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Review Article

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REVIEW ON INSITU GELLING SYSTEM

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ABSTRACT

The main aim of any drug delivery system is to modulate the pharmacokinetics and /or tissue distribution in better beneficial way. The development of in situ gelling systems has received significant attention over the past few years. It offers several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. The article presents a detailed review of these types of polymeric systems, their evaluation, advancements and their commercial formulations.

KEYWORDS: Insitu gel, Method of preparation, Recent advances.

INTRODUCTION

The main aim of any drug delivery system is to modulate the pharmacokinetics and /or tissue distribution in better beneficial way. Constantly there is an increase in demand for patient compliant dosage forms. The pharmaceutical companies are mainly focusing on development of new drug delivery system for already existing drug with improved efficacy and bioavailability and also with reduced dosage frequency to minimize side effects.

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

IN SITU GEL

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 patent 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 down by in situ forming polymeric 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 occur due to one or more stimuli like change in pH, Studies have been performed through various routes like oral, ocular, nasal, rectal and vaginal. 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 and development of in situ gel forming drug delivery systems.

In the current place of drug delivery technology in situ made an irreplaceable position due to their special characteristics. It is have unique properties Different type of polymers used, their formulation and evaluation. The various biodegradable polymers used are gellan gum, pectin, chitosan, alginic acid, xyloglucan, etc. Before administration in the body these are in sol form but one administered undergo gelation in situ to form a gel under physiological condition.

Importance

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

- Low dose is required for treatment
- Minimum local and systematic side effects
- Improved patient compliance and comfort
- Simple formulation and manufacturing so less investment and cost
- Reduced dose concentration
- Reduced dosing frequency
- Improved local bioavailability
- Increased residence time

- Ease of application
- It can also administered to unconscious patient

Approaches

1. In situ formation due to physiological stimuli

Thermally triggered systems

Temperature-sensitive hydrogels are most commonly studied class of environment sensitive polymer systems in drug delivery research. The use of biomaterial whose transition from sol-gel is triggered by increasing 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 facilitated and no external source of heat other than that of body is required for triggering gelation. A useful system should be tailorable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity

- They are classified into
- Positively thermo sensitive
- Negatively thermo sensitive
- Thermally reversible gels

Positively thermo sensitive

A positive temp sensitive hydrogel is having upper critical solution temperature (UCST), such hydrogel contracts upon cooling below UCST.

- Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic(cationic) groups
- The most anionic pH-sensitive polymers are based on PAA, carbopol-carbomer or its derivative likewise polyvinyl acetal diethyl amino acetate (AEA) Solutions with a low viscocity at pH 4 from hydrogel at natural pH condition.
- Anionic ex, Are PMMA, PEG, CAP latex, Pseudo latex, etc.

2. In situ formation based on *physical mechanism*

a. Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to cover desired space. One such substance is Myverol I899 (glycerol mono oleate). Which is polar lipid that swells in water to form lyo tropic liquid crystalline phase structure It has some bio adhesive properties and can be degraded in vivo enzymatic action

b. Solvent exchange-diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-

- Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated.

Photo polymerization

Ex. Poly acrylic acid (PAA), poly acryl amide (PAAm).

Negatively thermo sensitive

Has lower critical solution temperature (LCST), Contracts upon heating above LCST.

Ex. Poly(N-isopropyl acryl amide)

PNIPAAm is a water soluble polymer at it's low LCST, but hydrophobic above LCST, which result on precipitation of PNIPAAm from the solution at the LCST.

Mostly used thermo reversible gels are prepared from Pluronics and Tetronics

Pluronics are poly(ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPOPEO) triblock co-polymer that are fluid at low temperature, but forms thermo responsible gel when heated as a consequence of a disorder-order transition in micelle packing which makes these polymers suitable for in situ gelation.

b. pH triggered systems

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as poly electrolytes.

methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.

3. In situ formation based on *chemical reaction*

Following chemical reaction cause gelation

Ionic cross linking

Enzymatic cross-linking

Photo-polymerization

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-carrageenan forms in rigid , brittle gels in reply of small of k^+, i-carrageenan forms elastic gels mainly in the presence of ca^{2+} . Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono and Enzymatic cross linking
- In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

- Photo polymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application electromagnetic radiation used to form gel.

- Typically long wavelength ultraviolet and visible wavelengths are used.

4. 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 fluid the aqueous polymer solution forms a clear gel.
- The electrolyte present in the tear fluid especially Na+, Ca2+ and Mg2+ play an important role in initiation of gelling.
- Polymers that exhibit osmotically induced gelation include gallan gum, hyaluronic acid, alginate etc.

2. Gellan gum

It's a linear anionic de acetylated cellular polysaccharide secreted by the microbe pseudomonas elodea with a tetrasaccharide repeating units. The polysaccharide is produced by aerobic fermentation and then isolated from the fermentation broth by alcohol precipitation.

3. Alginic acid

It's a linear block copolymers polysaccharide consist of mannuronic acid and glucuronic acid residues joined by 1, 4- glycosidic linkage. Alginic acid is biodegradable and non toxic polymer due to which widely used as a vehicle for ophthalmic in situ gelling system.

4. Pectin

These are a family of polysaccharide. The polymers mainly consist of galacturonic residues. The main important advantage of pectin is that water soluble. Hence organic matters can be eliminated from the solution.

5. Xanthum gum

It's a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacteria xanthomonas compestris. The primary structure of this naturally obtained cellulose derivative contains a cellulose backbone.

METHOD OF PREPARATION

Different methods have been reported for the preparation of in situ gel.

1. 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 ultra violet light or by redox initiator system. Solvent present minimize the temperature control problem as well as serve as a heat sink. The finished hydro gel requires washing with distilled water for removal of unreacted materials, cross linking agents and initiator.

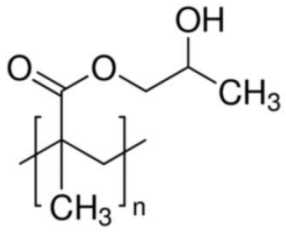
Example; poly (2-hydroxy ethyl methacrylate)

Polymer

Material exhibiting sol to gel transition based on the above mentioned Approaches are used as polymers in the in situ gelling system for sustained release drug some of the polymers are,

1. Pluronic F127

These polymers consist of more than 30 different surfactants. Their in situ gel formation is based on temperature change. These are co polymers consist of poly (oxy ethylene) and poly (oxy propylene) units. That may undergo alteration in solubility with alteration in surrounding temperature.



2. Suspension polymerization

This method is widely used for preparation of spherical hydro gel Micro particles with size ranging from 0.1mm to 1mm. In this method the monomer solution is dispersed in the non solvent forming fine droplet, which are stabilized by addition of stabilizers. The initiation of polymerization is by thermal decomposition of free radicals. The prepared micro particles require further washing to remove un reacted monomers, cross linking agents and initiator.

3. Polymerization by irradiation

High radiations such as gamma and electron beam are used to prepare the hydro gel of unsaturated compound. The irradiation of aqueous polymer solutions results in the formation of radical on the polymer chain, which result in the formation of micro radical. Recombination of micro radicals on different chains results in the formation of covalent bonds, and finally cross linked structure is formed. Polymerization micro radical may interact with oxygen during radiation, that's why radiation performed in an inert atmosphere using nitrogen and argon gas.

4. Chemically cross linked hydro-gel

Polymers which contain functional group such as –OH, -COOH, - NH2 are soluble in water. Due to presence of such functional group on polymer chain it can be used to prepare hydro gel by forming covalent linkage between polymer chain and complementary reactivity, such as amine- carboxylic acid, isocyanate- OH or NH2 or by Schiff`s base formation. Glutaraldehyde can be used as a cross linking agent for preparation of hydro gel of polymers containing –OH group such as poly (vinyl

alcohol) and also polymers containing amino group (albumin, gelatin, polysaccharides). The cross linking agent react with the functional group present on the polymer via addition reaction.

5. Physically cross linked hydro gel

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, hydro gels are prepared by reversible ionic cross linking. Chitosan a poly cationic polymer react with positively charged components either ions or molecule forming a network through ionic bridge between the polymeric chain. In case of anionic molecules, phosphate containing group particularly sodium tri phosphate widely studied.

Applications

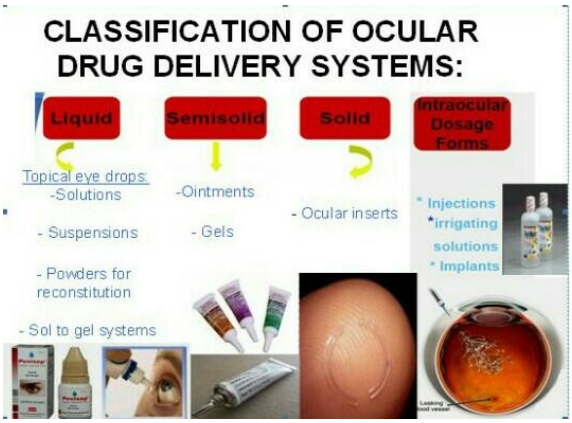
Depending on the rate of administration in situ gelling system can be classified as;

1. Oral drug delivery system

Potential uses of PH sensitive hydro gel for site specific delivery of drug to specific regions of GI tract have been widely studied. Polymers used for oral in situ gel delivery system are pectin, xyloglucogan and gellan gum. The potential of an orally administered in situ gelling pectin formulation for the sustained delivery of paracetamol have been reported. Hydro gel made of varying proportion of PAA derivatives and cross linked PEG assist in preparation of microspheres, which released prednisolone in the gastric medium and shows protective.

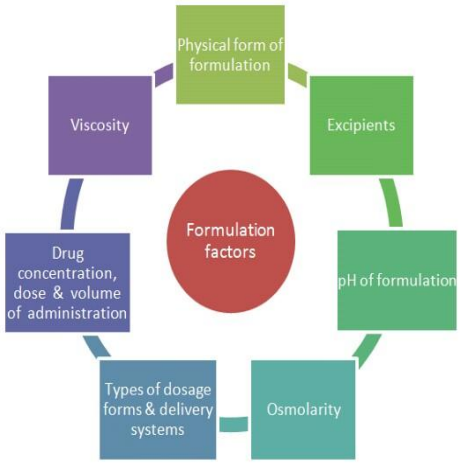
2. Ocular drug delivery system

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 antimicrobial agents, anti inflammatory agents and autonomic drugs used to relieve intraocular tension in glaucoma. Problems encountered with conventional drug delivery systems are poor bioavailability and low therapeutic response due to high tear fluid turnover and dynamic causing rapid elimination of the drug from the eye. Hence to overcome this problem, in situ gel were developed.



3. Nasal drug delivery system

For nasal in situ gel system, gellan gum and xanthan gum are used as in situ gel forming polymers. An in situ gel system for nasal delivery momethasone furate was developed and evaluated for its efficacy for the treatment of allergic rhinitis. In situ gel was found to inhibit the increasing in nasal symptoms compared to marketed preparation Nosonex 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, to sometimes they can migrate upwards to the colon which make them possible for drug to undergo the firstpass effect. Novel in situ gelling liquid preparation have gelation temperature 30^0c to 36^0c

5. Injectable drug delivery system

The development of injectable in situ forming drug delivery system has received a significant interest over the last decades. A novel, injectable thermo sensitive in situ gelling hydro gel was developed for tumour treatment. This hydro gel consisted of drug loaded Chitosan solution neutralized with B-glycerophosphate. Local delivery of paclitaxel from the formulation

injected intra tumorally was was investigated using EMT-6 tumours implanted subcutaneously on albino mice.

Recent Advances

One of the challenges in front of today's pharmaceutical industry centers 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, 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 deliver of drugs.

Commercial formulations of in situ polymeric system

1. Timoptic –XE

2. Azasite

3. Pilopine HS

4. Regel

5. Cytoryn

CONCLUSION

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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