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REVIEW ARTICLE

In Situ Gel: A Novel Approach of Gastroretentive Drug Delivery

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ABSTRACT

The oral delivery of drugs with a narrow absorption window in the gastrointestinal tract (GIT) is often limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the site of absorption. To overcome this drawback and to maximize the oral absorption of these drugs, novel drug delivery systems have been developed. Gastroretentive systems such as floating systems, mucoadhesive, high-density, expandable and have been developed, since they provide controlled delivery of drugs with prolonged gastric residence time. Among all oral dosage forms, liquid orals are more prone to low bioavailability as far as stomach specific drug deliveries are concerned, since they subjected to faster 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 floating gel system. The formation of gel 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. This comprehensive article contains approaches, polymers, marketed preparations, patents, herbal approaches and recent advances of in situ gel.

KEYWORDS: In situ floating gel, Sustained drug delivery, Ionic cross 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.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY:

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[4] Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.[5] This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[6]

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is

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swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.[7]

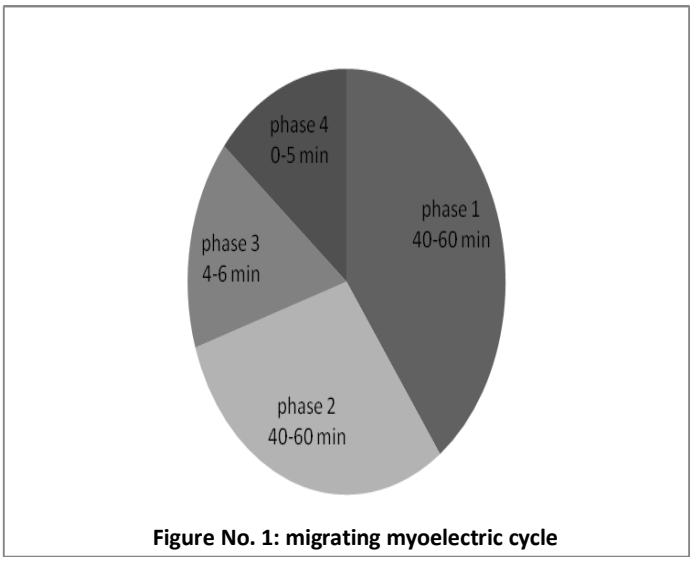

Figure No. 1: migrating myoelectric cycle

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

BENEFITS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS): [8, 9]

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.

✓ **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.

6. Improvement of bioavailability: Furosemide has poor bioavailability because its absorption is restricted to upper GIT. This was improved by formulating its floating dosage form. The floating system containing furosemide exhibit 42.9% bioavailability as compared to 33.4% shown by commercial tablet and 27.5% shown by enteric coated tablet.

7. Reduction in plasma level fluctuations: The reduced plasma level fluctuations results from delayed gastric emptying. For example bioavailability of standard madopar was found to be 60-70%, and the difference in the bioavailability of standard and HBS formulations was due to the incomplete absorption.

8. Reduction in the variability in transit performance: Floating dosage forms with sustained release characteristics are useful in reducing the variability in transit performance. For example formulating tacrine as HBS dosage form reduces its gastrointestinal side effects in Alzeihmer's patients.

9. Dosage reductions: The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. A conventional dose of 150 mg can inhibit gastric acid secretion upto 5 hrs only. If 300 mg is administered it leads to plasma fluctuations. On formulating ranitidine as floating system, the dosage has been reduced and sustained action was observed.

10. Enhancement of therapeutic efficacy: Floating systems are particularly useful for acid soluble drugs that are poorly soluble or unstable in intestinal fluids. For example bromocriptine used in the treatment of Parkinson's disease have low absorption potential that can be improved by HBS dosage form and thus itstherapeutic efficacy could be enhanced.

11. Eradication of Helicobacter pylori: H.pylori is responsible for chronic gastritis and peptic ulcers. This bacterium is highly sensitive to most antibiotics, and its eradication from patients require high concentrations of drug to be maintained within gastric mucosa which could be achieved by floating system.

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.[10] certain biodegradable lipid substance such as myverol (glycerol mono-oleate) forms in situ gel under such phenomenon.[11] 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.[12]

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^{+2}, Mg^{+2}, Na^+.[13] For e.g., 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.[14]

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]

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.[16] 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).[17,18] Polymers such as Pluronics (poly (ethylene oxide)-poly(propylene oxide)-poly (ethylene oxide)(PEO-PPOPEO) Triblock),[19] Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate).[20] Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature.[21] 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.[20]

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,[22] Polyvinylacetal diethylaminoacetate (AEA),[23] Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG)[24] 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.

POLYMERS USED FOR ORAL IN SITU GELLING SYSTEM

PECTIN:

Pectins are anionic polysaccharides extracted from cell wall of most plants. Pectin contains a backbone of α-(1-4)-D-galacturonic acid residues. 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. Pectin undergoes phase transition to gel state in presence of H^+ ion when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. [25]

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. Xyloglucan is composed of heptasaccharide, octasaccharide and nonasaccharide oligamers, which differ in the number of galactose side chains. 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.[26]

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. 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.[27]

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.[28] Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. 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). Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.[29]

Figure No. 2: Sequence of formation of floating in situ gel

EVALUATION OF IN SITU GELLING SYSTEM

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 of

administrations) were determined with different viscometer.[30]

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.[30]

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.

FUTURE PROSPECTS WITH RESPECT TO HERBAL DRUGS:

Herbal drug delivery is the emerging field in the pharmacy. The use of FDDS for herbal medicament is the novel approach for the better delivery. The drug release profile has been a major focusing area for the pharmaceutical research scientists for the past two decades. The scientists are finding it a great opportunity to work on GI transit profiles. This has given rise to new products with substantial benefits to the patients. Now with the advent of FDDS the products have been designed which could release drug for upto 24 hrs.

Some herbals that can be delivered as floating drug delivery systems:

BLACK MYROBALAN:

The aqueous extract of black myrobalan (Terminalia chebula Retz) has been shown to have uniform antibacterial activity against ten clinical strains of H. pylori.

GINGER:

Ginger root (Zingiber officinale Rosc.) has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and is also reported to have chemopreventative activity in animal models. The gingerols are a group of structurally related polyphenolic compounds isolated from ginger and known to be the active constituents.

TURMERIC:

Curcumin, a polyphenolic chemical constituent derived from turmeric (Curcuma longa L.), has been shown to prevent gastric and colon cancers in rodents. Many mechanisms had been proposed for the chemopreventative effects, although the effect of curcumin on the growth of H. pylori has not been reported.

LICORICE:

In a recent study at the Institute of Medical Microbiology and Virology, Ger-many, researchers found that licorice extract produced a potent effect against strains of H. pylori that are resistant against clarithromycin, one of the antibiotics typically used in the three antibiotic treatment regimens.

BERBERINE:

Berberine is a plant alkaloid isolated from the roots and bark of several plants including golden seal, barberry,Coptis chinensis Franch. and Yerba mansa. Berberine-containing plants have been used medicinally in ayurvedic and Chinese medicine, and are known to have antimicrobial activity against a variety of organisms including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. More recently, berberine had been demonstrated to be effective against H. pylori.

All these herbal drugs can be prepared as gastroretentive drug delivery system.[31]

RECENT ADVANCES:

DH Shastri, et al.

The present work describes the formulation development of ophthalmic in situ gelling system using thermo-reversible gelling polymer, i.e. Pluronic F 127 (PF127). Because of high concentration (20 to 25%w/v) of this polymer required for in situ gelation causes irritation to the eye. So, to reduce this concentration, an attempt

was made to combine the PF127 with other polymers like hydroxy propyl methyl cellulose (HPMC) as a viscosity increasing agent or with polymers like carbopol 940, xanthan gum, and sodium alginate (high glucuronic acid content) showing a pH and cation-triggered sol-gel transition, respectively.[32]

P.S. Rajnikanth et. al.,

They aimed to develop a new intra-gastric floating in situ gelling system for controlled delivery of amoxicillin for the treatment of peptic ulcer disease caused by Helicobacter pylori. Gellan based amoxicillin floating in situ gelling systems (AFIG) were prepared by dissolving varying concentrations of gellan gum in deionized water containing sodium citrate, to which varying concentrations of drug and calcium carbonate, as gas-forming agent, was added and dissolved by stirring. They found that the formulation variables like concentration of gellan gum and calcium carbonate significantly affected the in vitro drug release from the prepared AFIG.[33]

Dasharath M. Patel, et al.

Effective Helicobacter pylori eradication requires delivery of the antibiotic locally in the stomach. High dose of amoxicillin (750 to 1000mg) is difficult to incorporate in floating tablets but can easily be given in liquid dosage form. Keeping the above facts in mind, we made an attempt to develop a new floating in situ gelling system of amoxicillin with increased residence time using sodium alginate as gelling polymer to eradicate H. pylori. Methods. Floating in situ gelling formulations were prepared using sodium alginate, calcium chloride, sodium citrate, hydroxypropyl methyl cellulose K100, and sodium bicarbonate. The prepared formulations were evaluated for solution viscosity, floating lag time, total floating time, and in vitro drug release. The formulation was optimized using a 32 full factorial design. Dissolution data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables.[34]

Wataru Kubo et. al.,

The purpose of the study was to evaluate the potential for the oral sustained delivery of paracetamol of two formulations with in situ gelling properties. Oral administration of aqueous solutions of either gellan gum (1.0%, w/v) or sodium alginate (1.5%, w/v) containing calcium ions in complexed form resulted in the formation of gel depots in rabbit and rat stomachs as a consequence of the release of the calcium ions in the acidic environment.[35]

S. Miyazaki et. al.,

Assessed formulations with in situ gelling properties for their potential for the oral delivery of cimetidine. The formulations were dilute solutions of: (a) enzyme-degraded xyloglucan, which form thermally reversible gels on warming to body temperature; (b) gellan gum and; (c) sodium alginate both containing complexed calcium ions that form gels when these ions are released in the acidic environment of the stomach. The in vitro release of cimetidine from gels of each of the compounds followed root-time kinetics over a period of 6 hr. Plasma levels of cimetidine after oral administration to rabbits were compared with those resulting from administration of a commercial cimetidine/alginate suspension with an identical drug loading.[36]

MARKETED PRODUCTS:

Liquid Gaviscon - Al-hydroxide (95mg), Mg carbonate (385mg)
Topalkan - Al-Mg antacid
Conviron - Ferrous sulfate

Sr. No.	US Patent	Formulations
1	US20120009275	In situ forming hydrogel wound dressing containing antimicrobial agents[37]
2	US20050063980	Gastric raft composition[38]
3	US5360793	Rafting antacid formulation[38]
4	US20020119941	In situ gel formation of pectin[39]
5	US20110082221	In situ gelling system as sustained delivery for eye[40]

Table No. 1: List of patents

***SOME US PATENTS FOR FLOATING IN SITU GEL DRUG DELIVERY SYSTEM**

CONCLUSION:

Dosage forms with a prolonged GRT will bring about new and important therapeutic options. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the compliance level

of existing FDDSs. Many of the "Once-a-day" formulations will be replaced by products with release and absorption phases of approximately 24 hrs. Also, FDDSs will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at gastric mucosa which are sustained over a large period. Finally, FDDSs will be used as carriers of drugs with the "absorption window". 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. Use of FDDS and in situ floating gel for the delivery of herbal medicaments will be the subject of research in future.

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