FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLYMERS

A Dissertation submitted to

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

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch - I - PHARMACEUTICS

Submitted by

Name: R.KARTHI

REG.No:261510255

Under the Guidance of

Dr.S.BHAMA, M.Pharm., Ph.D

Associate professor,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU

OCTOBER - 2017

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLYMERS,** submitted by the student bearing **Reg.No:261510255** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND EVALUTION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLIMERS",** Submitted to "**The Tamil Nadu Dr. M.G.R. Medical University-Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** ,is a bonafied work carried out by the student bearing **Reg.No:261510255** during the academic year 2016-2017, under the guidance and supervision of **Dr.S.BHAMA,M.Pharm., Ph.D.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Dr.S. Bhama M.Pharm.,Ph.D.,
Associate Professor,
Dept.of Pharmaceutics,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam- 638 183.

Dr. R. Sambathkumar, M. Pharm., Ph.D.,
Professor, Head & Principal,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam- 638 183.

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled "**FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLIMERS"** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University- Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing **Reg.No:261510255,** during the academic year 2016-2017, under the guidance and supervision of **Dr.S.Bhama,M.Pharm., Ph.D.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalayam

Date:

Dr. R. Sambathkumar, M.Pharm., Ph.D.,
Professor & Head, Principal

Department of Pharmaceutics

J.K.K. Nattraja College of Pharmacy.

Kumarapalayam - 638 183.

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled "**FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLIMERS"** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University-Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing **Reg.No:261510255** during the academic year 2016-2017, under my guidance and direct supervision in the Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalayam

Date:

Dr.S.BHAMA, M.Pharm., Ph.D.,

Associate Professor,

Dept.of Pharmaceutics

J.K.K. Nattraja College of Pharmacy.

Kumarapalayam- 638 183.

DECLARATION

I do hereby declared that the dissertation **"FORMULATION AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE FLOATING TABLETS USING NATURAL POLIMERS"** submitted to "**The Tamil Nadu Dr.M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2016-2017, under the guidance and supervision of **Dr. S.BHAMA M. Pharm.,Ph.D.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **R.KARTHI**

Date: **Reg.No:261510255**

Dedicated to Parents, Teachers & My Family

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattaraja Chettiar,** providing the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt. N. Sendamaraai, B.Com.,** and Director **Mr.S.Omm Sharravana, B.Com., LLB.,** J.K.K. Nattraja Educational institutions, Kumarapalayam for their blessings, encouragement and support at all times.

It is my most pleasant duty to thank our beloved Principal and Professor **Dr. R. Sambathkumar, M. Pharm., PhD.,** of J.K.K.Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

My sincere thanks to **Dr. R. Shanmugasundaram, M.Pharm., Ph.D.,** Vice Principal & HOD, Department of Pharmacology for their valuable suggestions during my project work.

It is most pleasant duty to thank my beloved guide **Dr. S. BHAMA, M.Pharm., Ph.D.,** Associate Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam, for suggesting solution to problems faced by me and providing in dispensable guidance, tremendous encouragement

at each and every step of this dissertation work. Without her critical advice and deep-rooted knowledge, this work would not have been a reality.

Our glorious acknowledgement to our administrative officer **Dr. K. Sengodan, M.B.B.S.**, for encouraging using kind and generous manner to complete this work.

My sincere thanks to, **Mr. R. Kanagasabai, B.Pharm., M.Tech.,** Associate Professor, **Mr.K. Jaganathan, M.Pharm.,** Assistant Professor, **Ms. S. Manodhini Ilakiya, M.Pharm.,** Lecturer, **Mr. C. Kannan M.Pharm.,** Assistant Professor, **Dr. V. Kamalakannan M.Pharm., Ph.D.,** Assistant Professor, and **Ms. S. Sivashankari, M.Pharm.,** Assistant Professor, and **Mr. M. Subramani, M.Pharm.,** Lecturer, Department of pharmaceutics for the invaluable help during my project.

My sincere thanks to **Dr.V.Sekar, M.Pharm., Ph.D.,** Professor and Head, Department of Analysis, **Dr. I. Carolin Nimila, M.Pharm.,P h.D.,** Assistant Professor, and **Ms. V. Devi, M.Pharm.,** Lecturer, Department of Pharmaceutical Analysis for their valuable suggestions.

I greatly acknowledge the help rendered by **Mrs.K. Rani,** Office Superintendent, **Mr.E.Vasanthakumar, MCA.,** Assistant Professor, **Miss.M. Venkateswari, M.C.A.,** Typist**, Mrs.V.Gandhimathi, M.A., M.L.I.S.,** Librarian, **Mrs.S. Jayakala B.A., B.L.I.S.,** and Asst.

Librarian, **Mrs. Punitha, Lab Assistant** for their co-operation. I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

R.KARTHI

Reg.No:261510255

CONTENTS

1. INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. The design of oral controlled drug delivery systems (DDS) is primarily aimed to achieve more predictable and increased bioavailability. Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release from DDS leading to diminished efficacy of administered dose. Floating Drug Delivery Systems (FDDS) have a bulk density is lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result is increase in GRT and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two types, non-effervescent system and effervescent systems. Longer residence time in stomach could be advantageous for local action in the upper part of small intestine, for example treatment of peptic ulcer disease. Ciprofloxacin hydrochloride is a broad-spectrum antibiotic active against both Gram-positive and Gram negative bacteria. The dosage is equivalent of 250 to 750 mg of ciprofloxacin twice daily (116 mg of ciprofloxacin hydrochloride is approximately equivalent to 100 mg of ciprofloxacin). The aim of the present study is to formulation and evaluation of floating tablets of ciprofloxacin hydrochloride using HPMC (K100M, K4M and E50) in different ratio with sodium bicarbonate, magnesium stearate and talc by direct compression techniques[1].

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery system is also known as hydrodynamically balanced system (HBS). 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 results in an increased GRT and a better control of the fluctuations in plasma drug concentration[2].

Advantages of FDDS[3]:

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.
8. Site-specific drug delivery.

Limitations of FDDS[4]:

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed.

Factors affecting the floating time[5,6]:

a. Density: Floating is a function of dosage form buoyancy that is dependent on the density. Density of the dosage form should be less than the gastric contents (1.004gm/ml).
b. Shape of dosage form: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. Tetrahedron and ring shaped devices with flexural modules of 48 and 22.5 kilo pounds per square inch are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes.
c. Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
d. Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (mmc) that occurs in every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
e. Nature of meal: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
f. Caloric content and feeding frequency: Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of mmc.
g. Age: Elderly people, especially those over 70, have a significantly longer; floating. Disease condition such as diabetes and crohn's disease etc also affect drug delivery.
h. Gender: Mean ambulatory GRT in males (3.4 0.6 hours) is less compared with their age and race-matched female counter parts (4.6 1.2 hours), regardless of the weight, height and body surface.

i. Posture: Floating can vary between supine and upright ambulatory states of the patient.

Approaches to design floating drug delivery system:

Practical approaches in designing FDDS:

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm3, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system[6].

Approaches to design single and multiple unit dosage form[7,8]:

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

A. Single unit dosage form

In low density approaches, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier like popcorn, poprice, polystrol for the drug for its controlled release. The polymer of choice can be either Ethyl cellulose or HPMC depending on type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. Hydro dynamically balanced systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. To retain in stomach for a prolonged period of time the dosage form

must have bulk density of less than '1' and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation.

B. Multiple unit dosage form

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. However, potential drug loading of a multiparticulate system is lower because of the proportionally higher need for excipients (e.g., sugar cores). Most multiparticulate pulsatile delivery systems are reservoir devices coated with a reputable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by diffusion; while for water insoluble drug, the release is dependent on dissolution of drug.

Types of floating drug delivery system[9,10]:

Floating drug delivery systems can be divided in to non-effervescent and gas-generating system.

Non-effervescent systems: This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the

mixing of the 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. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types:

a) Colloidal gel barrier system such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g. hydroxypropyl cellulose, hydoxy ethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrixforming polymer such as polycarbophil, polyacrylateand polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

b) Microporous compartment system, this technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

c) Alginate beads, in which Multi-unit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40 ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12

hours. These floating beads gave a prolonged residence time which is more than 5.5 hours.

d) Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids, described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.

Gas-generating (effervescent) systems: These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g.chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology.

Hollow microspheres / Microballons loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the

evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours[10].

Bacterial infections

Ciprofloxacin hydrochloride is an antibiotic used to treat a number of bacterial infections. This includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others.

A fluoroquinolone antibiotic used to treat urinary infections and, as eye drops, for the treatment ofcorneal ulcers. The drug acts by binding to the enzyme gyrase. Mu tations lead to an alteration in the structure of thisenzyme leading to antibiotic resistan ce. Current research suggests the possibility of preventing this process. The drug is on the WHO official list. Brand names are Cifran and Cipfil[11,12].

Classification of quinolone antibiotics

Classification	*Agents*	*Antimicrobial Spectrum*	*General clinical indications**
First generation	Nalidixic acid (NegGram)	Gram-negative organisms (but not Pseudomonas species)	Uncomplicated urinary tract infections
	Cinoxacin (Cinobac)		
Second generation	Norfloxacin (Noroxin)	Gram-negative organisms (including Pseudomonas species), some gram-positive organisms (including*Staphylococcus aureus*but not *Streptococcus pneumoniae*) and some	Uncomplicated and complicated urinary tract infections and pyelonephritis, sexually transmitted
	Lomefloxacin (Maxaquin)		
	Enoxacin (Penetrex)		

Classification	*Agents*	*Antimicrobial Spectrum*	*General clinical indications**
	Ofloxacin (Floxin)	atypical pathogens	diseases, prostatitis, skin and soft tissue infections
	Ciprofloxacin (Cipro)		
Third generation	Levofloxacin (Levaquin)	Same as for second-generation agents plus expanded gram-positive coverage (penicillin-sensitive and penicillin-resistant *S. pneumoniae*) and expanded activity against atypical pathogens	Acute exacerbations of chronic bronchitis, community-acquired pneumonia
	Sparfloxacin (Zagam)		
	Gatifloxacin (Tequin)		
	Moxifloxacin (Avelox)		
Fourth generation	Trovafloxacin (Trovan)	Same as for third-generation agents plus broad anaerobic coverage	Same as for first-, second- and third-generation agents (excluding complicated urinary tract infections and pyelonephritis) plus intra-abdominal infections, nosocomial pneumonia, pelvic

Classification	*Agents*	*Antimicrobial Spectrum*	*General clinical indications**
			infections

Indications for quinolone antibiotics labeled by the U.S. food and drug administration

INDICATIONS	*AGENTS*
Uncomplicated urinary tract infections	Nalidixic acid (NegGram), cinoxacin (Cinobac), norfloxacin (Noroxin), lomefloxacin (Maxaquin), enoxacin (Penetrex), ofloxacin (Floxin), ciprofloxacin (Cipro), levofloxacin (Levaquin), gatifloxacin (Tequin), trovafloxacin (Trovan)
Complicated urinary tract infections and pyelonephritis	Norfloxacin, lomefloxacin, enoxacin, ofloxacin, ciprofloxacin, levofloxacin, gatifloxacin
Lower respiratory tract infections (limited)	Lomefloxacin, ofloxacin, ciprofloxacin, trovafloxacin
Skin and skin-structure infections	Ofloxacin, ciprofloxacin, levofloxacin, trovafloxacin
Urethral and cervical gonococcal infections	Norfloxacin, enoxacin, ofloxacin, ciprofloxacin, gatifloxacin, trovafloxacin
Urethral and cervical chlamydial and gonnococcal infections	Ofloxacin, trovafloxacin
Bone and joint infections, gram-negative bacterial infections	Ciprofloxacin

INDICATIONS	*AGENTS*
Infectious diarrhea	Ciprofloxacin
Typhoid fever	Ciprofloxacin
Prostatitis	Norfloxacin, ofloxacin, trovafloxacin
Acute sinusitis	Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin (Avelox), trovafloxacin
Acute exacerbations of chronic bronchitis	Levofloxacin, sparfloxacin (Zagam), gatifloxacin, moxifloxacin, trovafloxacin
Community-acquired pneumonia	Levofloxacin, sparfloxacin, gatifloxacin, Moxifloxacin, trovafloxacin
Intra-abdominal infections	Trovafloxacin
Gynecologic and pelvic infections	Trovafloxacin
Nosocomial pneumonia	Trovafloxacin

2. LITERATURE REVIEW

P. G. Yeole et al., presented a review article about floating drug delivery systems, need and development for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract to control the gastric residence time, using gastro retentive dosage forms that will provide us with new and important therapeutic option[13].

Shwetha A et al., made a reviewed on floating drug delivery systems with special focus on the principle mechanism of flotation to achieve gastric retention, including the physiological and formulation variables affecting gastric retention, approaches to design single – unit and multiple unit floating systems and their classification, summarized the in vitro techniques and in vivo studies to evaluate the performance and application of floating system and concluded that prolonging gastric retention of dosage form extends the time for drug absorption. Floating drug delivery system promises to be a potential approach for gastric retention[14].

Patel V. F et al., studied about formulation and evaluation of ciprofloxacin tablets and optimized the formulation for type of filler, different viscosity grades of HPMC and its concentration. The study revealed that type of filler adds significant effect on release of drug from hydrophilic matrix tablet and floating properties. It concluded that the different viscosity grades of HPMC had a major influence on drug release from hydrophilic matrices as well as on floating properties[15].

M.P.Venkatarajua et al., developed a controlled delivery system for propranolol hydrochloride (PPHCL) using the synergistic activity of locust bean gum (LBG) and xanthan gum (X). Granules of PPHCL were prepared by using different drug: gum ratios of X, LBG alone and a mixture of XLBG (X and LBG in 1: 1 ratios)[16].

Parikh bhavik anjankumar et al., prepared a floating drug delivery system of atenolol in order to increase the gastric residence time (GRT) and comparison of natural and synthetic polymer for better sustained effect. The tablets were prepared by direct compression. The pre and post compression studies were performed by using IP standard formula and procedure[17].

Mahesh chavanpatil et al., developed ofloxacin sustained release (SR) gastroretentive dosage forms (GRDF) for once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems[18].

Manoj et al., prepared a floating drug delivery system of diltiazem hydrochloride using polymers such as hydroxypropyl methylcellulose K100M CR and compritol 888 ATO, alone and in combination. The effect of sodium bicarbonate and succinic acid on drug release was investigated. The high level of both methocel K100M CR and compritol 888 ATO favours the preparation of floating controlled release of diltiazem tablets[19].

Inez Jimenez et al., developed a sustained delivery of captopril from floating matrix tablets. The study was done using metolose SH4000 sodium bicarbonate and at two different compaction pressures. The observation showed that the matrices compacted at lower pressure (55MPa) floated in the dissolution medium for more than 8hr while those compacted at (165MPa) floated only when sodium bicarbonate is included in the formulation[20].

Nur and zhanj et al., prepared captopril floating and bioadhesive tablets using two grade of HPMC (400 and l5000cps) and carbopol 934P. *In vitro* dissolution was carried out in simulated gastric fluid (enzyme free) at 37 ± 0.1°C using the USP type II method. Compared to conventional tablets, release of captopril from these floating tablets was apparently prolonged (24hrs). Tablet hardness was found to be a determining factor with regard to the buoyancy of the tablets[21].

Chen and hao et al., studied the *in vitro* performance of floating sustained release capsule of verapamil. Capsules filled with mixture of verapamil, HPC and effervescent materials are proposed to provide floating and sustained release for over 10 hrs. The effects of weight filled in the capsule, amount of HPC and the addition of effervescent material on the dissolution kinetics were studied[22].

Desai and bolton et al., developed controlled release floating tablets of the theophylline using agar and light mineral oil. Tablets were made by dispersing drug and mineral oil mixture in a warm agar solution. The resultant mixture was poured into tablets moulds, which on cooling and air-drying formed floated CR tablets[23].

Hilton and deasy et al., fabricated an oral sustain release floating tablets of amoxicillin trihydrate using various hydrophilic polymers like hydroxy Propyl cellulose, sodium alginate, sodium carboxymethylcellulose, HPMC and

methylcellulose. The report revealed that the intrinsic dissolution studies at P^H 2 showed a decreased drug residence time[24].

Park et al., developed and evaluated floating beads from sodium alginate solution containing CaCO3 or NaHCO3 as gas forming agents with riboflavin as a model drug. *In vitro* release studies revealed that CaCO3 is superior to NaHCO3 as gas forming agent in alginate bead preparations, with enhanced buoyancy and sustained release properties making them excellent for floating drug delivery system[25].

Patil UK et al., developed amlodipine besylate effervescent floating tablets in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms.

Baumgartner S et al., developed floating matrix tablets containing hydroxyl propyl methyl cellulose, which after oral administration are designed to prolong the gastric residence time, increased the bioavailability and diminished the side effects of irritating drugs. The importance of the composition optimization, the formulation effects and characterization of the tablets were examined.

Jimenez-casttellanos et al., designed and tested the *invitro* floating and bioadhesive property of sotalol for oral application. Tablets were prepared by mixing the active ingredient with sodium carboxy methyl cellulose, hydroxy propyl cellulose and sodium bicarbonate to generate gas.

Basak, S.C et al., have reviewed about development and *in vitro* evaluation of an oral floating matrix tablet formulation of ciprofloxacin which better absorbed in stomach and upper small intestine was formulated as floating matrix tablet using gas generating agent (sodium bicarbonate) and hydrophilic polymer (hydroxypropylmethyl cellulose) and concluded that *invitro* drug release study of these tablet indicated controlled sustained release for ciprofloxacin and 80-89% release at the end of 8 hrs.

K. Muthusami et al., prepared and evaluated of lansoprazole floating micropellets using HPMC, methyl cellulose and chitosan as a carrier and he concluded that drug loaded micropellets were found to float on stimulated gastric fluid and simulated intestinal fluid for more than 12 hrs.

Brijesh S.Dave et al., have reviewed about gastro retentive drug delivery system of ranitidine hydrochloride formulation and *invitro* evaluation. The result is of the full factorial design indicated that the addition of stearic acid reduces the drug dissolution due to it's hydrophobicity and shows sustained release of ranitidine hydrochloride from a gastroretentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride and concluded that addition of gel forming polymer HPMC K4M and gas generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy.

Jaimini,M et al., studied about formulation and evaluation of famotidine floating tablets by using different grades of methocel K100 and methocel K 15M by effervescent technique and showing good *in vitro* buoyancy.

Honglei jian et al., developed a controlled release tablets of theophylline using sustained release materials such as galactomannan (G) from gleditsia sinensis lam and xanthan gum (X), were mixed indifferent ratios of 7: 3, 5:5, and 3:7 to yield enhanced release-controlling performance. The polysaccharides content of tablets was 10% (w/w), either alone or in mixtures.

T.Akelesh et al., developed a gastro-retentive floating tablet of Acyclovir by direct compression method. The results of *in vitro* release studies showed that optimized formulation F7 could sustain drug release (99.08%) for 16 hr and remain buoyant for 24 hrs. Optimized formulation F7 contained 60% of locust bean gum and 40% sodium alginate out of total floating polymer while amount of xanthan gum is same in all 7 batches.

3. AIM AND OBJECTIVE

- The aim of the present work is to formulate and evaluate floating tablet of ciprofloxacin hydrochloride using natural polymers like xanthan gum and guar gum.

- Ciprofloxacin hydrochloride is a second generation fluroquinolone antibiotic. It inhibits the replication of DNA interfering with the action of DNA gyrase. It is weakly acidic drug and half life of 4 hours.

- According to BCS classification, ciprofloxacin hydrochloride coming under class4 category which has low solubility and low permeability.

- Ciprofloxacin is a FDA approved oral antibiotic drug, which has rapid and complete absorption after oral administration.

- Gastro –retentive delivery is one of the site specific delivery for the delivery of drug either at stomach or intestine.

- As ciprofloxacin hydrochloride has higher absorption site in the upper gastrointestinal tract and poor absorption in colon, suggest it is an ideal candidate for a gastroretentive drug-delivery system that will prolong the gastric residence time of the dosage form, giving prolonged drug release in the upper gastrointestinal tract, where absorption of ciprofloxacin hydrochloride is well confined.

- A systemic approach for design and development of gastroretensive drug delivery system of ciprofloxacin using polymers which increases the gastric residence time, decreases the diffusion distance and allow more of the antibiotic to penetrate through the gastric mucus layer and act locally at the infectious site to enhance the bioavailability and therapeautic efficacy of the drug.

- Naturally occurring polymers is preferred for controlled formulation because of its low cost, naturally available, biocompatible and better patient tolerance as well as public acceptance.

- So planned to formulate and evaluate floating tablets of ciprofloxacin hydrochloride using natural polymers.

4. PLAN OF WORK

The proposed work was carried out to formulate and evaluate floating tablets of ciprofloxacin hydrochloride in the following phases:

Phase-I:

- Pre-formulation study of ciprofloxacin hydrochloride
- Drug excipient compatibility study of ciprofloxacin hydrochloride by fourier transform infrared spectroscopy (FT-IR)
- Preparation of standard curve of ciprofloxacin hydrochloride in 0.1 N hydrochloric acid

Phase-II:

- Pre compression parameters
- Formulation of floating tablets of ciprofloxacin hydrochloride.
- Post compression parameters
  - Weight variation
  - Thickness
  - Friability Test
  - Hardness
  - Drug content
  - Tablet density
  - Floating test
  - Swelling study
  - *In-vitro* dissolution studies
  - Kinetics of drug release

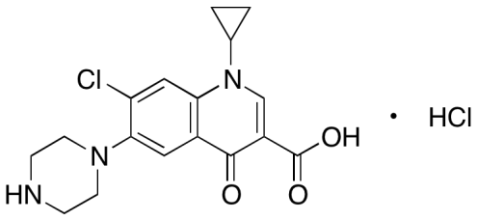
Phase-III:

Accelerated stability study of the optimized formulation as per ICH Guidelines.

5. THEORETICAL BACKGROUND PROFILES

DRUG PROFILE: Ciprofloxacin hydrochloride[26]

CHEMICAL STRUCTURE:



CHEMICAL NAME:

1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1, 4-dihydroquinoline-3-carboxylic acid hydrochloride.

Molecular formula **:** $C_{17}H_{18}FN_3O_3$.HCL

Molecular weight : 331.346 g/mol

Category **:** Ciprofloxacin is a broad spectum fluoroquinolone antibiotics.

Description **:** A pale yellow, crystalline powder

Solubility:

Ciprofloxacin hydrochloride is soluble in water, and slightly soluble in organic solvent.

Storage:

Store below 40˚C, preferably between 15˚C and 30˚C in a well-closed container, when otherwise specified by manufacture.

Clinical pharmacology[26]:

Mechanism of action

It is a broad-spectrum antibiotic of the fluoroquinolone class. It is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, and a type II topoisomerase, topoisomerase IV, necessary to separate bacterial DNA, thereby inhibiting cell division

Pharmacodynamics[27]:

The mean serum concentration of ciprofloxacin hydrochloride peaked approximately 1 h after the oral dose (0.94 mg/l). ... About 27% of the oral dose was excreted in urine, whereas the urinary recovery of the i.v. dose was 46%. The absolute bioavailability of ciprofloxacin hydrochloride was found to be approximately 60%.

Pharmacokinetics[28]:

Absorption

The absorption of ciprofloxacin from different regions of the human gastrointestinal tract was investigated in four healthy males using a remote-controlled drug delivery device (hf-capsule). Significant differences in AUC were observed in the control study (oral administration of ciprofloxacin solution without the hf-capsule = 100%) and after release of ciprofloxacin in the jejunum (geometric mean: 37%), the ileum (mean: 23%), the ascending colon (mean: 7%) and the descending colon (mean: 5%), whereas T_{max} showed no difference for any of the absorption sites. Ciprofloxacin release in the stomach resulted in the greatest AUC (mean: 140%). Thus, it is concluded that the main absorption site of ciprofloxacin is the upper gastrointestinal tract, up to the jejunum. Differences in presystemic metabolism of known drug metabolites along the gut could be excluded, as the pattern of urinary recovery of desethylene-, sulpho-, and oxo-ciprofloxacin and the parent compound was similar for all drug release sites.

Distribution:

The binding of ciprofloxacin hydrochloride to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs. After oral administration, ciprofloxacin hydrochloride is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism:

The drug is partially metabolized in the liver by modification of the piperazinyl group. ... The drug is partially metabolized in the liver by modification of the piperazinyl group to at least four metabolites. Ciprofloxacin and its metabolites are excreted in urine by both glomerular filtration and by tubular secretion.

Elimination:

The total renal elimination of the parent compound and its metabolites was approximately 60% over the 48-hour collection period in normal renal function and was reduced by about 20% in the group with clearances within the range of 10-30 ml/min. In renal impairment, there was a shift towards a higher proportion of the dose being eliminated as M2. M1 contributed only up to 2% of the dose in urine. Irrespective of the renal capacity, the amount of M3 recovered in urine was 3-4%

Contraindications:

- myasthenia gravis
- caution if QT prolongation
- caution if congenital long QT syndrome
- caution if QT prolongation family hx

- caution if torsades de pointes hx
- caution if ventricular arrhythmias

Marketed dosage forms:

Cifran 250(Sun pharma), Ciprokind 250(Mankind), Cipfil 250(Fourrts)

5.2 POLYMER PROFILE:

5.2.1 Xanthan gum[29]:

Nonproprietary Names

BP : Xanthan gum.

USPNF : Xanthan gum

Synonyms : Keltrol; Com sugar gum; Rhodigel; Xantural; Polysaccharide B-1459

Empirical formula and molecular weight:

Formula : $(C_{35}H_{49}O_{29})n$

Molecular weight : Approximately 2×10^6

Functional category

Stabilising agent, suspending agent, viscosity increasing agent.

Applications in pharmaceutical formulation or technology

Xanthan gum is widely used in oral and topical formulations, cosmetics and foods as a suspending agent and stabilising agent. It is also used as a thickening agent and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide P^H and temperature range. Xanthan gum gels show pseudo plastic behaviour, the shear thining being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

Recent studies have revealed that xanthan gum can also used as an excipient for spray drying and freeze drying processes for better results.

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained release matrix tablets. Xanthan gum has been incorporated

in an ophthalmic liquid dosage form, which interacts with mucin there by helping in prolonged retention of the dosage form in the precorneal area.

Xanthan gum can be used to increase the bio adhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum also used as a hydrocolloid in the food industry and in cosmetics it has been used a thickening agent in shampoos.

Description

Xanthan gum occurs as a cream or white colored, odourless, free-flowing, fine powder.

Typical properties

Acidity/alkalinity	:	p^H =6.0-8.0 for a l%w/v aqueous solution
Freezing point	:	0°C for al% w/v aqueous solution
Heat of combustion	:	4.6 j/g (3.5 cal/g)
Melting point	:	chars at 270°C

Solubility:

It is practically insoluble in ethanol and ether; soluble in cold or warm water.

Viscosity:

1200-1600 mPas(1200-1600 Cp) for a 1% w/v aqueous solution at 25°C.

Specific gravity:

1.600 at 25°C

Xanthan gum is a stable material aqueous solutions are stable over a wide P^H range (P^H 3-12), although they demonstate maximum stability at (P^H 4-10) and temperatures of 10-60°C. Xanthan gum solutions of less than 1% wlv concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids and bases.

Storage conditions:

The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Xanthan gum is incompatible with oxidising agents, some tablet film coatings, carboxy methylcellulose sodium, dried aluminium hydroxide gel and some active ingredients such as amitriptyline, tamoxifen and verampil.

Safety:

Xanthum gum is widely used in oral and topical pharmaceutical formulations,cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels empolyed as a pharmaceurtical excipient. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body weight.

Related substances:

Guar gum; ceratonia

5.2.2 GUAR GUM[30]:

Nonproprietary names

BP	:	Guar galactomannan;
PhEur	:	Guar galactomannanum;
USPNF	:	Guar gum.
Synonyms	:	Galactosol; Guar flour; Jaguar gum; Meyprogat; Meyprodor; Meyprofin.

Empirical formula and molecular weight

Formula	:	$(C_6, CH_{12,} O_6)n$
Molecular weight	:	2,20,000

Structural formula

Guar gum consists of linear chains of (1:4)-13-d-mannopyranosyl units with a-d-galactopyranosyl units attached by (1:6) linkages. The ratio of d-galactose to d-mannose is between 1: 1.4 and 1: 2.

Functional category

Suspending agent, tablet binder, tablet disintegrant, and viscosity increasing agent.

Applications in pharmaceutical formulation or technology

Guar gum used in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. It is used in solid dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled release carrier. Guar gum has also been examined for use in colonic drug delivery.

Table No.1: Uses of guar gum:

Use	Concentration (%)
Emulsion stabilizer	1
Thickener for lotions and creams	Up to 2.5
Tablet binder	Up to 10

Description

Guar gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L.) Taub. (Leguminosae). It consists chiefly of a high-molecular- weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a blend taste.

Typical properties

p^H = *5.0—7.0* (1% w/v aqueous dispersion)

Solubility:

It is practically insoluble in organic solvents. It swells almost immediately to form a highly viscous and thixotropic solution in cold or hot water,

Viscosity:

1.86 Pa s (4860 CP) for 1% w/v dispersion.

Stability and storage conditions[27]:

Guar gum powder should be stored in a well closed container in a cool and dry place.

5.3 EXCIPIENT PROFILE:

5.3.1 SODIUM BICARBONATE[31]:

Nomenclature

Non-proprietary names:

JP	:	Sodium bicarbonate
BP	:	Sodium bicarbonate
PhEur	:	Natriihydrogencarbonas
USP	:	Sodium bicarbonate

Chemical name : Carbonic acid monosodium salt

Formula:

Structural Formula : $NaHCO_3$

Physical and chemical properties:

Molecular weight	:	84.01
Color	:	Pale yellow
Nature	:	Crystalline powder
Odour	:	Odourless
Taste	:	Saline/slight alkaline
Density	:	0.869-2.173 g/cm3
Moisture content	:	less than 1 %w/w
Solubility	:	Soluble in water, practically insoluble in ethanol(95%) and ether.
Osmolarity	:	1.39% w/v aqueous solution is iso osmotic with serum.
Melting point	:	270 °C (with decomposition)

Functional category[30]:

Alkalizing agent, therapeutic agent

Applications:

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.

- Used to produce or maintain an alkaline pH in a preparation, like solution of erythromycin, lidocaine and niacin etc.
- Used to produce a sodium salt of the active ingredient that has enhanced solubility.
- Used as a freeze-drying stabilizer and in toothpaste.
- Used as a gas forming agent in alginate raft system and in floating drug delivery system.

Stability and storage:

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

Safety:

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

5.3.2 LACTOSE[32]:

Nonproprietary names:

Lactose (BP), Lactose monohydrate (PhEUR, USP-NF).

Synonym:

CapsuLac, GranuLac, Lactochem, lactosummonohydricum, monohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 3OGR, Tablettose.

Chemical name and CAS registry number:

O-b-D-Galactopyranosyl-(1 !4)-a-D-glucopyranose monohydrate,[10039-26-6]

Emprical formula and molecular weight:

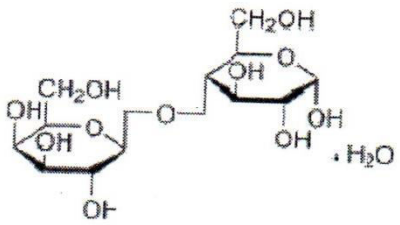
Formula : $C_{12}H_{22}O_{11}H_2O$,

Molecular weight : 360.31

Description[33]:

In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e a lactose monohydrate, 13-lactose anhydrous, and a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting

Structural formula:



P[H] : 5.5-8.9 (1%w/w aqueous solution at 25°)

Solubility : Insoluble in chloroform, ethanol, ether. Soluble in water in ratio of 1 in 5.24

Melting point : 201-202°C (for dehydrated a-lactose monohydrate)

Moisture content:

Lactose monohydrate contains normally had a range of 4.5-5.5% w/w water content.

Functional category:

Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

Applications in pharmaceutical formulation or technology[34]:

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.

Incompatibilities[35]:

A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amphetamines and lisinopril.

Stability and storage conditions[36]:

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.

Safety:

Lactose is widely used as a filler and filler-binder in orals and injections Adverse reactions to lactose are largely attributed to lactose intolerance, results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

5.3.3 MAGNESIUM STEARATE[37,38]:

Non proprietary name:

BP : magnesium stearate,

JP : magnesium stearate,

Pheur : magnesiistearas,

USPNF : magnesium stearate.

Synonyms:

Magnesiumocts decanoate; octadecanoicacid, magnesium salt; stearic acid, magnesium salt

Chemical name and CAS registry number:

Octadecanoic acid magnesium salt [557-04-0]

Emperical formula:

$C_{36}H_{70}MgO_4$

Molecular weight:

591.34

Functional category:

Tablet and capsule lubricant

Application in pharmaceutical formulation or technology:

Magnesium stearate is widely used in cosmetics, foods and in pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture.

Description:

Magnesium stearate is a very fine, light white, precipitated or mild, implantable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greesy to touch and readily adheres to the skin.

6. MATERIALS AND METHODS

The list of materials and equipments used were illustrated in the table no's 2&3.

LIST OF MATERIALS

Table no.2: Materials and their suppliers

S.No.	MATERIAL	SUPPLIED BY
1.	Ciprofloxacin hydrochloride	Fourrts India pvt, Ltd
2.	Xanthan gum	Cadila pharma pvt, Ahmedabad
3.	Guar gum	Zydus pharma pvt, Hosur
4.	Sodium bicarbonate	Medo pharm pvt. Ltd,
5.	Lactose	Orchid pharma pvt,ltd
6.	Magnesium stearate	Bafna pharma pvt,ltd
7.	Hydrochloric acid	Merck specialties pvt,ltd, Mumbai
8.	Methanol	Medo pharm pvt,ltd,Chennai

LIST OF INSTRUMENTS

Table No.3: Equipment and their manufacturer

S.No.	INSTRUMENTS	MANUFACTURER
1.	Electronic balance	Shimadzu ELB-300
2.	Sieve no 40	Jaico metals
3.	Proton mini press tablet punching machine	Proton
4.	Tablet hardness tester	Pfizer hardness tester
5.	Friability test apparatus	Roche Friabilator
6.	Tablet dissolution apparatus	Lab India Disso 2000
7.	Stability control oven	Biotechno lab, BTL
8.	UV-Visible spectrophotometer	Lab India,Lambda 25
9.	FTIR spectrophotometer	Bruker Alpha

6.1 PRE-FORMULATION STUDIES[39,40,41]:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

6.1.1 Organoleptic properties:

Colour : A small quantity of pure ciprofloxacin hydrochloride powder was taken in a butter paper and viewed in well illuminated place.

Taste and odour : Very less quantity of ciprofloxacin hydrochloride was used to get taste with the help of tongue as well as smelled to get the odour.

6.1.2 Solubility analysis[42]:

Solubility is important pre-formulation parameter because it affects the dissolution of drug bio availability of drug. Solubility of ciprofloxacin hydrochloride was determined in methanol, ethanol, dimethyl fluoride, methylchloride, 0.1N hydrochloric acid. Solubility studies were performed by taking excess amount of ciprofloxacin hydrochloride in different beakers containing the solvent.

6.1.3 Melting point[43]:

The melting point of ciprofloxacin hydrochloride was determined by capillary method, using small quantity of ciprofloxacin hydrochloride was taken and placed in apparatus and determined the melting point and matched with standards.

6.1.4 Loss on drying[44]:

Determined on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle(W_1). Put the sample in bottle, replace the cover, and accurately weighed the empty bottle with contents (W_2).

By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle(W_3). The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W_2 - W_3)}{(W_2 - W_1)} \times 100$$

Where, W_1 = Weight of empty weighing bottle

W_2 = Weight of weighing bottle + sample

W_3 = Weight of weighing bottle + dried sample

6.1.5 Drug powder characterization:

6.1.5.1 Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area and co-efficient of friction of the raw material[45,46].

$$\boldsymbol{\Theta = \tan^{-1} (h/r)}$$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Table-4: Limits:

Angle of repose	Flow property
<25°	Excellent
25-30°	Good
30-40°	Passable
>40°	Very poor

6.1.5.2 Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases[47].

A quantity of 5 gm of powder weighed and transferred to a measuring cylinder and observed the volume occupied by the sample. The initial volume was calculated. Bulk density was calculated using the formula[48].

Bulk density = Bulk mass / Bulk volume

6.1.5.3 Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes is observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tapping down[49,50].

The powder in the measuring cylinder were tapped for specific times at a height of 2.5 cm at a interval of 2 seconds. The powder in the graduated cylinder were tapped for specific times at a height of 2.5 cm at an interval of 2 seconds. The final volume occupied by the sample was noted and tapped density was calculated by using the formula:

$$\textbf{Tapped density} = \frac{m}{Vf}$$

Where, m = initial weight of material in gm, Vf = volume of material after tapping.

Generally replicate determinations are desirable for the determination of this property.

6.1.5.4 Measurement of powder compressibility[51]:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

$$\textbf{Compressibility index:} = 100\frac{(V_0 - Vf)}{V_0}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume

Table-5: Limits:

S.no	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremelypoor

$$\textbf{HausnerRatio:} = \frac{V_0}{Vf}$$

Where, Vf = final tapped volume, Vo = initial un tapped volume.

Table-6: Limits:

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

6.2 COMPATIBILITY STUDY:

Drug excipient compatibility studies by FT-IR[52,53]:

IR spectra of drug, polymer and drug and polymers, individual excipients, drug and polymers and excipients were obtained using FT-IR

Drug and excipients were analyzed by IR spectral studies using KBr pellet technique. In this method, the drug and KBr were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm^{-1}. Spectra were recorded for pure drug, pure excipients, and physical mixture of drug and polymer, drug, polymer and excipients.

6.3 STANDARD CURVE OF CIPROFLOXACIN HYDROCHLORIDE DRUG:

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 276nm. It obeyed Beer's law in the concentration range of 2-10 µg/mL.

Preparation of stock and standard solution[54,55,56]:

The stock solution was freshly prepared by dissolving 100mg of ciprofloxacin hydrochloride in few ml of methanol (5ml) in a 100ml volumetric flask and then made up the solution upto the mark using 0.1N hydrochloric acid for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100ml with 0.1N hydrochloric acid to obtain a solution of strength 100 µg/mL (stock II)

Preparation of various concentrations[57]:

10 ml stock solution was taken from stock solution-2 and volume made up to 100 ml by using 0.1N hydrochloric acid to get 10 µg/ml concentrations. From this solution with draw 2, 4, 6, 8, 10 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using 0.1N hydrochloric acid to get the concentrations 2, 4, 6, 8, 10 µg/ml.

6.4 Preparation method of ciprofloxacin hydrochloride floating tablets[58,59]:

Ciprofloxacin hydrochloride was mixed with the required quantities of polymers (xanthan gum and guar gum) sodium bicarbonate (12%), and lactose by geometric mixing. The powder blend was then lubricated with magnesium stearate (2%) and mixed for about 3 minutes. Finally this mixture was compressed on proton mini press tablet punching machine**.**

Formulation composition of gastroretentive tablets of ciprofloxacin hydrochloride

Table:7 Quantity of raw materials Per tablet (In mg)

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Ciprofloxacin HCL	250	250	250	250	250	250	250	250	250
2	Xanthan gum	10	10	-	15	15	-	20	20	-
3	Guar gum	10	-	10	15	-	15	20	-	20
4	Sodium bicarbonate	20	20	20	20	20	20	20	20	20
5	Lactose	25	35	35	15	30	30	5	25	25
6	Magnesium stearate	5	5	5	5	5	5	5	5	5
7	Total weight	320	320	320	320	320	320	320	320	320

6.5 Evaluation of floating tablets of ciprofloxacin hydrochloride[60,61]:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Following parameters were evaluated

- Tablet thickness
- Weight variation test
- Hardness
- Friability
- Content uniformity
- Buoyancy/floating test
- Swelling studies
- *In vitro* drug release studies

6.5.1 Tablet thickness:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

6.5.2 Weight variation:

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight and standard deviation were calculated and the results were expressed as compliance or non-compliance of set limits.

Table: 8: Weight variation tolerance

Average weight (mg)	% Deviation allowed
80 or less	10
80-250	7.5
More than 250	5

6.5.3 Tablet hardness:

Tablet hardness was measured using a Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness and standard deviation was reported.

6.5.4 Friability[62]:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

6.5.5 Content uniformity[63,64]:

The formulated ciprofloxacin hydrochloride floating tablets were assayed for drug content. From each batch of prepared tablets, ten tablets were collected randomly and powdered. a quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 100 ml of methanol was added and then the solution was subjected to sonication for about 2 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with methanol. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 276 nm by using UV-Visible spectrophotometer.

6.5.6 Buoyancy / Floating Test[65]:

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100-ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

6.5.7 Swelling Index[66]:

The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at $37^{o} \pm 0.5^{o}$c, rotated at 50 rpm. At selected regular intervals the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU).

$$\%WU = (Wt - Wo) * 100 / Wo$$

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

6.5.8 Dissolution study of tablets[67,68]:

Apparatus	:	Dissolution test apparatus -2; USP-32
Method	:	Paddle method
Dissolution medium	:	0.1N HCl
Volume	:	900 ml
Temperature	:	37 ± 0.5 °C
Speed	:	50 rpm

Procedure

The tablet was placed inside the dissolution vessel. 5ml of sample were withdrawn at time intervals of 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 10hr, 12hr. The

volume of dissolution fluid adjusted to 900 ml by replacing 5ml of dissolution medium after each sampling. The release studies were conducted with 6 tablets, & the mean values were plotted versus time.

Each sample was analyzed at 276 nm using double beam UV and visible spectrophotometer against reagent blank.

The drug concentration was calculated using standard calibration curve.

6.6 KINETIC DATA ANALYSIS[69,70]:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and peppas-Korsemeyer equation.

6.6.1 Zero order release kinetics[71]:

It defines a linear relationship between the fractions of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

6.6.2 First order release kinetics[72]:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from

most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{In\ (1\text{-}Q) = -\ K_1 t}$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

6.6.3 Higuchi's equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = \mathbf{K_2\ t^{½}}$$

Where, K_2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

6.6.4 Korsemeyer equation:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by peppas and korsmeyer equation (power law).

$$\mathbf{M_t/M_\alpha = K.\ t^n}$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent. A plot between log of M_t/M_α against log time will be linear if the release obeys peppas and korsmeyer equation and the slope of this plot represents "n" value.

Table-9: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent	**Overall solute diffusion mechanism**
0.45	Fickian diffusion
0.45<n<0. 89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super case II transport

6.7 Stability Studies:

The optimized formulation was subjected to stability studies as per I.C.H guidelines. Samples were kept at 40°c with 75% RH and analyzed for weight variation, hardness, friability, drug content and *In vitro* dissolutions study for every month for a period of three months.

7. RESULTS AND DISCUSSION

7.1 PREFORMULATION STUDY

These tests were performed as per procedure given in 6.2.1. The results were illustrated in table no 10.

7.1.1 Organoleptic properties:

Table-10: Observation of organoleptic properties:

TEST	SPECIFICATION	OBSERVATION
Colour	Pale yellow	Pale yellow
Odour	Odour less	Odourless
Taste	Tasteless	Tasteless

7.1.2 Solubility analysis:

Ciprofloxacin hydrochloride samples are examined and it was found to be soluble in water and slightly soluble methanol, soluble in dimethyl formamide. It also dissolves in dilute alkali and in dilute acids.

7.1.3 Melting point of drug:

The melting point of ciprofloxacin hydrochloride was determined by capillary method, melting point of ciprofloxacin hydrochloride was found to be 255°C. Melting point compared with USP standards that showed that drug is pure.

7.1.4 Loss on Drying:

It was determined as per procedure given in 6.2.4. The results was given in table no.11

Table-11: Observations for loss on drying

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.42%

The loss drying of drug was founded as 0.42 which is within the limit.

7.1.5 Drug powder characterization:

7.1.5.1 Angle of repose:

It was determined as per procedure given in 6.1.5.1. The results was given in table no.12

Table-12: Angle of repose

Material	Angle of repose
Ciprofloxacin hydrochloride	28.11

The results indicating that the raw material has excellent flow property.

7.1.5.2 Flow properties:

It was determined as per procedure given in 6.2.5.2 to 6.2.5.4. The results was given in table no.13

Table-13: Flow properties of pure drug

Material	Bulk density	Tapped density	Carr's index(%)	Hausner ratio (%)
Ciprofloxacin hydrochloride	0.23	0.46	11.02	1.134

The results are clearly indicating that the ciprofloxacin hydrochloride raw material has good flow property.

7.2 Drug-polymer compatibility study:

FTIR studies:

The FTIR spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}). No peaks are observed which interfere with the main drug peaks. The following spectrum and table shows IR spectrum for drug and polymer and the wave number of characteristic bands for the same.

The IR Spectrum preview pictures are as follows:

Fig. No: 1: IR Spectrum of ciprofloxacin hydrochloride standard

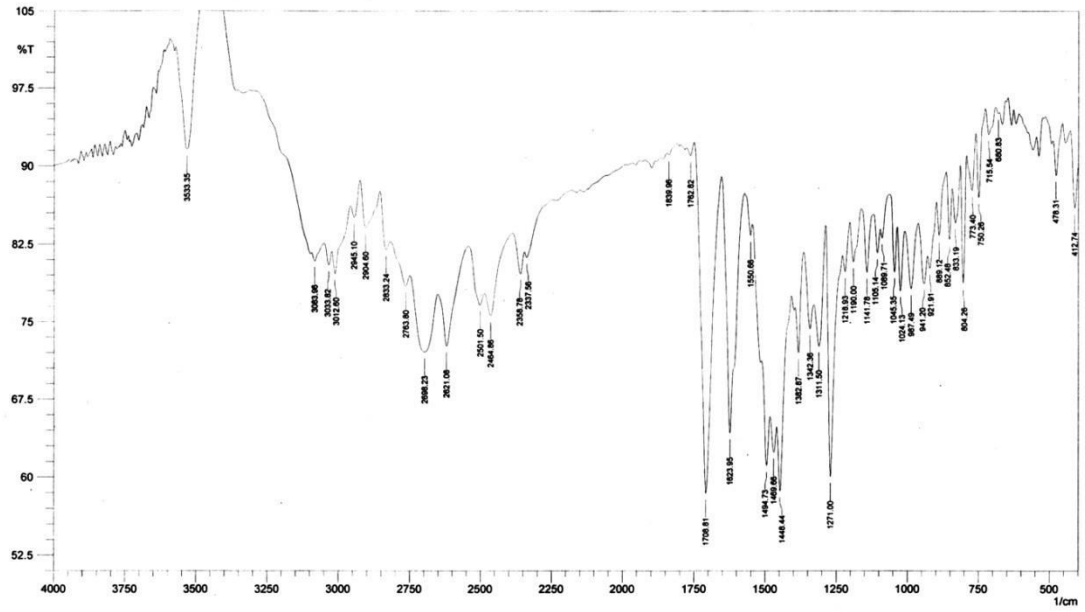


Fig. No: 2: IR Spectrum of xanthan gum

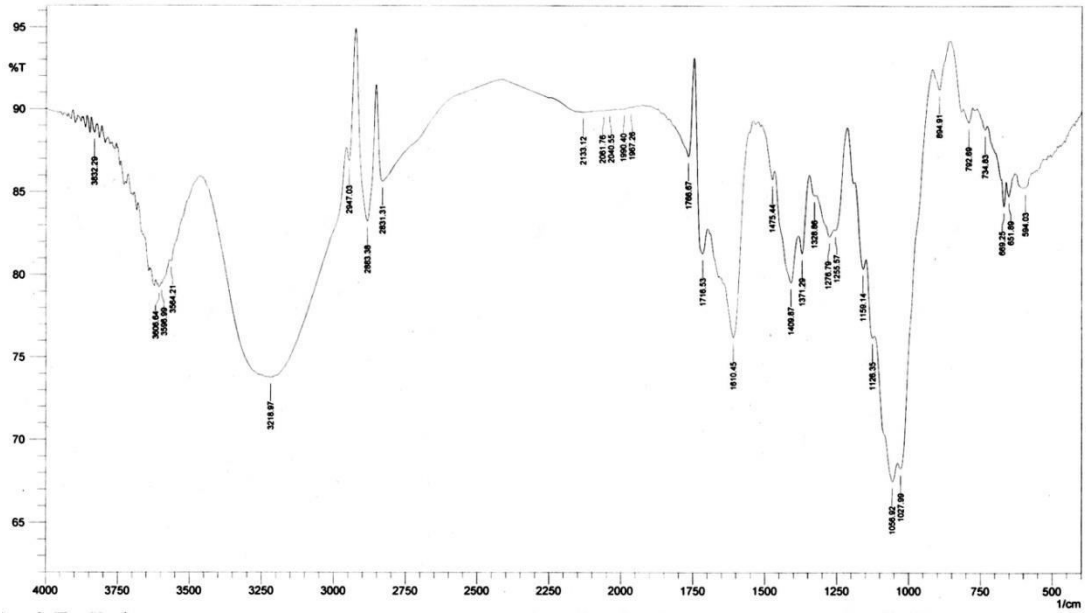


Fig. No: 3: IR Spectrum of guar gum

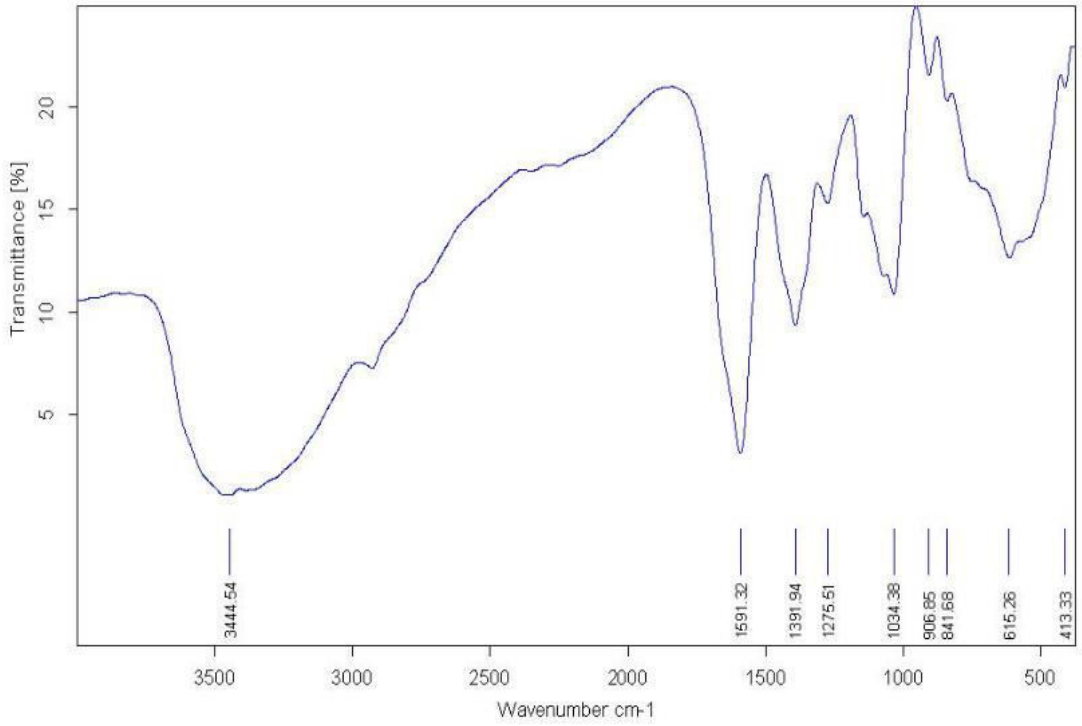


Fig. No: 4: IR Spectrum of magnesium stearate

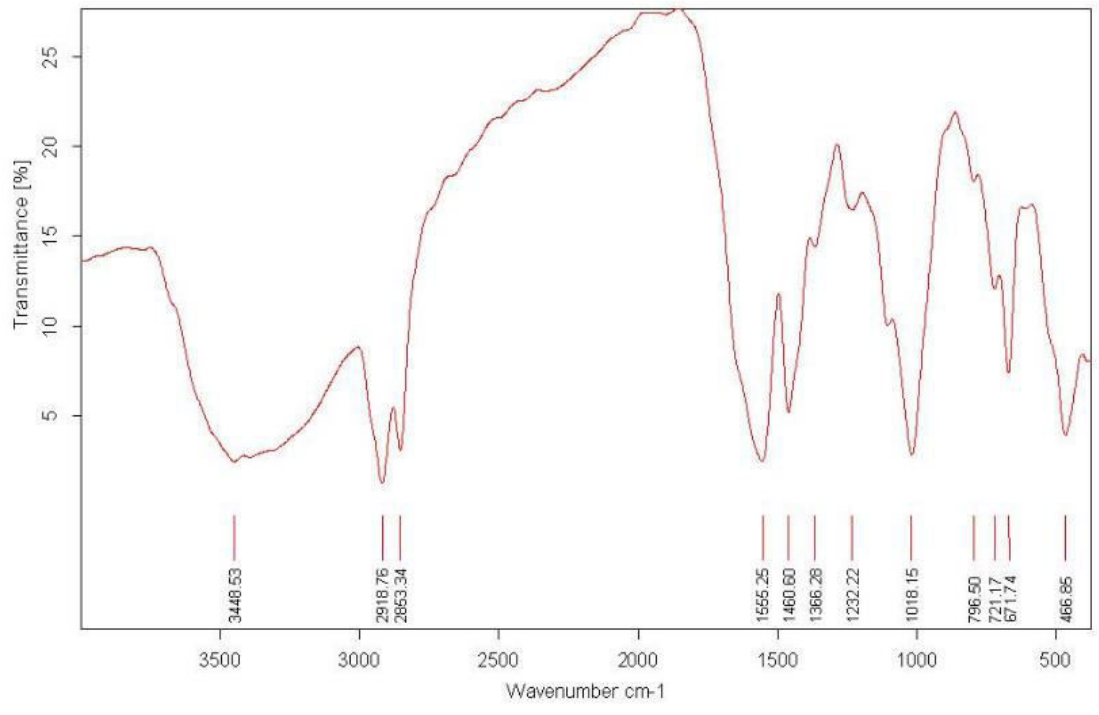


Fig. No: 5: IR Spectrum of lactose

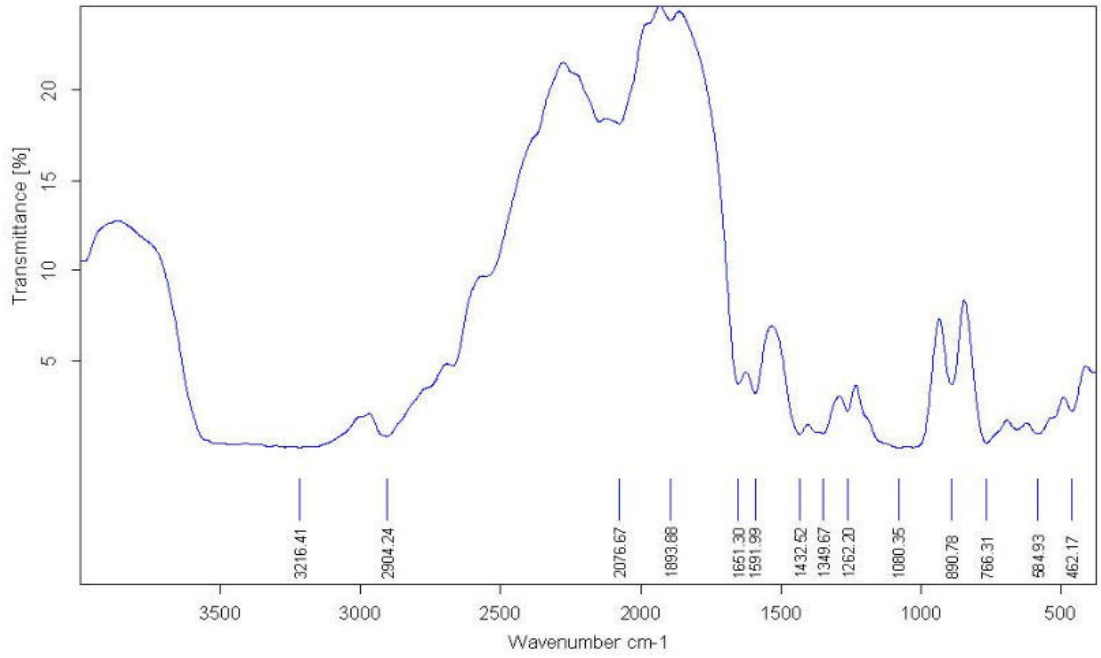


Fig. No: 6: IR Spectrum of ciprofloxacin hydrochloride and xanthan gum

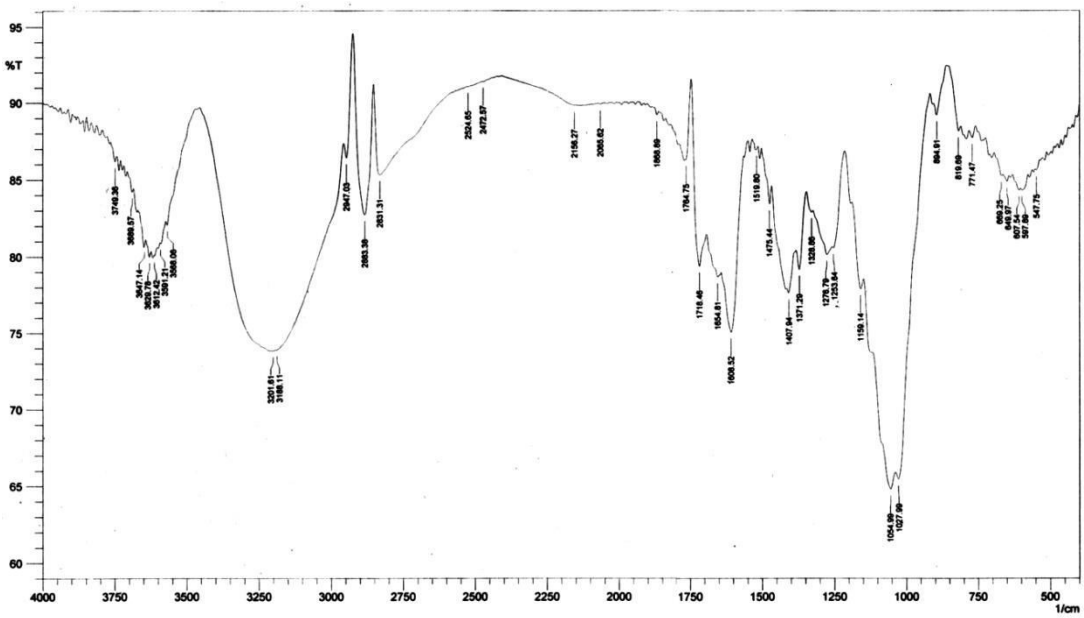


Fig. No: 7: IR Spectrum of polymers and excipients

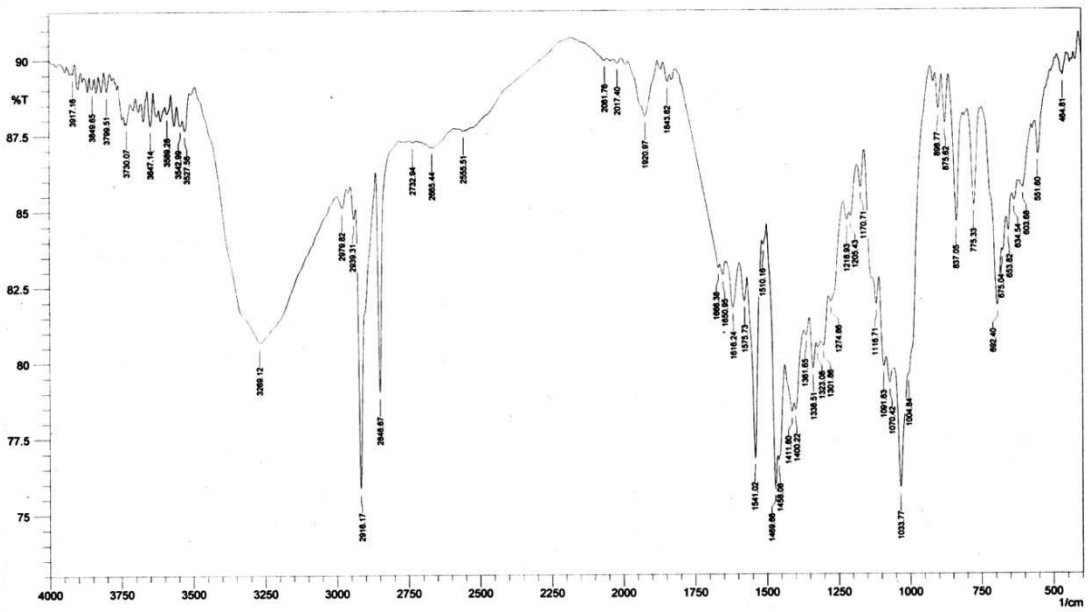


Table 14: FT-IR Peaks of various components

S.No	Peak in pure drug (cm^{-1})	Functional Group	Type of vibration	Peak in Physical mixture
1.	3533.35	Amine (N-H)	Stretch (medium)	3269.12
2.	1708.81	Ketone(C=O)	Stretch (medium)	1718.46
3.	1623.95	Alkene (C=C)	Stretch (Strong)	1608.52
4.	1271.00	Carbonyl(C-O)	Stretch (Scissoring)	1276.79

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

From the above results functional groups and type of vibrations are noted (Table no:14) In case of FTIR study there was no disappearance or appearance of already existing peaks. Hence drugs were found to be compatibles with excipients.

7.3 STANDARD CURVE OF CIPROFLOXACIN HYDROCHLORIDE PURE DRUG:

Calibration curve of ciprofloxacin hydrochloride was determined by plotting absorbance (nm) versus concentration (µg/ml) at 276 nm. The results obtained are as follows.

Table -15: Standard curve of ciprofloxacin hydrochloride

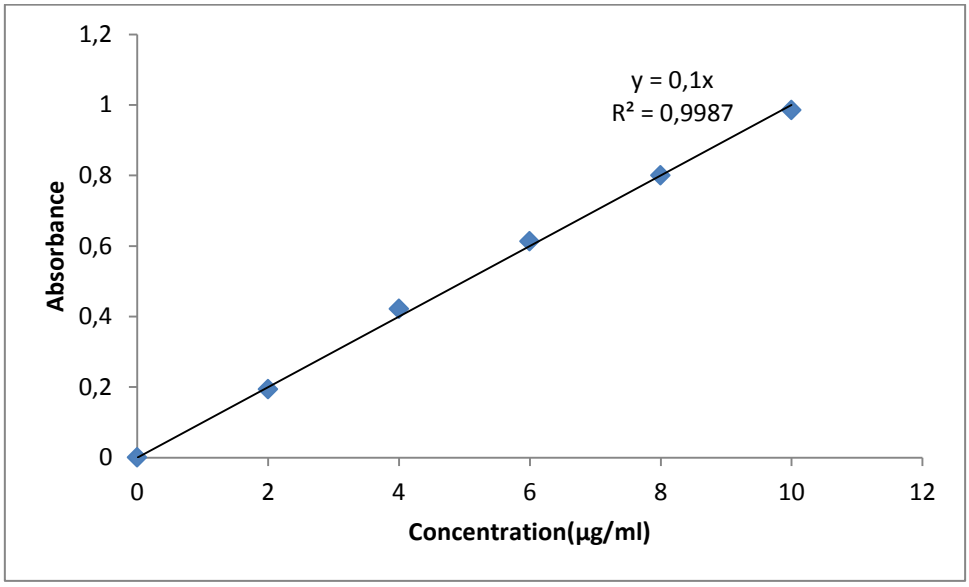
Concentration µg/ml	Absorbance
0	0
2	0.193
4	0.421
6	0.613
8	0.800
10	0.985

The linear regression analysis was done on absorbance data points. A straight line generated to facilitate the calculation of amount of drug, the equation is as follows:

$$Y = mx + c$$

Where Y=absorbance, m=slope, x=concentration

Fig No.8: Standard plot for ciprofloxacin hydrochloride in 0.1 N HCL



7.4 EVALUATION OF FORMULATED METHODS:

Before formulating floating tablets pre compression parameter were evaluated.

The following parameters were carried out by the procedure given in 6.1.5. The results were illustrated in table no.16

Table-16: Evaluation of powder characteristics:

Formulation code	Angle of repose (degree± SD)	BD (gm/ml± SD)	TD (gm/ml± SD)	Carr's index (%± SD)	Hausner ratio (%± SD)
F1	26.11±0.02	0.313±0.02	0.364±0.01	14.54±0.03	1.05±0.03
F2	27.01±0.01	0.324±0.05	0.381±0.02	15.11±0.04	1.06±0.02
F3	26.02±0.01	0.334±0.04	0.376±0.03	13.59±0.02	1.13±0.03
F4	25.04±0.02	0.342±0.02	0.384±0.02	16.42±0.04	1.37±0.05
F5	26.94±0.06	0.294±0.02	0.323±0.04	13.13±0.06	1.12±0.05
F6	25.32±0.06	0.263±0.01	0.334±0.04	15.23±0.03	1.13±0.04
F7	26.13±0.03	0.256±0.05	0.374±0.04	14.46±0.06	1.14±0.02
F8	27.10±0.06	0.305±0.05	0.332±0.03	13.31±0.07	1.14±0.04
F9	26.36±0.04	0.332±0.02	0.336±0.01	16.21±0.05	1.28±0.04

Angle of repose for all formulations were examined .the values were found to be with in the range from 25.04±0.02 to 27.10±0.06. This indicates that good flow property of powder blend.

The bulk density and tapped density values were found to be with in the range from 0.256±0.05 to 0.334±0.04 and 0.323±0.04 to 0.381±0.02 respectively.

The hausners ratio values were found to be with in the range from 1.05±0.03 to 1.37±0.05.this indicates that good flow property of powder blend.

Based on the results the physical mixture was found to be suitable for direct compression. So F1 to F9 batches were formulated accordingly to the composition given in table 7 of and kept in for evaluation.

7.5 EVALUATION OF FORMULATED TABLETS:

Table-17: Evaluation of formulated tablets

Formulation code	Weight variation (n=20) (mg ± SD)	Hardness (kg/cm^2± SD)	Friability (%)	Drug content (%± SD)	Thickness (%± SD)
F1	319±2.99	4.1±0.34	0.11	96.76±0.19	3.3±0.12
F2	320±1.98	4.0±0.71	0.23	95.14±0.23	3.2±0.20
F3	318±3.5	4.1±0.22	0.12	96.87±0.41	3.3±0.03
F4	320±6.1	4.1±0.32	0.26	97.23±0.22	3.3±0.14
F5	320±1.3	4.0±0.28	0.22	96.48±0.26	3.3±0.02
F6	319±6.59	4.1±0.37	0.14	95.67±0.17	3.2±0.53
F7	318±1.6	4.0±0.09	0.13	94.87±0.32	3.3±0.04
F8	319±3.06	4.0±0.42	0.25	96.28±0.33	3.2±0.16
F9	320±3.9	4.0±0.06	0.13	96.87±0.16	3.2±0.29

The formulated floating tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability and drug content. The weight variation of tablets was uniform in all formulations and ranged from 318±1.6 to 320±3.9. The % deviation is coming with in 5% to 7% range for this accepted % deviation should be 5 % for 320mg tablet. F1-F9 batches come with in limit and passed the test. The hardness of the prepared tablets was ranged from 4.0±0.06 to 4.1±0.37, friability values were ranged from 0.11 to 0.26 which falls with in the limit of standard (0.1 to 0.9%). Drug content of tablets was ranged from 94.87±0.32 to 97.23±0.22, F4 showed maximum drug content. Thickness of tablets was uniform and values are ranged from 1.2±0.20 to 1.3±0.14.

7.5.1 Buoyancy / Floating Test

On immersion in 0.1 N hydrochloric acid solution P^H (1.2) at 37^0C, The tablets floated, and remained buoyant without disintegration. Table-18 shows the results of buoyancy study and shows buoyancy character of prepared tablet.

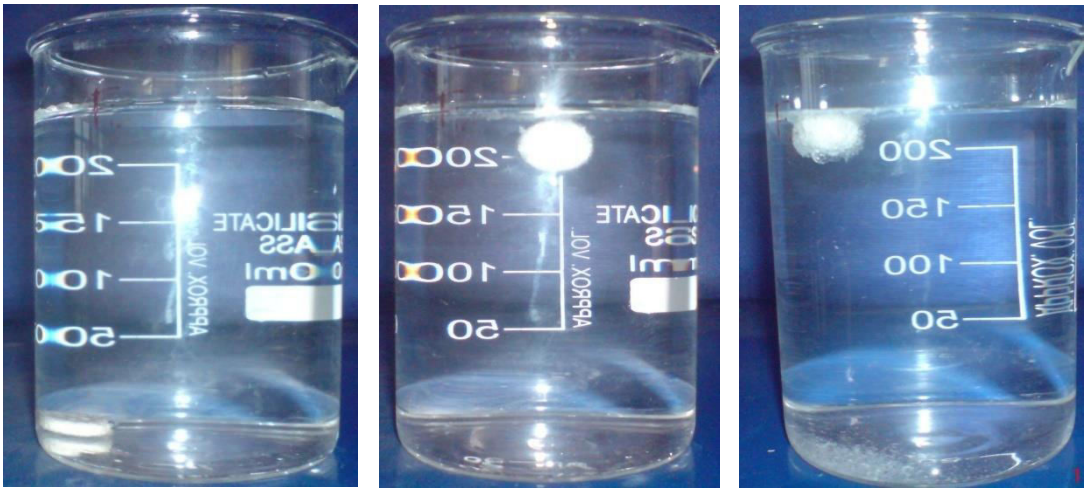
The buoyancy lag time for F1-F9 were ranging from 45-90 secs.

From the results it can be concluded that the batch containing both xanthan gum and guar gum showed good buoyancy lag time(BLT) and total floating time(TFT).

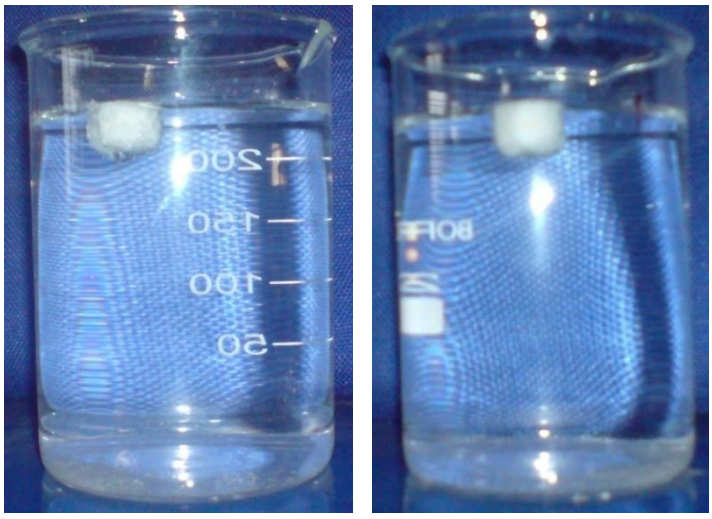
Formulation F4 containing xanthan gum and guar gum showed good BLT of 45 sec, while the formulation containing xanthan gum alone and guar gum alone showed highest BLT and TFT of greater than 8 hrs. This may due to the amount of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinious layer, and it escapes leading to variation in BLT and TFT.

Table 18: Buoyancy and floating time

S.No	Batch No	Buoyancy lag time (sec)	Floating duration (hrs)
1	F_1	55	>8 hrs
2	F_2	60	>8 hrs
3	F_3	50	>8 hrs
4	F_4	45	>8 hrs
5	F_5	70	>8 hrs
6	F_6	90	>8 hrs
7	F_7	60	>8 hrs
8	F_8	50	>8 hrs
9	F_9	55	>8 hrs



0 min **2 min** **4 hr**



6 hr **8 hr**

Fig No: 9: *In vitro* buoyancy study of ciprofloxacin hydrochloride floating

7.5.2 Swelling Index:

The percentage swelling obtained from the water uptake studies of the formulations is shown in Figure 10-12. The formulations with xanthan gum and guar gum showed the swelling and tablet integrity. The change in sodium bicarbonate concentration did not show any effect on swelling of the tablet. Complete swelling was achieved at the end of 6 hrs, then diffusion and erosion takes place. The formulation containing xanthan gum shows the higher swelling compared to that of the formulations containing both xanthan gum and guar gum alone. The swelling index of the tablets increases with an increase in the polymer viscosity grades.

Table 19: % swelling index of formulated floating tablets

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	19.54	25.15	18.22	20.1	19.99	19.26	13.05	16.12	11.15
2hr	32.22	42.1	33.15	28.98	32.14	30.9	18.55	28.76	17.01
3hr	44.1	56.16	46.1	42.1	45.88	41.1	27.85	43.1	21.85
4hr	61.12	70.11	63.01	52.9	58.22	53.1	39.75	51.1	31.96
6hr	69.02	76.12	71.11	63.89	71.03	60.8	46.1	59.65	43.11

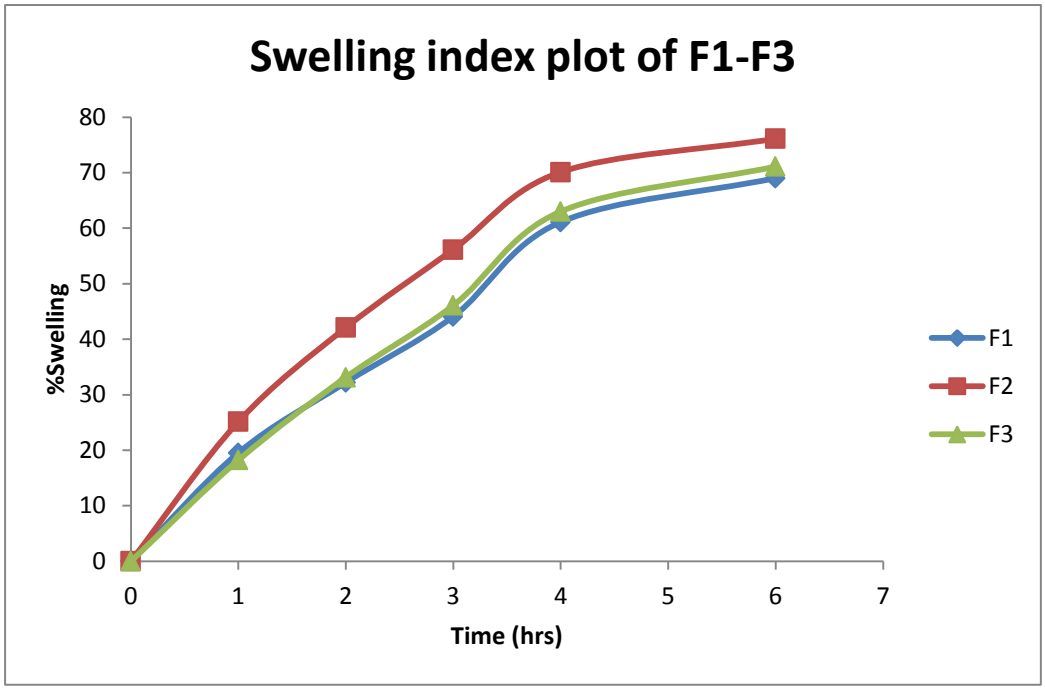


Fig No.10: Swelling index plot of F1-F3

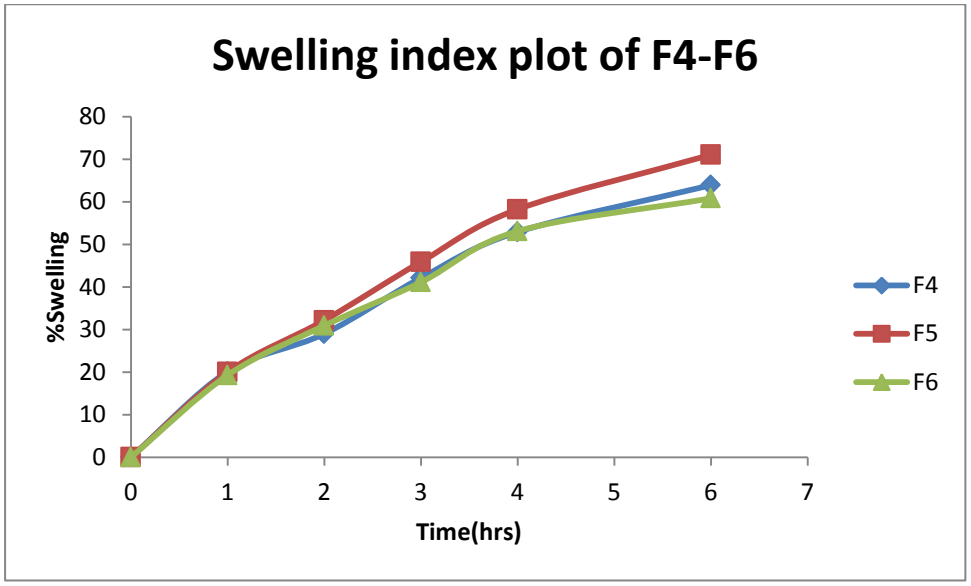


Fig No.11: Swelling index plot of F4-F6

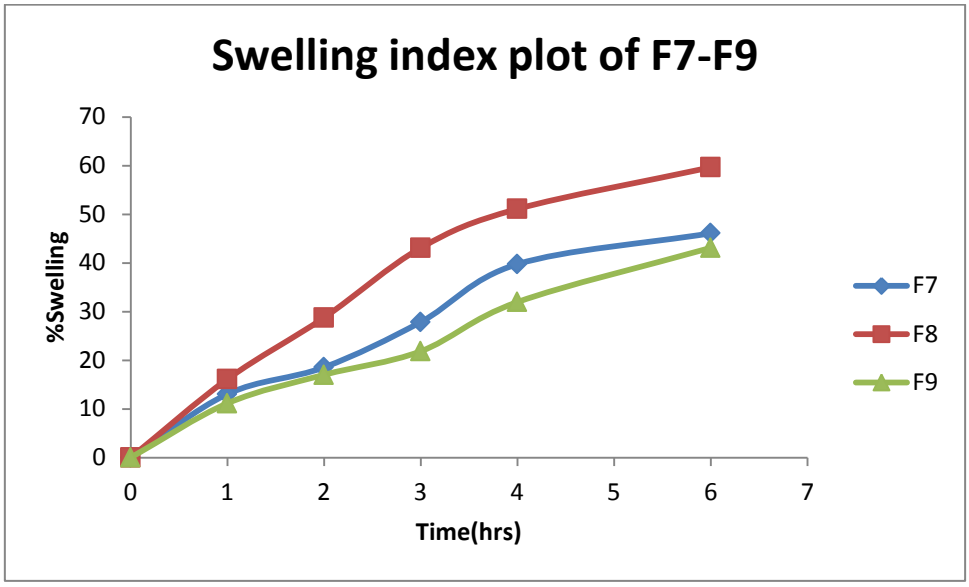


Fig No.12: Swelling index plot of F7-F9

7.5.3 *Invitro* drug release study of formulated floating controlled release formulations

Table 20: *Invitro* drug release study

TIME	CUMULATIVE PERCENTAGE DRUG RELEASE (%)								
	Fl	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	21.01	22.12	26.15	16.08	21.01	8.54	7.15	7.05	9.17
2	31.22	33.46	36.78	27.11	31.04	16.12	13.32	15.45	19.04
3	39.04	42.96	45.80	37.65	43.12	25.77	22.78	22.03	28.26
4	46.05	51.05	52.01	48.76	51.85	34.05	28.04	29.07	34.05
5	53.04	67.09	63.90	56.04	75.75	46.03	34.08	37.12	45.60
6	69.09	78.12	78.08	63.06	81.04	50.46	42.21	42.15	51.75
7	81.98	99.11	92.06	75.05	96.03	55.62	47.67	56.08	60.05
8	98.32	-	99.34	83.56	99.08	61.26	52.06	66.09	67.07
10	-	-	-	90.22	-	71.01	66.45	81.84	72.05
12	-	-	-	99.80	-	89.15	78.80	93.71	83.04

Average of n value n=3

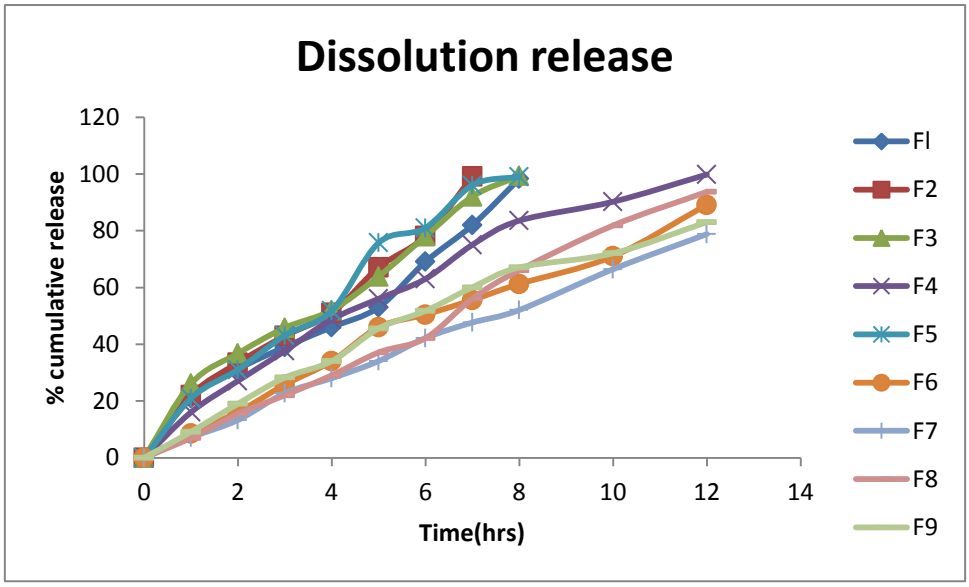


Fig No.13: *Invitro* drug release study

The formulated floating controlled release tablets were then subjected to *invitro* dissolution test for evaluating drug release from the formulation. The *invitro* dissolution test was carried out in 900 ml of 0.1N hydrochloric acid in USP-II paddle type apparatus at 50 rpm and 37±0.5^{o}C. The results of dissolution study was depends on polymer concentration. Formulation containing xanthan gum alone released fastly compared to that guar gum alone due to the less binding nature and controlled release property than that of guar gum. Formulation F4 containing xanthan gum (15 mg) and guar gum (15 mg) had given drug release 99.80% in 12 hrs. Then the formulations containing xanthan gum and guar gum were given better release profiles when compared with formulations containing xanthan gum alone and guar gum alone.

7.6 KINETIC STUDIES OF FLOATING TABLETS OF CIPROFLOXACIN:

Table-21: kinetic study of optimized formulation

Time (hrs)	Log Time	√Time	cumulative % drug release	Log cumulative % drug release	cumulative % drug remained	Log cumulative % drug remained
0	0	0	0	0	100	2.000
1	0	1.000	16.08	1.206	83.92	1.923
2	0.312	1.454	27.11	1.433	72.89	1.862
3	0.624	1.753	37.65	1.575	62.35	1.794
4	0.715	2.003	48.76	1.688	51.24	1.709
5	0.798	2.274	56.04	1.748	43.96	1.643
6	0.945	2.455	63.06	1.799	36.94	1.567
7	1.090	2.654	75.05	1.875	24.95	1.397
8	1.175	2.924	83.56	1.921	16.44	1.215
10	1.345	3.262	90.22	1.955	9.78	0.990
12	1.398	3.564	99.80	1.999	0.20	-0.698

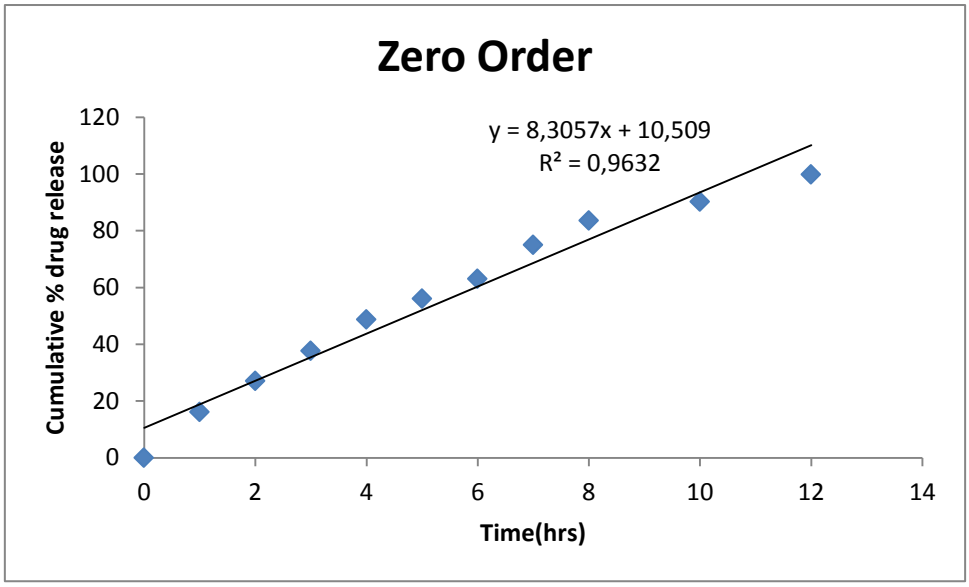


Fig No. 14: Zero order plot

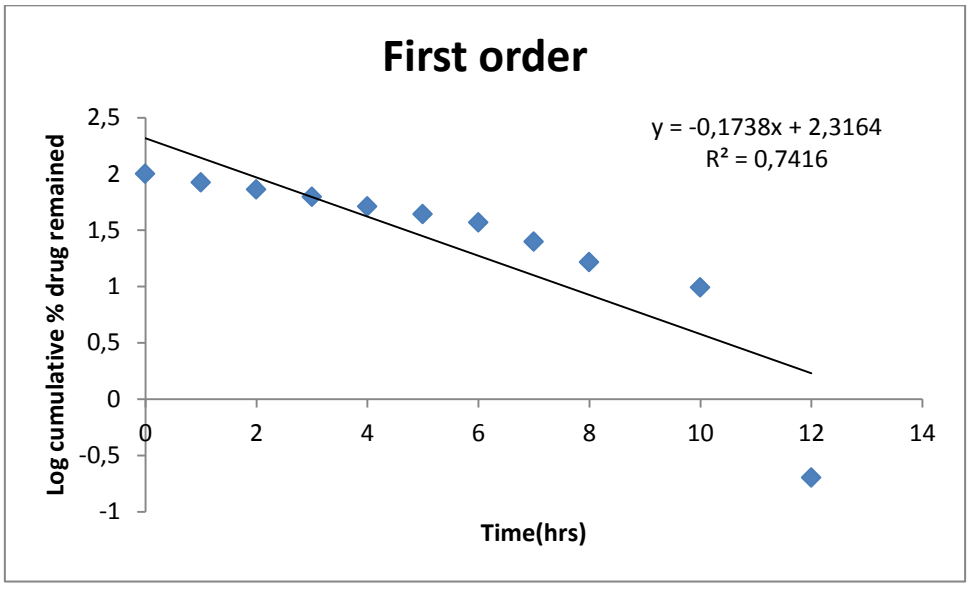


Fig No. 15: First order plot

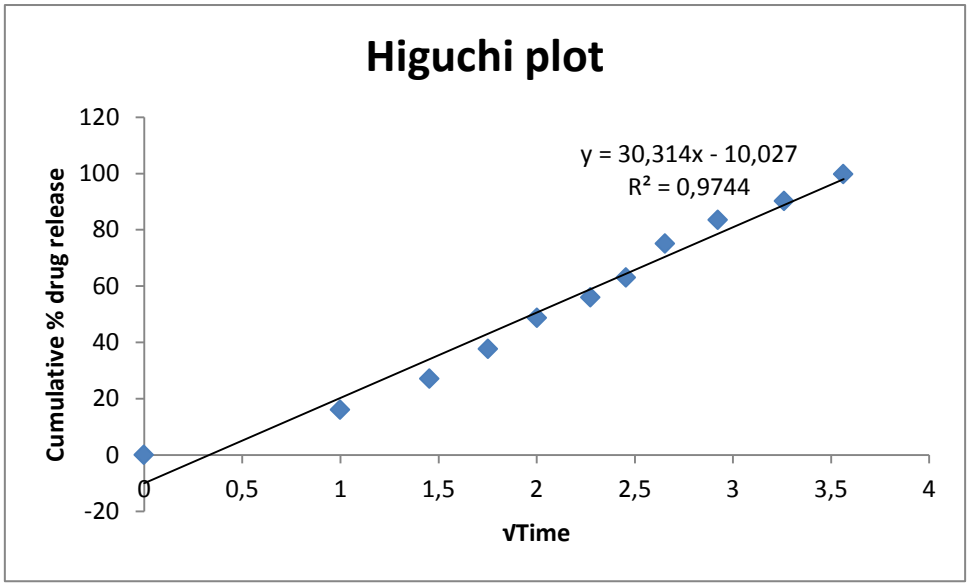


Fig No. 16: Higuchi plot

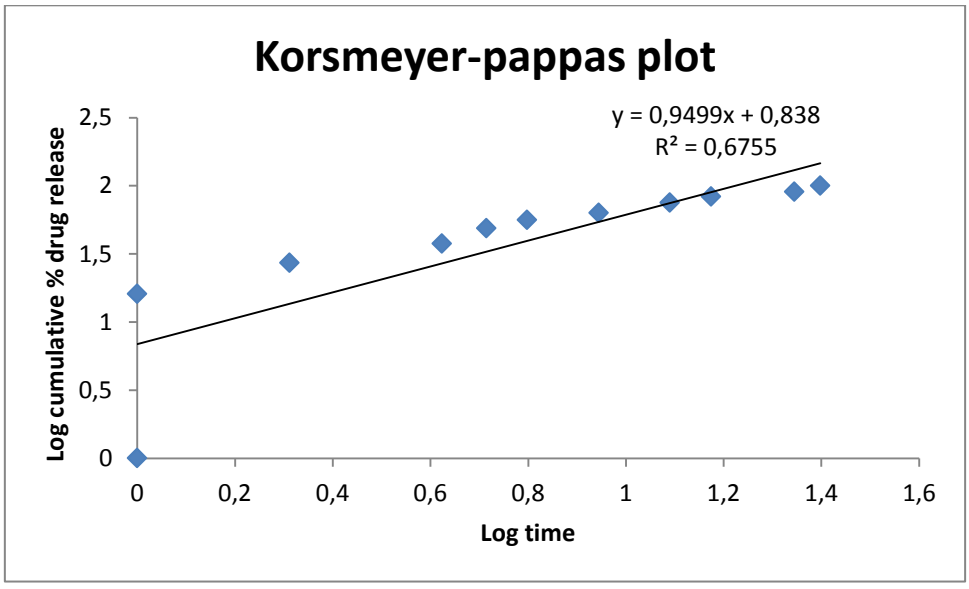


Fig No. 17: Korsmeyer peppas plot

KINETICS OF DRUG RELEASE

Table-22:

Formulation	Regression coefficient of zero order	Regression coefficient of first order	Order of release
F4	0.963	0.741	Zero order release

Table-23:

Formulation	Higuchi Model	Korsmeyer peppas model
	R^2	R^2
F4	0.974	0.675

In order to determine the mechanism of drug release form the formulations, the *Invitro* dissolution data was fitted to zero order, first order, higuchi plot and korsmeyer-peppas plot was drawn and interpretation of release exponent value (n) was calculated and results are shown in tables 22-23; figs 14-17. The results of R^2 for zero and first order were obtained as 0.963, 0.741. Based on that we will confirm the optimized formulation followed zero order release.

The drug release was diffusion controlled as the plot of optimized formulation F4 was found 0.974 as regression coefficient in higuchi plot. From korsmeyer peppas plot the release exponent value n was found as 0.675 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion.

7.7 STABILITY STUDIES:

The optimized formulation was subjected to stability studies at $40^{o}C \pm 2^{o}C$ / 75% RH ± 5% for 3 months.

The product was evaluated for following parameters:

- Weight variation
- Hardness
- Friability
- Drug content
- Dissolution analysis

1) Storage condition at 40°C±2°C/75%RH±5%:

Table-24:

TEST	0 days	30 days	60 days	90 days
Weight variation	99±0.87	99±0.55	98±0.84	99±0.76
Hardness	4.5	4.4	4.4	4.3
Friability	0.68	0.69	0.69	0.70
Drug content	99.83±0.04	99.59±0.07	99.39±0.07	99.28±0.06

7.7.1 Dissolution data of percent cumulative drug release for formulation F4

Table-25: Dissolution data of stability formulation F4

Time (hrs)	0 days	30 days	60 days	90 days
0	**0**	0	0	0
1	16.15	16.10	15.57	15.65
2	26.75	25.37	25.12	24.92
3	37.80	36.66	36.70	36.48
4	49.12	48.48	46.54	43.82
5	56.15	54.76	52.62	51.55
6	62.65	62.32	60.85	60.12
7	75.16	74.35	73.45	72.58
8	83.60	82.76	82.32	82.02
10	91.15	91.72	91.32	91.54
12	99.75	99.60	99.44	99.34

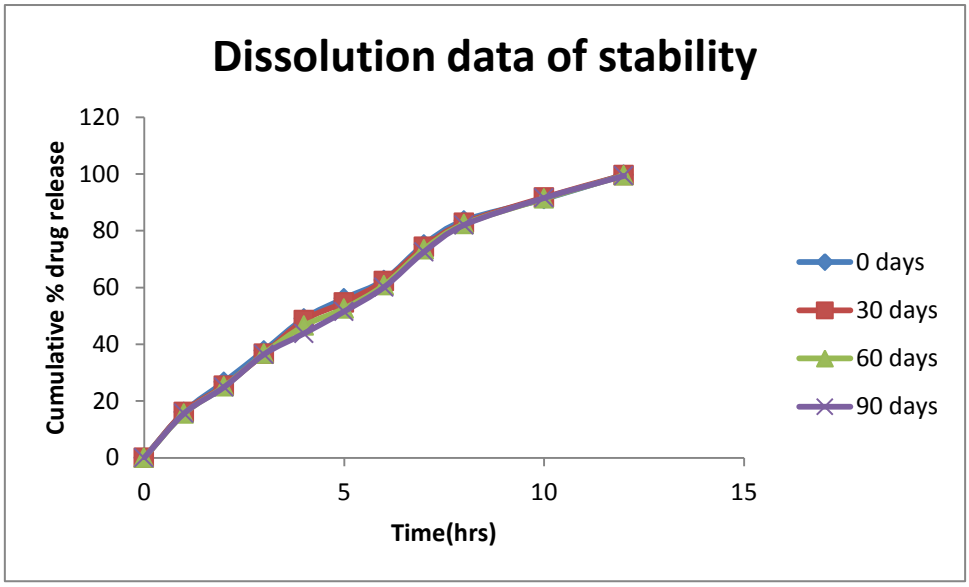


Fig. No. 18: Dissolution data of stability for formulation F4

The stability studies for optimized formulation F4 was carried out based accelerated stability conditions & study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that reveals that the optimized formulation was stable under accelerated condition.

8. SUMMARY AND CONCLUSION

The main objective of the present study was to develop floating formulation containing 250 mg of ciprofloxacin hydrochloride for twice therapy using natural polymers like xanthan gum and guar gum. GRDDS improved the bioavailability and therapeutic efficiency of drug.

In the preformulation, FTIR study was carried out for pure drug (ciprofloxacin hydrochloride), ciprofloxacin hydrochloride and excipients. It has not shown any interaction. Hence drugs were found to be compatible with excipients.

The formulations were prepared by direct compression method. The angle of repose values for formulations range from 25.04±0.02 to27.10 ±0.06. Bulk and tapped densities were used for the measurement of compressibility index. The bulk and tapped values for formulations range from 0.25±0.05 to 0.33±0.04 and 0.32±0.04 to 0.38±0.02 respectively the car's index and harusner's ratio values for formulations range from 1.05±0.03 to 1.37±0.05 respectively. Thus all formulations exhibited good flow characteristics.

The prepared floating tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. The thickness of tablets in all formulations were ranged from 3.2±0.16 to 3.3±0.14. The weight variation of tablets in all formulations were ranged from 318±1.6 to 320±6.1. The hardness and friability of all the formulations F1-F9 was found to be 4.0±0.6 to 4.1±0.4 and 0.11 to 0.26 respectively. Drug content of all the formulations were ranging from 95.14±0.23 to 97.23±0.22. The buoyancy lag time of all the formulations were ranging from 45sec to 90sec.

Compared to all formulations F4 showed the best buoyancy lag time, the buoyancy lag time for F4 was found to be 45sec. Total floating time of all formulations was found to be >8 hrs. The formulation containing xanthan gum shows the higher swelling compared to that of the formulations containing both xanthan and guar gum alone.

The prepared tablets were then subjected to dissolution test for evaluating the *invitro* drug release. The dissolution studies were carried out in 0.1N hydrochloric acid in USP-32 appatarus at 37±0.5°C. The results of the dissolution studies indicated that the polymer concentration was having a substantial effect on the drug release from the tablets. Formulation F4 gave better controlled drug release and floating properties in comparision to the other formulations. This formulation took 45sec to become buoyant.

The kinetic study was carried out for F4 formulation which showed that the drug release followed zero order kinetics followed by non-fickian diffusion.

The stability studies were carried out for F4 formulation at 45°C 175% RH for 3months. Data revelead that there was no considerable difference.

From the above study, concluded that F4 was the optimized formulation which has shown better buoyancy time 45sec and drug release 99.80% in 8hrs. However, further *invivo* studies can be carried out to support the results.

The overall results explained that the tablets prepared by combination of xanthan gum and guar gum could be more effective on floating tablets and has shown more sustained effect than floating tablets containing natural polymer alone.

BIBLIOGRAPHY

1. Leon Lachman, Herbert A. Liberman, the Theory and Practice of Industrial Pharmacy: P.293-302.
2. Robinson Jr, Lee V.H.L, Controlled drug delivery: Fundamentals and Applications, 2nd edn. Marcel Dekker, New york: 1978; P.24-36.
3. Brahmankar D.M, Jaiswal S.B, Biopharmaceutics and Pharmacokinetics a treatise, 1st ed. Vallabh prakashan; New Delhi: 1995; P.64-70.
4. Chein Y.W, Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York: 1992; P.4-56.
5. Ansel, Pharmaceutical Dosage form and Drug Delivery System, Lipincott, 7th edition: P. 553.
6. Gennaro R.A. Remington,The Science and Practice of Pharmacy., 20th ed. New york : Lippincott Williams: 2000; P.1045.
7. Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York: 1996; P.678-721.
8. Vyas S.P, Khar R.K, Controlled Drug Delivery: Concepts and Advances, 1st ed. Vallabh prakashan, New Delhi: 2002; P.345-376.
9. Friend DR. Oral delivery: A New approach to dosage forms. Pharmaceutical News 2002; 9: 375-80.
10. Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. The Eastern Pharmacist 1991; 45:25-28.
11. Hoffmann A.Pharmacodynamic aspects of sustained release preparations. Adv.Drug.Deliv.Rev 1998; 33:185-99.
12. Stanley SD, Lisbeth I.Drug delivery systems for challenging molecules.Int.j.Pharm.1998; 176:1-8.

13. P.G.Yeole, Floating Drug Delivery System: Need and Development, Ind. J. Pharm Sci., 2005; 67(3); 265-272.
14. Shweta Arora, Floating Drug Delivery: A Review, AAPS Pharmscitech., 2005; 47(11); P.268-272.
15. Patel VF, Patel NM. Intragastric floating drug delivery system of cefuroxime axetil: invitro evaluation. AAPS PharmSciTech. 2006; 7(1): Article 17.
16. M.P.Venkataraju, D.V.Gowda.Xanthan and locust bean gum matrix tablets for oral controlled delivery of proponolal chloride.Asian journal of pharmaceutical sciences. 2007; 2(6):239-24.
17. Parikh Bhavik Anjan kumar,Patel Ishvarc. Formulation and evaluation of floating tablet of atenolol:Funtionality of natural and synthetic polymer.*IJPI'S Journal of pharmaceutics and cosmetology*. 2011 voll:3:
18. Mahesh Chavanpatil, Paras Jam. Development of sustained release gastroretentive drug delivery systems for ofloxacin;Invitro and invivo evaluation. *Int J.Pharm* .304 2005; 178-184.
19. Manoj N. Gambhire, Kshitij W. Wmbade. development and invitro evaluation of an oral floating matrix tablets formulaton of Diltiazem hydrochloride. *AAPS. Pharm. Sci. tech.* 2007; 8(3) article 73: E1-E9.
20. Inez Jimenezmartinez, Tomas Quirino-Berreda. Sustained delivery of captopril from gloating matrix tablets. *Int.J.Pharm*. (2008); 362: 37-43.
21. Nur AO, Thang JS. Captopril Floating and/or bioadhesive Tablets: Design and Release kinetics. *Drug dev Ind Pharm* 2000; 26 (9): 965-9.
22. Chen GL, Hao WH. In Vitro performance of floating sustained-release capsule of Verapamil. D*rug Dev lnd Pharm* 1998; 24 (11): 1067-72.
23. Desai S, Bolton S. A floating controlled-release Drug Delivery system: In-vitro - in vivo Evaluation. *Pharma Res.*1993; 10:1321-5.
24. Hilton AK, Deasy PB. In vitro and In vivo evaluation of an oral sustained release floating dosage form of Amoxicillin trihydrate. *Int J Pharm* 1992; 86: 79-88.
25. Park HJ,Choi. preparation of alginate beads for floating drug delivery systems;effects of co2 gas forming agents.*Int.j.Pharm*. 2002;239:8 1-91.
26. en.wikipedia.org/wiki/Ciprofloxacin hydrochloride

27. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195:125-35.
28. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Dev Ind Pharm 1996; 22:631-9.
29. Wei Z, Yu Z, Bi D. Design and evaluation of a two-layer floating tablet for gastric retention using cisapride as a model drug. Drug Dev Ind Pharm 2001:27:469-74.
30. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm Res 1997; 14:815-9.
31. Mamajek RC, Moyer ES. Drug-dispensing device and method. Jun 1980. US patent 4,207,890.
32. Wong PS, Dong L–C, Edgren DE, Theeuwes F, Gardner PI, Jao F, *et al*. Prolonged release active agent dosage form adapted for gastric retention. Sept 2000. U S patent 6,120,803.
33. Conte U, Maggi L. Pharmaceutical tablet characterized by a showing high volume increase when coming into contact with biological fluids. Jul 1998. US patent 5,780,057.
34. Newton JM, O'Brien P. Slow release compositions. May 1995. US patent 5,415,878.
35. Lehr CM. Bioadhesion technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Crit Rev Ther Drug Carrier Syst 1994; 11:119-60.

36. Lehr CM, Bouwstra JA, Kok W, de Boer AG, Tukker JJ, Verhoef JC, Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin Prajapati, *et al*.: Polymers in floating drug delivery system Systematic Reviews in Pharmacy | January-June 2011 | Vol 2 | Issue 1 7 *et al*. Effect of the mucoadhesive polymer polycarbophil on the intestinal absorption of a peptide drug in the rat. J Pharm Pharmacol 1992; 44:402-6.
37. Lehr CM, Bouwstra JA, Tukker JJ, Junginger HE. Intestinal transit of bioadhesive microspheres in an *in situ* loop in the rat. (a comparative study with copolymers and blends based on polyacrylic acid). J Control Release 1990; 13;51-62.
38. Curatolo WJ, Lo J. Gastric retention system for controlled drug release. Mar 1991. US patent 5,002,772.
39. Curatolo WJ, Lo J. Gastric retention system for controlled drug release. Aug 1995. US patent 5,443,843.
40. Fix JA, Cargill R, Engle K. Controlled gastric emptying. III. Gastric residence time of a nondisintegrating geometric shape in human volunteers. Pharm Res 1993; 10:1087-9.
41. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gammascintigraphy. J Control Release 1999; 58:195-205.
42. Zatz JL, Woodford DW. Controlled release liquid pharmaceutical. Jan 1988. US patent 4,717,713.
43. Cremer K. Drug delivery: Gastro-remaining dosage forms. Pharm J 1997; 259:108.
44. Davis DW. Method of Swallowing a Pill, Dec 1968. US Patent No. 3,418,999.

45. Ichikawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage systems. I: Preparation and *in vitro* evaluation of floating and sustained-release characteristics. J Pharm Sci 1991; 80**:**1062-6.
46. Mitra SB. Sustained-Release Oral Medicinal Delivery Device. May 1984. US Patent No. 4,451,260.
47. Kawashima Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81:135-40.
48. Fell JT. Whitehead L. Collett JH. Prolonged Gastric Retention Using Floating Dosage Forms. Pharm Technol 2000; 24:82-90.
49. Iannuccelli V. Air compartment multiple-unit systems for prolonged gastric residence, Part I: Formulation study. Int J Pharm 1998; 174:47-54.
50. Sakr FM. A programmable drug delivery system for oral administration. Int J Pharm 1999; 184:131-9.
51. Michaels AS. Drug Delivery Device with Self-Actuated Mechanism for Retaining Device in Selected Area. Jan 1974.US Patent No. 3,786,813,
52. Michaels AS, Bashwa JD, Zaffaroni A. Integrated Device for Administering Beneficial Drug at Programmed Rate. Aug 1975. US Patent No. 3,901,232.
53. Hilton AK, Deasy PB. *In vitro* and *in vivo* Evaluation of an Oral Sustained-Release Floating Dosage Form of Amoxycillin Trihydrate. Int J Pharm 1992; 86:79-88.
54. Sheth PR, Tossounian JL. Novel Sustained- Release Tablet Formulations. May 1979.US Patent Nos. 4,167,558 and 4,140,755,
55. Sheth PR, Tossounian J. The Hydrodynamically Balanced System, A Novel Drug Delivery System for Oral Use. Drug Dev Ind Pharm 1984; 10:313-39.

56. Yang L, Esharghi J, Fassihi R. A new intra gastric delivery system for the treatment of *Helicobacter pylori* associated gastric ulcers, *in vitro* evaluation. J Control Release 1999; 57:215-22.
57. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: *In vitro* and *in vivo* evaluation of bilayer tablet formulation. Drug Dev Ind Pharm 2000; 26:857-66.
58. Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao 1997; 32:786-90.
59. Sheth PR, Tossounian J. Sustained release tablet formulations. Sept 1979. US Patent 4,167, 558,
60. Sheth PR, Tossounian, J. Sustained release tablet formulations. Feb 1979. US Patent 4,140, 755,
61. Penners G, Lustig K, Jorg PVG, inventors. Expandable pharmaceutical forms. Jul 1997. US patent 5 651 985.
62. Talwar N, Sen H, Staniforth JN, inventors. Orally administered controlled drug delivery system providing temporal and spatial control. Jul 2001. US patent 6261 601.
63. Foldager J, Toftkjor H, Kjornos K. Antacid composition. Nov 1991. US Patent 5, 068, 109.
64. Fabregas JL, Claramunt J, Cucala J, Pous R, Siles A. *In vitro* testing of an antiacid formulation with prolonged gastric residence time (Almagate Flot-Coat®). Drug Dev Ind Pharm .

65. Havelund T, Aalykke C, Rasmussen L. Efficacy of a pectin-based antireflux agent on acid reflux and recurrence of symptoms and oesophagitis in gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol 1997; 9:509-14.
66. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm .
67. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I: Preparation and *in vitro* evaluation of floating and sustained-release characteristics. J Pharm Sci.
68. Raymond C and Paul J Sheskey. "Handbook of Pharmaceutical Excipients". 6th edition. Pharmaceutical Press 2009;110-113, 298-300, 783-785, 317-322, 314-315, 118-121& 129-133.
69. Ernest W. Flick. "Water-soluble Resins: An Industrial Guide". Edition 2, William Andrew, 1991; 382.
70. Sheth PR, Tossounian JL. Sustained release tablet formulations. Feb 1979. US patent 4,140,755.
71. Dennis A, Timminis P, Lel K, inventors. Buoyant controlled release powder formulation. Dec 1992. US patent 5 169 638.
72. Gerogiannis VS, Rekkas DM, Dallas PP, Choulis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev Ind Pharm 1993; 19:1061-81.
73. Stockwell AF, Davis SS, Walker SE. Invitro evaluation of alginate gel systems as sustained release drug delivery systems. J Control Release 1986; 3:167-75.

74. Ishak RA, Awad GA, Mortada ND, Nour SA. Preparation, *in vitro* and *in vivo* evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. J Control Release 2007; 119:207-14.
75. Yotsuyanagi T, Ohkub T, Ohhashi T, Ikeda K. Calcium induced gelation of alginic acid and pH-sensitive reswelling of dried gels. Chem Pharm Bull 1987; 35:1555-63.
76. Hwang SJ, Shree GJ, Lee KM, Oh KH, Kim CK. Rlease characteristic of ibuprofen from excipients –loaded alginate gel beads. Int J Pharm 1995; 116:125-8.
77. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein gelatin beads floating properties. Int J Pharm 2000; 198:157-65.
78. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm 2001; 220:13-21.

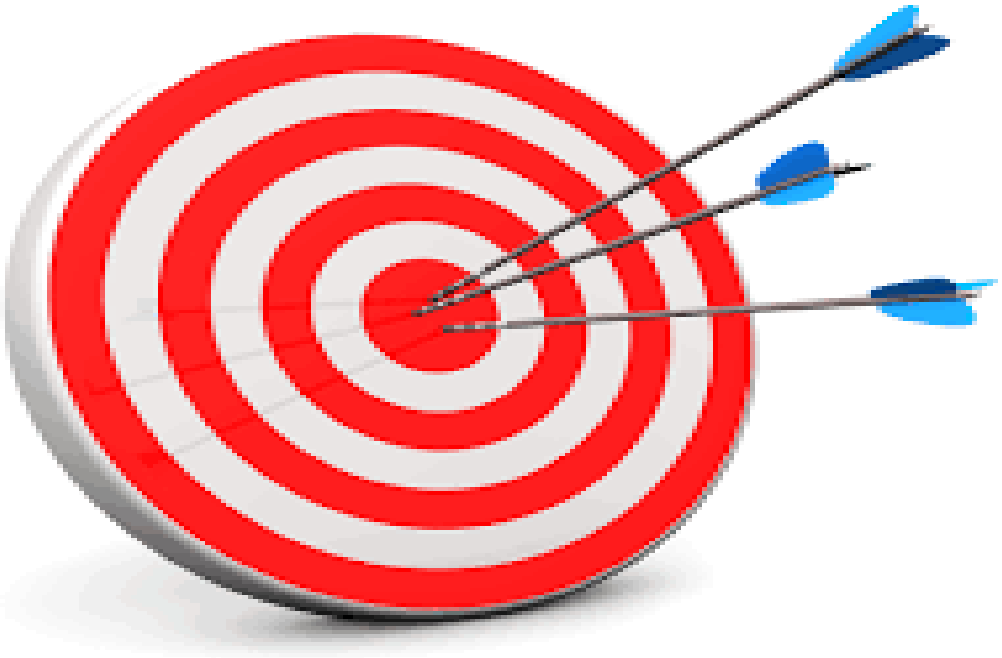
DECLARATION

LIST OF TABLE

INTRODUCTION

LITERATURE REVIEW

THEORITICAL BACKGROUND PROFILE



AIM AND OBJECTIVE

MATERIALS AND METHODS

RESULT AND DISCUSSION

SUMMARY AND CONCLUSION

BIBLIOGRAPHY

PLAN OF WORK