Administration Methods for Injectable Systems Involving Precipitation Mechanics

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Statement of Purpose: Injectable gel forming systems have come into wide use in a variety of fields such as cell scaffolding and drug delivery. These implants begin the treatment cycle in a solution (sol) form. This solution is then administered to the desired area of treatment through a syringe or port system. Once in place the implant then converts to the gel form. This transition is often called the sol-gel transition and the mechanism through which this change is effected is one of the distinguishing factors between systems. The majority of injectable *in situ* forming systems fall into one of three categories: (1) Crosslinking/Network formers, (2) Thermogelling systems, and (3) Precipitation systems[1]. Of these categories, precipitation systems appear to be valuable clinically as they can be designed to rely on the body's internal aqueous environment to induce the sol-gel transition[2], while also producing effective and reproducible depots. Therefore, work was undertaken to determine the feasibility and injectability of multiple diluent/polymer systems, in order to aid future device design. This communication reports the findings of this screening.

Methods: Multiple polymers were explored for this work. The first polymer used was a poly-ether-ester-carbonate urethane (PEECU) which has been identified as promising in terms of controlled release[2]. Following testing of these PEECU polymers, it was hypothesized that a polymer with a more hydrophobic main chain may respond better to the precipitation method employed. Therefore, a high-lactide copolymer (LAC) was polymerized for exceptional solution viscosity and quick depot formation. All of these polymers were combined with a diluent considered safe for *in vivo* injection. The solutions generated with these polymer/diluent combinations were then tested for injectability in the smallest diameter Leur-lok® needle available (30 gauge). A promising candidate was examined for complex viscosity using an Anton-Parr Rheometer (Physica MCR 301).

Results: Both polymers were successfully incorporated into solution forms of differing diluents. The resulting solutions were tested qualitatively for relational injectability and visual viscosity pre-gelation and stability post injectability on a scale of 1-5. Selected results of this testing can be seen in Table I. The system PEECU (30/70) was chosen for rheometric analysis to quantify gelation speed and stages due to the score of '5' in relation to gelation. This viscosity was analyzed from the time (t=0) that an excess of water was introduced into the chamber until gelation was achieved (~2500 PaS). This curve can be seen in Figure 1.

Table I: Summary of Properties from Different Injectable Systems

Composition	Injectability	Visual Viscosity	Visual Gelation Rating
Polymer: Diluent (%/%)	1 (water)-5 (solid)	1 (water)-5 (solid)	1 (water)-5 (solid)
PEECU (50/50)	3.5	3	2
PEECU (12.5/87.5)	1	1	2
PEECU (25/75)	2	1.5	3
*PEECU (30/70)	2	2	5
LAC (20/80)	2	1	4
LAC (15/85)	1	1	4
LAC (17.5/82.5)	1.5	1	5

*Polymer System Chosen for Rheometric Analysis

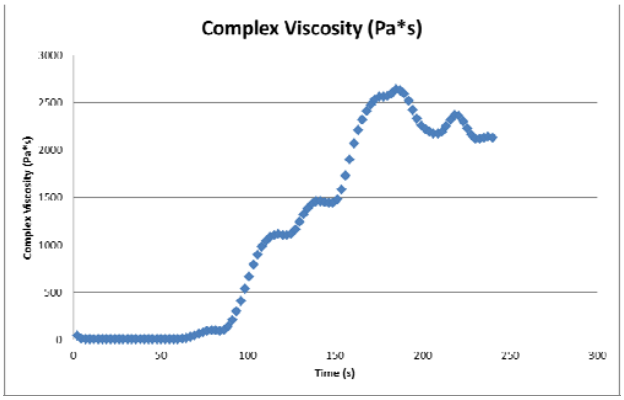

Figure 1: Complex Viscosity over Time for gelation of PEECU (30/70) system

Conclusions: Multiple injectable systems were identified. An improvement of gelation properties was found experimentally in the instance of the more hydrophobic LAC and an appropriate polymer to diluent ratio was identified for both polymer matrices. Gelation was quantified rheologically in one instance with the PEECU polymer and found to occur within 3 minutes following aqueous exposure. These systems appear to be useful for many indications where injectable gel formers are currently providing impact, such as drug delivery.

References:

1. Kretlow, J., Klouda, L., Mikos, "Injectable matrices and scaffolds for drug delivery in tissue engineering" Advanced Drug Delivery Reviews 59 (2007) 263–273
2. Olbrich, J.M et al. Trans. Soc. Bio. (2012).