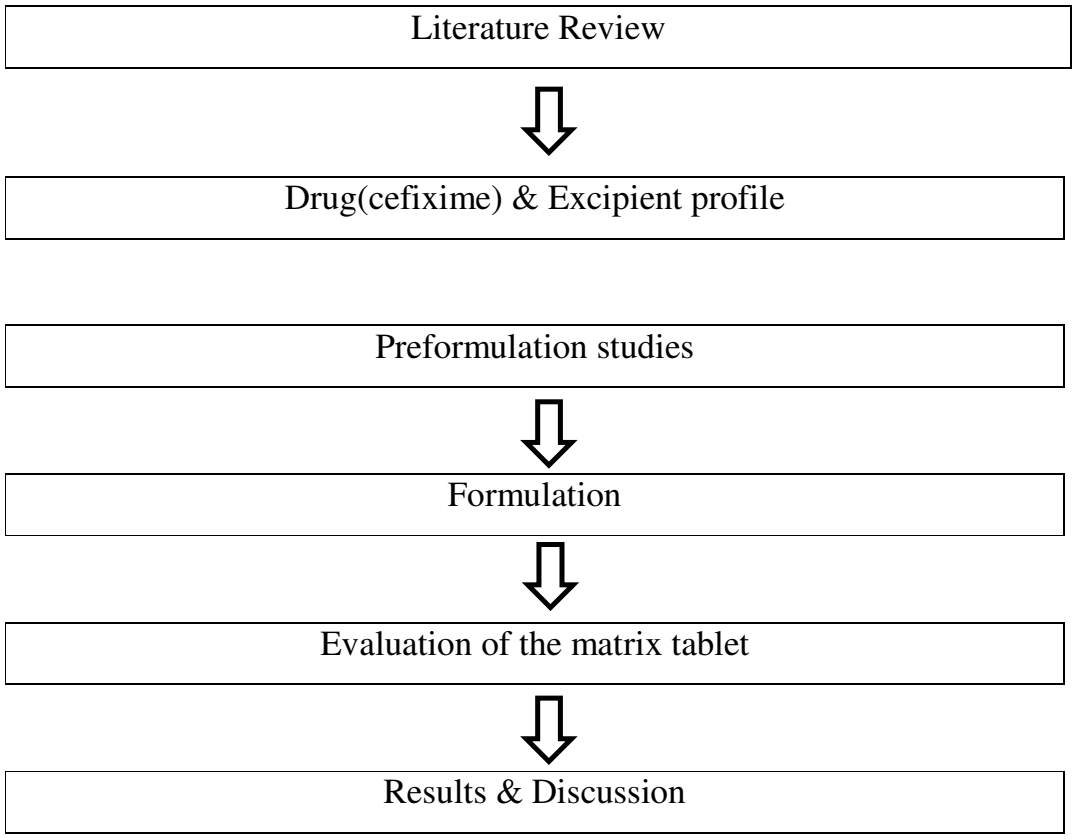


FIG-2: Process flow chart

DRUG PROFILE

CEFIXIME

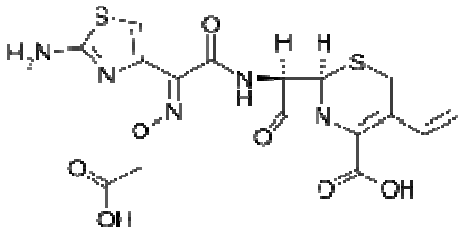
Synonym: Cefixim, Cefixima, Cefiximum

Chemical names: (6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(carboxymethoxy) imino]acetamido]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Molecular Weight: 453.45

Molecular formula: $C_{16}\ H_{15}\ N_5\ 07S_2$

Structure of compound:



Description: It is an orally active third generation cephalosporin highly active against Enterobactriaceae, H. influenzae and is resistant to may β-lactamases. However, it is not active on Staph, aureus, most pneumococci and Pseudomonas. It is a white to almost white, powder, odourless to practically odourless powder. With melting point at 207^0C.

Solubility: Practically insoluble in water soluble in HCL.

Storage: Store at 20^0 – 250^0C (68^0 – 77^0F). Dispense in well-closed containers with safety closures.

Category: β-lactum antibiotic .

Pharmacokinetics and Pharmacodynamics:

Absorption: Bioavailability40%- 50%, absorb from the GI tract. T_{max} is about 2 to 3 h.

Food: T_{max} increased and C_{max} and AUC are slightly decreased.

Distribution: V_d is 8.8 L. Protein binding is more than 99.5%.

Metabolism: Completely metabolized by oxidation via CYP-450 2C9. Major metabolites are cyclohexylhydroxymethyl (M1) (about one-third of the activity of the parent) and carboxyl (M2) derivatives.

Elimination: About 60% is excreted in urine and about 40% in faces as metabolites.

The half-life is about 3 to 4.2h.

Cefixime: is used with diet to reduce bacterial infections.

Pharmacology: Cefixime, an antibiotic, is a third-generation cephalosporin like ceftriaxone and cefotaxime. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall.

Uses: β-lactum antibiotic to treat bacterial infections.

Ear: Otitis caused by Haemophilus influenzae, Moraxella atarrhalis and Streptococcus pyongenes.

Sinuses: Sinusitis.

Throat: Tonsillitis, pharyngitis caused by Streptococcus pyogenes.

Chest and lungs: Bronchitis, pneumonia caused by Streptococcus pneumoniae and Haemophilus influenzae.

Dose: Adults – 200 – 400 mg daily (max 200 mg /day initial dose) with breakfast or the first main meal of the day. Increase by 200 to 400 mg /dose.

Adverse effects: Adverse drug reactions include diarrhea, dyspepsia, nausea and vomiting. Hypersensitivity reactions like skin rashes, urticaria and Stevens-Johnson syndrome have been reported. There is no specific antidote for Cefixime overdosage. Gastric lavage may perform. Dialysis will not remove Cefixime in significant quantities.

Contraindication: Cefixime is contraindicated in patients with known sensitivity or allergies to cephalosporin class of antibiotics. As Cefixime is a third generation cephalosporin, it is not contraindicated for patients with a true penicillin allergy.

Lactose:

Nonproprietary Names:

BP: Anhydrous Lactose, JP: Anhydrous Lactose, PhEur: Lactose, Anhydrous, USP-NF: Anhydrous Lactose.

Synonyms:

Anhydrous Impalpable; Anhydrous 60M; lactosumanhydricum; saccharumlactis; milk sugar

Chemical Name:

O-b-D-Galactopyranosyl-(14)-b-D-glucopyranose

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

Molecular Weight: 342.30

Physical Properties:

White to off-white powder or crystal particles. Lactose Contains 70-80% of β-Anhydrous Lactose and 20-30% of α- Anhydrous Lactose.

Solubility: Soluble in water and insoluble in chloroform, ethanol, and ether.

Melting Point: 232.0^0C

Applications and Uses:

Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous Injections. Used as lyophilization aid and Dry powder inhaler carrier.

HYDROXY PROPYL METHYL CELLULOSE[31]

Nonproprietary Names

BP: Hypromellose

USP: Hydroxy propyl methyl cellulose

Synonyms

Benecel MHPC, Cellulose, Hydroxy propyl methyl ether,E464,HPMC,Methocel,Methyl cellulose, Propylene glycol ether, methyl hydroxyl propyl cellulose, Metolose, Pharmacoat

Chemical name

Cellulose, 2-hydroxy propyl methyl ether

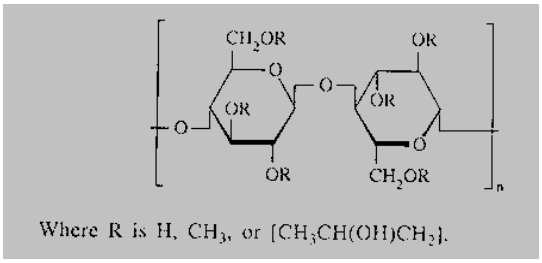
Empirical formula

[CH3CH(OH)CH2]

Molecular weight

10,000-1, 50,000

Structural formula



Where R is H, CH_3, or $[CH_3CH(OH)CH_2]$.

Functional Category

Coating agent, film-former, rate controlling polymer for sustained permeation, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

Application in pharmaceutical formulation technology

HPMC is widely used in oral and topical pharmaceutical formulation. In topical products, HPMC is also used as a suspending and thickening agent.

Description

It is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Typical properties

Bulk density: 0.341g/cc

Tap density: 0.557g/cc

True density:1.326g/cc

Viscosity: HPMC K4M, 4000 CPS; K10M 10,000 CPS

Methoxy content: 19-24%

Hydroxyl propoxy content: 7-12%

Melting point

Browns at 190-200 ºc, chars at 225-230ºc, glass transition temperature is 170-180ºc

Moisture content

Hydroxyl propyl methyl cellulose absorbs moisture from the atmosphere, the amount of water absorbed depending open the initial moisture content and temperature and relative humidity of the surrounding air.

Solubility

Soluble in cold water, mixtures of ethanol dichloromethane, mixtures of methanol and dichloromethane.

Specific gravity: 1.26

Stability and storage condition

Hydroxyl propyl methyl cellulose powder is stable material although it is hygroscopic after drying. Solutions are stable between PH 3-11.Increasing temperature reduce viscosity of solutions. Aqueous solutions are comparatively enzyme resistant, providing good viscosity stability.

Hydroxyl propyl methyl cellulose powder should be stored in a well closed container in a cool and dry place.

Incompatibilities

Hydroxyl propyl methyl cellulose is incompatible with some oxidizing agents. Since it is nonionic, hydroxyl propyl methyl cellulose will not complex with metallic salts or ionic organics to form insoluble precipitation.

CARBOPOL

Carbopols (carbomers) are synthetic high-molecular-weight polymers of acrylic acid that are cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 56% and 68% of carboxylic acid (COOH) groups calculated on the dry basis.

Types: Carbomer 910, 934, 934P, 940, 941, 971P, 974P and 1342

Nonproprietary Names

- BP : Carbomers
- PhEur : Carbomers
- USP-NF : Carbomer

Synonyms

Acrypol; Acritamer; acrylic acid polymer; carbomera; Carbopol; carboxypolymethylene; polyacrylic acid; carboxyvinyl polymer; Pemulen; TegoCarbomer.

Structure:

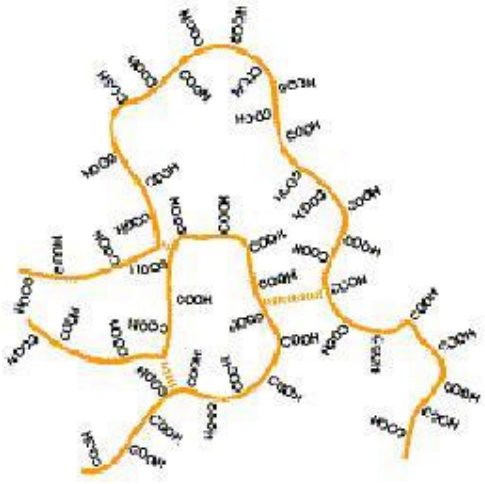


Figure : Chemical structure of carboxypolymethylene

Description:

White-Colored,'fluffy', Acidic, hygroscopic powders with slight characteristic odour.

Solubility:

Soluble in water after neutralization, in ethanolic (95%) and glycerin.

Density:

1.76-2.08 g/cm^3 (bulk); 1.4 g/cm^3 (tapped)

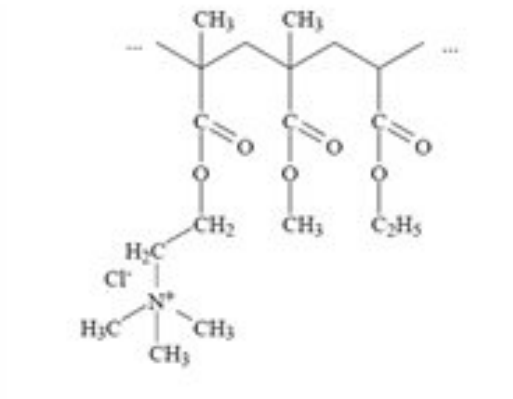
Stability:

Dry powder forms do not support the growth of molds and fungi. Microorganisms grow well in unpreserved aqueous dispersions and therefore an antimicrobial preservative such as chlorocresol (0.1%), methyl paraben (0.18%) & propyl paraben (0.02%), or thiomersol (0.1%) should be added. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.0-0.1% w/v of a water soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with 0.05-0.1% w/v edetic acid. The UV stability of carbomer gels may also be improved by using triethanolamine as the neutralizing base.

Uses:

- Suspending or viscosifier in liquid or semisolid dosage forms, Emulsifying agent for emulsions meant for external use.
- Dry or wet binder, rate controlling polymer and Sustained-release matrix beads.
- Bioadhesive for a cervical patch and magnetic granules for site specific drug delivery to the Oesophagus and in oral mucoadhesive controlled drug delivery system.

EUDRAGIT RS 100



Eudragit RS100 is copolymers of methacrylic acid esters containing an amount of quaternary ammonium groups between 4.5-6.8%. Eudragit RS 100 is insoluble in water and digestive juices,pbut permeable has pH-independent release profiles.

Class : Ammonio Methacrylate copolymer Type B"Ph. Eur.

Molecular wt : 150,000.

Description : Colourless, clear to cloudy granules with a faint amine-like odur

Solubility : miscible with methanol, ethanol and isopropyl alcohol (containing

Approx.3% water), as well as acetone, chloroform, ethyl acetate

And methylene chloride in a ratio of 1:1.

Viscosity : Max. 15 mPa.s

Stability : Stable under ordinary conditions of storage

Storage : Protect from warm temperatures and against moisture.

Keep in tightly closed containers.

Uses : time controlled release of active ingredients

Therapeutically customized release profiles

Higher patient compliance due to reduced

Number of doses to be taken

Application :

- Simple taste masking through gastric resistance to controlled drug release in all selections of the intestine insoluble but permeable in digestive fluids.
- Eudragit RS polymer with alkaline enable controlled release of active ingredient by pH-independent swelling.
- Delayed and sustain drug release

SODIUM BICARBONATE[53]

Non-proprietary Names	**:**	BP/EP: Sodium bicarbonate
Synonym	**:**	Baking soda, E-500, Monosodium carbonate.
Chemical name	**:**	Carbonic acid, Monosodium salt, Monosodium carbonate.
Empirical formula	**:**	NaHCO3
Molecular weight	**:**	84.01
Category	**:**	Alkalizing Agent, Therapeutic Agent.
Description	**:**	It is an odorless, white crystalline powder with slight alkaline taste.
Acidity/ Alkalinity	**:**	pH 8.3 for freshly prepared 0.1M aqueous solutions at 25^0C.
Density	**:**	2.159 g/cm^3
Solubility	**:**	Soluble in water, practically insoluble in ethanol.

Stability and Storage:

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

Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence.

CITRIC ACID ANHYDROUS

Nonproprietary Names

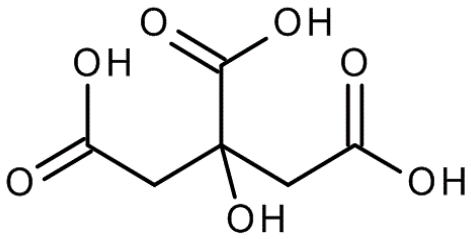
BP: Citric acid monohydrate, **IP:** Citric acid, **PhEur**: Acidumcitricummonohydricum**, USP:** Citric acid

Synonyms: E330; 2-hy droxypropane-1, 2,3-tricarboxyl ic acid monohydrate.

Chemical Name: 2-Hydroxy-1, 2, 3-propanetricarboxylic acid monohydrate

Empirical Formula and Molecular Weight: $C_6H_8O_7$_H20 210.14

Structure:



Functional Category: Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

Applications in Pharmaceutical Formulation or Technology

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products,

Primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric coated formulations for colon-specific drug delivery

Solubility: soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

Stability and Storage Conditions:

Citric acid loses water of crystallization in dry air or when heated to about 408C. It is slightly deliquescent in moist air. Dilute aqueous solutions of citric acid may ferment on standing. The bulk monohydrate or anhydrous material should be stored in airtight containers in a cool, dry place.

TALCUM POWDER(TALC)

Non-proprietary Names:

BP - Purified Talc

JP - Talc

PhEur - Talc

USP - Talc

Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrousmagnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogenmetasilicate; MagsilOsmanthus; Magsil Star; powdered talc;purified French chalk; Purtalc; soapstone; steatite; Superiore;talcum.

Chemical Name and CAS Registry Number:

Talc -14807-96-6.

Empirical Formula and Molecular Weight:

Talc is a purified, hydrated, magnesium silicate, approximating tothe formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variableamounts of aluminium silicate and iron.

Physical appearance :fine ,light and white colour powder.

Identification:

- **Microscopy:** Irregular plats , the majority less than 50µm in length.
- Melt 0.5gm in a metal crucible with 1gm of potassium nitrate and 3gm of anhydrous sodium carbonate, add 20ml of boiling water ,mix and filter . wash the residue with 50ml of water . mix residue with a mixture of 0.5ml of HCL acid and 5ml of water and filter. to the filtrate a 1ml of 9M ammonia and 1ml of ammonium chloride solution and filter .To the filtrate add 1ml of di-sodium hydrogen phosphate solution a white , crystalline precipitate is produced.

Description:

Talc is a very fine, white to greyish-white, odourless, impalpable,unctuous, crystalline powder. It adheres readily to the skin and issoft to the touch and free from grittiness.

Applications in Pharmaceutical Formulation:

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluents, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations.
- In a novel powder coating for extended-release pellets, and as an adsorbent.
- In topical preparations talc is used as a dusting powder, although it should not be used to dust surgical gloves.
- Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

MAGNESIUM STEARATE

Non-proprietary name:

BP, JP, PhEur, and USP: Magnesium stearate.

Synonym:

Dibasic magnesium stearate, magnesium distearate, magnesium octadecanoate, stearic acid.

Chemical name: Octadecanoic acid magnesium salt.

Empirical Formula and Molecular weight: $C_{36}H_{70}MgO_4$ - 591.24.

Structural Formula: $[CH_3 (CH_2)_{16}COO]2M$.

FunctionalCategory: Tablet and capsule lubricant.

Physical appearance: Fine, light, white precipitated or milled, impalpable powder.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility:

Practically insoluble in water, ethanol, and ether. Soluble in warm benzene, and warm ethanol.

Melting point: 117-150^{0}C.

Identification:

5mg of powder add 50ml of ether 20ml of 2M nitric acid and 20ml of distilled water and heat under a reflex condenser until dissolution is completed. Allow to cool, separate the aqueous layer and shake the ether layer with two quantities, Each 4ml of distilled water , combine the aqueous layer , wash with 15ml of ether & dilute to 50ml with distilled water. Evaporate the ether layer to dryness and dry the residue at 105^{o}C the freezing point of the residue is not lower than 53^{o}C .To 1ml of solution A obtained in test A given reaction A of magnesium salt.

Applications:

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is primarily used as at lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

MATERIALS AND METHODOLOGY

MATERIALS

List of drug and excipients

List of equipments/ instruments

METHODS

Pre-formulation Study

Standard plot of Cefixime in 0.1 N Hcl

Drug-excipients interaction study

Fourier transform infra-red (FTIR) spectroscopy

Formulation of floating tablets of Cefixime by direct compression method

Evaluation of floating matrix tablets of Cefixime

Pre compression parameters

Post compression parameters

MATERIALS

Table:3 List of materials

Materials	Supplier
Cefixime (API)	Lara Labs Ltd, Hyderabad, A. P., India
Lactose(Diluent)	Lara Labs Ltd, Hyderabad, A. P., India
HPMC K100 (Rate control in polymer)	Lara Labs Ltd, Hyderabad, A. P., India
Carbopol (Rate control in polymer)	Lara Labs Ltd, Hyderabad, A. P., India
Eudragit (Rate control in polymer)	Lara Labs Ltd, Hyderabad, A. P., India
Sodium bicarbonate (Gas Generating Agent)	Lara Labs Ltd, Hyderabad, A. P., India
Citric acid (Gas Generating Agent)	Lara Labs Ltd, Hyderabad, A. P., India
Magnesium stearate (Lubricant)	Lara Labs Ltd, Hyderabad, A. P., India
Talc (Lubricant)	Lara Labs Ltd, Hyderabad, A. P., India

EQUIPMENTS/INSTRUMENTS

Table 4 List of equipments/ instruments

Equipment's	Model/Company
Electronic balance	Shimadzu AUX220, Japan.
Tablet compression machine	Lab India Ltd., India
Tablet hardness tester	Pfizer hardness tester
Dissolution test apparatus	Electrolab, India
Friability test apparatus	Roche Friabilator(USP), Electrolab, India
UV-Visible Spectrophotometer	Shimadzu UV-1800, Japan
FTIR spectrophotometer	Bruker (Tensor 27)
Tap density taster	Electrolab, India

METHODS:

Preformulation study:

Estimation ofCefixime:

Preparation of standard solution:

Equivalent 500mg of the pure Cefixime trihydratewas weighed and transferred into 50ml volumetric flask. The drug was then dissolved and diluted up to the mark with 0.1N Hcl to get a concentration of 1000µg/ml of stock solution 1. 2ml of stock 1 solution was taken and diluted to 100 ml to give 20µg/ml solution.

Preparation of working standard solutions

From the stock solution 2 aliquots were pipetted out 2.5, 3.75, 5, 6.25, and 7.50ml and transferred to 25 ml volumetric flasks and diluted up to the mark with acidic buffer pH 1.2 to get concentration of 50, 75,100,125, and 150µg/ml, respectively. The absorbance of the solutions was measured at λ_{max}235.0 nm using double beam UV-visible spectrophotometer (UV1800, Shimadzu, Kyoto, Japan) against suitable mixture as a blank. The plot of absorbance vs. concentration (µg/ml) is plotted & data was subjected to linear regression analysis in Microsoft excel (2007).The obtained results are given in Table 5.1 and Figure 5.2.

0.1NHcl Preparation

8.5ml of concentrated Hcl measured and transfer in 1ltr beaker dil. with water mix properly then make up to 1000ml.

Drug-excipients interaction study:

Fourier Transform infra-red (FTIR) spectroscopy:

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of cefixime and 200-300 mg of dry powder of KBr(IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 2000-400cm^{-1} by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Table.5

Composition of Cefixime GRDDS by Direct Compression Method

Composition(mg/tab)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Cefixime	200	200	200	200	200	200	200	200	200
Lactose	90	40	90	40	90	40	140	140	140
Hpmc K100	100	150	-	-	-	50	-	-	-
Carbopol	-	-	100	150	-	-	-	50	-
Eudragit	-	-	-	-	100	150	-	-	50
Sodium bicarbonate	80	80	80	80	80	80	80	80	80
Citric acid	20	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Formulation of floating tablets of cefixime by direct compression method:

Procedure: Floating tablets of Cefixime were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. HPMC K100, Carbopol, and Eudragit were used as rate controlling polymers. The concentrations of the above ingredients were optimized on the basis of trial preparation of the tablets. All the ingredients [**Table**] were weighed accurately. The drug was mixed with the release rate retarding polymers and other excipients, except talc and Magnesium stearte, in ascending order of their weight. The powder mix was blended for 20 minutes to have uniformdistribution of drug in the formulation. Then, Magnesium stearate was added and mixed for not more than 1 minute (to ensure good lubrication.)About 500 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 12mm flat- surface punches.The hardness of the tablets was adjusted at 4-5 kg/cm^2 using a Pfizer hardness tester.

Pre compression parameters:

Angle of Repose: - The angle of repose is the constant, three dimensional angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.

Table 6 Angle of Repose with flow properties

Flow properties	Angle of Repose (degrees)
Excellent	up to 20
Good	20 to 30
Fair / Reasonable	30 to 40
Flow with difficulty	above 40

Bulk density, Tapped density, % Compressibility index & Hausner ratio:

a. Apparent Bulk Density: The bulk density was determined by transferring the accurately weighed sampleof powder to the graduated cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculatedby using the following formula.

Density = Mass/Volume.

b. Tapped Density: Weighed powder sample was transferred to a graduated cylinder and was placedon the tap density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the following formula.

Density = Mass/Tapped Volume.

c. Percentage Compressibility: Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by the following formula.

% Compressibility = Tapped density – Bulk density *100/ Tapped density

Table: 7 % Compressibility limits with respect to flowability

S.No	%Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than	Very very poor

d. Hausner's Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio = Tapped density/Bulk density

Table:8 Hausner ratio limits as per IP

Hausner's ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

e. Drug to Polymer compatibility Study:

The IR spectrums of Cefixime & dosage forms containing polymers (HPMC, Eudragit carbopol) were recorded using ???Alpha Brooker FTIR (Tokyo, Japan).using pellate technique. All these results are shown in figure

Post compression parameters:

Hardness

The hardness of ten tablets was found using Pfizer Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Friability

The friability of the tablets was determined using Roche friabilator(Remi Electronics, Mumbai, India). It is expressed in percentage.10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

$$\%of\ Friability = \frac{InitialWeight - FinalWeight x 100}{InitialWeight}$$

Acceptable weight loss: NMT 0.5-1%

Weight variation

Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit. The weight variation tolerance for uncoated tablets is as follows:

Table: 9 Standard weight variation limits (USP)

Average Tablet weight	% Deviation
130mg	10
>130mg-324mg	7.5
>324mg	5

% Deviation =Average weight – Tablet weight *100/. Average weight

1. **Thickness:** The thickness of the tablets was determined using. Vernier Calipers. Five tablets from each batch were used. The results are shown in Table ???.
2. **Content Uniformity Test:**

   For determination of drug content three tablets from each formulation were weighed individually, crushed and a quantity of powder equivalent to 100mg weighed and is dissolved in 100ml of water to give a solution of 1mg/ml. 1.0 ml of this solution was further diluted up to 10.0 ml with distilled waterto give a solution of concentrations 100 ugm/ml. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 258 nm against blank.

Amount of drug release = $\frac{\text{Conc} \times \text{dilution factor} \times \text{wt of tablet}}{1000 \times \text{wt of sample}}$ i.

%Drug release = $\frac{\text{Amount of drug release} \times 100}{\text{Label claim}}$ ii.

Table:10 Content uniformity limits

Number of tablets	Acceptable criteria
9 out of 10	85-115%
1 may be	75-125%
27 ut of 30	85-115%
2 may be	75-125%

Dissolution studies:

The in-vitrorelease of Cefiximefrom formulated tablets was carried out for 24 hours in 0.1N Hcl. The studies were performed in USP dissolution apparatus II (Electrolab, Mumbai, India) at 37 ± 0.5° C and 50 rpmspeed. Samples were taken at 2, 4, 8, 16, 20 & 24hours and diluted to suitable concentration and analyzed for Cefixime content at 235 nm by using UV–visible spectrophotometer The values are shown in Table 24 and plots for the same are shown in Figure 22&23.

% Drug release= $\frac{\text{Amount of drug released} \times 100}{\text{Label claim}}$

TABLE Standard dissolution parameters

Stage	No.of tablets	Acceptance criteria
S1	6	No tablet<D+5%
S2	6	Avg of 12tab ≥ D; No unit<D_15%
S3	12	Avg of 24 tab, S1+S2+S3≥D NMT 2 tab<D_15%, No unit<D_25%

Swelling Index[36] :

This was measured in terms of percentage(%) weight gain by the tablet. First prepare the 0.1NHcl take for each formulation separate Petri-dish and pour the buffer into the Petri-dish, insert the tablet in according the sequence and measure the % gain of the tablet with the interval .

S.No	Parameters	Specification for formulation's
1	Petri-dish	Glass material
2	Medium	0.1 Hcl
3	Time interval	2hours (up to 24 hours)

Table:16 list of parameter for Swelling Index

The % weight gain of the tablet was calculated by the following formula,

$$S.I=\{(M_t - M_o) / M_o\} \times 100$$

Where,

S.I = swelling index

M_t = weight of the tablet at the time(t) and

M_o=weight of the tablet at the time(t) = 0

Drug release kinetics:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

- **Zero-Order Kinetics:**

Zero order as cumulative amount of drug released vs time,

$$C = K_0 t$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration Vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

- **First order kinetics:**

First order as log cumulative percentage of drug remaining vs time,

$$Log\ C = Log\ C_o - k\ t / 2.303$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

A graph of log cumulative of % drug remaining vs time yields a straight line.

- **Higuchi Model:**

Higuchi's model as cumulative percentage of drug released vs square root of time

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

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

A graph of cumulative % drug released vs square root t yields a straight line

- **Korsemayer Peppas equations:**

To evaluate the mechanism of drug release from Disulfiram implant, data for the first 60% of drug release were plotted in Korsmeyer et al's equation log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$M_t / M_\infty = K t^n$

Where, M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

PREFORMULATION STUDY[10]:

Preformulation studies are the first step in development of dosage form of a drug substance. Preformulation studies are performed to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation.

"Preformulation" can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Goals of Preformulation:

1) To establish the necessary physicochemical parameters of a new drug substance
2) To determine its kinetic rate profile
3) To establish compatibility with common excipients

Physicochemical parameters:

- Solubility of drug
- Particle size
- Bulk density
- Tapped density
- Carr's index & Hausner ratio
- Flow property (Angle of Repose)
- F.T.I.R spectra

Organoleptic Properties:

Physical characterization of drug components was observed, such as color, odor, and appearances of the Active Pharmaceutical Ingredients(API) were examined.

Melting Point:

The point at which the drug or Active Pharmaceutical Ingredient was melts into liquid. This phenomenon helps in the characterization of the API polymorphism, presence of impurities, degradation and drug excipient compatibility.

Solubility:

It is the phenomenon that relates the drug in solid state, forms solution on contact with solvent. According to the BCS classification based on solubility the components are said to be given follow.

- very soluble (Class I and Class III) and
- poorly soluble (Class II and class IV).

The solubility of the API's (Active Pharmaceutical Ingredient)checked in 4 types of solvents such as water, 0.1N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer, and pH 7.2 Phosphate buffer

Density:

The ratio between weight to volume called as density. It is expressed as gm/cc.

Determination of bulk density:

Weigh accurately 25 g of blend (W), which was previously passed through 20 # sieve and transfer in 100 ml graduated measuring cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula;

Bulk density = Weight of powder / Bulk volume

Determination of tapped density:

Weigh accurately 25 g of blend, which was previously passed through 20 # sieve and transfer in 100 ml graduated measuring cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volume was less than 2 % then final the volume (V_2).

Tapped density = W/V_t gm/ml

W = weight of the blend

V_t = Tapped volume

Carr's compressibility index &Hausner's Ratio:

The compressibility index and Hausner ratio were measure the propensity of powder to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows;

$$Carr's index = \frac{Tappeddensity - Bulkdensity}{Tappeddensity} * 100$$

$$Hausnerratio = \frac{Tappeddensity}{Bulkdensity}$$

Compressibility index (%)	Flow character	Hausner 's Ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Table: Flow character related to Compressibility index and Hausner ratio

Angle of repose:

The maximum possible angle between the height of the pile to the surface of the plane. The frictional force in the powder can be measured by the angle of repose. Angle of repose was calculated by **fixed funnel method**. The funnel was fixed to a measured height. The powder blend was allowed to flow through funnel onto the surface until the apex of the heap touches the tip of the funnel. And the diameter of the heap was measured. Angle of repose was calculated by following formula;

$$\tan\theta = \frac{h}{r}$$

Where,

h = Height of the powder heap in cm.

r = Radius of heap in cm.

Angle of repose (Ɵ)	**Predicted flow property**
25-30	Excellent
31-35	Good
36-40	Fair (Aid not needed)
41-45	Passable (May hang up)
46-55	Poor (Must agitate or vibrate)
56-65	Very poor
>66	Very very poor

Table: Angle of Repose related Flow Property

Angle of repose were calculate by given above methods and the flow property will decided according the above table.

F.T.I.R SPECTRA:

IR spectra of bulk drugs were taken using F.T.I.R Spectrophotometer (F.T.I.R: Shimadzu 1200 S, JAPAN). F.T.I.R spectrum of drug was taken by using KBr pellet method. Pellets of drug and KBr (1:10) were prepared using hydraulic press and analyzed in F.T.I.R spectrophotometer. Drug –Excipient Incompatibility studies were carried out to detect the incompatibility between API and Excipients such that drug stability can be predicted at storage conditions. The studies were carried by different methods used, F.T.I.R spectra interpretation gives the picture about the incompatibility between drug and excipient.

RESULT AND DISCUSSION

Preformulation Studies:

Physical Characterization:

Cefixime:

Color	Whitish
Odour	Odour less
Appearance	Powder

Table:11 Physical Characterization of Cefixime

Melting Point Determination:

Drug	Reported Melting Point	Observed Melting Point
Cefixime	205 – 207^{0}C	205.8^{0}C

Table: 12 Melting point determination of the Cefixime

Conclusion: the drug melting point range in value.

Solubility:

The solubility was checked in different mediums for Cefixime which was a Class II drug it was found to be insoluble in water and the solubility decreased with increasing pH .

The solubility of the cefixime as followed;

0.1N HCl< pH 4.5 Acetate Buffer < pH 6.8 < pH 7.4 Phosphate buffer

Conclusion: The appropriate medium for the drug was found to be pH 0.1 Hcl. So it was used as the dissolution medium for the further evaluation.

Density and Flow Properties:

Bulk density	0.59g/c.c
Tapped density	0.65 g/c.c
Carr's Compressibility index	9.52%
Hausner's ratio	1.10

Table:13 Flow properties of Cefixime

Conclusion: The drug having poor flow property.

F.T.I.R of The Drug And Excipients:

F.T.I.R OF CEFIXIME

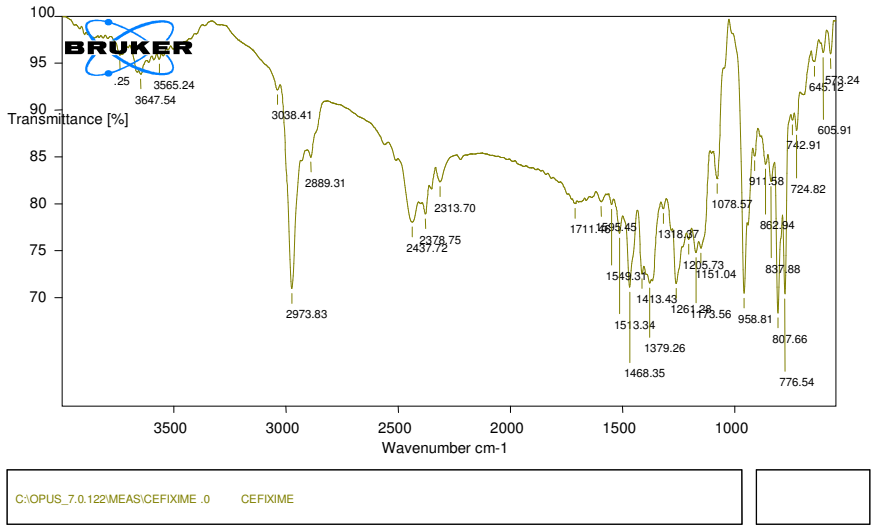


Fig.6

DRUG+EUDRAGIT

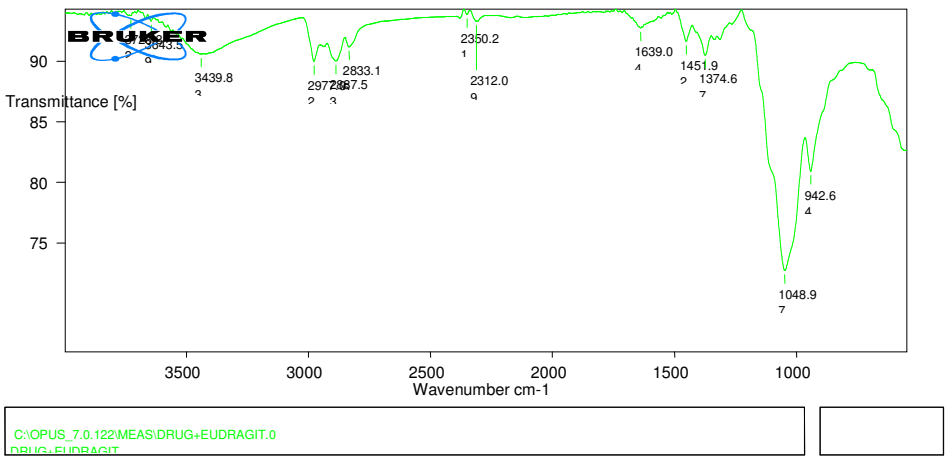


Fig.7

DRUG+LACTOSE

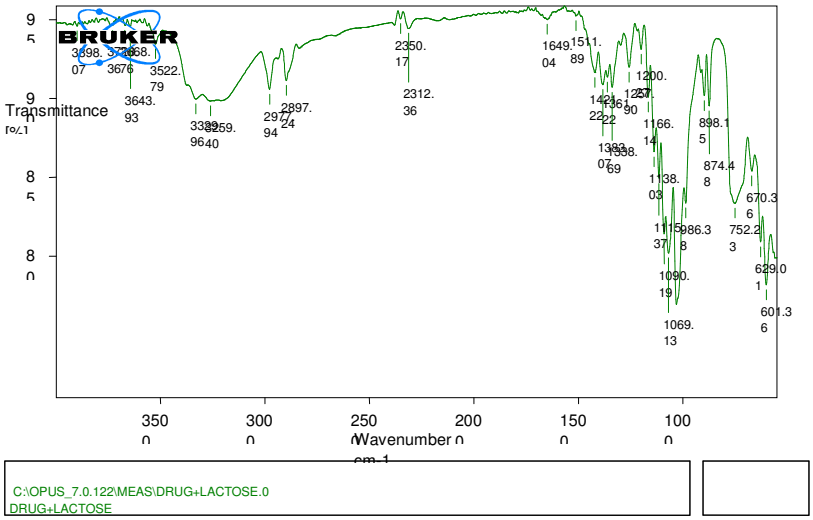


Fig.8

DRUG+CARBOPOL

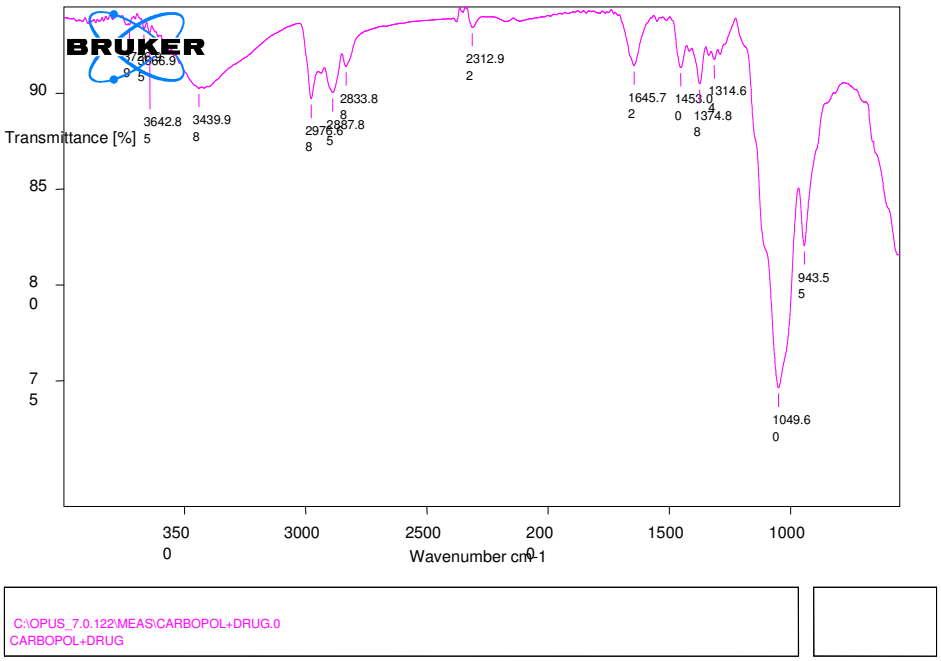


Fig.9

DRUG+MG.STERATEFfi

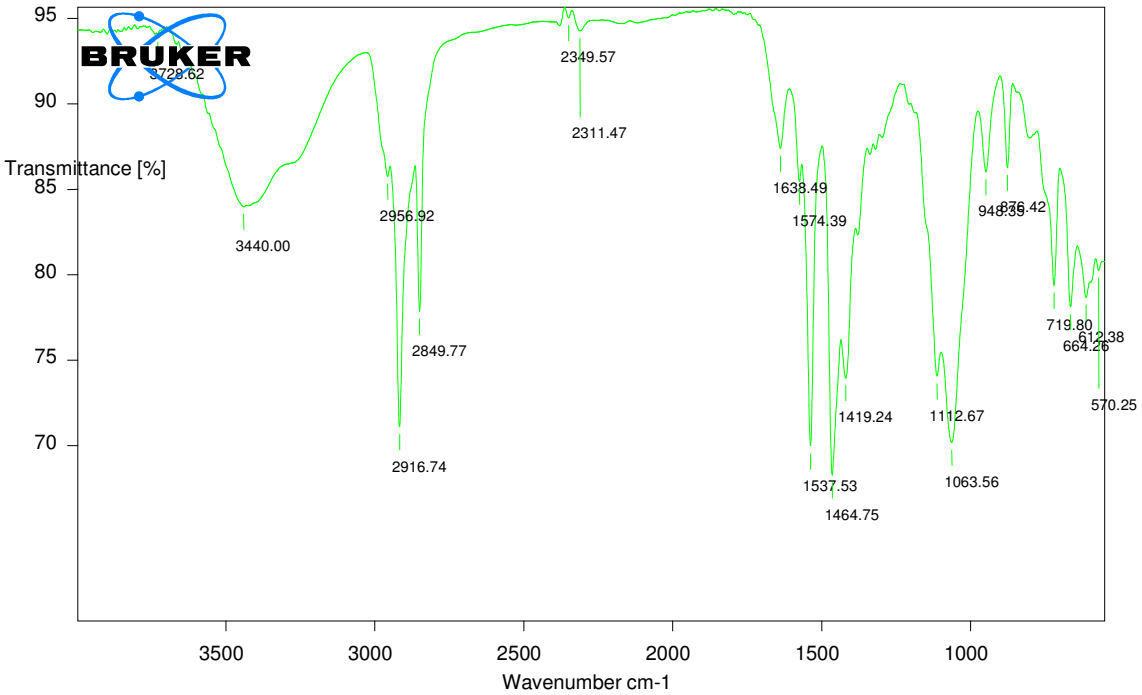


Fig.10

DRUG+HPMC

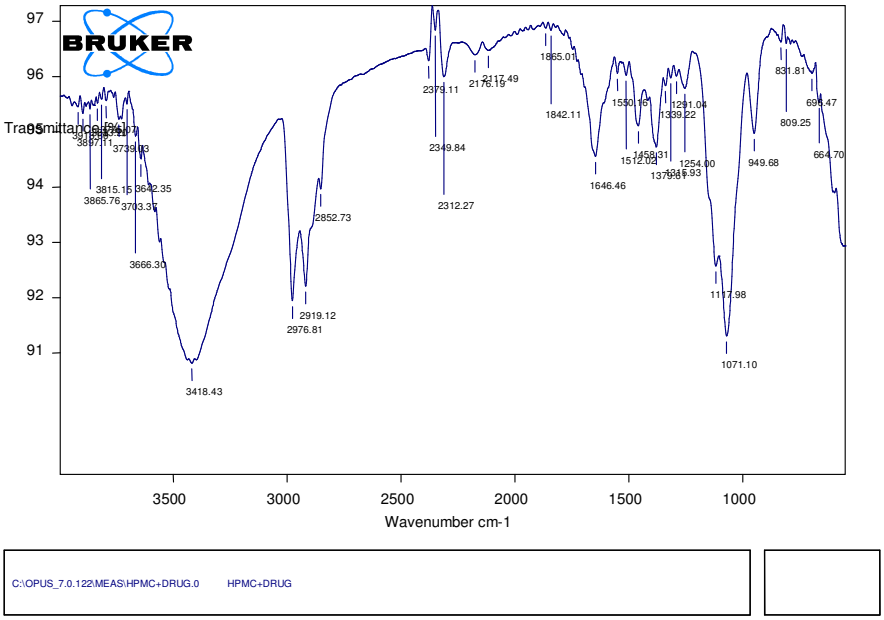


Fig.11

DRUG+SODIUM BICARBONATE

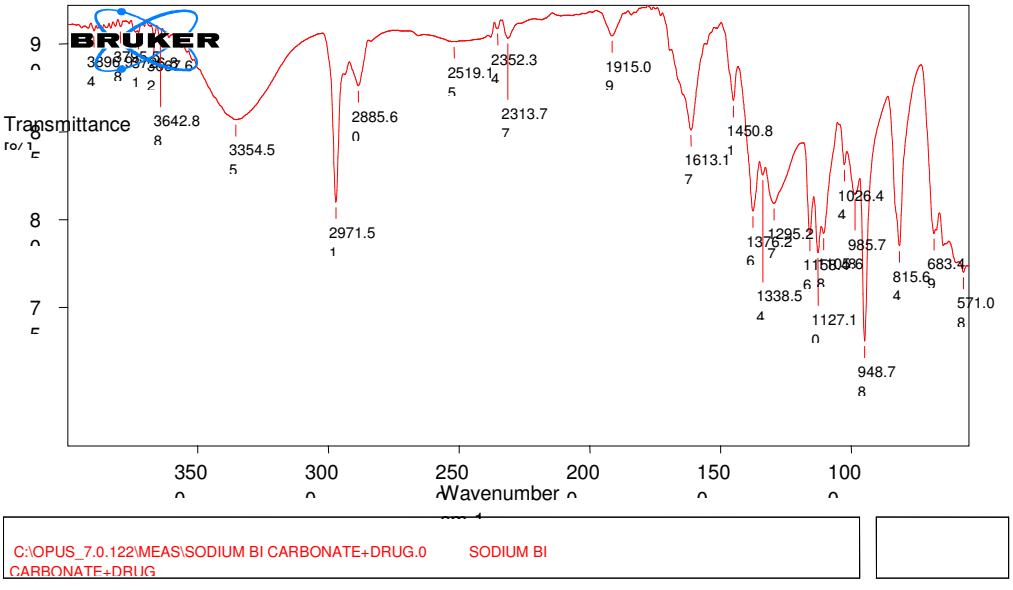
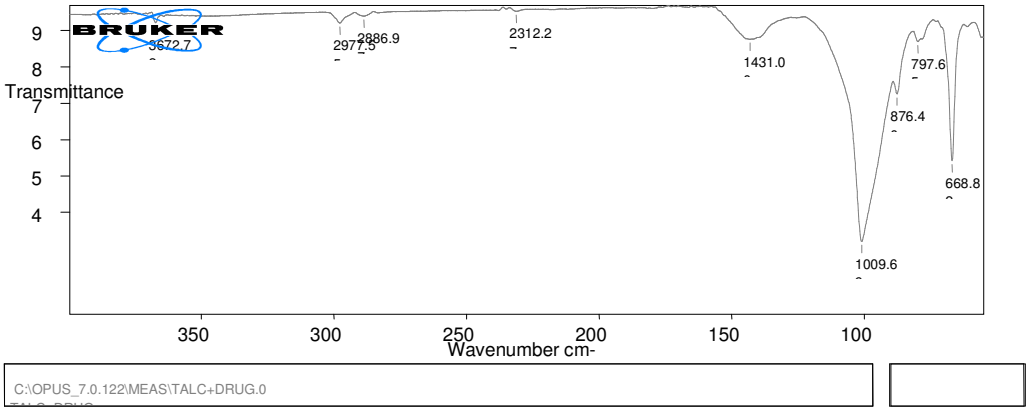


Fig.12



TALC+DRUG

Fig.13

Conclusion: There is noappearance or disappearance of characteristic peaks in above spectrum .

Evaluation Of Formulated Blend:

Batch code	Bulk density gm/cc	Tapped density gm/c.c	Carr's index %	Hausner ratio	Angle of repose θ
F1	0.5208	0.6250	16.666	1.2000	21.32
F2	0.5434	0.6250	13.0434	1.1500	23.51
F3	0.5434	0.6250	13.0434	1.1500	23.14
F4	0.5208	0.5682	8.3333	1.0909	21.24
F5	0.5952	0.6579	9.5238	1.1052	21.26
F6	0.5952	0.6579	9.5238	1.1052	21.65
F7	0.5208	0.6579	20.833	1.2631	21.75
F8	0.5952	0.6944	14.2857	1.1666	22.42
F9	0.5952	0.6944	14.2857	1.1666	22.55

Table: Evaluations of the Formulation Blend

Conclusion: The formulation blend was good flow property.

Evaluation of Cefixime Matrix Tablet:

Batch code	Average Weight mg	Thickness mm	Diameter mm	Hardness Kg/c.m	Friability %	Drug content %	Swelling index %
F1	503.55	4.13	12.16	7.0	0.51	97.15	92.05
F2	505.33	4.15	12.10	7.1	0.55	96.12	94.06
F3	506.43	4.19	12.11	7.3	0.45	97.03	98.02
F4	507.51	4.10	12.13	6.8	0.47	95.21	94.22
F5	501.37	4.12	12.05	6.9	0.60	96.36	95.55
F6	502.21	4.11	12.12	6.9	0.47	95.01	92.05
F7	501.05	4.14	12.10	7.5	0.62	97.36	93.45
F8	500.00	4.05	12.12	7.2	0.26	97.21	97.35
F9	498.83	4.20	12.14	7.4	0.65	96.25	98.25

Table:14 Evaluations of the Cefixime Matrix Tablet

Conclusion: The weight variation of each formulation not out of limit ±7.5, Hardness of the formulation is studied and values are not less than 5 kg/cm^2 limits. Friability is not more than 1% of the original weight and disintegration also studied.

Photos of Formulation F-3&F-5:

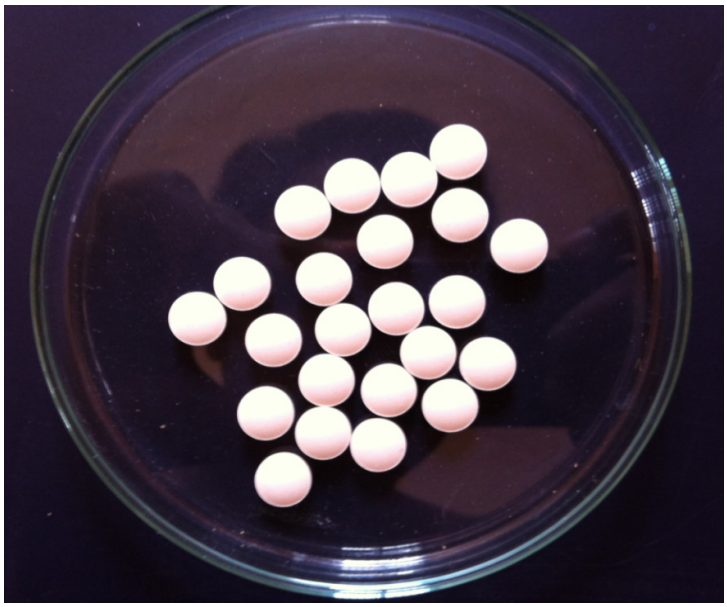


FIG-: photo of F-3 formulation

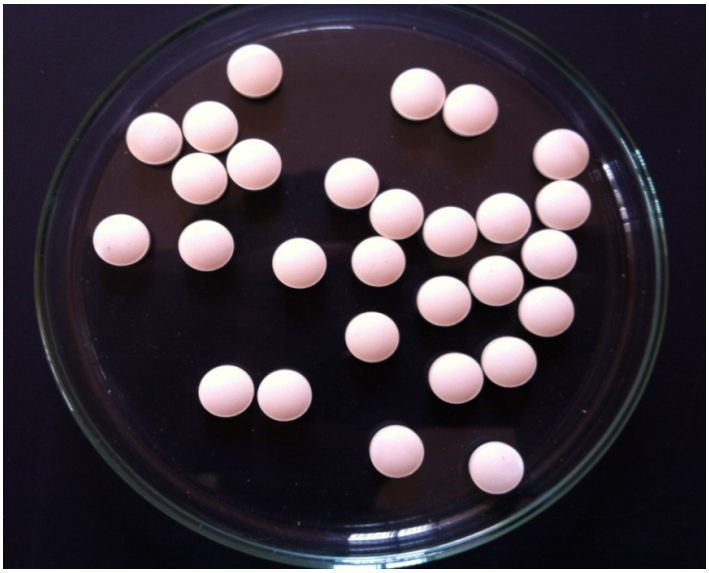


FIG-: photo of F-5 Formulation

In-Vitro Drug Release :

Standard Calibration Curve Of Drug:

Calibration Curve values of Cefixime:

S.No	Concentration(µg/ml)	Absorbance
1	50	0.312
2	75	0.458
3	100	0.625
4	125	0.781
5	150	0.937

Table:15 Calibration curve values of Cefixime

Standard Graph of Cefixime:

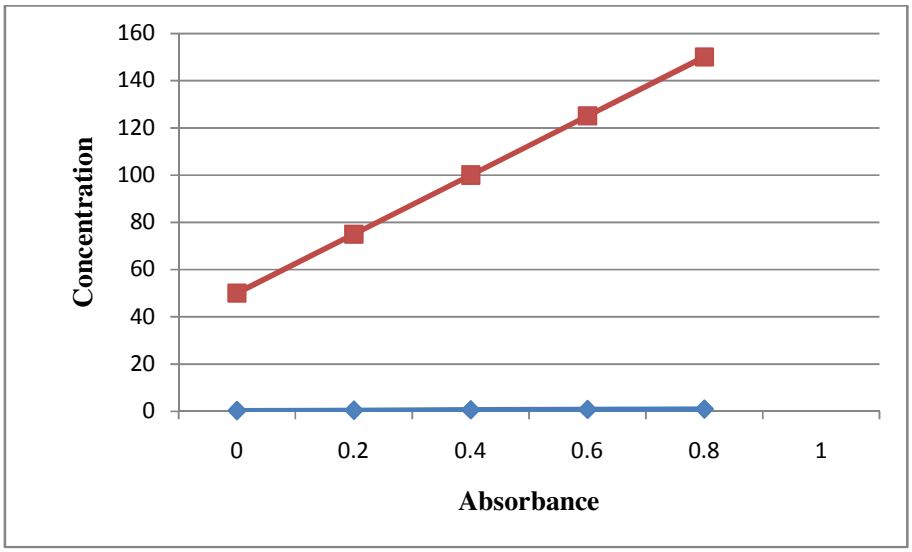


FIG: 16 Standard graph of Cefixime

Dissolution Profile Of CefiximeTablet:

Apparatus: USP- type (6-paddle)

Medium : pH0.1N Hcl buffer

Rpm : 50 rpm

Volume : 900ml(1000ml-100ml)

Absorption maxima: 235nm

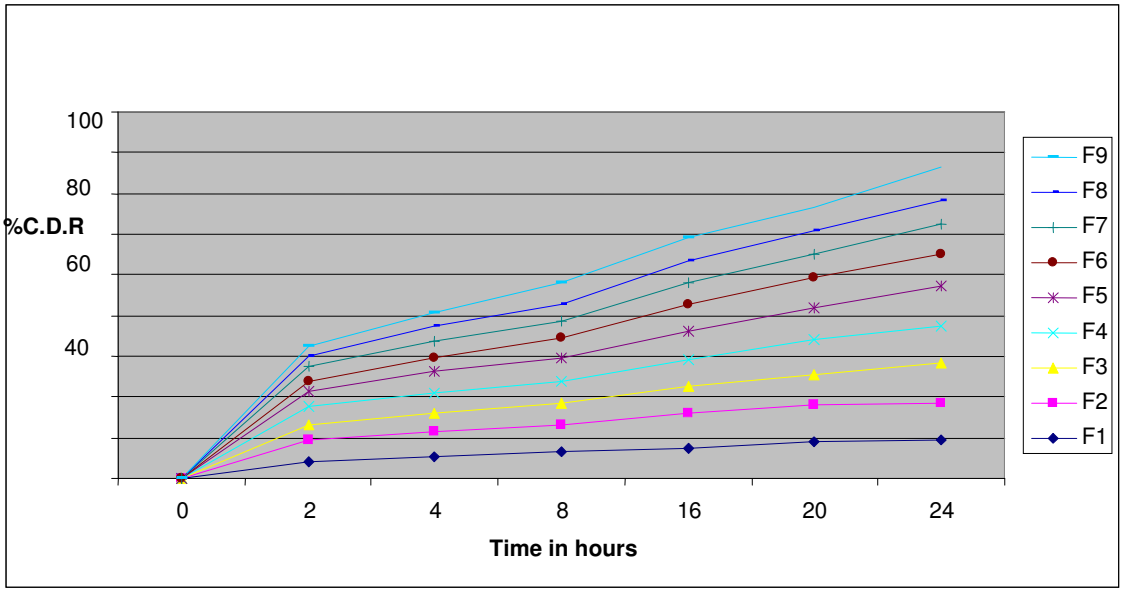
In-Vitro Drug Release:

% Cumulative Drug Release:

% Cumulative Drug Released(C.D.R)									
Time(hr)	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**
0	0	0	0	0	0	0	0	0	0
2	40.25	55.23	37.52	42.89	39.05	23.56	35.06	28.25	23.25
4	55.27	60.25	46.49	48.32	50.99	35.96	40.25	35.62	33.62
8	66.25	65.54	52.49	55.65	55.144	50.25	42.65	40.25	52.25
16	75.28	85.62	64.82	67.89	67.47	65.23	55.98	52.36	55.95
20	90.25	89.85	74.56	87.32	78.33	72.35	58.61	56.25	56.28
24	92.55	94.32	96.96	90.41	97.06	80.45	71.12	60.21	79.28

Table no-29: % C.D.R of F-1 to F-9

FormulationsFIG-24: %C.D.R of F-1 to F-9



Swelling Index of the F-3&F-5 Formulations:

S.No	Time in hours	F-3%	F-5%
1	0	0	0
2	2	35	36
3	4	40	45
4	8	50	55
5	16	74	85
6	20	85	90
7	24	96	94

Table:15 Swelling properties of the F-3 & F-5 Formulations

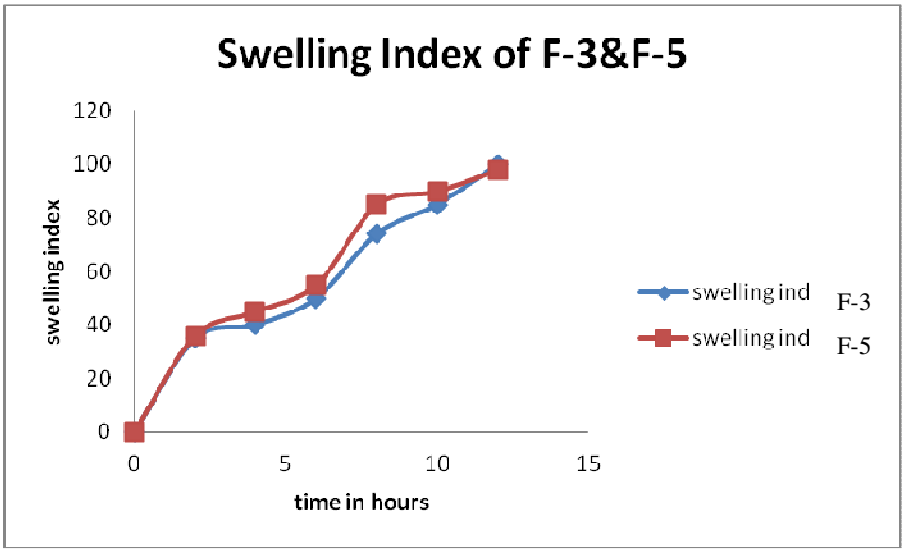


FIG-:16 Swelling property of F-3 & F-5 Formulations

Photo Graphs Of S.I Of F-3&F-5:

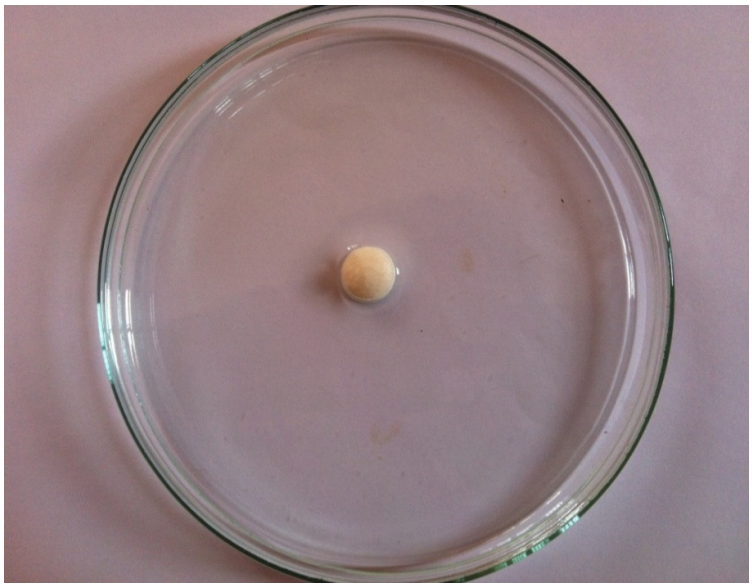


FIG-: Photo of F-5 before S.I

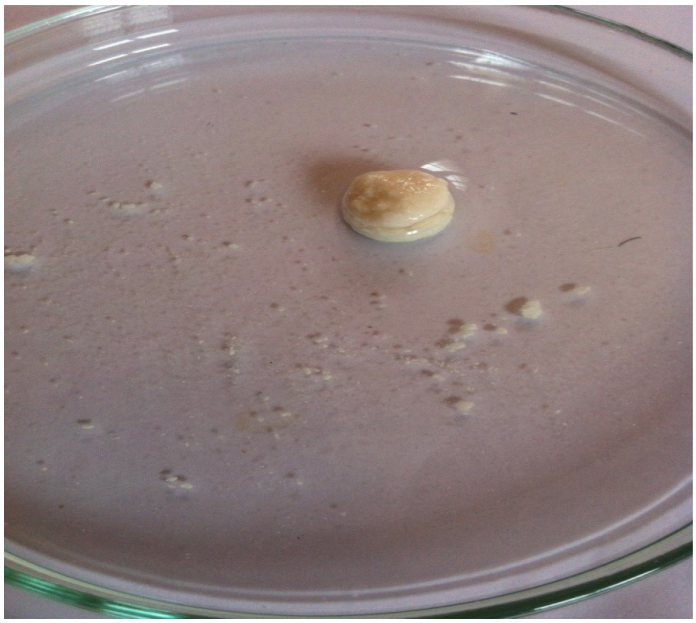


FIG-: Photo of F-3 at 24th hour of S.I

FIG-: Photo of F-5 before S.I

FIG-: photo of F-5 at 24th hour of S.I

Assay of F-3&F-5 Formulations:

Assay(%)	Formulation -3	Formulation-5
Value	96.96%	97.06%

Table: Assay of F-3& F-

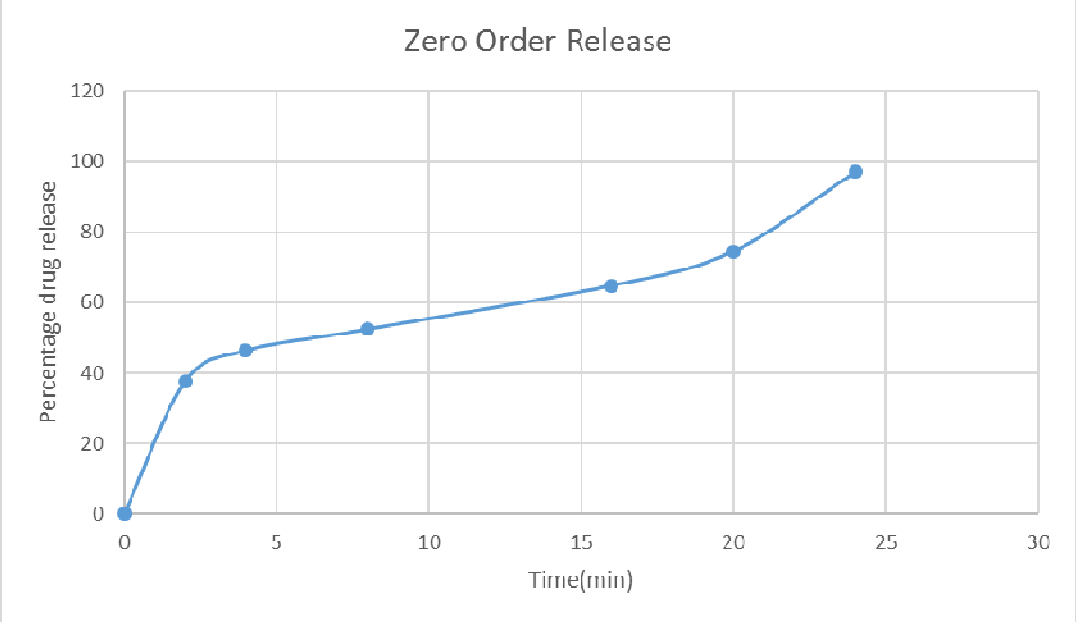
Conclusion: The assay value is within limits only.

Releaseof Kinetics:

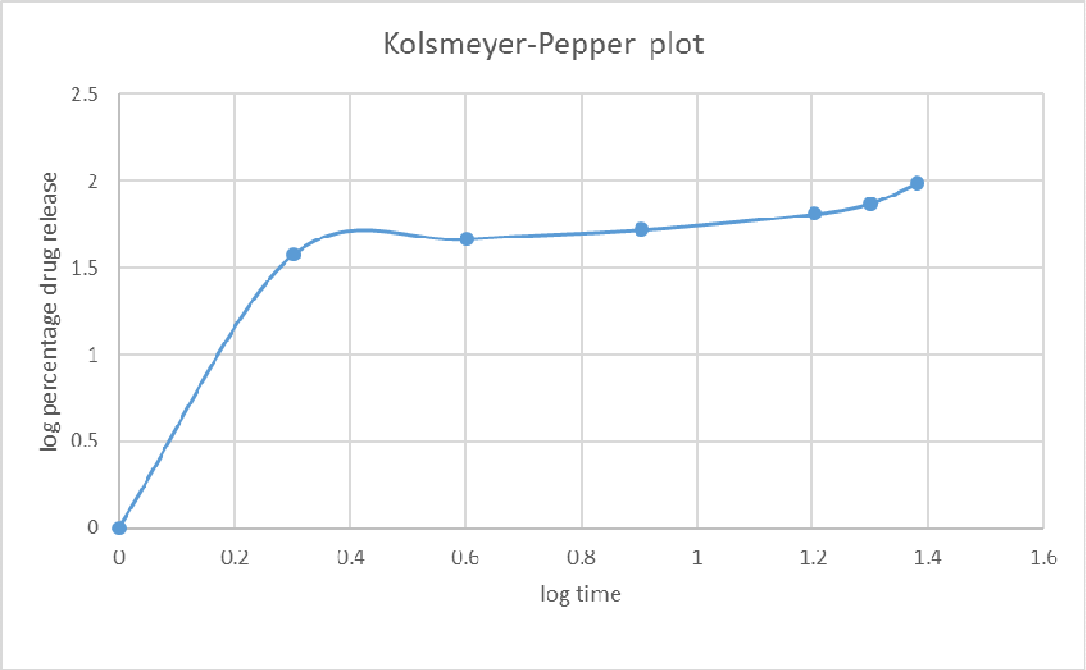
Release Kinetics of F-3 Formulation:

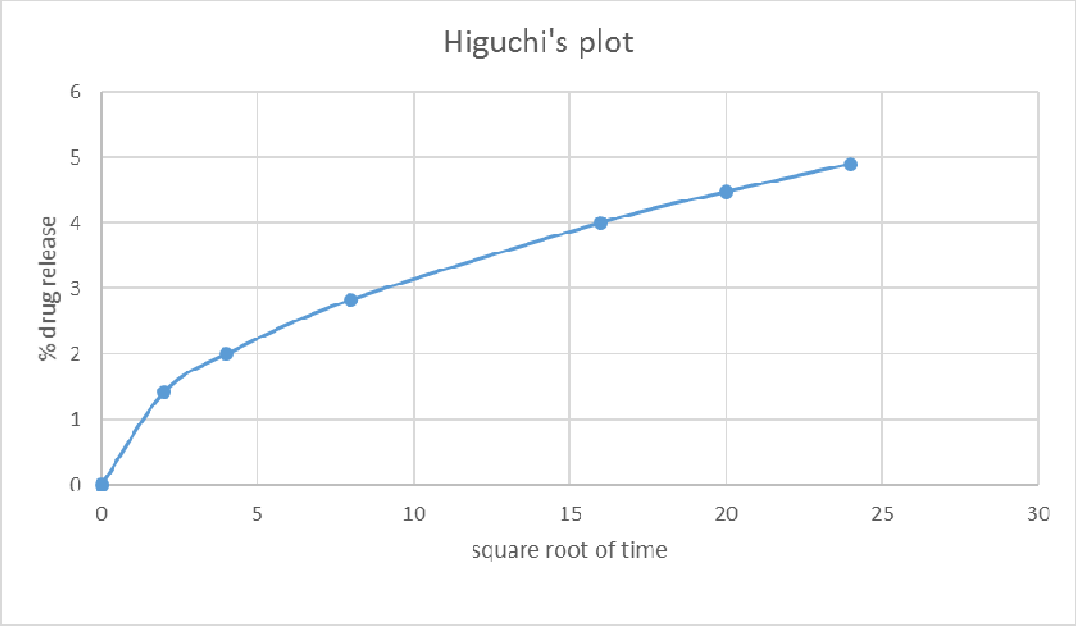
S.No	Time	SQRT	Log time	%C.D.R	Log %C.D.R	SQR of %C.D.R
1	0	0	0	0	0	0
2	2	1.41	0.30	37.52	1.5742	6.1253
3	4	2.00	0.60	49.49	1.6673	6.8183
4	8	2.45	0.90	52.49	1.72	7.245
5	16	2.83	1.20	64.82	1.8117	8.0510
6	20	3.16	1.30	74.56	1.8725	8.6348
7	24	3.46	1.38	96.96	1.9865	9.8468

Table: Release Kinetics of




First Order release
Percentage drug release
2.5
2
1.5
1
0.5
0
0
5
10
15
20
25
30
Time (min)





Conclusion:

- In Formulation-3, the R^2 values of Zero order and First order showing equal and the values are more than Higuchi and Korsmeyerpeppas values.

Stability Study:

Result of stability conducted of F-3 , Sample at 25°C±2°C 60%±5%RH & 40°C±2°C 75%±5% RH storage condition

Product: F-3 (CEFIXIME Matrix Tablet-500mg)

At25°C±2°C 60%±5%RH storage condition:

Parameters	Initial values	One month	Two months	Three months
Appearance	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour
Thickness (mm)	4.13	4.13	4.13	4.13
Hardness (kg/ cm^2)	7.3	7.3	7.3	7.4
Friability (%)	0.4	0.4	0.4	0.4
Dissolution test in hours (2,4,8,16,20,24hr)	2-37.52% 4-49.49% 8-52.49% 16-64.82% 20-74.56% 24-96.96%	2-35.52% 4-46.25% 8-50.25% 16-64.32% 20-72.51% 24-93.25%	2-32.25% 4-42.25% 8-48.25% 16-62.36% 20-70.21% 24-92.25%	2-30.25% 4-40.25% 8-41..25% 16-61.25% 20-69.21% 24-92.25%
Assay (%)	97.80	96.89	96.50	95.50

Table: **Stability studies of F-3 at 25°C±2°C and 60%±5%RH storage condition**

- **At 40°C±2°C and 75%±5% RH storage condition:**

Parameters	Initial values	One month	Two months	Three months
Appearance	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour
Thickness (mm)	3.2	3.2	3.2	3.2
Hardness (kg/ cm^2)	7.3	7.3	7.3	7.4
Friability (%)	0.4	0.4	0.4	0.4
Dissolution test in hours(2,4,8,16,20,24hr)	2-37.52% 4-49.49% 8-52.49% 16-64.82% 20-74.56% 24-96.96%	2-35.52% 4-46.25% 8-50.25% 16-64.32% 20-72.51% 24-93.25%	2-32.25% 4-42.25% 8-48.25% 16-62.36% 20-70.21% 24-92.25%	2-30.25% 4-40.25% 8-41..25% 16-61.25% 20-69.21% 24-92.25%
Assay (%)	97.80	97.67	97.03	97.45

Table : Stability studies of F-3 at 40°C±2°C and 75%±5% RH storage condition

Product: F-5(CEFIXIME Matrix Tablet-10mg)

At25°C±2°C 60%±5%RH storage condition:

Parameters	Initial values	One month	Two months	Three months
Appearance	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour
Thickness (mm)	4.13	4.13	4.13	4.13
Hardness (kg/ cm^2)	7.3	7.3	7.3	7.3
Friability (%)	0.4	0.4	0.4	0.4
Dissolution test in hours(2,4,8,16,20,24hr)	2-37.52% 4-49.49% 8-52.49% 16-64.82% 20-74.56% 24-96.96%	2-35.62% 4-46.25% 8-50.25% 16-62.26% 20-73.25% 24-95.26%	2-31.12% 4-42.25% 8-49.25% 16-60.21% 20-72.24% 24-93.36%	2-30.21% 4-40.21% 8-48.25% 16-69.65% 20-72.21% 24-93.20%
Assay (%)	96.4	96.4	95.6	96.1

Table: Stability studies of F-5at 25°C±2°C and 60%±5%RH storage condition

- **At 40°C±2°C 75%±5% RH storage condition:**

Parameters	Initial values	One month	Two months	Three months
Appearance	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour	Light brownish-white colour
Thickness (mm)	4.13	4.13	4.13	4.13
Hardness (kg/ cm^2)	7.3	7.3	7.3	7.3
Friability (%)	0.4	0.4	0.4	0.4
Dissolution test in hours(2,4,8,16,20,24hr)	2-37.52% 4-49.49% 8-52.49% 16-64.82% 20-74.56% 24-96.96%	2-35.62% 4-46.25% 8-50.25% 16-62.26% 20-72.25% 24-95.26%	2-31.12% 4-42.25% 8-49.25% 16-60.21% 20-71.24% 24-93.36%	2-30.21% 4-40.21% 8-48.25% 16-69.65% 20-70.21% 24-93.20%
Assay (%)	97.4	96.21	96.6	95.1

Table: stability studies of F-5 at 40°C±2°C and 75%±5% RH storage condition

DISCUSSION

Buoyant drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

In the present work efforts have been made to develop Floating drug delivery system for Cefixime containing HPMC of viscosity grade (HPMC $K_{100}M$) and Lactose CarbopolEudragit.

The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug Cefixime in the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers.

all formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The angle of repose value ranged from 21^{o} 14" ± 0.15 to 23^{0} 51" ±0.19. The results were found to be below 30^{0} and hence the blend was found to have poor flow ability. Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.44±0.04 to 0.51±0.04 and 0.50 ± 0.07 to 0.59 ± 0.04respectively. The compressibility index (%) was then calculated form the LBD and TBD and it ranged from 8.33±0.6 to 14.28±0.8 . The blend was found to have free flowing property as the result were found to be below 19%. The Hausner ratio ranged from 1.11±0.04 to 1.18±0.08. The result indicates the free flowing properties of the Powder as the value was below 1.2.

The floating tablets of Cefixime were prepared by effervescent technique using HPMC grade of viscosity (HPMC $K_{100}M$), sodium bicarbonate and citric acid, Lactose, Carbopol, Eudragit to. The magnesium stearate and talc were used as lubricant and glidant, respectively. The tablets of all formulation were subjected to various evaluation parameters such as thickness, diameter, weight variation, hardness, friability, drug content, in-vitro buoyancy lag time, total floating time, tablets density, swelling index and in-vitro dissolution study.

The results of all these tests were found to be satisfactory. The thickness of the tablets was uniform in all formulations and ranged from 5.16±0.054mm to 5.5±0.018mm. The hardness of tablets in all batches ranged from 4.0±0.45 to 6.4±0 . All the formulations (F1-F9) passed weight variation test as per the Pharmacopoeial limit of ±5%. The percentage friability of all batches ranged from 0.37 to 0.72 %, which was well below the pharmacopeial limit of 1 %. Drug content was also found to be uniform among the all formulations and ranged from 98.91± 0.35% to 99.94± 0.19 %.

There has been considerable interest in using different Types of polymers controlled release drug delivery system due to their hydrophilic nature and fast hydration. It has been reported that polymers of different viscosity grades can yield different drug absorption.

To know the kinetic drug release, the data was treated according to different model. The drug release data of F1-F9 fitted to Higuchi plots were best fit into Higuchi equation and diffusion mechanism. The diffusion is related to the transport of drug from the dosage form into *in-vitro* fluid depending upon concentration of the gradient varies the drug release the distance for diffusion increases.

In the present study *in-vitro* release profile could be expressed by Higuchi for all formulation showed good linearity indicates that diffusion is dominant mechanism of drug release with these formulations.

The performance of floating formulation has been reported to be greatly affected by physiological conditions such as food, transport, gastrointestinal motility and so on. In- vitro dissolution studies of all the formulations of floating tablets of Cefixime were carried out in 0.1NHcl. The study was performed for 24 hours and cumulative drug release was calculated at every hour time interval. In- vitro dissolution studies of all the formulations are shown. Three different polymers and their combination were used to prepare floating tablets. It was observed that the type of polymer influences the drug release pattern. Al the formulations contain equal amount of gas generating agent (Sodium Bicarbonate) and Citric Acid.

Drug release from F3 is high due to high permeabilty. Although combination of significantly release the drug as compared with F3. As expected drug release depend upon viscosity grade and concentration of polymer used. Tablet containing Lactose,Carbopol (F3) showed better drug release upto 24hours. As Carbopol has greater tendency to water, it can sustain the drug for 24 hours.

Polymeric system with low viscosity polymer (HPMC $K_{100}M$) yielded a faster initial burst effect. **Dortunc and Gunal (1997)** has reported that increased viscosity resulted in a corresponding decrease in the drug release. Wan et al. reported similar results, in which they have demonstrated that HPMC with higher viscosity resulted in thicker gel layer formation. Once the gel layer of polymeric system is formed, there appears to be no difference in release rate from delivery system.

From results of *in- vitro*drug release studies using USPXXIII dissolution apparatus, it concludes that F3 had better-sustained release than the other formulation (F1, F2, F4, F5, F6, F7,F8& F9).

In order to understand the complex mechanism of drug release from the floating tablets, the *in- vitro*Cefixime release data were fitted to Korsmeyer-peppa's release model and interpretation of release exponent values (n) enlightens us in understanding the release mechanism from the dosage form. The release exponent values thus obtained were from 2.471to 2.7586. Based on these values we can say that the formulations F1 to F9 exhibited Case II transport.

The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear (r>0.9230). All formulations F3 values for zero order plot indicating that drug release followed zero order kinetics and drug release from these floating tablets were by both diffusion and erosion.

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SUMMARY AND CONCLUSION

The aim of study was the**"Formulation and Evaluations of Cefixime Floating Matrix tablet using different type of polymers"** having Controlled release **Cefixime** Matrix system.

In this,The main objective of the study was to develop a stable product which provides controlled drug release profiles. The optimum Formulation of **F-3**was given the best Preformulation studies and post compression studies such as Angle of repose, compressibility index, and thickness, hardness, content uniformity, drug release.The Matrix tablets were subjected to test for accelerated stability (25°C±2°Cat 60%±5% RH & 40°C±2°C at 75%±5% RH for 3months) studies.

The release kinetics profile had also given a best result. the optimum Formulation of F-3drug was following mixed-order kinetics .

In this formulation, The combination of Lactose and Carbopol wasimproved the % cumulative release of the drug. This was given the best release of drug within the limits tablet up to 20th hrs. (94.09%), ourformulation had given a good drug releaseup to 24th hour(96.96%). The swelling behaviour is also within the limits only.

So, our formulation had produceda best result using theLactose and Carbopol combination in Formulation **F-3**.

1) **Gwen M. Jantzan., Joseph R. Robinson..** "Sustained and Controlled Release Drug Delivery Systems" In: Gilbert S. Banker.Editors. *Modern Pharmaceutics***.**4th Edition Revised And Expanded. Marcel Dekker Inc; New York. USA.2008 Pg.503-530
2) **Vyas S.P., Roop. K. Khar.**,Essentials of Controlled Drug Delivery In: S. P. Vyas. Editors. *Controlled Drug Delivery – Concepts And Advances***.** VallabhPrakashan, Delhi.2006, Pg. 1 – 53
3) **Julan U Desai., Jolly R Parikh., Rajesh H Parikh.,** "Floating Drug Delivery Systems:An Approach To Gastro Retention" *Pharma Info.Net*Vol 5 Issue 1 200
4) **PoojaKone R., Saudagar R B., Daharwal S J., "**Gastro-Retentive Drugs: A Novel Approach Towards Floating Therapy" *Pharma Info.Net*Vol 5 Issue 1 2007
5) **GarimaChawla., PiyushGupta,A.,. Bansal K.,**" Gastroretentive Drug Delivery System", In: Progress *In Controlled And Novel Drug Delivery System***,** N. K. Jain First Edition, 2004; 76-97.
6) **Desai S, Bolton S**."A Floating Controlled Release System: In-Vitro – In-Vivo Evaluation". *Pharm. Res*. 1993; 10: 1321-1325
7) **Singh B N., Kim H.,** " Floating Drug Delivery System An Approach To Control Drug Delivery Via Gastric Retention" *Journal Of Controlled Release*, 63 (2000); 235-259.
8) **Deshpande AA., Shah NH., Rhodes CT., Malick W.,**"Development Of A Novel Controlled Release System For Gastric Retention". *Pharm. Res*. 1997; 14(6): 815-819.
9) **Roma Patel.**, "Recent Development In Floating Drug Delivery System For Gastric Retention Of Drugs": An Overview.
10) **Sivakuma H G.,**" Floating Drug Delivery System For Prolonged Gastric Residence Time": A Review, *Ind. J. Pharm. Edu*; Oct-Dec-2004.
11) **Harrigan R M**, Novel Drug Delivery System, Yie W. Chein, 50; 168- 169.
12) **Brahmankar D M.,Jaiswal S B.**. "Controlled Release Medication. In BrahmankarDM. EDITORS. *BiopharmaceuticsAnd Pharmacokinetics* A Treatise. 1st Ed VallabhPrakashan. New Delhi: 1995, Pg. 64-70.

13) **Michaels A S., Bashwa J D.,** Novel Drug Delivery, Yie W. Chein, 50; 169.

14) **Brahma N. Singh, Kwon H. Kim.,** "Floating Drug Delivery Systems: An Approach to Oral Controlled Drug Delivery Via Gastric Retention" *Journal Of Controlled Release* 63 (2000) 235–259.

15) **Abubakr O. Nur; Jun S. Zhang**: "Captopril Floating And/OrBioadhesive Tablets: Design And Release Kinetics**"***Drug Dev. And Ind. Pharm.*, 2000,26(9); 965 – 969.

16) **Sanjay Garg**, Gastroretentive Drug Delivery System, NIPER, 2003; 160-166.

17) **ShwetaArora., "**Floating Drug Delivery: A Review", *AAPSPharmscitech*, 2005; Article 47.

18) **Baumgartner S., Kristl J., Vrecer F., Vodopivec P., ZorkoB..** "Optimization 0f Floating Matrix Tablets And Evaluation Of Their Gastric Residence Time" *Int. J. Pharm*., 2000,195; 125-135.

19) **GuojieXu And Michael J Groves.**, "Effect Of FITC-Dextran Molecular Weight On Its Release From Floating Cetyl Alcohol And HPMC Tablet" *J. Pharm. And Pharmaco*. 2001, 53; 49-56.

20) **El-Kamel A H.,Sokar M S, Al Gamal S S** "Preparation And Evaluation Of Ketoprofen Floating Oral Delivery System" *Int. J. Pharm*, 2001, 220; 13-21.

21) **Shoufeng Li, Senshang Lin, Bruce P.Daggy, Haresh L. Mirchandani, Yie W Chien**, " Effect Of HPMC And Carbopol On The Release And Floating Properties Of Gastric Floating Drug Delivery System Using Factorial Design "*Int. J. Pharm*, 2003, 253; 13-22.

22) **Brijesh S. Dave, Avani F. Amin, And Madhabhai M. Patel**: "Gastroretentive Drug Delivery System Of Ranitidine Hydrochloride:Formulation And In- vitro Evaluation "*AAPS Pharmscitech.* 2004,5 (2); Article 34.

23) **Mahesh Chavanpatil, Paras Jain, PradeepVavia**, " Development Of Sustained Release Gastroretentive Drug Delivery System For Ofloxacin - In- vitro And In-Vivo Evaluation " *Int. J. Pharm*., 2005,304(1-2); 178-184.

24) **XiaoqiangXu, Minjie Sun, FengZhi and Yiqiao Hu., "**Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In- vitro and in vivo evaluation in healthy volunteers" *International Journal of Pharmaceutics,*Volume 310, Issues 1-2, 9 March 2006, Pages 139-145.

25) **Christian Fernandes., Roberto Gonçalves., Junqueira., Ligia Maria Moreira Campos and GersonAntônioPianetti.,** "Dissolution test for lamivudine tablets: Optimization and statistical analysis" Journal of Pharmaceutical and Biomedical AnalysisVolume 42, Issue 5, 16 November 2006, Pages 601-606.

26) **Viral F.Patel and NatavarlalM.Patel** " Intragastric floating drug delivery system of cefuroxime Axetil: - In- vitro evaluation ", *AAPS Pharm. sci. tech*., 2006, 7(1); E_1-E_7

27) **ZiyaurRahman**: **"**Design And Evaluation Of Bilayer Floating Tablets Of Captopril *" Acta Pharm*., 2006,56; 49–57

28) **Samuel B. Philip A, Pathak.K**. " Preparation And Evaluation Of Gastro Retentive Delivery System Of Flurbiprofen " 2006, *The Indian Pharm*2006,47; 76-78.

29) **Narendra, M. S. Srinath, Ganesh Babu**, " Optimization Of Bilayered Floating Tablets Containing Metoprolol Tartrate As A Model Drug For Gastric Retention ", 2006, 7(2); E_1-E_7.

30) **Ali, J., Hasan, S., Ali, M.:**" Formulation And Development Of Gastroretentive Drug Delivery System For Ofloxacin ":*Methods Find ExpClinPharmacol***,** 2006, 28(7); 433.

31) **Sanjay S. Patel, S.Ray,And R. S. Thakur,** " Formulation And Evaluation Of Floating Drug Delivery System Containing Clarithromycin For Halicobector Pylori ", *ActaPoloniae Pharm*., 2006,63; 53-61.

32) **Girish S. Sonar, Devendra K. Jain, Dhananjay M. More**, " Bilayer And Floating Bioadhesive Tablet Of Rosiglitazone Maleate **"** ***Asian J. Pharm. Sci.***, 2007,2(4); 161-169.

33) **Patel V F., PateN M.,**" Statistical Evaluation Of Influence Of Viscosity Of Polymer And Types Of Fillers On Dipyridamol Release From Floating Matrix Tablets " *Ind. J. Pharm .Sci*, 2007; 51- 57.

34) **Raval J A., Patel J K., Patel M M.,** "Ranitidine Hydrochloride Floating Matrix Tablets Based On Low-Density Powder: Effect Of Formulation Processing Parameter On Drug Release ", *Asian J. Pharm. Sci*., 2007, 2(4); 130-142.

35) **Basak S C.,Rahman J., Ramalingam M.,** "Design And *In- vitro* Testing Of A Floatable Gastroretentive Tablet Of Metformin Hydrochloride "*Pharmazie*2007,62 (2); 145-148.

36) **DasarathM.Patel., NatvarlalM.Patel., NiteshN.Pandya.,**" Gastro Retentive Drug Delivery System Of Carbamazepine: Formulation Optimization Using Simplex Lattice Design ": *AAPS Pharm Sci*, 2007, 8 (1): Article 11.

37) **Javed Ali, PuneetTyagi,AlkaAhuja**., " Development & Evaluation Of Gastro Retentive Drug Delivery System For Celecoxib " *PDA Jour.Sci.And Tech*., 2007; 89-96.

38) **Manoj N. Gambhire., KshitijW.Ambade., Sushma D. Kurmi, Vilasrao J. Kadam.,** " Development And In-Vitro Evaluation Of An Oral Floating Matrix Tablets Formulation Of Diltiazem HCL ", *AAPS Pharm Sci Tech*, 2007, 8(3), Article-73.

39) **Shivakumar H N., Desai B G., Patel M.,** " Optimization Of Gastroretentive System For Oral Controlled Delivery Of Cinnarizine Using Response Surface Methodology ": *Ars Pharm 2007*; 48 (1): 55-81.

40) **Tejas Patel., Patel L D., Timir Patel., Kirit Patel**., " Design And Development Of Gastric Floating Drug Delivery System Using Factorial Design", *Pharma Buzz*, 2008,3; 21-27.

41) **Praveen Chaudhri., ChaudhriShilpa., BarhateNilesh., MistryChetan**., " Design And Evaluation Of Bilayer Floating Tablet Of Tizanidine HCL " *Ind J Pharm Educ Res.*, 2008,42(1); 36-47.

42) **Swamy P.V., Bhosale U.V., Hiremath S.N., Raju S.A.,** " Formulation And Optimization Of Gastric Floating Drug Delivery System Of Atenolol Using 3^2 Full Factorial Design " *Ind. Drugs*, 2008, 45(4); 293-300

43))**Ravi Kumar.,Patil M. B., Sachin R. Patil., Mahesh S. Paschapur.,** "Formulation And Evaluation Of Effervescent Floating Tablet Of Famotidine" *InternationalJournalOf Pharmtech Research*., Vol.1, No.3, Pp 754-763 , July-Sept 2009.

44) **Ferdous Khan., Md. ShaikhulMillatIbnRazzak., Md. ZiaurRahman Khan., KaziRashidulAzam., Sams Mohammad Anowar Sadat And Md. Selim Reza** "Preparation And *In- vitro*Evaluation Of Theophylline Loaded Gastroretentive Floating Tablets OfMETHOCEL K_4M*" Dhaka Univ. J. Pharm. Sci*. 7(1): 65-70, 2008 (June).

45) www.drugbank.com

46) **Yukari ohta and Ichiro Shinkai**., "New Drugs-Reports of New Drugs Recently Approved by The FDA- LAMIVUDINE" *Bioorganic and medicinal chemistry,* Vol 5,No 4,pp 639-640,1997.

47) **Robert M. Silverstein., Francis X. Webster.,**"Infrared Spectrometry. In: Robert M. Silverstein". Editors. *Spectrometric Identification Of Organic Compounds*. 6th Ed. John Wiley And Sons. Inc. New York. Pg. 71 – 143.

48) **John R. Dyer.,** "Infrared Spectroscopy. In: John R. ". Editors. *Applications OfAbsorption Spectroscopy Of Organic Compounds*. Eastern Economy Edition. Prentice – Hall Of India. New Delhi. Pg. 22 – 57.

49) **USP 31 / NF 26.** 2008, Asian ed. Volume – 2, Official Monographs. Pg. 1820 – 1822.

50) **SinghSk, Pandit J.K, Mishra DN**: Formulation And *Invitro* Evaluation Of Carbopol 934p Matrix Tablets: **J. Pharm. Res**, 2007:6(1): 20-23.

51) **Banker G S., Anderson N R.,** and Tablets In: LachmanL.Lieberman HA, Kanig JL, And Editor. *The Theory And Practice Of Industrial Pharmacy*.3rd Edition 1986, 293-335.

52) **Chawla F., gupta F., koradia. V., bansal A.K.**, "Gastroretention: a means to address regional variability in intestinal drug absorption". Pharmtech (serial online) 2003, JUL: 27(7). 50-68. Fromwww.pharmtech.com/pharmtech/article.

53) **Manoj N. Gambhire, KshitijW.Ambade, Sushma D. Kurmi, Vilasrao J. Kadam**, " Development and In-Vitro Evaluation of an Oral Floating Matrix Tablets Formulation of Diltiazem HCL ", *AAPS Pharm Sci Tech*, 2007, 8(3), Article-73.

54) **Robert M. Silverstein, Francis X. Webster**. Infrared Spectrometry. In: Robert M. Silverstein. Editors. *Spectrometric Identification of Organic Compounds*. 6th Ed. John Wiley and Sons. Inc. New York. Pg. 71 – 143.

55) **Korsmeyer R. W., Gurny R. Peppas**, "Mechanism of Solute Release From Porous Hydrophilic Polymers." *Int J Pharm***.** 1983, Pg. 25-35.

56) **Higuchi T.**, "Mechanism of Sustained Action Medication: Theoretical Analysis of Rate of Release of Solid Drug Dispersed in Solid Matrix**."** *J Pharm.Sci*, 1963, Pg. 1145-1149.

57) **Wei ZP., Huang L., Han J, Li Y**., "Preparation Of The 5-Fu Floating Sustained Release Tablet For Gastric Retention" Beijing Da XueXueBao. 2004 Aug 18;36(4):439-42.

58) **Jaimini.M.,Rana A.C., And Tanwar Y. S**., "Formulation And Evaluation Of Famotidine Floating Tablets", *Current Drug Delivery*, 2007, 4, 51-55.

59) **Fursule R.A., Patra2 CH. N., Patil G.B., Kosalge S.B., Patil P.O., Deshmukh P. K.,** "Study OF Multiparticulate Floating Drug Delivery System Prepared By Emulsion Gelation Technique" *International Journal Of Chemtech Research*, Vol.1, No.2, Pp 162-167 , April-June 2009.

60) **Shah S.H., Patel J.K., Patel N.V.,** "Stomach Specific Floating Drug Delivery System: A Review" *International Journal OfPharmtech Research* Vol.1, No.3, pp 623-633, Jul-Sep 2009.

61) **Sanjay S. Patel., Ray .S And Thakur R.S.,** "Formualtion And Evaluation Of Floating Drug Delivery System Containing Clarithromycin For Helicobacter Pylori"*ActaPoloniaePharmaceutica Ñ Drug Research*, Vol. 63 No. 1 Pp. 53ñ61, 2006.

62) **Ravi Kumar.,Patil M. B., Sachin R. Patil, Mahesh S. Paschapur** "Formulation And Evaluation Of Effervescent Floating Tablet Of Famotidine" *International JournalOf Pharmtech Research*., Vol.1, No.3, Pp 754-763 , July-Sept 2009.

63) **Thakkar V T., Shah P A., Soni1 T G, Parmar1 M Y., Gohel M C and Gandhi T R.,** "Fabrication And Evaluation Of Levofloxacin Hemihydrate Floating Tablet" *Research In Pharmaceutical Sciences*, October 2008; 3(2): 1-8.

64) **Girish S. Sonara., Devendra K. Jaina., Dhananjay M. More.,** "Preparation And *In-vitro*Evaluation Of Bilayer And FlOating-Bioadhesive Tablets Of Rosiglitazone Maleate" *Asian Journal Of Pharmaceutical Sciences* 2007, 2 (4): 161-169.

65) **IlonaMartı´NezGonza´Lez, LeopoldoVillafuerte Robles.,** "Influence Of Enteric Citric Acid On The Release Profile Of 4-Aminopyridine From HPMC Matrix Tablets" *International Journal Of Pharmaceutics* 251 (2003) 183_ 193.

66) **Frances Stops A., John T. Fell., John H. Collett., Luigi G. Martini.,Harbans L. Sharma., Anne-Marie Smith.,** "The Use Of Citric Acid To Prolong The In Vivo Gastro-Retention Of A Floating Dosage Form In The Fasted State" *International Journal Of Pharmaceutics* 308 (2006) 8–13.

67) **Hilton A K.,and P.B. Deasy P B.,** "In- vitro And In Vivo Evaluation Of An Oral Sustained-Release Floating Dosage Form Of AmoxycillinTrihydrate" *international .Journul*Of *Phrrrmuceutics,* X6 F 1992) 7948

68) **Alfred Martin**., "Diffusion and Dissolution". In: Alfred Martin, Pilar Bustamante and A.H.C Chun. *Physical Pharmaceutics*,4th edition,Lippincott Williams andWilikins. Maryland. USA.2001 pg 324-361.

69) **Brahma N. Singh, Kwon H. Kim.,** "Floating Drug Delivery Systems: An Approach To Oral Controlled Drug Delivery Via Gastric Retention" *Journal Of ControlledRelease* 63 (2000) 235–259.

70) **Monica RP Rao, Girish S Sonar, Rachana R Mandsaurwale, Swapnila D Vanshiv.,** "Evaluation Of Effervescent Floating Matrix Tablet Formulations Of Salbutamol Sulfate Using Full Factorial Design" *Asian Journal Of Pharmaceutics*