FORMULATION AND OPTIMIZATION OF FLOATING DRUG DELIVERY SYSTEM OFLEVOFLOXACIN HEMIHYDRATE

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

R.KOWSALYA

(REG. NO. 261511451)

Under the guidance of

Dr.D. KUMARASAMYRAJA,M.Pharm.,Ph.D.

Associate Professor, Department of Pharmaceutics

PGP COLLEGE OF PHARMACEUTICAL SCIENCE AND RESEARCH INSTITUTE

NH-7, Karur Main Road, Namakkal-637207

OCTOBER– 2017

CERTIFICATE OF APPROVAL

The foregoing thesis entitled **"FORMULATION AND OPTIMIZATION OF FLOATING DRUG DELIVERY SYSTEM OF LEVOFLOXACIN HEMIHYDRATE"** is hereby approved as creditable study of research topic and has been presented in satisfactory manner to warrant its acceptance as prerequisite to the degree for which it has been submitted.

(INTERNAL EXAMINER) **(EXTERNAL EXAMINAR)**

Prof.Dr. G. ARUNACHALAM. M. Pharm., Ph.D. FIC.,
Principal
PGP College of Pharmaceutical Science and Research Institute,
Namakkal-637207.

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND OPTIMIZATION OF FLOATING DRUG DELIVERY SYSTEM OF LEVOFLOXACIN HEMIHYDRATE "**was carried out by **KOWSALYA.R. (REG. NO: 261511451),** under the guidance of **Dr. D. KUMARASAMYRAJA,M.Pharm., Ph.D.**Associate Professorin the Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637 207, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

Prof.Dr. G. ARUNACHALAM

Place: Namakkal

Date:

Dr. D.KUMARASAMYRAJA,M.Pharm., Ph.D**,**

Associate Professor

Department of Pharmaceutics

PGP College of Pharmaceutical Science andResearch Institute,

Namakkal-637207.

CERTIFICATE

This is to certify that the dissertation entitled**"FORMULATION AND OPTIMIZATION OF FLOATING DRUG DELIVERY SYSTEM OF LEVOFLOXACIN HEMIHYDRATE"**was carried out by **KOWSALYA. R. (REG. NO: 261511451),** inthe**Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637207, Affiliated to The TamilnaduDr. M.G.R Medical University, Chennai - 32** under my direct supervision and guidance to my fullest satisfaction.

Dr. D.KUMARASAMYRAJA

Place: Namakkal

Date:

DECLARATION

We hereby declare that the matter embodied in the dissertation entitled **"FORMULATION AND OPTIMIZATION OF FLOATING DRUG DELIVERY SYSTEM OF LEVOFLOXACIN HEMIHYDRATE"**is a bonafide and genuine research work carried by us under the guidance of **Dr. D.KUMARASAMYRAJA,**M.Pharm.,Ph.D**.,** Assistant Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science & Research Institute, NH-7, Karur Main Road, Namakkal-637207.

KOWSALYA.R (REG. NO: 261511451)……

Place: Namakkal

Date:

ACKNOWLEDGEMENT

Gratitude is one of the least articulate of emotions especially when it is deep. Words are not enough to express my gratitude towards the people who stood behind me during my project work.

The highest appreciation is not to utter words but to live by them. Wewill be indebted throughout our life to our guide, **Dr. D.KUMARASAMYRAJA,** M.Pharm., Ph.D., Associate Professor, Department of Pharmaceutics, PGP College Pharmaceutical of Science and Research Institute, Namakkal-637 207 whose guidance, invaluable encouragement, innovative ideas and quest of knowledge beyond present frontiers, enabled me to accomplish this thesis with zest and zeal. We are extremely grateful for his infallible determination, untiring patience and emotional strength that he instilled in us.

We are highly grateful to **Prof. Dr. G. ARUNACHALAM**, M.Pharm., Ph.D.,FIC., Principal, PGP College of Pharmaceutical Science and Research Institute, Namakkal-637 207 for providing all the facilities for this project work and for his constant encouragement given throughout the work.

We express our sincere thanks to our honorable chairman **Dr.PALANIG. PERIASAMY,** M.A., M.A., Ph.D., (USA), Vice Chairman **Mrs.VISALAKSHI PERIASAMY.,** B.B.A.,and **Mr.M.GANAPATHI**, **IFS®** Correspondent, PGP Group of Educational Institutions, Namakkal–637 207 for providing the all necessary facilities.

We are highly obliged to our respected **Dr. M. ALAGARRAJA,**M.Pharm,Ph.D., Professor cum Vice Principal, Department of Pharmaceutical Analysis,**Dr**. **A.CHANDRAN**, M.Pharm, Ph.D., Department of Pharmaceutical Chemistry, **Dr. S.JAYARAMAN,** M.Pharm, Ph.D**.,** Department of Pharmacognosy, **Mr. G.RATHINAVEL,** M.Pharm**, (**Ph.D)., Department of Pharmaceutical Chemistry, **Mr. D.SAKTHIVEL,** M.Pharm., (Ph.D). Department of Pharmaceutics **Dr.M.K.SENTHIlKUMAR**, M.Pharm, Ph.D., Department of Pharmacognosy, **Dr. M. RANGAPRIYA,** M.Pharm., Ph.D., and **Mr. P. ODAYAKUMAR,** M.Pharm., Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207, who have a profound influence in shaping my orientation for research.

It is our privilege to express our sincere thanks to **Mr.R.BALAN, MA. MLIS**., Librarian PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207 for providing the library facilities and co-operation to complete this work. Also express our sincere thanks to Lab Assistants **Mr.J.RAMESH,MA.,B.Ed.,Mr. K.T. SHIVANESAN, M.Sc., B.Ed.,** and **Mr. S. MANIKANDAN M.Com.,** PGP College of Pharmaceutical Science and Research Institute, Namakkal–637 207 for their timely help.

We find ourselves lacking in words to express our deepest sense of gratitude towards our beloved parents for their unconditional support, encouragement and motivation. It's all because of their belief and the optimism that they instilled in us that we have been able to complete this work successfully.

By

KOWSALYA.R

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVATIONS

GIT	**Gatrointestinal tract**
Hr	**Hour**
GRT	**Gastric retention time**
HPMC	**Hydroxyl propyl methyl cellouse**
W/V	**Weight/Voulme**
Mg	**Milligram**
FLT	**Floating lag time**
TFT	**Total floating time**
FDDS	**Floating Drug Delivery System**
HBS	**Hydrodynamicaly Balanced System**

1. INTRODUCTION

The traditional use of excipients in drug formulations was to act as inert vehicles to provided necessary weight, consistency and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms they often full fill multi- functional rules such as modifying release, improvement of this ability and bioavailability of the active ingredient, enhancement of patient acceptability and ensure ease of manufacture. New and improved excipients continue to be developed to meet the needs of Advanced Drug Delivery Systems[1,2].

Polymers have been successfully investigated and employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of novel drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose[3]. Synthetic polymers are toxic, expensive, have environment related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers. However the use of natural polymers for pharmaceutical applications is fast increasing because they are economical, easily available, non toxic, capable of chemical modifications, biodegradable and biocompatible.

A large number of plant-based pharmaceutical excipients are available today. Many researchers have explored the use fullness of plant-based materials as pharmaceutical Excipients. Due to their ability to produce a wide range of material based on their properties and molecular weight, natural polymers are used in majority of investigations in various drug delivery systems [4]. The natural gums can also be modified based on their chemical structure to produce newer excipients that can meet the requirements of novel drug delivery systems which can competitive with synthetic excipients.

The plant based polymers have been studied for their application in different pharmaceutical dosage forms like matrix controlled systems, film coating agents, Nanoparticles, microspheres, buccal films, ophthalmic solutions, suspensions, implants and their applicability and efficiency has been proven[5-7]. They have also been utilized as stabilizers, viscosity enhancers, disintegrants, solubilizers, gelling agents, suspending agents in above mentioned dosage forms.[8]

Natural gums and mucilage are composed of many constituents. In several cases, the polysaccharides, resins or the tannins present in the gum are responsible for imparting release retard and properties to the dosage form. Gums are obtained from various parts of the plants. The source of the gums may be the epidermis, leaf, bark or roots or any other part of the plant.

Gastro retentive drug delivery systems significantly improve therapeutic efficacy of drugs that act locally in stomach, drugs that have narrow absorption window in stomach or drugs that are unstable in the intestinal or colonic environment. Hydration and swelling ability of polymers are the key performers in gastro retentive drug delivery system or which various synthetic, natural and semi synthetic polymers materials have been investigated.[9] many natural polymeric materials have been successfully used in formulation of gastro retentive drug delivery systems. These materials include: guar gum, is apghula husk, pectin, galactomannon from *Mimosascabrella*, *Gleditsiatri acanthus Linn*(honey locustgum),Sesbaniagum, mucilage from the pods of *Hibiscusesculenta*,Tamarindseed gum, Tara gum obtained from seed of *Caesal piniaspinosa*, okra gum obtained from pods *Abelmoschusescu lentus*, gum Karaya obtained from fruits of *Streculiaurens* etc.

1.1 Gastro Retentive Drug Delivery System

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastro retentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach. Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size.

1.2 Gastrointestinal Tract

1.2.1 Anatomy of the gastrointestinal tract:

The gastrointestinal tract is divided into three main regions namely[9]: Stomach, Small intestine (Duodenum, Jejunum and Ileum) and large intestine. The GIT is a muscular tube, from the mouth to the anus, which functions to take in nutrients and eliminate waste by secretion, motility, digestion, absorption and excretion, which are known as physiological processes. The stomach is a J-shaped enlargement of the GIT which is divided into 4 anatomical regions: cardiac, fundus, body and antrum[10] (Fig.2.1). The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption. During empty state, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 liter when full. The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, intermuscular plane, longitudinal muscle, submucosa, circular

muscle, lamina propria, muscularis mucosae, and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit.

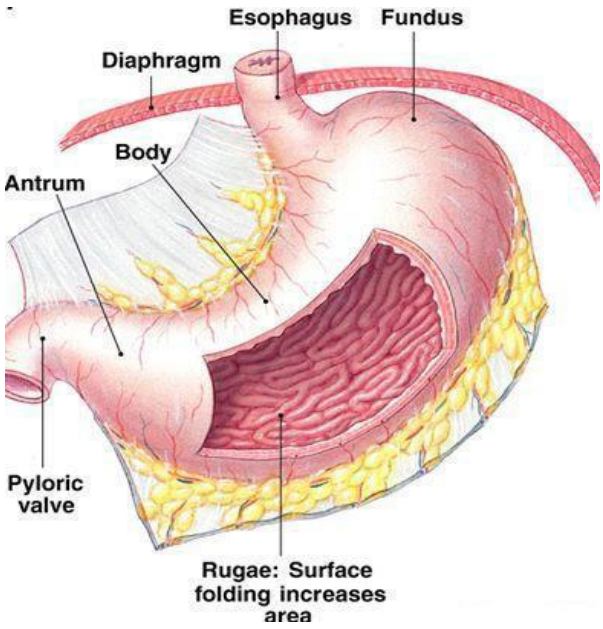


Figure 1.1: Anatomy of the gastrointestinal tract

1.2.2 Basic gastrointestinal tract physiology.

The stomach is divided into 3 regions anatomically:fundus, body, and antrum pylorus. The proximal partis the fundus and the body acts as a reservoir forundigested material, where as the antrum is the mainsite for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestivemyloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases[10] (fig.2.1).

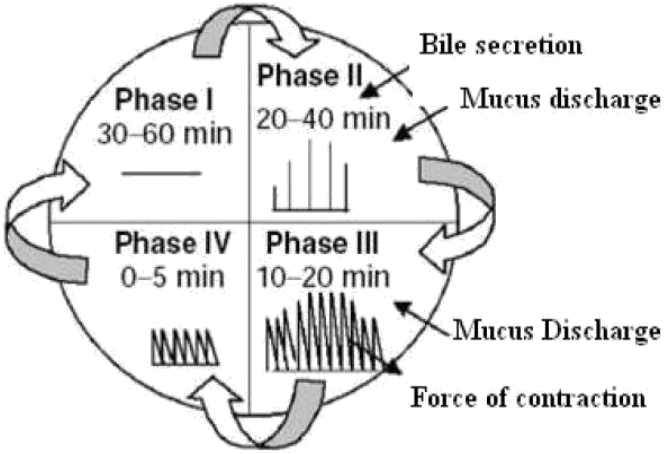


Figure 1.2: Schematic representation of interdigestive motility

- **Phase I:** This period lasts about 30 to 60 minutes with no contractions.
- **Phase II:** This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
- **Phase III:** This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20minutes these contractions, also known as „„house-keeper wave,"" sweep gastric contents down the small Intestine.
- **Phase IV:** This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

1.3 Need for gastroretention[10]

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline p^H.
- Drugs that are absorbed due to variable gastric emptying time.

- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of gastric ulcers caused by H.Pylori infections.

1.4 Formulation considerations for GRDDS[11]

- It must be effective for retention in the stomach to suit the clinical demand.
- It must be convenient for intake to facilitate patient compliance.
- It must have sufficient drug loading capacity and control drug release profile.
- It must have full degradation and evacuation of the system once the drug release is over.
- It should not have effect on gastric motility including emptying pattern.
- It should not have other local adverse effects.

1.5 Certain types of drugs can benefit from using gastroretentive devices[12]

- Drugs acting locally in the stomach.
- Drugs those are primarily absorbed in the stomach.
- Drugs those are poorly soluble at an alkaline P^H.
- Drugs with a narrow window of absorption.
- Drugs absorbed rapidly from the GI tract.
- Drugs those degrade in the colon.

1.6Drugs those are unsuitable for Gastro retentive drug delivery systems[13]

- Drugs that have very limited acid solubility e.g. Phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.

- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Drugs that are good candidates[14] for GRDDS and some gastro retentive products available in market, [12, 15] are listed in table 2.1 and table 2.2respectively.

Table 1.1: Good candidates for Gastro retentive Drug Delivery Systems

S.NO	Drug	Category	Half life	Peak time(hrs)	Bioavailability
1	Atenolol	Antihypertensive	4	3	40-50%
2	Clarithromycin	Antibiotic	3-4	2-2.5	50%
3	Diltiazem	Calcium channel blocker	3-4.5	50min	40%
4	Lidocaine	Local anaesthetic	1.5-2	4	35%
5	Nifedipine	Calcium channel blocker	2	0.5-0.2	45-65%
6	Omeprazole	Proton pump inhibitor	1-2	1	35-60%
7	Propranolol	Antihypertensive	4-5	4	26%
8	Ramipril	ACE inhibitor	2-4	3-5	28%
9	Verapamil	Calcium channel blocker	6	1-2	20-35%

Table 1.2: Marketed formulations available as GRDDS

S.NO:	Brand Name	Drug(dose)	Company, Country	Remarks
1	AlmagateFlot coat®	Al-Mg antacid	----------	Floating dosage form.
2	Cifran OD®	Ciprofloxacin (1gm)	Ranbaxy, India	Gas generating floating form.
3	Conviron®	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS.
4	Cytotech®	Misoprostol (100µg/200µg)	Pharmacia, USA	Bilayer floating capsule.
5	Liquid Gavison®	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithKline, India.	Effervescent floating liquid alginate preparations
6	Madopar®HBS (Propal® HBS)	Levodopa (100mg) and Benserazide (25mg)	Roche Products, USA	Floating CR capsules
7	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet.
8	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Effervescent floating liquid alginate preparation.
9	Valrelease®	Diazepam (15mg)	Hoffmann-LaRoche, USA	Floating Capsules

1.7 Various Factors affecting gastricretention[12]

Various factors that affect the bioavailability of dosage form and efficacy of the gastro retentive system are:

- **Density:** Gastric retention time (GRT) is a function of buoyancy of dosage form that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or Multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state:** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occur are every 1.5 to 2hrs. 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.
- **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.

- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface).
- **Age:** Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine, propantheline, opiates like codeine and prokinetic agents like Metoclopramide and Cisapride can affect floating time.
- **Biological factors:** Diabetes and Crohn‟s disease etc.

1.8 Approaches to Gastric retention

Various approaches for gastro retentive drug delivery systems are:

Floating drug delivery

Floating Drug Delivery Systems(FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach[12], (fig.2.3), for a prolonged period of time, without affecting the gastric emptying rate and the drug is released slowly at a desired rate from the system, results in an increase in the gastric residence time and a better control of fluctuations in the plasma drug concentrations and after complete release of the drug, the residual system is emptied from the stomach.

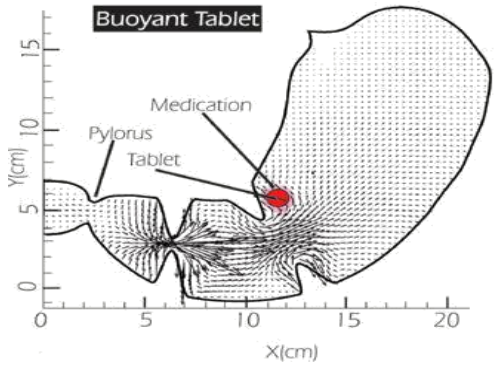


Figure 1.3: Graphic of the buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus.

Bio/Muco-adhesive systems

Bio/muco-adhesive systems, [12] bind to the gastric epithelial cell surface or mucin, which extends the GRT of drug delivery system in the stomach. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug delivery system to the gastrointestinal wall provides longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three categories:

1. Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

2. Bonding-mediated adhesion:

The adhesion of polymers to a mucus/epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the folds or crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as

hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

3. Receptor-mediated adhesion:

Certain polymers bind to specific receptor sites on the cell surfaces, thereby enhancing the gastric retention of dosage forms. Various investigators have proposed different mucin-polymer interactions, [11] such as:

- ✓ Wetting and swelling of the polymer to permit intimate contact with the biological tissue.
- ✓ Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.
- ✓ Formation of weak chemical bonds.
- ✓ Sufficient polymer mobility to allow spreading.
- ✓ Water transport followed by mucosal dehydration.

The bioadhesive coated system when comes in contact with the mucus layer, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occurs between the complimentary structures and these interactions last only until the turnover process of mucin and the drug delivery system should release its drug contents during this limited adhesion time, in order for a bioadhesive system to be successful.

Raft-forming systems:

These systems, [16] contain gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates), which on contact with the gastric contents, swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles, releases drug slowly in stomach by forming the raft layer on the top of gastric fluid (fig.2.4). These formulations contain antacids such as calcium carbonate or aluminum hydroxide to reduce gastric acidity.

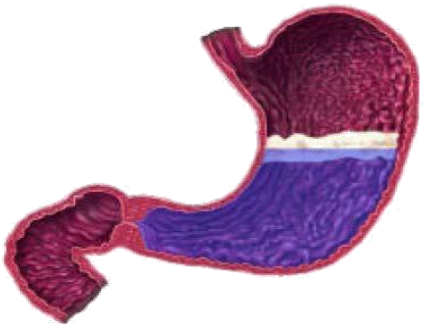


Figure 1.4: Barrier formed by a raft-forming system

Low density systems:

Low density systems, [11] (<1 g/cm3) which have immediate buoyancy have been developed because, the gas-generating systems have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. These are made of low density materials, entrapping air or oil. Most of the low density systems are multiple unit systems, also called as „„microballoons"" because of the low-density core (Sato and Kawashima, 2004). The preparation of these hollow microspheres (fig.2.5), involves simple solvent evaporation or solvent diffusion methods. Polycarbonate, cellulose acetate, Eudragit S, calcium alginate, low methoxylated pectin and agar are commonly used as polymers. Drug release and buoyancy are dependent on the plasticizer-polymer ratio, quantity of polymer, and the solvent used.

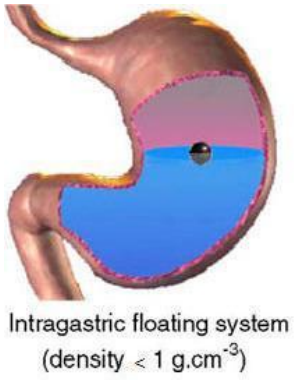


Figure 1.5: Foam-particles

Swelling/Expanding/Unfoldable systems:

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter, also the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system in order to prolong the gastric retention time (GRT) [16]:

1) A small configuration for oral intake.

2) An expanded gastroretentive form.

3) A final small form enabling evacuation following drug release from the device.

Thus, gastro retentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery.

- Unfoldable systems, [16] are made of biodegradable polymers. They are available in different geometric forms (fig.2.6), like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach.

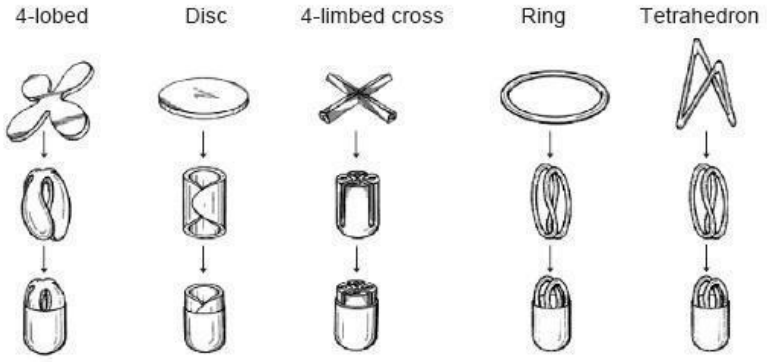


Figure 1.6: Different geometric forms of unfoldable systems.

- Swellable systems, [16](fig.2.7), are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid.
- Expandable systems, [16] have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

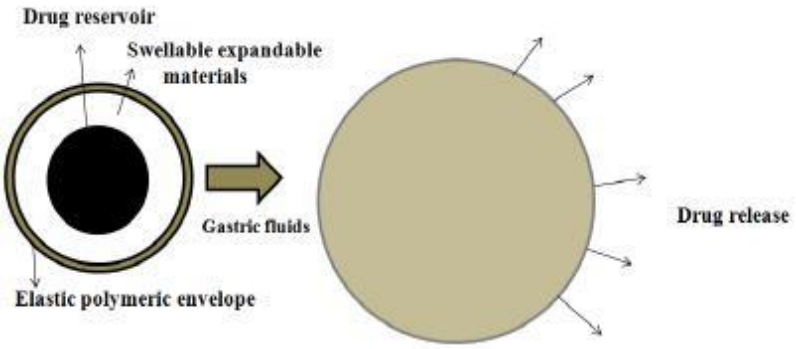


Figure 1.7: Drug release from swellable systems

Superporous Hydrogels:

Conventional hydrogels, with pore size ranging between 10 nm and 10 µm has very slow process of water absorption and require several hours to reach an equilibrium state during which premature evacuation of the dosage form may occur while the superporous hydrogel (fig.2.8), having average pore size (>100 µm), swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium) [11].

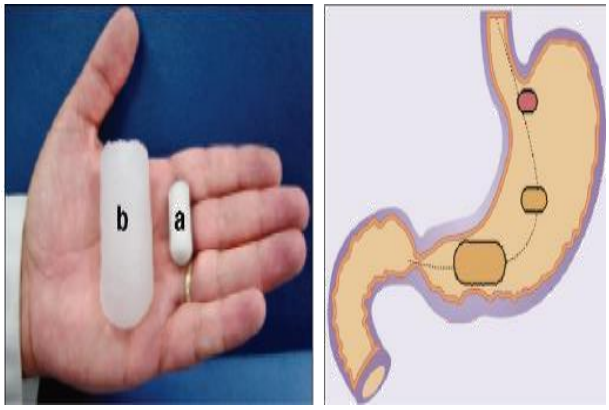


Figure 1.8: On the left, Superporous Hydrogels in its dry (a) and water-swollen (b) state. On the right, schematic illustration of the transit of Superporous Hydrogel.

Magnetic systems:

This approach is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach to enhance the gastric retention time (GRT) [11]. The external magnet must be positioned with a degree of high precision that might compromise patient compliance.

Self-unfolding systems:

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing through the pylorus and retains for a prolonged period of time in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods, [11] were suggested to provide for the self-unfolding effect:

1. The use of hydrogels swelling in contact with the gastric juice.
2. Osmotic systems, comprising an osmotic medium in a semi-permeable membrane.
3. Systems based on low-boiling liquids converting into a gas at the body temperature.

i.)High density systems:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach, [12] (fig.2.9).

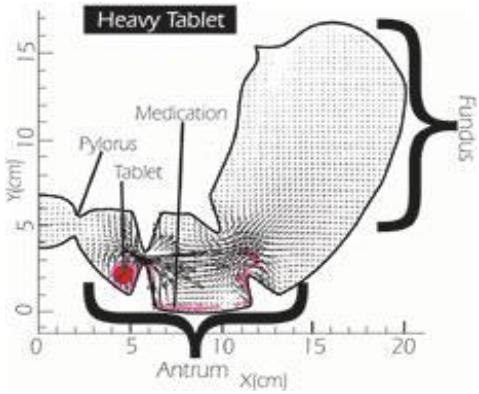


Figure 1.9: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum

1.9 Floating drug delivery systems:

A floating dosage form is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble (or) unstable in intestinal fluids. The floating properties of these systems help to retain in the stomach for a long time. Various attempts have been made to develop floating systems, which float on the gastric contents and release drug molecules for the desired time period. After the release of a drug, the remnants of the system are emptied from the stomach.

Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems. These include:

a) Effervescent system.

b) Non- Effervescent system.

a) Effervescent Systems

Effervescent systems,[12] include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types:

1) Gas generating systems.
2) Volatile liquid or vacuum containing systems.

1) Gas generating systems

a) Tablets:

i. Intragastric single layer floating tablets or Hydrodynamically Balanced System

These formulations have bulk density lower than gastric fluids and thus float in the stomach that increases the gastric emptying rate for a prolonged period,[12] (fig.2.10). These are formulated by intimately mixing the gas (CO_2) generating agents and the drug within the matrix tablet. The drug is released slowly at a desired rate from the floating system and the residual system is emptied from the stomach after the complete release of the drug. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration.

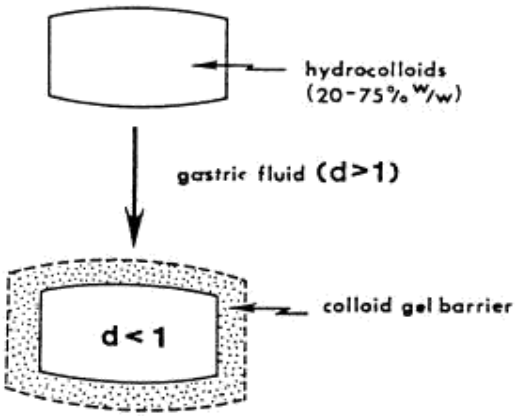


Figure 1.10: Intragastric single layer floating tablet

ii. Intragastric bilayer floating tablets

These are also compressed tablets, [12] containing two layers (fig.2.11):

- Immediate release layer and
- Sustained release layer.

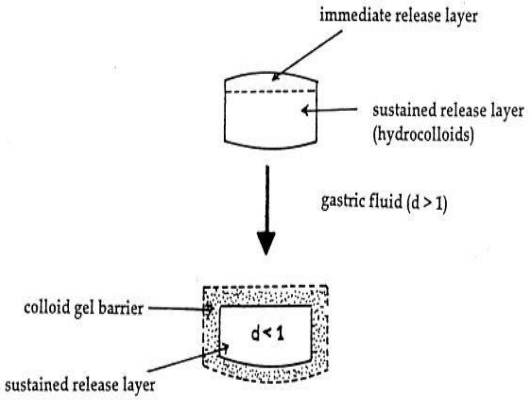


Figure 1.11: Intragastric bilayer floating tablet.

b) Floating capsules

These floating capsules, [11] are formulated by filling with a mixture of sodium alginate and sodium bicarbonate. The systems float as a result of the generation of CO_2 that was trapped in the hydrating gel network on exposure to an acidic environment.

c) Multiple unit type floating pills

These multiple unit type floating pills, [12] are sustained release pills, known as „seeds", which are surrounded by two layers (fig.2.12). The outer layer is of swellable

membrane layer while the inner layer consists of effervescent agents. This system sinks at once and then it forms swollen pills like balloons which float as they have lower density, when it is immersed in the dissolution medium at body temperature. The lower density is due to generation and entrapment of CO_2 within the system.

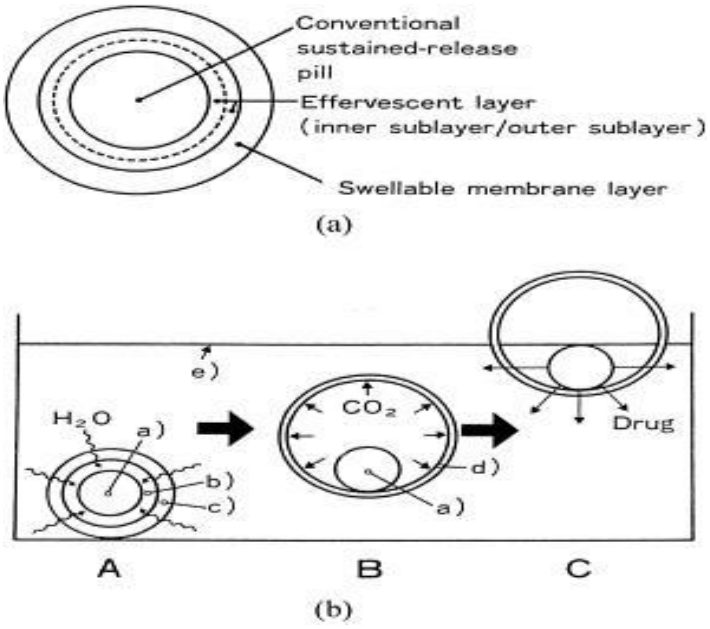


Figure 1.12: (a) A multiple-unit oral floating dosage system. (b) Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

d) Floating system with Ion-Exchange resins

Floating system using bicarbonate loaded ion exchange resin was made by mixing the beads with 1M sodium bicarbonate solution, and then the semi-permeable membrane is used to surround the loaded beads to avoid sudden loss of CO_2. On contact with gastric contents an exchange of bicarbonate and chloride ions takes place that results in generation of CO_2 that carries beads towards the top of gastric contents and producing a floating layer of resin beads[11].

2) **Volatile liquid or vacuum containing systems**

a) Intragastric floating gastrointestinal drug delivery system

This system floats in the stomach because of floatation chamber, which is vacuum or filled with a harmless gas or air, while the drug reservoir is encapsulated by a microporous compartment, [12] (fig.2.1).

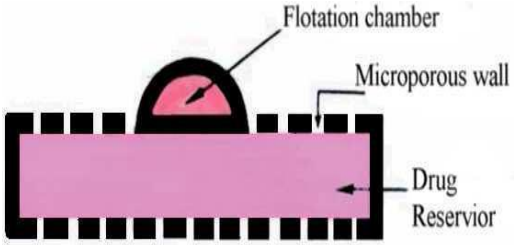


Figure 1.13: Intragastric floating gastrointestinal drug delivery device

b) Inflatable gastrointestinal delivery systems

These systems are incorporated with an inflatable chamber, which contains liquid ether that gasifies at body temperature to inflate the chamber in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule, [12] (fig.2.14). After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is released continuously from the reservoir into gastric fluid.

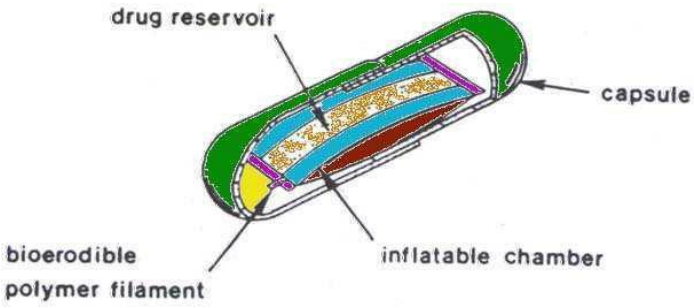


Figure 1.14: Inflatable gastrointestinal delivery system

c) Intragastricosmotically controlled drug delivery system

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule, [12] (fig.2.15). On contact with the gastric contents in the stomach, the capsule disintegrates quickly to release the intra gastric osmotically controlled drug delivery device. The inflatable support inside forms a hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag and it is deformable.

The osmotic pressure controlled drug delivery device consists of two components, osmotically active compartment and a drug reservoir compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to liquid and vapor and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing.

In the stomach, the osmotically active salt present in the osmotically active compartment is dissolved by absorbing the water continuously present in the GI fluid through the semi-permeable membrane. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

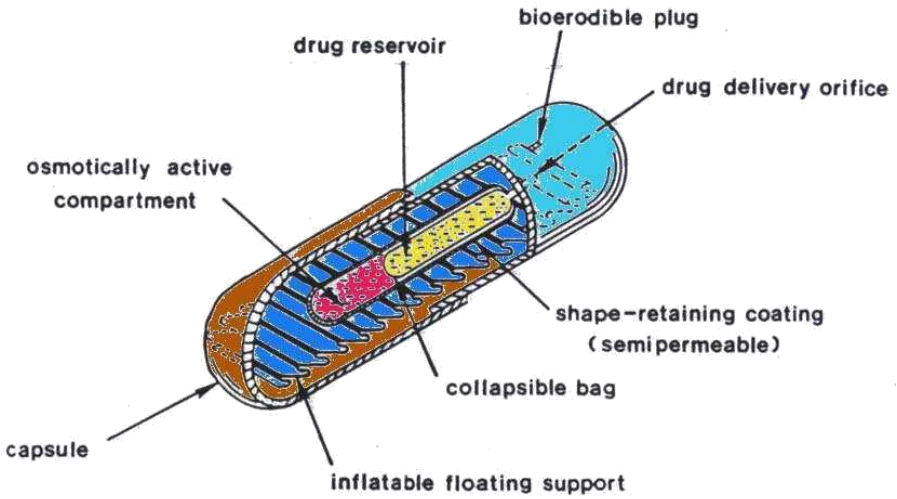


Figure 1.15: Intragastricosmotically controlled drug delivery system

b) Non-Effervescent systems

The Non-Effervescent floating drug delivery systems are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The various types of this system are:

1. Single layer floating tablets

These are formulated by intimate mixing of drug with a gel forming hydrocolloid, that swells on contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms[12].

2. Bilayer floating tablets

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach[12].

3. Alginate beads

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of $cacl_2$, causing

precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave ashort residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hours[12].

4. Hollow microspheres

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method (fig.2.16). The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*[12].

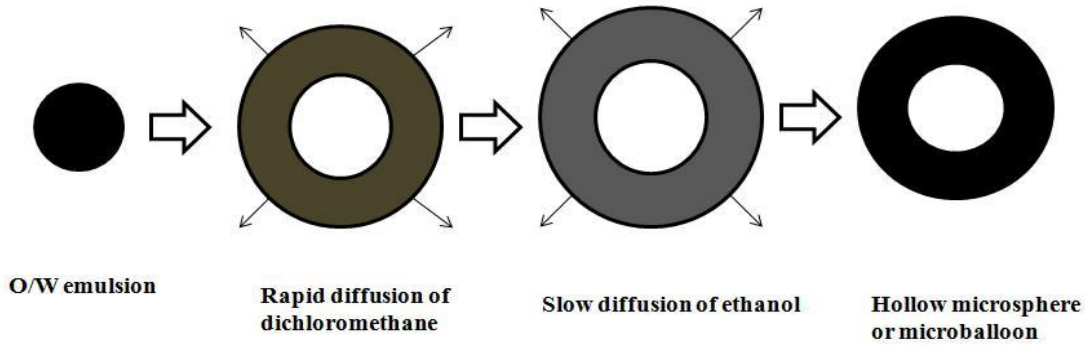


Figure 4.16: Formulation of floating hollow microsphere or microballoon.

1.10 Advantages of floating drug delivery system[12]

- The principle of Hydro dynamically Balanced System (HBS) can be used for any particular medicament or class of medicament. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine. E.g. Chlorpheniramine maleate.
- The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
- Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug is available for absorption in the small intestine, therefore it is expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline p^H of the intestine.
- Many drugs categorized as once-a-day delivery have been demonstrated tohave suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.
- When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption isexpected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

1.11 Limitations of floating drug delivery system[18]

- The floating system requires, sufficiently high level of fluid in the stomach for the system to float, this can be overcome by administering dosage form with a glass full of water (200-250 ml) or coating the dosage form with bioadhesive polymer which adhere to gastric mucosa.
- Aspirin and non steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Drugs, such as Isosorbidedinitrate, that are absorbed equally throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system.
- Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.
- Drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa are not suitable.
- Drugs that have multiple absorption sites or which undergo first pass metabolism were not desirable.
- The single unit floating dosage form is associated with “all or none concept”. This problem can be overcome by formulating multiple unit system like floating microballons or microspheres.

1.12Applications of floating drug delivery system[18]

1) Sustained drug delivery

Hydrodynamically Balanced System (HBS) type dosage forms which have bulk density less than one, relatively large in size and did not easily pass through pylorus, release the drug over a prolonged period of time by retaining in the stomach for several hours and by increasing the gastric residence time. MadoparHBS formulation has shown torelease levodopa for up to 8 hour in vitro, whereas the standard formulation released levodopa in less than 30 min.

2) Site specific drug delivery

Floating drug delivery systems are particularly useful for drugs having specific absorption from stomach or proximal part of the small intestine e.g. riboflavin, furosemide etc. The absorption of Captopril has been found to be site specific, stomach being the major site followed by duodenum. This property prompts the development of a monolithic floating dosage form of Captopril which prolongs the gastric residence time and thus increases the bioavailability, which has shown AUC, approximately 1.8 times than that of conventional tablets.

3) Absorption enhancement

Drugs that have poor bioavailability, because of their absorption is restricted to upper GIT are potential candidates to be formulated as floating drug delivery systems, thereby improving their absolute bioavailability.

4) **Minimized adverse activity at the colon**

Retention of the drug at the stomach (HBS system), minimizes the amount of drug that reaches the colon, that prevents the undesirable activities of the drug in colon. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small

intestine, and whose presence in the colon leads to the development of microorganism‟s resistance.

5) There are some cases in where the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsules. In such cases, the reduction in bioavailability is compensated by the advantages offered by FDDS e.g. patients with advanced Parkinson‟s disease, experienced pronounced fluctuations in symptoms while treatment with standard L-dopa. A HBS dosage form provided a better control of motor fluctuations although its bioavailability was reduced by 50-60% of the standard formulation.

6) Helicobacter Pylori, causative bacterium for peptic ulcers and chronic gastritis. Patients require high concentration of drug, to be maintained at the site of infection that is within the gastric mucosa. The floating dosage form due to its floating ability was retained in stomach and maintained high concentration of drug in the stomach. A sustained liquid preparation of Ampicillin, using sodium alginate was developed that spreads out and adheres to gastric mucosal surfaces and releases the drug continuously.

7) Floating drug delivery systems are particularly useful for drugs which are poorly soluble or unstable in intestinal fluids and acid stable drugs and for those which undergo abrupt changes in their pH-dependent solubility due to pathophysiological conditions of GIT, food and age, e.g. floating system for furosemide lead to potential treatment of Parkinson‟s disease. Approximate 30% drug was absorbed after oral administration.

1.13 Drug release Control and Mechanism in Swellable Matrix tablets.

1.13.1) Water penetration, swelling of matrix and gel layer formation Dynamics:

Swellable matrix tablets are activated by water and drug release mechanism depends on interaction between water, polymer and drug. The first step involved is water penetration in to matrix leading to polymer swelling and polymer and drug dissolution. In presence of water the glass rubber, transition temperature is decreased which results in formation of rubbery gel layer from glassy polymer. The polymer relaxation phenomenon determines the swelling or volume increased in the matrix tablet.

The thickness of gel layer formed depends on extent of water penetration, chain disentanglement and mass (polymer and drug) transfer in the water. Initially the water penetration is more rapid than chain disentanglement leading to quicker build up of gel layer, but later when water penetration is slow a little change in gel layer thickness is observed because water penetration and chain disentanglement rates are similar[19.] The gel layer thickness dynamics in swellable matrix tablets shows different three regions[20]:

a) Initially it increases when water penetration is fastest phenomenon.
b) Stays constant when rates of water penetration and chain disentanglement rates are similar.
c) Decreases when the entire polymer converts to rubbery phase.

The gel layer formed should prevent the matrix erosion and control additional water penetration. The factors influencing gel layer formation and drug release are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion.

1.13.2 Boundaries of gel layer and relevant fronts:

The boundaries of gel layer correspond to the fronts separating different matrix phases. The dynamics of gel layer formed is determined by the movements of different fronts. In swellable matrix tablets the following three fronts can be presented by same time:

a) The swelling front which is the boundary layer between glassy polymer and rubbery polymer.

b) The diffusion front which is the boundary between undissolved drug and dissolved drug in the gel layer.

c) The erosion front which is the boundary between matrix and dissolution medium.

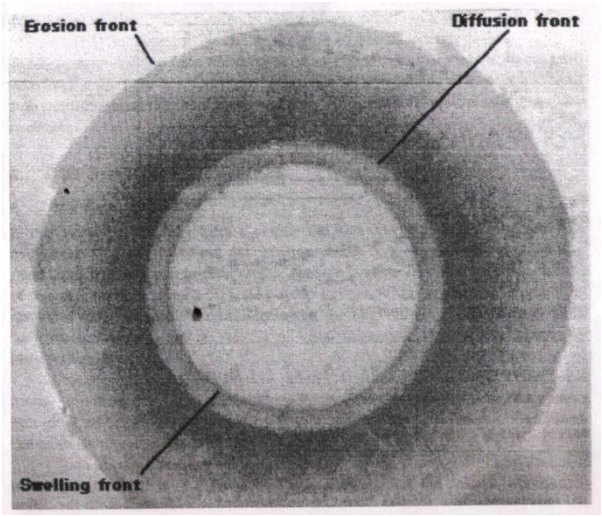


Fig 1.17 Relative fronts of Swellable matrix tablet during drug release

1.13.3 Swelling behavior front movements and drug release:

Due to dependence of gel layer thickness on the movement of swelling, diffusion and erosion fronts the analysis of front movement is use to interpret drug release in relation to swelling. The kinetics of drug release depends on the relative positions of erosion and swelling or diffusion forms. The rate of drug delivery is also dependent on the velocity of diffusion fronts. The drug release rate is inversely proportional to the dynamics of dissolved drug gel layer thickness. In swellable matrix tablets the erosion front movement determines the kinetics and diffusion front movement determines rate of drug release.Ritger and Peppas[21] proposed an equation to describe drug release kinetics from swelling controlled drug delivery system. The equation is as follows:

$$\frac{M_t}{M_\infty} = kt^n$$

Where M_t is drug released at time t,

M_∞ is amount of drug released at infinite time,

K is kinetic constant,

N is diffusion exponent.

Table: 1.3. Drug release mechanisms from swelling controlled systems based on sample Geometry.

'n' value (Diffusional exponent)			**Transport Mechanism**
Plane sheet	Cylinder	Sphere	
0.5	0.45	0.43	Fickian
>0.5	>0.45	>0.43	Anomalous
<1.0	<0.89	<0.85	Anomalous
1.0	0.89	0.85	Case II
>1.0	>0.89	>0.85	Super case II

REFERENCES

1. RaymondCR, (Ed.), Handbook of Pharmaceutical Excipients. 5th ed. London (UK): The Pharmaceutical Press; 2006.
2. PatelDM,. Seed mucilage from Ocimum americanumlinn. As disintegration tablets: Separation and evaluation. Indian JPharmSci 2007; 69:431-35.
3. VarshosazJ, TavakoliN, EramSA. Use of naturalgums and cellulose derivatives in production of sustained release dosage forms. Drug Deliv 2006; 13: 113-119.
4. Banker GS, Anderson NR. Tablets. In: LachmanL, Lieberman HA,KanigJL. (Ed.), the theory and practice of industrialpharmacy .3rd Ed., Mumbai: Varghese Publishinghouse; 1987.336.
5. PandeyR, Khuller GK. Polymer based drug delivery systems for *mycobacterial* infections.CurrDrugDeliv 2004; 1:195-201.
6. Chamarthy S.P.,Pinal R. Plasticizer concentration and the performance of a diffusion controlled polymeric drug delivery system. Colloids surf.A. Physio chem.Eng Asp 2008; 331: 25 -30
7. Alonso MJ. Glucomannan, A promising polysaccharide for Biopharmaceutical purposes.EurJ PharmBiopharm2009; 72(2): 453-62.
8. GuoJ, Skinner GW, Pharmaceutical applications of naturally occurring water-soluble polymers. Pharm S ci Technol Toda y1998; 1:254-61.
9. Morkhade DM, Fulzele SV, Satturwar PM, Joshi SB. Gum Copaland Gum Damar: Novel Matrix Forming Materials for Sustained Drug Delivery. IndianJPharm Sci 2006; 68(1):53-58.
10. S.U. Zate, P.I. Kothawade, "Gastroretentive Bioadhesive Drug Delivery System: A Review", International Journal of Pharm Tech Research Res, 2010, 2(2): 1227-1235.

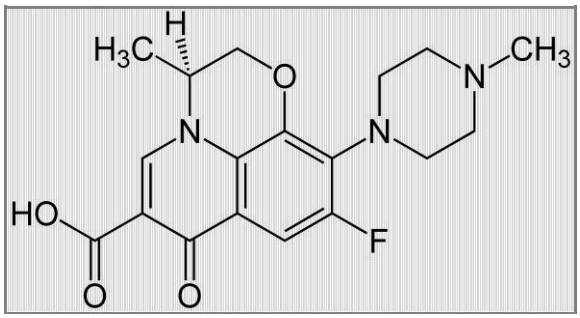
11. Vinod K.R., Santhosh Vasa, Anbuazaghan S, David Banji1, Padmasri A, Sandhya S,"Approaches for Gastroretentive Drug Delivery Systems", 2010;1(2): 589-601.
12. Debjit Bhowmik, Chiranjib. B. Jayakar, K.P.Sampath Kumar, "Floating Drug Delivery System: A Review", Der Pharmacia Lettre, 2009, 1(2), 199-218.
13. Amit KumarNayak, RumaMaji, Biswarup Das,"Gastroretentivedrug delivery systems: A review", 2010, 3(1), 2-10.
14. Praveen NASA, Sheefali Mahant, Deepika Sharma. Floating Systems, "A Novel Approach towards Gastroretentive Drug Delivery Systems", Int J Pharmacy and Pharm Sci, 2010,2(3), 2-7.
15. S. B. Gholap, S. K. Banarjee, R. M. Thorat,"Hollow Microsphere: A Review", 2010,1(1), 74-79.
16. Hetangi Rathod, Vishnu Patel, Moin Modasia, "Floating Drug Delivery System: Innovative Approach of Gastroretention", 2010, 4(3) 183-192.
17. ShwetaArora, Javed Ali, AlkaAhuja, Floating Drug Delivery Systems: A Review", AAPS PharmSciTech, 2005, 6 (3), 372-390.
18. Singh Sanjay, Joshi Vaibhav, and BarpetePravin Kumar,"Gastroretentive Drug Delivery System: Current Approaches", Journal of Pharmacy Research, 2009; vol 2(5): 881-886.
19. Lee, P.I. Controlled drug release from polymeric matrices involving moving boundaries, In: D.H. Levis (Ed), Controlled release of pesticides and pharmaceuticals 1981. Plenum publishing,NewYork. 39-48.
20. Harland R.S., Gazzaniga A, Peppas N.A. *etal.* Drug /Polymer matrix swelling and dissolution. Pharm res 1988; vol 5: 488-494.
21. Ritger P.L. ,Peppas. A simple equation for description of solute release. II .Fickian andanomalous release from swellable devices. JCR 1987; 5: 37-42

2. DRUG AND POLYMER PROFILE

2.1 LEVOFLOXACIN HEMIHYDRATE[1].

Molecular Formula: $C_{18}H_{20}FN_3O_4$

Chemical Structure:



(2S)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5(13),6,8,11-tetraene-11-carboxylic acid

Molecular Weight: 361.368

Drug Category:

- Anti-bacterial agent.
- Nucleic acid synthesis inhibitor.
- Anti infective agent.

Description: Stable, yellowish amorphous powder.

Solubility: Readily soluble in water (25mg/ml)

Melting Point: 163-164^{0}C.

Mechanism of Action:

Levofloxacin inhibits bacterial type II topoisomerases, topoisomerase IV and DNA gyrase. Levofloxacin, like other fluoroquinolones, inhibits the A subunits of DNA gyrase, two subunits encoded by the gyrA gene. This results in strand breakage on a bacterial chromosome, super coiling, and resealing, DNA replication and transcription is inhibited.

Pharmacokinetic profile of Levofloxacin

- **Absorption**: Levofloxacin is rapidly and, in essence, completely absorbed after oral administration. The amount of drug absorbed increases proportionately with the dose.
- **Peak plasmaconcentration**: Occurs 2 hours after oral administration.
- **Protein binding**: 24-38% (to plasma proteins).
- **Metabolism**: Mainly excreted as unchanged drug (87%); undergoes limited metabolism in humans. metabolism occurs by glucuronidation and hydroxylation.
- **Route of elimination**: Mainly excreted as unchanged drug in the urine.
- **Half life**: 6 hours.

Pharmacology

Levofloxacin is the L-isomer of the racemate ofloxacin, a quinolone antimicrobial agent. In chemical terms Levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance Ofloxacin.

Dose: Levofloxacin is used in doses of 250mg, 500mg and 750mg.

Therapeutic uses:

Levofloxacin is used in treatment of the following:

- Respiratory tract infections.
- Urinary tract infections.
- Anthrax
- Meningitis
- *Helicobacter pylori* infections.

Contraindications:

Levofloxacin hemihydrate is contraindicated in:

- Hepatic diseases.
- Pregnancy.
- Epilepsy.
- Arthritis, Arthralgia in case of children.

Drug Interactions:

- Caffeine: Metabolism affected by inhibiting cytochrome P-450.
- NSAID‟S: Severe CNS adverse reactions.
- Corticosteroids: Increased risk of Achilles tendon rupture.
- Concomitant use with cardiac antidysrhythmics: Increased risk of torsades and R on T syndrome.
- Quinidine barbiturates: Increased risk of cardio toxicity and arrhythmias.
- Warfarin: Levofloxacin may increase the anticoagulant effect of warfarin.
- Iron: Levofloxacin forms insoluble complexes with iron.
- Levofloxacin on coadminstration with orange juice can reduce the plasma quinoline levels.

Adverse Effects:

- Hypersensitivity.
- Peripheral neuropathy.
- Acute pancreatitis.
- Auto immune hemolytic anemia.
- Corneal perforation.
- Stevens-Johnson s

2.2. HYDROXYL PROPYL METHYL CELLULOSE (HPMC) [2]

Synonym:

Hypromellose, Hydroxyl propyl methyl cellulose,Methocel, Methyl cellulose propylene glycol ether, Metolose, Tylopur.

Chemical name:

Cellulose hydroxyl propyl methyl ether

Description:

Metolose is a white to slightly off-white powder and practically odorless and tasteless.

Solubility:

It is soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol, but soluble in mixtures of ethanol and dichloromethane.

Functional Category

- Coating agent.
- Film-former.
- Rate-controlling polymer.
- Stabilizing agent.
- Suspending agent.
- Tablet binder.
- Viscosity increasing agent.

Applications

- Hypromellose is used in oral, ophthalmic and topical pharmaceutical formulations.

- In oral products hypromellose is used as a tablet binder, in film coating and as a matrix for use in extended release tablet formulations.
- Hypromellose is also used as a suspending and thickening agent in topical formulations.

2.3.GUM KARAYA [3,4]

Source:

Gum Karaya, sometimes known as Sterculia gum, is the dried exudation of the Sterculia Urens tree and other species of Sterculia and belong to Sterculiaceae family. The tree is native to India.

Description:

The highest grade sorts of Gum Karaya are white, translucent and almost free of bark. Powdered Gum Karaya is white to greyish white.

Solubility:

Powdered gum karaya swells in cold water to an extent that a 3% to 4% sol will produce a heavy gel of uniform smoothness and texture.

Chemical Constituents:

Gum Karaya is a complex polysaccharide of high molecular weight. A molecular weight as high as 9.500.000 has been reported. On hydrolysis it yields galactose, rhamnose and galacturonic acid. Gum Karaya occurs as a partially acetylated derivative. Gum Karaya contains 12% to 14% moisture and less than 1% acid insoluble ash.

pH:

The pH of a 1% Gum Karaya solution is 4.6. If small amounts of alkali are added to change the pH to 7 or 8, the gum tends to have a buffering action effect and will gradually reduce the pH again to the acid size.

Pharmaceutical Applications:

A large part of the Karaya is used in two products. In the first product, bulk laxative, Karaya is usually processed 8-30mesh in size. In absorbing water the coarse particles swell enormously, forming a discontinuous type of mucilage that is very effective as a laxative. The second important product is a denture adhesive in which the finely powdered gum is dusted on the dental plate and swells when it touches the moist surface of the gums. This gives a comfortable and tight fit of the plate.

2.4. GUM KONDAGOGU [5]

Source:

It is natural gum exudates, obtained from stems and branches of *"Cochlospermum gossypium"* and belongs to Bixaceae family. **Description:** It occurs as pale brown to brown in colour.

Solubility: It is swellable in water.

pH:

The pH of 1 %w/v gum solution ranged from 4.9 to 5.1.

Chemical Constituents:

It Consists of high molecular weight acetylated polysaccharides, which on hydrolysis yield galactose, rhamnose, and galacturonic acid, together with minor amounts of glucuronic acid.

Pharmaceutical Applications:

Gum is sweet, cooling and useful in diarrhoea, dysentery, cough, pharyngitis, and also used as a pharmaceutical aid. Gum kondagogu was used as a substitute for gum tragacanth. Gum kondagogu is used as a drug delivery biopolymer and nano-composite material for removal of toxic metals.

2.5. XANTHAN GUM[6]:

Source:

It is obtained by fermentation of glucose,sucrose or lactose by using *Xanthomonas campestris* bacterium.

Description:

Pale to off-white colored powder

Solubility:

Highly soluble in cold and hot water

Chemical composition:

Chemically, Xanthan gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches.

Applications in Pharmaceutical Formulation

It is used in controlled release and sustained release formulations as matrix former.

1. Used as a thickening agent and stabilizing agent in emulsions.
2. In cosmetics, it is used to prepare water gels, usually in conjunction with bentonite clays.

2.6. NEEM GUM[7]

Source:

Neem gum is the bark extract of the plant *Azadirachta indica*. It is purified by dissolving it in cold water followed by precipitation with ethanol. **Family**: Meliaceae

Description:

Neem gum is clear bright amber coloredmaterial which on extraction with ethanol gives white amorphous powder.

Solubility: Readily soluble in cold water.

Chemical composition:

Neem gum is composed of three bitter agents‟ nimbin, nimbinin and nimbidin. These are chemically triterpinoids.

Applications in Pharmaceutical Formulation

1. Binding agent in tablet formulations.
2. Used as stabilizing and thickening agent in jells.
3. Used in formulation of antiseptic creams.

REFERENCES

1. Tripathi K D. Anti hypertensive drugs.In, Tripathi K D(ed). Essentials of Pharmacology, 5th edition, New delhi, Jaypee Publication, 2003; 688-690.
2. Kabir MA, Reo JP.In, Ray C Rowe, Paul JSheskey, Paul J Weller(ed)., Hand Book of Pharmaceutical excipients, 6th edition, London, Pharmaceutical press, 2009;346-348.
3. Anupama Setia, S. Goyal , N. Goyal. Applications of Gum Karaya in Drug Delivery Systems: A Review on Recent Research. Der Pharmacia Lettre. 2010; 2(5): 39-48.
4. Munday DL, Cox PJ. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm . 2000; 203:179-192.
5. Janaki, B Physicochemical analysis of gum kondagogu (cochlospermum gossypium): A potential food additive. Food Chmistry, 1998:61:231-236.
6. HC Shah, KK Singh. In, Ray C Rowe, (ed). Hand Book of Pharmaceutical excipients, 6th edition, London, Pharmaceutical press, 2009; 782-785.
7. Gangurde A. B, Malode S , Bha mbar R. S. Preliminary Evaluation of Neem Gum as Tablet Binder.Indian J.Pharm. Educ. Res 2008; vol 42(4):344-47.

3. LITERATURE REVIEW

3.1. PAST STUDIES ON FLOATING DRUG DELIVERY SYSTEMS OF LEVOFLOXACIN HEMIHYDRATE.

- **Thakkar V.T *et al.*,2008** formulated and evaluated Levofloxacin hemihydrate floating tablets using Gelurice and Methocel HPMC K4M. As the concentration of HPMC was increased the floating lag time was found to decrease and as concentration of Gelurice was increased the drug release rate decreased. The release rate of Levofloxacin hemihydrates was mainly governed by the hydrophilic and the hydrophobic polymer ratio. Formulations containing 25% HPMC and 15% Gelurice showed controlled release and good floating behavior. Optimal batch was found by regression analysis which followed Higuchi kinetics.

- **Arunachalam. A*et al.*, 2010** formulated floating effervescent floating tablets of Levofloxacin hemihydrate employing melt granulation using bees wax, HPMC K4M and Ethyl cellulose. Sodium bicarbonate was used as gas generating agent. Bees wax is selected to provide hydrophobic melt able support to give sufficient integrity to tablets.Formulations containing higher amount of bees wax F_6-F_7 showed less than 80% of drug release in 12 hours. As the concentration of bees wax was increased the release of Levofloxacin was sustained.

- **Shreeraj H. Shah *et al.*,2010** formulated floating tablets of Levofloxacin hemihydrate for treating Helicobacter pylori infections using combinations of different viscosity grades of Hpmc and carbopol by wet granulation employing PVP-k30M as binder. The combination of polymers showed good swellabilityand HPMC K4M when used alone showed good floating lag time.

They compared the drug release profile of formulated product with marketed product and established that formulated product showed better controlled release rate.

- **Nagesh C *et al.*,2011**formulated floating microspheres of Levofloxacin hemihydrates employing emulsion solvent evaporation technique. The drug was encapsulated in HPMC and Eudragit S 100 in different polymer ratios i.e. 1:1, 1:2, 1:3. The % yield of microspheres was higher with HPMC than Eudragit S 100 and the particle size of microspheres increased with an increase in increase in polymer concentration. From the percentage buoyancy studies of microspheres it was found that the microspheres remain buoyant in buffer for more than 12 hours. Microspheresof Levofloxacin formulated with HPMC showed enhanced release rate when compared to microspheres with Eudragit S 100.

3.2 PAST STUDIES ON FLOATING DRUG DELIVERY SYSTEMS OF XANTHAN GUM.

- **Brijesh S. Dave *et al.*,2004** prepared and evaluated gastro retentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxyl propyl methylcellulose were evaluated for gel-forming properties. The times required for 50% (t50) and 80% drug dissolution (t80), and the similarity factor f2 were selected as dependent variables. The results of the full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation.

- **Viral F. Patel *et al.*,2007** studied influence of xanthan gum and guar gum blends on dipyridamole release from floating matrix tablets. The content of polymer blends ($X1$) and ratio of xanthan gum to guar gum ($X2$) were selected

as independent variables. The diffusion exponent (*n*), release rate constant (*k*), percentage drug release at 1 hr (Q1) and 6 hr (Q6) were selected as dependent variables. Tablets of all batches had desired buoyancy characteristics. Multiple regression analysis with two ways ANOVA revealed that both the factors had statistically significant influence on the response studied ($p < 0.05$). Results of Tukey testshowed the relative contribution of each level of different factors for the response studied. It was concluded that the ratio of xanthan to gaur gum had equal or dominant role as controlling factor on kinetics of drug release compared to content of polymer blends.

- **Rajeev das *et al.*, 2009** used Sylimarin as model drug to prepare gastro retentive floating tablets employing Xanthan gum. . In-vitro drug release studies were performed and drug release kinetics were evaluated by Linear regression method and the formulations followed both Peppas and Higuchi equations. The drug release mechanism was found to follow Fickian type in most of the formulations. The formulated floating tablets prolonged the drug release for 24 hours improving bioavailability and patient compliance.

- **S. Verma *et al.*,2011**prepared gastroretentive drug delivery system of Stavudine. Guar gum, xanthan gum, and hydroxypropyl methylcellulose were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. Tablets were prepared by the dry granulation (slugging). Tablets were evaluated for their physical characteristics, invitrobuoyancy & drug release studies using United State Pharmacopoeia (USP) 24 paddle type dissolution type apparatus using 0.1N HCl as a dissolution medium for 12 hours. The tablets exhibited controlled and prolonged drug release profiles while floating

over the dissolution medium. Non-Fickian diffusion was confirmed as the drug release mechanism from these tablets.

3.3. PAST STUDIES ON FLOATING DRUG DELIVERY SYSTEMS OF GUM KONDAGOGU

- **Lakshmi Narasaiah.V*et al.*,2010** developed an optimized gastric floating drug delivery system containing Metformin Hydrochloride using Gum Kondagogu and investigate the effect of formulation and processing parameters. The effervescent granules were prepared by wet granulation technique using Gum Kondagogu as a controlled release natural polymer. Tablets were characterized for physical properties, floating characteristics (floating lag-time, floating time), swelling index, wetting time, drug content and evaluated for in vitro release characteristics for 10 hrs. The similarity factor, t_{50} and t_{90} were used as parameters for selection of the best formulation compared with commercial product.The drug release from all the formulations followed zero order kinetics and Korsmeyer-Peppas mechanism.

- **Lakshmi AP *et al.*,2011** prepared gastro retentive tablets of verapamil HCl by using different polymers like HPMC K4M, HPMC K100M and Gum Kondagogu. Sodium bicarbonate is used as gas generating agent. The tablet exhibits controlled and prolonged drugrelease profile while floating over the dissolution medium. A combination of sodium bicarbonate (36mg) and citric acid (10mg) was found to achieve optimum in vitro buoyancy. Formulations of F1-F4 were prepared with HPMC K4M, and F5-F8 was prepared with HPMC K100M and F9-F11 was prepared with a combination of HPMC K4M and gum kondagogu.Out of the formulations F-1 to F-15, the best formulation (F9) was selected based on in vitro characterization. The drug release

mechanism from formulation F-9 confirmed to fallowed Non-Fickian diffusion .

- **Lakshmi P J *et al.*,2012** studied the influence of formulation variables on the release profile of diclofenac sodium from gum kondagogu matrix tablets.

  Matrix tablets were prepared by wet granulation method. Physical properties and drug release studies were carried out for the prepared tablets. The physical properties indicated good handling properties of the prepared matrixtablets. Polynomial equations and response surface plots were generated for all dependent variables. This study indicates that both the factors have a significant effect on drug release profile. The dissolution studies indicate the release behavior of all the formulations was super case II transport mechanism with zero order kinetics.

- **Ravi V*et al.*,2013** prepared floating tablets of diltiazem HCl using kondagogu gumas matrix forming carrier. The tablets were prepared by direct compression technique using PVP K-30 as a binder, hydroxypropyl methyl cellulose (HPMCK4M) was employed in the formulation as a gel forming polymer and sodiumbicarbonate for development of CO_2. The prepared matrix tablets were evaluated for properties such as hardness, thickness, friability, weight variation, floating lag time, compatibility using DSC and FTIR. In vitrodissolution was carried out for 12 hrs in 0.1N HCl buffer at 37±0.5 °C using USP basket type dissolutionapparatus. The drug release from prepared tablets was found to vary with varyingconcentration of the polymer, kondagogu gum.

3.4 PAST STUDIES ON FLOATING DRUG DELIVERY SYSTEMS OF GUM KARAYA.

- **Gangadharappa HV*et al.*,2010**developed a single unit gastric floating drug delivery system of verapamil hydrochloride using karaya gum and hydroxypropyl methylcellulose (HPMC) as polymers. The feasibility of karaya gum was used for the rate controlling of drug release in the development of floating drug delivery system, evaluating the prepared dosage forms for its sustained release, in vitro buoyancy, swelling index, drug content, and in vitro drug release. The floating matrix tablets were prepared by direct compression technique using a combination of hydroxyl propyl methyl cellulose (HPMC) and karaya gum as polymers and sodium bicarbonate as generating agent. The prepared floating tablets were evaluated for weight variation test, hardness, thickness, swelling index, in vitro floating capabilities, floating lag time, compatibility studies, and in vitro drug release. This swellable hydrophilic natural karaya gum was used to control the release of drug. The results showed that the optimized formulation F8 containing 23.3% of karaya gum (70 mg) and 13.3% of HPMC (40 mg) had good floating capability, shorter Floating lag time and sustained drug release for the period of 8 hrs

- **Sreenivasa Reddy N *et al.*,2010**developed Captoprilfloating matrix tablets by using Xanthan gum, Gum karaya, Gellan gum & Pullulan gum alongwith HPMC K4M, PVP K-30, and Sodium bicarbonate . Sodiumbicarbonate was added as a gas generating agent, produced carbon dioxide in the gastric acidicenvironment which helped in maintaining the buoyancy. The prepared tablets were evaluated forphysical properties, content uniformity, hardness, friability, floating lag time and in vitro drug release.Among the studied

formulations, F9 was found to be suitable for gastric retention based on evaluationparameters, which was considered desirable for the drugs with absorption window in upper GIT. Thelinear regression analysis and model fitting showed that all these formulations followed Higuchi model,which had a higher value of correlation coefficient (r). Stability studies of all formulations werecarried out at elevated temperature and humidity conditions of 40±2 o C/75±5% RH and a controlsample was placed at ambient conditions for 12 months. There was no significant change in buoyancyproperty and drug content, indicating that the formulations are stable

- **PK Lakshmi*et al.*,2013** prepared and evaluated the gastro retentive floating drug delivery system of Diltiazem hydrochloride by using natural polymers.

  Thirteen tablet formulations were prepared by wet granulation usingdifferent concentrations of xanthan gum, karaya gum, guar gum, carrageenan as release-retarding polymers and sodium bicarbonate as a gas former. Swelling ability, floating behavior and drug release studies were conducted in 0.1N HCL (pH 1.2) at 37±0.5°C.The tablets showed acceptable physicochemical properties. Gastro retentive floating drug delivery system of Diltiazem hydrochloride using karaya gum, xanthan gum with drug to polymer ratio 1:5 (F1) and 1: 3 (F3) respectively are final optimized formulations as these formulations produced better sustained drug release (99.96%, 99.27% release in 24 h) and having good floating properties. From the results of kinetic modeling of drug release, it can be concluded that the optimized formulations F1 follows zero order and F3 follows non-Fickian diffusion mechanism.

REFERENCES

1. V.T. Thakkar, P.A. Shah, T.G. Soni1 *et al*. Fabrication and Evaluation of Levofloxacin Hemi hydrate floating tablet. Research in Pharmaceutical Sciences 2008; 3(2): 1-8.
2. Arunachalam, Stephen Rathinaraj*et al.* Design and Evaluation of Levofloxacin Hemihydrate floating tablets. International journal of Applied Biology and Pharmaceutical Technology 2010; 1(2):260-268.
3. Shreeraj h Shah, Jayvadan k Patel *et al*. Formulation and Evaluation of Effervescent floating tablet of Levofloxacin against *H Pylori* Infection. Der Pharmacia Sinica 2010; 1(3):232-234.
4. Nagesh C, Venkatesh J S, Santosh M etal. Intragastric floating drug delivery system of Levofloxacin: Formulation and evaluation. Journal of pharmaceutical science and research 2011; 3 (6):1265-1268.
5. Brijesh S. Dave, Avani F. Amin, Madhabhai M. Patel. Gastroretentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. AAPS PharmSciTech 2004; 5 (2):1-6.
6. Viral F. Patel, Statistical evaluation of influence of xanthan gum and guar gum blends on dipyridamole release from floating matrix tablets. Drug Development and Industrial Pharmacy, 2007; 33:327–334.
7. Rajeev das and Gana syam gupta. Preparation and evaluation of gastro retentive floating tablets of Sylimarin. Chem.pharm.bull 2009; 57(6):545-549.
8. S. Verma, N. Narang, G. Upmanyu, J. Sharma.Preparation and In Vitro Evaluation of Gastro retentive Tablets of Anti Retroviral Drug Using Different Polymers. Current Parma Research, 2011; 1(3): 245-249.
9. Lakshmi Narasaiah.V, Kalyan Reddy.B,, Kiran Kumar.A,, Govinda Rao.Y, Ramu.Y.Formulation and In Vitro Evaluation of Metformin Hydrochloride

Floating Tablets by Using Natural Polymer.J. Chem. Pharm. Res., 2010, 2(4):333-342.

10. Abbaraju Prasanna Lakshmi, Giddam Ashwini Kumar, KarnaKer Reddy T, Anand Kumar M.Development and invitro evaluation of gastroretentive verapamil hcl floating tablets.Int J Pharm Pharm Sci,2011; 4(1): 360-363.
11. Lakshmi Prasanna J, Deepthi B, Rama Rao N.Influence of Diluents on Diclofenac Sodium Release from Gum Kondagogu Based Matrix Tablets.IJPRR 2012; 1(4):12-17
12. Ravi V, .Investigation of Kondagogu Gum as a Pharmaceutical Excipients: A Case Study in Developing Floating Matrix Tablet.Int.J.PharmTech Res.2013;5(1):70-78.
13. Gangadharappa HV, Rahamath-Ulla M, Pramod-Kumar TM, Shakeel F. Clinical Research and Regulatory Affairs. 2010; 2(1): 13–20.
14. Sreenivasa Reddy N, Mahendra Kumar C B, Rohith ,Chandrashekhar M S.Development of floating matrix tablets: an approach using natural gums.IJPWR .2010; 3(1):1-16.
15. Shailaja T, Ramachandra S , Kishore C, Sasi Bhushan Y , Lakshmi PK.Formulation and In Vitro Evaluation of Gastro Retentive Delivery of Diltiazem Hydrochloride Using Natural Polymers. International Journal of Pharma Sciences.2013; 3(1):129-135.

4. AIM AND OBJECTIVES

Levofloxacin is a synthetic flouroquinoline antibacterial agent that inhibits bacterial DNA replication. It is L-isomer of Ofloxacin. It has a half life of 6hrsand the absorption of Levofloxacin is dose dependant, which increases with increase in dose. It is used in treating various infections caused by microorganisms like bacillus anthracis, Chlamydia infection, cystitis, epidydimitys, gonorrhea etc. The dose ranges from 250mg to 750mg.It is first choice drug used for treatment of *Helicobacter pylori* infections. Floating drug delivery system of Levofloxacin hemihydrates can localize the drug action within the stomach to treat gastric ulcers caused by *Helicobacter pylori.*

In the present study, natural polymers such as gum kondagogu, gum karayaandxanthumgum are selected for the preparation of floating tablets of Levofloxacin hemihydrates. Sodium bicarbonate was used as gas generating agent. Tablets were prepared by wet granulation method using these polymers.

The main objectives of this investigation are as follows:

1. To isolate and extract natural polymers from their natural sources.
2. To study the effect of sodium bicarbonate concentration and to optimize the concentration of gas generating agent.
3. To conduct the compatibility studies of Levofloxacin hemihydrates with natural polymers by IR spectral studies.
4. To formulate and evaluate Levofloxacin hemihydrate extended release floating tablets by Wet granulation method.
5. To evaluate the formulated tablets according to the pharmacopeia standards.

6. To study the influence of natural polymers on release rate and to select the best release retarding polymer among them.
7. To conduct comparative release studies among the natural polymers.
8. To evaluate the mechanism and release kinetics of drug from the prepared tablets.

PLAN OF WORK

The plan of work of the present studies are follows:

To isolate and extract natural polymers from their natural sources.

To conduct the compatibility studies of Levofloxacin hemihydrates with natural polymers by IR spectral studies.

To formulate and evaluate Levofloxacin hemihydrate extended release floating tablets by Wet granulation method.

To evaluate the formulated tablets according to the pharmacopeia standards.

To study the influence of natural polymers on release rate and to select the best release retarding polymer among them.

To conduct comparative release studies among the natural polymers.

To evaluate the mechanism and release kinetics of drug from the prepared tablets.

5. EXPERIMENTAL INVESTIGATION

5.1 Materials

Table 5.1: Materials used in the present research work

S.no	Name of the product	Name of the supplier
1.	Gum karaya	Yarrow Chem. Products, Mumbai.
2.	Gum kondagogu	Yarrow Chem. Products, Mumbai.
3.	HPMC K100M	Hetero labs, Hyderabad
4.	Hydrochloric acid	Qualigens fine chemicals, Mumbai.
5.	Isopropyl alcohol	Qualigens fine chemicals, Mumbai.
6.	Levofloxacin hemihydrate	Hetero labs, Hyderabad.
7.	Magnesium stearate	SD fine chemicals, Mumbai.
8.	PVP K 30	Qualigens fine chemicals, Mumbai.
9.	Sodium bicarbonate	Qualigens fine chemicals, Mumbai.
10	Talc	SD fine chemicals, Mumbai.
11	Xanthum gum	Yucca enterprises, Mumbai.

5.2Instrumentation

Table 5.2: Instruments used in the present work

S. No.	Name of the Instrument	Model And Manufacturer/Supplier
1.	Centrifuge	Cooling centrifuge C-24. Remi motors, Hyderabad.
2.	Electronic balance	Shimadzu, A×200, Japan
3.	Glassware	Borosil
4.	Hot air oven	Thermolab, Mumbai.
5.	Rotary tablet compression machine	Cadmach, Ahemadabad.
6	Tablet dissolution test apparatus	Electrolab TDT 08L, dissolution tester, U.S.P.
7	Tapped density apparatus	Campbell electronics, Mumbai.
8	U.V/Visible spectrophotometer	ELICO SL 159, shimadzu UV spec 1700.
9	Viscometer	Brookfield viscomerter, DV III Ultra, Brookfield inc, Brookfield, U.S.A.

5.3 M ethods

5.3.1. Analytical methods of Levofloxacin hemihydrate.

The following analytical methods are reported for the estimation of Levofloxacin hemihydrate.

- UV Spectroscopy.
- Visible Spectroscopy.
- Gas Liquid Chromatography.
- High Pressure Liquid Chromatography.
- Thin Layer Chromatography.
- Paper Chromatography.
- Column Chromatography.
- Polarography.
- Titrimetry.

In this investigation, UV method is used for the estimation of Levofloxacin hemihydrate.

5.3.2 Construction of calibration curve for Levofloxacin hemihydrate.

The calibration curve was constructed with 0.1N HCl. Accurately weighed 100 mg of Levofloxacin hemihydrate was transferred into 100 ml volumetric flask and dissolved in 0.1N HCl. Then volume was made up to the mark with 0.1N HCl to give a stock solution1 mg/ml. Further dilutions were made with 0.1N HCl to obtain 2 to 10 µg/ml concentrations of Levofloxacin hemihydrate and the absorbance was measured at 293 nm.

5.4 Viscosities of 1%w/v dispersions ofkaraya, gum kondagogu, xanthan gumand HPMC K 100 M IN 0.1N HCL.

Viscosities of 1%w/v dispersion of gum karaya,gum kondagogu, xanthan gum and HPMC K 100 M in 0.1N HCl were measured by using Brookfield viscometer.

5.5Infra Red Spectral analysis

IR Spectral analysis was used to study the interactions between the drug, polymer and the excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe.

5.6 Process optimization

To study the influence of process variables such as concentration of sodium bicarbonateand drug release, floating tablets were prepared by employing effervescent technology. Different concentration of $NaHCO_3$ were used (15%, 20% and 25%) for process optimization.

5.7. Preparation of Levofloxacin hemihydrate floating tablets

Floating tablets of Levofloxacin hemihydrate were prepared by using different drug: polymer (Levofloxacin hemihydrates+HPMC K100M+Natural polymer) ratios. The tablets were formulated by employing wet granulation method using PVP K 30 as binder and isopropyl alcohol as granulating fluid. All the formulations contain250 mg of Levofloxacin hemihydrate, sodium bicarbonate as gas generating agent, magnesiumstearate as lubricant and talc added as glidant. The details of composition of each formulation are given in Tables 5.3-5.7.

5.3: Composition of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum karaya

Ingredients	**F_1(mg)**	**F_2(mg)**	**F_3(mg)**	**F_4(mg)**	**F_5(mg)**
Levofloxacin hemihydrate	250	250	250	250	250
HPMC K 100 M	120	90	60	30	0
Gum karaya	0	30	60	90	120
Sodium bicarbonate	100	100	100	100	100
PVP K 30	5	5	5	5	5
Magnesium stearate	12	12	12	12	12
Talc (2%)	13	13	13	13	13
Total weight	500	500	500	500	500

Table 5.4: Composition of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthan gum.

Ingredients	F_6 (mg)	F_7 (mg)	F_8(mg)	F_9 (mg)
Levofloxacin hemihydrates	250	250	250	250
HPMC K100M	90	60	30	0
Xanthan gum	30	60	90	120
Sodium bicarbonate	110	110	115	115
PVP K 30	5	5	5	5
Magnesium stearate	7.5	7.5	5	5
Talc	7.5	7.5	5	5
Total weight	500	500	500	500

Table 5.5: Composition of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu.

Ingredients	**F_{10} (mg)**	**F_{11} (mg)**	**F_{12} (mg)**	**F_{13} (mg)**
Levofloxacin hemihydrate	250	250	250	250
HPMC K 100 M	90	60	30	0
Gum Kondagogu	30	60	90	120
Sodium bicarbonate	100	110	110	110
PVP K 30	5	5	5	5
Magnesium stearate	12	7.5	7.5	7.5
Talc	13	7.5	7.5	7.5
Total	500	500	500	500

5.10 Evaluation Parameters

5.10.1 Flow properties of granules.[3]

a) **Bulk Density (D_b):** It is the ratio of total mass of granules to the bulk volume of granules. It was measured bypouring the granules (passed through standard sieve # 20) into a measuring cylinder and initial weight will be noted. This initial volume is called bulk volume. From this the bulkdensity was calculated according to the formula mentioned below. It is expressed in g/ml and isgiven by

Bulk Density (g/ml) = Mass of the powder/Bulk Volume

b) **Tapped Density (D_t):** It is the ratio of total mass of the granules to the tapped volume of the granules. Volume was measured by tapping the granules for 750 times and the tapped volume will be noted, if thedifference between these two volumes is less than 2%. If it is more than 2%, tapping wascontinued for 1250 times and tapped volume was noted. Tapping was continued until thedifference between successive volumes is less than 2 % (in a bulk density apparatus). It isexpressed in g/ml and is given by

Tapped density (g/ml) = Mass of the powder/Tapped volume

c) **Angle of Repose (ɵ):** The friction forces in greanules can be measured by the angle of repose (ɵ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was calculated by measuring the height and radius of the heap of granules formed.

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

Where, θ is the angle of repose.

h is the height in cms

r is the radius in cms

d) **Carr's index (or) % compressibility:** It indicates granule flow properties. It is expressed in percentage and is given by

Carr's Index (%) = [(Tapped density – Bulk Density) / Tapped Density] × 100

e) **Hausner ratio:** Hausner ratio is an indirect index of ease of granules flow. It is calculated by the followingformula.

Hausner's Ratio = Tapped density / Bulk Density

5.10.2 Evaluation of tablets

a) **Hardness[4]:** The hardness of the tablet was measured by 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 tuning a threaded bolt untilthe tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The hardness was measured in terms of kg/cm^2.

b) **Drug content[4]:**20 tablets were weighed and powderedthe powder weight equivalent to 100mg of Levofloxacin trihydrate was dissolved in 100ml of 0.1N HCl and filtered. 5ml of this was diluted to 50ml with water and drug content was estimated using UV-VISIBLE spectrophotometer at 293nm.

c) **Weight variation[4]:**Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\%\text{Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X 100$$

d) **Friability[4]:** The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X\ 100$$

e) **Swelling Index[5]:** Formulated tablets were weighed individually (W_0) and placed separately in Petri dish containing 50 ml of 0.1 N HCl. The Petri dishes were placed in an incubator maintained at 37±0.5^{o}C. The tablets were removed from thepetri dish, at predefined intervals of time and reweighed (Wt), and the % swelling index was calculated using the following formula:

$$\% W_U = (Wt\text{-}Wo/Wo) \times 100$$

Where:

W_U – Water uptake

Wt – Weight of tablet at time t

Wo – Weight of tablet before immersion

f) **In vitro buoyancy study[6]:** This test is characterized by floating lag time and total floating time. The test was performed using USP-Type II paddle apparatus using 900 ml of 0.1N HCl at paddle rotation of 100 rpm at 37 ± 0.5^{0} C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium was noted as floating lag time and total floating time.

g) **In vitro dissolution test[7]:**The release of Levofloxacin hemihydratefrom the tablet was studied using USP-Type II paddle apparatus. Drug release profile was carried out in 900 ml of 0.1N HCl maintained at 37 ± 0.5°C temperatures at 100 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples was replaced by its equivalent volume of dissolution medium and was filtered through 0.45 µm Whatman filter paper and analyzed at 293 nm by UV spectrophotometer.

References:

1. Gangurde A. B, Malode S , Bhambar R. S. Preliminary Evaluation of Neem Gum as Tablet Binder**.**Indian J.Pharm. Educ. Res 2008; 42(4):344-47.
2. Rishabha Malviya, Pranati Srivastava, Vipin Bansal, Pramod Kumar Sharma, Formulation, Evaluation and Comparison of Sustained Release Matrix Tablets of Diclofenac Sodium Using Natural Polymers as Release Modifier, International Journal of Pharma and Bio Sciences, 2010; 1(2): 01-08.
3. Shivanand Pandey, Viral Devmurari1. Development and *In Vitro* Evaluation of Propranolol Hydrochloride Based Gastro-Retentive Floating Tablet. Der Pharmacia Lettre 2010; 2 (1): 75-86.
4. Indian Pharmacopoeia 2010.Vol 2.Indian Pharmacopoeial Commission. Ghaziabad.
5. V.T. Thakkar, P.A. Shah, T.G. Soni1. Fabrication and Evaluation of Levofloxacin Hemihydrate floating tablet .Research in Pharmaceutical Sciences 2008; 3(2): 1-8.
6. Baumgartner, JulijanaKristl. Optimisation of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics 2000; 195: 125-35.
7. Shreeraj h Shah, Jayvadan K Patel. Formulation and Evaluation of Effervescent floating tablet of Levofloxacin against *H Pylori* Infection. Der Pharmacia Sinica 2010; 1(3):232-234.

6. EXPERIMENTAL RESULTS

6.1 Construction of calibration cure for Levofloxacin hemihydrate in 0.1N HCl

S.NO	Concentration (µg/ml)	Absorbance ($\overline{X}$ ± s d)
1.	0	0
2.	2	0.194±0.005
3.	4	0.385±0.008
4.	6	0.580±0.003
5.	8	0.762±0.002
6.	10	0.940±0.007

Fig 6.1: Standard Calibration Curve of Levofloxacin hemihydrate in 0.1 N HCl

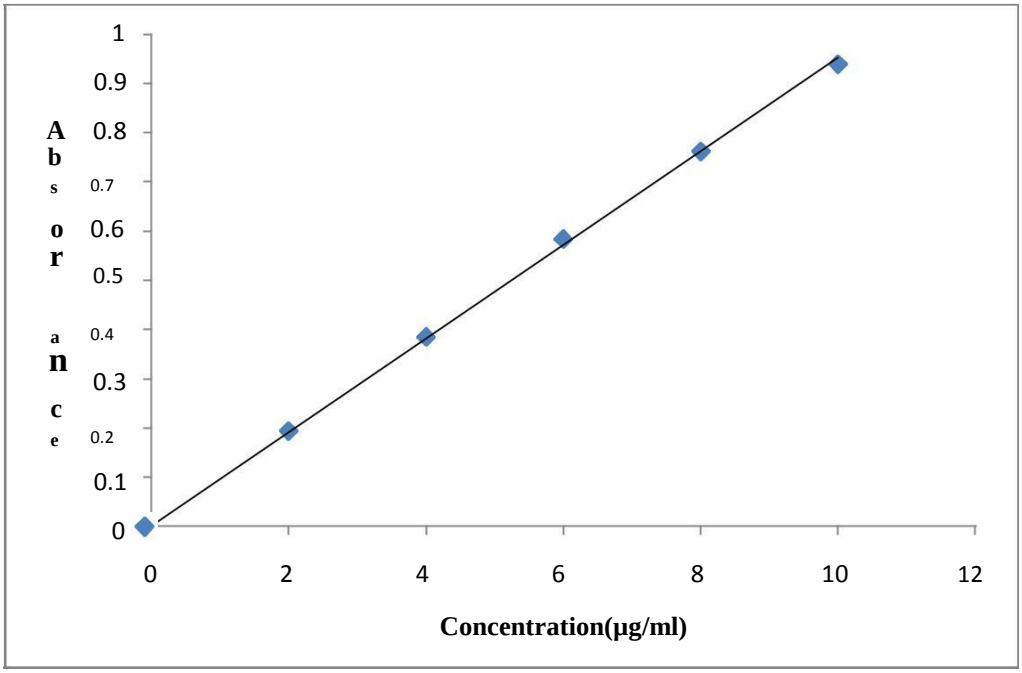


Table 6.2.Viscosities of 1%w/v dispersions ofXanthum gum, Gum kondagoguand Gum karaya.

S.NO	POLYMER	VISCOSITY(Cps)
1	Xanthum gum	2171.54
2	Gum kondagogu	450.54
3	Gum karaya	385.95

Table 6.3.Viscosities of 1%w/v dispersions of HPMC K 100 M .

S.NO	POLYMER	VISCOSITY(Cps)
1	HPMC K 100M	1205.74

Table 6.4: Micromeritic properties of Levofloxacin hemihydrate granules formulated with different concentrations of gum karaya

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Haussners ratio
F_1	26.94±0.021	0.276±0.014	0.314±0.013	12.10±0.024	1.137±0.012
F_2	25.6±0.031	0.350±0.012	0.408±0.011	14.21±0.022	1.161±0.014
F_3	25.42±0.052	0.320±0.020	0.370±0.009	11.89±0.009	1.134±0.017
F_4	26.85±0.024	0.319±0.005	0.362±0.021	11.87±0.017	1.130±0.024
F_5	27.01±0.035	0.351±0.009	0.393±0.019	10.68±0.014	1.119±0.014

Table 6.5: Physical properties of Levofloxacin hemihydrates floating tablets formulated with different concentrations of gum karaya.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_1	4.7±0.021	501.32±0.24	0.40±0.010	100.14±0.13	1.25 min	>14
F_2	4.5±0.025	500.65±0.28	0.34±0.018	99.78±0.15	2.12 min	>14
F_3	4.8±0.032	499.83±0.39	0.45±0.024	99.56±0.11	3.35 min	13
F_4	4.6±0.038	500.12±0.45	0.61±0.036	100.15±0.38	4.40 min	11
F_5	5.1±0.042	499.76±0.54	0.67±0.048	100.78±0.87	7.30 min	10

Table 6.6: *In vitro* release data of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum karaya

Time (hrs)	% Levofloxacin Released ($\bar{x}$ ± s.d.)				
	F_1	**F_2**	**F_3**	**F_4**	**F_5**
0	0.00	0.00	0.00	0.00	0.00
0.5	5.14±0.12	5.79±0.21	18.92±0.12	20.21±0.15	20.45±0.14
1	7.68±0.09	8.91±0.19	20.70±0.14	23.34±0.11	23.57±0.09
1.5	9.75±0.11	11.50±0.11	22.84±0.18	25.38±0.14	25.58±0.15
2	12.43±0.06	15.67±0.09	24.57±0.09	28.92±0.09	29.15±0.07
2.5	15.35±0.08	19.76±0.16	27.83±0.05	31.60±0.05	31.83±0.16
3	18.62±0.15	22.88±0.11	31.35±0.13	33.76±0.07	33.99±0.14
3.5	21.66±0.17	25.95±0.14	35.75±0.17	36.19±0.16	36.43±0.17
4	23.42±0.15	28.88±0.13	38.24±0.11	44.48±0.09	46.78±0.07
4.5	26.00±0.06	30.98±0.18	45.36±0.18	47.78±0.12	50.09±0.09
5	29.27±0.03	34.55±0.14	50.56±0.14	49.94±0.08	52.65±0.14
5.5	34.39±0.07	38.25±0.16	54.27±0.21	55.56±0.14	57.90±0.13
6	35.57±0.12	39.37±0.06	56.09±0.15	60.82±0.19	63.17±0.11
6.5	39.00±0.15	50.27±0.05	61.74±0.17	68.78±0.16	71.14±0.09
7	48.34±0.19	55.89±0.19	65.50±0.13	71.06±0.09	73.43±0.05
7.5	52.03±0.09	59.24±0.15	71.20±0.18	76.02±0.07	78.41±0.10
8	56.13±0.06	64.14±0.18	77.68±0.16	82.91±0.16	85.31±0.07
8.5	58.72±0.18	67.15±0.14	80.39±0.18	85.64±0.14	88.44±0.16
9	62.09±0.14	70.18±0.12	82.72±0.14	87.62±0.16	91.20±0.17
9.5	65.47±0.26	73.99±0.11	85.45±0.16	89.23±0.06	93.59±0.06
10	67.35±0.18	76.67±0.08	87.04±05	91.60±0.09	--
10.5	70.37±0.20	78.99±0.06	89.03±0.19	93.99±0.14	--
11	73.03±0.11	81.69±0.20	90.63±0.15	95.63±0.09	--
11.5	75.71±0.09	85.17±0.18	92.63±0.14	--	--
12	78.78±0.13	87.15±0.14	94.26±0.18	--	--

Table 6.7: *In vitro*drug release kinetic data of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum karaya.

Formulation	Correlation CoefficieSnt Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9958	0.9620	0.9065	0.9907	16.5772	0.9411	7.5	13.6
F_2	0.9961	0.9531	0.9179	0.9939	18.8651	0.9202	6.6	11.9
F_3	0.9706	0.9611	0.9628	0.9674	22.2475	0.6221	5.6	10.1
F_4	0.9688	0.9452	0.9621	0.9653	24.3660	0.5957	5.1	9.2
F_5	0.9752	0.9339	0.9549	0.9584	26.4037	0.5921	4.7	8.5

Figure 6.2: Comparative *in vitro*drug release profile of Levofloxacin hemihydrate floating tablets formulatedwith different concentrations of gum karaya.

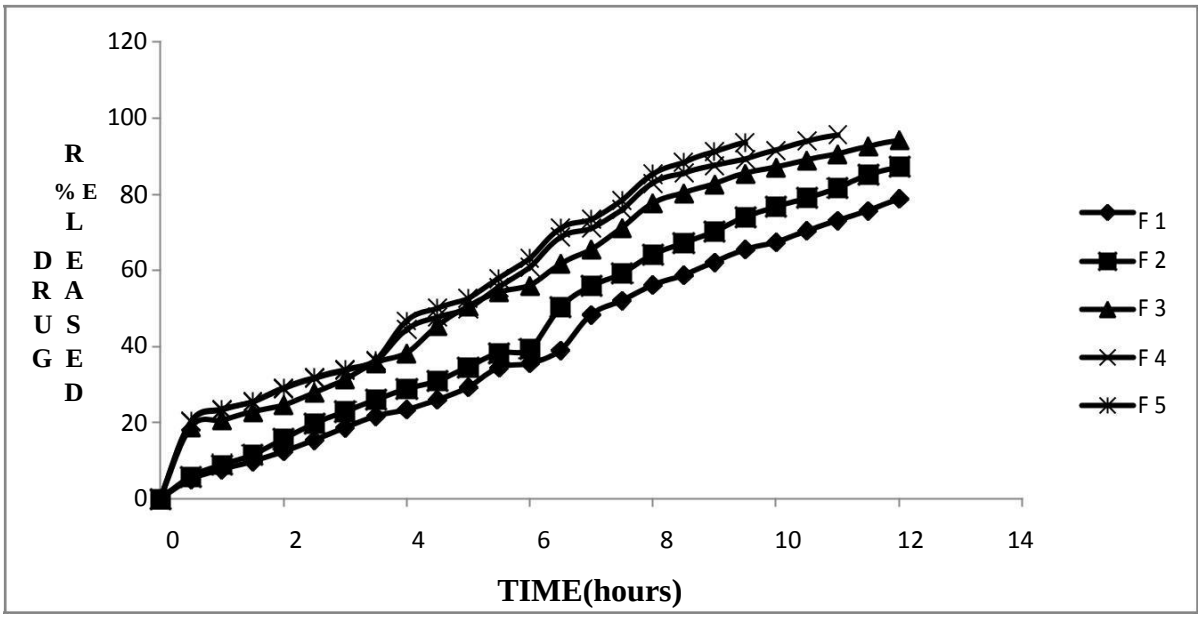


Figure 6.3: Comparative Zero order plots of Levofloxacin hemihydrate floatingtablets formulated with different concentrations of gum karaya

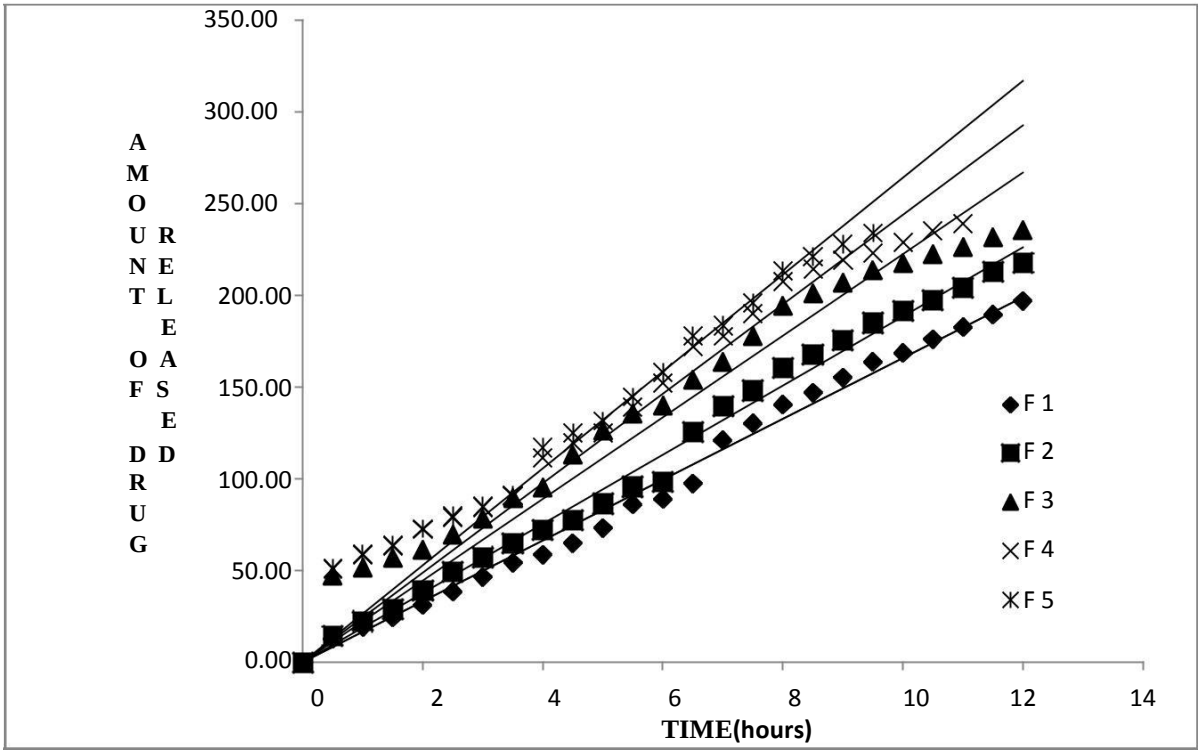


Figure 6.4: Comparative Peppas plots of Levofloxacin hemihydrate floatingtablets formulated with different concentrations ofgum karaya

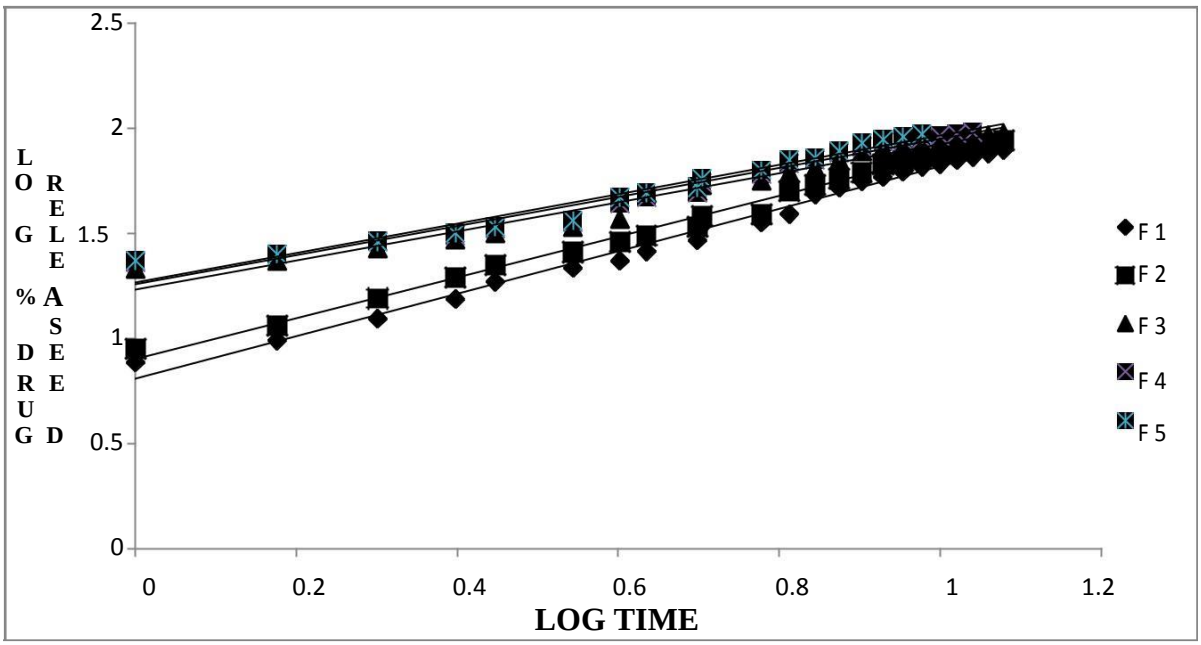


Table 6.8:Swelling index values of Levofloxacin hemihydrate tablets formulated withdifferent concentrations of gum karaya

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_1	63.22	79.59	118.00
F_2	81.63	87.62	120.21
F_3	82.00	98.00	132.42
F_4	86.50	100.39	148.97
F_5	94.68	104.77	157.62

Figure 6.5. Comparative swelling index plot of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum karaya

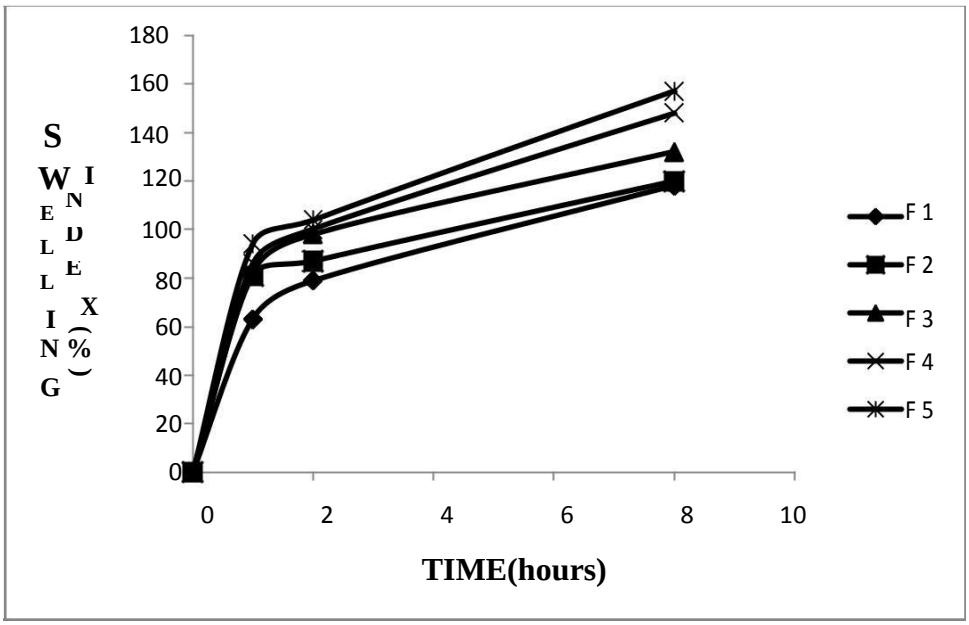


Table 6.9: Micromeritic properties of Levofloxacin hemihydrate granules formulated with different concentrations of xanthum gum.

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Haussners ratio
F_6	25.76±0.05	0.255±0.025	0.291±0.005	12.37±0.024	1.142±0.014
F_7	26.40.0±0.07	0.271±0.021	0.316±0.011	14.240±0.019	1.166±0.019
F_8	27.32±0.09	0.314±0.018	0.366±0.019	14.207±0.027	1.165±0.011
F_9	26.54±0.13	0.353±0.027	0.400±0.014	11.750±0.017	1.133±0.027

Table 6.10: Physical properties of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum.

Formulation	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Floating Lag time	Total floating time (hrs)
F_6	4.6±0.048	501.36±0.54	0.39±0.025	101.52±0.23	1.98 min	>15
F_7	4.4±0.032	501.66±0.49	0.35±0.019	99.87±0.41	3.25 min	>18
F_8	4.7±0.029	499.91±0.39	0.42±0.026	101.93±0.16	5.02 min	>22
F_9	5.2±0.054	500.08±0.51	0.40±0.032	100.23±0.46	6min	>22

Table 6.11: *In vitro* release data of Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum.

Time(hrs)	% Levofloxacin Released (x̄±s.d.)				
	F_1	**F_6**	**F_7**	**F_8**	**F_9**
0	0.00	0.00	0.00	0.00	0.00
0.5	5.14±0.12	6.36±0.09	5.25±0.08	3.99±0.15	4.64±0.06
1	7.68±0.09	8.26±0.12	7.30±0.17	6.07±0.04	6.35±0.04
1.5	9.75±0.11	11.48±0.15	8.87±0.16	8.25±0.16	8.02±0.11
2	12.43±0.06	13.79±0.08	10.43±0.12	9.90±0.09	9.71±0.19
2.5	15.35±0.08	15.44±0.14	13.1±0.06	14.00±0.20	11.11±0.20
3	18.62±0.15	16.89±0.17	15.77±0.04	16.21±0.16	13.19±0.16
3.5	21.66±0.17	19.28±0.21	18.18±0.09	19.01±0.11	14.59±0.18
4	23.42±0.15	20.91±0.16	20.27±0.16	21.40±0.14	16.39±0.14
4.5	26.00±0.06	22.97±0.07	24.23±0.11	23.77±0.07	18.31±0.09
5	29.27±0.03	24.47±0.09	27.08±0.19	25.66±0.18	23.22±0.17
5.5	34.39±0.07	27.32±0.14	27.41±0.15	28.51±0.16	26.21±0.13
6	35.57±0.12	29.60±0.16	30.20±0.14	31.41±0.14	29.21±0.20
6.5	39.00±0.15	34.56±0.18	33.49±0.03	35.02±0.05	32.23±0.09
7	48.34±0.19	37.92±0.21	35.610±0.18	37.11±0.09	34.24±0.05
7.5	52.03±0.09	54.12±0.06	38.97±0.21	43.76±0.07	38.32±0.17
8	56.13±0.06	59.37±0.11	56.17±0.16	47.82±0.13	39.97±0.13
8.5	58.72±0.18	60.45±0.19	57.62±0.07	49.98±0.18	38.66±0.11
9	62.09±0.14	62.69±0.09	59.84±0.09	52.54±0.11	40.77±0.04
9.5	65.47±0.26	64.17±0.07	61.30±0.18	55.11±0.07	42.52±0.08
10	67.35±0.18	66.42±0.18	62.39±0.11	56.12±0.04	43.89±0.16
10.5	70.37±0.20	69.06±0.09	65.39±0.04	59.13±0.12	47.17±0.07
11	73.03±0.11	71.71±0.13	67.65±0.09	62.88±0.19	50.47±0.14
11.5	75.71±0.09	73.62±0.06	70.29±0.05	66.26±0.16	55.32±0.19
12	78.78±0.13	75.53±0.18	73.33±0.15	69.28±0.09	60.57±0.20

Table 6.12: Comparative *in vitro*drug release profile of Levofloxacin hemihydrate floating tablets formulatedwith different concentrations of xanthum gum.

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50}	T_{90}
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9958	0.9620	0.9065	0.9907	16.5772	0.9411	7.5	13.6
F_6	0.9806	0.9476	0.8822	0.9689	16.0000	0.8777	7.8	14.1
F_7	0.9849	0.9499	0.8835	0.9790	15.1187	0.9330	8.3	14.9
F_8	0.9973	0.9716	0.9081	0.9943	14.1717	0.9607	8.8	15.9
F_9	0.9936	0.9764	0.9135	0.9845	11.7362	0.8705	10.7	19.2

Figure 6.6: Comparative *in vitro*drug release profile of Levofloxacin hemihydrate floating tablets formulatedwith different concentrations of xanthum gum

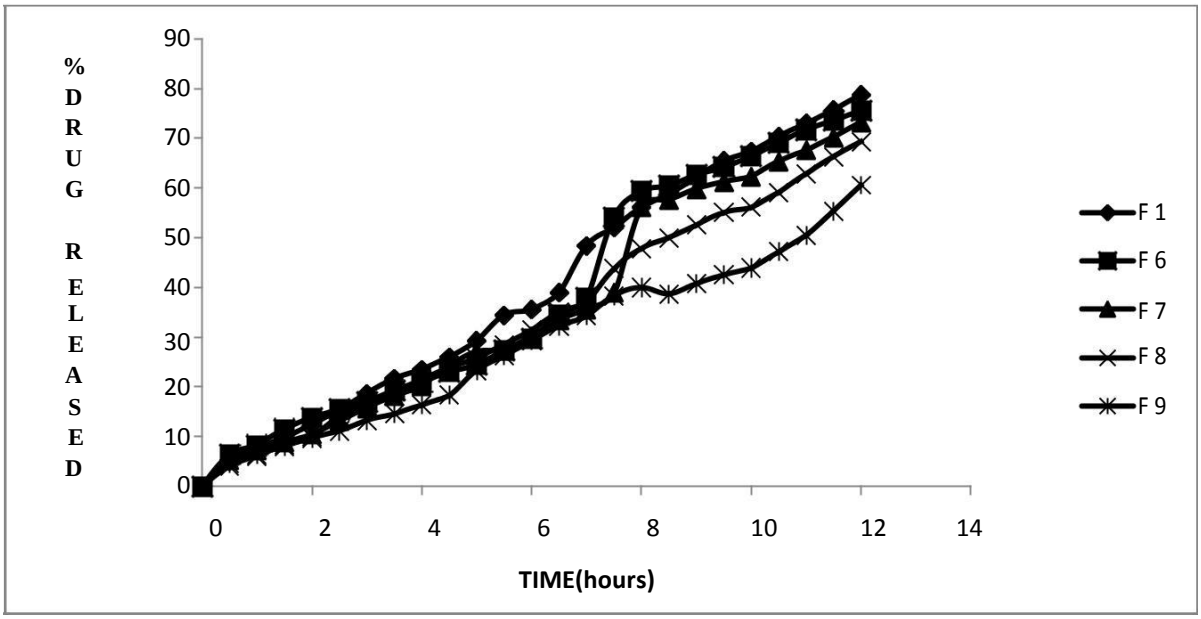


Figure 6.7: Comparative Zero order plots of Levofloxacin hemihydrate floatingtablets formulated with different concentrations of xanthum gum

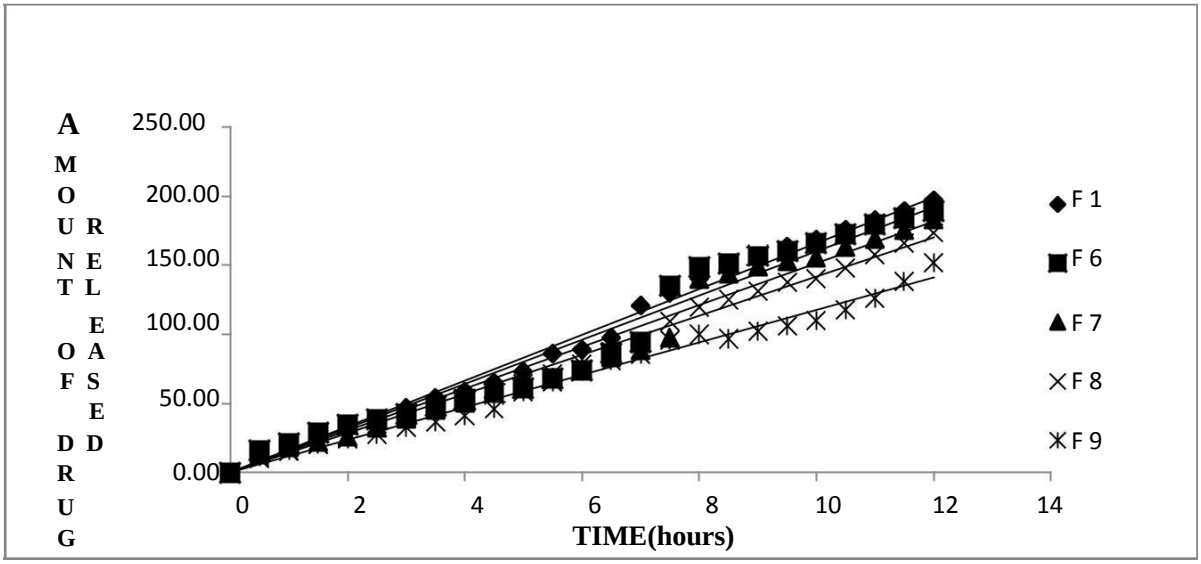


Figure 6.8: Comparative Peppas plots of Levofloxacin hemihydrate floatingtablets formulated with different concentrations ofxanthum gum.

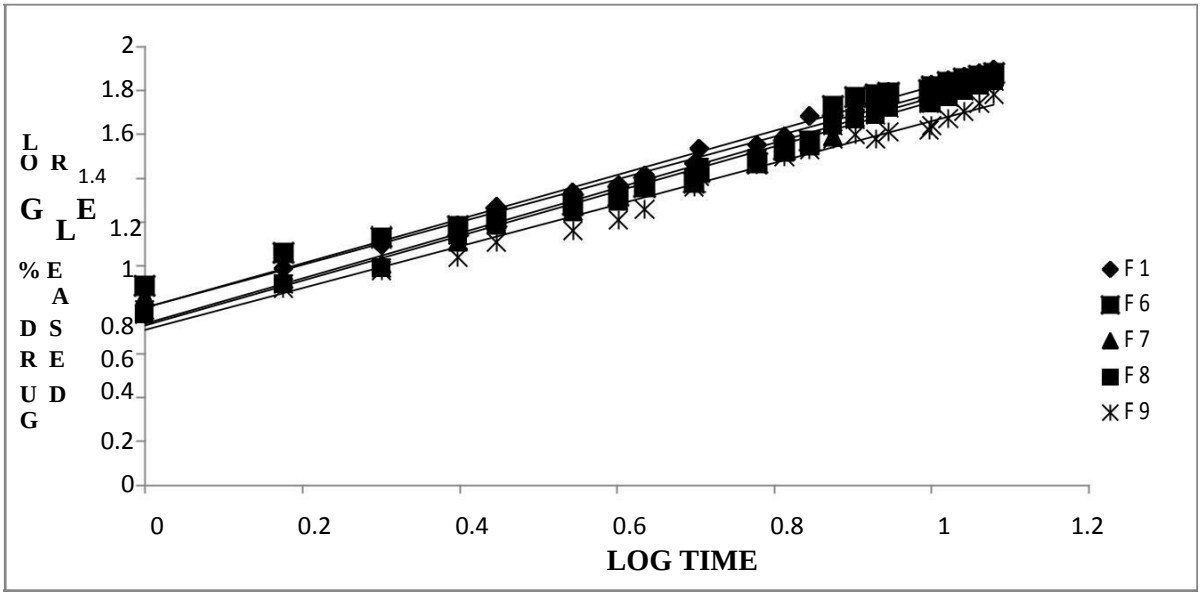


Table 6.13:Swelling index values of Levofloxacin hemihydrates tablets formulated with different concentrations of xanthum gum.

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_6	52.69	76.64	145.00
F_7	53.53	89.89	154.00
F_8	58.53	96.10	168.50
F_9	65.33	105.41	171.34

Figure 6.9:Comparative swelling index plot of Levofloxacin hemihydrate floating tablets formulated with xanthum gum.

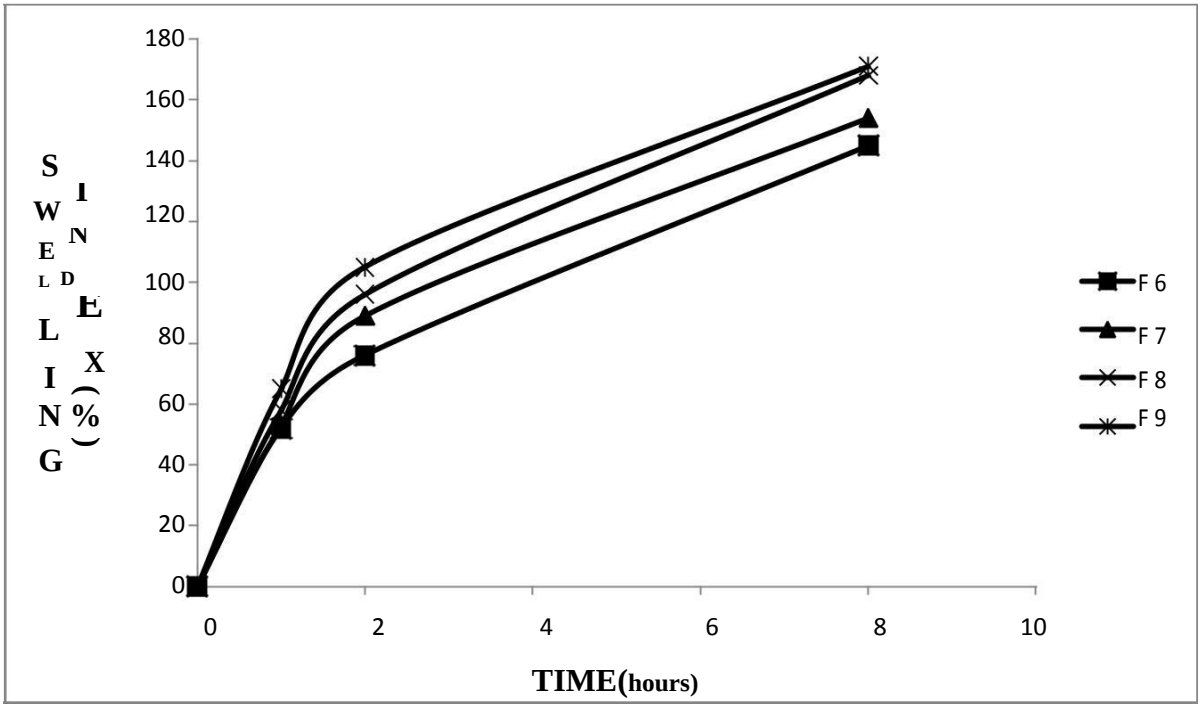


Table 6.14: Micromeritic properties of Levofloxacin hemihydrate granules formulated with different concentrations of gum kondagogu.

Formulation code	Angle of repose	Bulk density	Tapped density	Compressibility index	Haussners ratio
F_{10}	29.89±0.241	0.268±0.011	0.307±0.025	12.70±0.019	1.145±0.019
F_{11}	28.41±0.250	0.271±0.021	0.313±0.017	13.41±0.011	1.154±0.014
F_{12}	29.33±0.214	0.280±0.017	0.320±0.031	12.50±0.024	1.142±0.025
F_{13}	30.81±0.233	0.281±0.015	0.319±0.019	12.70±0.016	1.146±0.017

Table 6.15: Physical properties of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

Formulation	Hardness (kg/cm^2)	Weight variation(mg)	Friability (%)	Drug content(%)	Floating lag time (min)	Total floating time
F_{10}	4.8±0.044	500.47±0.44	0.62±0.024	99.45±0.15	1.40	>14
F_{11}	4.7±0.027	501.39±0.94	0.37±0.012	101.89±0.16	2	13
F_{12}	4.2±0.082	499.54±0.55	0.37±0.101	99.58±0.17	2.15	13
F_{13}	4.5±0.023	500.34±0.60	0.39±0.124	101.45±0.13	3.15	11

Table 6.16: *In vitro* release data of Levofloxacin hemihydrate floating tablets formulated with different concentrations of gum kondagogu

Time (hrs)	% Levofloxacin Released (X±s.d.)				
	F_1	**F_{10}**	**F_{11}**	**F_{12}**	**F_{13}**
0	0.00	0.00	0.00	0.00	0.00
0.5	5.14±0.12	8.42±0.05	15.79±0.09	16.25±0.15	18.05±0.17
1	7.68±0.09	10.44±0.08	17.67±0.013	18.82±0.018	20.35±0.19
1.5	9.75±0.11	12.84±0.10	19.87±0.12	21.02±0.17	22.30±0.20
2	12.43±0.06	14.78±0.10	23.07±0.15	24.15±0.19	24.48±0.21
2.5	15.35±0.08	17.95±0.08	26.40±0.12	27.53±0.15	28.21±0.021
3	18.62±0.15	21.53±0.15	28.38±0.16	29.67±0.18	29.58±0.19
3.5	21.66±0.17	23.93±0.12	30.25±0.15	31.09±0.17	32.80±0.20
4	23.42±0.15	26.58±0.14	32.82±0.16	34.00±0.21	34.23±0.19
4.5	26.00±0.06	28.33±0.13	34.83±0.16	38.77±0.19	37.13±0.21
5	29.27±0.03	31.08±0.16	38.34±0.12	47.76±0.18	53.52±0.20
5.5	34.39±0.07	33.84±0.12	42.17±0.14	53.36±0.016	56.86±0.12
6	35.57±0.12	36.09±0.10	48.89±0.18	58.99±0.015	55.26±0.15
6.5	39.00±0.15	38.08±0.08	55.6±0.19	62.37±0.09	59.75±0.18
7	48.34±0.19	45.04±0.06	60.14±0.21	63.46±0.08	63.13±0.21
7.5	52.03±0.09	55.97±0.05	64.28±0.14	66.47±0.05	66.14±0.17
8	56.13±0.06	63.14±0.12	66.53±0.17	72.17±0.0.17	77.56±0.19
8.5	58.72±0.18	66.53±0.13	68.79±0.20	74.46±0.13	80.26±0.16
9	62.09±0.14	68.41±0.17	70.68±0.19	77.53±0.14	82.60±0.13
9.5	65.47±0.26	70.31±0.17	72.96±0.12	80.23±0.10	86.09±0.10
10	67.35±0.18	72.97±0.21	74.87±0.15	82.56±0.09	88.07±0.15
10.5	70.37±0.20	76.03±0.20	77.56±0.10	84.90±0.06	90.44±0.19
11	73.03±0.11	78.34±0.16	81.01±0.16	86.49±0.12	93.20±0.21
11.5	75.71±0.09	80.27±0.18	83.72±0.14	88.46±0.15	--
12	78.78±0.13	82.98±0.14	85.69±0.16	91.21±0.20	--

Table 6.17: Comparative *in vitro*drug release profile of Levofloxacin hemihydrate floating tablets formulatedwith different concentrations of gum kondagogu

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50}	T_{90}
	Zero Order	First Order	Matrix	Peppas				
F_1	0.9958	0.9620	0.9065	0.9907	16.5772	0.9411	7.5	13.6
F_{10}	0.9892	0.9490	0.9038	0.9742	17.7442	0.8250	7	12.7
F_{11}	0.9761	0.9756	0.9552	0.9671	19.4295	0.6271	6.4	11.6
F_{12}	0.9733	0.9725	0.9602	0.9708	21.1625	0.6449	5.9	10.6
F_{13}	0.9788	0.9416	0.9451	0.9543	22.7780	0.6307	5.5	9.9

Figure 6.10: Comparative *in vitro*drug release profile of Levofloxacin hemihydrate floating tablets formulatedwith different concentrations of gum kondagogu

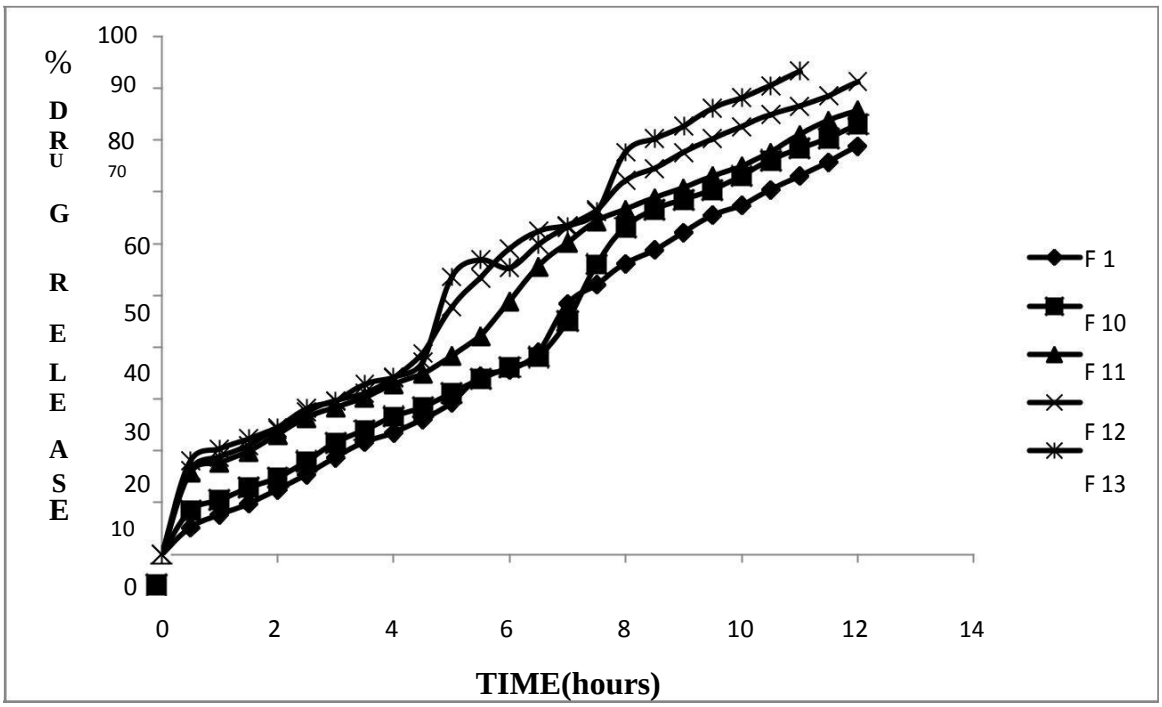


Figure 6.11: Comparative Zero order plot of levofloxacin hemihydrate floatingtablets formulated with different concentrations of gum kondagogu

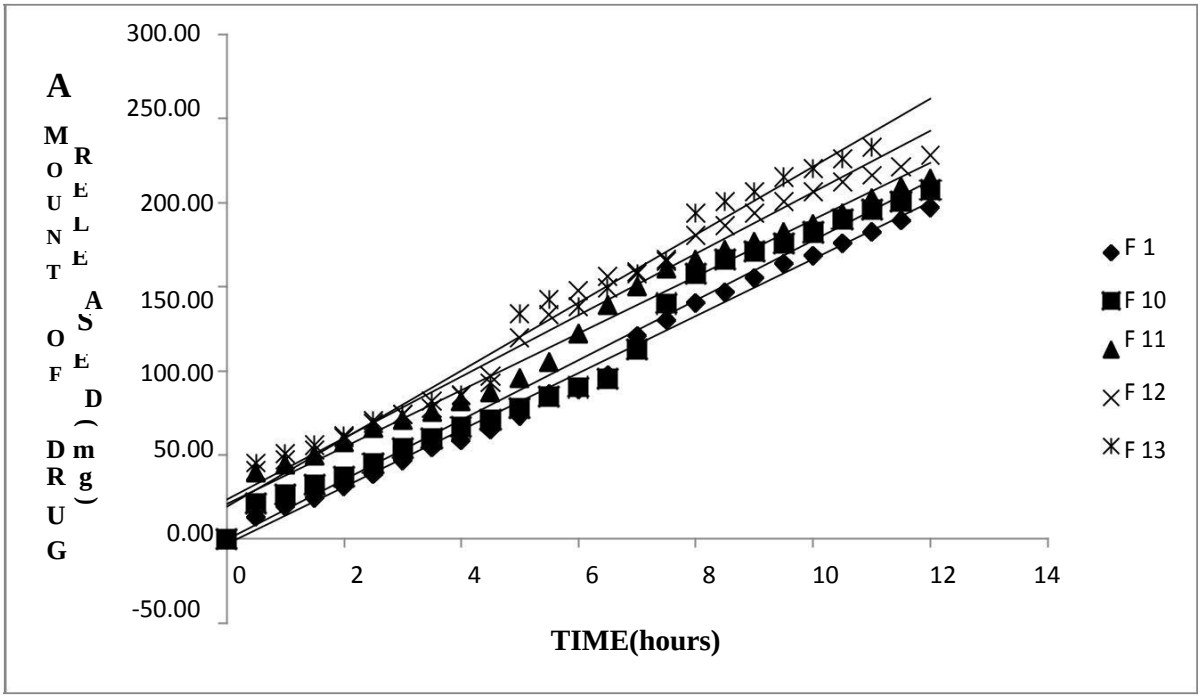


Figure 6.12: Comparative Peppas plots of Levofloxacin hemihydrate floatingtablets formulated with different concentrations ofgum kondagogu

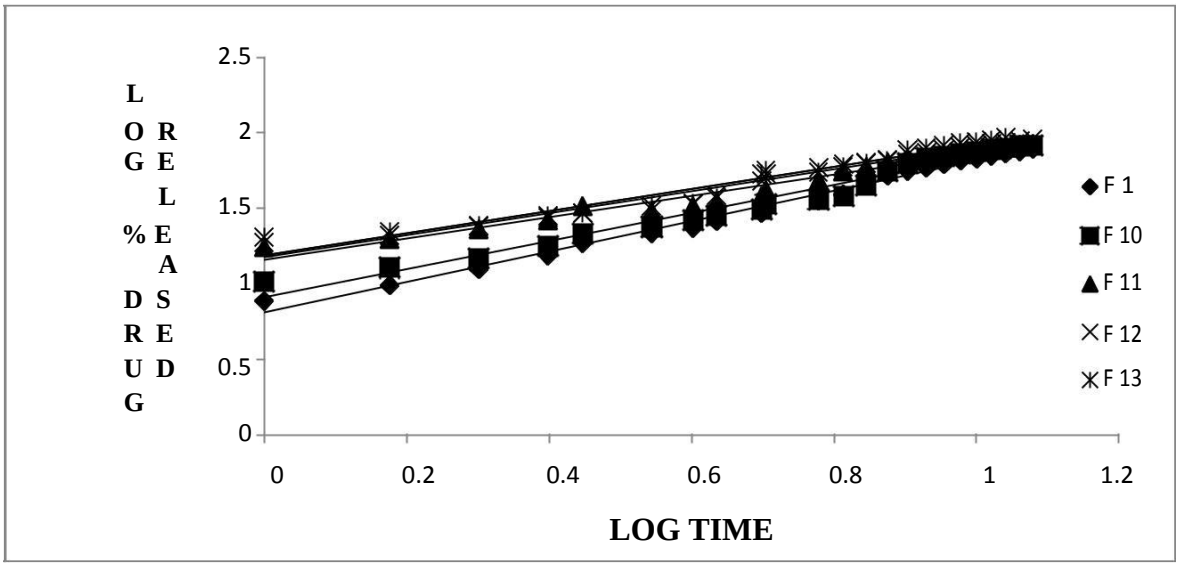
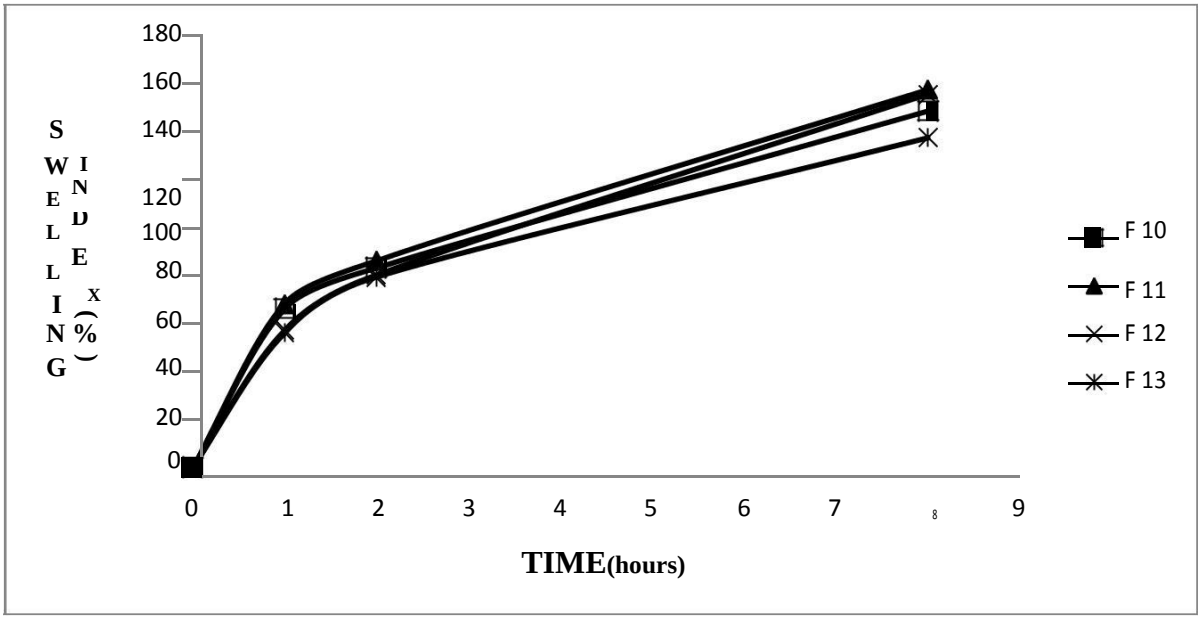


Table 6.18:Swelling index values of Levofloxacin hemihydrates tablets formulated with different concentrations of gum kondagogu

Formulation code	Swelling index		
	Time in hours		
	after 1 hour	after 2 hours	after 8hours
F_{10}	66.99	83.89	148.50
F_{11}	68.34	86.49	157.05
F_{12}	57.06	80.91	155.46
F_{13}	56.31	79.35	137.42

Figure 6.13: Comparative swelling index plot of Levofloxacin hemihydrate floating tablets formulated with gum kondagogu



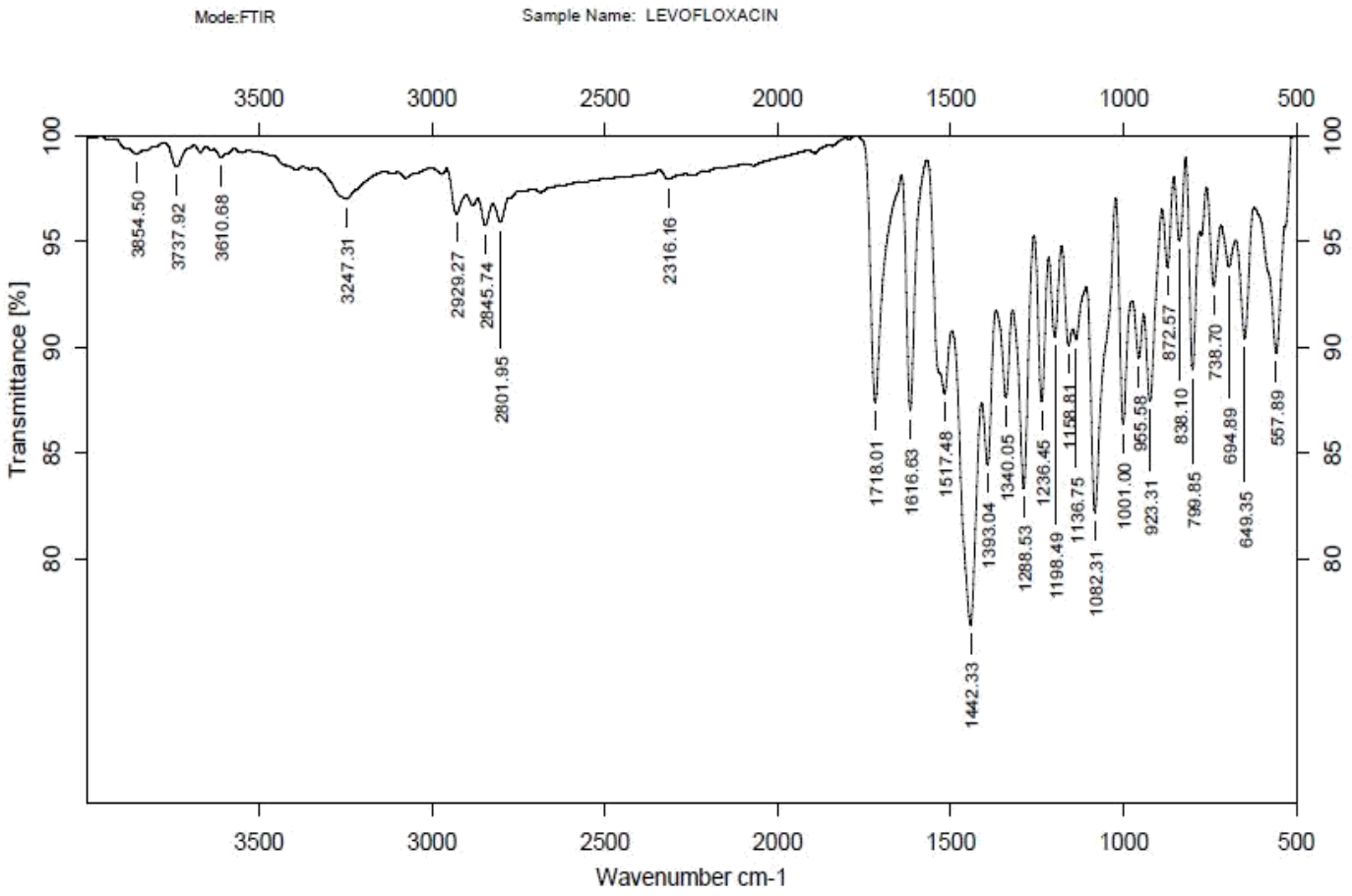


Figure: 6.14. IR spectrum of Levofloxacin hemihydratre.

Figure: 6.15. IR spectrum of Levofloxacin+ gum karaya.

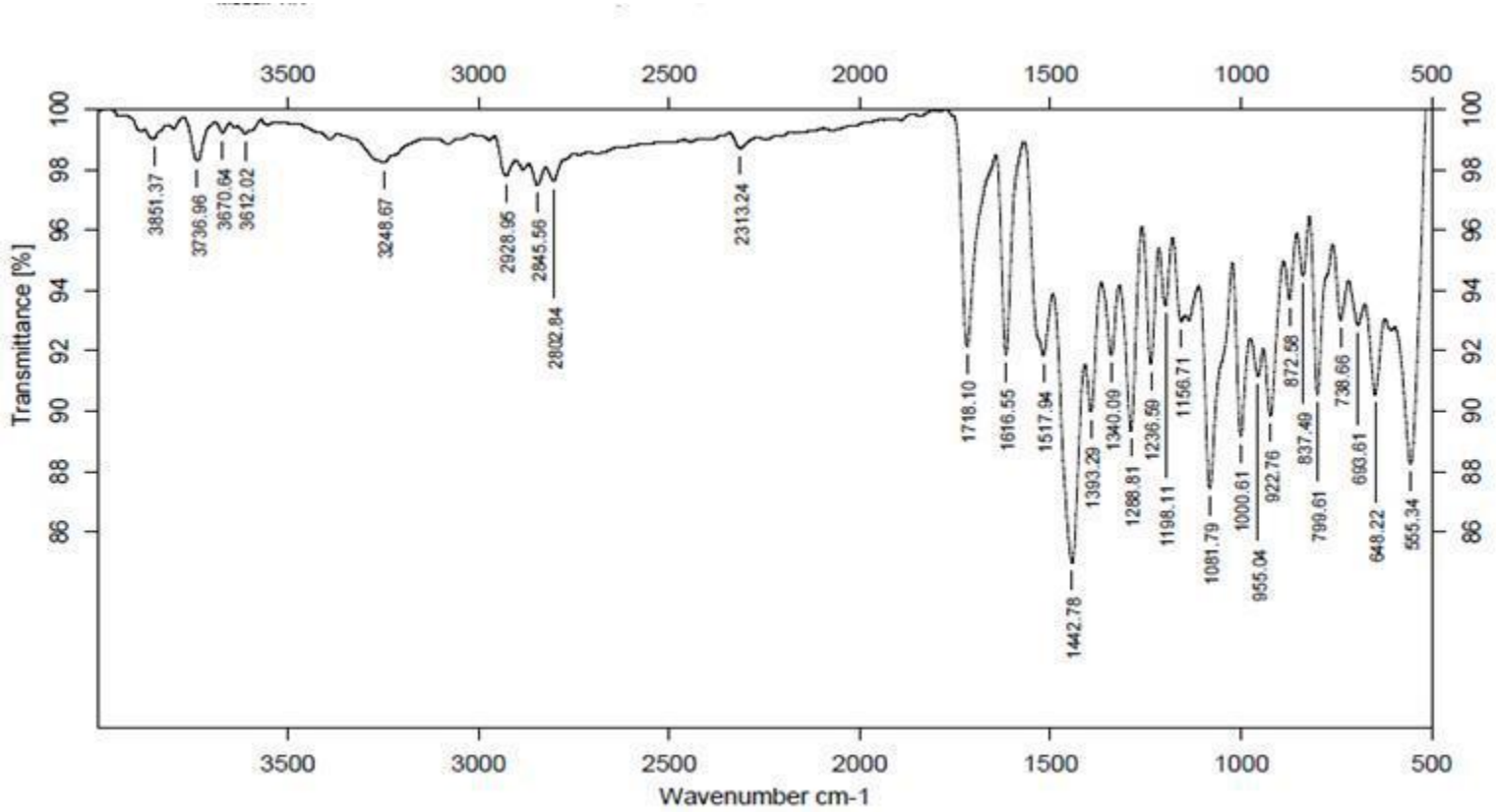


Figure: 6.20. IR spectrum of Levofloxacin + xanthum gum

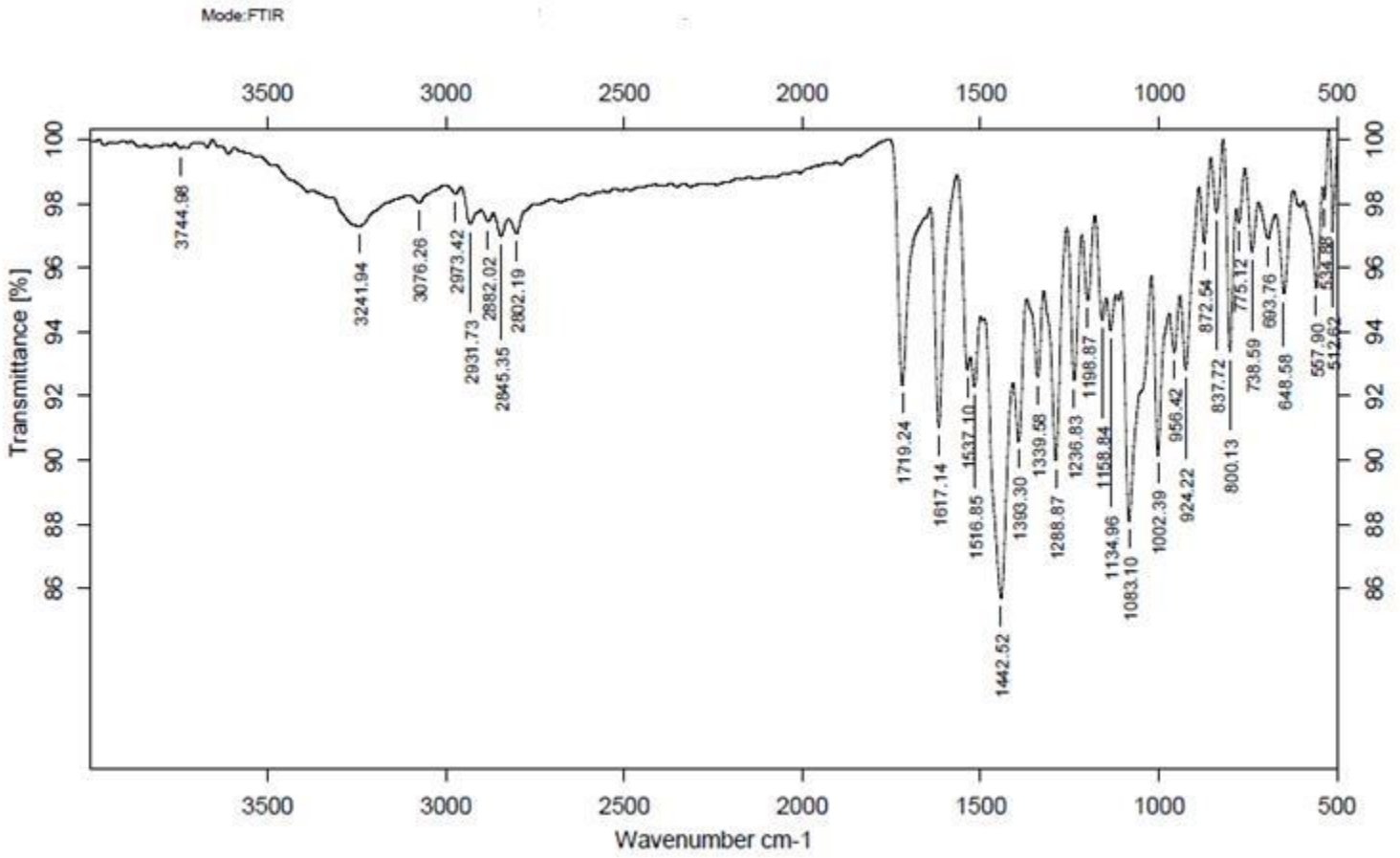
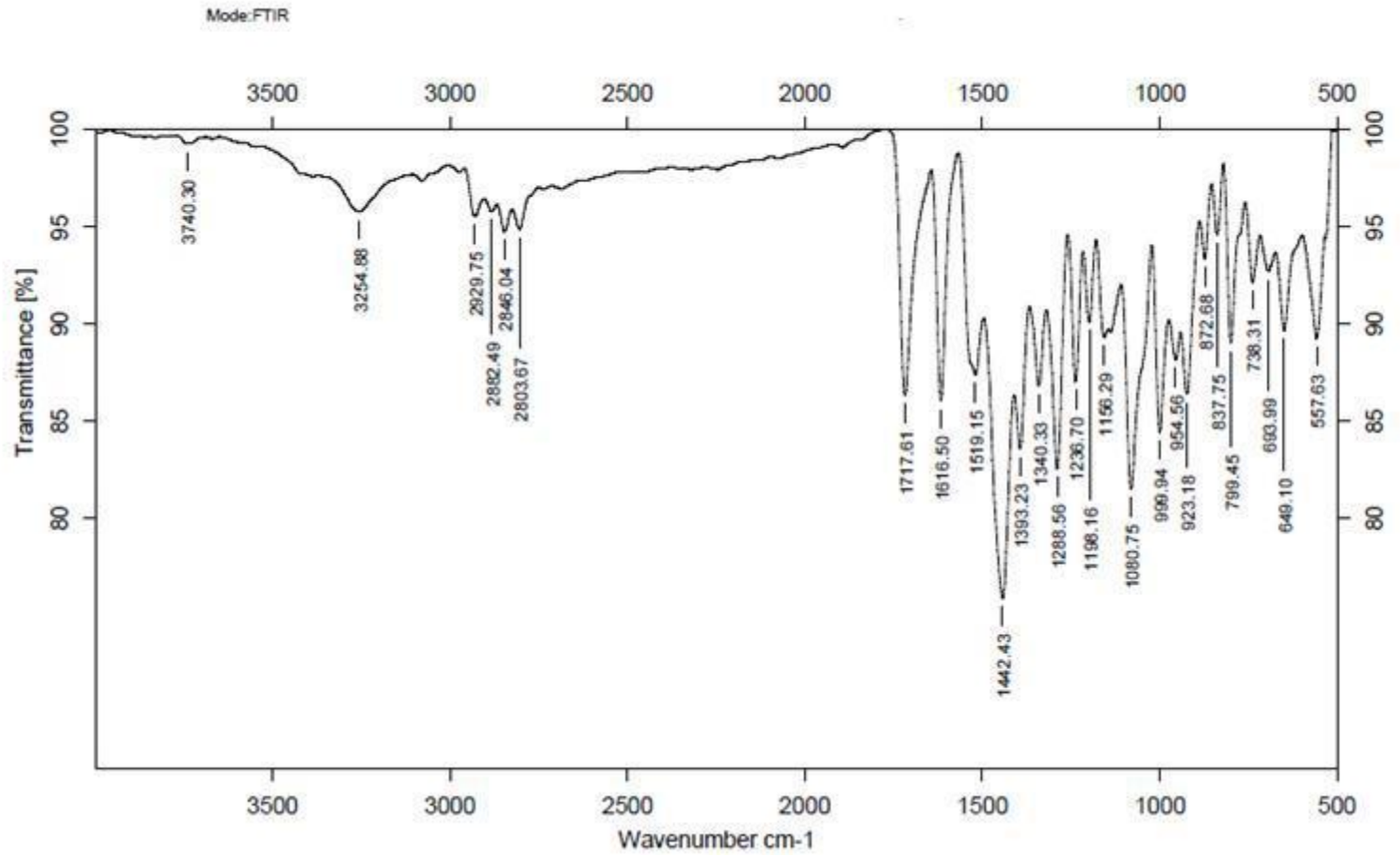


Figure: 6.21. IR spectrum of Levofloxacin+ gumkondagogu



7. RESULTS AND DISCUSSION

7.1 Calibration curve

The absorbance values and standard plots were shown in table 6.1 and fig 6.1. From these results it was found that there exists a good correlation between concentration and absorbance values.

7.2 Process optimization

The process optimization studies were carried out to determine the concentration of $NaHCO_3$ based on lag time and drug release. The gas generating components such as carbonates and composition. Increasing the concentration of sodium bicarbonate decreases the floating lag time because of faster and higher carbon dioxide generation.

In the present investigation 20-23%w/w $NaHCO_3$ was selected as optimized concentration, as it showed less lag time when compared with other concentrations of $NaHCO_3$.

7.3 Viscosity of polymers

Viscosities of 1%w/v HPMC K 100 M, xanthum gum, gumkondagogu and gum karayawere measured in 0.1N HCl.Viscosity values were in order of xanthum gum >HPMC K 100 M>gumkondagogu>gum karaya.Viscosity values were showed in table 6.2 and table 6.3.

7.4 Studies on Levofloxacin hemihydrates floating tablets formulated with different concentrations of gum karaya.

Floating tablets (F_1-F_5) of Levofloxacinhemihydrate were prepared by varying the concentration of HPMC K 100 M and gum karaya. The composition of the formulations is shown in table 5.3.

The formulated granules were evaluated for various flow properties.The bulk density for all theformulations ranged from 0.276 to 0.351. The angle of repose for all the formulations was found to be in the range of $25^0 42^1$-$27^0 01^1$. The Carr's index for all the formulations ranged from 10.68 – 12.01%. The value of bulk density indicates good packing characters. The value of angle of repose (25^0-30^0) for all the

formulations indicates good flow property. The value of Carr's index (10-16%) indicates free flowing material. The values of Hausner's ratio were found to be between 1.119-1.161. The powder blend with Hauser's ratio of 1.25 has good flow properties. So the values indicate that the granules had acceptable flow properties. The flow properties were shown in table 6.4

Floating matrix tablets were evaluated for hardness and friability. The hardness was found to be in between 4.5 – 5.1 kg. The tablets satisfied friability requirement, as the % friability values were less than 1%.The drug content estimations showed values in the range of 99.56 to 100.78%, which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ±5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

All the tablets were formulated using sodium bicarbonate as effervescent agent. It was observed that the carbon dioxide generated from sodium bicarbonate in presence of dissolution medium(0.1N HCL) was trapped in the polymer gel matrix formed by the hydration of polymers(HPMC K100M orgum karaya) which decreases the density(<1) and makes the tablet buoyant. The tablets formulated with gum karaya(F_1-F_5) contained the same amount of Sodium bicarbonate as effervescent agent but showed a increased in floating lag time with increase in concentration of natural polymer. The buoyancy studies results showed that the formulations containing higher concentration of HPMC K 100M, showed good floating lag time (FLT) and total floating time (TFT) when compared to formulations containing higher concentrations of natural polymer. The results of various physical properties and*invitro* buoyancy studies were tabulated in table 6.5.

In vitro dissolution studies of all the formulations of floating matrix tablets were carried out in 0.1N HCl. The study was performed for 12 hrs and the cumulative drug release was calculated. All the formulations remained floating and intact throughout the dissolution studies. The formulations(F_2-F_4) containing gum karayain combination with HPMC K100M showed increase in drug release with increase in concentration of gum karayawhen compared formulation containing only HPMC

K100M. The drug release from formulation F_5 containing only gum karayashowed a maximum drug release at end of 10 hours. Drug release from the formulation containing HPMC K100M was lesser owing to its high viscosity and also due to less permeability of water, as the drug release rate is dependent on the viscosity grade and the concentration of the polymers used. The dissolution profile for the formulations is tabulated in table 6.6 and shown in figure 6.2.

To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) revealed that the dissolution profiles follows Zero order kinetics and the mechanism of drug release was governed by Peppas model. The n values are found to be more than 0.5 (n>0.5) indicted that the drug release was predominantly controlled by non fickian diffusion. . The in-vitro drug release kinetic data was shown in table 6.7 and figures 6.3 and 6.4.

The swelling index studies showed a gradual increase with increase in concentration of gum karayawhich indicates the natural tendency of it to swell 5-10 times of its original value. The swelling index values are shown in table 6.8 and figure 6.5.

7.5 Studies on Levofloxacin hemihydrate floating tablets formulated with different concentrations of xanthum gum.

To study the influence of xanthum gum concentration on drug release, formulations (F_6-F_9) were prepared using different concentrations of xanthum gum with HPMC K100M by wet granulation method. The composition of formulations F_6-F_9 is shown in table 5.4 .The formulated granules were subjected to various micromeritic properties and the values were shown in table 6.9. All the formulations exhibited the desirable flow properties.

The formulated tablets were subjected to various quality control tests like hardness, friability, weight variation and drug content. All the tablets complied with the pharmacopoeia standards. In the case of tablets formulated with guar gum (F_6-F_9) amount of sodium bicarbonate required for floating increased with increase in xanthum gumconcentration which indicated that the molecular weight distribution or viscosity of the gel forming polymers influenced the *in vitro* buoyancy. The various physical properties are shown in table 6.10.

The formulations(F_6-F_9) containing xanthum gum in combination with HPMC K100M showed decrease in drug release with increase in concentration of xanthum gum when compared formulation containing only HPMC K100M(F_1). The drug release from the formulations (F_6-F_9) showed very slow release as compared to other formulations. The in vitro release data for formulations (F_6-F_9) was presented in table 6.11 and fig 6.6. The release rate followed zero-order release kinetics (fig 6.7) and the data was fitted in the Peppas plots (fig 6.8).The exponential coefficient from the Peppas plots was found to be in between 0.75 to 0.88, indicating non fickian mechanism of drug release. Drug release kinetic data was presented in table 6.12. The release rate of Levofloxacin hemihydrate was found to be retarded by xanthum gumwith an increase in its concentration.

The swelling indexof tablets formulated with xanthum gum(F_6-F_9) was found to be higher than that of other formulations which can be attributed tohigh viscosity and high water retention property of both HPMC K100M and xanthum gum. The values of swelling index are tabulated in table 6.13 and shown in figure 6.9.

7.6 Studies on Levofloxacin hemihydrate floating tablets formulated with different concentrations of gumkondagogu.

To study the influence of gum kondagoguconcentration on drug release, formulations (F_{10}-F_1) were prepared using different concentrations of gum kondagoguand HPMC K 100 M by wet granulation method as given in table 5.5

The granules were subjected to various micromeritic properties and the values were shown in table 5.14. All the formulations exhibited the desirable flow properties. The formulated tablets were subjected to various quality control tests and the values were shown in table 6.15. All the tablets complied with the pharmacopoeial standards. All the formulations showed good floating lag time and remained buoyant for more than 12 hours except formulation F_{13} which remained buoyant for 11 hours. The in vitro release data for formulations (F_{10}-F_{13}) was presented in table 6.16 and fig 6.10. The release rate followed zero-order release kinetics (fig 6.11) and the data was fitted in the Peppas plots (fig 6.12).The exponential coefficient from the Peppas plots was found to be in between 0.63 to 0.94, indicating non fickian mechanism of drug release. Drug release kinetic data was presented in table 6.17. The release rate of Levofloxacin hemihydrate was found to be affected by the concentration of the polymer used in the preparation of tablets.Based on the release rate, the order of drug release from the formulations was in order of F_{12}>F_{11}>F_{10} after 12 hours.

The results of swelling index studies for tablets formulated with gum kondagoguare shown in table 6.18 and figure 6.13. The formulation containing HPMC K 100 M and gum kondagoguin a ratio of 1:1 showed higher swelling index.

Table 7.1: Comparativeinvitro release parameters of Levofloxacin hemihydrates floating tablets formulated with various natural polymers and HPMC K 100 M.(1:1 ratio)

Formulation	% Drug release at end of 12 hours.	Release Rate Constant k_0 (mg/hr)
F_3(Levofloxacin+ gum karaya)	94.26	22.77
F_7 (Levofloxacin+xanthumgum)	73.33	15.11
F_{11}(Levofloxacin+ gum kondagogu)	85.69	19.43

From the above table (7.1) it is clearly evident that the invitro release of drug from the floating tablet was influenced by nature of natural polymer. Based on the release rate constant and % of drug release at the end of 12 hours the release retarding capacities of the natural polymers were arranged in the following order. Xanthum gum> gum kondagogu>gum karaya.

7.7. IR Spectral studies.

The IR Spectrum of Levofloxacin hemihydrates and Levofloxacin hemihydrates were shown in figures 6.18-6.22.

S.No.	Formulation	Characteristicstretching		
		Carbonyl C=O	Aromatic C-H	Carbonyl O-H
1	Levofloxacin hemihydrate	1724.8cm^{-}	2935.62cm^{-}	3247.31cm^{-}
2	Levofloxacin + gum karaya	1718.10cm^{-}	2928.95cm^{-}	3248.67cm^{-}
3	Levofloxacin +xanthum gum	1719.24cm^{-}	2931.73cm^{-}	3241.94cm^{-}
4	Levofloxacin +gumkondagogu	1717.61cm^{-}	2929.75cm^{-}	3254.88cm^{-}

The obtained IR spectra of Levofloxacin hemihydrate and combination of Levofloxacin hemihydrate with natural polymers were identical. The IR spectra of the pure drug and drug in combination with natural polymers indicated that, no chemical interaction occurred between the drug, Levofloxacin hemihydrate and the excepients used.

8. SUMMARY AND CONCLUSION

- Floating tablets of Levofloxacin hemihydrate prepared usinggumkaraya, xanthumgumandgumkondagogu showed controlled release for a prolonged period of time.
- The natural polymers used showed drug release retarding nature and the release retarding nature was in order of Xanthum gum> gum kondagogu> gum karaya.
- Compared to other gums used Xanthumgumhashigh viscosity value and good drug release retarding capacity.
- There is a similarity between the viscosities of the polymers and their release retarding profiles.
- The floating tablets prepared only with HPMC K 100 M had shown much lesser drug release than the combination of natural polymer (gum kondagogu/ gum karaya) and HPMC K 100 M.Whereas in case of formulations prepared with xanthum gum and HPMC K 100 M shows much lesser drug release than the formulations prepared with HPMC K 100 M alone.
- The concentration of $NaHCO_3$ influences the lag time. In this investigation 20-23% $NaHCO_3$ was selected as optimized concentration.
- The FT-IR studies clearely indicates that there are no drug and polymer interactions.
- PreparedLevofloxacin hemihydrate floating tablets complies with the specifications of the Pharmacopoeial standards.

From this study it could be concluded that natural polymers can be used in the preparation of floating tablets and in combination with synthetic polymers. Floating tablets of Levofloxacin hemihydrate prepared by employing natural polymers could be used for treatment of gastric ulcers caused by *H.pylorii* infection by prolonging the gastric residence time and its controlled release in the gastric environment thus completely eradicating the *Helicobacter pylori*from GIT.

Recommendations

The following recommendations are suggested for future extension of this experimental work.

- Selection of suitable packaging materials.
- Stability studies on the finished dosage form.
- In vivo studies on suitable animal and assessment of various pharmacokinetic and pharmacodynamic evaluation of drug.
- Physico-chemical characterization of extracted natural polymers.