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ORAL IN-SITU FLOATING GELLING SYSTEM: REVIEW ON

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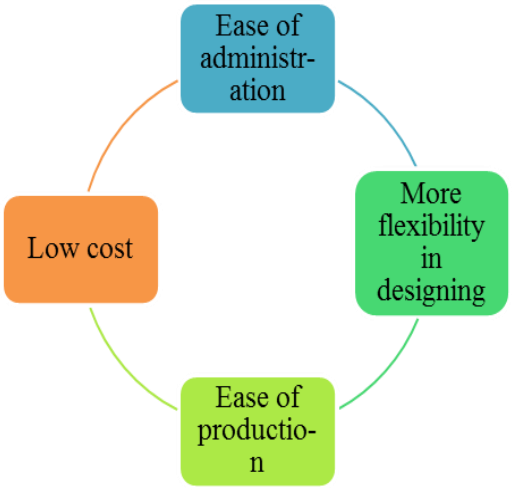
ABSTRACT

In-situ gelling system explains about gels which are defined as intermediate state of matter consists of liquid and solid components. Hydrogels is defined as three dimensional structures which has capacity to retain bulk amount of water and also biological fluids to swell. Conventional oral dosage forms pose low bioavailability problems due to their rapid gastric transition from stomach, especially in case of drugs which are less soluble at alkaline pH of intestine. Similarly, drugs which produce their local action in stomach get rapidly emptied and do not get enough residence time in stomach. So, frequency of dose administration in such cases is increased. In-situ gels are type of hydrogels that are solution in form and undergo gelation in contact with body fluids or change in pH. Some of the polymers that are used in in-situ gelling system are guar gum, Xanthan gum, Sodium alginate, Sodium Benzoate, Sodium Citrate, Polyethylene glycon and Hydroxy Propyl methyl cellulose.

KEYWORDS: In situ gel, Approches, Polymers, Evaluation.

INTRODUCTION

Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used these days include oral, parentral, topical, nasal, rectal, vaginal, ocular etc. But out of these routes, oral route of drug delivery is considered as the most favoured and practiced way of drug delivery, because of following reasons.[1,2,3]



Most of the drugs given via oral route subjected to absorption throughout the gastrointestinal tract, with major absorption from stomach and intestine.[1,4,5] Various processes occur after the drug release from the dosage form, which affect the absorption of drugs, e.g. degradation of drug by enzymatic or microbial action, precipitation etc.

In situ-forming systems that do not require organic solvents or copolymerization agents have gained increasing attention. These are liquid aqueous solutions before administration, but gel under physiological conditions. Gelation can occur in situ by ionic cross-linking[16,17,18] or after a change in pH[16,19,20] or temperature. The latter approach exploits temperature-induced phase transition.

Gels:- Gels are an intermediate state of matter containing both liquid and solid components. It consists of three dimensional solid networks. As it has three dimensional solid network, gels are classified into two types based on the nature of the bonds. They are.

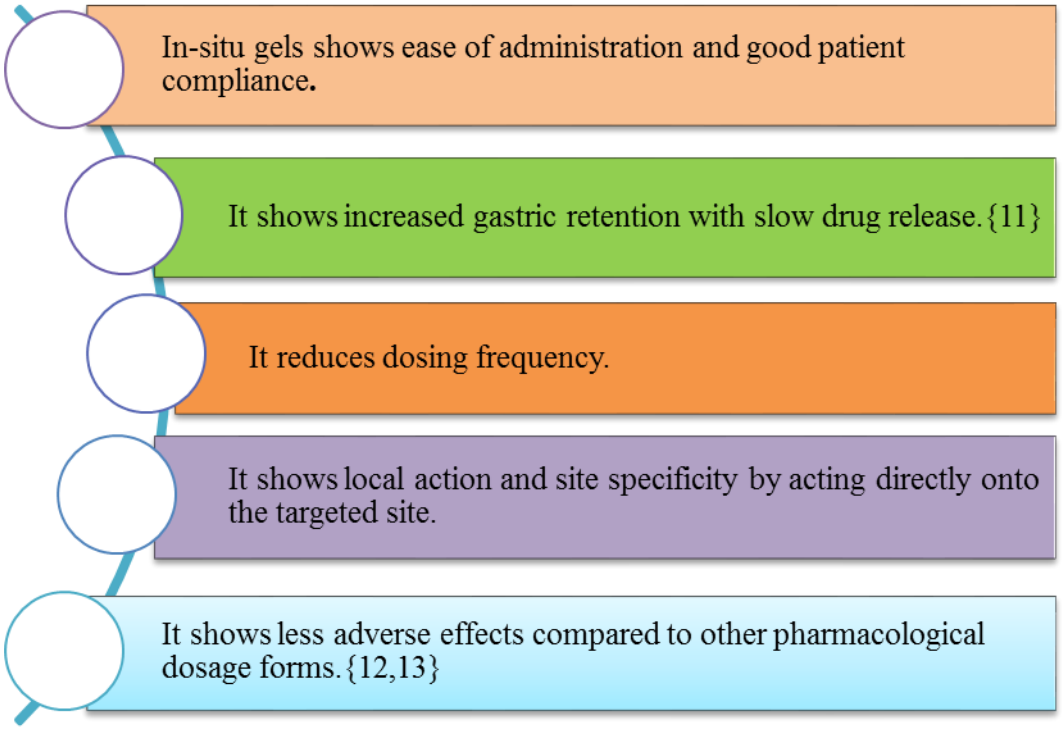
- Physical gels arise when weak bonds like hydrogen bonds, electrostatic bonds and vanderwaal bonds constitute together to maintain the gel network.
- Chemical gels arise when strong covalent bonds1 constitute to maintain the gel network. The network indicates the presence of cross-links which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.[6,7]

PRINCIPLE OF *INSITU* GEL

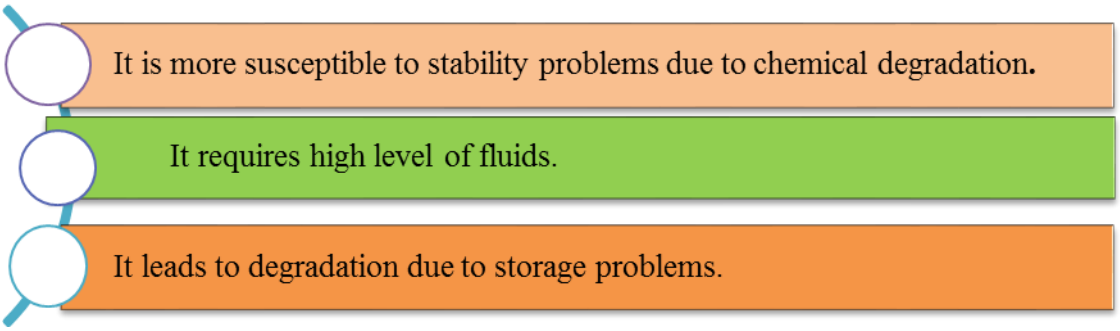
Formulation of *insitu* gel system involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a gellan gum or sodium

alginate solution containing calcium chloride and sodium citrate, which complexes the free Calcium ions and releases them only in the acidic enviorment of stomach. Gellan gum or sodium alginate acts as gelling agent and can produce textures in the final product that vary from hard, non elastic, brittle gels to fluid gels.[8,9] The free calcium ions gets entrapped in polymeric chains of gellan gum or sodium alginate thereby causing crosslinking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water.[8,10]

ADVANTAGES OF *IN-SITU* GELLING SYSTEM



DISADVANTAGES OF *IN-SITU* GELLING SYSTEM[14]



SUITABLE DRUG CANDIDATES FOR IN SITU GEL[15]

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- Drugs that degrade in the colon, e.g. ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

IDEAL CHARACTERISTICS OF POLYMERS[8]

1. It should be biocompatible.
2. It should be capable of adherence to mucus.
3. It should have pseudo plastic behavior.
4. It should have good tolerance and optical activity.
5. I should influence the tear behavior.
6. The polymer should be capable of decrease the viscosity with increasing shear rate offering lowered viscosity during blinking and stability of tear film during fixation.

Anatomy And Physiology Of Stomach

The stomach is anatomically situated in the upper left part of the abdominal cavity immediately under the diaphragm and is composed of three regions: the fundus, the body, and the antrum.(fig.no.1) It is made up of goblet cells, parietal cells, and chief cells, which secrete mucus, hydrochloric acid, and pepsinogen, respectively, amounting to 2 to 3 L of gastric juice daily. The contraction forces of the stomach churn the chyme (a milky mixture of food) and mix it with the digestive gastric juices. The proximal part of the stomach, composed of the fundus and the body, acts as a reservoir for undigested material and propulses chyme to the antrum. The antrum is the main site for trituration and grinding of the food particles by mixing motions, and it also acts as a pump to regulate gastric emptying by its propelling actions. The average length of the stomach is about 0.2 mm, and the apparent absorbing surface area is about 0.1 mm.[21,22,23]

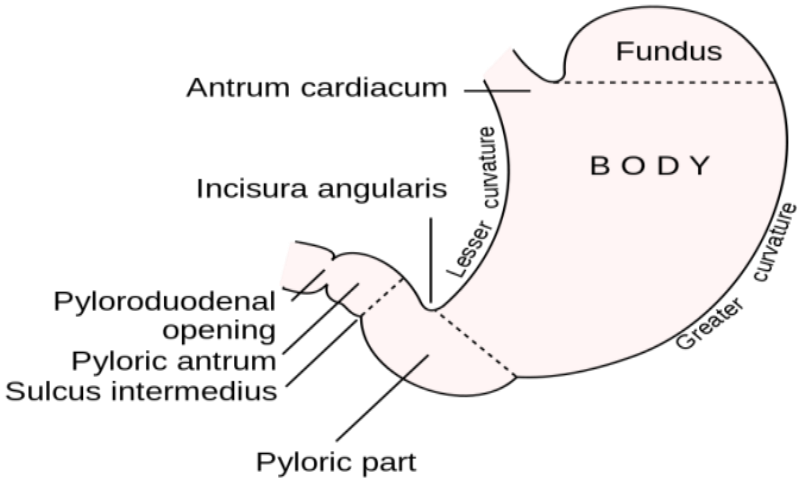


Fig no.1: Anatomy of stomach.

pH:- The physiologic gastric pH in humans is not constant and varies across different sections of the GIT.[21,24] It also exhibits large intra-and inter-subject variability due to differences in the state of the stomach during measurement (fed or fasted) and other physiological and biological factors. The mean value of gastric pH in fasted healthy subjects is reported to be 1.1 ± 0.15.[21,22] In the fed state, the pH initially falls below 5.0, and then gradually reaches the fasting state values over a period of a few hours. The mean fed-state pH in healthy males is reported to be 3.6 ± 0.4.[21,25]

Gastric Emptying:- Gastric emptying is a motility-driven process whereby the dosage form is emptied from the stomach into the small intestine. In drug delivery, gastric emptying determines the length of time that the dosage form remains in the stomach. Therefore, this process is signifi cant for drugs with a narrow absorption window that have their primary site of absorption in the stomach and proximal small intestine. Any factors that affect gastric emptying will also infl uence the time that the drug remains in contact with the target site, and will therefore affect its oral bioavailability. Because gastric emptying is an extremely variable process, the ability to control or regulate it can widen the stomach's potential as a drug-absorbing organ and also broaden the scope for the design of novel controlled-release drug-delivery systems.

FACTORS AFFECTING GASTRIC RETENTION[26,27,28]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing theretention time. These attempts include the use of 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. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastroretentive system. These factors are as follows.

Density:- Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density. The density of the dosage form should be less than the gastric contents (1.004 gm/ml).

Size:- Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form:- Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

Single or multiple unit formulation:- Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles compared with single unit dosage forms.

Fed or unfed state:- Under fasting conditions, gastro intestinal motility is characterized by periods of strong motor activity that occurs every 1.5 to 2 hours and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal:- Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate.

Caloric content:- GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed:- The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender:- Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

Age:- Elderly people, especially those over 70 years, have a significantly longer GRT.

Posture:- GRT can vary between supine and upright ambulatory states of the patients.

Concomitant drug administration:- Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and cisapride decrease GRT.

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

DIFFERENT APPROACHES FOR IN SITU GELLING SYSTEM

There are different mechanisms used for triggering the in situ gel formation: physical changes in biomaterials (e.g., Diffusion of solvent and swelling), chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization) and Physiological stimuli (e.g., temperature and pH).

IN SITU FORMATION BASED ON PHYSICAL MECHANISM

SWELLING AND DIFFUSION

Swelling of polymer by absorption of water causes formation of gel.[15,29] certain biodegradable lipid substance such as myverol (glycerol mono-oleate) forms in situ gel under such phenomenon.[15,30] Solution of polymer such as N – methyl pyrrolidone (NMP) involves diffusion of solvent from Polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix.[15,31]

IN SITU GELLING BASED ON CHEMICAL STIMULI

IONIC CROSSLINKING

Certain ion sensitive polysaccharides such as carrageenan, Gellan gum, Pectin, Sodium Alginate undergo phase transition In presence of various ions such as k+, Ca+2, Mg+2, Na+.[15,32] For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with guluronic acid block in alginate chains.[15,33]

ENZYAMATIC CROSSLINKING

Certain natural enzymes which operate efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation in situ.[15,34]

PHOTO-POLYMERISATION

A solution of monomers such as acrylate or other polymerizable functional groups and initiator such as 2,2 dimethoxy-2-phenyl acetophenone, camphorquinone and ethyl eosin can be injected into a tissues site and the application of electromagnetic radiation used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo.[15,35] Typically long wavelength ultraviolet and visible wavelengths are used.

IN SITU GEL FORMATION BASED ON PHYSIOLOGICAL STIMULI

TEMPERATURE DEPENDANT IN SITU GELLING

These are liquid aqueous solutions before administration, but gel at body temperature. These hydrogels are liquid at room temperature (20ºC -25ºC) and undergo gelation when in contact with body fluids (35ºC -37ºC), due to an increase in temperature This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST).[15,36,37] Polymers such as Pluronics (poly (ethylene oxide)-poly(propylene oxide)-poly (ethylene oxide)(PEO-PPOPEO) Triblock),[15,38] Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate).[15,39] Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature.[15,40] A positive temperature- sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acryl amide-co-butyl methacrylate) have positive temperature dependence of swelling.[15,39]

pH DEPENDANT GELLING

Another formation of in situ gel is based on Change in pH. Certain polymers such as PAA (carbomer) or its derivatives, Polyvinylacetal diethylaminoacetate (AEA), Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) shows change from sol to gel

with change of pH. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.[15,41]

MECHANISM OF IN-SITU GELATION[26]

These are aqueous liquid solutions before administration, but gel under physiological conditions. Several possible mechanisms lead to in-situ gel formation are: Ionic cross linkage, pH change and temperature modulation. Polymer solutions of gellan, pectin & sodium alginate, etc. contain divalent ions complexed with sodium citrate that are breakdown in the acidic environment of stomach to release free divalent ions (Ca+2) causes the in-situ gelation of orally administered solution. It involves the formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations and hydrogen bonding with water.

MECHANISM OF FLOATING IN-SITU GEL

While the system is floating on 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 besides a minimal gastric content 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 for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side (Fig.1). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[26,42]

F = F buoyancy - F gravity

=(Df - Ds) gv

Where, F = total vertical force, Df = fluid density, Ds = object density, v = volume,

g = acceleration due to gravity.

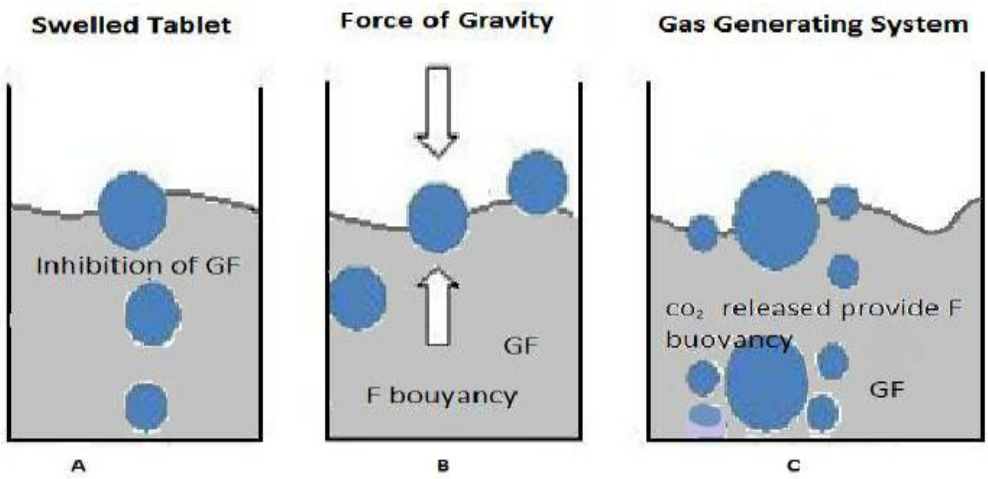


Figure 1: Mechanism of floating system, GF = Gastric Fluid.

APPLICABILITY OF IN SITU POLYMERIC DRUG DELIVERY SYSTEM[8]

1. Ocular drug delivery system:- In ocular delivery system natural polymers like gallan gum, alginic acid & xyloglucan are most commonly used. For local ophthalmic delivery system various compoundslike antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra ocular tension in glaucoma. Conventional delivery system often result in poor availability & therapeutic response because high tear fluid turn over & dynamics which cause rapid elimination of the drug from the eye so, the overcome the bioavailability problem ophthalmic in-situ gel was developed.

2. Nasal drug delivery system:- In nasal in-situ gel system gallan gum & xanthan gum are used as in-situ gel forming polymers Momethasone furoatewas evaluated for it„s efficacy for the treatment of allergic rhinitis. Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%).

3. Rectal drug delivery system:- The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate up-wards to the colon that makes them possible for drug to undergo the first-pass effect.

4. Vaginal drug delivery system:- The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins62. Chang et al. have recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

5. Injectable drug delivery system:- One of the most obvious ways to provide sustained release medication is to place the drug in delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs in vitro.

6. Dermal and transdermal drug delivery system:- Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin73. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

7. Oral drug delivery system:- For the oral in situ gel delivery system pectin, xyloglucan & gellan gum natural polymers are used. Pectin formulation for sustained delivery of paracetamol has been reported. Advantages of pectin is water soluble so, no need to add organic solvent. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system. W. Kubo et al. developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied. Hydrogels made of varying proportions of PAA derivatives and crosslinked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property.

POLYMERS FREQUENTLY USED FOR INSITU GELLING FOR FLOATING DRUGDELIVERY SYSTEM

1.Chitosan[43]

Chitosan is a natural and versatile polymer obtained by alkaline deacetylation of chitin. It has favorable biological properties such as non toxicity, biocompatiblity, and biodegradability**.** These properties make chitosan a good candidate for the development of various ventional and novel gastrointestinal dosage forms. Being a bioadhesive polymer and having antibacterial activity, this polymer is a excellent agent for site specific drug delivery.

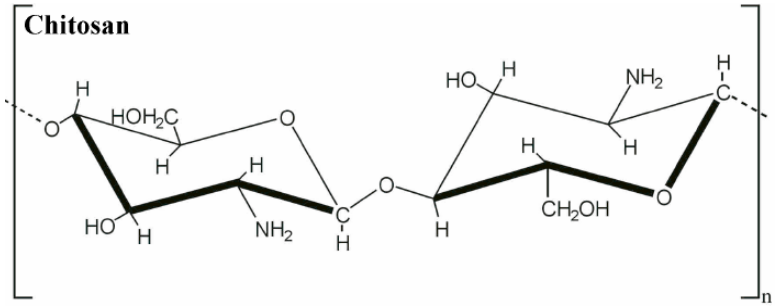


Fig. no.1 structure of chitosan.

2.Pectin[43]

Pectins are non-starch, linear polysaccharides present in the walls that surround growing and dividing plant cells. They are predominantly linear polymers of primarily a-(1,4)-linked D-galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues having an average molecular weight of about 50,000 to about 180,000.

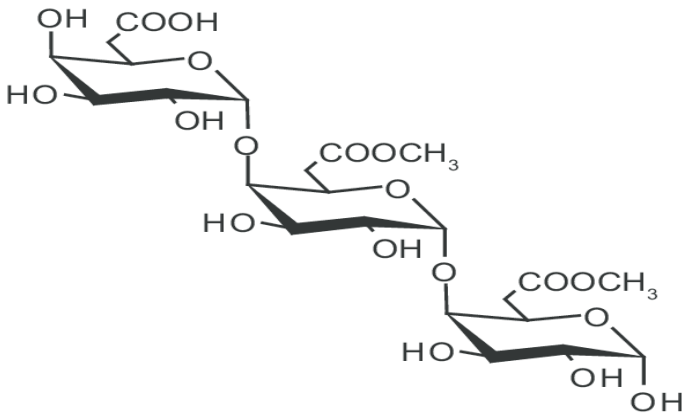


Fig. no.2 structure of pectin.

Pectin was first isolated in the 1820s and the first commercial production of a liquid pectin extract was recorded in 1908 in Germany, and the process spread rapidly to the United States.

Pectin is widely found in plant tissues where it serves, in combination with cellulose, as intercellular structural substance (membranes, middle lamellae).

3.Xanthan Gum[43]

Xanthan gum is a high molecular weight extracellular polysaccharide produced by pure culture aerobic fermentation of carbohydrate with *Xanthomonas campestris* bacteria.Xanthan is a long chained polysaccharide with large number of trisaccharide side chains. The main chain consists of b-(1,4)-linked D-glucose units. The side chains are composed of two mannose units and one glucuronic acid unit. This gum develops a weak structure in water, which creates high viscosity solutions at low concentration. Viscosity remains fairly constant from 0°C to 100°C.29.

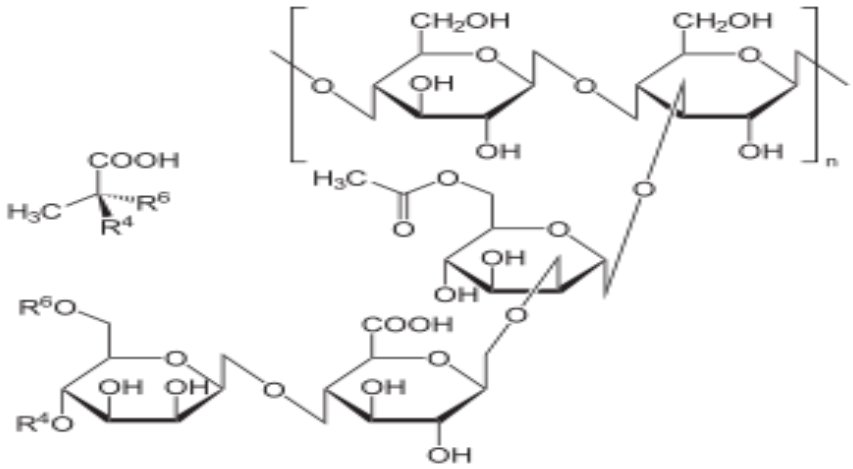


Fig. no.3: structure of xanthan gum.

4.Guar Gum[43]

Guar gum is naturaly occurring galactomannan polysaccharide, made up of linear chain of β-D-mannopyranose joined by ß-(1-4) linkage with α-D-galactopyranosyl units attached by 1,6-links in the ratio of 1:2.It is obtained from the ground endosperms of the leguminous plant *Cyamopsis tetragonolobus* (L.) Taub., a species cultivated in India as a fodder crop. Guar gum hydrates and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retard the drug release and make it a flexible carrier for extended release dosage forms.51-54 It is practically insoluble in organic solvents.

5.Gellan Gum[43]

Gellan gum is an anionic, high molecular weight, deacetylated extracellular linear polysaccharide comprising glucuronic acid, rhamnose and glucose. It is produced as a

fermentation product by a pure culture of Pseudomonas elodea. Gellan gum, also commercially known as Phytagel or Gelrite. It is capable of gelation in the presence of mono- and divalent ions.63 It is available in two forms (high or low acyl content). This gum has an outstanding flavor release, high gel strength, an excellent stability, process flexibility, high clarity, good film former and thermally reversible gel characteristics.

6.Sodium alginate[26]

Sodium alginate is a widely used polymer of natural origin. Chemically, it is alginic acid salt, consisting of Lglucuronic acid and D-mannuronic acid residues, connected by 1,4-glycosidic linkages. Solution of alginates in the water form firm gels in the presence of di or trivalent ions (E.g. Calcium and magnesium ions). Alginate salts, specifically, sodium alginate is mostly used for preparation of gel forming solution, for delivery of the drugs and proteins.

7.Carbopol[26]

Carbopol is a well-known pH dependent polymer, which stays in solution form at acidic pH, but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo changes in solubility with change in environmental temperature. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week.

8.Pluronic F-127[26]

Poloxamers or pluronic are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides of the blocks of relatively hydrophilic poly ethylene oxide. Due to the PEO-PPO ratio of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEO-PPO-PEO copolymers. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in-situ gelation by temperature change.

EVALUATION OF IN SITU GELLING SYSTEM[15,44]

CLARITY:- The clarity of formulated solutions can be determined by visual inspection under black and white background.

VISCOSITY: The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route administrations) were determined with different viscometer.

SOL-GEL TRANSITION TEMPERATURE AND GELLING TIME: For in situ gel forming systems, the sol-gel transition temperature and pH should be determined. Gelling time is the time required for first detection of gelation of in situ gelling system.

GEL-STRENGTH: A specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe of rheometer slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

FOURIER TRANSFORM INFRA-RED SPECTROSCOPY AND THERMAL ANALYSIS: Fourier transform infra-red spectroscopy is performed to study compatibility if ingredients. Differential scanning calorimetry is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

IN-VITRO DRUG RELEASE STUDIES: The drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique.

CONCLUSION

In present scenario, it's a challenging task for prolonging the gastric retention and physiological compatibility with the stomach. So, amongst various approaches one of the most promising approach is insitu floating gel drug delivery system. Which form sol to gel formation in various physiological environments like pH, temperature and ionic condition. So, it proved as a site specific release formulation. Several biodegradable polymers are used

for this formulation. In-situ floating gel have a good biocompatibility, bioavailability and stability. So, it's become more reliable over conventional dosage form.

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