



Original Research Paper

Preparation of hydroxypropyl methyl cellulose phthalate nanoparticles with mixed solvent using supercritical antisolvent process and its application in co-precipitation of insulin

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ABSTRACT

To obtain hydroxypropyl methyl cellulose phthalate (HPMCP)/insulin nanospheres by supercritical antisolvent process, the formation of HPMCP nanoparticles was first investigated. The effects of ratio of the mixed solvent, pressure, temperature, concentration, flow rate of CO₂ and solution on forming HPMCP nanoparticles are discussed. It was found that different morphologies of HPMCP could be produced by varying the ratio of DMSO to acetone in the solvent. The operating parameters were optimized for making HPMCP nanoparticles. Formation of HPMCP/insulin nanospheres was further inspected. The nanospheres with the size ranging from 138 nm to 342 nm were obtained. The loading of insulin in the nanospheres ranged from 10.76% to 16.04% and the encapsulation efficiency reached 100%. The release of insulin is also discussed.

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1. Introduction

In recent years, more attentions have been paid to the generation of biopolymer particles encapsulating additives, such as pharmaceuticals, natural products, and cosmetics. In particular, the formation of biopolymer particles containing pharmaceuticals is a good way to produce drugs with controlled release and targeted locations. Supercritical fluid technology has been one of the most promising methods because it can form superfine particles at mild conditions with a narrow size distribution and no organic solvent remains.

The supercritical fluid based techniques for producing micro/nanoparticles can be classified into two main processes: rapid expansion of supercritical solutions (RESS) and supercritical antisolvent process (SAS). According to the properties of the selected biopolymers and additive compounds, a suitable process can be chosen in order to produce the designed particles or co-precipitates. For example, the RESS process is suitable for highly soluble biopolymer in supercritical fluid.

Supercritical antisolvent process (SAS) and its multiform modifications, such as GAS, ASES, PGSS, SAA and SEDS, have been widely used in preparing micro/nanoparticles and micro/nanospheres [1–5]. Song et al. [6] and Sarkari et al. [7] successfully produced L-PLA particles by the SAS process. Their studies high-

lighted that temperature, pressure, and concentration affected the particle size and morphology. Taki et al. [8] encapsulated diuron in L-PLA by SAS process. The biopolymer and additive compound were dissolved in dichloromethane. The degree of loading was obviously affected by the initial concentration of polymer and diuron.

However, most pairs of biopolymers and additive compounds can not be dissolved in one solvent, so mixed solvents must be used to dissolve two substances. Elvassore et al. [9] used the mixture solvent of DMSO and dichloromethane with 50% ratio to dissolve L-PLA and insulin. After SAS process, it was shown that more than 80% of insulin initially sprayed into vessel was encapsulated in the L-PLA particles. Grassi et al. [10] loaded theophylline into poly(hydroxypropyl methylcellulose) (HPMC) particles by SAS process using a mixture of dichloromethane and ethanol (50/50). It was found that the drug release of the processed samples was slower than that of unprocessed ones. From these results, we can see that the application of mixed solvent can broaden the choice of coating materials in SAS.

Insulin is the most effective drug in diabetes therapy. Generally, diabetes patients have to take it for their whole life. Injection is the most common way to deliver insulin, but it is not convenient for patients. Now oral administration of insulin is regarded as a promising way. Encapsulation is a good method in which insulin could be protected from biodegradation by oral administration. The rate of release can be controlled and the duration of bioactive protein could be prolonged [11–14].

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