FORMULATION DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF ORAL FLOATING *IN SITU* GELLING LIQUID SYSTEM OF RIVASTIGMINE TARTRATE

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032.

in partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

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COLLEGE OF PHARMACY

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MAY- 2019

DEPARTMENT OF PHARMACEUTICS
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DATE:

CERTIFICATE

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ABBREVIATIONS AND SYMBOLS

CR	Controlled Release
ER	Extended Release
SR	Sustained Release
SGF	Simulated Gastric Fluid
GIT	Gastrointestinal tract
GRDDS	Gastroretentive Drug Delivery System
MMC	Migrating Myoelectric Complex
GRT	Gastric Retention Time
FDDS	Floating Drug Delivery System
HBS	Hydrodynamically Balanced Systems
HPMC	Hydroxy Propyl Methyl Cellulose
GRDF	Gastroretentive Dosage Form
GERD	Gastro Esophageal Reflux Disease
NSAID	Non-Steroidal Anti Inflammatory Drug
PVA	Poly-Vinyl Alcohol
HEC	Hydroxy Ethyl Cellulose
Na CMC	Sodium Carboxy Methyl Cellulose
CO_2	Carbon dioxide
3D	Three dimensional
cps	Centipoise
$CaCO_3$	Calcium carbonate
QbD	Quality by Design
AUC	Area Under the Curve
RPM	Revolutions per minute
USP	United states pharmacopeia
g	Gram
w/v	weight/volume
λ max	Wave length with maximum absorbance

AD	Alzheimer's Disease
CSF	Cerebro-spinal Fluid
BP	British Pharmacopoeia
Ph Eur	European Pharmacopoeia
USP-NF	United States Pharmacopoeia - National Formulary
USP	United States Pharmacopoeia
HCl	Hydrochloric Acid
NC	No Change
FTIR	Fourier Transform Infra-Red Spectroscopy
API	Active Pharmaceutical Ingredient
RH	Relative Humidity
RPM	Revolution Per Minute
S.D	Standard Deviation
UV	Ultra Violet
Vis	Visible
%	Percentage
^{0}	Degree
^{0}C	Degree Celsius
cm	Centimeter
Cum.	Cumulative
Hrs.	Hours
L	Litre
M.W	Molecular Weight
mg	Milli Gram
min.	Minutes
nm	Nano Meter
sec	Seconds
µg	Micro gram
ICH	International Council for Harmonization
pH	Negative logarithm of hydrogen ion concentration

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INTRODUCTION

1. INTRODUCTION

1.1. DOSAGE FORMS[1]

Dosage forms are the means by which drug molecules are delivered to sites of action within the body. Drug substances are formulated in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions. The proper design and formulation of a dosage form requires consideration 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.

1.1.1. Need for dosage forms[1]

- To provide accurate dosing of the drug
- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules)
- Protection from gastric environment (Enteric coating)
- Masking taste and odour of drugs (bitter taste of drugs)
- Placement of drugs within body tissues
- Insertion of drugs into body cavities (rectal, vaginal)
- Providing sustained and controlled release of medication
- To obtain optimal drug action
- Use of desired vehicle for insoluble drugs

1.1.2. Types of dosage forms[1]

Based on their 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

1.2. ROUTES OF DRUG ADMINISTRATION[2]

Administration of drugs by various routes is described in the Fig. 1.1

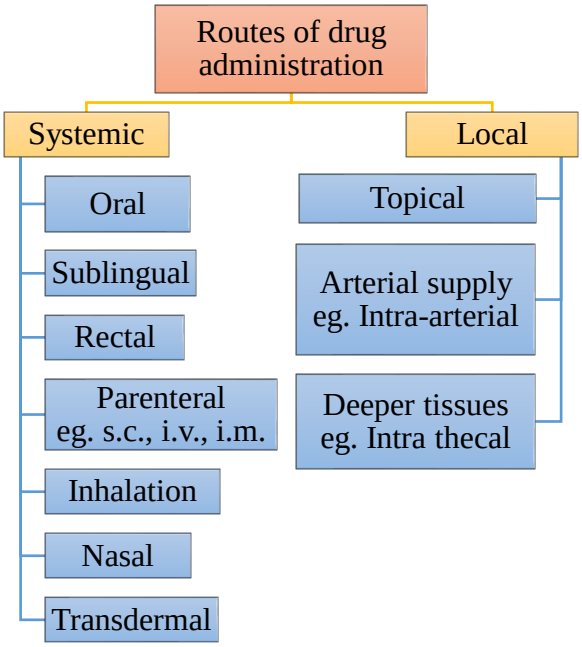


Fig. 1.1 : Routes of Drug Administration

1.3. ORAL DRUG DELIVERY[3]

Oral delivery is typically considered the most favourable and preferred route of drug administration in case of conscious and co-operating patients, because of convenience, possibility of self-administration and enhanced compliance. More than 60% of drugs are marketed in the form of oral products.

1.4. LIQUID DOSAGE FORMS[4]

Liquid preparations for oral use are usually solutions, emulsions or suspensions containing one or more active ingredients in a suitable vehicle; they may in some cases consist simply of a liquid active ingredient used as such. The vehicle for any liquid preparation for oral use is chosen having regard to the nature of the active ingredient(s) and to provide organoleptic characteristics appropriate to the intended use of the preparation. Liquid preparations for oral use may contain suitable antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing, flavouring and sweetening agents and authorized colouring 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.

1.4.1. Advantages of Oral Liquids

- Ease of dose adjustment by dilution, thus making it easier to swallow than solids and acceptable for paediatric and geriatric use.
- Immediate drug availability after absorption, hence faster therapeutic response than the solid formulations, which has to disintegrate for the drug to be dissolved in the gastrointestinal fluid before the absorption begins.[4,5]
- 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.[5]

1.4.2. Disadvantages of Liquid Preparations

- Liquids being bulky, are inconvenient to transport and store.
- The stability of drugs are poor when formulated as liquids than that of solids like tablets or capsules, especially if the drugs are susceptible to hydrolysis. Hence, shorter shelf life of the formulations.
- Preservatives are necessary as the solutions are widely prone to microbial growth.[5]

1.4.3. Classification of Oral Liquid Dosage Forms

Oral liquid dosage forms can be classified as:

1.4.3.1. Conventional oral Liquid dosage form:

- This drug delivery system results in suboptimal therapy and/or systemic side effects.[6] Several preparations are distinguished including: oral solutions, emulsions, suspensions, elixirs, oral drops, spirits and syrups.[7]

1.4.3.2. Non-conventional oral Liquid dosage forms

- **Extended /Sustained release dosage form (ER/SR):** The attractiveness of ER dosage form is the success to ensure safety, improve the efficiency of drug, reduce the dose frequency and thus reduction in the side effects and improvement of bioavailability could be expected. As a result more patient compliance especially for paediatric and geriatric patients or patients that are unable to tolerate solid dosage forms.[8]

- **Controlled/Gastroretentive release dosage form (CR/GR):** It offers an alternative and novel strategy for achieving extended release profile, where the formulation will remain in the stomach for a prolonged period, releasing the drug *In situ*, which will then dissolve in the liquid contents and slowly pass into the small intestine.[9]

1.5. STOMACH - AN OVERVIEW[10]

The stomach is 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.

1.5.1. Anatomy of stomach[10]

The stomach has four regions: 1) Cardia (2) Fundus (3) Body (4) Pylorus as shown in Fig. 1.2.

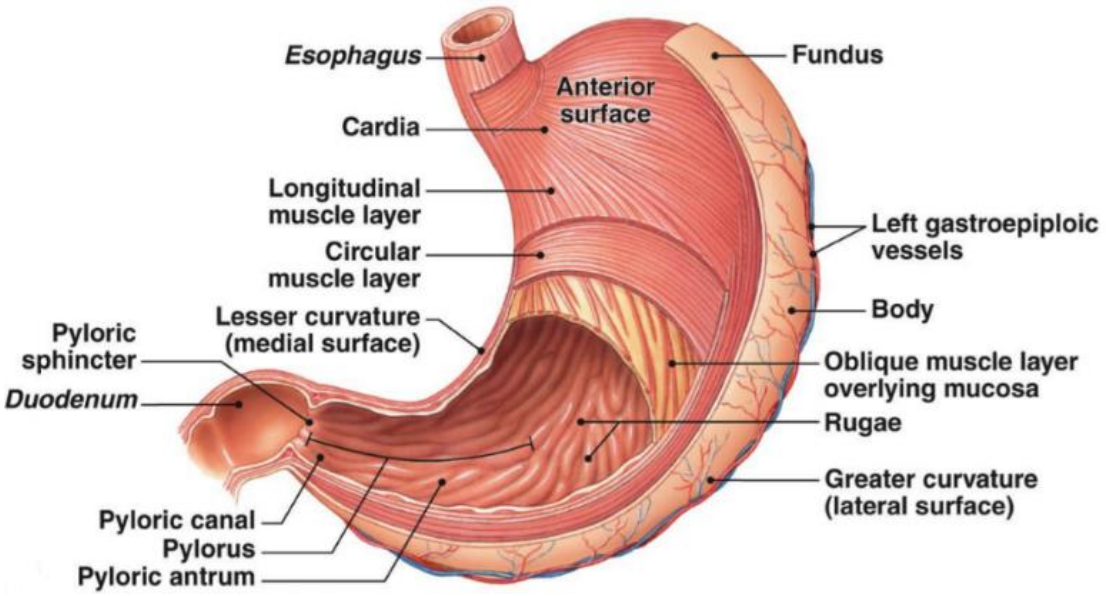


Fig. 1.2: Anatomy of the stomach

Gastric emptying: The process of gastric emptying happens both during fasting and 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 in Fig 1.3 and described in the table 1.1.

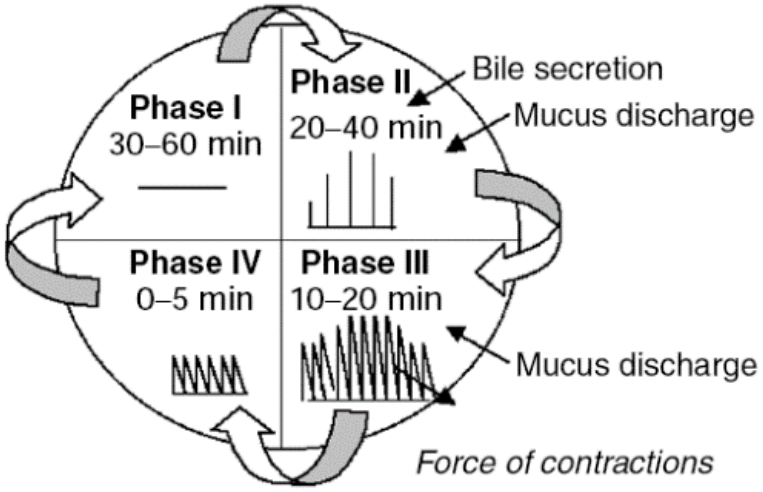


Fig. 1.3: Phases of gastric emptying

Table 1.1: Different phases of gastric emptying

Phase	**Duration**
Phase-I (Basal Phase)	30-60 min with infrequent contractions
Phase-II (Preburst Phase)	20-40 min with irregular action potential and 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 & one of two 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 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 that leads to decreased systemic bioavailability of numerous drugs.

1.6. GASTRORETENTIVE DRUG DELIVERY SYSTEMS(GRDDS)[11]

Drugs which are easily absorbed from the gastrointestinal tract and those with short 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 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 is shown in Fig. 1.4.

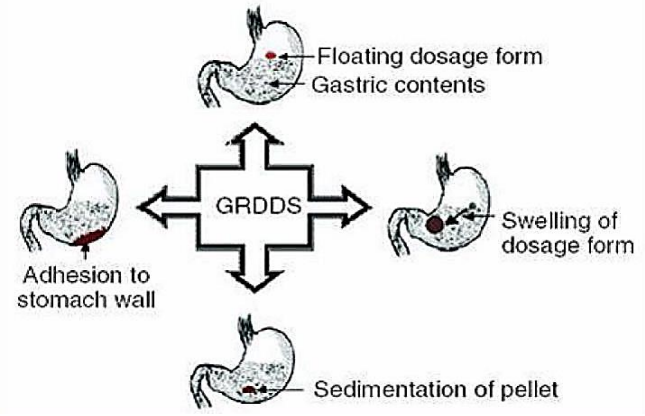


Fig. 1.4: Approaches to GRDDS

1.6.1. Factors Affecting Gastric Retention[12]

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 (1.004 gm/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, allow co-administration of units that have dissimilar release profiles related with single unit dosage forms.

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) is less 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 decrease GRT.

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

1.6.2. Advantages Of Gastroretentive Drug Delivery Systems[11,13]

- Maintenance of constant therapeutic level over longer period of time. E.g. Beta lactam 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, etc.
- 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.
- Bioavailability enhances despite the first pass effect as a result of variations in plasma drug concentration are escaped; a required plasma drug concentration is retained by the continuous drug release.
- Controlled drug delivery of drugs.

1.6.3. Disadvantages Or Limitation Of Gastroretentive Drug Delivery Systems[11]

- Drugs, that undergo significant first pass metabolism, are not desirable candidate.
- 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.
- The dosage form must be taken with a full glass of water.
- Violent gas generation, disintegration of dosage forms, burst release, dose dumping, and alkaline microenvironment are the limitation 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 is 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 takes longer time to swell.

1.6.4. Need Of Gastroretentive Drug Delivery Systems[11]

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 an 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 problem floating drug delivery system has been developed.

1.6.5. Approaches For GRDDS[14]

The classification and different approaches for formulating dosage form to produce gastric retention and release within gastric region shown in fig 1.5 and fig 1.6

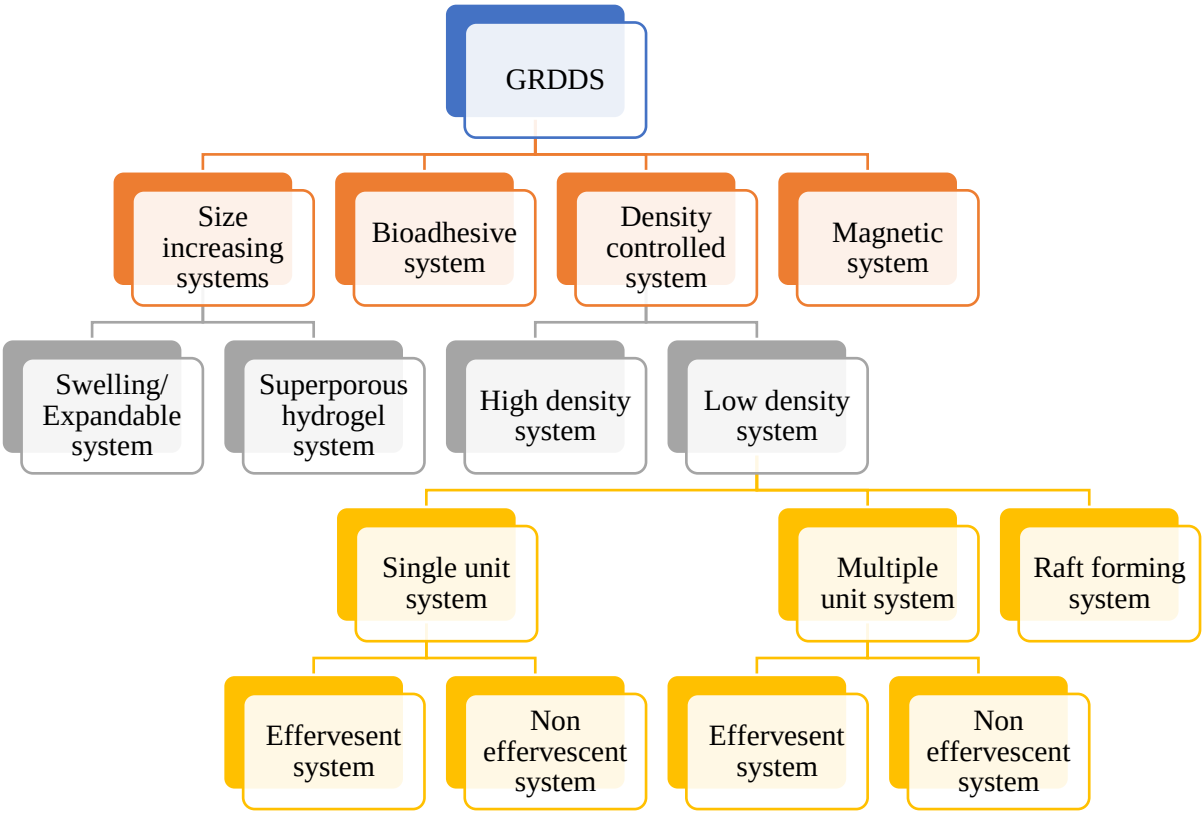


Fig. 1.5: Classification of GRDDS

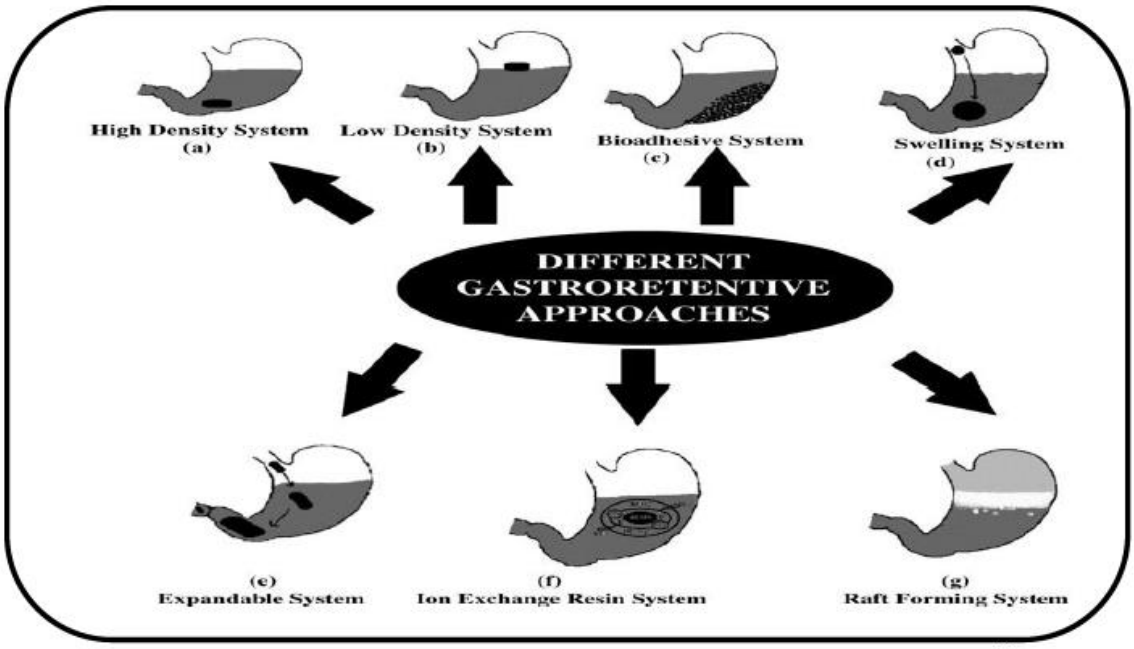


Fig. 1.6: Different approaches of the gastroretentive drug delivery system[15]

1.6.6. Merits and Demerits of GRDDS[16,17]

Merits and demerits of Gastroretentive drug delivery are given in Table 1.2.

Table 1.2: Merits and Demerits of GRDDS

Approaches	Merits and Demerits
Expandable system	**Merits:** Small in size and can be easily swallowed, also increases in size to prevent passing through pylorus for prolonged stay in the stomach. **Demerits:** Time consuming, difficulty in formulation, not widely used.
Super porous hydrogel system	**Merits:** Fast swelling property, high swelling ratio, good mechanical strength and short swelling time **Demerits:** Weak mechanical properties.
Bio adhesive/ Mucoadhesive system	**Merits:** Improves patient compliance, excellent accessibility, rapid onset of action, reduce the frequency of dosing, rapid absorption. **Demerits:** Bio adhesion is difficult to maintain due to rapid turnover of mucin in GIT, occurrence of local ulcerous effects due to prolonged contact of the drug in stomach.
High density system	**Merits:** Density higher than gastric fluids so retained in the antrum part of the stomach and capable of withstanding its peristaltic movements thus allows the release of drug for a prolonged period of time. **Demerits:** Not marketed because difficult to manufacture with high amount of drug (>50%) also difficult to achieve a density of about 2.8 g/cm$_3$.
Raft forming system	**Merits:** • Forms a low density viscous layer on gastric contents so more surface area that lead to more drug release and improve therapeutic efficacy. • Improve patient compliance by once a day therapy and its action is within seconds for long duration. **Demerits:** • Stability problem that will lead to change in the pH on prolonged storage also chemical degradation or microbial degradation.
Low density system/ Floating Systems	**Merits:** • Better compliance so widely used, no dose dumping, and improve efficacy due to sustained release of drugs by reducing the frequency of dosing. • Floats on gastric fluid that release drug slowly thus improve drug absorption because of increasing GRT that enhance bioavailability and reduce irritation. • Specific drug delivery for drugs that are absorbed and local action through the stomach e.g. ferrous salts and antacids. **Demerits:** • Buoyancy cannot be predicted that may cause obstruction in the GI tract producing irritation. • Float requires high level of fluids in the stomach with a minimum of full glass of water (200-250 ml). • Not taken before going to bed because gastric emptying occurs randomly and highly dependent on the diameter and size in supine position.

1.7. STOMACH SPECIFIC FLOATING DRUG DELIVERY SYSTEM (FDDS)[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 take 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 form transit in the GIT or indirectly by pharmacokinetic studies with drug tracer.

1.7.1. Mechanism Of Floating Drug Delivery System[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 coadministration 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 for a prolonged period of time as given in fig. 1.7. 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.

$F = (Df - Ds)\, gv$ ……..(1)

Where, F= total vertical force,

Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity

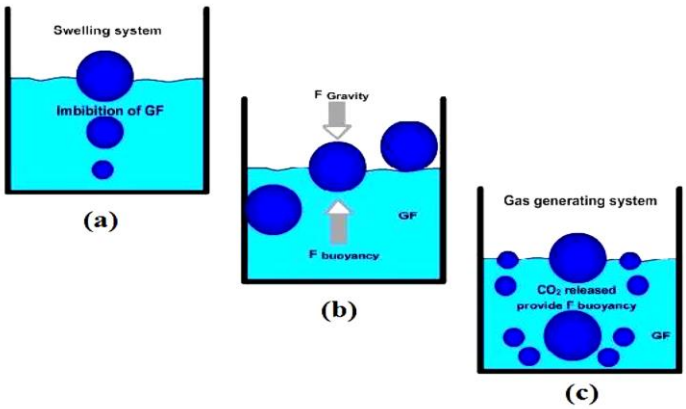


Fig. 1.7: Mechanism of floating system in Gastric Fluid a) Swelling system b) Non-Effervescent system c) Effervescent system

1.7.2. Classification Of FDDS[20]

A. Effervescent Systems

a) Volatile liquid containing systems
b) Gas-generating systems

B. Non-effervescent Systems

a) Colloidal gel barrier system
b) Alginate beads
c) Hollow microspheres
d) Intragastric/ Microporous compartment system

C. Raft-Forming Systems

A. EFFERVESCENT SYSTEMS[20]

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, $C0_2$ 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:

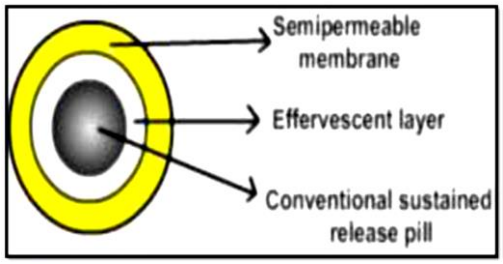


Fig. 1.8: a) Different layers (i) Semi-permeable membrane, (ii) Effervescent Layer (iii) Core pill layer

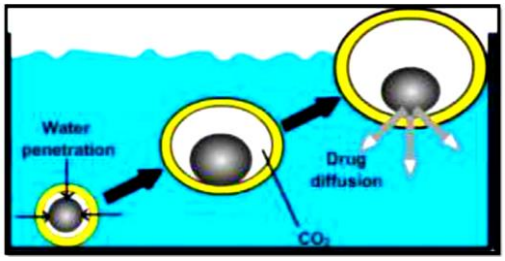


Fig. 1.9: b) Mechanism of floatation via CO_2 generation.

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

B. NON-EFFERVESCENT SYSTEMS[20]

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 design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, NaCMC, Polysacchacarides 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 these dosage form.

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.

c) Hollow Microspheres: Hollow microspheres are regarded as the most promising buoyant systems, as they've 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 contain simple solvent evaporation, solvent diffusion & 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.

d) 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[21]

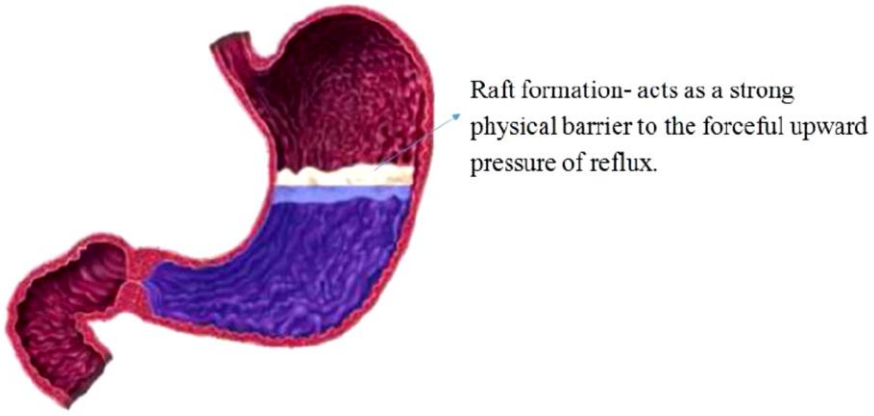


Fig. 1.10: Raft forming system

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 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 formed as 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.

1.8. *IN SITU* GELLING SYSTEMS[23,24]

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 and the 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 ease of 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 and potentially can be used for oral, buccal, rectal, vaginal, ocular, intraperitoneal and parenteral drug delivery.

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 on the 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 Vander walls interaction maintain the gel network[25].

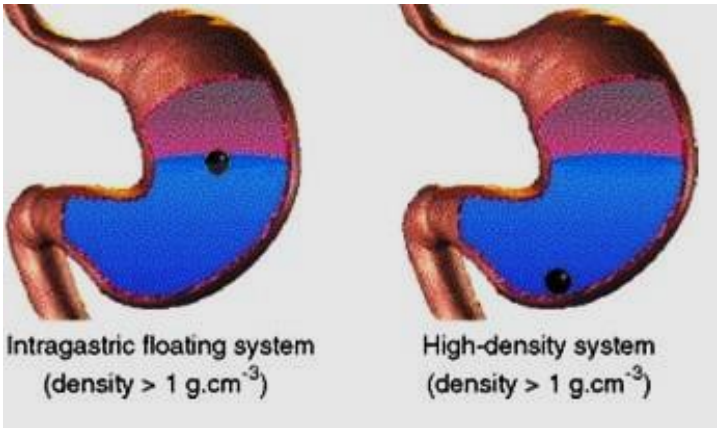


Fig. 1.11 : Floating systems

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 as shown in fig. 1.11 is produced.

1.8.1. Advantages of *In situ* gelling system[26]

- *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 targeted site.
- It shows less adverse effects compared to other pharmacological dosage forms.

1.8.2. Disadvantages of *In situ* gelling system[26]

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

1.8.3. Approaches of Designing *In situ* Gel System[27]

Various approaches for *In situ* gelling systems described in Fig. 1.12

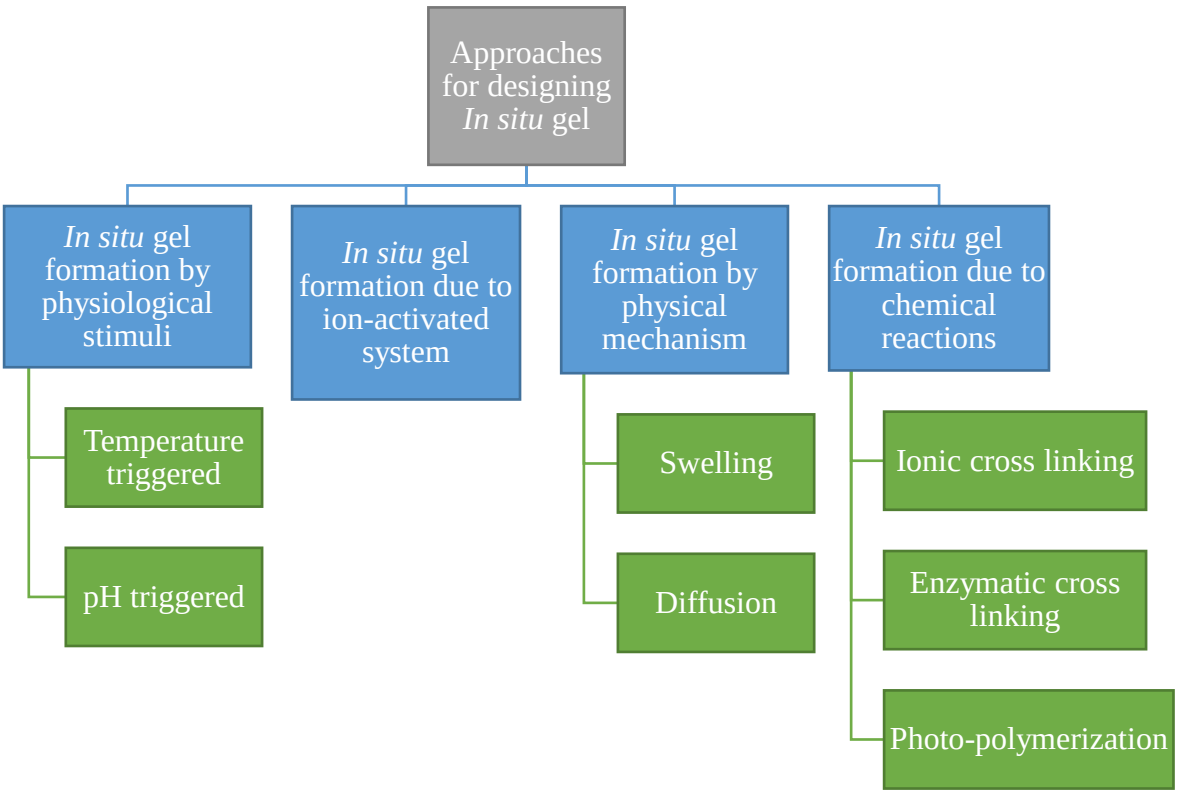


Fig. 1.12: Approaches for *In situ* Gelling system

I) Physically induced *In situ* gel systems[27]

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 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 enzymatic action.

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 useful solvent for such system.

II) *In situ* gel formation due to ion activated system[27]

Here, gelling of the instilled solution is induced by the change in ionic strength. It is 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 present 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.

III) Chemically induced *In situ* gel systems[28]

A- Ionic crosslinking: 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^+. *Insitu* gel formation involves administration of aqueous liquid solutions, once administered they form gel under certain conditions involve 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 contains divalent-ions complexed 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 causes the *In situ* gelation of orally administered solution as shown in equation:

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 crosslinking: *In situ* gel formation catalysed 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 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.

IV) *In situ* gel formation based on physiological stimuli[29]

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 drug release. These hydrogels exists in liquid form at room temperature (20- 25°C) and undergo gelation when comes in contact with body fluid (35-37°C). The use biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach *In situ* 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.4 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 (hydroxy ethyl) cellulose (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 acidic or 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 ionisable 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, polyvinylacetal diethylaminoacetate (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, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, etc.

1.8.4. Mechanisms of Drug Release from *In situ* Gel System[30,31]

1.8.4.1. 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:

1- Diffusion of water into the matrix followed by the dissolution of the drug and finally the diffusion of the dissolved drug from the matrix.

2- Polymers interact with drugs leading to modulate the release of the drug.

3- 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.

1.8.4.2. Swelling-controlled mechanism

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 modelled 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.

1.8.4.3. Chemically-controlled mechanism

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

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 systems.

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 polymers.

1.8.5. Criteria of Drugs Suitable for *In situ* Gel Drug Delivery System[32]

• 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.

1.8.6. Criteria of Drugs Unsuitable for *In situ* Gel Drug Delivery System[33]

• 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).

1.9. POLYMERS OF *IN SITU* GEL SYSTEM[34,35]

1.9.1. Polymers Selection for *In situ* Gel System

The polymers selection for preparation of *In situ* gel drug delivery system should be soluble, biologically compatible, biodegradable, having good drug polymer linkage, good mechanical strength and inert.

1.9.2. Classification of Polymers of *In situ* Gel System

Polymers used for *In situ* gel system can be classified according to:

1. Interaction with water: This include soluble polymers (e.g. polyethylene glycol (PEG)), cellulose based polymers (e.g. HPMC) and hydrocolloids (e.g. carrageenan, sodium alginate).

2. Natural polymers: (e.g. Gellan Gum).

3. Bio-stability: This includes biodegradable polymers (e.g. chitosan).

1.10. POLYMERS USED IN THIS STUDY[34,35]

1.10.1. Sodium Alginate:

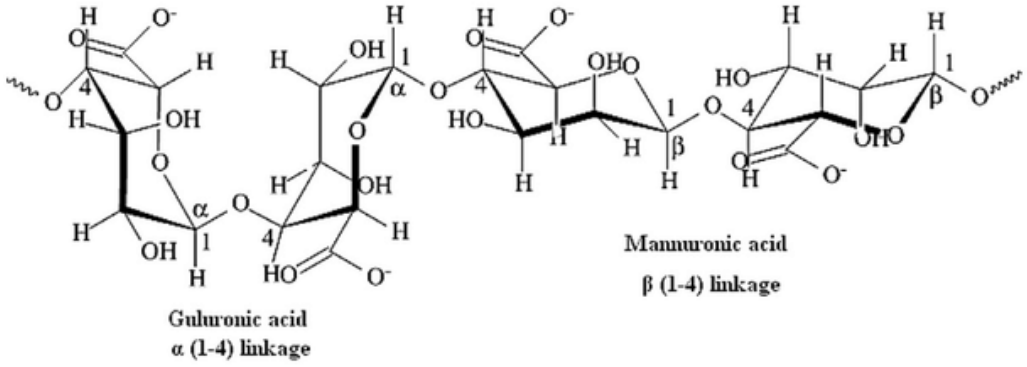


Fig. 1.13: Structure of Sodium Alginate

Properties: It is a linear polysaccharide extracted from brown seaweed consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues joined by 1,4-glycosidic linkage.

Gelation of dilute solutions of sodium alginate takes place upon contact with simulated gastric fluid; when divalent cations (usually calcium ions) interact ionically by a co-operative process involving consecutive blocks of guluronic residues in the α -l-guluronic acid (G) blocks of the alginate chain, resulting in the formation of a three dimensional network that is usually described by an 'egg-box' model as in fig 1.13. It is the ion exchange process between sodium and calcium ions that is supposed to be responsible for the swelling and subsequent degradation of sodium alginate in the colon.

Sodium alginate applied pharmaceutically as a water soluble polymer so useful in SR liquid preparations for oral administration, act as a stabilizing agent; viscosity-increasing agent, as a hydrogel systems for delivery of proteins and peptides, as tissue engineering matrices, as both a binder and disintegrant in tablet formulations and as a diluent in capsule formulations.

Mechanism: Alginate is a copolymer with two types of monomers used, β- D-mannuronic acid (M) and αL-guluronic acid (G), arranged as homopolymeric blocks of M-M blocks or G-G blocks together with blocks of alternating sequence (M-G). The polymer forms 3- dimensional ionotropic hydrogel matrices, mostly by the interaction of calcium ions with G moieties which leads the formation of

inhomogeneous gel. The characteristic properties of these hydrogels, such as mechanical strength and porosity, are dependent upon the G:M ratios, concentration and viscosity of the initial alginate solution and type of ionic cross-linker (bi- or poly-valent cations) etc. Alginate with a high G content will improve the gelling properties and reduce the total polymer to be introduced into the eyes.

1.10.2. Gellan Gum:

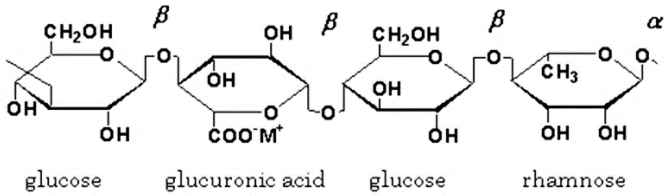


Fig. 1.14: Structure of Gellan gum

Properties : Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and are linked together to give a tetrasaccharide unit as in fig 1.14. Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Upon instillation, gelrite forms gel due to the presence of calcium ions. The gelation involves the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexation with cations and hydrogen bonding with water. Because of its thixotropy, thermo plasticity, pseudo plasticity are widely use in ophthalmology. In food industry, used as suspending and stabilizing agent.

Mechanism : Gellan gum produce a cation induced *In situ* gelation (Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) due to the cross linking between negatively charged helices and mono or divalent cations (Na^{+}, Ca^{+}). Divalent ions superior to promoting gelation as compared to monovalent cations. Gelation prolongs the residence time of drug at absorption site and bioavailability of the drug is increased.

1.10.3. Iota Carrageenan (*i*-carrageenan):

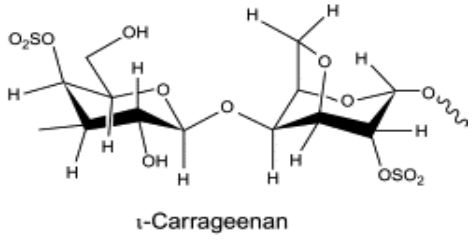


Fig. 1.15: Structure of *i*-carrageenan

Properties: Carrageenan is a sulphated linear polysaccharide of D-galactose and 3, 6-anhydro-D-galactose obtained by extraction of certain red seaweeds of the Rhodophyceae class. λ -Carrageenan (lambda-carrageenan) is a non-gelling polymer, *i* -Carrageenan (iota-carrageenan) is a gelling polymer and *k* -Carrageenan (kappa-carrageenan) is a strongly gelling polymer which has a helical tertiary structure that allows gelling as in fig 1.15.

Carrageenan has strong negative charge; thus it has been used as a gelling agent/viscosity enhancing agent for controlled drug release and prolonged retention.

Mechanism: 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 SeaSpen PF is used, it must be at about 0.75% w/v level, which requires no additional calcium.

1.10.4. Hydroxypropyl Methyl Cellulose (HPMC):

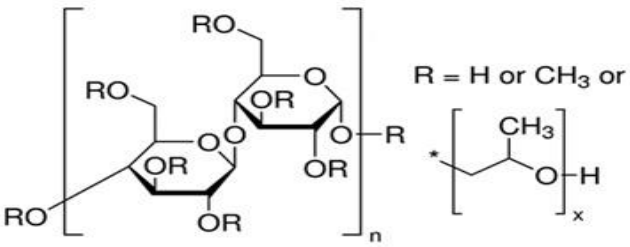


Fig. 1.16: Structure of HPMC

Properties : Hydroxypropyl Methyl Cellulose (HPMC) as a partly O-methylated (OCH3) and O-(2-hydroxypropylated) (OCH2CH (OH) CH3) cellulose conforming to the limits for the various types of HPMC as shown in fig. 1.16. It is available in several grades that vary in viscosity (50-100000 cps) and extent of substitution (OCH3) either E or K. Molecular weight is approximately 10000–1500000. It is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations as coating agent, controlled-release agent, dispersing agent, dissolution enhancer, extended-release agent, film forming agent, release-modifying agent, solubilizing agent, stabilizing agent, sustained-release agent, thickening agent and viscosity-increasing agent.

Mechanism : Gelation of cellulose solution is caused by hydrophobic interactions between molecules containing methoxy substitution. At low temperature, molecules are hydrated and little polymer-polymer interaction occurs, whereas at high temperature, polymers lose their water of hydration.

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

1. **Pashikanti SP et al.**[36] 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 h. 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 h. They concluded that the drug release from the formulations followed First order kinetics with Fickian diffusion.

2. **Solanki R et al.**[37] formulated and evaluated of Floatable *In situ* Gel of Ofloxacin using different concentrations of HPMC-K 4 M, HPMC-K 15 M, and HPMC-K 100 M. On the basis of results, they observed that if the final concentration of $CaCO_3$ increases, then it decreases the lag time for floating and if there is increase in concentration of sodium alginate and HPMC K4M, the viscosity increases. They concluded that Ofloxacin *In situ* gel formulation has better performance than conventional formulation and also makes better compliance and improved efficacy.

3. **Bhushan I et al.**[38] briefly discussed Alzheimer disease and its clinical features that there are four stages of Alzheimer disease in series i.e., predementia, mild, moderate and severe. They explained various risks factors like age, genetics, education etc. are associated with Alzheimer disease. Positron emission toronography, Computed toronography and Magnetic resonance imaging are the techniques available for detection of Alzheimer's disease in patients. They concluded that the cause of Alzheimer disease can be explained on Amyloid hypothesis and Cholinergic hypothesis and the delay in neurodegeneration by targeting neurotic plaques and Neurofibrillary tangles is future potential mechanism for treatment of Alzheimer disease.

4. **Priya S et al.**[39] formulated gastroretentive *In situ* gel of Lafutidine by pH-triggered ionic gelation method using different concentrations of gelling polymer such as sodium alginate, gellan gum and xanthan gum. The drug was released from the all the formulations in a sustained manner. *In vivo* studies confirmed the gastroretention of the formulation in mice stomach for 8 h. Stability studies indicated that the there was no significant change in the visual appearance, floating behaviour, and drug content.

5. **Patel HP et al.**[22] reviewed Gastroretentive Drug Delivery Systems: From Conception To Commercial Success about recent innovations and techniques regarding fabrication and evaluation of Gastro Retentive Drug Delivery Systems. They explained that variable gastric emptying time is also one of the crucial factor for variable *in vivo* data for GR dosage forms and depends upon type of food, caloric content, gender, age etc. They concluded that better *in vivo* drug release profile with enhanced bioavailability can be achieved by employing essential QbD principles and utilizing various experimental design (DOE) techniques.

6. **Vineetha K et al.**[40] 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.

7. **Wiwattanapatapee R et al.**[41] 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 h period.

8. **Adimoolam S et al.**[42] 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. Formulation F4 with Diclofenac sodium, Sodium alginate and Fenugreek seed mucilage in a ratio of 1:1.25:1.2 showed floating lag time of eight seconds and released 51% of drug within eight hours. They concluded that it follows zero order kinetics and fit to Korsmeyer-Peppas model with release exponent of 0.6434, revealed non-fickian diffusion mechanism.

9. **Kajale AD et al.**[43] formulated and evaluated oral floating *insitu* gel of Ilaprazole using Sodium Alginate, HPMC K100M, Eudragit RSPO, Ethyl cellulose and Rosin. In the optimized batch Sodium Alginate 2% and Ethyl cellulose 2% (1:1) ratio gave gastric retention of drug Ilaprazole for 12 hours. *In-vivo* study performed by providing the formulation to rabbit and then X-ray confirmed the formation of gel in stomach and floating of dosage form for 12 hrs. They observed that gas forming agent sodium bicarbonate and calcium carbonate 2% each (1:1) proportion gives floating of gel for >12 hrs.

10. **Nikode S et al.**[35] presented a brief introduction to *In situ* gels, various approaches for *In situ* gelling system, different types of polymers used and evaluation of *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.

11. **Devasani SR et al.**[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 parameters involved in the formulation of *In situ* gels. They concluded that the use of biodegradable and water soluble polymers for the *In situ* gel formulations makes them more acceptable and excellent drug delivery system.

12. **Tandle RL et al.**[44] 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.

13. **Bobade NN et al.**[45] formulated Controlled Release Gastro- Retentive *In situ* gel for Diltiazem Hydrochloride using various concentrations (0.5,1,1.5% w/v) of Sodium Alginate, HPMC K4M and Gellan Gum as polymers which released the drug in controlled manner. It was concluded that sodium alginate (1.5%)w/v, HPMC K4M (0.5%)w/v, Gellan gum (1.5%)w/v, which could be most promising gastro-retentive *In situ* gel formulation and the prepared controlled release *In situ* gel of Diltiazem Hydrochloride may prove to be potential candidate for safe and effective controlled drug delivery for extended period of time.

14. **Shastri D et al.**[46] developed and evaluated of 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 along with sodium citrate. Mucoadhesion was enhanced with the help of polymer HPMC K4M. 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 hour and optimum viscosity. The results revealed that as the concentration of Sodium alginate was directly proportional to mucoadhesion, inversely proportional to drug release while concentration of pectin directly proportional to drug release and hence *In situ* oral gel is a better formulation in terms of ease of administration, better patient compliance and prolonged gastro-retention.

15. **Rao MRP et al.**[47] formulated Controlled Release Ion Sensitive Floating Oral *In situ* Gel of a Prokinetic Drug Itopride Hydrochloride using Gellan Gum as a gel forming polymer and calcium carbonate as cross linking agent and Ca^{2+} ion source, and HPMC K100M as release retardant. They performed 32 factorial designs and the effect of variation in concentration of gellan gum and HPMC K100M on drug release at 1 h, 6 h, and viscosity was evaluated. The gel was evaluated for other parameters like floating lag time, floating duration, gel strength, density, pH, *In vitro* drug release, drug content, and *In vitro* gelling capacity. The results revealed that the concentration of gellan gum and HPMC K100M significantly affected the dependent variables i.e. drug release at 1 h, at 6 h and viscosity. The drug release mechanism followed Korsmeyer - Peppas model. *In vivo* studies revealed higher T_{max} of gel compared to plain drug indicating slower absorption and the AUC 0-12 h was found to be nearly 90% higher than plain drug.

16. **Kumar KK et al**.[48] formulated and evaluated of floating *In situ* gelling system of losartan potassium using sodium alginate and guar gum as polymers and $CaCO_3$ as a crosslinking agent. Evaluations showed that the formulation containing 2% of sodium alginate and 1.5% of Guar gum controlled the release of drug for longer duration. They concluded that the *In situ* gel exhibited the expected viscosity, drug content, pH, *In vitro* gelling capacity, *In vitro* floating ability and sustained drug release and followed the Fickian diffusion type of release.

17. **Nautiyal U et al.**[12] presented 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.

18. **Rewar S et al.**[49] 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 devices from developmental level to the manufacturing and commercial level.

19. **Alhamdany ATN et al.**[50] developed a Floating *In situ* Gelling Oral Liquid Extended Release Formulation of Furosemide using Iota carrageenan (0.2, 0.25, 0.3% w/v) with Sodium Alginate (1% w/v) which undergoes gelation when it is in direct contact with gastric fluid. Different variables that affect drug release profile like cross linking agent, combination of polymer, gas generating agent and drug concentrations were studied to optimize the best formulation through measuring their effects on viscosity, gel strength, floating lag time and floating duration. The best formulation exhibited 94.9% release of the drug after 5 h with effective floating property. They concluded that *In vivo* test demonstrated good indication to the gastroretentive property of the optimum formulation through its relation to the diuretic property of the drug, and it agreed with *In vitro* release and the proposed kinetic mathematical modeling.

20. **Ma T et al.**[51] formulated *In situ* gel of Ranitidine for Oral sustained delivery using 0.2%, 0.5%, and 1.0% concentration (w/v) of gellan gum. Characterization in terms of preparation, viscosity and *In vitro* release showed increase in viscosity of the formulations with increasing concentrations of gellan gum. *In vitro* study showed that the release of ranitidine from these gels was characterized by an initial phase of high release (burst effect) and translated to the second phase of moderate release. Single photon emission computing tomography technique suggested that *In situ* gel had feasibility of forming gels in stomach and sustained the ranitidine release from the gels over the period of at least 8 hours. They concluded that the *In situ* gel system is a promising approach for the oral delivery of Ranitidine for the therapeutic effects improvement.

21. **Thomas LM at al.**[52] performed the formulation and evaluation of floating oral *In situ* gel of Metronidazole by using sodium alginate along with varying concentrations of methylcellulose, hydroxypropyl methylcellulose, or sodium carboxymethylcellulose and gas forming agent calcium carbonate and sodium bicarbonate. The concentration of viscosity enhancing polymer and the concentration of gas-forming agents affected the formulation viscosity, floating behaviour and *In vitro* drug release. The prepared *In situ* gelling formulations of Metronidazole floated in the gastric conditions and released the drug in controlled manner. They concluded that the prepared formulations appeared to be promising drug delivery system for localized delivery of metronidazole for better treatment of peptic ulcer disease caused by *H. pylori*.

22. **Sharmila SK et al.**[53] developed and validated of UV-Spectrophotometric Method for the Estimation of Rivastigmine Tartrate dissolved in 0.1 N HCl, the resulting solution was then scanned in the UV range (200-400nm) in a 1cm quartz cell in a double beam UV spectrophotometer. The λ_{max} of Rivastigmine tartrate was found to be 263.1 nm. The method obeys Beers law in the concentration range from 10-90 µg/ml. The correlation coefficient was found to be 0.999 (r^2= 0.999). The LOD and LOQ were found to be 2.68 and 8.12 µg/ ml respectively. The result of estimation of marketed formulation (Exelon) was found to be 99.02 %.

23. **Basu B et al.**[54] formulated and characterized of novel floating *In situ* gelling system for controlled delivery of Ramipril prepared by using different concentration of gelling polymer such as sodium alginate, gellan gum and calcium carbonate. Formulation containing 0.50 % of sodium alginate, 0.50 % of gellan gum and 1.0 % of calcium carbonate showed the best gelling ability. For optimization of *In situ* gelling system, 32 full factorial design was employed to study the effect of independent variables. F8 batch was selected as optimized batch based on buoyancy time (71 sec), viscosity 356.9 cp, drug content 99.06 % and drug release 99.80 % at 12 hrs. They concluded that controlled release of Ramipril from *In situ* gelling system was observed and good fit to the Zero order and Korsmeyer Peppas model which shows fickian diffusion (n=0.351) mechanism.

24. **Sivannarayana T at al**.[55] performed the formulation and evaluation Of oral floating *In situ* gel of Moxifloxacin Hydrochloride using sodium alginate and pectin as polymers. Tri sodium citrate and calcium carbonate are the main ingredients for the formation of gelling solution as calcium ions released from calcium carbonate complexes with citrate ions. They concluded that the prepared formulation enhances the residence time and thereby improves patient compliance.

25. **Singh B et al.[56]** developed Once-a-day Gastroretentive Controlled Release tablets of Rivastigmine using optimized polymer blends exhibited excellent bio adhesive and flotational characteristics besides possessing adequate drug release control. Pharmacokinetic studies carried out in rabbits showed the absence of any sharp peaks or troughs in the plasma drug levels, and various levels of *In vitro/In vivo* correlation (IVIVC) were successfully established. *In vivo* gamma scintigraphic studies in human volunteers ratified the gastroretentive characteristics of the optimized formulation with retention time of 6 h or more.

26. **Patel MJ at al.[57]** presented the Strategy for Development of pH Triggered Floating *In situ* Gel of Levetiracetam to provide controlled delivery for the treatment of partial onset seizures. They prepared Sodium alginate-based *In situ* gelling systems. A 32 full factorial design was used for optimization. The gels were studied for their viscosity, *in-vitro* buoyancy and drug release. They concluded that the drug release from the *In situ* gel follows the Higuchi model and Korsemeyer-peppas model, which indicates a diffusion-controlled release.

27. **Gupta G et al.[21]** presented a short review on stomach specific drug delivery system about the research and development of rate - controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). They discussed about the various approaches to produce gastro retention of drug delivery system, with current & recent developments of Stomach Specific floating drug delivery system.

28. **Wamorkar V et al.**[58] formulated and evaluated Stomach Specific *In situ* Gel of Metoclopramide Using Natural, Bio-Degradable Polymers such as sodium alginate and guar gum. The optimized formulations were able to release its contents upto 8 hours. From designed set of experiments, they concluded that guar gum plays a vital role in not only producing viscous solution but also controlling the release for longer duration than that of sodium alginate and the prepared *In situ* gel exhibited the expected viscosity, drug content and sustained drug release.

29. **Jha VN et al.**[59] developed a rapid, accurate and sensitive UV spectroscopic method for estimation of rivastigmine tartrate entrapped in nanoparticles. RT was estimated at 264 nm in acetonitrile and in distilled water. The linearity range was found to be 50-500 ug/ml in acetonitrile according to the regression equation of absorbance=0.0015× (concentration in μg/ml) +0.0042and for distilled water the regression equation of absorbance=0.0012× (concentration in μ/ml)+0.0027. The LOD for the assay of RT using ACN and distilled water was found to be 1.095 and 3.6148 respectively. The method was found to be accurate (mean percentage accuracy 99.65) in ACN and method was found to be accurate (mean percentage accuracy 99.57) and precise with % RSD less than 1.97 (for intra-day) and less than 1.36 (for inter-day). They concluded that the developed method was successfully employed for the determination of RT in pharmaceutical dosage forms (nanoparticles).

30. **Patel DM et al.**[60] formulated and evaluated floating oral *In situ* gel of Amoxicillin using sodium alginate, calcium chloride, sodium citrate, hydroxypropyl methyl cellulose K100, and sodium bicarbonate. The prepared formulations were evaluated for solution viscosity, floating lag time, total floating time, and *In vitro* drug release. The formulation was optimized using a 3^2 full factorial design. They concluded that concentration of sodium alginate and HPMC K100 had significant influence on floating lag time, cumulative percentage drug release in 6 h and 10 h and floating *In situ* gelling system of amoxicillin can be formulated using sodium alginate as a gelling polymer to sustain the drug release for 10 to 12 h with zero-order release kinetics.

31. **Patel RP et al.**[61] formulated, optimized and evaluated of sodium alginate based *In situ* gel of clarithromycin and metronidazole benzoate. Sodium alginate used as a polymer and $CaCO_3$ was used as a cross-linking agent, this formulations exhibits good viscosity properties and sustained drug release and explained accelerated stability studies.

32. **Nirmal HB et al.**[62] designed and researched on *In situ* forming polymeric drug delivery system to reduce the frequency of administration, improved patient compliance and comfort, formulations developed based on the factors are temperature modulation, pH range, presence of ions and ultraviolet irradiation.

33. **Moin KM et al.**[63] designed and evaluated oral *In situ* gelling system for sustained release drug delivery of Famotidine, *in-vitro* release study revealed that drug released from the *In situ* gel followed non-fickian diffusion. *In vivo* study in rats, showed gel formation in gastric juice and reduction in ulcer index. Stability study was also carried out for three months, which showed no major changes from their initial state.

34. **Madan M et al.**[64] 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.

35. **Ramesh CN et al.**[65] 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 (X_1), sodium alginate (X_2) and anti-diabetic drug Metformin (X_3). 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 variables.

AIM AND PLAN OF WORK

3.1. AIM OF THE WORK

To develop a stable oral gastroretentive *In situ* gelling liquid formulation of Rivastigmine tartrate for Geriatric patients in the treatment of Alzheimer's disease, thereby providing ease of administration, reducing the frequency of dosing and thus, better patient compliance.

3.2. OBJECTIVES

I. To carry out **Pre-formulation** studies.

II. To select suitable type and quantity of **polymers along with other excipients** for developing floating *In situ* gel of Rivastigmine tartrate.

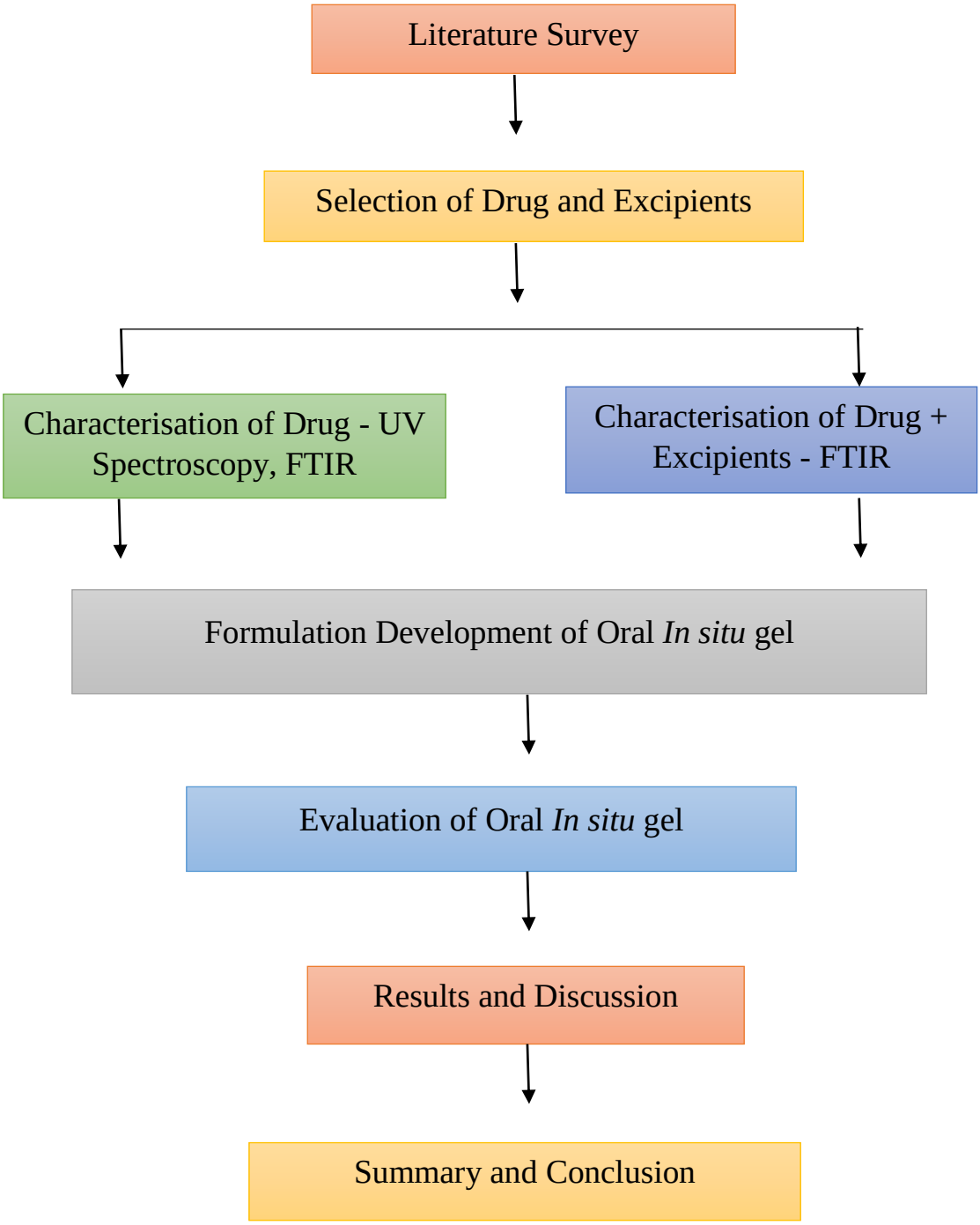
III. To develop optimized oral floating *In situ* gelling system of **Rivastigmine**, thereby **increasing patient compliance.**

IV. To carry out ***In vitro* characterization** of the optimized formulations.

V. To achieve a **controlled release** of the drug for a long period to **reduce the frequency of dosing.**

VI. To carry out **stability studies,** on the most satisfactory formulation as per ICH guidelines.

3.3. PLAN OF WORK:



RATIONALE OF THE STUDY

4.1. RATIONALE FOR THE SELECTION OF DOSAGE FORM

- Oral drug administration still remains the route of choice for the majority of clinical applications. Oral delivery of drugs with a narrow absorption window in gastro intestinal tract is often limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption.
- *In situ* gel forming systems have been widely investigated as vehicles for controlled drug delivery. Since administration of highly viscous gel formulations by oral route is difficult, it is preferred that a liquid drug polymer formulation would gel at the targeted site, since *In situ* gelling systems undergo reversible sol-gel transitions in response to temperature, pH, or ion composition of the fluids. Drug retention and bioavailability can be achieved by gelation.[66,67]
- Gastroretentive *In situ* gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed from *In situ* gelling system, being lighter than gastric fluids, floats over the stomach contents, produces gastric retention of the dosage form and increase gastric residence time, resulting in prolonged drug delivery in gastrointestinal tract.[68,69]

4.2. RATIONALE FOR THE SELECTION OF DRUG

- Rivastigmine, a drug extensively prescribed for the treatment of mild to moderate Alzheimer's disease, has recently been recommended for the treatment of mild to moderate dementia associated with Parkinson's disease as well.[70]
- Rivastigmine has elimination half-life of about 1.5 - 2 hours. The efficacy of rivastigmine is dose-related, with the total oral dose ranging between 6 and 12 mg administered 2 to 3 times a day.[71] Rivastigmine is associated with severe central cholinergic gastrointestinal (GI) side effects.[72,73]
- A rapid increase in brain acetylcholine levels has been believed to precipitate these side effects.[74,75] Moreover, the twice- or thrice daily dosage regimen associated with a drug like Rivastigmine tends to reduce its patient compliance.[76]

4.3. RATIONALE FOR THE SELECTION OF GELLING AGENTS[77]

- Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and αL-guluronic acid residues joined by 1,4-glycosidic linkages. Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions (e.g. calcium and magnesium ions).
- Gellan gum is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetra saccharide repeating unit of one α-L-rhamnose, one β- D-glucuronic acid and two β-D-glucuronic acid residues. 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.

DISEASE PROFILE

5.1 ALZHEIMER DISEASE[2,78]

Alzheimer's disease is a neurological brain disorder. Alzheimer's disease is the most common form of dementia, a group of disorders that impairs mental function. It is a progressive, degenerative disorder that attacks the brain nerve cells or neurons, resulting in loss of memory which is the earliest symptoms, along with a gradual decline of other intellectual thinking abilities, often called as cognitive functions and other changes in personality or behavior. These neurons which produce the brain chemical or neurotransmitter, Acetylcholine, break connections with other nerve cells and ultimately die. For example, short term memory fails when Alzheimer's disease first destroys nerve cells in the hippocampus and language skills and judgment decline when neurons die in the cerebral cortex. Two types of abnormal lesions clog the brains of individuals with Alzheimer's disease as in fig. 5.1. Beta- amyloid plaques - sticky clumps of protein fragments and cellular material that form outside and around neurons . Neurofibrillary tangles - insoluble twisted fibers composed of the protein that build up inside nerve cells. Although these structures are hallmarks of the disease, scientist are unclear whether they cause it or a byproduct. The disease was first described by Dr. Alois Alzheimer, a German physician in 1906.

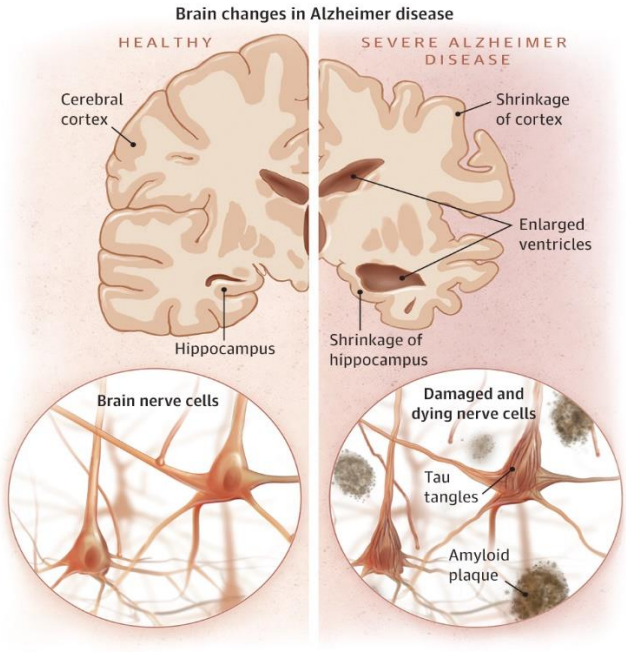


Fig. 5.1 : Brain changes in Alzheimer disease[78]

About 3% of men and women aged 65 to 74 have AD and nearly half of those aged 85 and older may have the disease. About 3,60,000 new cases of Alzheimer's are diagnosed each year.

5.1. 1. Causes

The cause of AD is unknown. However several factors are thought to implicated this

1. Neurological factors
2. Acetylcholine
3. Somatostain
4. Substance P
5. Nor epinephrine
6. Environmental Factors
7. Cigarette smoking
8. Certain Infections
9. Metals, industrial or other toxins
10. Use of cholesterol lowering drugs (statins)

5.1.2. Genetic and Immunological Factors:

1. Formation of plaques in brain
2. Risk Factors
3. Down's syndrome

5.1.3. Family

1. Chronic high BP
2. Head Injuries
3. Gender
4. Smoking and Drinking

5.2. PATHOPHYSIOLOGY

Alzheimer's disease attacks the brain nerves and nerve cells as well as neurotransmitters. The destruction of these parts causes clumps of protein to form around the brain cell. These clumps are known as "plaques" and "bundles". The presence of the bundles or plaques starts to destroy the more connection between the brain cells which makes conditions worst as in fig 5.2.

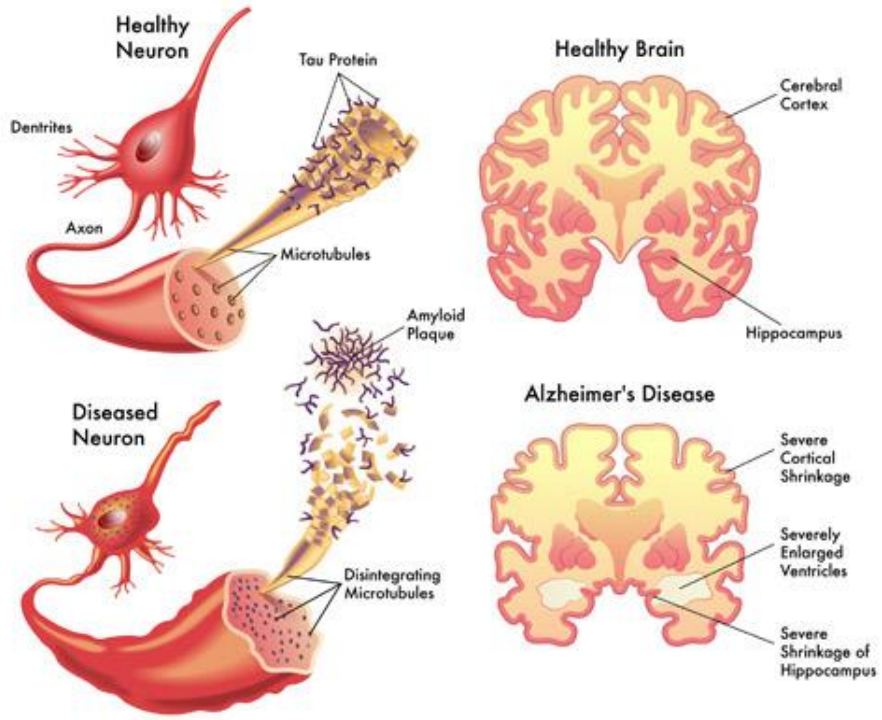


Fig. 5.2: Alzheimer's brain cells

5.3. SYMPTOMS

5.3.1 Worsened ability to take in and remember new information, for example

- Repetitive questions or conversations
- Misplacing events belongings
- Forgetting events or appointments
- Getting lost on a familiar route

5.3.2 Impairments to reasoning, Complex tasking, exercising judgment

- Poor understanding of safety risks
- Inability to manage finance
- Poor decision making ability
- Inability to plan complex or sequential activities

5.3.3 Impaired visuospatial abilities (but not due to eye sight problems):

- Inability to recognize faces or common objects or to find objects in direct view
- Inability to operate simple implements, or orient clothing to the body.

5.3.4 Impairment speaking, reading and writing:

- Difficulty thinking of common words while speaking, hesitations

  Speech, spelling and writing errors.

5.3.5 Changes in personality and behavior, for example

- Out of Character mood changes, including agitation, less interest, motivation or initiative, social withdrawal
- Loss of empathy
- Compulsive, obsessive or socially unacceptable behavior.

5.4. Diagnostic Criteria:

While they cannot be seen or tested in the living brain affected by Alzheimer's disease postmortem / autopsy will always show tiny inclusions in the nerve tissues called plaques and tangles.

5.6 STAGES OF ALZHEIMER'S DISEASE[79]

The stages and conditions of Alzheimer's disease is described in Fig. 5.3 and Fig. 5.4.

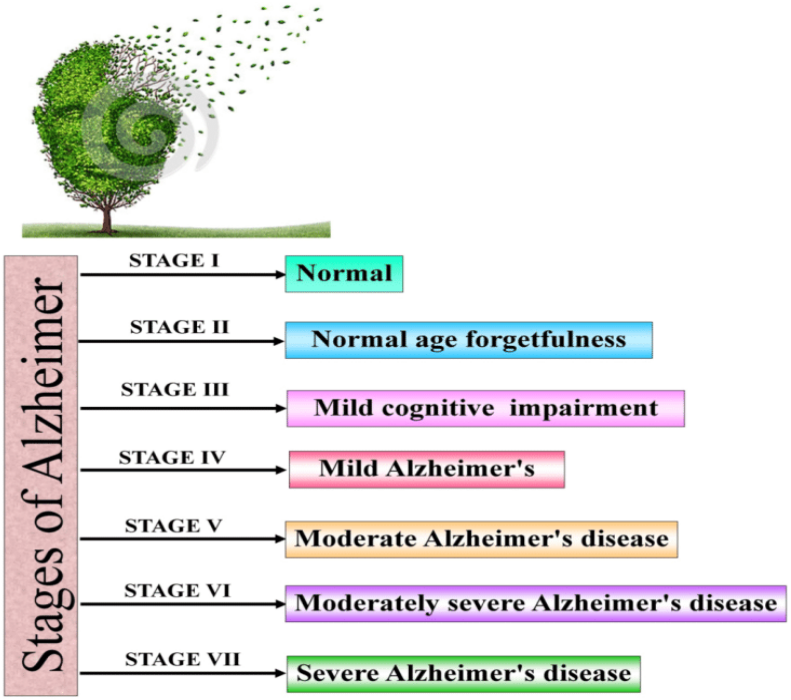


Fig. 5.3 : Stages of Alzheimer's Disease

Stage 1: No Impairment

During this stage, Alzheimer's is not detectable and no memory problems or other symptoms of dementia are evident.

Stage 2: Very Mild Decline

The senior may notice minor memory problems or lose things around the house, although not to the point where the memory loss can easily be distinguished from normal age-related memory loss. The person will still do well on memory tests and the disease is unlikely to be detected by loved ones or physicians.

Stage 3: Mild Decline

At this stage, the family members and friends of the senior may begin to notice cognitive problems. Performance on memory tests are affected and physicians will be able to detect impaired cognitive function.

People in stage 3 will have difficulty in many areas including:

- Finding the right word during conversations
- Organizing and planning
- Remembering names of new acquaintances

People with stage three Alzheimer's may also frequently lose personal possessions, including valuables.

Stage 4: Moderate Decline

In stage four of Alzheimer's, clear-cut symptoms of the disease are apparent. People with stage four of Alzheimer's:

- Have difficulty with simple arithmetic
- Have poor short-term memory (may not recall what they ate for breakfast, for example)
- Inability to manage finance and pay bills
- May forget details about their life histories

Stage 5: Moderately Severe Decline

During the fifth stage of Alzheimer's, people begin to need help with many day-to-day activities. People in stage five of the disease may experience:

- Difficulty dressing appropriately
- Inability to recall simple details about themselves such as their own phone number

On the other hand, people in stage five maintain functionality. They typically can still bathe and toilet independently. They also usually still know their family members and some detail about their personal histories, especially their childhood and youth.

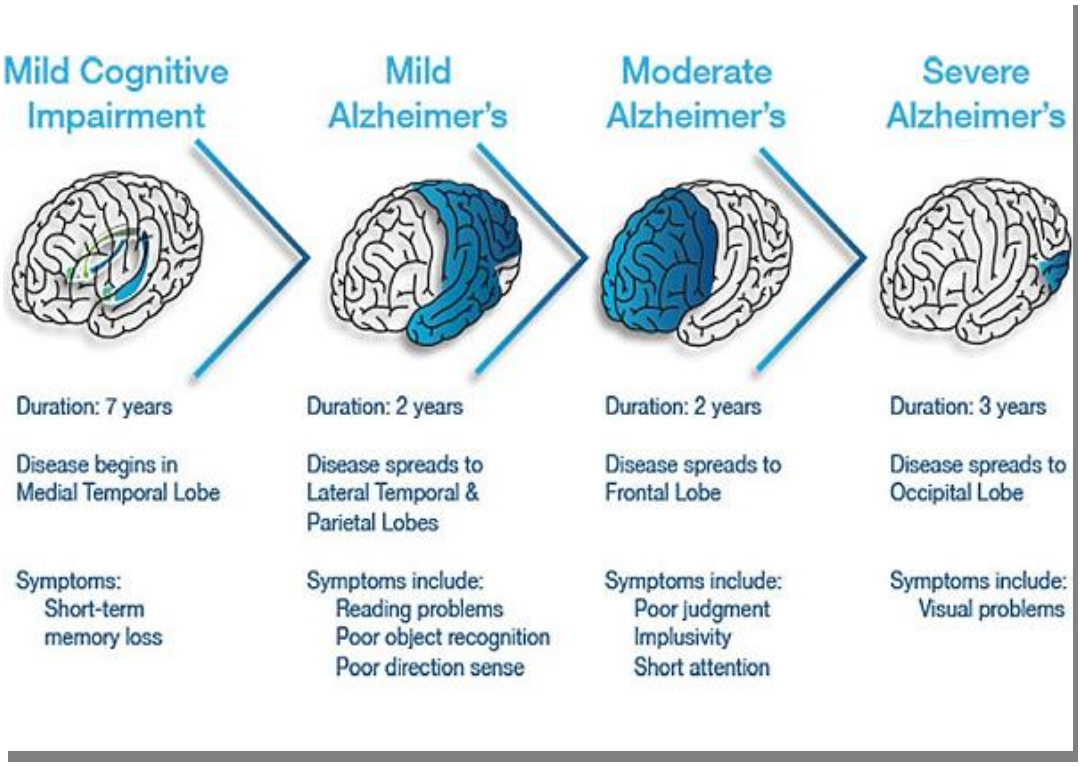


Fig. 5.4: Conditions in various stages of Alzheimer's disease

Stage 6: Severe Decline

People with the sixth stage of Alzheimer's need constant supervision and frequently require professional care. Symptoms include:

- Confusion or unawareness of environment and surroundings
- Inability to recognize faces except for the closest friends and relatives
- Inability to remember most details of personal history
- Loss of bladder and bowel control
- Major personality changes and potential behaviour problems
- Wandering
- The need for assistance with activities of daily living such as toileting and bathing

Stages 7: Very Severe Decline

Stage seven is the final stage of Alzheimer's. Because the disease is a terminal illness, people in stage seven are nearing death. In stage seven of the disease, people lose the ability to communicate or respond to their environment. While they may still be able to utter words and phrases, they have no insight into their condition and need assistance with all activities of daily living. In the final stages of Alzheimer's, people may lose their ability to swallow.

5.7 DETECTION METHODS FOR ALZHEIMER'S DISEASE[80]

- Neuroimaging is a promising and widely expanding area of research for detecting Alzheimer's disease.
- Structural imaging provides information about the shape, position or volume of brain tissue which include magnetic resonance imaging (MRI) and computed tomography (CT).
- Functional imaging reveals how well cells in various brain regions are working by showing how actively the cells use sugar or oxygen which include positron emission tomography (PET) and functional MRI (fMRI).
- Molecular imaging uses highly targeted radiotracers to detect cellular or chemical changes linked to specific diseases which include PET, fMRI and single photon emission computed tomography (SPECT).
- Each scan involves a unique technique and detects specific structures and abnormalities in the brain and associated parts. Several potential biomarkers are being studied for their ability to indicate early stages of Alzheimer's disease. Examples being studied include beta-amyloid and tau levels in cerebrospinal fluid (CSF) and brain changes detectable by imaging.

5.7 TREATMENT

Oral Alzheimer's Drugs[2]

- **Donepezil** is available in 5 mg or 10 mg tablets. It is taken once a day, usually at bed time. Treatment is started at 5 mg a day and then increased to 10 mg a day after one month if necessary. The maximum licensed total daily dose is 10 mg.

- **Rivastigmine** is available as capsule or transdermal patch. It is taken twice a day. People start with 3 mg a day in two divided doses, which will usually increase (at intervals of at least two weeks) to between 6 mg and 12 mg a day. The maximum licensed total daily dose for oral Rivastigmine is 12 mg. Rivastigmine patches are also available daily doses of patches is 4.6 mg, 9.5 mg or 13 mg with fewer side effects than the capsules. Patches are suited to people who struggle in taking medication through oral route. Only one patch should be applied at any time and it should be put on different parts of the skin each time, to avoid the person getting a rash.

- **Galantamine** is recommended at a dose of 8 mg each day for four weeks, increasing to 16 mg a day for another four weeks, and then kept at a dose of between 16 mg to 24 mg daily. Galantamine is made in a variety of forms including a 4 mg/ ml (twice daily) oral solution and tablets of 8 mg and 12 mg. Slow release (XL) capsules are available in doses of 8 mg, 16 mg and 24 mg. These are popular because they only need to be taken once a day. The maximum licensed total daily dose for Galantamine is 24 mg.

- **Memantine** comes in two forms as 10 mg and 20 mg tablets. The 10 mg tablets can be broken in half (into 5mg doses) and taken with or without food. The recommended dose is 5 mg a day, increasing every week by 5 mg, up to 20 mg a day after four weeks. The maximum licensed total daily dose for Memantine is 20 mg.

DRUG PROFILE

6.1. RIVASTIGMINE TARTARATE[81,82,83]

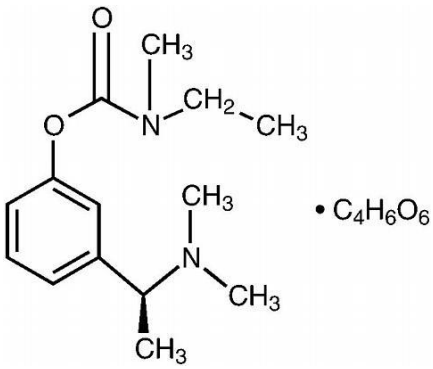
Rivastigmine belonging to BCS class I, is a parasympathomimetic and a reversible cholinesterase inhibitor for the treatment of Alzheimer's disease (AD), the most common form of dementia. Rivastigmine inhibits both Butyrylcholinesterase and Acetylcholinesterase.

Use:

Alzheimer's Disease: Management of mild to moderate dementia of the Alzheimer's type**.**

Dementia Associated with Parkinson's Disease: Management of mild to moderate dementia associated with Parkinson's disease.

Chemical structure :



Chemical Name : 3- [(1S)-1-(dimethylamino)Ethyl] phenyl N-ethyl-N-Methylcarbonate

Molecular formula : $C_{14}H_{22}N_2O_2$

Molecular weight : 250.3367

Description: A white, hygroscopic, crystalline compound.

Solubility : Freely soluble in water, soluble in ethyl alcohol, very slightly soluble in ethyl acetate.

6.1.1. Mechanism of action

Reversible anticholinesterase – carbamate that is structurally related to physostigmine acts by mechanism as described in fig. 6.1.

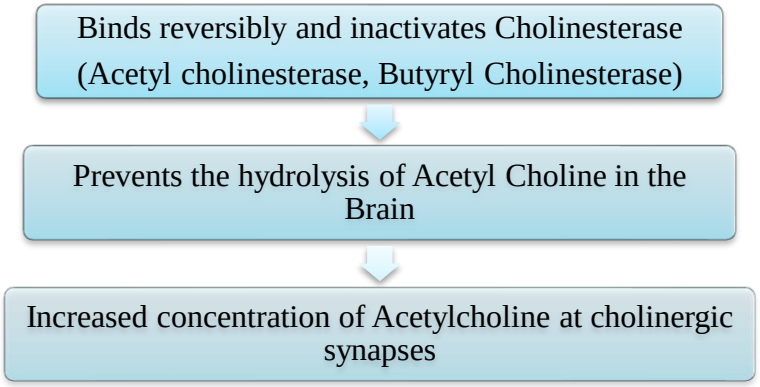


Fig. 6.1: Mechanism of action of Rivastigmine tartrate

6.1.2. Pharmacokinetics:

Absorption

- Rivastigmine is rapidly and completely absorbed from the GI tract. Absolute bioavailability is approximately 36-40%.
- Peak plasma concentrations attained in approximately 1 hour following oral administration

Distribution

- Widely distributed throughout the body; peak CSF concentrations attained within 1.4-2.6 hours

Plasma Protein Binding

- The drug is stable, bind to plasma proteins at about 40%.

Metabolism

- Rapidly and extensively metabolized, principally via cholinesterase-mediated hydrolysis to the decarbamylated metabolite.

Excretion

- Excreted principally in urine as metabolites.

Half-life

- Oral administration: Approximately 1.3-2 hours.
- Transdermal system: Approximately 3.4 hours.

Actions

- An intermediate-acting, reversible cholinesterase inhibitor.
- Increases acetylcholine at cholinergic synapses by inactivating cholinesterases, thereby inhibiting hydrolysis of acetylcholine.
- Relatively specific for brain acetylcholinesterase and butyrylcholinesterase.

Common Adverse effect

- Nausea, vomiting, diarrhea, anorexia, dyspepsia, asthenia .

6.1.3. Dosage and Administration

Alzheimer's Disease

Oral: Initially 1.5 mg twice daily. Increased to maximum 6 mg twice daily.

Transdermal: Maximum one system delivering 13.3 mg/24 hours once daily.

6.1.4. Drug Interactions

Table 6.1: Drug interactions

Drug	Interaction
Anticholinergics	Antagonistic effects
Cholinomimetics and other cholinesterase inhibitors	Additive effects
Muscle relaxants (succinylcholine-type)	Exaggerated response to muscle relaxant during surgery
Nicotine	Increased Rivastigmine clearance

6.1.5. Available form

Table 6.2: Marketed formulations of Rivastigmine tartrate

Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Topical	**Transdermal System**	4.5 mg/24 hours (9 mg/5 cm^2)	Exelon®	Novartis
		9.5 mg/24 hours (18 mg/10 cm^2)	Exelon®	Novartis
		13.3 mg/24 hours (27 mg/15 cm^2)	Exelon®	Novartis
Oral	**Capsules**	1.5 mg (of Rivastigmine)	Exelon®	Novartis
		3 mg (of Rivastigmine)	Exelon®	Novartis
		4.5 mg (of Rivastigmine)	Exelon®	Novartis
		6 mg (of Rivastigmine)	Exelon®	Novartis

EXCIPIENT PROFILE

7.1. SODIUM ALGINATE[34,84]

1. **Nonproprietary Names**

   BP: Sodium Alginate

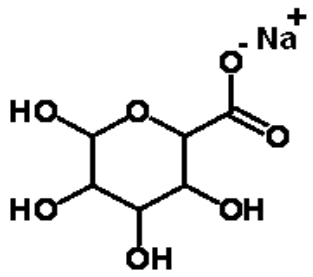
   Ph Eur: Sodium Alginate

   USP-NF: Sodium Alginate

2. **Synonyms**

   Alginato sodico; algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; natrii alginas; Protanal; sodium polymannuronate.

3. **Chemical Structure:**



4. **Molecular weight:** 216.121 g/mol

5. **Functional category**

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

6. **Description**

   Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

7. **Solubility**

   Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

8. **Viscosity**

   Various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 208ºC, will have a viscosity of 20–400 mPa (20–400 cPs). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions.

9. Stability

Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years. Solutions should not be stored in metal containers.

10. Incompatibility

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

11. Applications

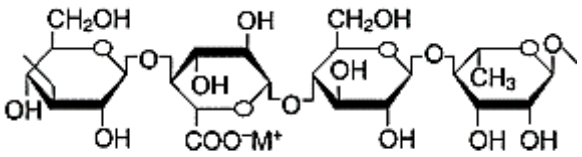
- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has been used as a diluent in capsule formulations.
- Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions at a concentration of 1-5 %. The effects of particle size, viscosity and chemical composition of sodium alginate on drug release from matrix tablets have been described.
- Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formation of nanoparticles.

7.2. GELLAN GUM[85,86,87]

1. **Synonyms**

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

2. **Chemical Structure:**



Gellan gum

3. **Molecular weight :** 646.5442

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 > 250º C.

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 in the concentration range of 1.5 to 2.25% in preparation of oral medicated jellies.

12. Applications:

- **Ophthalmic delivery:** Low acetyl gellan gum has been used to devise novel ophthalmic formulations, significantly improving drug ocular bioavailability resulting from the unique gelling property of gellan gum in the presence of tear fluid cations.

- **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 microspheres and *in situ* gels for prolonged drug delivery.

7.3. IOTA CARRAGEENAN[34]

1. **Nonproprietary Names**

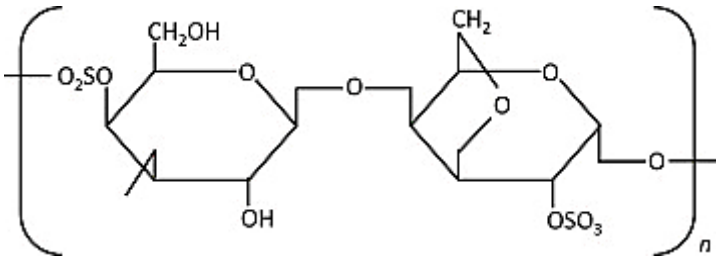
   USP-NF: Carrageenan

2. **Synonyms**

   Chondrus extract; E407; 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:**



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

5. **Functional category:** 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-brown to 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. The acid hydrolysis takes place only when the carrageenan is dissolved, and the hydrolysis is accelerated as the processing temperature and/or the processing time is increased. 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 the i-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 SeaSpen 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 the product to control the rate of gelation.

7.4. HYDROXY PROPYL METHYL CELLULOSE[34]

1. **Nonproprietary Names**

   BP: Hypromellose

   JP: Hypromellose

   PhEur: Hypromellose

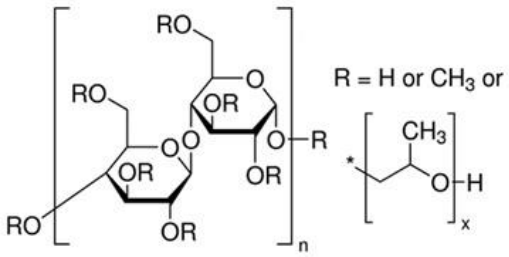
   USP: Hypromellose

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:**



5. **Molecular weight:** Molecular weight is approximately 10,000–15,00,000.

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**

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

8. **Solubility**

   Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, 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 50–908C, 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 processes.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.
- HPMCK4M has viscosity of about 4000 mPa s.

7.5. SODIUM CITRATE DIHYDRATE[34]

1. **Nonproprietary names**

   BP: 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

5. **Functional category**

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

6. **Solubility**

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

7. **Incompatibility**

   Aqueous solutions are slightly alkaline and will react with acidic substances. Alkaloidal salts may be precipitated from their aqueous or hydro-alcohol solutions. Calcium and strontium salts will cause precipitation of the corresponding citrates. Other incompatibilities include bases, reducing agents, and oxidizing agents.

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 used as a sequestering agent. It is used in effervescent tablet formulations.
   - It is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen citrate.

7.6. CALCIUM CARBONATE[34]

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

5. **Functional category**

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

6. **Description**

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

7. **Solubility**

   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 in solid-dosage forms as a diluent.
   - It is also used as a base for medicated dental preparations, as a buffering agent, and as a dissolution aid in dispersible tablets.
   - Calcium carbonate is used as a bulking agent in tablet sugar-coating processes and as an opacifier in tablet film-coating.
   - Calcium carbonate is also used as a food additive and therapeutically as an antacid and calcium supplement.

7.7. SODIUM BICARBONATE[34]

1. **Nonproprietary Names**

   BP: Sodium Bicarbonate

   JP: Sodium Bicarbonate

   Ph Eur: Sodium Hydrogen Carbonate

   USP: Sodium Bicarbonate

   Synonyms

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

2. **Chemical Name:** Carbonic acid monosodium salt
3. **Empirical Formula and Molecular Weight :** $NaHCO_3$, 84.01.
4. **Functional category:** Alkalizing agent; therapeutic agent.
5. **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.

6. **Solubility**

   Practically insoluble in ethanol (95%) and Ether. Solubility in water: 1 in 10 at 25ºC.

7. **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.

8. **Applications**

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

7.8. SODIUM SACCHARIN[34]

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**

   Soluble in ethanol 1in 102 at 20°C

   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 mouthwashes;
   - 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.

7.9. METHYLPARABEN SODIUM[34]

1. **Nonproprietary Names**

   BP: Sodium Methyl hydroxybenzoate

   PhEur: Sodium Methyl Parahydroxybenzoate

   USP-NF: Methyl paraben sodium

2. **Synonyms**

   E219; methyl 4-hydroxybenzoate sodium salt; sodium methyl hydroxybenzoate; soluble methyl 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**

   A 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 agents.
   - 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.

7.10. PROPYL PARABEN SODIUM[34]

1. **Nonproprietary Names**

   BP: Sodium Propyl hydroxybenzoate

   PhEur: Sodium Propyl Parahydroxybenzoate

   USP-NF: Propyl paraben Sodium

2. **Synonyms**

   E217; 4-hydroxybenzoic acid propyl ester, sodium salt; Nipasol M Sodium; parasept; propyl 4-hydroxybenzoate, sodium salt; propyl p-hydroxybenzoate, sodium salt; propylis parahydroxybenzoas natricus; sodium 4-propoxycarbonylphenolate; sodium propyl phydroxybenzoate; soluble propyl hydroxybenzoate.

3. **Chemical Name:** Sodium 4-propoxycarbonylphenolate

4. **Empirical Formula and Molecular Weight:** $C_{10}H_{11}NaO_3$, 202.2

5. **Functional category:** Antimicrobial preservative

6. **Description**

   Propylparaben sodium occurs as a white, crystalline, odourless or almost odourless powder.

7. **Solubility**

   Soluble in ethanol 90% 1 in 50 at 20°C

   Soluble in water 1 in 1 at 20°C

8. **Incompatibility**

   The activity of propylparaben sodium can be adversely affected by the presence of other excipients or active ingredients, such as atropine, essential oils, iron, magnesium trisilicate, talc, polysorbate 80 and other non-ionic surfactants, sorbitol, weak alkalis, and strong acids.

9. **Applications**

   - Propylparaben sodium is used as an antimicrobial or antifungal preservative in oral pharmaceuticals and in many water-based cosmetics.
   - It is generally used in combination with other paraben esters.
   - It is used at the concentration of 0.01-0.02% in Oral solutions and Suspensions.

MATERIALS AND METHODS

8.1. MATERIALS USED

Table 8.1: Materials used in the formulation

Chemicals	Manufacturer/Supplier	Use In Formulation
Rivastigmine Tartrate	Dr. Reddys Laboratories Pvt. Ltd., A.P	Active Ingredient
Sodium Alginate	Signet Chemical Corporation, Mumbai	Gelling Agent
Gellan Gum	Signet Chemical Corporation, Mumbai	
Iota Carrageenan	Signet Chemical Corporation, Mumbai	
HPMC K4M	Saimirra Innopharm, Chennai.	Release Retardant
Calcium Carbonate	Saimirra Innopharm, Chennai.	Crosslinking Agent
Sodium Bicarbonate	Saimirra Innopharm, Chennai.	Gas Generating Agent
Sodium Saccharin	Saimirra Innopharm, Chennai.	Sweetening Agent
Sodium Citrate	Pharmafabrikon, Madurai.	Buffering Agent
Methyl Paraben Sodium	Pharmafabrikon, Madurai.	Preservative
Propyl Paraben Sodium	Pharmafabrikon, Madurai.	

8.2. INSTRUMENTS USED

Table 8.2: List of Equipment used

INSTRUMENTS	SUPPLIERS
UV spectrophotometer	Shimadzu 1800, Japan
Weighing balance	MC Dalal, Chennai
Magnetic Stirrer	REMI Instruments, Mumbai
pH meter	MC Dalal, Chennai
Brookfield viscometer	LV5 ka
Dissolution Apparatus	Thermonik, Campbell Electronics, Mumbai
Stability chamber	Remi che-6 plus
FT-IR	8400S, Shimadzu, Japan

8.3. PREFORMULATION STUDIES

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.[88]

8.3.1. CHARACTERIZATION OF RIVASTIGMINE TARTRATE

8.3.1.1 Determination of Melting Point of Rivastigmine Tartrate

The melting point of Rivastigmine tartrate was determined by the capillary tube method according to the USP. A sufficient quantity of Rivastigmine tartrate powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in 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 Rivastigmine tartrate in the tube passed into liquid phase**.**[89]

8.3.1.2. Determination of UV Absorption Maxima (λ max) of Rivastigmine Tartrate

100 mg of Rivastigmine tartrate was accurately weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 0.1 N HCl, and the volume was made up to 100 ml to obtain a stock solution of 1000 µg/ml. 1 ml of this stock solution was again diluted with 0.1 N HCl up to 10 ml to obtain a solution of 100 µg/ml. The resulting solution was scanned between 200 nm and 400 nm in a double beam UV-visible spectrophotometer.[90]

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

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 40° C and 75 ± 2 % RH. Any change in colour of the physical mixture was observed visually.[91]

8.3.2.2. Chemical Compatibility Study

Fourier transform infrared (FTIR) spectroscopy was performed using a Shimadzu FTIR 8400 Spectrophotometer from 4000 to 400/cm region, the spectrum was recorded. The procedure consists of dispersing the sample (drug alone, Mixture of drug and excipients and the optimized formulation) in KBr (200– 400 mg) and made into disc form by compressing it with a pressure of 5 tons in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.[92]

8.3.3. PREPARATION OF 0.1 N HCl (pH 1.2)

8.5 mL of Hydrochloric acid was transferred to a 1000 mL standard flask and then diluted with distilled water and made up to the volume. The pH was adjusted to 1.2 using 0.1 M sodium hydroxide solution.[93]

8.3.4. PREPARATION OF CALIBRATION CURVE FOR RIVASTIGMINE TARTRATE

Standard solution of Rivastigmine tartrate ranging from 5-25 ml (1ml=1000µg) was transferred into a series of 50 ml volumetric flasks. To each flask required amount of 0.1N HCl was added and finally the volume in each flask was brought up to the 50 ml with the 0.1N HCl. The absorbance was measured at 263 nm against the reagent blank. Then, Calibration curve was plotted by taking Concentration on X-axis and Absorbance on Y-axis.[53]

8.4 PREPARATION OF ORAL *IN SITU* GEL OF RIVASTIGMINE TARTRATE

- Sodium Alginate, Gellan Gum, Iota Carrageenan, HPMC K4M, Sodium Citrate, Calcium Carbonate, Sodium bicarbonate, Sodium Saccharin, Propyl paraben sodium and Methyl paraben sodium were weighed accurately.
- Various concentrations of gelling polymer (Sodium Alginate or Gellan Gum) were dissolved in deionized water with a weighed amount of Sodium Citrate on a magnetic stirrer at 70°C.
- Iota carrageenan solution was prepared separately by dissolving in deionized water containing Sodium Citrate and heating to 80º C while stirring.
- In another beaker, the required quantity of release retardant polymer HPMC K4M was soaked in deionized water until completely dissolved.
- Then, all the three solutions were mixed together with continuous stirring.
- After the above solution has cooled down to 40°C, Calcium Carbonate, Sodium bicarbonate and Rivastigmine tartrate were added.
- Sodium Saccharin and Preservatives were mixed.
- Finally, the volume was adjusted with the deionized water, and the resultant solution was stirred well and stored in amber-coloured bottles until further use.

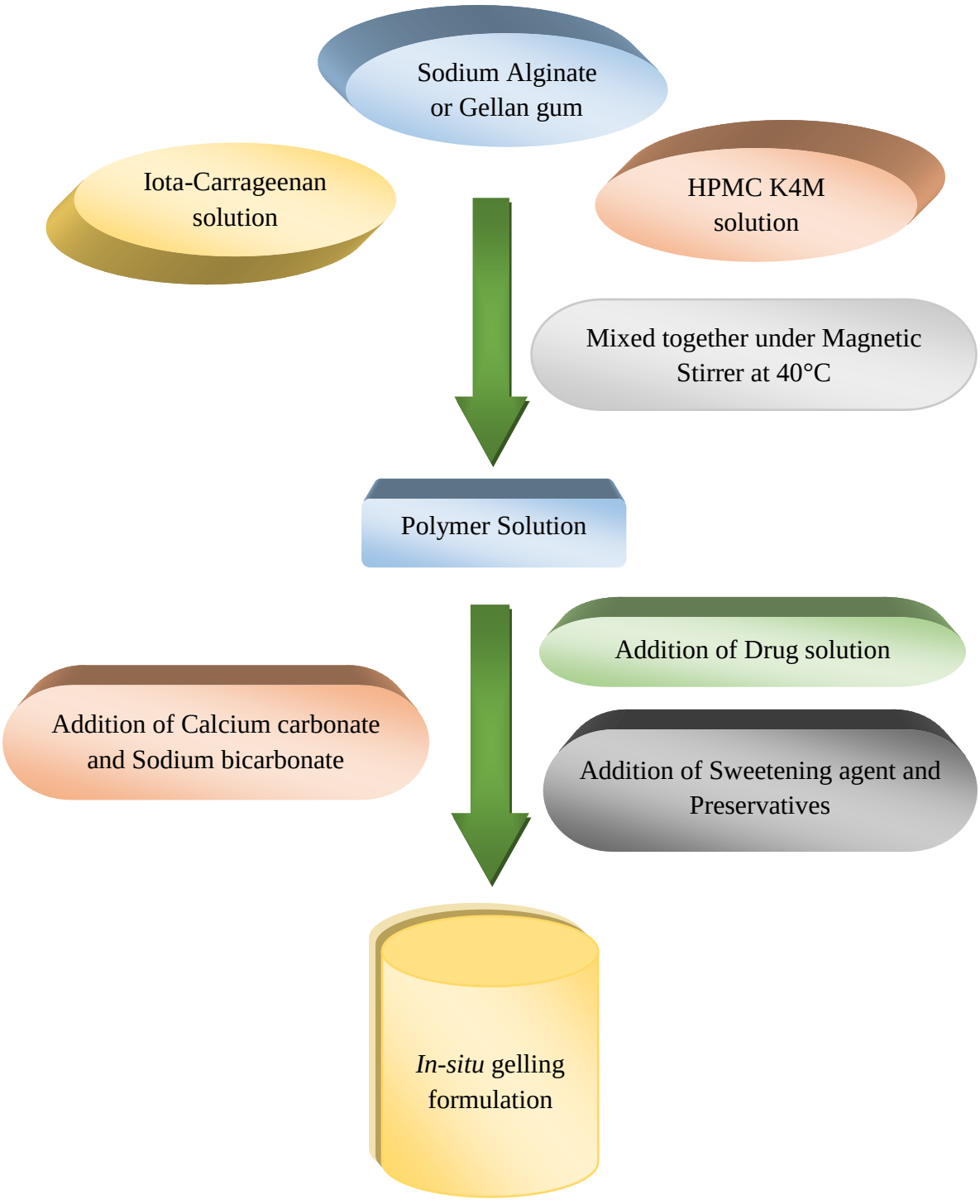


Fig. 8.1: Schematic representation of the preparation of Oral *In situ* gel

Table 8.3: Composition of the *In situ* gelling formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Rivastigmine tartrate (mg)	60	60	60	60	60	60	60	60	60	60
Sodium alginate (%w/v)	1.0	-	0.5	-	1.0	-	1.0	-	0.5	0.5
Gellan gum (%w/v)	-	0.3	0.15	-	-	0.3	-	0.3	0.15	0.15
Iota carrageenan (%w/v)	-	-	-	0.25	0.2	0.2	0.25	0.25	0.2	0.25
HPMC K4M (%w/v)	0.1	0.1	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	0.5	0.5
Calcium carbonate (% w/v)	0.5	0.5	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	0.25	0.25
Sodium Saccharin (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Methyl paraben sodium (% w/v)	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Propyl paraben sodium (% w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Deionized water (to produce ml)	100	100	100	100	100	100	100	100	100	100

8.5. CHARACTERIZATION OF *IN SITU* GEL

8.5.1. Visual appearance[39]

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

8.5.2. Measurement of pH[39]

The pH for each 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.

8.5.3. *In vitro* gelation study[39]

5 ml of the simulated gastric fluid (0.1N HCl, pH 1.2) was taken in a 15ml test tube, maintained at 37°C, 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* gelling capacity was investigated.

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

- (+) : Gels in few seconds, disperse immediately
- (++) : Gelation immediate remains for few hours
- (+++) : Gelation after few minutes remains for extended periods

8.5.4. Determination of viscosity[39]

Viscosities 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 for done for 3 times with fresh samples used each time and the average reading was taken.

8.5.5. *In vitro* buoyancy study[39]

The studies were conducted in a USP Type II dissolution apparatus using simulated gastric fluid (pH 1.2) as the medium at 37±0.5°C. 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.

8.5.6. Measurement of water uptake by the gel[39]

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

8.5.7. Measurement of density of gel[39]

30 ml of the *In situ* formulation was poured into a beaker containing 50 ml of 0.1N HCl. 10 ml of the gel formed was taken in measuring cylinder and the weight 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.

8.5.8. Measurement of gel strength[39]

30 g of the gel was taken in a 50 ml beaker and a 50 g weight was placed on the centre of the surface of the gel and allowed to penetrate through the gel. The time taken by the 50 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.

8.5.9. Determination of the drug content[39]

5 ml of the formulation equivalent to 3 mg of the drug was added to 80 ml 0.1N HCl (pH 1.2) in a 100 ml standard flask and stirred for 1 h in a magnetic stirrer. After 1 h, the solution was filtered and diluted with 0.1 N HCl (pH 1.2). The drug concentration was then determined by ultraviolet (UV) visible spectrophotometer at 263 nm against a suitable blank solution.

8.5.10. *In vitro* drug release study of the *In situ* gel formulation[39]

The dissolution studies were performed using a USP type II (paddle method) dissolution apparatus. The dissolution medium used was 500 ml of 0.1 N HCl (pH 1.2), maintained at 37ºC. The stirring rate was adjusted to 50 rpm. This speed was believed to simulate the *in vivo* existing mild agitation and was slow enough to avoid the breaking of the gelled formulation. At predetermined time intervals, 10 ml samples were withdrawn and replaced by fresh dissolution medium, filtered through Whatman filter paper, diluted, and assayed at maximum absorbance at 263 nm using UV-Visible Spectrophotometer.

8.6. RELEASE KINETICS OF THE OPTIMIZED FORMULATION[94]

To study the *In vitro* release kinetics of the optimized formulation of Rivastigmine tartrate oral *In situ* gel, data obtained from dissolution study were plotted in various kinetics models.

8.6.1. Zero-order equation

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

$$C=K_0t$$

Where,

K_0= Zero order constant

t= Time in hours

8.6.2. First order equation

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

8.6.3. Higuchi kinetics

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

$$\mathbf{Q = Kt^{½}}$$

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

8.6.4. Hixson and Crowell erosion equation

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.

$$\mathbf{Q_0^{1/3} - Qt^{1/3} = K_{HC}t}$$

Where,

Qt= amount of drug released in time t.

Q_0= Initial Amount of drug

K_{HC}= Rate constant for Hixson Crowell equation

8.6.5. Korsmeyer-Peppas equation

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

$$M_t/M_\alpha = Kt^n$$

Where

M_t/M_α = Fraction of drug released at time t

t = Release time

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 and 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

8.7. Stability studies[95]

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 guideline, 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 behaviour, gelling capacity, drug content as well as *In vitro* drug release.

RESULTS AND DISCUSSION

9.1. PREFORMULATION STUDIES

9.1.1. CHARACTERIZATION OF THE DRUG

9.1.1.1. Melting point of Rivastigmine tartrate

Melting point was measured using capillary tube method. It was found to be 124ºC. The melting point of Rivastigmine tartrate is within the limits (123 - 125 º C).[81]

9.1.1.2. Determination of λ max of Rivastigmine tartrate

The maximum absorbance of the Rivastigmine tartrate was studied and found to be 263 nm as given in fig 9.0. Hence, the wavelength of 263 nm was selected for estimation of drug content and analysis of drug in dissolution media as determined by Sharmila SK et al.[53]

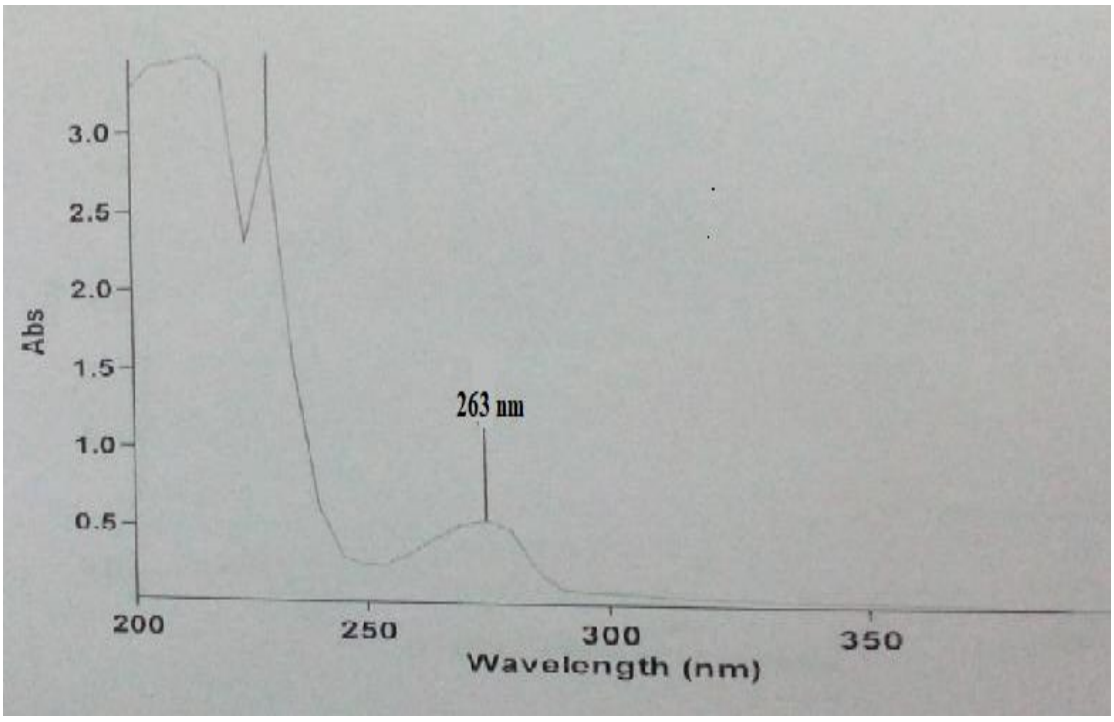


Fig. 9.0 : UV spectrum of Rivastigmine tartrate

9.1.2. DRUG - EXCIPIENT COMPATIBILITY STUDY

The drug-excipient study was conducted to reveal the excipient compatibility with the drug.

9.1.2.1. PHYSICAL COMPATIBILITY STUDY:

Table. 9.1. Physical Compatibility of Drug and Excipients

S. No.	Drug and Excipients	Description and Condition						
		Initial	At room temperature			At 40°C ± 2°and 75% RH± 2% (in days)		
			10	20	30	10	20	30
1.	Rivastigmine tartrate (API)	White Granular Powder	NC	NC	NC	NC	NC	NC
2.	API + Sodium Alginate	Off-White Powder	NC	NC	NC	NC	NC	NC
3.	API + Gellan Gum	Dull-White Powder	NC	NC	NC	NC	NC	NC
4.	API + Iota carrageenan	Dull-White Powder	NC	NC	NC	NC	NC	NC
5.	API + HPMC K4M	White Powder	NC	NC	NC	NC	NC	NC
6.	API + Calcium Carbonate	White Powder	NC	NC	NC	NC	NC	NC
7.	API + Sodium bicarbonate	White crystalline Powder	NC	NC	NC	NC	NC	NC
8.	API + Sodium Citrate	White crystalline Powder	NC	NC	NC	NC	NC	NC
9.	API + Sodium Saccharin	White crystalline Powder	NC	NC	NC	NC	NC	NC
10.	API + Methyl Paraben Sodium	White Powder	NC	NC	NC	NC	NC	NC
11.	API + Propyl Paraben Sodium	White Powder	NC	NC	NC	NC	NC	NC

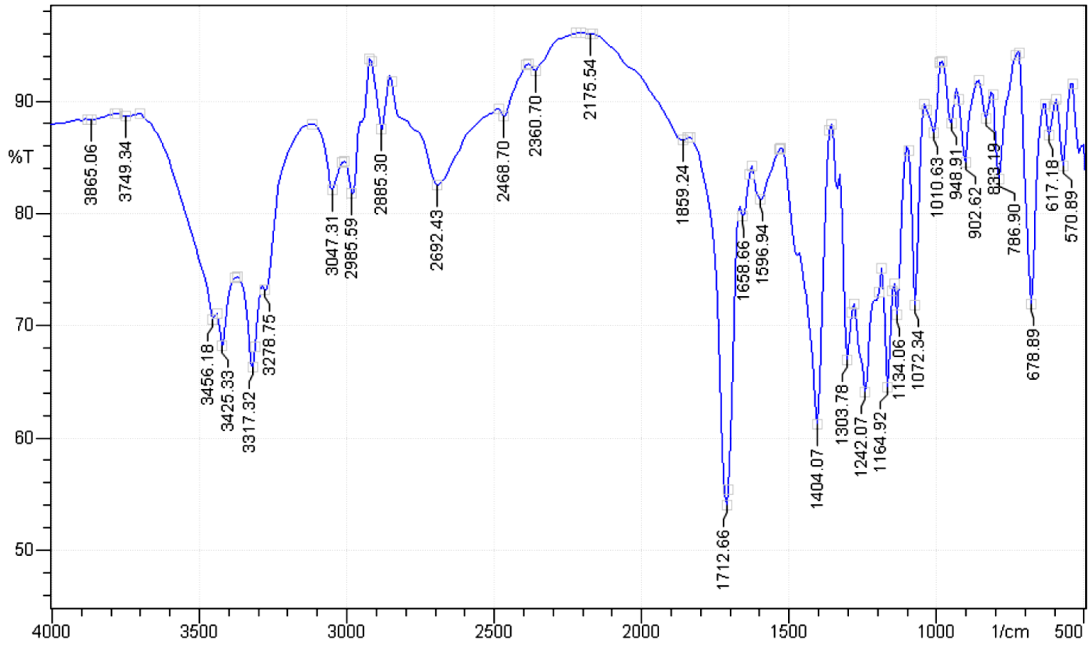
*NC - No Change

Inference

- ✓ The Physical compatibility was evaluated for 10, 20 and 30 days at room temperature and at 40˚C±2˚C/75±5% RH. There was no change of colour.
- ✓ Therefore, the drug and excipients are physically compatible with each other.

9.1.2.2. CHEMICAL COMPATIBILITY STUDY:

Fig. 9.1: FTIR SPECTRA OF RIVASTIGMINE TARTRATE:

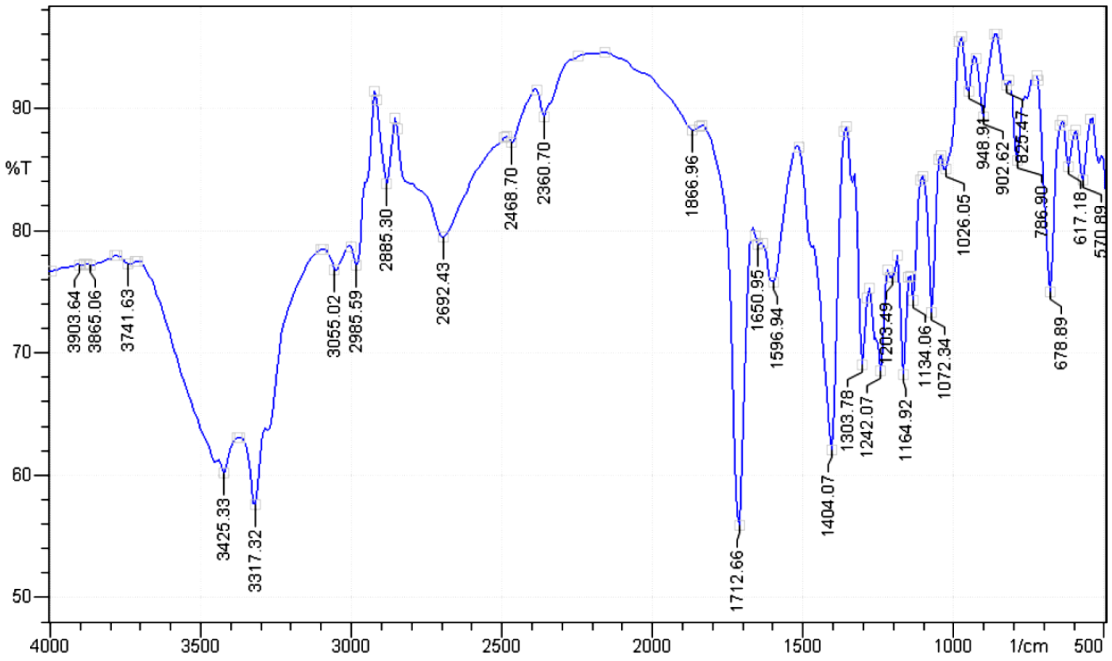


Observation:

Table 9.2: FTIR spectral interpretation of Rivastigmine tartrate

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1658.66	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Fig. 9.2: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + SODIUM ALGINATE



Observation:

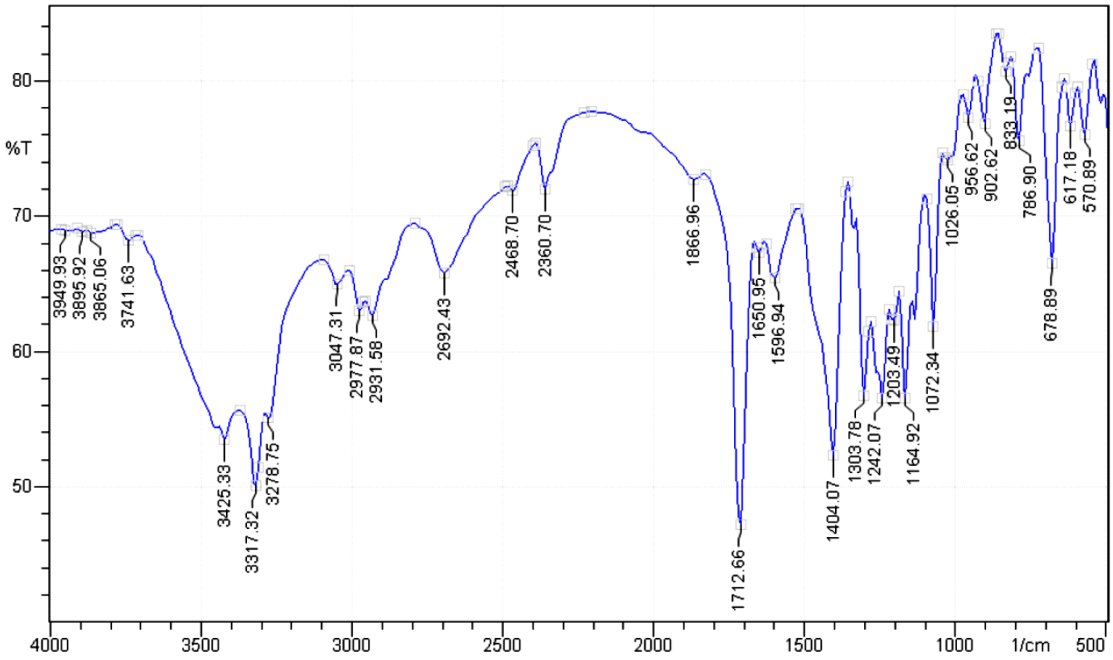
Table 9.3: FTIR spectral interpretation of Rivastigmine tartrate and Sodium Alginate

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1650.95	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Sodium Alginate is shown in figure 9.2.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium Alginate.[92]

Fig. 9.3: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + GELLAN GUM



Observation:

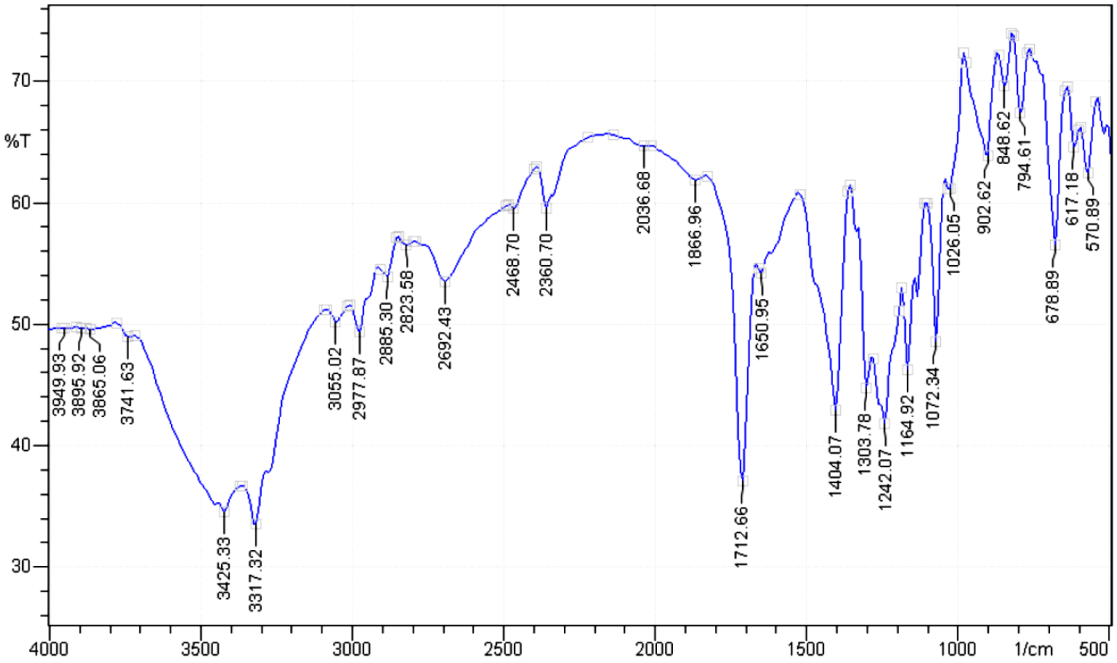
Table 9.4: FTIR spectral interpretation of Rivastigmine tartrate and Gellan gum

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2931.58	-
3	C=C	1675-1600	-	1650.95	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Gellan gum is shown in figure 9.3.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Gellan gum. [92]

Fig. 9.4: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + IOTA CARRAGEENAN



Observation:

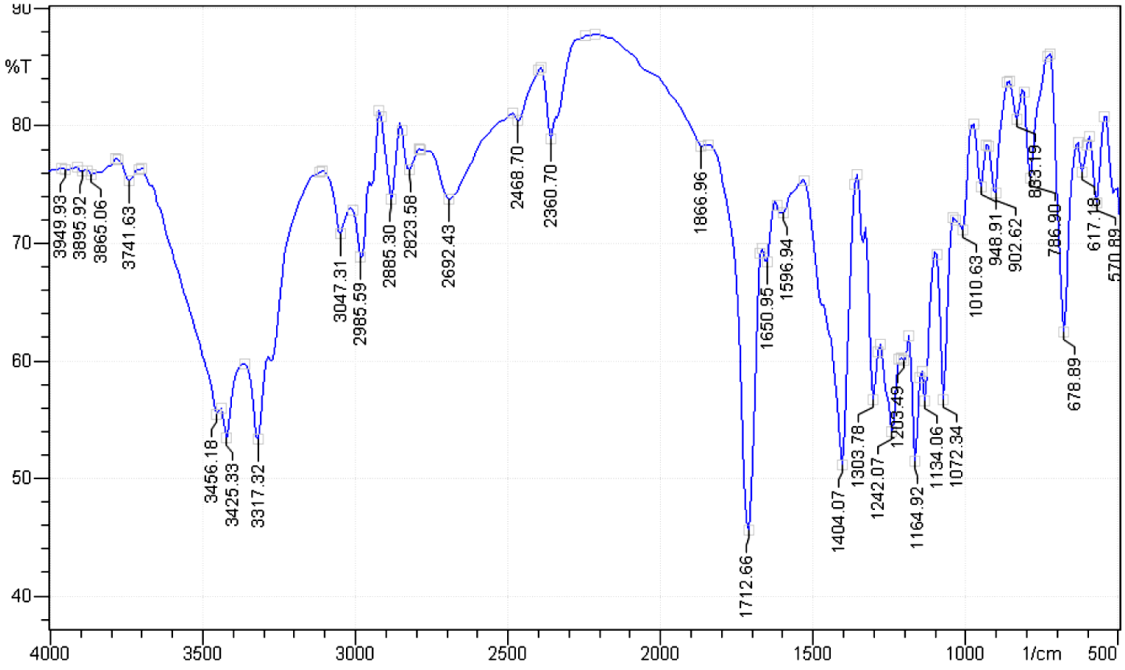
Table 9.5: FTIR spectral interpretation of Rivastigmine tartrate and Iota carrageenan

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1650.95	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Iota carrageenan is shown in figure 9.4.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Iota carrageenan. [92]

Fig. 9.5: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + HPMC K4M



Observation:

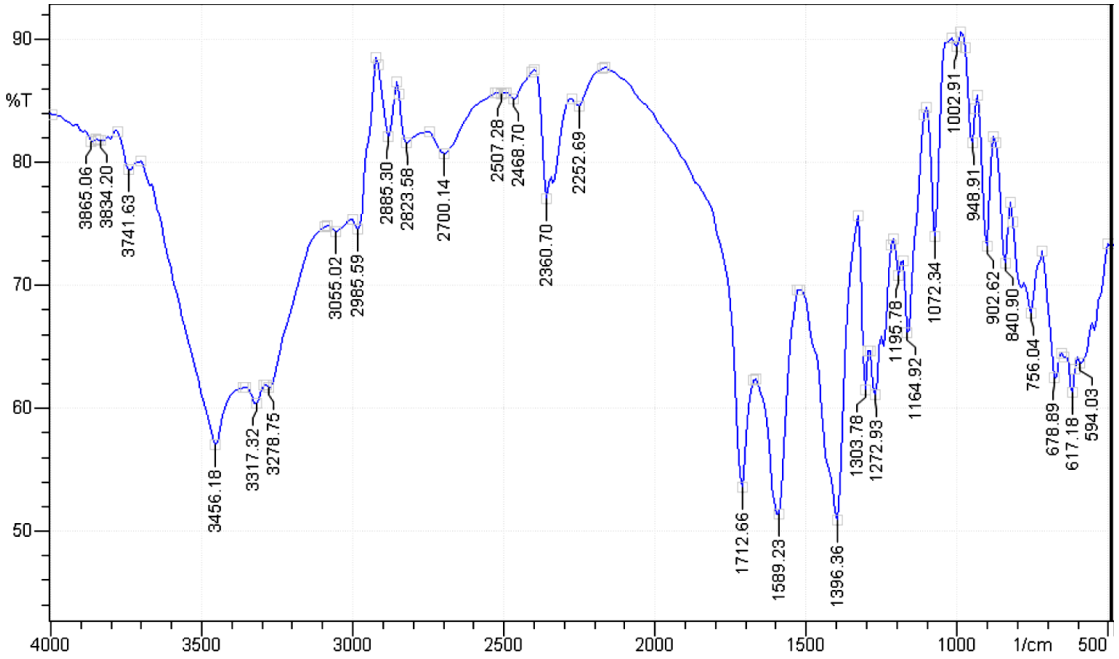
Table 9.6: FTIR spectral interpretation of Rivastigmine tartrate and HPMC K4M

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1650.95	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and HPMC K4M is shown in figure 9.5.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and HPMC K4M. [92]

Fig. 9.6: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + SODIUM CITRATE



Observation:

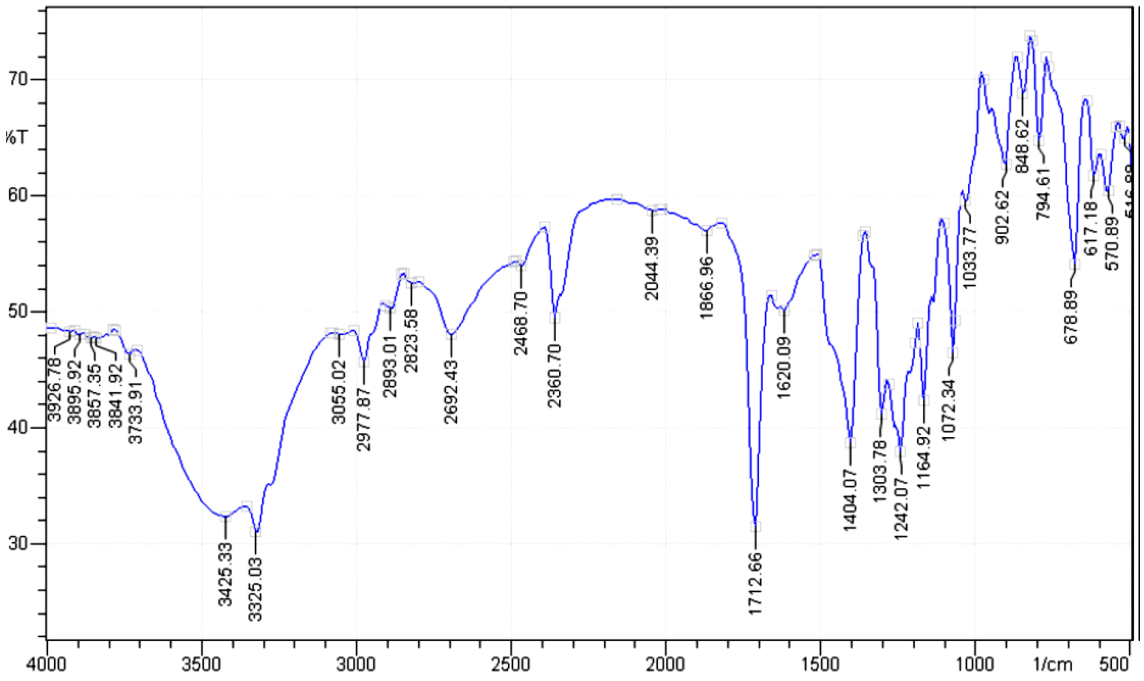
Table 9.7: FTIR spectral interpretation of Rivastigmine tartrate and Sodium Citrate

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3456.18	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1589.23	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Sodium citrate is shown in figure 9.6.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium citrate. [92]

Fig. 9.7: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + CALCIUM CARBONATE



Observation:

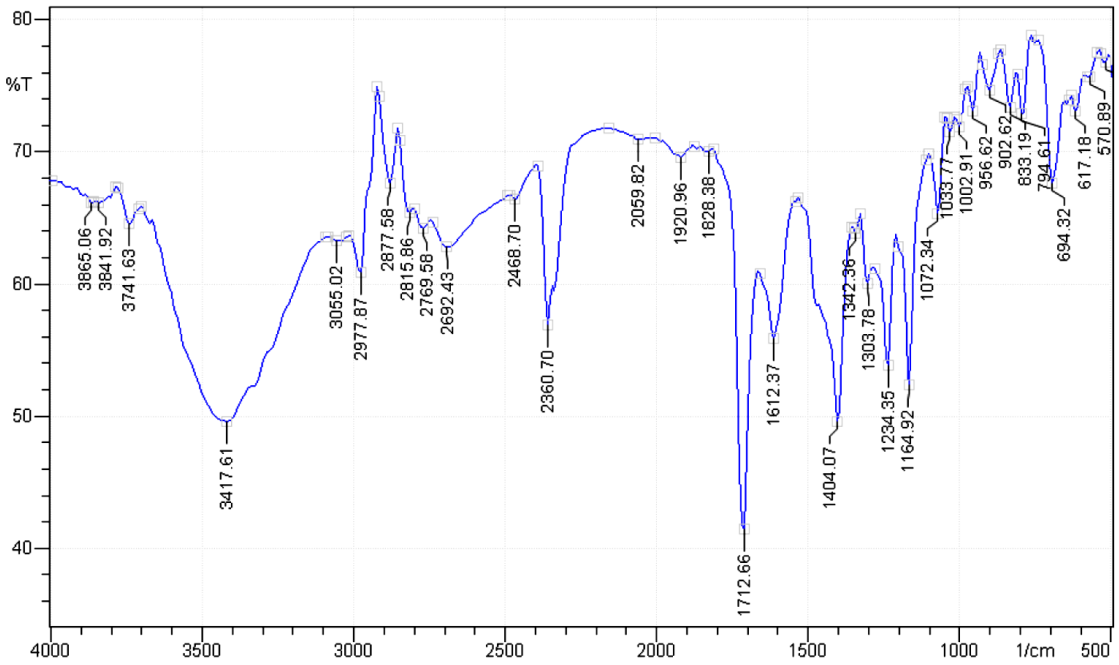
Table 9.8: FTIR spectral interpretation of Rivastigmine tartrate and Calcium carbonate

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2893.01	-
3	C=C	1675-1600	-	1620.09	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Calcium carbonate is shown in figure 9.7.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Calcium carbonate. [92]

Fig. 9.8: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + SODIUM BICARBONATE



Observation:

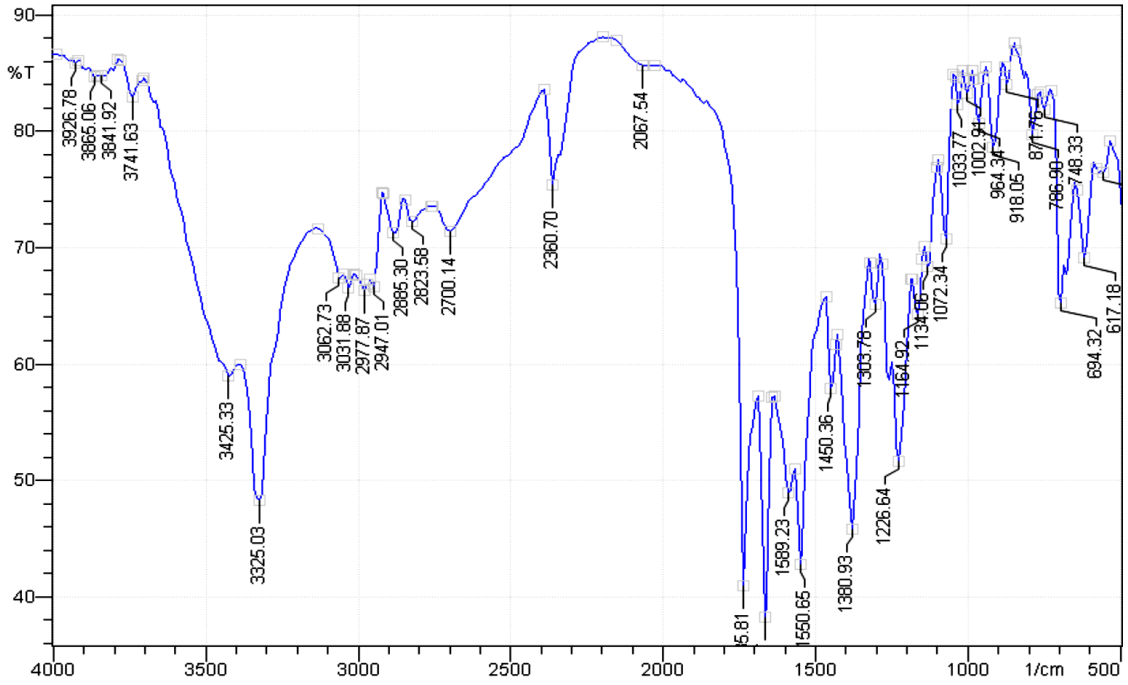
Table 9.9: FTIR spectral interpretation of Rivastigmine tartrate and Sodium Bicarbonate

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3417.61	-
2	C-H	2962-2853	-	2877.58	-
3	C=C	1675-1600	-	1612.37	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	694.32	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Sodium Bicarbonate is shown in figure 9.8.
- ✓ There is no disappearance characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium Bicarbonate. [92]

Fig. 9.9: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + SODIUM SACCHARIN



Observation:

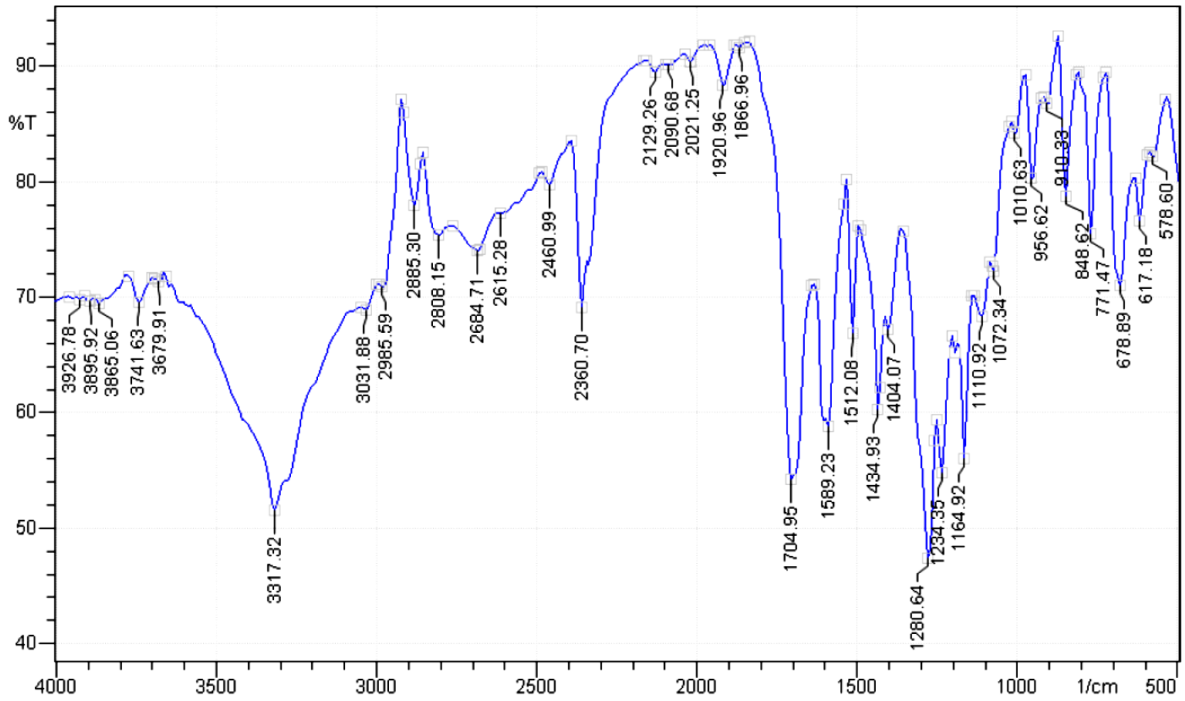
Table 9.10: FTIR spectral interpretation of Rivastigmine tartrate and Sodium Saccharin

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1589.23	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	694.32	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Sodium Saccharin is shown in figure 9.9.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium Saccharin. [92]

Fig. 9.10: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + METHYL PARABEN SODIUM



Observation:

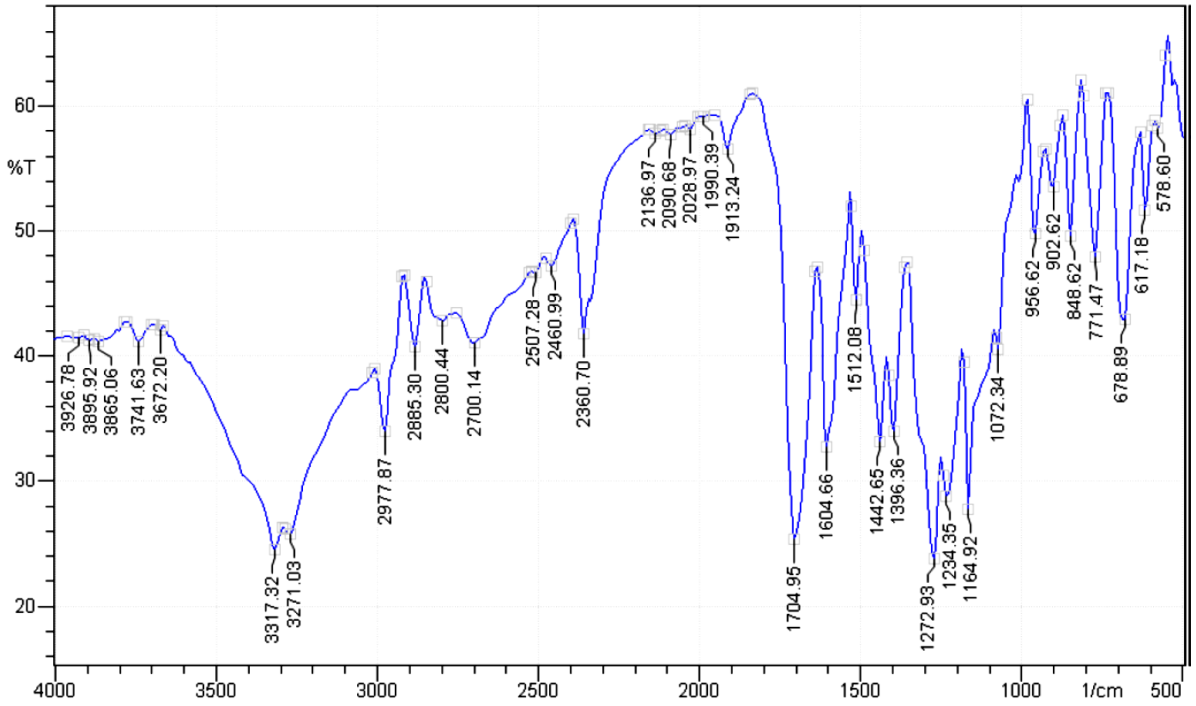
Table 9.11: FTIR spectral interpretation of Rivastigmine tartrate and Methyl Paraben sodium

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3317.32	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1589.23	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Methyl Paraben sodium is shown in figure 9.10.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Methyl Paraben sodium. [92]

Fig. 9.11: FTIR SPECTRA OF RIVASTIGMINE TARTRATE + PROPYL PARABEN SODIUM



Observation:

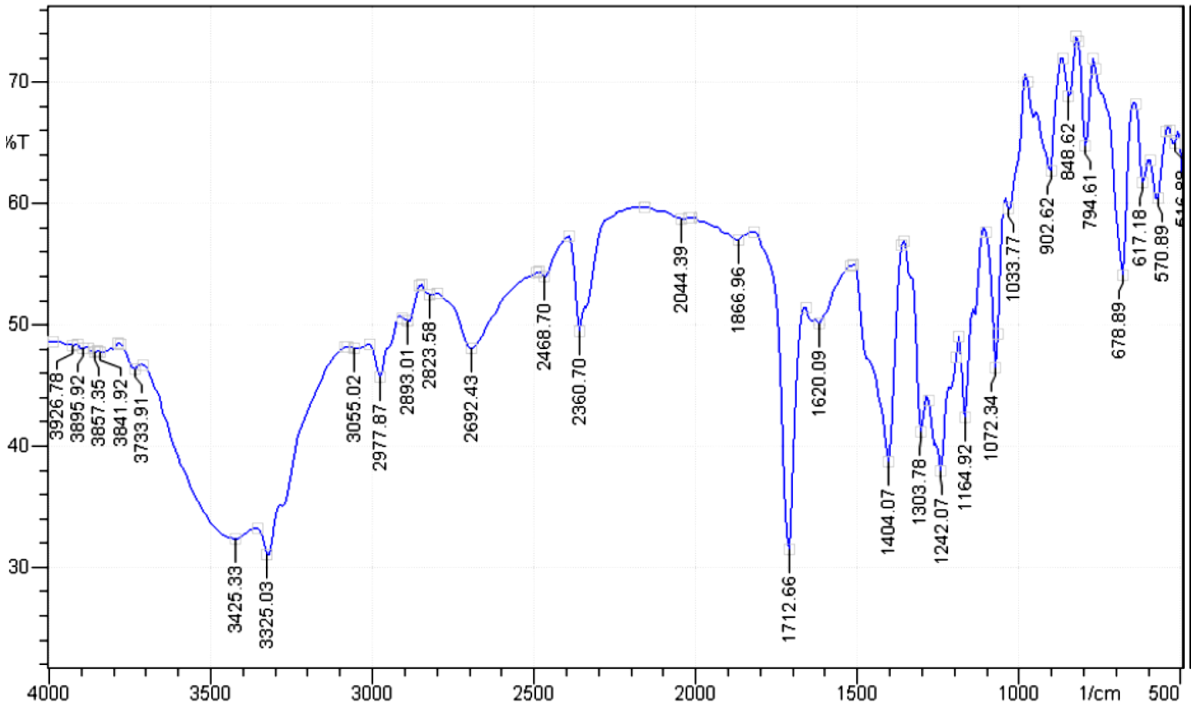
Table 9.12: FTIR spectral interpretation of Rivastigmine tartrate and Propyl Paraben sodium

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3317.32	-
2	C-H	2962-2853	-	2885.30	-
3	C=C	1675-1600	-	1604.66	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Rivastigmine tartrate and Propyl Paraben Sodium is shown in figure 9.11.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Propyl Paraben sodium. [92]

Fig. 9.12: FTIR SPECTRA OF OPTIMIZED FORMULATION



Observation:

Table 9.13: FTIR spectral interpretation of Optimized formulation

S. No.	Functional Group	Characteristic Peaks		Observed Peaks	
		Stretching	Bending	Stretching	Bending
1	N-H	3500-3410	-	3425.33	-
2	C-H	2962-2853	-	2893.01	-
3	C=C	1675-1600	-	1620.09	-
4	C-O	1200-1050	-	1164.92	-
5	C-H	800-600	-	678.89	-

Inference

- ✓ The peaks observed in the FT-IR spectrum for Optimized formulation of *In situ* gel is shown in figure 9.4.
- ✓ There is no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and the excipients. [92]

9.1.3. CALIBRATION CURVE OF RIVASTIGMINE TARTRATE

The UV/Vis spectrophotometric method was used to analyse Rivastigmine tartrate. The absorbance of the drug in 0.1N HCl (pH 1.2), was measured at a wavelength of 263 nm. The results are given in Table 9.14 and Fig 9.13.

Table. 9.14: Concentration and absorbance of Rivastigmine tartrate

Concentration (µg/ml)	Absorbance at λ 263 nm
0	0
100	0.1210 ± 0.005
200	0.2504 ± 0.01
300	0.3699 ± 0.01
400	0.4987 ± 0.02
500	0.6342 ± 0.01

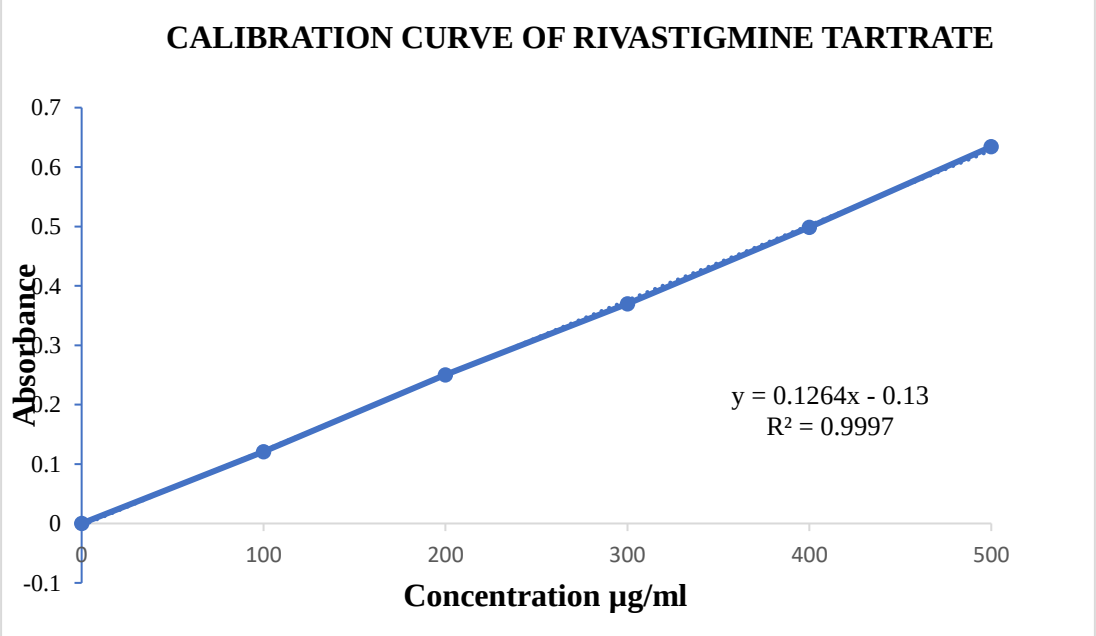


Fig. 9.13: Calibration curve of Rivastigmine tartrate

Inference

- ✓ It was found that the solutions of Rivastigmine tartrate in 0.1 N HCl (pH 1.2) showed linearity (**R^2=0.9997**) in absorbance at concentrations of 100 to 500 µg/ml.
- ✓ It obeys Beer - Lambert's Law.

9.2. FORMULATION OF RIVASTIGMINE TARTRATE ORAL *IN SITU* GEL

The prepared formulations (F1-F10) of Rivastigmine tartrate oral *In situ* gel are shown in Fig.9.14.

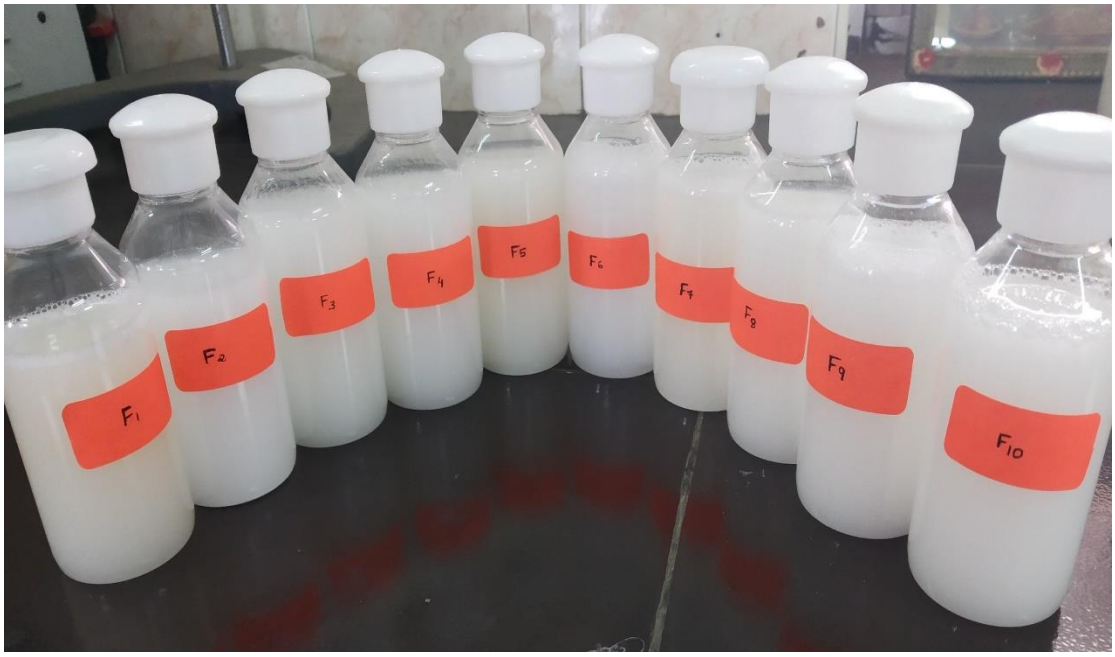


Fig.9.14: Prepared formulations of Rivastigmine tartrate oral *In situ* gel

9.3. EVALUATION OF RIVASTIGMINE TARTRATE ORAL *IN SITU* GEL

9.3.1. Physical Appearance of Rivastigmine Tartrate Oral *In situ* Gel

The visual appeal 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 9.15

Table 9.15: Physical appearance of formulated *In situ* gel

S.No.	Formulation Code	Appearance	Pourability
1	F1	Dull - white	Pourable
2	F2	Dull - white	Easily Pourable
3	F3	Dull - white	Easily Pourable
4	F4	Dull - white	Easily Pourable
5	F5	Dull - white	Pourable
6	F6	Dull - white	Pourable
7	F7	Dull - white	Pourable
8	F8	Dull - white	Pourable
9	F9	Dull - white	Easily Pourable
10	F10	Dull - white	Pourable

Inference

- ✓ All the prepared formulations had dull-white appearance.
- ✓ The formulations were free flowing and did not produce any gelation at room temperature.

9.3.2. pH of Rivastigmine Tartrate Oral *In situ* Gel

Table 9.16: pH of *In situ* gel formulations

S. No.	Formulation Code	pH*
1	F1	6.94 ± 0.02
2	F2	7.18 ± 0.02
3	F3	7.33 ± 0.02
4	F4	7.08 ± 0.02
5	F5	7.16 ± 0.02
6	F6	6.98 ± 0.02
7	F7	7.20 ± 0.02
8	F8	7.28 ± 0.02
9	F9	7.39 ± 0.02
10	F10	7.05 ± 0.02

*n=3

Inference:

- ✓ The pH of all the formulations was found to be satisfactory in the range of 6.94 - 7.39 as depicted in Table 9.16.
- ✓ The pH of all the formulations was within the orally acceptable range (i.e. salivary pH range : 6.2 - 7.6) which is comparable to the conclusions given by Priya S. et al.[39]
- ✓ Therefore, it will not cause any irritation on administration of the formulations.

9.3.3. *In vitro* Gelation Study of Rivastigmine Tartrate 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 9.17.

Table 9.17: Gelling capacity of formulated *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	+++
9	F9	+++
10	F10	+++

(+) : Gels in few seconds, disperses rapidly

(++) : Gelation immediate, remains for few hours

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

Fig. 9.15: *In vitro* gelation study of the *In situ* gel formulations

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 calcium citrate complex gets entrapped in polymeric chains resulting in the cross-linking of polymer chains to form a gel matrix.[50]
- ✓ Thus, **stiff gels were formed with all the formulations** containing polymers such as Sodium alginate and Gellan gum as the main polymer with or without Iota Carrageenan, **except formulation F4** containing only Iota carrageenan as the gelling polymer where the gel formed dispersed rapidly.

9.3.4. Viscosity of Rivastigmine Tartrate Oral *In situ* Gel

The viscosity of all the *In situ* gelling formulations determined at 50 rpm at 25°C using Brookfield Viscometer DV-II+Pro. The results of viscosity measurement of all the formulations are shown in Table 9.18.

Table 9.18: Viscosity of formulated *In situ* gel

S.No.	Formulation Code	Viscosity (centipoise)*
1	F1	186 ± 2.65
2	F2	165.67 ± 1.53
3	F3	111.33 ± 2.62
4	F4	67 ± 4.58
5	F5	238.33 ± 2.52
6	F6	208.67 ± 2.52
7	F7	253.33 ± 6.03
8	F8	236.67 ± 4.16
9	F9	175.67 ± 3.51
10	F10	194.33 ± 3.21

*n=3

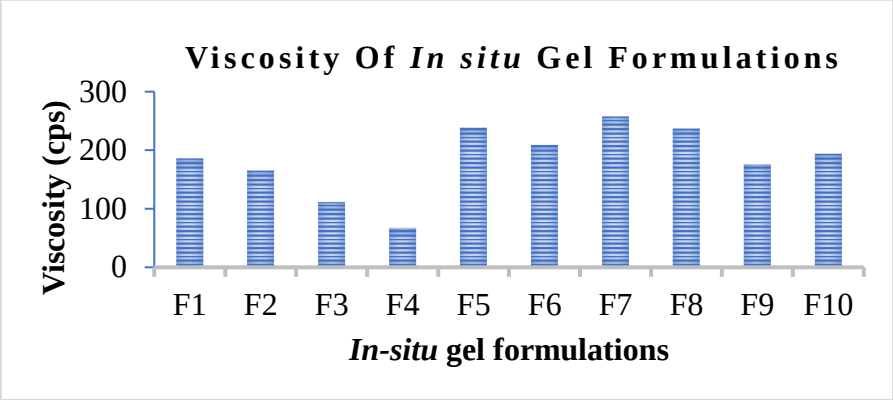


Fig. 9.16: Viscosity of *In situ* gel formulations

Inference

- ✓ All formulations exhibited good consistency, which was dependent on concentration of gelling agents. The results are similar to the inferences given by Shastri D et al.[46]
- ✓ The increase in viscosity was observed in formulations containing high concentration of Sodium alginate and Gellan gum.
- ✓ Formulations containing combination of polymers i.e. Sodium alginate and Gellan gum along with Iota carrageenan showed less viscosity than the formulations with high concentration of single polymer.

9.3.5. *In vitro* Buoyancy of Rivastigmine tartrate 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 floated on the surface of the medium is known as floating duration. The results of buoyancy studies are given in Table 9.19.

Table 9.19: *In vitro* buoyancy of formulated *In situ* gel

S. No.	Formulation Code	Floating lag time (s)*	Floating duration (hrs)
1	F1	13 ± 2	>12
2	F2	15 ± 4	>12
3	F3	12 ± 2	>12
4	F4	8 ± 2	>12
5	F5	20 ± 4	>12
6	F6	12 ± 2	>12
7	F7	16 ± 2	>12
8	F8	22 ± 4	>12
9	F9	13 ± 2	>12
10	F10	17 ± 2	>12

* (n=3)

Inference:

- ✓ When the formulation comes in contact with the acidic environment, gelation as well as cross-linking of the calcium ions takes place providing a gel barrier on the surface of formulation.
- ✓ The carbon dioxide released is entrapped in the gel matrix giving buoyancy to the formulation. Then, the polymeric network further restricts the diffusion of carbon dioxide as well as drug release. The floating ability of the formulations mainly depends on concentration of the gelling polymer, carbon dioxide and cation source as given in earlier reports.[39]
- ✓ All the *In situ* gel formulations had a floating lag time of <2 min and all the formulations floated for more than 12 h.
- ✓ Therefore, the extended duration of floating may be responsible for the controlled release of drug.

9.3.6. Density of Rivastigmine Tartrate 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. 20: Density of formulated *In situ* gel

S. No.	Formulation Code	Density (g/cm^3)*
1	F1	0.659 ± 0.001
2	F2	0.641 ± 0.002
3	F3	0.461 ± 0.002
4	F4	0.303 ± 0.001
5	F5	0.734 ± 0.001
6	F6	0.648 ± 0.001
7	F7	0.771 ± 0.001
8	F8	0.658 ± 0.001
9	F9	0.486 ± 0.001
10	F10	0.532 ± 0.001

* n=3

Inference

- ✓ The density of all the formulations are less than that of the gastric fluid (~1.004 gcm−3).[12]
- ✓ As a result, the floating of the gastroretentive *In situ* gel is promoted in the stomach.

9.3.7. Measurement of Gel Strength of Rivastigmine Tartrate Oral *In situ* Gel

Table 9.21: Gel strength of formulated *In situ* gel

S. No.	Formulation Code	Average gel Strength (s)*
1	F1	20.3 ± 0.6
2	F2	17.6 ± 1.15
3	F3	29.7 ± 0.58
4	F4	14.7 ± 0.58
5	F5	29.3 ± 1.53
6	F6	23.6 ± 1.15
7	F7	34.3 ± 1.53
8	F8	29.0 ± 1.00
9	F9	44.3 ± 1.53
10	F10	52.6 ± 1.53

*n=3

Inference

- ✓ Gel strength gives an indication about the tensile strength of the gelled mass. It demonstrates the ability of the gelled mass to withstand the peristaltic movement in *in vivo*. Table 9.21 gives the gel strength of all the formulations.
- ✓ All the formulations showed good gel strength which ranged from as low as 14.7 s for formulation F4 which contains only Iota carrageenan as main polymer to higher values of 44.3 s and 52.6 s for formulations F9 and F10 respectively, which contains combination of three polymers i.e. Sodium Alginate, Gellan gum and Iota carrageenan.
- ✓ 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 Rivastigmine Tartrate *In situ* Gel

Table 9.22 : Percentage water uptake of *In situ* gel formulations

TIME (mins)	PERCENTAGE WATER UPTAKE BY THE FORMULATIONS									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
30	4.92	2.9	3.44	4.72	5.02	4.48	7.89	5.88	6.78	8.47
60	7.79	5.81	8.6	7.48	9.48	7.94	13.38	11.13	14.36	16.14
90	12.3	8.71	12.89	10.63	15.61	14.86	17.67	18.07	24.12	25.13
120	14.55	12.24	16.91	14.17	22.3	19.96	24.01	23.74	29.27	31.22

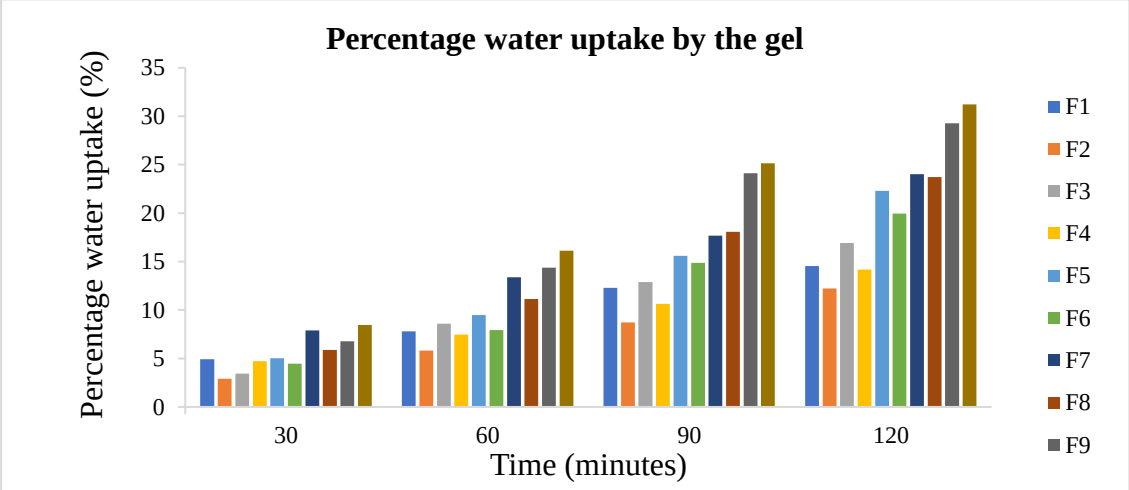


Table 9.17 : Percentage water uptake of *In situ* gel formulations

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 drug release involves the penetration of water into the matrix and simultaneous release of the drug through diffusion or dissolution.
- ✓ The percentage water uptake of all the formulations is given in Table 9.22 and Fig. 9.17. When compared with other formulations, F9 and F10 showed a better water uptake of 29.27% and 31.22% respectively. The high water uptake may be because of the high swelling capacity of the polymers used.
- ✓ As the formulations F9 and F10 contain combination of Sodium alginate, Gellan gum, Iota carrageenan and HPMC K4M. This results in high water uptake.

9.3.9. Drug Content of Rivastigmine Tartrate 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 are given in Table 9.23 and Fig. 9.18.

Table 9.23: Percentage drug content of formulated *In situ* gel

S. No.	Formulation Code	Drug content (%)
1	F1	98.20
2	F2	98.04
3	F3	98.20
4	F4	98.36
5	F5	98.04
6	F6	98.51
7	F7	98.69
8	F8	98.36
9	F9	99.83
10	F10	99.53

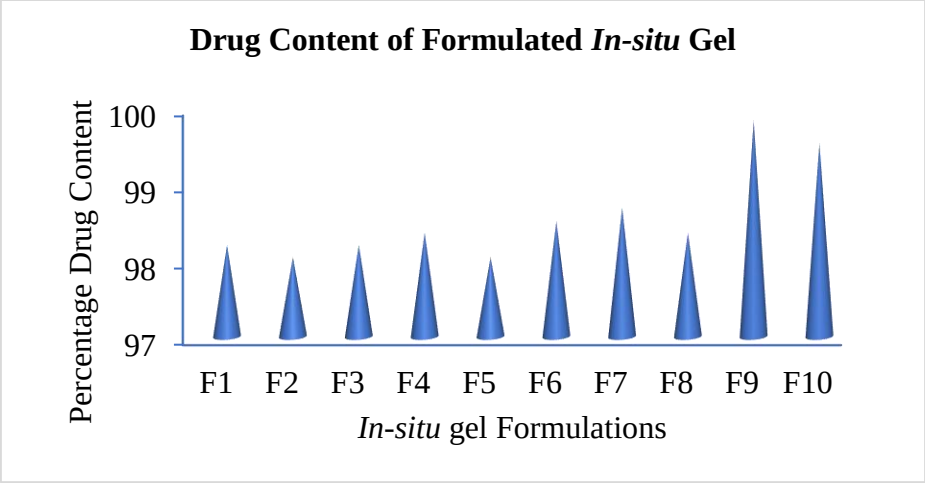


Fig 9.18: Percentage drug content of formulated *In situ* gel

Inference

- ✓ The percentage drug content of all the formulations was in the range of 98.04 - 99.83 % indicating uniform distribution of drugs in all formulations.
- ✓ The results are comparable to that of Rivastigmine capsules (Acceptance criteria : 94.0% – 105.0%).[96]

9.3.10. *In vitro* Dissolution Study of Formulated Rivastigmine Tartrate Oral *In situ* Gel

The results of *In vitro* drug release study of the *In situ* gel formulations are given in Table 9.24, Fig. 9.19 and Fig. 9.20.

Table 9.24: *In vitro* Drug release of formulated *In situ* gel

Time	PERCENTAGE DRUG RELEASE									
(min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	18.42	14.03	11.83	33.86	14.03	11.83	9.61	9.61	7.42	7.44
1	29.81	25.34	20.87	49.95	20.92	20.89	16.39	14.22	12.0	9.61
1.5	48.04	34.64	27.9	70.77	27.94	25.72	21.17	23.27	18.83	14.39
2	55.59	50.74	43.86	80.99	35.11	37.22	28.17	30.33	21.39	21.27
3	72.08	64.94	53.55	97.97	51.12	53.39	39.78	35.39	30.61	32.67
4	88.91	75.03	69.99	-	58.78	65.39	49.33	42.66	37.81	39.94
5	97.71	83.07	77.94	-	68.71	73.28	56.83	50.11	45.17	47.33
6	-	89.01	86.02	-	85.44	81.28	66.78	55.44	52.55	54.83
7	-	97.27	94.24	-	95.83	89.39	70.22	60.89	60.21	60.22
8	-	-	98.17	-	-	95.44	78.11	68.56	65.72	68
9	-	-	-	-	-	99.39	81.72	76.44	71.33	73.67
10	-	-	-	-	-	-	87.61	82.26	81.46	79.39
11	-	-	-	-	-	-	98.00	99.14	87.33	83.0
12	-	-	-	-	-	-	-	-	99.91	91.11

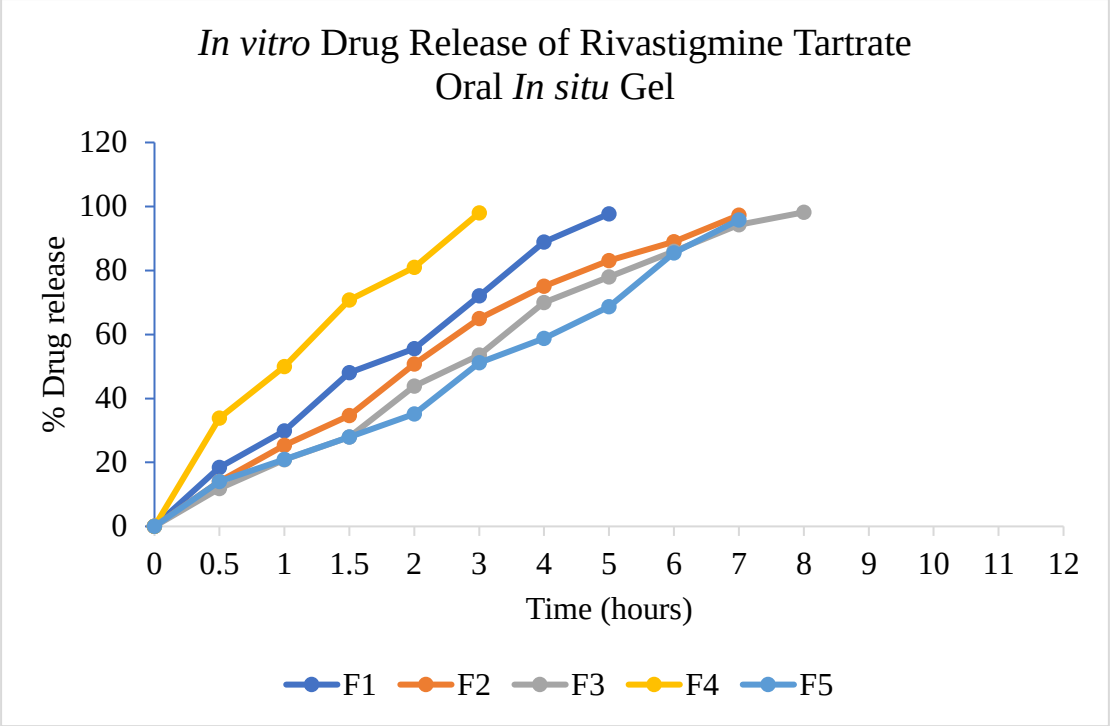


Fig. 9.19: *In vitro* drug release study of *In situ* gel formulations (F1 - F5) of Rivastigmine tartrate

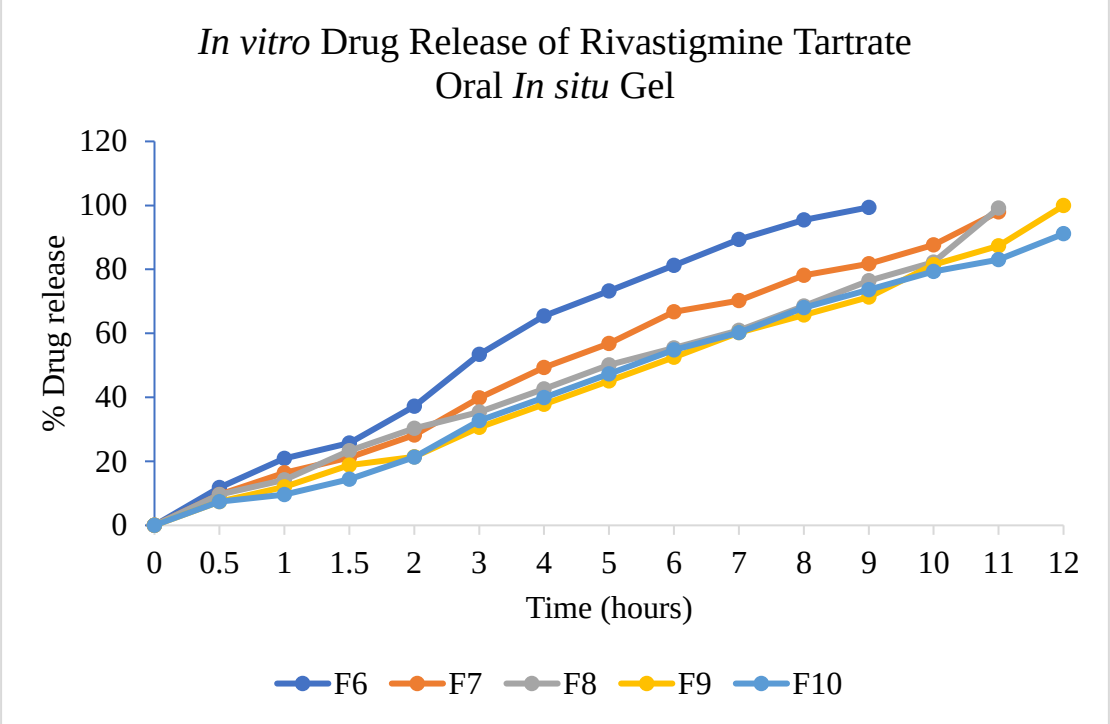


Fig. 9.20: *In vitro* drug release study of *In situ* gel formulations (F6 - F10) of Rivastigmine tartrate

Inference

- ✓ From the *In vitro* drug release studies of the *In situ* gel formulations (F1 - F10), it was observed that only the Formulations F9 and F10 containing the combination of all three polymers (Sodium Alginate, Gellan gum and Iota carrageenan) provided prolonged release of the drug upto 12 hours.
- ✓ Other formulations (F1 - F8) released the drug even before the period of 12 hours.
- ✓ Formulation F9 containing Sodium alginate (0.5 % w/v), Gellan gum (0.15 % w/v) and Iota carrageenan (0.2 % w/v) showed 99.91 % of drug release at the end of 12 hours.
- ✓ Formulation F10 containing Sodium alginate (0.5 % w/v), Gellan gum (0.15 % w/v) and Iota carrageenan (0.25 % w/v) showed 91.11 % of drug release at the end of 12 hours.

9.4. SELECTION OF OPTIMIZED FORMULATION

- ❖ Based on the *In vitro* drug release studies of the *In situ* gelling formulations, formulation F9 and F10 were considered to be suitable for providing prolonged delivery of Rivastigmine tartrate as it extended the drug release up to 12 hours.
- ❖ Comparing other evaluation parameters like pourability, viscosity, density and drug content of both the formulation F9 and F10, the formulation F9 was found to be a better formulation than F10.
- ❖ Hence, Formulation **F9** is chosen as the optimized formulation.

9.5. *IN VITRO* RELEASE KINETICS

Table. 9.25: *In vitro* release kinetics of optimized formulated (F9)

Time in minutes	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
0.5	0.7071	-0.3010	7.42	92.58	1.9665	0.8704	4.524
1	1	0	12	88.0	1.9444	1.0792	4.448
1.5	1.2247	0.1761	18.83	81.17	1.9094	1.2749	4.329
2	1.4142	0.3010	21.39	78.61	1.8955	1.3302	4.284
3	1.7320	0.4771	30.61	69.39	1.8413	1.4859	4.109
4	2.0000	0.6020	37.81	62.19	1.7937	1.5776	3.962
5	2.2360	0.6989	45.17	54.83	1.7390	1.6549	3.799
6	2.4495	0.7781	52.55	47.45	1.6762	1.7206	3.62
7	2.6458	0.8450	60.21	39.79	1.5998	1.7797	3.414
8	2.8284	0.9031	65.72	34.28	1.5350	1.8177	3.248
9	3.0000	0.9542	71.33	28.67	1.4574	1.8533	3.061
10	3.1623	1.0000	81.46	18.54	1.2681	1.9109	2.647
11	3.3166	1.0414	87.33	12.67	1.1028	1.9412	2.331
12	3.4641	1.0792	99.91	0.09	-1.0458	1.999	2.331

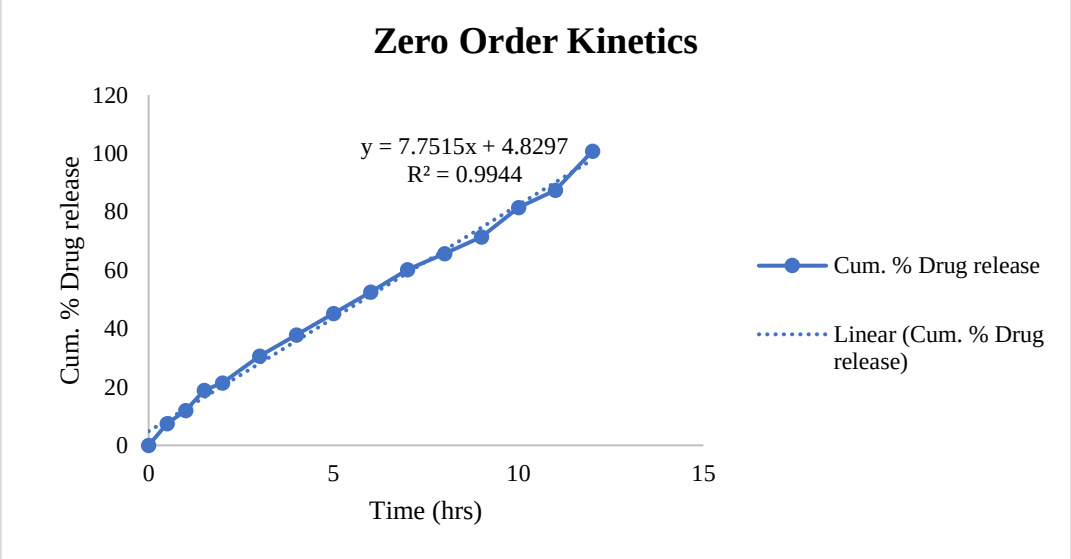


Figure 9.21: A plot of zero order kinetics of optimized formulation (F9)

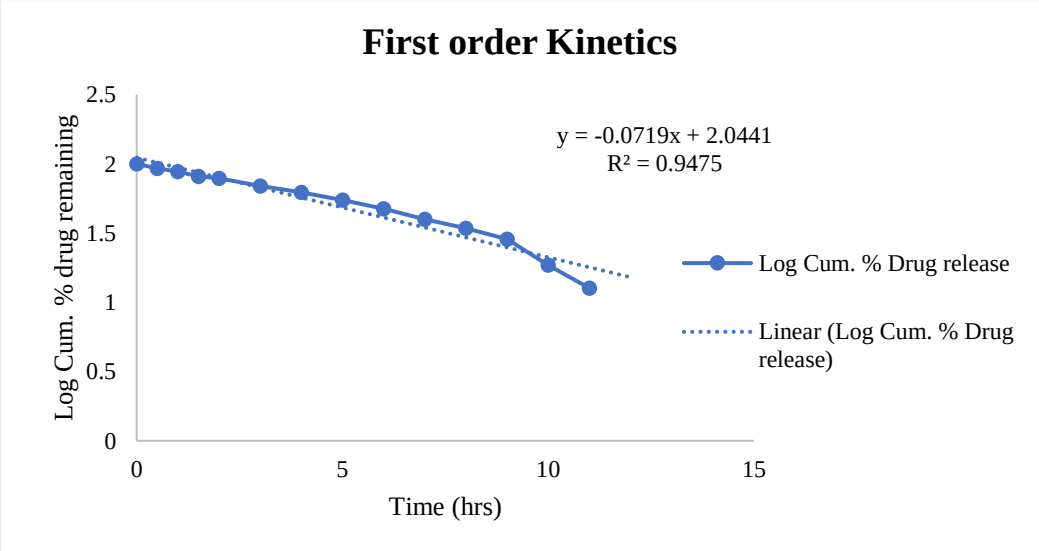


Figure 9.22: A plot of first order kinetics of optimized formulation (F9)

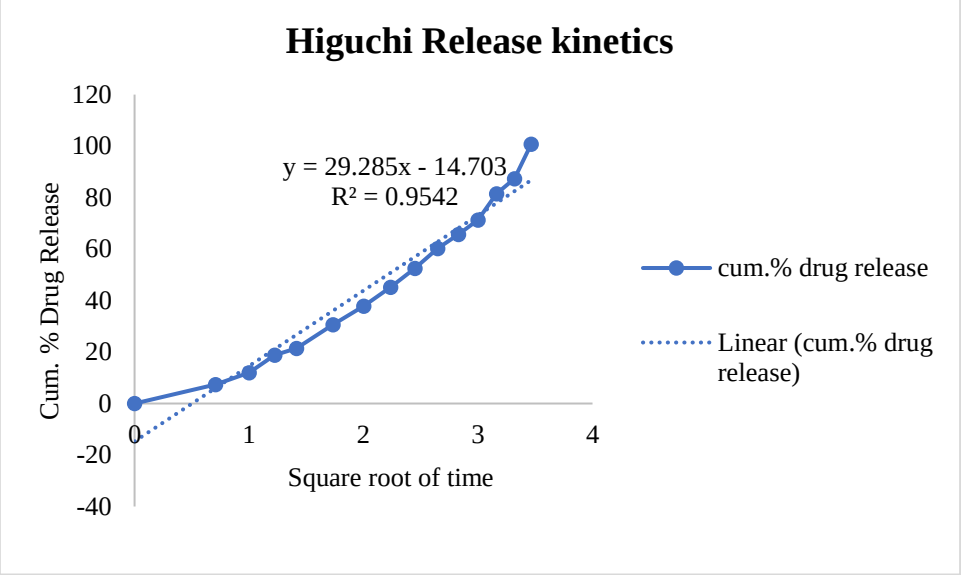


Figure 9.23: A plot of Higuchi release kinetics of optimized formulation (F9)

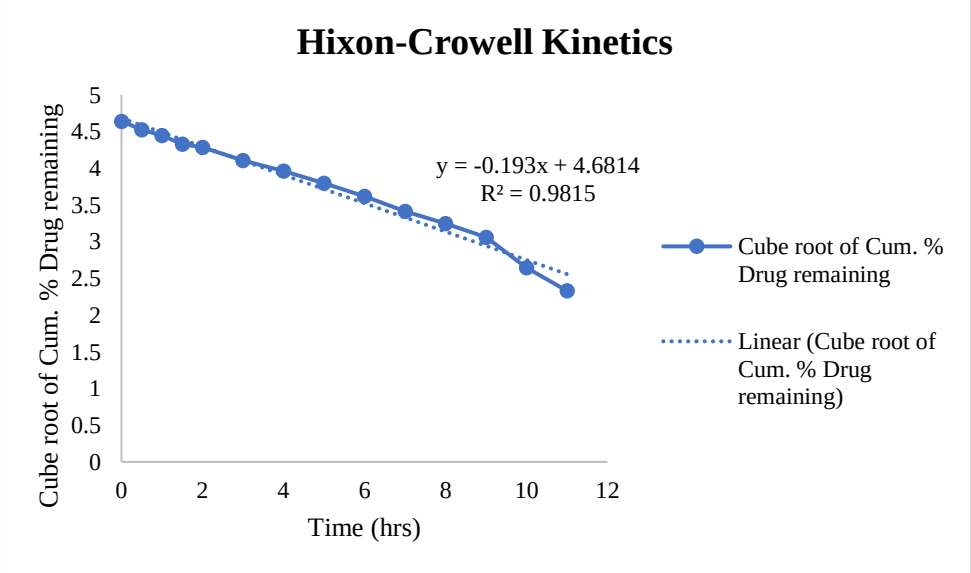


Figure 9.24: A plot of Hixon-Crowell kinetics of optimized formulation (F9)

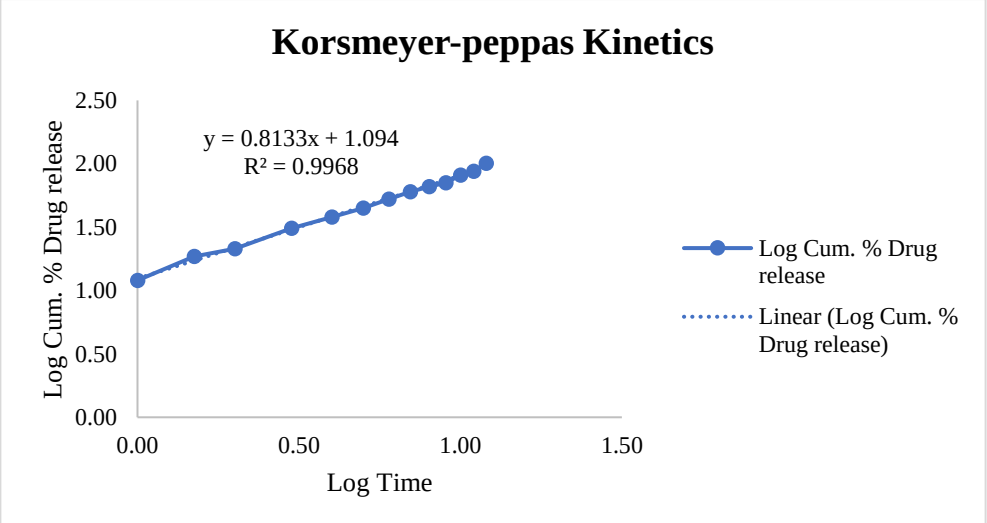


Figure 9.25: A plot of Korsmeyer-Peppas kinetics of optimized formulation (F9)

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2values of various models are given in the table 9.26.

Table 9.26: R^2Values of various Kinetic Models of Optimized formulation (F9)

Kinetic Models	**Coefficient of Determination (R^2)**
Zero order	0.9944
First Order	0.9475
Higuchi	0.9542
Hixon-Crowell	0.9815
Korsmeyer - Peppas	0.9968

- The *In vitro* release of optimized formulation F9 data was fit into various kinetic models to find out the mechanism of drug release from Rivastigmine tartrate oral *In situ* gel.
- A good linearity was observed with the zero order (R^2=0.9944). 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=0.9542) and Hixson-Crowell plot (R^2=0.9815) indicates the rate of drug release follows both diffusion and dissolution mechanisms.

- The data was fitted into the Korsmeyer-Peppas equation which showed good linearity and the slope of the Korsmeyer-Peppas plot (n= 0.8133) was found to be more than 0.45 indicating Anomalous diffusion (Non Fickian diffusion).
- Thus, the release kinetics of the optimized formulation showed zero order drug release with Non-Fickian diffusion mechanism.

9.6. STABILITY STUDIES

The optimized formulations (F9) subjected to stability studies as per ICH guidelines and shown in Table. 9.27 & Table. 9.28.

Table 9.27: Stability data for Optimized Formulation – F9

Parameter	Condition: 40±2ºC/75±5%RH	
	Initial	After 1 month
Visual Appearance	Dull-white	Dull-white
Pourability	Easily pourable	Easily pourable
pH*	7.39 ± 0.2	7.37 ± 0.2
Gelling capacity	+++	+++
Floating Lag time (s)*	13 ± 2	15 ± 2
Floating duration (hours)	>12	>12
Viscosity (cps)*	175.67 ± 3.51	178.3 ± 1.15
Drug content (% w/v)	98.69	98.36

* n=3

Table 9.28: Stability data for Optimized Formulation (Cumulative % drug release of Optimized formulation) - F9

Time (hrs)	Condition: 40±2ºC/75±5%RH	
	Initial	After 1 month
0.5	7.42	9.61
1	12.0	16.42
1.5	18.83	25.57
2	21.39	32.66
3	30.61	42.12
4	37.81	51.74
5	45.17	62.72
6	52.55	67.11
7	60.21	72.72
8	65.72	76.33
9	71.33	82.11
10	81.46	85.77
11	87.33	91.72
12	95.52	95.50

Inference

No significant changes in Physical appearance, pH, viscosity, gelling capacity, floating lag time, drug content and *In vitro* drug release were observed at storage condition of 40°C ± 2°C / 75 ± 5% RH at the end of 1 month.

SUMMARY AND CONCLUSION

10. SUMMARY AND CONCLUSION

The Rivastigmine tartrate oral *In situ* gel was developed using gelling agents such as Sodium Alginate, 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 FT-IR studies revealed that there was no change in major peaks, thus confirming no interaction between the drug and excipients.
- Calibration curve of Rivastigmine tartrate was constructed in Simulated Gastric Fluid (SGF) of pH 1.2 and it obeys Beer Lambert law.
- 10 formulations (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10) of Rivastigmine tartrate *In situ* gel were prepared using varying concentrations of different polymers such as Sodium Alginate, Gellan Gum and Iota Carrageenan along with HPMC K4M (0.1 % w/v) as the release retardant.
- The prepared formulations (F1 - F10) 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, free flowing and did not produce any gelation at room temperature.
- All the formulations except F4 exhibited good gelling capacity. In the formulation F4 containing only Iota carrageenan as the main polymer, the gel that was formed dispersed rapidly.
- All the formulations showed floating lag time of less than 2 minutes and duration of floating was greater than 12 hours.
- Formulation F9 and F10 exhibited lower density than the density of gastric fluid (~1.004 gcm−3) and higher gel strength when compared to other formulations.
- The percentage water uptake was higher for formulations F9 and F10 due to the presence of combination of 3 polymers i.e. Sodium alginate, Gellan gum and Iota carrageenan.
- The percentage drug content of all the formulations was in the range of 96.08-98.69 % indicating uniform distribution of drugs.

- *In vitro* drug release study showed that only the Formulations F9 and F10 released 99.91 % and 91.11% 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.
- Based on the results of evaluation of *In situ* gel, the Formulations F9 and F10 was considered suitable for providing prolonged delivery of Rivastigmine tartrate. Since the Formulation F9 had lower viscosity and was easily pourable than the formulation F10 without significant differences in other parameters, Formulation F9 containing Sodium alginate (0.5 % w/v), Gellan gum (0.15 % w/v), Iota carrageenan (0.2 % w/v) and HPMC K4M (0.1%) was chosen as the optimized formulation.
- The *In vitro* release kinetic study of the optimized formulation F9 showed that the formulation followed Zero-order kinetics and Non-Fickian diffusion mechanism.
- The stability studies indicated that the optimized formulation F9 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 1 month.

The overall results indicate that formulation of Rivastigmine tartrate 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 Alzheimer's disease in patients.

FUTURE PLAN

- Scale-up studies of the optimized formulation.
- Bioequivalence studies with the marketed formulations.
- *In vivo* studies and *In vitro-In vivo* correlation studies.

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ANNEXURES

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This is to certify that.....Mrs. C.K. Aarthi..... has participated as Delegate/Speaker in the CME on " PHARMACOKINETICS" conducted by the Department of Pharmacology, Govt. Kilpauk Medical College, Chennai on 17th August, 2018.

This CME is accredited within 10 credit points under Category II by The TN.Dr.M.G.R Medical University, Guindy, Chennai.

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