Preparation and Characteristics of Novel Porous PLGA Microsphere by Gas Foaming Method Using Hydrogen Peroxide

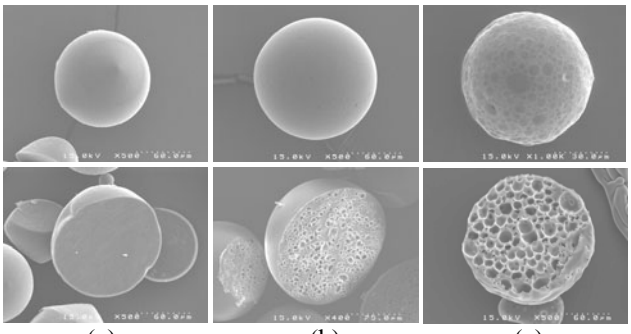
Jun Sik Son[a,b], Sunho Oh[b], Kwideok Park[a], Dong Keun Han[a]

[a]Biomaterials Research Center, Korea Institute of Science and Technology, P.O.Box 131, Cheongryang, Seoul 130-650, Korea.
[b]University of Texas at San Antonio, San Antonio, TX, USA

Statement of Purpose: The goal of this study is to fabricate porous biodegradable microcarriers with sustained release for drug delivery. Hydrogen peroxide (H_2O_2), a strong oxidizing agent, is a colorless liquid that is decomposed into water and oxygen when heated over 80°C. It also decomposes in the presence of numerous catalysts, e.g., most metals, acids, or oxidizable organic materials, and catalase. In this study, porous poly(lactide-co-glycolide) (PLGA) microspheres were fabricated by a double emulsion solvent evaporation method using H_2O_2 as a gas foaming agent. H_2O_2 was mixed in the polymer emulsion droplets to generate oxygen gas bubbles during the solvent evaporation process. Catalase was used as a H_2O_2 decomposition catalyst. This method is simple and environment-friendly, eliminating the use of salts. Sterilizing effect is also expected from this process. In this study, various conditions were tested and the resultant porous microspheres were characterized.

Methods: Porous PLGA microspheres were fabricated by a water-in-oil-in-water ($W_1/O/W_2$) double emulsion solvent evaporation method. PLGA was dissolved in methylene chloride as an oil phase. H_2O_2 aqueous solution (W_1 phase) containing different amounts of H_2O_2 was added to a PLGA solution. The first water-in-oil (W_1/O) emulsion was prepared by a homogenizer. This primary emulsion was immediately poured into a beaker containing polyvinyl alcohol (PVA) solution and catalase as a H_2O_2 decomposition catalyst (W_2 phase). The resultant emulsion solution was placed in a hood under a magnetic stirring condition, allowing the solvent to evaporate. The hardened microspheres were centrifuged, washed three times with deionized water and lyophilized using a freeze dryer. The surface and internal structure of porous microsphere were analyzed by scanning electron microscopy (SEM). The size distribution and the average diameter of microspheres were measured by a particle size analyzer.

Results: Porous PLGA microspheres were fabricated by using a $W_1/O/W_2$ double emulsion solvent evaporation method with H_2O_2 aqueous solution as a gas foaming agent (Fig. 1. (c)). The pores were uniformly distributed and well interconnected throughout the inner part of the microsphere. It was demonstrated that H_2O_2 in the W_1 droplets generated oxygen bubbles upon contacting the catalase in the W_2 phase, thereby creating porous morphology throughout the PLGA microspheres. In the case of pure water as the W_1 phase, the surface of the microsphere had no pores and the inner core had very tiny pores (Figure 1 (b)). One of the interesting points in this study is that when using H_2O_2 as a gas foaming agent to generate a porous PLGA microsphere, the outer surface of the microsphere becomes covered with a thin PLGA membrane. It is postulated that such phenomena happens by chemical reactivity of the H_2O_2, but the exact causes are still under research. These covered microspheres represent a novel structure with the benefit that when a drug-loaded microsphere is introduced to the human body, it arrives at the target without initial burst release and dissolves the membrane covering the microsphere to create a sustained drug release. Ultimately, covered microspheres have characteristics that can control the release of drugs with more precise and effective behavior. As a result, hydrogen peroxide, as a new environment-friendly gas foaming agent for porous microspheres, can produce a unique encapsulated structure more rapidly and easily with the benefit of a sterilizing effect.



(a) (b) (c)

Figure 1. SEM images of the surface (top) and cross-section (bottom) of microspheres prepared at various condition (x 500): (a) control PLGA, (b) water, (c) H_2O_2 aqueous solution.

Conclusions: Porous PLGA microspheres were successfully prepared by double emulsion solvent evaporation method using H_2O_2 as a gas foaming agent. Therefore, the porous biodegradable PLGA microsphere is applicable to drug and cell delivery as a biodegradable microcarrier with controlled surface encapsulation for sustained drug release.

References:
1. T. K. Kim et al., *Biomaterials*, **27**, 152-159 (2006).
2. X. –Q. Chen et al., *J. Microencapsulation*, **18**, 637-649 (2001).