IN-SITU GEL: A NOVEL PATH OF GASTRORETENTIVE DRUG DELIVERY

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ABSTRACT
In recent times, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been stimulate 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. In situ gelling systems (type of mucoadhesive drug delivery system) are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. Advances in in-situ gel technologies have encourage development in many medical and biomedical applications including controlled drug delivery. Many novel in situ gel-based delivery matrices have been designed and fabricated to fulfill the ever-increasing needs of the pharmaceutical and medical fields. The formulations are designed with an objective to retain in stomach for an extended time period to obtain better bioavailability. In-situ forming polymeric formulations drug delivery systems is in sol form before administration in the body, but once administered, undergoes gelation in-situ to form a gel. Many natural, biodegradable, biocompatible and synthetic polymers are used in the preparation of in situ gelling system. Mainly in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. In situ gels were evaluated for their visual appearance, clarity, pH, viscosity, gelling strength, drug content analysis, in-vitro gelation, rheological studies, sterility testing, texture analysis and in-vitro drug release studies.

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INTRODUCTION

In-situ gel forming drug delivery systems are a revolution in oral drug delivery system. 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.

The goal in designing and sustained drug delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, decreasing the dose required or providing uniform drug delivery. Polymers have historically been the keys to the great majority in drug delivery systems. [1]

Oral in situ gel forming system also known as stomach specific or raft forming systems have provided a suitable way of providing the controlled drug delivery within stomach with enhanced gastro-retention. The tablet/capsule floating dosage forms are stable as compare to liquids but the problem with them is that they are needed to swallow as whole unit. In case of dosage 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 patient with certain conditions suffer from dysphasia, so it becomes difficult for them to swallow tablet/capsule dosage forms. Also in case of dosage adjustments these floating solid dosage forms are needed to be available in different strengths. Where an environment specific gel forming solution, on conversion to gel, floats on the surface of the gastric fluids (due to less density than gastric contents). In this technique, a solution of low viscosity is used which on coming in contact with the gastric fluids, undergo change in polymeric conformation and a viscous gel of density lower than the gastric fluids is produced. This low density gel formation called as raft not only provide the much desired gastro retention to prolong the contact time, but also produce the continuous and slow drug release. [2]

This is a more desirable dosage form which can be deliver drug in solution form & create little to no problem of vision & frequently doses are not needed. This in situ gelling system is when exposed to physiological condition will shift to a gel phase. This new concept of production a gel in-situ was suggested first time in the early 1980s. Gelation occurs via the cross linking of polymer chain that can be achieved covalent bond formation (chemical cross linking) or non covalent bond formation (physical cross linking). This system described as low viscosity solution that undergoes phase transition in conjuctival cul-de-sac to form visco-elastic gel due to conformational changes of polymer in response to physiological environment. The rate of in situ gel formation is important because between instillation in eye & before a strong gel is formed; the solution or weak gel is produced by the fluid mechanism of eye. [3]

In situ gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can be inconvenient or oral route, which can result in unacceptably low bioavailability and passes the hepatic first-pass metabolism, in particular of proteins and peptides. This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semisolid dosage forms. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Recent development in technology has provided viable dosage alternatives that can be administered via different routes of administration. Various routes that are used include oral, topical, nasal, rectal, vaginal and ocular, etc. The hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. [4] The in situ gelling system being one among them is a type of mucoadhesive drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively constant plasma profile.

![Fig.1: In-Situ Formation of Floating Gel.](https://www.iajpr.com)
The solid component comprises a three dimensional network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified based on the nature of the bonds involved in the 3-D solid network. [4]

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. Gastroretentive in situ gelling system helps to increase bioavailability of drug compared to conventional liquid dosage form. Sodium alginate used as a polymer and calcium carbonate was used as a cross-linking agent. Oral administration is most convenient and preferred means of any drug delivery to the systemic circulation. [5]

These in situ gel preparations can be easily formulated in bulk and these formulations give homogeneity of drug distribution when compared to other conventional suspensions. These in situ gels also have good mucoadhesion property, which helps in coating of the ulcer lining once the solution comes in contact with the gastric pH.

**DEFINITION: [6]**

**Gel:**

Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a three dimensional network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified based on the nature of the bonds involved in the 3-D solid network. Chemical gels arise when strong covalent bonds hold the network together and physical gels when hydrogen bonds and electrostatic and vander-waals interaction maintain the gel network.

**Hydrogels:**

Hydrogels are polymeric networks that can absorb and retain large amounts of water and biological fluids and swell, still maintaining their three-dimensional structure. These polymeric networks contain hydrophilic domains that are hydrated in an aqueous environment, thereby creating the hydrogel structure. The term network indicates the presence of cross-links, which help avoid the dissolution of the hydrophilic polymer in an aqueous medium.

**ADVANTAGES: GASTRORENTITIVE DRUG DELIVERY SYSTEM (GRDDS) [7, 8]**
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) 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 its therapeutic efficacy could be enhanced.

4) 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.

5) 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.

6) 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.

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 Alzheimer’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 up to 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) GRDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

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 requires high concentrations of drug to be maintained within gastric mucosa which could be achieved by floating system.

**IMPORTANCE OF IN SITU GELLING SYSTEM [8]**

1) In-situ forming polymeric delivery system such as ease of administration & reduced frequency of administration improved patient compliance & comfort.

2) Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.

3) The possibilities of administrating accurate & reproducible quantities compared to already formed gel.

4) Poor bioavailability & therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye &undergoes a sol-gel transition from instilled dose.

5) Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.
MECHANISM OF IN-SITU GELATION: DIFFERENT APPROACHES

These are aqueous liquid solutions before administration, but gel under physiological conditions. Several possible mechanisms lead to in-situ gel formation is (mechanisms used for triggering the in-situ gel formation):

[1] Diffusion of solvent and swelling (Physical changes in biomaterials)
[2] Ionic cross-linkage (Chemical reactions)
[3] pH change & Temperature modulation (Physiological stimuli)

Polymer solutions of gellan, pectin & Na-alginate etc contains divalent-ions complexed with Na-citrate that are breakdown in acidic environment of stomach to release free divalent ions (Ca$^{2+}$).causes the in situ gelation of orally administered solution. It involves formation of double helical junction zones by aggregation of double helical segments to form dimensional network by complexation with cations & hydrogen bonding with water.

[1] IN SITU FORMATION BASED ON PHYSICAL MECHANISM: [9]

SWELLING AND DIFFUSION:

Swellling of polymer by absorption of water causes formation of gel. Certain biodegradable lipid substance such as myverol 18-99 (glycerol mono-oleate), which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded in vivo by enzymatic action; that’s forms in situ gel under such phenomenon. 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.

[2] IN SITU GELLING BASED ON CHEMICAL STIMULI: [10]

(a) 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$. For e.g., alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca2+ due to the interaction with guluronic acid block in alginate chains & stomach specific in situ gel of Ranitidine hydrochloride.

(b) ENZYMATIC 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.

(c) 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.

[3] IN SITU GEL FORMATION BASED ON PHYSIOLOGICAL STIMULI: [11, 12]

(a) TEMPERATURE DEPENDANT IN SITU GELLING:

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. Polymers such as Pluronics [poly-(ethylene oxide)-poly (propylene oxide)-poly-(ethylene oxide) (PEO-PPO-PEO, Triblock) used. 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.

E.g. In situ gelling formulation based on methylcellulose/pectin system for oral-sustained drug delivery to dysphagic patients.

(b) pH DEPENDANT GELLING:

Certain polymers such as PAA (Carbopol®, carboemer) or its derivatives, Polyvinylactel 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. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel.

E.g. The influence of variation of gastric pH on the gelation and release Characteristics of in situ gelling sodium alginate formulations.
IDEAL CHARACTERISTICS OF POLYMERS: [13]
A polymer used to in situ gels should have following characteristics-
A. It should be biocompatible.
B. It should be capable of adherence to mucus.
C. It should have pseudo plastic behaviour.
D. It should be good tolerance & optical activity.
E. It should influence the tear behaviour.
F. The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking & stability of the tear film during fixation.

CLASSIFICATIONS OF IN SITU POLYMERIC SYSTEMS
PECTIN [14]
Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-1,4-Dgalacturonic acid residue. Low methoxy pectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free Ca\(^{2+}\) ions, which crosslink the galacturonic acid chains in a manner described by egg-box model. Although the gelation of pectin will occur in the presence of H\(^{+}\) ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. Divalent cations present in the stomach, carry out the transition of pectin to gel state when it is administered orally. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Sodium citrate may be added to the pectin solution to form a complex with most of calcium ions added in the formulation. By this means, the formulation may be maintained in a fluid state (sol), until the breakdown of the complex in the acidic environment of the stomach, where release of calcium ions causes gelation to occur. The quantities of calcium and citrate ions may be optimized to maintain the fluidity of the formulation before administration and resulting in gelation, when the formulation is administered in stomach. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of Paracetamol has been reported.

XYLOGLUCAN [15]
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-galactosyllose. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains. The sol-gel transition temperature varies with the degree of galactose elimination. It forms thermally reversible gels on warming to body temperature. 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. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery.

GELLAN GUM [15]
Gellan gum (commercially available as Gelrite TM or Kelcogel TM) 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. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation consists of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ. In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported.

ALGINIC ACID [16]
Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di- and tri-valent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favourable biological properties such as biodegradability and non-toxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties.

XANTHUM GUM [16]
Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose- β-D-glucuronicacid-α-D-mannose attached with alternate glucose residues of the main chain. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.
CHITOSAN

Chitosan is a biodegradable, thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.

CARBOPOL

Carbopol is a well known pH dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution. Various water soluble polymers such as carbopol system, hydroxy propyl methyl cellulose system, poly (methylacrylic acid)-poly (ethylene glycol) come under the category of pH induced in-situ precipitating polymeric systems. Based on this concept, the formulation and evaluation of an ophthalmic delivery system for indomethacin for the treatment of uveitis was carried out. A sustained release of indomethacin was observed for a period of 8 h in vitro thus considering this system as an excellent candidate for ocular delivery.

PLURONIC F-127 [17]

Poloxamers or pluronic, marketed by BASF Corporation, are the series of commercially available difunctional triblock copolymers of non-ionic nature. They comprise of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide. Due to the PEO/PPO ration of 2:1, when these molecules are immersed into the aqueous solvents, they form micellar structures above critical micellar concentration. They are regarded as PEOPPO-PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω-hydroxypropoxy (oxyethylene) a poly (oxypropylene)-b-poly (oxyethylene) a block copolymer. The pluronic triblock copolymers are available in various grades differing in molecular weights and physical forms. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronics or Poloxamers also undergo in situ gelation by temperature change. They are triblock copolymers consisting of poly (oxyethylene) and poly (oxypropylene) units that undergo changes in solubility with change in environment temperature. Pluronic™ F127. A 25-40% aqueous solution of this material will gel at about body temperature, and drug release from such a gel occurs over a period of up to one week. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol-934 and hydroxy propyl methyl cellulose to ensure long residence time at the application site. Controlled release of drug was achieved in vitro indicating antimycotic efficacy of developed formulation for a longer period of time.

There are a number of synthetic and natural polymers which are used to increase the controlled and sustained release of the gel as defined in the table no.1.

<table>
<thead>
<tr>
<th>Table 1: Polymers used in in-situ gelling system [17, 18]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural polymers</td>
</tr>
<tr>
<td>Gelatin, Carrageenan, Gum copal, Sesbania gum, Gum damber, Tragacanth, Moi gum, Pectin, Na-algininate, Tara gum, Gellan gum, Hibiscus rosasinensis, Xanthum gum, Guar gum, Okra gum, Xyloglucan, Locust gum, Carbopol, Isapgulla (Psyllium), Pluronic F-127</td>
</tr>
<tr>
<td>Synthetic polymers</td>
</tr>
<tr>
<td>HPMC KAM, Polyvinyl ethers, HPMC K 15M, Esters and halides, Poly(methacrylic acid, HPMC K 100M, Poly(methacrylic acid (PMMA), Ethyl cellulose, Carbopol 934 p, Soda. Carboxy methyl cellulose, Poly-alkylene glycols, Polyvinyl alcohol, Polycarbonates, Polyamides, HEC, HPC</td>
</tr>
</tbody>
</table>

Synthetic polymers [18]

Synthetic polymers are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, requiring no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-co-glycolide), poly (decalactone), and poly-ε-caprolactone have been the subject of most extensive recent investigations. Various other polymers like triblock polymer systems composed of poly(D,L-lactide)-block poly(ethylene glycol), block poly(D,L-lactide), blends of low molecular weight poly(D,L-lactide) and poly(ε-caprolactone) are also in use. These polymers are mainly used for the injectable in situ formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven. Thermosetting systems are in the sol form when initially constituted, but upon heating, they set into their final shape. This sol-gel transition is known as curing. But if this cured polymer is heated further, it may lead to degradation of the polymer. Curing mainly involves the formation of covalent cross links between polymer chains to form a macromolecular network.

Thermosetting system using biodegradable copolymers of DL-lactide or L-lactide with ε-caprolactone for prosthetic implant and slow release drug delivery systems. This system is liquid outside the body and is capable of being injected by a syringe and needle and once inside the body, it gels. In situ precipitating polymeric systems, the polymer precipitation from solution may lead to gel formation in situ and this precipitation can be induced by change in temperature (thermosensitive systems), solvent removal or by
change in pH. An important example of thermosensitive polymer is poly-(N-isopropyl acrylamide), [poly (NIPAM)], which is used for the formation of in situ gels. It has lower critical solution temperature phase separation at about 32°C. The polymers such as poly (D-L lactide), poly (D-L-lactide-co-glycolide) and poly (DL-lactideo-ε-caprolactone) form solvent-removal precipitating polymeric systems.

IN SITU POLYMERIC DRUG DELIVERY SYSTEM: APPLICABILITY [19-22]

1. Oral drug delivery system:
   The pH-sensitive hydrogels have a potential use in site specific delivery of drugs to specific regions of the GI tract. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and insulin were investigated in order to develop a potential colon-specific drug delivery system. Hydrogels made of varying proportions of PAA derivatives and cross-linked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property. Developed formulations of gellan and sodium alginate both containing complexed Ca2+ ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. For the oral in situ gel delivery system pectin (water soluble so, no need to add organic solvent), xyloglucan & gellan gum natural polymers are used. Pectin formulation for sustained oral delivery of paracetamol has been reported.

2. Ocular drug delivery system:
   Conventional delivery systems often result in poor availability & therapeutic response because high tear fluid turns over & dynamics which cause rapid elimination of the drug from the eye so, to overcome the bioavailability problem ophthalmic in-situ gel was developed. Natural polymers like gellan gum, alginic acid & xyloglucan are most commonly used. Various compounds like antimicrobial agent, anti-inflammatory agent & autonomic drugs are used to relieve intra-ocular tension in glaucoma. To improve the bioavailability, viscosity enhancers such as Hydroxypropyl Methyl Cellulose, Carboxy Methyl Cellulose, Carbomers, Poly Vinyl alcohol used to increase the viscosity of formulation in order to prolong the precorneal residence time & improve the bioavailability, ease to manufacture. Penetration enhancer such as preservatives, chelating agent, surfactants are used to enhance corneal drug penetration.

3. Nasal drug delivery system:
   In nasal in-situ gel system gellan gum & xanthan gum are used as in-situ gel forming polymers. Momethasone furoate was evaluated for its efficacy for the treatment of allergic rhinitis. In-situ gel was found to inhibit the increase in nasal symptoms are compared to marketed preparation nosonex (Momethasone furoate suspension 0.05%). Animal study were conducted using allergic rhinitis model & effect of in-situ gel on antigen induced nasal symptoms in sensitizes rats was observed.

4. Rectal drug delivery system:
   In-situ gel possesses a potential application for rectal & vaginal route. Conventional suppositories often cause discomfort during insertion and sometimes they can migrate upwards to the colon that makes them possible for drug to undergo the first-pass effect. In-situ gelling liquid suppositories with gelation temperature at 30–36°C in which Poloxamer-407 or poloxamer-188 were used to confer the temperature-sensitive gelation property. For better therapeutic efficacy & patient compliance, mucoadhesive, thermo-sensitive, prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrins complex formulated for treatment of vaginitis. Ex.: Xyloglucan based thermo reversible gel for rectal drug delivery of Indomethacin. Administration of Indomethacin loaded xyloglucan based system to rabbit indicated broad drug absorption & a longer drug residence time as compared to that resulting after administration of commercial suppository.

5. Vaginal drug delivery system:
   The vagina, an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermo-plastic graft-copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins. Recently reported a mucoadhesive thermo-sensitive gel (combination of poloxamers and polycarbophil), which exhibited, increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

6. Injectable drug delivery system:
   In-situ forming Injectable drug delivery system, cross linking of hydrazide modified by aluronic acid with aldehyde modified version of cellulose derivatives such as CMC, MC and HPMC are used. The suitability of poloxamer gel alone or with the addition of hydroxyl propyl methylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran for epidural administration of drugs in vitro. The compact gel depot acted as the rate limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions. Thermoreversible gels mainly prepared from poloxamers are predominantly used. These in-situ forming gel were used for preventing postoperative peritoneal adhesion thus avoiding pelvic pain, bowel obstruction & infertility. For a better therapeutic efficacy & patient compliance, mucoadhesive, thermo-sensitive, prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrin complex was designed for treatment of virginity.
   - Pluronic F127 gels, which contained either insulin or insulin-PLGA nanoparticles, useful for the preparation of a controlled delivery system.
Poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone or a long acting single dose injection of lidocaine.

ReGel® (triblock copolymer PLGAPEGPLGA) was used as a drug delivery carrier for the continuous release of human insulin. Steady amounts of insulin secretion from the ReGel® formulations up to day 15 of the subcutaneous injections were achieved.

7. Dermal and Transdermal drug delivery system:

Thermally reversible gel of Pluronic-F127 was evaluated as vehicle for the percutaneous administration of Indomethacin. In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

IN-SITU POLYMERIC SYSTEMS: COMMERCIAL FORMULATIONS [22, 23-26]

Regel: depot-technology:

Regel is one of the Macromed's proprietary drug delivery system and based on triblock copolymer, composed of poly (lactide-co-glycolide)-poly (ethylene glycol)-poly (lactide-co-glycolide). It is a family of thermally reversible gelling polymers developed for parenteral delivery that offers a range of gelation temperature, degradation rates and release characteristics as a function of molecular weight, degree of hydrophobicity and polymer concentration. Following injection, the physical properties of polymer undergo a reversible phase change resulting in formation of a water insoluble, biodegradable gel depot.

Oncogel:

Oncogel is a frozen formulation of paclitaxel in Regel. It is a free flowing liquid below room temperature which upon injection forms a gel in situ in response to body temperature.

HGHD-1:

HGHD-1 is a novel injectable depot formulation of human growth hormone (hGH) utilizing Macromed's Regel drug delivery system for treatment of patients with hGH deficiency.

Timoptic-XE:

It is a timolol maleate ophthalmic gel formulation of Merck and Co. Inc., supplied as a sterile, isotonic, buffered, aqueous gel forming solution of timolol maleate. This formulation is available in two dosage strengths 0.25% and 0.5% in market. The pH of the solution is approximately 7.0, and the osmolarity is 260-330 mOsm. Each ml of Timoptic-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Inactive ingredients include gellan gum, tromethamine, mannitol, and water for injection and the pH may be adjusted to 5.5 to 7.5 with Hydrochloric Acid and/or Sodium Hydroxide. Dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure and reapplied to maintain anesthetic effect.

Cytorn:

This is one of the novel Macromed's products, is a peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy using Regel drug delivery system. It is a free flowing liquid below room temperature that instantly forms a gel depot upon injection from which the drug is released in a controlled manner. It enhances the immunological response by safely delivering four times the maximum tolerated dose allowed by conventional IL-2 therapy. It also activates the systemic antitumor immunity. Regel system stabilizes and releases IL-2 in its bioactive form. The release of drugs is controlled by the rate of diffusion from and degradation of the depot. These are easy to install at the same time improves ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular therapy.

Akten™:

Akten™ is an HPMC-based gel of lidocaine hydrochloride for ocular surface anesthesia, contains 35 mg of lidocaine hydrochloride (per ml) as the active ingredient and also contains Hypromellose, Sodium Chloride, and Purified Water as inactive ingredients. The pH may be adjusted to 5.5 to 7.5 with Hydrochloric Acid and/or Sodium Hydroxide. Dose of Akten™ is 2 drops applied to the ocular surface in the area of the planned procedure and reapplied to maintain anesthetic effect.

AzaSite:

Marketed product of InSite Vision. AzaSite is a topical sterile aqueous ophthalmic solution of azithromycin formulated in DuraSite (polycarbophil, edetate disodium, sodium chloride). The recommended initial dose of the drug is instill 1 drop in the affected eye(s) twice daily, 8-12 hrs apart for the first two days and then in still 1 drop in the affected eye (s) once daily for the next five days.

Pilopine HSi:

Pilopine HSi (pilocarpine hydrochloride ophthalmic gel) is a marketed product of Alcon Laboratories Inc., is a 4% sterile topical ophthalmic aqueous gel which contains more than 90% water and employs Carbopol-940 (to impart a high viscosity).
Virgan:

Virgan (ganciclovir) is an ophthalmic antiviral that is indicated for the treatment of acute herpetic keratitis. It contains carbomer-974. The recommended dosing regimen is 1 drop in the affected eye 5 times/day (approximately every 3 hours while awake) until the corneal ulcer heals, and then 1 drop 3 times/day for 7 days. The carbomers are polyacrylic acid derivatives that impart high viscosity to their aqueous solutions at neutral pH (above their pKa values).

IN SITU GELLING SYSTEM: EVALUATIONS [27, 28-30]

In-situ gel evaluated & characterized by the following parameters:

Clarity
The Formulated solution’s clarity determined by visual inspection under black & white Background.

Texture Analysis
The consistency, firmness & cohesiveness of in situ gel are assessed by using texture profile analyzer which mainly indicated gel strength & easiness in administration in vivo higher value of adhesiveness of gel are needed to maintain an intimate contact with mucus surface.

pH of Gel
pH is checked by using pH meter. The pH can be determined formulation is taken in beaker & 1ml NaOH added drop wise with continuous stirring.

Gelling Capacity
In-situ gel is mix with simulated tear fluid (in the proportion of 25:7 i.e. application volume 25μl & normal volume of tear fluid in eye is 7μl) to find out gelling capacity of ophthalmic product. The gelation assessed visually by noting the time for & time taken for dissolution of the formed gel.

Rheological Studies
The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling & after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.

Isotonicity Evaluation
Isotonicity is important characteristics of ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All ophthalmic preparation are subjected to isotonicity testing, science they exhibited good release characteristics & gelling capacity & the requisite velocity. Formulation mixed with few drops of blood & observed under microscope at 45x magnification & compared with standard marketed ophthalmic formulation.

Determination of drug content
Certain weight of formulation equivalent to an amount of drug has to be dissolved in a suitable medium, stirred for required time, filtered and analysed for drug content.

Swelling Studies
Swelling studies are conducted with a cell equipped with thermo jacket to maintain a constant temperature. The cell contains artificial tear fluid (composition-0.67g NaCl, 0.20g NaHCO3, 0.008g CaCl2.2H2O & distilled water q.s. to 100g). Swelling medium equilibrating at 370c one millilitre of formulated solution is placed in dialysis bag & put into the swelling medium. At specific time interval the bag is removed from the medium & weight is recorded. The swelling of the polymer gel as a function of time is determined by using the following relationship:

\[
\text{% St} = \left( \frac{W_t - W_0}{W_0} \right) \times 100
\]

Where,
- \( St \) = Swelling at time ‘t’.
- \( W_0 \) = Initial weight of gelling solution.
- \( W_t \) = Final weight of gel.

Drug polymer interaction study and thermal analysis
Interaction study can be performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric Analysis (TGA) can be conducted for in situ forming polymeric system to quantitate the percentage of water in hydrogel. Differential Scanning calorimetry (DSC) conducted to observe if there are any changes in thermograms as compared with pure active ingredients used for gelation.
Water uptake study

Once the 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 thus formed gel has to be noted. Again the gel has to be exposed to the medium/distilled water and the same process is repeated for every 30 min to note down the weights of the gel at each interval after removing the excess amount of medium/distilled water, using filter paper. The weight gain due to water uptake has to be noted from time to time. 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 formulations.

Tastical Analysis

Analysis of variance (ANOVA) is used the testing the difference between calculated parameters using SPSS statistical package. Statistical difference yielding P≤0.05 is considered. Duncan multiple comparison is applied when necessary to identify which of the individual formulations are significantly different.

High Performance Liquid Chromatography

The HPLC system is used in reversed phase mode. Analysis is performed on a Nova pack C18 packed column (150 mm length X 3.9 mm i.d).

Thermal Analysis

Thermo gravimetric analysis can be conducted for in situ forming polymeric system to quantitative the percentage of water in hydrogel. Different scanning calorimetry is used to observed, if there are many changes in thermograms as compared with pure ingredients used thus indicating the interaction.

In Vitro Drug Release Studies

In vitro release study of in situ gel solution is carried out by using Franz diffusion cell. The formulation is placed in donor compartment & freshly prepared simulated tear fluid in receptor compartment. Between receptor & donor compartment dialysis membrane is placed (0.22 μm pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37±0.5°C. 1ml sample is withdrawn at predetermined time interval of 1hr for 6hrs the sample volume of fresh medium is replaced. The withdrawn sample is diluted to 10ml in volumetric flask with respective solvent & analyzed by UV spectrophotometer at respective nm using reagent blank. The drug content calculated using an equation generated from standard calibration curve. The percentage cumulative drug release (% CDR) calculated. The obtained data is further subjected to curve fitting for drug release data. The best fit model is checked for Krosmeyers peppas & Fickinian diffusion mechanism for their kinetics.

Ocular Irritancy Studies

Ocular irritancy studies are performed on male albino rabbits, weighing 1-2 kg. The modified Draize technique is used for ocular irritation potential of ophthalmic products. The formulation is placed in lower cul-de-sac & irritancy is tested at time interval of 1hr, 2hrs, 48hrs, 72hrs, & 1 week after administration. The rabbits are observed periodically for redness, swelling & watering of eyes.

Antimicrobial Activity

Antimicrobial efficacy studies are carried out to ascertain the biological activity of sol-gel-system against microorganisms. This is determined in agar diffusion medium employing ‘Cup Plate Techniques’. The microbial growth of bacteria is measured by conc. Of antibiotic & compared with that produced by known conc. Of standard preparation of antibiotic & carried out the microbial assay serial dilution method is employed.

Sterility Testing

Sterility testing is carried out as per the IP 1996. The formulation is incubating for not less than 14 days at 300-350c in the fluid thioglycolate medium to find the growth of bacteria & at 200-250 c in Soya bean casein digest medium to find the growth of fungi in formulation.

Accelerated Stability Studies

Formulation is replaced in amber colours vials & sealed with aluminium foil for the short term accelerated stability study at 40± 20 c & 75 ±5% RH as per International Conference of Harmonization (ICH) State Guidelines. Sample is analyzed at every month for clarity, pH, gelling capacity, drug content, rheological evaluation & in vitro dissolution.

Histopathological studies

Two mucosa tissue pieces (3 cm2) were mounted on in vitro diffusion cells. One mucosa was used as control (0.6 ml water) and the other was processed with 0.6 ml of optimized organogel (conditions similar to in vitro diffusion). The mucosa tissues were fixed in 10% neutral carbonate formalin (24 hours), and the vertical sections were dehydrated using graded solutions of ethanol. The subdivided tissues were stained with hematoxylin and eosin. The sections under microscope were photographed at original magnification ×100. The microscopic observations indicate that the organogel has no significant effect on the microscopic structure of
the mucosa. The surface epithelium lining and the granular cellular structure of the nasal mucosa were totally intact. No major changes in the ultra-structure of mucosa morphology could be seen and the epithelial cells appeared mostly unchanged.

RECENT RESEARCHES IN IN-SITU GEL DRUG DELIVERY SYSTEMS

Stubbing et al investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate) based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm² were investigated regarding drug release in 0.1 mol. litres HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, bench top MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm² SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. [31] The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Jang et al has prepared a gastro-retentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA- 6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizer and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastro-protective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Rajinikanth and Mishra have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionised water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti-H. Pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of H. pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. Pylori. [32]

One of the challenges facing today's pharmaceutical industry centers on coming up with efficient treatment options that are readily acceptable to physicians and patients. Delivery systems must also contribute to a better therapeutic outcome if they are going to provide viable alternatives to pharmaceuticals currently delivered by other routes. In situ gel formulations are one of the challenging drug delivery systems. Various biodegradable polymers are used for formulation of in situ gels, but there are fabrication problems, difficult processability, and use of organic solvents for their preparation (especially for synthetic polymer based systems), burst effect and irreproducible drug release kinetics. Natural polymers satisfy the characteristics of an ideal polymer but batch to batch reproducibility is difficult therefore synthetic polymers are used.

The recent advancement of biotechnologies has led to the development of labile macromolecular therapeutic agents that require complex formulations for their efficient administration N-stearoyl L-alanine (m) ethyl esters when mixed with a vegetable oil and a biocompatible hydrophilic solvent led to the formation of injectable, in situ forming organogel. [33]

CONCLUSION

Nowadays, in situ gelling system has become the alternative of conventional dosage form because of its controlled drug release, use of water soluble and biodegradable polymers, biocompatibility and better patient compliance by reducing dosing frequency. In-situ drug delivery provides a great potential for development of liquid orals for their sustained drug release. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. In situ gelling system also becomes convenient for pediatric and geriatric patient. The utility of in situ gelling system in drug delivery and biomedical application is massive. Different types of functional polymers have been investigated for series of drugs in vitro or in vivo. These polymers have been widely investigated as a drug carrier for many possible routes of administration because of their favorable biological properties, such as non-toxicity, biocompatibility, biodegradability, and antibacterial characteristics. The Captivative properties of the polymers seem promising in many future applications and offer possible use as the next generation of materials in biological, biomedical and pharmaceutical products. This floating in-situ gel approach is suitable for drugs having absorption window in stomach or drugs showing local effect in stomach. These types of drugs which are currently present in market as their solid dosage forms will be available as their floating-insitu-gel-in-recent-future.
REFERENCES


12) Sterile ophthalmic gel forming solution, Timoptic-XE. 0.25% and 0.5%, (Timolol maleate ophthalmic gel forming solution), Merck and Company Inc. NJ 08889: Whitehouse Station, USA.


