Formulation and Evaluation of Floating Matrix Tablet Captopril

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ABSTRACT: The present study involves preparation and evaluation of floating matrix tablet of Captopril as model drug for prolongation of gastric residence time. The tablets were prepared by direct compression method using polymers HPMC (K4M), HPMC (K4M), Xantham gum and Guar gum. The tablet were evaluated for angle of repose, bulk density, tapped density, carr's index, hausner's ratio. The prepared tablets were characterized by hardness, thickness, friability, weight variation and drug content respectively. *In-vitro* drug release studies were performed by using an USP dissolution test apparatus (Basket type II) at 37±0.5ºC and 50 rpm speed. To study the release behavior, kinetic analyses were performed on the optimized formulation. The dissolution data were fitted to zero order, first order, matrix, Hixson-Crowell, Peppas model. The prepared tablet exhibited prolonged drug release (~ 12 h) and remained buoyant for > 12 h. The optimized formulations F13 were kept for short term stability study. The conditions for stability study were 40ºC and relative humidity of 75% from the study; it was observed that there is no significant change in stability and drug release rate.

Key-words: Floating matrix tablet, Captopril, In-vitro release.

INTRODUCTION:

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attain the desired therapeutic concentration of drug in plasma and maintains its concentration for the entire duration of treatment. This is possible through the administration of conventional dosage forms in a particular dose and at particular frequency. The frequency of administration or dose interval of any drugs depends upon its half-life or mean residence time and its therapeutic index. In most cases, dosing interval is much shorter than the half-life of the drug resulting in number of limitations associated with such conventional dosage forms, which are as follows:

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- A typical peak valley plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the concentration may lead to under medication or overmedication as the steady state concentration (C_{ss}) value fall or rise beyond the therapeutic range.
- The fluctuating drug level may lead to precipitation of adverse effect especially of a drug with small therapeutic index whenever over medication occurs.

1.1 Need of non-conventional drug delivery:

To overcome above discussed limitations of conventional dosage forms, it indicates the need of the development of non-conventional dosage forms.

There are two ways to overcome such a situation, which are

- Development of new, better and safer drugs with long half-life and large therapeutic indices.
- Effective and safer use of existing drugs through concepts and techniques of sustained/ controlled and targeted drug delivery systems.
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The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper Site in the body to achieve promptly and then maintain the desired drug concentration. The Most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Oral sustained drug delivery system is complicated by limited gastric residence times (grts). Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in Stomach or the upper part of small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the Upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS) Swelling or expanding systems, mucoadhesive systems, modified-shape systems, High-density system and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used [1].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this Physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the Dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by Delivering drug in a controlled and reproducible manner. Gastro retentive Systems can remain in the gastric region for several hours and hence significantly prolong the gastric Residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and Improves solubility of drugs that are less soluble in high ph environment. Gastric retention provides new therapeutic

possibilities and substantial benefits to patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs [2].

1.2 Basic gastrointestinal tract:

Anatomy:

Anatomically the stomach is divided into 3 regions: funds, body, and antrum (pylorus) showed in fig-1. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases shown in fig-2.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

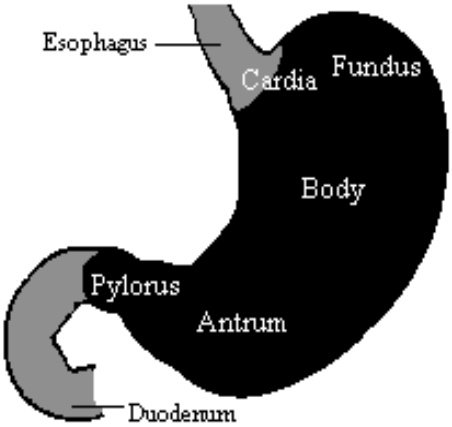
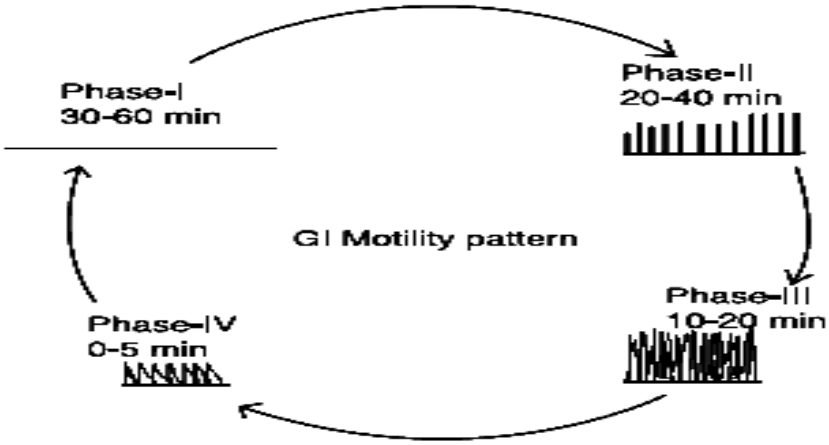


Figure 1.1: Structure of stomach

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate. [3]



Physiology:

Various factors like the absorption ability, pre-systemic clearance, gastric motility; gastrointestinal transit time and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form. Absorption ability of the absorption

capability of various segments or parts of gastrointestinal tract differs from each other. Most of the absorption takes place in small intestine and lesser extent in colon and stomach. Unless drugs are absorbed equally in both the colon and in small intestine, the duration for most of the drugs is 3-8 hours. This will be the major limiting factor for sustained release and controlled release drug delivery systems. Pre-systemic clearance Even if the drugs that can be absorbed equally well throughout the gastrointestinal tract, bioavailability is significantly reduced by the site-specific changes in pre-systemic clearance. Degradation of the drug is also carried out by hydrolysis in the stomach, enzymatic digestion, and metabolism in the brush border of the gut wall and by the microorganisms. Such degradation may leads to high variation in plasma drug concentration and poor absorption of drug in to the systemic circulation.

Gastric motility:
Gastric emptying occurs during fasting as well as fed states. During the fasting state an inter-digestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hours.

Gastrointestinal transit time:
Food content remains in each segment of the gastrointestinal tract for different periods of time. The resident time for both liquid and solid foods in each segment of the gastrointestinal tract is as reported by park.

Table 1.1: Transit time of food in each segment of the gastrointestinal tract

Segment	Liquid	Solid
Stomach	10-30 min	1-3 hrs
Duodenum	<60 sec	<60 sec
Jejunum and ileum	3 Hrs ± 1.5 hrs	4 Hrs ± 1.5 hrs
Colon	…….	20-50 hrs

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So, one has to take most of the drugs 3-6 times a day.

Factors affecting the gastric emptying time:

i. State of the stomach: gastric emptying time depends upon the fed state of the stomach, which increases the gastric emptying time as compared to unfed state.
ii. Circadian rhythms: which are increased in daytime and less during night, also affects the gastric retention time (GRT).
iii. Size of the dosage form: greater the energy content of the meal (carbohydrate and high fat content), longer the duration of emptying.
iv. Density of the oral dosage form: The density of the gastric fluid is reported to be 1.2g/cm^3. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for longer period of time.
v. Diseased state: State of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.
vi. Drug therapy: Plays an impotent role in gastric emptying e.g. Prokinetic drugs like cisapride and mosapride increase the gastric emptying time.
vii. Age: Increase in age decreases the gastric motility thereby increasing the gastric emptying time.
viii. Posture: It was seen that the supine posture on the right side showed better results than on the left side.

1.3 Approaches to gastric retention:
Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include:

A. Floating systems
B. Bioadhesive systems
C. Swelling and expanding systems
D. High density systems
E. Modified systems

A. Floating drug delivery systems:
Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have bulk density less than gastric fluids and so remain Buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. This delivery system is further divided into in to no effervescent and effervescent (gas-generating system).

(a) Non-effervescent systems:

I. Colloidal gel barrier systems:

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheth and Tossounian in 1975. These systems incorporate a high level (20- 75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.

II. Micro porous compartment systems:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.

III. Multiparticulate system: floating beads:

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet.

IV. Micro balloons:

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric micro balloons as carrier for drugs. Hollow microspheres are known as the micro balloons. Micro balloons were floatable in vitro for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that micro balloons orally administered to human were dispersed in the upper part of stomach and retained there for three hr against peristaltic movements.

(b) Effervescent systems:

A drug delivery system can be made to float in the stomach by incorporating a floating chamber which may be filled with vacuum, air or inert gas.

I. Volatile liquid containing systems:

These have an inflatable chamber which contains a liquid e.g. Ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid.

II. Gas generating systems:

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate Salts and citric/tartaric acid to liberate CO2 , which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate CO_2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus, carbon-dioxide is released, causing the beads to float in the stomach. [4, 5]

1.4 Methods for preparing floating dosage form:

Following approaches can be used for preparing floating dosage forms [6,7].

1. Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.
2. Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.
3. By reducing particle size and filling it in a capsule.
4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.
6. By incorporation of inflatable chamber which contained in a liquid e.g. Solvent that gasifies at body temperature to cause the chambers to inflate in the stomach.

Figure no: 1.3 Floating drug delivery system

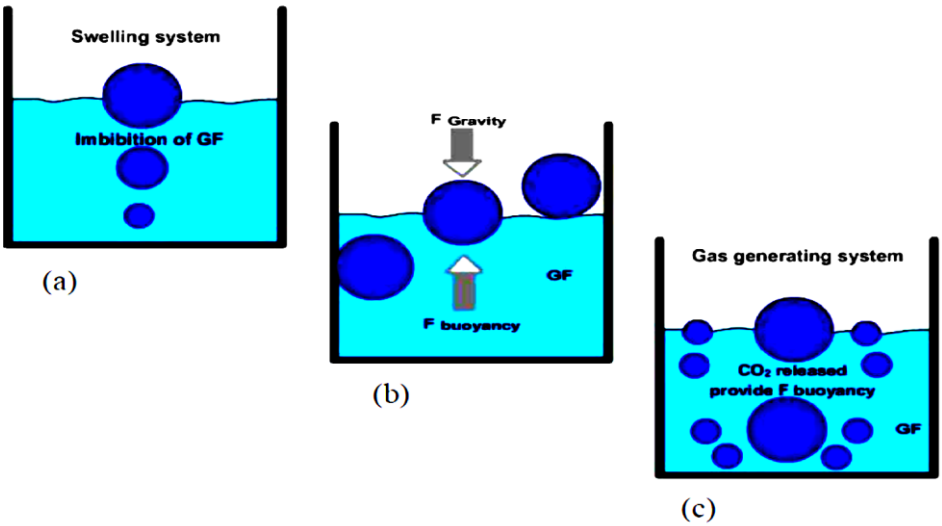


Figure no: 1.4 Mechanism of floating drug delivery system

1.5. Mechanism of floating drug delivery system [8]:

- Swelling matrix system
- Gas generating system

Swelling matrix system:

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered:

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other routes are adaptable)
- The release kinetic model.

1.5.1. Principal of modified drug release:

Following either of the two principles can modify drug release:

(a) Barrier principal:

In this method the retardant material is imposed between the drug and elusion medium. Drug release is by diffusion of the drug through the barrier and /or erosion of the barrier or permeation of the barrier by moisture.

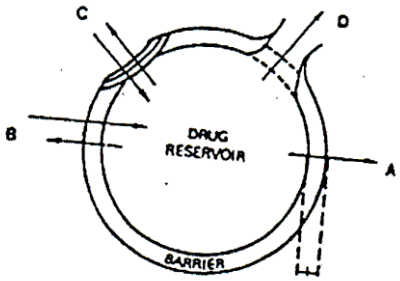


Figure no: 1.5 Barrier mediated models of sustained release dosage form regimen. A. Drug diffusion through the barrier, B. Permeation of barrier by elution media followed by drug dissolution, C. Erosion of barrier releasing drug, D. Rupture of permeation of elutiomedia.

(b) Embedded matrix:

In this drug is dispersed / embedded in a matrix of retardant material that may be encapsulated in a particulate form or compressed into the tablet. Drug release occurs by permeation of water leaching extraction of diffusion of drug from the matrix and erosion of matrix material.

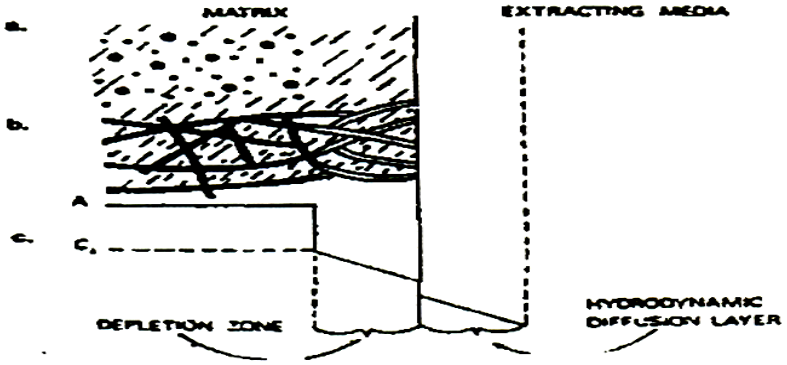


Figure no: 1.6 embedded matrix concept as a mechanism of controlled released in sustained release dosage form design network model a drug is insoluble in the retardant material. B Drug is soluble in the retardant material. Diffusion profile etc. Characterize drug release from matrix system.

1.5.2. Swellable matrices as system for oral delivery:

Monolithic devices or matrices represent a substantial part of drug delivery systems. Matrices containing swellable polymers are referred to as

- Hydrogel matrices
- Swellable control release systems.
- Hydrophilic matrix tablet

Swell able matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic microparticulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablet. They are constituted of a blend of drug and one or more hydrophilic polymers.

The release of drug from swellable matrix tablet is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug–polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The central element mechanism of drug release in the gel layer (rubbery polymer), is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration. Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.

DRUG AND POLYMER PROFILE:

4.1 Drug Profile

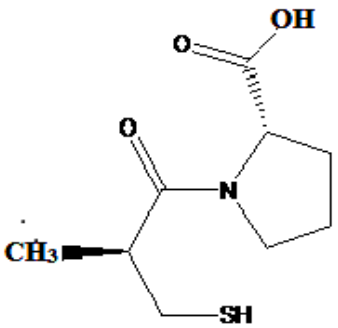
4.1.1 Captopril [59, 60]

It is official in IP and USP.

Physicochemical Profile

Synonyms : Capoten, Captolane, Captoril

Chemical structure :



IUPAC name : (2S)-1-[(2S)-2-methyl-3-Sulfanylpropanoyl] pyrrolidine-2-carboxylic acid.
Molecular formula : $C_9H_{15}NO_3S$.
Molecular weight : 217.285 g/mol
Description : Captopril is a white hygroscopic Crystalline Powder which is sulphide-like odour.
Melting point : 104˚-108°C
Solubility : Captopril is freely soluble in water, Ethanol, Chloroform, Methylene chloride and Methanol. Dissolves in dilute solutions of alkali hydroxide.
Category : An antihypertensive drug.
Pharmacokinetic
Bioavailability : 50 to 60%
Protein binding : About 30%.
Half life : About 1 to 2 h.
Absorption : Absorption of Captopril is in the gastrointestinal tract.
Distribution : Total protein binding to rhein is about 99%
Metabolism : Liver is the primary site of Captopril methylation where as the intestine plays only a minor role. Kidney may contribute substantially to the hepatic methylation of Captopril.

Pharmacodynamics profile
Mechanism of action :

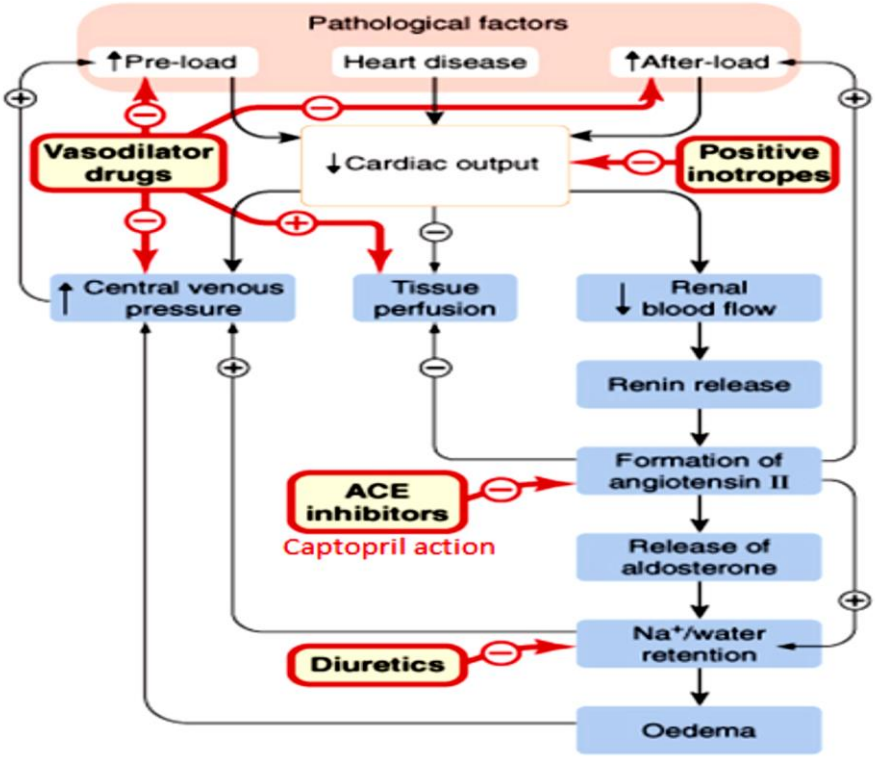


Figure: 4.1 Mechanism of action of Captopril

Captopril competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. As angiotensin II is a vasoconstrictor and a negative feedback mediator for renin activity, lower angiotensin II levels results in a decrease in blood pressure, an increase in renin activity and stimulation of baroreceptor reflex mechanisms. Kinase II, an enzyme which degrades the vasodilator bradykinin, is identical to ACE and may also be inhibited which is shown in figure 6.

Indications : 1) Treatment of hypertension
2) Cardiac conditions such as post myocardial infarction and congestive heart failure.
3) Preservation of kidney function in diabetic nephropathy.

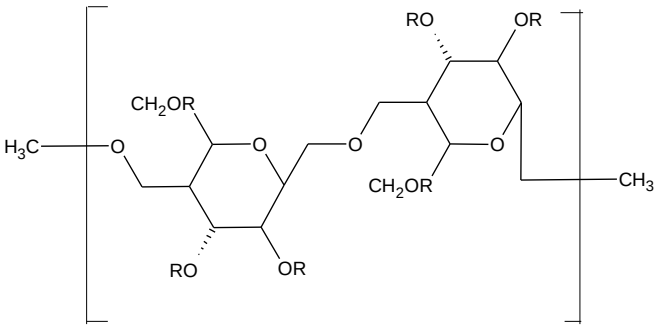
Adverse effects : Adverse effects of Captopril include cough due to increase in the plasma levels of bradykinin, angioedema, agranulocytosis, proteinuria, hyperkalemia, taste alteration, teratogenicity, postural hypotension, acute renal failure.

Dose : Captopril is available in potencies of 12.5 mg, 25 mg, 50 mg as conventional tablets for three times in a day.

4.2. Excipients profile

4.2.1 Hydroxy Propyl Methyl Cellulose [61]

Structure



Where: - R=H, CH_3 or CH_3 CH (OH) CH2

Synonym : HPMC, Methocel, Pharmacoat

Molecular weight: Approx 10,000-15, 00,000

Chemical name: Cellulose, 2-Hydroxypropyl methyl ether.

Category : Coating agent, film former, stabilizing -agent, suspending agent, tablet binder, viscosity- increasing agent.

Description : It is odourless and tasteless, white or creamy white colour, fibrous or granular powder.

Solubility : Swells in water, insoluble in alcohol, etherand Chloroform but soluble in a mixture of methylene chloride and methanol.

Table no: 4.1Different grades of HPMC

Methocel product	Nominal viscosity (cps)
HPMC K100 LV	100
HPMC K4M	4,000
HPMC K15M	15,000
HPMC K 100M	1, 00,000

Stability and storage condition : Very stable in dry condition, solutions are stable at pH 3.0-11.0. Aqueous solutions are liable to be affected by microorganisms.

Safety: Human and animal feeding studies have shown hydroxypropyl methyl cellulose to be safe.

Applications in pharmaceutical formulation or technology:

Hypromellose is widely used in oral, ophthalmic and topical Pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix polymer in extended-release tablet formulations. Concentrations between 2% w/w and 5% w/w may be used as a binder in either wet or dry-granulation process. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used as a suspending and thickening agent in topical formulations. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Table no: 4.2Application of HPMC in pharmaceutical formulation

Use	Concentration (%)
Tablet coating	1.0–3.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0-3.0
Tablet granulation	1.0-3.0

4.2Xanthamgum [62]

Nonproprietary names

BP : Xantham gum
PhEur : Xanthamgummi
USPNF : Xanthamgum

Synonyms : Corn sugargum; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural.

Functional category : As a stabilizing agent, suspending agent and viscosity-increasing agent.

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

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

Typical properties

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

Freezing point : 0˚C for a 1% w/v aqueous solution.

Melting point : Chars at 270˚C.

Refractive index : 1.333 (1% w/v aqueous solution)

Viscosity:1200-1600 cps for a 1% w/v aqueous solution at 25˚C.

Applications in pharmaceutical formulation or Technology:

- Xantham gum is widely used in oral and topical Pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other Pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range.
- Xantham gum is also used as a hydrocolloid in the food industry and in cosmetics it has been used as a thickening agent in shampoo. Xantham gum gels show pseudo plastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.
- Xantham gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.
- Recent studies have revealed that Xantham gum can also be used as an excipient for spray-drying and freeze drying process for better results.
- Xantham gum has also been used to prepare sustained-release matrix tablets.
- Xantham gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems.

4.5 Guar gum [62]:

Nonproprietary names:

BP : Guar galactomannan
PhEur : Guar galactomannan
USPNF : Guar-gum

Synonyms : *Galactosol;* Guar flour; guar

Chemical name : Galacyomannan polysaccharide

Empirical formula : $(C_6H_{12}O_6)n$

Structural formula : Guar gum consists of linear chain of the (1 → 4) β-D-mannopyranosyl units with α-D-galactopyranosyl units attached bythe (16) linkages. The ratio of D-galactose to D-mannose is between 1:1.4 and 1:2.

Functional category : Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.

Description : Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

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, thyrotrophic solution. The optimum rate of hydration occurs at pH 7.5-9.0. Finally milled powder swells more rapidly and is more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.

Viscosity:

Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation and particle size of the guar gum powder. Synergistic rheological effects may occur with other suspending agents such as Xantham gum.

Typical properties

Acidity/alkalinity pH : 5.0-7.0 (1% w/v aqueous dispersion)

Density : 1.492 gm/cm^3

Applications in pharmaceutical formulation or technology

- Guar gum is galactomannan commonly used in cosmetics, food products and Pharmaceutical formulations. Guar gum has been also investigated in the preparation of sustained-release matrix tablet.
- In Pharmaceuticals, guar gum is used in solid-dosage form such as binder and disintegrant. In oral and topical products, as a suspending, thickening and stabilizing agent and also as a controlled-release carrier.
- Guar gum has been also examined in colonic drug delivery.
- Guar gum based three layer matrix tablet have been used experimentally in oral controlled-release formulation.
- Therapeutically, guar gum has been used as a part of the diet of patients with diabetes mellitus. It has also been used as appetite suppressant.

EXPERIMENTAL:

Table No: 5.1List of chemicals

Sr. No.	Chemical and Reagents	Suppliers
1	Captopril	Inventia Healthcare Ltd., Mumbai, India.
2	Xantham gum	Rajesh Chemicals, Mumbai, India.
3	HPMC (K4M and K15M)	SD Fine Chemicals, Mumbai, India.
4	Guar Gum	SD Fine Chemicals, Mumbai, India.
5	Lactose	Loba Chem., Mumbai, India.
6	Magnesium Stearate	Fischer Chem., Mumbai, India.
7	Citric acid	Fischer Chem, Mumbai, India.
8	Manitol	Fischer Chem., Mumbai, India
9	Talc	SD Fine Chemicals, Mumbai, India.

Table No: 5.2List of instruments

Sr. No.	Instrument	Make
1	Tablet compression machine	Cadmach, Ahmedabad.
2	USP tablet dissolution apparatus	Electrolab Ltd., Mumbai, India.
3	UV Visible double beam spectrophotometer	Systronic 2201, India.
4	Fourier Transform Infra- Red Spectrophotometer	Shimatzu, Mumbai, India.
5	Hardness tester	Monsanto Tester, India.
6	Friability tester	Roche, India.
7	Electronic balance	Shimatzu, Japan.
8	Verniercaliper	Aerospace, Mumbai, India.

Characterization of Captopril:

5.1.1 Melting point determination [37]

The melting point of Captopril was determined using thiel's tube method.

5.1.2 Determination of λ max

Stock solution of Captopril was prepared by dissolving 10 mg of drug in 100 ml of solvent pH 1.2 after proper dilutions analyze spectrophotometrically to determine the λ max.

5.2 Preparation of calibration curve in 0.1 N HCl (pH 1.2)[38]

Accurately weighed amount of Captopril 10 mg was dissolved in 100 ml 0.1 N HCl. A series of standard solution containing 5-25 µg/ml of Captopril was prepared and analyzed using UV-visible spectrophotometer at 210.2 nm.

5.3 Drug-polymer compatibility study [39]

To determine possible incompabilities between pure drug and polymers the sample of pure drug, HPMC K4M, HPMC K15M, Xantham gum, Guar gum and its physical mixture were subjected to FTIR studies and the spectrum was recorded in the stretching frequency range of 400- 4000 cm^{-1}. The samples were prepared by KBr press pellet technique.

5.4 Characterization of tablet blend [40-45]

5.4.1 Angle of repose

The angle of repose of each powder blend was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated by using the following equation.

$$\tan \theta = h/r$$

Where, h = height of cone and r = radius of powder cone

5.4.2 Bulk density

Bulk density of the powder blend was determined by pouring gently 2gm of sample through a glass funnel into a 10ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated by the following formula.

$$\text{Bulk Densily} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

5.4.3 Tapped density

About 2 gram of powder blend was poured gently through a glass funnel into a 10ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after 100 tapping were recorded and tapped density was calculated by the following formula,

$$\text{Tapped Density} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

5.4.4 Carr's index

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index I, which is determined by the following equation,

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5.4.5 Hausner ratio

Hausner ratio is related to inter particle friction and as such used to predict powder flow properties.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

5.5 Formulation design [45-50]

In order to investigate the drug release profile, the formulations (F1-F12) were prepared in the ratio of Drug: Polymer in 1:1, 1:1.5, and 1:2.and (F13) 1:1.5 with combination of HPMC K4M and HPMC K15M. and (F14) with combination ofXantham gum and Guar gum respectively. The dose of the Captopril which is 50 mg was kept constant.

5.5.1 Preparation of floating matrix tablet

Different tablets formulations F1-F14 were prepared by the direct compression technique. All the powders were passed through 18 mesh sieve. The required quantity of drug, matrix polymer and low-density powder were mixed thoroughly. Magnesium stearate was added as a lubricant. The blend was compressed (10 mm diameter, concave punches) using a rotary tablet compression machine. Each tablet contained 50 mg Captopril and other excipients as listed in table 5.3

Table No: 5.3 Composition of tablets

Formulation (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Drug	50	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	50	75	100	-	-	-	-	-	-	-	-	-	35.5	-

HPMC K15M	-	-	-	50	75	100	-	-	-	-	-	-	35.5	-
Xantham gum	-	-	-	-	-	-	50	75	100	-	-	-	-	35.5
Guar Gum	-	-	-	-	-	-	-	-	-	50	75	100	-	35.5
Sodium bicarbonate	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Lactose	60	35	10	60	35	10	60	35	10	60	35	10	35	35
Total Weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200

5.6Evaluation of tablet [51, 52]

5.6.1 Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester (Nevtex). The hardness was measured in terms of kg/cm^2.

5.6.2 Thickness:

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernire caliper.

5.6.3 Friability:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ Loss} = \frac{\text{Initial weight of tablets - Final weight of tablets}}{\text{Initial weight of tablets}} \text{ X } 100$$

5.6.4 Weight variation:

Weigh 20 tablets at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown and none deviates by more than twice that percentage.

5.6.5 Determination of drug content:

For drug content, accurately weighed tablets was selected and ground to fine powder. An amount equivalent to 50 mg drug was dissolved in 0.1N HCl and filtered through filter paper. The filtered solutions of appropriate dilutions were analyzed at 210.2 nm using UV spectrophotometer. The amount of Captopril was determined by measuring the absorbance at 210.2 nm.

7.4.5. Swelling index [53]:

The swelling index of tablets was determined n 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index WU} = \frac{(W_t - W_0)}{W_0} \text{ x } 100$$

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

7.4.6. Buoyancy lag time [54]:

The in vitro buoyancy was determined by floating lag time method described as The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy lag time (BLT) and total duration of time by which dosage form remain buoyant is called Total floating time (TFT).

5.7*In-vitro* dissolution studies [55-58]:

The release of Captopril for different formulations of floating tablets was determined using USP dissolution test apparatus (type II). The dissolution medium was 900 ml in 0.1N HCl at 37±0.2 °C with a stirring speed of 50 rpm. Aliquots of 10 ml were withdrawn at predetermined intervals of 1 hr, filtered and replaced by equivalent volume of fresh dissolution media. The test sample was filtered through membrane filter, (0.45 µm) and the concentration of drug release was determined by using UV- Visible Spectrophotometer at λmax 210.2 nm.

5.8 Stability studies:

The optimized formulation was kept for short term stability study. The conditions for stability study were 40°C and. All tablets were suitably packed in group of 10 in aluminum foil. The stability study condition was maintained at 40°C using saturated solution of sodium chloride. At the end of one month the sealed tablets were opened and evaluated for hardness, thickness, friability, uniformity of weight, determination of drug content and dissolution studies. [57]

RESULT AND DISCUSSION:

6. Result and discussion:

6.1 Characterization of captopril:

A. Melting point determination:

Melting point of captopril was found in the range of 106-108ºC which is in the reported range that is 104ºC to 108ºC which indicates purity of drug sample.

B. Determination of λ_{max} :

The Wavelength of maximum absorbance (λ_{max}) of solution of captopril prepared in 0.1N HCl i.e. pH 1.2. The λmax for captopril was observed at 210.2 nm which was reported in the literature. The spectrum is shown in figure 6.1

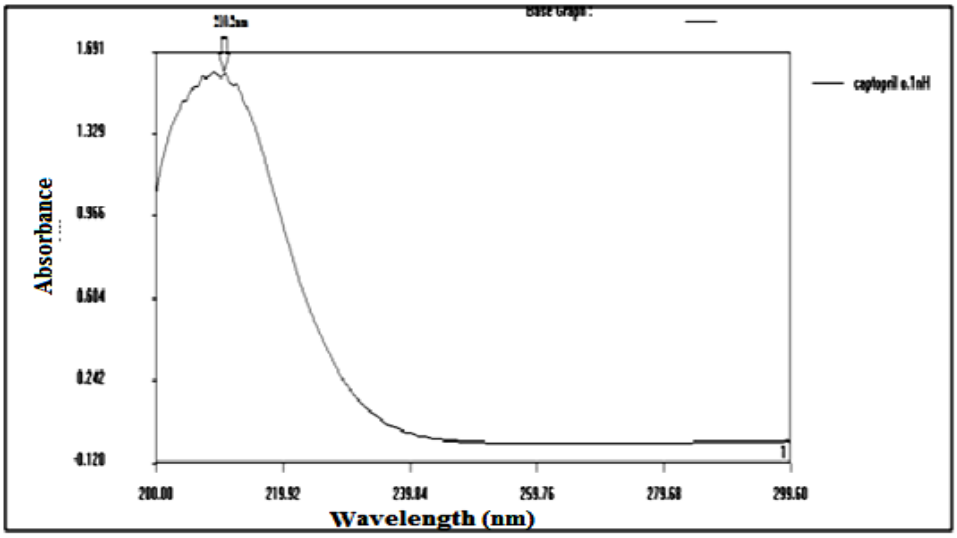


Figure 6.1: UV spectrum of captopril

6.2 Calibration curve for captopril in pH 1.2 (0.1N HCl):

The calibration curve for captopril in pH 1.2 was prepared in the range of 5-25 µg/ml and the results are shown in table 6.1 and figure 6.2.

Table 6.1: Result of calibration curve in pH 1.2

Concentration (µg/ml)	Absorbance
5	0.134
10	0.266
15	0.419
20	0.550
25	0.683

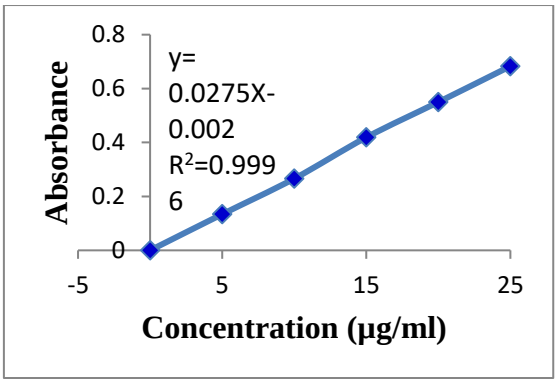


Figure 6.2: Calibration curve in pH 1.2

The prepared calibration obeyed Beer Lambert's law in the concentration range of 5-25 µg/ml. The value of regression coefficient (0.9996) shows the linearity relationship between concentration and absorbance.

6.3 Drug and polymer compatibility study:

6.3.1 FTIR spectroscopy:

The FTIR spectrum of captopril, HPMC K4M, HPMC K15M, Xantham gum, Guar gum and its physical mixture are shown in figure 6.3-6.11 and table 6.2

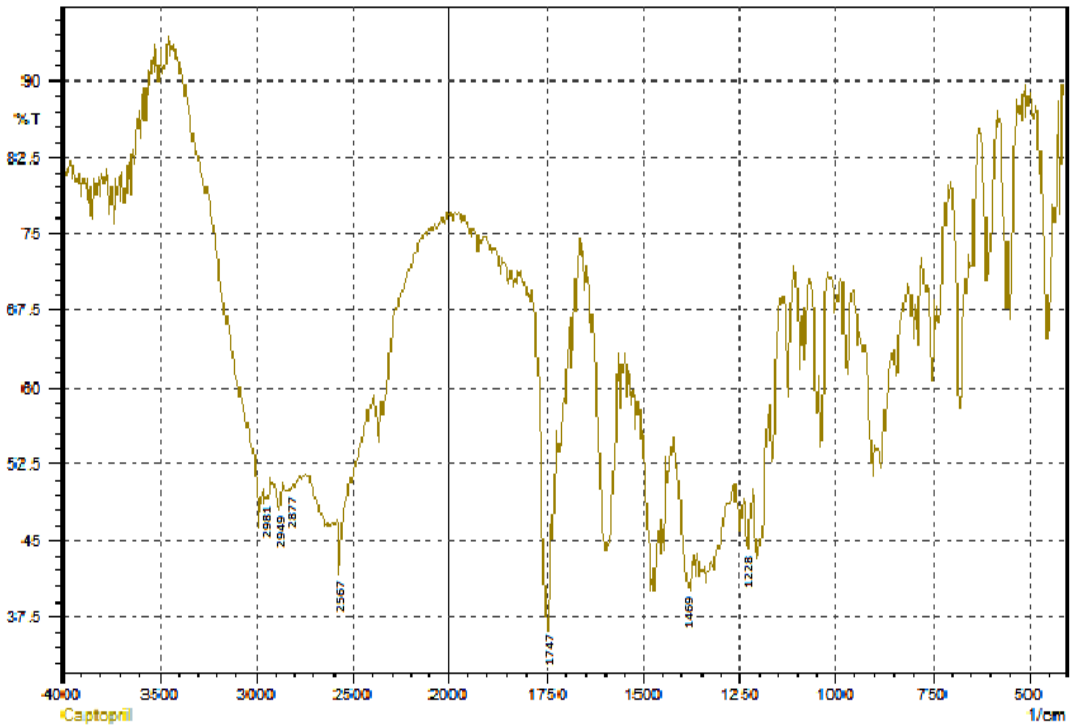


Figure no: 6.3 FTIR spectra of Captopril

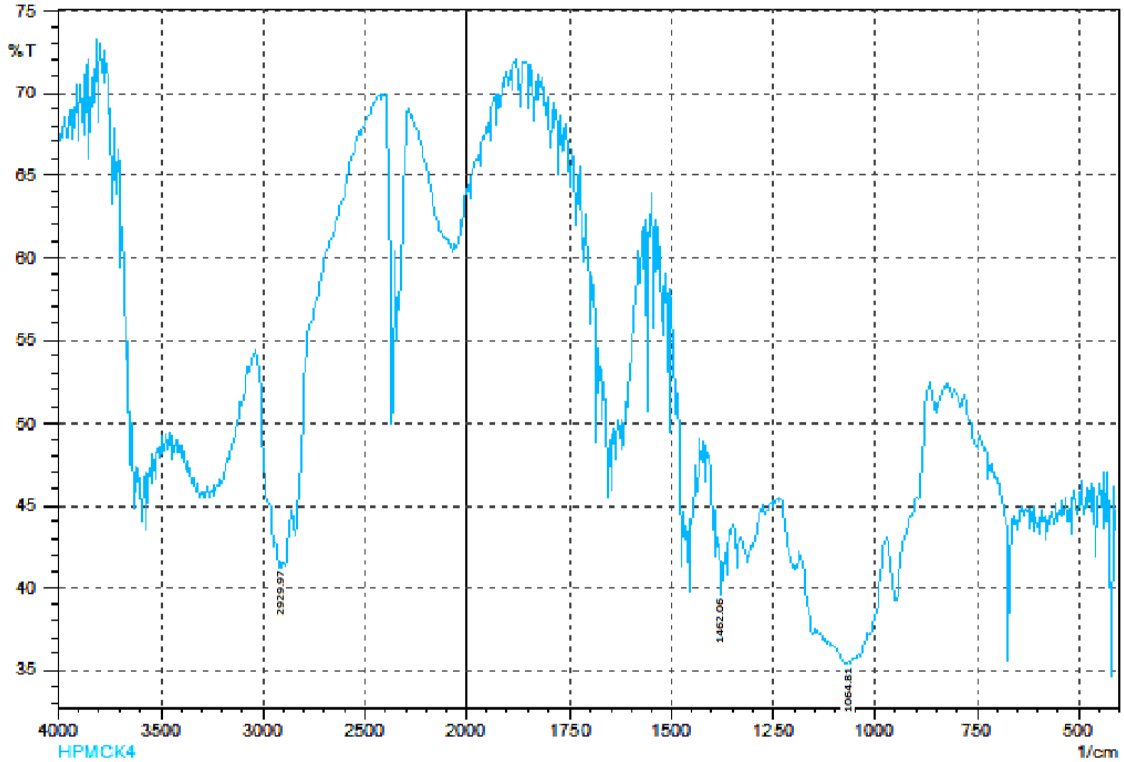


Figure no: 6.4 FTIR spectra of HPMC (K4M)

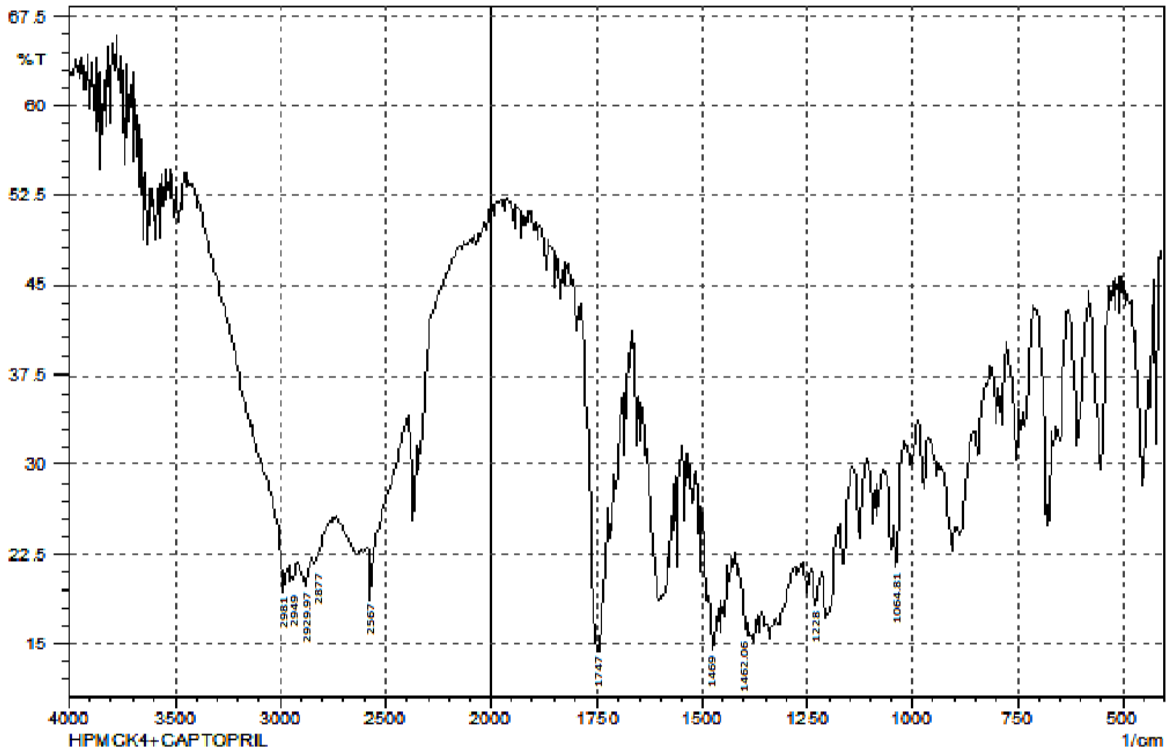


Figure no: 6.5 FTIR spectra of HPMC K4M+Captopril

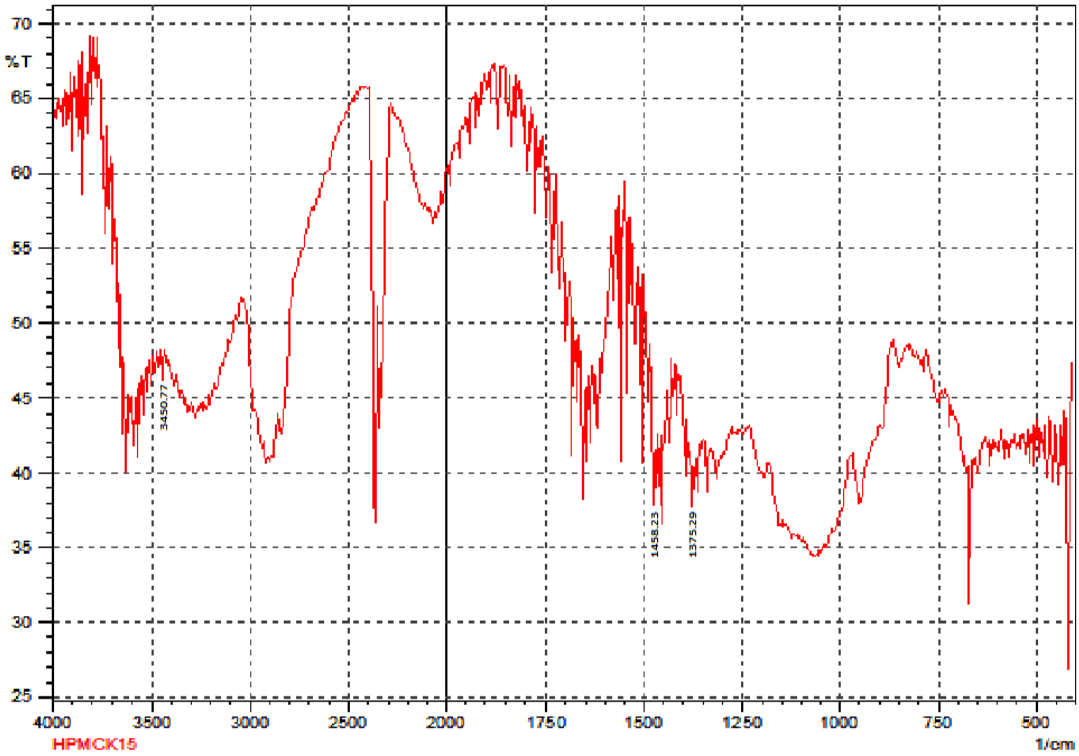


Figure no: 6.6 FTIR spectra of HPMC (K15M)

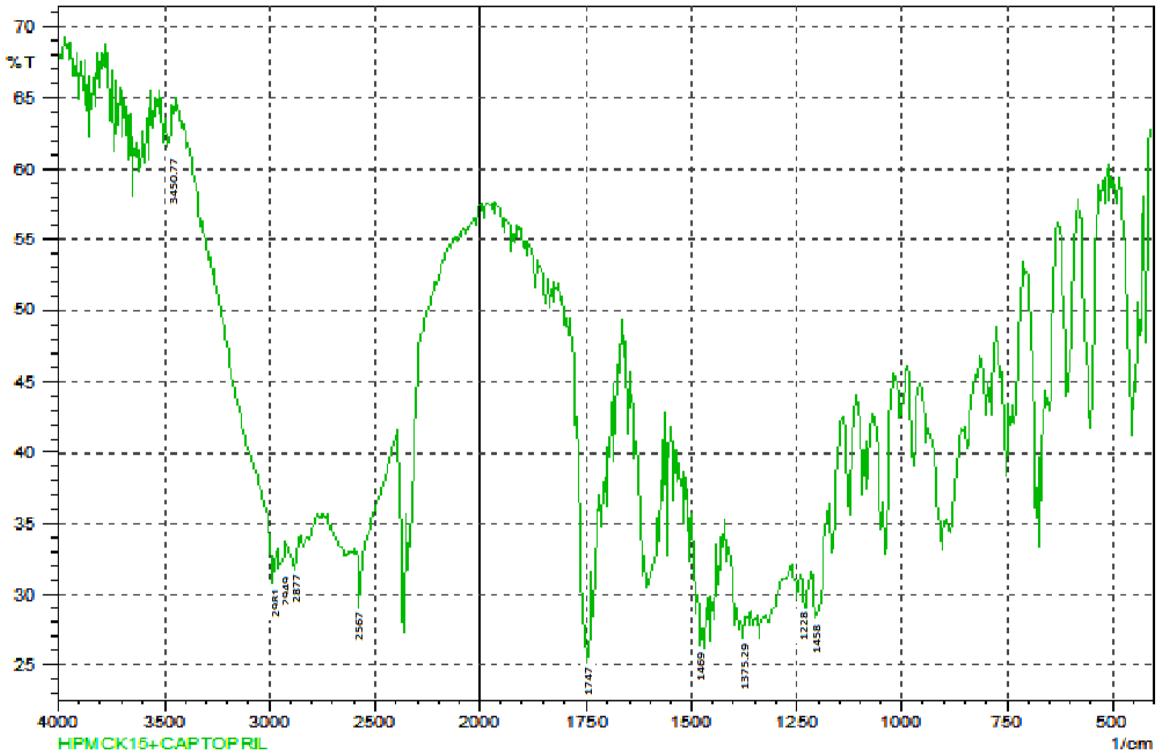


Figure no: 6.7 FTIR spectra of HPMC K15M+Captopril

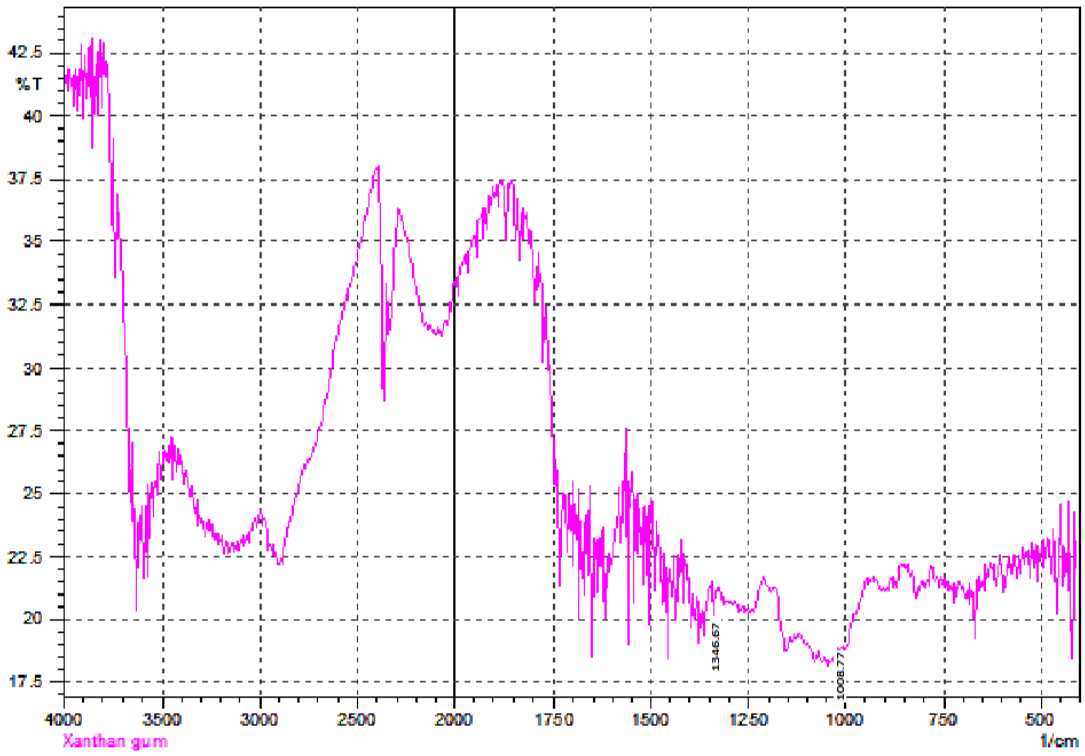


Figure no: 6.8 FTIR spectra of xantham gum

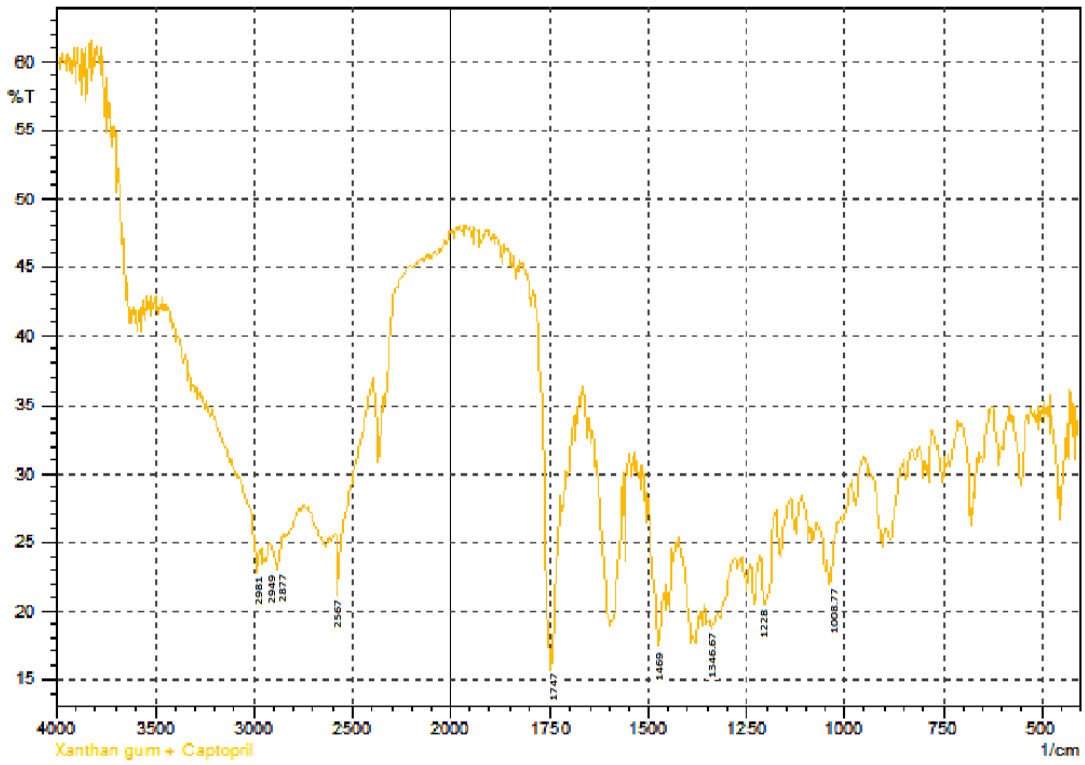


Figure no: 6.9 FTIR spectra of xantham gum+Captopril

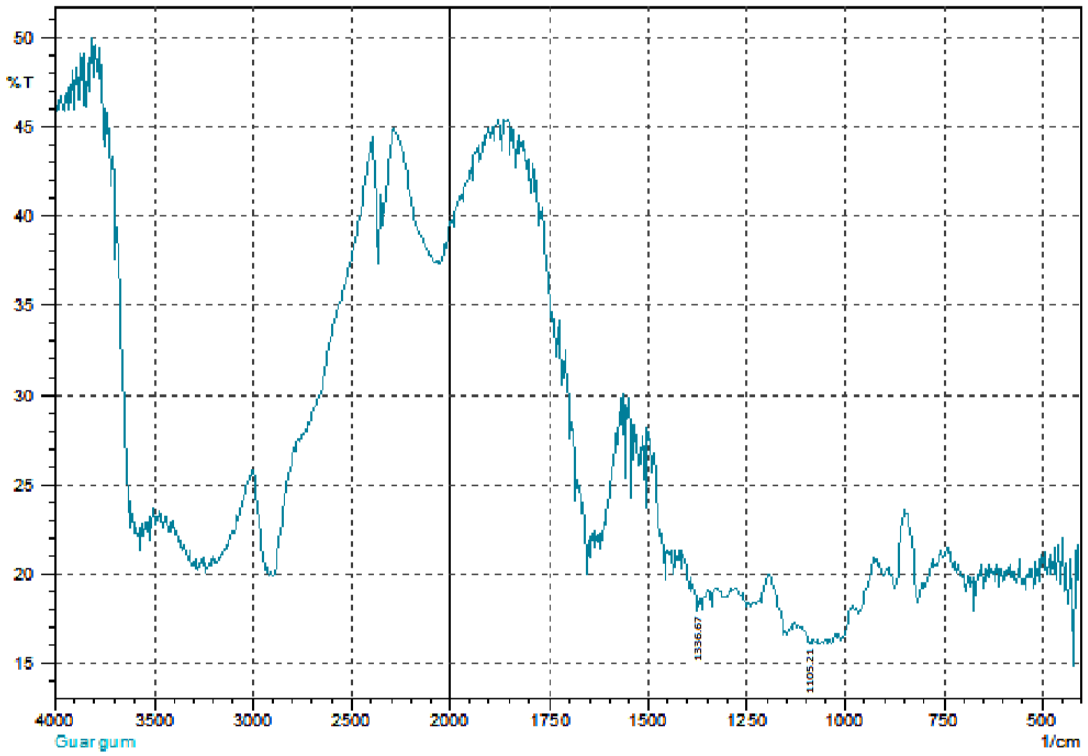


Figure no: 6.10 FTIR spectra of guar gum

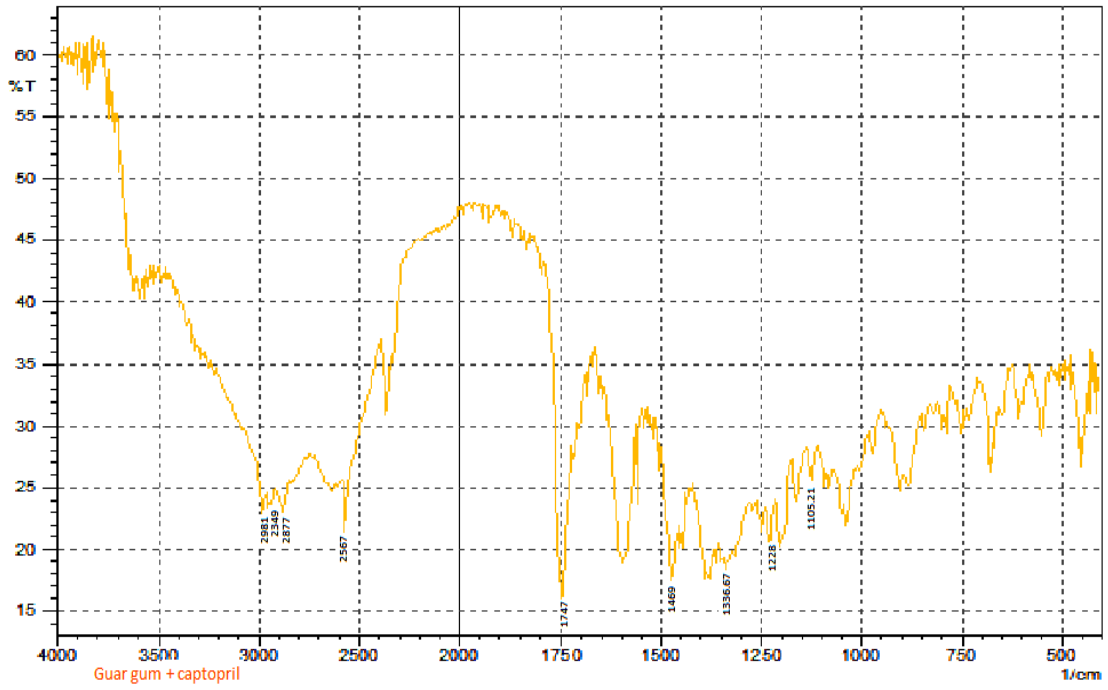


Figure no: 6.11 FTIR spectra of guar gum + captopril

Table 6.2 Results of FTIR study

Material	Peaks (cm^{-1})	Characteristic Functional Groups
Captopril	2981, 2949 2877 2567 1747 1469 1228	CH_3 and CH_2 asymmetric stretching CH_3 symmetric stretching SH stretching C=O stretching CH_3 bending CN stretching
HPMC (K4M)	2929.97 1064.81 1462.09	C-H stretching C-O stretching C-OH stretching
HPMC (K15M)	3450.77 1458.23 1375.29	O-H stretching C-H bending C-O stretching
Xantham gum	1346.67 1008.77	C-H bending C-O stretching
Guar gum	1336.67 1105.21	C-H bending C-O stretching

From the figure 9.13 and table 6.2 the Captopril showed 2981, 2949 cm^{-1} for CH_3 and CH_2 asymmetric stretching, 2877 cm^{-1} for symmetric CH_3 stretching mode, 2567 cm^{-1} for SH stretching vibration, 1747 cm^{-1} for C=O stretching vibration of carboxylic acid, 1469 cm^{-1} for CH_3 bending vibration, 1228 $cm^{-1}$for C-N stretching vibration. In IR spectra HPMC (K4M) showed 2929.97 cm–1 for C-H Stretching, 1064.81cm–1 for C-O Stretching, 1462.09 cm–1 for C-OH stretching. . In IR spectra of HPMC (K15M) the peak showed 3450.77 cm-1 for O-H Stretch, 1458.23 cm-1 for C-H Bending, 1375 cm-1 for C-O Stretching. Xantham gum C-O stretching occurs at 1008.77 and C-H bending occurs at 1359.82. Guar gum C-O stretching occurs at 1105.21 and C-H bending occurs at 1336.67.
From the results there is no significant changes were observed, when physical mixture was subjected to FTIR studies.

6.4 Evaluation of tablet:

6.4.1 Characterization of tablet blend:

All the formulation powder mixtures were evaluated for pre-compression parameters such as Angle of the repose, Loose bulk density, Tapped bulk density, Carr's index and Hausner's ratio and results obtained are shown in the table 6.3

Table 6.3. Results of tablet blend

Formulations	Angle of Repose	Bulk Density (gms/cm^3)	Tapped Density (gms/cm^3)	Carr's Index (%)	Hausner's Ratio
F1	28.90±1.29	0.59±0.03	0.69±0.04	13.81±2.36	1.16±0.03
F2	28.07±1.18	0.60±0.03	0.70±0.03	14.50±1.00	1.17±0.01
F3	28.61±1.58	0.57±0.02	0.67±0.02	14.16±2.21	1.17±0.03
F4	28.85±0.35	0.58±0.01	0.68±0.01	15.68±1.88	1.19±0.03
F5	29.28±1.06	0.61±0.02	0.71±0.00	14.68±2.67	1.17±0.04
F6	29.25±0.60	0.61±0.01	0.70±0.02	13.48±2.41	1.16±0.03
F7	28.27±1.85	0.58±0.04	0.67±0.02	13.12±3.44	1.15±0.04
F8	29.28±1.26	0.59±0.02	0.68±0.03	12.08±1.40	1.14±0.02
F9	27.27±0.32	0.60±0.01	0.68±0.03	12.89±2.14	1.15±0.03
F10	28.23±0.93	0.58±0.01	0.68±0.02	14.71±0.99	1.17±0.01
F11	29.67±0.34	0.59±0.02	0.70±0.02	15.14±0.20	1.18±0.00
F12	30.04±0.70	0.62±0.02	0.71±0.02	12.44±0.83	1.14±0.01
F13	28.43±1.46	0.61±0.02	0.70±0.03	13.14±1.15	1.15±0.02
F14	27.68±1.80	0.60±0.01	0.72±0.01	16.50±2.35	1.20±0.03

*All values are expressed as mean± S.D, n=3

From the result, the angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio were found to be within the limits. The compressibility index was the lowest for all the formulations which had good flow properties. Also, lower values for Hausner ratio indicate excellent flow properties of the formulations.

6.5. Characterization of formulation:

The hardness, thickness, friability, weight variation and drug content of all the formulations were determined and the results obtained are mentioned in the Table 6.4. The tablets evaluated for the weight variation showed within limit and thus passed the test. The friability of the tablets was found to be less than 1% which was considered within the limit. The drug content of the optimized formulation was found to be within the limits (98 – 102%).

Table 6.4. Results of characterization of floating matrix tablets

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	201.85±0.22	3.17±0.06	6.67±0.29	0.77±0.19	96.53±0.12
F2	201.68±0.18	3.20±0.09	6.40±0.53	0.67±0.20	97.54±0.29
F3	201.22±0.19	3.08±0.11	6.57±0.40	0.90±0.14	96.80±0.29
F4	201.00±0.41	3.25±0.09	6.83±0.35	0.59±0.21	95.93±0.22
F5	200.72±0.48	3.20±0.06	6.83±0.29	0.58±0.20	97.57±0.16
F6	202.55±0.51	3.03±0.23	6.40±0.53	0.45±0.19	97.37±0.29
F7	201.00±0.41	3.21±0.13	6.50±0.62	0.66±0.28	95.63±0.29
F8	200.72±0.48	3.09±0.14	6.73±0.64	0.38±0.03	96.50±0.45
F9	202.55±0.51	3.18±0.15	6.57±0.40	0.63±0.20	97.57±0.33
F10	200.58±0.57	3.04±0.15	6.30±0.17	0.61±0.31	95.36±0.29
F11	200.88±0.19	3.08±0.13	6.47±0.31	0.75±0.12	95.99±0.34
F12	200.60±0.35	3.22±0.10	6.77±0.25	0.80±0.26	97.59±0.25
F13	200.65±1.04	3.08±0.18	6.60±0.17	0.69±0.22	99.36±0.16
F14	200.45±0.15	3.21±0.13	6.93±0.51	0.72±0.27	97.70±0.21

*All values expressed as mean± are S.D., n=3

6.6. Swelling Index:

The swelling of the polymers used could be determined by 0.1N HCl uptake of the microspheres. The complete swelling was achieved by the end of 6 hours, so percent swelling was determined at the end of 6 hours for all the developed formulation. The values of swelling index of various batches were evaluated as shown in table 6.5 to 6.9. There was a significant increase in the percent swelling of the microspheres with increase in concentration of polymers. After 6 hours swelling index was observed between 70.76±2.74 to 86.99±1.22 %.

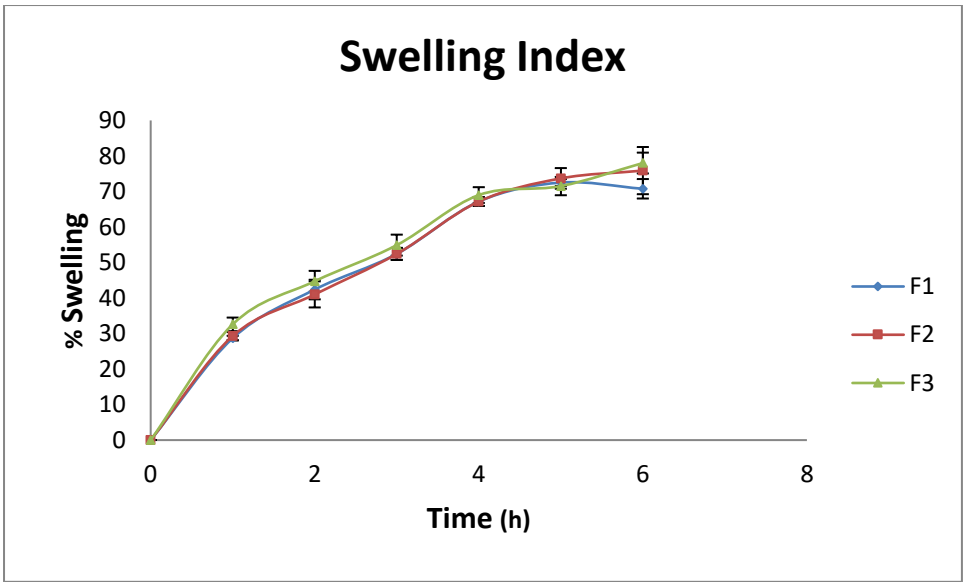


Figure no: 6.12 Results of swelling index of formulation F1 to F3

Table no: 6.5 Results of swelling index of formulations F1 to F3

Time (h)	F1	F2	F3
1	28.69±0.65	29.31±1.14	32.58±1.92
2	42.39±2.76	41.02±3.67	44.73±2.92
3	52.42±1.68	52.42±1.68	54.90±2.95
4	67.17±1.24	67.17±1.24	68.99±2.22
5	72.50±0.99	73.68±2.91	71.52±2.57
6	70.76±2.74	75.88±6.65	78.01±2.93

Mean ± S.D., n=3

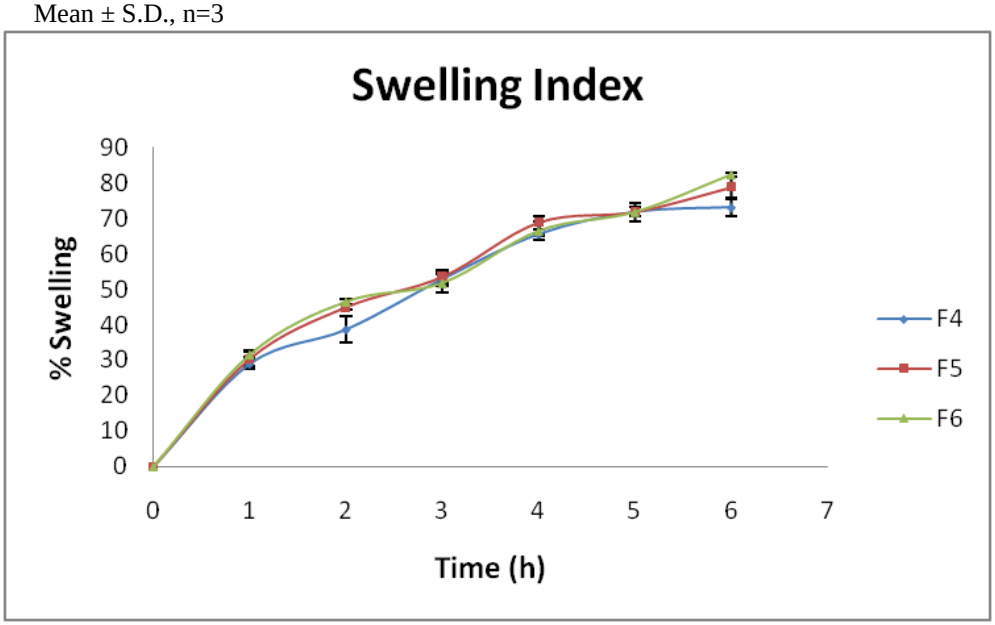


Figure no: 6.13 Results of swelling index of formulation F4 to F36

Table no: 6.6 Results of swelling index of formulations F4 to F6

Time (h)	F4	F5	F6
1	28.95±1.64	30.40±1.27	31.60±2.18
2	38.62±2.10	44.92±3.71	46.46±0.77
3	52.85±1.07	53.51±1.84	51.74±1.79
4	65.54±1.24	68.84±0.39	66.47±1.83
5	71.76±1.74	71.75±1.33	71.75±1.33
6	73.07±1.84	78.73±2.34	82.33±2.83

Mean ± S.D., n=3

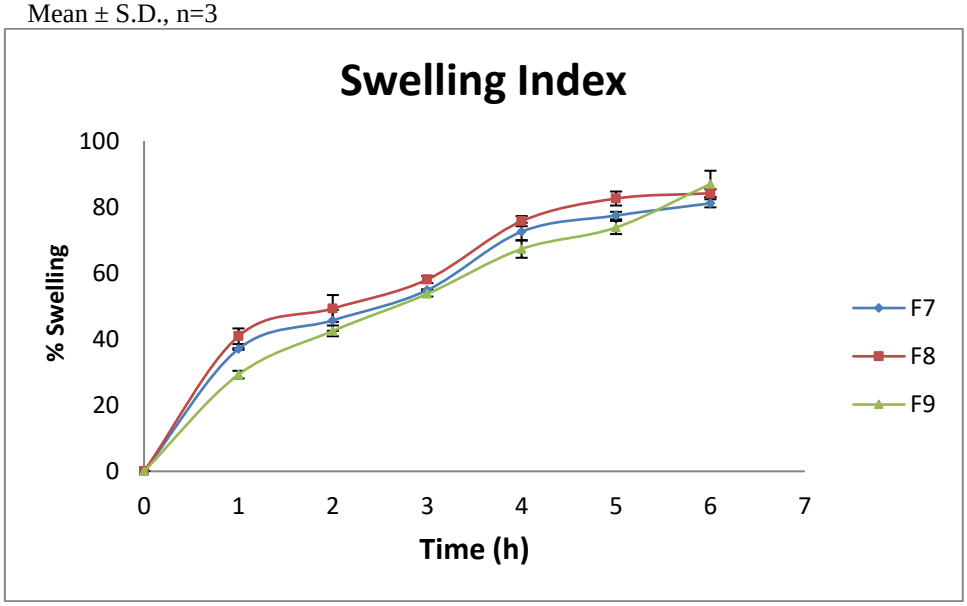


Figure no: 6.14 Results of swelling index of formulation F7 to F9

Table no: 6.7 Results of swelling index of formulations F7 to F9

Time (h)	F7	F8	F9
1	37.02±0.77	40.88±1.77	29.27±0.25
2	45.71±0.83	49.29±3.05	42.51±3.18
3	54.84±2.58	58.06±1.23	53.72±0.27
4	72.55±2.73	75.72±0.86	67.31±2.69
5	77.42±2.59	82.58±0.85	73.80±1.14
6	81.12±0.61	84.17±2.10	86.99±1.22

Mean ± S.D., n=3

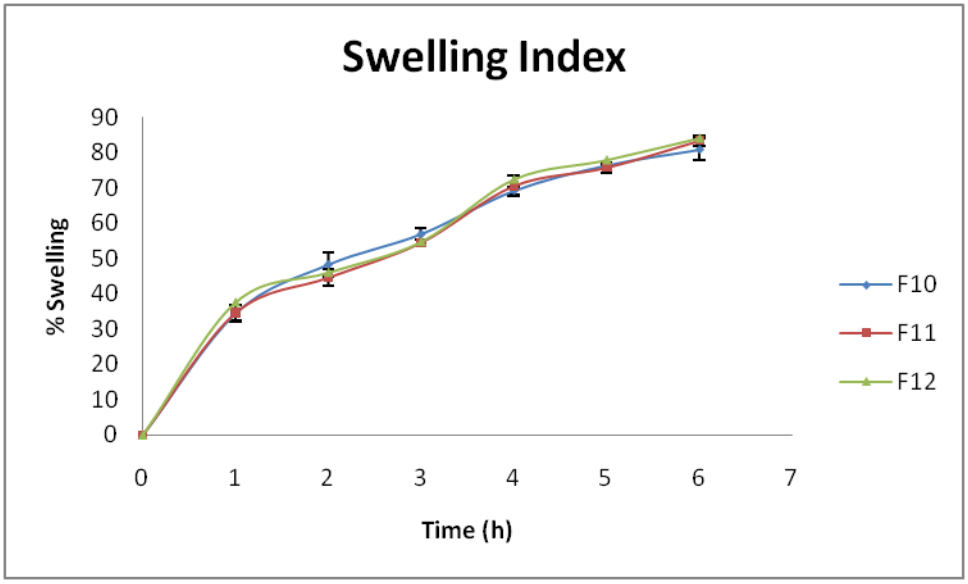


Figure no: 6.15 Results of swelling index of formulation F10 to F12

Table no. 6.8:- Results of swelling index of formulations F10 to F12

Time (h)	F10	F11	F12
1	34.49±2.37	34.63±1.16	37.62±2.32
2	48.29±4.07	44.60±1.63	46.03±2.77
3	56.93±1.09	54.51±0.82	54.76±3.35
4	69.22±1.53	70.59±2.67	72.47±3.02
5	76.41±2.12	75.77±1.99	77.97±3.92
6	80.85±1.20	83.41±4.00	84.17±2.97

Mean ± S.D., n=3

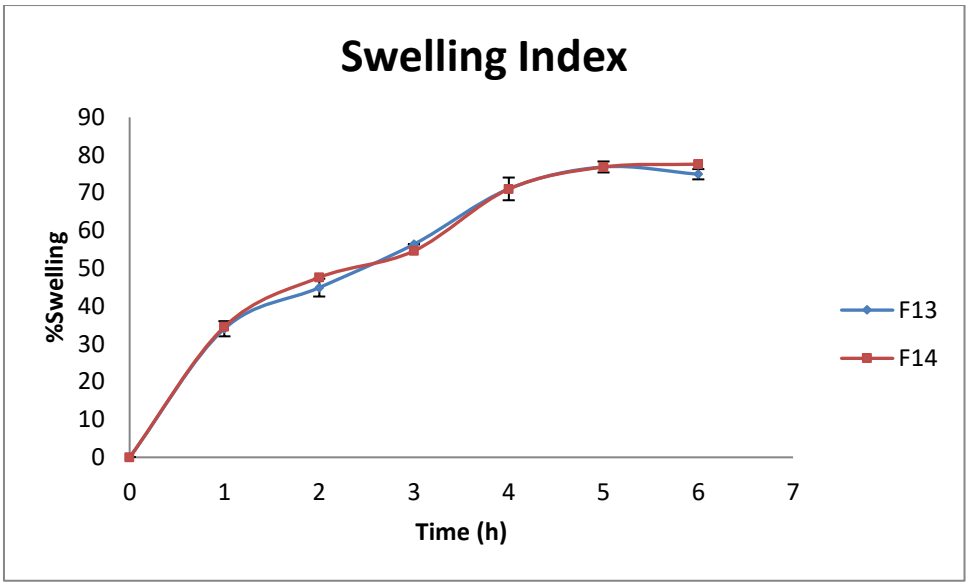


Figure no: 6.16 Results of swelling index of formulation F13 to F14

Table no: 6.9 Results of swelling index of formulations F13 to F14

Time (h)	F13	F14
1	34.04±2.31	34.56±2.01
2	44.92±3.50	47.61±2.36
3	56.40±1.66	54.63±0.06
4	71.05±1.22	71.01±3.00
5	76.86±0.52	76.84±1.46
6	74.94±3.04	77.60±1.36

The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. It was observed that the swelling indices were increased with increase in polymer concentration. The direct relationship was observed between swelling index and polymer concentration. It has been observed that the cumulative percent drug release decreases with increasing concentration of polymer and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amount of polymer. For floating the tablets, there should be appropriate balance between swelling and water uptake. It was observed that HPMC grade also affect the swelling. No effect of effervescence on the swelling index was observed. Swelling index values starts decreasing when polymer erosion starts in medium.

8.6.6. Buoyancy lag time:

Buoyancy of the tablet were influenced by both the swelling of the hydrocolloid particle on surface when it contacts the gastric fluid which in turn results in an increase in the bulk volume and porosity buoyancy lag time will increases when the hardness increases, at high compressed, reduces of porosity of tablets occurs, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result, the capability of the tablet to float is significantly reduced. The results are shown in table 6.10.

Table no: 6.10 Results of lag time and floating time

Sr. No.	Buoyancy time in seconds	Floating Time (hr)
F1	30	>12
F2	18	>12
F3	25-30	>12
F4	15-25	>12
F5	30	>12
F6	15-18	>12
F7	25-30	>12
F8	20	>12
F9	30	>12

F10	15-18	>12
F11	25-30	>12
F12	20-25	>12
F13	15-20	>12
F14	35	>12

6.6 *In-vitro* drug release studies:

6.6.1 Effect of HPMC (K4M):

In order to investigate the release rate with HPMC (K4M) this is prepared in the ratio of 1:1, 1:1.5 and 1:2.

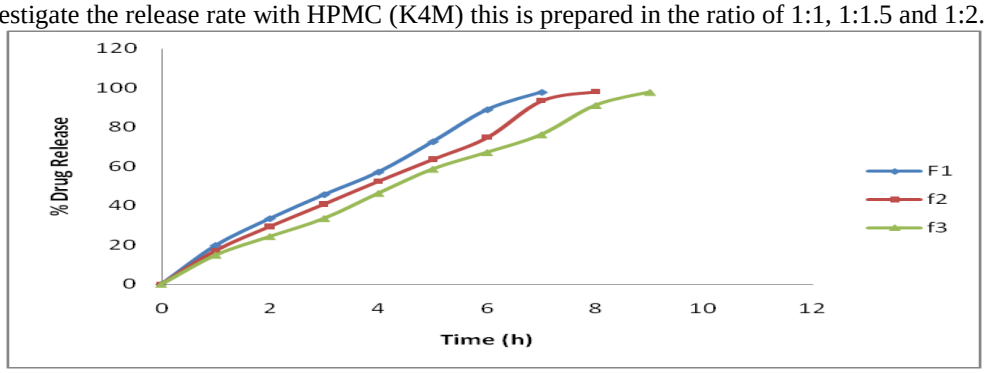


Figure no: 6.17 Results of *in-vitro* drug release rate profile of F1- F3

Table 6.11 Results of % Drug Release Rate of F1-F3

Hours	F1	F2	F3
1	19.77±0.46	17.17±0.68	14.81±1.46
2	33.49±0.26	29.45±0.27	24.30±2.77
3	45.71±0.26	40.86±0.27	33.49±2.77
4	57.20±0.64	52.51±0.67	46.32±0.95
5	72.67±0.62	63.59±0.52	58.62±0.67
6	89.01±1.64	74.74±3.27	67.09±4.54
7	97.87±0.34	93.42±0.69	76.14±5.94
8		97.98±0.11	91.06±6.05
9			97.78±1.31

Mean, ± S.D., n=3

From the figure 9 and table 10, the formulation F1 showed drug release rate 97.87 % in 7 hr, F2 showed 97.98 % drug release rate in 8 hr and F3 showed 97.78 % drug release rate in 9 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

6.6.2 Effect of HPMC (K15M):

In order to investigate the release rate with HPMC (K15M), which were prepared in the ratio 1:1, 1:1.5 and 1:2. The formulations F4-F6 were subjected to dissolution studies as shown in figure 6.18 and table 6.12.

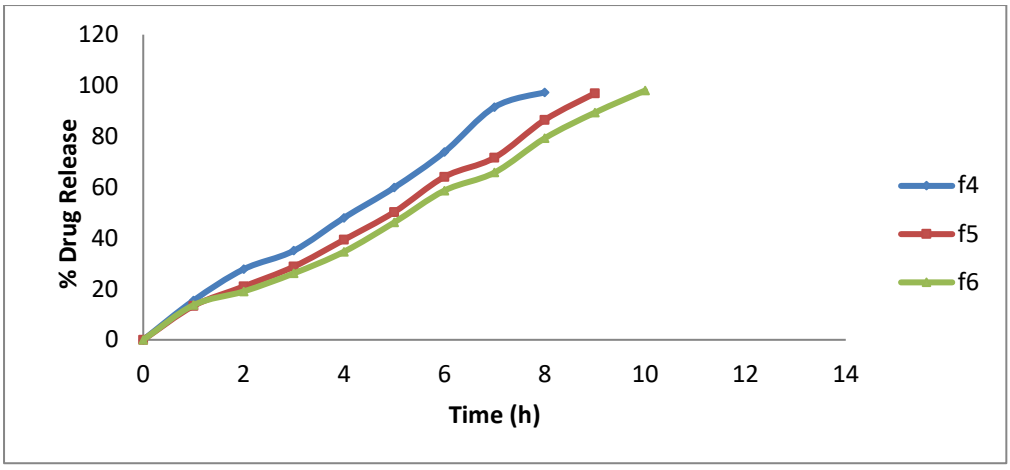


Figure no: 6.18. Results of *in-vitro* drug release rate profile of F4- F6

Table 6.12 Results of % drug release rate of F4-F6

Hours	F4	F5	F6
1	15.42±0.58	13.31±0.39	13.64±0.51
2	27.75±0.57	20.97±0.92	19.02±0.23
3	35.04±0.57	28.78±0.92	26.14±0.23
4	48.00±0.79	39.34±1.62	34.64±0.21
5	59.84±1.04	50.22±0.83	46.14±0.13
6	73.83±2.16	64.07±1.41	58.66±0.04
7	91.54±2.77	71.62±1.19	65.78±0.00
8	97.32±0.54	86.46±1.52	79.26±0.57
9		96.93±0.80	89.34±0.23
10			98.02±0.04

Mean, ± S.D., n=3

From the figure 6.18 and table 6.12, the formulation F4 showed drug release rate 97.32 % in 8 hr, F5 showed 96.93 % drug release rate in 9 hr and F6 showed 98.02 % drug release rate in 10 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

6.6.1 Effect of xantham gum:

In order to investigate the release rate with Xantham gum this is prepared in the ratio of 1:1, 1:1.5 and 1:2. The formulations F7-F9 were subjected to dissolution studies as shown in Figure 6.19 and Table 6.13.

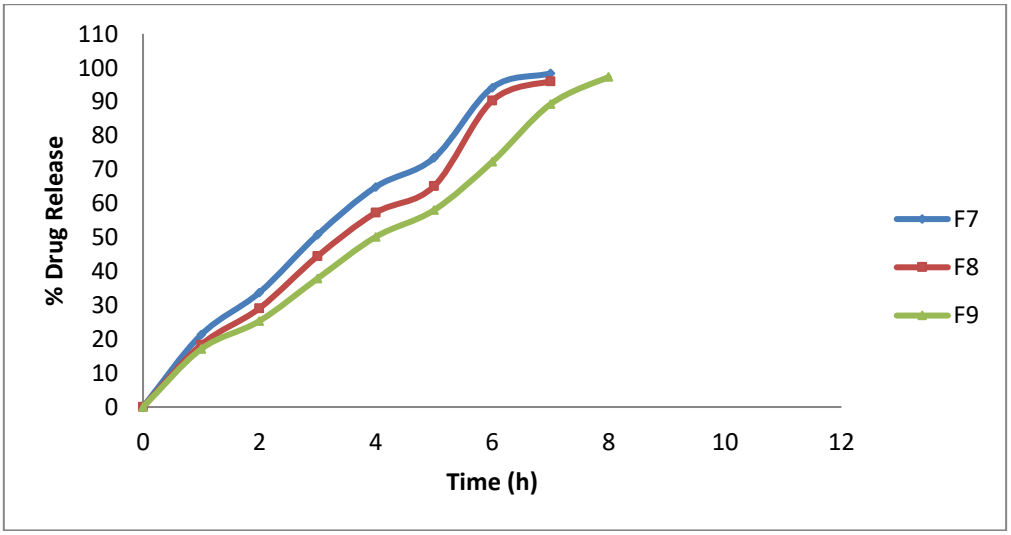


Figure no: 6.19. Results of *in-vitro* drug release rate profile of F7- F9

Table 6.13 Results of % drug release rate of F7-F9

Hours	F7	F8	F9
1	21.31±0.85	18.37±0.33	17.10±0.08
2	33.75±1.04	29.10±1.19	25.35±1.84
3	50.79±1.04	44.48±1.19	37.90±1.84
4	64.88±0.49	57.29±0.27	48.72±0.69
5	73.41±1.01	65.10±0.10	58.03±0.85
6	94.14±1.18	90.30±2.32	72.28±0.15
7	98.35±1.10	96.01±0.40	89.25±1.09
8			97.28±0.15

Mean, ± S.D., n=3

From the figure 6.19 and table 6.13, the formulation F1 showed drug release rate 98.35 % in 7 hr, F2 showed 96.01 % drug release rate in 7 hr and F3 showed 97.28 % drug release rate in 8 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

6.6.1 Effect of guar gum:

In order to investigate the release rate with HPMC (K4M) this is prepared in the ratio of 1:1, 1:1.5 and 1:2. The formulations F10-F12 were subjected to dissolution studies as shown in figure 6.20 and table 6.14.

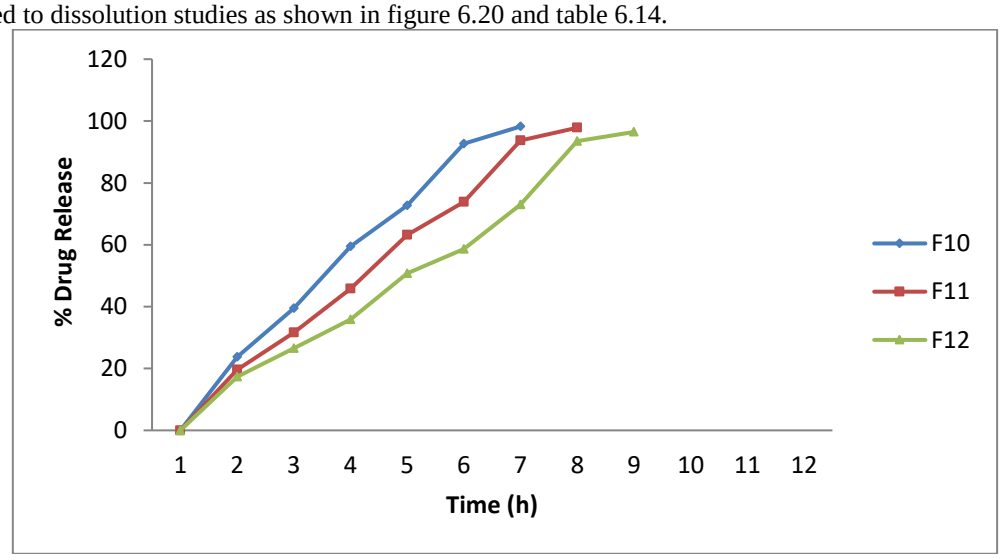


Figure no: 6.20 Results of *in-vitro* drug release rate profile of F10- F12

Table 6.14 Results of % drug release rate of F10-F12

Hours	F10	F11	F12
1	23.76±0.79	19.57±0.24	17.39±0.16
2	39.53±0.64	31.61±0.26	26.53±0.26
3	59.43±0.64	45.84±0.26	35.91±0.26
4	72.74±0.04	63.22±0.52	50.77±0.48
5	92.68±0.41	73.85±0.42	58.64±0.52
6	98.26±0.53	93.77±0.69	73.02±0.30
7		97.85±0.45	93.53±0.56
8			96.47±0.90

Mean, ± S.D., n=3

From the figure 6.20 and table 6.14, the formulation F1 showed drug release rate 98.26 % in 6 hr, F2 showed 97.85 % drug release rate in 7 hr and F3 showed 96.47 % drug release rate in 8 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

6.6.1 Effect of combination:

In order to investigate the release rate with HPMC (K4M): HPMC (K15M) and Xantham gum: Guar gum this is prepared in the ratio of 1:1.5. The formulations F13-F14 were subjected to dissolution studies as shown in figure 6.21 and table 6.15

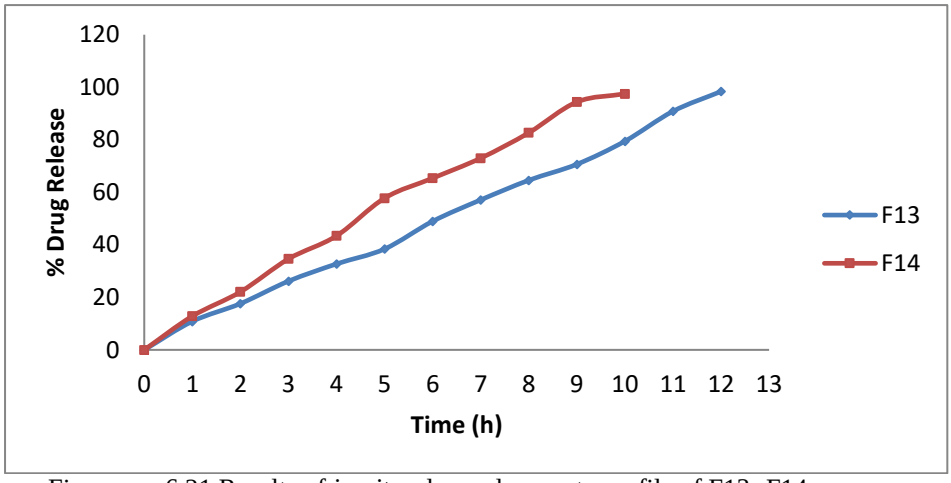


Figure no: 6.21 Results of *in-vitro* drug release rate profile of F13- F14

Table 6.15 Results of % drug release rate of F13-F14

Hours	F13	F14
1	10.84±0.43	12.83±0.61
2	17.61±1.01	22.08±0.88
3	26.16±1.01	34.62±0.88
4	32.72±1.53	43.41±1.38
5	38.42±3.52	57.77±0.85
6	48.96±1.25	65.36±0.88
7	57.12±1.04	73.00±0.75
8	64.58±0.16	82.66±1.94
9	67.13±0.15	94.38±1.48
10	79.46±0.63	97.50±0.46
11	90.84±0.79	
12	98.70±0.30	

Mean, ± S.D., n=3

The formulation F13 showed drug release rate 98.70 % in 12 hr, F14 showed 97.50 % drug release rate in 10 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

6.7. Drug release kinetics:

Dissolution data of the all formulations was fitted to various mathematical models (Zero-order, First order, matrix, Peppas and Hix. Crowell) in order to describe the kinetics of drug release rate. Higher the value of regression coefficient (R^2) was chosen as criteria for selecting the most appropriate model. The dissolution data of was found to fit well into zero order release kinetics as shown in table 6.16.

8.9 Release kinetics:

Table: 6.16 Kinetic data of captopril floating tablets

Batch code	Zero order (R)	First order (R)	Higuchi model (R)	Hixson- Crowell (R)	Korsmeyer Peppas (n)
F1	0.995	0.816	0.977	0.925	0.995
F2	0.994	0.827	0.974	0.926	0.996
F3	0.997	0.808	0.976	0.921	0.994
F4	0.994	0.817	0.960	0.936	0.989

F5	0.976	0.785	0.955	0.929	0.985
F6	0.994	0.777	0.951	0.921	0.973
F7	0.987	0.839	0.981	0.922	0.993
F8	0.989	0.844	0.961	0.946	0.988
F9	0.995	0.803	0.96	0.932	0.985
F10	0.985	0.868	0.987	0.926	0.995
F11	0.993	0.862	0.987	0.931	0.997
F12	0.99	0.829	0.953	0.945	0.982
F13	0.997	0.740	0.964	0.909	0.994
F14	0.993	0.862	0.987	0.924	0.997

6.8. Stability studies:

The optimized formulation was kept at temperature 40°C for 30 days. Then tablets were evaluated for physical properties and dissolution studies, the results are shown in table 6.17.

Table 6.17 Results of stability study

Parameters	Results
Hardness (kg/cm^2)	6.38±0.13
Thickness (mm)	3.08±0.16
% Friability (%w/w)	0.69±0.48
Weight variation (mg)	200.01±0.3
Drug Content (%w/w)	99.36±0.05

The stability study of formulation F13 showed no significant changes in the hardness, % friability, weight variation, content uniformity of the formulation.

SUMMARY AND CONCLUSION:

Gastro retentive drug delivery system is designed with the aim to target the drug to its absorption site and to maintain the dosage form at that site for an extended period of time. To develop a floating matrix tablet to prolong the gastric retention time for effective drug delivery system.

The present study is aimed to formulate floating drug delivery system using effervescent agent Sodium bicarbonate and Citric acid and the tablet continuously floats for more than 12 hrs. Floating tablet was prepared using HPMC (K4M), HPMC (K15M), Xantham gum, Guar gum by varying concentration. The blends were prepared by direct compression technique. The tablets were evaluated for hardness, thickness, drug content uniformity, swelling index, buoyancy time, *in-vitro* drug release studies for 12 hours in 0.1 N HCl i.e. pH 1.2. The concentration of Captopril released from the tablet formulations was estimated at 210.2nm using a UV spectrophotometer.

Evaluation parameters indicated that powder blend used for preparing tablets was free flowing. Tablet evaluation parameters (hardness, friability, weight variation, thickness and drug content) were within the acceptable limits.

Swelling studies were indicated significant water uptake and contributed in drug release and could be significant in gastro retention. Proper equilibrium between swelling and gel nature of the polymer provides tablet to maintain its integrity and total floating time.

The formulation F1-F3 contained a polymer HPMC (K4M) with drug and polymer ratio 1:1, 1:1.5 and 1:2 respectively and drug release rate was 97.87 %, 97.98 % and 97.78 % in 12 h.From the dissolution study, it was observed that the rate and extent of drug release decreases with increase in polymer concentration.

The formulation F4-F6contained a polymer HPMC (K15M) with drug and polymer ratio 1:1, 1:1.5 and 1:2 respectively and drug release rate was 97.32 %, 96.93 % and98.02 % in 12 h.From the dissolution study, it was observed that the rate and extent of drug release decreases with increase in polymer concentration.

The formulation F7-F9contained a polymer Xantham gum with drug and polymer ratio 1:1, 1:1.5 and 1:2 respectively and drug release rate was 98.35 %, 96.01 % and 97.28 % in 12 h.From the dissolution study, it was observed that the rate and extent of drug release decreases with increase in polymer concentration.

The formulation F10-F12contained a polymer Xantham gum with drug and polymer ratio 1:1, 1:1.5 and 1:2 respectively and drug release rate was 98.26 %, 97.85 % and 96.47 % in 12 h.From the dissolution study, it was observed that the rate and extent of drug release decreases with increase in polymer concentration.

The formulation F13contained a polymer HPMC (K4M)+HPMC (K15M) in combination with drug and polymer ratio 1:1.5 and drug release rate was 98.70 % in 12 h.formulation F14contained a polymer Xanthamgum+Guar gum in combination with drug and polymer ratio 1:1.5 and drug release rate was 97.50 % in 12 hrs.From the dissolution study, it was observed that the rate and extent of drug release decreases with increase in polymer concentration.

The formulation F13 shows a desire drug release rate and from the results, it could be considered as optimized formulation of floating drug delivery system for captopril.

The stability study of formulation F13 showed no significant changes in its physical properties.

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