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ADVANCES IN INSITU GELLING SYSTEM: A REVIEW

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ABSTRACT
Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. 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. Mainly in situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. The in situ gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. The article presents a detailed review of these types of polymeric systems, their evaluation, advancements and their commercial formulations. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing cost.

KEYWORDS: *Biodegradable polymers, controlled release, in situ gels, poly (lactic-co-glycolic acid), sustained release, ocular, controlled drug delivery systems.*

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INTRODUCTION

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. The goal in designing these 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.

Extensive research has been carried in designing of polymeric drug delivery systems. The development of in situ gel systems has received considerable attention over the past few years[1]. This interest has been sparked by the advantages shown by in

situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort [2]. In the past few years, increasing number of in situ gel forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered [3]. 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. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems.

This review attempts to discuss the newer developments and strategies for this drug delivery including physiological factors, physiochemical factors and formulation factors to be considered in the development of in-situ drug delivery system. Also, different types of smart polymers, their mechanisms of gel formation from the sol forms, evaluation and characterization of in situ polymeric formulations are discussed.

METHOD OF PREPARATION

Several techniques have been reported for the synthesis of hydrogels. The first approach involves co-polymerization/cross-linking of co-monomers using multifunctional co-monomer, which acts as cross-linking agent. The polymerization reaction is initiated by chemical initiator. The polymerization reaction can be carried out in bulk, in solution, or in suspension. The second method involves cross linking of linear polymers by irradiation, or by chemical compounds. The monomers used in the preparation of ionic polymer network contain an ionizable group, a group that can be ionized or a group that can undergo a substitution reaction after polymerization is completed. As a result, hydrogels synthesized contains weakly acidic group like carboxylic acid, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids or quaternary ammonium compounds. Some of commonly used cross-linking agents include N, N '– methylenebisacrylamide, divinyl benzene and ethylene glycol dimethacrylate.

1. Solution Polymerization/Cross-linking
2. Suspension Polymerization
3. Polymerization by Irradiation
4. Chemically Cross-linking Hydrogels
5. Physically Cross-linked Hydrogels [4].

CLASSIFICATION OF POLYMERS

Pectin

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α--1-4--Dgalacturonic acid residue. Low methoxypectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium 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 [5].

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose [6]. 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.

Gellangum

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 [7]. It has the tendency of gelation which is temperature dependent or cations induced.

Alginic acid

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 trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain [8].

Xanthum gum

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 glucuronicacid and pyruvic acid groups in the side chain [9].

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 [10]. 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 [11].

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 (methacrylic acid)-poly (ethylene glycol) come under the category of pH-induced in-situ precipitating polymeric systems [12].

Pluronic F-127

Poloxamer 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 [13]. Depending upon the physical designation for the grades are assigned, as F for flakes, P for paste, L for liquid. Pluronic or Poloxamer also undergo in situ gelation by temperature change [14]. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxypropylmethylcellulose 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 [15].

Synthetic polymers

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- coglycolide), Poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations. 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- coglycolide), Poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations.

A. In situ hydrogels

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical cross-linking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility [16].

B. Smart hydrogels

Smart hydrogels, or stimuli-sensitive hydrogels, are very different from inert hydrogels in that they can sense changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume-changing behavior of smart hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes.

CLASSIFICATION

Insitu gel forming systems have been classified in two categories as below:

1. **Based on mechanism of gelation**
   - Physiological stimuli
   - Physical mechanism
   - Chemical reactions
   - Photo-initiated polymerization

2. Based on route of administration

- Insitu forming polymeric systems for oral administration
- Insitu forming polymeric systems for ocular administration
- Insitu forming polymeric systems for recta and vaginal delivery
- Insitu forming injectable drug delivery systems
- Insitu forming nasal drug delivery systems
- Insitu forming transdermal drug delivery systems

BASED ON MECHANISM OF GELATION

IN SITU FORMATION BASED ON PHYSIOLOGICAL STIMULI

Thermally trigged system

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research [17]. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is fascinated and no external source of heat other than that of body is required for trigger gelation. A useful system should be optimize to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity. Three main strategies are exists in engineering of thermo responsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive, and thermally reversible gels.

pH triggered systems

Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH change[17]. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH .The polymers with a large number of ionizable groups are known as polyelectrolytes. 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[18]. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives[19]. Likewise polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition[20].

IN SITU FORMATION BASED ON PHYSICAL MECHANISM

Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space[21]. One such substance is Myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some Bioadhesive properties and can be degraded invivo by enzymatic action[22].

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-Methyl Pyrrolidone (NMP) has been shown to be useful solvent for such system[23].

IN SITU FORMATION BASED ON CHEMICAL REACTIONS

Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

Ionic Cross-linking

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones[24]. While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, i-carrageenan forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+.

Enzymatic Cross-Linking

In situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

PHOTO-POLYMERISATION

Photo-polymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo-polymerization in the presence of suitable photo initiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful.

BASED ON ROUTE OF ADMINISTRATION

Depending on the route of administration, these in situ polymeric systems may be classified as illustrated in following sections.

INSITU FORMING POLYMERIC SYSTEMS FOR ORAL ADMINISTRATION

Pectin, xyloglucan and gellan gum are the natural polymers used for in situ forming oral drug delivery systems. Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-D-galacturonic acid residues[25]. Low methoxypectins (degree of esterification <50%) readily form gels in aqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model[26]. 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 potential of an orally administered in situ gelling pectin formulation for the sustained delivery of paracetamol has been reported. 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 [26]. 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 the stomach.

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. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains [27]. The sol-gel transition temperature varies with the degree of galactose elimination. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery [28-32]. 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. In situ gelling gellan formulation as vehicle for oral delivery of Theophylline is reported [33]. The formulation consisted 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. An increased bioavailability with sustained drug release profile of Theophylline in rats and rabbits was observed from gellan formulations as compared to the commercial sustained release liquid dosage form.

INSITU FORMING POLYMERIC SYSTEMS FOR OCULAR ADMINISTRATION

For in situ gels based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. Local ophthalmic drug delivery has been used for various compounds such as antimicrobial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over and dynamics cause rapid elimination of the drug from the eyes [34, 35]. So, to overcome bioavailability problems, ophthalmic in situ gels were developed [36]. Aqueous solution of gellan dropped into the eye undergoes transition into the gel state due to the temperature and ionic condition (Ca^{++}) in the tear fluid [37]. Much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery [38-40]. Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops.

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 trivalent 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 favorable biological properties such as biodegradability and non-toxicity[43, 44]. 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[41, 42].

INSITU FORMING POLYMERIC SYSTEMS FOR RECTAL AND VAGINAL DELIVERY SYSTEMS

In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Miyazaki et al. investigated the use of xyloglucan based thermoreversible gels for rectal drug delivery of indomethacin. Administration of indomethacin loaded xyloglucan based systems to rabbits indicated broad drug absorption peak and a longer drug residence time as compared to that resulting after the administration of commercial suppository. For a better therapeutic efficacy and patient compliance, mucoadhesive, thermosensitive, prolonged release vaginal gel incorporating Clotrimazole-β-cyclodextrin complex was formulated for the treatment of vaginitis[45]. In addition, a significant reduction of drug C-max was observed after administration of in situ polymeric system thus indicating the avoidance of adverse effects of indomethacin on nervous system [46].

INSITU FORMING INJECTABLE DRUG DELIVERY SYSTEMS

The development of injectable in-situ forming drug delivery systems has received a considerable interest over the last decade. A novel, injectable,

thermosensitive in situ gelling hydrogel was developed for tumor treatment. Chitosan is a biodegradable, thermosensitive, poly-cationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell[47]. 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 main problem with chitosan is its non-biodegradability. 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. This transformation has solved the non-biodegradability problem of chitosan.

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), poly ε-caprolactone have been the subject of the most extensive recent investigations [30]. Various polymers like triblock polymer systems composed of poly(D,L-lactide)-block-poly(ethylene glycol)-block-poly(DL-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.

A pH induced in situ precipitating polymeric system (an aqueous solution of carbopol-HPMC system) was designed and developed for plasmid DNA delivery[48]. Mixture of poly (methacrylic acid) and poly (ethylene glycol) dissolved in NMP-ethanol-buffer (1:1:2) was also tried out as polymeric system. It was found that physical stability of pDNA from these systems was not maintained. A high burst effect was also observed with this polymeric system. The reason for less release or no release after burst effect may be attributed to strong interaction between pDNA and polymers used. The removal of the ethanol from the delivery system would have led to a significant reduction in the volume of system thus causing the burst effect.

INSITU FORMING NASAL DRUG DELIVERY SYSTEMS

An in-situ gel system for nasal delivery of Mometasone furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis[49]. Gellan gum and xanthan gum were used as in situ gel forming polymers. Animal studies were conducted using an allergic rhinitis model and the effect of in situ gel on antigen induced nasal symptoms in sensitized rats was observed. In-situ gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation Nasonex (Mometasone furoate suspension 0.05%). Intact ciliated respiratory epithelium and normal goblet cell appearance indicated from histopathology of rat nasal cavity proved that these formulations were safe for nasal administration. Thermosensitive hydrogel by simply mixing N-[(2-hydroxy-3- methyltrimethylammonium) propyl]chitosan chloride and poly (ethylene glycol) with a small amount of α-β- glycerophosphate; for nasal delivery of insulin. The formulation was in solution form at room temperature that transformed to a gel form when kept at 37^{o}c. Animal experiments demonstrated hydrogel formulation to decrease the blood-glucose concentration by 40-50% of the initial values for 4-5 h after administration with no apparent cytotoxicity. Therefore, these types of systems are suitable for protein and peptide drug delivery through nasal route[50].

INSITU FORMING DERMAL AND TRANSDERMAL DELIVERY SYSTEMS

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 [51]. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

Recent developments of the hydrogels based formulations using respective drug and polymers are given below in table 1.

TABLE.1 RECENT DEVELOPMENTS OF THE HYDROGELS BASED FORMULATIONS

DRUG	POLYMER	MECHANISM OF GELATION
Pefloxacin mesylate	Gelrite gellan gum	Ion
Gatifloxacin	Alginate and HPMC	Ion
Indomethacin	Gelrite (gellan gum)	Ion
Ciprofloxacin HCL	Gelrite gellan gum and sodium alginate	Ion
Timolol maleate	Gellan gum	Ion
Ofloxacin	Carbopol 940 and HPMC	pH
Puerarin	Carbopol/HPMC-based gel	pH
Puerarin	Poloxamer analogs/carbopol	pH
Fluconazole	In-situ gelling eye drops	---
Ganciclovir	In-situ gelling eye drops	---
Timolol maleate	Pluronic F127	Temperature
Timolol maleate	poly(Nisopropylacrylamide)-chitosan	Temperature
Pilocarpine	Alginate and Pluronic-based in situ gelling	Ion and temperature
Timolol maleate	Pluronic F-127 and chitosan	pH and temperature
Gatifloxacin	Pluronic F127-g-poly(acrylic acid) copolymers	pH and temperature
Pilocarpine	Xyloglucan	Temperature

EVALUATION AND CHARACTERIZATIONS OF IN SITU GEL SYSTEM

In situ gels may be evaluated and characterized for the following parameters;

Clarity

The clarity of formulations determined by visual inspection under black and white background.

Texture analysis

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringeability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surfaces like tissues[52].

Sol-Gel transition temperature and gelling time

For in situ gel forming systems incorporating thermoreversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first detection of gelation as defined above.

Gel-Strength

This parameter can be evaluated using a Rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface [46].

Viscosity and rheology

This is an important parameter for the in situ gels, to be evaluated. The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid (depending upon the route of administrations)

instead of 5% Mannitol, were determined with Brookfield Rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by the patient, especially during parenteral and ocular administration [53].

Fourier transform infra-red spectroscopy and thermal analysis

During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide pellet method. Thermo gravimetric analysis can be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. Differential scanning Calorimetry is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions [53].

In-vitro drug release studies

For the in situ gel formulations to be administered by oral, ocular or rectal routes, the drug release studies are carried out by using the plastic dialysis cell .The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analyzed for the drug release using analytical technique. For injectable in situ gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed [54].

Histo-pathological 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 [54].

COMMERCIAL FORMULATIONS OF INSITU POLYMERIC SYSTEMS AT A GLANCE

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 preservative used is benzododecinium bromide 0.012%. Timoptic-XE, when applied topically on the eye, reduces the elevated, as well as normal intraocular pressure, whether or not accompanied by glaucoma[55].

Regal depot technology

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

body temperature. hGHD-1 is a novel injectable depot formulation of human growth hormone (hGH) utilizing Macromed's Regal drug delivery system for treatment of patients with hGH deficiency[56].

Cytoryn

This is one of the Macromed's products, which is a novel, peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy using regal 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. Cytoryn enhances the immunological response by safely delivering four times the maximum tolerated dose allowed by conventional IL-2 therapy. Cytoryn also activates the systemic antitumor immunity. Regal 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 [57, 58].

CONCLUSION

In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the in situ gels offer. Exploitation of polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

REFERENCES

1. Peppas NA, Langer R. New challenges in biomaterials. Science. 1994; 263:1715–20.
2. Zhidong L, Jaiwei L, Shufang N, Hui L, Pingtian D, Weisan P. Study of an alginate/HPMC based in situ gelling ophthalmic delivery system for Gatifloxacin. Int J Pharm. 2006; 315:12–7.
3. Al-Tahami K, Singh J. Smart polymer based delivery systems for peptides and proteins. Recent Pat Drug Deliv Formul. 2007; 1:66–71.
4. Vyas jigar, ghedia vishal, Christian vishal, upadhyay umesh, a review on novel in situ polymeric drug delivery system; IJPRD, 2O11; 5(3), 53-9.
5. Miyazaki S, Suisha F, Kawasaki N., Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Rel 1998; 56:75-83.
6. Miyazaki S, Hirotatsu A, Kawasaki N, Wataru K, Attwood D., In situ gelling gellan formulations as vehicles for oral drug delivery. J Control Rel 1999; 60:287-95.
7. Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C., A new long acting ophthalmic formulation of carteolol containing Alginic acid. Int J Pharm 2000; 207:109-16.
8. Al-Shamklani A, Bhakoo M, Tuboku MA, Duncan R., Evaluation of the biological properties of alginates and gellan and xanthan gum. Proc Int Symp Control Release Bioact Mater 1991; 18:213-4.
9. Hatefi A, Amsden B., Biodegradable injectable in situ forming drug delivery systems. J Control Release 2002; 80:9-28.
10. Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD et al., Novel injectable solution of chitosan form biodegradable gels in situ. Biomaterials 2000; 2:2155-61.
11. Ismail FA, Napaporn J, Hughes JA, Brazean GA., In situ gel formulation for gene delivery: release and myotoxicity studies. Pharm Dev Technol 2000;5:391-7.
12. Schmolka IR. Artificial skin, Preparation and properties of pluronic F127 gels for the treatment of burns. J. Biomed. Mater. Res. 1972;6:571-582.
13. Kabanov A, Batraoka E, Alakhov V., Pluronic block copolymers as novel polymer therapeutics for oral and gene delivery. J. Control. Rel. 2002;82:189-212.
14. Alexandridis P, Hatton TA., Poly (ethylene oxide)- poly (propylene oxide)-poly (ethylene oxide) block copolymer surfactants in aqueous solutions and interfaces: thermodynamics,

structure, dynamics and modeling. Colloid Surfaces 1995; A96:146.
15. Nirmal H.B., Bakliwal S.R., Pawar S.P., In-Situ gel: New trends in Controlled and Sustained Drug Delivery System. International Journal of PharmTech Research 2010; 2(2): 1398-408.
16. Qiu Y, Park K., Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev 2001;53: 321-39.
17. Soppimath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski WE., Stimulus-responsive "smart" hydrogels as novel drug delivery systems. Drug Dev Ind Pharm 2002;28: 957-74.
18. Aikawa K, Mitsutake A, Uda H, Tanaka S, Shimamura H, Aramaki Y, et al., Drug release from pH-response polyvinylacetal diethyl aminoacetate hydrogel, and application to nasal delivery. Int J Pharm 1998;168:181-8.
19. Esposito E, Carratto V & et al., Comparative analysis of tetracycline containing dental gels; poloxomers and mono-glycerides based formulation . Int.J.Pharm.1996;142:9-23.
20. Geraghaty P,Attwood D, et al., An investigation of parameters influencing the Bioadhesive properties of Myverol 18-99/ water gels.Biomaterials 1997, 18:63-7.
21. Motto F, Gailloud P, et al., In-vitro assessment of new embolic liquids prepared from preformed polymers and water miscible solvents aneurysm treatment. Biomaterials 2000,21:803-11.
22. Bhardwaj TR, Kanwar M, Lal R, Gupta A., Natural gums and modified natural gums as sustainedrelease carriers. Drug Devel Ind Pharm 2000;26:1025-38.
23. Meqi SA, Deshpande SG., Ocular drug delivery: Controlled and novel drug delivery. New delhi:CBS Publishers; 2002; 82-84.
24. Eva M, Amo D, Urtti A., Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov Today 2004; 13:135-143.
25. Wataru K, Yasuhiro K, Miyazaki S, Attwood D. In situ gelling pectin formulations for oral sustained delivery of paracetamol. Drug Develop Ind Pharm. 2004;30:593–9.
26. Dumitriu S, Vidal PF, Chornet E. Hydrogels based on polysaccharides. In: Dumitriu S, editor.Polysaccharides in medical applications. New York: Marcel Dekker Inc; 1996. pp. 125–242.
27. Ni Y, Kenneth MY. In-situ gel formation of pectin. United States Patent. 2004. 6777000.
28. Miyazaki S, Kawasaki N. Comparison of in situ gelling formulations for the oral delivery of cimetidine. Int J Pharm. 2001;220:161–8.
29. Kawasaki N, Ohkura R, Miyazaki S, Uno Y, Sugimoto S, Attwood D. Thermally reversible xyloglucan gels as vehicles for oral drug delivery. Int J Pharm. 1999;181:227–34.
30. Suisha F, Kawasaki N, Miyazaki S, Shirakawa M, Yamotoya K, Sasaki M, et al. Xyloglucan gels as sustained release vehicles for intraperitoneal administration of mitomycin C. Int J Pharm. 1998;172:27–32.
31. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int J Pharm.2001;229:29–36.
32. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Rel. 1998;56:75–83.
33. Miyazaki S, Hirotatsu A, Kawasaki N, Wataru K, Attwood D. In situ gelling gellan formulations as vehicles for oral drug delivery. J Control Rel. 1999;60:287–95.
34. Mikkelson TJ. Ophthalmic drug delivery. Pharm Tech. 1984;8:90–8.
35. Schoenwald RD. Ocular drug delivery: Pharmacokinetic considerations. Clin Pharmacokinet.1990;18:255–69.
36. Patton TF, Robinson JR. Ocular evaluation of poly vinyl alcohol vehicle in rabbits. J Pharm Sci.1975;64:1312–6.
37. Choenwald RD, Ward RL, De Santis LM, Roehrs RE. Influence of high viscosity vehicles on miotic effects of pilocarpine. J Pharm Sci. 1978;67:1280–3.
38. Rozier A, Mazuel C, Grove J, Plazonnet B. Gelrite: A novel, ion activated, In situ gelling polymer for ophthalmic vehicles: Effect on

bioavailability of Timolol. Int J Pharm. 1989;57:163–8.
39. Rozier A, Mazuel C, Grove J, Plazonnet B. Functionality testing of gellan gum, a polymeric excipient material for ophthalmic dosage forms. Int J Pharm. 1997;153:191–8.
40. Sanzgiri YD, Maschi S, Crescenzi V, Callegaro L, Topp EM, Stella VJ. Gellan based systems for ophthalmic sustained delivery of methylprednisolone. J Control Rel. 1993;26:195–201.
41. Sechoy O, Tissie G, Sebastian C, Maurin F, Driot JY, Trinquand C. A new long acting ophthalmic formulation of carteolol containing Alginic acid. Int J Pharm. 2000;207:109–16.
42. Shamklani A, Bhakoo M, Tuboku MA, Duncan R. Evaluation of the biological properties of alginates and gellan and xanthan gum. Proc Int Symp Control Release Bioact Mater. 1991;18:213–4.
43. Smart JD, Kellaway IW, Worthington HE. An in vivo investigation of mucosa adhesive materials for use in controlled drug delivery. J Pharm Pharmacol. 1984;36:259–99.
44. Fuongfuchat A, Jamieson AM, Blackwell J, Gerken TA. Rheological studies of interaction of mucins with alginates and polyacrylate. Carbohyd Res. 1996;284:85–99.
45. Bilensoy E, Rouf MA, Imran V, Murat S, Hincal AA. Mucoadhesive thermosensitive prolonged release vaginal gel for clotrimazole: β-cyclodextrin complex. AAPS Pharm Sci Tech 2006;7:38.
46. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Rel 1998;56:75-83.
47. Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. J Control Release. 2002;80:9–28
48. Ismail FA, Napaporn J, Hughes JA, Brazean GA. In situ gel formulation for gene delivery: release and myotoxicity studies. Pharm Dev Technol. 2000;5:391–7.
49. Cao S, Ren X, Zhang Q, Chen E, Xu F, Chen J, et al. In situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate. Int J Pharm 2009;365:109-15.
50. Wu J, Wei W, Wang LY, Su ZG, Ma G. A thermosensitive hydrogel based on quaternized chitosan and poly (ethylene glycol) for nasal delivery system. Biomaterials 2007;28:2220-32.
51. Pillai O, Panchagnula R. Transdermal delivery of insulin from poloxamer gel: ex vivo and in vivo skin permeation studies in rat using iontophoresis and chemical enhancers. J Control Release 2003;89:127-40.
52. Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar MNV. Design and evaluation of biodegradable, biosensitive in situ gelling systems for pulsatile delivery of insulin.Biomaterials 2007; 28:2051-60.
53. Chandrashekhar G, Udupa N. Biodegradable injectable implant system for long term drug delivery using poly (lactic-co-glycolic) acid copolymers. J Pharm Pharmacol 1998; 48:669-74.
54. Sambhaji Pisal,1 Vijay Shelke, et al., Effect of Organogel Components on In Vitro Nasal Delivery of Propranolol Hydrochloride, AAPS PharmSciTech 2004; 5 :4,63
55. Sterile ophthalmic gel forming solution, Timoptic-XE®, 0.25% and 0.5%, (Timolol maleate ophthalmic gel forming solution) Whitehouse Station, USA: Merck and Company Inc.; NJ 08889.
56. Ramesh CR, Zentner GM, Jeong B. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co- glycolide) polyethylene glycol copolymers having reverse thermal gelation properties.US patent. 2001. 6201072.
57. Rathi R, Zentner C, Gaylen M, Jeong B. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co-glycolide) polyethylene glycol copolymers having reverse thermal gelation properties. US patent. 2000. 6117949.
58. Rathi R, Zentner C, Gaylen M. Macro med, Inc. Biodegradable low molecular weight triblock poly (lactide-co-glycolide) polyethylene glycol copolymers having reverse thermal gelation properties. US patent. 1999. 6004573.

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