

INJECTABLE DRUG DELIVERY SYSTEMS WITH CYCLODEXTRIN-POLYMER BASED HYDROGELS

Field of the Invention

5 The invention is directed to injectable drug delivery systems with cyclodextrin-poly(ethylene glycol) polymer based hydrogels.

Background of the Invention

 A variety of polymers used for controlled release and delivery of drugs have
10 been developed in the past 20 years. Most of the polymers are formed into implants or injectable microspheres. Such polymers are, and must be, biodegradable and biocompatible.

 In order to form suitable forms of polymers, complicated fabrication processes are required which typically involve organic solvents. The use of organic solvents,
15 however, may cause denaturation of some protein drugs and even traces of an organic solvent may be toxic.

 Polymer hydrogels have been explored for drug delivery and controlled release. For example, chemically cross-linked polymer hydrogels have been used as implants. Some injectable drug delivery systems form chemically cross-linked hydrogels in the
20 body after injection. However, the chemical reactions occurring in the body may cause tissue irritation and damage.

 In situ formed hydrogels from thermosensitive block copolymers have also been proposed as sustained release matrix for drugs. They have the advantage that there is no chemical reaction involved in the gel formation. These copolymer
25 hydrogels are usually designed for macromolecular drugs such as protein and hormone drugs. The disadvantage of such temperature sensitive hydrogels is the practicality of using such a gel in injection.

 In 1994, June Li and co-workers reported the formation of hydrogels between linear poly(ethylene glycol)s and cyclodextrin. However, since then, there has been
30 few articles on injectable drug delivery systems. In recent years, S.W. Kim et al

published a few papers on injectable drug delivery systems using thermosensitive or electrically sensitive hydrogels formed from biodegradable block copolymers.

The article describes poly(ethylene glycol)s (PEG) of high molecular weight which was found to form complexes with alpha-cyclodextrin (alpha-CD) in aqueous solutions to give gels in a wide range of concentration. The time of gelation decreased with increase in alpha-CD and PEG concentration, indicating that the gel formed during complex formation between alpha-CD chains. The time of gelation increases in the molecular weight of PEG, indicating that the PEG chains penetrate alpha CD cavities from the ends of PEG and are included in alpha-CDS. X-Ray powder diffraction studies showed that the gel consists of both complexed alpha-CD and uncomplexed alpha CD, indicating partial inclusion of PEG chains by alpha-CD. Further, the gel-melting temperature increased with increases in PEG molecular weight and alpha-CD concentration, and decreased with increase in PEG concentrations, suggesting that gelation results from the formation of longer or shorter domains of alpha-CD-PEG inclusion complexes respectively. (Li J, Harada A, Kamachi M., Sol-Gel Transition During Inclusion Complex-Formation between Alpha-Cyclodextrin and High Molecular-Weight Poly(ethylene glycol)s in Aqueous Solution. Polymer Journal 26:(9) 1019-1026 1994.

A further article explores polymers as potential drug delivery systems that display a physicochemical response to stimuli. Stimuli studied to date include chemical substances and changes in temperature, pH, and electric field. Homopolymer or copolymers of N-isopropylacrylamide and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) are typical examples of thermosensitive polymers, but their use in drug delivery is problematic because they are toxic and non-biodegradable.

Biodegradable polymers used for drug delivery to date have mostly been in the form of injectable microspheres or implant systems, which require complicated fabrication processes using organic solvents. Such systems have the disadvantage that the use of organic solvents can cause denaturation when protein drugs are to be encapsulated. Furthermore, the solid form requires surgical insertion, which often results in tissue irritation and damage. Thermosensitive, biodegradable hydrogels may be synthesized using blocks of poly(ethylene oxide) poly(L-lactic acid). Aqueous

solutions of these copolymers form a sol around 45°C. In this form, the polymer is injectable. On subsequent rapid cooling to body temperature, the loaded copolymer forms a gel that act as a sustained release matrix for drugs. (Jeong B, Bae YH, Lee DS, Kim SW Biodegradable Block Copolymers as Drug Delivery Systems Nature 5 388:(6645) 860-862 August 28, 1997.)

Another article (Kwon IC, Bae YH, Kim SW, Electrically Erodible Polymer Gel for Controlled Release of Drugs Nature 354:(6351) 291-293 November 28 1991) is directed to new controlled drug-delivery systems being explored to overcome the disadvantages of conventional dosage forms. For example, stimulated drug delivery 10 has been used to overcome the tolerance problems that occur with a constant delivery rate, to mimic the physiological pattern of hormonal concentration, and to supply drugs on demand. Stimuli sensitive polymers, which are potentially useful for pulsed drug delivery, experience changes in either their structure or their chemical properties in response to change in environmental conditions. Environmental stimuli include 15 temperature, pH, light (ultraviolet or visible), electric field or certain chemicals. Volume changes of stimuli sensitive gel networks are particularly responsive to external stimuli, but swelling is slow to occur. Such systems also provide insight into intermolecular interactions. The polymeric system rapidly changes from a solid state to solution in response to small electric currents, by disintegration of the solid polymer 20 complex into water-soluble polymers. The modulated release of insulin, and by extension other macromolecules, can be achieved with this polymeric system.

It is desired to have an improved hydrogel system for the delivery and controlled release of drugs into the body. It is desired that the process of forming the hydrogel be simple and easy. It is also desired that the properties of the hydrogels be 25 tunable with different copolymers thus allowing delivery and controlled release of a variety of drugs, including protein drugs, and vaccines.

Summary of the Invention

The invention is directed to a cyclodextrin polymer-based injectable 30 composition comprising cyclodextrin, a polymer which is capable of forming a hydrogel with the cyclodextrin, and a pharmacologically effective amount of at least

one drug; wherein the polymer is selected from poly(ethylene glycol), derivatives thereof, or a copolymer with a poly(ethylene glycol) segment. The copolymer with a poly(ethylene glycol) segment may include a polymer selected from the group consisting of polyesters, polyurethanes, polyamides, polyethers, polysaccharides, poly(amino acid)s, polypeptides, and proteins. The cyclodextrin may be naturally synthesized by microorganisms or artificially synthesized. The drug is preferably in a pharmaceutically acceptable injectable aqueous fluid.

The invention is further directed to the cyclodextrin polymer-based injectable composition described above and further containing a secondary polymer which complexes with the drug, conjugates the drug, or both. The secondary polymer may be a polymer selected from the group consisting of polyesters, polyurethanes, polyamides, polyethers, polysaccharides, poly(amino acid)s, polypeptides, and proteins. The secondary polymer may be a di- or mono-functional polymer or polyionic polymer with poly(ethylene glycol) segments.

The invention is further directed to a method of treating a condition requiring pharmacological treatment which comprises injecting into the body a cyclodextrin polymer-based injectable composition comprising cyclodextrin, a polymer which is capable of forming a hydrogel with the cyclodextrin, and a pharmacologically effective amount of at least one drug; wherein the polymer is selected from poly(ethylene glycol), derivatives thereof, or a copolymer with a poly(ethylene glycol) segment. The injection may be subcutaneous or intramuscular.

Brief Description of the Drawings

Figure 1 depicts the release of dextrin-FITC from a hydrogel formed from alpha-cyclodextrin and linear poly(ethylene glycol) with different molecular weights.

Figure 2 depicts the release of dextrin-FITC from hydrogels formed from alpha-cyclodextrin and Pluronic polymer poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) with different molecular weights and different ratios between poly(ethylene glycol) and poly(propylene glycol) segments.

Detailed Description of the Invention

The invention is based on the discovery that gel formation during supramolecular self-assembly between the components forms an injectable hydrogel.

5 Supramolecular self-assembly concerns the spontaneous association of multiple molecular components into a specific phase having well-defined microscopic organization and macroscopic characteristics. It was discovered that drugs can be delivered in a sustained manner from an *in vivo* matrix or carrier formed from a cyclodextrin polymer-based injectable hydrogel. The injectable composition is a
10 physically cross-linked hydrogel that carries a drug to be released.

The hydrogel is bioabsorbable, thermosensitive, and thixotropic, and undergoes reversion between gel and sol under certain conditions. Bioabsorbable means the polymer can disappear from its initial application site in the body with or without degradation of the dispersed polymer molecules. The gel-sol transition temperature is
15 generally above room temperature, which depends on the composition of the gel, as well as on the chemical structure and molecular weight of PEG or PEG copolymers.

The formation of the hydrogel is generally very simple and easy. In addition, the properties of the hydrogels are tunable with different copolymers thus allowing delivery of a variety of drugs, including protein drugs, and vaccines, and also allows
20 for the sustained, controlled release of the drugs, genes, vaccines, and the like. For example, the hydrogel gel may be adjusted to be a more flexible hydrogel or a more rigid hydrogel. The hydrogel structure can be tailored to have variable viscosity and drug release rates. Structures with positive charge or with higher hydrophobicity could be used to yield a more sustained release.

25 The invention is directed to a cyclodextrin polymer-based injectable hydrogel prepared from a cyclodextrin, a polymer capable of forming hydrogel with the cyclodextrin, and at least one drug. The hydrogel provides a sustained, controlled release matrix for the drug.

The drug is in a pharmaceutically acceptable injectable aqueous fluid and may
30 be any drug suitable for injection. Suitable drugs include, but are not limited to, analgesics, anesthetics, antiarthritics, antiasthmas, anticoagulants, anticonvulsants,

antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, antibiotics, antihistamines, decongestants, anti-inflammatories, muscle relaxants, peptide drugs, anti-parasitic drugs, antiviral drugs, genes, and vaccines.

The drug is in a macromolecular form or in a low molecular weight form. Low
 5 molecular weight drugs may be conjugated to, for example, poly(ethylene glycol) to form a macromolecule. The drug used herein is defined to encompass not only compounds or species which are inherently pharmaceutically or biological active but also material which include one or more of these active compounds or species.

The hydrogel may also carry DNA nanospheres for sustained, controlled
 10 release of the DNA nanospheres. DNA nanospheres are nanoparticles synthesized by salt-induced complex coacervation of DNA and polycations such as gelatin and chitosan as gene delivery vehicles (Leong, KW, et al., DNA-polycation nanospheres as non-vial gene delivery vehicles, Journal of Controlled Release 53: 183-193, 1998). PEG copolymers, while the polymers condense or bind DNA and form DNA
 15 nanospheres in the hydrogels.

The pharmaceutically acceptable injectable aqueous fluid may be, but is not limited to, injectable saline. If desired, the aqueous fluid may also contain buffering agents and/or preservatives. Suitable buffering agents include, but are not limited to, alkali or alkali earth carbonates, phosphates, bicarbonates, citrates, borates, acetates,
 20 and succinates. Suitable preservatives include, but are not limited to, sodium bisulfite, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimersol, phenylmercuric borate, parabens, benzyl alcohol and phenylethanol.

Cyclodextrins are a series of natural cyclic oligosaccharides composed of six, seven, eight, or more D (+) glycopyranose units linked by alpha 1, 4 linkages.
 25 Cyclodextrins are biodegradable and biocompatible and may be naturally or artificially synthesized. Cyclodextrin may be synthesized naturally by microorganisms, for example. Artificially modified cyclodextrins allow manipulation of its properties to improve their solubility, complex-forming capability, and specificity, and other properties. Cyclodextrin used herein refers to all forms of the natural and artificially
 30 modified forms. Suitable cyclodextrins include α -cyclodextrin, β -cyclodextrin, γ -

cyclodextrin and derivatives thereof, including hydrophobic derivatives, hydrophilic derivatives, charged cyclodextrins, and the like.

The polymer is bioabsorbable/biodegradable, biocompatible, and is capable of forming hydrogel with cyclodextrin. Bioabsorbable means the polymer can disappear
 5 from its initial application site in the body with or without degradation of the dispersed polymer molecules. Biodegradable means that the polymer can break down or degrade within the body to nontoxic components by hydrolysis or enzymatic degradation. Biocompatible means that all of the components are nontoxic in the body.

The polymer is a poly(ethylene glycol), a derivative thereof, or a copolymer
 10 that reacts with the poly(ethylene glycol) segment. The polymer can also be poly(propylene glycol) or other poly(alkylene glycols). Higher molecular weight poly(ethylene glycol) is also called poly(ethylene oxide). Preferably the polymer is poly(ethylene glycol). The copolymer may be any one of a variety of biodegradable and biocompatible copolymers that contain ethylene glycol units which can form
 15 hydrogels with cyclodextrins such as polyesters, polyurethanes, polyamides, polyethers, polysaccharides, poly(amino acids), polypeptides, or a proteins.

The poly(ethylene glycol) may have different forms and different end groups. For example, the poly(ethylene glycol) derivatives may have different structures, e.g. star-shaped poly(ethylene glycol), comb-like poly(ethylene glycol), etc. The
 20 poly(ethylene glycol) may be modified molecules, e.g. pegylated polysaccharides, pegylated poly(amino acid)s, pegylated proteins, etc. The poly(ethylene glycol) derivatives or copolymers may have poly(ethylene glycol) or poly(propylene oxide) segment(s) at the end(s), in which the middle segment carries positive charge. In addition polyamine derivatized poly(ethylene glycol), e.g. pegylated poly(ethylene
 25 imine), pegylated polylysine may be used.

Poly(ethylene glycol) block copolymers with poly(propylene oxide), including all pluronic polymers (Pluronic) may also be used. Different molecular weight of each segments, and weight ratio of the blocks, and different sequences may be used such as PEO-PPO-PEO (Pluronic), PPO-PEO-PPO (Pluronic-R), PEO-PPO, etc.

The molecular weight of the polymer is preferably between 1,000 and 50,000, more preferably between 5,000 and 35,000. Preferably the polymer is in an aqueous solution. For example, typical aqueous solutions contain about 1% to about 80% polymer, preferably about 10% to about 40%. A non-limiting example commercially
5 available is 28% poly(ethylene glycol).

The cyclodextrin and polymer are combined in sufficient amounts and ratios to provide an injectable hydrogel. The hydrogel can be made to pass through needles up to 27 G. Typically, the amount of cyclodextrin to polymer is, but not limited to, 0.275 in weight.

10 Suitable polymers useful in the invention include PLURONIC (BASF Corp.) surfactant which is a group of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymers also known as poloxamers. The PEG block at both ends is able to complex with α -cyclodextrin, just like the PEG molecules. PLURONIC polymers have unique surfactant abilities and extremely low toxicity and
15 immunogenic responses. These products have low acute oral and dermal toxicity and low potential for causing irritation or sensitization, and the general chronic and subchronic toxicity is low. In fact, PLURONIC polymers are among a small number of surfactants that have been approved by the FDA for direct use in medical applications and as food additives (BASF (1990) Pluronic & Tetronic Surfactants,
20 BASF Co., Mount Olive, NJ). Recently, several PLURONIC polymers have been found to enhance the therapeutic effect of drugs, and the gene transfer efficiency mediated by adenovirus. (March KL, Madison JE, Trapnell BC. (1995) "Pharmacokinetics of adenoviral vector-mediated gene delivery to vascular smooth muscle cells: modulation by poloxamer 407 and implication for cardiovascular gene
25 therapy." Hum Gene Therapy 6(1): 41-53, 1995).

One skilled in the art recognizes that other related hydrogels can be used. Two functional domains are essential: a poly(ethylene glycol), derivative or copolymer thereof, and a cyclodextrin moiety threaded onto the polymer. A bulky blocking group may be conjugated to the end of polymer chain via a biodegradable linkage, e.g. L-
30 phenylalanine, L-tryptophan, nicotinyl groups, etc.. A biodegradable linkage is required for the end group conjugation.

The composition may also contain a secondary polymer which may complex with the drug, conjugate the drug, or both. The secondary polymer may be a polyester, polyurethane, polyamide, polyether, polysaccharide, poly(amino acid), polypeptide, or a protein. Preferably the secondary polymer is a di- or mono-functional polymer or
5 polyionic polymer with poly(ethylene glycol) segments. In the case where drugs conjugate or complex to the hydrogels, then the hydrogel formulations act not only as a matrix but also a carrier of the drugs. This means that the drug is not only physically entrapped in the hydrogel but also complexed or conjugated to the molecules that form the hydrogel. The secondary polymer may also be used to alter the properties, such as
10 porosity and viscosity, of the matrix hydrogel. The amount of the second polymer should be sufficient to achieve the desired result, e.g. a sufficient amount to complex with and/or conjugate the drug.

The injectable composition may be injected into the body of the patient in any suitable manner. For example, the hydrogel may be administered by subcutaneous,
15 intramuscular, intradermal, and intracranial injection. The hydrogel can be administered to a confined area or tissue to achieve a higher local concentration of the drug. The particular drug used in the hydrogel is the type which a patient would require for pharmacological treatment of the condition from which the patient is suffering.

20 The cyclodextrin-polymer based injectable composition may be prepared in any suitable manner. Generally, the drug in aqueous solution is combined with the cyclodextrin. The solution is mixed and then the poly(ethylene glycol) component is added. The mixture is cooled, generally to a temperature of 0°C to 25°C, preferably to refrigeration temperatures such as 4°C. The resulting product is a white viscous
25 hydrogel.

The pH of the hydrogel is generally, about 6.5 to about 7.8, which are suitable pH levels for injection into the body. The pH level may be adjusted by any suitable acid or base such as hydrochloric acid or sodium hydroxide.

The following examples are offered by way of illustration and are not intended
30 to limit the invention in any manner.

Examples

Example 1:

Preparation of the injectable hydrogel formulation with linear poly(ethylene glycol) with different molecular weight. In a 0.30 ml of α -cyclodextrin aqueous solution (0.145 g/ml) was dissolved 3.0 mg of fluorescein isothiocyanate labeled dextran (dextran FITC, molecular weight 20,000). The solution was mixed with 0.15 ml of an aqueous solution of PEG (molecular weight from 8,000 to 100,000) with a typical concentration of 0.40 g/ml. The mixture was placed into a 0.6-ml cuvette, and then incubated in a 40°C water bath for one hour. The cuvette was then kept in a refrigerator at 4°C overnight, allowing the composition to form a viscous gel. The resulting gels were injectable hydrogel formulations. The gel can pass through needles with different gauges.

15 **Example 2:**

Release of dextran-FITC from hydrogel forming from alpha cyclodextrin and linear poly(ethylene glycol) with different molecular weights (Fig-1). For *in vitro* release studies, the cuvettes with hydrogels prepared in Example 1 were placed upside down in a test tube with 12 ml of water and incubated in a 37°C water bath. The water was changed in determined intervals of time. The fluorescence intensity was read from 200 microliters samples. Results are plotted in Fig. 1 as cumulative fluorescence released versus time. The values plotted in the figure represent the average of samples from three separate hydrogels. The release rate decreases sharply with an increase in the molecular weight of PEG up to 35,000, presumably because of the chain entanglement effect and different complex stability. The release rate is quite steady with time for gels formed with PEG 35,000 and 100,000.

Example 3:

Preparation of the injectable hydrogel formulation with Pluronic polymer poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) with different molecular weights and different ratio between poly(ethylene glycol) and

poly(propylene glycol) segments. In 0.30 ml of α -cyclodextrin aqueous solution (0.145 g/ml) was dissolved 3.0 mg of fluorescein isothiocyanate labeled dextran (dextran-FITC, molecular weight 20,000). The solution was mixed with 0.15 ml of an aqueous solution of Pluronic polymer (molecular weight from 2,900 to 35,000, PPG/PEG ratio between 0 and 3.0) with a typical concentration of 0.40 g/ml. The mixture was placed into a 0.6-ml cuvette, and then incubated in a 40°C water bath for one hour. The cuvette was then kept in a refrigerator at 4°C overnight, allowing the mixture to form a viscous gel. The resulting gels were injectable hydrogel formulations. The gel can pass through needles with different gauges.

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Example 4:

Release of dextran-FITC from hydrogels forming from alpha-cyclodextrin and Pluronic polymer poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) with different molecular weights and different ratios between poly(ethylene glycol) and poly(propylene glycol) segments. (Fig. 2). For *in vitro* release studies, the cuvettes with hydrogels prepared in Example 3 were placed upside down in a test tube with 12 ml of water and incubated in a 37°C water bath. The water has changed in determined intervals of time. The fluorescence intensity was read from 200 microliters samples. Results are plotted in Fig. 2 as cumulative fluorescence released versus time. The values plotted in the figure represent the average of samples from three separate hydrogels. The result shows that more sustained release kinetics may be obtained with Pluronic polymer PEG-PPG-PEG of lower molecular weight over PEG homopolymer. The higher ratio of PPG segment provides extra intermolecular hydrophobic interaction and reduces the dissolution rate of the gel.

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We Claim:

1. A cyclodextrin polymer-based injectable composition comprising cyclodextrin, a polymer which is capable of forming a hydrogel with the cyclodextrin, and a pharmacologically effective amount of at least one drug; wherein the polymer is
5 selected from poly(ethylene glycol), derivatives thereof, or a copolymer with a poly(ethylene glycol) segment.
2. The composition of claim 1 wherein the drug is in a pharmaceutically acceptable injectable aqueous fluid.
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3. The composition of claim 1 or claim 2 wherein the cyclodextrin is naturally synthesized by microorganisms.
4. The composition of claim 1 or claim 2 wherein the cyclodextrin is artificially
15 synthesized.
5. The composition of any of claims 1-4 wherein the polymer capable of forming a hydrogel with cyclodextrin is a copolymer of poly(ethylene glycol) and a polymer selected from the group consisting of polyesters, polyurethanes, polyamides,
20 polyethers, polysaccharides, poly(amino acid)s, polypeptides, and proteins.
6. The composition of any of claims 1-5 further comprising a secondary polymer which complexes with the drug, conjugates the drug, or both.
- 25 7. The composition of claim 6 wherein the secondary polymer is a polymer selected from the group consisting of polyesters, polyurethanes, polyamides, polyethers, polysaccharides, poly(amino acid)s, polypeptides, and proteins.

8. The composition of claim 6 wherein the secondary polymer is a di- or mono-functional polymer or polyionic polymer with poly(ethylene glycol) segments.
9. The composition of any of claims 1-8 wherein the drug is in a macromolecular
5 form.
10. The composition of any of claims 1-9 wherein the composition is injected subcutaneously, intramuscularly, intradermally, or intracranially.
- 10 11. The composition of any of claims 1-9 further comprising a buffering agent or a preservative.
12. A use of a cyclodextrin polymer-based injectable hydrogel comprising cyclodextrin, a polymer which is capable of forming a hydrogel with the
15 cyclodextrin, and a pharmacologically effective amount of at least one drug; wherein the polymer is selected from poly(ethylene glycol), derivatives thereof, or a copolymer with a poly(ethylene glycol) segment for the manufacture of a medicament for the treatment of a condition requiring pharmacological treatment.
- 20 13. The use of claim 12 wherein the polymer capable of forming a hydrogel with cyclodextrin is a copolymer of poly(ethylene glycol) and a polymer selected from the group consisting of polyesters, polyurethanes, polyamides, polyethers, polysaccharides, poly(amino acid)s, polypeptides, and proteins.
- 25 14. The use of claim 12 or 13 wherein the composition further comprises a secondary polymer which complexes with the drug, conjugates the drug, or both.