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FLOATING ORAL *IN-SITU* GEL, A COMPREHENSIVE APPROACH OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT: Conventional oral dosage forms posses low bioavailability problems due to their rapid gastric transition from the stomach. Especially some drug which is less soluble in alkaline pH and producing local action in the stomach gets rapidly emptied and do not get enough residence time in the stomach. As a result, there is a requirement of increased frequency of dose. To overcome such type of problems various efforts have been made by developing the gastro-retentive drug delivery system. The gastro-retentive drug delivery system comprised mainly of floating, mucoadhesive, swellable and high-density systems have emerged as a current approach of enhancing the bioavailability and controlled delivery of drugs that exhibit an absorption window. So, oral controlled release and site-specific drug delivery system has been of great interest in the pharmaceutical field to achieve an improved therapeutic advantage. In this review, we have discussed the various approaches to produce gastro retention of drug delivery system, with special discussion on floating *in-situ* gel system for stomach specific drug delivery. As it offers several advantages like sustained and prolonged action in comparison to conventional drug delivery systems and increases the bioavailability of drug as well as produce patient compliance by reducing dosing frequency.

INTRODUCTION: Despite the tremendous advancement in drug delivery, the oral route is the most preferred route of drugs administration because of the following reasons;

- Easy for administration.
- Patient acceptability is more.
- Flexibility in the formulation.
- Production is easy.[1]

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1.1 Types of Oral Dosage Forms:

Oral route differentiates into two categories:

- Liquids, *i.e.* solutions, suspensions.
- Solid, *i.e.* tablets, capsules, powders, granules, lozenges, pills, *etc.* [2]

Oral Liquid Dosage Form: Oral liquid dosage forms are homogenous preparations containing one or more active ingredients in a suitable vehicle intended to be swallowed either diluted or after dilution of concentrated liquid preparations. They may contain suitable preservatives, antioxidants and other excipients such as suspending, emulsifying, buffering, solubilizing, flavoring, sweetening and coloring agents.

Needs for Oral Liquid Dosage Form: Although solid dosage forms like tablets and capsules are widely used, the selection of oral liquid preparations is due to:

- Makes it easier to swallow than solids and is therefore acceptable for pediatric and geriatric use.
- Drugs are immediately available for absorption; therefore the therapeutic response is faster than solid dosage form.
- It is a homogenous system and therefore the drug will be uniformly distributed throughout the preparation.

Classification of Oral Liquid Dosage Forms: [2]
Conventional Oral Liquid Dosage Form: This drug delivery system results in suboptimal therapy and systemic side effects. Several preparations are distinguished including oral solutions, emulsions, suspensions, elixirs, oral drops, spirits, and syrups.

Non-conventional Oral Liquid Dosage Forms Including Extended/Sustained release dosage form (ER/SR). The attractiveness of ER dosage form is the success to ensure safety, improve the efficiency of the drug, reduce the dose frequency and Improvement of bioavailability could be expected. As a result, more patient compliance, especially for pediatric and geriatric patients or patients those, are unable to tolerate solid dosage forms.

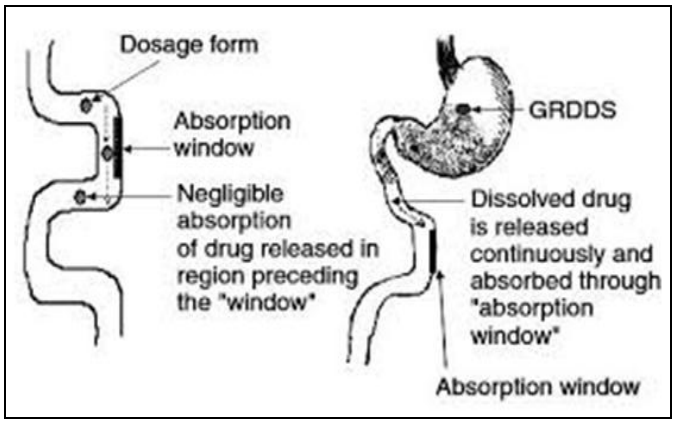

FIG. 1: SHOWS THE ABSORPTION OF DRUG

Controlled/Gastro Retentive Release Dosage Form (CR/GR): It becomes an alternative and novel strategy for achieving extended release profile of drug, 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 so that the drug is continuously supplied to the absorption sites in the gastrointestinal tract (GIT) as shown in **Fig. 1** and for this, the therapeutic drugs concentration will be maintained in the systemic circulation for an extended period.

Advantages of Oral Gastro retentive Release Dosage Form:

- In the stomach, it produces the local action.
- Drugs having a narrow absorption window in the small intestine are more suitable dosage form.
- Frequency of dose can be reduced.
- The bioavailability of the drug can be improved.

Disadvantages of Oral Gastro Retentive Release Dosage Form:

- These require sufficiently high levels of stomach fluids, for the system to float.
- The drugs having stability or solubility problem in the stomach are not suitable.
- It is not suitable for drugs those which are undergoing extensive first-pass metabolism.
- Not suitable for drugs having an irritant effect.

1.2. Biological Aspects of Gastro retentive Dosage Form (GRDF):
1.2.1. GIT [3]**:** The gastrointestinal tract is divided into three main regions as shown in **Fig. 2**:

1. Stomach
2. Small intestine: duodenum, jejunum, and ileum.
3. Large intestine.

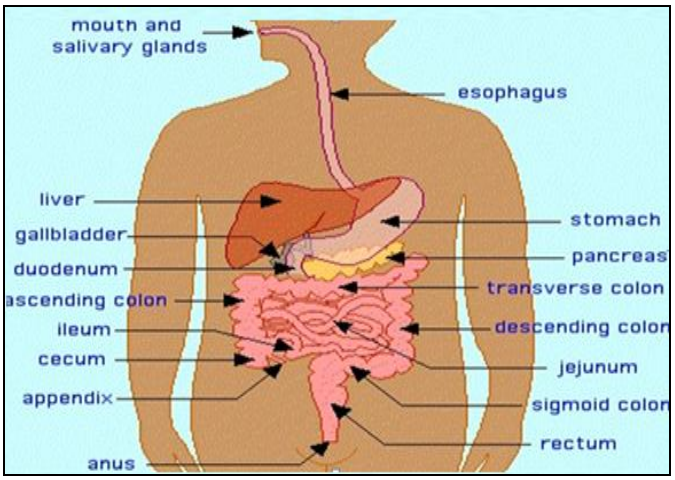

FIG. 2: ANATOMY OF GIT

The walls of the GI tract, from the stomach to large intestine, have very much similar basic arrangement of tissues, from outside to inside. The exception is for the stomach that has three different smooth muscle layers which are responsible for performing the motor functions of the GI tract; Stomach is divided into 3 parts: as shown in **Fig. 3.**

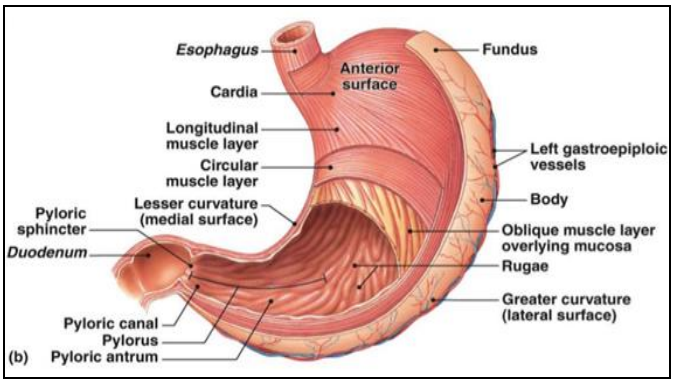

FIG. 3: ANATOMY OF STOMACH

a) Fundus: Also called the proximal stomach, which exerts pressure on the gastric contents by pressing them towards the distal region.

b) Body: The central part, acts as a reservoir for undigested materials.

c) Pylorus or Antrum: Also called distal part of the stomach, which is the site of mixing motions to propel gastric contents for emptying.

The gastric smooth muscle contraction serves two basic functions:

- Ingested food is crushed, grounded and mixed to form chyme.
- Chyme is forcefully pass through the pyloric canal into the small intestine in a process called gastric emptying.

1.2.2 Salient Features of Upper GIT [3]: The characteristic features of upper GIT is shown in **Table 1**.

Concerning the Stomach:

Gastric pH: Healthy volunteers in fasted 1.1 ± 0.15 while in fed healthy subject 3.6 ± 0.4 and may rise to 6 in the presence of water and food.

Volume: Resting volume (collapsed state) is about 25-50 ml while after the meal the volume of distention may reach to 1500 ml.

Gastric Secretion: About 60 ml of acid, pepsin, gastrin, mucus and some enzymes are secreted.

Effect of Food on Gastric Secretion: About 3 liters of secretions are added to the food during gastrointestinal transit time.

TABLE 1: FEATURES OF UPPER GIT

Section	Length (m)	Transition time (hr)	pH	Absorbing surface area (m^2)	Absorption pathway
Stomach	0.2	Veriable	1-4	0.1	PD, ACT, AT
Small intestine	6-7	3±1	5-7.5	120-200	FT, IPT, E, CM

PD – Passive diffusion; ACT – Aqueous channel transport; AT – Active transport; FT – Facilitated transport; IPT – Ion-pair transport; E – Entero-or pinocytosis; CM – Carrier mediated transport

1.3 Physiological Factors Affecting Drug Absorption:

1.3.1 Gastric Motility: The motility of the stomach is mostly contractile, controlled by a complex set of neural and hormonal signals. Thus gastric motility comes from smooth muscle cells integrating a large number of inhibitory and stimulatory signals which causes food grinding into smaller particles, mixing with gastric juices, forward and backward movements of gastric contents and emptying, with all of the actions occurring together.

There are two marked differences between gastric motility:

a) **In the Fasting State:** The motoric activity termed Interdigestive Myoelectric Motor Complex (IMMC) or Migrating Myoelectric Cycle (MMC) which is a series of electrical events happening every 2-3 h, which serves as housekeeping & sweep the undigested foods also this cycle of peristaltic movements generated to clear the stomach and the small intestine of indigested debris, swallowed saliva and sloughed epithelial cells.

b) **In the Fed State:** The digestive mode comprises continuous contractions. As a result of contractions, it reduces the size of food particles (<1 mm), which are propelled

towards the pylorus in suspension form. In the presence of food in the stomach onset of MMC is delayed resulting in a slowdown of gastric emptying rate [3, 4].

1.3.2 Gastric Emptying Rate: The passage of drug from the stomach to the small intestine is called gastric emptying, and it occurs during fasting as well as fed states. In the stomach, the drug absorption is very less because the major site for absorption is the intestine. Delayed gastric emptying promotes the dissolution of the poorly soluble drugs and useful for the drugs that are majorly absorbed from the stomach or proximal part of the intestine. In general, the rate of gastric emptying depends mainly on viscosity and volume. However, the increase in acidity slows down gastric emptying time. In the case of elderly persons, gastric emptying is slowed down. Generally, females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.MMC is organized in cycles of activity and quiescence. Each cycle reoccurs every 90-120 min and consists of four phases.

1.3.3 MMC is Further Divided into the following 4 Phases as in Fig. 4: The presence of the hormone mottling in the blood which controls the duration of the phases

- **Phase 1:** It is a quiescent period lasting from 30 to 60 min during which there are only rare action potential and no contraction.
- **Phase 2:** A period roughly 30 min in which peristaltic contraction occurs and progressive increase in the frequency peristalsis originate in stomach & propagate through the small intestine. Gastric discharge of fluid occurs in this phase.
- **Phase 3:** This phase lasting for 5 to 15 min in which rapidly spaced peristaltic contract occurs. In contrast to the digestive period (4-5 contraction per min), the pylorus remains open during this peristaltic contraction, allowing many indigestible materials to pass to the small intestine. These contractions, also known as "housekeeper waves" gastric sweep content down the small intestine.
- **Phase 4:** This is a short period of transition between the last part of phase 3 and quiescence of phase 1 with a period of 0 to 5 min. The empty stomach performs rhythmic peristaltic contractions known as hunger contractions. The regulation of gastric emptying is by neural and hormonal reflexes like vagal tone and mottling which increase the gastric motility [3, 4].

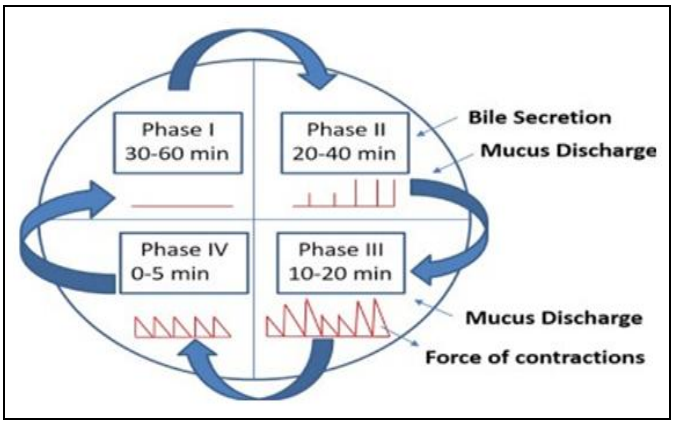

FIG. 4: GASTROINTESTINAL MOTILITY PATTERN

1.4. Factors Controlling Gastro retentive Drug Delivery System (GRDDS): [4] Various factors which affect gastric retention time (GRT) that influence on the development of gastro-retentive dosage forms and prolong the dosing intervals and thus improve patient compliance, these factors can be classified into:

❖ **Factors Related to the Dosage Forms:**

- **Size of the Dosage Form:** To allow the dosage form to pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. In most cases, the larger the dosage form, the greater will be the GRT.
- **The density of Dosage Form:** The density of the dosage form affects the gastric emptying rate. A buoyant dosage form is having a density of less than that of the gastric fluids (1.004g/ml). Thus the dosage unit is retained in the stomach for a prolonged period. Factors related to food intake and its nature.
- **Fed & Unfed State:** Gastric motility is higher in the empty stomach which depicts less gastric retention time.

- **Nature of food:** In the gastrointestinal tract usually the presence of food and feeding of indigestible polymers or fatty acid can change the motility pattern of the stomach to a fed state. Thus, decreasing the gastric emptying rate improves the gastric retention time of the dosage form & will increase absorption of drugs by allowing its stay at the absorption site for a longer period.

❖ **Frequency of Feed:**

- Higher the frequency of taking food, the longer will be the gastro retention time.

❖ **Patient-Related Factors:**

- **Gender & Age:** Gastric emptying rate may differ in the male & female. Generally, the gastric emptying in women was slower than in men. In the case of geriatric patients, especially those over 70 years have a longer gastro-retentive time. Thus gastric emptying time is slowed down.

- **Body Posture:** Gastric retention time are different in supine and upright patient states. In the upright position, the floating systems floated to the top of the gastric fluid and remained for a longer time, showing prolonged GRT. However, in the supine position, the floating units are emptied faster than the non-floating units of similar size.

- **Disease State:** In the case of partial or total gastrectomy and duodenal ulcers there is a decrease in gastric residence time. Diseases like gastroenteritis, pyloric stenosis, and diabetes show an increase in gastric residence time.

- **The volume of the GI Fluid:** The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. Cold fluids delay gastric emptying while warmer fluids fasten gastric emptying.

- **Effect of Gastrointestinal Fluid:** On comparison between the floating and non-floating dosage form, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents protected from the peristaltic waves during the digestive phase, while the non-floating units stayed close to the pylorus and were sink; thus they are subjected to propelling by the digestive phase for emptying.

1.5 Requirements for Gastric Retentive Dosage Form: Major key issues taken for consideration to achieve gastric retention by:

1. Satisfying factors like density, size, *etc*. of the dosage form in the stomach.
2. The formulation must be able to withstand against the peristaltic waves, constant contractions and grinding of the stomach.
3. It must resist premature gastric emptying.
4. Furthermore, once its purpose has been served, it should easily leave the stomach.

1.6 Approaches for Gastric Retentive Dosage Form: Various technological approaches have been developed to increase the GRT of dosage forms, and the Classification of gastro retentive drug delivery system is given in the following **Fig. 5**.

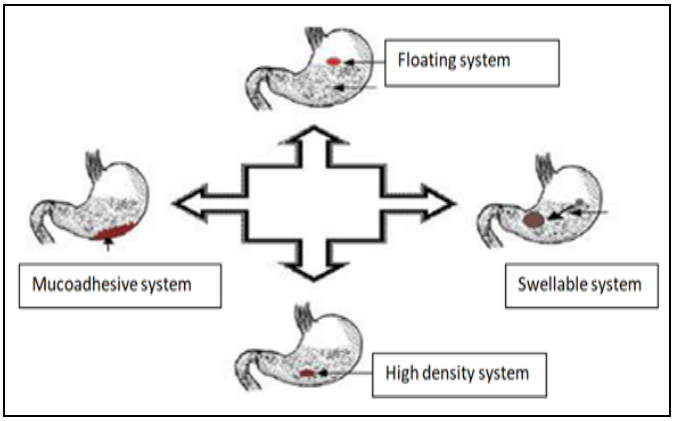

FIG. 5: DIFFERENT APPROACHES OF GRDDS

1.6.1 Swellable/Expandable System: These are a type of non-floating gastro retentive drug delivery system which when enters to stomach, swells (due to presence of swellable polymers) to an extent that cannot pass through the pyloric sphincter leading to retained in the stomach for a long period of time referred to as "plug type systems" because they tend to remain lodged at the pyloric sphincter. Thus three arrangements are required:

A. Oral intake swallowed in a small configuration.

B. Expanded to a size that prevents their passage through the pylorus as shown in **Fig. 6**.

C. Finally, after the drug release at a predetermined time, it becomes ready for an evacuation since the device is no longer can attain or retain the expanded configuration. This is because the system will lose its integrity as a result of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures as a result of continuous expansion, also, it may erode in the presence of gastric juice [5].

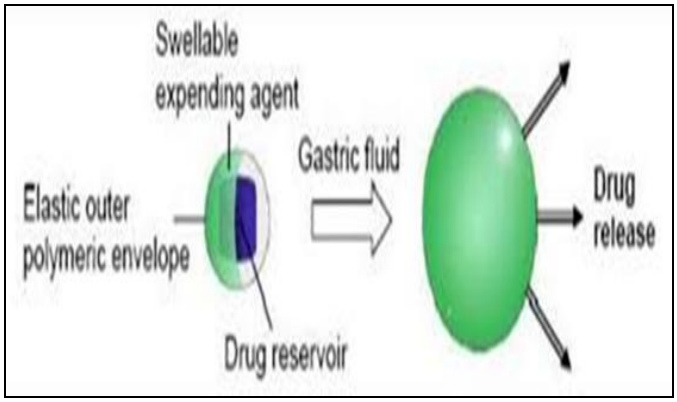

FIG. 6: DRUG RELEASE FROM SWELLABLE SYSTEM

1.6.2 Mucoadhesive/Bioadhesive Systems: These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in the stomach for its prolonged release as shown in **Fig. 7**.

These systems are formulated using bioadhesive polymers. Mucoadhesive controlled release systems increase the effectiveness of the drug by maintaining the drug concentration within a therapeutic level, inhibiting the dilution of drugs in body fluids, and allowing targeting and localization of drugs at specific site [6, 7].

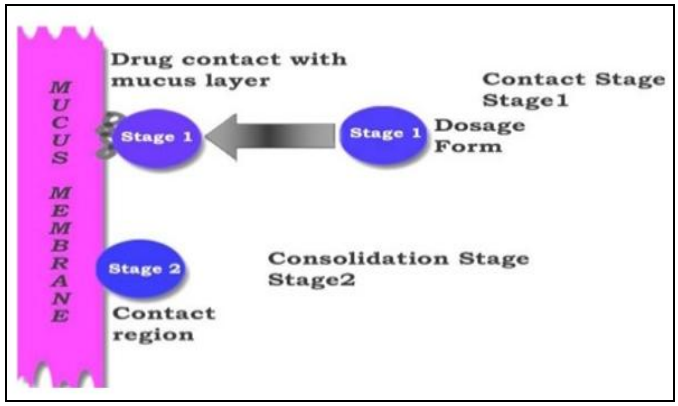

FIG. 7: THE TWO STEPS OF MUCOADHESION PROCESS

1.6.3 High-Density Systems: These systems possess density greater than the gastric fluids due to which sedimentation has been employed as a retention mechanism in the stomach as shown in **Fig. 8**. This approach involves the formulation of dosage forms with the density that must exceed the density of normal stomach content (~ 1.004 g/cm^3). These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, *etc*. as these materials increase the density by up to 1.5-2.8 g/cm^3. [8]

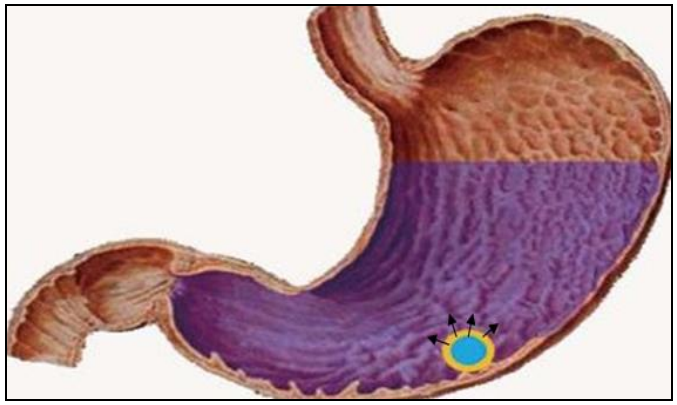

FIG. 8: DRUG RELEASE FROM HIGH-DENSITY SYSTEM

1.6.4 Merits and Demerits of GRDDS: [9, 10, 11] The advantages and disadvantages of different GRDDS approaches are presented in **Table 2**.

TABLE 2: MERITS AND DEMERITS OF DIFFERENT GRDDS APPROACHES

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 a prolonged stay in the stomach Demerits: Time consuming, difficulty in the formulation, not widely used
Mucoadhesive system/Bioadhesive	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 the rapid turnover of mucin in GIT, the occurrence of local ulcerous effects due to prolonged contact of the drug in the 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 (50)
Demerits: Not marketed because difficult to manufacture with a high amount of drug (>50%) also difficult to achieve a density of about 2.8 g/cm^3

1.7 Floating Drug Delivery System (FDDS): Classification of floating drug delivery system, Based on the mechanism of buoyancy two distinctly different technologies have been utilized for the development of floating drug delivery system including

1.7.1 Non-Effervescent System: [12, 13] The formulation methods of the non-effervescent floating drug delivery system involve mixing of the drug with a polymer, which swells upon contact with gastric fluid due to air trapped by the swollen polymer that confers buoyancy to these dosage forms after oral administration. Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix forming polymers. The excipients widely used in these systems are HPMC, sodium alginate and calcium chloride. There are many types of non-effervescent system including:

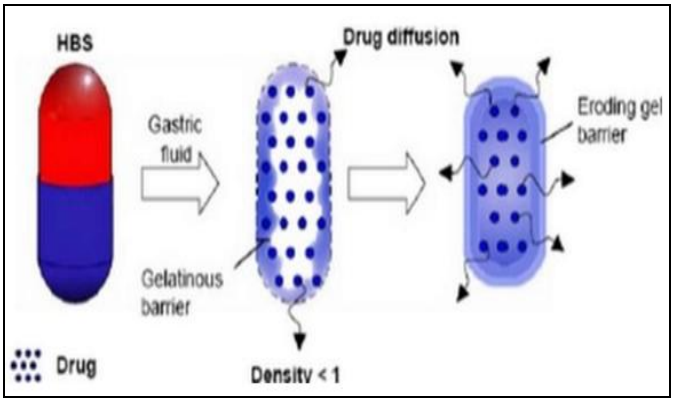

FIG. 9: HYDRO DYNAMICALLY BALANCED SYSTEM (HBS)

- **Hydro Dynamically Balanced Systems (HBS):** In this system gel-forming hydrocolloid polymer mixed with the drug administered in a gelatinous capsule to remain buoyant on the stomach content. The capsule shell dissolves in contact with water and the mixture swells to form gelatinous barrier, which imparts buoyancy to a dosage form in gastric juice for a long period. Continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy of the dosage form, as shown in **Fig. 9**. These systems contain one or more gel-forming hydrophilic polymers like HPMC, NaCMC, agar, carrageenan and alginic acid.

- **Hollow Microspheres / Micro balloons:** Microspheres are spherical, homogeneous and monolithic particles having a size range of about 0.1-1000 μm and are widely used as drug carriers for controlled release. They float on the stomach contents and then adhere to the mucous linings as the stomach empties as shown in **Fig. 10**. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, eudragit S, agar and pectin.

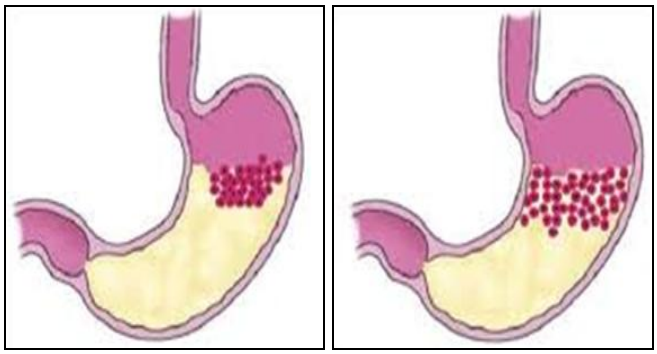

FIG. 10: RETENTION OF MICROSPHERES IN THE STOMACH

- **Alginate Beads:** In this approach generally, sodium alginate solution is dropped into an aqueous solution of calcium chloride and causes the precipitation of calcium alginate with the formation beads. To develop a floating system based on cross-linked beads, spherical beads of approximately 2.5 mm in diameter can be formulated. These beads are then separated and dried by air convection and freeze-drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 h. These beads improve GRT for more than 5.5 h.

- **Microporous Compartment System:** This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls as shown in **Fig. 11**. The peripheral walls of the device were completely sealed to prevent any direct contact of the

gastric surface with the undissolved drug. The entrapped air in the stomach is responsible for the floating of the delivery system. Gastric fluid enters through the aperture, dissolves the drug and causes continuous transport of the drug across the intestine.

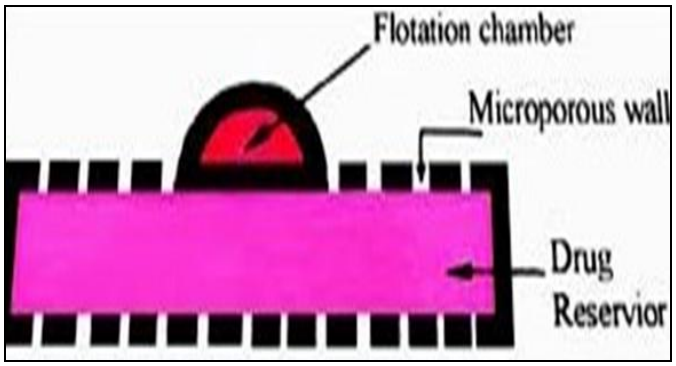

FIG. 11: MICROPOROUS COMPARTMENT MODEL

❖ **Floating Tablets:**

➢ **Single Layer Floating Tablets:** They are formulated by uniform mixing of a drug with low-density gel-forming hydrocolloid enteric materials such as cellulose acetate phthalate and hydroxyl propyl methyl cellulose, which swells in contact with the gastric fluid and maintains specific gravity less than one.

➢ **Bi-layer Floating Tablets:** A bi-layer tablet contains two layers, one is an immediate release layer which releases loading dose from the system while the other is a sustained release layer which releases dose by absorbing gastric fluid to form an impermeable colloidal gel barrier on its surface, and maintains a specific gravity less than unity and thereby remains buoyant in the stomach.

1.7.2 Effervescent System: Gas-generating Systems; Floatability achieved when the system reached stomach and came in contact with gastric fluids, then entrapment of liquid in the gelled hydrocolloid layer matrices prepared with swellable polymers such as methylcellulose (MC) and HPMC. The reactions occur between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 gas at body temperature, thus decreasing its specific gravity making it float in the stomach and release the drug slowly at a desired rate [14]. Effervescent substances incorporated in the hydrophilic polymer, and CO_2 bubbles are trapped in the swollen matrix as in **Fig. 12**.

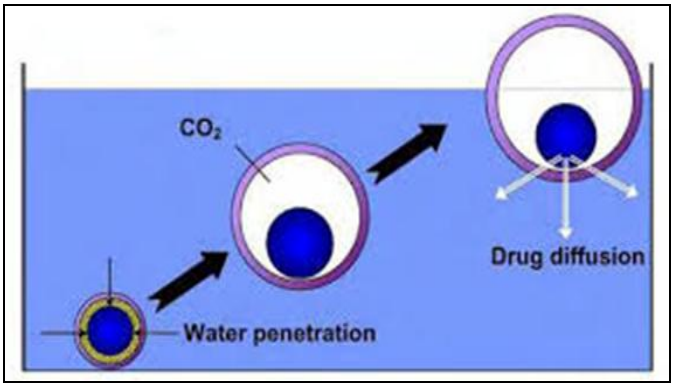

FIG. 12: GAS GENERATING SYSTEM

There are many types of gas generating system including intragastric single-layered floating tablet, intragastric bi-layered floating tablets and multiple-unit type of floating pills.

❖ **Volatile Liquid Containing System:** This device is a controlled floating system which increases GRT and sustains the release of the drug. It contains a hollow deformable unit that can be transformed from a collapsed to an expanded position and returned to collapse position after an extended period. The deformable unit consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber loaded with the drug and the second chamber loaded with the volatile liquid shown in **Fig. 13**. There are several types of volatile liquid containing system including inflatable gastrointestinal delivery system and intragastric osmotically controlled drug delivery system [15].

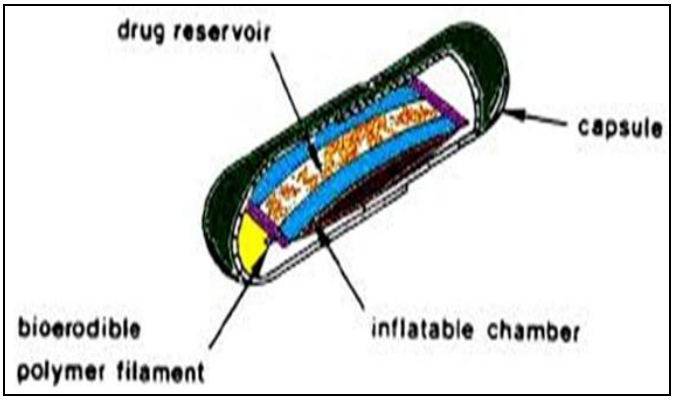

FIG. 13: VOLATILE LIQUID CONTAINING SYSTEM

1.8 *In-situ* Gelling System: [16] *In-situ* in Latin word means 'In its original place or position.' Giving priority for the development of new drug delivery systems with improving efficacy and bioavailability together, thus reducing the

frequency of dose to minimize side effects. As a progress, the designing of *in-situ* forming polymeric delivery systems sparked by the advantages of

- Easy administration
- Enhance bioavailability.
- Sustain drug delivery.
- Improved patient compliance and comfort.
- Reduce the frequency of dosing.
- Reduce the fluctuation of drug concentration.
- Extended effective concentration.
- Minimize adverse activity at the colon.

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

Floating oral *in-situ* gel is a polymer solution of low viscosity which upon coming in contact with the gastric fluids; changes polymeric conformation and with the formation of a strong viscous gel of density lowers than the gastric fluids. The gelation can be triggered by temperature modulation, pH change, and ionic cross-linking. In-situ gels can be administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes.

1.8.1 Approaches to Designing Floating Oral *in-situ* Gel System:

I) physically Induced *in-situ* Gel Systems: [16]

A. Swelling: *In-situ* gel formation occurs when polymeric lipid absorbs water from the 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 bioadhesive properties, and it can be degraded *in-vivo* by the enzymatic action of the stomach.

B. Diffusion: In this method the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of the polymer matrix. The solvent of N-methyl pyrrolidone (NMP) is useful for such a system.

II) Chemically Induced *in-situ* Gel Systems: [17]

A. Ionic Cross-linking: Many ion sensitive polysaccharides such as sodium alginate, iota carrageenan, gellan gum(Gelrite®), pectin undergo a phase transition in the presence of various ions such as K^+, Ca^{2+}, Mg^{2+}, Na^+. The formation of *in-situ* gel involves administration of solutions, once administered they form a gel inside the stomach under certain conditions involving the use of a gelling agent which can form a system that contains the dispersed drug and other excipients. The gelling of this system is achieved by using polymer solutions such as sodium alginate triggered by ionic complexation that contains divalent-ions complexed with Na-citrate which breakdown in the acidic environment of the 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 the orally administered solution as shown in equation: *In-situ* gel involves the formation of double helical junction zones by aggregation of double helical segments to form a 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. The residual system is emptied from the stomach after the release of the drug.

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

C. **Photo-Polymerization:** A solution of monomers such as acrylate or other polymerizable functional groups and initiator can be injected into tissue site and the application of electromagnetic radiation 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 [18].

III) *In-situ* Gel Formation based on Physiological Stimuli: [19, 20]

A. **Temperature Dependent *in-situ* Gelling:** These hydrogels are liquid at room temperature (20 ºC - 25 ºC) and undergo gelation when contact body fluids (35 ºC-37 ºC), due to an increase in temperature. This approach exploits the temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST) and formation of negative temperature sensitive hydrogel in which hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer-polymer and water-water interactions. Also, an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. Alternatively, some amphiphilic polymers increase LCST, where self-assembles in solution show more micelle packing and gel formation because of polymer-polymer interactions when the temperature is increased for *e.g.,* cross-linked N-isopropylacrylamide-co-butylmetha-crylate {P(NIPAAmco-BMA)} polymer.

B. **pH-Dependent *in-situ* Gelling:** Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH. The polymers with a large number of ionizable groups are known as a polyelectrolyte. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if the polymer contains weakly basic (cationic) groups. For example carbomer and its derivatives as anionic polymer.

1.8.2 Drug Release Mechanisms of *in-situ* Gel System: [21, 22]

1. Diffusion- Controlled Mechanism:

- **Matrix Devices:** The active agent is homogeneously dispersed as a solid into a hydrogel inert bio-degradable polymers matrix as in **Fig. 14**. The release of the 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. The 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.

- **Reservoir Devices:** The drug is contained in a core (often termed as a reservoir) which is surrounded by a rate-controlling polymeric membrane of hydrogel which allows the diffusion of the drug as shown in **Fig. 15**. As the system comes in contact with water, water diffuses into the system and dissolves the drug. The drug then transports (from the core through the external polymer membrane) by dissolution at one interface of the membrane and diffusion driven by a gradient in the 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 the 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.

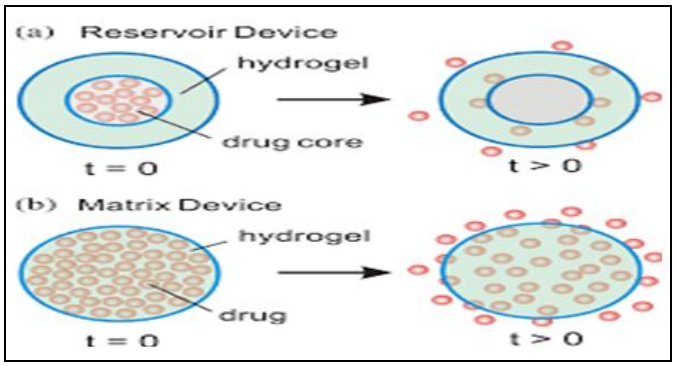

FIG. 14: DRUG DELIVERY SYSTEM A- RESERVOIR DEVICE, B-MATRIX DEVICE

2. Swelling-Controlled Mechanism: [23]

- **Solvent Activated System:** It occurs when diffusion of the drug is faster than hydrogel swelling. When a hydrogel is placed in an aqueous solution, water molecules will penetrate the polymer network that occupies some space, and as a result, some meshes of the network will start expanding, allowing other water molecules to enter within the network. But, swelling is not a continual process; the elasticity of the covalently or physically cross-linked network will counter-balance the infinite stretching of the network to prevent its destruction. For example, the release of drugs from (HPMC) hydrogel is commonly modeled using this mechanism.

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

1.8.3. Criteria of Drugs Suitable for *in-situ* Gel Drug Delivery System: [25] The right selection of drugs for oral *in-situ* drug delivery systems are drugs that have poor colonic absorption and Drugs that having better absorption properties at the upper parts of the GIT, so the following few points are taken into consideration:

- Drug acting locally in the stomach like Antacids and drugs for *H. pylori, e.g.* Misoprostol.
- Drugs that are maximum absorbed from the stomach like chlordiazepoxide and cinnarizine.
- Drugs those are poorly soluble at alkaline pH like verapamil HCl and diazepam.
- Drugs with a narrow window of absorption like levodopa and riboflavin.
- Drugs which are rapidly absorbed from the GIT like tetracycline.
- Drugs that degrade in the colon like ranitidine and metronidazole.
- Drugs that disturb normal colonic microbes like ampicillin.
- Poor soluble of drugs at alkaline pH *e.g.* Furosemide, Diazepam, Verapamil, *etc*.

1.8.4 Criteria of Drugs not Suitable for *in-situ* Gel Drug Delivery System; Drugs that have minimal acid solubility *e.g.* phenytoin.

- Drugs that suffer instability in the gastric environment *e.g.* erythromycin or solubility problem in GIT, *e.g.*, phenytoin.
- Drugs intended for selective release in the colon, *e.g.* 5- aminosalicylic acid and corticosteroids.
- Drugs that are absorbed along entire GIT, which undergo first-pass metabolism, *e.g.* nifedipine, propranolol.

1.8.5. Polymers of *in-situ* Gel System: [26]

1.8.5.1 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.

1.8.5.2 Classification of Polymers of *in-situ* Gel System: [26] Polymers used for in-situ gel system can be classified according to:

1. **Natural Polymer:** *e.g.*, Protein, collagen, keratin, albumin, carbohydrates, starch, cellulose, alginate, gellan gum.

2. **Biodegredable Polymers:** *e.g.*, Polyesters, protein, carbohydrate, chitosan, *etc*.

3. **Interaction with Water:**
   - **A. Soluble Polymer:** these are moderate mol-wt un-crosslinked polymers that dissolved in water. *e.g.*, HPMC, PEG.
   - **B.** Biodegradable polymers; these are slowly disappearing from the site of administration in response to a chemical reaction such as hydrolysis. *e.g.*, polyacrylic acid, polyglycolic acid.
   - **C. Hydrogel:** They swell but do not dissolve when brought in contact with water. *e.g.*, polyvinyl pyrrolidone.

1.8.5.3 Polymers Used in this Study:

Sodium Alginate (Na Alginate): 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 as shown in **Fig. 15**.

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. It is the ion exchange process between sodium and calcium ions that are supposed to be responsible for the swelling and subsequent degradation of sodium alginate in the colon [26, 27].

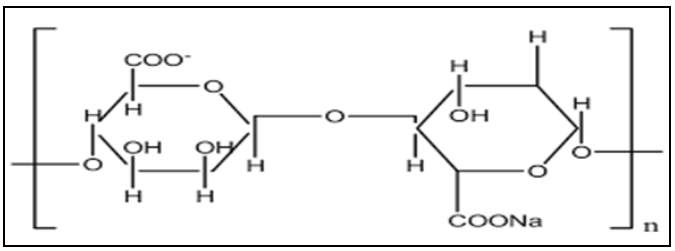

FIG. 15: STRUCTURE OF SODIUM ALGINATE

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.

Gellan Gum: (Gelrite®) It is an anionic, deacetylated extracellular linear polysaccharide with a tetrasaccharide is repeating unit of one α-L-rhamnose, 1β-D-glucuronic acid and 2β-D-glucose obtained from the cultured solution of Pseudomonas species as shown in **Fig. 16**. In an ion-free aqueous medium; the polymer chains form double helices, resulting in a fluid that has a viscosity close to that of water. In the presence of gel-promoting cations (K^+, Mg^{2+}, Ca^{2+}, and Na^+), the portion of the helices associates and the cation-mediated aggregates cross-link the gel network. A rapid gelling can be expected upon contact with the mucosa since, even at low polymer concentrations, small quantities of ions sufficient for the formation of a strong gel within GIT.

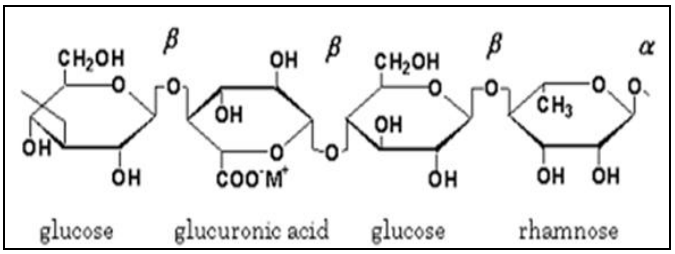

FIG. 16: STRUCTURE OF GELLAN GUM

Gellan gum can be applied pharmaceutically as a water-soluble polymer acts as a potential carrier for different oral floating sustained delivery dosage forms.

Iota-Carrageenan (i-carrageenan): Carrageenan is a sulfated linear polysaccharide of D-galactose and 3, 6-anhydro-D-galactose obtained by extraction of certain red seaweeds of the Rhodophyceae class. The carrageenans are divided into three families as shown in **Fig. 17**.

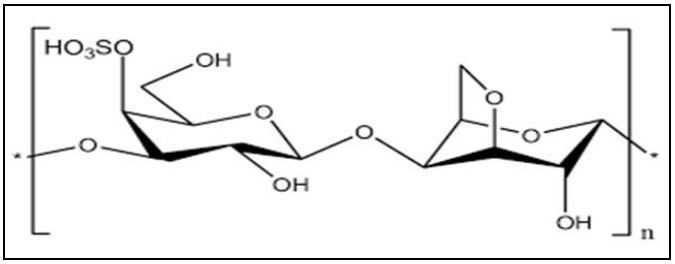

FIG. 17: STRUCTURE OF CARRAGEENAN

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 [26].

Application of carrageenan included as an excipient in the pharmaceutical industry, for example, as the polymer matrix in oral extended-release tablets. Moreover, carrageenan has a strong negative charge; thus it has been used as a gelling agent/viscosity enhancing agent for controlled drug release and prolonged retention.

Hydroxypropyl Methyl Cellulose (HPMC): Hydroxypropyl Methyl Cellulose (HPMC) as a partly O-methylated (OCH_3) and O-(2-hydroxy-propylated) (OCH_2CH (OH) CH_3) cellulose conforming to the limits for the various types of HPMC as in **Fig. 18**. It is available in several grades that vary in viscosity (50-100000 cps), and Molecular weight is approximately 10000-1500000.

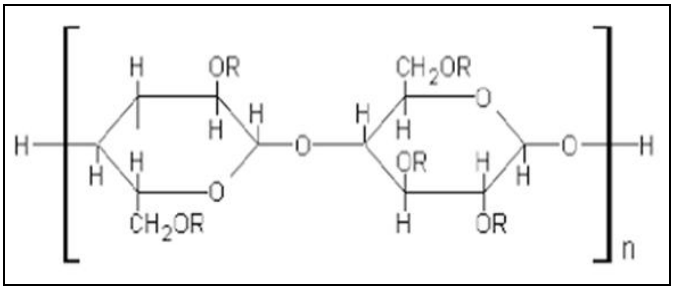

FIG. 18: STRUCTURE OF HPMC

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, modified-release agent, release-modifying agent, solubilizing agent, stabilizing agent, sustained-release agent, thickening agent, and viscosity-increasing agent.[26]

CONCLUSION: The literature searched during the review of the topic reviled that gastro retentive drug delivery have various prospective advantages for drugs with poor bioavailability due to rapid transition and small absorption window at the upper gastrointestinal tract (GIT). It greatly improves the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which is sustained over a longer period. So far as *in-situ* gel drug delivery system is a concern, it can be the potential tools towards the treatment of diseases like chronic gastritis and peptic ulcers caused by *H. pylori*. It is not only helpful for sustained drug delivery of oral liquid dosage form but also become convenient for pediatric and geriatric patients having a swallowing problem. The exploitation of polymeric *in-situ* gels for controlled release of various drugs may provide several advantages over conventional dosage forms. Good stability and biocompatibility characteristics also make the *in-situ* gel dosage forms very reliable. The application of these tools for the delivery of herbal medicaments will be the subject of research in the future.

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