CONTROLLED RELEASE OF BUPIVACAINE FROM INJECTABLE HYDROGEL COMBINED WITH MICROSPHERES: POTENTIAL USE FOR DISCOGENIC BACK PAIN CONTROL

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Introduction

Previously, we reported that it is feasible to formulate a microsphere (MS)-dispersed *in situ* forming hydrogel matrix which is percutaneously injectable into the intervertebral disc (IVD)[1]. It is desirable for long-term control of discogenic back pain if this matrix can deliver a local anesthetic (LA). The purpose of this study is to show the controlled release of bupivacaine (BC) *in vitro* from a gel combined with MS.

Methods

1. *In situ* forming matrix: MS was first made by melting the mixture of 170mg of Poly(ε-caprolactone) (PCL) with 30mg of alkalized BC at 70°C in a oven for 20mi. It was transferred the molten mixture into 300ml of aqueous polyvinyl alcohol (3%) at 65°C for 2hrs, and then stayed for 3hrs at 5°C. MS was collected by centrifugation and drying. (mean diameter ± SD: 4.77±1.49 μm by SEM). Twenty percent of Poly(EO_{95}-PO_{62}-EO_{95}) (F127) and 0.8% of sodium hyaluronate were dissolved in deionized water at cold room (15°C) while mixing with MS, where the ratio of gel to MS was determined by weight.

2. Viscosity: The matrix consisting of gel and MS was measured at a shear rate of 1 sec^{-1} with a temperature elevation using a viscometer (Viscometer II+, Brookfield Eng. Lab.) equipped with a 1.0mm gap cone and plate (CP 52).

3. *In vitro* drug release: A vial containing 2g matrix in 20ml of deionized water was placed in a reciprocal water bath (Precision 50, Thermo Electron Inc.) at 50rpm and 37˚C. At regular time intervals, 200μl supernatant solution was collected and then diluted to 1/5 before measurement. The same amount of fresh water was added to the vial. The amount of BC released was analyzed at 274nm using UV/VIS spectrophotometer (Lambda 20, PerkinElmer).

Results/Discussion

The viscosity of matrix showed highly relied not only on the temperature and concentration, but also on the ratio of gel to MS. The viscosity variation ranged from 50Pa·s at 20°C to above 300Pa·s at 37°C (Fig 1), showing *in situ* forming property. When the more MS was added to gel at 25 and 37°C, the higher viscosity was seen in tested samples but did not significantly vary in individual sample except for pure gel (100:0).

Figure 2 shows that the BC from tested samples was released significantly slower than the control. In 100:0 sample, a marginal burst effect was observed over the first 7 days, but BC was released almost linearly thereafter. In contrast, 0:100 sample showed no burst effect and released BC gradually with time, indicating the effect of miscroencapsulation.

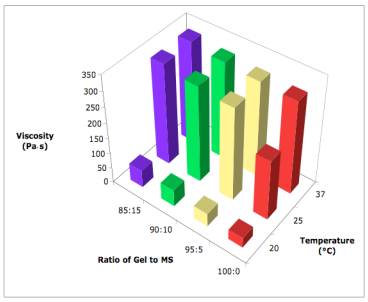

Figure 1.

The limitation of this drug release study was done *in vitro*. Because the absolute amount of BC released may vary depending on the media, an *in vivo* study should be followed. For example, for the degenerated IVD, most amide-based LA are readily dissolved in acidic condition (≅pH 5.7)[2]. However, slower release of BC due to the effect of microencapsulation clearly demonstrated the possibility of adequate control of drug release rate using microspheres.

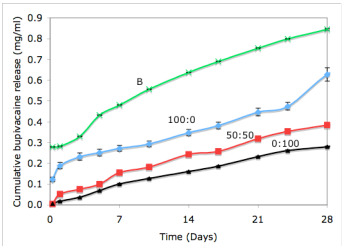

Figure 2. BC released from the matrix produced by 90% gel and 10% MS (n=3): 3% BC are loaded in deionized water (B) for control, in gel only (100:0), evenly in gel and MS (50:50), and in MS only (0:100).

Conclusion

Preliminary *in vitro* drug release studies showed that the injectable hydrogel combined with MS can control the release rate of BC, whch could have potential as a long-acting control of discogenic back pain.

References

(1). Lee, JW et al., Society for Biomaterials Transactions, 2005(30):180 (2). Lotz JC et al., Biochem Society Transaction 2002(30)829