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In situ gel as a novel approach of gastroretentive drug delivery

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Abstract

Among oral dosage form, liquid dosage forms are more prone to low bioavailability because of their quick transit from the stomach/ duodenum. To produce sustained release formulation of an oral liquid formulation could be successfully augmented substantially through a strategy of liquid in-situ gelling system. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. The in situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems and increase bioavailability of drug as well as produce patient compliance by reducing dosing frequency.

Keywords: In situ gel, Sustained drug delivery, Ionic crosses linking.

Introduction

In situ gel forming systems have been widely investigated as vehicles for sustained drug delivery. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort.[1] In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange[2]. So, In situ gelling system via different route such as oral, nasal, ophthalmic etc can be formulated. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone are used for formulation development of in situ forming drug delivery systems [3]. Gastroretentive in situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. The gel formed from in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract. This review attempts to discuss stomach specific in situ gelling system in detail including formulation factors to be considered in the development of in-situ drug delivery system. Also, different types of smart polymers, their mechanisms of gel formation from the sol forms, evaluation and characterization of in situ polymeric formulations are discussed.

Benefits of gastroretentive drug delivery system (GRDDS) [4, 5]

The principle of GRDDS can be used for any particular medicament or class of medicament.

1. The GRDDS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
2. The efficacy of the medicaments can be increased utilizing the sustained release.
3. When there is 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 advantage drug in gastroretention to get a relatively better response.

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4. GRDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
5. The GRDDS are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.

Suitable drug candidates for gastroretentive dusage form

- 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

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.[6] certain biodegradable lipid substance such as myverol 18-99 (glycerol mono-oleate) forms in situ gel under such phenomenon.[7] 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.[8]

In situ gelling based on chemical stimuli

Ionic crosslinking

Certain ion sensitive polysaccharides such as carrageenan, Gellan gum(Gelrite®), Pectin, Sodium Alginate undergo phase transition In presence of various ions such as k^+ , Ca^+, Mg^+, Na^+.[9] For eg., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with guluronic acid block in alginate chains.[10]

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.[11]

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. [12] Typically long wavelength ultraviolet and visible wavelengths are used. A photopolymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney [13]

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).[14,15] At the LCST, hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions, and an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. [16,17] Alternatively, some amphiphilic polymers, that self-assemble in solution, show micelle packing and gel formation because of polymer–

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polymer interactions when temperature is increased.[18] Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research.[19] Polymers such as Pluronics (poly (ethylene oxide)-poly(propylene oxide)-poly (ethylene oxide)(PEO-PPOPEO) Triblock),[20] Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate).[21] Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature.[22] 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. [21]

pH dependant gelling

Another formation of in situ gel is based on Change in pH. Certain polymers such as PAA (Carbopol®, carbomer) or its derivatives,[23] polyvinylacetal diethylaminoacetate (AEA),[24] Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG)[25] shows change from sol to gel with change of pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. 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.

Polymers used for oral in situ gelling system

Pectin, xyloglucan, Sodium Alginate and gellan gum are the natural polymers used for in situ forming oral drug delivery systems.

Pectin

Pectins are anionic polysaccharides extracted from cell wall of most plants.Pectin contains a backbone of α-(1-4)-D-galacturonic acid residues.(Figure 1). It readily form gels in aqueous solution in the presence of divalent ions such as free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box mode[26] Pectin undergoes phase transition to gel state in presence of H^+ ion when it is administered orally[27]. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Pectins are commercially available as low methoxy (LM) pectin (degree of esterification (DE) < 50%) and high methoxy (HM) pectin (DE > 50%)[28] LM pectins form a gel in the presence of divalent ions such as Ca2+, and can also gel in the absence of Ca2+ when the pH is below about 3.3.[29] Kubo at al developed in situ gel using pectin, Gels formed in situ following oral administration of dilute aqueous solutions of pectin (1.0 and 1.5%, w/v) were evaluated as vehicles for the sustained release of the expectorant drug Ambroxol hydrochloride. The solutions contained calcium ions in complexed form, which on release in the acidic environment of the stomach caused gelation of the pectin. In vitro studies demonstrated diffusion-controlled release of Ambroxol from the gels over a period of 6 h. A bioavailability of Ambroxol of approximately 64% of that of a commercially available formulation could be achieved from gels containing an identical dose of Ambroxol formed in situ in the stomachs of rats, with appreciably lower peak plasma levels and a sustained release of drug over a period of at least 6 h. The influence of added sorbitol (17%, w/v) on the rheological and drug release properties of the formulations has been examined. [30]

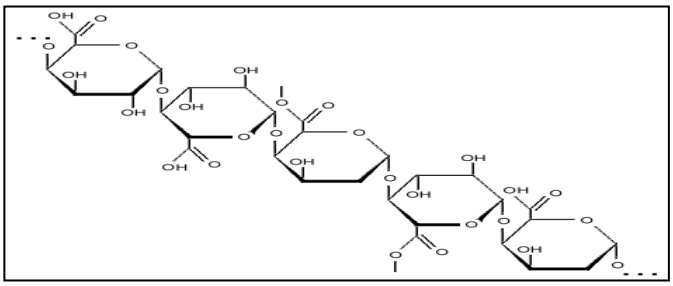

Fig. 1: Structure of pectin

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose[31] Xyloglucan is

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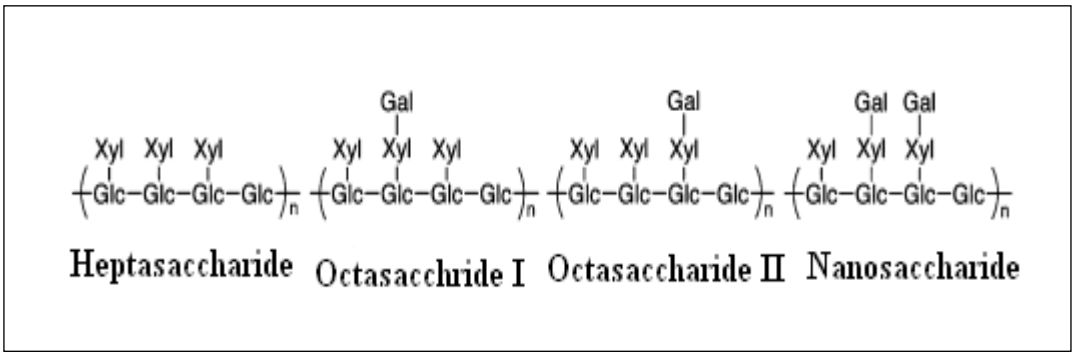
composed of heptasaccharide, octasaccharide and nonasaccharide oligamers, which differ in the number of galactose side chains.[32] (Fig. 2)

Fig. 2: Backbone structure of xyloglucan. Glc,xyl,Gal indicate β-D xylopyranosyl and β-D-galactopyranosyl residues respectively

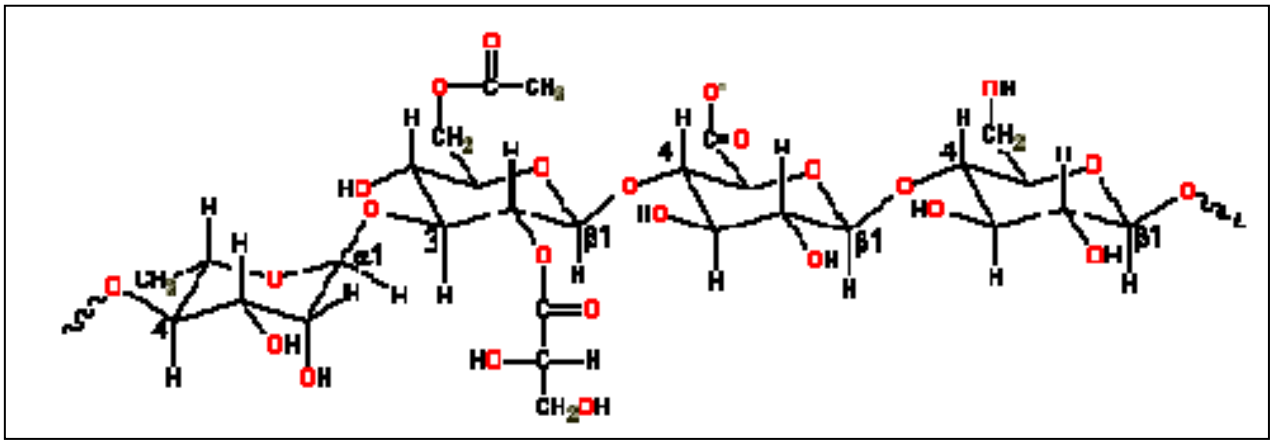


Although xyloglucan itself does not gel, dilute solutions of xyloglucan which has been partially degraded by galactosidase exhibit a thermally reversible sol–gel transition on heating. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery. [33, 34, 35, 36] Its potential application in oral delivery exploits the proposed slow gelation time (several minutes) that would allow in situ gelation in the stomach following the oral administration of chilled xyloglucan solution. Itoh K examined the gelation and release characteristics of mixtures of xyloglucan, which has thermally reversible gelation characteristics, and pectin, the gelation of which is ion responsive, with the aim of formulating an in situ gelling vehicle suitable for oral sustained drug delivery.[37]

Gellan gum

Gellan gum (commercially available as Gelrite™ or Kelcogel™) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues[38] Chemical structure of the polysaccharide has a tetrasaccharide repeat unit consisting of two glucose (Glc) residues, one glucuronic acid (GlcA) residue, and one rhamnose (Rha) residue. These are linked together to give a tetrasaccharide repeat unit (Fig. 3) [39]

Fig. 3: Structure of gellan gum



Toxicological study of Gellan gum has been performed in rats.Male and female Sprague-Dawley rats (20/sex/group) were fed dietary levels of Gellan Gum ranging from 0-6% for 13 weeks. Although the animals on this study experienced symptoms of a sialodacryoadenitis viral infection, all animals survived treatment and there were no

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adverse effects associated with the feeding of Gellan Gum.[40] Gellan gum produces temperature dependent or cations induced in situ gelling[41]. An increased bioavailability with sustained drug release profile of theophylline in rats and rabbits was observed from gellan formulations as compared to the commercial sustained release liquid dosage form.[40] Effect of Mg^2 and Ca^2 on gel hardness has been shown in following graph. (Fig. 4)

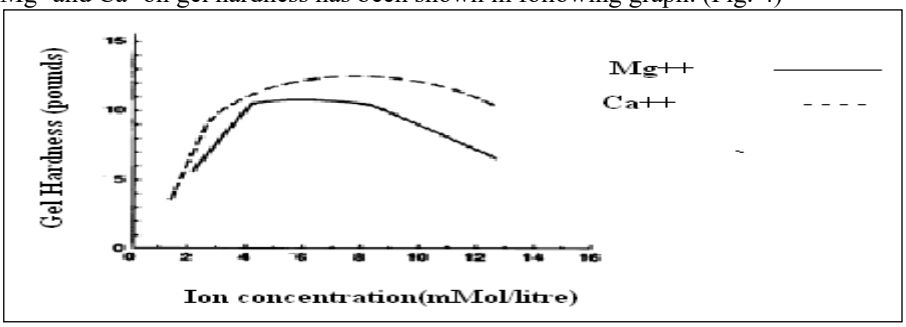

Fig. 4: Effect of divalent cations on gel Hardness of 1% Gelrite gel

Rajinikanth prepared stomach specific in situ gelling system of Clarithromyci to eradicate *H. pylori* infection using gellan gum as a polymer. Gellan based formulation was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The formulation parameters like concentrations of gellan gum and sucralfate influenced the rate and extent of in vitro drug release significantly from FIGC. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. [42]

Sodium Alginate

Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages.[43] (Fig. 5). Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. Nakamura et al. investigated the thermal properties of water insoluble alginate films containing di and trivalent cations. The results indicated that the alginates form compact structures when the ionic radii of the cation are lower. Changes in the film structure during ionic exchange were studied on the basis of its glass transition temperature (Tg) and heat capacity using differential scanning calorimetry (DSC).[44] Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.[45] Rohit *et al.*, developed a gastroretentive in situ gelling liquid formulation for controlled delivery of ranitidine using sodium alginate (low, medium and high viscosity grades), calcium carbonate (source of cations) and ranitidine. Prepared formulations were evaluated for viscosity, buoyancy lag time and buoyancy duration, drug content and in vitro drug release. Formulation variables such as concentration of sodium alginate, calcium carbonate and drug significantly affected the formulation viscosity, floating behavior and in vitro drug release. Analysis of the release pattern showed that the drug release from in situ gel followed a diffusion mechanism[46]. It exhibits favorable biological properties such as biodegradability and nontoxicity[47] and mucoadhesive properties.[48, 49]

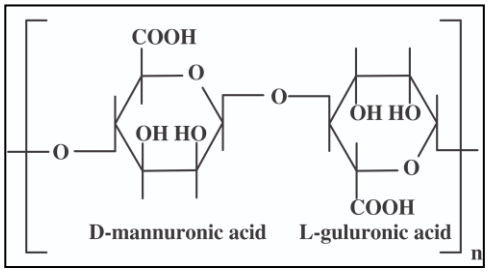

Fig. 5: Structure of Alginic acid

Evaluation of in situ gelling system

Clarity

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

Viscosity

This is an important parameter for the in situ gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations) were determined with different viscometer The viscosity of these formulations should be such that it should be patient complient.[50]

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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.[36] Thermosensitive in situ gel should be checked for in situ gelling at body temperature.

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.[36]

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.[50]

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 situ gelling system becomes helpful as an alternative of oral solid dosage form with an advantage of liquid dosage form. Sustained release formulation can be prepared in liquid form using in situ gelling approach. In situ gelling system not only helpful for sustained drug delivery, but also become convenient for pediatric and geriatric patient. Exploitation of polymeric in- situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Good stability and biocompatibility characteristics also make the in situ gel dosage forms very reliable.

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