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RECENT ADVANCES IN DEVELOPING INJECTABLE *IN-SITU* GEL MATRIX SYSTEM FOR CONTROLLED DRUG RELEASE-ON REVIEW

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ABSTRACT

The drug which have poor bioavailability it can be administered through parenteral route is regarded the most suitable for drug delivery. Parenteral delivery provides quick onset of action even for the drug with narrow therapeutic index, but patient discomfort will be cause due to the maintenance of systemic drug level repeated installation are required. This type of discomfort can be overcome by developing the drug into a system, which improves patient compliance. Injectable *in-situ* gelling system is one of the types of such system. This biodegradable injectable in-situ gelling drug delivery system offer attractive opportunities for protein (eg: Albumin), Anti-cancer (eg: Melphalan, Cyclophosphamide), NSAIDs (eg: Diclofenac, Indomethacin) drug delivery and may be possibly extend patent life of these drugs. In this article investigate the injectable *in-situ* gelling system for extended release parenteral drug delivery system and their preparation, mechanism and evaluation are discussed.

KEYWORDS

Injectable *in-situ* gel, Strategies of parenteral systems, Biodegradable injectable polymers and Preparation of *in-situ* gel.

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INTRODUCTON

Over the past series of years greater interest has been concentrated on designing of sustained and controlled drug delivery systems. Developing of polymeric drug delivery system is extensive research. The designing of *in-situ* gel systems has received substantial focused over the past few years. The advantages demonstrate by *in-situ* forming polymeric delivery systems such as simple manufacture, ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In-situ* gel formulations

proposals an exciting another for succeeding systemic drug effects of parenteral routes, which can be difficult or oral route, which can result in permits the hepatic first-pass metabolism and unacceptably short bioavailability, in particular of proteins and peptides. This novel drug delivery system encourages the significantly ease and convenience of administration, release of accurate dose as well as to extend residence time of drug in contact with mucosa. *In-situ* gel formation happens due to one or combination of different stimuli like solvent exchange, pH change and temperature modulation. From initially 1970's natural and synthetic polymers began to be examined for controlled release formulations. This type of polymers undergoes sol-gel transition once it wills administer to the body. Several natural and synthetic polymers are used for development of *in-situ* forming drug delivery systems[1].

TYPES OF PARENTERAL CONTROLLED DRUG DELIVERY SYSTEMS

There are mainly three ways to attain extended release of parenteral dosage form viz. physical methods, chemical and Pharmacological. Physical methods contain the choice of the correct vehicle, thus giving extended release (use of oleaginous solutions as an alternative of aqueous solutions); the additions of adsorbents; the use of solutions from which, upon administration, the drug is precipitated when it contacts body fluids; and the use of implants. Chemical methods consist of the use of esters, salts, and complexes of the active ingredient with low solubility. Pharmacological methods contain subcutaneous or intramuscular administration as an alternative of intravenous; the concurrent administration of vasoconstrictors (ephedrine in heparin solutions; adrenaline in local anesthetics); and blocking the exclusion of drugs through the kidneys by concurrent administration of a blocking agent, such as probenecid with p-amino salicylic acid.

- Microspheres
- Surgical implants
- Liposomes
- Injectable gels

Microspheres

Microspheres developed for parenteral delivery, it can also be injected into the body using conventional syringes. Therefore, they have been the most broadly accepted biodegradable polymer system for parenteral use. However, microspheres manufacturing processes are often complex and hard to control. As a consequence, there are often questions including costs and batch-to-batch product uniformity.

Surgical implants

Surgical implant scan be prepared from decomposable polymers using skillful manufacturing processes, such as compression moulding and injection moulding. However, since their size, they need surgical implantation, which regularly limits the product's market potential due to patient and physician approval disputes.

Liposomes

Liposomes on the other hand are versatile carriers for both hydrophilic and lipophilic drug molecules but suffer from several disadvantages like, high production cost, leakage of drug, short half-life and low solubility. Biodegradable injectable *in-situ* gel forming drug delivery systems represent an attractive alternative to implants and microspheres as parenteral depot systems. It involves biocompatible carrier dissolved in a biodegradable polymers. When using standard needles and syringes liquid polymer system is placed into the body, it solidifies upon contact with aqueous body fluids to form solid implant. Biodegradable polymers used in these systems are polyorthoesters, Polyhydroxyacids, polyesteramides polyanhydrides, and others.

Injectable *In-Situ* Gels

Injectable *In-Situ* Gels polymeric delivery systems pose the attractive capability to control the release of drug substances to obtain define blood levels over a specified time. In several cases this capability would provide a significant advantage. For example, permanent medication thereby often advantage from long-term delivery systems to increase patient compliance. For permanent medication and numerous other applications in humans and in animals, the want for proper depot systems exists. Injectable *in-situ* forming depots include a specific class of polymeric delivery

systems that possess the benefits of a straight forward manufacturing even for sensitive molecules and ease of administration as a liquid, which solidifies after application by phase separation. Presently, there are two injectable *in-situ* gelling system on the market: Atridox® and Eligard®. Injectable *in-situ* setting semi-solid drug depot are being deigned as alternative delivery system. These implants are made of biodegradable products, which can be injected via a syringe into the body and once injected; solidify to form a semi-solid depot. The main prerequisite features of the solvent of an injectable *in-situ* depot system include polymers having good solubility properties, biocompatibility, chemical compatibility and stability. Furthermore, a suitable solvent for intramuscular (i.m.) or subcutaneous (s.c.) injection should be slightly irritating to the injection site, and its metabolic products should not have any side effects on the organism. The ICH classification of solvents in pharmaceutical products narrows the use by the permitted daily exposure (PDE) of excipients[2].

ADVANTAGES OF INJECTABLE *IN-SITU* GELS

This system serves many advantages over conventional methods of drug delivery systems;

1. Ease of administration, comfort.
2. Reduced frequency of administration further.
3. Improved patient compliance.
4. Can be administered to unconscious patients.
5. Drug becomes released in a controlled and sustained manner.
6. Natural polymers usually have inherent properties of biodegradability, biocompatibility, and biologically identifiable moieties that support cellular activities.
7. Synthetic polymers have clear structures that can be changed to yield tailor able functionality and degradability.

Limitation

1. Ease of administration is questionable sometimes as some hydrogels are not adequately deformable, so injectable route may not be possible.
2. The homogeneity and quantity of drug loading into hydrogels may be limited, mainly for hydrophobic drugs. Only drugs with small dose necessity can be given.
3. The large pore size and high water content of maximum hydrogels often result in relatively rapid drug release[3].

POLYMERS USED AS INJECTABLE *IN-SITU* GELLING AGENTS

Gellangum

Gellan gum is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea by a tetra saccharide repeating unit of one α-L-rhamnose, one β- D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is cations induced or temperature dependent. This gelation contains the formation of double helical junction zones followed by aggregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water. The formulation involved of gellan solution with calcium chloride and sodium citrate complex. It is administered orally; the calcium ions are released in acidic media of stomach leading to gelation of gellan therefore forming a gel *in-situ. In-situ* gelling gellan formulation used as vehicle for oral delivery of theophylline is reported.

Alginic acid

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues combined by 1, 4-glycosidic linkages. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a helpful process connecting consecutive glucuronic residues in α- L glucuronic acid blocks of the alginate chain. Alginic acid can be selected as a vehicle for ophthalmic formulations, since it shows favorable biological properties such as biodegradability and nontoxicity. A extended 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.

Chitosan

Chitosan is a biodegradable, polycationic, thermo sensitive polymer obtained by alkaline

deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible, pH dependent and cationic polymer, which remains dissolved in aqueous solutions upto a pH of 6.2. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical change or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, fructose, sorbitol or glucose phosphate salts to chitosan aqueous solution.

Pluronic F-127

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

Xanthum gum

Xanthan gum is a high molecular weight extra cellular polysaccharide formed by the fermentation of the gram negative bacterium Xanthomonas campestris. The primary structure of this naturally formed cellulose derivative comprises a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D mannose attached with alternative glucose residues of the main chain. The anionic character of this polymer is due to the existence of both glucuronic acid and pyruvic acid groups in the side chain.

Synthetic polymers

Synthetic polymers are general choice mainly for parenteral preparations. Synthetic polymers are popular choice mainly for the parenteral preparations. These polymers are mainly used for the injectable *in-situ* formulations. The trend in drug delivery technology has been towards biodegradable polymers, demanding no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly (glycolic acid), poly ε-caprolactone, poly (lactide- coglycolide), poly (lactic acid), poly (decalactone), have been the subject of the most extensive current examinations. Different other polymers like triblock polymer systems composed of poly(D,L-lactide) block-poly(ethylene glycol)- blockpoly (DL-lactide), blends of low molecular weight poly(ε-caprolactone) and poly(D,L-lactide) are also in use. The feasibility of lactide/glycolide polymers as excipients for the sustained and 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 correctly prepared under GMP conditions from purified monomers, the polymers exhibit no evidence of inflammatory response or other side effects upon implantation. Alternative 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 or heat (thermosetting systems) or light (photopolymerizable systems). Thermosetting systems are in the solution form when primarily 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 comprises the formation of covalent cross links between polymer chains to form a macromolecular network. Dunn *et al*. Developed a thermosetting system using biodegradable copolymers of L-lactide or DL-lactide with ε-caprolactone for artificial implant and slow release drug delivery systems. This system is liquid form in outside the body and is capable of being injected by a syringe and needle and once it will inside the body, it gets gel form. In *in-situ* precipitating polymeric systems, the polymer precipitation from solution may lead to gel formation *in-situ* and this precipitation can be induced solvent removal or by change in pH, by change in temperature (thermo sensitive systems)[4].

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 and photo-initiated polymerization).

***In-situ* formation based on Physiological Stimuli**

Thermally trigged system

In drug delivery research temperature-sensitive hydrogels are maybe the most commonly studied class of environment-sensitive polymer systems. 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 helped and there is no external source of heat is required other than body temperature for trigger gelation. A beneficial system should be tailor able to account for small differences in local temperature, such as might be bump into in appendages at the surface of skin or in the oral cavity. There are mainly three main strategies are exists in engineering of thermo responsive sol-gel polymeric system. For convenience, temperature-sensitive hydrogels are classified into positively thermo sensitive, negatively thermo sensitive, and thermally reversible gels. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and bond upon heating above the LCST. Polymers with low critical temperature (LCST) transition between physiological temperature and ambient is used for this purpose.

pH triggered systems

The pH-sensitive polymers comprise pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. Polyelectrolytes are the polymers with a large number of ionizable groups. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer comprises weakly basic (cationic) groups. The most of anionic pH-sensitive polymers are based on poly (acrylic acid) (PAA) (carbomer, Carbopol) or its derivatives. Likewise polyvinylacetal diethyl amino acetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have numerous limitations, including limited bioavailability and propensity to be easily removed by tear fluid. A poly (acrylic acid) (PAA) solution that would be gel at pH 7.4 for reduces this factor and maximizes this drug delivery. At high concentrations sufficient 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 by partially by combining PAA with HPMC, a viscous enhancing polymer, which resulted in pH responsive polymer combinations that was sol at pH 4 and gel at pH 7.4. Mixtures of poly (ethylene glycol) (PEG) and poly (methacrylic acid) (PMA) also has been used as a pH sensitive system to attain gelation.

***In-situ* formation based on Physical mechanism**

Swelling

The formation of *in-situ* may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol (glycerol mono-oleate), which is polar. Lyotropic liquid crystalline phase structures will form when lipid swell in water. It has some bioadhesive properties and can be degraded *in-vivo* by enzymatic action.

Diffusion

This method includes the diffusion of solvent from polymer solution into surrounding tissue and results in solidification or precipitation of polymer matrix. N- Methyl pyrrolidone (NMP) has been displayed to be useful solvent for such system.

***In-situ* formation based on Chemical Reactions**

Chemical reactions that results *in-situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, photo-initiated processes and enzymatic 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. While k-carrageen an forms rigid, brittle gels in reply of small amount of K+, i-carrageen an forms elastic gels mainly in the presence of Ca2+. Gellan gum commercially available as Gel rite is an anionic polysaccharide that undergoes *in-situ* gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca2+. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca2+ due to the interaction with guluronic acid block in alginate chains.

Enzymatic cross-linking

In-situ formation catalyzed by natural enzymes has not been examined widely but seems to have some benefits over photochemical and chemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially injurious chemicals such as initiators and monomers. Hydrogels that can release insulin from stimuli-responsive delivery systems 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 appropriate mechanism for controlling the rate of gel formation, which permits the mixtures to be injected before gel formation.

Photo-polymerisation

The commonly used for *in-situ* formation of biomaterials by Photo-polymerisation. Solution of monomers or reactive macromer and initiator can be injected into a tissues site and the use of electromagnetic radiation used to form gel. Acryl ate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo polymerisation in the presence of suitable photo initiator. Usually long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used frequently because it has limited penetration of tissue and biologically dangerous. A ketone, such as 2, 2 dimethoxy-2-phenyl acetophenone, is regularly 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 developed readily to be degraded by enzymatic or chemical processes or can be designed for long term persistence *in-vivo*. Photopolymerizable systems when introduced to the preferred site via injection get photo cured *in-situ* with the help of fiber optic cables and then release the drug for prolonged period of time. The photo-reactions offer rapid polymerization rates at physiological temperature. Additionally, the systems are easily placed in complex shaped volumes leading to an implant formation[5].

METHOD OF PREPARATION

***In-situ* forming drug delivery systems (ISFD)**

Injectable *in-situ* forming implants are classified into five categories, according to their mechanism of depot formation:

i. Thermoplastic pastes
ii. *In-situ* cross linked systems
iii. *In-situ* polymer precipitation
iv. Thermally induced gelling system
v. *In-situ* solidifying organogels.

Thermoplastic pastes (TP)

Thermoplastic pastes are semisolid polymers, it is injected as a melt and form a depot upon cooling to body temperature. They are considered as having a low melting point or glass transition temperature in the range of 25-65˚C and an intrinsic viscosity in the range of 0.05-0.8 dl/g. Below the viscosity of 0.05 dl/g, no delayed release could be observed, whereas above 0.8 dl/g the ISFD was no longer injectable using a needle. At injection temperature above 37˚C but below 65˚C these polymers perform

like viscous fluids which solidify to highly viscous depots. Drugs are combined into the molten polymer by mixing without the application of solvents. Bioerodible thermoplastic pastes could be prepared from monomers such as E-caprolactone, glycolide, D, L-lactide, dioxanone and orthoesters. Polymers and copolymers of this monomer have been widely used in surgical sutures, ocular implants, soft tissue repair etc. Zhang et al designed a thermoplastic ABA triblock polymer system composed of poly (D,L-lactide)- poly(ethylene glycol)-poly(D,L-lactide) and blend of ABA triblock copolymer and polycaprolactone (PCL) delivery of Taxol within tumor resection sites. Both provide release of Taxol for more than 60d but the rate of release was very slow. Additional drawback associated with this polymeric system was the high melting temperature of thermoplastic pastes requiring injection temperature at least 60˚C. Poly (orthoesters) POE have well matched properties for TP due to their good biocompatibility, relatively low softening temperatures in the range of 35-45˚C and degradation by surface erosion.

***In-situ* cross linked polymer systems**

The formation of a cross-linked polymer network is beneficial, to control the diffusion of the hydrophilic macromolecules. Cross-linked polymer network can be establish *in-situ* by free radical reactions initiated by heat (thermosets) or ionic interactions or absorption of photon between small cation and polymer anions. Dunn et al, used biodegradable copolymers of L-lactide or D, L-lactide with E-caprolactone to formulate a thermosetting system for prosthetic implants and slow release drug delivery systems it requires free radical producing agents such as benzoyl peroxide into the body which may induce tumor promotion Hibbell *et al*. defined a photopolymerizable biodegradable hydrogel as a tissue contacting material and controlled release carrier. This system involved of a macromer, PEG (polyethylene glycol) -oligo-glycol-acrylate, using a photo initiator, such as eosin and visible light. These hydrogel are restricted to surgical sites accessible to a light source as they form with difficulty after injection into the body. Ion-mediated gelation has been described for a number of polymers, e.g. chitosan/phosphate ions or alginates/calcium ions. The concentrations of the counter ion available under physiological situations are usually lacking for cross-linking of the above mentioned polymers. Even with these applications, there are two important factors which limit the use of calcium-alginate. The first factor is their potential immunogenicity and the second one is longer time *in-vivo* degradability.

***In-situ* polymer precipitation**

A water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent to which a drug is added forming a suspension or solution after mixing. When this formulation is injected into the body, the water miscible organic solvent dissolves and water penetrates into the organic phase. This leads to precipitation and phase separation of the polymer forming the depot at the site of injection. This method has been developed as Atrigel TM technology, which used as a drug carrier for Eligard TM, contains the leuteinizing hormone releasing hormone (LHRH) agonist leuprolide acetate (7.5, 22.5 or 30mg) and poly(lactide-co-glycolic acid)(PLGA) 75/25 dissolved in N-methyl-2-pyrrolidone (NMP) in a 45:55 (m/m) polymer: NMP ratio. This system led to suppression of testosterone levels in dogs for approximately 91d. One of the problems with this system is the possibility of a burst in drug release especially during the first few hours after injection into the body. In order to control the burst effect, four factors have been investigated, the concentration of polymer in the solvent, the molecular weight of the polymer, the solvent used and the addition of surfactant. Also the drug burst is directly related to the dynamics of the phase inversion. Himmelstein and joshi studied that polymer complex of PEG, polyacrylic acid (PAA), and polymethacrylic acid (PMA) is stable below pH≤5.7, the complex is insoluble in water but dissolves in a hydroalcoholic solvent to yield a clear viscous solution. After injection the diffusion of ethanol from the liquid transforms the system into a gel form upon contact with physiological situation. The gel disappears from the site of application with time due to complex dissociation into water soluble and low molecular weight component, which can be eliminated by glomerular filtration. Carbopol is a pH dependent polymer, which forms a low viscosity

gel in alkaline environment e.g. pH-7.4 and stays in solution in acidic pH. The addition of HPMC, a viscosity prompting agent, to carbopol reduces the carbopol concentration and hence the solution acidity while conserving the viscosity of the *in-situ* gelling system. This system gels upon an increase in pH when injected.

Thermally induced gelling system

Many polymers undergo rapid changes in solubility as a function of environmental temperature. The thermo sensitive polymer, poly (N-isopropylacrylamide) [poly (NIPAAM)] exhibit sharp lower critical solution temperature, LCST at about 32˚C, which can be shifted to body temperature by formulating poly NIPAAM based gels with salt and surfactant. Unfortunately, poly NIPAAM is not suitable for biomedical applications due to its well-known non-biodegradability and cytotoxicity (activation of platelets). Triblock poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) copolymer, pluronics or poloxamers, have shown gelation at body temperature when highly concentrated polymer solution >15% w/w were injected. These polymer concentration shown drawback of changing the osmolarity of the formulation, kinetics of the gelation, and causes discomfort in ophthalmic applications due to vision blurring and crusting. Macromed produced thermo sensitive biodegradable polymers based on ABA and BAB triblock copolymers. Where A is hydrophobic polyester block and B denotes the hydrophilic PEG block. The aqueous polymer solution of PEG-PLA-PEG is loaded with drug at 45˚C after injected into animal form a gel at body temperature, which constantly releasing hydrophilic model substances fluorescein isothiocyanate dextran (FITC-dextran), over 10-20d.An aqueous solution of low molecular weight PEGPLGA- PEG (550-2810-550) triblock copolymers becomes gel at body temperature.

***In-situ* solidifying organogel**

This organogels are composed of water insoluble amphiphilic lipids, which swell in water and forms various types of lyotropic liquid crystals. The amphiphilic lipids studied for drug delivery are glycerol monooleate, glycerol monopalmitostearate, glycerol monolinoleate, sorbitan monostearate (SMS) and different gelation modifiers (polysorbates 20 and 80) in various organic solvents and oils. These compound forms a cubic liquid crystal phase upon injection into an aqueous medium which is gel like and highly viscous. Sorbitan monostearate organogels having either w/o or vesicular in water in oil (v/w/o) emulsion were examined *in-vivo* as delivery vesicles for vaccines using albumin (BSA) and haemagglutin (HA) as model anigens. Intramuscular administration of the v/w/o gel yielded the extended depot effect for 48hrs. Controlled releases of contraceptive steroids ethinyl estradiol and levonorgestrel were achieved by Gao *et al*. In these work biodegradable organogel formulations prepared from glycerol palmitostearate (precirol) in derivatized vegetable oil, show *in-vitro* release of levonorgestrel up to 14d74, while subcutaneous injection into rabbits demonstrated an estrus blockage for up to 40d75[6].

EVALUATION AND CHARACTERIZATION OF *IN-SITU* GEL SYSTEM

Physical parameters

Physical parameters to be tested for *in-situ* gel solution are clarity, pH, gelling capacity, and drug content estimation.

Gelling capacity

The gelling capacity test was done by placing a drop of the prepared formulation in a vial containing 2.0 ml of freshly prepared buffer solution and visually observe[7].

Drug content

The drug content was determined by accurately placing 10gm of formulations in a volumetric flask and suitably diluted with buffer solution to obtain a concentration of 10µg/ml. By using UV-Visible spectrophotometer the drug concentration was determined[8].

Viscosity

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) were determined with different viscometer like Brookfield viscometer, Cone and Plate viscometer.

Texture analysis

The consistency, firmness and cohesiveness of formulation are measured using texture analyzer which mainly shows the syringe ability of solution

so the formulation can be easily administered *in-vivo*. To achieve the intimate contact with surfaces like tissues the gel should be in higher values of adhesiveness.

Sol-Gel transition temperature and gelling time

For *in-situ* gel forming systems, the sol-gel transition temperature and pH should be determined. Gelling time is the time required for first detection of gelation of *in-situ* gelling system. Thermo sensitive *in-situ* gel should be checked for *in-situ* gelling at body temperature.

Gel-Strength

The gel strength can be evaluated by using a remoter. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker, from the solution 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.

Drug-polymer interaction study and thermal analysis

This study can be performed by using Fourier Transform Infra-Red (FTIR) spectroscopy. During gelation process, the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo gravimetric Analysis (TGA) can be conducted for *in-situ* forming polymeric system to quantitate the percentage of water in hydrogel. Differential Scanning Calorimetry (DSC) conducted to observe if there are any changes in thermo grams as compared with pure active ingredients used for gelation[9].

Syringe ability Study

This study can be performed by taking a disposable syringe, with desirable amount of formulation in it, and then pass the formulation through 21-gauge needle. The formulations that passed easily from the needle it pass the syringe ability test.

***In-vitro* dissolution study**

In-vitro release profile was studied using USP apparatus II at 37˚ ± 10˚ C with a rotating speed of 100 rpm in dissolution media which containing pH 7.4 buffer. During the study, 5 ml of aliquots were removed at fixed time intervals (0.5, 1, 2, 4, 6, 8, 10, and, 24 hr) from the dissolution medium and replaced with fresh buffer to ensure sink condition and drug content can be determined by spectrophotometrically.

***In-vitro* diffusion studies**

In-vitro diffusion test was determined by using Franz diffusion cell. In Franz diffusion cell, cellophane membrane is sandwiched securely between donor and receptor compartment with the epidermis site facing the donor compartment. The receptor compartment is filled with buffer solution, which is continuously stirred and maintained the temperature at 37˚C ±1˚C throughout the experiment. Before starting the experiment the donor cell was sealed with paraffin film and covered with aluminum foil to prevent exposure to light. At predetermined time interval (0.5, 1, 2, 4, 6, 8, 10, and 24 hr) 5ml of aliquots are withdrawn and are replaced with an equal volume of fresh buffer to maintained sink condition and drug content can be determined by spectrophotometrically[10].

CONCLUSION

The injectable *in-situ* gelling system for prolonged release through parenteral delivery ensures that a promising system which can control as well as target the region where it is required. This compilation completely discusses the method of preparation, physical characterization and other issues in detail.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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