DESIGN AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AN ANTIHYPERTENSIVE DRUG USING DIFFERENT NATURAL POLYMERS

THESIS

Submitted to

The Tamil Nadu Dr .M.G.R Medical University, Chennai

in partial fulfillment for the award of Degree of

DOCTOR OF PHILOSOPHY

IN

FACULTY OF PHARMACY

Submitted by

Mrs. D. VANI, M. Pharm.,

Under the guidance of

Prof. Dr. V. VAIDHIYALINGAM, M. Pharm., Ph. D.,

DIRECTOR

K.K.COLLEGE OF PHARMACY

JANUARY 2018

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD, THASILDAR NAGAR

MADURAI - 20

Dr.V.Vaidhiyalingam M.Pharm., Ph.D.,

Director-Cum-Professor

Department of Pharmaceutical Chemistry,

K.K.College of Pharmacy

KRA Campus, 1/161,

Sankaralinganar Road, Gerugambakkam,

Chennai – 600122.

TamilNadu.

CERTIFICATE

This is to certify that the Ph.D., dissertation entitled **" DESIGN AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AN ANTIHYPERTENSIVE DRUG USING DIFFERENT NATURAL POLYMERS"** being submitted to the TN. Dr. M.G.R. Medical University, Chennai for the award of **Doctor of Philosophy** in **Faculty of Pharmacy** was carried out by **Mrs. D.Vani** at Ultra college of pharmacy , Madurai under my direct supervision and guidance to my fullest satisfaction. The content of this thesis in full or in parts have not been submitted to any other institute or university for the award of any degree or diploma.

Dr.V.Vaidhiyalingam M.Pharm. Ph.D.,

Guide

Place : Chennai

Date :

Dr.A.Babu Thandapani M.Pharm., Ph.D.,
Pricipal and Professor
Department of Pharmaceutical Biotechnology,
Ultra College of Pharmacy
4/235, College Road, Thasildar Nagar,
Madurai – 625020., TamilNadu.

CERTIFICATE

This is to certify that the Ph.D., dissertation entitled **" DESIGN AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AN ANTIHYPERTENSIVE DRUG USING DIFFERENT NATURAL POLYMERS"** being submitted to the TN. Dr. M.G.R. Medical University, Chennai for the award of **Doctor of Philosophy** in **Faculty of Pharmacy** was carried out by **Mrs. D.Vani** at Ultra College of Pharmacy , Madurai under the supervision and guidance of **Prof. V. Vaidhiyalingam**, Director, K.K.College of Pharmacy, Chennai – 600122.

Dr.A.Babu Thandapani, M.Pharm. Ph.D.
Principal / Co-Guide

Place : Chennai
Date :

DECLARATION

I hereby declare that the Ph.D., dissertation entitled **" DESIGN AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF AN ANTIHYPERTENSIVE DRUG USING DIFFERENT NATURAL POLYMERS"** being submitted to the TN. Dr. M.G.R. Medical University, Chennai for the award of **Doctor of Philosophy** in **Faculty of Pharmacy** was carried out under the direct supervision and guidance of **Dr.V.Vaidhiyalingam M.Pharm., Ph.D.,** Director, K.K. College of Pharmacy, Chennai during the academic year **2013 - 2017.** The content of this thesis in full or in parts have not been submitted to any other institute or university for the award of any degree or diploma.

Mrs.D.VANI, M.Pharm.

Place : Chennai

Date :

ACKNOWLEDGEMENT

I wish to express my sincere gratitude to my guide **Prof.V.Vaidhiyalingam, M.Pharm., Ph.D., Director** K. K. College of Pharmacy, Chennai for his continue support of my Ph.D., study and related research, for his patience, motivation and immense knowledge. His guidance helped me in all the time of research and writing of thesis. I could not have imagined having better guide and mentor for my Ph.D., studies.

First and foremost, I wish to express my deepest gratitude to respected **Prof.K.R.Arumugam, M.Pharm., Chairman** K.K.College of Pharmacy,Chennai for his help and support.

I would like to Extend my Gratitude to **Prof.Dr.A.Meena, M.Pharm., Ph.D., Principal** K.K.College of Pharmacy, Chennai for her heartily cooperation and encouragement, valuable ideas and timely support whenever needed.

I express my deep sense of gratitude to **Prof.Dr.A.Babuthandapani, M.Pharm., Ph.D., Head of the Department, Department of pharmaceutical Biotechnology,** Ultra college of pharmacy for his valuable guidance and providing facilities to work successfully.

It's my Privilege and honor to extend my profound gratitude and express my indebted to my professor **Dr.C.Vijaya , M.pharm., Ph.D.,Dean,** Ultra college of pharmacy, Madurai for her precious guidance, encouragement and abundant help, her enthusiastic and inspiring discussion and timely suggestion which proved for the success of this research work.

I am grateful to my friends **Dr.D.Krishnarajan, M.Pharm., Ph.D., Mr.T.Ethiraj, M.Pharm., Ph.D., Mrs.R.Revathy, M.Pharm., Dr.S.Palanisamy, M.Pharm., Ph.D., Dr. N. Tamilselvi, M.Pharm., Ph.D.,** and for their stimulating discussion, valuable advices, throughout my research. Without their precious support, I would not be possible to complete this results.

My heartfelt thanks to **Mr.K.Karthik, M.Pharm., Dr.R.Prakash. M.Pharm., Ph.D., Head,** Department of Pharmacology , K.K. College of Pharmacy, all other helped us throughout this research.

I extend my heartfelt thanks to all my colleagues for their encouragement and support. I take this occasion to owe my indebted gratitude towards all those who have continued to support me accomplished this work. This thesis is the result of unbounded and immense contribution and support by many people.

Last but not the least, I would like to thank my family, my parents and to my husband for supporting me spiritually throughout writing this thesis.

D.VANI, M.Pharm.

CONTENTS

LIST OF ABBREVIATIONS AND SYMBOLS

Avg	Average
λmax	Absorption maximum
ρ_b	Bulk density
CO_2	Carbon di oxide
cm	Centimetre
CMC	Carboxy Methyl Cellulose
Cps	Centipoise
CR-GRDF	Controlled Release Gastro Retentive Dosage Forms
CRDDS	Controlled Release Drug Delivery System
ºC	Degree centigrade / Celsius
CNS	Central Nervous System
DDS	Drug Delivery System
FDDS	Floating Drug Delivery System
FTIR	Fourier Transform Infra Red
FLT	Floating Lag Time
GI	Gastro Intestine
GIT	Gastro Intestinal Tract
GRT	Gastro Retentive Time
GRDDS	Gastro Retentive Drug Delivery System
g/cm^3	Gram per Cubic centimetre
HBSTM / HBS	Hydro-dynamically balanced system
Hcl	Hydrochloric Acid
HEC	Hydroxy Ethyl Cellulose
HPMC	Hydroxy Propyl Methyl Cellulose
HPLC	High Performance Liquid Chromatography
HPTLC	High Performance Thin Layer Chromatography
h	Hour
NMR	Nuclear Magnetic Resonance
IMMC	Interdigestive Migration Myloelectric Complex
ICH	International Conference on Harmonization
KBr	Potassium bromide
MC	Methyl Cellulose

MCC	Micro Crystalline Cellulose
MMC	Migration Myloelectric Complex
ml	Millilitre
mm	Millimetre
mg	Milligram
mmHg	Millimetres of Mercury
NaCMC	Sodium Carboxyl Methyl Cellulose
µg	Micro gram
min	Minute
No	Number
nm	Nano Meter
non GRDF-CR	Non controlled release Gastro Retentive Dosage Forms
NSAID	Non Steroidal Anti Inflammatory Drugs
PVA	Poly Vinyl Alcohol
PMMA	Poly Methyl Methacrylate
%	Percentage
rpm	Rotations per Minute
RH	Relative Humidity
Na	Sodium
o/w	Oil in water
SEM	Scanning Electron Microscope
SGF	Simulated Gastric Fluid
sec	Seconds
S.D	Standard Deviation
ρ_t	Tapped Density
TFT	Total Floating Time
USP	United States Pharmacopeia
UV	Ultraviolet
w/v	Weight per Volume
>	Greater than
<	Smaller than
≥	Greater than or equal to

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

The objective of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve and maintain a desired drug concentration. Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration include oral, topical, nasal, rectal, vaginal and ocular, etc.[1] Out of these routes, oral route of drug delivery is considered as the most promising route of administration due to reasons like ease of administration, ease of production, reduction in cost of therapy and high level of patient compliance.[2,3]

In humans, the relative gastric emptying time ranges in between 2-3 h through the major absorption zone like stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leads to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. The contact of the DDS with the membrane in which the drug is absorbed increases the rate of drug absorption which leads to the development of a unique oral controlled release dosage form with gastro-retentive properties.[4,5,6]

Drugs that get absorbed from stomach or show local effect should spend maximum time in stomach which is very difficult to occur in case of conventional dosage forms. Conventional dosage form achieves and maintains the drug concentration within the therapeutically effective range for treatment, only after it is taken several times a day. The development of oral sustained-controlled release formulations is an challenge to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in systemic circulation for a long time[1]. Drugs with absorption window in a particular region of GIT are difficult to be designed as oral controlled release drug delivery system (CRDDS). This is because only the drug released in the region prior and surrounding area of the absorption window is available for absorption. The drug released from CRDDS after the absorption window will be waste or negligible absorption takes place. The CRDDS

with ability to retain in stomach is called as gastro retentive drug delivery system (GRDDS). It can assist in controlling the release of drug before absorption window for prolonged period of time thus ensures increased bioavailability.[6]

1.1 Gastrointestinal retention:[1]

Gastro retentive systems can stay in the gastric region for number of h to prolong the gastric residence time (GRT) of drugs. Prolonged gastric retention increases bioavailability, minimizes drug waste to other parts of the body, increases solubility for drugs that are less soluble in a high pH environment, local drug delivery of the drug to the stomach and proximal small intestines. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) for maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT.

1.1.1 Gastrointestinal Tract Physiology:

The stomach is divided into three parts: fundus, body and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material and antrum is for mixing motions and acts as a pump for gastric emptying by propelling actions.

1.1.2 Stomach Physiology:

The stomach is an expanded section of the digestive tract between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that it has an additional, oblique layer of smooth muscle inside the circular layer that assists in the performance of complex grinding motions.

In fasting state, the stomach is constricted and its mucosa and sub mucosa are thrown up into distinct folds called rugae shown in fig. 1.

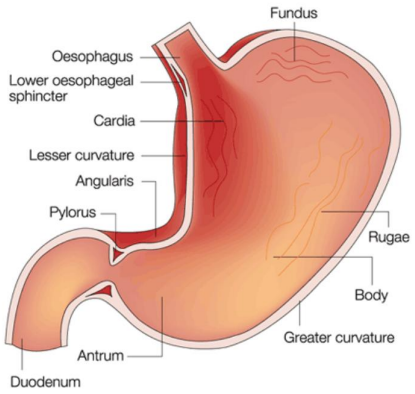


Fig. 1: Physiology of stomach

There are 4 types of secretary epithelial cells that cover the surface of the stomach and extended down into gastric pits and glands[3,4]:

- Mucous cells : Secrete alkaline mucus that protects the epithelium against shear stress and acid.
- Parietal cells : Secrete hydrochloric acid.
- Chief cells : Secrete pepsin, a proteolytic enzyme.
- G cells : Secrete the hormone gastrin.

The contraction of gastric smooth muscle serves two basic functions:

- Ingested food is crushed into large pieces, grounded in fine state, mixed and liquefied to form **Chyme**.
- Chyme is pumped through the pyloric canal into the small intestine (gastric emptying).

1.1.3 Gastric motility:

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility, for e.g. both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The patterns of gastric motility results from the

integtaion of smooth muscle cells with more of inhibitory and stimulatory signals. Liquid readily pass through the pylorus in spurts, but solids should be reduced to a diameter of less than 1-2 mm before passing pyloric gatekeeper. The gastric volume is important for dissolution of the drug in dosage form *in vivo*. The resting volume of the stomach is 25-50 ml. There is a huge dissimilarity in gastric secretion of normal and achlorhydric individuals. Gastric pH also has pronounced effect of absorption of drug from delivery system. The pH of fasting stomach is 1.2-2.0 and in fed condition 2.0-6.0.

1.1.4 Gastric emptying rate:

Gastric emptying occurs in both fasting and fed state. The pattern of motility is separated into two stages. During the fasting stage, an inter-digestive series of electrical events takes place that pass through the gastrointestinal area every 2 to 3 h. This is known as inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC). This MMC is further seperated into 4 phases as described by *Wilson* and *Washington*.

- ✓ **Phase I** (Basal phase) lasts for 40 to 60 min with rare contractions.
- ✓ **Phase II** (Preburst phase) lasts for 40 to 60 min with irregular action potential and contractions. As the phase advances, the intensity and frequency increases gradually.
- ✓ **Phase III** (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period due to the wave that all the undigested material is sweep out of the stomach into the small intestine. It is also called as the housekeeper wave.
- ✓ **Phase IV** lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles. After the ingestion of meal, the pattern of contractions changes from fasted to fed state. This is also called as digestive motility pattern and consists of continuous contractions as in Phase II of fasted state. These contractions result in decreasing the size of food particles less than 1

mm, propelled into the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in decelerate of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates found that orally administered controlled release drug delivery system has two troubles like short gastric residence time and erratic gastric emptying rate.

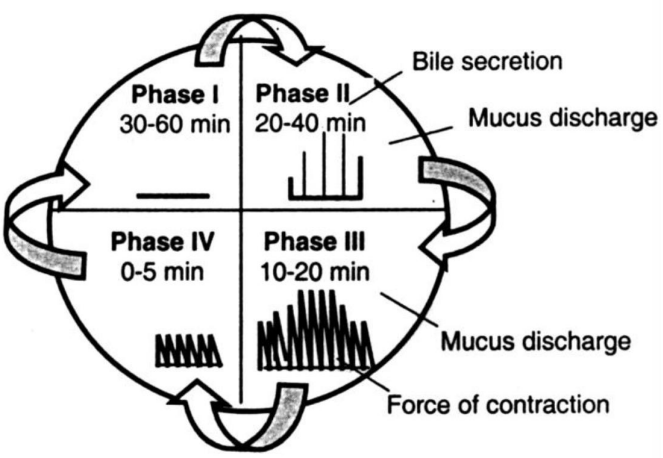


Fig. 2: Motility pattern in gastrointestinal tract

1.2 APPROACHES TO GASTRIC RETENTION:[2,7-10]

Various types of systems have been developed to increase the GRT of dosage forms by employing range of concepts. These systems have been classified on the basis of principle of gastric retention.

- ✓ High density systems
- ✓ Swellable and expanding systems
- ✓ Incorporating delaying excipients
- ✓ Modified systems
- ✓ Mucoadhesive and bioadhesive systems
- ✓ Floating systems

1.2.1 High density systems:

It has density of approximately 3 g/ml are retained in the rugae of stomach and is capable of withstanding its peristaltic movements. The main difficulty in these systems is difficult to prepare with a large amount of drug (>50%) and attain necessary density of 2.4-2.8 g/ml. Diluents such as barium sulphate, zinc oxide, titanium oxide and iron powder should be used to prepare such systems.

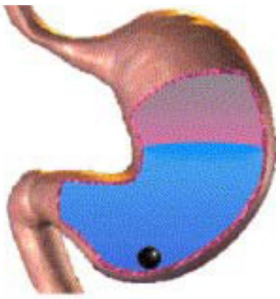


Fig. 3: High density system

1.2.2 Swelling and expanding systems:

Such systems absorb water and enlarge in size. These systems are also called as plug type system as they remain in the pyloric sphincters. These polymeric matrix dosage forms stay in the gastric cavity for more number of h even in fed state. Focus should be given for the selection of polymer with the appropriate molecular weight and swelling properties could attain controlled and sustained drug release. When this system comes in contact with gastric fluid, the polymer absorbs water and swells. The extensive swelling of these polymers is due to the presence of cross linking in the hydrophilic polymer network. The cross linking stops the dissolution of polymer and sustain the physical integrity of the dosage form. High degree of cross linking prevent the swelling ability of the dosage form and maintains its physical integrity for prolonged period. Low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.

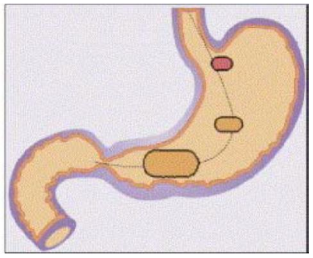


Fig. 4: Swellable system

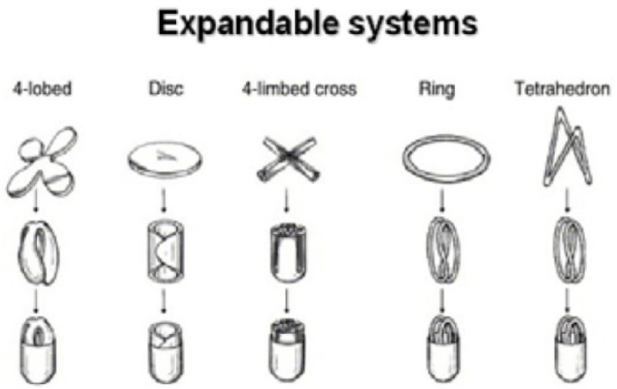


Fig. 5: Different geometric forms of unfoldable systems

1.2.3 Incorporating delaying excipients:

It consist of feeding of digestible polymers or fatty acid salts that changes the motility pattern of the stomach to a fed stage decreases the gastric emptying rate and allow the prolongation of the drug release. Prolongation of GRT of this system is due to incorporation of delaying excipients like trietanolamine myristate in a dosage form.

1.2.4 Modified systems:

It is the system with non-disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends which increases the GRT depending on size, shape and flexural modules of dosage form.

1.2.5 Mucoadhesive & bioadhesive systems:

It is used to localize a dosage form within the lumen to enhance the drug absorption in a site specific approach. This system involves the use of bioadhesive polymers, which can stick to the epithelial surface in the stomach include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

On the basis of binding of polymers to the mucin-epithelial surface, the adhesion is subdivided into two broad categories[11]

a) Hydration mediated adhesion:

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

b) Bonding mediated adhesion:

   The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding [may be either covalent (primary) or ionic (secondary) in nature]. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions (i.e., hydrogen bonds). The hydrophilic functional groups are responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

1.2.6 Floating systems:

It has bulk density less than that of gastric fluids and remains floating in the stomach without changing the gastric emptying rate for a prolonged period of time. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system and the residual system is pushed out from the stomach after the drug is released. Floatation of this system in stomach can be achieved by incorporation of floating chamber filled with vacuum, air or inert gas.

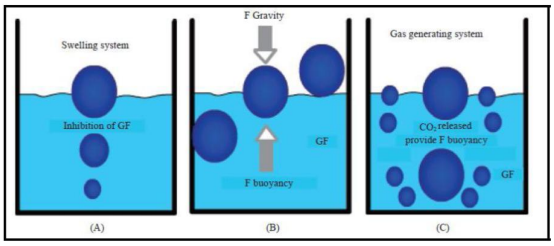


Fig. 6: The mechanism of floating systems

1.3 Floating Drug Delivery System (FDDS):

Floating drug delivery systems or hydro dynamically controlled systems are low density systems that remain buoyant over the gastric contents without disturbing the gastric emptying rate for a prolonged period of time. These are useful for drugs that are poorly soluble or unstable in intestinal fluids[2]. When the system is floating on the gastric contents, the drug is released at the controlled rate from the system and is emptied from the stomach after the release of drug results in an improved gastric retention time had control of the fluctuations in plasma drug concentration, achieve greater therapeutic benefit of the drug substance. For example, drugs that are absorbed in the proximal part of the GIT and drugs that are poorly soluble in or degraded by the alkaline pH may benefit from prolonged gastric retention. In addition, for local and sustained delivery of drug to the stomach and proximal small intestine is used to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability and therapeutic efficacy and possible reduction of dose size.[2]

Minimum gastric content is needed for proper attainment of the floating. A minimum floating force (F) is also required to keep the dosage form buoyant on the surface of the meal.

To measure the floating force, a novel apparatus for determination of resultant weight was used which operates by measuring continuously the force equivalent to F (as a function of time require) required to maintain the submerged object. The object floats better if F is on the higher positive side.

$$F = F \text{ buoyancy} - F \text{ gravity}$$
$$= (DF - Ds)\, gv \text{--- (1)}$$

where,

F= total vertical force, DF = fluid density, Ds= object density, v = volume and g = acceleration due to gravity[7,12]

1.4 The major requirements for FDDS:[7,9,10]

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 g/cm^3).
- It must form a cohesive gel barrier.

The approach to design floating dosage forms of single and multiple-unit systems with inherent low density system could be entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils or foam powder). The single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of systems could be successfully combined with accurate control of the resulting drug release patterns. Single unit dosage form suffers from some difficulties like sticking together or being obstructed in the GIT that produces irritation. Multiple-unit floating systems had advantages like reduce inter and intra-subject availabilities in drug absorption and low dose dumping. Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (micro-balloons) prepared by the emulsion solvent diffusion method, micro particles based on low density foam powder, beads prepared by emulsion gelatin method etc., can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs.

1.5 Classification of Floating Drug Delivery System:[1,2, 7-17]

A. Effervescent system

- Volatile liquid containing system
- Gas generating system

B. Non-effervescent system:

- Colloidal gel barrier system.
- Alginate beads.
- Hollow microspheres / Micro-balloons.
- Intragastric Floating Drug Delivery Device / Microporous compartment System

1.5.1 Effervescent Systems:

These systems are manufactured with swellable polymers such as methylcellulose and chitosan with various effervescent compounds, eg, sodium bicarbonate, citric acid and tartaric acid or matrices containing chambers of liquid that gasify at body temperature. When these systems come in contact with the acidic gastric contents, carbon dioxide is liberated and gas entrapped in swollen jellified hydrocolloids which provides buoyancy to the dosage forms. Other materials include mixture of sodium alginate and sodium bicarbonate.

1.5.1.1 Volatile liquid containing systems:

The GRT of this system is sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane) that gasifies at body temperature to cause the inflatation of the chamber in the stomach. It consist of a bio-erodible plug made up of PVA, polyethylene, etc. that progressively dissolves and causes the inflatable chamber to release gas and collapses after a predetermined time to allow the spontaneous ejection of the inflatable systems from the stomach. The device inflates and the drug is continuously released from the reservoir into the gastric fluid.

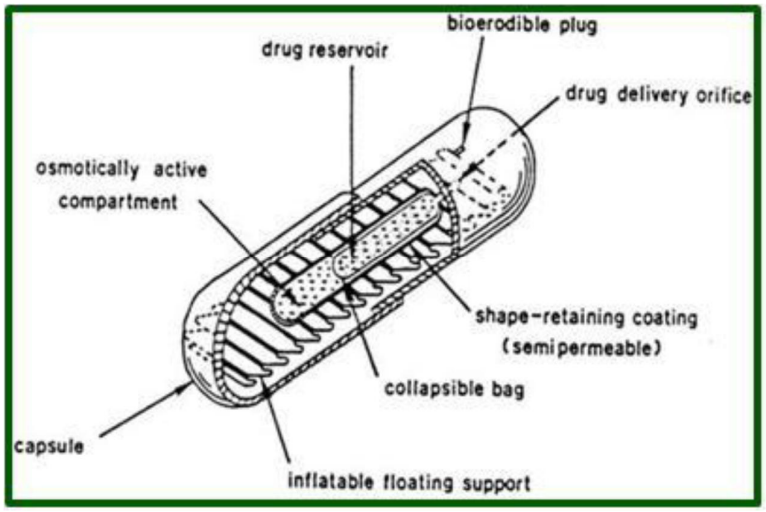


Fig. 7: Volatile liquid containing system

1.5.1.2 Gas-generating Systems:

It utilizes effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate carbon dioxide that gets entrapped in the gellified hydrocolloid layer of the systems thus reduces its specific gravity and make it to float over chyme.

It utilizes matrices formulated with swellable polymers like methocel, polysaccharides like chitosan and effervescent components like sodium bicarbonate, citric acid and tartaric acid. The multiple type of this system is composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents contains separated sodium bicarbonate and tartaric acid to avoid direct contact between the two agents. These sub layers were surrounded by a swellable polymer contains polyvinyl acetate and purified shellac. When this system was placed in the buffer at 37^{o}C, it settles down and the solution permeate dinto the effervescent layer through the outer swellable membrane. CO_2 generated by the neutralization reaction between the two effervescent agents, producing swollen pills or balloons with density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and viscosity and the Para-amino benzoic acid was released in a sustained manner.

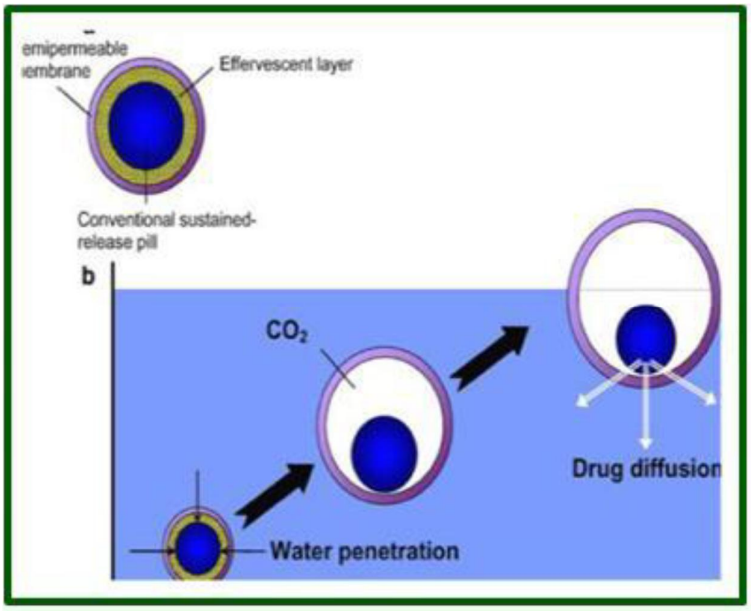


Fig. 8: Principle mechanism of floating by CO_2 gas releasing method

1.5.2 Non-effervescent systems:

These systems utilize gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. In this system, the drug is mixed with gel-forming hydrocolloid. After oral administration, this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. This swollen gel-like structure act as reservoir and allow sustained release of drug through the gelatinous mass. Excipients used include HPMC, polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

1.5.2.1 Colloidal gel barrier systems or Hydro-dynamically balance system (HBS^{TM}):

It was first developed by *Sheth* and *Tossounian* in 1975. It contains drug with more amount of one or more gel forming hydrocolloids (HEC, HPMC, NaCMC, polysacchacarides) and matrix forming polymer (polycarbophil, polyacrylates and polystyrene) usually administered in HB-capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts

buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydro dynamically balanced system.

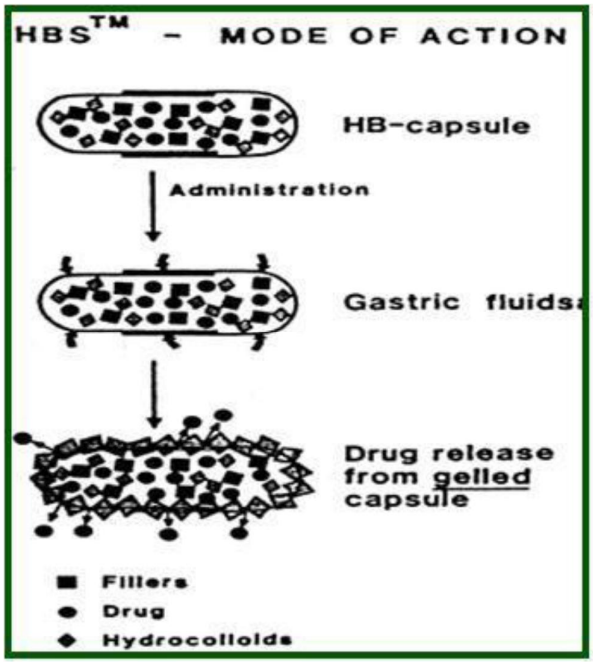


Fig. 9: Working principle of hydro-dynamically balanced system

1.5.2.2 Alginate beads:

It is a multi-unit floating systems prepared from freeze-dried calcium alginate. Spherical beads (2.5 mm in diameter) are formulated by dropping sodium alginate solution into aqueous solution of calcium chloride which causes precipitation of calcium alginate. The beads are separated, snap-frozen in liquid nitrogen and freeze-dried at -40ºC for 24 h, lead to the formation of a porous system maintains the floating for 12 h. It gave prolonged GRT of more than 5.5 h. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, eudragit, agar and low methoxylated pectin etc. Floating

and drug release from dosage form are dependent on quantity of polymers, the plasticizer-polymer ratio and the solvent used for formulation. These micro-balloons floats constantly on the surface of an acidic dissolution media containing surfactant for more than 12 h. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

1.5.2.3 Hollow microspheres:

Hollow microspheres (micro-balloons) are formulated by emulsion solvent diffusion method. In this method a solution or dispersion of drug and polymer is prepared in solvent (like dichloromethane, ethanol, isopropanol or a combination of these). This dispersion/solution is introduced into an aqueous solution of PVA (polyvinyl alcohol) forms an O/W type emulsion. This emulsion is agitated using propeller type agitator to remove the organic solvent, which produces the micro-balloons, size between 500-1000 mm. Hollow microspheres with a drug loaded in their outer shells by an emulsion solvent diffusion method. Ibuprofen loaded micro-balloons are prepared with the ethanol/dichloromethane solution of a drug and to this an enteric acrylic polymer was poured into an aqueous solution of PVA that was maintained at 40°C, with constant stirring. The gas generated in the dispersed polymer droplet by the evaporation of dichloromethane forms an internal core in the microsphere with drug. The prepared micro-balloons floated continuously on the surface of acidic dissolution media containing surfactant for more than 12 h *in vitro*. The mechanism of formation of microsphere is reported that ethanol was a good solvent for acrylic polymer, preferentially diffuses out of dispersed droplets (organic phase) into an aqueous phase, the acrylic polymer instantly solidifies as a thin film at the interface between the aqueous phase and organic phase. It has also been reported that when the diffusion rate of solvent out of emulsion droplet was too slow, microspheres coalesced together. Conversely, when the diffusion rate of solvent was too fast, the solvent diffused into the aqueous phase before stable emulsion droplets could form, causing the aggregation of embryonic microsphere droplets.

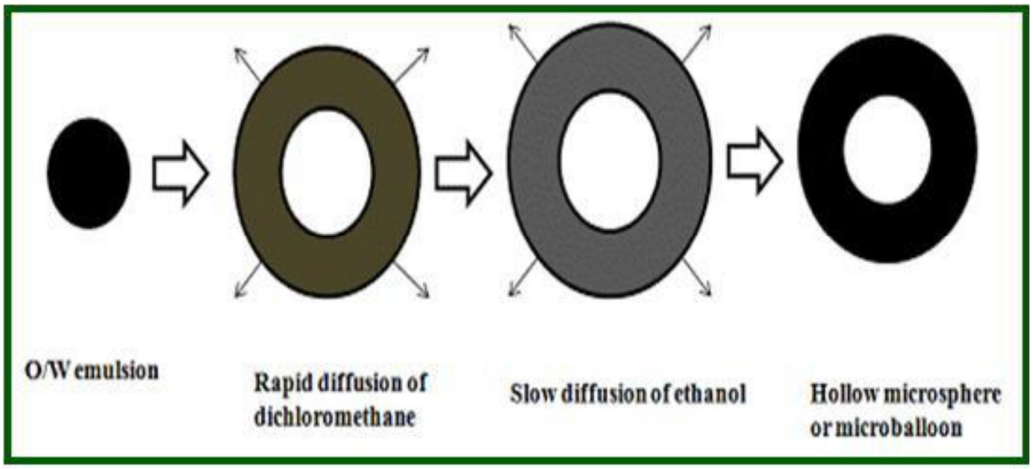


Fig. 10: Formulation of floating hollow microsphere or micro-balloon

1.5.2.4 Intragastric / Microporous compartment system:

This system composed of a drug encapsulated in a microporous compartment contains pores on top and bottom surfaces. The marginal walls of the reservoir compartment were completely sealed to avoid any physical contact of the undissolved drug with walls of the stomach. In the stomach, the floatation chamber containing entrapped air causes this system to float over the gastric content. Gastric fluid enters through the aperture into system, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption. Novel Levodopa gastro-retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. *In vitro* studies showed that unfolded form reached within 15 min after administration and it was confirmed *in vivo* in beagle dogs. The unfolded form was maintained for at least 2 h. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

1.5.3 Raft forming systems:

This system is used in the delivery of antacid and for drugs used to treat local diseases in stomach. On contact with gastric fluid, a gel forming solution swells and

forms a viscous cohesive gel containing entrapped CO_2 bubbles which forms raft layer on top of gastric fluid which releases drug slowly in stomach.

1.5.4 Other techniques: [5,18-21]

Two patents on FDDS were issued to the Alza Corporation to drug delivery devices for the controlled administration of drug.

1.5.4.1 Inflatable gastrointestinal drug delivery system:

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber which consists of a liquid (e.g., ether) that gasifies at body temperature to cause the chamber to inflate in the stomach and float. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.

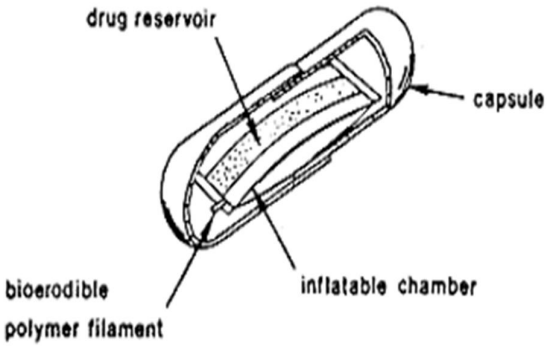


Fig. 11: Inflatable gastrointestinal drug delivery system

1.5.4.2 Intragastric osmotically controlled drug delivery system:

This system composed of an osmotic pressure controlled gadget and an inflatable floating support in a bio erodible capsule. When this system reaches the

site of drug administration, e.g., the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled gadget. The inflatable floating support is made from a deformable hollow polymeric bag which contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled gadget consists of two components: drug reservoir compartment and an osmotically active compartment. The drug reservoir is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a orifice for drug delivery. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is then created which acts on the collapsible bag and in turn forces the bag reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflat the support. The deflated drug delivery system is then emptied from the stomach

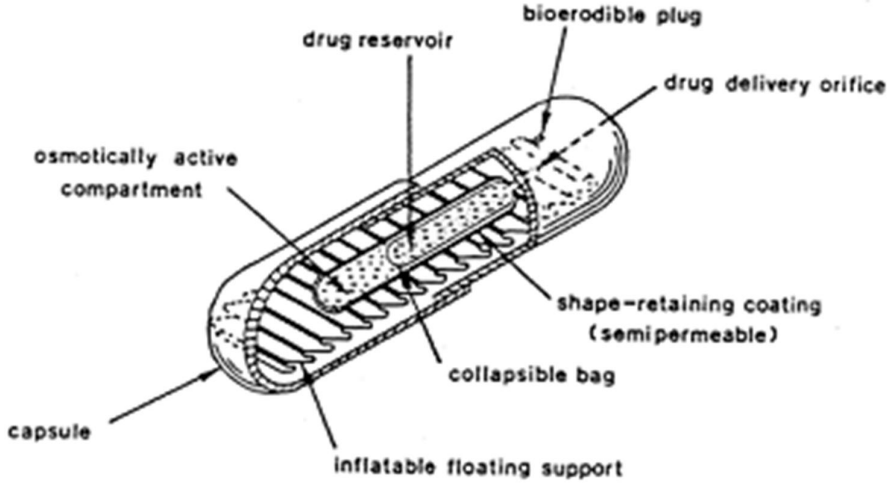


Fig. 12: Intragastric osmotically controlled drug delivery system

1.6 Advantages of FDDS:[1,2,12,22-23]

- ✓ It is very useful for drugs that are particularly absorbed from stomach or the proximal part of the small intestine, e.g., Riboflavin and Furosemide
- ✓ It minimizes the fluctuations in plasma drug concentration and prevents concentration dependent adverse effects associated with peak concentrations of drug found useful for drugs with a narrow therapeutic index
- ✓ It is advantageous for drugs with poor bioavailability because of site-specific absorption from the upper part of the GIT thereby maximizing their absorption.
- ✓ It is useful for drugs with short half life to get an appreciable therapeutic activity
- ✓ Enhancement of the bioavailability for drugs which can metabolized in the upper GIT
- ✓ It is used to overcome the adversities of gastric retention time as well as the gastric emptying time
- ✓ The duration of treatment through a single dose is efficient that releases drug over an extended period of time
- ✓ Site-specific drug delivery minimises or eliminating the side effects
- ✓ Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine
- ✓ It is advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach for better response
- ✓ Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of Aspirin and other similar drugs
- ✓ It is advantageous for drugs absorbed through the stomach eg: Ferrous salts and antacids by increasing absorption of drug due to increased GRT
- ✓ It minimizes the mucosal irritation by releasing drug slowly
- ✓ It is useful in the treatment of gastrointestinal disorders such as gastro esophageal reflux

1.7 Disadvantages of floating drug delivery system:[1,2,8-10,21-24]

- ✓ It is not feasible for those drugs that suffers from solubility or stability problem in GI tract
- ✓ It requires a high level of gastric fluid in the stomach for drug delivery to float and work efficiently in fluid. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach
- ✓ GRT is influenced by many factors like gastric motility, pH and presence of food which are never constant and could not predict the buoyancy
- ✓ It offers high variability in gastric emptying time
- ✓ The dosage form should be administered with a minimum of glass full of water (200-250 ml)
- ✓ The drugs, which are absorbed throughout GIT, which under go first-pass metabolism (Nifedipine, Propranolol etc.), are not desirable candidate
- ✓ The ability of drug to remain in the stomach depends upon the subject being positioned upright
- ✓ The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal
- ✓ It is not suitable for drugs that cause gastric lesions e.g. Non steroidal anti inflammatory drugs.
- ✓ It is not advantageous for the drugs that are unstable in the strong acidic environment and complete absorbtion throughout the gastro intestinal tract
- ✓ The mucus on the walls of the stomach is in the state of constant renewal, resulting in the unpredictable adherence
- ✓ Faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time

- ✓ The ability to float relies in the hydration state of dosage form
- ✓ In all the above, the most important and primary requirement for the success is the physical integrity of the dosage form

1.8 DRUG CANDIDATES SUITABLE FOR FDDS:[2,3,7,12]

- ❖ Drugs with narrow absorption window in gastrointestinal tract

  e.g. L-DOPA, Para-aminobenzoic acid, Furosemide, Riboflavin

- ❖ Absorption from upper gastrointestinal tract

  e.g. Ciprofloxacin

- ❖ Drugs with low pKa and remains unionized in stomach for better absorption.

- ❖ Drugs that act locally in the stomach

  e.g. Misroprostol, Antacids

- ❖ Drugs which are principally absorbed in the stomach

  e.g. Calcium supplements, Chlordiazepoxide and Cinnarazine.

- ❖ Drugs that disturb normal colonic microbes

  e.g. Antibiotics used for the eradication of *Helicobacter pylori* such as Tetracycline, Clarithromycin, Amoxicillin

- ❖ Drugs with low solubility at high pH values

  e.g. Rosiglitazone maleate, Diazepam, Chlordiazepoxide, Verapamil, Captopril, Ranitidine Hcl, Metronidazole

- ❖ Drugs that gets degraded in alkaline pH

  e.g. Doxifluridine, which degrades in small intestine

- ❖ Drugs that causes sudden increase of drug concentration in the stomach

  e.g. NSAID

- ❖ Drugs with variable bioavailability.

  e.g. Sotalol Hcl

1.9 FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS:[1,12,23-25]

1.9.1 Formulation factors:

1.9.1.1 Size of tablets:

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves. Floating and non-floating capsules of 3 different sizes with diameter of 4.8 mm (small unit), 7.5 mm (medium unit) and 9.9 mm (large unit) were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their GRT, while the non-floating dosage units sank and settled in the lower part of the stomach. Floating systems were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retro-pelling waves of the digestive phase.

1.9.1.2 Density of tablets:

It is the main factor influencing the gastric residence time of dosage form. A floating dosage form have density less than that of the gastric fluids floats, since it is away from the pyloric sphincter and the dosage unit is retained in the stomach for a prolonged period.

1.9.1.3 Shape of tablets:

It also affects the gastric residence time of floating systems. Six shapes of this dosage forms like ring, tetrahedron, cloverleaf, string, pellet and disk were screened *in vivo* for their gastric retention potential. From the results it was concluded that he tetrahedron (each leg 2cm long) and rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 h.

1.9.1.4 Viscosity grade of polymer:

Drug release and floating properties of this system are influenced by viscosity of polymers and their interaction. Low viscosity polymer like HPMC K100 LV were more beneficial than high viscosity polymer like HPMC K4M in improving floating properties and also decreases the drug release rate.

1.9.2 Idiosyncratic factors:

1.9.2.1 Gender:

Women have slower gastric emptying time than do men regardless of the weight, height and body surface.

1.9.2.2 Age:

Low gastric emptying time and longer GRT are observed in elderly than in younger subjects. Intrasubject and intersubject variations also observed in gastric and intestinal transit time.

1.9.2.3 Posture:

- **Upright position:**

  An upright position protects floating dosage forms against postprandial emptying because the floating dosage form s remains buoyant on the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.

- **Supine position**:

  It does not offer protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of these dosage forms appear to remain floating anywhere between the lesser and greater curvature of the stomach. On distal movement, these dosage

forms may be swept away by the peristaltic movements that drive the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

1.9.2.4 Concomitant intake of drugs:

Drugs like prokinetic agents (e.g., Metoclopramide and Cisapride), anti-cholinergics (e.g., Atropine or Propantheline), opiates (e.g., Codeine) affects the performance of FDDS. The co-administration of gastrointestinal motility decreasing drugs increases the gastric emptying time.

1.9.2.5 Feeding regimen:

- **Fed or Unfed State:**

  Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. The GRT of 4-10 h has been reported after a meal of fats and proteins. Under fasting conditions, the gastrointestinal motility is evaluated by periods of strong motor activity or the migrating myloelectric complexes (MMC) which occurs every 1.5 to 2 h. The MMC pushes undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the gastro residence time of the dosage form can be very short. But in the fed state, MMC is delayed and GRT is considerably longer.

- **Nature of the Meal:**

  The motility pattern of the stomach is changed to a fed state by feeding of indigestible polymers of fatty acid salts decreases the gastric emptying rate and prolonging the drug release.

- **Caloric Content:**

  A meal rich in proteins increases the GRT of 4 to 10 h.

1.10 EVALUATION PARAMETERS OF GASTRORETENTIVE SYSTEM:[1,12-15, 20-22,26]

1.10.1 Size and Shape Evaluation:

The particle size and shape plays an important role in determining solubility rate of the drugs and thus its bioavailability determined using Sieve analysis, Air elutriation analysis, Photo analysis, Optical microscope, Electro resistance counting methods, Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc.

1.10.2 Hardness, Friability, Assay and Content uniformity (Tablets):

These tests for tablets are performed as per described in specified individual monographs.

1.10.3 Floating Properties: (Floating lag time and total floating time determination)

It is noted by the time between the introduction of the tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in gastric fluid or 900 ml of 0.1 mole/litre hydrochloric acid as the dissolution medium maintained at 37^{o} C using USP dissolution apparatus.

1.10.4 Resultant weight determination:

Bulk density and floating duration are primary parameters of a dosage form's buoyancy. The floating of the dosage forms operates by force equivalent to the force F required to keep the object totally submerged in the fluid. The magnitude, direction of the force and the resultant weight corresponds to the *Victoria* sum of buoyancy (Fbuoy) and gravity (Fgrav) forces acting on the objects as shown in the equation below

$$F = Fsbuoy – Fgra F$$

$$= dfgV – dsgV$$

$$= (df\text{-}ds)\ gV$$

$$F = (df - M/V)\ gV$$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, df is the fluid density, ds is the object density or the object mass and V is the volume of the fluid.

1.10.5 Surface Topography:

The surface topography and structures of the formulation especially floating microspheres (multi units) were determined using scanning electron microscope operated with an acceleration voltage of 10kv, Contact angle meter, Atomic Force Microscopy (AFM) and Contact portfolio-meter.

1.10.6 Swelling Studies:

Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using USP dissolution apparatus, optical microscopy, ^{1}HNMR imaging, Confocal laser scanning micro and fats scopy (CLSM), Cryogenic Scanning Electron Microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using dissolution apparatus (USP dissolution apparatus) was calculated as per the following formula.

Swelling ratio = Weight of wet formulation / Weight of formulations

1.10.7 Determination of the Drug Content:

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by spectroscopy, HPLC, HPTLC methods, near infrared spectroscopy (NIRS), Micro-titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES).

1.10.8 Percentage Entrapment Efficiency:

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation and pressure Ultra filtration.

1.10.9 *In vitro* Release Studies:

It is performed in gastric fluids and intestinal fluids maintained at $37^{O}C$ by using the USP dissolution apparatus. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before the blade starts to rotates and standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors.

1.10.10 Floating microspheres and beads:

Drug loading is determined by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium and centrifuged, filtered and analyzed by analytical methods like spectrophotometry.The size and shape calculated by optical microscopy method. The external and cross-sectional morphology is done by scanning electron microscope (SEM). The total percentage yield of floating microspheres was determined by dividing weight of prepared microspheres by total amount of all non-volatile components used for the preparation of microspheres.

1.10.11Fourier Transforms Infrared Analysis:

Fourier transform infrared spectroscopy is a technique used to identify organic, polymeric and some inorganic materials as well as for functional group determination for drug and excipient and also to identify interaction between drug and excipient. The pellets were prepared on KBr press under hydraulic pressure of 150 kg/cm^2; the spectra were scanned over the wave number range of 3600 to 400 cm^{-1} at the ambient temperature.

1.10.12Differential Scanning Calorimetry (DSC) :

It is used to characterize water of hydration of pharmaceuticals. Thermograms of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min over a temperature range of 25° C – 65°C by maintaining inert atmosphere by purging nitrogen gas at the flow rate of 50 ml/min.

1.10.13 X Ray/Gamma scintigraphy:

It is used to evaluate floating ability of dosage form *in vivo*. In each experiment, the animals are allowed to fast overnight with free access to water, in a formulation allows indirect external observation using a γ-camera or scintiscanner. But the main drawback of γ-scintigraphy is limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.

1.10.14 Pharmacokinetic studies:

It includes AUC (Area under Curve), C_{max} (maximum plasma concentration of the drug) and time to reach maximum (T_{max}) and radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation was administered by natural swallowing followed by 50 ml of water. Gastric radiography was done at 30 min interval for 5 h using an X-ray machine. The inclusion of a γ-emitting radionuclide plasma concentration (T_{max}) was analyzed using a computer. Statistical analyses were carried out using a Student t test with p, 0.05 as the minimal level of significance.

1.10.15 Specific Gravity:

The displacement method is used to evaluate the specific gravity of floating system using compound benzene as a displacing medium.

1.11 LIST OF DRUGS EXPLORED FOR VARIOUS FLOATING DOSAGE FORMS:[1,2,7,12,18-20]

- Microspheres, Tablets /Pills: Chlorpheniramine maleate, Aspirin, Griseofulvin, Acetaminophen, p-Nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxycillin trihydrate, Terfenadine, Ampicillin, Tranilast, Atenolol, Theophylline, Captopril, Isosorbide di nitrate, Sotalol and Isosorbide mononitrate.
- Films: P-Aminobenzoic acid, Cinnarizine, Piretanide, Prednisolone and Quinidine gluconate.
- Granules: Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate and Isosorbide dinitrate.
- Powders: Riboflavin, Sotalol and Theophylline.
- Capsules: Verapamil Hcl, Chlordiazepoxide Hcl, Diazepam, Furosemide, L-Dopa, Benserazide, Misoprostol, Propranolol Hcl, Ursodeoxycholic acid and Nicardipine .

Table 1: Marketed Preparations of Floating Drug Delivery system [2,4]

Brand name	Drug	Dosage form
Cifran O.D	Ciprofloxacin	Tablet
Liquid Gavison	Mixture of Alginates	Liquid
Madopar HBS	Levodopa and Benserazide	Capsule
Glumetza	Metformin Hydrochloride	Tablet
Valrelease	Diazepam	Capsule
Topalkan	Antacids (Aluminium and Magnesium mixture)	Liquid
Conviron	Ferrous sulphate	Gel
Cytotech	Misoprostol	Bilayer capsule

1.12 APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS:[1,2,7-10]

1.12.1 Enhance bioavailability:

The bioavailability of controlled release gastroretentive dosage form is significantly enhanced in comparison to the administration of non-controlled release gastroretentive dosage form. There are different activities, related to absorption and transit of the drug in the gastrointestinal tract, that act concurrently to influence the magnitude of drug absorption.

1.12.2 Sustained drug delivery:

In this system, the dose larger in size is forbidden passing from the pyloric opening. *In vivo* studies, plasma concentration time curves found a longer duration for administration (16 h) in the sustained release floating capsules of Nicardipine hydrochloride as compared with conventional MICARD capsules (8 h). Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done it shown the drug was released up to 8 h *in vitro* in the Madopar HBS and the release completed in less than 30 min in Madopar standard formulation.

1.12.3 Site–specific drug delivery systems:

These drug delivery systems are particularly advantageous for drugs those are specifically absorbed from the stomach or the proximal part of the small intestine. The controlled delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. It reduces the side effects which are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site specific delivery system reduces the dosing frequency.

1.12.4 Absorption enhancement:

Drugs with poor bioavailability are made advantageous by formulating in floating dosage forms due to its site specific absorption from the upper part of the GIT there by maximizing their absorption.

1.12.5 Minimize adverse activity in the colon:

Retention of the drug in the hydro-dynamically balanced system at the stomach restricts the amount of drug that reaches the colon. Thus, undesirable effects of the drug in colon may be prevented. This pharmacodynamic feature provides the rationale for gastroretentive formulation for Beta-lactam antibiotics that are absorbed only from the small intestine and whose availability in the colon leads to the development of microorganism's resistance.

1.12.6 Reduce fluctuations of drug concentration:

The blood drug concentrations was maintained within a narrower range by slow continuous input of the drug following controlled release gastro-retentive dosage form administration than immediate release dosage forms reduces fluctuations of adverse effects of high concentrations of drug which is of special importance for drugs with a narrow therapeutic index.

ANTI-HYPERTENSIVE AGENTS

1.13 Hypertension[27]:

Hypertension, particularly essential or primary hypertension, is a predominant risk factor for cardiovascular morbidity and mortality especially that associated with stroke and control of hypertension reduces cardiovascular risk.

1.13.1 Definitions:

Blood pressure generally means arterial blood pressure, that is, the pressure of the blood on artery walls. It is usually measured indirectly in the brachial artery just above the elbow using an appropriately calibrated sphygmomanometer and is expressed in mmHg.

Two measurements are made:

- *systolic* or maximum blood pressure achieved during ventricular contraction of the heart
- *diastolic* or minimum blood pressure achieved during ventricular dilatation

Hypertension means a higher than 'normal' blood pressure; it has been defined as the level of blood pressure above which intervention has been shown to reduce the associated cardiovascular risk. Ambulatory blood pressure monitoring may have advantages in some situations and automated devices for home monitoring may also have a role. However, home and ambulatory blood pressures tend to be lower than those measured in healthcare settings, and different thresholds for normal and abnormal values apply.

Normal adult blood pressure has been arbitrarily defined as a systolic pressure below 130 mmHg together with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg), but more recent studies have suggested that optimal blood pressure, in terms of cardiovascular risk, may be lower than this. US guidelines now define normal blood pressure as below 120/80 mmHg, while European and British guidelines classify this as optimal. Blood pressures of 130–139/85–89 mmHg are

regarded as high normal or included in the classification of **prehypertension**. Although hypertension was formerly defined in terms of diastolic blood pressure alone, it is now recognised that systolic pressure is also important in determining risk and current guidelines give equal emphasis to both. Blood pressure above 140 mmHg systolic, and/or 90 mmHg diastolic is generally considered to represent **hypertension**. Although classifications of mild, moderate and severe hypertension have been widely used, these terms may be misleading since absolute cardiovascular risk is more important in determining the need for treatment and depends on other factors in addition to blood pressure.

Most guidelines therefore use a grading system to classify hypertension, as follows:

grade 1: 140–159/90–99 mmHg;

grade 2: 160–179/100–109 mmHg;

grade 3: ≥180/≥110 mmHg.

In the US guidelines, stage 1 hypertension corresponds to grade 1, whereas stage 2 includes both grades 2 and 3. When systolic and diastolic pressure falls into different categories the higher value is used for classification purposes.

The term **malignant or accelerated hypertension** has been used for rapidly progressing severe hypertension associated with retinopathy and often renal impairment.

Isolated systolic hypertension occurs mainly in the elderly and has been defined as systolic pressure of 140 mmHg or more and diastolic pressure under 90 mmHg.

1.13.2 Origins:

In the majority of cases of hypertension the cause is unknown, and such **primary or essential hypertension** is probably multifactorial in origin, with genotype, as well as external factors such as diet and body-weight, playing a role. Hypertension may also be associated with surgery or pregnancy and is prevalent in diabetics. In a limited number of cases **hypertension is *secondary*** to some other

condition, such as renal disease, Cushing's syndrome, phaeochromocytoma or the adverse effects of drugs such as Oestrogens and such causes may be suspected particularly in resistant or malignant hypertension. Although treatment of the underlying condition will generally be desirable, the resultant hypertension will not necessarily be abolished by this.

1.13.3 Management of hypertension:

Hypertension may be discovered because of adverse vascular events, especially in the eyes, brain, kidneys, or heart but is more often asymptomatic and only discovered on routine measurement of blood pressure. It is well-established that hypertension is a risk factor for the development of stroke, heart failure and renal damage and to a lesser extent, ischaemic heart disease and a reduction in blood pressure is generally beneficial although mortality remains higher than in non-hypertensives. However, it is important to assess hypertension in the context of overall cardiovascular risk, including the presence of target-organ disease, such as left ventricular hypertrophy or renal disease, associated conditions such as atherosclerosis or diabetes and other risk factors such as hyperlipidaemia or smoking. Treatment of hypertension may involve both non-pharmacological and pharmacological interventions to reduce blood pressure, as well as assessment and treatment of any other cardiovascular risk factors, any co-existing diseases should also be treated.

1.13.3.1 Non-pharmacological treatment:

A healthy lifestyle is encouraged for patient with raised blood pressure that reduces their cardiovascular risk by following below said strategies for termed as primary prevention of high blood pressure.

Interventions that have been shown to reduce blood pressure include:

- reduction in excess weight
- reduction in excess alcohol consumption
- reduction in sodium intake
- adequate exercise

• reduced fat intake

• increased fruit and vegetable consumption

Other interventions that have been tried, but with less evidence of benefit, include:

- increased intake of potassium, magnesium, and calcium
- increased polyunsaturated fat intake with reduced saturated fat intake
- relaxation therapies for stress reduction.

1.13.3.2 Pharmacological treatment:

- Patients with grade 3 hypertension (180/110 mmHg or higher) should receive prompt drug treatment.
- In grade 2 hypertension, drug therapy is indicated if blood pressure remains at 160/100 mmHg or higher after a period of lifestyle modification, a prompt drug therapy is advised for those at high or very high risk.
- For patients with grade 1 hypertension, the need for treatment is less well established; those with associated risk factors should be given drug therapy if lifestyle modification is inadequate, but some guidelines suggest that anti-hypertensives are not indicated in those at lower risk, or state that priority should be given to those at highest risk.
- Lower thresholds may apply in patients with renal disease or diabetes but whether there is any benefit in treating uncomplicated patients with prehypertension is controversial.

For elderly patients (over 60 years) there is evidence to support the benefit of treating hypertension, including isolated systolic hypertension and this applies up to at least 80 years of age, suggesting a strict age limit to drug therapy is inappropriate.

Target blood pressures of below 140/90 mmHg or below 140/85 mmHg are now recommended; lower targets may be considered if tolerated by the patient, particularly in patients at high risk. A lower target of below 130/80 mmHg has also been suggested for patients with established ischaemic heart disease and lower targets may also be appropriate in diabetics and patients with renal disease.

1.13.3.3 The drug regimen:

Historically, thiazide diuretics and beta blockers have been the basis of drug therapy for hypertension, but calcium-channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and alpha blockers are now also widely used.

1.13.4 Classification of anti-hypertensive drugs:[28]

1. Diuretics

Thiazides	:	Hydrochlorothiazide, Chlorthalidone, Indapamide
Loop diuretics	:	Frusemide, Bumetanide, Torsemide
Potassium sparing diuretics	:	Spiranolactone, Amiloride, Triamterene

2. Drugs acting on rennin-angiotensin system:

Angiotensin converting enzyme Inhibitors	:	Captopril, Enalapril, Lisinopril, Ramipril, Perindopril, Fosinopril, Trandolapril, Quinapril, Benazepril
Angiotensin II receptor blockers	:	Losartan, Candesartan, Valsartan, Eprosartan, Irbesartan, Olmesartan
Renin inhibitor	:	Aliskiren

3. Sympatholytics:

Centrally acting drugs	:	Clonidine, Methyldopa, Guanabenz, Guanfacine
Ganglion blockers	:	Trimethaphan
Adrenergic neuron blockers	:	Guanethidine, Reserpine
Adrenergic receptor blockers		
α-blockers	:	Prazosin, Terazosin, Doxazosin Phenoxybenzamine, Phentolamine
β- blockers	:	Acebutolol, Propranolol, Atenolol, Esmolol, Metoprolol
Mixed α – and β – blockers	:	Labetalol, Carvedilol
4. **Calcium channel blockers**	**:**	Nifedipine, Nicardipine, Nimodipine, Amlodipine, Verapamil,

5. Vasodilators

Arteriolar dilators	:	Hydralazine, Minoxidil, Diazoxide
Arteriolar and venular dilators	:	Sodium nitroprusside

Choice of initial therapy depends on anti-hypertensive efficacy, safety and long term effects on morbidity and mortality. Angiotensin II receptor antagonists effectively reduce blood pressure. Tolerance of the drug groups is also similar, although there has been concern about the metabolic effects of Thiazides and beta blockers. Alpha blockers (specifically Doxazosin) have been associated with an increased risk of heart failure, which may limit their use. The safety of short-acting Dihydropyridine calcium-channel blockers has also been questioned, and they are no longer generally recommended for hypertension; long-acting Dihydropyridines, however, are of established benefit.

All of the main drug groups are therefore established as effective anti-hypertensives, but their effects on long-term mortality and morbidity have been less clear. The different drug groups have differing effects on several substitute outcomes, such as left ventricular hypertrophy and endothelial dysfunction, but the clinical significance of this has not been established, although there is some evidence that regression of left ventricular hypertrophy is associated with a reduction in clinical events. Diuretics (particularly thiazides) and beta blockers were the first drugs to demonstrate an effect on mortality in long-term studies and preferred for initial therapy. Long-term studies with other drug groups showed comparable effects on mortality and morbidity. In general, guidelines acknowledge that lowering blood pressure appears to be more important than which drug is chosen for initial therapy and that most patients will require a combination of drugs. Thiazide diuretics, ACE inhibitors, Angiotensin II receptor antagonists or calcium-channel blockers may all be used and choice should take into account individual patient characteristics, including age, ethnicity, contra-indications or compelling indications for specific drugs, adverse effects and relative cost-effectiveness. Strict guidance is therefore not generally given, although for uncomplicated patients US and international guidelines recommend thiazide diuretics as first-line, whereas in the UK diuretics or calcium-channel blockers are recommended for older patients (55 years or over) and black patients, while in younger, non-black patients ACE inhibitors or angiotensin II receptor antagonists are preferred. Compelling indications in all the guidelines include the use of ACE inhibitors or angiotensin II receptor blockers in patients with nephropathy, diuretics or calcium-channel blockers in elderly patients and beta blockers in patients who have had a myocardial infarction. The use of beta blockers as initial therapy in patients who have not had a myocardial infarction remains controversial; UK guidelines issued since the publication of ASCOT-BPLA suggest that they should be avoided except in younger patients who are unable to take ACE inhibitors or angiotensin II receptor antagonists and in women of child-bearing potential, whereas more recent European guidelines allow their use in all patients other than those at risk of metabolic effects.

After decision of drug used for treatment the next will be the lowest recommended dose. If this is ineffective or only partially effective the dose may be increased (except in the case of thiazide diuretics where there is generally no additional benefit, but more adverse effects); alternatively another first-line drug may either be substituted (sequential therapy) or added (combination therapy). Two-drug combinations will control blood pressure in a higher proportion of patients and may be necessary in most patients to achieve optimal levels, although the effects of the two drugs may not be fully additive. Combination therapy also allows lower doses of the individual drugs to be used with a consequent reduction in adverse effects. Initial treatment with a low-dose combination may be considered in some patients. The most effective combinations involve drugs that act on different physiological systems.

Appropriate combinations therefore include:

- diuretic plus beta blocker
- diuretic plus ACE inhibitor
- diuretic plus angiotensin II receptor antagonist
- calcium-channel blocker plus ACE inhibitor
- calcium-channel blocker plus angiotensin II receptor antagonist
- calcium-channel blocker (except Verapamil) plus beta blocker

Alpha blockers may be used with any of the other classes but are usually reserved for third-line therapy unless specifically indicated for another reason. A 3-drug combination is often required, especially in severe hypertension. In patients who maintain an elevated diastolic blood pressure despite triple therapy the possibility of secondary hypertension should be considered, although factors such as non-compliance, NSAID use or alcohol abuse may contribute to resistance.

Other classes of anti-hypertensive drugs that are sometimes used include:

- Centrally acting drugs such as Clonidine, Methyldopa and the less sedating Moxonidine; direct-acting vasodilators such as Hydralazine and Minoxidil;

- The aldosterone antagonist, Eplerenone; and

- The renin inhibitor, Aliskiren.
- Older drugs like the adrenergic neurone blocker Guanethidine and the Rauwolfia alkaloid Reserpine are rarely recommended now.
- Endopeptidase inhibitors and endothelin antagonists are among various drug groups that are under investigation.

1.13.5 Withdrawal of drug treatment:

It has been standard that drug treatment for hypertension is continued indefinitely. In case of withdrawal in selected patients, monitoring of blood pressure and lifestyle measures should be continued indefinitely.

1.13.6 Hypertension in children:

Hypertension is less common in children than in adults but is evident in increase in childhood obesity. Lifestyle measures are the mainstay of treatment, particularly in children with less severe hypertension and no evidence of target organ damage, since the benefits of treatment and the risks of long-term drug therapy are not established. However, drug treatment may be required in some cases and should generally be based on individual patient characteristics.

1.13.7 Hypertensive crises:

Patients with severe hypertension may be divided into those in whom there is evidence of rapid or progressive CNS, cardiovascular or renal deterioration (hypertensive emergencies) and those with no evidence of target-organ damage (urgent hypertensive crises or hypertensive urgencies). In the former case the goal is a reduction in mean arterial blood pressure by 25%, or a fall in diastolic blood pressure to 100 to 110 mmHg, over a period of several min to several h depending on the clinical situation; intravenous therapy is often required although oral therapy may be adequate. In the latter case a drastic reduction in blood pressure is inappropriate and oral therapy is preferred, with the aim of a reduction in blood pressure over several h to days. In both situations too rapid a reduction of blood pressure may be detrimental and may lead to cerebral infarction and blindness, to deterioration in renal function, and to myocardial ischaemia.

If oral treatment can be given and there is no evidence of ongoing target-organ damage, beginning standard anti-hypertensive therapy is appropriate, although the patient should be closely monitored. Short-acting drugs with a rapid effect are often used, although caution is required since they may lower blood pressure abruptly. Drugs that have been recommended include the beta blocker Labetalol, the centrally acting drug Clonidine, the ACE inhibitor Captopril, and the alpha blocker Prazosin (especially when there are increased circulating Catecholamines); calcium-channel blockers such as Amlodipine, Felodipine, and Isradipine may also be suitable. Diuretics may have a role in volume overload but many patients with hypertensive crises are volume depleted and diuretics may therefore be less appropriate in the initial stages. Nifedipine and Captopril have been given sublingually for a faster onset, but there appears to be no clearly defined clinical advantage for this route and it is generally considered that Nifedipine should not be used.

In the emergency situation, when parenteral therapy is required, choice of therapy depends on concomitant clinical conditions. Sodium nitroprusside given by intravenous infusion, has most often been the drug of choice, but close monitoring is required as toxicity may be a problem. Intravenous Labetalol, Nicardipine, or Fenoldopam are suitable alternatives in most situations. Other drugs that are used in specific indications include Glyceryl trinitrate (in patients with coronary ischaemia), Phentolamine (in phaeochromocytoma and other states associated with catecholamine excess such as the MAOI-tyramine interaction), Enalaprilat (in acute heart failure), Esmolol (particularly in aortic dissection or perioperatively) and Hydralazine (in eclampsia). Trimetaphan and Urapidil have also been used. Hypertensive emergencies in children are managed similarly to those in adults.

1.13.8 Hypertension during surgery:

Giving anti-hypertensive drugs to patients about to undergo surgery is not only safe but probably best continued up to and including the morning of surgery. Pre-operative hypertension may occur as a result of surgery and often needs to be controlled with parenteral anti-hypertensives since the oral route may not be available.

The parenteral drug of choice is often Sodium nitroprusside; others include Glyceryl trinitrate (especially after coronary artery bypass), Labetalol, Enalaprilat, Esmolol, Fenoldopam, and Nicardipine; Diazoxide, Hydralazine and Methyldopa have also been used.

1.13.9 Hypertension in diabetic patients:

Hypertension is twice as common in diabetic as in nondiabetic subjects, and up to 50% of patients with type 2 diabetes mellitus become hypertensive. The reasons proposed for this increased prevalence are controversial, but insulin resistance has been implicated. In addition to being a major risk factor for atherosclerosis in large blood vessels, hypertension in diabetes appears to contribute to small vessel disease and is a risk factor for diabetic nephropathy and possibly for diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) Group has reported that tight control of blood pressure (with a target of below 150/85 mmHg) reduces the risk of diabetes-related death and diabetic complications, including diabetic retinopathy, in type 2 diabetics. The threshold for intervention with drug treatment may be lower in diabetic than in non-diabetic hypertensive patients and treatment targets are also lower. An initial target of 140/80 mmHg has been suggested, while a target below 130/80 mmHg may be optimal and is recommended in many guidelines; the lower target is particularly advised in type 1 diabetics with nephropathy. All the main groups of anti-hypertensive drugs can be used in diabetics, and most patients will require at least two drugs to achieve target blood pressure. ACE inhibitors (with angiotensin II receptor antagonists as an alternative) have been particularly recommended, as there is evidence of benefit in preserving renal function in patients with nephropathy. However, a systematic review found limited evidence to support a specific renoprotective action in diabetics, independent of their effect on blood pressure.

Diuretics and beta blockers have often been avoided because of their potential adverse effects on glucose and lipid metabolism, but may be used where indicated. In the UKPDS treatment with an ACE inhibitor (Captopril) or a beta blocker (Atenolol) was equally effective in reducing the risk of diabetic complications, although the ACE inhibitor appeared to be better tolerated. Although

there has been concern regarding the safety of calcium-channel blockers, long-acting calcium-channel blockers have been shown to be a suitable choice.

1.13.10 Hypertension and renal disease:

Hypertension is closely linked with the kidney. The kidney may have a role in the pathogenesis of hypertension and it may also be a prime target of damage caused by hypertension. Both renal parenchymal disorders and renovascular disorders may be associated with hypertension. In the former, hypertension is often resistant to treatment and a combination of drugs, including vasodilators, may be required. Anti-hypertensive therapy is also important in these patients since it may slow the decline in renal function in patients with nephropathy. There is some evidence that ACE inhibitors may have a greater protective effect than other anti-hypertensives, although this is not certain and they have been recommended as the basis of therapy (with angiotensin II receptor antagonists as an alternative), usually with a diuretic. The effect of blood pressure reduction appears to be related to the degree of proteinuria, and studies have shown that patients with proteinuria higher than 1 g/day benefit from lower blood pressures. Current guidelines recommend a target blood pressure of below 130/80 mmHg in patients with nephropathy, with a lower target of 125/75 mmHg in those with proteinuria of 1 g/day or over.

Renovascular hypertension has been defined as arterial hypertension resulting from obliteration or compression of one or both renal arteries, the commonest cause being stenosis due to atherosclerosis. The perfusion of the kidney leads to increased release of renin and consequent rise in blood pressure. However, the relationship between renovascular hypertension and renal artery stenosis is not clear cut; the two conditions may simply co-exist or hypertension may cause the stenosis rather than the other way round.

Renovascular hypertension may be difficult to distinguish clinically, but carries a worse prognosis than essential hypertension, may be less willing to treatment, carries a higher risk of progression to accelerated or malignant hypertension, and may result in irreversible ischaemic failure of the affected kidney. Diagnostic methods used to detect renovascular hypertension include imaging

studies such as ultrasonography and angiography, and functional tests such as the Captopril test; renal scintigraphy with and without ACE inhibition is also used.

Although blood pressure in renovascular hypertension can often be controlled by anti-hypertensive drugs, patients with renal artery stenosis are often treated by angioplasty of the affected artery. There is some evidence that angioplasty lowers blood pressure more effectively than drug therapy, particularly in patients with bilateral stenosis, but the relative effects on other outcomes are less clear. Renal function may deteriorate in patients given anti-hypertensives since blood flow to the kidney is reduced; however, sudden restoration of blood flow by angioplasty may also have deleterious effects. Reduced blood flow is a particular concern with the use of ACE inhibitors or angiotensin II receptor antagonists, since renal perfusion may be dependent on angiotensin II in patients with renal artery stenosis, and renovascular hypertension is often considered a contra-indication to the use of these drugs, particularly in patients with bilateral stenosis or stenosis affecting the functioning kidney. However, they may be required in patients with resistant hypertension, although they must be used cautiously and in low doses, with careful monitoring of renal function.

1.13.11 Hypertension in pregnancy:

Hypertension in pregnancy may be life-threatening to both mother and fetus. It may be pre-existing or may develop for the first time during pregnancy. Definitions vary, but hypertension presenting before 20 weeks of gestation generally continues long-term and is considered chronic hypertension. After the twentieth week (gestational hypertension) it may be transient (pregnancy-induced hypertension), chronic, or represent pre-eclampsia. Gestational hypertension is usually defined as a blood pressure of 140/90 mmHg or more on at least two occasions in a previously normotensive woman; it is considered transient hypertension if the blood pressure has returned to normal limits by the twelfth week postpartum. In pre-eclampsia, increased blood pressure occurs with proteinuria; abnormal coagulation, liver dysfunction, and oedema may also be present. Pre-eclampsia may progress to eclampsia, a convulsive phase. Recommendations about the treatment of ***gestational*** or ***pre-existing hypertension*** during pregnancy have been controversial. Most women with chronic or transient hypertension will have

grade 1 or grade 2 hypertension and a low risk of cardiovascular complications during the short period of pregnancy, and the benefits of treatment in such patients are not established. It is usually agreed that blood pressures of 170/110 mmHg or above should be treated as an emergency, but recommendations for management of lower blood pressures are less clear. Although treatment of patients with blood pressures of 140/90 mmHg or above has been suggested, there is little evidence that this improves maternal or neonatal outcomes, although the incidence of severe hypertension is reduced. Some guidelines allow withdrawal of anti-hypertensives in pregnant women with pre-existing hypertension, with treatment restarted if the blood pressure exceeds specific threshold values. However, women with mild hypertension are at an increased risk of developing pre-eclampsia, regardless of whether they receive anti-hypertensives, and should be closely monitored.

For women with mild to moderate hypertension in whom the decision is made to give anti-hypertensives, optimum choice of drug therapy is unclear. Women with pre-existing hypertension usually continue their existing treatment, although ACE inhibitors and angiotensin II receptor antagonists are contra-indicated in pregnancy and should be changed to an alternative. For gestational hypertension, methyldopa or beta blockers have generally been preferred, although there is little evidence that outcomes differ for any of the main drug groups. A systematic review found no evidence of substantive benefits with beta blockers, but another review found that they reduced the risk of severe hypertension more effectively than Methyldopa. Methyldopa has the advantage of reassuring long-term safety results in the infant, whereas there have been concerns about fetal growth retardation with beta blockers, particularly with Atenolol. Nifedipine or Hydralazine may also be used. Diuretics are not generally recommended for controlling hypertension in pregnancy because of the theoretical risk of exacerbating the volume depletion of pre-eclampsia; however, they appear to be safe in practice and may be used if necessary.

For patients with **pre-eclampsia** the definitive treatment is delivery (although pre-eclampsia may also develop post-partum), but where the maternal condition allows this is usually delayed to allow fetal maturation. Anti-hypertensive therapy is therefore given to reduce the risk of maternal complications, and prophylactic anticonvulsants, particularly Magnesium sulfate, may also be given in

those at high risk for eclampsia. Evidence to guide choice of anti-hypertensive in severe hypertension is limited. Oral therapy may be appropriate, in which case Methyldopa or beta blockers (preferably Labetalol) are usually first-line; calcium-channel blockers such as Nifedipine are an alternative. However, in acute pre-eclampsia or if delivery is imminent, parenteral anti-hypertensives are required. Intravenous Hydralazine is widely used, although there is some evidence that it may be less effective and have more adverse effects than other drugs and some guidelines recommend that it should be avoided. Intravenous Labetalol and oral Nifedipine are also used and Sodium nitroprusside may be required in some patients. Glyceryl trinitrate may be used if there is pulmonary oedema. Other drugs that have been given include Diazoxide and Clonidine.

1.13.12 Prevention of pre-eclampsia:

It was hoped that prevention of pre-eclampsia might be possible by reducing the local platelet aggregation thought to be responsible for some of its manifestations. Several small studies suggested that low-dose aspirin reduced the risk of pregnancy-induced hypertension and intra-uterine growth retardation in high risk patients. However, larger studies in women at lower risk generally failed to confirm this benefit and in one the risk of placental abruption was higher in those who take Aspirin. Findings of the CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) multicentre study involving over 9000 women considered to be at increased risk of pre-eclampsia or intra-uterine growth retardation did not support the routine prophylactic or therapeutic use of antiplatelet therapy in all such women. A further study in high-risk women also failed to show any benefit, although Aspirin appeared to be safe for mother and fetus. However, systematic reviews have concluded that antiplatelet therapy provides a small to moderate benefit in patients at risk of developing pre-eclampsia, although it is not clear which women are most likely to benefit. Calcium supplementation has also been shown to reduce the risks of pregnancy-induced hypertension and pre-eclampsia, although its role is not yet established. Preliminary evidence suggested that supplementation with vitamins C and E might be beneficial in women at high risk, but further studies were unable to confirm this effect.

2. AIM AND OBJECTIVE OF THE STUDY

2.1 AIM:

Nowadays, the researchers focus is more on oral novel controlled site specific drug delivery systems, in which the release of active drug can be controlled for a longer period at a particular site of action reducing the wastage of drugs and side effects to other area of the body. Even though the release of drug is controlled in the controlled drug delivery, the drug absorption is insufficient and highly erratic in the individuals due to its physiological variability such as gastrointestinal transit as well as gastric residence time (GRT) of the dosage forms[29]. Gastroretentive technology provides an alternative to solve the above said problem. Such technology is called as gastro-retentive drug delivery system (GRDDS) which makes the drug available in the gastric fluid for prolonged time and thus prolong the gastric residence time of drugs due to its lower bulk density compared to the gastric medium. Prolonged gastric retention improves bioavailability, minimizes drug waste and increases solubility of drugs that are less soluble in acidic pH environment and also have a better control of fluctuations in the plasma drug concentrations[30] is achieved. It is also suitable for local drug delivery to the stomach and proximal small intestines[31].

The present investigation aimed to formulate and evaluate the floating tablets of Eprosartan mesilate and Acebutolol hydrochloride separately using natural and synthetic polymers for prolonging gastric residence time.

2.2 OBJECTIVE:

2.2.1 Reason for selecting Acebutolol hydrochloride:

Acebutolol is one of the commonly prescribed angiotensin drugs[32]. Acebutolol is a cardioselective beta blocker. It is used in the management of hypertension, angina pectoris, and cardiac arrhythmias. Acebutolol is completely absorbed from GIT and undergoes extensive first-pass hepatic metabolism[33]. The short half life of acebutolol is 3-4 h[34] necessities frequent dosing daily results in fluctuations of drug levels in body and need for constant monitoring and counseling of patient for adherence to dose regimen. The major challenge in the treatment of hypertension is minimizing fluctuations of drug levels in blood by using sustained dosage form releases drug in steady state. The objective of the study is to formulate gastro-retentive dosage form to reduce the plasma drug fluctuations due to frequent dosing of conventional dosage form by increasing gastric retention time and site-specific delivery in stomach can be achieved.

2.2.2 Reason for selecting Eprosartan mesilate:

Eprosartan is an angiotensin II receptor antagonist used in the management of hypertension. The oral bioavailability of Eprosartan is only 13-15% due to pH-dependent solubility in combination with the degree of ionization of the dissolved active substance at different pH values encountered in the gastro-intestinal tract results in erratic absorption throughout the gastrointestinal tract. Above pH 2, the drug starts ionizing to become negatively charged ion and gets 2 or 3 negative charges as pH increases which reduce the permeability of drug into biomembranes[35]. Eprosartan dose is increased upto 800 mg per day may be required for an effective treatment of hypertension, congestive heart failure and renal failure and short half life of Eprosartan is 5-9 h[36] necessitates the need for the present study is to prolong the drug release in acidic pH for longer time that enhances the bioavailability of Eprosartan.

2.3 PLAN OF THE WORK:

- Preformulation study for Eprosartan mesilate and Acebutolol hydrochloride with and without excipients to find the chemical interaction using Fourier Transform Infra Red Spectroscopy
- To optimize and characterize plain floating tablets prepared with various synthetic and natural polymers like different grades of hydroxyl propyl methyl cellulose (HPMC E15 and HPMC K15), different grades of Carbopol (Carbopol 934P and Carbopol940), Ethyl cellulose (synthetic polymers) and Xanthan gum, Guar gum, Karaya gum, Chitosan, Sodium alginate (natural polymers) by direct compression method with respect to various parameters like
    - Effect of polymer on swelling index
    - Effect of increasing concentration of natural polymer on *in vitro* buoyancy studies
    - Effect of effervescent agent on *in vitro* buoyancy studies
- Develop and evaluate floating tablets of Eprosartan mesilate and Acebutolol hydrochloride
    - Pre compression studies like bulk density, tapped density, hausner ratio and carr's compressibility index
    - Post-compression studies like general appearance, thickness, hardness, friability, weight variation, swelling index, *in vitro* buoyancy studies and uniformity of drug content
    - *In vitro* dissolution of floating tablets of Eprosartan mesilate and Acebutolol hydrochloride
    - Fitting the *in vitro* dissolution data to various kinetic models and optimize the best formulation
- To perform the stability studies for best formulation of floating tablets of Eprosartan mesilate and and Acebutolol hydrochloride
- To perform *in vivo* X-ray studies and pharmacokinetic studies for best formulation of Eprosartan mesilate floating tablet and Acebutolol hydrochloride floating tablet

3. REVIEW OF LITERATURE

Syed Iftequar. *et al.,* (**2016**)[37] developed and evaluated floating matrix tablet of Ramipril using HPMC K4M and carbopol 934NF as polymer, sodium bicarbonate and citric acid as gas generating system and sodium carboxy methyl cellulose as gelling agent and evaluated for various pre and post compression parameters. From the results it was concluded that formulation containing highest amount of HPMC K4M showed increased floatation duration for more than 18h.

Narendar Dudhipala. *et al.,* (**2016**)[38] prepared floating bioadhesive tablets of Amoxycillin trihydrate by direct compression method using hydroxy propyl methyl cellulose (HPMC K4M) / chitosan (CH), carbopol (CP974P) / polymethacrylic acid (PMA) as release retarding agent / bioadhesive respectively, sodium bicarbonate (NaCO3) as a gas-former and evaluated for various pre compression and post compression parameters. From the results it was concluded that formulation containing carbopol (CP974P) / polymethacrylic acid (PMA) floated with a lag time of 32 ± 2.7 sec and floated for 12 h and followed non-Fickian diffusion mechanism (n = 0.625).

Prasuna Sundari PJ. *et al.,* (**2015**)[39] formulated and evaluated sustained release floating micro-balloons of Eprosartan mesilate using solvent evaporation technique. From the results it was concluded that formulation containing HPMC and EC in ratio 1:4 in ethanol–dichloromethane at ratio of 1:1 at temperature 40^{o}C exhibited increased oral bioavailability due to increase in gastric residence time of the drug. Eprosartan mesilate release from floating micro-balloons was diffusion controlled confirmed by fitting the data into different kinetic models.

Sarkar rao. *et al.,* (**2015**)[40] formulated and evaluated gastro-retentive drug delivery system of Losartan potassium by raft forming technique using HPMC K4M, xanthan gum and carbopol 971P at various concentrations by direct compression method. Sodium bicarbonate as gas generating agent, sodium alginate as foaming agent, magnesium stearate and talc as lubricants, lactose as sweetening agent and microcrystalline cellulose as binding agent. FTIR spectroscopy study revealed no chemical interaction between drug and polymers. The prepared

formulations were evaluated for various pre compression and post compression parameters. The *in vitro* cumulative % drug release of all formulations ranged from 94.28 to 98.88% at 12 h. The *in vitro* cumulative % drug release and floating time and lag time for best formulation containing drug and xanthan gum in ratio of 1:1 was found to be 98.88%, 20 min and 12 h, respectively.

Ying-Chen Chen. *et al.,* (**2015**)[41] prepared and characterized swelling and floating behavior of floating tablets using hydroxyl ethyl cellulose (HEC 250HHX) and sodium carboxy methyl cellulose (NaCMC) as polymers in different ratios with three model drugs with different solubilities (Metformin, Ciprofloxacin and Esomeprazole). All the batches were evaluated for various pre and post compression parameters. The release mechanism of the freely water-soluble drug, Metformin, was mainly diffusion-controlled, while those of the water-soluble drug, Ciprofloxacin and the slightly water-soluble drug, Esomeprazole, were mainly anomalous diffusion. Overall results showed that the developed floating tablet composed of HEC 250HHX and NaCMC of 450 cps possessed proper swelling extents and desired floating periods with sustained-release characteristics.

Senjalia HK. *et al.,* (**2014**)[42] prepared and characterized once daily sustained release tablet of Eprosartan mesilate using dissolution enhancement approach by solid dispersion using polyvinyl pyrolidine (PVP K30) in ratio of 1:0.25 with drug by solvent evaporation technique using methanol as solvent. Sustained release tablets were prepared with different polymers like Ethocel 10FP, Eudragit RSPO and Eudragit RLPO in different ratios by direct compression method and evaluated for pre compression and post compression parameters. From the results it was confirmed that tablets containing blend of Ethocel 10FP and Eudragit RSPO showed good drug release than other tablets further confirmed erosion was a predominant mechanism controlling drug release. There was no significant change in evaluation parameters after stability studies conducted at $40^{o}C \pm 2^{o}C$ / 75 ± 5 % RH.

Satyavathi K. *et al.,* (**2014**)[43] formulated and evaluated immediate release tablets of Eprosartan mesilate using solid dispersion technique with polyethylene glycol 6000 as carrier in different ratios like 2:1, 1:1, 2:3 with drug as physical mixtures (kneading) and as inclusion complexes with β-cyclodextrin in 1:1 ratio

with drug and compressed as tablets. The prepared tablets were evaluated for various pre compression and post compression parameters. From the results it was revealed that formulation containing β-cyclodextrin showed highest drug release when compared with marketed product (Teveten).

Neeta Choudhary. *et al.,* (**2014**)[44] conducted *in vivo* analysis of self emulsifying drug delivery system (SEDDS) of Eprosartan mesilate with oil phase of Labrafac Lipophile WL 1349, Tween 80 as surfactant and Capryol 90 as cosurfactant. The preparation were subjected to various evaluation parameters like percentage transmittance, spontaneous emulsification test, robustness to dilution, emulsification time, thermodynamic stability studies and globule size analysis and concluded that this formulation showed 98.3% drug release from SEDDS.

Venkata Srikanth Meka. *et al.,* (**2014**)[45] formulated and evaluated the gastroretentive floating drug delivery system of Propranolol hydrochloride using a synthetic hydrophilic polymer polyethylene oxide of different grades such as PEO WSR N-12 K and PEO 18 NF as release retarding polymers and calcium carbonate as gas generating agent by direct compression and evaluated for physico-chemical properties, *in vitro* buoyancy, swelling studies, *in vitro* dissolution studies and release mechanism studies. From the dissolution and buoyancy studies, formulation PEO WSR N-12 K and PEO 18 NF based formulations at the drug: polymer ratio 1:4 and 1:1.5 respectively retarded the drug release promptly than all other formulations. High molecular weight PEO grade exhibited higher retarding property and good buoyancy properties. Best formulation (F 9) when characterized with FTIR studies showed no interactions between drug and polymer. Hence, it can be concluded that, PEO is a suitable polymer for the development of gastroretentive floating drug delivery systems.

Asha Spandana K M. *et al.,* (**2013**)[46] formulated and evaluated bilayer floating tablet containing Verapamil hydrochloride using HPMC K100 and Carbopol as release retarding polymer with sodium bicarbonate and citric acid as gas generating agents by direct compression technique. The results concluded that increase in concentration of effervescent agents decreased the floating lag time.

Initial burst of drug release followed by slow release confirmed from *in vitro* release studies and release follows Fickian diffusion.

Shivanand K. *et al.,* (**2013**)[47] formulated and evaluated gastroretentive floating drug delivery tablets of an Acyclovir, using hydroxypropyl methylcellulose (HPMC K15M, HPMC K100M), xanthan gum as release-retarding polymers and sodium bicarbonate and tartaric acid as a gas former by direct compression method. Formulation F3 containing all the polymers prolonged the drug release for 12 h confirmed by higher correlation with zero order plot and selected as best formulation. Swelling studies indicated significant water uptake and contributed in drug release and gastroretention. The higher viscosity polymer had been seen to inhibit the release of Acyclovir from the floating drug delivery system. Best formulation was checked for stability studies for 2 months which showed no significant changes in the parameters.

Udayakumar. *et al.,* (**2013**)[48] designed and developed bioadhesive gastro retentive drug delivery system of Metoprolol succinate using mucoadhesive hydrophilic and hydrophobic polymers like PEO, Hydrophylic polymer (Carbopol 71G, HPMC E15, Methacrylic acid, Pectin, Carragenan and Guargum) and gas forming agent Sodium bicarbonate. Metoprolol succinate bioahesive gastric drug delivery system was proved to be attained the effective plasma concentration higher than the marketed formulation. Metoprolol succinate bioahesive gastric drug delivery system using PEO and HPMC E15 polymers could be effective sustained release formulation.

Hemanth kumar G. *et al.,* (**2012**)[49] formulated bilayer floating tablets of Metformin hydrochloride and Sitagliptin phosphate using hydrophilic polymers like HPMC K100 and sodium CMC with crospovidone, croscarmellose sodium and sodium starch glycolate as superdisintegrants and evaluated for various pre and post compression parameters. From the results of *in vitro* dissolution study, formulation containing combination of HPMC K100 and sodium CMC % drug release of Sitagliptin and Metformin was found to be 99.15% and 97.65% at 12 h and concluded that it possess good sustained release for 12 h and sodium starch glycolate was found to be good superdisintegrant for Sitagliptin layer.

Mohan Varma M. *et al.,* (**2012**)[50] developed floating tablets of Atenolol using HPMC100 cps, sodium alginate, carbopol 940 and guargum as the polymers by direct compression method and evaluated for various quality control tests. The results revealed that formulation containing sodium alginate in ratio of 1:4 of drug : polymer extended the drug release up to 8 h. It follows fickian diffusion and its release profile was similar with that of marketed extended release tablet.

Navjot Singh. *et al.,* (**2012**)[51] developed floating tablets of Tizanidine hydrochloride using HPMC by wet granulation technique in various concentration and best formulation was characterized by *in vivo* gamma scintigraphic studies using TC-99M tracer. The results confirmed that floating tablet of Tizanidine hydrochloride can maintain its integrity under harsh gastric conditions in the human stomach confirmed it as sustained release formulations.

Nirav Patel. *et al.,* (**2012**)[52] formulated floating tablets of Glipizide employing different polymers like HPMC K100M, sodium alginate, Carbopol 940 and PVP K30 by effervescent technique. Sodium bicarbonate and citric acid were incorporated as a gas generating agent and evaluated for various pre-compression and post-compression parameters. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 16-24 h. From the results it was concluded that formulation containing HPMC K100 M and sodium alginate separately were found to be best formulations and found that there was no change in stability studies.

Satishbabu BK. *et al.,* (**2010**)[53] formulated and evaluated cod liver oil entrapped calcium alginate floating beads of Famotidine. Separately floating sodium alginate beads containing carbopol 934P and hydroxyl propyl methyl cellulose K15M prepared in different ratios with Famotidine by emulsion gelation method and evaluated. The results suggested that cod liver oil entrapped calcium alginate beads were promising as a carrier for intragastric floating drug delivery of Famotidine by sustaining the drug release up to 8 h when compared to sodium alginate beads.

Kharia AA. *et al.,* (**2010**)[54] designed floating tablet of Acyclovir using psyllium husk and hydroxypropylmethylcellulose K4M as the polymers and sodium bicarbonate as a gas generating agent by wet granulation technique and best by 3^2 full factorial design. The results of this study revealed that the hydrophilic polymer such as HPMC K4M and psyllium husk plays an important role for the formulation of floating tablet. The results indicated that the proper balance between psyllium husk and hydroxypropylmethylcellulose K4M can produce a drug dissolution profile similar to the predicted dissolution profile. As the amount of the polymer in the formulations increases, the drug release rate decreases. The best formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix. The formulation F2 was best may be used once a day administration in the management of viral diseases.

Ramesh Bomma. *et al.,* (**2009**)[55] developed and evaluated floating tablets of Norfloxacin by wet granulation technique using HPMC K4M, HPMC K100M and xanthan gum. From the results it was concluded that formulation containing HPMC both grades floated with lag time less than 1 minutes and continued to float for 24 h. *In vivo* radiographic studies concluded that formulation containing HPMC K4M increases gastric residence time thereby improving bioavailability of drugs.

Havaldar VD. *et al.,* (**2009**)[56] formulated and evaluated floating matrix tablets of Atenolol various concentrations of different rate controlling polymers like HPMC K4M, HPMC K100M and xanthan gum with sodium bicarbonate as gas generating agent by direct compression technique. Swelling studies of all formulations showed formulation containing xanthan gum has higher swelling index than HPMC K4M and HPMC K100M. From the results it was concluded that formulation with higher swelling indices retard the release of drugs more than those with lower swelling index. It was also confirmed that formulation containing xanthan gum has lesser floating lag time and prolonged floating duration thereby increases the gastric residence time.

Vishnu M Patel. *et al.,* (**2009**)[57] formulated and evaluated controlled release gastroretentive tablets of Verapamil hydrochloride using HPMC K4M, HPMC

K15M, HPMC E15, carbopol (CP 934P and CP 940P) and xanthan gum as rate controlling polymers by direct compression technique. The results revealed that formulation containing xanthan gum sustained the drug release up to 24 h and follows non-fickian release, buoyancy lag time was 24.6 sec remained buoyant for more than 24 h.

Ravi kumar. *et al.,* (**2009**)[58] formulated and evaluated effervescent floating tablet of Famotidine using polymers like different viscosity grades of HPMC and Carbopol 934P with sodium bicarbonate, citric acid as effervescent agents by wet granulation technique. The results revealed that formulation containing combination of all the polymers with effervescent agents sustained the drug release and remain buoyant up to 24 h and mechanism for drug release was predominantly diffusion controlled.

Manoj N Gambhire. *et al.,* (**2007**)[59] developed and evaluated oral floating matrix tablet of Diltiazem hydrochloride using rate controlling polymers like Methocel K100M CR, Compritol 888 ATO only or combined with sodium bicarbonate as gas generating agent by direct compression technique and best by 3^2 factorial design. The results concluded that formulations containing either Methocel K100M CR or Compritol 888 ATO showed minimal variation in drug release and floating lag time.

Raval JA. *et al.,* (**2007**)[60] formulated and characterized floating matrix tablets of Ranitidine hydrochloride by direct compression technique with HPMC K4M, HPMC K15M, HPMC K100M, sodium alginate, psyllum, sesbania gum, guar gum and gum acacia with or without low density copolymer (poly(styrene-divinyl benzene) copolymer). The results indicated that floating behavior is sustained for 8 h by HPMC K100M assisted by low density copolymer at 15% concentration.

Narendra C. *et al.,* (**2006**)[61] best bilayer floating tablets of Metoprolol tartrate as model drug using different viscosity grades of HPMC (K4M and K10M) by 2^3 factorial design. The results revealed that formulation containing HPMCK4M remained buoyant up to 24 h.

Asha patel. *et al.,* (**2006**)[62] best and evaluated controlled release floating microspheres of Metformin hydrochloride using ethylcellulose as rate controlling polymer and acetone as solvent by non-aqueous emulsification solvent evaporation technique. The results revealed that sustained floating time and drug release up to 8 h was obtained in the ratio of drug: polymer: solvent was 250:750:12 and 25:146.45:9 (mg:mg:ml).

Ziyaur Rahman. *et al.,* (**2006**)[63] designed and evaluated bilayer floating tablets of Captopril by direct compression method using HPMC K15M, PVP K30 and carbopol 934P alone or in combination with effervescent mixture of citric acid and sodium bicarbonate. *In vitro* dissolution studies revealed controlled release of drug for 24 h. The drug release follows diffusion controlled mechanism and *in vivo* studies showed increased gastric residence time.

4. MATERIALS & METHODS

4.1 List of materials used:

Table 2: List of materials used

S.No	Name of the ingredients	Manufacturer
1.	Eprosartan mesilate	Hetero Pharmaceuticals, Hyderabad.
2.	Acebutolol hydrochloride	Sigma Aldrich, Chennai.
3.	Carbopol 934P	Yarrow Chemicals Ltd, Mumbai.
4.	HPMC E 15	Granules India Pvt Ltd, Hyderabad.
5.	Ethyl cellulose	Granules India Pvt Ltd, Hyderabad
6.	HPMC K15	Granules India Pvt Ltd, Hyderabad
7.	Carbopol 940	Yarrow Chemicals Ltd, Mumbai.
8.	Guar gum	Yarrow Chemicals Ltd, Mumbai.
9.	Xanthan gum	Yarrow Chemicals Ltd, Mumbai.
10.	Karaya gum	Yarrow Chemicals Ltd, Mumbai.
11.	Sodium alginate	Yarrow Chemicals Ltd, Mumbai.
12.	Chitosan	Ranbaxy Research Laboratories, Gurgaon
13.	Sodium bicarbonate	Merck Ltd, Mumbai.
14.	Citric acid	Granules India Pvt Ltd, Hyderabad
15.	Microcrystalline cellulose	Granules India Pvt Ltd, Hyderabad
16.	Talc	Scientific Lab, Erode
17.	Magnesium stearate	Loba Chemicals, Mumbai
18.	Sodium chloride	Finar Chemicals Ltd, Ahmadabad
19.	Concentrated hydrochloric acid	Merck Ltd, Mumbai

4.2 List of equipments used:

Table 3: List of equipments used

S. No.	Equipment	Manufacturer
1	Electronic balance	R.R.Scientifics
2	UV Spectrophotometer	Elico Limited
3	Tablet punching machine	Kambert Machinery Co. (P) Ltd.
4	Vernier caliper	Madras Scientifics
5	Hardness tester	Asian Scientific Instruments
6	Friabilator	Lab India
7	USP dissolution apparatus	Lab India
8	FT-IR Spectrometer	Perkin Elmer
9	Stability chamber	Scigenics Biotech

4.3 DRUG PROFILE

4.3.1 Acebutolol hydrochloride[34]

Other names : Acébutolol; Acebutololum; Asebutolol; Asebutololi.

Chemical name : (±)-3′-Acetyl-4′-(2-hydroxy-3-isopropylaminopropoxy) butyranilide.

Molecular formula : $C_{18}H_{28}N_2O_4$.Hcl.

Molecular weight : 372.9 g/mol

Chemical structure:

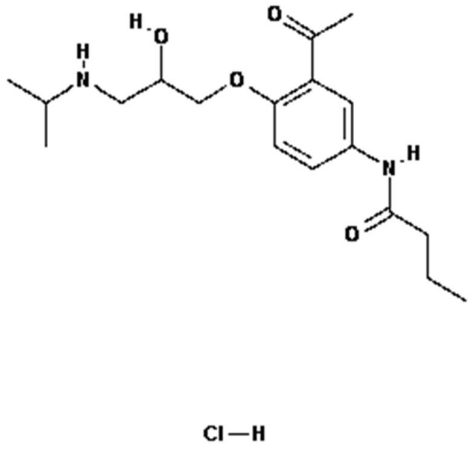


Fig. 13: Structure of Acebutolol hydrochloride

Description:

It is a white or almost white crystalline powder. It is soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane; practically insoluble in ether. The pH of a 1% solution in water is between 4.5 and 7.0. It should be stored in airtight containers.

Adverse Effects:

Breast feeding:

Concentrations of Acebutolol and its active metabolite Diacetolol in breast milk are higher than those in maternal plasma. The adverse effects in the neonate include hypotension, bradycardia and tachypnoea and therefore care should be taken for the administration of Acebutolol to breast-feeding mothers.

Effects on the liver:

The syndrome consisted of markedly elevated transaminase concentrations, moderately elevated alkaline phosphatase concentrations, and other constitutional symptoms such as fever, nausea, abdominal pain and headache. The duration of therapy before onset of symptoms ranged from 10 to 31 days; 5 patients received a daily dose of 400 mg; the dose was unspecified in the sixth patient. The syndrome resolved when Acebutolol was stopped but reappeared in 2 patients who were rechallenged.

Effects on respiratory function:

Bronchospasm is a familiar adverse effect of beta blockers, but other respiratory disorders have also been reported. Pleurisy and pulmonary granulomas developed in a patient given Acebutolol and a diuretic; Acebutolol was considered to be responsible.

Hypersensitivity:

Hypersensitivity pneumonitis has also been reported in a patient taking Acebutolol.

Lupus:

An increase in antinuclear antibodies has been seen with Acebutolol. A report of a lupus syndrome in an elderly patient given Acebutolol and Clonidine described remission of symptoms when Acebutolol was withdrawn, but the high antinuclear antibody titre persisted for more than 9 months. Acebutolol was also

reported to have caused subacute cutaneous lupus erythematosus in a 57-year-old woman. The condition had resolved completely 4 months after Acebutolol was stopped. The authors noted that there had been previous reports of lupus in patients taking Acebutolol, but only one had skin manifestations.

Pregnancy:

Both Acebutolol and its active metabolite Diacetolol cross the placenta evidenced bradycardia and tachypnoea.

Interactions:

Both pharmacodynamic and pharmacokinetic interactions have been reported with beta blockers. **Pharmacodynamic** interactions may occur with drugs whose actions enhance or antagonise the various effects of beta blockers at beta1 and beta2 receptors, including their anti-hypertensive effect, cardiodepressant effect, effect on carbohydrate metabolism or effect on bronchial beta2 receptors.

Use of beta blockers with other cardiac depressants such as antiarrhythmics and rate-limiting calcium channel blockers can precipitate bradycardia and heart block; the combination of intravenous Verapamil and beta blockers should especially be avoided. Beta blockers may potentiate bradycardia due to Digoxin.

The interaction between beta blockers and sympathomimetics is complex and depends on the selectivity of both drugs. Patients taking beta blockers may have an exaggerated hypertensive response to Adrenaline, caused by unopposed alpha-mediated vasoconstriction, while the bronchodilator effects are inhibited; the response to Adrenaline given for anaphylaxis may also be reduced in patients on long-term treatment with beta blockers. In diabetic patients beta blockers can reduce the response to Insulin and oral hypoglycaemics through their effects on pancreatic beta receptors.

Pharmacokinetic interactions occur with drugs that alter the absorption or metabolism of beta blockers. Although these interactions may alter the beta blocker plasma concentration, they are not usually clinically significant since there is little association between plasma concentrations and therapeutic effect or toxicity and

there are wide inter-individual differences in steady-state plasma concentrations of beta blockers. Drugs that reduce absorption include Aluminium salts and bile-acid binding resins such as Colestyramine. Metabolism of some beta blockers can be increased by drugs such as Barbiturates and Rifampicin and decreased with drugs such as Cimetidine, Eythromycin, Fluvoxamine and Hydralazine. Drugs that alter hepatic blood flow also affect metabolism of some beta blockers.

Antiarrhythmics:

Use of beta blockers with antiarrhythmic drugs and other drugs affecting cardiac conduction can precipitate bradycardia and heart block.

Antimalarials:

Antimalarials such as Halofantrine, Mefloquine and Quinine can cause cardiac conduction defects and caution is necessary if they are used with beta blockers.

Anxiolytics and antipsychotics:

Plasma concentrations of some beta blockers may be reduced by Barbiturates.

Calcium-channel blockers:

Use of calcium-channel blockers with beta blockers has resulted in hypotension, bradycardia, conduction defects and heart failure.

General anaesthetics:

The hypotensive effects of beta blockers may be potentiated by general anaesthetics, and anaesthetics that cause myocardial depression, such as Ether, Cyclopropane and Trichloroethylene should preferably be avoided.

NSAIDs**:**

The anti-hypertensive effect of beta blockers may be impaired by some NSAIDs, possibly due to their inhibition of renal synthesis of vasodilating

prostaglandins. This interaction probably occurs with all beta blockers but may not occur with all NSAIDs. For example, Sulindac appears to affect blood pressure control less than Indomethacin.

Opioid analgesics:

Bioavailability of Propranolol and Metoprolol was increased in subjects given Dextropropoxyphene; Dextropropoxyphene is an inhibitor of the cytochrome P450 isoenzyme CYP2D6 and was reported to increase serum concentrations of Metoprolol, a CYP2D6 substrate, in a patient given both drugs, resulting in bradycardia. Intravenous Morphine may increase serum concentrations of Esmolol.

Pharmacokinetics:

Acebutolol is well absorbed from the GIT but undergoes extensive first-pass metabolism in the liver. Although the bioavailability of Acebutolol is reported to be only about 40%, the major metabolite Diacetolol is active. After oral doses, peak plasma concentrations of Acebutolol and Diacetolol are reached in about 2 and 4 h, respectively. Acebutolol and Diacetolol are widely distributed in the body, but they have low to moderate lipid solubility and penetration into the CSF is poor. They cross the placenta and higher concentrations are achieved in breast milk than in maternal plasma. Acebutolol is only about 26% bound to plasma proteins, but is about 50% bound to erythrocytes. The plasma elimination half-lives for Acebutolol and Diacetolol are 3 to 4 h and 8 to 13 h respectively. Half-life values for Acebutolol and Diacetolol may be increased in the elderly and the half-life for Diacetolol may be prolonged up to 32 h in patients with severe renal impairment. Acebutolol and Diacetolol are excreted in the urine and in the bile and may undergo enterohepatic recycling; Acebutolol is also reported to be excreted directly from the intestinal wall and more than 50% of an oral dose can be recovered from the faeces. Acebutolol and Diacetolol are removed by dialysis.

Uses and Administration:

Acebutolol is a cardioselective beta blocker. It is reported to have some intrinsic sympathomimetic activity and membrane stabilising properties. Acebutolol

is used in the management of hypertension, angina pectoris and cardiac arrhythmias. Acebutolol is used as the hydrochloride, but doses are usually expressed in terms of the base; 110.8 mg of Acebutolol hydrochloride is equivalent to 100 mg of base. It is generally given orally although slow intravenous injection has been used for the emergency treatment of arrhythmias.

In **hypertension** the usual initial oral dose is 400 g once daily or 200 mg twice daily, increased if necessary after 2 weeks to 400 mg twice daily. Doses up to 1.2 g daily in divided doses may be given. The usual oral dose for **angina pectoris** is 400 mg once daily or 200 mg twice daily, but up to 300 mg three times daily may be required for severe cases and total daily doses of 1.2 g have been given. The usual initial oral dose for **cardiac arrhythmias** is 200 mg twice daily, increased according to response; up to 1.2 g daily in divided doses has been required. Reduced doses may be required in patients with impaired renal function. Elderly patients may also require lower maintenance doses; doses greater than 800 mg daily should be avoided.

Action:

Acebutolol is generally considered to be a cardioselective beta blocker but there has been considerable controversy as to the degree of its selectivity and the selectivity of its primary metabolite, Diacetolol. Acebutolol was less cardioselective than other drugs such as Atenolol or Metoprolol because the metabolite accumulates during chronic dosage to reach concentrations that affect both beta1 and beta2 receptors since cardio selectivity are only a relative and dose-related phenomenon.

Administration in renal impairment**:**

The dose of Acebutolol should be reduced in patients with renal impairment. It is recommended that the dose should be reduced by 50% in patients with a creatinine clearance between 25 and 50 ml/min and by 75% in those with a creatinine clearance of less than 25 ml/min. The dose frequency should not exceed once daily.

4.3.2 Eprosartan Mesilate[36]

Other names : Éprosartan, Mésilate d'; Eprosartan Mesilate *(USAN)*; Eprosartani Mesilas; Mesilato de eprosartán; SKF-108566-J. (*E*)

Chemical name : 2-Butyl-1-(*p*carboxybenzyl)-α-2-thenylimidazole-5-acrylicacid methanesulfonate.

Molecular formula : $C_{23}H_{24}N_2O_4S,CH_4O_3S$.

Molecular weight : 520.6.

Chemical structure:

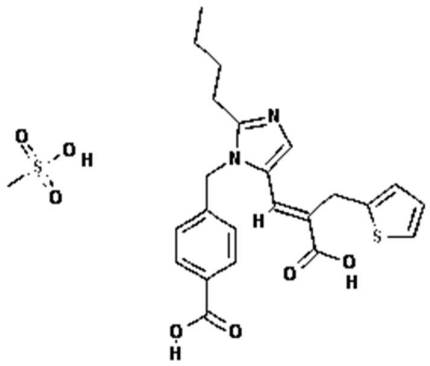


Fig. 14: Structure of Eprosartan mesilate

Description:[64]

It is a white to off-white crystalline powder that is insoluble in water, freely soluble in ethanol and melts between 248°C and 250°C.

Adverse Effects:

Adverse effects of Eprosartan have been reported to be usually mild and transient and include dizziness, headache and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example

those who have received high dose diuretics). Impaired renal function and rarely, rash, urticaria, pruritus, angioedema and raised liver enzyme values may occur. Hyperkalaemia, myalgia and arthralgia have been reported. Eprosartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue and neutropenia. Rhabdomyolysis has been reported rarely.

Angioedema:

Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. Although angiotensin II receptor antagonists were thought to lack effects on bradykinin.

Effects on the blood:

Symptomatic anaemia, decreased haemoglobin and immune thrombocytopenia are reported with Eprosartan. Acute, reversible hepatotoxicity also occurred in a patient who had been taking Eprosartan 150 mg daily for 6 weeks.

Effects on the skin:

Atypical cutaneous lymphoid infiltrates, Henoch-Schonlein purpura, purpuric rash with evidence of vasculitis developed in patients receiving Eprosartan for hypertension.

Effects on taste:

Taste disturbances, in some cases progressing to complete taste loss, have occurred in patients receiving Eprosartan for hypertension and taste is returned to normal after stopping Eprosartan therapy.

Migraine:

Severe migraine has been occured in a patient after use of Eprosartan.

Pancreatitis:

Acute pancreatitis has been reported in patients receiving Eprosartan.

Precautions:

Eprosartan is contra-indicated in pregnancy. It should be used with caution in patients with renal artery stenosis. Eprosartan is excreted in urine and in bile and reduced doses may therefore be required in patients with renal impairment and should be considered in patients with hepatic impairment. Patients with volume depletion (for example those who have received high-dose diuretic therapy) may experience hypotension; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium- sparing diuretics should generally be avoided.

Diabetes mellitus:

The symptomatic and hormonal responses to hypoglycaemia are associated with Eprosartan therapy. Angiotensin II receptor antagonists may prevent the development of diabetes in non-diabetic patients.

Pregnancy:

Eprosartan is contra-indicated in pregnancy since it has been associated with fetal toxicity in animal studies and other drugs that act on the renin-angiotensin system, such as ACE inhibitors, have been associated with fetal toxicity in humans. Oligohydramnios with subsequent fetal death occurred in a patient received Eprosartan during weeks 20 to 31 of pregnancy; the effects on the fetus were similar to those reported with ACE inhibitors.

Interactions:

The anti-hypertensive effects of Eprosartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics or other drugs that can cause hyperkalaemia; Eprosartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking

Eprosartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of Eprosartan. Eprosartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Pharmacokinetics:

Eprosartan is absorbed from the gastrointestinal tract with an absolute oral bioavailability of about 13%. Peak plasma concentrations occur about 1 to 2 h after an oral dose in the fasted state; giving doses with food delays absorption but this is not clinically significant. Eprosartan is about 98% bound to plasma proteins. It is excreted in the bile and in the urine, primarily as the unchanged drug; after oral doses approximately 7% of the drug is excreted in the urine, with about 2% as the acyl glucuronide. The terminal elimination half life is about 5 to 9 h.

Uses and Administration:

Eprosartan is an angiotensin II receptor antagonist used in the management of hypertension. Eprosartan is given orally as the mesilate but doses are expressed in terms of the base; Eprosartan mesilate 1.2 mg is equivalent to about 1 mg of Eprosartan. The onset of anti-hypertensive effect occurs about 1 to 2 h after administration and the maximum effect is achieved within 2 to 3 weeks after initiating therapy. In the management of hypertension, Eprosartan is given in an initial dose of 600 mg once daily. A lower initial dose of 300 mg once daily may be used in elderly patients over 75 years and has been recommended in renal or hepatic impairment. The dose should be adjusted according to response; the usual maintenance dose is 400 to 800 mg daily in a single dose or in two divided doses.

Administration in hepatic or renal impairment:

A lower initial dose of 300 mg daily of Eprosartan is recommended in patients with renal impairment (creatinine clearance less than 60 ml/min) or mild to moderate hepatic impairment; this seems to be due to lack of clinical experience in such patients. A maximum dose of 600 mg daily is recommended for patients with moderate or severe renal impairment.

4.4 EXCIPIENT PROFILE

Hydroxy Propyl Methyl Cellulose (HPMC)[65]

Synonyms : Hypromellose, Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose, propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

Chemical name : Cellulose 2- hydroxy propyl methyl ether.

Empirical formula : $[C_6H_7O_2(OH)_3—(OCH_3)—(OCH_3CH(OH)—CH_3)]_n$

Molecular weight : 10, 000–1, 500, 000

Chemical structure:

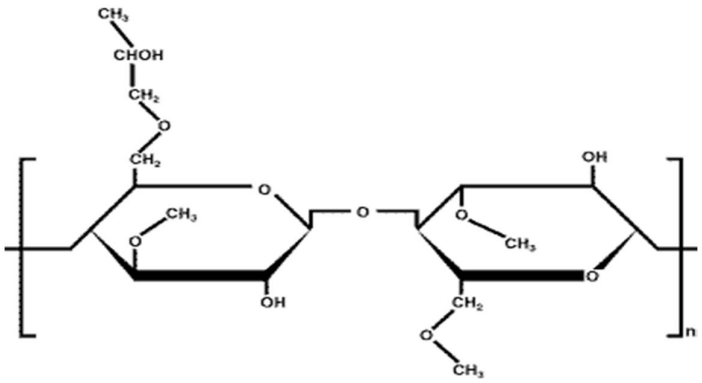


Fig. 15: Structure of Hydroxy propyl methyl cellulose

Functional Category : Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

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

Solubility	**:**	It is soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, methanol and dichloromethane and water and alcohol.
Acidity/ alkalinity	**:**	5.5 – 8.0 for 1% w/w aqueous solution.
Viscosity	**:**	HPMC E15 15 mPa s. HPMC K15M 15000 mPa s.
Stability	**:**	It is a stable material, although it is hygroscopic after drying.
Storage conditions	**:**	It is stored in a well-closed container in a cool, dry place.
Applications	**:**	It is used as tablet binder in film-coating in the concentrations between 2% and 5% w/w and as a matrix for use in extended-release tablet formulations in the concentration of 10–80% w/w in tablets and capsules. It is also used as emulsifier, suspending and thickening agent in topical gels and ointments.

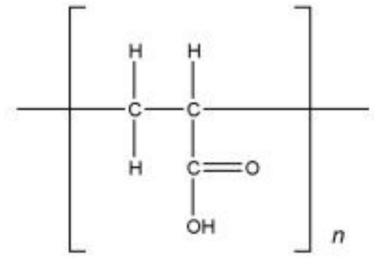
Carbopol[66]

Synonyms : Acritamer; acrylic acid polymer; Carbomer; carboxy polymethylene, polyacrylic acid; carboxyvinyl polymer; Pemulen; Ultrez.

Molecular weight : Mc (molecular weight between crosslinks) 2, 37, 600 g/mol for Carbopol 941 and of 1, 04, 400 g/mol for Carbopol 940.

Chemical Name : Poly (acrylic acid).

Chemical structure:



Acrylic acid monomer unit in carbomer resins.

Fig. 16: Structure of Carbopol

Functional Category : Bioadhesive; emulsifying agent; release-modifying agent; suspending agent; tablet binder; viscosity-increasing agent.

Description : It is white-colored, 'fluffy', acidic, hygroscopic powders with a slight characteristic odor.

Solubility : Soluble in water and, after neutralization, in ethanol (95%) and glycerin.

Acidity/ alkalinity	**:**	pH = 2.7–3.5 for a 0.5% w/v aqueous dispersion. pH = 2.5–3.0 for a 1% w/v aqueous dispersion.
Viscosity	**:**	Carbomer 934P 29400 - 39400 mPa s. Carbomer 940 40000 - 60000 mPa s.
Stability	**:**	It is a stable hygroscopic material.
Storage conditions	**:**	It is stored in an airtight, corrosion-resistant container in a cool, dry place.
Applications	**:**	It is used in liquid or semisolid pharmaceutical formulations in the concentration of 0.5 – 1% as suspending agent, 0.5 – 2% as jelling agent and 0.1-0.5% as emulsifiers include creams, gels, and ointments for use in ophthalmic, rectal and topical preparations. It is also used as tablet binder in the concentration of 5-10%.

Ethyl cellulose[67]

Synonyms	**:**	Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.
Chemical name	**:**	Cellulose ethyl ether.
Empirical Formula	**:**	$C_6H_7O_2(OR_1)(OR_2)$ where $R_1$and R_2 may be any of the following:—H or $C_{20}H_{38}O_{11}$.
Molecular weight	**:**	454.513 g/mol.

Chemical structure:

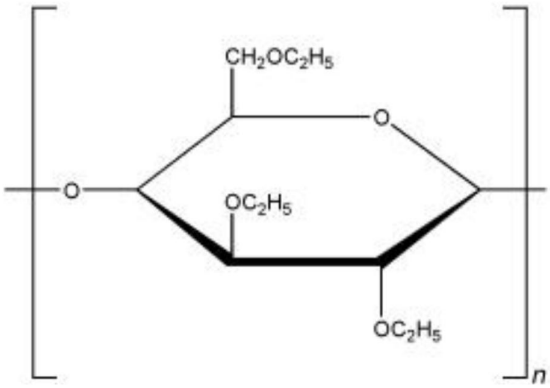


Fig. 17: Structure of Ethyl cellulose

Functional Category	**:**	Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.
Description	**:**	It is tasteless, free-flowing, white to light tan-colored powder.
Solubility	**:**	It is practically insoluble in glycerin, propylene glycol, and water.
Viscosity	**:**	7-100 mPa s.

Stability	**:**	It is a stable and slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.
Storage conditions	**:**	It is stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat.
Applications	**:**	It is widely used in oral and topical pharmaceutical formulations in the concentration of 1-3% in tablet granulation and coating, 3-20% in sustained release coating of tablet and 10 – 20 % in microencapsulation.

Guar gum [68]

Synonyms : E412; Galactosol; guar flour; jaguar gum; Meyprogat; Meyprodor; Meyprofin.

Chemical name : Galactomannan polysaccharide.

Empirical Formula : $(C_6H_{12}O_6)_n$

Molecular weight : 2, 20, 000

Chemical structure:

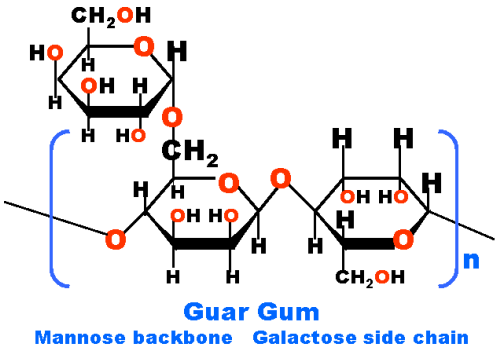


Fig. 18: Structure of Guar gum

Functional Category : Suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent.

Description : It is a gum obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (Fam. Leguminosae). It consists chiefly of a highmolecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. It appears as off-white or yellowish powder.

Solubility	**:**	It is practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol.
Acidity/ alkalinity	**:**	pH = 5.0–7.0 (1% w/v aqueous dispersion).
Viscosity	**:**	4.86 mPa s for a1% w/v dispersion.
Stability	**:**	Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5.
Storage conditions	**:**	It is stored in a well-closed container in a cool, dry place.
Applications	**:**	Guar gum is a galactomannan, commonly used in cosmetics, food products and pharmaceutical formulations. It is used in the concentration of 1% as emulsion stabilizer, upto 10% as tablet binder and upto 2.5% as thickening agent in lotions and creams. It has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose and for use in colonic drug delivery in oral controlled-release formulations.

Karaya gum[69]

Synonyms : Karaya , sterculia , Indian tragacanth , Bassora tragacanth , kadaya, mucara , kadira , katila , kullo, Suavioside H.

Scientific name : Sterculia urens Roxb

Description : The gum also may be obtained from S. villosa, S. tragacantha or other species of Sterculia Family: Sterculiaceae**.** It appears as tan off-white colour or pale yellow to pinkish brown fine granules with acidic odour.

Empirical Formula : Kaur-15-en-18-oic acid,
13 - (b-D-glucopyranosyloxy) - 17-oxo-,
b-D-glucopyranosyl ester, (4a)-$C_{32}H_{48}O_{14}$.

Chemical structure:

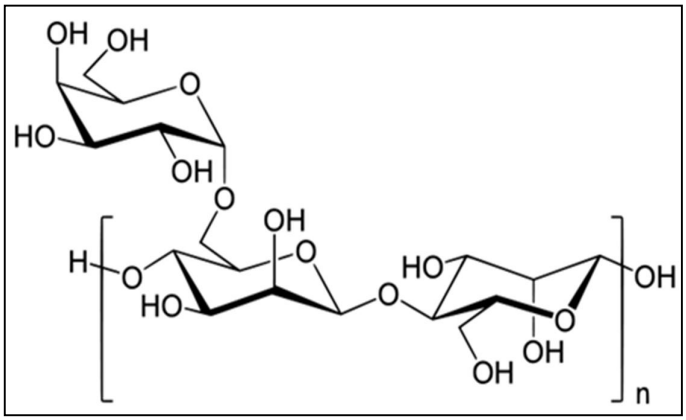


Fig. 19: Structure of Karaya gum

Acidity : pH 7-8.

Viscosity : 5600 mPa s.

Solubility : Karaya gum is the least soluble of the commercial plant exudates, but it absorbs water rapidly and swells to form viscous

colloidal solutions even at low concentrations (1%). The swelling behavior of karaya gum is dependent upon the presence of acetyl groups in its structure. Deacetylation through alkali treatment results in a water soluble gum. When used in higher concentrations in water (up to 4%), Karaya forms gels or pastes. Unlike other gums, Karaya swells in 60% alcohol, but remains insoluble in other organic solvents. Karaya may absorb up to 100 times its weight in water. It is very slightly soluble in cold water.

Functional Category : Gelling agent, stabilizing agent, suspending agent, sustained release agent and thickening agent.

Stability : It is a stable material. Aqueous solution are stable over a wide pH range (3-12) at temperature of 10-60^{o}C.

Storage conditions : It is stored in a well closed container and in a cool, dry place.

Applications : Karaya gum is used in cosmetics and food, and in pharmaceuticals as a laxative and adhesive. It is also used in making of medical jellies and pastes. Backing and dairy industries are widely used gum karaya for dressing and binding. Karaya gum is used in the production of adhesives for ileostomy and colostomy. It is also used in hair dressing preparation lotions as cosmetic purpose. It is also used in different type of drug delivery systems.

Xanthan gum[70]

Synonym : Corn sugar E415; keltrol, polysaccharide B1459, Rhodigel; Vanzan NF; Xantural.

Chemical name : Xanthan gum.

Empirical formula : $(C_{35}H_{49}O_{29})_n$

Molecular weight : 20, 00, 000

Chemical structure:

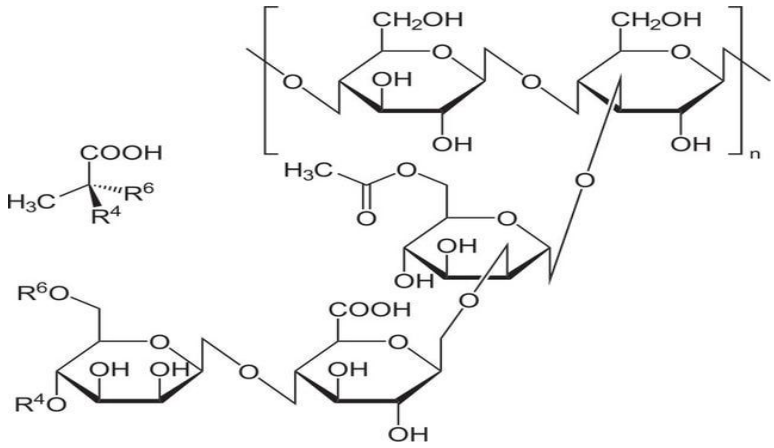


Fig. 20: Structure of of Xanthan gum

Functional category : Stabilizing agent, suspending agent, viscosity increasing agent, thickening agent.

Description : Xanthan gum occurs as a cream (or) white coloured, odourless, free flowing, fine powder.

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

Acidity / alkalinity : pH= 6.8 – 8.0 for a 1% w/v aqueous solution.

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

Stability	**:**	It is a stable material. Aqueous solution are stable over a wide pH ranges (pH 3-12) although they demonstrate maximum stability at pH 4-10 and temperature of 10-60ºC.
Storage conditions	**:**	It should be stored in a well closed container in a cool, dry place.
Applications	**:**	It is usually used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending, emulsifying, thickening and stabilizing agent. It is also used to prepare sustained-release matrix tablets and also be used as an excipient for spray drying and freeze-drying processes.

Chitosan[71]

Synonyms : 2-Amino-2-deoxy-(1,4)-ß0-D-glucopyranan; deacetylated chitin; deacetylchitin; ß0-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-ßÅ-D-glucopyranosamine).

Chemical name : Poly-ß-(1,4)-2-Amino-2-deoxy-D-glucose.

Chemical formula : $C_{56}H_{103}N_9O_{39}$

Molecular weight : 10,000–1,000,000

Chemical structure:

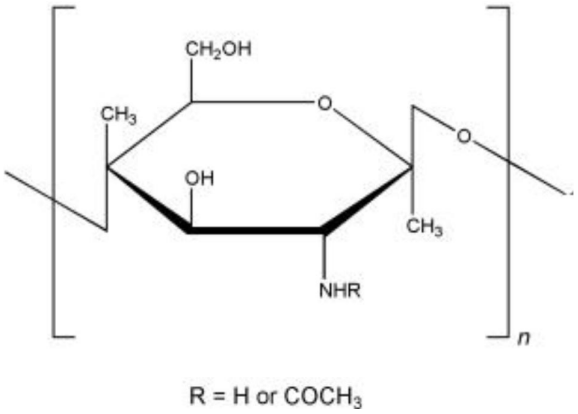


Fig. 21: Structure of Chitosan

Functional Category : Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

Description : It is an odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cottonlike'.

Solubility : It is sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents and neutral or alkali solutions at pH above approximately 6.5.

Acidity/ alkalinity	**:**	pH = 4.0–6.0 (1% w/v aqueous solution).
Viscosity	**:**	In acetic acid 260 mPa s. In citric acid 35 mPa s.
Stability	**:**	It is a stable material at room temperature, although it is hygroscopic after drying.
Storage conditions	**:**	It is stored in a tightly closed container in a cool and dry place.
Applications	**:**	It is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations include controlled drug delivery applications such as use as a component of mucoadhesive dosage forms, rapid release dosage forms, gels, films, beads, microspheres, tablets and coatings for liposomes, enhanced peptide delivery, colonic drug delivery systems, gene delivery and also in several techniques including spraydrying, coacervation, direct compression and conventional granulation processes.

Sodium alginate[72]

Synonyms : Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

Chemical name : Sodium alginate, alginic acid mono sodium salt.

Empirical formula : $C_6H_9NaO_7$

Molecular weight : 216.121 g/mol.

Chemical structure:

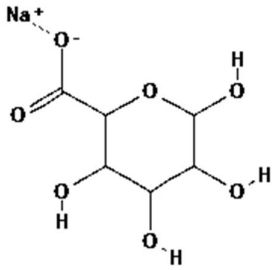


Fig. 22: Structure of Sodium alginate

Functional category : Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

Description : It is an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility : It is practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%.

Acidity/ alkalinity	**:**	pH 7.2 for a 1% w/v aqueous solution.
Viscosity	**:**	20–400 mPa s.
Stability	**:**	It is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature.
Storage conditions	**:**	It is stored in an airtight container in a cool and dry place.
Applications	**:**	It is used in oral and topical pharmaceutical formulations. In tablets, it is used as both a binder and disintegrant and in capsule it is used as diluents. It is also used in the preparation of sustained-release oral formulations. In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams and gels and as a stabilizing agent for oil-in-water emulsions. It is also used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems, in formation of nanoparticles, ophthalmic solutions that form a gel in situ when administered to the eye and a freeze-dried device intended for the delivery of bone-growth factors.

Citric acid[73]

Synonym : E330; 2-hydroxy propane-1,2,3,tri-carboxlic acid monohydrate.

Chemical name : 2-hydroxy-1,2,3-propanetricarboxlic acid monohydrate.

Empirical formula : $C_6H_8O_7.H_2O$

Molecular weight : 210.14 g/mol

Chemical structure:

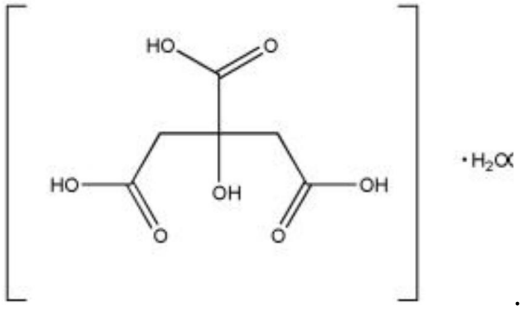


Fig. 23: Structure of Citric acid

Functional category : Acidifying, antioxidant, buffering agent, chelating, flavour enhancer.

Description : It is colourless (or) translucent (or) as a white crystalline efflorescent powder. It is odourless and has strong acid flavor. The crystal structure is orthorhombic.

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

Acidity / alkalinity : pH 2.2 for a 1% w/v aqueous solution.

Viscosity (dynamic)	**:**	6.5 mPa s for 50% w/v aqueous solution at 25ºC.
Stability	**:**	Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40°C. It is slightly deliquescent in moist air.
Storage conditions	**:**	It should be stored in airtight container in a cool and dry place.
Applications	**:**	It is usually used in pharmaceutical formulations and food products, in the concentration of 0.1 – 0.2% to adjust the pH of solutions, tablet matrices in enteric-coated formulations for colon-specific drug delivery, to improve the stability of spray-dried insulin powder in inhalation formulations, 0.3-2% as a flavor enhancer for its acidic taste, sequestering agent and antioxidant synergist.

Sodium bicarbonate[74]

Synonym	**:**	Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; Sodium hydrogen carbonate
Chemical name	**:**	Carbonic acid monosodium salt.
Empirical formula	**:**	$NaHCO_3$
Molecular weight	**:**	84.01 g/mol.

Chemical structure:

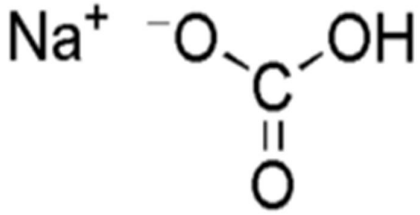


Fig. 24: Structure of Sodium bicarbonate

Functional category	**:**	Alkalizing agent, therapeutic agent.
Description	**:**	Odourless, white crystalline powder, slightly alkaline nature.
Solubility	**:**	Soluble in water, practically insoluble in ethanol and ether.
Acidity / alkalinity	**:**	pH 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C alkalinity increase on standing, agitation (or) heating.
Stability	**:**	Sodium bicarbonate is stable in dry air but slowly decomposes in moist air.
Storage conditions	**:**	It should be stored in a well-closed container in a cool, dry place.

Application **:** It is generally used as a source of carbon dioxide in effervescent tablet and granules in the concentration of 25-50%. It is also widely used to provide (or) maintain an alkaline pH in a preparation in the concentration of 10-40%. Therapeutically sodium bicarbonate may be used as an antacid and source of bicarbonate anion in the treatment of metabolic acidosis. It is also used as a component of oral rehydration salt and as a source of bicarbonate in dialysis fluids.

Microcrystalline cellulose[75]

Synonyms : Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Empirical name : Cellulose.

Chemical formula : $(C_6H_{10}O_5)n$

Molecular weight : 36, 000 g/mol.

Chemical structure:

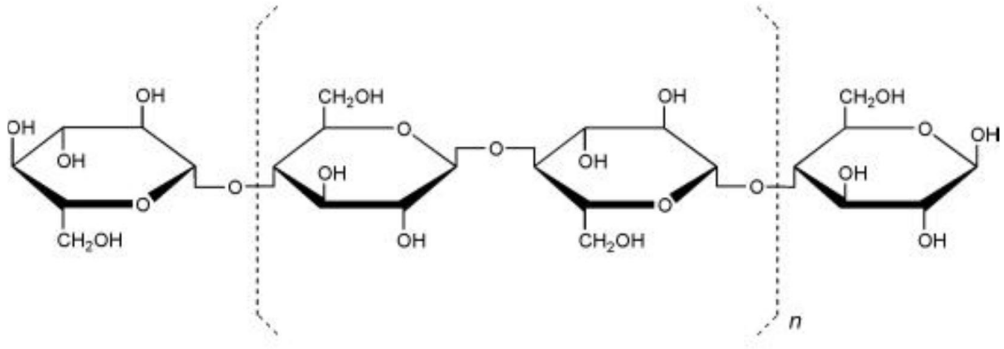


Fig. 25: Structure of Microcrystalline cellulose

Functional category : Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description : It is a white, odorless, tasteless, crystalline powder composed of porous particles.

Solubility : It is slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

Stability : Microcrystalline cellulose is a stable though hygroscopic material.

Storage conditions	**:**	It should be stored in a well-closed container in a cool and dry place.
Applications	**:**	Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder or diluent in oral tablet and capsule formulations of 20-90% where it is used in both wet-granulation and direct compression processes. It also used as lubricant in 5-20% and disintegrant in 5-15% in tablet.

Talc[76]

Synonyms : Altalc; E553b; Hydrous magnesium calcium silicate, Hydrous magnesium silicate, Magnesium hydrogen metasilicate, Magsilstar, powdered talc, purified French chalk, steatite; Superiore.

Chemical name : Talc.

Empirical Formula : $Mg_6(Si_2O_5)_4(OH)_4$

Molecular weight : 379.27 g/mol.

Chemical structure:

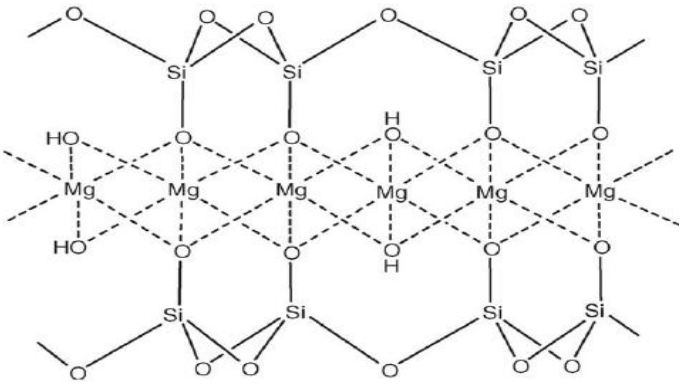


Fig. 26: Structure of Talc

Functional category : Anticaking agent, Glidant.

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 the touch and free from grittiness.

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

Stability	**:**	It is a stable material and may be sterilized by heating at 160°C for not less than 1 h. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.
Storage conditions	**:**	It should be stored in a well-closed container in a cool and dry place.
Applications	**:**	It is usually used in oral solid dosage formulations as a glidant and lubricant in 1-10%, and diluents in 5-30%. It is also used as dusting powder in 90-99% concentration.

Magnesium stearate[77]

Synonyms	**:**	Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.
Chemical name	**:**	Octadecanoic acid magnesium salt.
Empirical formula	**:**	$C_{36}H_{70}MgO_4$
Molecular weight	**:**	591.34 g/mol.

Chemical structure:

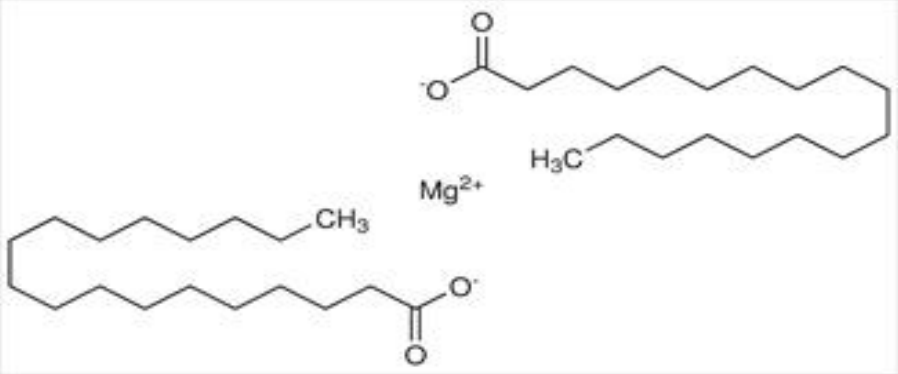


Fig. 27: Structure of Magnesium stearate

Functional category	**:**	Tablet and capsule lubricant.
Description	**:**	It is a very fine, light 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 the touch and readily adheres to the skin.
Solubility	**:**	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in *warm benzene and warm ethanol (95%).
Stability	**:**	It is stable material.

Storage conditions	**:**	It should be stored in a well closed container in a cool and dry place.
Applications	**:**	It is usually used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

4.5 EXPERIMENTAL SECTION

4.5.1 Preparation of simulated gastric fluid pH 1.2 (SGF)[78]:

About 2.0 g of sodium chloride and 7.0 ml of hydrochloric acid (concentrated) were dissolved in small amount of distilled water and made up to 1000 ml with distilled water whose pH should be 1.2.

4.5.2 Determination of λ max for Acebutolol hydrochloride in simulated gastric fluid pH 1.2:

About 100 mg of Acebutolol hydrochloride was accurately weighed into 100 ml volumetric flask and dissolved in small amount of SGF pH 1.2. Then it was made upto 100 ml using SGF pH 1.2. From this solution 10 ml was pipetted out, diluted to 100 ml in a volumetric flask using SGF pH 1.2. From this solution 1ml was withdrawn and made upto 10 ml with SGF pH 1.2 and scanned in the range of 200-400 nm using UV-Spectrophotometer with SGF pH 1.2 as blank. From the spectrum obtained, the λ max for Acebutolol hydrochloride in SGF pH 1.2was confirmed to be 234 nm.

4.5.3 Standard graph for Acebutolol hydrochloride in SGF pH 1.2:

About 100 mg of Acebutolol hydrochloride was weighed accurately and taken in a 100 ml volumetric flask. Then it was dissolved in small amount of SGF pH 1.2 and the volume was made upto 100 ml with SGF pH 1.2. From this, 10 ml was withdrawn and made upto 100 ml with SGF pH 1.2. From this solution, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8 and 2 ml was withdrawn and made upto 10 ml individually with SGF pH 1.2 (2 to 20 µg/ml) and their absorbances were measured at λ max of 234 nm using UV spectrophotometer with SGF pH 1.2 as blank. Standard graph of the drug was plotted with concentration (µg/ml) as x-axis and absorbance at 234 nm as y-axis is shown in table 4 and fig. 28.

Table 4: Standard curve for Acebutolol hydrochloride in SGF pH 1.2

S.No	Concentration (µg/ml)	Absorbance at 234 nm
1	0	0
2	2	0.082
3	4	0.187
4	6	0.268
5	8	0.375
6	10	0.442
7	12	0.582
8	14	0.624
9	16	0.751
10	18	0.864
11	20	0.921

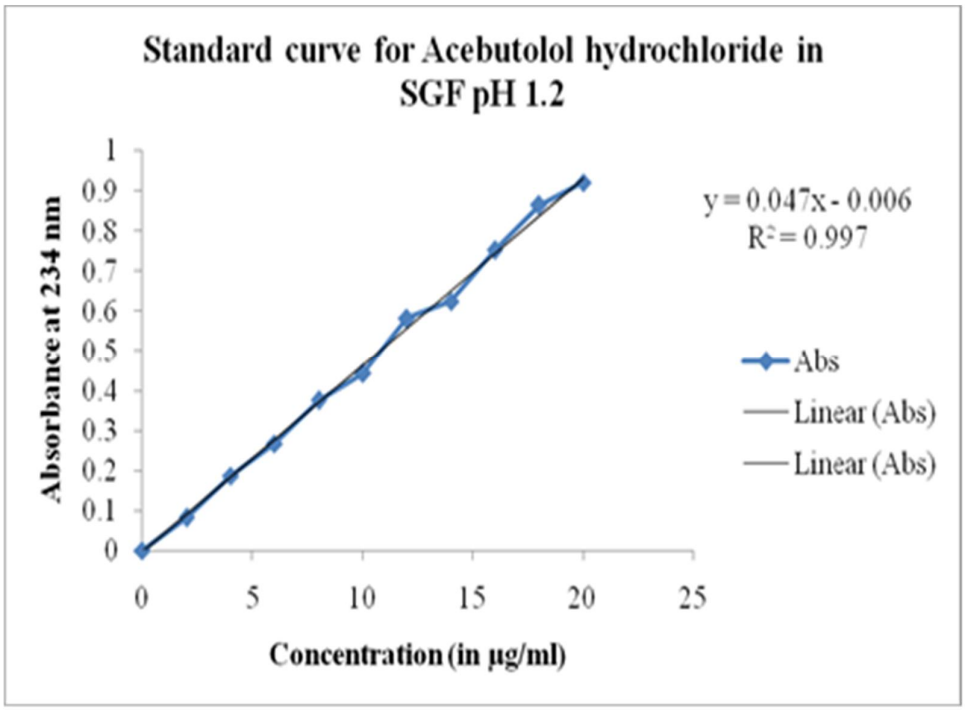


Fig. 28: Standard curve for Acebutolol hydrochloride in SGF pH 1.2

4.5.4 Determination of λ max for Eprosartan mesilate in simulated gastric fluid pH 1.2:

About 10 mg of Eprosartan mesilate was accurately weighed into 100 ml volumetric flask and dissolved in small amount of SGF pH 1.2. Then it was dissolved in 10 ml of methanol and made upto 100 ml with SGF pH 1.2. From this solution 1ml was withdrawn and made upto 10 ml with SGF pH 1.2 and scanned in the range of 200-400 nm using UV-Spectrophotometer with SGF pH 1.2 as blank. From the spectrum obtained, the λ max for Eprosartan mesilate in SGF pH 1.2 was confirmed to be 233 nm.

4.5.5 Standard graph for Eprosartan mesilate in SGF pH 1.2:

About 10 mg of Eprosartan mesilate was weighed accurately and taken in a 100 ml volumetric flask. Then it was dissolved in 10 ml of methanol and made upto 100 ml with SGF pH 1.2. From this solution, 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.4, 2.7 and 3 ml was withdrawn and made upto 10 ml individually with SGF pH 1.2 (3 to 30 µg/ml) and their absorbances were measured at λ max of 233 nm using UV spectrophotometer with SGF pH 1.2 as blank. Standard graph of the drug was plotted with concentration (µg/ml) as x-axis and absorbance at 233 nm as y-axis is shown in table 5 and fig. 29.

Table 5: Standard curve for Eprosartan mesilate in SGF pH 1.2

S.No	Concentration (µg/ml)	Absorbance at 233 nm
1	0	0
2	3	0.157
3	6	0.248
4	9	0.345
5	12	0.392
6	15	0.476
7	18	0.583
8	21	0.647
9	24	0.784
10	27	0.835
11	30	0.962

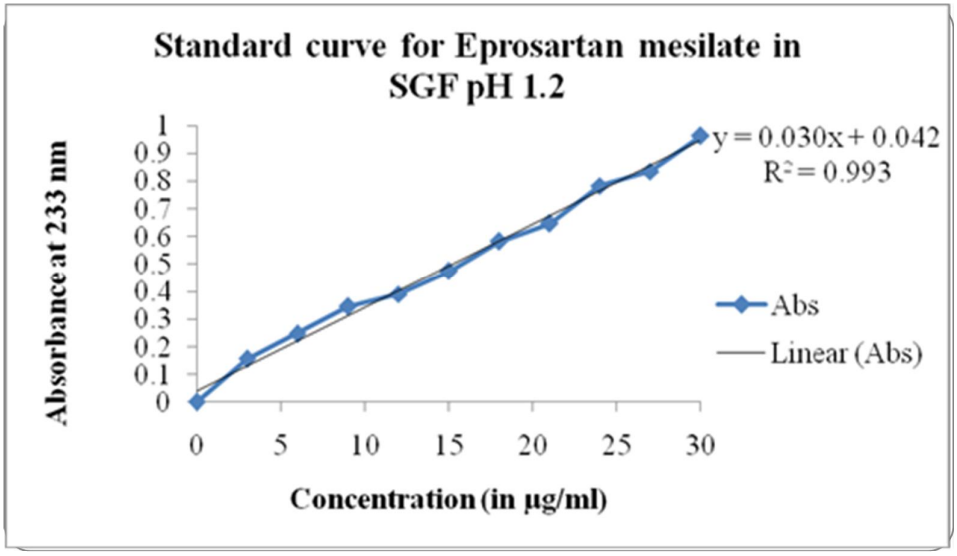


Fig. 29: Standard curve for Eprosartan mesilate in SGF pH 1.2

4.6 Pre formulation studies:

4.6.1 Drug excipient compatibility studies[79]

Fourier transform infrared (FTIR) spectroscopic analysis:

FTIR was used to assess the interaction between carrier and drug molecule in the solid state. The IR spectra were recorded using an FTIR specto-photometer. The moisture free samples were scanned over the frequency range of 4000-400 cm^{-1}. FTIR spectras of Eprosartan mesilate and Acebutolol hydrochloride are shown in fig. 30 and 32.

4.7 Development of Eprosartan mesilate and Acebutolol hydrochloride floating tablets separately[79]:

Floating tablets were prepared by direct compression method according to the formula altering with respect to various parameters are shown below from table 6 to 9. Floating tablet of Eprosartan mesilate was prepared as per the table 6 - 8 and for Acebutolol hydrochloride as per table 9. Weighed amount of drug was mixed with remaining excipients which were already passed through sieve no.60 seperately in a geometrical order except talc and magnesium stearate. Finally, talc and magnesium stearate were added and mixed well which was compressed into tablets using flat round punch in 8-station tablet compression machine.

Table 6: Effect of polymer on swelling index

Name of the ingredients in a tablet/ Formulation Code	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
Eprosartan mesilate*	360	360	360	360	360	360	360	360	360	360
Carbopol 934P	50	-	-	-	-	-	-	-	-	-
HPMC E 15	-	50	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	50	-	-	-	-	-	-	-
HPMC K15	-	-	-	50	-	-	-	-	-	-
Carbopol 940	-	-	-	-	50	-	-	-	-	-
Guar gum	-	-	-	-	-	50	-	-	-	-
Xanthan gum	-	-	-	-	-	-	50	-	-	-
Karaya gum	-	-	-	-	-	-	-	50	-	-
Sodium alginate	-	-	-	-	-	-	-	-	50	-
Chitosan	-	-	-	-	-	-	-	-	-	50
Microcrystalline cellulose	75	75	75	75	75	75	75	75	75	75
Talc	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Total	500	500	500	500	500	500	500	500	500	500

* 1.2 mg of Eprosartan mesilate is equivalent to 1 mg of Eprosartan

Note: All the ingredient are mentioned in mg/tablet

Table 7: Effect of effervescent agent on *in vitro* buoyancy studies

Name of the ingredients in a tablet/ Formulation Code	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)
Eprosartan mesilate*	360	360	360	360	360
Karaya gum	50	50	50	50	50
Sodium bicarbonate	5	10	15	20	25
Citric acid	10	10	10	10	10
Microcrystalline cellulose	60	55	50	45	40
Talc	10	10	10	10	10
Magnesium stearate	5	5	5	5	5
Total	500	500	500	500	500

* 1.2 mg of Eprosartan mesilate is equivalent to 1 mg of Eprosartan

Note: All the ingredient are mentioned in mg/tablet

Table 8: Development of floating tablets of Eprosartan mesilate

Name of the ingredients in a tablet/ Formulation Code	E1 (mg)	E2 (mg)	E3 (mg)	E4 (mg)	E5 (mg)	E6 (mg)	E7 (mg)	E8 (mg)
Eprosartan mesilate*	360	360	360	360	360	360	360	360
Carbopol 934P	50	-	-	-	-	-	-	-
HPMC E 15	-	50	-	-	-	-	-	-
HPMC K15	-	-	50	-	-	-	-	-
Carbopol 940	-	-	-	50	-	-	-	-
Guar gum	-	-	-	-	50	-	-	-
Xanthan gum	-	-	-	-	-	50	-	-
Karaya gum	-	-	-	-	-	-	50	-
Chitosan	-	-	-	-	-	-	-	50
Sodium bicarbonate	25	25	25	25	25	25	25	25
Citric acid	10	10	10	10	10	10	10	10
Microcrystalline cellulose	40	40	40	40	40	40	40	40
Talc	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5
Total	500	500	500	500	500	500	500	500

* 1.2 mg of Eprosartan mesilate is equivalent to 1 mg of Eprosartan

Note: All the ingredient are mentioned in mg/tablet

Table 9: Development of floating tablets of Acebutolol hydrochloride

Name of the ingredients in a tablet/ Formulation Code	A1 (mg)	A2 (mg)	A3 (mg)	A4 (mg)	A5 (mg)	A6 (mg)	A7 (mg)	A8 (mg)
Acebutolol hydrochloride*	443.2	443.2	443.2	443.2	443.2	443.2	443.2	443.2
Carbopol 934P	60	-	-	-	-	-	-	-
HPMC E 15	-	60	-	-	-	-	-	-
HPMC K15	-	-	60	-	-	-	-	-
Carbopol 940	-	-	-	60	-	-	-	-
Guar gum	-	-	-	-	60	-	-	-
Xanthan gum	-	-	-	-	-	60	-	-
Karaya gum	-	-	-	-	-	-	60	-
Chitosan	-	-	-	-	-	-	-	60
Sodium bicarbonate	30	30	30	30	30	30	30	30
Citric acid	6	6	6	6	6	6	6	6
Microcrystalline cellulose	42.8	42.8	42.8	42.8	42.8	42.8	42.8	42.8
Talc	12	12	12	12	12	12	12	12
Magnesium stearate	6	6	6	6	6	6	6	6
Total	600	600	600	600	600	600	600	600

* 110.8 mg of Acebutolol hydrochloride is equivalent to 100 mg of Acebutolol

Note: All the ingredient are mentioned in mg/tablet

4.8 Characterization of floating tablets:

4.8.1 Fourier transform infrared (FTIR) spectroscopic analysis:

FTIR spectra for best floating tablet of Eprosartan mesilate and Acebutolol hydrochloride are shown in fig. 31 and 33.

4.8.2 Pre-Compression parameters:[80]

4.8.2.1 Bulk density:

Bulk density is defined as ratio of mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and in size blending equipment.

An accurately weighed amount of powder blend was introduced into a 100 ml measuring cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled bulk volume, Vo, was recorded. The bulk density was calculated using the formula $\boldsymbol{\rho_b = M / Vo}$ where ρ_b , M and Vo are bulk density, weight of sample and bulk volume of powder respectively.

4.8.2.2 Tapped density:

The sample taken for bulk density determination in a 100 ml measuring cylinder was tapped for 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the formula $\boldsymbol{\rho_{tap} = M / V_f}$ where ρ_{tap}, M and V_f are tapped density, weight of sample and tapped volume of powder respectively.

4.8.2.3 Compressibility index:

The Compressibility Index (Carr's Index) is a measure of the tendency of a powder to be compressed. It is determined from the bulk and tapped density. Less compressibility index, the flow of the material is excellent. For poor flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed and the differences are reflected in the compressibility index which is calculated using the following formula **Carr's Index = $100(\rho_{tap} - \rho_b) / \rho_{tap}$,** where **$\rho_b$ and ρ_{tap}** are bulk density and tapped density respectively.

Table 10: Official limits for Carr's index

Carr's index	Flow Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Very Poor

4.8.2.4 Hausner's ratio:

Hausner's ratio is determined from the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better will be the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively. Hausner's ratio was calculated from formula, **Hausner's Ratio = ρ_{tap} / ρ_b,** where **ρ_b** and **ρ_{tap}** are bulk density and tapped density respectively.

Table 11: Official limits for Hausner's ratio

Hausner's ratio	Flow Properties
< 1.18	Excellent
1.19-1.25	Good
1.3-1.5	Fair to Passable
> 1.5	Poor
Above 2	Very Poor

The results of pre-compression parameters of blend of floating tablets of Eprosartan mesilate are shown in table 13. The results of pre-compression parameters of blend of floating tablets of Acebutolol hydrochloride are shown in table 14.

4.8.3 Post-Compression parameters:

4.8.3.1 General appearance:[81]

All the tablets from different formulations were checked for its general appearance like size, shape, color, odor, surface texture, physical flaws and consistency.

4.8.3.2 Thickness:[81]

The thickness of the tablets from each batch was determined by using vernier caliper.

Limit: Tablet thickness should be controlled within a ± 5% variation from the standard value.

The results for thickness for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 15, 16 and 18 respectively.

4.8.3.3 Hardness test:[81]

Tablets will require a definite amount of strength or hardness and resistance to withstand mechanical shocks while handling during manufacture, packaging & shipping. The instrument used for measuring the tablet hardness is "Monsanto Hardness Tester". Hardness for six tablets from each batch was determined using Monsanto tablet hardness tester.

Limit: Tablets with hardness of 3-5 kg/cm^2 were generally considered acceptable.

The results for hardness for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 15, 16 and 18 respectively.

4.8.3.4 Friability test[82]**:**

Friability of the tablets was determined using Roche friabilator in which the tablets are subjected to the combined effects of abrasion & shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each revolution. For the tablets with unit weight equal to or less than 650 mg the sample of whole tablets corresponding as near as possible to 6.5 g should be taken for analysis. The weighed sample of whole tablets were dusted, placed in the friabilator and operated for 100 revolutions. After rotation, the tablets were re-dusted and weighed. Percentage loss was calculated using the following formula

$$\text{Percentage loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Limit: Conventional compressed tablets that lose less than 0.5-1% of their weight were generally considered acceptable.

The results for friability for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 15, 16 and 18 respectively.

4.8.3.5 Weight variation test:[83]

Weight of each tablet was measured to ensure that a tablet contains the proper amount of drug. Twenty tablets were selected at random from each batch and average weight was calculated. Then the tablets were individually weighed which was compared with that of average weight and the variation in weight was expressed in terms of percentage deviation. The average weight and its percentage deviation is shown in table 12. The results for weight variation for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 15, 16 and 18 respectively.

Limit: Not more than two of the individual weights deviate from the average weight by more than 5% & none deviates by more than twice that percentage.

Table 12: I.P limit for average weight of a tablet and its percentage deviation

S.No.	Average weight of tablet in mg	Percentage deviation
1.	80 mg or less	± 10 %
2.	More than 80 mg and less than 250 mg	±7.5%
3.	250 mg or more	± 5 %

4.8.3.6 Uniformity of drug content:[51, 58]

The drug content in each formulation was analyzed by the following method. About twenty tablets were taken at random, crushed and powder equivalent to average weight was dissolved in 100 ml of simulated gastric fluid pH 1.2 (SGF). The solution was filtered through whatmann filter paper no.41, diluted suitably and absorbance of diluted solution was measured spectrophotometrically at 234 nm and 233 nm for Acebutolol hydrochloride and Eprosartan mesilate individually using SGF pH 1.2 as blank.

The tablet comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is

outside the limits 75 to 125 % of the average value. If two or three of the individual values are outside the limits 85 to 115.5 of the average value and none is outside the limits 75 to 125 %, repeat the determination using another 20 tablets. The tablet comply with the test if in the total sample of 30 tablets not more than three of the individual values are outside the limits 85 to 115 % and none is outside the limits 75 to 125 % of the average value.

The results for uniformity of drug content for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 16 and 18 respectively.

4.8.3.7 Determination of swelling index:[58]

It was determined in simulated gastric fluid pH 1.2 at room temperature. The swollen weight of the tablet was determined at over a period of 24 h. The swelling index (SI) was expressed as percentage and was calculated from the following equation

$$SI = \frac{\text{Final weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

The results for swelling index for floating tablet of Eprosartan mesilate is shown in table 15.

4.8.3.8 *In vitro* buoyancy studies:[58]

This test was performed by placing randomly selected tablet from each formulation in beaker containing 100 ml simulated gastric fluid pH 1.2 as a testing medium maintained at 37^0C. The time taken for the tablet to ascend to the surface and float on the surface was taken as floating lag time (FLT). The duration of time the tablet constantly remained on the surface of medium was determined as the total floating time (TFT) (including floating lag time). The results for *in vitro* buoyancy studies for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 15, 16 and 18 respectively.

4.8.4 *In vitro* dissolution studies:[58]

The release rate of Acebutolol hydrochloride from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of simulated gastric fluid pH 1.2 at 37 ± 0.5^0C and 50 rpm. At specified time intervals, aliquot of sample was withdrawn from the dissolution apparatus every h for 10 h and replaced with fresh dissolution medium. The samples were filtered through whatman filter paper no. 41. Absorbance of these solutions was measured at 234 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The same procedure was repeated using Eprosartan mesilate floating tablets and absorbance was measured at 233 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The results for *in vitro* dissolution studies for floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 17 and 19 with graphical representation in fig. 34 and 39, respectively.

4.8.4.1 *In vitro* drug release kinetics:[56, 58, 84]

Kinetic model had described drug dissolution from solid dosage forms in which the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer – Peppas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Zero order equation

% drug released = kt where k is constant and t is time

First order equation

Log % unreleased = kt/2.303 where k is constant and t is time

Korsmeyer – Peppas equation

$M_t / M_\infty = kt^n$

where M_t / M_∞ represents the fraction of drug release at time t, k is the release rate constant and n is the diffusion coefficient.

or

Log drug released = log k + n log t where n is release exponent

Higuchi equation

% drug released = $kt^{0.5}$

The results for *in vitro* drug release kinetics for best formulation of floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in fig. 35-38 and 40-43, respectively.

4.8.5 Stability studies for best formulation of Acebutolol hydrochloride and Eprosartan mesilate:[85]

Best floating tablet of Acebutolol hydrochloride and Eprosartan mesilate separately were packed in HDPE bottles and loaded at accelerated conditions like $40^{O}C \pm 2\ ^{O}C$ / 75% ± 5% RH for 3 months. Various post-compression parameters were evaluated for a period of initial stage and at the end of every one month. The results for stability studies for best formulation of floating tablet of Eprosartan mesilate and Acebutolol hydrochloride separately are shown in table 20 and 21.

4.8.6 *In vivo* X-ray studies or radiographic studies:[86-88]

The protocol for *in vivo* study was approved by the Institutional Animal Ethics Committee of C. L. Baid Metha College of Pharmacy, Chennai (IAEC/XL VIII/05/CLBMCP/2016) and is in accordance with guidance of Committee for the Purpose of control and supervision of experiments on animals, Ministry of social justice and empowerment, Government of India. All the *in vivo* experiments were performed under permission from animal ethical committee.

The floating tablet of best formulation of Acebutolol hydrochloride (A7) and Eprosartan mesilate (E7) were made X-ray opaque by replacing the amount of the drug incorporated already with equal amount of barium sulphate (BaSO4) with all other ingredients were kept constant so that the tablet weight remained same. The

floating property of the best floating tablet was studied by X-ray technique. Albino male rabbits with weight of 1.5 kg and with age of 12 months were selected. The animal was housed individually under environmental condition (12 h light and dark cycle). The rabbit was fasted 36 h and allowed free accesses to water only. The rabbit was administrated with best formulation of Acebutolol hydrochloride. The tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulb. X-rays were taken a time- interval of 0, 1, 2, 3, 4, 5 and 10 h. The same procedure was repeated with best floating tablet of Eprosartan mesilate. The X-ray photographs are shown in fig. 44 and 45 for Eprosartan mesilate and Acebutolol hydrochloride, respectively.

4.8.7 *In vivo* pharmacokinetic studies:[89-91]

4.8.7.1 Method:

The protocol for *in vivo* study was approved by the Institutional Animal Ethics Committee of C. L. Baid Metha College of Pharmacy, Chennai (IAEC/XL VIII/05/CLBMCP/2016) and is in accordance with guidance of Committee for the Purpose of control and supervision of experiments on animals, Ministry of social justice and empowerment, Government of India. All the *in vivo* experiments were performed under permission from animal ethical committee.

Albino male rabbits with weight 1.5 kg were selected for i*n vivo* pharmacokinetics studies. The animal was housed individually under environmental condition (12 h light and dark cycle). The rabbit was fasted 36 h and allowed free accesses to water only. Six male albino rabbits were administered orally with best formulation of floating tablets of Acebutolol hydrochloride. Water was administered whenever necessary during fasting and throughout the experiment. Blood samples (2 ml) were collected from marginal ear vein at just before dosing and at 1, 2, 4, 6, 8, 10, 12, 18 and 24 h post oral dose into heparinized centrifuge tubes. Plasma was separated by centrifuging at 4000 rpm for 15 min and stored at –20°C until analysis. An undosed plasma sample was kept as blank. The same method mentioned above was repeated with selected best formulation of floating tablet of Eprosartan mesilate.

4.8.7.2 Determination of drug content:

Plasma concentrations of drug from above samples were determined by HPLC method. To 1 ml of plasma sample, 1 ml of acetonitrile was added and centrifuged for 10 min at 4000 rpm and the supernatant liquid was separated and 20 ml was injected in to the system. The analysis was carried out using HPLC equipped with C18 column and UV detector. The mobile phase consisted of acetonitrile and water (1:1). The eluents were examined at wavelength of 234 nm for Acebutolol hydrochloride and 233nm for Eprosartan mesilate at a flow rate of 0.8 ml/min and the results is shown in table 22 and fig. 46.

4.8.7.3 Pharmacokinetic analysis:

Pharmacokinetic parameters calculated are peak plasma concentration (Cmax), time to reach peak plasma levels (Tmax) and the area under the curve (AUC) for best formulation of floating tablets of Acebutolol hydrochloride and Eprosartan mesilate are shown in table 23.

5. RESULT & DISCUSSION

5.1 Preformulation study

5.1.1 Drug excipient Compatibility study by Fourier transform infra red (FTIR) analysis

Fourier transform infra red spectrum for Eprosartan mesilate, Acebutolol hydrochloride individually and best floating tablets of Eprosartan mesilate and Acebutolol hydrochloride were recorded and analyzed for chemical interaction.

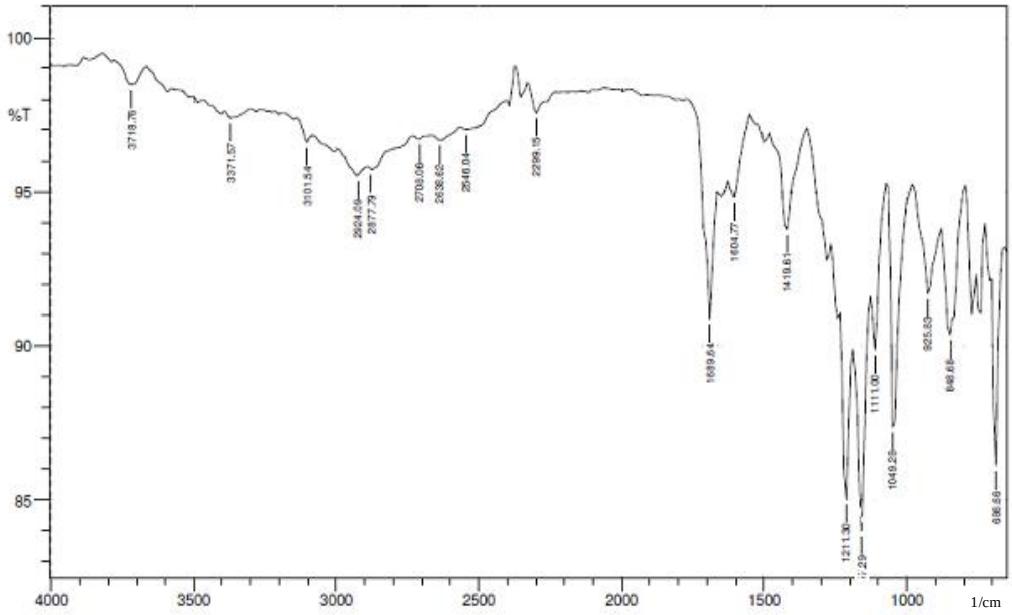


Fig. 30: FTIR spectrum of Eprosartan mesilate

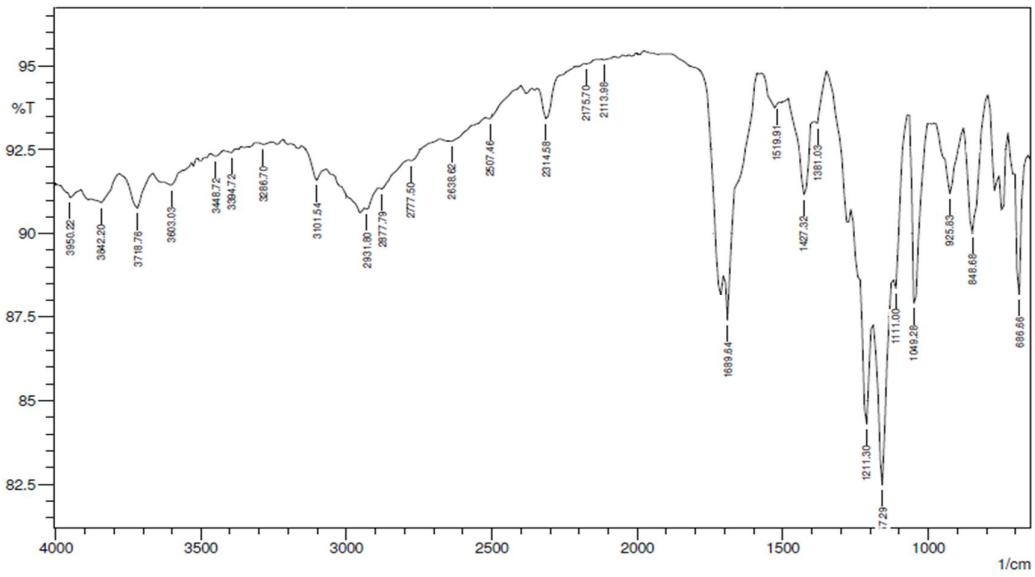


Fig. 31: FTIR spectrum of best formulation of Eprosartan mesilate

Discussion:

In the FTIR spectrum of Eprosartan mesilate in fig. 30, NH stretching was appeared in 3371cm^{-1}, aromatic CH stretching was appeared in 3101 cm^{-}1, carboxylic acid was appeared in 2924 cm^{-1}, C=C aromatic stretching was appeared in 1639 cm^{-1}, S=O stretching was appeared in 1111 cm^{-1} and C-N vibration was appeared in 1049 cm^{-1}. From the results it was found that there was no remarkable change in position of major peaks represented above in fig. 31 when compared with spectra of pure Eprosartan mesilate in fig.30 and concluded that there was no chemical interaction between drug and excipients in best formulation of Eprosartan mesilate.

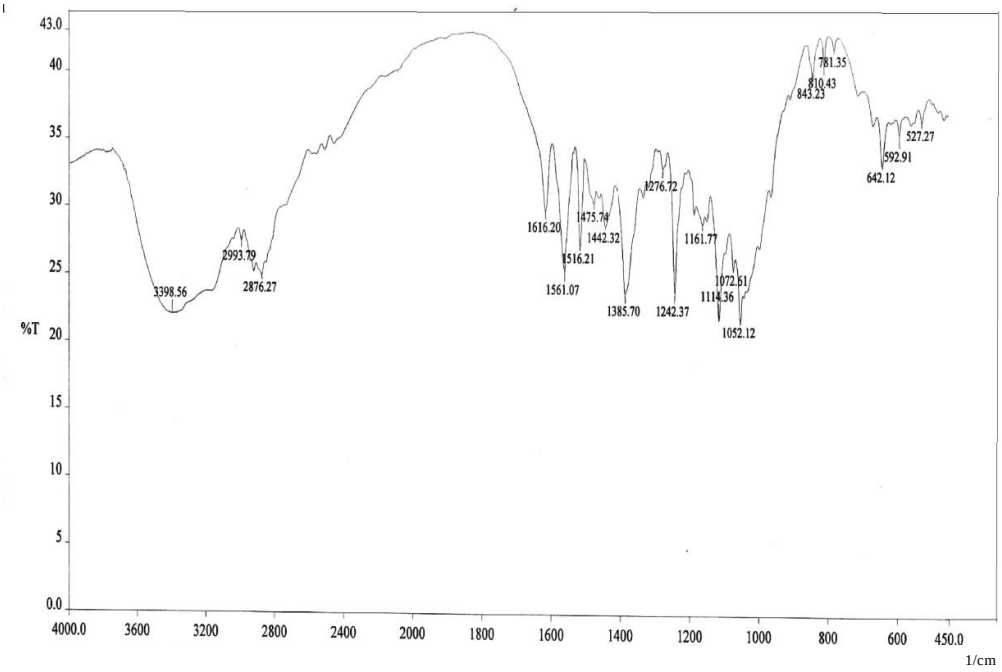


Fig. 32: FTIR spectrum of Acebutolol hydrochloride

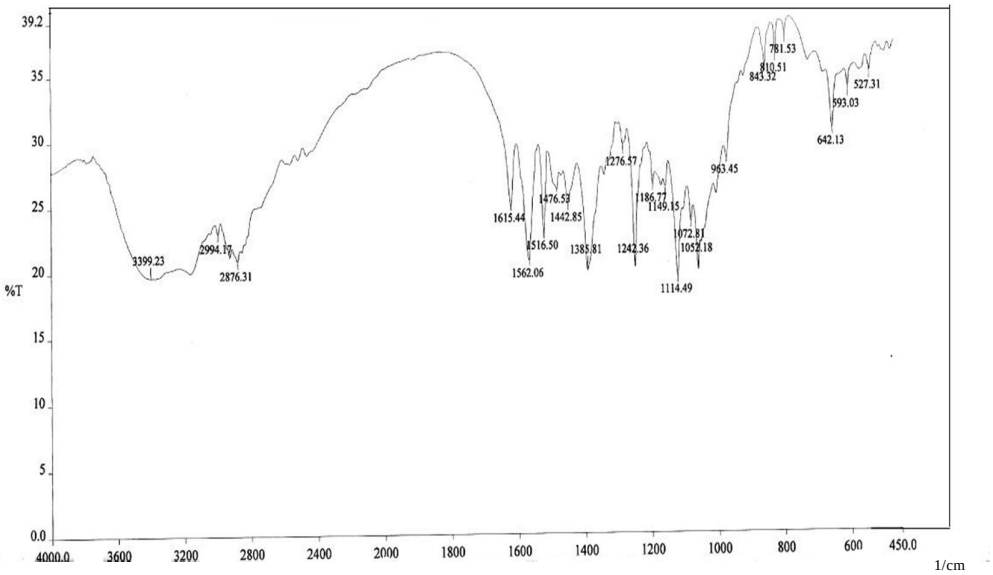


Fig. 33: FTIR spectrum of best formulation of Acebutolol hydrochloride

Discussion:

In the FTIR spectrum of Acebutolol hydrochloride in fig. 32, NH stretching was appeared in 3398 cm^{-1}, carboxylic acid was appeared in 2993 cm^{-1}, C=C aromatic stretching was appeared in 1616 cm^{-1}, methyl and methylene was appeared in 1475 cm^{-1}, C-O was appeared in 1276 cm^{-1}, secondary alcohol was appeared in 1114 cm^{-1} and aromatic unsaturated C=C was appeared in 843 cm^{-1}. From the results it was found that there was no remarkable change in position of major peaks represented above in fig. 33 when compared with spectra of pure Acebutolol hydrochloride in fig.32 and concluded that there was no chemical interaction between drug and excipients in best formulation of Acebutolol hydrochloride.

5.2 Characterization of powder blend of Acebutolol hydrochloride and Eprosartan mesilate:

5.2.1 Pre-compression parameters of powder blend of Eprosartan mesilate:

Table 13: Pre-compression parameters of powder blend of Eprosartan mesilate

Formulation Code	Bulk Density (g/ml)	Tapped density (g/ml)	Carr's Compressibility index (%)	Hausner's ratio
F 1	0.66	0.72	8.59	1.09
F 2	0.42	0.45	7.01	1.08
F 3	0.68	0.72	5.59	1.06
F 4	0.72	0.79	8.98	1.10
F 5	0.69	0.79	10.12	1.12
F 6	0.44	0.49	10	1.11
F 7	0.67	0.71	5.49	1.06
F 8	0.74	0.82	10.09	1.11
F 9	0.45	0.49	8	1.09
F10	0.47	0.51	7.99	1.09
F11	0.71	0.79	9.50	1.11
F12	0.47	0.51	7.99	1.09
F13	0.68	0.75	9.20	1.10
F14	0.44	0.49	9.99	1.11
F15	0.74	0.81	9.14	1.10
E1	0.69	0.73	9.12	1.06
E2	0.44	0.48	7.65	1.08
E3	0.72	0.79	8.97	1.10
E4	0.47	0.51	8	1.09
E5	0.73	0.81	9.14	1.10
E6	0.46	0.50	8	1.09
E7	0.72	0.82	11.85	1.13
E8	0.43	0.47	9.99	1.11

5.2.2 Pre-compression parameters of powder blend of Acebutolol hydrochloride:

Table 14: Pre-compression parameters of powder blend of Acebutolol hydrochloride

Formulation Code	Bulk Density (g/ml)	Tapped density (g/ml)	Carr's Compressibility index (%)	Hausner's ratio
A1	0.68	0.72	5.59	1.06
A2	0.74	0.81	9.14	1.10
A3	0.72	0.79	8.97	1.10
A4	0.47	0.51	7.99	1.09
A5	0.44	0.48	7.65	1.08
A6	0.67	0.71	5.49	1.06
A7	0.71	0.79	9.50	1.11
A8	0.45	0.49	7.9	1.09

Discussion:

Physical evaluation of blend of floating tablet of Eprosartan mesilate and Acebutolol hydrochloride were done by determining bulk density, tapped density, compressibility index and hausner ratio. From the results, the flow property of all formulations containing synthetic and natural polymer (F1 - F 15, E1 – E8 and A1 and A8) were found to be excellent for both Acebutolol hydrochloride and Eprosartan mesilate.

5.3 Characterization of floating tablet of Acebutolol hydrochloride and Eprosartan mesilate:

5.3.1 Post-compression parameters of floating tablets of Eprosartan mesilate:

Table 15: Evaluation of floating tablets of Eprosartan mesilate

Formulation Code	Thickness (mm) (n = 6) Avg ± S.D	Hardness (kg/cm^2) (n = 6) Avg ± S.D	Friability (%) (n = 20)	Weight variation (g) (n = 20) Avg ± S.D	Swelling index (%)	Floating lag time (FLT) (sec)
F 1	3 ± 0	5.20 ± 0.16	0.28	0.495 ± 0.008	72	-
F 2	3.03 ± 0.008	5.18 ± 0.18	0.30	0.496 ± 0.003	86	-
F 3	3 ± 0	4.90 ± 0.11	0.45	0.496 ± 0.003	46	-
F 4	2.78 ± 0.004	5.20 ± 0.20	0.34	0.495 ± 0.008	88	-
F 5	2.72 ± 0.004	4.76 ± 0.12	0.54	0.497 ± 0.004	79	-
F 6	3 ±0	4.84 ± 0.18	0.23	0.494 ± 0.008	86	-
F 7	2.97 ± 0.005	4.90 ± 0.11	0.25	0.495 ± 0.26	87	-
F 8	2.8 ± 0.004	4.76 ± 0.14	0.56	0.494 ± 0.008	92	-
F 9	2.8 ± 0.004	5.06 ± 0.21	0.16	0.498 ± 0.005	62	-
F10	2.8 ± 0.005	4.76 ± 0.14	0.52	0.496 ± 0.003	80	-
F11	3 ± 0	4.90 ± 0.11	0.19	0.495 ± 0.006	-	8
F12	2.97 ± 0.005	4.86 ± 0.14	0.18	0.496 ± 0.18	-	6
F13	3 ± 0	5.18 ± 0.18	0.48	0.495 ± 0.008	-	5
F14	2.82 ± 0.004	4.90 ± 0.11	0.24	0.493 ± 0.005	-	3
F15	2.97 ± 0.005	4.84 ± 0.18	0.37	0.495 ± 0.26	-	1

Table 16: Evaluation of floating tablets of Eprosartan mesilate

Formulation Code	Thickness (mm) (n = 6) Avg ± S.D	Hardness (kg/cm^2) (n = 6) Avg ± S.D	Friability (%) (n = 20)	Weight variation (g) (n = 20) Avg ± S.D	Floating lag time (FLT) (sec)	Total floating time (TFT) (min)	Drug content (%)
E 1	2.97±0.005	4.94±0.12	0.29	0.495±0.008	1	270	91.77
E 2	3 ± 0	4.62±0.13	0.45	0.494±0.008	1	340	88.2
E 3	2.82±0.004	4.70±0.16	0.28	0.496±0.003	1	315	90.25
E 4	2.97±0.005	4.91±0.11	0.22	0.495±0.26	1	260	86.49
E 5	2.78±0.004	4.89±0.18	0.16	0.494±0.008	1	320	86.32
E 6	2.97±0.005	4.88±0.13	0.32	0.493±0.005	1	390	90.14
E 7	**2.8±0.004**	**4.71±0.19**	**0.31**	0.495±0.008	**1**	**580**	**93.14**
E 8	2.82±0.004	4.94±0.12	0.26	0.495±0.26	1	450	89.90

5.3.2 *In vitro* dissolution studies data for floating tablets of Eprosartan mesilate:

Table 17: *In vitro* dissolution studies data for floating tablets of Eprosartan mesilate

Time (min)	% Drug released							
	E1	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**
0	0	0	0	0	0	0	0	0
5	16.54	17.14	15.29	18.28	11.61	11.24	2.58	4.72
10	28.24	28.91	21.67	22.32	24.19	24.91	7.48	10.96
30	36.32	36.27	31.28	34.17	35.29	35.64	13.27	21.24
60	48.65	41.78	47.35	59.41	48.61	46.14	25..60	32.62
90	56.87	49.45	56.27	71.56	54.73	58.91	32.69	41.24
120	65.62	58.27	68.62	78.81	60.81	62.27	41.09	51.33
180	71.36	65.34	72.41	84.67	72.14	75.69	48.33	59.71
240	84.27	78.54	85.21	90.65	84.27	81.42	55.24	67.36
300	92.68	84.82	92.32		91.84	88.13	64.54	72.96
360		89.65				92.54	72.57	80.02
420							79.68	86.27
480							84.48	94.68
540							89.76	
570							93.24	
600							98.47	

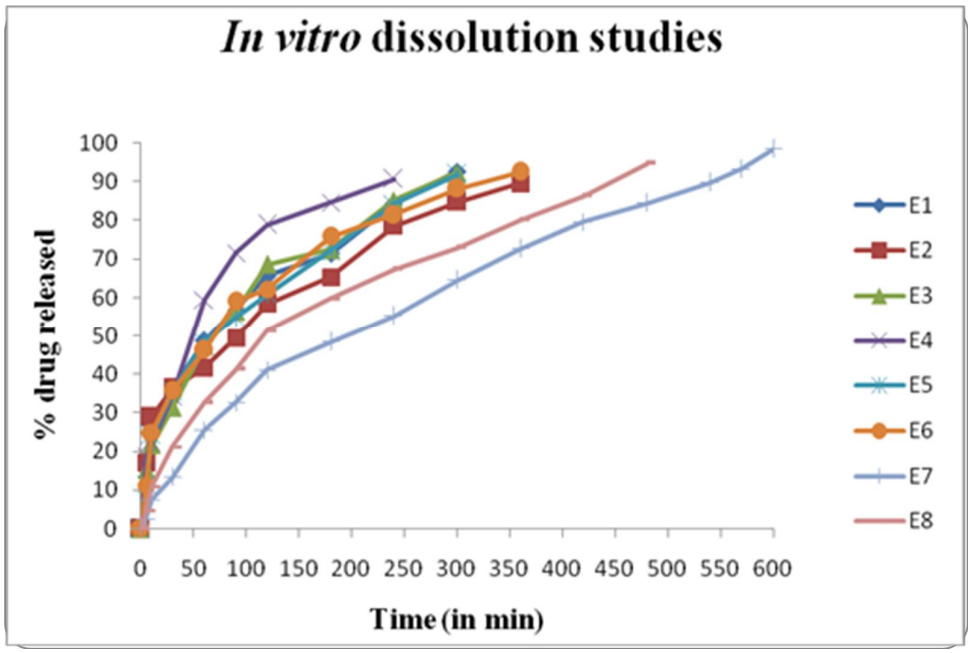


Fig. 34*: In vitro* dissolution profile for floating tablet of Eprosartan mesilate

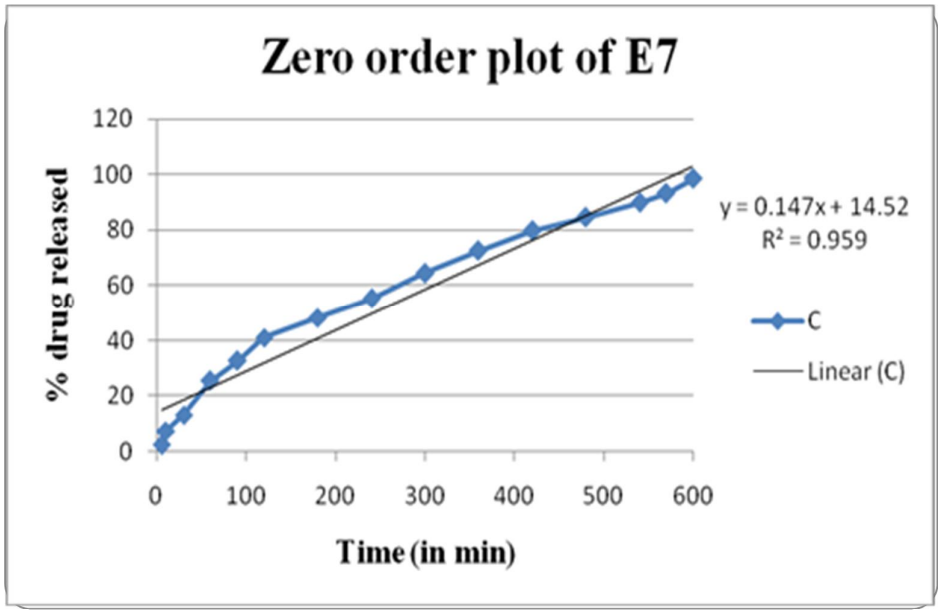


Fig.35: Zero order plot for best formulation of floating tablet of Eprosartan mesilate (E7)

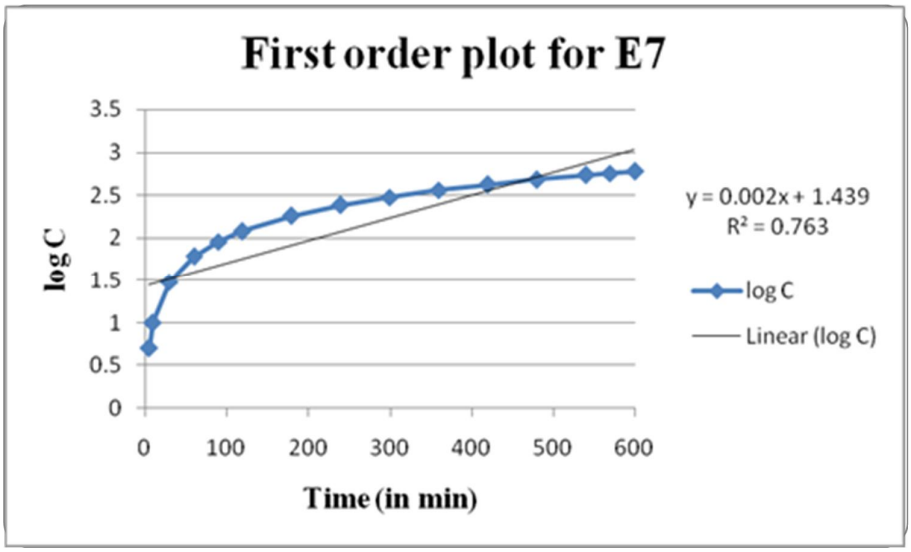


Fig. 36: First order plot for best formulation of floating tablet of Eprosartan mesilate (E7)

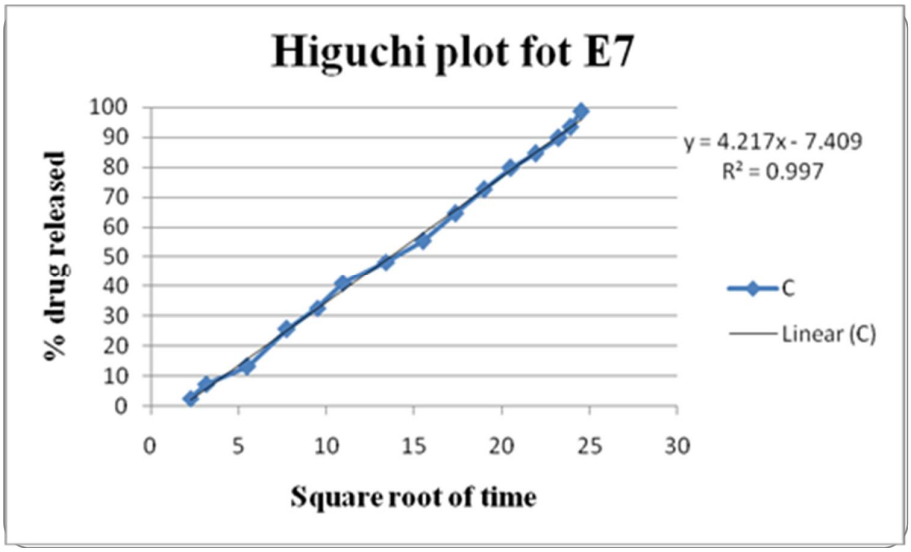


Fig. 37: Higuchi plot for best formulation of floating tablet of Eprosartan mesilate (E7)

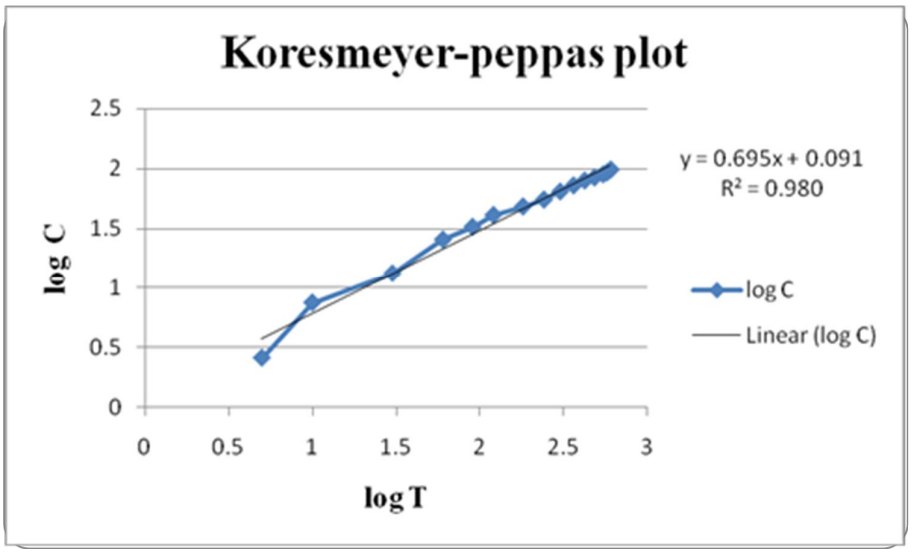


Fig. 38: Koresmeyer peppas plot for best formulation of floating tablet of Eprosartan mesilate (E7)

Discussion:

The design of floating tablet of Eprosartan mesilate included three stages like effect of different polymer without effervescent agent on swelling index of floating tablet, effect of varying concentrations of effervescent agent on *in vitro* buoyancy of floating tablet, effect of different polymer on *in vitro* buoyancy and dissolution studies. The above three parameters are selected on their importance on success of the formulation *in vivo* also. Swelling index of polymers is the identity of their efficiency of hydration in aqueous media to form porous or non porous gel which affects the drug release from the dosage form both *in vitro* and *in vivo*. Buoyancy is generally related to the reduction of the density of the dosage form less than the density of water (density of water is always 1 g/ml) which is related to the density of gastric fluids. *In vitro* drug release study usually gives an idea about the drug release *in vivo*. This is an important parameter to be conducted for all types of dosage forms. Therefore the formulations are best initially by swelling index to get an idea about inclusion and exclusion of the polymers (natural and synthetic) selected for further screening.

In the first stage, floating tablets containing Eprosartan mesilate (F1 – F10) were prepared various synthetic (HPMC (E15 and K15), Carbopol (934P and 940) and Ethyl cellulose) and natural polymers (Guar gum, Xanthan gum, Karaya gum, Chitosan and Sodium alginate) to find the effect of polymer on swelling index of the formulations. From the results in table 15, all the tablets were good in appearance without cracking with thickness in the range of 2.72 to 3.03 mm. These tablets had hardness between 4.76 to 5.20 kg / cm^2, friability in the range of 0.16 - 0.56 % w/w and weight variation within the range of 5%w/w. Based on the results in the table 15 for swelling index, formulation containing ethyl cellulose and sodium alginate were omitted for next trials due to their low swelling index (F3 and F9) than formulations containing other polymers. The reason for low swelling index may be due to ethyl cellulose is a hydrophobic polymer which could not able to absorb aqueous media and not hydrated and for sodium alginate may be due to formation of less viscous gel when compared to other polymers which gives higher index than this of higher viscosity grades.

In second stage, floating tablets containing Eprosartan mesilate (F11 – F15) were prepared with other polymers synthetic (HPMC (E15 and K15), Carbopol (934P and 940)) and natural polymers (Guar gum, Xanthan gum, Karaya gum and Chitosan) in same concentration with varying concentrations of effervescent agent (sodium bicarbonate only) keeping concentration of citric acid constant to find the effect of effervescent agent on *in vitro* buoyancy studies especially floating lag time. From the results in table 15, all the tablets were good in appearance without cracking with thickness in the range of 2.82 to 3 mm. These tablets had hardness between 4.84 to 5.18 kg / cm^2, friability in the range of 0.18 - 0.48 % w/w and weight variation within the range of 5%w/w. Based on the results in the table 15 for *in vitro* buoyancy, formulation containing highest ratio of sodium bicarbonate with citric acid (5:2) showed lowest floating lag time of 1 sec than other formulations with various ratios of 1:2, 2:2, 3:2 and 4:2 which concluded that increase in concentration of sodium bicarbonate gradually reduces the floating lag time due to fastest evolution of carbon dioxide by interaction of sodium bicarbonate with citric acid forms hollow space inside the tablet reduces the density of the tablet less than less than the density of gastric fluid allows to float immediately.

In third stage, floating tablets containing Eprosartan mesilate (E1-E8) were prepared with same polymers as second stage formulations maintaining constant ratio of sodium bicarbonate and citric acid in 5:2 and were evaluated for effect of polymer on total floating time, drug content and *in vitro* release studies. From the results tabulated in table 16, all the tablets were good in appearance without cracking with thickness in the range of 2.78 to 3 mm. These tablets had hardness between 4.70 to 4.94 kg / cm^2, friability in the range of 0.16 - 0.45 % w/w and weight variation within the range of 5%w/w. All the formulations showed floating lag time of 1 sec and total floating time in between 260-580 min. All the formulations contain drug in the range of 86.32 – 93.14 %. Based on the results in the table 15 for *in vitro* dissolution studies, formulation containing karaya gum (E7) floated for long time in simulated gastric fluid pH 1.2 than other formulations due to highest swelling index of Karaya gum which induces the formation of porous gel than other polymers. The results of *in vitro* dissolution studies in table 17 and fig. 34 showed sustained release of drug from floating tablet for 600 min and further confirmed by its release kinetics follows zero order non-fickian diffusion controlled represented by kinetic plots of dissolution data are shown from fig. 35 to 38.

5.3.3 Post-compression parameters of floating tablets of Acebutolol hydrochloride:

Table 18: Post-compression parameters of floating tablets of Acebutolol hydrochloride

Formulation Code	Thickness (mm) (n = 6) Avg ± S.D	Hardness (kg/cm^2) (n=6) Avg ± S.D	Friability (%) (n = 20)	Weight variation (g) (n=20) Avg ± S.D	Floating lag time (FLT) (sec)	Total floating time (TFT) (min)	Drug content (%)
A 1	2.97±0.005	4.76±0.12	0.56	0.597±0.004	1	275	96.52
A 2	2.72±0.004	4.90±0.11	0.23	0.604±0.003	1	365	101.54
A 3	3.03±0.008	5.06±0.21	0.16	0.602±0.005	1	320	95.16
A 4	2.8 ± 0.004	4.86±0.14	0.19	0.595±0.008	1	280	98.52
A 5	3 ± 0	4.84±0.18	0.32	0.594±0.008	1	335	98.74
A 6	2.72±0.004	4.76±0.12	0.55	0.606±0.004	1	400	102.97
A 7	**2.78±0.004**	**4.90±0.11**	**0.51**	**0.598±0.005**	**1**	**590**	**97.84**
A 8	2.97±0.005	4.84±0.18	0.39	0.605±0.008	1	465	91.68

5.3.4 *In vitro* dissolution studies data for floating tablets of Acebutolol hydrochloride:

Table 19: *In vitro* dissolution studies data for floating tablets of Acebutolol hydrochloride

Time (min)	% Drug released							
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**
0	0	0	0	0	0	0	0	0
5	14.48	15.54	13.48	16.54	13.28	14.45	3.25	5.38
10	25.84	25.15	25.54	25.29	28.68	26.25	6.54	14.21
30	32.84	33.98	36.87	39.35	36.64	32.49	12.45	22.51
60	46.45	39.46	52.15	58.48	41.38	41.57	21.49	31.67
90	52.15	46.38	61.68	66.68	46.59	49.24	29.57	44.18
120	61.64	55.19	69.18	75.27	58.49	56.49	36.16	55.91
180	68.87	61.65	78.29	83.15	66.67	69.15	42.98	62.24
240	79.57	76.58	82.67	87.98	79.48	77.28	55.46	69.43
300	88.74	84.82	87.49	90.54	87.24	83.84	62.32	76.57
360		88.84	90.35		91.37	89.45	70.42	82.19
420		92.45				93.48	77.29	88.73
480							81.37	93.82
540							88.61	
570							94.42	
600							98.81	

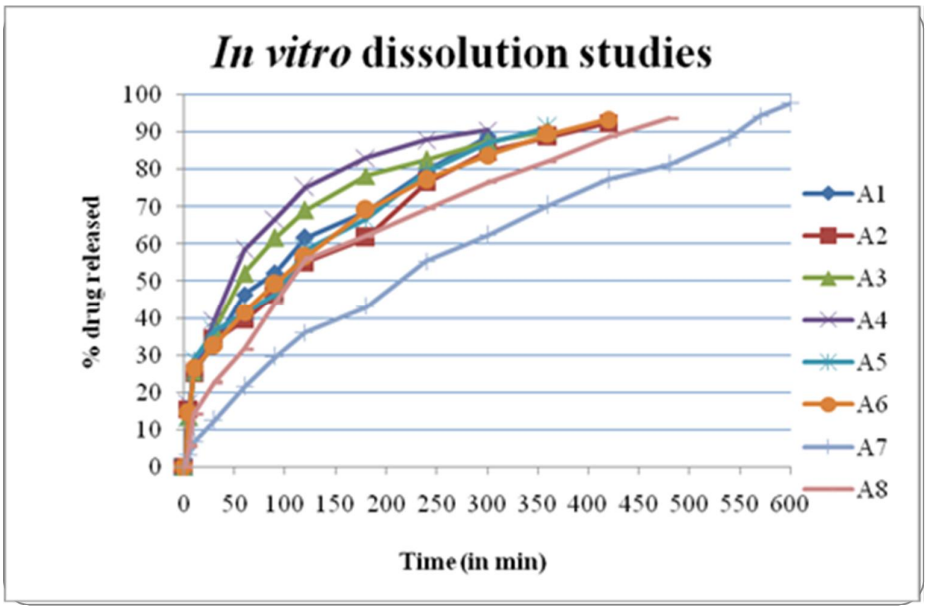


Fig. 39*: In vitro* dissolution profile for floating tablet of Acebutolol hydrochloride

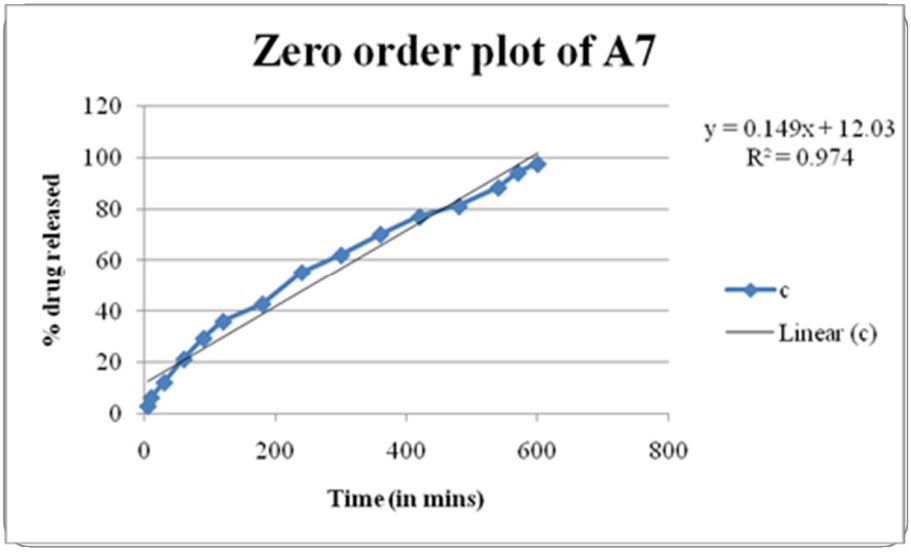


Fig.40: Zero order plot for best formulation of floating tablet of Acebutolol hydrochloride (A7)

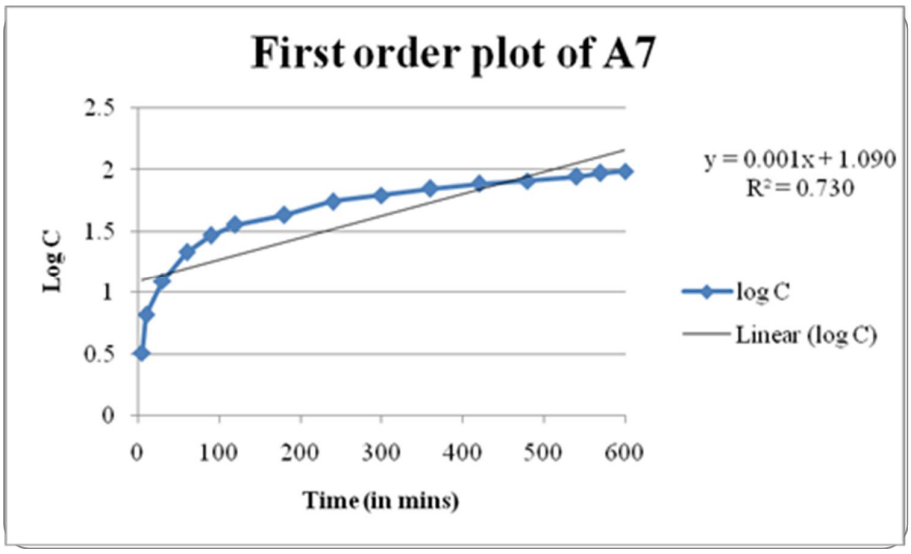


Fig. 41: First order plot for best formulation of floating tablet of Acebutolol hydrochloride (A7)

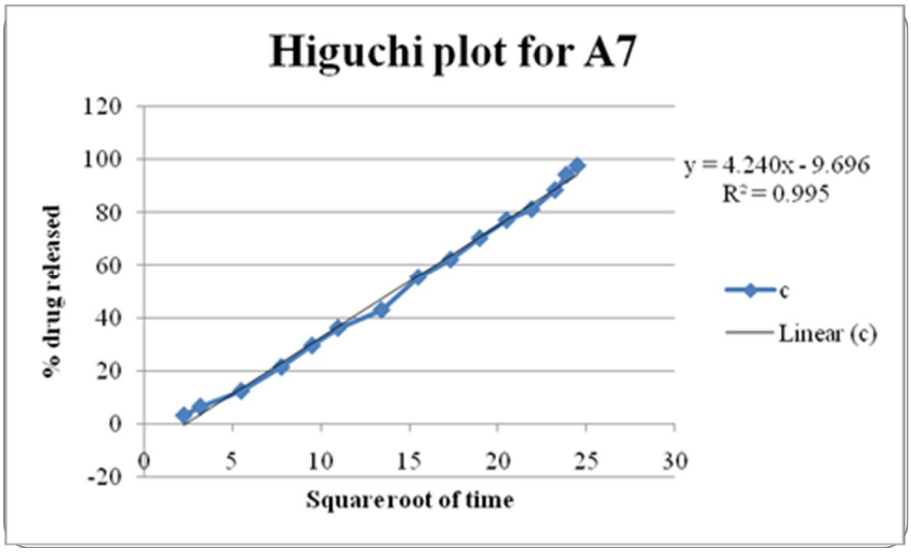


Fig. 42: Higuchi plot for best for/n bmulation of floating tablet of Acebutolol hydrochloride (A7)

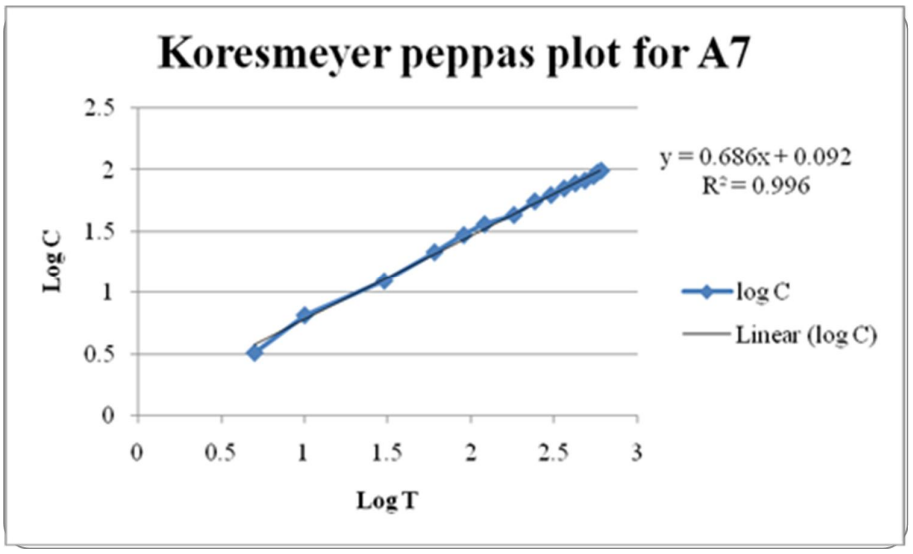


Fig. 43: Koresmeyer peppas plot for best formulation of floating tablet of Acebutolol hydrochloride (A7)

Discussion:

The floating tablet of Acebutolol hydrochloride (A1 – A8) was formulated with various synthetic (HPMC (E15 and K15), Carbopol (934P and 940)) and natural polymers (Guar gum, Xanthan gum, Karaya gum, Chitosan) in same concentration (10% w/w of total tablet weight) with highest ratio of effervescent agent (sodium bicarbonate and citric acid). From the results tabulated in table 18, all the tablets were good in appearance without cracking with thickness in the range of 2.72 to 3.03 mm. These tablets had hardness between 4.76 to 5.06 kg / cm^2, friability in the range of 0.16 – 0.56 % w/w and weight variation within 5%w/w deviation. All the formulations showed floating lag time of 1 sec and total floating time in between 275-590 min. All the formulations contain drug in the range of 91.68 – 102.97 %. Based on the results in the table 19 for *in vitro* dissolution studies, formulation containing Karaya gum (A7) floated for long time in simulated gastric fluid pH 1.2 than other formulations due to highest swelling index of karaya gum which induces the formation of porous gel than other polymers. The results of *in vitro* dissolution studies in table 19 and fig. 39 showed sustained release of drug from floating tablet for 600 min. The sustained floating of the dosage form may be due to the increased swelling and viscosity of the gel that retards the drug release

from the matrix. This high degree of swelling of the polymer is due to increased uptake of water from the medium surrounding it. It was further confirmed by its release kinetics follows zero order non-fickian diffusion controlled represented by kinetic plots of dissolution data are shown from fig. 40 to 43.

5.3.5 Stability studies:

Table 20: Stability studies data for best floating tablet of Eprosartan mesilate

Parameters	Initial	After three months
Hardness (kg/cm^2)	5.20	5.32
Friability (%)	0.38	0.32
Floating lag time (sec)	1	1
Total floating time (min)	580	585
Drug content (%)	92.78	92.45

Table 21: Stability studies data for best floating tablet of Acebutolol hydrochloride

Parameters	Initial	After three months
Hardness (kg/cm^2)	4.90	5.1
Friability (%)	0.51	0.58
Floating lag time (sec)	1	1
Total floating time (min)	590	592
Drug content (%)	97.84	97.28

Discussion:

The optimtized formulation of Eprosartan mesilate (E7) and Acebutolol hydrochloride (A7) were subjected to stability studies revealed that there was no drastic change in post-compression parameters before and after stability period represented in table 20 and 21.

5.3.6 *In vivo* X-ray studies or Radiographic studies

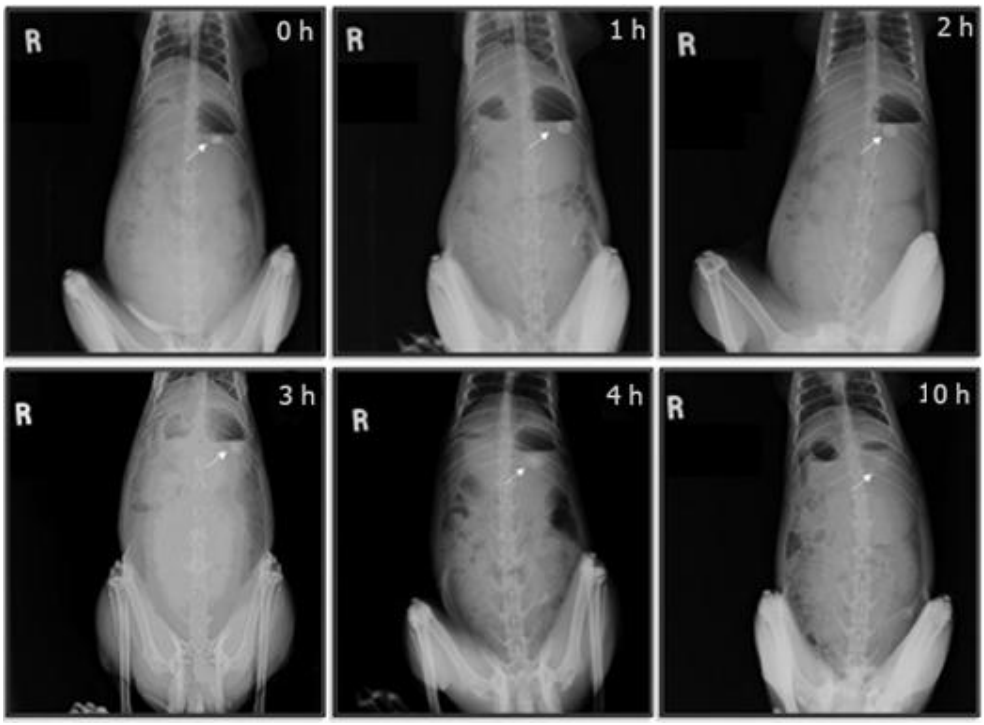


Fig. 44: *In vivo* X-ray photographs for best formulation of floating tablet of Eprosartan mesilate (E7)

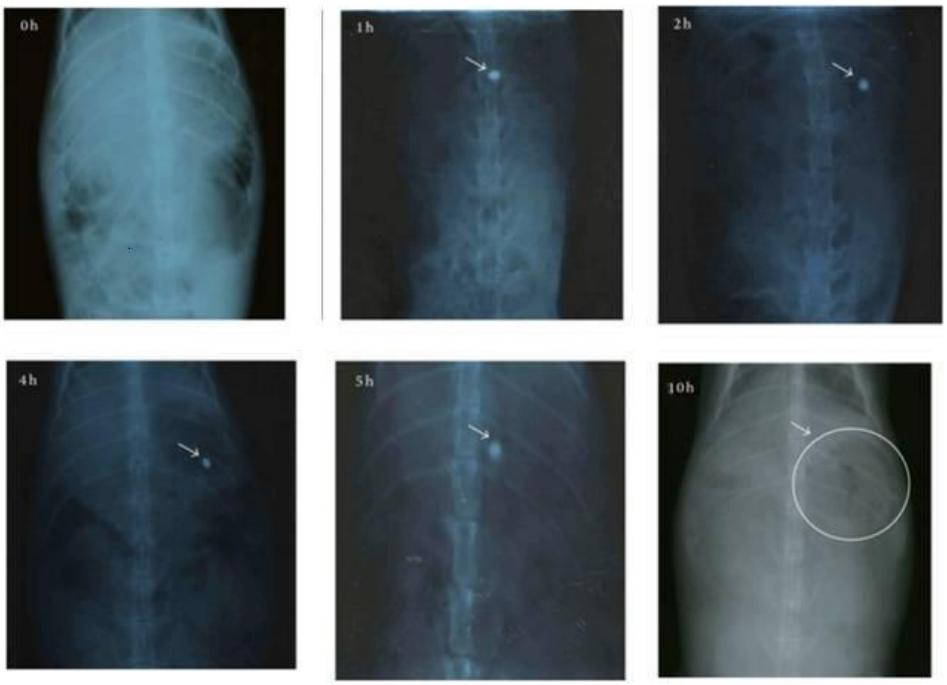


Fig. 45: *In vivo* X-ray photographs for best formulation of floating tablet of Acebutolol hydrochloride (A7)

Discussion:

The *in vivo* X- ray studies was performed for best formulation of Eprosartan mesilate (E7) and Acebutolol hydrochloride (A7) individually shown in fig. 44 and 45 revealed that the formulation was found intact till 10 h in the gastric region of the rat confirms that there was no change in the floating behavior of best floating tablet of Eprosartan mesilate (E7) and Acebutolol hydrochloride (A7) in both *in vitro* and *in vivo* studies.

5.3.7 *In vivo* pharmacokinetic studies:

Table 22: Plasma concentration of Acebutolol hydrochloride and Eprosartan mesilate after administration of respective best formulation of floating tablets

Time (in h)	Plasma concentration of Acebutolol hydrochloride (in ng/ml) Avg ± S.D	Plasma concentration of Eprosartan mesilate (in ng/ml) Avg ± S.D
0	0	0
1	28.12 ± 0.81	12.07 ± 7.64
2	41.66 ± 5.15	31.48 ± 4.07
4	64.37 ± 2.17	45.01 ± 5.12
6	45.33 ± 1.53	38.31 ± 6.94
8	34.35 ± 7.51	29.33 ± 2.19
10	27.91 ± 4.01	17.63 ±1.10
12	21.37 ± 1.53	13.22 ± 0.41
18	15.25 ± 2.16	8.48 ± 1.53
24	9.74 ± 1.32	5. 62 ± 4.08

Table 23: Pharmacokinetic parameters of best formulation of floating tablets of Acebutolol hydrochloride and Eprosartan mesilate

Pharmacokinetic parameters	Floating tablets of Acebutolol hydrochloride	Floating tablets of Eprosartan mesilate
Cmax (ng/ml)	64.37	45.01
Tmax (h)	4	4
AUC_{0-24} (ng.h/ml)	979.75	671.02

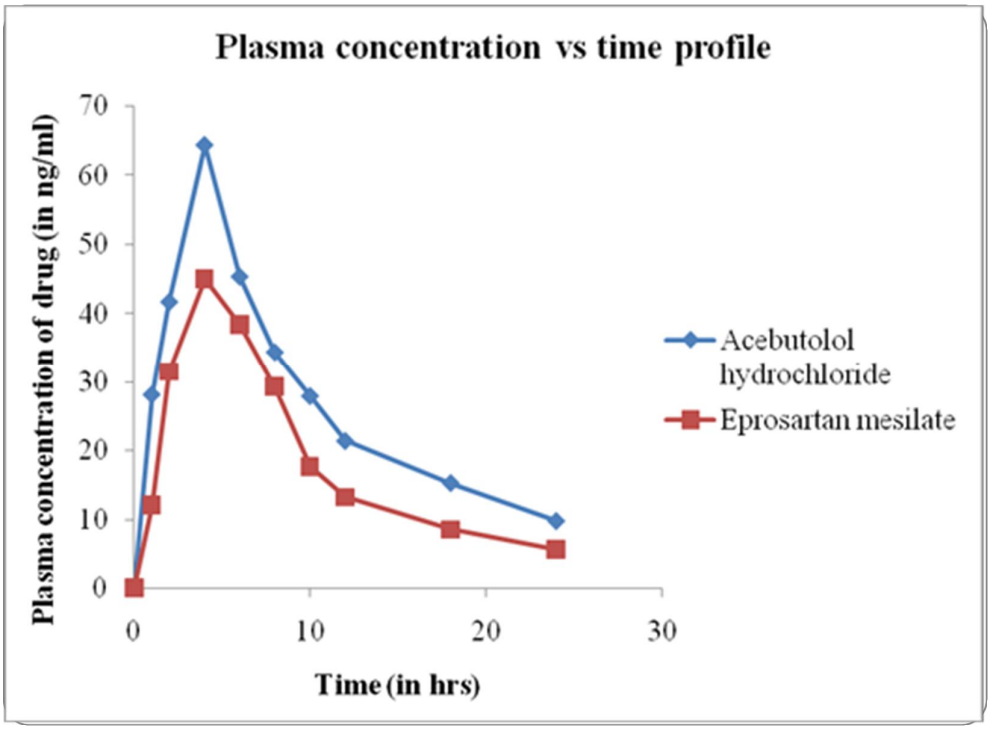


Fig. 46: Mean plasma concentration – time curves of best formulation of floating tablet of Acebutolol hydrochloride and Eprosartan mesilate following oral administration

Discussion:

The best formulation of floating tablets of Acebutolol hydrochloride and Eprosartan mesilate showed prolonged drug release *in vivo* also almost similar to *in vitro* drug release studies. This showed that formulated floating tablet released the drug in sustained fashion with gastro-retentive properties inducing more amount of drug available for absorption in local gastric area.

6. SUMMARY & CONCLUSION

In the present study, an attempt was made to formulate individually the floating tablet of Eprosartan mesilate and Acebutolol hydrochloride by effervesecent approach comparing various synthetic and natural polymers by direct compression method to increase the gastric retention of the drug and thus increases the bioavailability of the drug. The principle of gastro-retentive dosage form is to reduce the density of the dosage form less than the density of gastric fluid to increase the gastric residence time by means of effervescent approach using sodium bicarbonate and citric acid as effervescent agent with different natural and synthetic polymers in this research.

Intiallly, the procured drugs were identified by FTIR. Then, formulation of floating tablets of Eprosartan mesilate was done in three different stages with Eprosartan mesilate like to study the effect of different polymer on swelling index of the floating tablet, effect of effervescent agent on *in vitro* buoyancy studies. The results of above two stages were used to eliminate each one polymer from natural and synthetic sources and also to determine the concentration of effervescent agent in terms of ratio used to formulate floating tablets of Eprosartan mesilate in the third stage of formulation development. The result of third stage was used to formulate floating tablets of Acebutolol hydrochloride.

From the results of the first stage of formulation development of floating tablets of Eprosartan mesilate, based on swelling index, ethyl cellulose in synthetic source and sodium alginate in natural source were omitted for further screening due to its low swelling index than formulations containing other polymers which may be due to no water absorption capacity of hydrophobic polymer, ethyl cellulose to swell and less water absorption capacity of hydrophillic polymer, sodium alginate to hydrate and swell because of less viscosity of polymer.

From the results of the second stage of formulation development of floating tablets of Eprosartan mesilate, based on *in vitro* buoyancy studies, the highest ratio of sodium bicarbonate and citric acid was used for further formulation devolpment.

From the results of the first and second stage of formulation development of floating tablets of Eprosartan mesilate, shortlisted polymers and highest ratio of sodium bicarbonate and citric acid were used to formulate floating tablets of Eprosartan mesilate. From these formulations based on *in vitro* buoyancy (floating lag time and total floating time), uniformity of drug content and *in vitro* dissolution studies, formulation containing karaya gum (E7) was selected as best formulation in terms of least floating lag time of 1 sec, total floating time of 580 min, 98.47% released at the end of 600min. It was then subjected to release kinetics analysis and confirmed from the highest correlation coefficient that it follows zero-order non-fickian diffusion controlled system. The best formulation was subjected to drug–excipient compatibility studies and compared with FTIR of pure drug found that there was no interaction with drug and excipients. It was then subjected to stability studies and found that there was no drastic changes in analysed post-compression parameters. It was then analyzed for *in vivo* experiments like *in vivo* X-ray studies and *in vivo* pharmacokinetic studies for predicting its buoyancy and drug release and comparing with *in vitro* parameters. From the results it was found that buoyancy and was maintained for 10 h *in vivo* similar to *in vitro* results and sustained drug release was noticed *in vivo* similar to *in vitro* results concluded sustained drug delivery system was achieved.

From the above discussed results it was concluded that floating tablet of Eprosartan mesilate containing karaya gum (E7) prolongs the retention of dosage form in gastric area for longer time and thus minimizes the fluctuation in plasma concentration of the drug by frequent dosing of conventional immediate release dosage form.

From the results of formulation development of floating tablets of Eprosartan mesilate, shortlisted polymers and highest ratio of sodium bicarbonate and citric acid were used to formulate floating tablets of Acebutolol hydrochloride. From these formulations based on *in vitro* buoyancy (floating lag time and total floating time), uniformity of drug content and *in vitro* dissolution studies, formulation containing karaya gum (A 7) was selected as best formulation in terms of least floating lag time of 1 sec, total floating time of 590 min, 98.91% released at the end of 600 min. It

was then subjected to release kinetics analysis and confirmed from the highest correlation coefficient that it follows zero-order non-fickian diffusion controlled system. The best formulation was subjected to drug–excipient compatibility studies and compared with FTIR of pure drug found that there was no interaction with drug and excipients. It was then subjected to stability studies and found that there was no drastic change in analysed post-compression parameters. It was then analyzed for *in vivo* experiments like *in vivo* X-ray studies and *in vivo* pharmacokinetic studies for predicting its buoyancy and drug release and comparing with *in vitro* parameters. From the results it was found that buoyancy and was maintained for 10 h *in vivo* similar to *in vitro* results and sustained drug release was noticed *in vivo* similar to *in vitro* results concluded sustained drug delivery system was achieved.

From the above discussed results it was concluded that floating tablet of Acebutolol hydrochloride containing karaya gum (A7) prolongs the retention of dosage form in gastric area for longer time and thus minimizes the fluctuation in plasma concentration of the drug by frequent dosing of conventional immediate release dosage form.

.

7. IMPACT OF THE STUDY

Floating drug delivery system offers various future potential like reducing fluctuations in the plasma level of drug resulted from delayed gastric emptying and also by reducing frequent administration of the drug. This delivery system is a beneficial strategy for the local treatment of gastric and duodenal cancers. The buoyancy concept can be utilized in the development of various anti-reflux formulations and these are potential to treat the Parkinson's disease.

In the present research an attempt was made to solve a common critical issue related to the rational development of FDDS include the correlation between prolonged GRT and sustained release and pharmacokinetic characteristics. This created a path of transition from developmental level to the manufacturing and commercial level of gastro-retentive drug delivery system.

Further trials could be attempted in future on clinical studies for these best formulations of floating tablet of Acebutolol hydrochloride and Eprosartan mesilate separately.

BIBLIOGRAPHY

1. Anupama Sarawade, Ratnaparkhi MP, Shilpa Chaudhari. Floating drug delivery system: an overview, International Journal of Research and Development in Pharmacy and Life Sciences, 2014; 3(5): 1106-15

2. Neha Narang. An updated review on Floating drug delivery dystem (FDDS), International Journal of Applied Pharmaceutics, 2011; 3(1): 1-7

3. Purnima Tripathi, Ubaidulla U, Roop Kishan Khar, Vishwavibhuti. Floating drug delivery system, International Journal of Research and Development in Pharmacy and Life Sciences, 2012; 1(1): 1-10

4. Manju Maria Mathew, John Joseph, Teena Mohan. Review article on floating drug delivery system, International Journal of Pharmaceutical and Chemical Sciences, 2014; 3(3): 775-790

5. Abhishek Suryawanshi, Hiremath HP. Floating drug delivery systems - a review, Americal Journal of Pharmtech Research, 2012; 2(1): 138-53

6. Kataria Sahil, Middha Akanksha, Bhardwaj Sudeep, Sandhu Premjeet. Floating drug delivery system: a review, International Research Journal of Pharmacy, 2011; 2(9): 18-24

7. Srujana Katta, Mettu Srikanth Reddy, Raghavendra Rao NG. Overview on floating drug delivery system, American Journal of Pharmtech Research, 2013; 3(2): 145 - 69

8. Arunachalam A, Karthikeyan M, Kishore Konam, Pottabathula Hari Prasad, Sethuraman S, Ashuthoshkumar S, Manidipa S. Floating drug delivery system: A review, International Journal of Research in Pharmaceutical Sciences, 2011; 2(1): 76-83

9. Juhi Dubey, Navneet Verma. Floating drug delivery system: A review, International Journal of Pharmaceutical Science and Research, 2013; 4(8): 2893-99

10. Shailaja pant, Ashutosh badola, Preeti kothiyal. A review on gastroretentive drug delivery system, International Journal of Research and Development in Pharmacy and Life Sciences, 2016; 5(4): 2178-87

11. Kadam shashikant M, Kadam SR, Patil US, Ratan GN, Jamkandi VG. Review on floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. International Journal of research in Ayurveda and Pharmacy, 2011; 2(6): 1752-55

12. Pooja Gupta, Gnanarajan, Preeti Kothiyal. Floating drug delivery system: a review, International Journal of Pharma Research and Review, 2015; 4(8): 37-44

13. Jain NK. Advances in Controlled & Novel Drug Delivery, CBS Publishers & Distributers ,New Delhi: 76-95

14. Brahmankar DM. Biopharmaceutics and Pharmacokinetics , Vallabh Prakashan, New Delhi: 335-70

15. Kamalakkannan V, Puratchikody A, Prasanth VV and Masilamani K. Enhancement of drugs bioavailability by floating drug delivery system – A review, International Journal of Drug Delivery, 2011; 1: 558-70

16. Joseph R. Robinson and Vincent HL Lee, Controlled Drug Delivery, Fundamentals and Applications, 2nd ed., Revised and Expanded, Marcell. Dekker Inc., New York, 2009: 501-23

17. Vyas SP, Roop K Khar. Controlled Drug Delivery, Concepts & Advances, 1st ed.,Vallabh Prakashan, New Delhi, 2002: 196-217

18. Vishal Bhardwaj, Nirmala, Harikumar SL. Floating drug delivery system: a review, Pharmacophore, 2013; 4(1): 26-38

19. Gupta GD, Garg R. Gastroretentive floating microspheres of Silymarin: Preparation and *in vitro* evaluation. Trop,ical Journal of Pharmaceutical Research 2010; 9 (1): 59-66.

20. Geetha A, Rajendra kumar J, Krishna Mohan CH, Sateesh V, Raju PN. A review on floating drug delivery systems, International Journal of Pharmaceutical Research and Biomedical Analysis, 2012; 1(1): 1-13

21. Shweta Arora, Javed Ali, Alka Ahuja, Roop K Khar, Sanjula Baboota. Floating drug delivery system: A review, AAPS PharmSciTech, 2005, 6(3): E372-E390

22. Abhishek Chandel, Kapil Chauhan, Bharat Parashar, Hitesh Kumar, Sonia Arora. Floating drug delivery systems: A better approach, International Current Pharmaceutical Journal, 2012; 1(5): 110-18

23. Azhar Danish Khan, Meenakshi Bajpai. Floating drug delivery system: An overview, International Journal of PharmTech Research, 2010; 2(4): 2497-505

24. Kaushik Avinash, Dwivedi Abha, Kothari Praween, Govil Abhinav. Floating drug delivery system a significant tool for stomach specific release of cardiovascular drugs, International Journal of Drug Development and Research, 2012; 4(4): 116-29.

25. Sarvesh D Parsekar, Shruthi Prabhu, Amitha Shetty, Mohd Azharuddin, Shabaraya AR. A brief review on floating bilayer tablet as a convenient gastroretentive drug delivery system, International Journal of Pharmaceutical and Chemical Sciences, 2014; 3(2): 420-30

26. Paresh D Parmar, Saikat Pande, Saumil H Shah, Shailesh N Sonara. Floating drug delivery system: A novel approach to prolong gastric retention, World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(4): 418-44

27. Sean C Sweetman, editor. Martindale: The complete drug reference, 36th ed, Pharmaceutical press, London-Chicago; 2009: 1171-74

28. Padmaja Udayakumar, Medical Pharmacology, Chapter 18: Antihypertensive drugs, 5th ed, CBS Publishers and Distributors Pvt Ltd., New Delhi; 2017; 188-89

29. Srikanth MV, Janaki Ram B, Sunil SA, Sreenivasa Rao N, Ramana Murthy KV. Gastroretentive drug delivery systems: novel approaches and its evaluation: a review, International Journal of Pharmaceutical Sciences Review and Research, 2011; 10(1): 203-16.

30. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: a review., Research Journal of Pharmaceutical Technology, 2008; 1(4): 345-48.

31. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention a means to address regional variability in intestinal drug absorption, Pharmaceutical Technology, 2003; 27(7): 50-68.

32. Ramakrishna P, Mallikarjuna B, Chandra Babu A, Sudhakar P, Chowdoji Rao K, Subha MCS. Interpenetrating polymer network of crosslinked blend microspheres for controlled release of Acebutolol hydrochloride, Journal of Applied Pharmaceutical Science, 2011: 1(6): 212-19

33. Ranjitha, Zaheer Abbbas, Swamy NGN. Formulation and in vitro evaluation of Acebutolol hydrochloride microballoons for sustained drug delivery, Indian Journal of Novel Drug Delivery, 2014; 6(2): 124-31

34. Sean C sweetman, editor. Martindale-the complete drug reference. 36th ed. Pharmaceutical press, London-Chicago; 2009: 1200 - 01

35. Atmakuri, D & Attari, Zenab, Pai, G, Koteshwara KB. Enteric coated capsules of Eprosartan mesylate with pH-modifier for augmenting the dissolution, International Journal of Research in Pharmaceutical Sciences, 2016; 7 (1): 34-38

36. Sean C sweetman, editor. Martindale-the complete drug reference. 36th ed. Pharmaceutical press, london-chicago; 2009; 1281

37. Syed Iftequar, Maria Saifee, Lahoti Swaroop, Zahid Zaheer, Sabina Meraj, Furqan khan, Sarfraz Khan, Qazi Yasar, Shaikh Abdulla. Formulation and evaluation of floating drug delivery system of Ramipril, Journal of Innovations in Pharmaceuticals and Biological Sciences, 2016; 3(1): 85-95

38. Narendar Dudhipala, Arjun Narala, Karthik Yadav Janga, Ramesh Bomma. Amoxycillin Trihydrate floating bioadhesive drug delivery dystem for eradication of *Helicobacter pylori*: preparation, *in vitro* and *ex vivo* evaluation. Journal of Bioequivalence, 2016; 8:118-24.

39. Prasuna sundari PJ, Raju Gangadhari, Prathima Srinivas. Formulation and evaluation of sustained release floating microballons of Eprosartan mesylate, World Journal of Pharmaceutical Research, 2015; 4(9): 2260-74

40. Sarkar Rao K, Gnana prakash K, Kumar B, Prasad K, Madhavi C, Gobinath M. Formulation and evaluation of gastro-retentive drug delivery system of Losartan potassium by using raft-forming approach, International Journal of Research in Pharmaceutical Sciences, 2015; 6(2): 204-12

41. Ying-Chen Chen, Hsiu-O Ho, Der-Zen Liu, Wen-Shian Siow, Ming-Thau Sheu. Swelling/floating capability and drug release characterizations of gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose, 2015; 10 (1): e0116914 available in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4305323/

42. Senjalia HK, Shah S. Formulation and evaluation of once daily sustained release tablet of Eprosartan mesylate involving dissolution enhancement approach, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2014; 5(4): 345-358

43. Satyavathi K, Annapurna KVSS, Gayathri P, Bhojaraju P, Kanthal LK, Veerraju T. Formulation and evaluation of immediate release tablets of Eprosartan mesylate, International Journal of Pharmaceutical Sciences Review and Research, 2014; 25(1): 36-40

44. Neeta Choudhary , Rathore DS. *In vivo* study of self emulsifying drug delivery system (SEDDS) of Eprosartan, The Pharmaceutical and Chemical Journal, 2014; 1(1): 10-4

45. Venkata Srikanth Meka, Senthil Rajan Dharmanlingam, Venkata Ramana Murthy Kolapalli. Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and its *in vitro* characterization, Brazilian Journal of Pharmaceutical Sciences, 2014; 50 (2): 1-16

46. Asha spandana KM, Senthil kumar SK, Parthiban S. Formulation and evaluation of bilayer floating tablet containing antihypertensive agent, Asian Journal of Pharmaceutical Science & Technology, 2013; 3(1): 32-9

47. Shivanand K, Kishor S, Divakar Goli. Formulation and evaluation of gastroretentive floating drug delivery system of an Acyclovir, RGUHS Journal of Pharmaceutical Science, 2013; 3(3): 35 – 40

48. Udayakumar.T, Chordia Mayor Ashok, Udhumansha Ubaidulla. Design and development of bioadhesive gastro retentive drug delivery system of Metoprolol succinate, International Journal of Research and Development in Pharmacy and Life Sciences, 2013; 2(2): 355-62

49. Hemanth kumar G, Jaganathan K, Sambath kumar R, Perumal P. Formulation and *in vitro* evaluation of bilayer floating tablets of Metformin hydrochloride and Sitagliptin phosphate, International Journal of Advanced Phamaceutics, 2012; 2(2): 64-81

50. Mohan Varma M, Vijaya S. Development and evaluation of gastroretentive floating drug delivery system of Atenolol, International Journal of Pharmaceutical and Chemical Sciences, 2012; 1(2): 867-76

51. Navjot Singh, Anirbandeep Bose, Rakesh K Mishra, Vivek Jain, Sanjay Dhakar, Dileep Bharati. Development and evaluation of gastroretentive floating drug delivery system for Tizanidine hydrochloride and its *in vivo*

gamma-scintigraphic studies using tc-99m tracer, Asian journal of pharmaceutical and clinical research, 2012; 5(3): 56-61

52. Nirav Patel, Jinal Patel, Moin Modasiya. Formulation and *In vitro* evaluation of Glipizide as Floating Drug Delivery System Asian Journal of Pharmaceutical Technology 2012; 2(2): 67-73

53. Satishbabu BK, Sandeep VR, Ravi RB, Shrutinag R. Formulation and evaluation of floating drug delivery system of Famotidine, Indian Journal of Pharmaceutical Sciences, 2010; 738-44

54. Kharia AA, Hiremath SN, Singhai AK, Omray K, Jain SK. Design and optimization of floating drug delivery system of Acyclovir, Indian Journal of Pharmaceutical Sciences, 2010; 599-606

55. Ramesh Bomma, Rongala Appala Swamy Naidu, Madhusudan Rao Yamsani, Kishan Verabrahma. Development and evaluation of gastroretentive Norfloxacin floating tablets, Acta pharmaceutica, 2009; 59: 211-21

56. Havaldar VD, Kulkarni AS, Dias RJ, Aloorkar NH, Mali KK. Floating matrix tablets of Atenolol: Formulation and *in vitro* evaluation, Asian Journal of Pharmaceutics, 2009, 3(4): 286-291

57. Vishnu M Patel, Bhupendra G Prajapati, Anand K Patel. Controlled release gastroretentive dosage form of Verapamil hydrochloride, International Journal of PharmTech Research, 2009; 1(2): 215-21

58. Ravi kumar, Patil MB, Sachin R Patil, Mahesh S Paschapur. Formulation and evaluation of effervescent floating tablet of Famotidine, International Journal of PharmTech Research, 2009; 1(3): 754-63

59. Manoj N Gambhire, Kshitij W Ambade, Sushma D Kurmi, Vilasrao J Kadam, Kisan R Jadhav. Development and *in vitro* evaluation of an oral floating matrix tablet formulation of Diltiazem hydrochloride, AAPS PharmSciTech, 2007; 8(3): E1-E9

60. Raval JA, Patel K, Naihong Li, Patel MM. Ranidine hydrochloride floating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release, Asian Journal of Pharmaceutical Sciences, 2007; 2(4): 130-42

61. Narendra C, Srinath MS, Ganesh Babu. Optimization of bilayer floating tablet containing Metoprolol tartrate as a model drug for gastric retention, AAPS PharmSciTech, 2006; 7(2): E1-E7

62. Asha Patel, Subhabrata Ray, Ram Sharnagat Thakur. *In vitro* evaluation and optimization of controlled release floating drug delivery system of Metformin hydrochloride, DARU, 2006; 14(2): 57-64

63. Ziyaur Rahman, Mushir Ali, Khar RK. Design and evaluation of bilayer floating tablets of Captopril, Acta Pharmaceutica, 2006; 56: 49-57

64. Available from https://www.drugs.com/pro/Eprosartan.html

65. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 916- 25

66. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients,.286-97

67. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 737-53

68. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 845-51

69. Available from www.drugs.com

70. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 2180-88

71. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 411-9

72. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 1736-43

73. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 478-85

74. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 1756-66

75. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 341-52

76. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 2033-40

77. Raymond C Rowe, Paul J Sheskey and Sian C Owen, editor. Handbook of pharmaceutical excipients, 1122-31

78. Shreesh Kiran R, Chander Shekar B, Nagendra Babu B, Ranitidine hydrochloride gastroretentive floating tablets based on hydrophilic polymers, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010; 1 (4) : 964-76

79. M Mohan varma, S Vijaya. Development and evaluation of gastroretentive floating drug delivery system of Atenolol, Int J Pharm Chem Sci, Jun 2012, 1(2): 867-76

80. United states pharmacopeia 30. Asian ed. Rockville (Maryland): United states pharmacopeial convention, twinbrook parkway; 2007; 1: 242.

81. Leon Lachman, Hebert A Libermann, Joseph L Kanig, editor. Theory and Practice of Industrial Pharmacy. 3rd ed. Vargheese Publishing House; 296-303

82. United states pharmacopeia 30. Asian ed. Rockville (Maryland): United states pharmacopeial convention, twinbrook parkway; 2007; 1: 674

83. Ansel's Tablets, pharmaceutical dosage pharma and drug delivery, 8th edition, Wolters Kluwer (India), New Delhi :234-38

84. Kishore Babu A, Ramana MV. Development and *in vivo* evaluation of gastro retentive floating tablets of antipsychotic drug Risperidone. International Journal of Pharmacy and Pharmaceutical Sciences 2016; 8(11): 43-52.

85. International conference on harmonization: ICH harmonized tripartite guideline for stability testing of new drugs substances and products Q1A (R2). 2003:1-15

86. Ramesh Bomma, Kishan Veerabrahma. Development, intragastric performance and pharmacokinetic study of gastroretentive drug delivery system for Cefdinir in human volunteers, International Journal of Drug Delivery, 2013; 5(1): 63-72.

87. Patil SH, Talele GS. Formulation development and *in vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of Lafutidine. Asian Journal of Pharmacy, 2013; 7: 68-74.

88. Dinesh Kumar P, Grace Rathnam, Prakash CR, Saravanan G, Karthick V and Panneer Selvam T. Formulation and characterizatioin of bilayer floating tablets of Ranitidine. Rasayan Journal of Chemistry, 2010; 3(2): 368-74

89. Vemula SK, Venisetty RK, Veerareddy PR. Formulation and pharmacokinetics of Ketorolac tromethamine floating compression coated mini-tablets, Journal of Bioequivalence & Bioavailability, 2017; 9(5): 493-98

90. Mastiholimath VS, Dandagi PM, Gadad AP, Rashmi mathews, Kulkarni AR. *In vitro* and *in vivo* evaluation of Ranitidine hydrochloride ethylcellulose floating microparticles, Journal of Microencapsulation, 2008; 25(5): 307-14.

91. Chowdary KPR, Udaya Chandra D. Pharmacokinetic evaluation of Pioglitazone floating tablets formulated employing various polymers, JPR:BioMedRx: An International Journal, 2013; 1(9): 888-91.