INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

REVIEW ON POLYMERS USED FOR IN SITU GEL FOR OPHTHALMIC DRUG DELIVERY SYSTEM

VIDYA KAKAD[1], RACHANA KUMAR[2], SMITA RUPVATE[3], RUPALI NAGARE[1], JAYSHRI MADAGUL[1]

1. MET Institute of pharmacy, Bhujbal Knowledge City (University of pune), Nasik 422003, Maharashtra.
2. Assistant professor, MET Institute of pharmacy, Bhujbal Knowledge City (University of pune), Nasik.
3. Assistant professor, MET Institute of pharmacy, Bhujbal Knowledge City (University of pune), Nasik.

Accepted Date: 26/04/2015; Published Date: 27/06/2015

Abstract: In the present update 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 because of sustained and prolonged action in comparison to conventional drug delivery systems. 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. Various biodegradable polymers that are used for the formulation of *in situ* gels include chitosan, pluronics, xyloglucans, hydroxyl propyl methyl cellulose, carbopol, gelrite, gellan gum, and alginates. From a manufacturing point of view, the production of such systems is less complex and thus lowers the investment and manufacturing cost. The present study focused on the polymers used in the preparation of *in situ* gelling system for the ophthalmic drug delivery.

Keywords: *In situ* gel, Natural polymers, Synthetic polyers, Thermoreversible, pH sensitive.

Corresponding Author: MS. VIDYA KAKAD

Access Online On:

www.ijprbs.com

How to Cite This Article:

Vidya Kakad, IJPRBS, 2015; Volume 4(3): 52-68

PAPER-QR CODE

INTRODUCTION

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems[1]. 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. Polymers have historically been the keys to the great majority in 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[2, 3]. 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. 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[4, 5, 6].

Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered, i.e. they are in solution phase before administration, but gels under physiological condition[7,8]. These systems are refer to polymer solution which can be administered as liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. There are various physical and chemical stimuli leading to *in situ* gel formation viz. temperature, pH, electric field, magnetic field and light Stimuli responsive polymer mimics biological system in a crude way where an external stimulus (pH and temperature) result in a change in the properties of the formulation. These changes may be in the conformation, solubility, alteration of hydrophilic/hydrophobic balance or release of a drug molecule. This also includes a combination of several responses at the same time. Both natural and synthetic polymers can be used for the production of *in situ* gels. So, *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes. Recent advances in *in situ* gels have made it possible to exploit the changes in physiological uniqueness in different regions of the GI tract for the improved drug absorption as well as patient's convenience and compliance[9,10,11].

This review presents a brief introduction to *in situ* gels, various approaches for *in situ* gelling systems. Also different types of smart polymers, their mechanisms of gel formation from the sol forms and evaluation of polymeric *in situ* gel.

IMPORTANCE OF *IN SITU*GELLING SYSTEM[7,12,13]

- The major importance is the possibilities of administrating accurate & reproducible quantities compared to already formed gel.

- In-situ forming polymeric delivery system such as ease of administration & reduced frequency of administration improved patient compliance & comfort.
- 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.
- Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the naso lacrimal duct may result in some undesirable side effects.

VARIOUS APPROACHES OF IN-SITU GEL

Depending upon the method employed to cause sol to gel phase transition on the ocular surface, the following types of systems are recognized

• TEMPERATURE DEPENDENT SYSTEMS[14,15]

Temperature dependent in-situ gel system is probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. These in-situ gels are able to swell or deswell as a result of changing in the temperature of the surrounding fluid. This type of formulation is liquid at room temperature (20°-25°c) which undergoes gelation in contact with body fluid (35-75°c)..

Example: chitosan, pluronics, tetronics, xyloglucans, hydroxyl propylmethyl cellulose

• PH- TRIGGERED SYSTEMS[16,17]

In case of pH sensitive in-situ gels, the pH sensitive polymer contains pendent acidic or basic groups that either accept or release protons in response to change in environmental pH. Swelling of *in situ* gel increases as the external pH increase in the case of weakly basic groups. Sol to gel transition takes place when pH is raised from 4.2 to 7.4 (eye pH). At higher pH polymer forms hydrogen bonds with mucin which leads to formulation of hydrogen network.

Example: cellulose acetate phthalate (CAP) latex, carbopol, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudo latexes.

• ION-ACTIVATED SYSTEMS[18,19]

In this polymer may undergo phase transition in presence of various ions. Gellan gum commercially available as gelrite is an anionic polysaccharide Ca^{2+}, Mg^{2+}, k^{+} and Na^{+}.

Formulation undergo liquid- gel transition under influence of an increase in ionic strength and gel formation take place because of complexation with polyvalent cations in lacrimal fluid.

Example: gelrite, gellan, hyaluronic acid, alginates.

_IN SITU_FORMING POLYMERIC SYSTEMS FOR OCULAR DELIVERY:

Some of the most important polymers used as in-situ gelling agents are described here.

***Ideal Characteristics of Polymers*[20,21,22]**

- A polymer used to *in situ* gels should have following characteristics-
- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be good tolerance & optical activity.
- It should influence the tear behavior.
- 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.

TEMPERATURE DEPENDENT POLYMER

Thermo reversible polymers are a novel state of matter having both solid and liquid like properties. Thermosetting systems are in the sol form when initially constituted, but upon heating, they set into their final shape. This polymer can be delivered as a fluid and solidifies within the body's microenvironment where the temperature is higher than the sol-gel transition temperature[23].

Mechanism of Gelation

A number of polymers exhibit abrupt changes in their physical properties like solubility and viscosity with increases in temperature; the resulting sol-gel transition occurring at the lower critical solubility temperature (LCST) is characterized by minimal heat production and absence of byproducts. Let us consider the free energy of association (G) between the polymer chains:

$$G = H - T.S$$

Where, H is the enthalpy term, S the entropy term and T temperature.

Increase over a critical temperature results in a larger value of T S than the positive enthalpy term (H), and thus a negative G favoring polymer association: chain-chain interactions (hydrophobic effects, hydrogen bonding) dominate over chain-water hydrogen bonding[6,24].

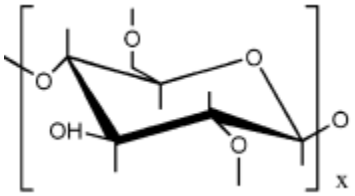
Individual polymer followed a different theory of gel formation[24]

1. Cubic crystalline phase:
2. Micellar aggregation:
3. Micelle-micelle cluster formation:

SYNTHETIC POLYMERS

CELLULOSE

Methylcellulose

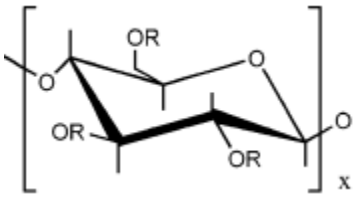


Methylcellulose (MC) is water-soluble polymer which is known to undergo thermoreversible gelation in aqueous solution upon heating[25].

Mechanism of gelation of methyl cellulose

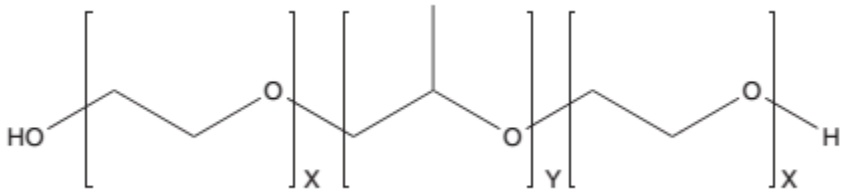
At low temperature, water molecules are presumed to form "cagelike" structures to surround the hydrophobic methoxyl groups, causing the MC to become water-soluble. Upon heating, these structures distort and break to expose the hydrophobic regions, inducing the formation of aggregates. Thus, the gelation is a manifestation of the hydrophobic effect and co-solutes that are readily soluble in water[24,26].

Hydroxypropyl methylcellulose



Transition temperature can be lowered by reducing the hydroxy propyl molar substitution[25]

Poloxamer

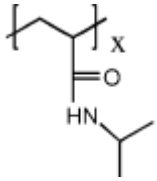


Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They are regarded as PEO-PPO-PEO copolymers. Chemically they are Oxirane, methyl-, polymer with oxirane or α-Hydro-ω- hydroxypoly(oxyethylene)a poly(oxypropylene)b poly(oxyethylene)a block copolymer. It is biocompatible and has been approved by FDA for use in human body[25,27]. ***Mechanism of gelation of poloxamer***

Due to the PEO/PPO ratio of 2:1, when the poloxamer is placed into cold water, at low concentration; hydration layer surrounds the poloxamer molecule as hydroxyl groups of the copolymer forms hydrogen bond which surrounds the hydrophobic portions are separated due to hydrogen bonding. They undergo change in solubility with change in environment temperature. With increasing temperature, desolvation of the hydrophilic chains occurs as the result of breakage of hydrogen bonds. This results into hydrophobic interactions amongst the polyoxypropylene domains and gel gets formed. The molecular weight and percentage of hydrophobic portion are determinant factors for gelling behaviour. The gel formation occurs only when concentration is above critical micellar concentration. Reverse thermal gelation is the unique property of pluronic copolymers which makes it useful in the various drug delivery systems such as oral, ocular, nasal, topical, dental, and other biomedical fields. Poloxamer 407 forms transparent gel without syneresis, and also undergoes quick dissolution. Because the length of the polymer blocks can be customized, the pluronic triblock copolymers are available in various grades differing in molecular weight and physical form[7,24,26].

Acryl amides

Poly-(N-isopropylacrylamide) PNIPAM

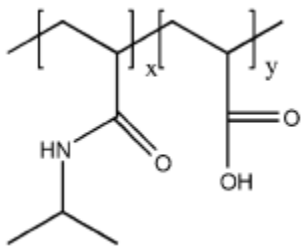


Poly-(N-isopropylacrylamide), a typical thermosensitive polymer, has been widel studied, chiefly because of its phase transition at 32-33°C. The LCST of PNIPAM can be changed by copolymerization with a second monomer which shifts upon shifting the hydrophilic/hydrophobic balance. Hydrophobic co monomers (isopropyl) increase the LCST, whereas hydrophilic co-monomers (amide) have the opposite effect[24,28].

Mechanism of gelation of PNIPAM

Wang et al. have investigated the coil-to-globule transition of PNIPAM in water. They found a hysteresis between the radius of gyration during the heating and the cooling curve. Two intermediate states were observed, which gives in total four different, thermodynamically stable states viz. coil, crumpled coil, molten globule, and globule .The toxicity of PNIPAAm in the body is unknown and the lack of compatibility with cells and blood, thus its application in drug delivery systems may be extremely restricted[24,28].

Poly (N-isopropylacrylamide-co-acrylic acid)



PNIPAMco-AA Copolymerization of acrylic acid (AA) prevents syneresis of PNIPAM [26].

Poly (acrylic acid-co-acrylamide)

An interpenetrating network of poly (acrylic acid) and polyacrylamide is one of the few examples of a system with UCST behavior within the biomedical setting. The transition temperature is at 25°C. The UCST behavior is caused by the cooperative effects coming from the hydrogen bonding between AAc and AAm units[28].

NATURAL POLYMERS

Xyloglucan

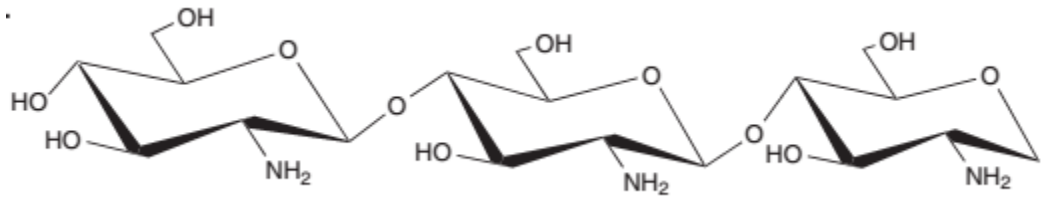
Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1 -4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose. When xyloglucan is partially degraded by β-galactosidase, the resultant product exhibits thermally 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[1,25].

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. It shows thermoreversible gelation with locust bean gum at appropriate gum concentration[1,29]

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. 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 dpendent gel forming aqueous solutions, without any hemical modification or cross inking by addition of olyol salts bearing a single anionic head such as lycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution[6,24]

Mechanism

The mucoadhesive property is due to the formation of ionic interaction between the positively charged amino groups of chitosan and negatively charged sialic acid residues of

mucins, depends on environmental pH. Because of its bioadhesive, hydrophilic, good spreading properties, is used as viscosifying agent in artificial tear formulations[30].

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-glucose 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[1,25].

CLASSIFICATION OF TEMPERATURE SENSITIVE *IN SITU* GEL BASED ON IT'S ENGINEERING[31]

Negative Thermosensitive

Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST), such hydrogel contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between ambient and physiologic temperature is used for this purpose. E.g. poly (N-isopropylacrylamide) (PNIPAAm). It 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.

Positive Thermosensitive

A positive temperature sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. E.g. poly(acrylic acid) (PAA), polyacrylamide (PAAm)/poly(acrylamide-cobutyl methacrylate) have positive temperature dependence of swelling.

Thermally Reversible Gels

Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature. E.g. Pluronics

PH SENSITIVE *IN SITU* GELLING SYSTEM

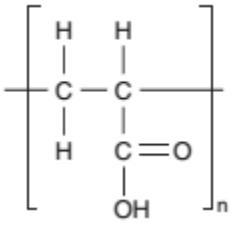
In this system, gelling of the solution is triggered by change in pH, when pH is raised from 5-7.4. At higher pH, polymer forms hydrogen bond with mucin, which leads to hydrogel formation. Cellulose acetate phthalate latex, Carbopol, Polyacrylic Acid,Polyethylene Glycol are pH dependent polymers[32].

Mechanism for pH sensitive gelling System

All pH sensitive polymers contain pendant acidic or basic groups that can either accept or release protons in response to changes in environmental pH. In case of weakly acidic group, swelling of hydrogel increases as the external pH increases, while decreases in case of weakly basic groups[33].

POLYMERS USED IN PH SENSITIVE *IN SITU*GELLING SYSTEM

Carbomer



Carbomers are the poly (acrylic acid)-based high-molecularweight polymers commercially known as Carbopol. These polymers exhibit sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopols are available in a range of molecular weights with linear, branched and cross-linked side chains. Carbopols exhibit excellent mucoadhesive property in comparison with other natural or synthetic polymers (e.g., cellulose derivatives) and hence studied extensively in ocular drug delivery. Among the carbopols, Carbopol 934 is the most commonly reported polymer composed of 62% of carboxyl groups formed by repeating units of acrylicacid, cross-linked with either allylsucrose or allylethers of pentaerythritol. Different grades of carbomer are available in market which includes carbopol 934(lowest cross linking density), carbopol 940 (highest cross linking density), and carbopol 981 (intermediate cross linking density). Carbopol is used as gelling, emulsifying and suspending agent[6,25].

Mechanism

Mucoadhesive property is due to hydrogen bonding, electrostatic interaction or hydrophobic interaction. Carbopol molecule is tightly coiled acidic molecule. Once dispersed in water, carboxylic group of the molecule partially dissociates to form flexible coil. Being a pH sensitive polymer, increase in solution pH results swelling of polymer. In acidic medium, it is in collapsed state due to hydrogen bonding, as the pH increases, electrostatic repulsion occur between the anionic groups, results gel swelling. The gelling effect is activated in two stages: Dispersion and hydration of carbopol, neutralizing the solution by addition of sodium hydroxide, Triethanolamine, or potassium hydroxide. As the concentration of

carbopol increases, due to its acidic nature it causes irritation to the eye. Addition of viscosity enhancer like HPMC, MC will reduce the concentration without affecting its gelling property[33].

Polycarbophil

Polycarbophil is lightly cross linked polyacrylic acid having excellent mucoadhesive property[33].

Mechanism

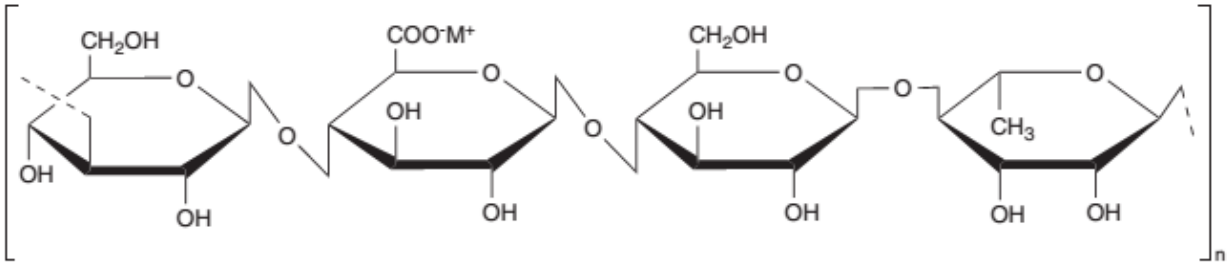
It is insoluble in water but its swelling capacity in neutral medium permits the entanglement of polymer chain with mucus layer. The carboxylic acid group of polycarbophil binds to mucin by hydrogen bonds. Noveon® AA-1 polycarbophil, is a high molecular weight polyacrylic acid polymer cross linked with divinyl glycol and exhibit sol-gel transition.Cellulose acetate latex (CAP latex) another pH sensitive Polymers these are flowing liquid at pH 4.8 and gel at pH 7.4[27,32].

ION SENSITIVE GELLING SYSTEM

Gelation is triggered by the presence of cations (Na^+, Mg^{++}, Ca^{++}) in the tear fluid. These can be achieved by polymers like sodium alginate, gellan gum. Gelation is occurred by ionic interaction of polymer and divalent ions of tear fluid. When anionic polymers come in contact with cationic ions, it converts to form gel[35].

POLYMERS USED FOR ION SENSITIVE *IN SITU*GELLING SYSTEM

Deacetylated Gellan Gum (Gelrite)



Gellan gum is an anionic hetero polysaccharide, secreted by microbe Sphingomonas elodea. It consists of glucose, rhamnose, glucuronic acid and are linked together to give a tetrasaccharide unit. Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the molecule. Upon instillation, gelrite forms gel due to the presence of calcium ions. The gelation involves the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexaton with cations and hydrogen bonding with water. Because of its

thixotropy, thermo plasticity, pseudo plasticity are widely use in ophthalmology. In food industry, is used as suspending and stabilizing agent[1,25].

Mechanism

Gellan gum produce a cation induced in situ gelation(Ca^{2+}, M^{2+}, K^{+}, Na^{+}) due to the cross linking between negatively charged helices and mono or divalent cations (Na^{+}, Ca^{+}, Mg^{+}). Divalent ions superior to promoting gelation as compared to monovalent cations. Gelation prolongs the residence time of drug at absorption site and bioavailability of the drug is increased[33].

Sodium Alginate

Sodium alginate is a gum extracted from brown algae. It is a salt of alginic acid. It is a linear block polysaccharide consisting of two type monomers β –D- Mannuronic acid and α-L-glucuronic acid residues joined by 1,4 glycosidic linkages. It exhibit good mucoadhesive property due to its carboxylic group. It is biodegradable and non toxic[25].

Mechanism

The monomers of alginate (β-D-mannuronic acid (M) and α-L- glucuronic acid (G) are arranged as M-M block or G-G block with alternating sequence (M-G) block. Upon interaction of G block of polymer with calcium moieties resulting in the formation of homogenous gel. Mechanical strength and porosity of hydrogel depends on G: M ratio, type of cross linker used and concentration of alginate solution[36].

EVALUATION OF IN-SITU GEL

1. pH of Formulation

1ml quantity of each formulation was transferred to the 10ml volumetric flask and diluted by using distilled water to make 10ml. pH of resulting solution was determined by using pH meter[37].

2. Viscosity and rheology

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[1].

3. Measurement of gelation temperature

a. Visual inspection: 10 ml volume of solution is transferred to 20 ml transparent vial containing a magnetic stirrer bar. The vial is heated at an increasing rate of 1°C/min with constant stirring at 100 rpm. The temperature at which rotation of bar stopped is taken as the gelation temperature[36]

b. Rheological method: A rheological study is performed with a thermostatically controlled Brookfield Programmable Rheometer fitted with CP-52 spindle. The cone/plate geometry is used. The shear stress is controlled to maintain a shear rate of 10/sec shear rate for precise determination of the gelling temperature. The temperature is increased in steps of 1°C/min, from 20-40°C to locate the solution/gel transition point. The gelling temperature is determined graphically as the inflection point on the curve of the apparent viscosity (mPas) as a function of the temperature (°C)[38].

4. Gel-Strength

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. The probe is slowly pushed through the gel by placing the weights on the probe, resulting in rising of gel in a beaker at certain rate. 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[39].

5. In vitro drug release:

In vitro drug release can be carried out using cellophane membrane, modified USP XXII dissolution apparatus, Circular teflon cup, Franz diffusion cell, Dialysis tube. The formulation is kept in the donor compartment and freshly stimulated tear fluid in receptor compartment. Between the donor and receptor compartment dialysis member is placed (0.22 um pore size). The whole assembly is placed on thermostatically controlled magnetic stirrer. Temperature of the medium was maintained at $37^0C \pm 5^0C$. 1ml of sample is withdrawn at predetermined time interval of 1 hour for 6 hours and same volume of fresh medium is replaced[40].

COMMERCIAL FORMULATIONS OF IN-SITU 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 thesolution 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[41].

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 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 is a novel injectable depot formulation of human growth hormone (hGH) utilizing Macromed's Regel drug delivery system for treatment of patients with hGHdeficiency[42].

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 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. 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. 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[43].

CONCLUSION

Development of polymeric in situ gels for delivery of various drugs provides a number of advantages over conventional dosage forms. Various natural, synthetic, semi synthetic polymers are developed for controlled release of drug. Use of biodegradable and water soluble polymers for the *in situ* gels formulations can make them more acceptable and excellent drug delivery systems. Thus sustained and prolonged release of drug, biocompatibility characteristics makes *in situ* gel dosage form reliable. In recent technology, polymer combinations focus the development of safe ophthalmic delivery system.

REFERENCES

1. Nirmal H et al. *In situ* gel: New trends in controlled and sustained drug delivery system. International Journal of Pharm Tech Research, 2, 2010, 1398-1408.

2. Peppas N, Langer R. New challenges in biomaterials. Science1994, 263,171520.

3. Swapnil S et al. A Review on polymers used in novel *in situ* gel formulation for ocular drug delivery and their evaluation Journal of biological and scientific opinion, 1(2), 2003, 132-137.

4. Kant A et al. *In situ* gellig system - an overview, Pharmacologyonline 2, 2011, 28-44.

5. Sharma N et al. Mucoadhesive thermoreversible nasal delivery system. Journal of Pharmacy Research, 3, 2010, 991-997.

6. Prajapati N, Goyal A. Thermoreversible mucoadhesive *in situ* gel: a review, International Journal of Innovative Drug Discovery, 2(3), 2013, 67-84.

7. Saneesh G, Sujith A. A review on *in situ* drug delivery system, international journal of universal pharmacy and bio sciences, 3(4), 2014, 135-154.

8. Kalia N et al. *In situ* gelling system: a review, Journal of Drug Delivery and Therapeutics, 4(4), 2014, 93-103.

9. Patel N et al. ophthalmic *in situ* gel, pharmagene, 1(4), 21014, 29-33.

10. Jothi M et al. *In-situ* ophthalmic gels for the treatment of eye diseases, International journal of pharmaceutical science and research, 3(7), 2012, 1891-1904.

11. Pandya P et al. Opthalmic *in-situ* gelling system, international journal of pharmacy & life sciences, 2(5), 2011, 730-738.

12. Sable Namita V et al. *In-situ* gels for ocular drug delivery system: an Overview, world journal of pharmacy and pharmaceutical sciences, 2(6), 2013, 4878-4901.

13. Jain S et al. A Review on Triggered Gel for Ocular Drug Delivery, International Journal of Pharmaceutical & Biological Archives, 5(4), 2014, 19- 25.

14. Patil A et al. A novel ophthalmic drug delivery system: *in-situ* gel, international journal of pharmaceutical sciences and research, 3(9), 2012, 2938-2946.

15. Ganapaneni C et al. A review on design and development of thermosensitive occular *in situ* gel ophthalmic formulation, the pharma innovation – journal, 2(3), 2013, 133-140.

16. Agarwal K et al. In-Situ Gel Formation for Ocular Drug Delivery System an Overview, Asian Journal of Biomedical and Pharmaceutical Sciences 1 (4) 2011, 01-07.

17. Singh K and Verma S. Novel Polymeric *in situ* Gel Forming System for Ophthalmic Drug Delivery, International Journal of Drug Delivery Technology, 4(1), 2013,1-13.

18. Rathore K. *In-situ* gelling ophthalmic drug delivery system: an overview, International Journal of Pharmacy and Pharmaceutical Sciences, 2(4), 2010, 30-34.

19. Thakur R and Sharma M. An Insight ophthalmic to ophthalmic *in situ* gel: an overview, International research journal of pharmacy, 3(3), 2012, 16-21.

20. Nerkar T et al. *In-situ* gel: novel approach in sustained and controlled drug delivery system, An international journal of pharmaceutical sciences, 4(4), 2013,1-18.

21. Amaliyar P et al. *In situ* gel forming a novel approach for sustained ophthalmic drug delivery. International journal of pharmaceutical research and bio-science, 3(2), 2014, 502-524.

22. Saraswat R et al. A review on polymers used in *in-situ* gel drug delivery systems, international journal of pharmaceutical innovations, 1(2), 2011, 2249 –1031.

23. Gangadia B et al. Formulation and evaluation of thermo sensitive *in-situ* gel for local action: a review, international journal of pharmaceutical research and bio-science, 3(1), 2014, 217-228.

24. Tegeli V et al. A treatise on theory and applications of thermoreversible polymers. International Journal of Drug Formulation & Research, 2, 2011, 154-175.

25. Agrawal A.et al. *In situ* gel systems as 'smart'carriers for sustained ocular drug delivery, Expert Opinion. Drug Delivery, 9(4), 2012, 383-402.

26. Eve Ruel G and Jean-Christophe L. In situ-forming hydrogels-review of temperature-sensitive systems, European Journal of Pharmaceutics and Biopharmaceutics 58, 2004 409–426

27. Rajoria G and Gupta A. In-Situ Gelling System: A Novel Approach for Ocular Drug Delivery, American Journal of PharmTech Research, 2(4), 2012, 24-53.

28. Jun Li et al. Thermo-sensitive polymer for controlled release drug delivery systems, International journal of Pharmacology, 2(5), 2006, 513-519.

29. KELTROL®/ KELZAN® xanthan gum Book, 8th ed., A Huber Company, 5-25. www.cpkelco.com.

30. Lehr C et al. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers, International Journal of Pharmaceutics, 78, 1992, 43-48.

31. Peppas N et al. Hydrogels in pharmaceutical formulations, European Journal of Pharmaceutics and Biopharmaceutics 50, 2000, 27- 46

32. Rajas N et al. *In situ* opthalmic gels: a developing trend nternational Journal of Pharmaceutical Sciences Review and Research, 7(1), 2011, 8-14.

33. Kumar A et al. Polymers Used in Ophthalmic *in situ* Gelling System, International Journal of Pharmaceutical Sciences Review and Research, 20(1), 2013, 173-180.

34. Kumar L et al, *In situ* gel: a novel system for ocular drug delivery, International Journal of Pharmaceutical Sciences Review and Research, 9(2), 2011, 83-92.

35. Chandra Mohan E. et al, *In-situ* gels-a novel approach for ocular drug delivery, Scholars Research Library Journal, 1(1), 2009, 21-33.

36. Liu Z et al. Study of an alginate/HPMC-based *in situ* gelling ophthalmic delivery system for gatifloxacin, International Journal of Pharmaceutics 315, 2006, 12–17

37. Patel M et al. Preparation and evaluation of thermoreversible formulations of flunarizine hydrochloride for nasal delivery. International Journal of Pharmacy and Pharmaceutical Sciences, 2, 2010, 116-120.

38. Majithiya R et al. Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS pharm. Sci. Tech, 7, 2006.

39. Boddeda B et al. A Review on Mucoadhesive Polymers in Ophthalmics, International Journal of Pharmaceutical Sciences Review and Research, 24 (1), 2014, 237-245.

40. Suryawanshi S et al. Novel Polymeric *in situ* Gels for Ophthalmic Drug Delivery System, International Journal of Research in Pharmacy and Science, 2(1), 2012, 67-83.

41. 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.

42. 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 6201072. 2001.

43. Rathi R, Zentner C, Gaylen M, Jeong B. Macro med, Inc.Biodegradable low molecular weight triblock poly (lactide-co-glycolide) polyethylene glycol copolymershaving reverse thermal gelation properties. US patent 6117949. 2000.