

Novel Strategy In Controlled Gastroretentive Drug Delivery: *In-Situ* Floating Gel

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A b s t r a c t

Attempts are made in research and development of sustained and controlled drug delivery systems to overcome physiological and unpredictable gastric emptying time (GET). Such dosage forms are useful for the drugs with 'narrow therapeutic index'. Formation of gel depends on factors such as temperature, pH, ionic cross linking and UV irradiation, from which drug is released in controlled or sustained manner. In-situ gelling systems is prominent among other novel drug delivery systems (NDDS), due to advantages such as sustained and prolonged drug action, improved patient compliance and reduced frequency of drug administration as compared to conventional drug delivery system. These polymeric formulations are in solution form before administration and then turns to gel form when comes in contact with gastric fluids. Various natural, biodegradable, biocompatible and water soluble polymers such as pectin, gallen gum, chitosan, poly-caprolactone, xyloglucane, poly-D, L-lactic acid, pluronic F 127, carbopol, etc makes this drug delivery most acceptable and useful. In-situ gel is fabricated for both local and systemic drug delivery at specific site of action. Various evaluations are recommended for in-situ gels mostly viscosity, buoyancy, gelling capacity and dissolution studies are performed. This review presents current trends in fabrication, evaluation parameters and importance of various drugs formulated as in-situ gelling system.

Keywords: Hollow microspheres, Multiparticulate floating system, peroral delivery, Gastro retentive floating DDS.

Introduction

Floating is the Novel Drug Delivery System. Different dosage form are developed in gastro retentive floating system as microspheres, micro beads, tablets, capsules, films etc. *In-situ* gelling system is a new trend in floating DDS. In-situ gelling system have its application in different routes of administration like oral, nasal, ophthalmic, peroral, rectal, vaginal and also parenteral route. In-situ forming polymeric drug delivery systems has many advantages such as ease of administration, increased local bioavailability, reduced dose frequency, improved patient compliance and has less complex method of production and so is cost effective. [1, 2]

Gastro retentive FDDS have bulk density lower than gastric fluid and hence remain buoyant in stomach without affecting the gastric emptying rate for a long period of time. When the gel so formed float on gastric fluid the drug get released slowly at desired rate from the floating gel. After drug is released from floating system, the residual part is emptied from stomach. This may increase GRT and also control the fluctuations in plasma drug concentration (PCD). Floating system are the controlled or sustained release dosage form and have properties similar to hydrophilic matrices and so called as hydrodynamically balanced system (HBS) as they form a low density polymeric gel barrier at outer surface. Drug is slowly released from the matrices same as that in case of conventional hydrophilic matrices. This form may remain buoyant

(8-10 hours) on gastric contents without affecting the rate of gastric emptying. Different polymer systems are used in floating drug delivering dosage forms. Among those some are polysaccharides, polymethacrylates, hydrocolloids etc. in this cellulose ether polymers are most popular, especially HPMC. The formulation of floating in situ gelling solution may sustain and prolong drug action, improve patient compliance and reduce frequency of administration of the drug in comparison to conventional drug delivery system. [3-7]

Different Applications Of *In-Situ* Gelling Drug Delivery System

Parenteral delivery

It is most obvious way to provide sustained release medication is to place the drug in a delivery system and inject or implant the system into the body tissue. Poloxamers are predominantly used in these preparations to obtain the thermo reversible gel. Suitability of poloxamer gel alone or with combination with HPMC, Na-CMC or dextran was studied for epidural administration of drug in-vitro. Dang Wang *et al* (2014) prepared and developed a parenteral thermo-sensitive organogel or ganogel for treatment of schizophrenia by using long chain fatty acids in pharmaceutical oil. [8, 9]

Ocular delivery

Ophthalmic hydrogel have its efficacy based on increased ocular residence time via enhancing viscosity and mucoadhesive properties. In situ gels are preferred since they are conveniently dropped in the eye as a solution where it undergoes transition to for a gel. Thermo sensitive, specific ion sensitive or pH-sensitive hydrogels have been examined for their potential as vehicles for ocular drugs. Gellan gum containing formulations of pilocarpine HCl reduces drug concentration from 2% to 0.5% showing the same bioavailability. Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability.¹⁰ Malik APH et al (2014) studied pH induced in-situ gelling system of an anti-infective drug i.e. gatifloxacin for sustain ocular delivery.^[11] Lin T formulated another new in-situ gelling formulation consisting of 0.15% ganciclovir (GCV) for herpes simplex keratitis. They evaluated clinically the safety and efficacy of the ganciclovir. [13]

Rectal delivery

For the rectal administration all the drugs used as liquid, semisolid (ointments, creams or foams), and solid dosage form (suppositories) can be used. Suppositories cause discomfort during insertion which is minimized in case of *in-situ* preparations. Novel *in-situ* gelling liquid suppositories which form gel at temperature near 30-36°C are developed using poloxamers 407 and/or poloxamer 188 to obtain the temperature sensitive gelation property. Thermo reversible xyloglucan gels are useful for rectal drug delivery. Lin HR et al (2012) developed a novel in-situ gelling liquid suppository for site-targeting delivery of anti-colorectal cancer drugs.²⁵

Vaginal delivery

Thermoplastic graft copolymers develops *in-situ* gelation to prolong the release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins. Mucoadhesive thermo sensitive gel containing combination of poloxamers and polycarboxylic acid exhibited prolonged antifungal activity of clotrimazole compared to conventional formulation. Sayed I *et al* studied development and characterization of thermosensitive pluronic-based Metronidazole in-situ gelling formulations for vaginal application. [29]

Peroral delivery

The pH sensitive hydrogel have potential use in site-specific drug delivery to a particular region of stimuli sensitive hydrogels in controlled and sustained drug delivery to GI tract. Cross-linked hydrogels with faster swelling under high pH conditions, likewise other polysaccharides such as amidated pectin, guar gum and insulin were investigated in order to develop a potential colon specific drug delivery system. Rao PB studied the in-situ mucoadhesive peroral delivery of antifungal drug voriconazole for treatment of candidiasis using carbopol 934P and HPMC E50 polymers as independent variables. Formulation showed drug

release up to 12 hrs. Haoping Xu developed a novel in-situ gel for formulation of ranitidine for oral sustained delivery.^[36] Rao PB *et al* (2014) Design optimization and evaluation of mucoadhesive peroral in-situ gel containing anti fungal drug for candidiasis.^[37]

Dermal and Transdermal delivery

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of indomethacin. *In-vivo* study suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of drug. Poloxamer 407 was found to be suitable for transdermal delivery of insulin. The combination of chemical enhancers and iontophoresis result in synergistic enhancement of insulin permeation. Pillai O *et al* (2003) studied Transdermal delivery of insulin from poloxamer gel: ex vivo and in vivo skin permeation studies in rat using iontophoresis and chemical enhancers.^[39]

Nasal delivery

An *in-situ* gelling system for nasal delivery of mometasone furoate was developed and evaluated for the treatment of allergic rhinitis. Xanthan gum and gellan gum is used as gelling polymers. In situ gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation nasonex. Pre-clinical studies demonstrated that the hydrogel formulation to decrease the blood glucose concentration by 40-50% of initial values for 4-5 hrs after administration with no apparent cytotoxicity. Therefore, these types of systems are best suited for protein and peptide drug delivery. Abhirami M studied recently the nasal in-situ gelling system for administration of celecoxib to enhance its bioavailability and drug activity. The complex of drug was formed with β -cyclodextrin and polymer used where Pluronic F127 and carbopol934P. The addition of cyclodextrin complexed drug in formulation prove enhancement in dissolution of hydrophobic drug in aqueous environment which increases in-vivo bioavailability of drug. ^[42] Anuradha Nerella prepared the in-situ mucoadhesive nasal gel of montelukast sodium used in leukotriene antagonist used in treatment of asthma and allergic rhinitis. This formulation reduces the pre-systemic metabolism and is attractive alternative.^[43]

Mechanism Of Floating System

Various attempts are made to obtain retention of dosage form in stomach by increasing RT of stomach. These include introduction of different gastro retentive dosage forms as floating system (gas generating system and swelling and expanding system), mucoadhesive system, high density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric emptying delaying drugs. From this the floating drug delivery system (FDDS) is most commonly used. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. When the system floats on gastric contents the drug is released slowly at the desired rate from the system. After the drug is



released, the residue is emptied from the stomach. This results in increasing the gastric emptying time of stomach as well as controlling the fluctuations in PDC. [45]

$F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) gV$ (1)
Where,

F = total vertical force,
 D_f = fluid density
 D_s = object density
 V = volume
 G = acceleration due to gravity

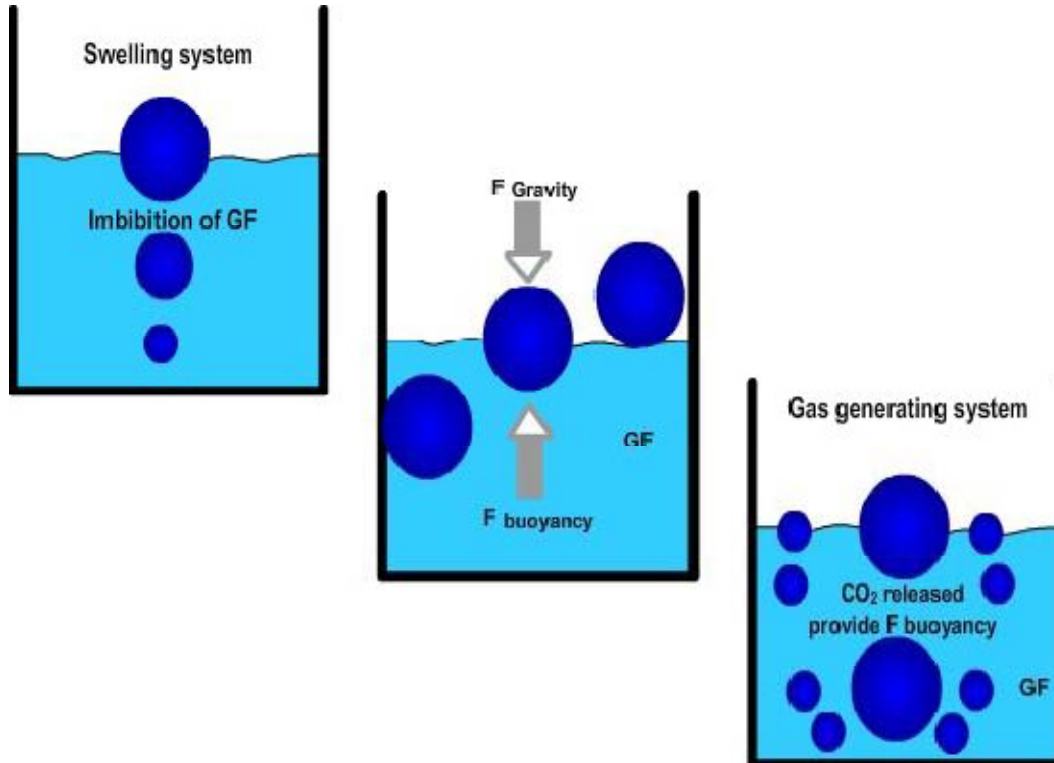


Figure.1. Mechanism of floating systems, GF= Gastric fluid

Formation Of In Situ Gelation Mechanism

These are aqueous liquid preparations that are in liquid state before administration, and turns to gel under physiological conditions. Different mechanisms which lead to in situ gel formation are:

- Ionic cross-linking
- pH change
- Temperature modulation

Polymers such as gellan gum, pectin and sodium alginate etc contains divalent ions which are complexed with sodium citrate which are braked down in acidic environment of stomach to release free divalent ions (Ca^{+2}) that causes in situ gelation of oral solution. It forms double helical junctions by aggregating double helical segments to form a dimensional network by complexation with cations and hydrogen bonding with water.

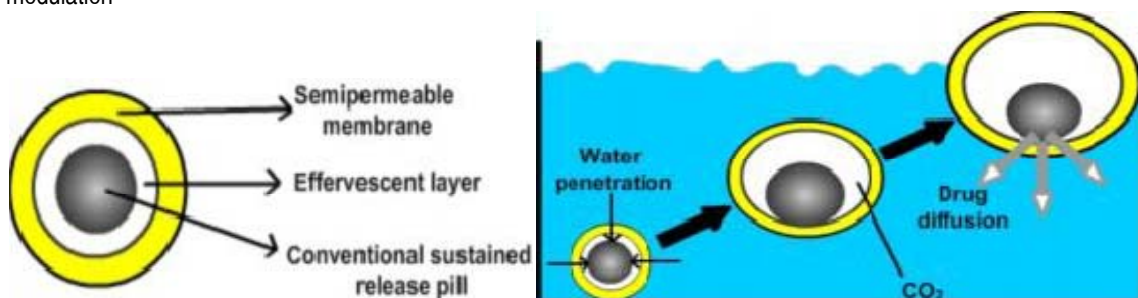


Figure.2 a) Different layers i) Semi-permeable membrane, ii) Core pill layer, b) Mechanism of floatation via CO₂ generation.



Based on the Mechanism of Buoyancy FDDS can be Classified as

- A. Single unit floating systems
 - a) Effervescent system (Gas-generating system)
 - b) Non-effervescent system
- B. multiple unit floating systems
 - a) Effervescent system (Gas-generating system)
 - b) Non-effervescent system
 - c) Microspheres
- C. Raft forming system

A. Single unit floating system

Effervescent Systems (Gas-generating Systems)

Effervescent systems utilizes matrices prepared with polymers like HPMC, polysaccharides as chitosan, effervescent agent as sodium bicarbonate, citric acid and tartaric acid or chambers that contains liquid which gasifies at body temperature. The optimum ratio of stiochiometry for citric acid and sodium bicarbonate to generate gas is reported to be 0.76:1. The resin beads of sodium bicarbonate coated with ethyl cellulose is a common method of preparation of these systems. The water permeation is possible from the coat which is insoluble but permeable one. Thus CO₂ is released which causes beads to float on the gastric fluid. Most commonly used excipients in such systems are polyacrylate polymers, polyvinyl acetate, HPMC, carbopol, sodium alginate, agar, calcium chloride, polyethylene oxide and polycarbonates. [47]

Non-effervescent systems

Due to imbibitions of gastric fluid this system swells upon swallowing and it also prevent their exit from the stomach. These systems are like plug as they are having tendency to remain lodged near to the polymeric sphincter. These dosage forms involves the mixing of drug with gels which has tendency to swell when comes in contact with gastric fluid when administered orally and maintains a relative integrity of shape and the bulk density less than one in a outer gelatinous barrier. The air trapped in polymer matrix give buoyancy to the dosage forms. These systems involve different types as microporous compartment, alginate beads, colloidal gels, hollow microspheres etc. Another system which incorporates the gas filled chamber in microporous compartment which consist of a drug reservoir which is fluid- filled floating chamber. On top and bottom of the walls different openings or apertures are present from which the GI fluids get entered into the chamber and drug diffuses slowly from it. The other two walls are sealed to undissolve the drug therein. The fluid present in it may be air in partial vacuum or other suitable sources as gases, liquids or solids having inert behavior and appropriate specific gravity. The device is swallowable and remain in the floating state for prolong period of time. After the drug is completely released the shell get disintegrate, passes to intestine and then get eliminated. 47

Multiple Units Floating System

To overcome the drawbacks of the hydrodynamically balanced system or floating systems are the variability in GI transit time then administered orally. Thus to overcome this problem the multiple unit floating system were developed, which reduce the inter-subject variability in absorption and minimize the probability of dose dumping. Research has been made in field of hollow microspheres which are capable of floating on GI fluid and also increase the gastric retention property.

Non-effervescent systems

Much work is not performed on non-effervescent multiple unit system in comparison to effervescent system. Some researchers have reported the possibility of developing systems containing indomethacin by using chitosan as polymer. Indomethacin in multiple unit HBS is a model drug prepared by extrusion process is already reported. The extrudate of mixture (drug, chitosan and acetic acid) is extruded though needle, then cut and dried. Chitosan hydrates and float in the acidic medium and the required multiple drug release could be obtained by modifying the drug polymer ratio. [47-48]

Effervescent Systems(Gas-generating system)

Floating minicapsules of pepstatin having diameter of 0.1-0.2 mm has been reported by Umezawa. These minicapsules contain a central core and a coating and the central core consist of granules composed of sodium bicarbonate, lactose and a binder which is coated with HPMC layer. Ikura *et al* reported sustained release floating granules containing tetracycline hydrochloride. A multiple unit system prepared by Iannuccelli et al comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Ichikawa *et al*/developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills. [49, 50, 51]

Hollow Microsphere

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microspheres. The techniques involved in the preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and floating property mainly depends on the type of polymer used, plasticizer and solvents used for preparation. Polymers such as polycarbonate, Eudragit S and cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. Semalty M. (2010) Prepared and characterized of floating microspheres of ofloxacin hydrochloride.52



C. Raft forming system

Raft forming systems are known for the delivery of antacids and drug delivery to GI infections or disorders. The formation of viscous cohesive gel in contact with gastric fluids, where each portion of liquid swells to form layer called raft is a main mechanism of its formation. The raft so formed floats on gastric fluids because of low bulk density created by CO₂ release. The system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float

on the gastric fluids. Jorgen *et al.* describes an antacid raft forming floating system. The gel forming agents as gellan gum or sodium alginate are included in the system along with calcium carbonate, sodium bicarbonate and acid neutralizers, which forms a foaming sodium alginate or gellan gel raft when come in contact with gastric fluids. The raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.[60]

Different Approaches For *In-Situ* Gelling System

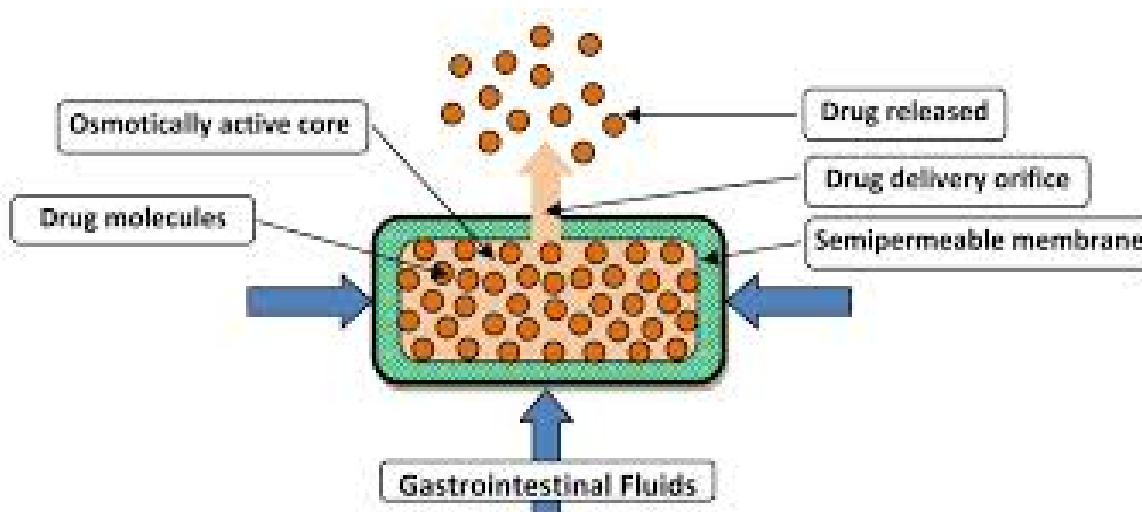


Figure.3. Mechanism of drug release from matrix

There are different mechanisms reported for the formation of in-situ gel formation:

- Chemical reaction (e.g., Ionic cross linking method)
- Physiological stimuli
- Temperature-sensitive.
- pH-sensitive.
- Ion-sensitive.
- Dilution sensitive.
- Electrical signal-sensitive.
- Light-sensitive.
- Glucose-sensitive.

In-Situ Gelling Based On Chemical Stimuli

Ionic Cross-Linking

Certain ion sensitive polysaccharides such as carrageenan, gellan gum (Gelrite), pectin, sodium alginate undergo phase transition in presence of different ions such as K⁺, Ca²⁺, Mg²⁺, Na⁺. e.g., Gelation of low-methoxy pectins can be caused by divalent

cations, especially Ca²⁺ ions, alginic acid undergo gelation in presence of divalent/ polyvalent cations, e.g., Ca²⁺ due to the interaction with guluronic acid block in alginate chains. E.g., Haoping Xu(2014) studied novel in-situ gel for formulation of ranitidine oral drug delivery.[35]

In-Situ Gel Formation Based On Physiological Stimuli

Temperature-sensitive

Temperature is one of the most widely used stimuli-sensitive *in situ* gels, because it is easy to control and has practical advantages both *in vitro* and *in vivo*. These formulations are liquid at room temperature (20-25°C) and undergo gelation when comes in contact with application site (35-37°C), due to increase in temperature. Temperature sensitive *in-situ* gel undergoes a volume phase-transition or a sol-gel phase transition at a critical solution temperature (UCST). The LCST polymers exhibit a hydrophilic to hydrophobic transition with increasing temperature, whereas the UCST systems undergo the opposite transition. There are different polymers used as LCST such as poly (N-isopropyl acryl amide)



(PNIPAM), poly (N,N diethylacrylamide) (PDEAM), poly(vinyl ether) (PVE), poly(N-vinylalkylamide) (PNVAAM), polyphosphazene derivatives and poly(N-(2-hydroxypropyl)methacrylamide mono/di lactate) (PHVAAM)-mono/dilactate). Among all poloxamers are the most commonly used thermosetting polymers in *in-situ* gel forming drug delivery system.

Mechanisms involved in sol to gel transition after an increase in temperature.

Gradual desolation of the polymer.

Increased micellar aggregation.

The increased entanglement of the polymeric network.

Thermo reversible gels can be prepared with naturally occurring polymers such as gelatin and carrageenan. At elevated temperature these polymers adopt a random coil conformation in solution. Upon cooling, a continuous network is formed by partial helix formation. Latest study on thermo-sensitive FDDS is preparation and development of organogel or ganogel for treatment of schizophrenia by using long chain fatty acids in pharmaceutical oil.[8, 63]

PH-sensitive

pH is one of the important environmental parameter for novel drug delivery system, because the pH change occurs at different body sites such as stomach, intestine, endosome, blood vessels, vagina and tumor extracellular sites. These formulations are polymeric dispersion in aqueous system which undergoes spontaneous gelation in response to change in pH after application at the target site. Generally the ionic polymers like polyacrylamide, polyacrylic acid, and polymethacrylic acid are used for preparation of pH sensitive *in-situ* gels. The entire pH sensitive polymers acidic or basic group either accepts or release protons in response to change in environmental pH. Swelling of *in-situ* gel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. Singh NK studied the pH and temperature sensitive biodegradable copolymer hydrogel for drug delivery.[63]

Ion-sensitive

In such type of *in-situ* hydrogels the sol to gel transition occurs due to presence of mono/di valent cations such as Na⁺, K⁺, Ca⁺⁺, and Mg⁺⁺ ions. Naturally occurring anionic polymers like gellan gum, sodium alginate, carrageenan and xyloglucan have properties of cationic induced gelation. Gellan gum is commercially available as Gelrite® is an anionic polysaccharide that undergoes *in-situ* gelling in the presence of mono and divalent cations including Ca²⁺, Mg²⁺, K⁺ and Na⁺.

Dilution sensitive

This type of hydrogel contains polymer that undergoes phase transition in presence of higher amount of water. System that undergoes phase transition as a consequence of dilution with water a higher amount of polymer can be used. E.g., Lutrol F68.

Electrical signal sensitive

This type of transmission occurs in presence of an applied electrical field. Chitosan gels can be used for electrically modulated drug delivery through gel matrix.

Light sensitive

Light- sensitive hydrogels can be used in the development of photo- responsive artificial muscle or as the *in-situ* forming gels cartilage tissue engineering. Polymerizable functional groups and their initiator like ethyl eosin and camphor quinone can be injected in to tissue and then electromagnetic radiations are applied to form a gel by enzymatic processes. For this purpose long ultraviolet wavelengths are used.

Glucose- sensitive

The stimuli-responsive system to release the insulin intelligently using hydrogels has been investigated. Cationic pH sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in pulsatile manner. Another approach is based on competitive binding of insulin or insulin and glucose to fix the number of binding sites in concanavatin A, where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system. An alternative route through phenyl borate-poly (vinyl alcohol) polymers is also possible.

novel trend in floating drug delivery system

Floating drug delivery system is mostly used system for controlled and sustained drug delivery. In situ gelling system is a novel trend in FDDS. Different polymers are used in floating in situ gelling preparation for different approaches.

Polymers used as *in situ* gelling agents

Materials which undergo sol to gel transition in aqueous solution at body temperature are used in the development of sustained release vehicle with in situ gelation property.

Some polymers are listed below which are used as in situ gelling agents

1. Pectin
2. Gellan gum
3. Sodium alginate
4. Xyloglucan
5. Pluronic F127
6. Xanthan gum
7. Chitosan
8. Carbomer

Pectin

Low methoxy pectin (degree of esterification < 50%) Low methoxypectins (degree of esterification <50%) readily form gels in



aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes

gelation to occur. The potential of an orally administered *in situ* gelling pectin formulation for the sustained delivery of Paracetamol has been reported.

Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an α -(1-4) chain. Pectin gelation characteristics can be divided into two types: high-methoxy and low-methoxy gelation. Gelation of high methoxy pectin usually occurs at $\text{pH} < 3.5$. Low-methoxy pectin is gelled with calcium ions and is not dependent on the presence of acid or high solids content.

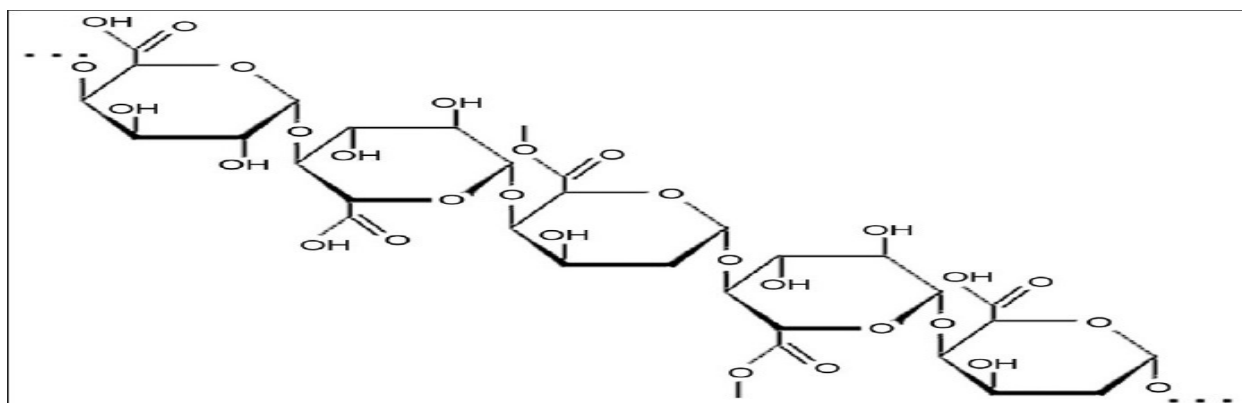


Figure. No.4: Chemical structure of pectin

Gellan gum

Gellan gum (GelriteR) is a linear, anionic heteropolysaccharide secreted by the microbe *Sphingomonas elodea* (formerly known as *Pseudomonas elodea*). The native polysaccharide is partially esterified with L-glycerate and acetate, but the commercial product Gelrite has been completely de-esterified by alkali treatment. GelriteR (deacetylated gellan gum) is one of the most interesting *in situ* gelling polymers that have been tested since it seems to perform very well in humans. Formulations with the Gelrite can be

administered to ocular mucosa as a low viscosity solution. On contact with cations in tear fluid the formulation will form a clear gel. This is caused by cross linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na^+ , K^+ , Ca^{2+}). Gellan gum produces temperature dependent or cations induced *in situ* gelling. It is a water soluble polysaccharide. It forms a gel via formation of double helices, followed by their ionic cross-linking. [60, 71]

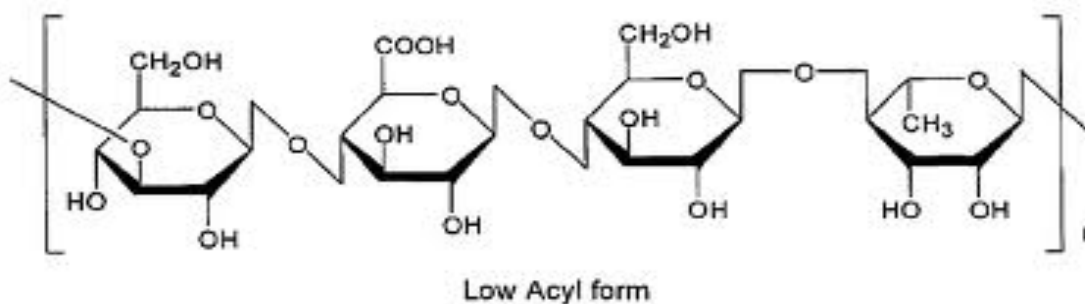


Figure. No.5: Chemical structure of Gellan gum

Sodium alginate: (Alginic acid)

Alginic acid is a polysaccharide consisting of β -D-mannuronic acid (M) and -L-guluronic acid (G) residues joined by 1,4-glycosidic

linkage. Alginate is a well known polysaccharide widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent



counter ions, such as calcium, lead, and copper; it is also possible to obtain an alginic acid gel by lowering the environmental pH value. Alginate has been proposed in the field of pharmaceuticals for its *in situ* gelation properties, particularly for the application of alginate gels for ocular drug delivery, since this dosage form is so effective as compared to solutions. A prolonged delivery of two different drugs (pilocarpine⁴⁰ and carteolol⁴¹) was obtained in

comparison to the same drugs instilled as solutions. Alginic acid is mucoadhesive, biodegradable and non toxic polymer. Because of these applications it is widely used as a vehicle for ophthalmic *in situ* gelling system. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins. [71]

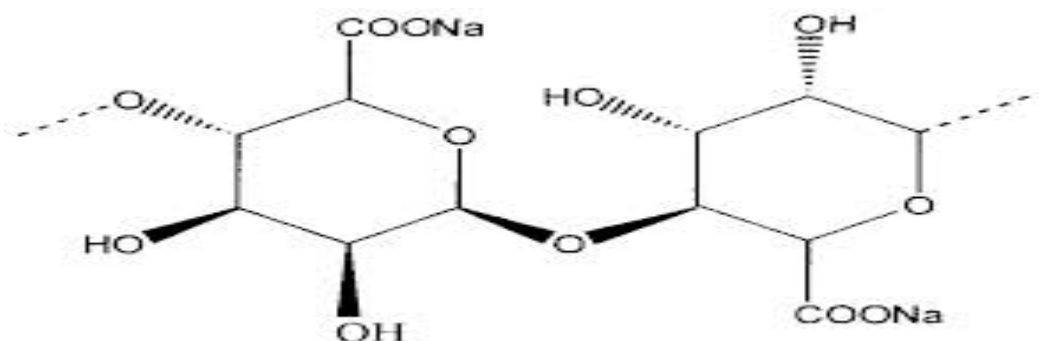


Figure. No.6: Chemical structure of Sodium alginate

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and it is composed of a (1 4)- β -D-glucan backbone which has (1 6)-D-xylose branches that are partially substituted by (1 2)- β -D-galactoxylose⁴⁶. Xyloglucan forms thermo responsive gels in water, under certain conditions. For example, the sol-gel transition of xyloglucan was shown to decrease from 40 C to 5 C when the galactose removal ratio increased from 35 to 58%. Xyloglucan formulations were assessed for ocular delivery of pilocarpine; using Poloxamer 407 as a positive thermosensitive control. The 1.5 wt. % xyloglucan formulation enhanced the miotic response to a degree

similar to that of a 25 wt. % Poloxamer 407 gel⁴⁹. In comparison with gellan and alginate, in the oral administration of cimetidine, xyloglucan gels appear to be the system with the widest application because its gelation does not require the presence of cations, as in the case of alginate, and its use is not restricted by the charged nature of the drug, as in the case of gellan. Xyloglucan gels have also been investigated for ocular delivery of pilocarpine and timolol. Xyloglucan gels have also been used as vehicles for a sustained release of percutaneous formulations of non-steroidal anti-inflammatory drugs. [73]

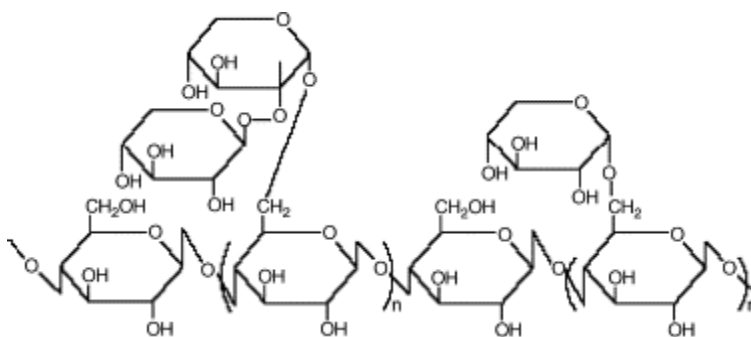


Figure. No.7: Chemical structure of Xyloglucan

Pluronic F127

The Poloxamers or pluronic consist of more than 30 different non-ionic surface active agents. Poloxamers, commercially available as PluronicR, are the most commonly used thermal setting polymers



in ophthalmology. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Pluronic F-127, which gives colorless and transparent gels, is the most commonly used polymer in pharmaceutical technology. Poloxamer formulation generally increased drug residence time at application sites, resulting in improved bioavailability and efficacy. (PluronicR F127) was found to gel at a concentration of 20 wt. % at 25 C, which is less than that of the other members of the

Poloxamer series. At room temperature (25 C), the solution behaves as a mobile viscous liquid, which is transformed into a semisolid transparent gel at body temperature (37 C). Pluronics or Poloxamers also undergo *in situ* gelation by temperature change. Pluronic F-127 was used as an *in situ* gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methylcellulose to ensure long residence time at the application site. [70-71] As shown in figure No. 8

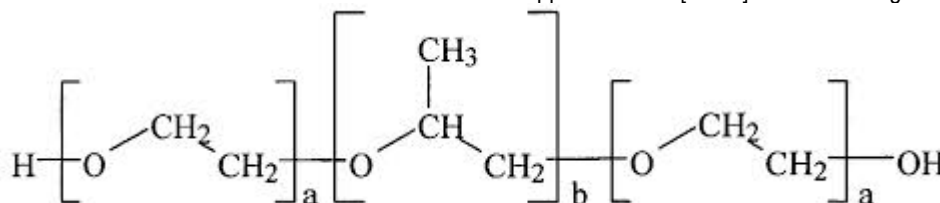


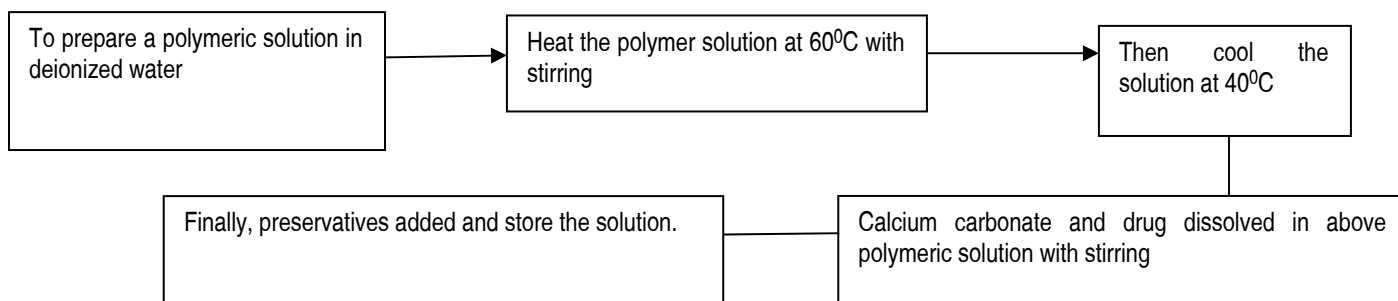
Figure.No.8 PEO-PPO-PEO (Poloxamer)

Synthetic polymers

Synthetic polymers are of increasing interest in drug delivery as therapeutic agent. Synthetic polymers are popular choice mainly for parenteral preparations. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide- coglycolide), poly (decalactone), poly -caprolactone have been the subject of the most extensive recent investigations. Various other polymers like

triblock polymer systems composed of poly (D,L-lactide)-block poly (ethylene glycol)-block-poly (DL-lactide), blends of low molecular weight poly (D,L-lactide) and poly (-caprolactone) are also in use. These polymers are mainly used for the injectable *in situ* formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven. [71]

FORMULATION



Evaluation Of Floating *In-Situ* Gelling System

Clarity

Clarity is inspected visually under black and white backgrounds.

Texture analysis

The consistency, cohesiveness and firmness are checked by texture analyzer which mainly indicates syringability of solution to know its ease of administration *in vivo*.

Drug polymer interaction and thermal analysis

Drug-polymer interaction studies can be done by FTIR spectroscopy. TGA can be done to quantitate the percentage of water in hydrogel. DSC is conducted to observe whether there are

any changes in thermograms as compared with pure active ingredients used for gelation purpose.

Determination of drug content

Certain amount of formulation is added to the amount equivalent to drug has to be dissolved in suitable medium and stir for required time and then filtered. Then analyze for drug content.

pH determination

The pH can be measured by using digital pH meter and at favorable condition. The influence of pH on the gelation property of sol can be determined by using different medium of various pH values.

In-vitro gelling capacity: Generally



gelling capacity of an in situ gel forming system can be determined by forming a colored solution of *in situ* gelling system for visual observation. By adding in situ gel to simulated gastric fluid we can estimate different parameters like in situ gel formation, its stiffness and the duration for which formed gel remain intact.

In-vitro buoyancy studies

After addition of *in-situ* gelling formulation to a simulated gastric fluid we can estimate parameters such as floating lag time and the time the gel float on system constantly.

In-vitro drug release studies

The release rate of drug from *in-situ* gel can be determined using USP dissolution rate testing apparatus II at 50 rpm. 900ml of 0.1 N HCl can be used as dissolution medium and temperature of 37±0.5 °C is maintained. 5ml samples can be withdrawn at various time points for estimating the drug release using UV-Visible spectrophotometer. The drug release studies from *in-situ* gel can also be done by using plastic dialysis cell.

Measurement of rheological property of sol and gel

Viscosity of *in-situ* formulation can be measured by using Brookfield viscometer, Cone and plate viscometer etc., the viscosity of the gel can also be determined to estimate the gel strength.

Water uptake study

When sol is converted to gel, it is collected from the medium and the excess medium was blotted using a tissue paper. The initial weight of gel so formed has to be noted. Again the gel has to be exposed to the medium and the same procedure is repeated for every 30 min to note down the weight of the gel at each interval after removing the medium using filter paper. Effect of pH, concentration of gelling agent/ cross linking agent on viscosity, in situ gelation character, floating ability and drug release can be studied for in situ gelling type of floating formulation.

Gel strength

Gel strength is evaluated by using rheometer with a specified amount of solution form gel where prepared in a beaker. This beaker is raised so pushing the probe of rheometer through the gel. Change in the load on probe can be measured as a function of depth of merge of the probe below the gel surface.

Sol-gel transition temperature and gelling time

Sol to gel transition temperature is the temperature at which the phase transition of sol meniscus is first noted when it kept in a sample tube at a specific temperature and then heated at a specified time. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the required for first detection of gel formation of sol formation.

Accelerated stability studies

Formulation are placed in amber color vials and sealed with aluminum foil for short term accelerated stability study at 40°C and 75 % RH as per ICH guidelines. Samples are tested for every month for clarity, pH, gelling capacity, drug content, viscosity and *in vitro* dissolution studies.

Application Of Floating In-Situ

To increase the absorption of drugs which are mostly absorbed from upper GIT to get prolonged contact time at their site of maximum absorption and so increase the extent of drug absorption.

As there is increase in absorption of drug from specific site the bioavailability of drug enhanced probably. Increase in gastric transit time also causes an increase in the bioavailability of drug.

As drug remain in stomach till completely release, so frequency of adverse effect on colon is reduced.

Drugs that are released in the stomach get enough residence time for absorption rate occurs. Local action of drug is prolonged, so less amount of dose is required for administration.

Advantages Of Fdds

The floating systems are important tool of stomach specific drug delivery, both for systemic as well as local drug action. E.g. antacids

Acidic substances generally cause irritation on the stomach wall when it comes in contact with it. So there is scope for the development of HBS formulation for acidic drugs like aspirin and some other drugs.

The prolong release dosage forms as tablets or capsules on administration will dissolve in gastric fluid. After dissolution they will be available in gastric fluid to be dissolved in small intestine after emptying of stomach contents. The drug will be fully absorbed from floating dosage form if it remains in solution form in alkaline pH of intestine.

The drugs meant for local action as H₂-receptor antagonist or some other drugs for local action have advantageous for GRDDS.

When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Dosing frequency is reduced in this system and thus increases the patient compliance.

The first pass effect is reduced as bioavailability of drug is enhanced by maintenance of desirable plasma drug concentration with continues drug release by this system.

Better therapeutic effect of short half-life drugs can be achieved.

Due to buoyancy gastric retention time is increased.

Drugs which have stomach as main absorption site, FDDS is advantageous for it.



Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping. Gastric irritation is minimized as these dosage forms show sustained drug release, buoyancy and uniform drug release through multi-particulate system.

Advantages Of Floating *In Situ* Gel

As the *in-situ* gel has low density it floats immediately on gastric fluid to form a layer on it. It has effective surface area which leads to high drug release and improved bioavailability. Buoyancy is faster than tablets and capsules. Easy method of preparation than other floating dosage forms.

Conclusion

It is challenge to prepare a dosage form which gives prolonged gastric retention as well as compatibility with stomach physiology. To obtain gastric retention researchers have worked from several years and had developed different approaches for GRDDS. Out of which floating *in-situ* gelling system is most promising technique which undergoes sol to gel transition when come in contact with

gastric fluid or stomach pH. These gels shows site specific drug delivery may be local or systemic delivery as it retain in stomach for long period of time by floating on gastric fluid. This reduces dosing frequency and hence patient compliance. *In-situ* gels are useful for sustained drug delivery and also beneficial for pediatric and geriatric drug delivery. Different biodegradable polymers are used in *in-situ* floating systems. The floating behavior of biodegradable polymer can be further studied for improvement of gastric retention and hence bioavailability of different drugs. *In-situ* gels are promising dosage for in the field of novel controlled drug delivery systems as it as good stability and bioavailability along with better drug release which makes it more reliable one amongst other conventional dosage forms.

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