In situ gelling systems for drug delivery

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ABSTRACT

The in situ delivery system method of sustained release of steroids, small molecular drugs, peptides and proteins as well as an array of other pharmacological actives has developed over the last 40 years. They have been used for release periods of days to months. Most systems have been patented so their use by the pharmaceutical industry in many cases requires a license. In general, the systems are liquid but form a gel depot following injection subcutaneously for some formulations or intramuscularly with others. Their ease of manufacture, biocompatibility, ability to scale - up, decreased frequency of administration and improved patient compliance are positives when compared to conventional delivery systems. This paper reviews some of the more thoroughly investigated systems to include SABER®, Atrigel®, ALZAMER®, and Poloxamer.
Research to develop sustained delivery systems was initiated in the 1930’s. Since that time many systems have been developed and depending on an active pharmaceutical agent’s (API) molecular weight, solubility, potency and duration of delivery needed, the system can be matched with the API. This chart illustrates the type of system that may be used for different delivery times.
In situ gelling systems have recently been developed for drug delivery using ocular, rectal, oral, vaginal, injectable and intraperitoneal routes. Multiple natural, biodegradable, biocompatible and synthetic polymers have been used to prepare in situ gels. In general, in situ systems can be used to deliver an API for 7 or more days.

Examples of synthetic polymers include the widely-used poly DL lactic acid, poly DL-Lactide-co Glycolide (PLGA), Poly-Caprolactone and Pluronic F127. The major advantages of in situ gel systems over implantable solid systems or microspheres is the ease of administration, local site delivery possibility, increase in drug stability and simplified manufacturing. The major problem with in situ gel systems is the overabundance of patent protection of the systems. In situ gelling systems can be used to provide sustained-release of proteins, peptides, small molecule drugs and steroids (1).

In situ gelling systems, in general, are liquid at room temperature but undergo gel formation when they come in contact with body fluids or pH changes. In some cases, gelation is initiated by a change in temperature (an example - thermosensitive gels) such as Polaxamer polymers the most widely marketed of which is Pluronic F127. In this example, the gel is a liquid at room temperature or cooler but gels when exposed to body temperature. Other systems are triggered by ion exchange. Still others are based on ion cross-links, or precipitation of the polymer. Very few in situ gelling systems have been used in veterinary medicine. Only one product, SUCROMATE EQUINE, has been FDA approved for reproductive application in mares. The API in this product is Deslorelin acetate and it is mixed with SAIB (Sucrose acetate iso Butyrate) and a low viscosity solvent which forms a gel when injected intra-muscularly. This system has been patented and is known as the SABER™ (SAIB extended release) depot system.
An intramuscular injection of 1.85 mg Deslorelin acetate (SUCROMATE EQUINE) is given intramuscularly when an ovarian follicle is 35+ millimeters in size. Ovulation generally occurs within 48 hours in 87+ % of mares. Because SABER™ is a patented delivery system, it must be licensed before it can be used in any in situ gelling system. SUCROMATE EQUINE is also patented.

Fully esterified sucrose molecule. Sucrose Acetate Isobutyrate (SAIB)

Properties of SAIB:

- High Viscosity Liquid
- Hydrophobic
- Biocompatible
- Biodegradable
- Adhesive
SAIB in the absence of a co-solvent is a highly viscous material. Note it will not run down the sides of the inverted vial.

SABER systems have been used to deliver small molecules, peptides, proteins and steroids. SAIB is non-polymeric and hydrophobic and its high viscosity can be reduced and delivery parameters affected by adding to it one or more low viscosity solvents such as ethanol or propylene carbonate. For example, SUCROMATE EQUINE formulation is 1.8 mg Deslorelin Acetate in a 70:30 w/w% ratio of SAIB: Propylene Carbonate (2). SABER formulas may be either suspensions or solutions depending on composition. This formulation is reported to be difficult to syringe under cold field conditions.

A major advantage to many In Situ gelling systems is the ease of manufacturing. Below is
a simplified, hypothetical overview of how a SAIB: Progesterone formulation could be manufactured. Production is rapid from beginning to end and no sophisticated equipment would be required.
Generally, drug formulations for In Situ gelling delivery systems can be either suspensions or solutions. Reports suggest stability may be reduced in solution formulas. However, the problem with suspensions is achieving uniform mixing prior to injection. One must be able to shake the product immediately before injection and have a uniform dispersion, thus a low viscosity solvent would be required.

An example of a polymeric based In Situ gelling system is one of the oldest in use. It is also patented. The delivery system was first reported by Atrix Laboratories in 1995 and is known as the Atrigel® System. Atrigel has been used as the delivery system for at least four approved products, three in humans and one in dogs (3). Three of the applications are in dental gels (API is Doxycycline) and one is in oncology for prostate and breast cancer treatment (API Leuprolide Acetate, a GNRH analogue). The general composition of Atrigel utilizes a water–insoluble polymer that is biodegradable, such as Poly Lactide Glycolic Acid (PLGA), which is dissolved in a solvent that is biocompatible, water miscible and organic like NMP (N-Methyl-2-Pyrrolidone). The API is mixed with polymer + solvent forming either a suspension or solution. When injected subcutaneously, a migration of solvent occurs into surrounding tissues and the polymer precipitates after water enters the organic phase at the injection site. Several additional organic solvents have been used for various APIs to include DMSO, Ethyl Acetate, Triacetin, Propylene Carbonate, Tetraglycol and Glycolfurol. Different solvents affect the phase inversion dynamics of PLGA from the organic phase. Even more importantly the release pharmacokinetics of the API is determined by its mass, the ratio of Lactide to Glycolide and the polymer concentration. In general, the greater the L: G ratio, the longer the duration of release of API (4).
Structure of PLGA which is a poly ester. PLGA is usually a linear chain and the ester bonds can be broken by water releasing API until the PLGA is completely absorbed.

The ALZAMER® system is also patented and uses PLGA as the biodegradable polymer since it is approved for parental use. There are at least 25 approved products that use PLGA as part of the delivery system components. Below is a flow chart of how an ALZAMER system drug would be made.

**FLOW CHART**

1. **BIODEGRADABLE POLYMER**
2. +
3. **BIOCOMPATIBLE SOLVENT** (miscible in water)
4. (ETHANOL OR N-METHYL-2-PYRROLIDONE (NMP))
5. +
6. **LOW MOLECULAR WEIGHT APIs, PEPTIDES AND PROTEINS**
7. SUSPENSION OF API
The resulting formula, depending on the solvent, polymer and API characteristics will release API for days to months. Biocompatibility of the system seems to be acceptable. Apparently, no products have been approved using the ALZAMER SYSTEM.

Poloxamer polymers are synthetic, biodegradable and are a thermo-reversible type of material. That is, they are liquid at room temperature or below but form gels at 37°C (reverse gelation) and have been used to deliver some protein drugs such as Human Growth Hormone.

The ReGel® system evolved based on these polymers. However, the polymers are available for purchase and can be used in other gel systems.

Hypothetical formula for poloxamar cold preparation method:

Poloxamer 407 + Poloxamer 188 + API + water + Polymer additives (such as polyvinyl pyrrolidone (PVP), hydroxyl methyl cellulose (HMP), or carbopol or a combination of all 3).

When no polymer additive was used the sol-gel transition temperature is 26 to 28°C. Stability of the API may be an issue in such formulas but may be greatly improved by lyophilization of the finished product.
References


