Development of Polymeric Carrier Systems with Multiple Burst Release Potential for Treatment of Osteoarthritis

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Statement of Purpose

Osteoarthritis (OA) is the most common form of arthritis, which is characterized by the degeneration of articular cartilage, changes of the subchondral bone, associated pain, and increasing disability of the affected joint. One of the treatments for early-stage symptomatic OA is viscosupplementation with hyaluronic acid (HA), which provides temporary relief of knee pain typically with 3-5 intra-articular injections[1]. The limitations of multiple injections of HA include poor patient compliance, multiple-injection associated complications such as infection, and the relatively short therapeutic effects. The aim of this study was to develop polymeric carrier systems that are capable of providing controllable multiple burst releases of pharmaceutical agents, which could provide persistent therapeutic effects with only one injection. Chondroitin sulfate (CS), an integral component of articular cartilage that has been also used for OA management (typically through oral administration), is used as a model agent to develop such carrier systems.

Methods

Four proprietary poly(lactide-co-glycolide) (PLGA) formulations with distinct lactide to glycolide ratios (between 50:50 and 100:0) were used for CS encapsulation. PLGA I (MW 40-75kDa), PLGA II (MW 40-75kDa), PLGA III (MW 66-107kDa), PLGA IV (MW 50-75kDa), chondroitin sulfate-A, poly(vinyl alcohol) (PVA), and isopropanol (IPA) were all obtained from Sigma. Blyscan GAG assay kit was purchased from Biocolor, Ltd. CS-encapsulated PLGA microspheres were prepared via a water-in-oil-in-water double emulsion technique with modifications[2]. Briefly, certain amount of freshly prepared CS aqueous solution was added to 12.5% (w/v) PLGA methylene chloride solution, and subsequently vortexed and sonicated to form the first emulsion. The CS-PLGA mixture was then poured into a 0.1% PVA solution and stirred at 300rpm to form the second emulsion. After 5 minutes, 2% IPA solution was added and the solution was stirred for additional 2 hours before the microspheres were isolated and dried. The resultant microspheres were further separated into different size ranges using stainless steel sieves. For CS release studies (n=3), approximately 100mg microspheres were added to 1.5ml PBS with 1% antibiotics and incubated at 37°C. At predetermined time points, 200µl of the releasing medium was withdrawn. Equal amount of fresh PBS was added to each tube to continue the release study. Blyscan GAG assay was performed on the microspheres and releasing medium at individual time points to determine the CS encapsulation efficiency and the amount of CS released, respectively.

Results

The encapsulation efficiencies of CS into different PLGA formulations ranged between 45% and 85%. For PLGA I, microspheres were separated into six size ranges (75-150µm, 150-212µm, 212-300µm, 300-355µm, 355-425µm, 425-500µm, as well as a mixture of all size ranges) and the CS release profile is shown in Fig. 1. PLGA I microspheres showed two burst CS releases – one occurring within the first day and the other between 14-35 days. The amount of CS released closely depended on microsphere size.

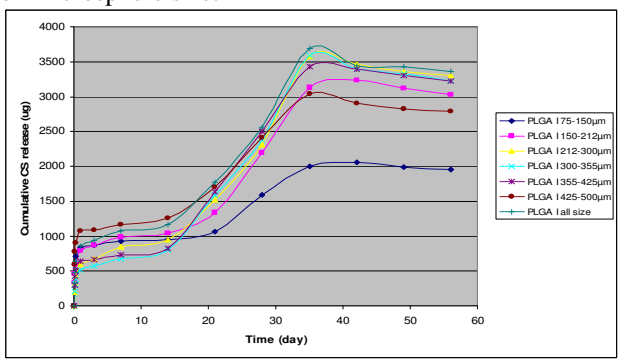

Fig.1. CS release from PLGA I microspheres of various sizes

The CS release from microspheres fabricated from different types of PLGAs also showed unique characteristics (Fig. 2). Each type of PLGA microspheres showed an initial burst release of CS within the first day. PLGA I showed a second burst CS release between 14-35 days; PLGA II showed a second burst CS release between 42-56 days; PLGA III showed a second burst CS release starting at ~70 days. PLGA IV showed the slowest CS release due to the slowest degradation rate and a second burst release from this polymer is anticipated at later time. Therefore, a combination of different types of PLGA microspheres with various sizes can be carefully designed to provide multiple burst releases at various times in a controllable manner, thus mimicking a series of intra-articular drug injections to maintain the therapeutic level of the pharmaceutic agents for a prolonged time period.

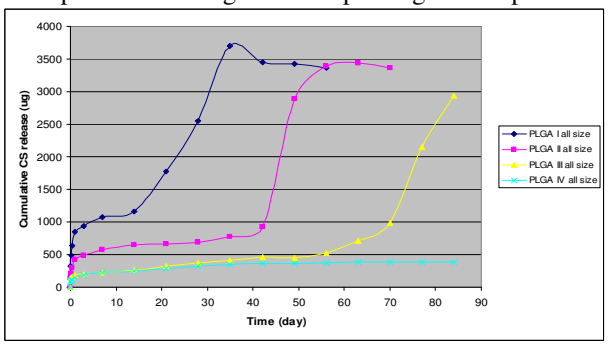

Fig. 2. CS release kinetics from different types of PLGA microspheres

Conclusion

This study established a method to achieve multiple burst drug releases from a single polymeric carrier system for persistent therapeutic effect mimicking the multiple-injection therapy currently used for treatment of OA.

References

1. Moreland LW. Arthritis Res Ther. 2003; 5: 54-67.
2. Billon A. et al. J Microencapsul. 2005; 22: 841-852.