FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS

A Dissertation submitted to

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

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: MAHENDRA BABU.J

REG.No. 261410270

Under the Guidance of

Dr. R. Sambathkumar, M.Pharm., PhD,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

OCTOBER – 2016

FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS

A Dissertation submitted to

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

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: MAHENDRA BABU.J

REG.No.261410270

Under the Guidance of

Dr.R.Sambathkumar, M.Pharm.,PhD,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

OCTOBER – 2016

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS",** submitted by the student bearing **Reg. No: 261410270** to "**The Tamil Nadu Dr. M. G. R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS",** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University**- **Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing **Reg.No. 261410270** during the academic year 2015-2016, under the guidance and supervision of **Dr. R. Sambathkumar, M. Pharm., PhD.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalayam
Date:

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

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS", submitted** to "**The Tamil Nadu Dr. M.G.R. Medical University** - **Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing **Reg.No. 261410270** during the academic year 2015-2016, under my guidance and direct supervision in the Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalayam
Date:

Dr. R. Sambathkumar, M. Pharm., PhD.,
Professor & Head,
Department of Pharmaceutics
J.K.K. Nattraja College of Pharmacy.
Kumarapalayam - 638 183.

DECLARATON

I do hereby declared that the dissertation **"FORMULATION DEVELOPMENT AND *INVITRO* EVALUTION OF GASTRORETENTIVE VENLAFAXINE HYDROCHLORIDE FLOATING TABLETS",** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2015-2016, under the guidance and supervision of **Dr. R. Sambathkumar, M. Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

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

Place: Kumarapalayam **Mr. MAHENDRA BABU. J**

Date: **Reg.no. 261410270**

Dedicated to

Parents,

Teachers &

My Family

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

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

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

It is most pleasant duty to thank for our beloved Principal and my guide **Dr. R. Sambathkumar, M.Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project and tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

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

My sincere thanks to **Mrs. S. Bhama, M. Pharm.,** Assistant Professor Department of Pharmaceutics, **Mr. R. Kanagasabai, B.Pharm, M.Tech.,** Assistant Professor, **Mr. K. Jaganathan, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, **Mr. C. Kannan M.Pharm.,** Assistant Professor, Department of Pharmaceutics and **Mr. V. Kamalakannan M.Pharm.,** Assistant Professor, Department of pharmaceutics for the in valuable help during my project.

My sincere thanks to **Mr. N. Venkateswaramurthy, M.Pharm.,** Professor and Head, Department of Pharmacy Practice. **Dr. Radhika,**

M.Pharm., Ph.D., Associate Professor, **Dr. K.Sattanathan, M.Pharm., Ph.D.,** Assistant Professor **Mrs. K. Krishna Veni, M.Pharm.,** Lecturer, Department of Pharmacy Practice, **Mrs. P. Kavitha M.Pharm** Lecturer, Department of Pharmacy Practice, **Mr. R. Kameswaran M.Pharm** Lecturer Department of Pharmacy Practice, **Dr. Taniya Jacob, Pharm.D.,** Lecturer, Department of Pharmacy Practice, **Dr. V. Viji Queen, Pharm.D.,** Lecturer, Department of Pharmacy Practice, **Mrs. M. Sudha M.Pharm.,** Lecturer, Department of Pharmacy Practice and **Mr . T.Thiyagarajan M.Pharm** Lecturer Department of Pharmacy Practice, for their help during my project.

It is my privilege to express deepest sense of gratitude toward **Dr. M. Vijayabaskaran**, **M.Pharm.,** Professor & Head, Department of Pharmaceutical chemistry, **Dr. S. P. Vinoth Kumar M.Pharm.,** Assistant professor, Department of Pharmaceutical chemistry, **Mrs. S. Gomathi M.Pharm.,** Lecturer, Department of Pharmaceutical chemistry, **Mrs. B. Vasuki M.Pharm.,** Lecturer, Department of Pharmaceutical chemistry, for their valuable suggestions and inspiration.

My sincere thanks to **Dr. V. Sekar, M.Pharm., Ph.D.,** Professor and Head, Department of Analysis, **Mr. S. Jayaseelan, M.Pharm.,** Associate Professor, **Dr. I. Caolin Nimila, M.Pharm., Ph.D.,** Assistant Professor, and **Mr. K. K. Senthil Kumar**, **M.Pharm.,** Assistant Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to **Dr. Senthilraja, M.Pharm., Ph.D.,** Associate Professor and Head, Department of Pharmacognosy, **Mrs. Meena Prabha M.Pharm.,** Lecturer, Department of Pharmacognosy and **Mrs.Seema, M.Pharm.,** Lecturer, Department of Pharmacognosy for their valuable suggestions during my project work.

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

I greatly acknowledge the help rendered by **Mrs. K. Rani,** Office Superintendent, Miss**. Venkateswari, M.C.A.,** typist**, Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian, Mrs**. S. Jayakala B.A., B.L.I.S.,** and Asst. Librarian for their co-operation. I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

Mr. MAHENDRA BABU. J

Reg.no. 261410270

FORMULATION DEVELOPMENT AND INVITRO EVALUTION OF GASTRORETENTIVE VENLAFAXINE FLOATING TABLETS

CONTENTS

1. INTRODUCTION

The design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hours (hr). This variability in turn may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2–3 hr through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled-release (CR) dosage forms possessing gastric retention capabilities.[1]

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[2]

1.1 Basic Gastrointestinal Tract Physiology: [1]

It is well recognized that the stomach may be used as a ‘depot’ for sustained-release (SR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for

ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter-digestive series of electrical events which cycle both through the stomach and small intestine every 2–3 hr. This activity is called the inter-digestive myoelectric cycle or MMC, which is often divided into four consecutive phases.

- **Phase I** is a quiescent period lasting from 40 to 60 min with rare contractions.
- **Phase II** is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses.
- **Phase III** is a short period of intense, large regular contractions lasting from 4 to 6 min. It is this phase, which gives the cycle the term 'housekeeper' wave, since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum.
- **Phase IV** is a brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying. Overall, the relatively brief GI transit time of most drug products, which is approximately 8–12 h, impedes the formulation of a once daily dosage form for most drugs. These problems can be exacerbated by alteration in gastric emptying that occur due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore, desirable to have a CR product that exhibits an extended GI residence and a drug release profile independent of patient related variables.

1.2 Factors Affecting Gastric Retention: [3]

- **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size** – dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those having diameter of 9.9mm.

- **Shape of dosage form** – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better GRT ≈ 90% to 100% retention at 24 hr compared with other shapes.
- **Fed or unfed state** – under fasting conditions, the GI motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 hr. The MMC sweeps undigested material from the end 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 hr 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 hr) is less compared with their age and race matched female counterparts (4.6±1.2 hr), 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 and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Biological factors** – diabetes and Crohn's disease, etc.

1.3 Gastroretentive forms:

1. Floating systems
2. High density systems
3. Expandable systems
4. Superporous hydrogels

5. Mucoadhesive or bioadhesive systems
6. Magnetic systems

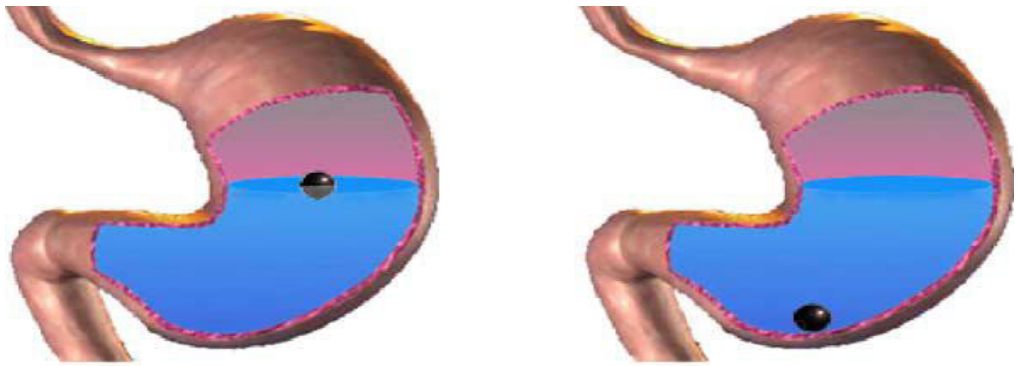
1. **Floating systems**

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

2.High density systems

Gastric contents have a density close to water (1.004 g/cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g /cm^3 seems to be necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

Fig:1 Schematic localization of an intragastric floating system and a high-density system in the stomach



3.Expandable systems

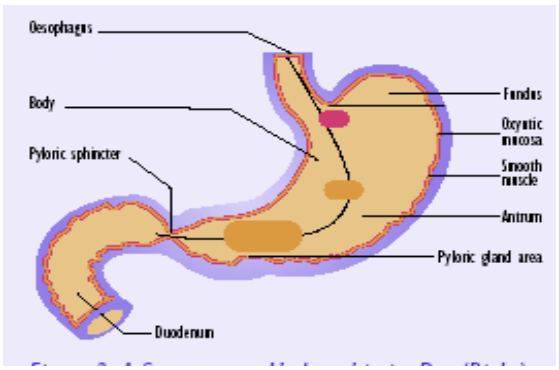
A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable and swellable systems have been investigated. Unfoldable

systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach.

4.Hydrogel systems

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10 nm and 10 Am, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >100 Am, 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 and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

Fig: 2 i) On the left, superporous hydrogel in its dry (a) and water-swollen (b) state. ii) On the right, schematic illustration of the transit of superporous hydrogel.



5.Mucoadhesive or bioadhesive systems:

The basis of mucoadhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous

structure of the polymer substrate. Materials commonly used for bioadhesion are poly(acrylic acid) (Carbopol\, polycarbophil), chitosan, Gantrez\ (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate) and polylactic acid.

6. Magnetic systems:

This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

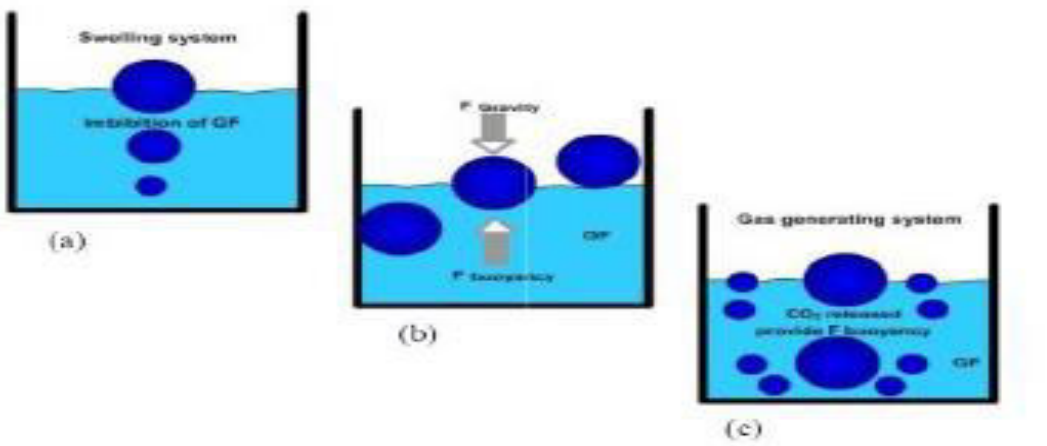
1.4 Mechanism of floating systems

While the system is floating on the gastric the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side (Fig. 3(b)). This apparatus helps in optimizing FDDS with respect to stability and durabilityof floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations 19.

F = F buoyancy - F gravity = (Df - Ds) gv---

Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.

Fig: 3. Mechanism of floating systems, GF=Gastric fluid



1.5 Technological developments in FDDS:

Based on mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non effervescent system.

A. Effervescent system:

Effervescent system include use of gas generating agents, carbonate(sodium bicarbonate) and other organic acids (citric acid and tartaric acid) to produce carbon dioxide(CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. The effervescent further classified into two types.

(I) Gas Generating Systems:

1. Intra Gastric Single Layer Floating Tablet:

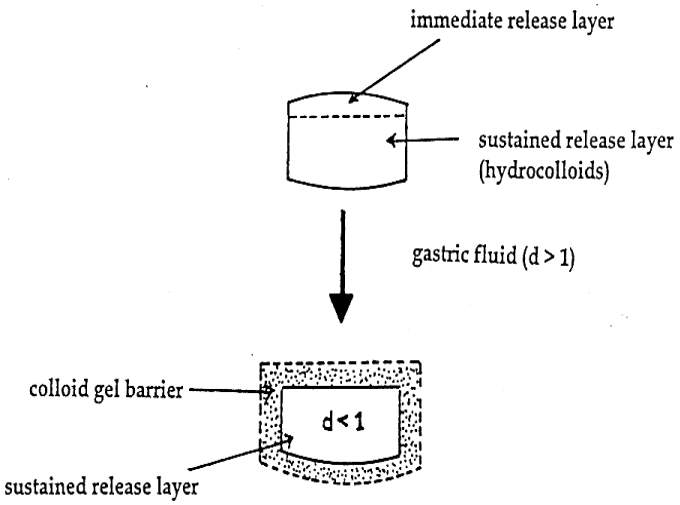
These are formulated by the CO_2 generating agents and the drug within matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the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

2. Intra Gastric Bilayered Floating Tablets:

These are also compressed tablets and contain two layers for:

Immediate release layer and Sustained release layer

Fig: 4 Intra Gastric Bilayered Floating Tablets



3. Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swllowen pills like balloon and float as the density decreases.

Fig: 5 multiple-unit oral floating dosage system

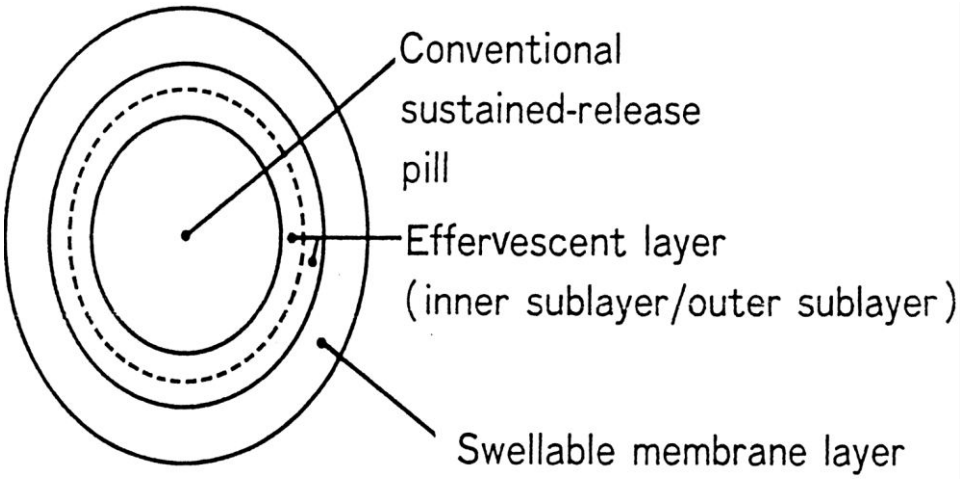
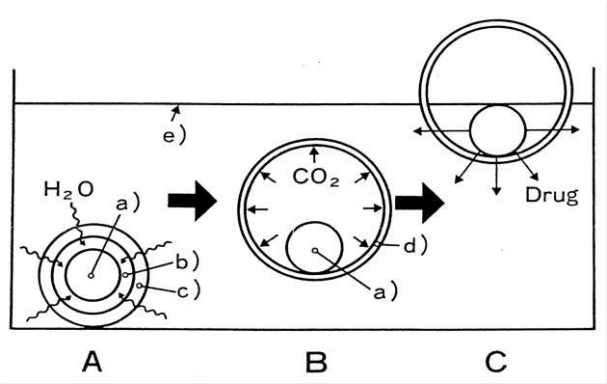


Fig: 6 Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker

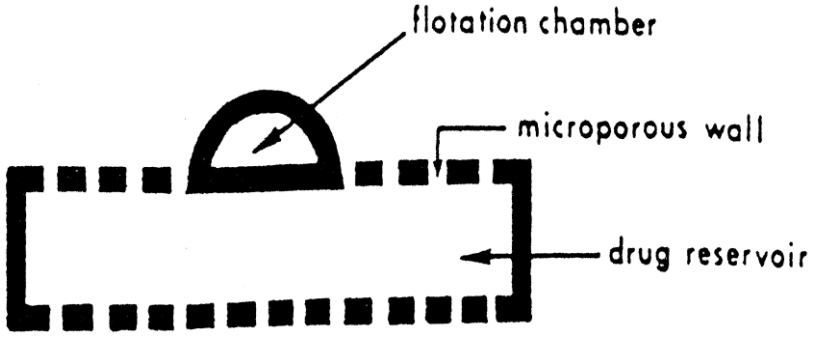


II. Volatile liquid/ vacuum containing systems:

1. Intragastric Floating Gastroretentive Drug Delivery System:

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

Fig: 7 Intragastric floating drug delivery device

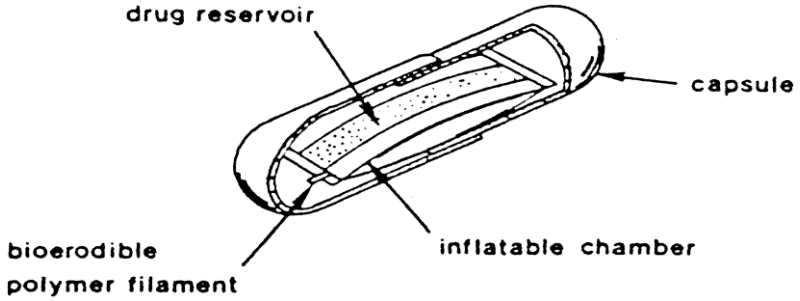


2. Inflatable Gastroretentive Delivery System:

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, impregnated polymeric matrix, and then encapsulated in a gelatin capsule. After oral administration of the capsule dissolve to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug

reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

Fig: 8 Gastro-inflatable drug delivery device

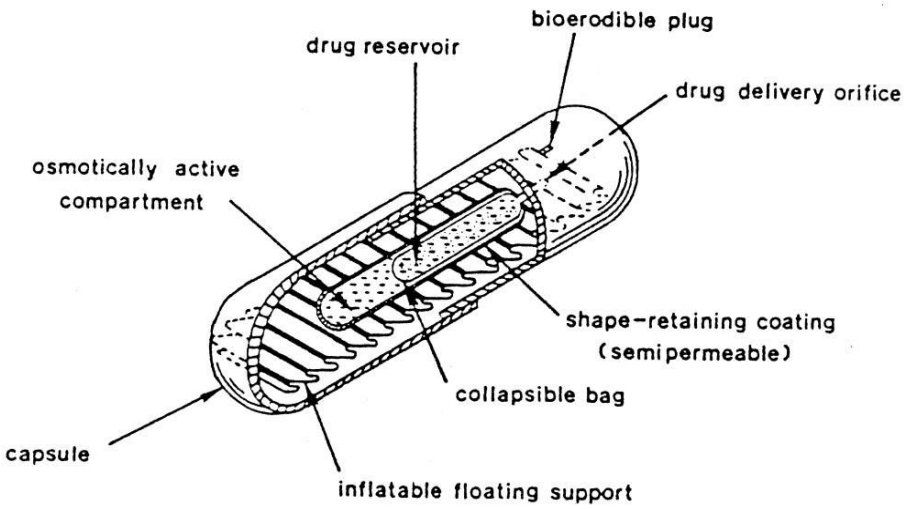


3. Intragastric Osmotically Controlled Drug Delivery System:

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

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

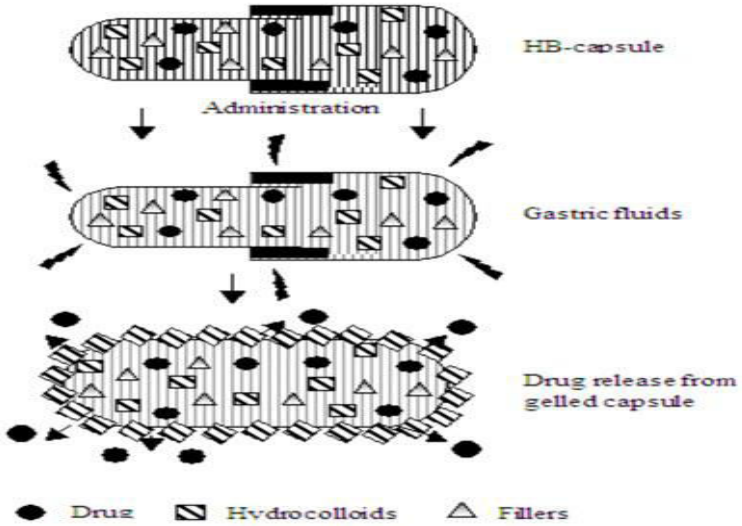
Fig: 9 Intragastric osmotic controlled drug delivery system



B. Non Effervescent Systems

The non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethaacrylates, polystyrenes etc. and bioadhesive polymer such as chitosan and carbopol

Fig: 10 Principle of hydrodynamically balanced system.



The various types of systems are:

- **Single Layer Floating Tablets:**

They are formed by intimate mixing of drug with a gel forming hydrocolloid, which swells in 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.

- **Alginate Beads:**

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5mm diameter can be prepared by dropping sodium alginate into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hr. These floating beads gave a prolonged residence time of more than 5.5 hr

- **Hollow Microspheres:**

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microballons were floatable in vitro for 12 hours when immersed in aqueous media. Radio graphical studies proved that microballons orally administered to humans were dispersed in the upper part of the stomach and retained there for 3 hours against peristaltic movements.

Drug Candidates Suitable for FDDS

- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin)[8]
- Drugs those are locally active in the stomach (e.g. misroprostol, antacids).
- Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole).
- Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin).
- Drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil).

Table NO.1: - List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems

DosageForm	Drugs
Tablets	Cholrpheniraminemaleate,Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCI Isosorbide di nitrate, Isosorbide mononitrate, Acetaminophen, Ampicillin, Cinnarazine, Dilitiazem Florouracil, Prednisolone
Capsules	Nicardipine, Chlordiazepoxide HCI, Furosemide,Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid.
Microspheres	Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Iboprufen, Terfenadine
Granules	Indomethacin, Diclofenac sodium, Prednisolone
Films	Cinnarizine

1.6 Advantages and Disadvantages of FDDS

Advantages of FDDS:

- Drugs that act locally in the stomach e.g. antacids, antibiotics for microbial based ulcer, etc.
- Drugs that are absorbed primarily in the stomach e.g. Albuterol
- Drugs those are poorly soluble in alkaline pH.
- Drugs that have narrow absorption window for absorption of the drugs which are absorbed from the proximal part of the small intestine. E.g. riboflavin, Levodopa, PABA.

- Drugs that degrade in colon e.g. Captopril, Metoprolol. The Floating systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
- The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
- It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

Disadvantages of FDDS:

- High variability in gastric emptying time due to variations in emptying process.
- Drugs that cause irritation and leisions to gastric mucosa and unstable in gastric fluid cannot be formulated as FDDS
- Drugs with unpredictable bioavailability, minimum effective concentration are achieved slowly.
- Gastric retention is achieved by many factors such as gastric motility, pH, and presence of food. These factors are never constant hence the buoyancy cannot be predicted.
- Floating system is not feasible for thosedrugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

Table No.2: MARKETED PRODUCT OF FDDS:

Sr. No.	Brand Name	Delivery system	Drug (dose)	Company, Country
1	Madopar	Floating, CR capsule	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA
2	Valrelease	Floating capsule	Diazepam (15 mg)	Hoffmann-LaRoche, USA
3	Liquid Gaviscon	Effervescent floating liquid alginate preparation	Al hydroxide (95mg), Mg carbonate (358 mg)	Glaxo Smith-Kline, India
4	Topalkan	Floating liquid alginate preparation	Al-Mg antacid	Pierre Fabre Drug, France
5	Almagate Flot Coat	Floating dosage form	Al-Mg antacid	----------
6	Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
7	Cifran OD	Gas-generating floating form	Ciprvenlafaxine hcl (1g)	Ranbaxy, India
8	Cytotec	Bilayer floating Capsule	Misoprostol (100mcg/200mcg	Pharmacia, USA

2. LITERATURE REVIEW

- **Anil G *et al.,* (2016),** prepared a controlled release tablet of Venlafaxine HCl, which releases the drug in a sustained manner over a period of 12 hrs. Three different viscosity grades of HPMC namely K4M, K15M, K100M were used for the tablets. The tablets were prepared by direct compression method and then evaluated. A combination of HPMC k100M was found to achieve optimum *in-vitro* buoyancy.[1]

- **Senthil A *et al*., (2011),** formulated the mucoadhesive microspheres of Venlafaxine HCl by single emulsification phase separation technique using different volumes of glutaraldehyde as crosslinking agent. The optimized formulation was selected based on the percentage of mucoadhesion and sphericity of microspheres.the optimized formulation exhibited a high drug entrapment efficiency of 70% and a swelling index 1.57%.Mucoadhesion after 1 hr was 91% and the drug release was also sustained for more than 12hrs. As the concentration of the glutaraldehyde increased, the mucoadhesiveness decreases and there was no significant effect in time.[17]
- **Pare. A *et al.,* (2011),** developed amlodipine besylate effervescent floating tablets by using hydrophilic polymers HPMC and cabopol934 along with effervescent agents like sodium bicarbonate and citric acid. It was found that carbopol has a negative effect on floating behavior but it was found that carbopol has a negative effect on floating behavior but it was used only for the drug release retardant charecteristics.[1]
- **Sreekanth S.K. *et al.,* (2015),** prepared floating matrix tablets using HPMC K100M as a polymer and sodium bicarbonate as gas generating agent. The compressed were then evaluated and there was no interaction between drug polymer and excepients, it was found out by IR studies. The *in-vitro* drug release study indicate that the release of the drug depends on the proportion of the polymer present in formulation .As the polymer ratio increases the release rate of the drug is prolonged.[19]

- **Subash C *et al.,* (2011),** designed a controlled release floating tablet of Diltiazem HCl using Xanthan gum as a polymer. It was noted that the drug

release from the prepared tablets was found to vary with varying concentration of the polymer. From the study it was concluded that floating tablets can be prepared by using Xanthan gum as a carrier.[20]

- **Bagherwal A *et al.,* (2013),** have formulated the floating tablets of Ciprofloxacin HCl with HPMC and carbomer in different proportions (4%, 8%,9 %) by direct compression technique. The formulations were then evaluated and the mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics. The results revealed the drug polymer ratio showed greater drug release than other formulations.[21]
- **Raja *et al*., (2011),** prepared a gastro retentive floating tablets of Glipizide by using two different polymers HPMC K4M and HPMC K15M at different concentration. It was found that as the concentration of polymer increased, floating lag time decreased. Use of high viscosity polymer can also decreases the floating lag time and viscosity of the polymer should directly proportional relationship with swelling characteristics of tablets.[22]
- **Garg, R *et al.,*(2008),** scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times.
- **Kotwal K *et al.,* (2012),** prepared intragastric buoyant tablets of Amoxicillin trihydrate by using different grades of HPMC polymer as gelling agent. It was found that hardness of the tablet will affect the buoyancy characteristics of the dosage form. The in-vitro release study was concluded that amoxicillin releases from the tablet followed peppa's model with non-fickian diffusion.[23]
- **Patel VM *et al.,* (2009),** were prepared gastroretentive tablets of Verapamil HCl by using different hydrocolloid polymer including carbopol (CP 934; CP 940), hydroxypropaxymethylcellulose (HPMC K4M; HPMC K15M; HPMC E15) and xanthangum by direct compression technology. The selected tablets containing xanthan gum released approximately 97.89% drug in 24 hours *in-vitro* dissolution study, while buoyancy lag time was 24.6 seconds and the tablet remained buoyant for more than 24 hours. [24]
- **Jaimini M *et al.,* (2007),** were formulated Famotidine floating tablets by using different grades of methocel (K100, K15M), PVP K-30, gas generating agent sodium bicarbonate and citric acid. The floating tablets were evaluated for

physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The effect of citric acid on drug release profile and floating properties was investigated. The tablets with methocel K100 were found to be float for longer duration as compared with formulation containing methocel K15.[25]

- **Prabhu P *et al.,* (2008),** were prepared a gastro retentive floating controlled drug delivery system containing Glipizide in the form of tablet. Ten formulations containing retardant materials such as HPMC4K and eudragit RS100, alkalizing agent sodium bicarbonate and other release promoters such as sodium lauryl sulphate and polyvinyl pyrrolidone were used. Tablets remained buoyant over 8 hours in the release medium, and the amount of sodium bicarbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet. Further the selected best formulations were compared with the marketed sustained release product and found to be comparable release of the drug. All the formulations exhibited diffusion dominated drug release.[26]
- **Deshmukh VN *et al.,* (2009),** were prepared theophylline anhydrous bioadhesive tablets by using different natural polymers such as xanthan gum, locust bean gum, guar gum, karaya gum and their combinations were used to formulate matrix tablets. The bioadhesive strength of the tablets were measured as the force of detachment against the porcine gastric mucosa. The combination of karaya gum: guar gum (6:4) Tablet showed greater biodhesive strength as compared with single gum and other gum combination tablets. Karaya gum: guar gum loaded tablets were not discharged from the mucous membrane and were dissolved in gastric fluid. An increase in the gum concentration increases the drug profile beyond 12 hours whereas there is no significant effect of gum concentration on bioadhesive strength of the tablet.[27]
- **Rahman *et al.,* (2006),** designed the bilayer floating tablets of captopril using HPMC-K15 M, K4M, PVP-K30 and Carbopol 934p alone or in combination with the drug in release layer and HPMC K grade, effervescent mixture of citric acid and sodium bi carbonate in the floating layer. It was found that 95 % of drug released in 24 hrs, tablet remained floatable throughout all studies and release followed the Higuchi model. In vivo X-ray studies indicated that

placebo formulation containing barium sulphate in the release layer significantly increased the gastric residence time.[28]

- **Gambhire *et al*., (2007),** Studied on Oral floating matrix tablets of Diltizem Hydrochloride by using Methocel K-100M CR, Compritol 888 ATO, Sodium bicarbonate, succinic acid and concluded that the effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using gel-forming polymer methocel K 100 CR and gas generating agent sodium bicarbonate. A high level of both Methocel K-100M CR and compritol 888 ATO favors the preparation of the floating controlled release of DTZ tablets.[2]
- **Arza RAK *et al.,* (2009),** were prepared Swellable and floating gastroretentive ciprofloxacin hydrochloride tablet by using a combination of hydrophilic polymer (hydroxypropylmethylcellulose), swelling agent (crosspovidone, sodium starch glycolate, and croscarmelose sodium) and effervescent substance (sodium bicarbonate). A combination of HPMC K100, crosspovidone, and sodium carbonate shows the good swelling, drug release, and floating character than the marketed product of ciprofloxacin hydrochloride CIFRAN OD.[30]
- **Prajapati ST *et al.,* (2009),** were prepared Floating matrix tablets of domeperidone were prepared by wet granulation technique, using polymer such as HPMC K4M, carbopol 934P and sodium alginate either alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics and *in vitro* release characteristics for 24 hours. Floating matrix tablet based on combination of three polymers exhibited desired floating and prolonged drug release for 24 hours. Carbopols loading showed negative effect on floating properties but were found helpful to control the release rate of drug.[31]
- **Sungthongjeen S *et al.,* (2008),** were designed Floating multi-layer coated tablets of theophylline based on gas formation. The system consists of a drug containing core tablet coated with a protective layer (hydroxypropylmethylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. The properties of acrylic polymers (eudragit RL 30D, RS 30D, NE 30D) and ethyl cellulose were characterized by the puncture test in order to screen a suitable film for the system. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its

high flexibility and high water permeability. The obtained tablets enabled to float due to the CO_2-gas formation and the gas entrapment by polymeric membrane.[32]

- **Singh S *et al.,* (2007),** were developed floating matrix tablets of metoclopramide hydrochloride using the polymers such as guar gum, karaya gum, HPMC E15 alone and in combination with HPMC K15M (HK) and gas generating agents such as calcium carbonate and citric acid. Tablets with gas generating agent and with HK floated for 24 hours without complete erosion and showed slower drug release. This indicates that the gas forming agent contributes towards the initial floating of tablets and faster drug release and HK for maintaining the integrity of the floating matrix tablet and sustaining the drug release.[33]
- **Vinay pandit *et al.,* (2010),** designed gastro retentive form of amoxicillin trihydrate floating tablets. The formulations were prepared as matrix tablets in the form of non effervescent tablets by using various grades of HPMC. The granules were prepared by wet granulation technique and tablets were evaluated. The optimized formulation of amoxicillin was found to have increased gastric residence prolonging the release of drug with 85% of drug release in 6 hrs by diffusion. The mechanism of drug release was found to be diffusion and followed combination of zero order and first order kinetics.[34]

- **Mokhopadhayats *et al.,* (2014),** formulated floating bioadhesevie tablets of ciprofloxacin Hcl by direct compression technique. Tablets were prepared by using polymers like HPMC, SCMC, carbopol in different ratios. The effervescent base was prepared by using 1: 1 ratio of sodium bycarbonate and citric acid. It was observed that tablets with 5% effervescent base shows greater control in drug release in comparison to that of 10%.[35]
- **Atul kumar sahu *et al.,* (2011),** prepared buoyant controlled release tablet of furosemide containing chitosan and HPMC as a polymer and evaluated. The effect of chitosan and HPMC concentration on drug release kinetics and buoyancy was also determined. The in vitro drug release of furosemide in all the formulations was best explained by zero order equation and followed mechanism of non-fickian diffusion. By combining HPMC with chitosan in

various blends, the formulation found to be more suitable for oral controlled release of furosemide.[36]

- **Srinivas reddy *et al.*, (2010),** developed floating matrix tablets of captopril by using natural gumd like xanthine gum, karaya gum, gellan gum along with HPMC K4M, PVP K30. The tablets were prepared by direct compression using sodium bicarbonate as gas generating agent and evaluated. The linear regression analysis and model fitting showed that all this formulation followed Higuchi model.[37]

3. AIM AND OBJECTIVE OF STUDY

- The aim of this present work is to formulate a gastro retentive floating tablet of Venlafaxine HCl by direct compression method using various polymers such as Carbopol 934, Xanthan gum, and HPMC K-100M.
- Venlafaxine HCl exhibits pH dependent solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt will be made to develop gastroretentive delivery system of Venlafaxine HCl which would increase the bioavailability of Venlafaxine HCl and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

Objectives of present work:

- Formulation and evaluation of sustained release tablet.
- To study the effect of mixture of drug, hydrophilic and hydrophobic cellulose polymers on release rate of sustained release tablet.
- To reduce the frequency of administration and to improve patient compliance by once daily sustained release formulation.
- To determine the chemical compatibility of formulation containing various ratio of polymer and drug.

4. PLAN OF WORK

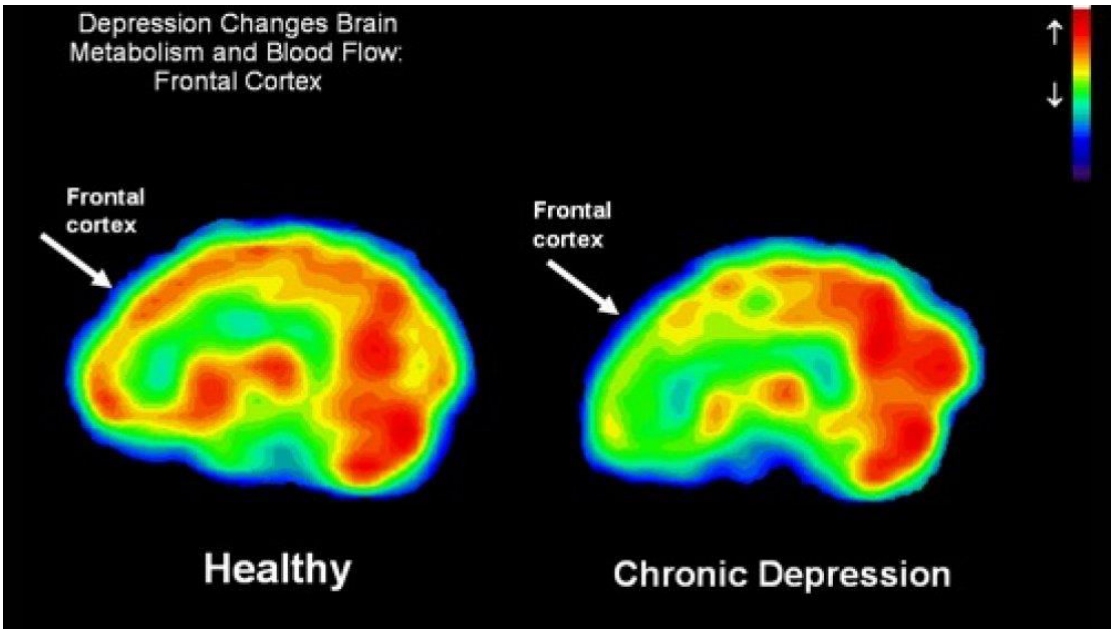
To achieve the objectives of the work, the following work was planned an undertaken:

1. Literature survey
2. Selection of excipients
3. Formulation of tablets with different polymers
4. Optimization of the selected formula
5. Comparison of in-vitro dissolution profile with that of a marketed formulation.
6. Completion of data and analysis of results.
7. Pre- formulation studies for possible drug or polymer interaction by IR analysis.
8. Preparation of floating tablets by direct compression method.
9. Evaluation of the various properties of floating tablets.
    - Evaluation of precompression parameters such as bulk density, tapped density, compressibility index etc.
    - Evaluation of post compression parameters like thickness, hardness, friability, drug content, *In vitro* buoyancy studies.
10. Drug release study using suitable *in-vitro* model.
11. Carry out short term stability studies on the most satisfactory formulation

5. DISEASE PROFILE

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Also called major depressive disorder or clinical depression, it affects how the person feel, think and behave and can lead to a variety of emotional and physical problems.

Figure No-11 – BRAIN METABOLISM IN BRAIN.



Sometimes physical problems can cause depression. But other times, symptoms of depression are part of a more complex psychiatric problem. There are several different types or subtypes of depression, including:

Major depressive disorder

Dysthymia and chronic depression (now called persistent depressive disorder)

Seasonal affective disorder

Psychotic depression

Bipolar depression

5.1. MAJOR DEPRESSION[56]

An individual with major depression, or major depressive disorder, feels a profound and constant sense of hopelessness and despair.

Major depression is marked by a combination of symptoms that interfere with the person's ability to work, study, sleep, eat, and enjoy once pleasurable activities. Major depression may occur only once but more commonly occurs several times in a lifetime.

5.2. WHAT ARE THE SYMPTOMS OF MAJOR DEPRESSION[57]?

Symptoms of depression include:

A. Sadness
B. Irritability
C. Loss of interest in activities once enjoyed
D. Withdrawal from social activities
E. Inability to concentrate
F. Disrupted sleep
G. Fatigue or loss of energy
H. Appetite changes
I. Thoughts of suicide

5.3. CAUSES[56,57,58]

It's not known exactly what causes depression. As with many mental disorders, a variety of factors may be involved, such as:

- **Biological differences.** People with depression appear to have physical changes in their brains. The significance of these changes is still uncertain, but may eventually help pinpoint causes.
- **Brain chemistry.** Neurotransmitters are naturally occurring brain chemicals that likely play a role in depression. Recent research indicates that changes in the function and effect of these neurotransmitters and how they interact with neurocircuits involved in maintaining mood stability may play a significant role in depression and its treatment.
- **Hormones.** Changes in the body's balance of hormones may be involved in causing or triggering depression. Hormone changes can result with pregnancy and during the weeks or months after delivery (postpartum) and from thyroid problems, menopause or a number of other conditions.
- **Inherited traits.** Depression is more common in people whose blood relatives also have this condition. Researchers are trying to find genes that may be involved in causing depression.

5.4. DYSTHYMIA[58]

- Dysthymia, sometimes referred to as a form of chronic depression, is a less severe form of depression but the depression symptoms linger for a long period of time, typically years. Those who suffer from dysthymia are usually able to function normally, but seem consistently unhappy.

- It is common for a person with dysthymia to also develop superimposed periods of depression, which then lessen without fully going away. This is called "double depression."

5.5. TYPES OF DEPRESSION[58]

Symptoms caused by major depression can vary from person to person. To clarify the type of depression you have, your doctor may add one or more specifiers. A specifier means that you have depression with specific features, such as:

- **Anxious distress —** depression with unusual restlessness or worry about possible events or loss of control
- **Mixed features —** simultaneous depression and mania, which includes elevated self-esteem, talking too much and increased energy
- **Melancholic features —** severe depression with lack of response to something that used to bring pleasure and associated with early morning awakening, worsened mood in the morning, major changes in appetite, and feelings of guilt, agitation or sluggishness
- **Atypical features —** depression that includes the ability to be cheered by happy events, increased appetite, excessive need for sleep, sensitivity to rejection, and a heavy feeling in arms or legs
- **Psychotic features —** depression accompanied by delusions or hallucinations, which may involve personal inadequacy or other negative themes
- **Catatonia —** depression that includes motor activity that involves either uncontrollable and purposeless movement or fixed and inflexible posture
- **Peripartum onset —** depression that occurs during pregnancy or in the weeks or months after delivery (postpartum)
- **Seasonal pattern —** depression related to changes in seasons and reduced exposure to sunlight

5.6. OTHER DISORDERS THAT CAUSE DEPRESSION SYMPTOMS[57,58]

Several other disorders, such as those below, include depression as a symptom. It's important to get an accurate diagnosis, so you can get appropriate treatment.

- **Bipolar I and II disorders.** These mood disorders include mood swings that range from highs to lows. It's sometimes difficult to distinguish between bipolar disorder and depression.
- **Cyclothymic disorder.** Cyclothymic (sy-kloe-THIE-mik) disorder involves highs and lows that are milder than those of bipolar disorder.
- **Disruptive mood dysregulation disorder.** This mood disorder in children includes chronic and severe irritability and anger with frequent extreme temper outbursts. This disorder typically develops into depressive disorder or anxiety disorder during the teen years or adulthood.
- **Persistent depressive disorder.** Sometimes called dysthymia (dis-THIE-me-uh), this is a less severe but more chronic form of depression. While it's usually not disabling, persistent depressive disorder can prevent you from functioning normally in your daily routine and from living life to its fullest.
- **Premenstrual dysphoric disorder.** This involves depression symptoms associated with hormone changes that begin a week before and improve within a few days after the onset of your period, and are minimal or gone after completion of your period.
- **Other depression disorders.** This includes depression that's caused by the use of recreational drugs, some prescribed medications or another medical condition.

5.7. TREATMENTS AND DRUGS[59]

Medications and psychological counseling (psychotherapy) are very effective for most people with depression. Your primary care doctor or psychiatrist can prescribe medications to relieve symptoms. However, many people with depression also benefit from seeing a psychologist or other mental health professional.

5.8. CLASSES OF ANTI-DEPRESSANT DRUGS[59]:

Table No: 3 CLASSES OF ANTI-DEPRESSANT DRUGS

S.No	Antidepressant type	Examples
1.	**SSRIs (selective serotonin reuptake inhibitors)**	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline
2.	**SNRIs (serotonin and norepinephrine reuptake inhibitors)**	Duloxetine **Venlafaxine** Desvenlafaxine
3.	**Noradrenaline reuptake inhibitor**	Reboxetine
4.	**TCAs (tricyclic antidepressants)**	Amitriptyline Nortriptyline Clomipramine Dothiepin Doxepin Imipramine Trimipramine
5.	**RIMA (reversible inhibitor of monoamine oxidase)**	Moclobemide
6.	**Tetracyclic antidepressant**	Mianserin
7.	**Tetracyclic analogue of mianserin (sometimes called noradrenergic and specific serotonergic antidepressant [NaSSA])**	Mirtazapine
8.	**MAOIs (monoamine oxidase inhibitors)**	Phenelzine Tranylcypromine
9.	**Melatonergic antidepressant**	Agomelatine

5.9. SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)[59]:

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are potent inhibitors of the reuptake of serotonin and norepinephrine. These neurotransmitters are known to

play an important role in mood. SNRIs can be contrasted with the more widely used selective serotonin reuptake inhibitors (SSRIs), which act mostly upon serotonin alone.

The human serotonin transporter (SERT) and norepinephrine transporter (NET) are membrane proteins that are responsible for the reuptake of serotonin and norepinephrine. Balanced dual inhibition of monoamine reuptake can possibly offer advantages over other antidepressants drugs by treating a wider range of symptoms.

SNRIs are sometimes also used to treat anxiety disorders, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), chronic neuropathic pain, and fibromyalgia syndrome (FMS), and for the relief of menopausal symptoms.

5.9.1. HOW DO SNRIS WORK?

Serotonin and noradrenaline are neurotransmitters — chemicals that relay signals between the cells in your brain. SNRIs increase the amount of these two neurotransmitters in your brain, and this is how they are thought to improve the symptoms of depression.

5.9.2. Mechanism of action[58]:

SNRIs are potent inhibitors of the reuptake of serotonin and norepinephrine. These neurotransmitters are known to play an important role in mood. SNRIs can be contrasted with the more widely used selective serotonin reuptake inhibitors (SSRIs), which act upon serotonin alone.

The human serotonin transporter (SERT) and norepinephrine transporter (NET) are membrane proteins that are responsible for the reuptake of serotonin and norepinephrine. Balanced dual inhibition of monoamine reuptake can possibly offer advantages over other antidepressant drugs by treating a wider range of symptoms.[1] SNRIs, along withselective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs), are second-generation antidepressants. Over the past two decades, second-generation antidepressants have gradually replaced first-generation antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) as the drugs of choice for the treatment of MDD. This is mainly because of their improved tolerability and safety profile.

6. DRUG PROFILE

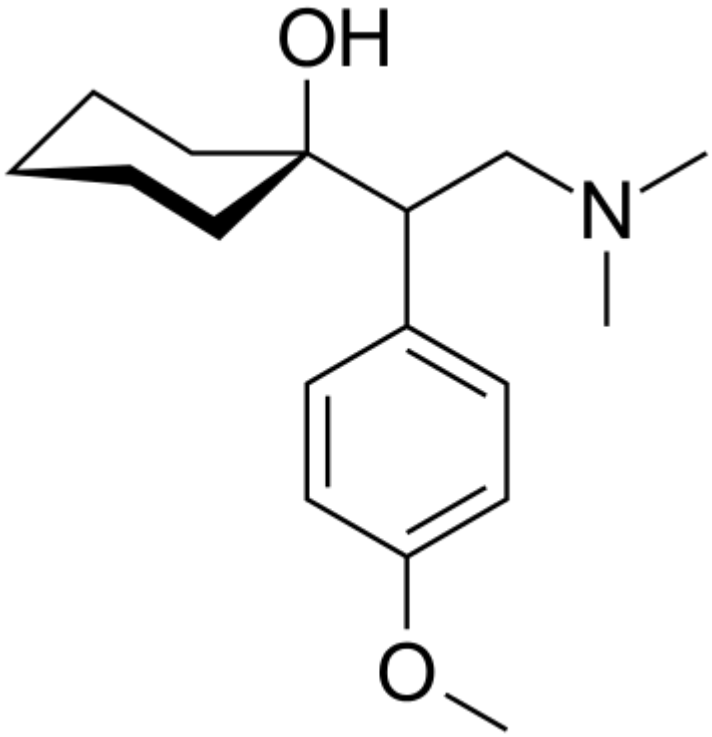
3.1 DRUG DATA- VENLAFAXINE HCL: [14, 15]

Venlafaxine HCl is a serotonin and norepinephrine reuptake inhibitors

Molecular formula: $CH_{27}NO_2$ HCl

Molecular weight: 313.87

Structure:



Chemical name: (*RS*)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol

Category: Anti-depressant

3.1.1Physico-chemical properties:

Description: white crystalline powder

Standards: venlafaxine HCl contains not less than 98.5 per cent and not more than of 101.5 per cent , calculated on the dried basis.

Solubility: venlafaxine HCl is considered to be soluble in aqueous solutions with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions with pH 7.

Melting point: Venlafaxine HCl melts at 207-209^{0}C

Bioavailability: 30%

Metabolism: Hepatic

Half life: 4hours

Execration: Renal

Mechanism of action:

The mechanism of the antidepressant action of Venlafaxine HCl in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that Venlafaxine HCl and its active metabolite, O-desmethyl venlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine HCl and ODV have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine HCl and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Dosage and Administration:

Extended release:

Daily dose: 75-150 mg orally

Maximum dose (moderately depressed outpatients): 225 mg/day

Maximum dose (severely depressed inpatients): 375 mg/day

Adverse effects:

Suicidal thinking (suicidality), sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision.

Contraindications:

Venlafaxine HCl hydrochloride tablets must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of

vital signs, and mental status changes that include extreme agitation progressing to delirium and coma.

7. EXCIPIENT PROFILE

POLYMER PROFILE: [15]

7.1. CARBOPOL934

1. Nonproprietary Names:

BP: Carbomer

USPNF: Carbomer

JP: carboxyvinyl polymer

2. Synonyms:

Carboxypolymethylene , polyacrylic acid.

3. Functional Category:

Controlled release agent, stabilizing agent, viscosity enhancing agent, binding agent.

4. Applications in pharmaceutical formulation or technology:

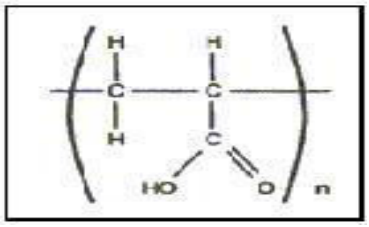
They are used in wide range of pharmaceutical applications which provide:

- Controlled release in tablets
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

5. Description:

It occurs as odorless, tasteless, fluffy white powder.

6. Structural Formula:



7. Solubility:

The Carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion.

Carbopol polymers are bearing very good water sorption property. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0 to 6.0.

8. Viscosity (dynamic):

Different grades of Carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (Mc), distributions of the Mc, and the fraction of the total units, which occur as terminal, i.e. free chain ends. The viscosity range of different Carbopol polymers are as follows

S.No	polymer	viscosity
1	Carbopol 934 NF	30500 – 39400
2	Carbopol 934 p NF	29400 – 39400
3	Carbopol 71G NF	4000 – 11000

7.2 XANTHAN GUM

1. Nonproprietary Names:

BP: Xanthan gum

USPNF: Xanthani gum

2. Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural

3. Chemical Name:

Xanthan gum

4. Functional Category:

Stabilizing agent; Suspending agent; Viscosity-increasing agent.

5. Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent.

6. Description:

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

7. Typical properties:

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.

Melting point : Chars at 270˚C.

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

8. Safety: It is safe when up to 15grams per day are taken. It can cause some side effects such as intestinal gas.

7.3. HYDROXYPROPYL METHYLCELLULOSE

1. Nonproprietary Name:

BP: Hypromellose

USP: Hypromellose

2. Synonyms:

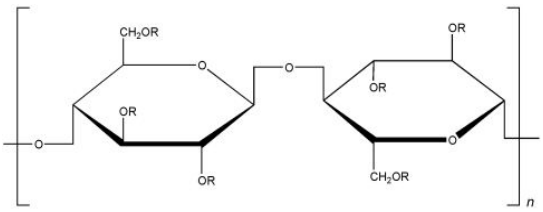
Hydroxy Propyl Methyl Cellulose, HPMC, Hypromellosum, Methocel, Methyl Cellulose Propylene Glycol Ether, Methyl Hydroxy Propyl Cellulose, Metolose, MHPC.

3. Chemical Name: Cellulose Hydroxy Propyl Methyl Ether

4. Empirical Formula and Molecular Weight:

The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. Molecular weight is approximately 10 000–1 500 000.

5. Structural Formula:



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

Fig: 11 Structure of HPMC

6. Applications in Pharmaceutical Formulation or Technology:

HPMC is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

7. Description:

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

8. Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane.

9. Viscosity (dynamic):

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared.

Typical viscosity values for 2% (w/v) aqueous solutions of methocel (Dow Chemical Co.) viscosities measured at 20ºC

Methocel grade	Viscosity(cps)
K4 M	4000
K15M	15000
K100M	100000

10. Stability and Storage Conditions:

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

11. Safety:

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.

7.4. SODIUM BICARBONATE

1. Nonproprietary Names:

BP: Sodium Bicarbonate

PhEur: Sodium Hydrogen Carbonate

USP: Sodium Bicarbonate

2. Synonyms:

Baking soda, E500, Effer-Soda, Sodium acid carbonate, Sodium hydrogen carbonate.

3. Chemical Name: Carbonic acid monosodium salt

4. Empirical Formula and Molecular Weight: $NaHCO_3$ and 84.01

5. Applications in Pharmaceutical Formulation or Technology:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis.

6. Descriptions:

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste.

7. Stability and Storage Conditions:

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

8. Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.

9. Safety:

When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material. Administration of excessive amounts of sodium bicarbonate may thus disturb the body's electrolyte balance, leading to metabolic alkalosis or possibly sodium overload with potentially serious consequences.

7.5. MICROCRYSTALINE CELLULOSE

1. Nonproprietary Names:

BP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

2. Synonyms: Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose, Vivacel.

3. Functional Category: Tablet and Capsule diluent, suspending agent, adsorbent, tablet disintegrant.

4. Applications: As a diluent in tablets (direct compression and direct compression) and capsule formulation. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

5. Description: White-colored, odourless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

6. Solubility: Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organic solvents.

7. Stability: It is a stable, though hygroscopic material.

8. Storage conditions: The bulk material should be stored in a well-closed container in a cool and dry place.

9. Incompatibilities: Incompatible with strong oxidizing agents.

10. Safety: It is generally regarded as a nontoxic and nonirritant material.

7.6. MAGNESIUM STEARATE:

1. Non-proprietary names:

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

2. Synonyms: Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

3. Chemical name: Octadecanoic acid magnesium salt

4. Structural formula: $[CH_3 (CH_2)_{16}COO]_2 Mg$

5. Molecular weight: 591.34

6. Functional category: Tablet and capsule lubricant.

7. Melting point: 117-150 ^0C

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

9. Solubility: It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

10. Applications: It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

11. Stability and storage conditions: It should be stored in a well closed container in a cool, dry place.

7.7. TALC

1. Non-proprietary names:

BP: Purified talc

PhEur: Talcum

USP: Talc

2. Synonyms: Altalc, powdered talc, purified French chalk, Purtalc, soapstone, steatite and Superiore.

3. Chemical name: Talc

4. Structural formula: $Mg_6 (Si_2O_5)_4(OH)_4$

5. Functional Category: Anticaking agent, glidant and lubricant.

6. Description:

It is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

7. Solubility:

It is practically insoluble in dilute acids and alkalis, organic solvents and water.

8. Applications:

It was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as dissolution retardant in the development of controlled release products. In topical preparations, it is used as a dusting powder, although it should not be used to dust surgical gloves. It is a natural material it may frequently contain micro-organisms and should be sterilized when used as a dusting powder. It is additionally used to clarify liquids and is also used mainly for its lubricant properties, in cosmetics and food products.

9. Stability and storage conditions:

It is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well closed container in a cool and dry place.

10. Incompatibilities:

It is incompatible with quaternary ammonium compounds

8. MATERIALS & INSTRUMENTS USED

8.1 MATERIALS USED:

Table 4: List of chemicals used with their grade and supplier

S. No.	INGREDIENTS AND REAGENTS	MANUFACTURER / SUPPLIERS
1	Venlafaxine HCl	Aurabindo pharma
2	Carbopol 934p	Himedia laboratories
3	Xanthan gum	Himedia laboratories
4	HPMC K100M	Aurabindo pharma
5	Sodium bicarbonate	Nice laboratories
6	MCC	S.D fine chemicals
7	Magnesium Stearate	S.D fine chemicals
8	Talc	Nice laboratories

8.2 INSTRUMENTS USED:

Table 5: Details of Equipments Used

Sr. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimadzu Corporation, AW220 &BX6205
2.	Tablet hardness tester	Pfizer hardness tester
3.	Friability tester	Roche Fribilator
4.	Vernier Caliper	Mitutoyo digimatic caliper
5.	Dissolution apparatus USP	Electrolab tablet dissolution apparatus
6.	Double beam UV Spectrophotometer	Lab India UV 3000
7.	Rotary tablet punching machine	Proton Multipress
8.	pH meter	Systonic 335

9. PREFORMULATION STUDIES

Preformulation studies are carried out in order to evaluate the physical and chemical properties of the drug alone and in the combined form with the excipients.

These studies are important to predict the physical and chemical properties and stability of the drug and excipients.

9.1. ORGANOLEPTIC PROPERTIES:

1. Colour:

Take a small quantity of sample and spread it on the white paper and examine it visually.

9.2. PHYSICAL PROPERTIES:

1. Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a file of the powder and the horizontal plan.

$$Ø = \text{Tan}^{-1} h/r$$

Where, h = height of file

R = radius of the base of the pile

Ø = angle of repose

Flow properties and corresponding Angle of Repose

Table No: 6. Flow properties and corresponding Angle of Repose

Flow property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	> 66

The ideal characteristics of a tablet that make it a popular and acceptable dosage form are compactness, physical stability, rapid production capability, chemical stability and efficacy. In general above characteristics of tablet are dictated by the

quality of the granulation from which it is made. Many formulation and process variables involved in the granulation step can affect the characteristics of the granulation produced. Therefore various methods to measure certain granulation characteristics have been developed to monitor granulation suitability for tablet formulation. The main characteristics required to be monitored in granulation are flow properties and compressibility.

2. Determinations of bulk density and tapped density:

An accurately weighed quantity of the powder (w) was carefully poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus) the density apparatus was set for 500 taps and after that, the volume (v_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk Density} = W/V_0$$

$$\text{Tapped Density} = W/V_f$$

Where, V_0= Initial volume,

V_f = final volume

3. Compressibility index

The compressibility Index and Hausner ratio are measures of the property of a powder to be compressed. As such, they measure the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner ratio.

The compressibility index and hausner ratio are calculated by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:

$$\text{Compressibility index} = P_{tapped} - P_{bulk}/P_{tapped} X\ 100$$

$$\text{Hausner ratio} = P_{tapped} / P_{bulk}$$

Scale of flowability

Table No: 7. Scale of flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.10-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

4. Melting point:

It is the characteristic to test the purity of the sample.

Procedure:

Take a small quantity of sample into the fusion tube. Place the tube in the mating point apparatus containing castor oil. Increase the temperature of castor oil gradually and note the temperature starts to melt and when all the powder completely melts.

9.3. Solubility:

Take a small quantity of sample and add the solvent until the sample completely dissolves. It is examined visually for the presence of any un dissolved particles.

9.4.Drug-excipient compatibility studies:

Drug-excipient compatibility studies are important to know the interaction between drug and excipients and in between excipients of the formulation, which could later affect the stability of the formulation and may interfere with the pharmacological action of the drug.

The physical examination of the formulation is done when alone and in combination with the excipients. If there is any change in the physical appearance, shows that there is interaction.

But some substances do not show any physical changes when combined in a formulation, for such FT-IR (Fourier transform-infrared) studies are conducted.

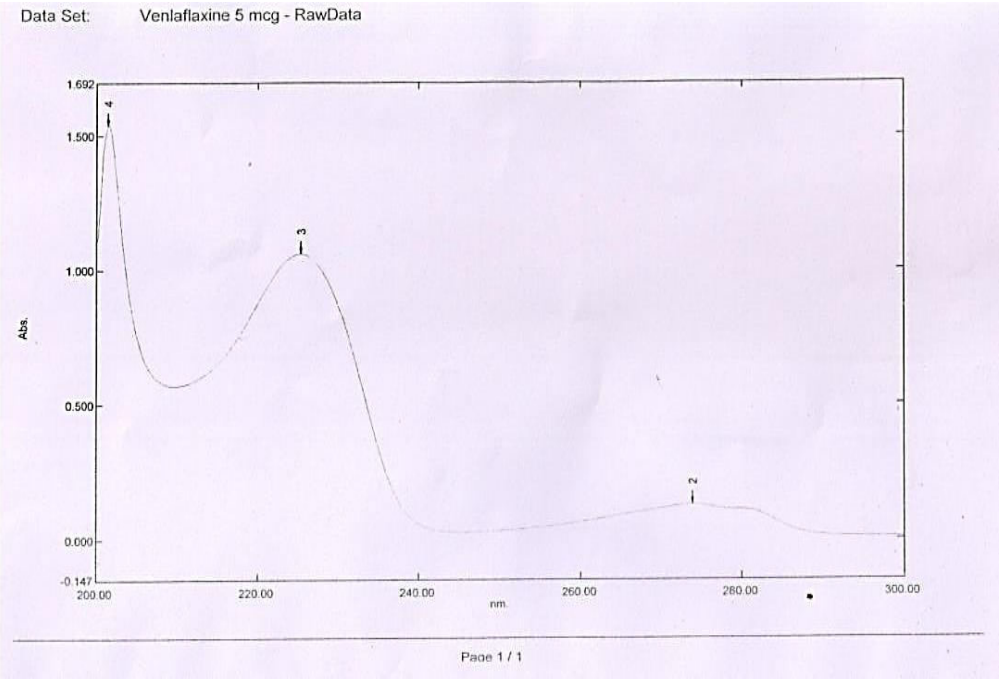
Procedure by FT-IR studies:

The FT-IR studies are conducted for Venlafaxine HCL and mixture of Venlafaxine HCL and excipients by preparing dispersion in potassium bromide discs. The peaks are obtained and compared with the standards by superimposing these spectra and observed for any difference in shape and size of spectrum. If there is any significant change represents interaction between drug and excipients.

9.5.PREPARATION OF STANDARD CURVE

DETERMINATION OF λmax OF Venlafaxine Hcl IN ACID BUFFER (pH 1.2)

Fig12: Spectrum of Venlafaxine HCl



Venlafaxine HCl drug solution in pH 1.2(0.1N HCl) was scanned using UV-Spectrophotometer between the range 210-400nm using pH 1.2 as blank and the maximum absorbance (λ max) was found at **224nm.**

Preparation of 0.1 M Hydrochloric acid:

Accurately measure 8.5 ml of hydrochloric acid and sufficient water to make upto 1000 ml.

Preparation of stock solution:

Accurately weigh 100 mg of Venlafaxine HCL and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl.

Preparation of standard solution:

Pipette out 10 ml of the above solution and transfer it to a 100 ml volumetric flask. Then make up the volume to 100 ml with 0.1 M Hcl. Then from the standard stock solution withdraw 2ml, 4ml, 6ml, 8ml, and 10ml into five 100 ml different volumetric flasks. Then make up the volume to 100 ml with 0.1M Hcl to get 2, 4, 6, 8, 10 µg/ml concentration.

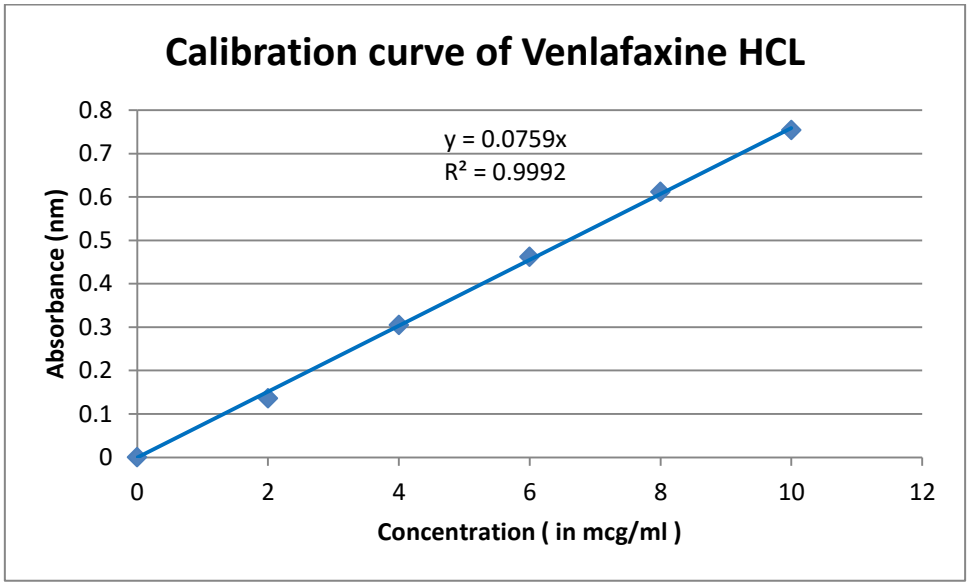
CALIBRATION CURVE OF VENLAFAXINE HCL:

The absorbance of the prepared stock solutions was measured at 224 nm in an UV spectrophotometer. Plot a graph between concentration (in µg/ml) vs absorbance (in nm) on X-axis and Y-axis respectively.

Table no. 8. Calibration curve of Venlafaxine HCL

S.no.	Concentration(in µg/ml)	Absorbance (in nm)
1.	0	0.000
2.	2	0.136
3.	4	0.305
4.	6	0.462
5.	8	0.612
6.	10	0.754
R^2	0.9992	

Fig.no.13 .calibration curve of Venlafaxine HCL



10. FORMULATION

TABLE NO. 9: The Composition of Tablets Prepared Using Venlafaxine HCl

INGREDIENTS / FORMULATION	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	150	150	150	150	150	150	150	150	150
Carbopol 934p	20	25	30	-	-	-	-	-	-
Xanthan gum	-	-	-	80	95	110	-	-	-
HPMC K100M	-	-	-	-	-	-	60	70	80
Sodium bicarbonate	7	7	7	7	7	7	7	7	7
MCC	147	142	137	87	72	57	107	97	87
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total	330	330	330	330	330	330	330	330	330

10.1. STEPS INVOLVED IN FORMULATION

Each tablet containing 300 mg Venlafaxine HCl were prepared by direct compression method. Accurately weighed amount of drug Venlafaxine HCl, Carbopol 934 p, Xanthan gum, HPMC K100M, PEO, Sodium CMC were mixed geometrically in a mortar. Then binder PVP K 30, MCC, Sodium bicarbonate, Sodium bicarbonate and MCC are passed through the sieve and thoroughly mixed for 15 minutes. The powder blend then lubricated with Talc and magnesium stearate for 2 minutes and compressed on a tablet punching machine using 9 mm punches. The total weight of the tablet is 330 mg.

11. EVALUATION

11.1. Pre-compression parameters:

1. Angle of repose:

Take a small quantity of powder (5 gm) in a cone shaped funnel and fix it to a holder at an appropriate height say 6 cm above the surface. Place a graph sheet below it. The sample was passed slowly through the funnel. The height of the powder heap was formed. Then measure the circumference of the heap by drawing with the pencil on the graph sheet. The radius of the heap was measured. The angle of repose is calculated by using the following formula. This is repeated five times for accurate results.

$$Ø = Tan^{-1} h/r$$

Where, h = height of file

R= radius of the base of the pile

Ø = angle of repose

The results were tabulated in table.

2.Bulk density and Tapped density:

Weigh a small quantity of the powder (w) was carefully poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus) set for 500 taps and after that, the volume (v_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk Density} = W/V_0$$

$$\text{Tapped Density} = W/V_f$$

Where, V_0= Initial volume,

V_f = final volume

The results were tabulated in table.

3. Compressibility index and Hausner ratio:

The compressibility index and hausner ratio are calculated by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:

$$\text{Compressibility index} = P_{tapped} - P_{bulk}/P_{tapped} X\ 100$$

Hausner ratio $= P_{tapped} / P_{bulk}$

The results were tabulated in table.

11.2. EVALUATION OF FORMULATED TABLETS OF VENLAFAXINE HCL

All the formulated sustained release tablets were evaluated for following official and unofficial parameters.

1. Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in a none deviate by more than twice the percentage shown.

$$\% \text{ deviation} = \frac{\text{tablet weight-average weight}}{\text{Tablet weight}} \times 100$$

Observation:

The average weight and standard deviation of the tablets of each batch were given.

Weight variations Specification

Table No: 10. Weight variations Specification

Average weight of tablets(X mg)	Percentage deviation
130 or less	±10
130 to 324	±7.5
More than 324	±5

2. Dimensions

Control of physical dimension of the tablets thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using digital Vernier calipers. The thickness of tablets is mostly related to the tablet hardness can be used as initial control parameter.

Six tablets were randomly selected from each batch and their thickness was measured by using Digital Vernier caliper.

3. Hardness[60]

It is determined to get perfect compactness during shipping, coating, and packaging and to get proper shape and design. Hardness was measured by using

hardness tester. (Pfizer hardness tester) for each batch six tablets were tested. The force required to break the tablet is recorded by the unit is Kg/cm^2.

Observation:

The measured hardness of tablets of each batch was range from 6-16Kg/cm^2.

4. Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for every 4 minutes. After revolution the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\%F = \{1-(W_t/W)\} \times 100$$

Where, %F=friability in percentage

W=initial weight of tablets after revolution

Observation:

All the formulated batches were found under acceptable limit of 0.1- 0.6 as specified in IP.

5. Buoyancy Lag Time[61]

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

The results were tabulated in table.

6. Floating Time[62]

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

7. **Dissolution study:**

Preparation of buffer:

Measure 8.5 ml of Hcl in a 1000 ml volumetric flask and make up the volume to 1000 ml using distilled water.

Requirements:

Medium: 0.1N Hcl

Volume: 900 ml

Apparatus: USP II (paddle)

RPM: 50

Time: upto 12 hrs

Temperature: 37^0 c $\pm$ 0.5^0c

λmax : 224 nm

Perform the test on six tablets one tablet in each dissolution vessel containing 900 ml of 0.1 N Hcl maintained at 37^0c $\pm$ 0.5^0c. at specific time withdrawn required amount of sample and replace same amount of 0.1N Hcl(maintain sink condition), then absorbance was taken and calculate percentage release.

$$\% \text{ purity} = \frac{\text{absorbance} * 900 * \text{dilution}}{\text{Slope} * 1000 * \text{label claim}} * 100$$

8. Assay:

Crush 20 tablets and weigh equivalent to 20 mg Venlafaxine HCL and dissolved in 0.1N Hcl and make up the volume to 100 ml. From that, withdraw 10 ml and diluted to 100 ml with 0.1 N Hcl. Read the absorbance at 232 nm in UV spectrophotometer.

9. **Kinetics of drug release**

The invitro dissolution profile of all batches were fitted to Zero order,

first order, Higuchi model and Koresmeyer-Peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

Zero-order kinetics

Zero order release would be predicted by the following equation:

$$\mathbf{A_t = A_o - K_o t}$$

A_t - Drug release at time‘t’

A_o - Initial drug concentration

K_o - Zero-order rate constant (hr^{-1})

When the data plotted as cumulative % drug release Vs time and the plot is linear, then the data obeys zero-order equal to K_o.

First order kinetics:

First order release would be predicted by the following equation:

$$\mathbf{Log\ C = log\ C_o - K_t / 2.303}$$

C - Amount of drug remained at time‘t’

C_o - Initial drug concentration

K - First-order rate constant (hr^{-1})

When data is plotted as log cumulative % remaining Vs time yields a straight line, and then the release obeys first order kinetics. The constant ‘K’ obtained by multiplying 2.303 with the slope values.

Higuchi’s Model:

Drug release from the matrix devices by diffusion has been described by Following Higuchi’s classical diffusion equation:

$$\mathbf{Q = [D\varepsilon/\tau\ (2A-\varepsilon CS)\ CSt]^{1/2}}$$

Q - Amount of drugreleased at time‘t’

D - Diffusion coefficient of the drug in the matrix

A - Total amount of drug in unit volume of matrix

CS - The solubility of drug in the matrix

ε - Porosity of the matrix

τ - Tortuosity

t - Time at which amount of drug released

When the data is plotted as Cumulative % drug released Vs square root of time yields a straight line, indicating that drug release follows diffusion mechanisms. The slope is equal to ‘K’.

Korsmeyer – Peppas model:

To study the mechanism of drug release from the microspheres, the invitro release data were fitted to the well known exponential equation (Korsmeyer – Peppas model), which is often used to describe the drug release behaviour from polymeric systems.

$$Mt/M\alpha = Kt^n$$

Mt/Mα - The fraction of drug released at time't'

K-Constant incorporating structural and geometrical characteristics of the drug/polymer system

N-Diffusion exponent related to the mechanism of drug release

When the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept.

Mechanism of drug release as per Korsmeyer-Peppasequation / Peppas model

Table. No. 11: Mechanism of drug release

S.No	n value	Drug release
1	0 –0.5	Fickian release
2	0.5 – 1.0	Non-Fickian release
3	>1.0	Class II transport

12.RESULT AND DISCUSSION

12.1. Preformulation studies:

12.1.1. Organoleptic properties:

The tests were performed as per the procedure. The results were tabulated below.

Table.no.12. organoleptic properties

Test	Specifications/limits	Observations
Colour	White to off-white powder	white to off-white crystalline solid
odour	Odourless	Odourless

The result complies as per specifications.

12.1.2. Physical properties:

Angle of repose:

It was determined as per procedure. The results were tabulated below.

Table.no.13. flow properties

Material	Angle of repose
Venlafaxine HCl	27.23^0

The results show that the drug having poor flow.

Bulk density and tapped density:

It was determined as per procedure. The results were tabulated below.

Table no. 14.bulk density and tapped density

Material	Bulk density(gm/ml)	Tapped density(gm/ml)
Venlafaxine HCl	0.53	0.56

Powder compressibility:

It was determined as per procedure. The results were tabulated below.

Table no. 15.powder compressibility

Material	Compressibility index	Hausner's ratio
Venlafaxine HCl	6.84	1.06

Melting point:

It was determined as per procedure. The results were tabulated below.

Table no.16. Melting point

Material	Melting point range	Result
Venlafaxine HCl	215-217^{0}c	215^{0}c

The result indicates that the Venlafaxine HCl drug was pure one.

12.1.3. SOLUTION PROPERTIES

Solubility:

It was determined as per procedure. The results were tabulated below.

Table no.17 . Solubility

Material	Test	Specification	observation
Venlafaxine HCl	Solubility	soluble in water, DMSO	Complies

The result complies as per specification.

8.3 FTIR STUDIES

TABLE NO. 18 Compatibility Studies of Venlafaxine HCl with Excipients

SL. NO	Excipients	Drug/ Excipients Ratio	Physical Description Initial	$35^0C \pm 2^0C$ / 60% ± 5% RH		
				1 Week	2 Week	3 Week
1	Venlafaxine HCl	-	White crystalline powder	*	*	*
2	Drug + carbopol934	1:1	White crystalline powder	*	*	*
3	Drug + xanthan gum	1:1	White crystalline powder	*	*	*
4	Drug + HPMC k100M	1:1	White crystalline powder	*	*	*

*** indicates no incompatibility**.

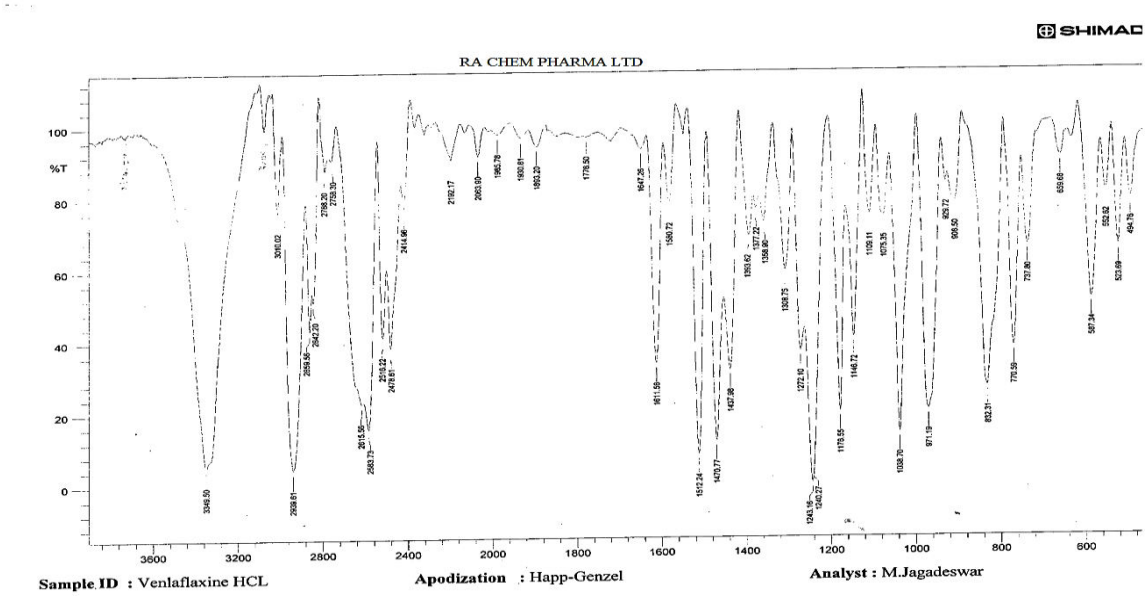


Fig14: FTIR Spectroscopy of pure drug

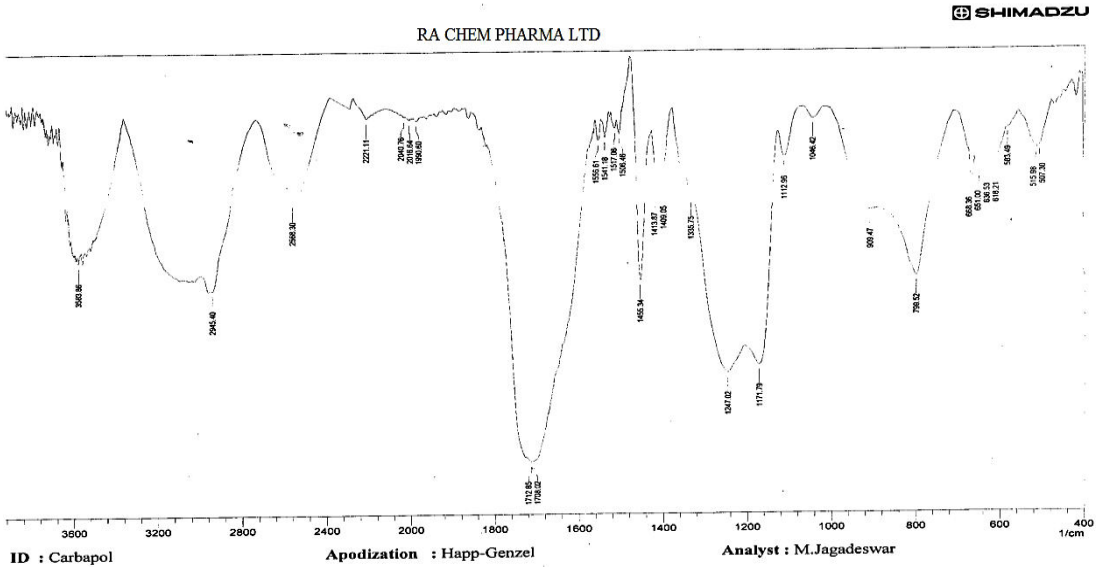


Fig15: FTIR Spectroscopy of Carbopol934

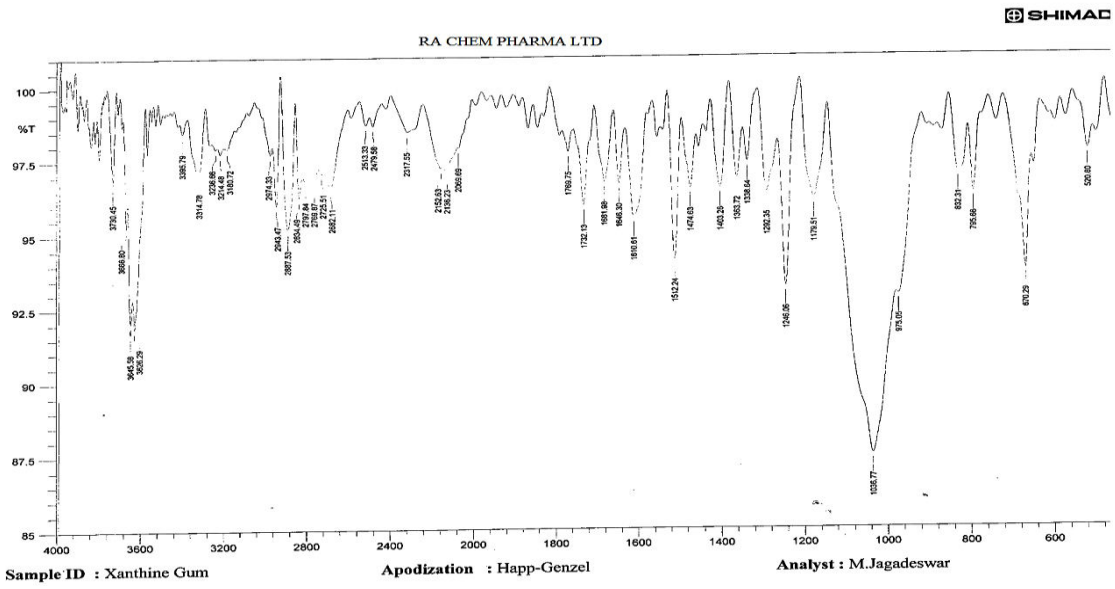


Fig16: FTIR Spectroscopy of Xanthan gum

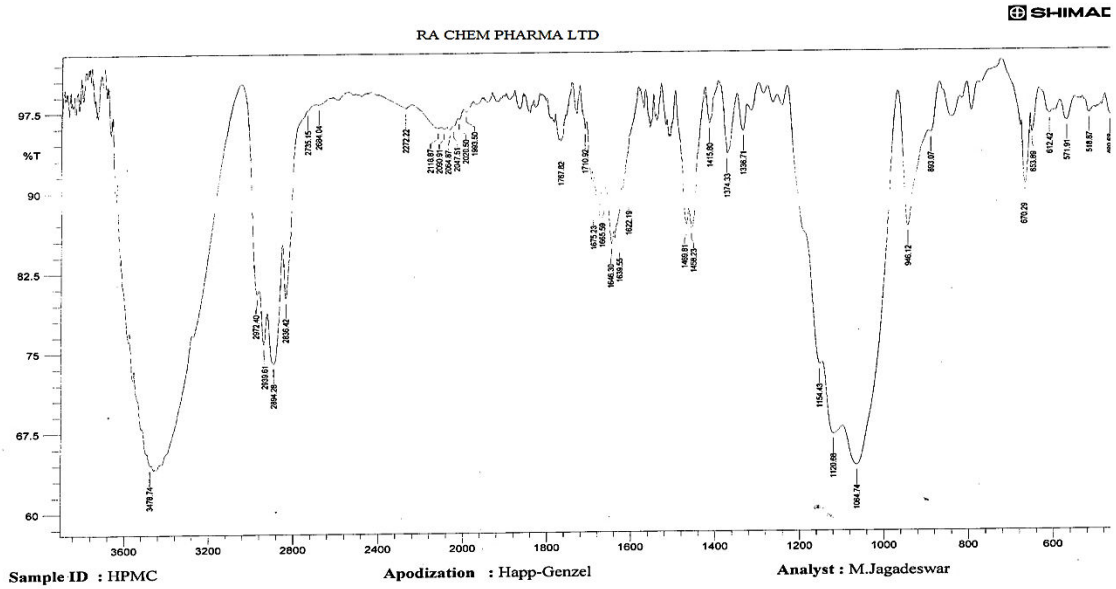


Fig17: FTIR Spectroscopy of HPMC K100M

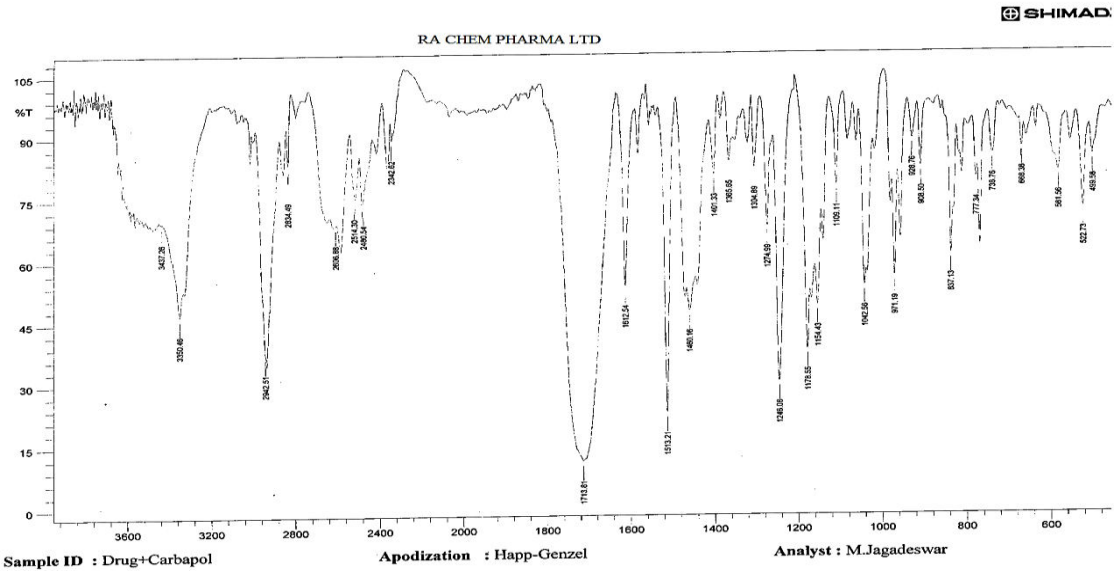


Fig18: FTIR Spectroscopy of pure drug+ Carbopol 934

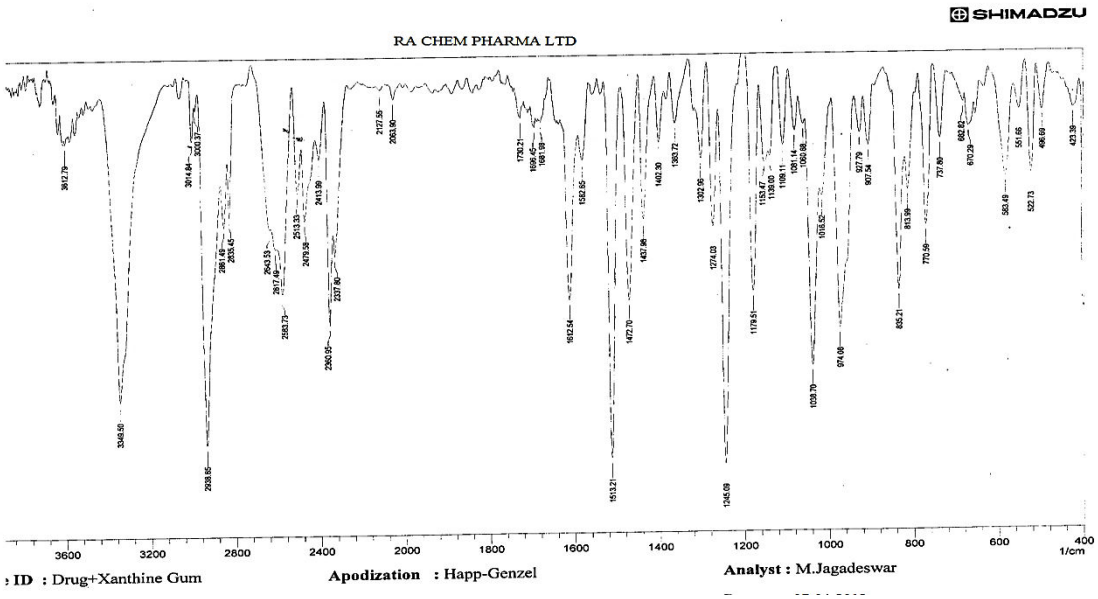


Fig19: FTIR Spectroscopy of pure drug+ Xanthan gum

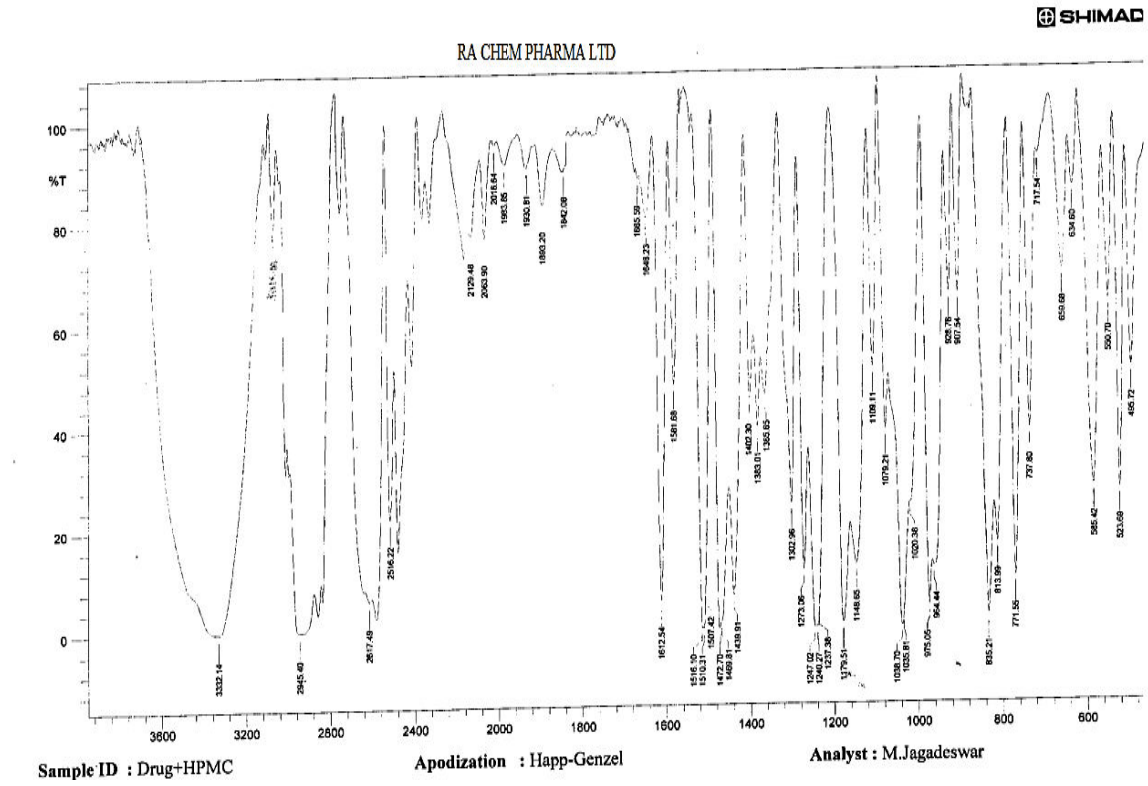


Fig20: FTIR Spectroscopy of pure drug+ HPMC K100M

Table No. 19: Comparison of the peak of functional groups of Venlafaxine HCl observed in IR spectra of compatibility studies:

S. No	Types of vibrations	IR absorption Ranges (cm^{-1})	Drug (cm^{-1})	Physical mixture(drug + polymer)		
				Drug + xanthan gum	Drug + carbopol 934	Drug + HPMC K100M
1	Aromatic C-H stretching	3000-2850	2939.6	2936.5	2942.5	2945.4
2	Aromatic C=C stretching	1680-1600	1647.2	1642.9	1632.4	1648.2
3	O-H stretching	3400-3600	3349.5	3349.5	3437.2	3332.1
4	C-O stretching	1300-1000	1243.16	1245.9	1246.6	1247.2
5	N-H stretching (1° & 2°amine)	3500-3100	3349.5	3349.5	3437.2	3332.1
6	C-N stretching	1350-1000	1308.7	1302.9	1304.5	1302.9

- In order to check the integrity of the drug in the formulation, FTIR spectra of pure drug(Venlafaxine HCl), Carbopol 934, HPMC K100M, Xanthan gum and mixture of drug with the above polymers were taken and compared. The FTIR spectrum of Venlafaxine HCl reveal the presence of peaks at 2939.6 due to the presence of C-H stretching, 1647.2 due to the presence of C=C aromatic stretching, 3349.5 due to the presence of O-H stretching, 1243.16 due to the

presence of C-O stretching, 3349.5 due to the presence of N-H stretching, 1308 due to the presence of C-N stretching.

- Major frequencies of functional groups of pure drug remain intact in powder containing Carbopol 934, HPMC K100M and Xanthan gum. Hence there is no major interaction between the drug and polymers used in the study.

8.4 EVALUATION PARAMETERS:

6.4.1 Pre Compression Parameters

Table No.20: Evaluation parameters of powder blend

Formulation	Angle of repose	Bulk density(gm/cc)	Tapped density(gm/cc)	Compressibility index (%)
F1	$29^{0}1^{1}$±0.1	0.36±0.004	0.41±0.018	11.8±0.8
F2	$30^{0}3^{1}$±0.2	0.37±0.001	0.44±0.017	13.4±0.8
F3	$32^{0}1^{1}$±0.5	0.38±0.005	0.44±0.004	13.3±0.6
F4	$30^{0}6^{1}$±0.3	0.35±0.005	0.41±0.003	14.2±1.4
F5	$32^{0}8^{1}$±0.5	0.34±0.004	0.40±0.018	14.8±1.2
F6	$33^{0}8^{1}$±0.1	0.35±0.002	0.42±0.001	16.2±0.7
F7	$28^{0}1^{1}$±0.7	0.35±0.002	0.40±0.005	12.6±0.9
F8	$28^{0}5^{1}$±0.3	0.36±0.003	0.41±0.002	12.7±1.1
F9	$31^{0}2^{1}$±0.1	0.36±0.005	0.42±0.004	14.2±1.3

- Floating tablets of Venlafaxine HCl was developed to increase the gastric residence time of the drug, so that they can be retained in the stomach for longer time and help in controlled release of drug up to 12 hrs.
- Different grades of viscosities of Carbopol 934, xanthan gum, HPMC K100M polymers is known to be beneficial in improving floating property and release charecteristics.
- The pre- compression parameters obtained for all formulations are tableted in the table no 13. The value of angle of repose was found to be in the range of $28^{0}1^{1}$ to $33^{0}8^{1}$. This indicates good flow property of powder blend. Carr's index value ranges between 11.8 to 16.2% indicates that the powder blend have the required flow property for direct compression.

8.4.2 Post Compression Parameters:

Table no.21: Evaluation parameters of formulations

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight variation(mg)	Drug content (%)
F1	3.76±0.04	5.33±0.02	0.65±0.07	331.2±1.3	98.06
F2	3.68±0.07	5.61±0.05	0.59±0.09	330.7±1.4	98.39
F3	3.62±0.02	5.44±0.03	0.53±0.05	331.5±1.7	97.22
F4	3.71±0.04	5.48±0.01	0.54±0.11	330.2±2.1	99.02
F5	3.67±0.09	5.86±0.04	0.47±0.08	329.8±2.3	97.18
F6	3.63±0.11	6.14±0.02	0.47±0.12	331.3±2.1	97.56
F7	3.74±0.02	5.42±0.03	0.57±0.04	329.2±1.4	97.19
F8	3.76±0.01	5.57±0.01	0.54±0.07	328.7±1.8	98.45
F9	3.69±0.05	5.72±0.05	0.53±0.06	331.4±1.2	98.28

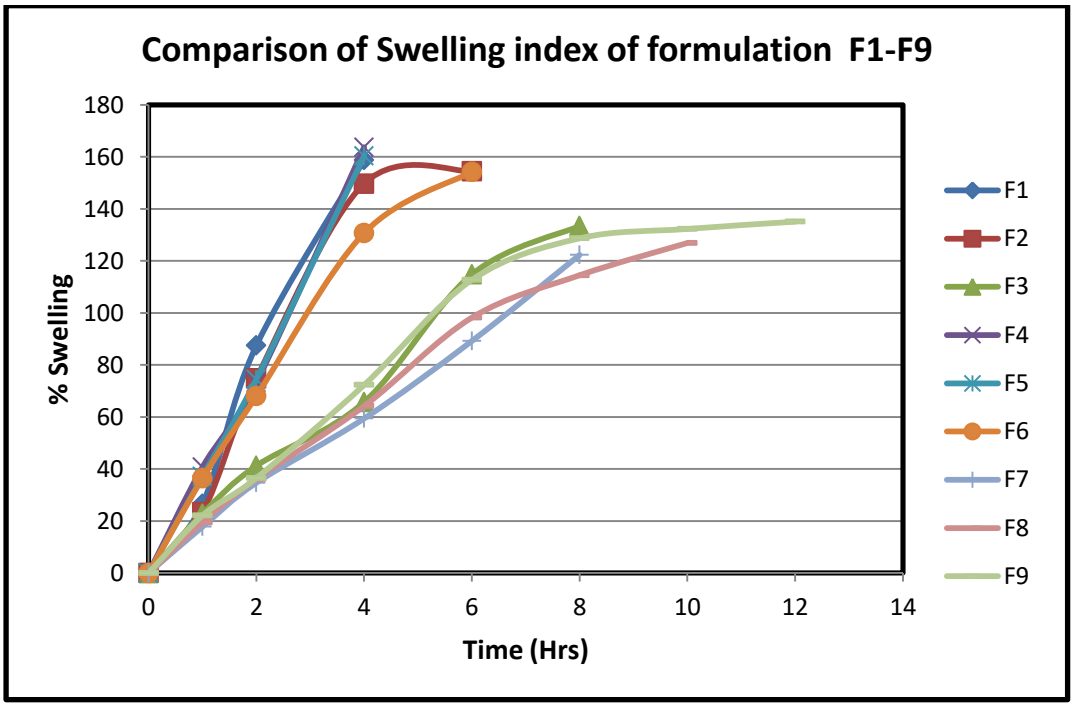
- The floating tablets were prepared by direct compression method using the polymers Carbopol 934, Xanthan gum, HPMC K100M to provide sufficient drug release retardation and provide sufficient buoyancy to the tablets .The results have shown in the table no.14.
- The prepared floating tablets were evaluated for thickness, hardness, friability, average weight variation, drug content, all the studies were performed in triplicates and the results were expressed in ± standard deviation.
- The measured hardness for the tablets for each batch arranged between 5.33 to 6.14 kg/cm, this ensures the good handling characteristics of all the batches.
- The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.
- The weight variation for different formulations was found to be 328.7 to 331.4, indicates consistency in each batch.
- The drug content was found to be 97.19 to 98.45, with low standard deviation indicates batch to batch consistency.

8.5 SWELLING INDEX:

Table no.22: Swelling index (%) of formulations

Time (hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	26.6	23.3	22.8	40.7	37.2	36.4	17.8	19.4	22.1
2	87.45	74.77	41.2	73.25	74.5	68	34.7	36.1	36.5
4	158.8	149.7	65.7	163.7	160.3	130.7	59.4	64.2	72.3
6		154.5	114.8			154.2	89.2	98.2	112.7
8			133.4				122.3	114.5	128.7
10								126.9	132.3
12									135.1

Fig 21: Graph for comparison of swelling index of all the formulation



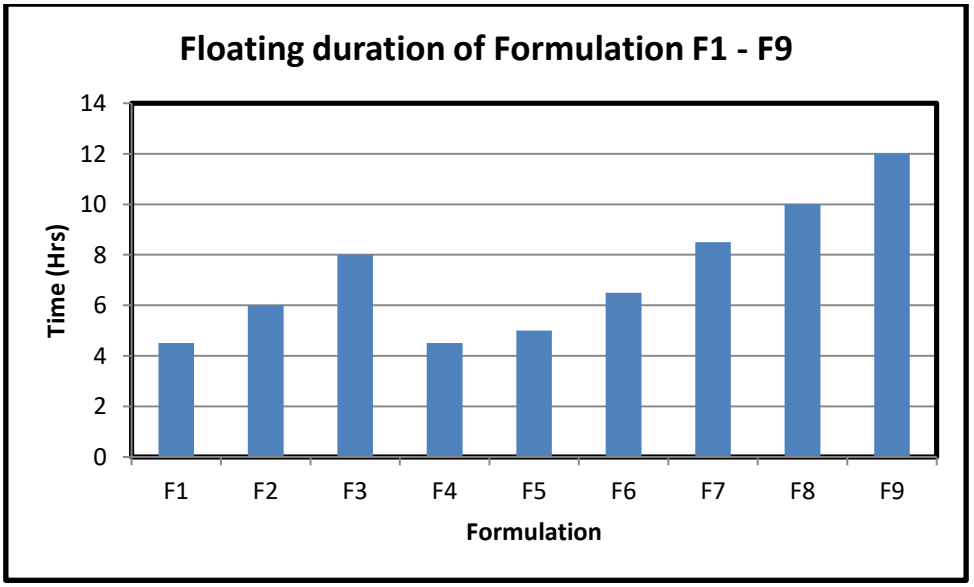
Swelling index for all the formulations was carried out in the 0.1N HCl. The formulations showed different indices in the swelling media and it is shown in the table. Tablets containing carbopol934 and HPMC K100M showed maximum swelling in 12 hr with sharp increase up to 8 hr this may due to increased concentration of HPMC K100M which retain water and form thick swollen mass.

8.6 BUOYANCY STUDIES:

Table no. 23: Buoyancy studies of formulations

Formulation code	Floating lag time (sec)	Floating duration (hrs)
F1	52	4.5
F2	58	6
F3	76	8
F4	29	4.5
F5	36	5
F6	34	6.5
F7	34	8.5
F8	32	10
F9	39	12

Fig 22: Floating duration of Formulation F1 - F9



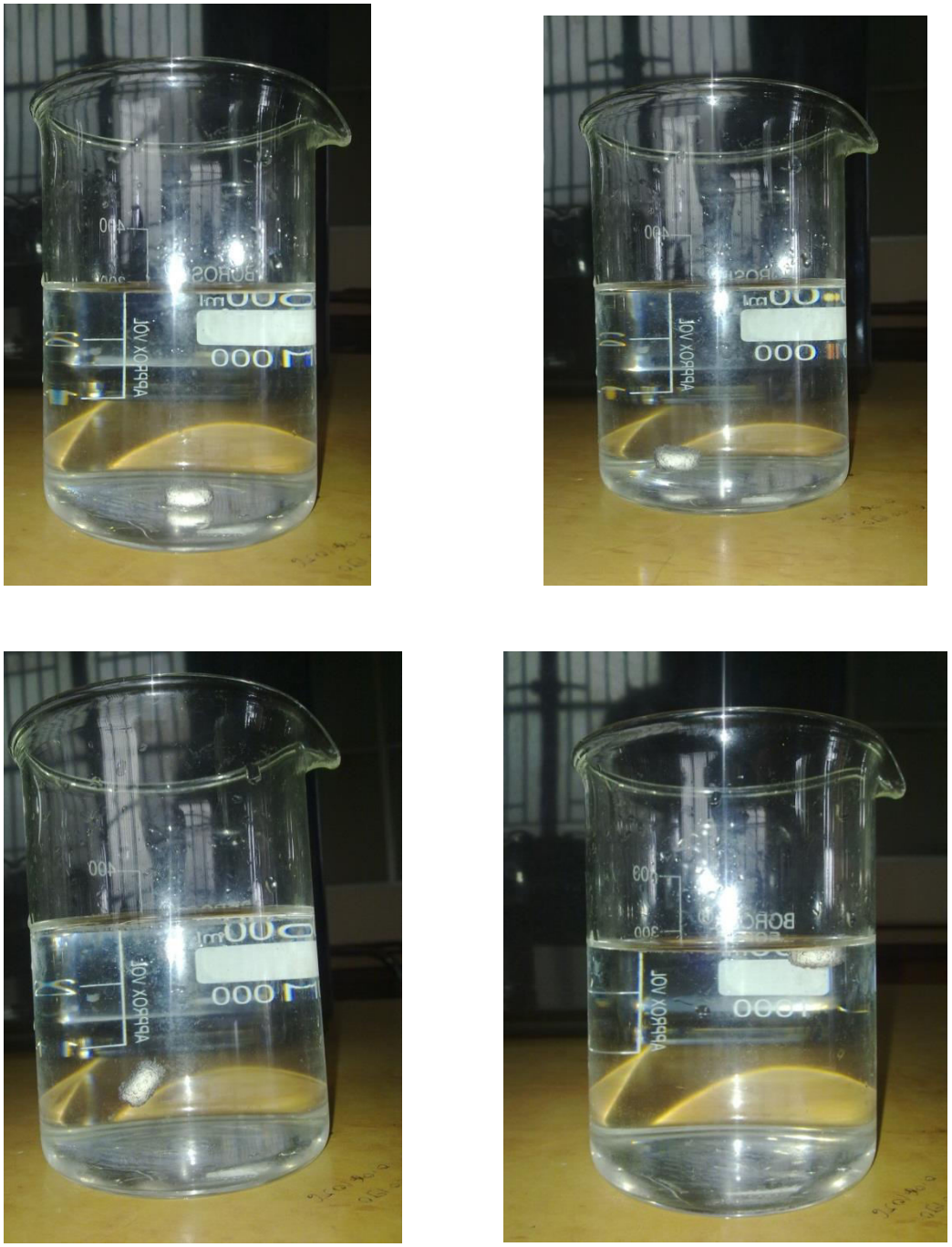


Fig 23: ***In vitro*** **buoyancy studies of optimized formulation**

- The *in-vitro* floating behavior of the tablets was studied by placing them in beaker containing 0.1 N HCl (pH 1.2). The gas generating agents immediately evolves carbon dioxide in presence of HCl solution generating sufficient porosity which helped the dosage unit to float. Formulation F1-F3 prepared with carbopol934p started floating after 52 seconds and remains buoyant for 8 hr till they were completely eroded.
- On the other hand formulation F4-F6 prepared with Xanthan gum which shows a floating time of 6.5 hrs and formulation of F7-F9 prepared with HPMC K100M show decrease in floating lag time to 34 seconds and increased floating duration time to 12 hrs. This might be due to high viscosity polymer HPMC K100M maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. The results are shown in table no.16.Thus it can be concluded that the batch containing HPMC polymers showed good floating lag time and total floating time.

8.7 *In-Vitro* DRUG RELEASE STUDIES:

In-vitro drug release studies were carried out using USP dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of pH 1.2 acid buffer (0.1N HCl), maintained at 37 $\pm$ 0.5^{0}C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer at 224 nm.

Table no.24: Percentage drug release of formulations

Time (hrs)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	24.87	22.92	20.06	38.34	32.28	27.54	23.46	22.43	18.84
2	58.16	55.27	48.07	62.15	45.38	41.15	39.87	31.11	24.18
4	96.53	71.18	69.18	98.1	94.19	76.77	67.82	53.67	43.67
6		96.11	78.92			96.13	82.09	65.28	61.08
8			98.33				97.12	76.59	72.49
10								98.76	83.54
12									98.03

Fig24: *In-vitro* dissolution profile of F1 to F3 formulations.

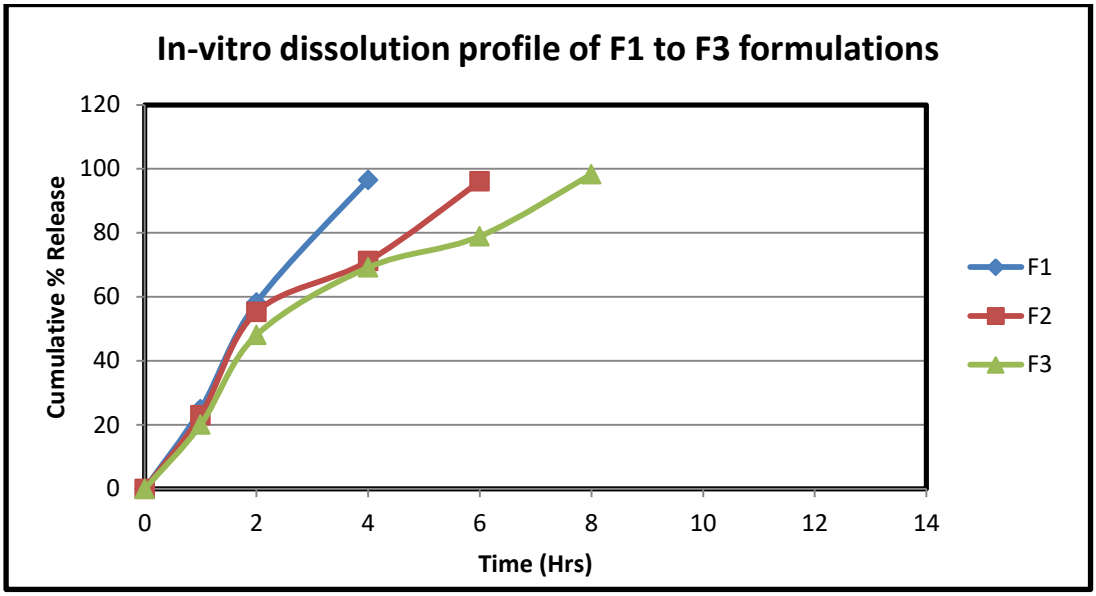


Fig25: *In-vitro* dissolution profile of F4 to F6 formulations.

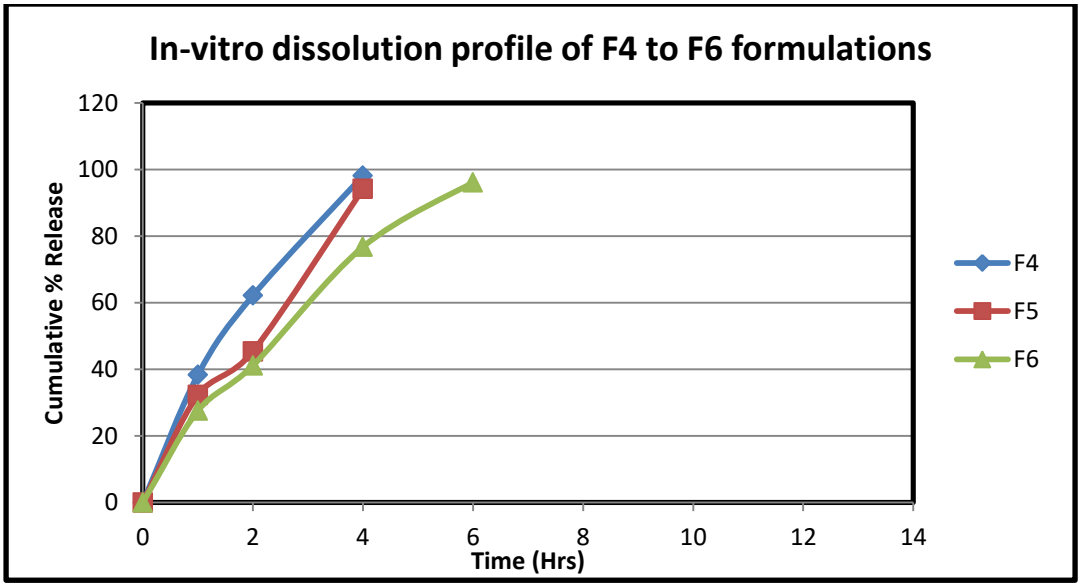


Fig26: *In-vitro* dissolution profile of F7 to F9 formulations.

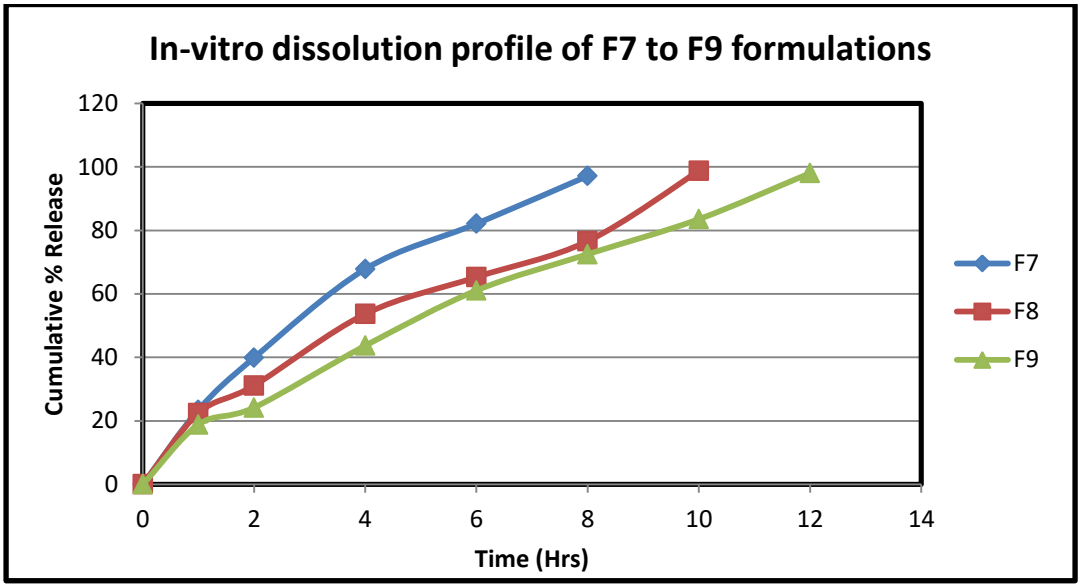
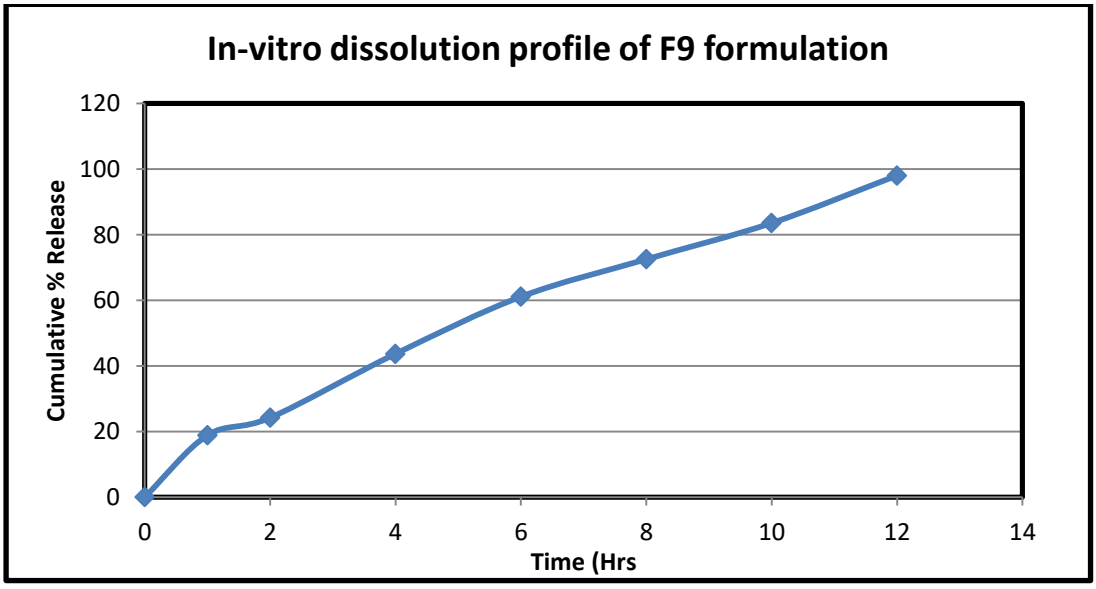


Fig27: *In-vitro* dissolution profile of F7 to F9 formulations.



- *In-vitro* dissolution studies were performed for all the formulations using USP dissolution apparatus II at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. The samples withdrawn and were analyzed by using UV spectrophotometer. The drug release from the formulations F1-F3 prepared with Carbopol 934P was found to be 96.53, 93.11 and 98.33%, where as formulation F4- F6 prepared with Xanthan gum was found to be 98.1, 94.19, 96.13 at the end of 4 & 6 hours. Formulations F7-F9 prepared with HPMCK100M was found to be 97.12, 98.76, 98.03% showed reasonable drug

release of formulation in F9. As per the results of dissolution study the formulations F1-F9 the drug release was sustained for 4 to 12hr.

- All the formulations were designed as dosage form for 12 hours. In order to check the 100% dissolution release profile, formulations were subjected to dissolution studies for 12 hours. Among the nine formulations F9 was best and shows 98.03% drug release in the end of 12 hours.
- It is evident from the *in-vitro* dissolution data that increase in HPMC K100M concentration decreases the release rate this might be due to increase in diffusional path length, which the drug molecule may have to travel. . So, formulation F9 was selected as the optimized formulation. The results are shown in table no.17.

8.8 RELEASE KINETICS:

Table No. 25 Model fitting for formulation F-9

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
1	**18.84**	81.16	1.414	1.909	0.301	1.275
2	**24.18**	75.82	2.000	1.880	0.602	1.383
4	**43.67**	56.33	2.449	1.751	0.778	1.640
6	**61.08**	38.92	2.828	1.590	0.903	1.786
8	**72.49**	27.51	3.162	1.439	1.000	1.860
10	**83.54**	16.46	3.464	1.216	1.079	1.922
12	**98.03**	1.97	3.464	0.294	1.079	1.991

Fig28: Zero order kinetic model of F9

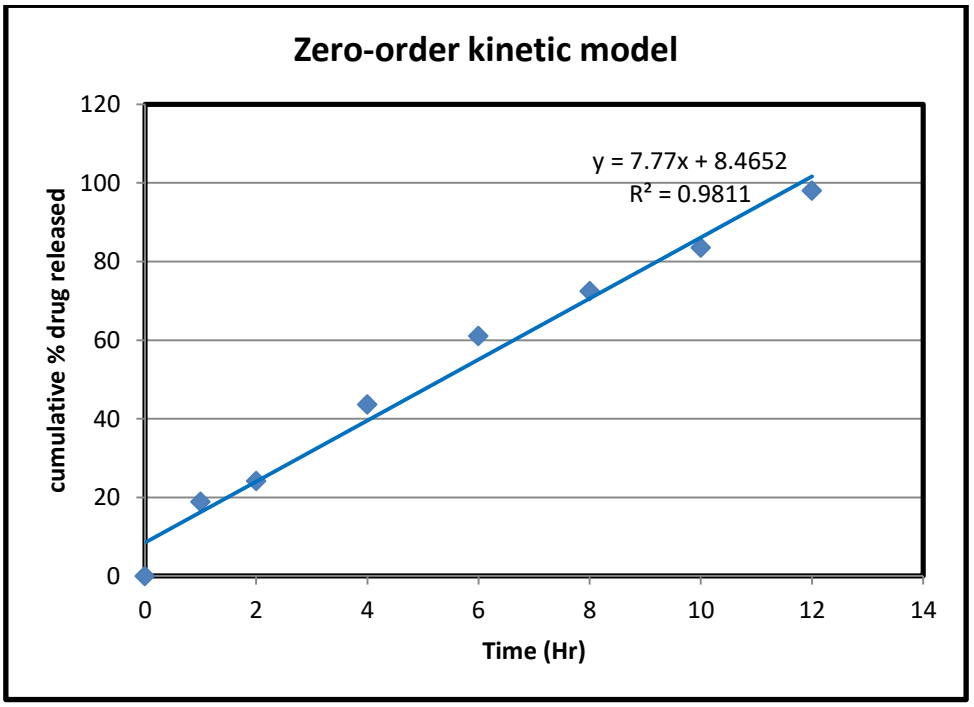


Fig29: First order kinetic model of F9

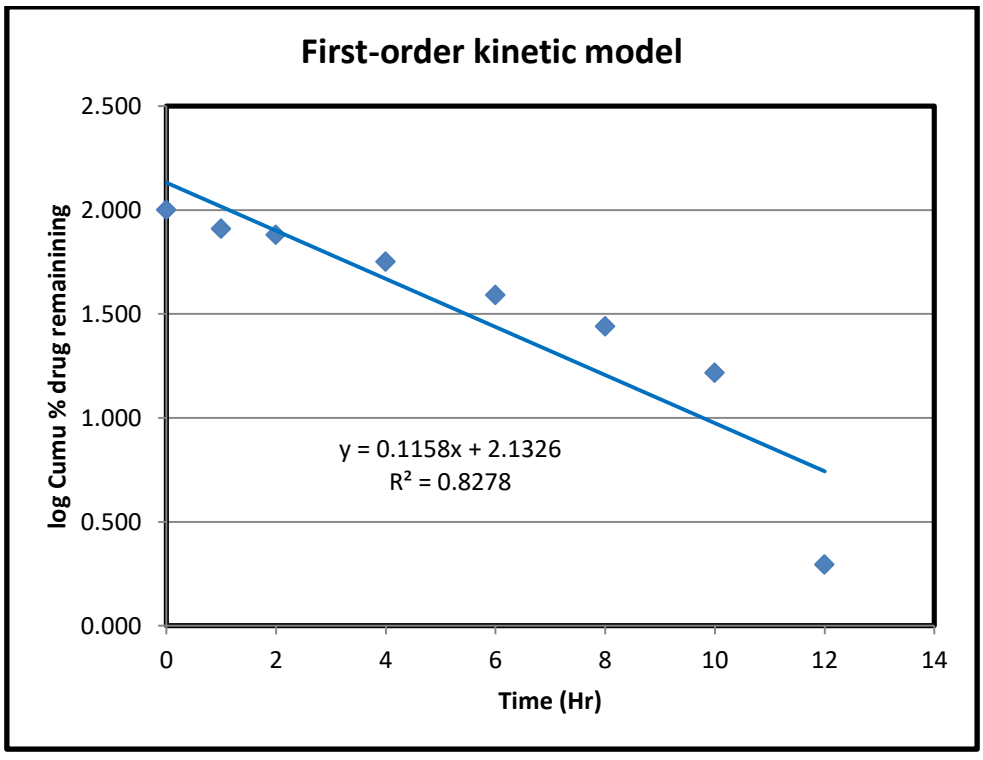


Fig30: Higuchi model of F9

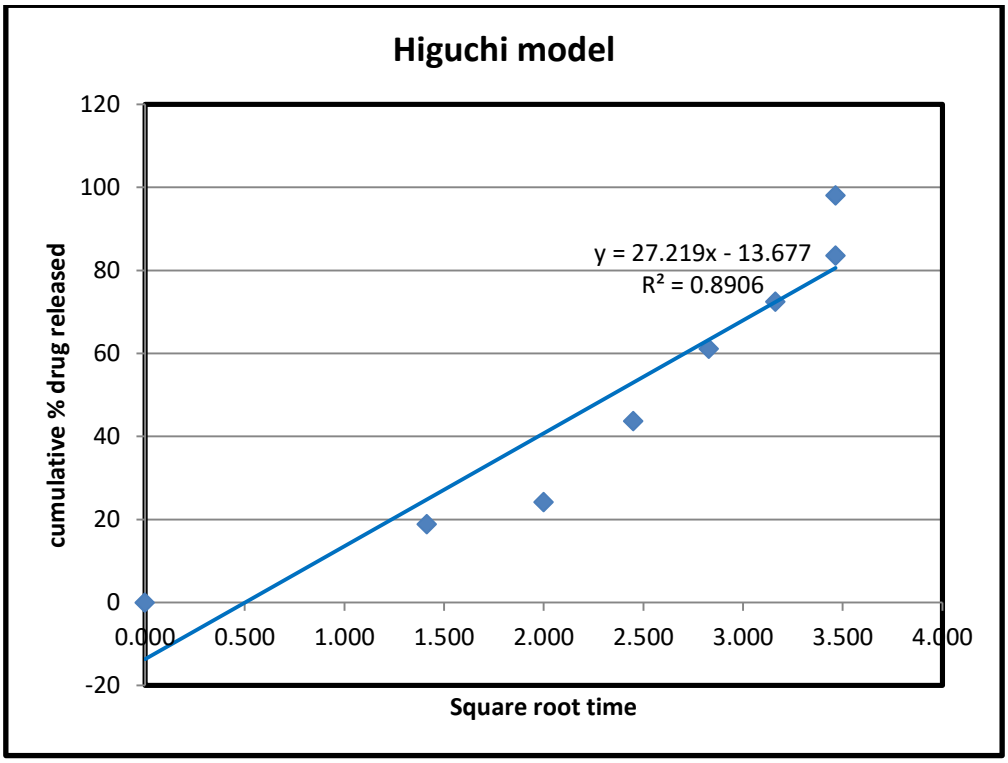
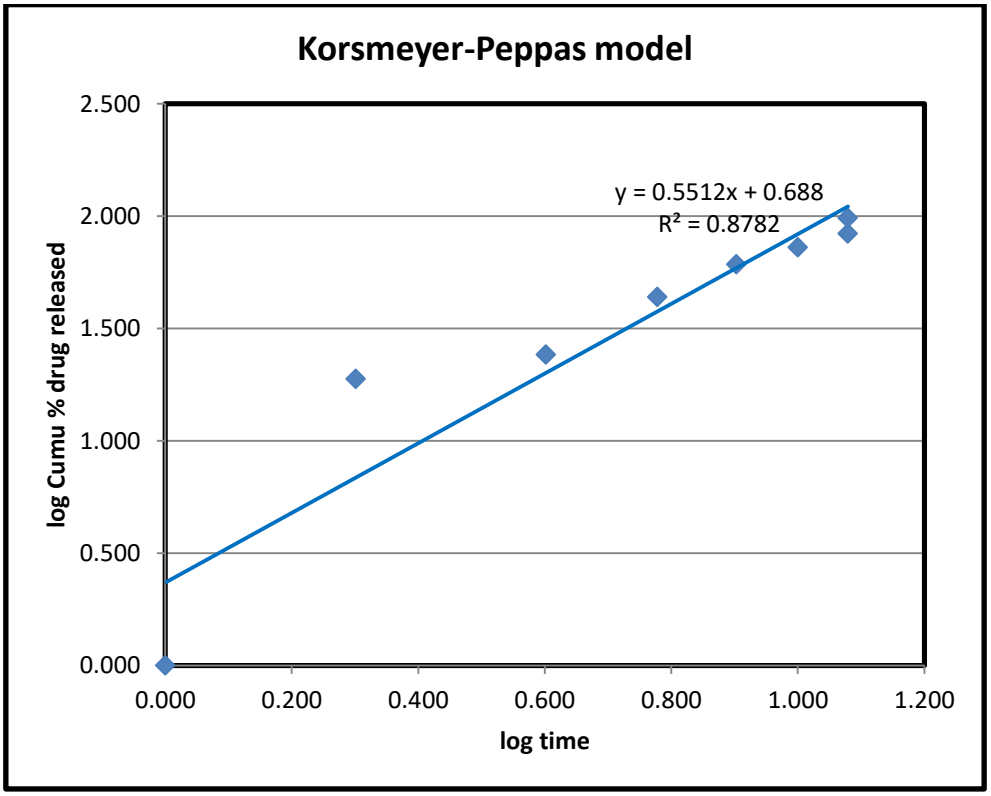


Fig31: Korsmeyer-Peppas model of F9



- The mechanism of drug release is predicted by using Korsmeyer–Peppas equation. The n value of optimized formulation F9 is 0.66 respectively and is between "0.45 to 0.85". This indicates that the drug release depends on swelling, diffusion, and erosion. All formulations follow the non-Fickian/anomalous type of diffusion.

8.9 STABILITY STUDIES:

Table no. 26: Stability studies of optimized formulation F9

Time (days)	$25^oC \pm 2^oC/60\%$ RH ± 5% RH, $30^oC \pm 2^oC/65\%$ RH ± 5% RH, $40^oC \pm 2^oC/75\%$ RH ± 5% RH			
	Hardness(kg/cm^2)	Drug content (%)	% Drug release	Total floating time
30	5.56	98.45	98.34	>12
60	5.56	98.42	98.27	>12
90	5.48	98.18	98.71	>12

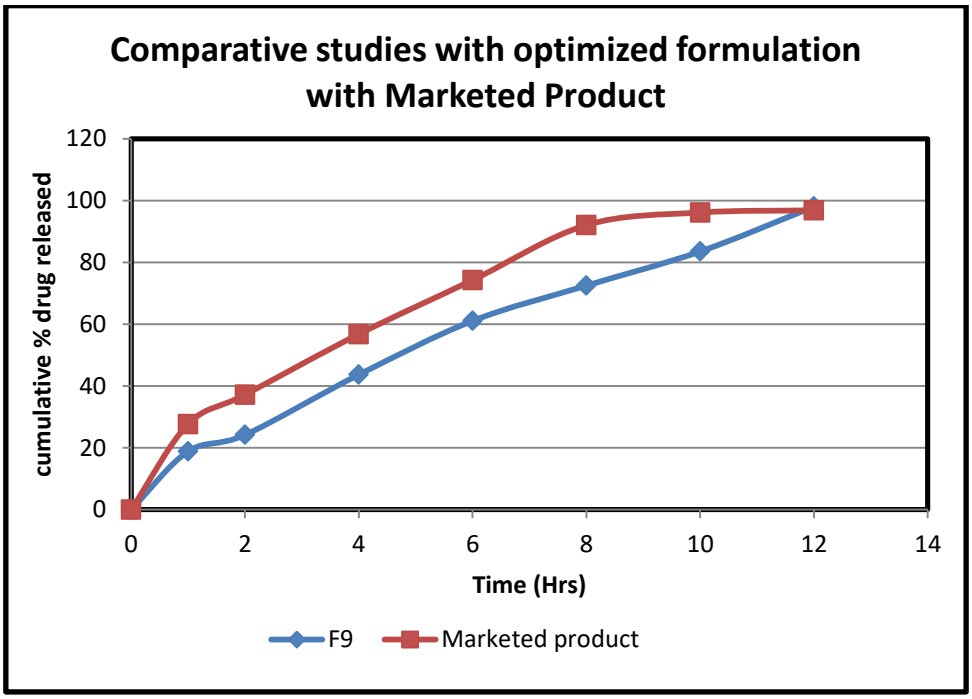
- Stability studies were carried out on selected formulations (F9) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability, drug release, floating lag time (Table 20) for the selected formulation F8 after 90 days at $25^oC \pm 2^0C$ / 60% ± 5% RH, $30^0C \pm 2^0C$ / 65% ±5% RH and $40^0C \pm 2^0$ / 75% ± 5% RH.

8.10 COMPARISON WITH MARKETED PRODUCT:

Table no.27: Comparative studies with optimized formulation

Time(hrs)	Cumulative % drug release	
	F9	Marketed product
1	18.84	27.64
2	24.18	37.18
4	43.67	56.79
6	61.08	74.28
8	72.49	92.08
10	83.54	96.16
12	98.03	96.87

Fig 32: Plot of comparative dissolution profile of optimized formulation (F8) and Marketed product



- The marketed product releases 96.16% drug in 10 hrs where as the optimized formulation F9 releases 98.03% of drug in 12 hrs. Thus comparison study of the marketed product of Venlafaxine HCl showed that the optimized

formulation F9 has better control over release rate in comparison to the commercial product.

13. SUMMARY

In the present work, 9 different formulations were prepared by direct compression, incorporating polymers like Carbopol934, Xanthan gum and HPMC K100M as swelling polymers, sodium bicarbonate as gas generating agent, MCC as a diluents, talc used as glidant and magnesium stearate used as lubricant.

Characterization of the drug was done by performing the UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all the excipients used in the study. The results showed that there was no drug-excipient interaction. The UV spectral analysis of the drug solution indicated that λmax value as 224 nm.

All the prepared floating formulations were evaluated for hardness, friability, uniformity of weight, drug content uniformity, drug-polymer interaction, *in-vitro* floating studies, *in vitro* drug release and short term stability studies.

The thickness of the formulations (F1-F9) was in the range of 3.62 $\pm$ 0.03 to 3.71 $\pm$ 0.05mm and the hardness was in the range of 5.3 $\pm$ 0.2 to 6.1 $\pm$ 0.3 Kg/ cm^2, indicated good mechanical strength of the tablets. Friability, weight variation and drug content uniformity was found to be within official limits for all the formulations.

The dissolution studies were carried out for 12 hrs. As per the result of dissolution study formulation F7, F8 and F9 showed reasonable release respectively. But F9 showed good floating lag time and total floating time, when compare to other formulations. Based on all these results, formulation F9 was selected as the optimized formulation. F9 was then compared to the marketed product and was found that the optimized formulation F9 has better control over release rate in comparison to the commercial product.

The release kinetics were fitted to different mathematical models like Zero order, First order, Higuchi's and Peppa's plot. The selected formulation F9 follows Higuchi's plot and slope (*n*) value of Peppa's for these formulations were found to be in the range of "0.45 to 0.85". This indicates that the drug release depends

on swelling, erosion, and diffusion. Thus follows the non-Fickian/anomalous type of diffusion.

The drug-polymer ratios, viscosity of polymers, were found to influence the drug release and floating properties of the prepared tablets. From the results it can be concluded that as the concentration of the polymer increased floating lag time decreased and the percentage drug release was prolonged. Viscosity of the polymer also showed a directly proportional relationship with swelling characteristics of the tablets.

The optimized formulation (F9) was subjected for stability studies as per ICH guidelines. Formulations subjected for short term stability studies were checked for drug content, hardness, friability and Total floating time for 90 days with an interval of 15 days. The formulations were found to be stable as no significant change was observed in the various evaluated parameters of the formulations.

14. CONCLUSION

Floating Drug Delivery System are retained in the stomach for a longer time and assist in improving the oral controlled delivery of drugs that have an absorption window in the particular region of the GI tract as well as for controlling the release of the drug having site-specific absorption limitation.

Venlafaxine HCl is a highly effective antidepressant was used as a model drug to develop a controlled release formulation. Venlafaxine HCl exhibits pH dependent solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt was made to develop gastroretentive delivery system of Venlafaxine HCl which increased the bioavailability of Venlafaxine HCl and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

15. BIBLIOGRAPHY

1. Neha narang. An updated review on floating drug delivery system. IJPR 2011; 3(1): 1-7.
2. Garg, R. and Gupta G.D., Progress in controlled gastroretentive delivery systems. Trop J Pharm Res., 7(3): 1055- 1066. 2008.
3. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS PharmSciTech 2005;6(3):E372-90.
4. Garg S, Sharma S. Gastroretentive Drug Delivery Systems. Pharmatech 2003; 160-6.
5. Bardonet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. J Control Rel 2006; 111:1-18.
6. Kluaunser A, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage form. J Control Rel 2003; 90:143-62.
7. Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. Int J Pharm 2000; 210(1-2):45-9.
8. Amit Kumar Nayak, Ruma Maji, Biswarup Das. Gastroretentive drug delivery system: a review. Asian Journal of Pharmaceutical and clinical Research 2010; 3(1):2-10.
9. Anand S. Surana, Rakhee K. Kotecha. An over review on various approaches to oral controlled drug delivery system via gastroretention. IJPR 2010; 2(2):68-72.
10. Praveen nasa, Sheefali mahant, Deepika sharma. Floating system: a novel approach towards gastroretentive drug delivery system. IJPP 2010; 2(3): 2-7.
11. Vaishali sharma, Lalit Singh, Vijay Sharma. A novel approach to combat regional variability: floating drug delivery system. Int. Jn. Of pharmaceutical science Review and Research 2011; 8(2): 154- 159.
12. Kumar D, Saini S, Seth N, Khullar R. Approaches, Techniques and evaluation of gastroretentive drug delivery system: An overview. IJRAP 2011; 2(3): 767-774.
13. KD Tripathi. Essential Of Medical Pharmacology, 6th edition, 2008, 447.
14. H L Sharma, K K Shrma. The textbook " principle of pharmacology", 2nd edition,2010,
15. Government of India, Ministry of health and family welfare, The Indian Pharmacopoeia commission, Ghaziabad; The Indian Pharmacopoeia 2007; vol 3.

16. Raymond C Rowe, Paul J Sheskey, Sian C Owen. Hand book of Pharmaceutical excipients. U.K, 5th edition.
17. Anil G, Satayanarayana T, Suresh Kumar P. Formulation and evaluation of gastroretentive floating tablets of Venlafaxine HCl. Int J Pharma 2011, 1(2), 76-82.
18. Adhimoolam Senthil, Thakkar Hardik Kumar Rajeshbhai, Dave Mehul Kumar Vinodbhai, Baghya Laxmi Bathu. Formulation and evaluation of mocoadhesive microspheres of venlafaxine Hcl. IRJP 2011, 2(4), 194-199.
19. Pare A, Yadav SK and Patil UK; Formulation and Evaluation of Effervescent Floating Tablet of Amlodipine besylate; Research J. Pharm. and Tech. 2008 1(4), Page 526-530.
20. S K Srikanth, S. Palanichamy, T. Raja Sekharan, A. Thanga Thirupathi; formulation and evaluation studies of floating matrix tables of nifedipine, International J. Pharma And Bio Sciences, 2010, 1(2), 1-8.
21. P Subhash Chandra Bose, P Srikanth Reddy, Valluru Ravi, D Sarita, T M Pramod Kumar; formulatin and evaluation of sustained release floating tablets of diltiazem Hcl using xanthan gum, RJPBCS, 2011, 2(2), 319-328.
22. Ajay Bagherwal, Dinesh Kumar Patidar, Pradeep Sharma; studies on formulation and evaluation of floating tablets of ciprofloxacin Hcl,IJCP, 2010, 5(2),1-4.
23. Raja Benhar Dickson, Thakkar Hardik Rajeshbai, Paramasivam Sureshkumar, Jamsheer Assin kk, Adimoolam Senthi; formulation and evaluation of gastro retentive floating tablets of glipizide, IJRAP, 2011, 2(3), 911-917.
24. A. Kotwal, A.K. Pathak, formulation and evaluation of intra gastric buoyant tablets of amoxicillin trihydrate; IJPLS, 2011, 2(2), 546-550.
25. Patel VM, Prajapati BG, Patel AK. Controlled release gastroretentive dosage form of verapamil hydrochloride. Int J Pharm Tech Res 2009; 1(2):215-21.
26. Jaimini M, Rana AC, Tanwar YS. Formulation and evaluation of famotidine floating tablets. Curr Drug Deliv 2007; 4(1):51-5.
27. Prabhu P, Harish NM, Guljar AM, Yadav B, Narayana CR, Satyanarayana D, Subrahmanayam EVS. Formulation and *In Vitro* Evaluation of Gastric Oral Floating Tablets of Glipizide. Indian J Pharm Educ Res 2008; 42(2):174-83.
28. Deshmukh VN, Jadhav JK, Sakarkar DM. Formulation and in vitro evaluation of theophylline anhydrous bioadhesive tablets. Asian J Pharm Sci 2009:54-8.

29. Rahman Z, Ali M, Khar R. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm 2006; 56(1):49-57.
30. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. Development and in vitro evaluation of an oral Floating matrix table formulation of diltiazem hydrochloride. AAPS Pharm Sci Tech. 2007; 8: E1. E9.
31. Arza RAK, Gonugunta CSR, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprvenlafaxine hcl hydrochloride tablets. AAPS PharmSciTech 2009;10(1):220-6.
32. Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: Design and optimization using combination of polymers. Acta Pharm 2008; 58: 221-9.
33. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur J Pharm Biopharm 2008; 69(1):255-63.
34. Singh S, Singh J, Muthu MS, Balasubramaniam J, Mishra B. Gastroretentive drug delivery system of metoclopramide hydrochloride: Formulation and in vitro evaluation. Curr Drug Deliv 2007; 4(4):269-75.
35. Vinay pandit, Suresh, Hemanth joshi. Formulation and invitro evaluation of amoxicillin. IJPBS 2010, 1(2), 1-10.
36. Mukopadhaya, Goswami,Satish. Formulation and evaluation of floating bioadhesive tablets of ciprofloxacin.Inter J pharmacy sci 2010,2(3),113-115.
37. Atul kumar, Shailandra kumar and Anita verma. Formulation and development of buoyant controlled release tablets containing chitosan. Optimization of invitro dissolution and release kinetics. Inter J pharmacy sci 2011, 3(2), 81-85.
38. Sreenivasa reddy, Mahendra kumar, Rohit, Chandra sekar. Development of floating tablets by using natural gums.IJPWR2010, 1(3), 1-18.
39. Lirong Liu, Wiliam R Porter. Developing solid oral dosage forms: pharmaceutical theory and practice, chapter IV, 125-135.
40. Pare A, Yadav SK, Patil UK. Formulation and Evaluation of Effervescent Floating Tablet Of Amlodipine besylate. Research J. Pharm. and Tech2008, 1(4), 526-530.
41. Peck, Baley, McCurdy, Banker. Tablet formulation and design, 88-120.
42. Herbert A. Liberman, Leon Lachman, Joseph B. Schwartz. Pharmaceutical dosage forms: tablets, U.K, volume 1, 1-5.

43. Lachman Leon, Lieberman Herbert A. Pharmaceutical Dosage Forms: Tablets. In: The Theory and Practice of Industrial Pharmacy. Lea and Febiger, U.S.A, 1991; 3rd edition: 293-345.
44. Subrahmanyam CVS. Textbook of physical pharmaceutics. 2nd ed. Delhi:Vallaba prakashan;2003.p.180-234.
45. Sameer Singh, Kalpana Prajapati,A K Pathak,A Mishra. Ormulation and Evaluation of Floating Tablet of Captopril. Int.J. PharmTech Res.2011,3(1), 333-341.
46. Aulton ME. Pharmaceutics: the science of dosage forms design, 2nd edition, Churchill.
47. Vishnu M Patel, Bhupendra G Prajapati, Anand K Patel. Controlled release gastroretentive dosage form of verpamil hydrochloride. Int.J. PharmTech Res.2009, 1(2), 215-221.
48. Vinay pandit, Sarasija suresh, Hemanth joshi. Gastroretentive drug delivery system of amoxycilin: formulation and in-vitro evaluation. IJPBS 2010, 1(2), 1-10.
49. Korsemeyer RW, Peppas N A. Macromolecular and modeling aspects of swelling – controlled Systems. In: Mansdrofsz, Roseman TJ, ad, Controlled Release Delivery systems. New – York, NY: Marcel Dekker; 1983:77.
50. ICH Q1A (R2) stability testing guidelines: stability testing of new drug substances and products.
51. Shah S.H, Patel J.K and Patel N.V., Stomach specific drug delivery systems: A review International Journal of PharmTech ResearchVol.1, No.3. 2009; 623-633.
52. Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985; 19:77- 83.
53. Deshpande A.A., Shah N.H., Rhodes C.T., Malick W., Development of a novel controlledrelease system for gastric retention, Pharm. Res. 1997; 14:815-819.
54. Kawashinia Y, Niwa T. Takcuchi H. Hino T, Itoh Y. Hallow microspheres for use as afloating controlled drug delivery system in the stomach. J.Pharm. Sci.1992; 81(2): 135-140.
55. Ichikawa M., .Watemblc S., Miyake V.A. Multiple unit oral floating dosage systems I: Preparation and in-vivo evaluation of' floating and sustained release characteristics. J.Pharm. Sci. l99l; 80:l062-1066.

56. Rossi S, ed. eAMH [online]. Adelaide: Australian Medicines Handbook, 2012.
57. Williams JW Jr, Mulrow CD, Chiquette E, et al. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med 2000;132:743–56.
58. Ellis P; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Australian and New Zealand clinical practice guidelines for the treatment of depression. Aust N Z J Psychiatry 2004;38:389–407.
59. National Collaborating Centre for Mental Health. Depression: the NICE guideline on the treatment and management of depression in adults (updated edition). London: National Institute for Health and Clinical Excellence, 2010.
60. R Garg*, GD Gupta, Progress in controlled gastroretentive delivery systems, Tropical Journal of Pharmaceutical Research, September 2008; 7 (3) : 1055-1066
61. Desai S, Bolton S, A Floating controlled release system: In-vitro – in-vivo evaluation, pharm. Res. 1993; 10:1321-1325
62. Patel, V.F., Patel N.M., Yeole, PG., Studies on formulation and evaluation of ranitidine floating tablets; Ind. J. Pharm. Sci., 2005,67(6), 703-709.