Available online through

www.jbsoweb.com

Review Article

A REVIEW ON POLYMERS USED IN NOVEL IN SITU GEL FORMULATION FOR OCULAR DRUG DELIVERY AND THEIR EVALUATION

Sonawane Swapnil D.[1]*, Patil Ravindra Y[2], Lad Meenal[3]

[1]PhD Scholar at Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan, India

[2]Shankarro Ursal Collage of Pharmaceutical Science and Research Centre, Kharadi, Pune, India

[3]Dept. of Dravyaguna and Research Methodology, P.D.E.A.'s Collage of Ayurveda and Research Centre, Akurdi, Pune, India

***Correspondence**

Sonawane Swapnil D

PhD Scholar at Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan, India

DOI: 10.7897/2321-6328.01221

Article Received on: 09/06/13

Accepted on: 16/08/13

Abstract

Ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientists, the major problem encountered to pharmaceutical scientist is rapid precorneal elimination of the drug, resulting in poor bioavailability and therapeutic response, because of high tear fluid turn over and dynamics. Newer research in ophthalmic drug delivery system is directed towards amalgamation of several drug delivery technologies which helps to extend the contact of the vehicle at the surface of the ocular system and slows down the removal of the drug. In situ-forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and these gels provide a response to environmental changes. In the past few years, an impressive number of novel temperature, pH, and ion induced in situ forming systems have been reported for sustained ophthalmic drug delivery. This review includes polymeric systems used in various temperatures, pH, and ion induced in situ gel formulation to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

Keywords: In-situ gels, pH dependent, temperature dependent, ion triggered.

INTRODUCTION

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. Amongst the 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. 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. This interest has been sparked by the advantages shown by in situ forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort[1]. In situ gel 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[2]. This novel drug delivery system promotes the importantly ease and convenience of administration, delivery 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[3]. Smart polymeric systems represent promising means of delivering the drugs. These polymers undergo sol-gel transition, once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems[4]. 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.

Approaches of in situ Gel Drug Delivery

There are four broadly defined mechanisms used for triggering the in situ gel formation of biomaterials:

1. Physiological stimuli (e.g., Temperature and pH),
2. physical changes in biomaterials (e.g., solvent exchange and swelling),
3. Chemical reactions (e.g. Enzymatic, chemical)
4. Photo-initiated polymerization.

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[5]. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way toapproach in situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A

useful system should be tailorable 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 exist in engineering of thermo responsive sol-gel polymeric system. For convenience, temperature sensitive hydrogels are classified into negatively thermo sensitive, positively thermo sensitive and thermally reversible gels. Negative temperature sensitive hydro gels have a lower critical solution temperature (LCST) and they contract upon heating above the LCST. Polymers with low criticalsolution temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. One of the most extensively investigated polymers that exhibit useful LCST transition is poly (N-isopropylacrylamide) (PNIPAAm). PNIPAAm is a water soluble polymer at its low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST. Pluronics are poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPOPEO) triblock co-polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequences of a disorder-order transition in micelle packing which makes these polymers suitable for in situ gelation[6]. A positive temperature sensitive hydro gel 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 (acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling[7]. The most commonly used thermoreversible gels are these prepared from poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (Pluronics®, Tetronics®, poloxamer). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature[8]. Cappello *et al*. developed novel "protein polymers" ProLastins, which undergo an irreversible sol gel transition. When injected as a solution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months. Such a system would be easy to administer into desired body cavity[9].

pH Triggered Systems

Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH changes. 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 ionisable groups are known as polyelectrolytes. Swelling of hydro gel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives[10]. Likewise polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition[11]. Drug formulated in liquid solutions have several limitations, including limited bioavailability and propensity to be easily removed by tear fluid. Kumar and Himmelstein sought to minimize these factors and maximize this drug delivery by making a poly (acrylic acid) (PAA) solution that would be gel at pH 7.4. The author found that at concentrations high enough to cause gelation, however, the low pH of PAA solution would cause damage to surface of eye before being neutralized by the lacrimal fluid. This problem was solved partially by combining PAA with HPMC, a viscosity enhancing polymer, which resulted in pH responsive polymer mixtures that was sol at pH 4 and gel at pH 7.4[12]. Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also have been used as a pH sensitive system to achieve gelation[13].

In Situ Formation Based on Physical Mechanism Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to acquire desired space[14]. 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 bio-adhesive properties and can be degraded in vivo by enzymaticaction[15].

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 pyrolidone (NMP) has been shown to be useful solvent for such system[16].

In Situ Formation Based on Chemical Reactions

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

Ionic Crosslinking

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones[17]. While k-carrageenan forms rigid, brittle gels in reply of small amount of K^+, i-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono and divalent cations, including Ca^{2+}, Mg^{2+}, K^+ and Na^+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent / polyvalent cations example Ca^{2+} due to the interaction with guluronic acid block in alginate chains[18].

Enzymatic Cross-Linking

In situ formation catalysed 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. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation[19].

Photo-Polymerisation

Photo-polymerisation 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 monomersand macromers because they rapidly undergo photo-polymerisation 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. A ketone, such as 2, 2 dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo- polymerization, whereas camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be designed readily to be degraded by chemical orenzymatic processes or can be designed for long term persistence *in vivo*[20]. Photopolymerizable systems when introduced to the desired site via injection get photo cured in situ with the help of fibre optic cables and then release the drug for prolonged period of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes eadingto an implant formation. A photopolymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported by Sawhney *et al*[21].

Classifications of in situ Polymericsystems

Pectin

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-dgalacturonic acid residues. Low methoxy pectin's (degree of esterification < 50 %) readily form gels inaqueous solution in the presence of free calcium ions, which crosslink the galacturonic acid chains in amanner 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[22]. The main advantage ofusing 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 complex form may be included in the formulation for the induction of pectin gelation[23]. 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[24,25].

Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbonechain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose[26]. 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[27]. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery[28,29]. Gellan gum (commercially available as Gelrite TM) is an ionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with atetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues[30]. 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[31]. The formulation consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ionsare released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ[32]. In situ gelling gellan formulation as vehicle for oral deliveryof theophylline is reported.

Alginic Acid

Alginic acid is a linear block copolymerpolysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidiclinkages. 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 diandtrivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-Lglucuronic acid blocks of the alginate chain[33]. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favourable biological properties such as biodegradability and nontoxicity. 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[34].

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 glucuronic acid and pyruvic acid groups in the side chain[35].

Chitosan

Chitosan is a biodegradable, thermo sensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component ofshrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2[36]. 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 asglycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution[37].

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 hydroxyl propylmethyl cellulose system, poly (methacrylic 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. A pH induced in situ precipitating polymeric system (an aqueous solution ofcarbopol-HPMC system) was designed and developed by Ismail *et al*. for plasmid DNA delivery[38].

Pluronic F-127

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 polyethylene oxide[39]. 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 PEO-PPO-PEO copolymers. Chemically they are oxirane, methyl-polymer with oxirane or α-Hydro-ω-hydroxyl poly (oxyethylene) a poly (oxypropylene) 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 insolubility with change in environment temperature. Pluronic™ F 127. 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[40]. Pluronic F-127 was used as an in situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxylpropylmethyl 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[41,42].

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-caprolactonehave 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) and poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations. Various other polymers like triblock polymer systems composed of poly (D,L-lactide)-block-poly (ethyleneglycol)-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. The feasibility of lactide / glycolide polymers as excipients for the controlled release of bioactive agents is well proven. These materials have been subjected to extensive animal and human trials without evidence of any harmful side effects. When properly prepared under GMP conditions from purified monomers, the polymers exhibit no evidence of inflammatory response or other adverse effects upon implantation[43]. Another type of synthetic polymeric system includes the in situ cross linked system, where the polymers form cross linked networks by means of free radical reactions that may occur by means of light (photopolymerizable systems) or heat (thermosetting systems). 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 macro molecular network. Dunn *et al*. designed a thermo setting system using biodegradable copolymers of DL-lactide or L-lactidewithε-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 formationin situ and this precipitation can be induced by change in temperature (thermo sensitive systems), solvent removal or by change in pH[44]. An important example of thermo sensitive polymer is poly-(N-isopropylacrylamide), [poly (NIPAAM)], which is used for the formation of in situ gels. It has lower critical solution temperature phase separation at about 32^0C. The polymers such as poly (DL-lactide), poly (DL-lactideco-glycolide) form solvent removal precipitating polymeric systems[45].

Evaluation and Characterizations of In Situ Gel System

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

Clarity

The clarity of formulated solutions determined by visual inspection under black and white background

Texture Analysis

The firmness, consistency and cohesiveness of formulation are accessed using texture analyser which mainly indicates the syringe ability 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.

Sol-Gel Transition Temperature and Gelling Time

For in situ gel forming systems incorporating thermo reversible 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.

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.

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 someother 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.

Fourier Transform Infra-red Spectroscopy and Thermal Analysis

During gelation process, the nature of interactingforces can be evaluated using this technique byemploying potassium bromide pellet method. Thermogravimetric 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 thermo grams as compared with the pure ingredients used thus indicating the interactions.

***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 areceptor 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 analysed for the drug release using analytical technique. For injectable insitu gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillationsrate. Samples are withdrawn periodically and analyzed.

Histopathological Studies

Two mucosa tissue pieces (3 cm^2) 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 Advances

One of the challenges facing today's pharmaceutical industry centre's 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 process ability 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 macro molecular 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.

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 N, Langer R. New challenges in biomaterials. Science 1994; 263: 171520. http://dx.doi.org/10.1126/science.8134835
2. Zhidong L, Jaiwei L, Shufang N, Hui L, Pingtian D, Weisan P. Study of an Pharm alginate-HPMC based in situ gelling ophthalmic delivery system for gatifloxacin. Int J 2006; 315: 12-7.
3. Sarasija S, Shyamala B. Nasal Drug Delivery: An Overview, Indian J Pharm.Sci 2005; 67(1): 19-25.
4. 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. http://dx.doi.org/10.1081/DDC-120037490 PMid:15285332

5. Marsha Ritter Jones, MS, Philip B. In-situ forming biomaterials, Oral Maxillo facial Surg Clin N Am 2002; 14: 29-38.
6. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur JPharm Biopharm 2000. http://dx.doi.org/10.1016/S0939-6411(00)00090-4
7. Qiu Y, Park K. Environment-sensitive hydrogelsfor drug delivery. Adv. Drug Deliv. Rev 2001; 53: 321-39. http://dx.doi.org/10.1016/S0169-409X(01)00203-4
8. Bromberg LE, Ron ES. Temperature-responsive gels and thermo gelling polymer matrices for protein and peptide delivery. Adv.drug Deliv. Rev 1998; 31: 197-221. http://dx.doi.org/10.1016/S0169-409X(97)00121-X
9. Cappello J, Crissman JW, Crissman M, Ferrari FA, Textor G, Wallis O, *et al*. In-situ self-assembling protein polymer gel systems for administration, delivery, and release of drugs. J Control Release 1998; 53: 105-17. http://dx.doi.org/10.1016/S0168-3659(97)00243-5
10. 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. http://dx.doi.org/10.1081/DDC-120006428 PMid:12378965
11. Aikawa K, Mitsutake A, Uda H, Tanaka S, Shimamura H, Aramaki Y, *et al*. Drug release from pH-response polyvinylacetal diethylaminoacetate hydrogel, and application to nasal delivery. Int J Pharm 1998; 168: 181-8. http://dx.doi.org/10.1016/S0378-5173(98)00096-9
12. Kumar S, Himmelstein K. Modification of in-situ gel behaviour of Carbopol solutions by hydroxypropylmethylcellulose. J.Pharm.Sci 1995; 84: 344-8. http://dx.doi.org/10.1002/jps.2600840315 PMid:7616375
13. Alexandridis P, Lindman B, Amphiphilic block polymers. Amsterdam: Elsvier; 2000.
14. Esposito E, Carratto V and *et al*. Comparative analysis of tetracycline containing dental gels; poloxomers and mono-glycerides based formulation. Int.J.Pharm 1996; 142: 9-23. http://dx.doi.org/10.1016/0378-5173(96)04649-2
15. Geraghaty P, Attwood D, *et al*. An investigation of parameters influencing the Bioadhesive properties of Myverol 18-99 / water gels. Biomaterials1997;18:63-7.http://dx.doi.org/10.1016/S0142-9612(96)00087-7
16. 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. http://dx.doi.org/10.1016/S0142-9612(99)00243-4
17. Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified natural gums as sustained release carriers. Drug Dev. Ind. Pharm 2000; 26:1025-38. http://dx.doi.org/10.1081/DDC-100100266 PMid:11028217
18. Guo JH, Skinner GW, Harcum WW, Barnum PE. Pharmaceutical applications of aturally occurring water-soluble polymers. Pharm Sci and TechnolToday 1998; 1: 254-61. http://dx.doi.org/10.1016/S1461-5347(98)00072-8
19. Podual K, Doyle III FJ, Peppas NA. Dynamic behaviour of glucose oxidase-containing microparticles of poly (ethylene) - grafted cationic hydrogels in an environment of changing pH. Biomaterials 2000; 21: 1439-50. http://dx.doi.org/10.1016/S0142-9612(00)00020-X
20. Burkoth AK, Anseth KS. A review of photo crosslinked polyanhydrides: In situ forming degradable networks. Biomaterials 2000; 21: 2395-404. http://dx.doi.org/10.1016/S0142-9612(00)00107-1
21. Sawhney AS, Pathak CP, Hubbell JA, Hill JL, Desai NP. Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled release carriers.US Patent 5410016; 1995.
22. Dumitriu S, Vidal PF, Chornet E. Hydrogels based on polysaccharides. In: Dumitriu S, editor. Poly saccharides in medical applications. NewYork: Marcel Dekker Inc; 1996. p. 125-242.
23. Ni Y, Kenneth MY. In-situ gel formation of pectin. United States Patent 6777000; 2004.
24. Miyazaki S, Kawasaki N. Comparison of in situ gelling formulations for the oral delivery of cimetidine. Int J Pharm 2001; 220: 161-8. http://dx.doi.org/10.1016/S0378-5173(01)00669-X
25. Bilensoy E, Rouf MA, Imran V, Murat S, Hincal AA. Mucoadhesive thermo sensitive prolonged release vaginal gel for clotrimazole: β-cyclodextrincomplex. AAPS Pharm Sci Tech 2006; 7: 38. http://dx.doi.org/10.1208/pt070238PMid:16796356 PMCid:PMC2750288
26. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Rel 1998; 56: 75-83. http://dx.doi.org/10.1016/S0168-3659(98)00079-0
27. 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. http://dx.doi.org/10.1016/S0378-5173(99)00026-5
28. Suisha F, Kawasaki N, Miyazaki S, Shirakawa M, Yamotoya K, Sasaki M, *et al*. Xyloglucan gels as sustained release vehicles for intra peritoneal administration of mitomycin C. Int J Pharm 1998; 172: 27-32. http://dx.doi.org/10.1016/S0378-5173(98)00157-4
29. 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 JPharm 2001; 229: 29-36. http://dx.doi.org/10.1016/S0378-5173(01)00825-0
30. 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. http://dx.doi.org/10.1016/S0168-3659(99)00084-X
31. Crescenzi V, Dentini M, Coviello T. Solutions and gelling properties of microbial polysaccharides of industrial interest: The case of gellan. In: Dawes EA, editor. Novel biodegradable microbial polymers. Dordrecht: Kluwer Academic Publishers; 1999. p. 227-84.
32. Grasdalen H, Smidsroed O. Gelation of gellan gum. Carbohydrate Polymers1987;7:371-93.http://dx.doi.org/10.1016/0144-8617(87)90004-X
33. 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. http://dx.doi.org/10.1016/S0378-5173(00)00539-1
34. Smart JD, Kellaway IW, Worthington HE. An *in vivo* investigation of mucosa adhesive materials for use in controlled drug delivery. J Pharm Pharmacol1984;36:259-99.http://dx.doi.org/10.1111/j.2042-7158.1984.t04377.x
35. 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.
36. Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. J Control Release 2002; 80: 9-28. http://dx.doi.org/10.1016/S0168-3659(02)00008-1
37. 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; 21: 2155-61. http://dx.doi.org/10.1016/S0142-9612(00)00116-2
38. 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.http://dx.doi.org/10.1081/PDT-100100555 PMid:10934739
39. Schmolka IR. Artificial skin, Preparation and properties of pluronic F127 gels for the treatment of burns. J. Biomed. Mater. Res 1972; 6: 571-582. http://dx.doi.org/10.1002/jbm.820060609 PMid:4642986
40. 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. http://dx.doi.org/10.1016/S0168-3659(02)00009-3
41. Alexandridis P, Hatton TA. Poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) block copolymer surfactants in aqueous solutions and interfaces: thermo dynamics, structure, dynamics and modeling. Colloid Surfaces 1995; A96: 146.
42. Liu F, Wilson BC. Hyperthermia and photodynamic therapy. In: Tannock I, Hill RP, editors. Basic science of oncology. New York: McGraw-Hill; 1998. p. 443-53.
43. Dunn RL, English JP, Cowsar DR, Vanderbelt DD. Biodegradable in situ forming implants and methods for producing the same. US Patent 5340849; 1994.
44. Siegel RA, Firestone BA. pH dependent equilibrium swelling properties of hydrophobicpoly electrolyte copolymer gels. Macro molecules 1988; 21: 3254-9. http://dx.doi.org/10.1021/ma00189a021
45. Eliassaf J. Aqueous solution of poly-(N-isopropylacrylamide). J App Polymer Sci 1978; 22: 873-4. http://dx.doi.org/10.1002/app.1978.070220328

Cite this article as:
Sonawane Swapnil D., Patil Ravindra Y, Lad Meenal. A review on polymers used in novel in situ gel formulation for ocular drug delivery and their evaluation. J Biol Sci Opin 2013; 1(2): 132-137 http://dx.doi.org/10.7897/2321–6328.01221