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Pluronic F127 gel effectively controls the burst release of drug from PLGA microspheres

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To investigate the controlled release effect of a thermosensitive gel, Pluronic® F127 (PF127) on microspheres, poly[D,L-lactic-co-glycolic acid] (PLGA) microspheres were coated with Pluronic F127 gel and the *in vitro* release was evaluated. The results demonstrated that PF127, which gelled at 37 °C, inhibited the initial burst release of drug from microspheres effectively.

Poly [D,L-lactic-co-glycolic acid] (PLGA) is a promising material for sustaining drug release which can degrade gradually without toxicity. Microparticles composed with PLGA are extensively used in gene therapy (Davda and Labhasetwar 2002; Panyam et al. 2003), anti-cancer drug delivery, and as drug carrier (Li et al. 2001). However, the initial burst in the release process limits its usage and might cause side-effects or toxic-effects (Wang et al. 2002).

On the other hand, an intelligent hydrogel, which is responsive to external circumstances like pH, light, temperature, magnetism, etc, is used in many fields (Jeong et al. 2002). Among the thermosensitive hydrogels, Pluronic F127 (PF127) exhibits a reversible sol-gel property above the concentration of 20% (w/v), which means that it can present a phase transition from solution to gel with the temperature rises to its lower critical solution temperature (LSCT) (Jeong et al. 1999). It owns a semi-solid property in body temperature. PF127 has been used in sustaining drug release (Kim and Park 2002).

Therefore, using PF127 to overcome the initial burst of PLGA microspheres was tried in the present study. We at first prepared PLGA microspheres containing BSA, subsequently dispersed PLGA microspheres into PF127, and the *in vitro* release was investigated. Here, considering the gel formulation and easy to be fulfilled, two concentrations (24% and 30%) of PF127 were evaluated. The results showed that the burst release of BSA from microspheres was inhibited effectively by this intelligent gel (Fig. 1). Thirty minutes after the release started, the release ratio of PLGA microspheres was $16 \pm 2\%$. In contrast, it is only $0.82 \pm 0.17\%$ and $0.31 \pm 0.05\%$ for microspheres coated with 24% PF127 and 30% PF127, respectively. At a concentration of 24%, PF127 coating microspheres showed a very stable release, and 30% PF127 sustained the drug release more effectively (Fig. 1).

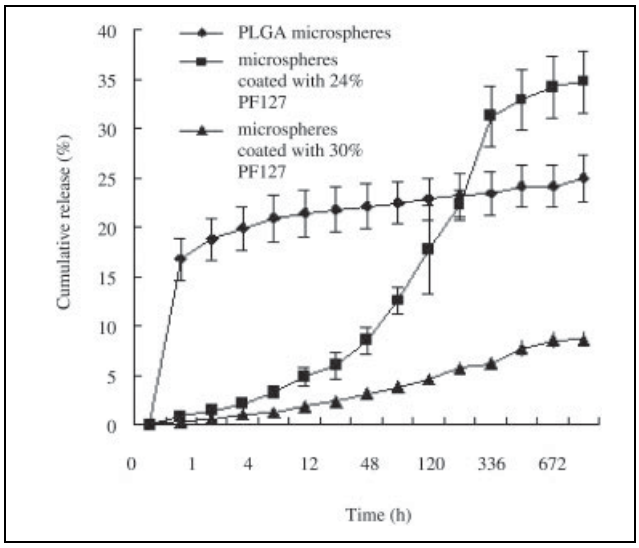

Fig. 1: *In vitro* release studies of PLGA microspheres coated with PF127 of different concentrations (mean ± SD, n = 3)

Initial burst of PLGA microspheres is correlated with many factors such as the physical-chemical property of PLGA, the preparation methods, additives, and so on (Huang et al. 1999). However, the drug adsorbed to the surface of microspheres is a main reason of initial burst. Therefore, while the coated PF127 gel retarded the direct contact of the microspheres and release media, the corrosion process of gel became the rate-limiting step, and the adsorbed drug could only release with the erosion of gel. 30% PF127 has a higher viscosity than that of 24% PF127 and showed more slowly sustained release effect on drug, and thus, the sustained release effect can be modulated by adjusting the viscosity of gel (Ricci et al. 2002).

Furthermore, the influence of pH on the release pattern of PF127 coated microspheres was investigated. Three pH conditions ranging from 4 to 10 were selected and the results showed that there was no significant difference among them (Fig. 2), suggesting that PF 127 is insensitive to pH change, and the control release effect could be modulated by temperature and concentration.

The inhibition of the initial burst of PLGA microspheres with an intelligent gel firstly demonstrated in our study

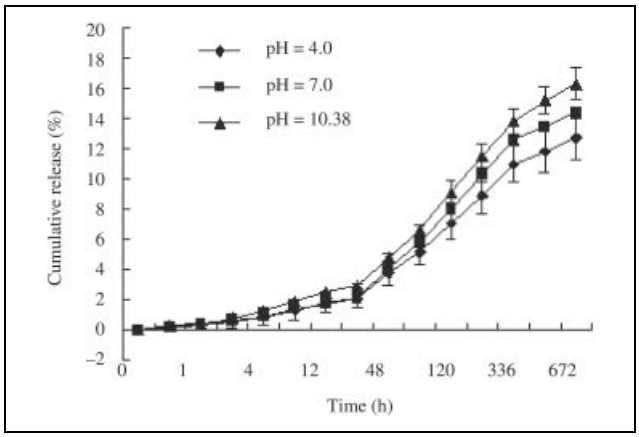

Fig. 2: *In vitro* release studies of PLGA microspheres coated with PF127 at different pH conditions (mean ± SD, n = 3)

suggested that (1) enlarged original drugs regardless of their own narrow therapeutic window can be used, (2) other microparticle preparations also might be improved by PF127. PF127 gelled at 37 °C which is just the normal body temperature, which provides a promising application of this polymer in controlling drug release *in vivo*. Though the interactions between PF127 and various kinds of drugs and materials are expected to be inspected, such a thermosensitive hydrogel is promising regarding the improvement in intensity, multi-response character and other properties (Ruel-Gariepy et al. 2004; Cho et al. 2003).

Experimental

1. Materials and instruments

Bovine serum albumin (BSA, Sino-American Biotechology Co. CHN), poly vinyl alcohol (PVA, Shanghai chemical reagent company, China National Pharmaceutical Group Corporation, CHN), BCA kit (Beyotime Institute of Biotechnology, Jiangsu, CHN), poly [D,L-lactic-co-glycolic acid] (PLGA, copolymer ratio 70 : 30, MW25000, Shandong Medical Instrument Institute, CHN), Pluronic F127 (BSAF, USA), enzyme crosslinked immunosorbent assay instrument (Bio-Rad, USA), probe ultrasonic instrument (Ningbo Xinzhi Science Instrument Institute, CHN), high speed homogenizer (Shanghai Specimen and Model Factory, CHN)

2. Preparation of microspheres

PLGA microspheres with a mean diameter of 4–5 μm were prepared by the double emulsion evaporation technique (Davda and Labhasetwar 2002; Sahoo et al. 2002). Briefly, 150 mg of BSA and 1000 mg of PLGA were dissolved in distilled water and dichloromethane, respectively. After these two solutions were mixed and ultrasounded by a probe (400 w, 60 s), this primary-emulsion was then poured into 100 ml of 1% PVA and homogenized (20000 rpm, 2 min) to obtain a w/o/w multiple-emulsion. The residue of dichloromethane was evaporated by stirring the emulsion for 3 h. The particles were isolated by centrifugation (20000 rpm, 5 min), and washed twice to remove PVA before lyophilization.

3. In vitro release study

In vitro release studies of microspheres dispersed in PF127 were performed by a membraneless model (Barichello et al. 1999). Microspheres (150 mg) were uniformly dispersed in 2 ml of PF127 solution and gelled at 37 °C. One ml saline pre-equilibrated to 37 °C was transferred into the surface of the gel. At certain intervals, the supernatant was completely removed and replaced with fresh saline. Release of the PLGA mircospheres without gel was performed as follows, a precise quantity of microspheres was weight to a release tube and suspended in 1.5 ml saline, at certain intervals, 1 ml medium was extracted after centrifugation and equally replenished. For evaluating the effect of pH conditions, release media were modulated and pH values were measured. BSA was detected with a Lowry-Peterson protein assay kit.

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