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Review Article

An Insight to In-Situ Gel Forming Stomach Specific Drug Delivery System

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ABSTRACT

The oral delivery of drugs having narrow absorption window in the gastro-intestinal tract is limited by poor bioavailability with conventional dosage forms due to incomplete drug release and short residence time at the time of absorption. To provide controlled delivery of drugs novel drug delivery systems have been developed. Different systems have been developed to increase the gastric residence time viz. floating system, mucoadhesive, high density, expandable. Among all oral dosage forms, liquid orals are more prone to low bioavailability due to fast transit time from stomach to duodenum. Sustained/Controlled delivery can be achieved by decrease in the transit time of the dosage form. This can be augmented by an approach of liquid *in-situ* gelling system. These *in-situ* formulations are the drug delivery systems that are in *sol* form before administration in the body, but when administered, undergo gelation, *in-situ*, to form a gel. Formation of gel depends on various factors viz. temperature modulation, pH change, presence of ions, ultra-violet irradiation, from which drug releases in a sustained and controlled fashion. Different polymers which can be used for formation of *in-situ* gel include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly-caprolactone, poly-lactic acid, poly-lactic-co-glycolide. This article presents a detailed review of introduction, approaches to achieve in situ gelling system, polymers used, evaluation parameters, advantages of in situ gelling system.

Keywords: In-situ gel, oral delivery, gelation, polymers, controlled release, floating system

INTRODUCTION

Controlled and sustained release drug delivery systems received considerable attention of all pharmacists/scientists from the last 30 years. Among them extensive research has been carried out in designing of polymeric drug delivery system. *In-situ* gel forming systems has been widely investigated as vehicle for the sustained delivery of drug. Also, the development of *in-situ* gel forming systems has drawn attention over the past few years [1]. The advantages shown by *in-situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, which increases patient compliance and comfort, has drawn considerable interest in their development [2].

Formation of *in situ* gel occurs by one or by the combination of different stimuli like pH change, temperature modulation, and solvent exchange [3]. *In-situ* gel forming system via different route such as orla, nasal, opthalmic etc. can be formulated. The system basically utilizes polymers that undergo transformation from sol to gel like consistency, due to the change in physicochemical properties. The formulation development of *in situ* forming drug delivery system can be done using various natural and synthetic polymers viz. gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly-lactic acid,

How to cite this article: D Kumar, P Kapoor, An Insight to In-Situ Gel Forming Stomach Specific Drug Delivery System, PharmaTutor, 2014, 2(2), 25-32

poly-lactic-co-glycolide and poly-caprolactone [4]. In situ gelling system increases the bioavailability of drug as compared to conventional liquid dosage form. The gel formed in situ being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to bioadhesive nature of polymer and produce gastric retention of dosage form and increases the gastric residence time which results in the prolonged drug delivery in gastrointestinal tract [5].

APPROACHES OF IN SITU GELLING SYSTEM

There are different approaches used for triggering the in situ gel formation viz. physical changes in biomaterial (diffusion of solvent and swelling), chemical reactions (enzymatic, chemical and photo- initiated polymerization), and physiological stimuli (temperature and pH). These are explained below:

In situ gel formation based on physical mechanism:

Swelling and Diffusion:

Polymer swells by the absorption of water. This swelling of polymer causes formation of gel [6]. The example of the polymer which undergoes swelling is myverol 18-99 (glycerol mono-oleate) [7].

Solution of the polymer such as N-methylpyrrolidone (NMP) uses diffusion mechanism which involves the 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 like carrageenan, gellan gum, pectin, sodium alginate undergo phase transitions in presence of various such as K^+, Ca^{2+}, Mg^{2+}, Na^+ [9]. In instance, alginic acid undergoes gelation in presence of divalent/polyvalent cations (Ca^{2+}) due to interaction with glucoronic acid [10].

Enzymatic crosslinking:

Certain natural enzymes operate under physiologic conditions without need for potentially harmful chemicals such as monomers, and initiators provide a convenient mechanism for controlling rate of gel formation, which facilitates the mixtures to be injected before gel formation in situ [11].

Photo-polymerisation:

A solution of the monomers such as acrylate or other polymerizable functional groups and initiator viz. 2, 2-dimethoxy-2-phenyl acetophenone, camphorquinone and ethyl eosin can be injected into a tissue site and the application of electromagnetic radiation used to form gel [12]. Ultraviolet and visible wavelengths are used for polymerization. Sawhney reported the controlled release carrier form a photopolymerizable-biodegradable hydrogel as tissue contacting material [13].

In situ gel formation based on physiological stimuli:

Temperature dependent in situ gelling:

These transform from solution form to gel after administration. These hydrogels remain liquid at room temperature (20-25^{0}C) and undergo gelation when comes in contact with body fluids (35-37^{0}C). This approach exploits temperature-induced phase transition. Some of the polymers undergo abrupt changes in solubility with the increase in environmental temperature (lower critical solution temperature, LCST)[14,15]. Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature[16]. A positive temperature sensitive hydrogel has an upper critical solution temperature (UCST). Such hydrogel contracts upon cooling below the UCST.

pH dependent gelling:

Another approach for formation of in situ gel is based on change in pH. Polymers which shows change from sol to gel with change of pH are Carbolpol or its derivatives[17], polyvinylacetaldiethylaminoacetate[18], mixtures of poly (methacrylic acid) and poly (ethylene glycol)[19]. Swelling of hydrogel increases as the external pH increases in case of weakly acidic groups, and decreases in case of weakly basic groups.

POLYMERS USED FOR IN SITU GELLING SYSTEM

Pectin:

Pectins are the class of polysaccharides which are anionic in nature, in which the polymer backbone is mainly comprise of α-(1-4)-D-galacturonic acid residues. Low methoxypectins readily form gels in aqueous solution in presence of Ca^{2+} ions, which crosslink galactouronic acid chain. Although gelation of pectin will occur in the presence of hydrogen ions, but calcium ions are required to produce the gels that are suitable as a vehicle for the delivery of drug[20]. The main advantage of using pectin is that it is water soluble, so organic solvents can be excluded. Also, the divalent cations present in the stomach carryout the phase transition of pectin when administered orally. Calcium ions may be included in the formulation in complexed form for the induction of gelation of pectin[21]. Sodium citrate can be added to which form a complex with calcium ions, due to which the formulation may be maintained in a sol state, until the complex breaks in acidic environment of the stomach. This breakdown of complex releases the calcium ions causing gelation to occur. The quantities of the calcium and citrate ions may be optimized to maintain the desired fluidity of the formulation before administration and when administered, results into gelation when comes in contact with stomach fluids. The potential of an orally administered *in situ* gelling pectin formulation for the sustained delivery of Paracetamol has been reported [22].

Xyloglucan:

Xyloglucoan is a class of polysaccharide derived from tamarind seeds. The polymer backbone is mainly comprises 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[23]. Xyloglucan is itself not a gel, dilute solutions of xyloglucan which has been degraded by galactosidase exhibit a thermally reversible sol-gel transition on heating. The sol-gel transition temperature varies with the degree of galactose elimination. Xyloglucan gels have been used for oral, intraperitoneal, ocular, and rectal drug delivery[23, 24, 25, 26]. Itoh K et al reported the gelation and release characteristics of mixtures of xyloglucan, which has thermally reversible gelation characteristics, and pectin (gelation is non-responsive), with the aim of formulating an in situ gelling vehicle for oral sustained drug delivery [27].

Gellan gum:

Gellan gum is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a repeating unit of one α-L-rhamnose, one β-D-glucoronic acid and two β-D-glucoronic acid residues residues [28]. Its tendency of gelation is either temperature dependent or cation induced. This gelation involves the formation of double helical segments followed by aggregation of the double heclical segment to form a 3-D network by complexation with cations and hydrogen bonding with water [29]. In situ gellan formulation as vehicle for oral delivery of theophylline is reported [28]. Formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered, calcium ions released in acidic environment of stomach leading to gelation of gellan thus forming gel. Increased bioavailability

with sustained effect was reported in rats and rabbits as compared to commercial sustained release liquid dosage form.

Sodium alginate:
Sodium Alginate is sodium salt of alginic acid. It is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic likages[30]. Dilute aqueous solutions of alginates form firm gels on addition of di- and tri-valent metal ions. Nakamura et al studied the thermal properties of water soluble alginate films containing di- and tri-valent cations. The results showed that the alginate form compact structures when the ionic radical of the cation are lower. These changes in the film structure were studied on the basis of its glass transition temperature (T_g) and heat capacity using differential scanning calorimetry (DSC) [31]. Alginate salts are considered most favorable because of biodegradable and non-toxic nature, with additional bio-adhesive property[32]. Sodium alginate has been used in the preparation of gel for the delivery of biomolecules such as drug, peptides, and proteins [33].

Xanthum gum:
Xanthum gum is a high molecular weight, anionic, extra cellular polysaccharide produced by fermentation of gram negative bacterium *Xanthomonas campestris*. It contains a cellulosic backbone (β-D-glucose residues) and a trisacchharide side chain of β-D-mannose-β-D-glucoronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic nature is due to the presence of both glucoronic acid and pyruvic acid groups in the side chain [34].

EVALUATION PARAMETERS OF IN SITU GELLING SYSTEM

Physical appearance [35]:
In situ solutions should be clear and be free from any particulate matter. Time taken by the solution to convert into gel in buffer pH 1.2 is measured. Consistency of the gel formed is checked visually.

Clarity:
The clarity of the final formulation can be easily examined by visual inspection under white and black background for the presence of any particulate matter.

pH[35]:
pH of gel forming solution can be easily determined by using calibrated pH meter at 27^0C.

Viscosity [35, 36]:
It is an important parameter to be determined for in situ solutions. The viscosity and rheologic characteristics of the formulation can be determined either in solution or in gel, made with artificial tissue fluid (depending on the route of administration). The viscosity can be determined with the help of Brookfield viscometer or cone and plate viscometer at temperature (25^0C), using 1-2 ml of sample aliquots.

Gel strength:
A specified amount of gel is prepared in a bealer from the sol form. This gel containing beaker is then raised at a rate and pushing a probe of rheemeter slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of probe below the gel surface [23].

Fourier transform infra-red (FTIR) spectroscopy and thermal analysis:
FTIR is performed to examine the compatibility of ingredients. Differential Scanning Calorimetry (DSC) is used to check if there are any changes in thermograms as compared to the pure

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ingredients used, which improved bioavailability indicates the interaction [36].

In-vitro drug release:

The in-vitro drug release study can be carried out using plastic dialysis cell. The cell is made up of two half cells, donor compartment and receptor compartment, separated with the help of cellulose membrane. The sol form is placed in donor compartment. The cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at different intervals and replaced with fresh media. This receptor solution is then analyzed for drug release using analytical technique [5].

ADVANTAGES OF STOMACH SPECIFIC IN SITU GEL [37]

● Increased absorption:

Drugs which mainly absorb from upper part of stomach get prolonged contact time, at their site of maximum absorption. This increases the extent of absorption.

● Improved bioavailability:

As the absorption of the drug is increased, bioavailability of the drug is enhanced. Prolongation of gastric transit time also increases the bioavailability of the drug.

● Less adverse effect of drug:

As the drug remains in the stomach till the complete release, frequency of the adverse effects that occur on the coon decreases to a greater extent.

● Site specific drug delivery:

The drugs which are absorbed from the stomach get enough residence time stomach in absorption. Hence absorption rate increases. So the drugs which act in the stomach can be formulated by this manner to achieve site specific drug delivery.

RECENT ADVANCEMENT

● Yawei Ni et al [38] have received a patent on Aug. 17, 2004 for in-situ gelation of pectic substance. They developed a method for sustained delivery of an active agent to an animal, comprising of providing a liquid solution or dispersion (containing a liquid carrier, a pectic substance, and one or more physiologically active agents) and applying the liquid solution or dispersion to the tissues or body fluids of the animal to form a gel.

● Xiaoqiang Qi et al [39] have received a patent on Jul. 5, 2011 for in situ gel casting machine, which comprises a gel casting stand, a rubber cushion, a locking base, a slab gel casting mold. They put two slab gel casting molds and insert the wedge frame against each, which form the gel casting stand. Locking base compresses the slab gel casting molds from two directions, which ensures sealing. Without moving the slab gel molds, an electrophoresis experiment can be started right after the gel has been solidified, which avoid the leakage of the gel solution and the production of air bubbles into the slab gel casting molds.

● Ana Rey-Rico et al [40] have filed a patent application P201000670 for oesteogenic efficacy of *in situ* gelling poloxamine systems with and without bone morphogenetic protein-2.

● Grober and his co-workers developed a method for *in-situ* gelation of poloxamer and chitosan by utilizing their property that poloxamer solution converts into gel at physiological temperatures and that of chitosan to undergo ion responsive gelation in presence of sodium tripolyphosphate. Differential scanning calorimetry and tube techniques were used to study the gelation of poloxamer solution. The critical gelation temperature of poloxamer was found to be reduced due to mixture of poloxamer and tripolyphosphate.

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This had shown a decrease in the dissolution rate and release characteristics of metoprolol, doxycycline and flufenamic acid [41].

● Kazarian et al formulated pH sensitive hydrogels by morpholine derivatives using homopolymers and copolymers of N-rthylmorpholine methacrylamide and N, N-dimethylacrylamide applied in the form of matrices for ibuprofen release. This prevents the damage of mucous membrane which may occur due to drug. Prepared hydrogels were evaluated for the release rate at temperature 37 ^{0}C and in different pH values 2, 5 and 7. From the results, they concluded that hydrogels were able to prevent crystallization of ibuprofen at all pH [42].

● Helicobacter pyroli requires local delivery of antibiotic in stomach. Since it is difficult to incorporate such a high dose of amoxicillin (750 – 1000 mg), Patel et al decided to use liquid dosage form. They developed a new floating in situ gelling system of amoxicillin with increased residence time by taking sodium alginate as gelling polymer. The prepared formulations were evaluated for solution viscosity, floating lag time, total floating time, and in-vitro drug release studies [43].

Table 1: Available market products [44, 45]:

Brand	Drug
Liquid Gaviscon	Aluminium hydroxide, Magnesium carbonate
Topalkan	Aluminum – Magnesium antacid
Conviron	Folic acid, Ascorbic acid, Vit. B_{12}, Dried Ferrous sulphate, Vit. B_6
Madopar	Levodopa, Benserazide hydrochloride
Cifran OD	Cifrofloxacin

CONCLUSION

In situ gelling system is one of the approaches of stomach specific drug delivery system which undergo sol to gel transition in acidic stomach conditions and provide stomach specific drug delivery for prolonged period of time. As the system remains in the stomach for longer period of time, the contact time to gastric mucosa is increased. This leads to less frequent dosing and improved efficacy of treatment. In situ gelling system becomes helpful as an alternative of oral solid dosage form with an advantage of liquid dosage form. It also becomes convenient for pediatric and geriatric patient. Good stability and bio-compatibility also make the in situ gelling system more reliable.

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