

Preparation of Ibuprofen-loaded Poly-(Methyl Vinyl Ether-co-maleic Anhydride) Nanoparticles by Solution-enhanced Dispersion by Supercritical CO₂

Ai-Zheng Chen^{a,b,*}, Guang-Ya Wang^a, Shi-Bin Wang^{a,b,*},
Jian-Gang Feng^a, Yuan-Gang Liu^{a,b}, Wei Zheng^a

^aCollege of Chemical Engineering, Huaqiao University, Xiamen 361021, China

^bInstitute of Pharmaceutical Engineering, Institute of Biomaterials and Tissue Engineering
Huaqiao University, Xiamen 361021, China

Abstract

Ibuprofen-loaded Poly-(methyl vinyl ether-co-maleic anhydride) (PVM/MA) nanoparticles were successfully prepared by Solution-enhanced Dispersion by Supercritical CO₂ (SEDS). Ibuprofen and PVM/MA were first homogeneously dissolved in acetone, and then the resulting solution was simultaneously sprayed with supercritical CO₂ through a coaxial nozzle, forming ibuprofen-PVM/MA nanoparticles. FTIR spectra demonstrated that ibuprofen was successfully incorporated into PVM/MA and the SEDS process was a typically physical process. The absolute value of the zeta potential of the obtained ibuprofen-PVM/MA nanoparticles was larger than 40 mV, indicating a good stability of the nanoparticles in aqueous suspension and suitability for oral administration. Analysis of Thermogravimetry-differential Scanning Calorimetry (TG-DSC) revealed that the effect of the SEDS process on the thermostability of the drug and the coating polymer was negligible. The results of Gas Chromatography (GC) analysis confirmed that the SEDS process could efficiently remove the organic residue. The drug dosage of 20% corresponded to a final drug load of $5.3 \pm 0.2\%$, which appeared to be relatively low and indicated that most of the ibuprofen was lost in the supercritical CO₂. Significant differences existed among the drug release profiles obtained from different release media; a medium with a low pH could efficiently prevent the release of ibuprofen from ibuprofen-PVM/MA nanoparticles, which works to reduce the adverse effects of ibuprofen on the stomach and makes ibuprofen-PVM/MA nanoparticles suitable for oral administration.

Keywords: PVM/MA, Ibuprofen; Nanoparticles; Supercritical CO₂, pH Response

1 Introduction

In the past few decades, drug-loaded nanoparticles/microspheres prepared by incorporating pharmaceutical agents into biodegradable polymers have aroused increasing interest [1-4]. This strat-

*Corresponding author.

Email addresses: azchen@hqu.edu.cn (Ai-Zheng Chen), sbwang@hqu.edu.cn (Shi-Bin Wang).

egy can combine the protection of active compounds with the release of drugs to specific tissues at a therapeutically optimal rate [5, 6]. The utilized polymers should possess an appropriate chemical composition and molecular weight to guarantee their biodegradability, low toxicity, and ideal bonding capacity with biologically active compounds [7]. The most frequently studied polymers that meet these requirements can be represented by chitosan [8] and several poly(esters), including Poly(Lactic Acid) (PLA) [9], Poly(Glycolic Acid) (PGA) [10], and poly(lactic-co-glycolic acid) (PLGA) [11, 12].

Among various biodegradable polymers, PVM/MA is a typical one with great potential for biomedical application [13–15]. It is a polyanhydride and can be employed as an ideal co-polymer for the fabrication of particulate dosage forms due to its bioadhesive and mucoadhesive properties [16]. Actually, when PVM/MA is hydrolyzed, each cleaved anhydride bond can generate two carboxylic groups, which can promote the formation of hydrogen bonds between the polymers and mucosal components [17]; furthermore, the hydrolyzation of PVM/MA can be affected by pH and thus is pH responsive to some degree. In the last few decades, PVM/MA has been widely used for pharmaceutical purposes, as a denture adhesive and an adjuvant for transdermal patches [18–24]. However, few studies have reported on the application of PVM/MA in fabricating drug-loaded polymer nanoparticles/microspheres.

A wide range of pharmaceutical agents take advantage of biodegradable polymers to provide targeted delivery of the drugs and control the drug release rate; nevertheless, most drug carrier system preparation strategies depend on either a high temperature process, like spray drying [25], or organic solvent evaporation-based techniques [26, 27] to incorporate pharmaceutical candidates into polymers and form composite nanoparticles/microspheres. A high temperature process is not suitable for temperature-sensitive compounds, and in organic solvent-based processes, complete removal of the organic solvent in a subsequent procedure is tedious and rather challenging.

Over the past few decades, supercritical CO₂-based techniques have been fully developed and widely utilized in particle engineering, especially for those in biomedical domains [28]. Compared with those conventional methods mentioned above, the unique advantages of supercritical CO₂-based techniques range from mild critical points ($T_c=304.1$ K, $P_c=7.38$ MPa), non-toxicity, non-flammability, and an absence of organic residue, to a relatively low price [29, 30]. Particle preparation methodologies based on supercritical CO₂ have involved a number of related methods, from a Rapid Expansion of Supercritical Solution (RESS) process [31], to a Supercritical Antisolvent (SAS) process [29,32], to Solution-enhanced Dispersion by Supercritical CO₂ (SEDS) [28, 30]. In the SEDS process, supercritical CO₂ and a solution of chemical compounds in organic solvent are simultaneously sprayed through a co-axial nozzle, where the spraying and dispersion of the initial solution can be significantly enhanced by that of supercritical CO₂. The moment the drug solution contacts supercritical CO₂, extremely rapid extraction of the organic solvent in the drug solution by supercritical CO₂ occurs, which causes instant drug precipitation and forms particles on a nano/micro-scale [33, 34].

Oral administration is accepted as an effective drug delivery route due to its convenient operation, fast absorption, and avoidance of pain. Ibuprofen, a non-steroidal anti-inflammatory analgesic and antipyretic drug widely used in the treatment of arthritis and mild to moderate pain, is usually administered orally, with a conventional drug dosage form including tablets, suspension, and capsules. However, the therapeutic effects of these drug forms are always undermined by the release of ibuprofen in the stomach and, in turn, its irritation of the gastric mucosa