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New gastroretentive medication delivery method using in situ gel

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Due to their rapid elimination from the stomach and duodenum, liquid dose forms are more likely to have poor bioavailability than other oral dosage forms. A liquid in-situ gelling device might be an effective way to increase the production of a sustained release formulation of an oral liquid formulation. Gels may be formed in response to variations in temperature, pH, ionic strength, and ultraviolet light, all of which influence the rate and duration of drug release. Advantages of in situ gel forming polymeric formulations include increased bioavailability of medicine and patient compliance via decreased dose frequency, as well as sustained and extended activity in contrast to traditional drug delivery methods.Keywords: In situ gel, Sustained drug delivery, Ionic crosses linking.

Introduction

There has been a lot of research on in situ gel forming systems as potential vehicles for long-term drug delivery. The benefits of in situ forming polymeric delivery methods, such as simple administration, decreased dosing frequency, increased patient compliance, and comfort, have inspired this interest.1 Changes in pH, temperature, and solvent exchange2 are all triggers that may lead to in situ gel formation. This allows for the development of In-Situ Gelling Systems for administration through various routes (oral, nasal, ophthalmic, etc.). Gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL- lactide-co-glycolide), and poly-caprolactone are only some of the natural and synthetic polymers employed in the formulation creation of in situ forming drug delivery systems. Compared to the standard liquid dose form, the bioavailability of the medicine is improved by the gastroretentive in situ gelling mechanism. Since the gel formed by the in situ gelling system is less dense than the gastric fluids, it is able to float on top of the stomach contents or adhere to the gastric mucosa thanks to the polymer's bioadhesive properties, resulting in the prolonged delivery of the drug. This article aims to explore the aspects to be addressed in the formulation of an in-situ drug delivery system, with a focus on stomach-specific in situ gelling systems. Evaluation and characterisation of in-situ polymeric formulations, as well as the processes of gel formation from sol forms of various smart polymers, are also covered. The upsides of using a GRDDS (gastric-retention drug-delivery system).

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The GRDDS framework is applicable to any drug or group of drugs.
medications that are absorbed in the stomach, such as ferrous salts, and medications that are intended for local action in the stomach, such as antacids, benefit from the GRDDS.Medications' effectiveness may be improved with the help of the continuous release.Poor absorption is to be anticipated when intestinal movement is rapid and transit time is short, as may occur in some types of diarrhea. In these cases, the medicine may be more effective when retained in the stomach by the process of gastroretention.

Drugs with tiny intestine absorption windows can be delivered using GRDDS, which is a benefit.Medicines absorbed primarily via the stomach are not the only substances affected by the GRDDS. This is because it
has been discovered that they are just as effective as orally ingested drugschlorpheniramine maleate, for instance.Medications that might work well in a gastroretentive dosage formSpecific gastrointestinal (GI) absorption window, such as for riboflavin and levodopaAbsorption occurs mostly in the stomach and upper GI tract; examples include calcium supplements, chlordiazepoxide, and cinnarazine. Locally acting drugs in the stomach, such as antacids and misoprostol Drugs include ranitidine HCl and metronidazole that break down in the gutMedications like amoxicillin trihydrate that kill off healthy colonic floraMethods that take use of in-situ gelling systemsIn situ gel formation may be triggered by a variety of processes, including chemical reactions (such as enzymatic, chemical, and photo-initiated polymerization), physiological stimuli (such as temperature and pH), and physical changes in biomaterials (such as diffusion of solvent and swelling).Physically based in situ formation Inflation and DispersionGel is formed when a polymer absorbs water and expands.Myverol 18-99 (glycerol mono-oleate), a biodegradable lipid molecule, produces an in situ gel under such conditions.7 Diffusion of the solvent from the polymer solution into the surrounding tissue causes the polymer matrix to precipitate or solidify when using a polymer such as N-methyl pyrrolidone (NMP).8Gelation triggered on-site by chemical agents Cross-linking of ionsPhase change occurs in ion-sensitive polysaccharides such carrageenan, Gellan gum (Gelrite®), pectin, and sodium alginate. As a result of the presence of ions like k+, Ca+, Mg+, and Na+.9 Because of its interaction with the guluronic acid block in alginate chains, alginic acid gels when divalent/polyvalent cations like Ca2+ are present.10 Cross-linking by enzymesThe rate of gel formation can be easily controlled by using specific natural enzymes that function well under physiological conditions without the use of potentially harmful chemicals like monomers and initiators, allowing the mixtures to be injected before gel formation in situ.11

Photo-polymerisation

The application of electromagnetic radiation can be used to form gel designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in vivo from 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 injected into a tissues site. 12 The utilization of UV and visible light with extended wavelengths is common. As a tissue-contacting material and controlled-release carrier, Sawhney 13 reports the use of a photopolymerizable, biodegradable hydrogel.Formation of gels on the spot in response to physiological cues In situ gelation is temperature dependent.Before administration, these aqueous solutions are liquid, but they solidify when heated to body temperature. These hydrogels are liquid at room temperature (about 20oC - 25oC) but gel when exposed to bodily fluids (around 35oC - 37oC). This method takes use of a phase transition that is temperature-dependent. The solubility of certain polymers suddenly shifts when the surrounding temperature rises (the polymer's LCST).14,15 In contrast to polymer-polymer and

water-water interactions, hydrogen bonding between the polymer and water becomes unfavorable at the LCST, causing a sudden transition as the solvated macromolecule rapidly dehydrates and transitions to a more hydrophobic structure. 16,17 On the other hand, certain amphiphilic polymers, which self-assemble in solution, exhibit micelle packing and gel formation at elevated temperatures due to polymer-polymer interactions.18 Among environment-sensitive polymer systems, temperature-sensitive hydrogels get the greatest attention in the field of drug delivery.19 Pluronics (poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) Triblock) polymers are one example.20 Networks of polymers consisting of poly(acrylic acid), poly(acrylamide), or poly(acrylamide-co-butyl methacrylate).At room temperature, polymer solutions flow freely but gel when near the human body. 22 Hydrogels with a positive temperature coefficient shrink when cooled below their upper critical solution temperature (UCST). There is a positive temperature dependency of swelling in polymer networks made of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acryl amide-co-butyl methacrylate). 21Gelling that depends on pH In addition, a shift in pH may trigger the development of in situ gel. Poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) mixtures25 and PAA (Carbopol®, carbomer) or its derivatives23 demonstrate a transition from sol to gel with a change in pH. Polyelectrolytes are polymers that include several ionizable groups. If the polymer has weakly acidic (anionic) groups, the swelling of the hydrogel will increase as the external pH rises, whereas it will decrease if the polymer contains weakly basic (cationic) groups.Gelling system polymers for use in the mouthOral medication delivery systems are formed in situ using natural polymers such pectin, xyloglucan, sodium alginate, and gellan gum.

Pectin

Almost all plant cell walls include pectins, which are anionic polysaccharides.Pectin has -(1-4)-D-galacturonic acid residues as its backbone.(See

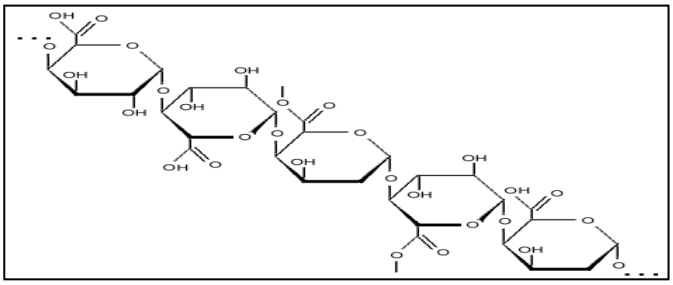


Figure 1). When divalent ions such free calcium ions are present, the galacturonic acid chains are crosslinked in an egg-box fashion, causing the aqueous solution to solidify.26 When taken orally, pectin undergoes a phase change to the gel state due to the presence of H+ ion27. For the purpose of inducing pectin gelation, the formulation may incorporate calcium ions in the complexed form. The degree of esterification (DE) of commercially available pectins ranges from low (LM) to high (HM).When divalent ions, such Ca2+, are present, LM pectins gel, but when the pH drops below roughly 3.3, they may also gel without the presence of Ca2+. In situ pectin gel was created by Kubo and colleagues, Pectin aqueous solutions (1.0 and 1.5%, w/v) were tested as carriers for the prolonged release of the expectorant medication Ambroxol hydrochloride because of their ability to form in situ gels after oral administration. Pectin gelation was triggered by the release of calcium ions from their complexes in the stomach's acidic environment. Ambroxol was shown to be released from the gels at a regulated pace by diffusion in in vitro trials spanning 6 hours. Gels containing an identical dose of Ambroxol formed in situ in the stomachs of rats achieved a bioavailability of approximately 64% of that of a commercially available formulation, with appreciably low wer peak plasma levels and a sustained release of drug for at least 6 h. Rheological and drug release features of the formulations have been studied to determine the impact of additional sorbitol (17%, w/v).

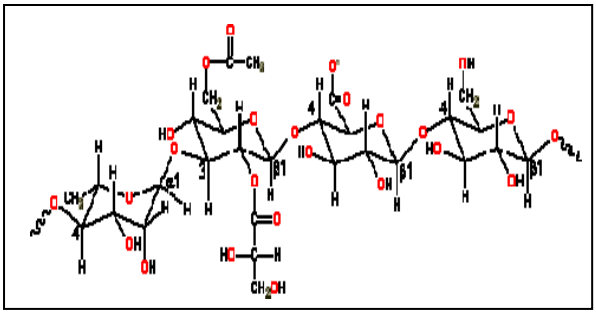
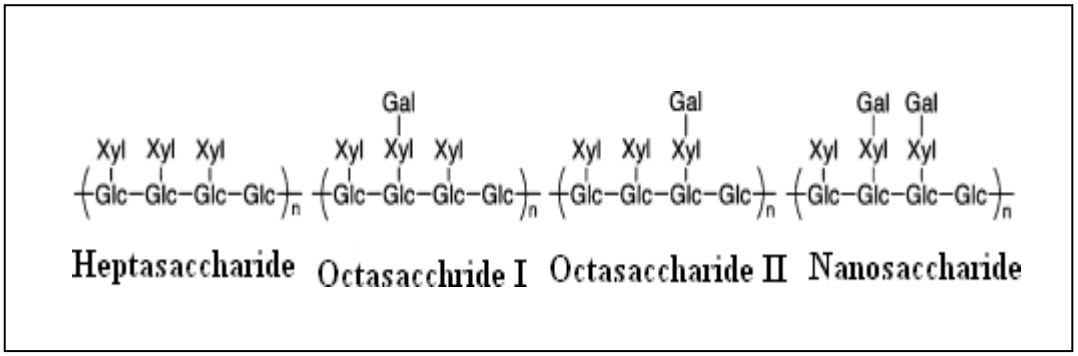


Fig. 1: Structure of pectin

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 iscomposed 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-galactopyranosylresidues 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 noadverse 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)

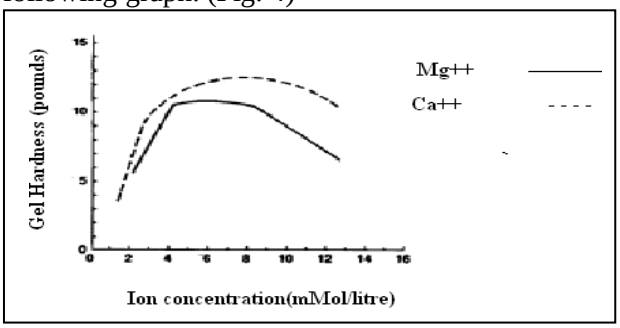
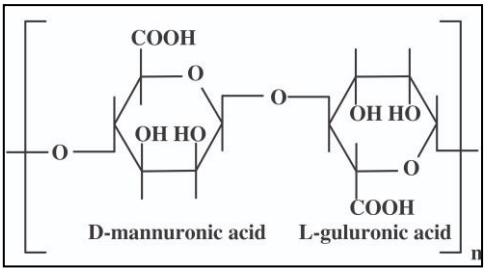


Fig. 4: Effect of divalent cations on gel Hardness of 1% Gelrite gel

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 gel



lan 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 diffe rential 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.Evaluati on of in situ gelling systemClarityThe clarity of formulated solutions can be determined by visualinspection under black and white background.

Viscosity

This is an important parameter for the in situ gels, to be evaluated.

Fig. 5: Structure of Alginic acid

The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made withartificial 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.Sol-Gel transition temperature and gelling timeFor 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-StrengthA 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]ourier 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 andiocompatibility characteristics also make the in situ gel dosage forms very reliable.

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