FORMULATION DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF ORAL FLOATING *IN SITU* GELLING LIQUID SYSTEM OF LOSARTAN POTASSIUM

A Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY
CHENNAI –600032

In partial fulfilment of the requirements

for the award of the Degree of

MASTER OF PHARMACY
IN PHARMACEUTICS

Submitted by

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OCTOBER 2021

DEPARTMENT OF PHARMACEUTICS
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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION DEVELOPMENT AND INVITRO CHARACTERIZATION OF ORAL FLOATING INSITU GELLING LIQUID SYSTEM OF LOSARTAN POTASSIUM"** submitted by **Reg. No: 261911259** to The Tamil Nadu Dr. M.G.R Medical university examinations is evaluated.

EXAMINERS

1.

Place: Chennai – 03
Date:

2.

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Place: Chennai-03

Date:

(Dr. A. JERAD SURESH, M. Pharm., Ph.D., M.B.A)

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Place: Chennai-03

Date:

(Mr. K. RAMESH KUMAR, M. Pharm.)

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"GIVE THANKS TO THE LORD, FOR HE IS GOOD, HIS LOVE ENDURES FOREVER."

- **PSALM 107:1**

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ABBREVIATIONS AND SYMBOLS

CR	Controlled Release
ER	Extended Release
SR	Sustained Release
SGF	Simulated Gastric Fluid
GIT	Gastrointestinal Tract
ODD	Oral Drug delivery
GRDDS	Gastroretentive Drug Delivery system
MMC	Migrating Myoelectric Complex
GRT	Gastric Retention time
FDDS	Floating Drug Delivery system
HPMC	Hydroxy Propyl Methyl Cellulose
GERD	Gastro Esophageal Reflux Disease
GRDF	Gastroretentive Dosage Form
BP	Blood Pressure
mmHg	Millimeter of Mercury
oz	Ounce
ACE	Angiotensin Converting Enzyme
PVA	Polyvinyl Alcohol
HEC	Hydroxy Ethyl Cellulose
Co_2	Carbon- di- oxide
$CaCo_3$	Calcium Carbonate
cps	Centipoise
AUC	Area Under Curve
RPM	Revolutions per minute
w/v	Weight/volume
v/v	Volume/volume
λ_{max}	Wavelength with maximum absorbance
BP	British Pharmacopoeia
IP	Indian Pharmacopoeia
HCL	Hydrochloric acid
USP	United states pharmacopoeia

USP-NF	United States Pharmacopoeia
PhEur	European Pharmacopoeia
NC	No Change
FTIR	Fourier Transform Infra-Red Spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
KBr	Potassium Bromide
API	Active Pharmaceutical Ingredient
RH	Relative Humidity
UV	Ultra violet
Vis	Visible
%	Percentage
º	Degree
º	Degree Celsius
cm	Centimeter
hrs	Hours
L	Litre
ml	Millilitre
M.W	Molecular Weight
g	Gram
mg	Miligram
min	Minutes
nm	Nanometer
sec	Seconds
µg	Microgram
ICH	International Council for Harmonization
pH	Negative logarithm of hydrogen ion concentration
WHO	World Health Organization

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1.1. ORAL DRUG DELIVERY SYSTEM[1]

An oral drug delivery system is believed to provide continuous oral release of the drug throughout the course of its gastrointestinal (GI) transit. Oral drug delivery (ODD) is the most preferred and convenient route of drug administration due to high patient compliance, cost-effectiveness, least sterility constraints, flexibility in the design of dosage form and ease of production. More than 60% of drugs are formulated in the form of oral products.

1.2. DOSAGE FORMS [1,2]

Dosage forms are the means by which drug molecules are delivered to the sites of action within the body. Drug substances are formulated in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical functions. The proper design and formulation of a dosage form requiresconsideration of the physical, chemical and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer and safe.

1.2.1 Types of dosage forms[1]

Based on the physical form, dosage forms are classified as:

1. Solid dosage forms
   - Powders, Tablets, Capsules
2. Liquid dosage forms
   - Syrup, Solution, Emulsion, Suspension
3. Semisolid dosage forms
   - Paste, Gel, Suppositories
4. Gaseous dosage forms
   - Inhalers, Aerosols

1.3. LIQUID DOSAGE FORMS[1,2]

Liquid preparations for oral use are usually solutions, emulsions or suspensions containing one or more active ingredients in a suitable vehicle; in some cases, they may consist simply of a liquid active ingredient used as such. The vehicle for any liquid preparation for oral use is chosen in regard to the nature of the active ingredients and to provide organoleptic characteristics appropriate to the intended use of the preparation. Liquid preparations for oral use may containsuitable antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing, flavoring and sweetening agents and authorized coloring matter. Liquid preparations for oral use may be supplied as multidose or as single-dose preparations. Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume.

1.3.1. ADVANTAGES OF ORAL LIQUIDS[3]

- Ease of dose adjustment by dilution, thus making it easier to swallow than solids and acceptable for pediatric and geriatric use.
- Immediate drug availability after absorption, hence faster therapeutic response than the solid formulations, which has to disintegrate for the drugto be dissolved in the gastrointestinal fluid before the absorption begins.
- Liquid dosage forms being homogenous systems, the drug will be uniformly dispersed in the preparation.
- Due to immediate dilution by the gastric contents it reduces the gastric irritation.

1.3.2. DISADVANTAGES OF LIQUID PREPARATIONS[3]

- Liquids being bulky are inconvenient to transport and store.
- The stability of drug is poor when formulated as liquids than that of solids like tablets or capsules, especially if the drugs are susceptible to hydrolysis. Hence shelf life of the formulations is shorter.
- Preservatives are necessary as the solutions are widely prone to microbial growth.

1.4. STOMACH - AN OVERVIEW[5,6,7]

The stomach is a J shaped enlargement of GIT directly inferior to the diaphragm in epigastric, umbilical and left hypochondriac regions of the abdomen. It connects oesophagus to the duodenum, the first part of the small intestine and provides a barrier to the delivery of drugs to the small intestine.

1.4.1 ANATOMY OF STOMACH[5,6]

The stomach has four main regions: 1) Cardia (2) Fundus (3) Body (4) Pylorus (Fig 1.1).

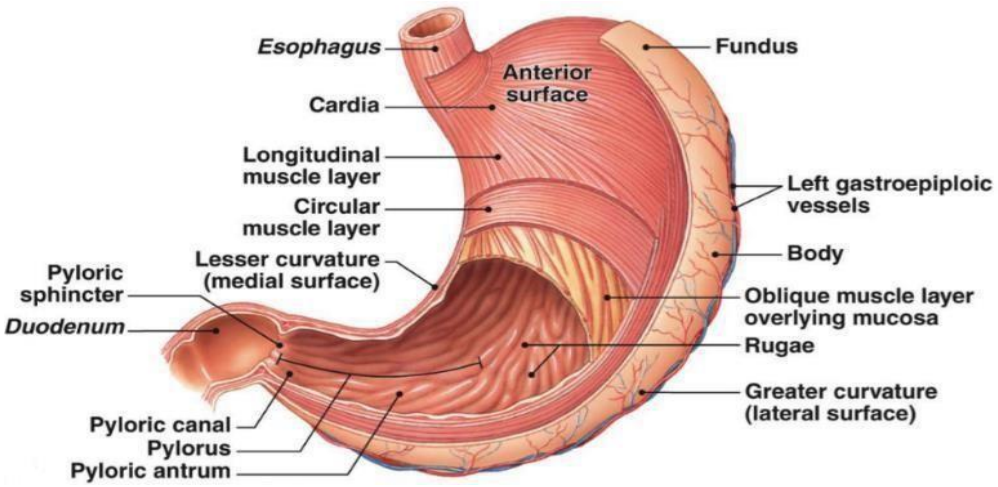


Fig 1.1 Anatomy of the stomach

GASTRIC EMPTYING[1,7,8]

Gastric emptying rate (GER) is the speed with which substances leave the stomach after ingestion. Liquids are retained for the shortest period, followed by small, then large solid particles. GER is also affected by food-specific factors including fat content. The process of gastric emptying happens both during fastingand fed state. In the fasted state, it is categorized by an interdigestive cycle both through the stomach and small intestine, every 2-3 hours. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC). It is composed of four phases as shown in Fig 1.2 and as described in Table 1.1.

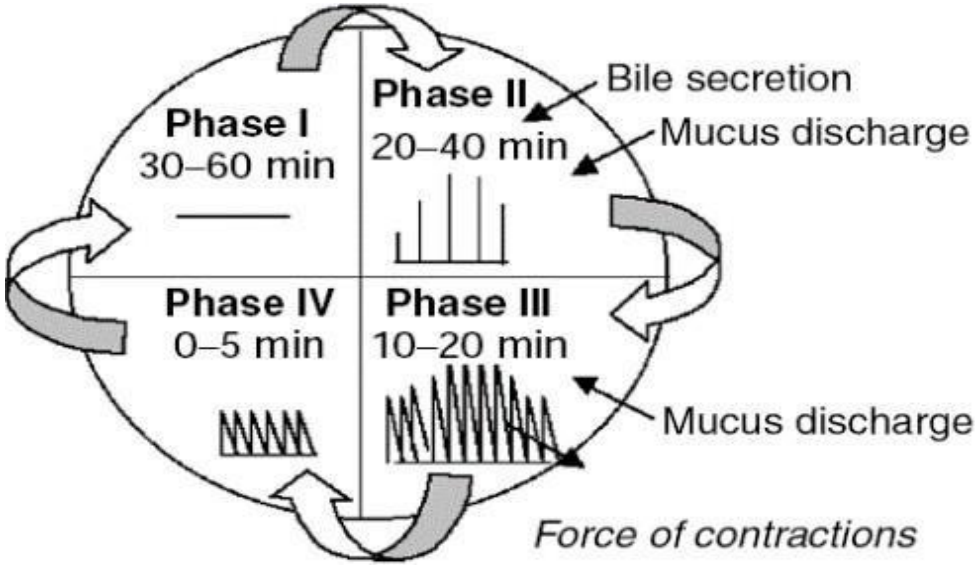


Fig 1.2 Phases of Gastric emptying

Table 1.1 Different Phases of Gastric Emptying

Phase	**Duration**
Phase-I (Basal Phase)	30-60 min with infrequent contractions
Phase-II (PreburstPhase)	20-40 min with irregular action potentialand contractions
Phase-III(Burst Phase)	10-20 min with intense and regular contractions for short periods. This phase sweeps undigested material form stomach to the small intestine.
Phase – IV	0-5 min and happens between phase three and one oftwo successive cycles

After the digestion of mixed meal, the pattern of contractions changes from fasted to fed state. This is also recognized as digestive motility pattern and contains endless contractions as in phase II of fasted state. The contractions result in decreasing the size of food particles (<1 mm), which are propelled towards the pylorus in the suspension form. Throughout the fed state, onset of Migrating myoelectric compass (MMC) is postponed resulting in a slowdown of the gastric emptying rate.

Scintigraphy studies including the measurements of the gastric emptying rate in healthy human subjects have discovered that an orally administered controlled release dosage form is primarily subject to two physiological difficulties:

1. Short GRT

2. Unpredictable gastric emptying rate

Yet another major difficulty encountered through the oral route is first pass effect thatleads to decreased systemic bioavailability of numerous drugs.

1.5. GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)[9,10,11]

Drugs which are easily absorbed from the gastrointestinal tract and those withshort half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastroretentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby, reducing the dosing frequency are being formulated. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner. If the drugs are poorly soluble in intestine because of alkaline pH, gastric retention may improve the solubility before they are emptied, resulting in GI absorption of drugs with narrow therapeutic absorption window and also monitoring the release of drugs that have site specific-absorption limitation. Drugs that might take benefit of gastric retention contain the drugs whose solubility is fewer in the higher pH of the small intestine than stomach (E.g., Cinnarizine, Chlordiazepoxide, etc.), the drugs prone to degradation in intestinal pH (E.g., Captopril), and drugs for local action in stomach(E.g., Misoprostol).

Gastroretentive drug delivery systems extend the dosing intervals and therefore improve patient compliance. The presence of drug in solution form is an important requisite for the drug to get absorbed. But if the drug solubility is poor, the time required for drug to dissolve within stomach will be high and transit time becomes most severe factor, which might consequently affect the absorption of the drug. So, dose of administration of such drugs should be kept at repeated intervals in a single day. Different approaches to Gastroretentive drug delivery are shown in Fig 1.3

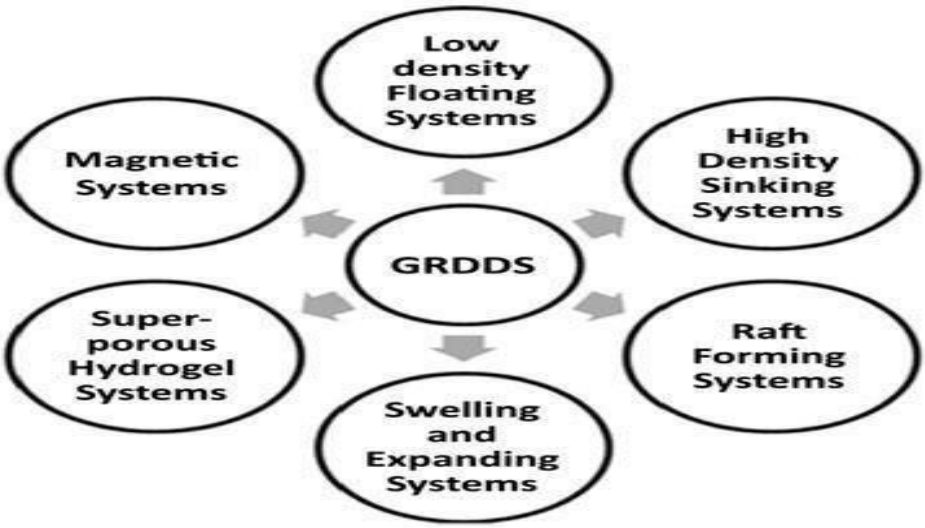


Fig 1.3 Approaches to GRDDS

Need of Gastroretentive Drug Delivery Systems[12]

Oral dosage forms pose low bioavailability problems because of their fast-gastric transition from the stomach, particularly in case of drugs that are less soluble at the alkaline pH of the intestine. Also, the drugs that produce their local action in the stomach get quickly emptied and do not get sufficient residence time in the stomach. Therefore, frequency of dose administration in such condition is increased. To avoid such problems, floating drug delivery system has been developed.

1.5.1. Factors Affecting Gastric Retention[9,12,13,14]

1. **Density:** Gastric retention time (GRT) is a function of dosage form buoyancy which is dependent on the density. The density of the dosage form must be lower than the gastric contents (1.004gm/cm^3).

2. **Size:** Dosage form units having a diameter of greater than 7.50 mm are stated to have an improved GRT related with those having a diameter of 9.90 mm.

3. **Shape of the dosage form:** Tetrahedron and ring-shaped devices having a flexural modulus of 48 and 22.50 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

4. **Single or Multiple unit formulation:** Multiple unit formulations show a more expectable release profile and insignificant damaging of performance because of

failure of units and allow co-administration of units that have dissimilar release profiles related with single unit dosage form.

5. **Fed/Unfed state:** In fasting conditions, gastrointestinal motility is categorized by periods of strong motor activity that occurs every 1.5 to 2h and if timing of administration of the formulation overlaps with that of the MMC, the gastric retention time of unit can be anticipated to be very short. However, in fed state, MMC is postponed and gastric retention time is significantly longer.

6. **Nature of meal:** Feeding of fatty acid salts or indigestible polymers can modify the motility pattern of stomach to a fed state, hence reducing the gastric emptying rate.

7. **Caloric content:** GRT can be improved by 4 to 10 h with a meal which is high in proteins and fats.

8. **Age:** Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.

9. **Frequency of feed:** Gastric retention time can rise by over 400 minutes, when consecutive meals are given related with a single meal because of the low frequency of MMC.

10. **Gender:** Mean ambulatory gastric retention time in males (3.4 ± 0.6 hours) isless correlated with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, body surface and height.

11. **Posture:** Gastric retention time can be differing between supine and upright ambulatory states of patients.

12. **Concomitant drug administration:** Anticholinergics like Atropine and Propentheline increase the GRT. Metoclopramide and Cisapride decreaseGRT.

13. **Disease state:** Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

Advantages of Gastroretentive Drug Delivery System[8,15,16]

- Maintenance of constant therapeutic level over longer period of time.

  E.g. Betalactum antibiotics.

- Enhanced bioavailability of drugs. E.g., Enhancement of bioavailability of controlled release gastroretentive dosage forms (CR-GRDF) of riboflavin in comparison of non-CR-GRDF polymeric formulation.

- Gastroretentive dosage form improves patient compliance by decreasing dosing frequency.

- Minimizing mucosal irritation of drugs, by releasing drug slowly at a controlled rate. E.g. NSAIDs

- Treatment of GI disorders like GERD, Helicobacter pylori infection.

- Floating drug delivery system is a feasible approach for the drugs that have limited absorption in the intestine.

- The floating drug delivery system can reduce the counter activity of body, leading to higher drug efficiency.

- For drugs that have comparatively short half-life, sustained release may result in a flip-flop pharmacokinetics.

- The floating drug delivery systems are beneficial for drugs that are absorbed through stomach. E.g. Antacids, Ferrous salts, etc.

- Sustained release drug delivery system reduces dosing frequency of drugs with short half-life.

Disadvantages of Gastroretentive Drug Delivery Systems[12,16,17]

- Drugs that undergo significant first pass metabolism, are not desirable candidates.

- Drugs having solubility or stability problems in the highly acidic gastric environment cannot be formulated as GRDDS.

- For swellable systems, the dosage forms must maintain size larger than the aperture of the resting pylorus for the required time period.

- These systems do not offer important advantages over the conventional dosage forms of drugs, which are absorbed throughout the gastrointestinal tract.
- Some drugs cause irritation to the gastric mucosa.
- Violent gas generation, disintegration of dosage forms, burst release, dose dumping, and alkaline microenvironment are the limitations for floating drug delivery.
- Patients cannot be dosed these formulations just before going to bed.
- It is effective only when the fluid level in the stomach is sufficiently high.
- However, as the stomach empties and the dosage form are at the pylorus, the buoyancy of the dosage form may be impeded.
- The major challenge for a bio adhesive system is the high turnover rate of gastric mucus. There is also the possibility of oesophageal binding with bio adhesive drug delivery systems. The Hydrogel based swelling system takeslonger time to swell.

1.6. STOMACH SPECIFIC FLOATING DRUG DELIVERY SYSTEM (FDDS)[15,18]

Stomach specific FDDS has a bulk density lesser than gastric fluids and therefore remain buoyant in the stomach without altering the gastric emptying rate for a longer period of time. However, as the system floats on gastric contents, the drug is released gradually at a preferred rate from the system. After releasing drug, the residual system is emptied from stomach. It results in an increased gastric residence time and a better control of variations in plasma drug concentration. The floating dosage forms present most of the characteristics of hydrophilic matrices and called 'hydrodynamically balanced systems' (HBS) as they are able to preserve their low apparent density however the polymer hydrates and builds a gelled barrier on the outer surface. The drug is released gradually from the swollen matrix, as in case of conventional hydrophilic matrices. These forms are anticipated to remain buoyant (3-4 hrs.) on the gastric contents without altering the intrinsic rate of emptying because their bulk density is lesser than that of the gastric contents. Amongst the different hydrocolloids suggested for floating form formulations, cellulose ether polymers are common, particularly hydroxyl propyl methyl cellulose (HPMC). A

fatty material with bulk density <1 may be added to the formulation to increase the buoyancy and reduce the water intake rate.

Similar to formulation studies, research has been done on humans and animals to evaluate intragastric retention performances of floating forms. These calculations were realized either directly by gamma scintigraphy and X-ray monitoring of the forms transit in the GIT or indirectly by pharmacokinetic studies with drug tracer.

1.6.1. Mechanism of Floating Drug Delivery System[15,19]

Various attempts have been made to increase the gastric retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high- density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate 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. A minimal gastric content is needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side.

$$F = (Df - Ds)\, gv$$

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

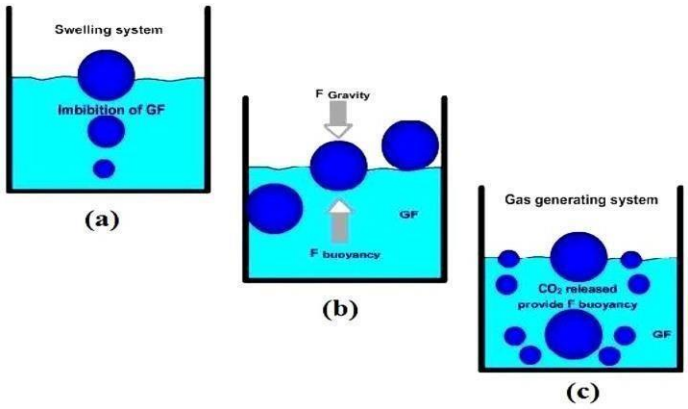


Fig 1.4 Mechanism of floating system in Gastric Fluid

a) Swelling system b) Non-Effervescent system c) Effervescent system

Classification of FDDS

Effervescent Systems

a) Volatile liquid containing system

b) Gas-generating system

A. Non- effervescent Systems

a) Colloidal gel barrier system

b) Alginate beads

c) Hollow microspheres

d) Intragastric/ Microporous compartment system

B. Raft- forming Systems

A. EFFERVESCENT SYSTEMS[9,20]

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gas

entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

a. Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

b. Gas-generating systems:

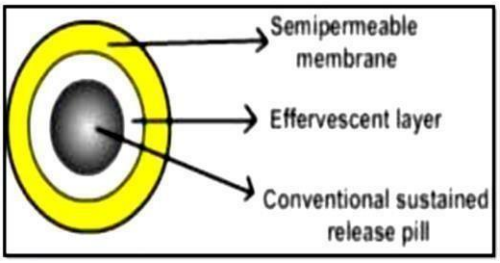


Fig 1.5 Different layers (i) Semi-permeable membrane, (ii) EffervescentLayer (iii) Core pill layer

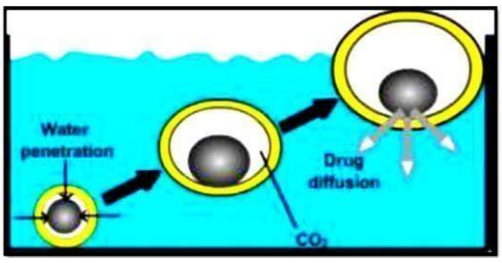


Fig 1.6 Mechanism of floatation via CO_2 generation.

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the systems, thus decreasing its specific gravity and making it to float over chyme.

B. NON-EFFERVESCENT SYSTEM [19]

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The swollen gel-like structure that is formed acts as a reservoir and allow sustained release of drug through the gelatinous mass.

a) Colloidal gel barrier systems: Hydrodynamically balance system (HBS) was first designed by Sheth and Tossounian in 1975. Such systems contain drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids. E.g., HEC, HPMC, Na-CMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to the dosage forms.

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

Hollow Microspheres: Hollow microspheres are regarded as the most promising buoyant systems, as they have exclusive advantages of multiple unit systems and also better floating properties, due to central hollow space inside microsphere. The general methods involved in their preparation consist of simple

solvent evaporation, solvent diffusion and evaporation. The drug release and better floating properties generally depend on plasticizer, type of polymer and solvents employed for preparation. Polymers like cellulose acetate and Eudragit are used in preparation of hollow microspheres, and drug release can be moderated by enhancing polymer quantity and polymer plasticizer ratio.

c) Intragastric / Microporous compartment system: In this type of systems, drug reservoir is encapsulated inside a micro porous compartment with pores along its top and bottom surfaces. To prevent any direct contact of gastric mucosal surface, the peripheral walls of the drug reservoir compartment are completely sealed. In stomach, the entrapped air of floatation chamber causes the delivery system to float over the gastric contents. Gastric fluid enters the system only through the pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

C. RAFT FORMING SYSTEMS

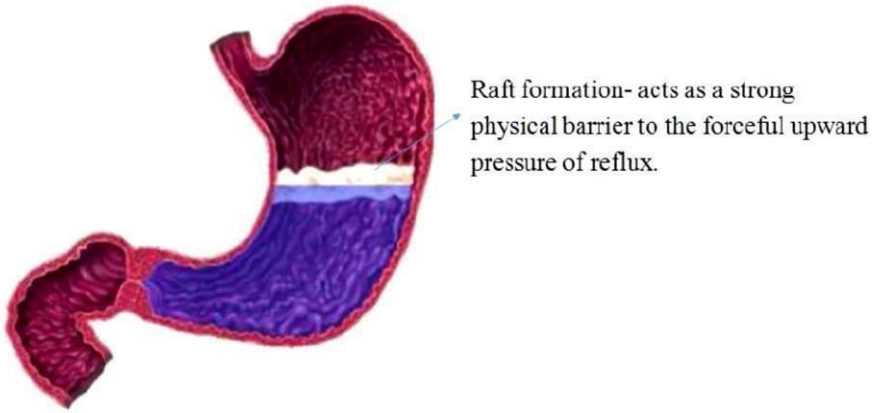


Fig 1.7 Raft forming system

These systems have established much attention for delivery of antacids and drug delivery for GI disorders and infections. The mechanism complied in the raft formation contains the development of viscous cohesive gel in contact with GI fluids, in which each portion of liquid swells forming a continuous layer known as raft. The raft floats on gastric fluids due to low bulk density produced by the development of CO_2. Generally, the system comprises a gel forming agent and alkaline carbonates or bicarbonates liable for the development of CO_2 to make the system fewer dense and float on the GI fluids. Antacid raft forming floating system comprises gel forming

agent, acid neutralizer and sodium bicarbonate that forms a foaming sodium alginate gel when in contact with GI fluids. The raft thus formedas shown in Fig. 1.10, floats on GI fluids and stops the reflux of the GI contents into the oesophagus by acting as a barrier amongst the oesophagus and stomach.

1.7 IN SITU GELLING SYSTEMS [21]

In situ is a Latin word which means 'In its original place or in position'. *In situ* gelling systems are polymeric formulations that are in sol forms before entering in the body, but change to gel forms under the physiological conditions. The sol- gel transition depends on one or a combination of different stimuli, like pH change, temperature modulation, solvent exchange, ultra violet irradiation andthe presence of specific ions or molecules. Drug delivery systems having such properties can be widely used for sustained delivery vehicle preparation of the bioactive molecules. Some important advantages of these smart systems are easeof application and reduced frequency of administration, as well as protection of drug from environmental condition changes. Various natural and synthetic polymers undergo *In situ* gel forming which can potentially be used for oral, buccal, rectal, vaginal, ocular, intraperitoneal and parenteral drug delivery.

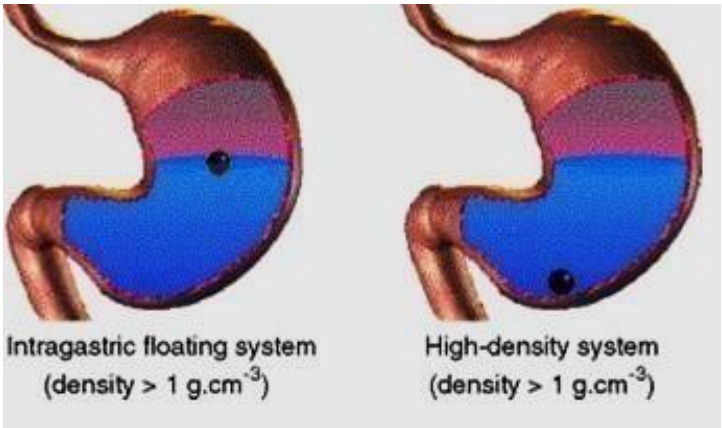


Fig 1.8 Floating systems

In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel

transition upon administration. Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a 3D network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified (based onthe nature of the bonds involved in the 3D solid network): chemical gels arises when strong covalent bonds hold the network together and physical gels when hydrogen bonds, electrostatic and van der Waals interaction maintain the gel network.

Gastroretentive floating *In situ* gel refers to a polymer solution of low viscosity which upon coming in contact with the gastric fluids undergoes change in polymeric conformation and a viscous strong gel of density lower than the gastric fluids.

1.7.1. Approaches of Designing *In situ* Gel System [22,23,24]

I) Physically induced *In situ* gel systems

A. Swelling: *In situ* gel formation occurs when material absorbs water from surrounding environment and expands to give the desired space. Example of substance is myverol 18-99 (glycerol mono-oleate), which is a polar lipid that swells in water to form liquid crystalline phase structures. It has some bio-adhesive properties and can be degraded *in vivo* by enzymaticaction[37].

B. Diffusion: This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be a useful solvent for such system.

***In situ* gel formation due to ion activated system**

Here gelling of the instilled solution is induced by the change in ionic strength. Itis believed that the osmotic gradient across the surface of the gel determines the rate of gelation. In presence of mono and divalent cations typically present in the tear fluids, the aqueous polymer solution forms a clear gel. The electrolyte presents in the tear fluid, especially Na^{+}, Ca^{2+} and Mg^{2+} cations play an important role in initiation of gelling when the solution is instilled in the conjunctival cul- de-sac. Polymers that exhibit osmotically induced gelation include Gelrite or Gellan gum, Hyaluronic acid, alginates etc.

II) Chemically induced *In situ* gel systems

A. Ionic cross linking: Certain ion sensitive polysaccharides such as Iota carrageenan, Gellan gum, Pectin, Sodium alginate undergo phase transition in presence of various ions such as K^+, Ca^{2+}, Mg^{2+}, Na^+. *In situ* gel formation involves administration of aqueous liquid solutions, once it is administered they form a gel under certain conditions involving the use of gelling agent which can form a system that contain the dispersed drug and other excipients. The gelling of this system is achieved by ionic complexation that contain divalent-ions complexes with Sodium citrate which breakdown in acidic environment of stomach to release free divalent ions (Ca^{2+}) due to change in pH. The free Ca^{2+} ions get entrapped in polymeric chains thereby causing cross linking of polymer chains to form matrix structure causing the *In situ* gelation of orally administered solution as shown in the equation[44]:

Sodium citrate + $NaHCO_3$ + $CaCl_2$ ----------→ Ca Citrate

Ca Citrate ----------→ Complex acidic environment Ca^{2+} + COO^-

In situ gel involves formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations & hydrogen bonding with water. While the system is floating in the stomach the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

B. Enzymatic cross linking: *In situ* gel formation catalyzed by natural enzymes. For example, cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin. Thus, adjusting the amount of enzyme controls the rate of gel formation, which allows the mixtures to be injected before gel formation.

C. Photo-polymerization: A solution of monomers such as acrylate or other polymerizable functional groups and initiator can be injected into tissue site and the application of electromagnetic radiation is used to form gel designed to be readily degraded by chemical or enzymatic processes or can be designed for long term persistence *in vivo*. Typically, long wavelength ultraviolet and visible

wavelengths are used, while short wavelength ultraviolet is not used because it has limited penetration of tissue and biologically harmful.

D. *In situ* gel formation based on Physiological stimuli

A. Temperature dependent *In situ* gelling: Temperature sensitive polymers are most extensively studied class of environmentally responsive polymer systems in drug delivery. This is because temperature is relatively easy to control and also easily applicable to both *in vitro* and *in vivo*. In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drugrelease. These hydrogels exist in liquid form at room temperature (20- 25°C) and undergo gelation when comes in contact with body fluid (35-37°C). The use of biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach *In situ* gel formation. The best critical temperature range for such systems is ambient and physiologic temperature; such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation. Three main strategies are used in engineering the thermosensitive sol-gel polymeric system. Hence, they are classified into

- Negatively thermosensitive, which contract upon heating
- Positively thermosensitive, which contract upon cooling

Polymers which show temperature induced gelation are poloxamers/pluronics, cellulose derivatives [HPMC, ethyl hydroxyethylcellulose (EHEC), methyl cellulose], xyloglucan, tetronics, etc.

B. pH dependent *In situ* gelling: Another physiological stimulus that induces formation of *In situ* gel is pH. Polymers included in this class contain an acidicor a basic group that either accept or release protons when they are exposed to different environmental pH. Hence these are called pH sensitive polymers. This type of mechanism is mostly used for ocular drug delivery system. The increase in the precorneal residence time of drug and consequently better bioavailability can be achieved by using *In situ* gelling systems. At pH 4.4, the formulation exists as a normal solution, but at pH 7.4, i.e., the pH of tear fluid, gelation occurs. The polymers having a large number of ionizable groups are

called as polyelectrolyte. In case of weakly acidic groups (anionic), increase in swelling of hydrogel with increase in external pH is observed, whereas polymers containing basic (cationic) groups exhibit decreased swelling. Most of the pH sensitive polymers containing anionic group are based on PAA (Carbopol®, Carbomer) and its derivatives. Whereas at neutral pH conditions, polyvinyl acetal diethyl aminoacetate (AEA) solutions which have a low viscosity at pH 4, forms hydrogel. Other polymers which show pH induced gelation are cellulose acetate phthalate (CAP) latex, poly methacrylic acid (PMMA), polyethylene glycol (PEG), pseudo latexes, etc.

Mechanisms of Drug Release from *In situ* Gel System[28,29]

Diffusion- controlled mechanism:

A. Matrix system: The active agent is homogenously dispersed as a solid into a hydrogel inert bio-degradable polymers matrix. The release of drug depends on:

- Diffusion of water into the matrix followed by the dissolution of the drug and finally the diffusion of the dissolved drug from the matrix.
- Polymers interact with drugs leading to modulate the release of the drug.
- Thickness of the hydrated matrix is considered as the diffusional path length of the drug. If we consider the polymer matrix to be inert and the drug release is diffusion- controlled, then the release rate of the drug could be described by Higuchi equation.

B. Reservoir devices: The drug is contained in a core (often termed as reservoir) which is surrounded by a rate-controlling polymeric membrane of hydrogel which allows the diffusion of drug. As the system comes in contact with water, water diffuses into the system and dissolves the drug, and then drug transport (from the core through the external polymer membrane) occurs by dissolution at one interface of the membrane and diffusion driven by a gradient in thermodynamic activity. Drug transport can be described by Fick's first law, if the activity of the drug in the reservoir remains constant and infinite sink conditions are maintained, then the drug release rate may be continued to be constant since it depends on the membrane permeability and it will be independent of time, thus zero-order

kinetics can be achieved. Once drug is exhausted, the release becomes concentration dependent following first order kinetics. These kinds of drug delivery systems are mainly used to deliver the active agent by oral routes.

1.7.1.1. Swelling-controlled mechanism[25]

A. **Solvent activated system**: It occurs when diffusion of drug is faster than hydrogel swelling. When a hydrogel is placed in an aqueous solution, water molecules will penetrate into the polymer network that occupy some space, and as a result some meshes of the network will start expanding, allowing other water molecules to enter within the network. For example, the release of drugs from (HPMC) hydrogel is commonly modeled using this mechanism.

B. **Osmotic swelling**: For hydrogels, the total swelling pressure of gel could be related to volume fraction, relaxed volume of network, and cross-link density while it is independent on gel pH and swelling time.

1.7.1.2. Chemically-controlled mechanism

It can be categorized according to the type of chemical reaction occurring during drug release within a delivery matrix.

A. **Pendant chain system** is the most common reaction where the drug is covalently attached to a polymer backbone. The bond between the drug and the polymer is labile and can be broken by hydrolysis or enzymatic degradation and then the drug release.

B. **Erodible drug delivery system** where the release of the drug is controlled by the dissolution during surface-erosion or bulk-degradation of the polymer backbone, then the drug diffuses from erodible system.

Depending on whether diffusion or polymer degradation controls the release rate, the drug is released following different mechanisms; if erosion of polymer is much slower than diffusion of the drug through the polymer, then drug release can be treated as diffusion-controlled process. While if diffusion of the drug from the polymer matrix is very slow, then polymer degradation or erosion is the predominate mechanism, for example hydrophobic erodible.

Criteria of Drugs Suitable for *In situ* Gel Drug Delivery System[15,26]

- Drugs that act primarily in the stomach like Misoprostol.
- Drugs that are primarily absorbed from the stomach like Amoxicillin trihydrate.
- Drugs those are poorly soluble at alkaline pH like Verapamil HCl and Diazepam.
- Drugs with a narrow window of absorption like Levodopa and cyclosporine.
- Drugs that degrade in the colon like Ranitidine and Metformin.
- Drugs that disturb normal colonic microbes like Ampicillin.

Criteria of Drugs Unsuitable For *In Situ* Gel Drug Delivery System[15,26]

- Drugs that have very limited acid solubility e.g. (Phenytoin).
- Drugs that suffer instability in the gastric environment e.g.(Erythromycin)
- Drugs intended for selective release in the colon e.g.(Corticosteroids).
- Drugs that are absorbed along entire GIT, which under go first-pass metabolism e.g. (Nifedipine, Propranolol).

1.7.1. Advantages of *In situ* gelling system[27]

- *In situ* gels shows ease of administration and good patient compliance.
- It shows increased gastric retention with slow drug release.
- It reduces dosing frequency.
- It shows local action and site specificity by acting directly onto the targetedsite.
- It shows less adverse effects compared to other pharmacological dosageforms.

1.7.2. Disadvantages of *In situ* gelling system[24]

- It is more susceptible to stability problems due to chemical degradation.
- It requires high level of fluids.

1. **Dindayal Darunde et al., (2020)[7]** performed a review on floating In Situ gelling system Dosage form with prolonged gastric retention and its compatibility with stomach physiology is the real challenge. So in order to achieve gastric retention various approaches have been done from several years. Out of which floating in-situ drug delivery system is the most promising technique which undergo sol to gel transition in acidic medium of stomach and provide site specific release for longer duration of time by floating on the surface of gastric fluid, due to which its contact time with gastric mucosa is increased. In situ gel have good stability and biocompatibility characteristics and better drug release which make it more reliable dosage form over the conventional one.

2. **Shaikh Siraj N et al., (2020)[88]** designed, developed and evaluated gastric floating In Situ gel of Piroxicam using Sodium Alginate, HPMC K 200 M and other ingredients. Most of the formulations floated within 1 min. All the formulations exhibited a basic pH in the range of 6.7 to 7.9 which is suitable for oral consumption and gastric delivery. Increasing the calcium carbonate content in the formulation simultaneously increased the viscosity at all polymer concentrations.

3. **Pashikanti SP et al.[20] (2019)** developed floating *In situ* gel formulations of Ciprofloxacin using varying concentrations of sodium alginate as *In situ* gel forming bio-degradable polymer and calcium carbonate as a cross-linking agent. Floating lag time of all formulations was between 32-70 seconds and floated for >12 hr. The *In vitro* gelling capacity increased with increasing the polymer and gelling agent concentrations. Increase in polymer concentration decreased the rate and extent of the drug release. Formulation containing 4% w/v of sodium alginate and 4% w/v of calcium carbonate showed sustained *in vitro* drug release (95.6%) over an extended period of 12 hr. They concluded that the drug release from the formulations followed First order kinetics with Fickian diffusion.

4. **Rohith Ganapathi Bhatta et al., (2019)[68]** formulated, optimized and evaluated in situ gelling liquid oral formulation of a novel Antidiabetic drug Canagliflozin. The effect of two independent factors namely concentration of sodium alginate and concentration of gas generating agent calcium carbonate on responses like floating lag time, viscosity and in-vitro drug release were considered for the optimization by plotting three-dimensional surface response plots. By considering the effect of calcium cations on the gelling properties of various concentration of sodium alginate, it was concluded that the effective gelling was achieved in the formulation comprised of 1 % sodium alginate with 0.5 %, 1.0 % and 1.5 % of calcium carbonate.

5. **Marwa A. Amer et al., (2019)[59]** performed development and evaluation of liquid oral controlled release systems for Losartan potassium by combination of the enteric coating technique with the in-situ gelling system is a promising strategy to develop a liquid oral sustained release system with close control of the release rate both in the gastric and intestine.

6. **Khan N.A et al., (2019)[57]** developed in situ gel of Losartan potassium was achieved through formulation designing of various formulations using various combinations of polymers and a cross linking agent. Optimization of the prepared formulations for gelling capacity and floating behaviour and evaluation of optimized formulations.

7. **Ashutosh Padhan et al., (2019)[1]** presented an review on floating oral In Situ gel in which they discussed the various approaches to produce gastro retention of drug delivery system, with special discussion on floating in-situ gel system for stomach specific drug delivery. As it offers several advantages like sustained and prolonged action in comparison to conventional drug delivery systems and increases the bioavailability of drug as well as produce patient compliance by reducing dosing frequency.

8. **Ramesh Pareek et al., (2019)[65]** developed sustained release of Glatifloxacin by using floating oral in situ gelling system using sodium alginate as gelling polymer and HPMC as thickening agent with a potential of H. Pylori

eradication. The formulations were evaluated on the basis of Pharmacopoeial specification. Clarity, visual appearance, pH, gelling capacity, viscosity, gelation, buoyancy, water uptake, density of gel, gel strength, drug content, assessment of drug release, release kinetics were carried out as per specifications and results were found to be complied with the Pharmacopoeial specification. The findings of prepared in situ gelling formulations of Gatifloxacin increased the gastric residence time and also float in the gastric condition.

9. **Solanki R et al., (2018)**[22] formulated and evaluated Floatable In Situ gel of Ofloxacin using different concentrations of HPMC K4M, HPMC K15M and HPMC K100M. On the basis of the results, they observed that if the final concentration of the CaCo3 increases, then it decreases the lag time for floating and if there is increase in concentration of sodium alginate and HPMCK4M, the vicosity increases. They concluded that Ofloxacin In Situ gel formulation has better performance than conventional formulation and also makes better compliance and improve efficacy.

10. **Adimoolam S et al., (2017)**[23] formulated and evaluated Diclofenac sodium *In situ* gelling system by fenugreek seed mucilage. Eight diclofenac sodium *In situ* gel formulations F1- F8 were formulated using different combinations of sodium alginate with Fenugreek seed mucilage and HPMC K4M together with other excipients and evaluated for floating properties and *in vitro* drug release. They concluded that it follows zero order kinetics and fit to Korsmeyer-Peppas model with release exponentof 0.6434, revealed non-fickian diffusion mechanism.

11. **Wiwattanapatapee R et al., (2017)**[24] developed and evaluated floating *In situ* gel for oral delivery of Propranolol HCl using three different types of main gelling polymers - Sodium alginate, Pectin and Gellan gum. HPMC K4M was used as the additional polymer to provide a sustained drug release pattern of formulations. They concluded that selected formulations formed gels and floated in the acidic medium with a sustained release pattern of Propranolol over an 8 hr period.

12. **Vineetha K et al., (2017)[25]** investigated Biodegradable injectable *In situ* Gelling Implantable system of Rivastigmine tartrate that provided prolonged drug release as an approach in the long term management of Alzheimer's disease and *ex vivo* drug permeation studies for over 27 h exhibited slower release patterns from the selected formulations as compared to *in vitro* release.

13. **Samyuktha Metta et al., (2017)[58]** performed invitro dissolution studies of gastroretentive floating tablets of Losartan potassium. It had been founded that increase in polymer concentration diminished drug release profile, the invitro cumulative percentage drug release of all formulations ranged from 79.92% -95.89% at the end of 10 hours with more than 12 hrs buoyancy. The invitro drug release followed 1st order kinetics and drug release mechanism was found to be non-ficksian type.

14. **Pasumarthy N. V. Gopal et al., (2017)[80]** presented a review on Gellan gum a multifunctional excipient in drug delivery. Gellan gum is one of the most widely explored one in the development of gels, microspheres, hydrogels, etc. Gellan gum's unique gelling properties in different vehicles have made it a cynosure among various natural gums these days. This review focuses on most recent literature on the use of gellan gum in optimizing drug release in various pharmaceutical dosage forms.

15. **Shastri D et al., (2016)[26]** developed and evaluated a Gastroretentive *In situ* oral gel of Cefuroxime axetil using Sodium alginate and Pectin as the ionic dependent gel forming polymer. Calcium chloride was used as complexing agent to increase cross linking alongwith sodium citrate. Mucoadhesion was enhanced with the help of polymer HPMCK4M. The *In situ* gel system was evaluated for the content uniformity, pH, gelling capacity, viscosity of gel, *in vitro* drug release and mucoadhesion study. Optimized formula showed more than 24% drug release after 1 hour and prolonged release up to 12 hours and optimum viscosity. The results revealed that as the concentration of Sodium alginate was directly proportional to mucoadhesion, hence *In situ* oral gel is a better formulation in terms of ease of administration, better patient compliance and prolonged gastro retention.

16. **Devasani SR et al., (2016)**[27] presented an overview of In Situ gelling systems in which they have explained the various approaches, polymers used in In Situ gels, methods of preparation, applications and evaluation parameter s involved in the formulation of In Situ gels. They concluded that use of biodegradable and water-soluble polymers for the In Situ gel formulations makes them more acceptable and excellent drug delivery system.

17. **Nikode S et al., (2016)**[28] presented a brief introduction to *In situ* gels, various approaches for *In situ* gelling system They described various biodegradable polymers that are used for the formation of *In situ* gels include Pectin, Guar Gum, Carbopol, Xyloglucan, Gellan Gum, Alginic Acid, Xanthum Gum, Chitosan, HPMC, Poloxamer etc. administered by oral ocular, rectal, vaginal, injectable and intraperitoneal routes.

18. **Tandle RL et al., (2016)**[29] presented a detailed review of Gastroretentive *In situ G*el Formulation System in which they have emphasized on the various approaches for *In situ* gel preparation and many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-coglycolide) and poly-caprolactone etc. used in the preparation of *In situ* gelling system.

19. **Rewar S et al., (2015)**[31] explained the novel approaches for floating drug delivery systems such as floating drug delivery systems (FDDS), swelling and expanding systems, bio-adhesive systems, modified shape systems, effervescent system, high density systems or other delayed gastric emptying devices. They concluded that we are as close as we have ever been to see a greater transition of gastric retention devicesfrom developmental level to the manufacturing and commercial level.

20. **Nautiya U et al., (2015)**[32] presented a review on gastroretentive drug delivery systems in which they have stressed about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastroretentive drug delivery systems. They

concluded that these systems not only provide controlled release of the drug but also present the drug in an absorbable form at the regions of optimal absorption.

21. **Vidyadhara Suryadevara et al., (2014)[87]** formulated and evaluated Losartan Potassium osmotic controlled matrix tablets. Losartan potassium matrix tablets were prepared by direct compression process using HPMC K 15M as polymeric material and mannitol as osmogen at varied concentrations. The matrix tablets were further coated with different compositions of ethylcellulose7cps and PEG-4000 by pan coating method. Physical parameters such as weight uniformity, drug content, hardness and friability were evaluated for uncoated tablets and were found to be within I.P limits.

22. **Thomas LM et al., (2014)[33]** performed the formulation and evaluation of floating oral In Situ gel of Metronidazole by using sodium alginate along with varying concentrations of methyl cellulose, hydroxy propyl methyl cellulose or sodium carboxy methyl cellulose and gas forming agent calcium carbonate and sodium bicarbonate. They concluded the prepared formulations appeared to be promising drug delivery system for localized delivery of Metronidazole for the better treatment of peptic ulcer disease caused by H. pylori.

23. **Patel R.P et al., (2010)[75]** formulated, optimized and evaluated sodium alginate based In Situ gel of Clarithromycin and Metronidazole benzoate. Sodium alginate was used as a polymer and calcium carbonate was used as a cross-linking agent, these formulations exhibited good viscosity properties and sustained drug release and explained accelerated stability studies.

24. **Madan M et al., (2009)[74]** formulated and developed *In situ* forming polymeric drug delivery systems by using various types of polymers including gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly caprolactone, poly (DL-lactic acid), poly (DL-lactide- glycoside) etc. and also explained selection of solvents (water, dimethylsulphoxide, N- methyl pyrrolidone,2-pyrrolidone etc.) depends on the solubility of polymers.

25. **Ramesh CN et al., (2009)[71]** developed, evaluated and optimised the *In situ* gel formulation by using 3^3 factorial design to retain in the stomach for extended period of time based on the three independent factors: concentrations of like gellan gum (X1), sodium alginate (X2) and anti-diabetic drug Metformin (X3). Three-dimensional surface response plots were drawn to evaluate the interaction of independent variables on the chosen dependent variables. Three factorial levels coded for low, medium and high settings (−1, 0 and +1, respectively) were considered for three independent values.

3.1 AIM

To develop a stable oral, gastroretentive *In situ* gelling liquid formulation of Losartan potassium for the treatment of hypertension, thereby providing ease of administration, reducing the frequency of dosing and thus better patient compliance.

3.2 PLAN OF WORK

- To carry out preformulation studies.
- To select suitable type and quantity of polymers along with other excipients for developing floating *In situ* gel of Losartan potassium.
- To develop optimized oral floating in situ gelling system of Losartan potassium, thereby increasing patient compliance.
- To carry out in vitro characterization of the optimized formulations.
- To achieve controlled release of the drug for a long period to reduce the frequency of dosing.
- To carry out stability studies on the most satisfactory formulation as per ICH guidelines.

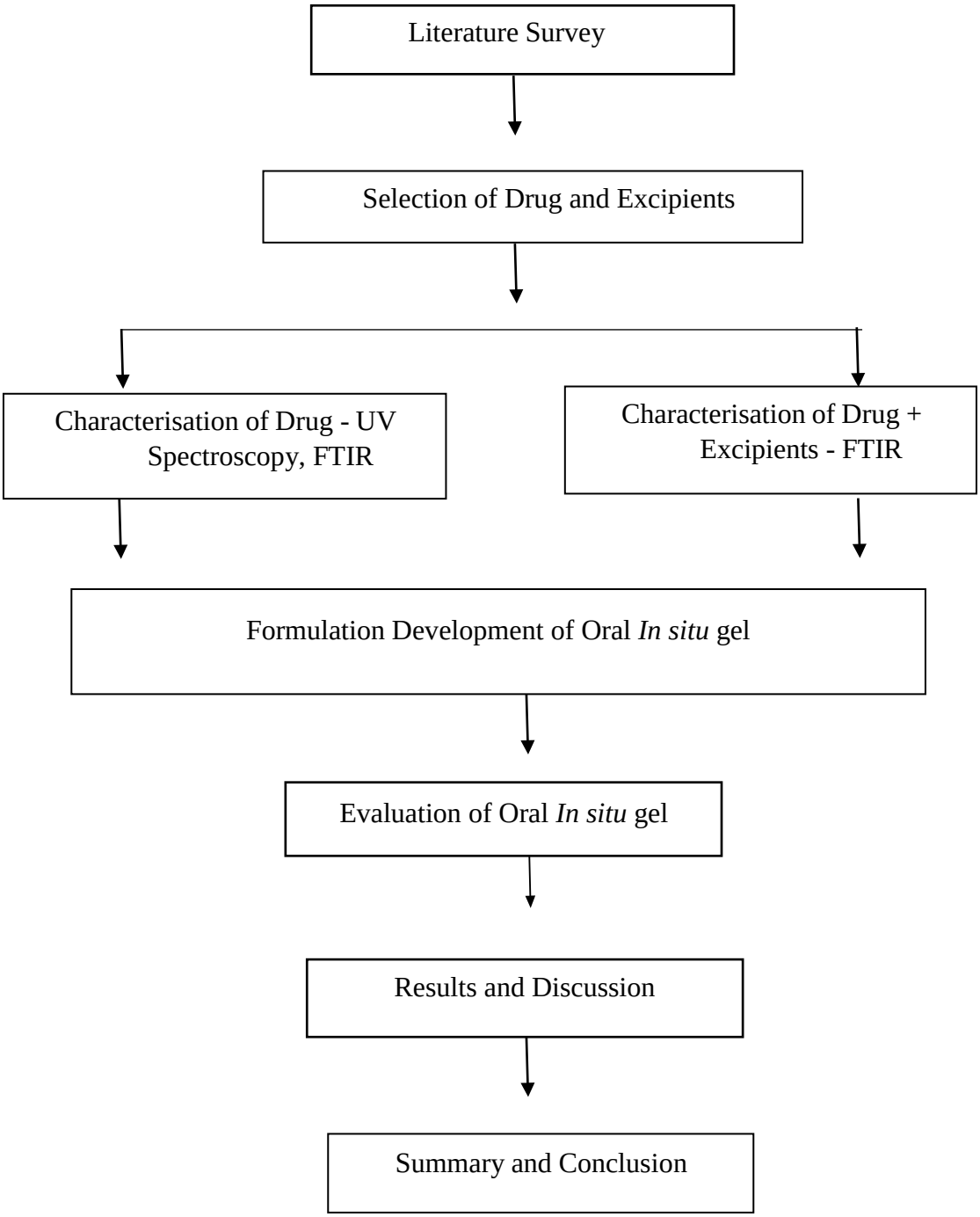


Fig 3.1 Plan of work

4.1. RATIONALE FOR THE SELECTION OF DOSAGE FORM[11, 19, 29]

- Oral drug administration still remains the route of choice for the majority of clinical applications.
- *In situ* gel forming systems have been widely investigated as vehicles for controlled drug delivery. It is preferred that a liquid drug polymer formulation would gel at the targeted site. Drug retention and bioavailability can be achieved by gelation.
- The gel formed from *In situ* gelling system, being lighter than gastric fluids, floats overthe stomach contents, produces gastric retention of the dosage form and increase gastric residence time, resulting in prolonged drug delivery in gastrointestinal tract.

4.2. RATIONALE FOR THE SELECTION OF DRUG[4]

- Losartan potassium is one of the Anti-hypertensive drug. It is a competitive antagonist and inverse agonist. It is more selective for AT2 receptor. All over actions of Ang II viz., vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adrenaline from adrenals, renal actions promoting salt and water reabsorption. Central actions like thirst, vasopressin release and growth promoting actions on heart and blood vessels are blocked.
- Losartan potassium has elimination half-life of about 2hrs. The efficacy of losartan is dose-related, with the total oral dose of 50mg/day. Oral absorption of Losartan is not affected by food, but bioavailability is only 33% due to first pass metabolism.
- The daily dosage-regimen associated with a drug tends to reduce its patient compliance. Thus, an optimal product would seek to provide the advantages of extended gastroretentive release of Losartan potassium.

4.3. RATIONALE FOR SELECTION OF GELLING AGENT[30,31,32]

- **Gellan gum** is an anionic deacetylated exocellular polysaccharide. It has the tendency of gelation which is cations induced.
- **Iota-carrageenan** forms elastic gels mainly in the presence of Ca^{2+}. The formulation consists of these gelling agents with calcium carbonate (or) calcium chloride and sodium citrate complex.
- When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of the polymers thus forming a gel *In situ*. **HPMC K4M** has been used as a release retardant.

5. DISEASE PROFILE:[33,34,35,36]

Hypertension is one of the most serious concerns of modern medical practices. Hypertension is a serious cardiovascular event which refers to rise in the arterial blood pressure. Due to raised blood pressure, heart has to work harder in order to pump adequate amount of blood to cope up with normal body functioning. If the same is not treated, it may lead to heart-related problems and may damage the organs like kidney, brain, and eyes. It is as such not a disease in itself but is a risk factor for major cardiovascular events like heart stroke, ischemic heart disease, myocardial infarction, and heart enlargement. According to WHO, Geneva, in 2008, hypertension resulted in 45% mortality rate because of ischemic heart disease and 51% mortality rate because of stroke. In 1980, 600 million people were suffering from hypertension while in 2008 this graph was raised to 1 billion raising a big concern for dealing with this condition effectively (WHO, 2013).

Table 5.1. Classification of Hypertension

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110

5.1 ETIOLOGY

Hypertension is either due to some cause or without identifiable cause. There are two types of hypertension.

1. Primary hypertension

2. Secondary hypertension

5.2 TYPES OF HYPERTENSION

Renal hypertension

Renal diseases like renal vascular hypertension produce renal hypertension, which is associated with the renal artery. Renal hypertension may be produced by any one of three interrelated mechanisms

a) Activation of Renin- Angiotensin system.

b) Sodium and water retention.

c) Decreased release of vasodepressor materials.

Endocrine hypertension

A number of hormonal secretions may produce secondary hypertension like Adrenal glands, parathyroid glands and oral contraceptives. Usually, hyper secretion of tumor of endocrine glands; e.g. Cushing's syndrome, primary hyper aldosteronism, Pheochromocytoma and oral contraceptives, use may lead to release of Angiotensin I.

Neurogenic

Psychogenic polyneuritis, increased intracranial hypertension and secretion of spinal cord are the uncommon causes of secondary hypertension.

Contraction of Aorta

It causes secondary hypertension in the upper part of the body due to constriction. Diastolic hypertension results from changes in circulation.

5.3 RISK FACTORS:

5.3.1 BEHAVIORAL RISK FACTORS

There are many behavioral risk factors for the development of hypertension including:

- Consumption of food containing too much salt and fat, and not eating enough fruit and vegetables
- Harmful levels of alcohol use
- Physical inactivity and lack of exercise
- Poor stress management.

5.3.2 Socio-economic factors

Social determinants of health, e.g., income, education and housing, have an adverse impact on behavioral risk factors and in this way influence the development of hypertension.

5.4 SYMPTOMS OF HIGH BLOOD PRESSURE

There is a common misconception that people with hypertension always experience symptoms, but the reality is that most hypertensive people have no symptoms at all. Sometimes hypertension causes symptoms such as,

- Headache
- Shortness of breath
- Dizziness
- Chest pain
- Palpitations of the heart
- Nose bleeds

It can be dangerous to ignore such symptoms, but neither can they be relied upon to signify hypertension. Hypertension is a serious warning sign that significant lifestyle changes are required. The condition can be a silent killer and it is important for everybody to know their blood pressure reading.

5.5 TREATMENT

- Diuretics
- Angiotensin Converting Enzymes (ACE) inhibitors
- Alpha adrenergic receptor blockers
- Beta adrenergic receptor blockers
- Calcium Channel Blockers
- Central adrenergic inhibitors
- Vasodilators

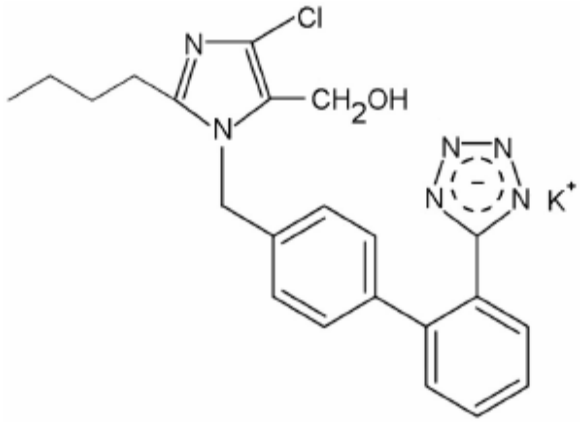
5.6 LIFE STYLE MODIFICATIONS

- Adoption of healthy lifestyles by all patients is an indispensable part of the management of all with hypertension and alone is sufficient for individuals with high normal blood pressure.
- Dietary approach – Diet rich in fruits and vegetables and low in fat, diary products, cholesterol, saturated and total fat.

- Regular physical activity – brisk walking atleast 30 minutes per day, most days of the week.
- Alcohol intake (preferably avoided)
  - Men – not more than 1 oz (30 ml).
  - Women – not more than 0.5 oz.
- Patients should be strongly counseled to quit smoking.

Name : Losartan potassium
Category : Angiotensin II Type 1 Receptor Blockers

Structure :



Physiochemical properties[37,38,39,40]

Molecular weight **:** 461.0 gm/ mol

Molecular formula **:** C_{22} H $_{22}$ Cl K N_6 O

IUPAC name **:** [2-butyl-4-chloro-1-[[2´-(1H-tertrazol-5-yl)[1,1´-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol.

Melting point **:** 268-271ºC

Solubility **:** Soluble in water, soluble in alcohols and slightly soluble in common organic solvents

Log P value **:** 4.48

Pharmacokinetics

Bioavailability **:** 33%

Half-life **:** 2hrs

Volume of distribution **:** 34 L

Protein binding **:** 98%

Metabolism **:** More selective AT2 receptor blocker.

Elimination **:** Oral administration about 4% of the doses excreted unchanged in the urine and about 6% is excreted in urine as active metabolite.

6.1. MECHANISM OF ACTION [34,36]

It is a competitive antagonist and inverse agonist, 10,000 times more selective for AT1 than for AT2 receptor; does not block any other receptor or ion channel, except thromboxane A2 receptor (has some platelet antiaggregatory property). All overt actions of Ang II, viz. vaso-constriction, central and peripheral sympathetic stimulation, release of aldosterone and Adrenaline from adrenals, renal actions promoting salt and water reabsorption, central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels are blocked. No inhibition of ACE has been noted.

Pharmacologically, ARBs differ from ACE inhibitors in the following ways:

- They do not interfere with degradation of bradykinin and other ACE substrates: rise in level or potentiation of bradykinin, substance P occurs. Consequently, ACE inhibitor related cough is rare.
- They result in more complete inhibition of AT1 receptor activation, because response to Ang II generated via alternative pathways and consequent AT1 receptor activation (which remain intact with ACE inhibitors) are also blocked.

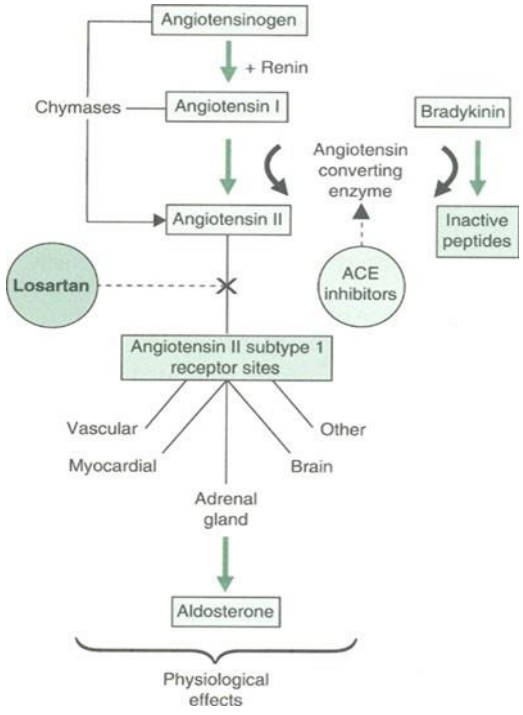


Fig 6.1 Mechanism of Action

7.1. GELLANGUM[41,42,43,44]

1. **Synonyms**

   Gum Gellan, Kelcogel, Gelrite, Phytagel, Gel-Gro.

2. **Chemical Structure:**

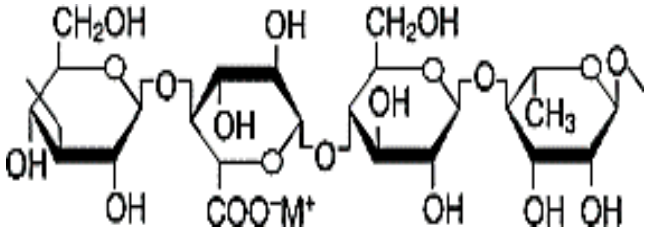


Fig 7.1 Structure of gellan gum

3. **Molecular weight:** 646.5442 g/mol.
4. **Functional Category**

   Gellan gum is a food additive that acts as a thickening or gelling agent.

5. **Description**

   Gellan gum is water soluble high molecular weight polysaccharide that is composed of repeating monosaccharide units, which appears as white to tan powder.

6. **Solubility**

   Soluble in hot water, forming viscous solution and becoming paste at higher concentrations greater than about 5%, Partially soluble in cold water and insoluble in non-polar organic solvent.

7. **Odour/Taste** **:** None.
8. **Melting Point** **:** Decomposes without melting > 250ºC.
9. **Solution pH** **:** 4.5 – 6.5 (as a 1%solution)
10. **Particle size** **:** 355µm –600µm.

11. **Chemical properties**

    Gellan gum is an anionic polysaccharide. It forms gels with polycations. It is used inthe concentration range of 1.5 to 2.25% in the preparation of oral medicated jellies.

12. Applications:

- **Ophthalmic delivery:** Low acetyl gellan gum has been used to devise novelophthalmic formulations, significantly improving drug ocular bioavailability resulting from the unique gelling property of gellan gum in the presence of tear fluidifications.
- **Nasal delivery:** It has been suggested than gellan gum is a promising polymer for use in nasal formulation.
- **Oral delivery:** Gellan gum is widely being used in the preparation of microspheresand *in situ* gels for prolonged drug delivery.

7.2. IOTACARRAGEENAN[45,46,47]

1. **Nonproprietary name**

   USP-NF **:** Carrageenan

2. **Synonyms**

   Chondrus extract; Gelcarin; Genu; Grindsted; Hygum TP-1; Irish moss extract;Marine Colloids; SeaSpen PF; Viscarin.

3. **Chemical Names** **:** Carrageenan; i-Carrageenan; k-Carrageenan; l-Carrageenan.

4. **Chemical Structure:**

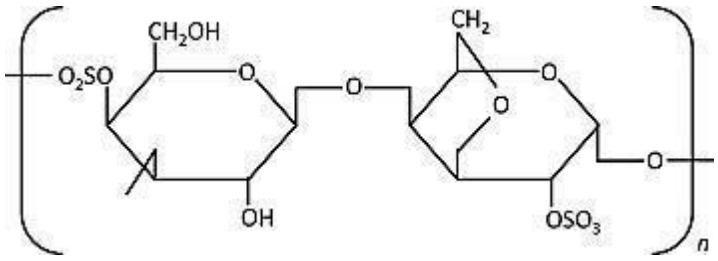


Fig 7.2 Structure of iota carrageenan

i-Carrageenan (iota-carrageenan) is a gelling polymer containing about 32% estersulfate by weight and approximately 30% 3,6- anhydro galactose.

5. **Functional category**

   It acts as emulsifying agent, gel base, stabilizing agent, suspending agent, sustained-release agent, viscosity increasing agent.

6. **Description**

   Carrageenan, when extracted from the appropriate seaweed source, is a

yellow- brownto white colored, coarse to fine powder that is odorless and tasteless.

7. **Solubility**

   Soluble in water at 80ºC.

8. **Stability**

   Carrageenan is a stable, though hygroscopic, polysaccharide and should be stored in a cool, dry place. Carrageenan in solution has maximum stability at pH 9 and should not be heat processed at pH values below 3.5. Acid and oxidizing agents may hydrolyze carrageenan in solution leading to loss of physical properties through cleavage of glycosidic bonds. Acid hydrolysis depends on pH, temperature and time. However, when the carrageenan is in its gelled state the acid hydrolysis no longer takes place.

9. **Incompatibility**

   Carrageenan can react with cationic materials. If complexation of cationic materials, with associated modification of the active compound's solubility is undesirable, the use of carrageenan is not recommended. Carrageenan may interact with other charged macromolecules, e.g. proteins, to give various effects such as viscosity increase, gel formation, stabilization or precipitation.

10. **Applications**

    - Carrageenan is used in a variety of nonparenteral dosage forms, including suspensions (wet and reconstitutable), emulsions, gels, creams, lotions, eye drops, suppositories, tablets and capsules. In suspension formulations, usually only thei- carrageenan and l-carrageenan fractions are used.
    - i-Carrageenan develops a shear-thinning thixotropic gel, which can be easily poured after shaking. When i-carrageenan is used, the presence of calcium ions is required for the gel network to become established.
    - With pure i-carrageenan, about 0.4% w/v is required for most suspensions plus the addition of calcium. However, if Sea Spen PF is used, it must be at about 0.75%w/v level, although no additional calcium is required as this is already present in theproduct to control the rate of gelation process.

7.3. HYDROXY PROPYL METHYLCELLULOS[48,49,50]

1. **Nonproprietary name BP :** Hypromellose
   JP : Hypromellose
   PhEur : Hypromellose
   USP : Hypromellose
2. **Synonyms**
   Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose;Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.
3. **Chemical Name :** Cellulose hydroxypropyl methyl ether.
4. **Molecular structure:**

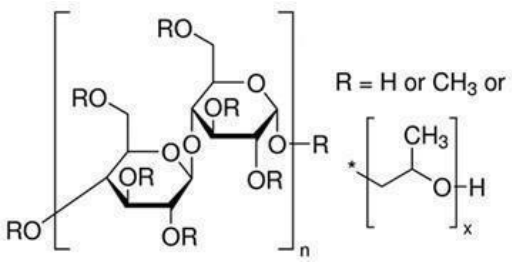


Fig 7.3 Structure of HPMC K4M

5. **Molecular weight :** Molecular weight is approximately 10,000–15,00,000 g/mol.
6. **Functional category**
   Bio adhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity- increasing agent.

7. Description

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

8. Solubility

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

9. Stability

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 75– 95^0 C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.

10. Incompatibility

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

11. Applications

- Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation 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 in liquid oral dosage forms as a suspending and/or thickening agent at concentrations rangingfrom 0.25–5.0%.

7.4. SODIUM CITRATE DIHYDRATE[51,52,53]

1. **Nonproprieta**

   ry namesBP:

   Sodium Citrate

   JP : Sodium Citrate Hydrate

   PhEur : Sodium Citrate

   USP : Sodium Citrate

2. **Synonyms**

   Citric acid trisodium salt; Natrii citras; sodium citrate tertiary; tri-sodium citrate.

3. **Chemical name:** Tri-sodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate

4. **Empirical formula and Molecular weight**

   $C_6H_5Na_3O_7.2H_2O$ / 294.10 g/mol.

5. **Functional category**

   Alkalizing agent; buffering agent; emulsifying agent; sequestering agent.

6. **Solubility**

   Practically insoluble in ethanol. Soluble 1 in 1.5 of water, 1 in 0.6 of boiling water.

7. **Incompatibility**

   Aqueous solutions are slightly alkaline and will react with acidic substances.

8. **Applications**

   - Sodium citrate, as either the dihydrate or anhydrous material, is widely used in pharmaceutical formulations. It is used to adjust the pH of solutions. It is also usedas a sequestering agent. It is used in effervescent tablet formulations.
   - It is additionally used as a blood anticoagulant either alone or in combination withother citrates such as disodium hydrogen citrate.

7.5. CALCIUM CARBONATE[54,55]

1. **Nonproprietary Names**

   BP : Calcium Carbonate

   JP : Precipitated Calcium Carbonate

PhEur : Calcium Carbonate

USP-NF: Calcium Carbonate

2. **Synonyms**

   Calcii carbonas; calcium carbonate (1 : 1); carbonic acid calcium salt (1 : 1); creta preparada; Destab; E170; MagGran CC; Micromite; Pharma-Carb; precipitated carbonate of lime; precipitated chalk; Vitagran; Vivapress Ca; Witcarb.

3. **Chemical Name:** Carbonic acid, calcium salt (1 : 1)

4. **Empirical Formula and Molecular Weight**

   $CaCO_3$ / 100.09 g/mol.

5. **Functional category**

   Buffering agent, coating agent, colorant, opacifier, tablet binder, tablet and capsule diluent and therapeutic agent.

6. **Description**

   Calcium carbonate occurs as odorless and tasteless white powder or crystals.

7. **Solubility**

   It is practically insoluble in ethanol (95%) and water. Solubility in water is increased by the presence of ammonium salts or carbon dioxide. The presence of alkali hydroxides reduces solubility.

8. **Incompatibility**

   Incompatible with acids and ammonium salts.

9. **Applications**

   - Calcium carbonate, employed as a pharmaceutical excipient, is mainly used insolid-dosage forms as a diluent.
   - It is also used as a base for medicated dental preparations, as a buffering agent, andas a dissolution aid in dispersible tablet.
   - Calcium carbonate is used as a bulking agent in tablet sugar-coating processes andas an opacifier in tablet film-coating.

     Calcium carbonate is also used as a food additive and therapeutically as an antacidand calcium supplement.

7.6. SODIUM BICARBONATE[56]

1. **Nonproprietary Names**

   BP : Sodium Bicarbonate

   JP : Sodium Bicarbonate

   Ph Eur : Sodium Hydrogen Carbonate

   USP : Sodium Bicarbonate

2. **Synonyms**

   Baking soda; E500; Effer-Soda; monosodium carbonate; natrii hydrogenocarbonas;Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

3. **Chemical Name :** Carbonic acid monosodium salt

4. **Empirical Formula and Molecular Weight**

   $NaHCO_3$ / 84.01 g/mol.

5. **Functional category**

   Alkalizing agent and therapeutic agent.

6. **Description:**

   Sodium bicarbonate occurs as an odourless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.

7. **Solubility**

   Practically insoluble in ethanol (95%) and ether; Solubility in water-1 in 10 at 25ºC.

8. **Incompatibility**

   Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates. In liquid mixtures, containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt.

9. **Applications**

   - Sodium bicarbonate is generally used in pharmaceutical formulations as a sourceof carbon dioxide in effervescent tablets and granules.

- It is also widely used to produce or maintain an alkaline pH in a preparation. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raftsystems and in floating, controlled release oral dosage forms for a range of drugs.

7.7. SODIUM SACCHARIN[57]

1. **Nonproprietary names**

   BP : Sodium Saccharin

   JP : Sodium Saccharin Hydrate

   Ph Eur : Sodium Saccharin

   USP-NF: Sodium Saccharin

2. **Synonyms**

   1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt; Crystallose; E954; gendorf 450; saccharinum natricum; sodium o-benzosulfimide; soluble gluside; soluble saccharin; sucaryl sodium.

3. **Chemical name:** 1,2-Benzisothiazol-3(2 H)-one 1,1-dioxide, sodium salt

4. **Empirical formula and Molecular weight**

   $C_7H_4NNaO_3S$ / 205.16

5. **Functional category**

   Sweetening agent.

6. **Description**

   Saccharin sodium occurs as a white, odourless or faintly aromatic, efflorescent, crystalline powder.

6. **Solubility**

   It is soluble in ethanol 1 in 102 at 20°C and soluble in water 1 in 1.2 at 20°C.

7. **Incompatibility**

   Saccharin sodium does not undergo Maillard browning.

8. Applications

- Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids and mouth washes.
- It is used in oral solutions at a concentration of 0.075 - 0.6 % and in oral syrup at 0.04 - 0.25 %.
- Saccharin sodium is considerably more soluble in water than saccharin, and is more frequently used in pharmaceutical formulations. Its sweetening power is approximately 300–600 times that of sucrose. Saccharin sodium flavour systems and may be used to mask some unpleasant taste characteristics.

7.8. METHYLPARABEN SODIUM[58,59]

1. Nonproprietary Names

BP : Sodium Methyl hydroxyl benzoate **PhEur :** Sodium Methyl Parahydroxy benzoate**USP-NF :** Methyl paraben sodium

2. Synonyms

Methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; solublemethyl hydroxybenzoate.

3. Chemical Name: Sodium 4-methoxycarbonylphenolate

4. Empirical formula and Molecular Weight

$C_8H_7NaO_3$ / 174.14

5. Functional category

Antimicrobial preservative

6. Description

White, odourless or almost odourless, hygroscopic crystalline powder.

7. Solubility

Soluble in ethanol 95% 1 in

50 at 25°C Soluble in water 1
in 2 at 25°C

8. Incompatibility

The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization. However, propylene glycol (10%) has been shown to potentiate the antimicrobial activity of the parabens in the presence of nonionic surfactants and prevents the interaction between methylparaben and polysorbate 80.

9. Applications

- It may be used either alone or in combination with other parabens or with other antimicrobial agent.
- Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore, a mixture of parabens is frequently used to provide effective preservation.
- It is used in the concentration of 0.015-0.2% in Oral solutions and Suspensions.

8.1. MATERIALS USED

Table 8.1: Materials used in the formulation

Chemicals	Manufacturer/Supplier	Use in Formulation
Losartan potassium	Saimirra Innopharm, Chennai.	Active pharmaceutical ingredient
Gellan Gum	Signet chemical corporation, Chennai	Gelling agent
Iota Carrageenan		
HPMC K4M	KNISS Labs, Chennai.	Release Retardant
Calcium carbonate	KNISS Labs, Chennai.	Crosslinking Agent
Sodium bicarbonate	KNISS Labs, Chennai.	Gas generating agent
Sodium saccharin	KNISS Labs, Chennai.	Sweetening agent
Sodium citrate	KNISS Labs, Chennai.	Buffering agent
Methyl paraben sodium	KNISS Labs, Chennai.	Preservative

8.2. INSTRUMENTS USED

Table 8.2: List of Equipments used

INSTRUMENT	SUPPLIER
UV-Vis Spectrophotometer	Shimadzu 1800, Japan
Weighing balance	MC Dalal, Chennai
Magnetic stirrer	REMI Instruments, Mumbai
pH meter	MC Dalal, Chennai
Brookfield viscometer	DV-II+ Pro
Dissolution apparatus	Thermonik, Campbell Electronics, Mumbai
Stability chamber	Remi-chi 6 plus, Mumbai
FT-IR	8400S, Shimadzu, Japan

8.3. PREFORMULATION STUDIES [60]

Preformulation study is defined as "investigation of physical and chemical properties of the drug substance alone and combined with the excipients". Preformulation studies are the first step in the rational development of dosage form of drugs. It involves the application of biopharmaceutical principles to the physicochemical parameters of the drug with the goal of designing an optimum delivery system that is stable, bioavailable and can be mass produced.

8.3.1. CHARACTERIZATION OF LOSARTAN POTASSIUM

8.3.1.1. Determination of melting point of Losartan potassium[61]

The melting point of Losartan potassium was determined by the capillary tube method according to the USP. A sufficient quantity of Losartan potassium powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in an electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of losartan potassium in the tube passed into liquid phase.

8.3.1.2. Determination of λ_{max} of Losartan potassium[62,63]

100 mg of Losartan potassium was accurately weighed and transferred to a 100 ml volumetric flask. The drug was dissolved in solvent and the volume was made up to 100 ml to obtain a stock solution of 1000 µg/ml (Stock I). 10 ml of this stock solution was again diluted with 0.1 HCl up to 100 ml to obtain a solution of 100µg/ml (Stock II). From the stock II, 10 ml of the solution again diluted with 100 ml of the 0.1 HCl. The resulting solution was scanned between 200 nm and 400 nm in a double beam UV-Visible spectrophotometer.

8.3.1.3. Solubility[61]

Solubility is an important parameter for preformulation studies. Because it affects the dissolution of the drug and the bioavailability of the drug is directly affected by dissolution and absorption of drug by oral administration.

8.3.2. Drug excipient compatibility studies

The drug and excipients selected for the formulation were evaluated for physical and chemical compatibility studies.

8.3.2.1. Physical compatibility study[65,66]

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting appropriate excipients for the formulation. It was done by mixing the drugs and the excipients and kept at room temperature and at 40ºC and 75 ± 2 %RH. Any change in colour of the physical mixture was observed visually.

8.3.2.2. Chemical compatibility study[67]

Fourier transform infrared (FTIR) spectroscopy was performed using a Shimadzu FTIR 8400 spectrophotometer from 4000 to 400 cm^{-1} region. The procedure consists of dispersing the sample (drug alone, mixture of drug and excipients) in KBr and made into disc form by compressing it with a pressure of 3 tons in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.

8.4. Preparation of calibration curve for Losartan potassium[68,69]

Standard solution was prepared by dissolving accurately 100 mg of bulk losartan potassium in 5 ml of methanol and made upto the volume with 0.1N HCl. 10 ml of the stock solution of was pipetted out in a separate 100 ml standard flask and the volume was made up using 0.1N HCl. From the resulting solution 2, 4, 6, 8 and 10 ml were pipetted out into separate 100 ml standard flask and made upto volume using 0.1N HCl. The absorbance was measured at 205 nm against the reagent blank. Then, the calibration curve was obtained by plotting concentration versus absorbance.

8.5. Preparation of oral *In situ* gel of losartan potassium

1. Various concentrations of gelling polymer gellan Gum was dissolved in deionized water with a weighed amount of sodium citrate on a magnetic stirrer at 70ºC.
2. Iota carrageenan solution was prepared separately by dissolving in deionized water containing sodium citrate and heating to 80ºC while stirring.
3. In another beaker, the required quantity of release retardant polymer HPMC K4M was soaked in deionized water until completely dissolved.
4. Then, all the three solutions were mixed together with continuous stirring.
5. After the above solution was cooled down to 40ºC, calcium carbonate, sodium bicarbonate and losartan potassium previously dissolved in water were added.
6. Sodium saccharin and preservative were then mixed.

7. Finally, the volume was adjusted with deionized water, and the resultant solution was stirred well and stored in bottles.

Table 8.3 Composition of the *In situ* gel formulation

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Losartan potassium (g)	1	1	1	1	1	1	1	1
Gellan gum %w/v	0.15	0.25	-	-	0.15	0.15	0.25	0.25
Iota carrageenan % w/v	-	-	0.2	0.4	0.2	0.4	0.2	0.4
HPMC K4M % w/v	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sodium citrate % w/v	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium carbonate % w/v	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate % w/v	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sodium saccharin % w/v	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Methyl paraben % w/v	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Deionized waterto produce (ml)	100	100	100	100	100	100	100	100

8.6. CHARACTERIZATION OF IN SITU GEL

8.6.1. Visual appearance[65,70]

All the formulations were visually inspected for their appearance, clarity and consistency.

8.6.2. Measurement of pH[67,70]

The pH of the formulations was measured using a calibrated pH meter. The readings were recorded three times for each of the formulations and the averages of the readings were considered.

8.6.3. *In vitro* gelation study[71]

5ml of the simulated gastric fluid (0.1N HCl, pH 1.2) was taken in a 10 ml test tube, maintained at 37ºC, followed by the addition of 1 ml of the formulation using a pipette. The pipette was positioned facing the surface of the fluid in the test tube and slowly the formulation was released from the pipette. When the formulation came in contact with the gelation medium, it was quickly converted into a gel-like structure. Based on the stiffness of gel as well as the duration for which the gel remains as such the *in vitro* felling capacity was investigated.

The *in vitro* gelling capacity was mainly divided into three categories based on gelation time and the time period of the formed gel remains.

- (+): gelation in few seconds, disperse immediately.
- (++): gelation immediate, remains for few hours
- (+++): gelation after few minutes, remains for extended period.

8.6.4. Determination of viscosity[72,73]

Viscosity of the formulations were determined with the help of Brookfield's Digital Viscometer (DV-II) + Pro using S21 spindle at 50 rpm and measurement was done for 3 times with fresh samples and the average reading was taken.

8.6.5 *In vitro* buoyancy study[73,74]

The studies were conducted in a USP Type II dissolution apparatus using simulated gastric fluid (pH 1.2) as the medium at 37±0.5ºC. About 10 ml of the *In situ* gel formulation was placed in the medium. The time taken by the *In situ* gel formulation to float on the surface of

the medium (floating lag time) and time period for which the formulation remained buoyant (duration of floating) was noted.

8.6.6. Measurement of water uptake by the gel[73,74]

To conduct this study, the *In situ* gel formed in 40 ml of 0.1N HCl (pH 1.2) was used. From each of the formulations, the gel part was separated from the buffer and the excess buffer was blotted out with the help of whatmann filter paper. The gel was initially weighed, followed by the addition of 10 ml of distilled water to it. After every 30 minutes interval, water was decanted and the weight of the gel was noted and the difference between initial and final weight was calculated.

8.6.7. Measurement of density of gel[75]

30 ml of the *In situ* formulation was poured into a beaker containing 50 ml of 0.1N HCl. 10 ml of the gel was measured. Using the weight as well as the volume of the gel, the density was calculated. This method was followed for all the formulations.

8.6.8. Measurement of gel strength[76,77]

10 g of the gel was taken in a 50 ml beaker and a 5 g weight was placed on the center of the surface of the gel and allowed to penetrate through the gel. The time taken by the 5 g weight to penetrate 5 cm down through the gel was noted for all the formulations. The same method was followed for 3 times for each fresh formulation and the average time was noted.

8.6.9. Determination of the drug content[63,64]

5 ml of the formulation equivalent to 50 mg of the drug was added to 100 ml of 0.1N HCl (pH 1.2) in a 100 ml standard flask and stirred well. After 1 hr, the solution was filtered. The drug concentration was then determined by UV-Vis spectrophotometer at 205 nm against a suitable blank solution.

8.6.10. *In vitro* drug release study of the *In situ* gel formulation[13,16]

The dissolution studies were performed using a USP was 500 ml of 0.1N HCl (pH 1.2), maintained at 37ºC. The stirring rate was adjusted to 50 rpm. This speed believed to stimulate the *In vivo* existing mild agitation and was slow enough to avoid the breaking of the gelled formulation. At the predetermined time intervals, 10 ml samples were withdrawn and replaced by fresh dissolution medium, filtered through whatmann filter paper, diluted and assayed at maximum absorbance at 205 nm using UV-Vis spectrophotometer.

8.7. Release kinetics of the optimized formulation[61]

To study the in vitro release kinetics of the optimized formulations of losartan potassium oral *In situ* gel, data obtained from dissolution study were plotted in various kinetic models.

8.7.1. Zero order kinetics

The zero-order release can be obtained by plotting cumulative % drug release vs. time in hours. It is ideal for the formulation to have a release profile of zero order to achieve pharmacological prolonged action.

$$\mathbf{C = K_0\, t}$$

Where,

K_0 = zero order constant

t = time in hours

8.7.2. First order kinetics

The graph was plotted as log cumulative % drug remaining vs. time in hours.

$$\mathbf{Log\ C = log\ C_0 - Kt/2.303}$$

Where,

C_0 = initial concentration of drug

K = first order

t = time in hours

8.7.3. Higuchi kinetics

The graph was plotted with cumulative % drug released vs. square root of time.

$$\mathbf{Q = Kt^{1/2}}$$

Where,

K = constant reflecting design variable system (differential rate constant)

t = time in hours

The drug release rate is inversely proportional to the square root of time.

8.7.4. Hixson and Crowell erosion kinetics

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by the cube root of % drug remaining vs. time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t$$

Where,

Q_t = Amount of drug release in time t

Q_0 = Initial amount of drug

KHC = Rate constant for Hixson – Crowell equation

T = Time in hrs

8.7.5 Korsmeyer – Peppas kinetics

To evaluate the mechanism of drug release, it was further plotted in Korsmeyer – Peppas equation as Log cumulative % of drug released Vs Log time.

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

Where,

Mt/Mα = Fraction of drug released at time t

t = Release kinetics

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

N = Diffusional exponent indicative of the mechanism of drug release

Table 8.4 Diffusion exponent band solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super case II transport

8.8 STABILITY STUDIES[76,86]

The optimized formulation of the *In situ* gel was placed in an amber colour bottle. It was tightly sealed. The stability study was carried out as per the ICH guidelines, i.e., Accelerated temperature 40 ± 2 °C / 75 ± 5 % RH for 1 month. Samples were withdrawn periodically (0 and 30 days) and evaluated for visual appearance, pH, floating behavior, gelling capacity, drug content as well as *In vitro* drug release.

9.1PREFORMULATION STUDIES

9.1.1. CHARACTERIZATION OF THE DRUG

9.1.1.1. Melting point of Losartan Potassium

Melting point was measured using capillary tube method. It was found to be 268ºC. The melting point of Losartan potassium is within the limits (268-271º C).

9.1.1.2. Determination of λ_{max} of Losartan Potassium

The maximum absorbance of the Losartan Potassium was studied and found to be 205 nm. Hence, the wavelength of 205 nm was selected for estimation of drug content and analysis of drug in dissolution media.

9.1.1.3. Calibration curve of Losartan potassium

The UV- Visible spectrophotometric method was used to analyze Losartan Potassium. The absorbance of the drug in 0.1N HC (pH 1.2), was measured at 205 nm. The results are given in Table 9.1. The calibration curve is shown in Fig 9.1.

Table 9.1 Calibration Data of Losartan Potassium

Concentration(µg/ml)	Absorbance (nm)
2	0.228 ± 0.00216
4	0.404 ± 0.001414
6	0.588 ± 0.00216
8	0.791 ± 0.001414
10	0.993 ± 0.00216

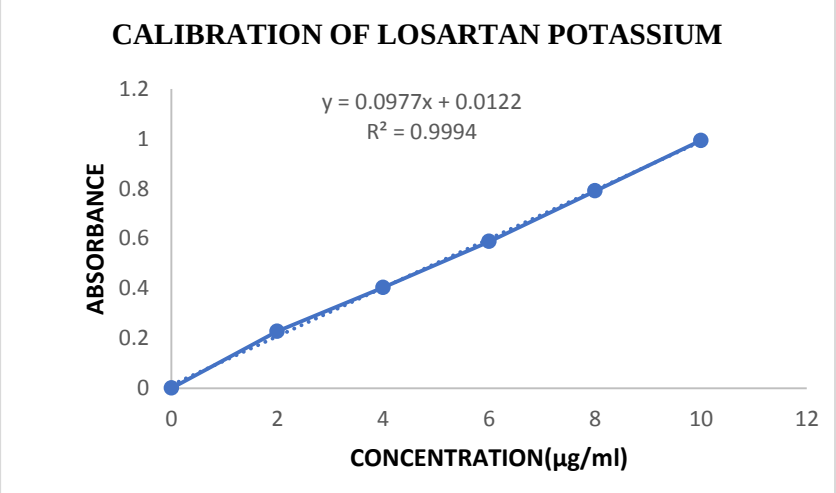


Fig 9.1 Calibration curve of Losartan Potassium

9.1.2. SOLUBILITY

The solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for the required pharmacological response. The Losartan potassium was found to be freely soluble in water. The solubility of Losartan potassium is essentially constant (approximately 100 mg/mL).

9.1.3. DRUG – EXCIPIENT COMPATABILITY STUDY

The drug – excipient compatibility study was conducted top reveal the excipient compatibility with the drug.

9.1.3.1 Physical Compatability Study

The virtual appearance of the formulation is an important parameter as it has an impact on the patient compliance. All the formulations were subjected to visual appearance and results are given in Table 9.2

Table 9.2 Physical Compatability of Losartan Potassium

S.No	Drug and Excipients	Description and Condition						
		Initial	At Room Temperature			At 40ºC ± 2º and 75% RH ± 2% (in days)		
			10	20	30	10	20	30
1.	Losartan Potassium (API)	White Powder	NC	NC	NC	NC	NC	NC
2.	API + Gellan Gum	Dull- White Powder	NC	NC	NC	NC	NC	NC
3.	API + Iota Carrageenan	Dull- White Powder	NC	NC	NC	NC	NC	NC
4.	API + HPMC K4M	White Powder	NC	NC	NC	NC	NC	NC
5.	API + Calcium Carbonate	White Powder	NC	NC	NC	NC	NC	NC
6.	API + Sodium bicarbonate	White Crystalline Powder	NC	NC	NC	NC	NC	NC

S.No	Drug and Excipients	Description and Condition						
		Initial	At Room Temperature			At 40ºC ± 2º and 75% RH ± 2% (in days)		
			10	20	30	10	20	30
7.	API + Sodium Citrate	White Crystalline Powder	NC	NC	NC	NC	NC	NC
8.	API + Sodium Saccharin	White Crystalline Powder	NC	NC	NC	NC	NC	NC
9.	API + Methyl paraben	White Crystalline Powder	NC	NC	NC	NC	NC	NC

*NC – No Change

9.1.3.2. Chemical Compatability Study

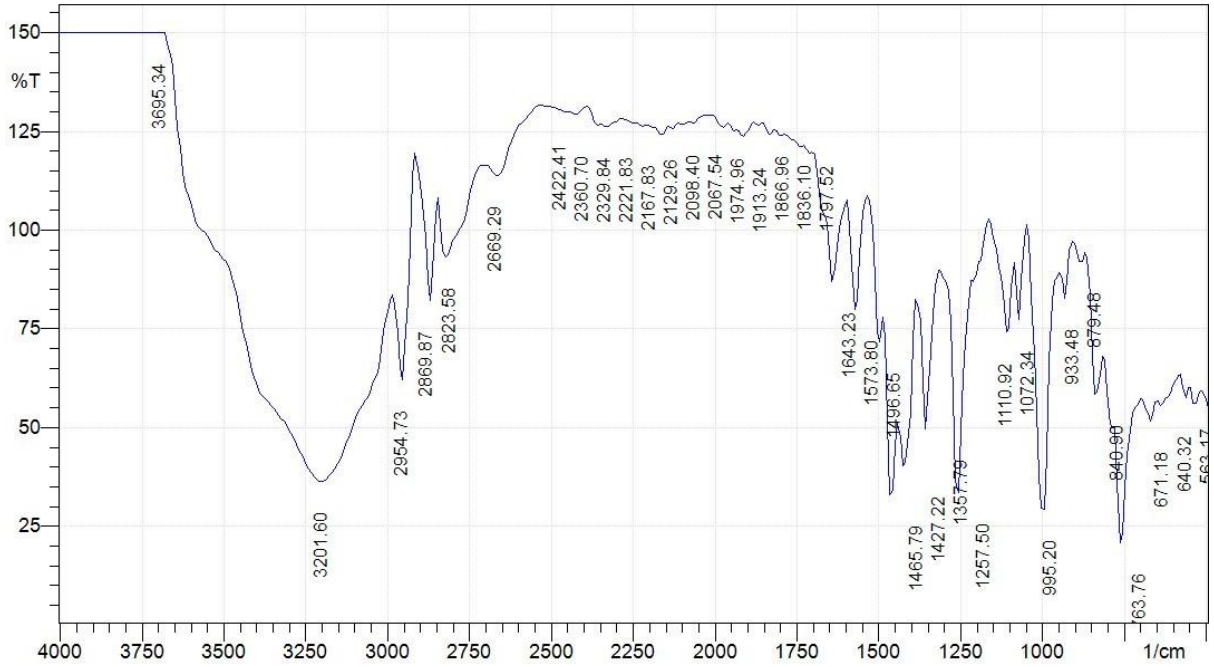


Fig 9.2 FTIR Spectra of Losartan Potassium

Table 9.3 FTIR Spectral Interpretation of Losartan Potassium

Wavenumber(cm^{-1})	Types of Vibrations
3201.60	OH Stretching
1465.79	-CH_2- Stretching
1573.80	Aromatic C=C Stretching
840.90	C-H Stretching
1110.92	C=O Stretching
1643.23	C=N Stretching
763.76	C-Cl Stretching

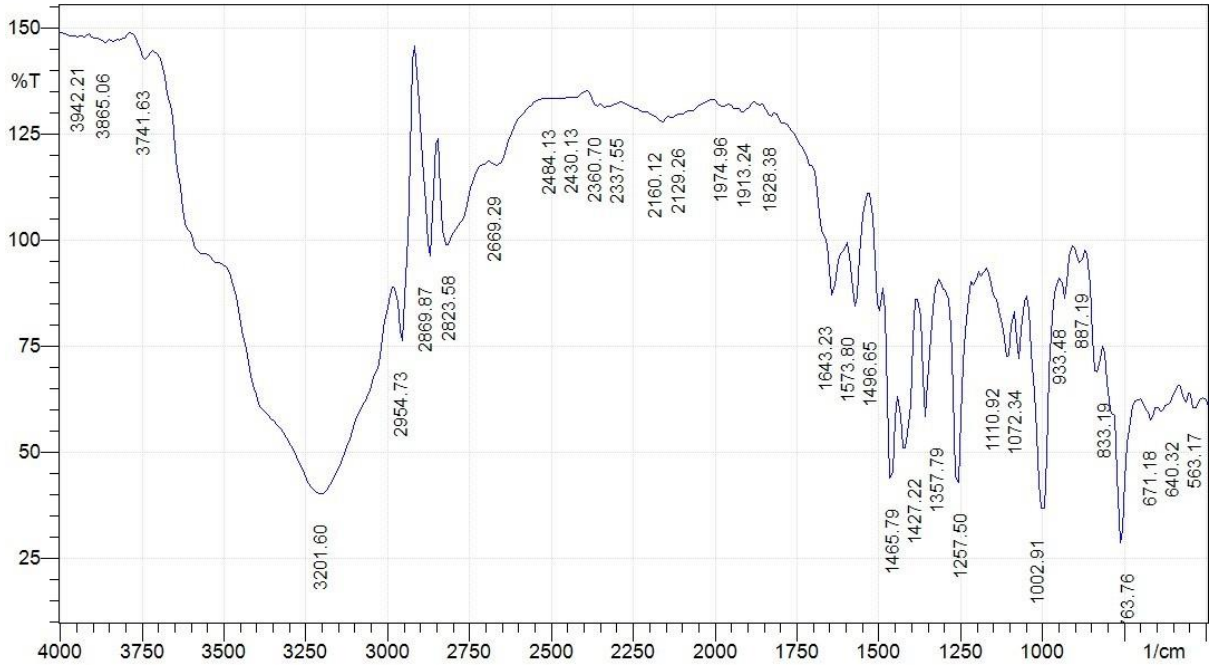


Fig 9.3 FTIR Spectra of Losartan Potassium and Gellan Gum

Table 9.4 FTIR Spectral Interpretation of Losartan Potassium and Gellan Gum

Wave number(cm^{-1})	Types of Vibrations
3201.60	OH Stretching
1465.79	-CH_2- Stretching
1573.80	Aromatic C=C Stretching
833.19	C-H Stretching
1110.92	C=O Stretching
1643.23	C=N Stretching
763.76	C-Cl Stretching

Inference

The peaks observed in the Fig 9.3 FT-IR spectrum for Losartan potassium and Gellan gum shown that there is no interaction between the drug and gellan gum.

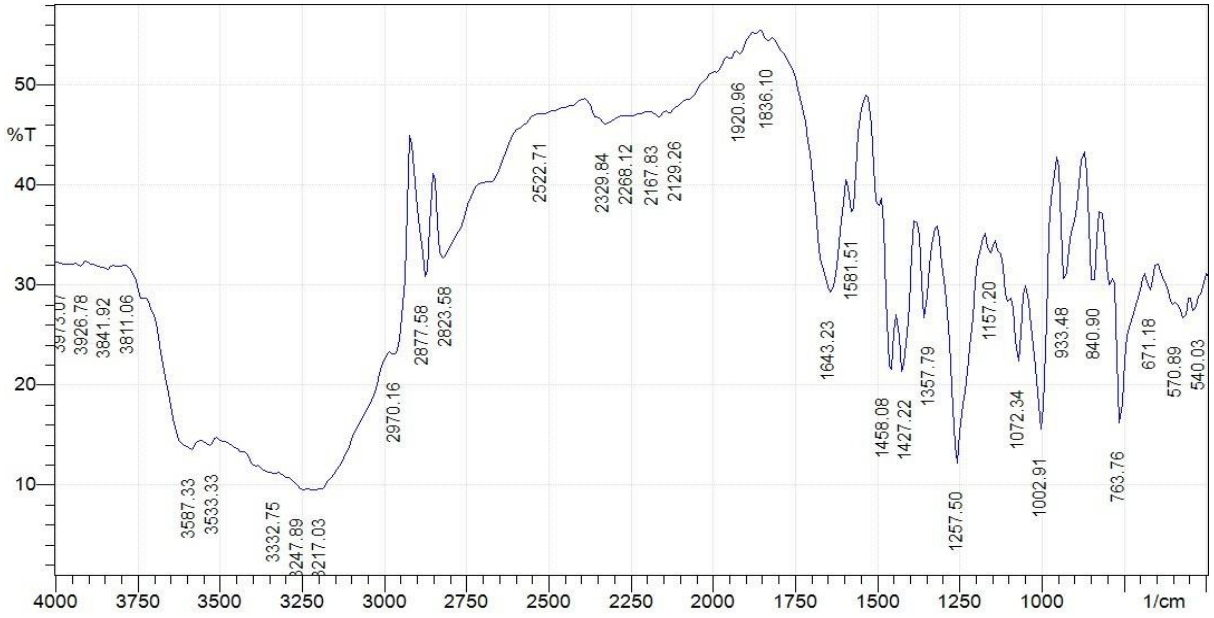


Fig 9.4 FTIR Spectra of Losartan Potassium and Iota Carrageenan

Table 9.5 FTIR Spectral Interpretation of Losartan Potassium and Iota Carrageenan

Wave number(cm^{-1})	Type of Vibrations
3217.03	OH Stretching
1581.51	Aromatic C=C Stretching
840.90	C-H stretching
1002.91	C=O Stretching
1643.23	C=N Stretching
763.76	C-Cl Stretching

Inference

The peak observed in the Fig 9.4 FT-IR spectrum of Losartan potassium and Iota carrageenan shown that there is no interaction between drug and Iota carrageenan.

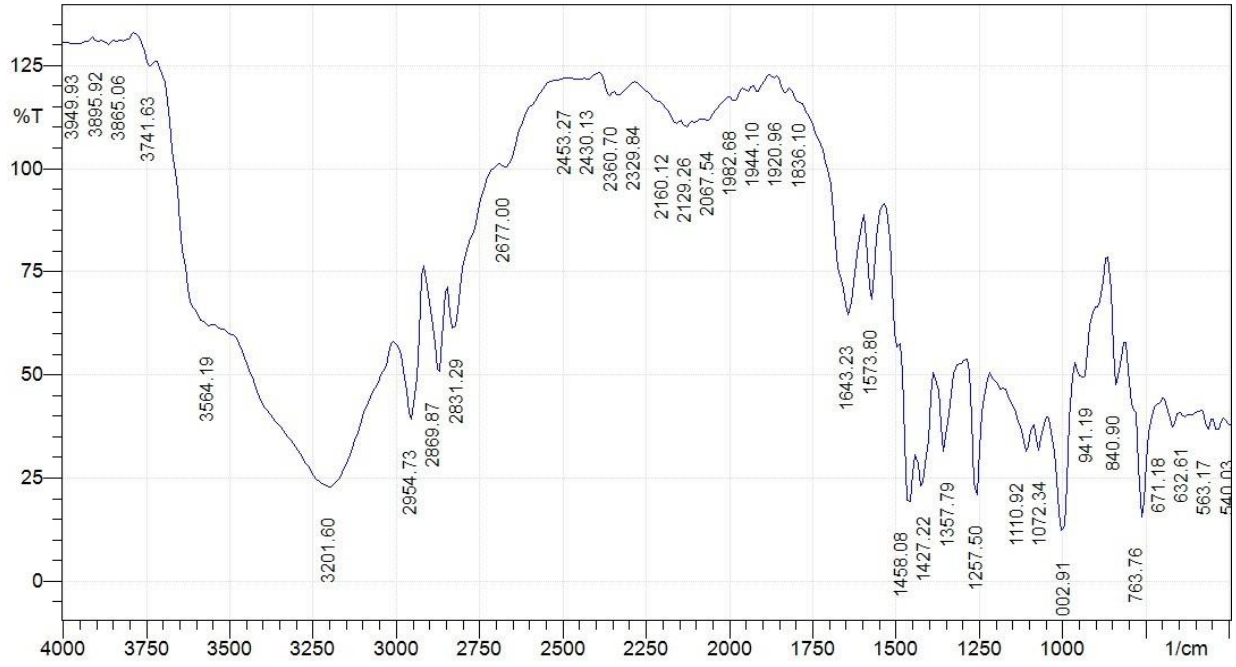


Fig 9.5 FTIR Spectra of Losartan potassium and HPMC K4M

Table 9.6 FTIR Spectral Interpretation of Losartan Potassium and HPMC K4M

Wave number(cm^{-1})	Type of Vibrations
3201.60	OH Stretching
1573.80	Aromatic C=C Stretching
840.90	C-H Stretching
1110.92	C=O Stretching
1643.23	C=N Stretching
763.76	C-Cl Stretching

Inference

The peak observed in the fig 9.5 FT-IR spectrum for Losartan potassium and HPMC K4M shown that there is no interaction between drug and HPMC K4M.

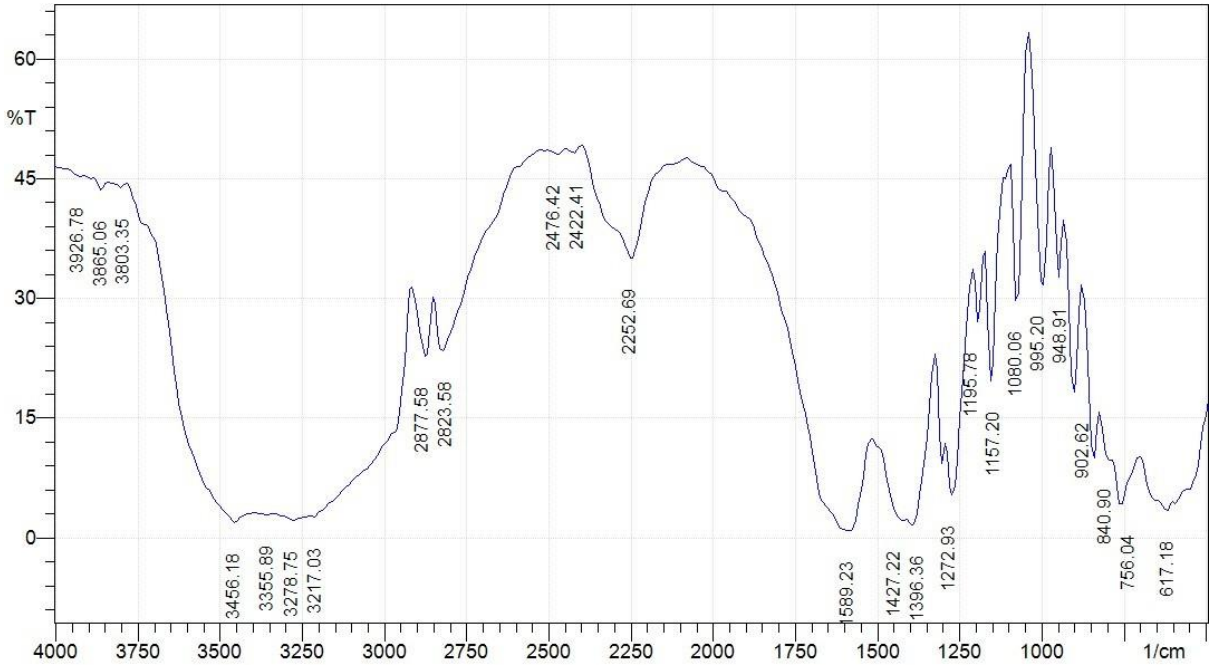


Fig 9.6 FTIR spectra of Losartan potassium and Sodium Citrate Dihydrate

Table 9.7 FTIR Spectral Interpretation of Losartan Potassium and Sodium Citrate Dihydrate

Wave number(cm^{-1})	Type of Vibrations
3217.03	OH Stretching
1589.23	Aromatic C=C Stretching
840.90	C-H Stretching
1157.20	C=O Stretching
756.04	C-Cl Stretching

Inference

The peaks observed in fig 9.6 FT-IR spectrum for Losartan potassium and Sodium Citrate Dihydrate shown that there is no interaction between drug and sodium citrate dihydrate.

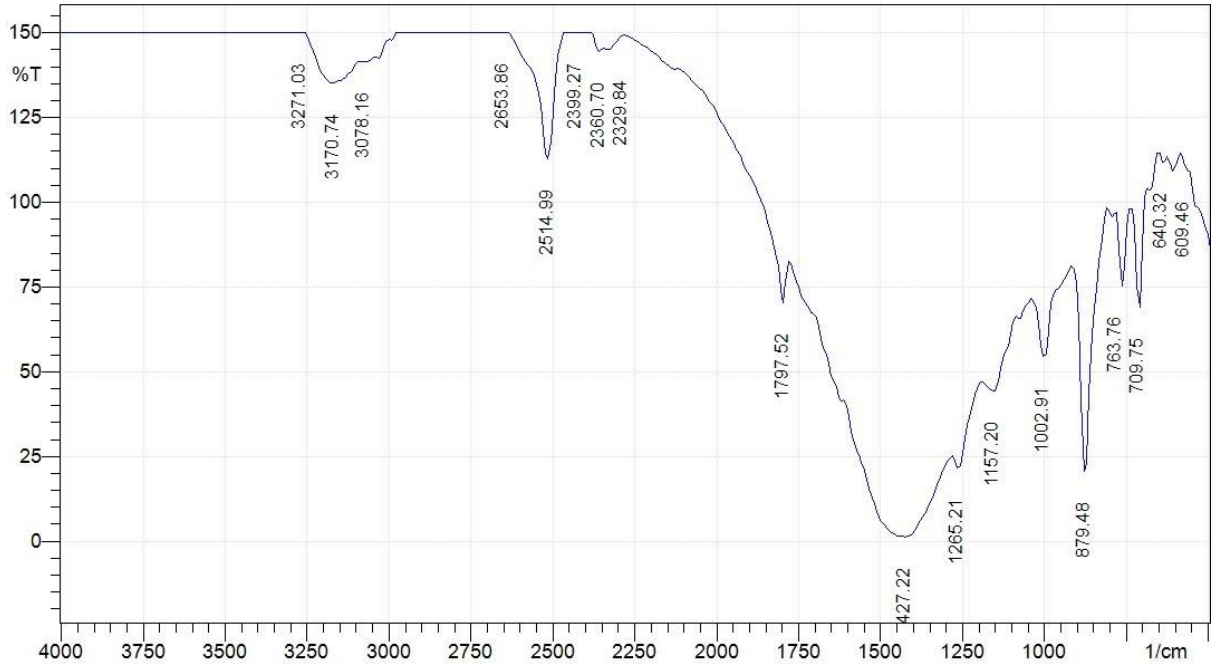


Fig 9.7 FTIR Spectra of Losartan potassium and Calcium carbonate

Table 9.8 FTIR Spectral Interpretation of Losartan Potassium and Calcium carbonate

Wave number(cm^{-1})	Type of Vibrations
3170.74	OH Stretching
879.48	C-H Stretching
1002.91	C=O Stretching
1797.52	C=N Stretching
763.76	C-Cl Stretching

Inference

The peaks observed in fig 9.7 FT-IR spectrum for Losartan potassium and Calcium carbonate shown that there is no interaction between drug and calcium carbonate.

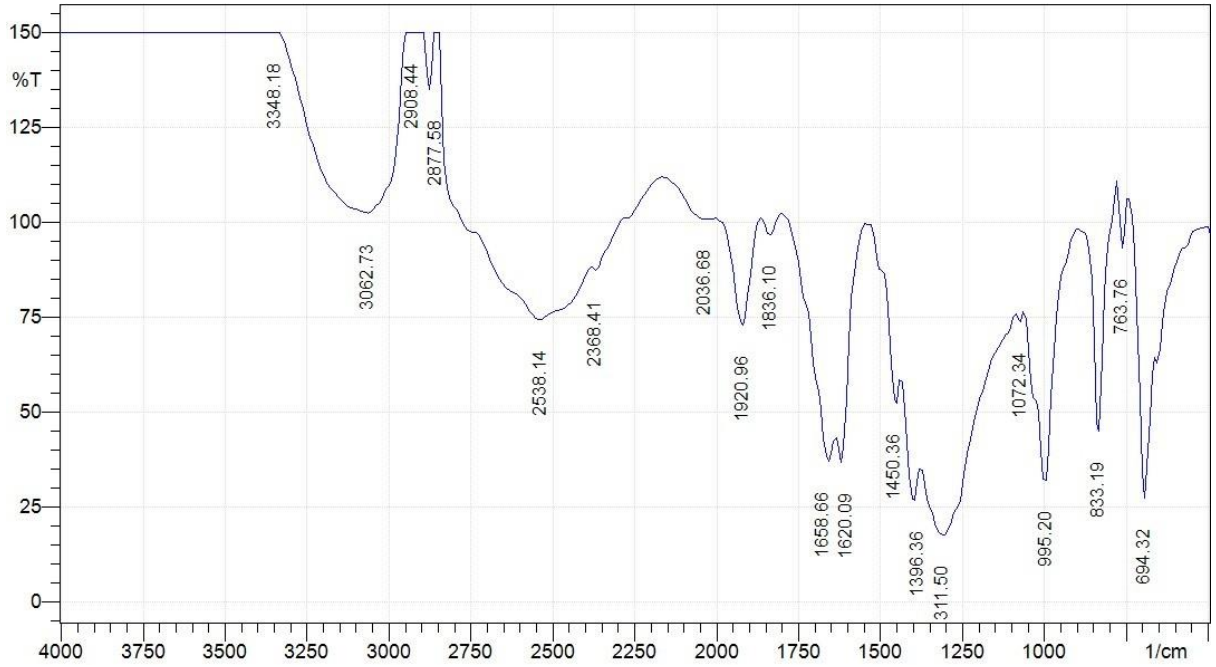


Fig 9.8 FTIR Spectra of Losartan Potassium and Sodium bicarbonate

Table 9.9 FTIR Spectral Interpretation of Losartan Potassium and Sodium Bicarbonate

Wave number(cm^{-1})	Type of Vibrations
3348.18	OH Stretching
1620.09	Aromatic C=C Stretching
694.32	C-H Stretching
1072.34	C=O Stretching
1658. 66	C=N Stretching
763.76	C-Cl Stretching

Inference

The peaks observed in the fig 9.8 FT-IR spectrum for Losartan potassium and Sodium bicarbonate shown that there is no interaction between drug and sodium bicarbonate.

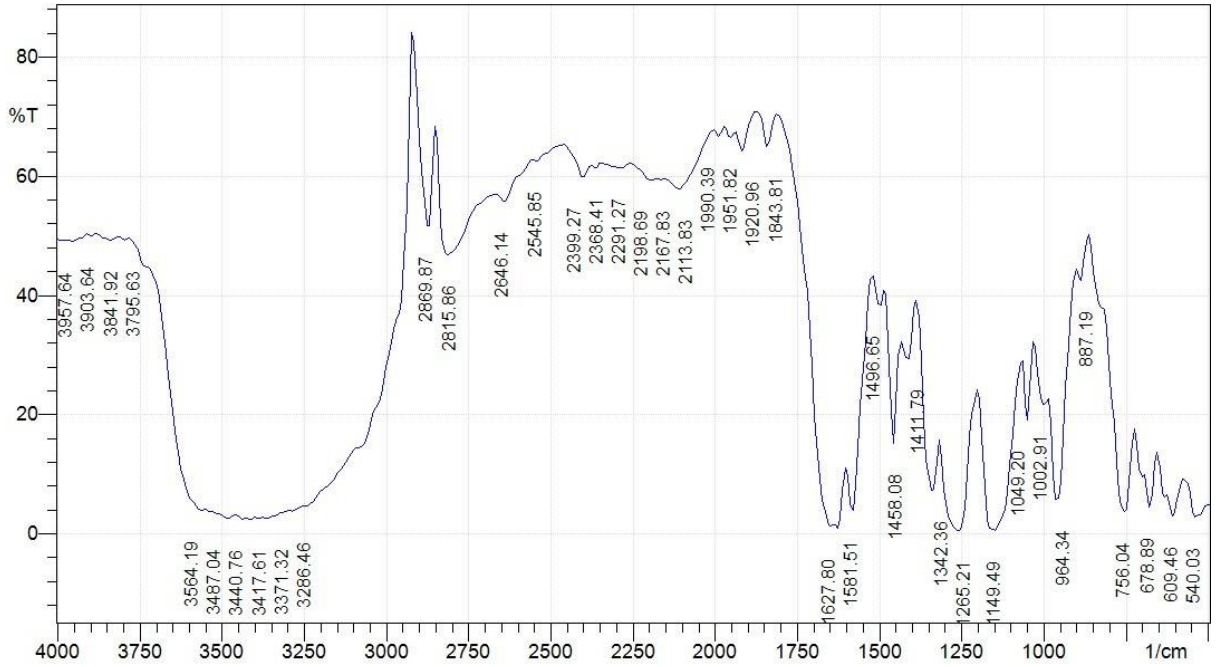


Fig 9.9 FTIR Spectrum of Losartan potassium and Sodium Saccharin

Table9.10 FTIR Spectral Interpretation of Losartan Potassium and Sodium Saccharin

Wave number(cm^{-1})	Type of Vibrations
3440.76	OH Stretching
1589.23	Aromatic C=C Stretching
887.19	C-H Stretching
1149.49	C=O Stretching
1627.80	C=N Stretching
756.04	C-Cl Stretching

Inference

The peaks observed in fig 9.9 FT-IR spectrum for Losartan potassium and Sodium saccharin shown that there is on interaction between drug and sodium saccharin.

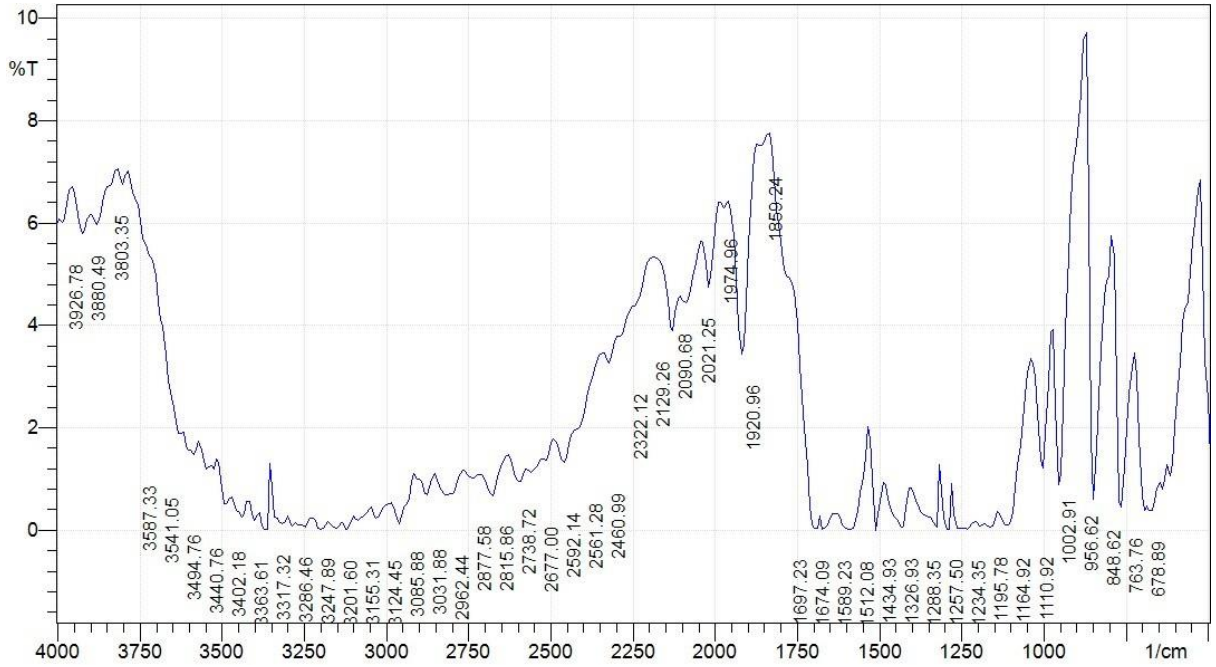


Fig 9.10 FTIR Spectra of Losartan potassium and Methyl paraben sodium

Table 9.11 FTIR Spectral Interpretation of Losartan Potassium and Methyl Paraben Sodium

Wave number (cm^{-1})	Type of Vibrations
3201.60	OH Stretching
1589.23	Aromatic C=C Stretching
3085.88	C-H Stretching
1110.92	C=O Stretching
1674.09	C=N Stretching
763.76	C-Cl Stretching

Inference

The peaks observed in fig 9.10 FT-IR spectrum for Losartan potassium and Methyl paraben sodium shown that there is no interaction between drug and methyl paraben sodium.

9.2 FORMULATION OF LOSARTAN POTASSIUM ORAL *IN SITU* GEL

The prepared formulations of Losartan potassium oral *In situ* gel (F1 – F8) are shown in fig 9.11.

Fig 9.11 Losartan potassium *In situ* gel

9.3 CHARACTERIZATION OF *IN SITU* GEL

9.3.1 Physical Appearance of Losartan potassium oral *In situ* gel

The visual appearance of the formulation is an important parameter as it has an impact on the patient compliance. All the formulations are visually inspected for their appearance, clarity and consistency. The results are given in Table 9.13.

Table 9.12 Physical appearance of *In situ* gel

S. No	Formulation Code	Appearance	Pourability
1	F1	Dull White	Pourable
2	F2	Dull White	Pourable
3	F3	Dull White	Easily Pourable
4	F4	Dull White	Pourable
5	F5	Dull White	Pourable
6	F6	Dull White	Pourable
7	F7	Dull White	Pourable
8	F8	Dull White	Pourable

Inference

All the prepared formulations had dull white appearance.

9.3.2 pH of Losartan Potassium oral *In situ* Gel

The pH of each of the formulations was measured using a calibrated pH meter.

Table 9.13 pH of *In situ* gel

S. No	Formulation code	pH
1	F1	6.529 ± 0.002944
2	F2	7.326 ± 0.00216
3	F3	7.296 ± 0.00216
4	F4	6.681 ± 0.002944
5	F5	7.473 ± 0.00432
6	F6	6.457 ± 0.002944
7	F7	6.973 ± 0.002944
8	F8	7.185 ± 0.004546

Inference

- The pH of all the formulations was within the orally acceptable range (i.e., salivary pH range 6.6- 7.6).
- Therefore, it will not cause any irritation on administration of the formulations.

9.3.3 In vitro gelation study of Losartan potassium Oral In situ gel

The gelation characteristics of the formulations were assessed in 0.1N HCl (pH 1.2) on an ordinal scale ranging between + and +++ as shown in Table 9.14.

Table 9.14 In vitro gelling capacity of Oral In situ gel

S. No	Formulation Code	Gelling Capacity
1	F1	++
2	F2	++
3	F3	+
4	F4	++
5	F5	+++
6	F6	+++
7	F7	+++
8	F8	+++

Inference

(+) – Gelation in few seconds, disperses rapidly.

(++) – Gelation immediate, remains for few hours.

(+++)- Gelation after few minutes, remains for extended period.

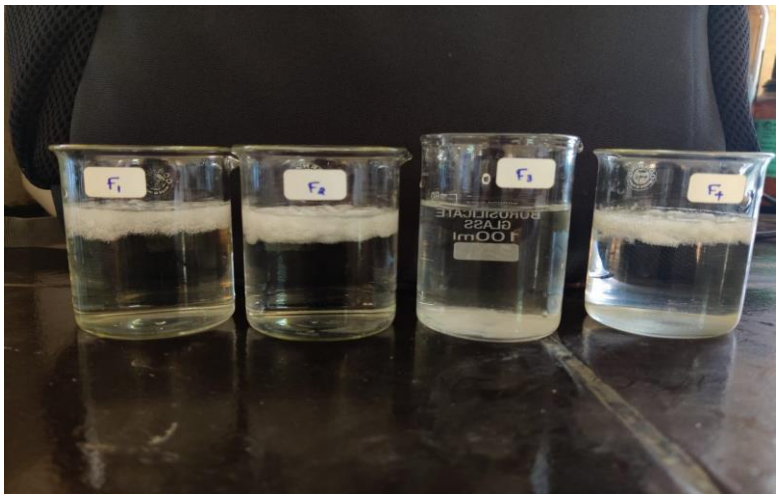


Fig 9.12 In vitro gelation study of the *In situ* gel formulation (F1 – F4)

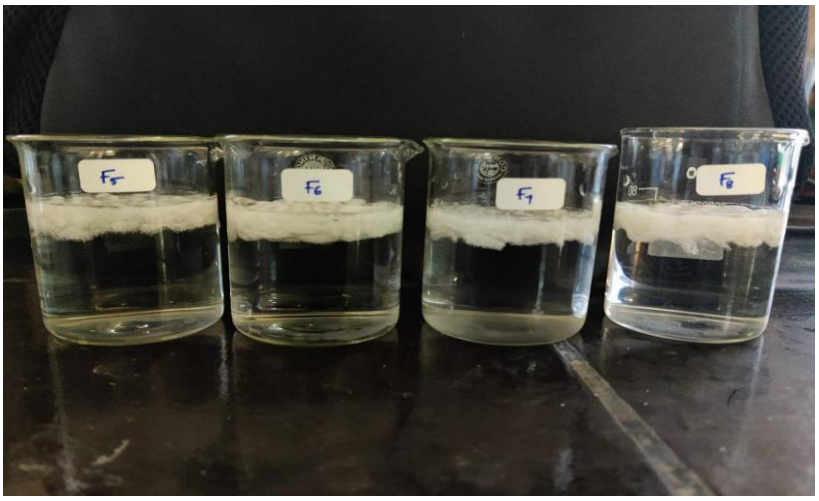


Fig 9.13 *In vitro* gelation study of the *In situ* gel formulation (F5 – F8)

Inference

- All the formulations on contact with the gelation medium had undergone sol-to-gel transition in the presence of gel forming polymers.
- The *In situ* released calcium ion from the calcium citrate complex gets entrapped in polymeric chains resulting in the cross- linking of polymer chains to form a gel matrix.
- Thus, stiff gels were formed with all the formulations containing polymers such as gellan gum, Iota carrageenan and with both gellan gum and Iota carrageenan except formulation F3 containing only Iota carrageenan as the gelling polymer where the gel formed dispersed rapidly.

9.3.4 Viscosity of Losartan potassium Oral In situ gel

The viscosity of all the *In situ* gelling formulations was determined at 50 rpm at 25º C using Brookfield Viscometer DV-II^{+} Pro. The results of viscosity measurement of all the formulations are shown in Table 9.15

Table 9.15 Viscosity of formulated gel

S. No	Formulation Code	Viscosity(centipoise)
1	F1	187
2	F2	160.41
3	F3	102.31
4	F4	168
5	F5	243.22
6	F6	200.36
7	F7	240.24
8	F8	235.9

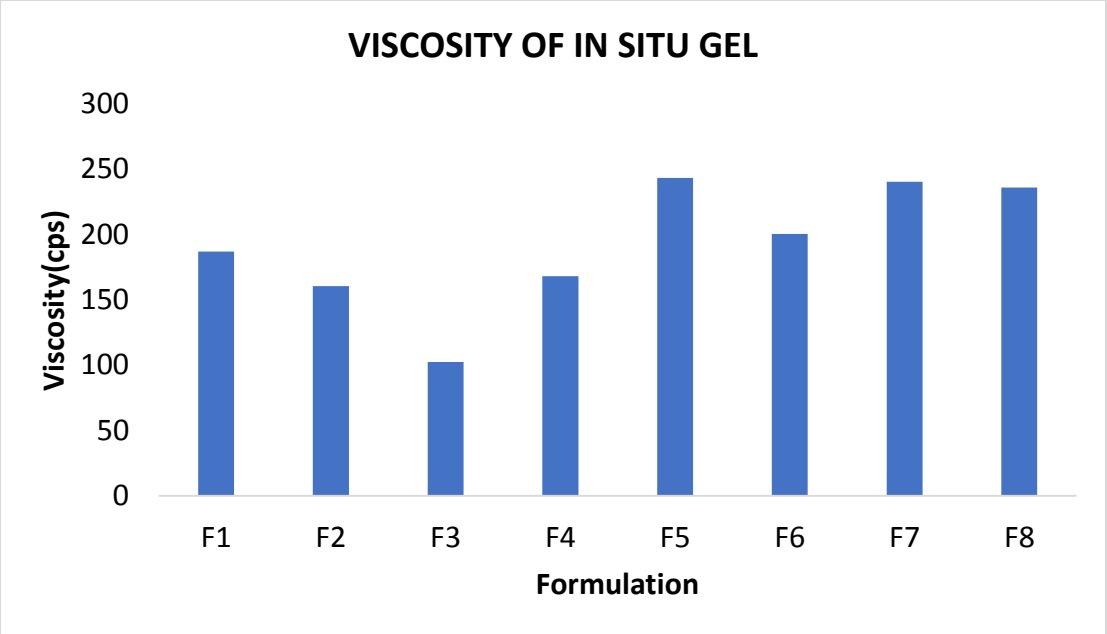


Fig 9.14 Viscosity of *In situ* gel formulation

9.3.5 In vitro Buoyancy of Losartan potassium Oral In situ Gel

The time taken by the formulation to emerge on the surface of the medium is the floating lag time and the time period for which the formulation constantly floats on the surface of the medium is known as floating duration. The results of buoyancy studies are given in Table 9.16.

Table 9.16 In vitro buoyancy of Oral In situ Gel

S. No	Formulation Code	Floating Lag Time(min)	Floating Duration (hrs)
1	F1	<1	>12
2	F2	<1	>12
3	F3	<1	<12
4	F4	<1	>12
5	F5	<1	>12
6	F6	<1	>12
7	F7	<1	>12
8	F8	<1	>12

Inference

- All the *In situ* gel formulations had a floating lag time of <1 min and all the formulations floated for more than 12 hours except, formulation F3.
- Therefore, the extended duration of floating may be responsible for the controlled release of drug.

9.3.6 Density of Losartan potassium Oral In situ Gel

Density is an important evaluation parameter as far as the buoyancy ability of the gastroretentive dosage form is concerned. For the formulation to float on the gastric contents, it should have a density less than or equal to that of the gastric contents (□1.004 gcm^{-3})

Table 9.17 Density of Oral In situ Gel

S. No	Formulation Code	Density of Oral In situ Gel (g/cm^3)
1	F1	0.623
2	F2	0.642
3	F3	0.598
4	F4	0.628
5	F5	0.685
6	F6	0.697
7	F7	0.701
8	F8	0.752

Inference

- The density of all the formulations are less than that of the gastric fluid (□ 1.004 gcm^{-3}).
- As a result, the floating of the gastroretentive *In situ* gel is promoted in the stomach.

9.3.7 Measurement of gel strength of Losartan potassium Oral *In situ* gel

The ability of the gelled mass to withstand the peristaltic movement in vivo is determined by measuring gel strength.

Table 9.18 Gel strength of oral *In situ* gel

S. No	Formulation Code	Average Gel Strength (Time in seconds)
1	F1	28.3
2	F2	24.2
3	F3	15.9
4	F4	20.4
5	F5	35.6
6	F6	32.7
7	F7	40.8
8	F8	42.1

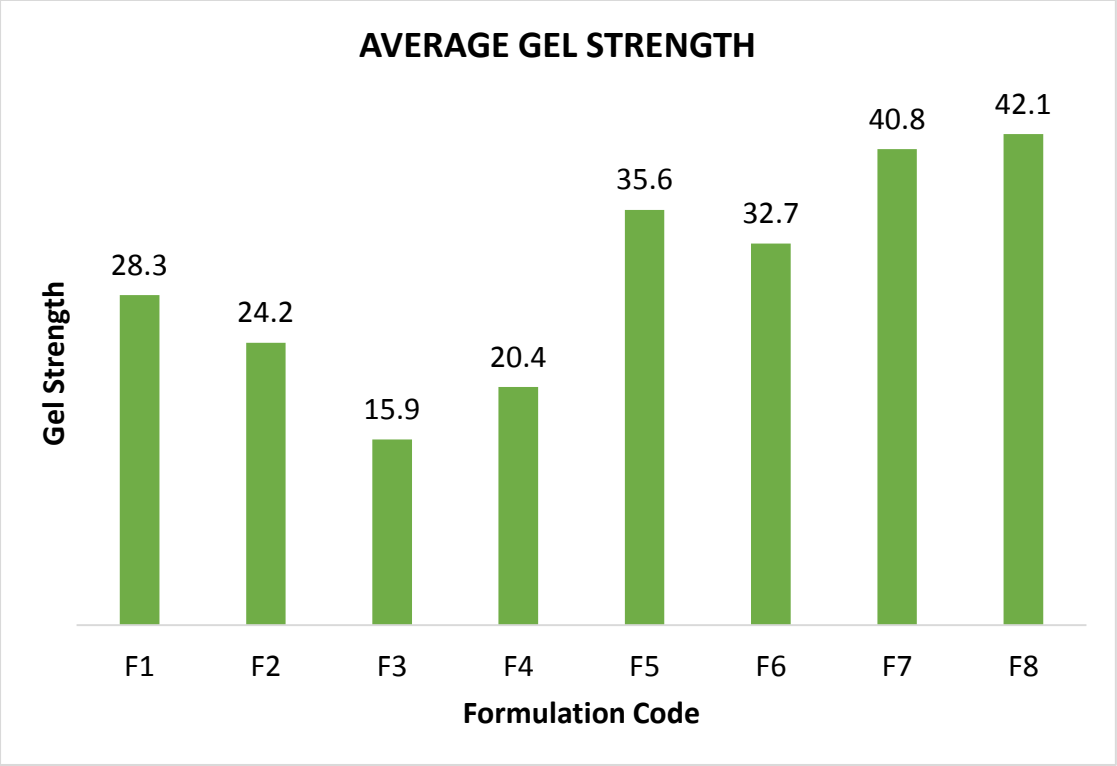


Fig 9.15 Average gel strength of Oral *In situ* gel

Inference

- All the formulations showed good gel strength which ranged from as low as15.9 sec for formulation F3 which contains only Iota carrageenan as main polymer to of 42.1 sec for formulation F8 respectively, which contains combination of both polymers.
- When the gel strength is more, the formulation may retain its consistency for a prolonged period of time. Thus, the release of the drug may also be prolonged.

9.3.8 Percentage water uptake by Losartan potassium Oral *In situ* Gel

The percentage water uptake of all the formulations is given in table 9.19

Table 9.19 Percentage water uptake of *In situ* Gel formulations

Time (min)	Percentage water uptake by the formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
30	4.03	2.15	2.83	6.73	5.91	4.27	8.19	6.52
60	6.84	6.82	6.67	8.56	8.92	10.84	12.20	11.78
90	9.93	9.90	10.0	9.76	11.73	14.44	15.49	16.19
120	14.38	13.05	13.10	13.64	14.41	17.59	20.72	25.19

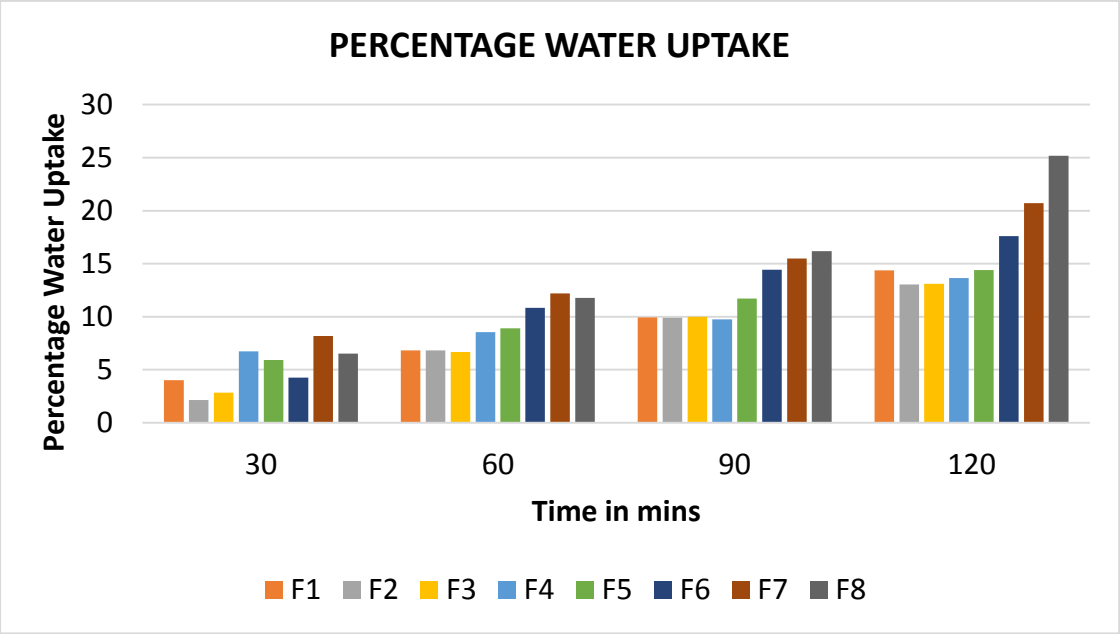


Fig 9. 16 Percentage water uptake of the *In situ* gel

Inference

- ✓ The quantity of water associated with the drug delivery system plays an important role in determining the release of the drug from the polymer matrix.
- ✓ The percentage water uptake of all the formulations is given table 9.19 and fig9.16. When compared with other formulations F8 showed better water uptake of 25.19% respectively. The high-water uptake may be because of the high swelling capacity of the polymers used.

9.3.9 Drug content of Losartan potassium Oral *In situ* gel

Drug content is one of the important evaluation parameters for any type of dosage form. The percentage drug content of the formulations is given in table 9.20

Table 9.20 Percentage drug content of formulated *In situ* gel

S. No	Formulation Code	Drug Content (%)
1	F1	87.5
2	F2	88.41
3	F3	90.33
4	F4	89.72
5	F5	90.03
6	F6	91.33
7	F7	95.77
8	F8	99.69

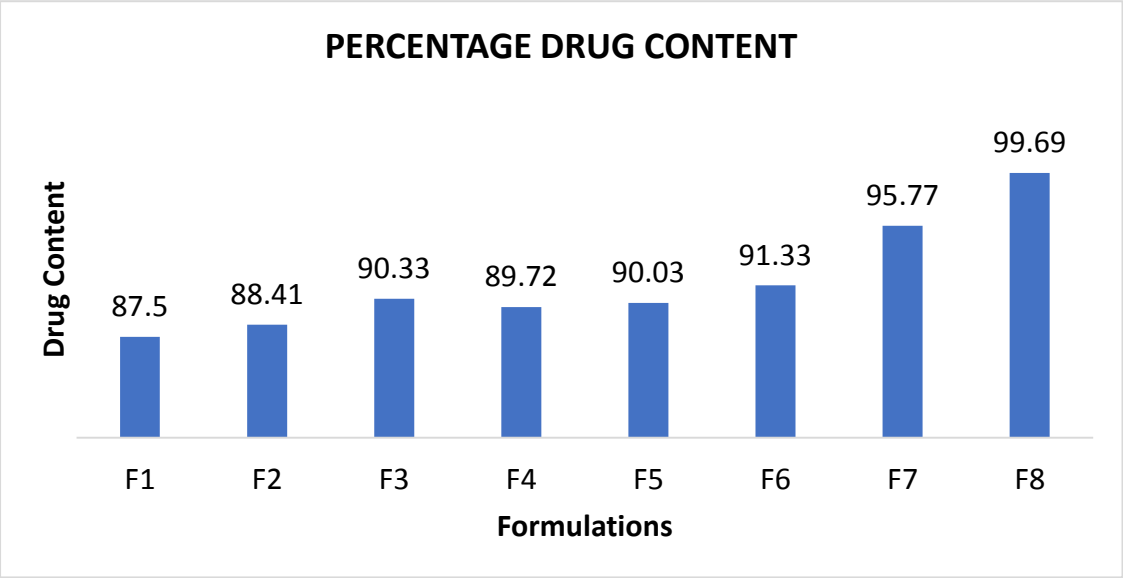


Fig 9.17 Percentage drug content of *In situ* gel

Inference

- The percentage drug content of all the formulations was in the range of 87.5 – 99.69% indicating equal distribution of drugs in all the formulations.
- The results are comparable to that of Losartan potassium tablets (Acceptance criteria: Not less than 70%).

9.3.10 *In vitro* Dissolution study of Losartan potassium Oral In situ Gel

The results of In vitro drug release study of the In situ gel formulations are given in Table 9.21

Table 9.21 In vitro release of oral *In situ* gel

Time (hr)	Control	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0	0
1	33.5	11.35	14.03	19.37	12.03	13.37	13.16	8.58	7.54
2	49.56	26.89	24.83	31.14	24.32	26.94	24.28	12.06	13.29
3	72.31	35.45	35.21	48.04	37.67	35.11	35.95	21.11	20.31
4	83.79	49.64	51.33	59.65	47.77	48.16	43.19	25.84	28.39
5	98.03	62.13	64.80	71.01	56.32	60.81	56.31	36.11	35.72
6		75.23	75.09	86.32	67.04	69.21	64.92	42.19	46.21
7		86.47	89.32	96.02	74.39	82.32	75.08	54.39	58.48
8		96.93	97.01		87.18	95.02	81.98	65.03	66.23
9					94.59		88.46	74.31	75.23
10							97.28	83.62	87.62
11								89.83	95.95
12								98.24	99.64

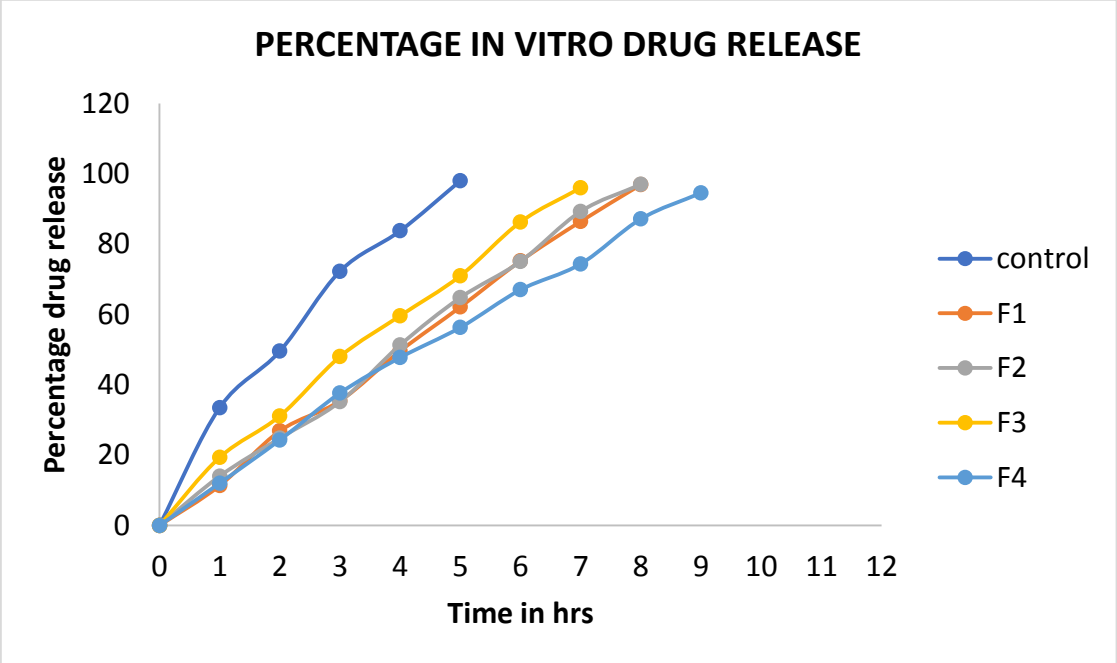


Fig 9.18 *In vitro* drug release study of control and *In situ* gel formulations (F1 – F8) of Losartan potassium.

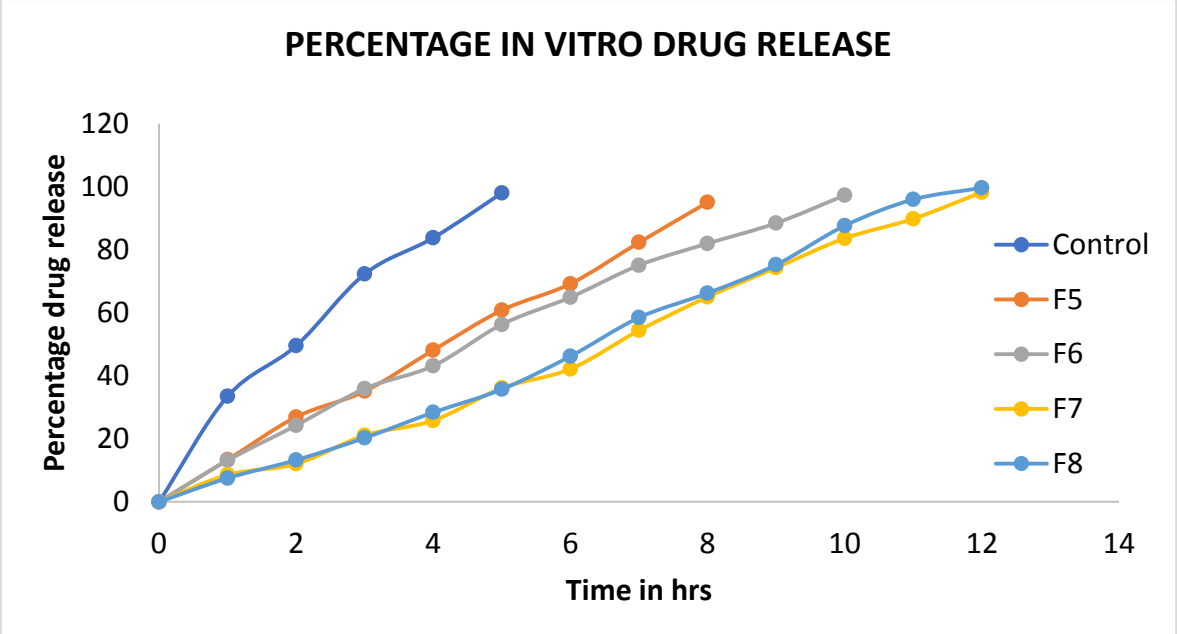


Fig 9.19 *In vitro* drug release study of control and *In situ* gel formulations (F4 – F5) of Losartan potassium

Inference

- From the *In vitro* drug release studies of *the In situ* gel formulations, it was observed that only the formulation F8 containing the combination of both the polymers in higher concentration (Gellan gum and Iota carrageenan) provided prolonged release of the drug up to 12 hours. Other formulations released the drug even before the period of 12 hours.
- Formulation F8 containing both Gellan gum (0.25%w/v) and Iota carrageenan (0.4 %w/v) showed 99.64 % of drug release at the end of 12 hours.

9.4 *IN VITRO* RELEASE KINETICS

Fig 9.22 *In vitro* release kinetics of the optimized formulation (F8)

Time	Square root of time	Log time	Cum. % Drug release	Cum. % Drug Remaining	Log Cum. % drug remaining	Log cum. % Drug Release	Cube root of % Drug Remaining
0	0	∞	0	100	2	∞	4.641
1	1	0	7.54	92.46	1.9659	0.8773	4.5219
2	1.4142	0.3010	13.29	86.71	1.9380	1.1235	4.4261
3	1.7320	0.4771	20.31	79.69	1.9014	1.3077	4.3032
4	2.0000	0.6020	28.39	71.61	1.8549	1.4531	4.1526
5	2.2360	0.6989	35.72	64.28	1.8080	1.5529	4.0058
6	2.4495	0.7781	46.21	53.79	1.7307	1.6647	3.7749
7	2.6458	0.8450	58.48	41.52	1.6182	1.7670	3.4627
8	2.8284	0.9031	66.23	33.77	1.5285	1.8210	3.2322
9	3.0000	0.9542	75.23	24.77	1.3939	1.8763	2.9150
10	3.1623	1.0000	87.62	12.38	1.0927	1.9426	2.3133
11	3.3166	1.0414	95.95	4.05	0.6075	1.9820	1.5939
12	3.4641	1.0792	99.64	0.36	- 0.4437	1.9984	0.7114

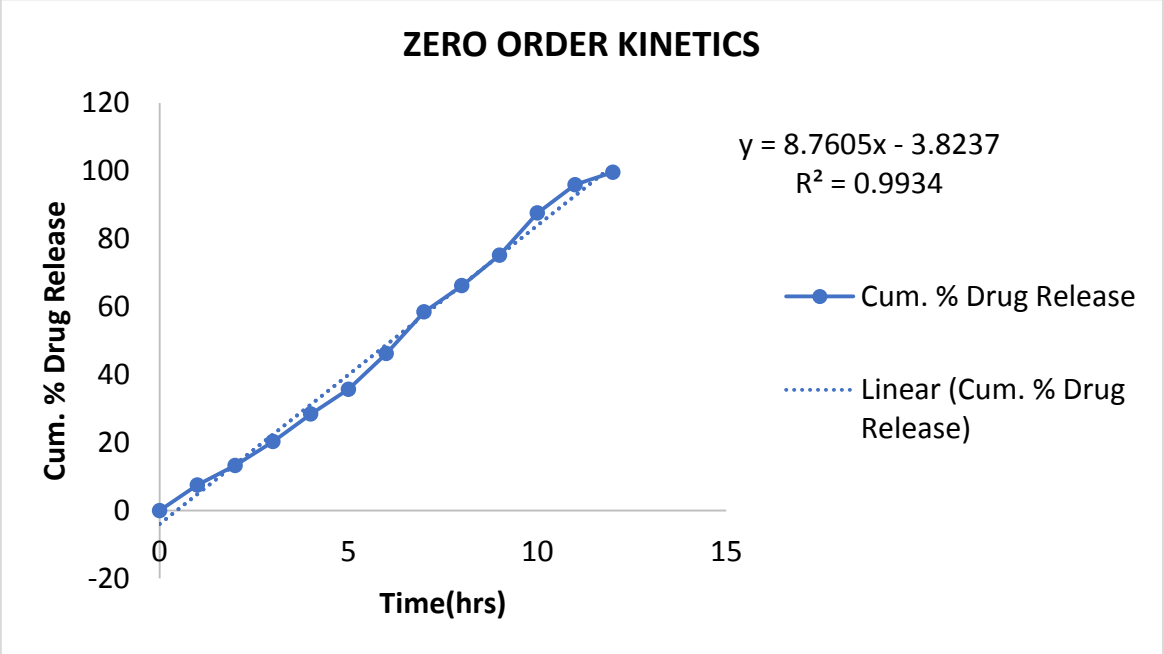


Fig 9.20 Plot of Zero order kinetics of optimized formulation (F8)

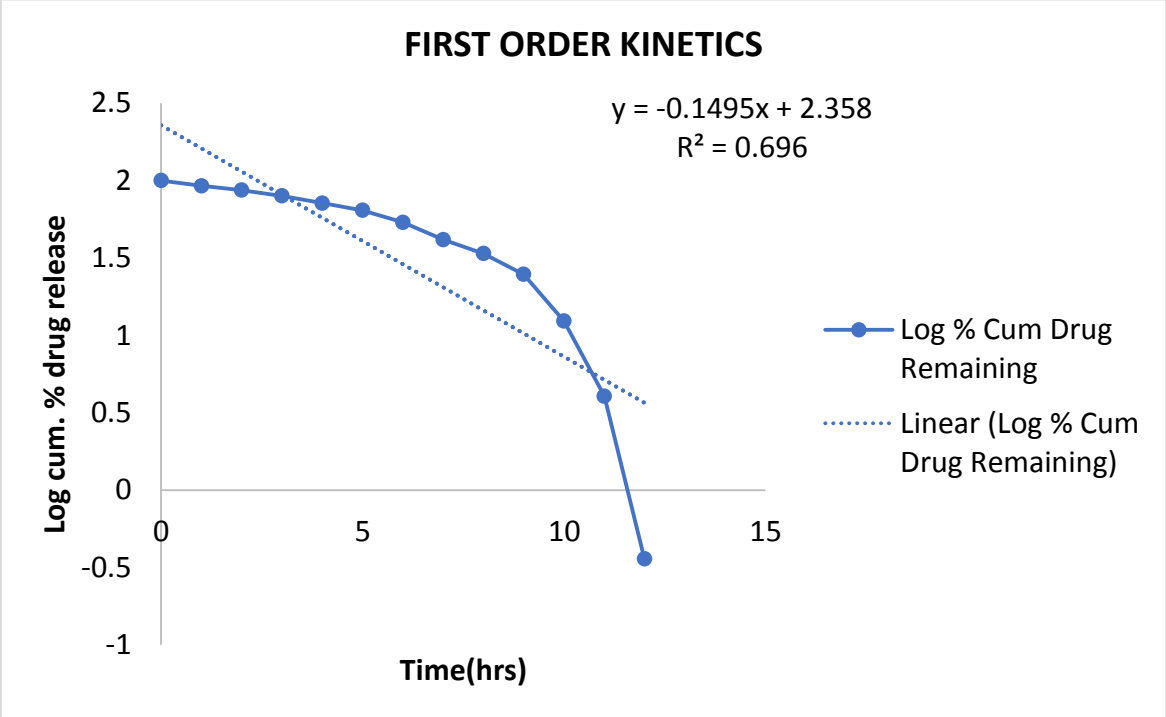


Fig 9.21 Plot of first order kinetics of optimized formulation (F8)

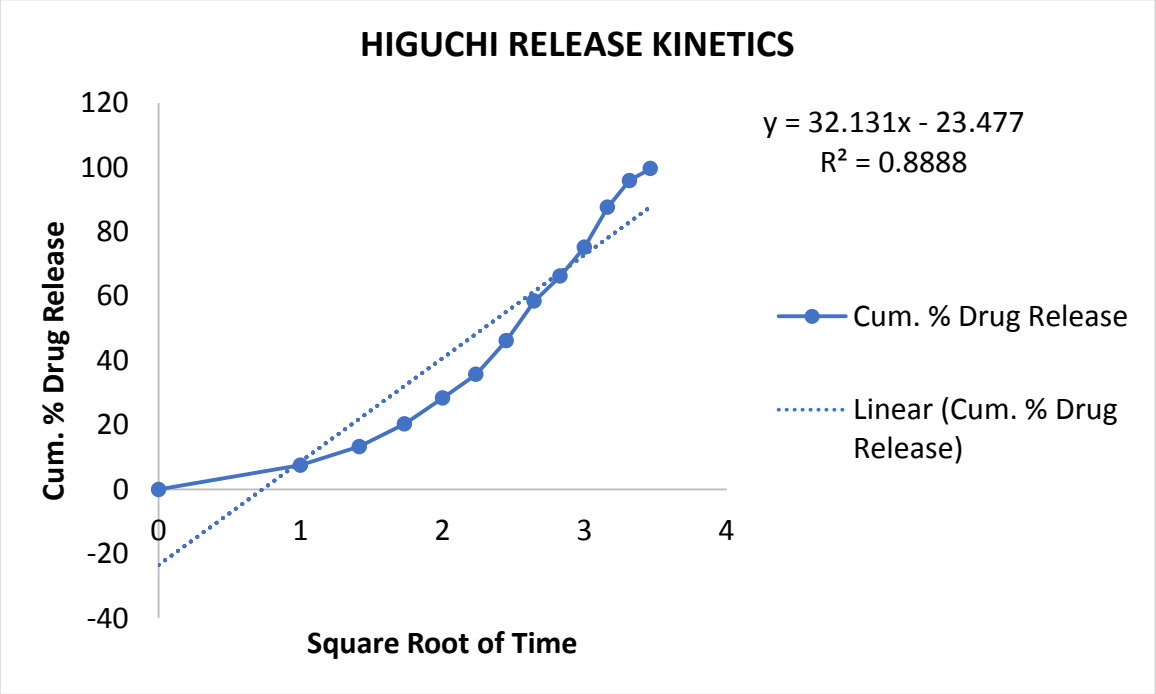


Fig 9.22 Plot of Higuchi release kinetics of optimized formulation(F8)

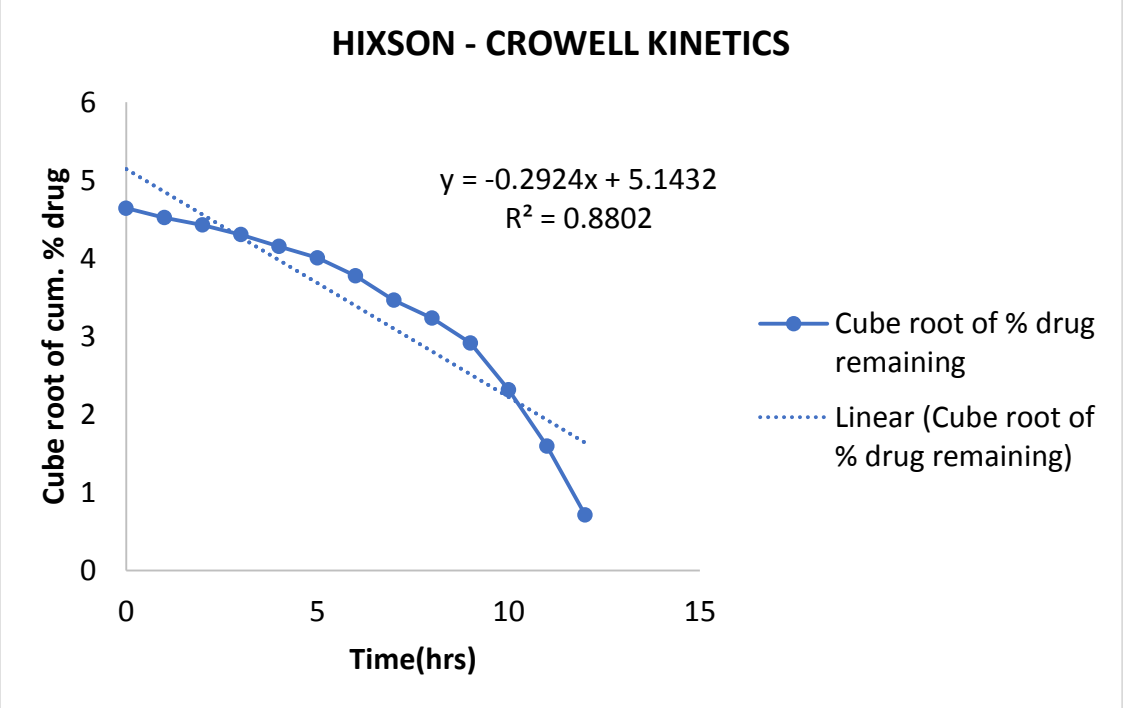


Fig 9.23 Plot of Hixson Crowell kinetics of optimized formulation (F8)

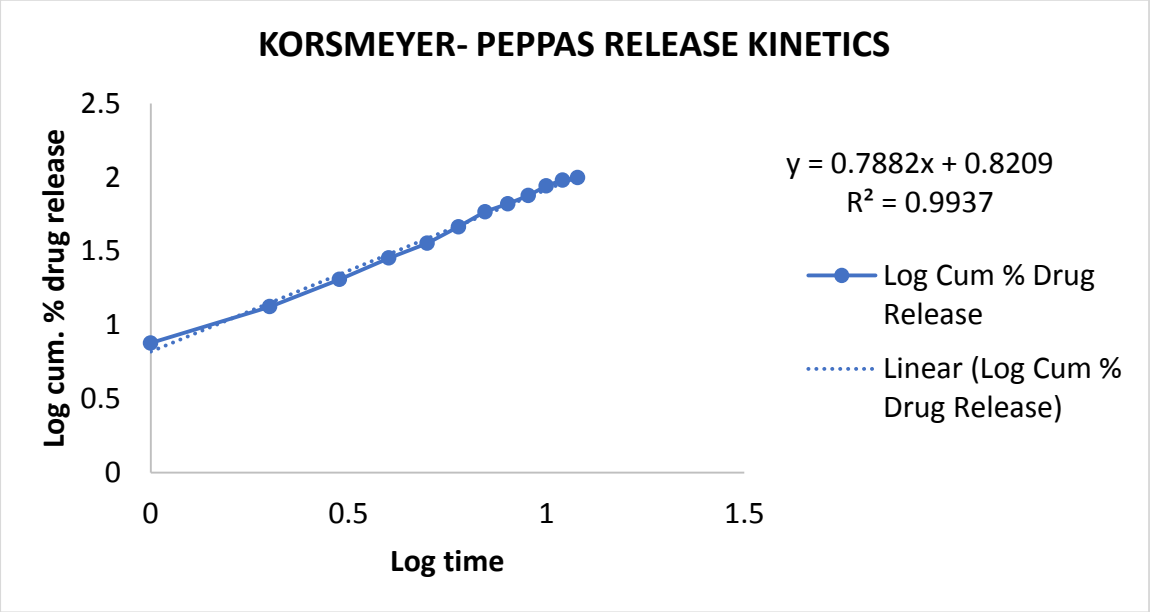


Fig 9. 24 Plot of Korsmeyer- peppas kinetics of optimized formulation

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2 values of various models are given in table 9.23

Table 9.23 R^2 values of various models of optimized formulation (F8)

Kinetics Models	Coefficient of Determination (R^2)
Zero Order	0.9934
First Order	0.693
Higuchi	0.8888
Hixson – Crowell	0.8802
Korsmeyer - peppas	0.9937

The *In vitro* release of optimized formulation F8 data was fit into various kinetic models to find out the mechanism of drug release from Losartan potassium oral *In situ* gel.

Good linearity was observed with the zero order (R^2 = 0.9934). The zero-order kinetics explains the controlled release of drug in the prepared *In situ* gel over the period of 12 hours.

The slope of the regression line from the Higuchi plot (R^2 = 0.8888) and Hixson- Crowell plot (R2 = 0.8802) indicates that the rate of drug release follows both diffusion and dissolution mechanism.

The slope of the Korsmeyer- Peppas plot (n= 0.7882) was found to be more than 0.45 indicating the diffusion was anomalous diffusion (Non – Fickian diffusion).

Thus, the release kinetics of the optimized formulation showed zero order drug release with non fickian diffusion mechanism.

9.5 STABILITY STUDIES

The optimized formulation (F8) was subjected to stability studies as per ICH guidelines and shown in Table 9.25

Parameter	**Condition: 40 ± 2º C / 75 ±5% RH**				
	Day 0	**Day 15**	**Day 30**	**Day 60**	**Day 90**
Visual appearance	Dull white	Dull white	Dull white	Dull white	Dull white
Pourability	Pourable	Pourable	Pourable	Pourable	Pourable
pH	7.185 ± 0.004546	7.193 ± 0.001414	7.184 ± 0.001826	7.190 ± 0.001633	7.193 ± 21.579
Gelling capacity	+++	+++	+++	+++	+++
Floating lag time (min)	<1	<1	<1	<1	<1
Floating duration(hrs)	>12	>12	>12	>12	>12
Viscosity (cps)	235.9	233.1	231.5	230.3	233.8
Drug content (% w/v)	99.69	99.54	99.35	99.24	99.44

SUMMARY AND CONCLUSION

The Losartan potassium oral *In situ* gel F1.F2.F3.F4.F5.F6.F7 and F8 was developed using gelling agents such as Gellan gum, Iota carrageenan and HPMC K4M.

- ✓ Physical compatibility study showed that the drug and excipients are physically compatible with each other.
- ✓ Chemical compatibility study was performed using FT-IR spectroscopy and its studies revealed that there was no change in major peaks, thus confirming no interaction between the drug and excipients.
- ✓ Calibration curve of Losartan potassium was constructed in simulated gastric fluid of pH 1.2 and it obeys Beer Lambert's law.
- ✓ 8 formulations of Losartan potassium *In situ* gel was prepared using varying concentrations of different polymers such as Gellan gum, Iota carrageenan along with HPMC K4M as the release retardants.
- ✓ The prepared formulations (F1- F8) were evaluated for physical appearance, pourability, pH, viscosity, *In vitro* gelation study, *In vitro* buoyancy study, density, gel strength, percentage water uptake, drug content and *In vitro* drug release.
- ✓ All the formulations had good physical appearance.
- ✓ All the formulations except F3 exhibited good gelling capacity. The gel that was formed dispersed rapidly in the formulation F3 containing only Iota carrageenan as the main polymer.
- ✓ All the formulations showed floating lag time of less than 1 minute and duration of floating are greater than 12 hours.
- ✓ All the formulation exhibited lower density than the density of gastric fluid (1.004 gcm^{-3}).
- ✓ Formulations F7 and F8 showed higher gel strength when compared to the other formulations.
- ✓ The percentage water uptake was higher for formulations F7 and F8 due to the presence of combination of polymers Gellan gum and Iota carrageenan.
- ✓ The percentage drug content of all the formulations was in the range of 87.5 – 92.74 % indicating uniform distribution of drugs.

- ✓ *In vitro* drug release study showed that only the formulations F7 and F8 released 98.24 % and 98.64 % of drug respectively at the end of 12 hours, while the other formulations showed more than 90 % of drug release even before the period of 12 hours.
- ✓ *The In vitro* release kinetics study of the optimized formulation F8 showed that the formulation followed Zero order kinetics and Non- fickian diffusion mechanism.
- ✓ The stability studies indicated that the optimized formulation F8 was stable and did not show any significant changes in the physical appearance, pH, gelling capacity, floating time, viscosity, drug content and *In vitro* drug release at the end of 3 months.

The overall results indicate that the formulation of Losartan potassium as oral floating *In situ* gel provides controlled release of the drug. This may improve the patient compliance due to ease of administration and reduction in dosing frequency. Hence, the developed formulation can be used as an alternative to the conventional dosage form for the treatment of Hypertension in patients.

FUTURE PLANS:

- Scale-up studies of the optimized formulation
- *In vivo* and *In vitro- In vivo* correlation studies
- To perform Bioequivalence studies

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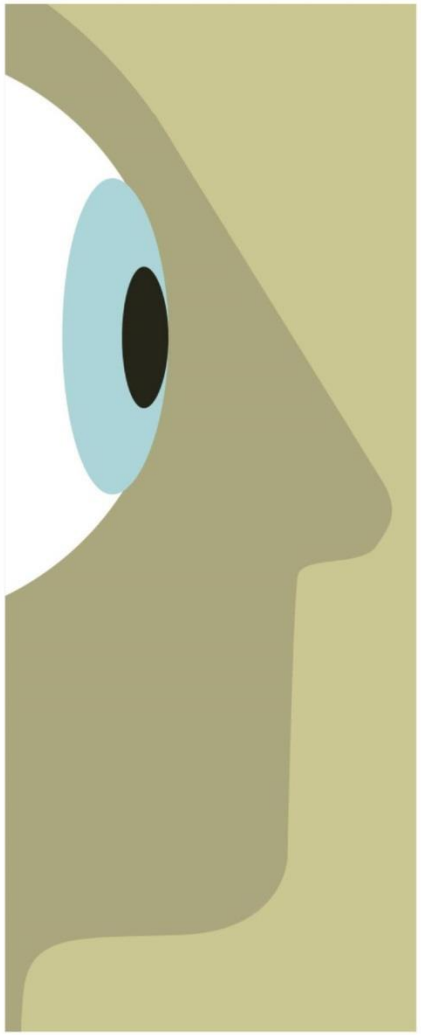

Researcher Academy On Campus

Certificate of Attendance

ELSEVIER

This certifies that

SHENI OBEL D

has attended the following

360 degree view on research management & academic journal publishing

at Indian Council of Medical Research,
on Friday 12 November, 2021

Presented by Priyanka Chatterjee Software Solutions Manager, Dr. Vishnu Vardhan Rao Director ICMR-National Institute of Medical Statistics (NIMS)

Suzanne BeDell
Managing Director, Education
Reference & Continuity Books

Philippe Terheggen
Managing Director, Science,
Technology & Medical Journals

Indian Pharmacy Graduates' Association

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IPGA Kerala State Branch

Certificate

This Certificate is presented to

SHENI OBEL.D

for attending the webinar conducted in the topic

Recent Trends in Quality Assurance in the In-Vitro Diagnostic Reagents

By Mr. Sanjaymon, K.R., Associate Vice President (Quality), Agappe Diagnostics Ltd.,

held on **Sunday, the 30th January 2022,** with Thanks.

Dr. Satheesh Kumar, C.S.,
President,
IPGA-Kerala State

Dr. Dileep. G.,
Secretary,
IPGA-Kerala State

Dr. Atul Kumar Nasa
Hon'ble President,
IPGA

Dr. Arun Garg
General Secretary,
IPGA

SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY

(Deemed to be University)

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School Of Pharmacy

CERTIFICATE OF PARTICIPATION

This is to certify that

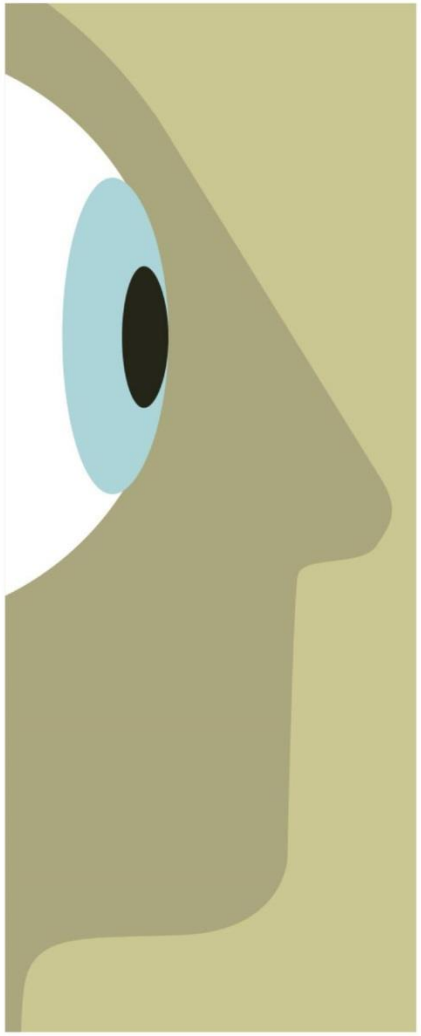
Ms. SHENI OBEL. D

School of Pharmacy, Sathyabama Institute of Science and Technology

has actively participated in the International webinar on "**Nanomedicine: Tiny is Mighty**" organized by **School of Pharmacy, Sathyabama Institute of Science and Technology, Chennai** on **June 30, 2020**.

ORGANISER	DEAN -SCHOOL OF PHARMACY	PRO VICE CHANCELLOR
Dr. Marslin Gregory	Dr. P. Shanmuga Pandiyan	Dr. Wilson Aruni

E-Certificate No. SOP/June2020/Web03/



Researcher Academy On Campus

Certificate of Attendance

ELSEVIER

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SHENI OBEL D

has attended the following

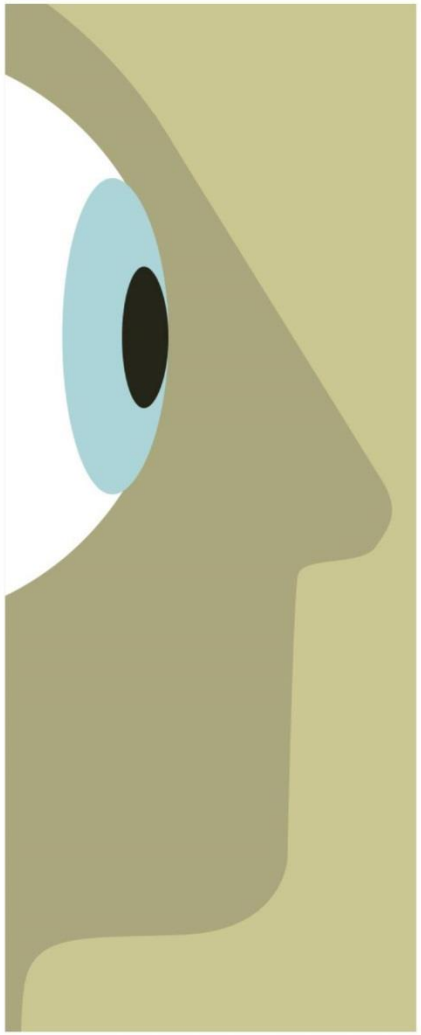
Ethics of publication

at Indian Council of Medical Research,
on Tuesday 23 November, 2021

Presented by Catriona Fennell Director Journal Service, Dr. Roli Mathur Scientist F and Head, ICMR Bioethics Unit

Suzanne BeDell
Managing Director, Education
Reference & Continuity Books

Philippe Terheggen
Managing Director, Science,
Technology & Medical Journals



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This certifies that

SHENI OBEL D

has attended the following

"Effective writing skills for promoting research - what do we need to know?"

at Indian Council of Medical Research,
on Monday 13 December, 2021

Presented by Fernanda Ogochi Executive Publisher Pharmacology, Dr. Beena Thomas Former Head, Department of Social and Behavioral Research, National Institute for Research in Tuberculosis and Dr. Jeyashree Kathiresan Scientist D

Suzanne BeDell
Managing Director, Education Reference & Continuity Books

Philippe Terheggen
Managing Director, Science, Technology & Medical Journals

CHEBROLU HANUMAIAH
INSTITUTE OF PHARMACEUTICAL SCIENCES

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INDIAN PHARMACEUTICAL ASSOCIATION, EDUCATION DIVISION

CERTIFICATE OF PARTICIPATION

This is to certify that Ms.SHENI OBEL. D

has participated in ***A Webinar on "Importance of Regulatory and Corporate Affairs and their Pharmaceutical Perspectives"*** *on* ***12th July, 2020,*** *organised by* ***Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur*** *in Association with* ***Indian Pharmaceutical Association, Education Division.***

Dr. Y. A. Chowdary CEC Member, Indian Pharmaceutical Association	**Dr. T. E. G. K. Murthy** CEC Member, Indian Pharmaceutical Association	**Dr. S. Vidyadhara** Chairman, IPA, Education Division	**Dr. T. V. Narayana** President, Indian Pharmaceutical Association

71st Indian Pharmaceutical Congress

Theme: Healthcare System - Role of Regulators

Certificate

This is to certify that Prof./Dr./Mr./Ms.....SHENI OBEL D.....
of ..COLLEGE OF PHARMACY, MADRAS MEDICAL COLLEGE..... has participated in the 71st Indian Pharmaceutical Congress held at Sri Ramachandra Institute of Higher Education and Research (DU), from 20th to 22nd December 2019, Chennai, Tamil Nadu.

Shri. Ravi Uday Bhaskar	Dr. P.V.Vijayaraghavan	Dr. M. Dhilip Kumar	Dr. T.V. Narayana
President - 71st IPC 2019	Chairman - LOC	Secretary - LOC	General Secretary - IPCA

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