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ORAL IN-SITU GEL: A REVIEW

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ABSTRACT

The difficulties in oral drug delivery system prompted the researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable time. One novel approach in this area is gastroretentive floating drug delivery system. Oral in-situ gel forming system provided a suitable way of providing the controlled delivery of drug within the stomach with enhanced gastric retention. This gives benefit of increased residence as well as sustained release. In-situ gel gives advantages such as ease of administration, reduced frequency of administration, improved patient compliance and comfort. In-situ gel formation occurs due to one or combination of different stimuli such as PH change, temperature modulation and ionic cross linking. In-situ gels are the solutions that undergo gelation after reaching the particular site due to physico- chemical changes. The gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time.

KEYWORDS: In-situ gel, ionic cross-linking, gastric retention.

INTRODUCTION[1-2]

The oral drug delivery system is considered to be one of the most convenient and commonly employed drug delivery system as it poses some advantageous characteristics such as ease of administration, least aseptic constraints and flexibility in the design of dosage form. However, this route has several physiological problems such as unpredictable gastric emptying rate, existence of narrow absorption window. These difficulties have prompted the researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. One novel approach in this area is gastroretentive floating drug delivery system. This can improve the delivery of drugs by continuously releasing the drug for a prolonged period of time before it reaches the absorption site.

The tablet/capsule floating dosage forms are more stable than liquids, but the problem is that they need to swallow as a whole unit. In case of dose adjustment these cannot be broken in halves as these are also designed for controlled release and floating ability also depends on dimensions of tablets. Elderly patients, children, some adult persons and patients with certain disease conditions face difficulties in swallowing tablet/capsule dosage forms. In case of dosage adjustments these dosage forms are required to be prepared in different strengths.

Oral in-situ gel forming system, also known as stomach specific have provided a suitable way of providing the controlled delivery of drug within the stomach with enhanced gastric retention. The in-situ gel forming drug delivery systems are capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. This gives benefit of increased residence as well as sustained release.

Gels[3]

Gels are an intermediate state of matter containing both liquid and solid components. It consists of three dimensional solid networks. Gels are classified into two types based on the nature of the bonds.

a) Physical gels arise when weak bonds like hydrogen bonds, electrostatic bonds and vanderwaal bonds constitute together to maintain the gel network.
b) Chemical gels arise when strong covalent bonds constitute to maintain the gel network. The network indicates the presence of cross-links which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

Hydrogels

Hydrogels are the three dimensional structures that has polymeric networks which has the capacity to absorb and retain large amounts of water and biological fluids to swell.

Hydrogels are of two types.

a) **Preformed hydrogels** are simple viscous solutions which do not undergo any modification after administration.

b) **In-situ gels** are the solutions or suspensions that undergo gelation after reaching the particular site due to physico- chemical changes.

In-Situ Gelling System

In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration. 'In-situ' is a Latin word which means 'in position'.

There are many triggering mechanisms in in-situ gel formation some of them are pH change, temperature modification and ionic cross linking. As the gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time. In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel. Various routes administration of in-situ gelling systems is oral, nasal, ophthalmic, vaginal, injectable, intraperitoneal and rectal route.

Advantages of In-Situ Gelling System

In-situ gels shows ease of administration and good patient compliance.
It shows increased gastric retention with slow drug release.
It reduces dosing frequency.
It shows local action and site specificity by acting directly onto the targeted site.
It shows less adverse effects compared to other pharmacological dosage forms.

Disadvantages of In-Situ Gelling System

It is more susceptible to stability problems due to chemical degradation.
It requires high level of fluids.
It leads to degradation due to storage problems.

Suitable Drug Candidates For Gastroretentive Dosage Form[4]

a) Narrow absorption window in GI tract, e.g., riboflavin, cyclosporine, levodopa, etc.
b) Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide, cinnarazine, etc.
c) Drugs that act locally in the stomach, e.g., antacids and misoprostol.
d) Drugs that degrade in the colon, e.g. ranitidine HCl and metronidazole.
e) Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.
f) Drugs those are poorly soluble at alkaline pH. e.g. verapamil, diazepam, etc.
g) Drugs that are primarily absorbed from the stomach. e.g. amoxicillin.
h) Drugs which are rapidly absorbed from the GIT. e.g. tetracycline.

Approaches To Produce In Situ Gel[5]

Different approaches and mechanisms utilized or involved in producing the *in situ* gel formation are as follows

A. Based on producing physical changes
B. Based on producing chemical changes
C. Based on physiological stimuli
D. Dilution-sensitive.
E. Electrical signal-sensitive.
F. Light-sensitive.
G. Glucose-sensitive

A. In Situ Formation Based On Physical Changes[6]

This approach involves either swelling or diffusion phenomenon.

Swelling and Diffusion

In swelling, polymer in the system absorbs water from the surrounding environment and swells to form a viscous gel (e.g. glycerol mono-oleate). In diffusion, solvent in which the drug and polymer is dissolved or dispersed, diffuse into the surrounding tissues causing the precipitation of the polymer to form gel (e.g. N-methyl pyrrolidone).

B. In Situ Formation Based On Chemical Changes

Ionic Crosslinking[7-8]

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+**.** For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with alginate chains.

Enzyamatic Crosslinking[9]

Enzymes present in the body fluids may also cause cross linking to form a polymer network and is considered, as the most convenient mode of gel formation. 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.

Photo-Polymerisation[10]

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. Typically long wavelength ultraviolet and visible wavelengths are used.

C. In Situ Gel Formation Based on Physiological Stimuli[11]

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

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, Polyvinylacetal diethylaminoacetate (AEA), Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) 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.

D. Electrical Signal-Sensitive[12]

Hydrogels sensitive to electric current are usually made of polyelectrolytes such as the pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. Chitosan gels as matrices can be used for electrically modulated drug delivery.

E. Light-Sensitive[12]

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

F. Glucose-Sensitive[12]

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have 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 a pulsatile fashion. Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system. An alternative route through phenylborate-poly (vinyl alcohol) polymers is also possible.

Evaluation of Floating In-Situ Gelling System[13-14]

1) Clarity

Clarity of solution is one of the most important characteristic features of preparation. Clarity is inspected visually under black and white backgrounds.

2) 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.

3) 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 thermogram as compared with pure active ingredients used for gelation purpose.

4) 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.

5) pH determination

pH is the one of the most important factors involved in the formulation. The pH of formulation should be such that the formulation will be stable at the pH and at the same time there would be no irritation to the patient upon administration of the formulation. 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 valves.

6) 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.

7) 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.

8) 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+0.50 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.

9) 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.

10) 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.

11) 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.

12) 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.

13) Accelerated stability studies
Formulation are placed in amber color vials and sealed with aluminum foil for short term accelerated stability study at 40oC 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.

14) In-vitro gelation time
The in-vitro gelling capacity of prepared formulations is measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube and maintained at 37±1^{o}C temperature. One ml of formulation solution is added with the help of pipette. The formulation was transferred in such a way that places the pipette at surface of fluid in test tube and formulation was slowly released from the pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The in-vitro gelling capacity is graded in three categories on the basis of gelation time and time period for which the formed gel remains.
(+) Gels after few minutes and dispersed rapidly.
(++) Gelation immediate and remains for 12 hours.
(+++) Gelation immediate and remains for more than 12 hours.

15) Kinetics of Drug Release
Dissolution profile of all the formulations are fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetics modelling of dug release by using a dissolution apparatus.

Principle of in Situ Gel Formation[15]
Formulation of gastro retentive in situ gel system involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension system is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a sodium alginate solution containing calcium carbonate (as a source of ca 2+) and releases them only in the acidic environment of the stomach.

Sodium alginate acts as a gelling agent. The free Ca2+ ions gets entrapped in polymeric chains of sodium alginate thereby causing cross linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed byreaggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.

Sodium citrate + Ca. carbonate (Ca)

Ca citrate complex Acidic Ca + COO
Environment

In this way, the formulation remains in liquid form until it reaches the stomach, where gelation of sodium alginate is instantaneous.

The gelling agent serves as a dispersion medium in the form of aqueous solution to contain the drug in dispersed form along with the cross linking agent.

The gas forming agent employed serves two functions

1. Act as a source of divalent cations that triggers gelation at gastric pH.
2. Produces co2 that gets entrapped in the gelled matrix to impart buoyancy.
3. The gelling agent employed in this case is the sodium alginate, It is one of the widely used polymer in cases where ion triggered gelation of *in situ* gelling agent is desired. Its aqueous solution serves as the medium for containing the drug in dispersed form along with the gas forming agent.
4. Calcium carbonate is incorporated as the gas forming agent that act as source of divalent cat ions and produces CO2 at gastric pH.

Anhydrous Calcium chloride is employed as a source of Ca2+ which is added to the sol just to impart sufficient viscosity to the solution, so as to form uniform dispersion.

Polymers Used For Oral in Situ Gelling System

i. Pectin[16]

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.

ii. Xyloglucan[17]

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.

iii. Gellan Gum[18]

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.

iv. Sodium Alginate[19-20]

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. 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.

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. Use of in situ floating gel for the delivery of herbal medicaments will be the subject of research in future.

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