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Review Article

An overview of *in situ* gelling systems

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ABSTRACT

Recently controlled and sustained drug delivery has become the new standard in modern pharmaceutical design and a thorough research has been undertaken in achieving much better drug product effectiveness, reliability and safety. In situ gelling system has become an outstanding among novel drug delivery system (NDDS) in recent years due to its advantages like sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug compared to conventional drug delivery system (DDS). In this system the formulation is in the form of solution and when comes in contact with body fluids it undergoes gelation to form a gel. The formation of gels depends on factors like temperature changes, pH changes, presence of ions and ultraviolet irradiation. Various biodegradable polymers like gellan gum, pectin, alginic acid, chitosan, xyloglucan, etc are used. In situ gels are administered through various routes like oral, ocular, nasal, rectal, vaginal, injectable and intraperitonial. The production of such devices is also less complex and thus lowers the investment and manufacturing cost.

Keywords: NDDS, Gelling systems, Gelation

Introduction

The main aim of any drug delivery system is to modulate the pharmacokinetic and/or tissue distribution of the drug in a beneficial way.[1] Constantly there is an increase in demand for more patient compliant dosage forms. Hence the demand for their technologies has been increased. Due to very high development cost of new chemical entity, the pharmaceutical companies are focussing on development of new drug delivery systems for existing drugs with an improved efficacy and bioavailability together with reduced dosage frequency to minimize side effects.

Over the past few decades, greater attention has been given to development of controlled and sustained drug delivery systems, amongst which extensive research have been carried in designing polymeric drug delivery systems. The development of in situ gelling systems has received significant attention over the past few years.

In situ is a Latin word meaning 'in its original place' or 'in position'. In situ gelling drug delivery system is capable of releasing drug in a sustained manner, maintaining relatively constant plasma profiles. In the past few years, increasing number of in situ gelling systems have been investigated and many patents have been registered for their use in various biomedical applications, including drug delivery have been reported. This interest has been sparked by the potential advantages shown by in

situ forming polymeric delivery systems such as simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort, compared to conventional dosage form. It also promotes deliverance of accurate dose as well as prolongs residence time of drug at the site of administration. In situ gel formation occurs due to one or combination of different stimuli like change in pH, temperature or solvent exchange, ionic cross linkage, ionization, UV irradiation. Studies have been performed through various routes like oral, ocular, nasal, rectal, vaginal, injectable, parenteral and intraperitonial. Smart polymeric systems show capable means of delivering the drugs. These polymers undergo sol-gel transition, once administered. Since the early 1970's, natural and synthetic polymers began to be investigated for controlled release formulations. The reward of using biodegradable polymers in clinical application is apparent. Various natural and synthetic polymers are used for formulation development of in situ gel forming drug delivery systems.[4]

In the current place of drug delivery technologies, in situ gels have made an irreplaceable space due to their unique characteristics. The following review presents a brief introduction to in situ gels, various approaches for in situ gelling system, different types of polymers used, their evaluation and applications.

Importance

The major importance of the in situ gel is the opportunity of administering precise and reproducible quantities of drug compared to an already formed gel. Other advantages of in situ forming gel include:

- low dose is required for treatment
- minimum local and systemic side effects
- ease of application
- reduced frequency of drug administration
- improved patient compliance and comfort
- increased residence time
- improved bioavailability
- It can also be administered to unconscious patient

In controlled drug delivery system, the release of drug is extended over a period of time by zero order kinetics and hence constant plasma drug concentration can be obtained. Natural polymers have inherent properties of biocompatibility, biodegradability and biologically recognizable moieties that maintain cellular activities. Synthetic polymers often have well-defined structures which can be altered to obtain tailorable degradability and functionality.

In situ gels offer an important "stealth" characteristic in vivo, owing to their hydrophobicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.[7] In situ gels can be engineered to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration.

Approaches

There are 4 mechanisms for triggering the in situ gelling formation of biomaterials. These include:

1. *In situ* gel formation due to physiological stimuli:
a) Temperature triggered in situ gel systems
b) pH triggered in situ gelling systems
2. *In situ* gel formation due to ion-activated system
3. *In situ* gel formation due to physical mechanism
a) Swelling
b) Diffusion
4. *In situ* gel formation due to chemical reactions
a) Ionic cross-linking
b) Enzymatically cross linking
c) Photo-polymerization

1. In situ gel formation due to physiological stimuli:

There are some polymers which undergo large and unexpected physical and chemical changes in response to small external changes in their environmental conditions. Such polymers are called Stimuli-responsive polymers. They are

also called as stimuli-sensitive, intelligent, smart or environmentally sensitive polymers. These polymers recognize a stimulus as a signal, judge the degree of the signal and then transform their chain confirmation in response.[3]

a) Temperature triggered in situ gel system

Temperature sensitive polymers are most extensively studied class of environmentally responsive polymer systems in drug delivery. This is because temperature is relatively easy to control and also easily applicable to both in vitro and in vivo. In this system, gelling of solution is triggered by alteration in temperature, thus sustaining the drug release. These hydrogels exists in liquid form at room temperature (20-25°C) and undergo gelation when comes in contact with body fluid (35-37°C). The use biomaterial whose transition from sol-gel is triggered by increase in temperature is an attractive way to approach in situ formation. The best critical temperature range for such systems is ambient and physiologic temperature; such that clinical manipulation is facilitated and no external source of heat other than that of body is required to trigger gelation.[4]

Three main strategies are used in engineering the thermosensitive sol-gel polymeric system. Hence they are classified into

- Negatively thermosensible, which contract upon heating
- Positively thermosensible, which contract upon cooling
- Thermally reversible gel

Polymers which show temperature induced gelation are poloxamers/pluronics, cellulose derivatives [HPMC, ethyl (hydroxy ethyl) cellulose (EHEC), methyl cellulose], xyloglucan, tetronics, etc.

b) pH triggered in situ gelling systems

Another physiological stimulus that induces formation of in situ gel is pH. Polymers included in this class contain an acidic or a basic group that either accept or release protons when they are exposed to different environmental pH. Hence these are called pH sensitive polymers. This type of mechanism is mostly used for ocular drug delivery system. The increase in the precorneal residence time of drug and consequently better bioavailability can be achieved by using in situ gelling systems.[9] At pH 4.4, the formulation exists as a normal solution, but at pH 7.4, i.e. the pH of tear fluid, gelation occurs. The polymers having a large number of ionisable groups are called as polyelectrolyte. In case of weakly acidic groups (anionic), increase in swelling of hyrogel with increase in external pH is observed, whereas polymers containing basic (cationic) groups exhibit decreased swelling. Most of the pH sensitive polymers containing anionic group are based on PAA (Carbopol®, Carbomer) and its derivatives. Whereas at neutral pH conditions, polyvinylacetal diethylaminoacetate (AEA) solutions which have a low viscosity at pH 4, forms hydrogel. Other polymers which show pH induced gelation are cellulose acetate phthalate (CAP) latex, polymethacrilic acid (PMMA), polyethylene glycol (PEG), pseudolatexes, etc.

2. In situ gel formation due to ion activated system

Here, gelling of the instilled solution is induced by the change in ionic strength. It is believed that the osmotic gradient across the surface of the gel determines the rate of gelation. In presence of mono and divalent cations typically present in the tear fluids, the aqueous polymer solution forms a clear gel. The electrolyte present in the tear fluid, especially Na^+, Ca^{2+} and Mg^{2+} cations play an important role in initiation of gelling when the solution is instilled in the conjunctival cul-de-sac. Polymers that exhibit osmotically induced gelation include gelrite or gellan gum, hyaluronic acid, alginates, etc.

3. In situ gel formation due to physical mechanism

a) Swelling

In this method gelling occurs as the material absorbs water present in the surrounding environment and then expands to occupy desired space. Example of such a substance is myverol 18-99 (glycerol mono-oleate)

b) Diffusion

This method involves diffusion of solvent from polymer solution into surrounding tissue and results in precipitation of polymer matrix. N-methyl pyrrolidone (NMP) is one of the useful solvent for such system.

4. In situ gel formation due to chemical reaction

a) Ionic cross-linking

There are some ion sensitive polysaccharides such as gellan gum, pectin, sodium alginate which undergo phase transition in presence of various ions.[3] An anionic polysaccharide, Gellan gum, undergoes in situ gelling in occurrence of mono- and divalent cations, i.e. Ca^{2+}, Mg^{2+}, K^{+} and Na^{+}.

b) Enzymatically cross linking

In situ formation catalysed by natural enzymes has not been studied widely but it has some advantages over chemical and photochemical approaches.[3] For example, under physiologic conditions, an enzymatic process operates efficiently without need for potentially harmful chemicals like monomers and initiators. Adjusting the amount of enzyme provides a convenient mechanism for controlling the rate of gelling, which allows the mixture to be injected before gel formation.

c) Photo-polymerization

For in situ formation of biomaterials, photo-polymerization is usually used. A solution of monomer or reactive macromer and initiator is injected into a tissue site and electromagnetic radiation is applied to form gel. Acrylate and related polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers since they rapidly undergo photo-polymerization in presence of suitable photoinitiator. Particularly long wavelength UV and visible wavelengths are used. Short wavelength UV is not often used because of its limited penetration into tissue and since it is biologically harmful.

Photo-polymerizable systems when introduced to the desired site via injection get photocured in situ with help of fibre optic cables and then release the drug for prolonged period of time. At physiological temperature, the photo-reactions provide rapid polymerization rates. A photo-polymerizable, biodegradable hydrogel as a tissue contacting matter and controlled release carrier is reported by Sawhney et al.

Polymers used

Materials exhibiting sol to gel transition based on the above mentioned approaches are used as polymers in the in situ gelling system for sustained release of drug. Some of the polymers include:

1) Pluronic F127

Pluronics or Poloxamers consists of more than 30 different non-ionic surfactants. Their *in situ* gel formation is based on temperature change. These are triblock copolymers consisting of poly(oxyethylene) and poly (oxypropylene) units that undergo alteration in solubility with alteration in surrounding temperature. Their structure consists of central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Based on the ratio and distribution along the chain of the hydrophobic and hydrophilic subunits, many molecular weights are present, leading to different gelation properties.[3] Pluronic F217 gives colourless and transparent gel, and is one of the most commonly used polymer in pharmaceutical technology. A concentration of 20% weight of Pluronic® F217 at 25°C is required for gelation. The solution behaves as a mobile viscous liquid at room temperature (25°C), which is altered into a semisolid transparent gel at body temperature (37°C).[3] Formulations contaning Poloxamer usually increase drug residence time at the application site which results in improved bioavailability and efficacy.

2) Gellan gum

Gellan gum (Gelrite®) is a linear, anionic deacetylated exocellular polysaccharide secreted by the microbe *Pseudomonas elodea* with a tetrasaccharide repeating unit of one α-L-

rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. The polysaccharide is produced by aerobic fermentation and then isolated from the fermentation broth by alcohol precipitation. Gelation of gellan gum is based on change in temperature or cation induced. This gelation is due to formation of double helical junction zones followed by aggregation of the double helical segments which gives rise to a 3-dimensional network by complexation with cations and hydrogen bonding with water. In case of oral administration, the calcium ions are released in acidic environment of stomach leading to gelation of gellan, thus forming a gel in situ. In case of ophthalmic administration, on contact with cations in tear fluid, it forms a clear gel. This is due to cross linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na^+, K^+, Ca^{2+})

3) Alginic acid

Alginic acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-guluronic acid residues joined by 1,4-glycosidic linkage. Depending on the algal source, the proportion of each block and the arrangement of blocks along with the molecule varies. Dilute aqueous solutions of alginates form firm gels on addition of di- and tri-valent metal ions by a cooperative process involving consecutive glucoronic residues in the α-L-guluronic acid blocks of the alginate chain.[4] Alginic acid is mucoadhesive, biodegradable and non-toxic polymer, due to which it is widely used as a vehicle for ophthalmic in situ gelling system.

4) Pectin

Pectins are a family of polysaccharides, where the polymer backbone mainly comprises α-(1,4)-D-galacturonic acid residues. Low methoxy pectins (degree of esterification <50%) readily form gels in aqueous solution in presence of free calcium ions, which cross link the galacturonic acid chains in a manner described by egg-box model.[4] 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 fit as vehicles for drug delivery. One of the important advantages of Pectin is that it is water soluble, hence organic solvents can be eliminated from the formulation. When administered orally, divalent cations present in stomach carry out the gelation of Pectin. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of Paracetamol has been reported.[3]

5) Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and it is composed of a (1-->4)-β-D-glucan backbone 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 reultant product exhibits thermally reversible gelation by the lateral stacking of the rod like chains.[4] Thermally reversible gels are formed on warming to body temperature. Xyloglucan gels have potentially been used for oral, intraperitonial, ocular and rectal drug delivery.[4]

6) Xanthum gum

Xanthum gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacteria *Xanthomonas campestris*. The primary structure of this naturally obtained cellulose derivative contains a cellulose backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-guluronic acid-α-D-mannose attached with alternate glucose residues of the main chain. For delivery of proteins and peptides through the nasal cavity, xanthum gum has been tested for the preparation of sponge like in situ gelling inserts. Bioadhesive polymers can be used to increase the nasal residence time for overcoming the problem of mucociliary clearance in nasal delivery. This ensures the formation of highly porous polymeric sponges into which drug can be embedded.

Synthetic polymers

Synthetic polymers are of increasing interest in drug delivery as therapeutic agents. These are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, with no follow up required for

surgical removal after the depletion of drug supply. Aliphatic polyesters such as poly (lactic acid), poly(glycolic acid), poly(lactide-co-glycolide), poly(decalactone), poly ε-caprolactone have been subject of the most extensive investigations recently.[4]

Various other polymers like triblock polymer systems composed of poly (D, L-lactide)-block-poly(ethylene glycol)-block-poly(D,L-lactide) and poly (ε-caprolactone) are also used. These polymers are mainly used in injectable in situ formations. The practicability of lactide/glucolide polymers as excipients for controlled release of bioactive agents is well proven.[4]

Another type of synthetic polymeric system includes the in situ cross linking system, where the polymers from cross linked networks by means of light (photopolymerizable systems) or heat (thermosetting system)

Methods of preparation

Different methods have been reported for preparation of in situ gel. Some of these methods involves cross linking of co-monomers using cross linking agent or polymerization while some other methods involves cross linking of polymers by irradiation or by chemical means.

a) Solution polymerization or cross linking

In this method, multifunctional cross linking agents are mixed with ionic or neutral monomers. The polymerization is initiated thermally or by UV light or by redox initiator system. Solvent present minimizes the temperature control problem as well as serves as heat sink. The finished hydrogels requires washing with distilled water for removal of the unreacted materials, cross linking agent and the initiator. One of the best example of this method is poly (2-hydroxyethyl methacrylate) hydrogels from hydroxyethyl methacrylate, using ehtylene glycol dimethacrylate as cross linking agent.[2]

b) Suspension polymerization

This method is widely used for preparation of spherical hydrogel microparticles with size ranging from 1µm to 1mm. In this method, the monomer solution is dispersed in the non-solvent forming fine droplets, which are stabilised by addition of stabilizer.[2] The initiation of the polymerization is by thermal decomposition of free radicals. The prepared microparticles require further washing to remove unreacted monomers, cross linking agent and initiator.[2] Hydrogel microparticles of poly(vinyl alcohol) and (hydroxyl ethyl methacrylate) have been prepared by suspension polymerization method.

c) Polymerization by irradiation

High energy radiations such as gamma and electron beam are used to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains, which results in formation of microradicals.[2] Recombination of the microradicals on different chains results in the formation of covalent bonds, and finally a cross linked structure is obtained.[2] Polymerization microradicals may interact with oxygen during radiation, that's why radiation is performed in an inert atmosphere using nitrogen or argon gas.[2] Example of this method include poly (vinyl alcohol), poly(ethylene glycol) and poly (acrylic acid)

d) Chemically crossed linked hydrogels

Polymers which contain functional groups like -OH, -COOH, $-NH_2$ are soluble in water. Due to presence of such functional groups on the polymer chain, it can be used to prepare hydrogels by forming covalent linkages between polymer chains and complimentary reactivity, such as amine-carboxylic acid, isocyanate -OH or $-NH_2$ or by Schiff's base formation. Gluteraldehyde can be used as a cross linking agent for preparation of hydrogels of polymers containing -OH groups such as poly (vinyl alcohol) and also polymers containing amine groups (albumin, gelatin, polysaccharides).[2] This cross linking agent reacts with the functional groups present on the polymer via addition reaction. Since cross linking agents are highly toxic, unreacted agents have to be extracted. Also the reaction has to carried out in organic solvents since water can react with the cross

linking agent. The drugs are loaded after the formation of hydrogel, hence the release is typically first order.

e) Physically cross linked hydrogel

Almost all of the covalent cross linking agents are known to be toxic, even in small traces. Hence to overcome this problem and to avoid a purification step, hydrogels are prepared by reversible ionic cross linking.[2] Chitosan, a polycationic polymer reacts with positively charged components, either ions or molecules forming a network through ionic bridges between the polymeric chains. In case of anionic molecules, phosphate containing groups, particularly sodium triphosphate is widely studied. Ionic cross linking is an effortless and easy-going procedure. Compared to covalent cross linking, no auxillary molecules such as catalysts are required.[2] Chitosan is also known for forming polyelectrolyte complex with poly (acrylic acid)

Applications of *in situ* polymeric drug delivery system

Depending on the rate of administration, in situ gelling system can be classified as:

1) Oral drug delivery system

Potential uses of pH-sensitive hydrogels for site specific delivery of drugs to specific regions of GI tract have been widely studied. Polymers used for oral in situ gel delivery system are pectin, xyloglucan and gellan gum. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of paracetamol have been reported.[4] In situ gelling gellan formulation as vehicle for oral delivery of theophyllin has been reported.[4] Hydrogels made of varying proportions of PAA derivatives and cross linked PEG assist in preparation of silicone microspheres, which released Prednisolone in the gastric medium and showed protective property.

2) Ocular drug delivery system

In ocular delivery system, natural polymers like gellan gum, alginic acid and xyloglucan are mostly used. Local ophthalmic drug delivery has been used for various compounds such as anti-microbial agents, anti-inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma.[4] Problems encountered with conventional drug delivery systems are poor bioavailability and low therapeutic response due to high tear fluid turnover and dynamics causing rapid elimination of the drug from the eye. Hence to overcome this problem, in situ gels were developed. To further increase the bioavailability, viscosity enhancers like HPMC, CMC, Carbomers, PVA are used which prolong the precorneal residence time and hence improved bioavailability. And also they are easy to manufacture. Penetration enhancer such as preservatives, chelating agents and surfactants are also used to enhance corneal drug penetration. Much of the significance in the pharmaceutical application of gellan gum has concentrated on its application on ophthalmic drug delivery. A drug used in ophthalmic in-situ gelling system is Indomethacin.

3) Nasal drug delivery system

For nasal in situ gel system, gellan gum & xanthan gum are used as in situ gel forming polymers.[2] An in-situ gel system for nasal delivery Momethasone furoate was furoate was developed and evaluated for its efficacy for the treatment of allergic rhinitis.[2] In-situ gel was found to inhibit the increase in nasal symptoms compared to marketed preparation Nosonex (Momethasone furoate suspension 0.05%) in-situ gel drug delivery systems are suitable for protein and drug delivery.

4) Rectal drug delivery system

The rectal route may use for delivery of many types of drugs that are formulated as liquid, semisolid and solid dosage forms. Some conventional suppositories often cause discomfort during insert. Moreover, suppositories are not capable of sufficiently retaining at a specific position in rectum, sometimes they can migrate up-wards to the colon which makes them possible for drug to undergo the firstpass effect. Novel in-situ gelling liquid preparation have gelation temperature 30°C to 36°C.[2] Poloxamer 407 and /or

poloxamer 188 were used to confer the temperature sensitive gelation property.[2] Xyloglucon based thermo reversible gel for rectal delivery of Indomethacin is one of the example.

5) Vaginal drug delivery system

Besides being an important organ of reproductive tract, vagina also serves as a potential route for drug administration. For better therapeutic efficacy and patient compliance, mucoadhesive, thermosensitive, prolonged release vaginal gel incorporated with Clotrimazole-β-cyclodextin complex has been formulated for treatment of vaginitis.[4]

6) Injectable drug delivery system

The development of injectable in situ forming drug delivery system has received a significant interest over the last decade. A novel, injectable, thermosensitive in situ gelling hydrogel was developed for tumour treatment. This hydrogel consisted of drug loaded Chitosan solution neutralized with β-glycerophosphate.[4] Local delivery of Paclitaxel from the formulation injected intratumorally was investigated using EMT-6 tumours implanted subcutaneously on albino mice.[4] Poloxamer gels were tested for i.m. and s.c. administration of growth hormone or with the aim to formulate a long acting single dose injection of Lidocain.

Evaluation and characterization

Following parameters are used for evaluation and characterization of in situ gel:

i. Clarity:

The clarity of the formulated solution is determined by visual inspection under black and white background.[2]

ii. Texture analysis:

The firmness, consistency and cohesiveness of hydrogels are examined using texture analyzer which significantly indicates the syringeability of sol so that the formulation can be easily administered in vivo. Higher values of adhesiveness of gels are required to maintain an intimate contact with surface.

iii. pH of gel:

Formulation is taken in a beaker and 1ml NaOH added dropwise with continuous stirring, pH is checked by using pH meter.

iv. Sol-Gel transition temperature and gelling time:

For in situ gelling systems with thermoreversible polymers, the sol-gel transition temperature may be defined as the 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 specific rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube.

v. Gel strength:

This parameter is evaluated using a Rheometer. Depending on the mechanism of gelling of the gelling agent used, a defined amount of gel is prepared in a beaker form the sol form. This gel containing beaker is raised at a definite rate, so pushing a probe slowly through the gel. The changes in the load on the probe are measured as a function of depth of immersion of the probe below the gel surface.

vi. Rheological studies:

This is one of the important parameter to be evaluated for in situ gels. Viscosity and rheological properties of in situ gelling drug delivery systems are assessed using Brookfield rheometer, or some other viscometers like Ostwald's viscometer. The viscosity of in situ gelling systems should be such that no difficulties are encountered during their administration by the patient, especially in parenteral and ocular administration. The formulation should have viscosity of 5-1000 mPas.

vii. High performance liquid chromate-graphy:

The HPLC system if used in reversed phase mode.[2] Analysis is performed on a Nova pack C18 packed column (150 mm length X 3.9 mm i.d)

viii. Drug-polymer interaction study and thermal analysis:

Interaction studies are performed with Fourier Transform Infra Red (FTIR) spectroscopy. During gelation process, the nature of interacting forces can be determined using this technique by employing KBr pellet method. Thermo gravimetric analysis (TGA) can be used for in situ gelling system to determine the percentage of water in hydrogel. Differential scanning calorimetry (DSC) used to observe if there are any changes in thermograms as compared to pure active ingredients used for gelation.

ix. In vitro drug release studies:

For the in situ gel formulations administered by oral, ocular or rectal routes, the drug release studies are done by using plastic dialysis cell. The cell is made up of 2 half cells, donor compartment and receptor compartment and both these compartments are separated with the help of cellulose membrane. The sol form of the formulation is sited in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution is analyzed for the drug release using analytical methods. For injectable in situ gels, the formulation is sited into vials containing receptor media and placed in a shaker water bath at required temperature and oscillation rate, samples are withdrawn periodically and analyzed.

x. Antimicrobial activity:

Antimicrobial studies are carried out to determine the biological activity of sol-gel-system against microorganisms. This is done using agar diffusion medium employing *'Cup Plate Techniques*'. The microbial growth of bacteria is measured by concentration of antibiotic and compared with that produced with known concentrations of standard preparation of antibiotic and carried out the microbial assay serial dilution method is employed.

xi. Sterility Testing:

Sterility testing is carried out as per IP 1996. The formulation is incubated for not less than 14 days at 30-35°C in the fluid thioglycolate medium to find the growth of bacteria and at 20-25°C in Soya casein digest medium to find the growth of fungi in formulations.[2]

xii. Accelerated stability studies:

Formulation is replaced in amber coloured vials and sealed with aluminium foil for the short term accelerated study at 40 ± 2°C and 75 ± 5% RH as per International Conference of Harmonization (ICH) Guidelines. Sample is analyzed at every month for clarity, pH, gelling capacity, drug capacity, drug content, rheological evaluation and in vitro dissolution.

Recent advances

One of the challenges in front of today's pharmaceutical industry centres on coming up with efficient treatment options that are readily tolerable to physicians and patients. Delivery systems should also have contribution in better therapeutic outcome is they are going to provide possible alternatives to pharmaceuticals currently delivered by other routes. In situ gelling formulations are one of the challenging drug delivery systems. Various biodegradable polymers are used for formulation of in situ gels, but there are manufacture problems, difficult processability, use of organic solvents for their preparation (particularly for synthetic polymer based systems), burst effect and irreproducible drug release kinetics. Natural polymers suit the characteristics of an ideal polymer but batch to batch reproducibility is difficult, hence synthetic polymers are used. But all these problems are

being overcome day by day and these in situ forming gels are becoming a major tool for site specific delivery of drugs.

Marketed preparations

a) Timoptic-XE
b) Azasite
c) Pilopine HS
d) Regel
e) Cytoryn

Conclusions

The primary requirement for a successful controlled release product is focusing patient compliance, which is offered by in situ gels. Each drug having its own therapeutic effects can be administered through various routes as in situ gels. Exploitation is polymeric in situ gels for controlled release of various drugs provide many advantages over conventional dosage forms and are very reliable due to its sustained and prolonged drug release, good stability and biocompatibility characteristics. Use of biodegradable and water soluble polymers for the in situ gel formulations makes them more acceptable and excellent drug delivery system.

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