Reverse Thermo-responsive Polymers for Sustained Delivery

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ABSTRACT

Delivery of a therapeutic agent where needed *in vivo* (on site) at the required dose is a key issue faced in a number of interventions. Effective strategies to resolve this offer significant benefits, one of the key advantages being the use of lower doses compared to traditional administration methods such as in oral capsules or intravenus injections. This advantage coupled with sustained release of the agent on site at the required level over a long period of time eliminates the need for repeated interventions and set new standards in drug delivery technolgies. Such novel strategies lead to significant economic benefits, less toxic after effects (use of lower doses), minimal organ damage and most importantly less trauma to the patient. CSIRO has developed a series of aqueous polymer solutions capable of encapsulating a range of therapeutic agents, that are injectable through a fine needle, and form instantaneous gels at physiological temperatures.

Keywords: sustained release therapeutic, injectable, degradable

INTRODUCTION

Sustained release of bioactives, particularly therapeutics, in patients represents a very large market opportunity. If the system is also injectable, offering sustained release of the therapeutic over at least 3 months, there may be significant advantage versus existing delivery systems. CSIRO has developed a novel, thermosetting, biodegradable polymer gels that solidify when injected into the body and are designed to provide high local concentrations of an active drug for a sustained period.

Such a system has a multitude of potential applications in the biomedical area, including ophthalmic drug delivery, cancer therapeutic delivery and tissue engineering. Ophthalmic (eg macular degeneration) and cancer therapeutic delivery are rapidly gowing markets, usually requiring repeated, very precise, injectable delivery of a therapeutic. Sustained release systems are very attractive for these markets to both improve patient outcomes and cut costs.

Tissue engineering applications may include minimally invasive repair of injuries using bioactive molecules and cell delivery. Minimally invasive surgery is growing rapidly with large opportunities in general and thoracic surgery such as resections. There are also a growing number of applications within gynecology, urology, cardiothoracic, orthopaedic and head and neck surgery,

where it would be desirable to combine minimally invasive surgery and sustained bioactive delivery.

The clinician would need a new delivery gel to be easy to use – ideally it would be a stable at room temperature and ready to use in a solution form, via injection through a fine-gauge needle. It will also need to form a gel instantaneously upon injection, to avoid unintended leakage. Naturally any new system must also be completely biocompatible with the body and produce non-toxic by-products.

A stable, easy to use system would also offer potential opportunities in 3rd world settings where patient compliance is often an issue, such as vaccines, and one-off treatment of infectious diseases.

Reverse thermo-responsive polymers (RTPs) are those that change their phase from a liquid to a gel as the temperature is increased – for example as they are injected *in vivo*. They have potential utility as injectable, sustained delivery systems. The most well known and widely investigated RTPs are poly(*n*-isopropyl acrylamides), ReGel™ [1] and a series of block copolymers commonly referred to as Pluronic. The major drawback of these classes of polymers is their relative non-degradability and, hence, the inability to filter the eroded polymer through the kidneys. The low strength and rapid erosion of the *in vivo* deposited gel are other well known issues with typical Pluronic polymers. ReGel™ was being evaluated in a product named OncoGel, but appears to have been withdrawn from development since 2011.

METHODS AND MATERIALS

The range of polymers used in the technology are completely degradable and resorbable in vivo and composed of FDA approved GRAS (generally regarded as safe) materials. The *in vitro* release data shown are for a low molecular weight enzyme and for a common small molecule drug. The release medium was tested over the shown time points for the released enzyme encapsulated in the polymer gel by using standard assay methods in triplicate. All samples were incubated at physiological temperature and repeatedly shaken to stimulate as extreme conditions as possible.

Physical and mechanical characterization of these polymers has been carried out (NMR, GPC, TGA, DSC, DMTA etc.) and their gelation characteristics investigated. The phase diagrams for each polymer has been plotted and more advanced light scattering studies carried out to ascertain the size of micelles formed in aqueous media. In addition, extensive rheological characterisation of these polymers have also been completed (SAXS, Light scattering, surface tension, cryo-TEM) and structure property relationships (shape of micelles at CMC, gelation kinetics, activation energy for gelation) established. The formulations were designed to have greater solids densities with low viscosities. CSIRO has also established sterilization procedures for these polymer formulations. These results have established, that sterilization does not cause chemical or physical modification or degradation to polymer compositions and does not cause a loss in reversible gelation characteristics or the LCST.

RESULTS

CSIRO has developed new Reverse thermo-responsive polymers (RTPs) composed of FDA approved biocompatible monomers: lactic acid; glycolic acid; caprolatone and poly(ethylene glycol) (PEG) block copolymers. They are biocompatible, and expected to be biodegradable *in vivo*. Aqueous solutions of the CSIRO RTPs demonstrate spontaneous physical gelation and rapid sol-gel transformations, between 30-45 °C. Below this the solutions are free flowing liquids, have low viscosities and are easily injectable through a 25 gauge needle. We have demonstrated that these therapeutic containers by example to function as sustained release drug depots.

In-vitro gelation of the CSIRO RTPs and encapsulation efficiency of a model protein (enzyme) was investigated and established to be >99% after 1 hour at 37 °C. Comparative short term release profiles for this model enzyme at 3% loading encapsulated in Pluronic or ReGel™ demonstrated a significantly lower 24 hour burst release of 24% for the CSIRO RTPs, as compared to 42% for non-degradable Pluronic F127 and 65% for Regel™ [1] (Figure 2). Long term release studies have established sustained release of the same enzyme. Figure 2 also demonstrates the tunability of the CSIRO polymers with a delivery window ranging from 35 to 140 days with 82 and 70% released respectively. CSIRO is now able to tailor the polymer formulations between these two extremes to optimize delivery to suit required applications. The release kinetics following the burst release period was demonstrated to be zero order (linear), independent of the encapsulated concentration of the enzyme. The activity of enzyme in the released medium was found to be comparable to that of the unencapsulated enzyme used in the experiment, confirming the stability of the enzyme during encapsulation.

Release studies conducted on model small molecular cancer therapeutic drugs have established sustained release over a period of 91 days (Figure 1), indicating the CSIRO RTPs may be useful sustained delivery systems for a wide variety of therapeutic agents.

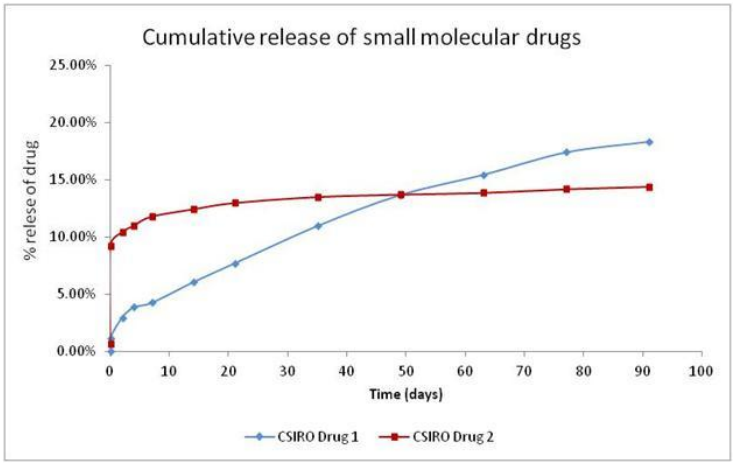

Figure 1: Release of small molecules using the CSIRO system

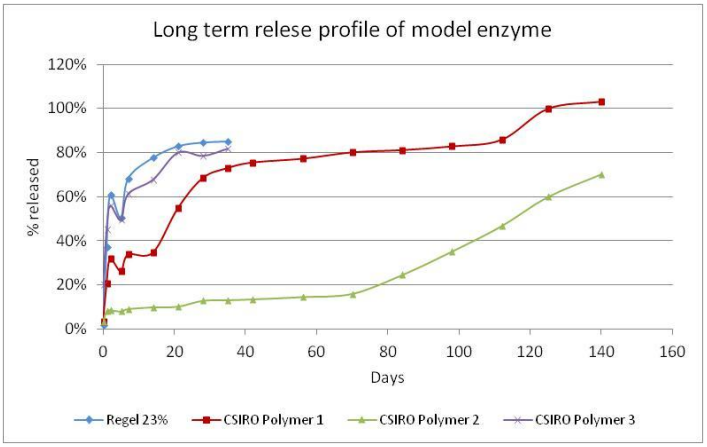

Figure 2: Release of an enzyme – comparison of CSIRO system with ReGel™

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