Reactive and Functional Polymers 107 (2016) 46–53

Contents lists available at ScienceDirect

Reactive and Functional Polymers

journal homepage: www.elsevier.com/locate/react

Poly(lactide-*co*-glycolide)/cyclodextrin (polyethyleneimine) microspheres for controlled delivery of dexamethasone

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ARTICLE INFO

Article history:
Received 20 April 2016
Received in revised form 28 July 2016
Accepted 26 August 2016
Available online 31 August 2016

Keywords:
Poly(lactide-co-glycolide)
Poly(ethyleneimine)
Cyclodextrin
Microsphere
Drug delivery

ABSTRACT

Water-in-oil-in-water ($w_1/o/w_2$) solvent evaporation method is a technique for encapsulation and protection of water soluble and chemically sensitive bioactive molecules.
One of the most important disadvantages of this method is the diffusion of bioactive molecule, during synthesis, from the primary to the secondary aqueous phase, reducing dramatically the encapsulation yield. Therefore, dexamethasone sodium phosphate (DM), a corticosteroid water soluble drug, which is sensitive to degradation, was first complexed with hydroxypropyl cyclodextrin (HPCD), γ-cyclodextrin (γ-CD) or polyethyleneimine (PEI) and then entrapped in poly(lactic-*co*-glycolic acid) (PLGA) microspheres obtained by $w_1/o/w_2$ solvent evaporation method. Association equilibrium constants for the formation of the HPCD/DM and γ-CD/DM inclusion complexes were also calculated, being $1.420 \times 10^3\ M^{-1}$ and $1.447 \times 10^4\ M^{-1}$, respectively. PEI was proved to be the most efficient DM trapper, retaining the highest amount of the drug in microspheres, followed by γ-CD and HPCD. Despite the high values of the association equilibrium constants for DM binding to HPCD and γ-CD, both cyclodextrins are not able to protect the drug against UV irradiation. The morphology of the microspheres as well as the drug entrapment efficiency and the release rates are influenced by complexing agents and the ratio between the primary aqueous phase and the organic phase.

1. Introduction

Controlled drug delivery systems based on polymeric micro- and nano-spheres have seen a tremendous development over the last twenty years [1–3]. The most important advantages of these systems are the prolonged delivery of drugs, maintaining a therapeutic concentration and reduce side effects; moreover, they are easy to prepare and handle and can be administered by any route in the organism [4]. Furthermore, drug binding to a polymeric matrix protects the drug against premature degradation. Drugs are usually linked covalently [5], by electrostatic and hydrogen bonds [6], or they are physically embedded in the polymeric matrix [7]. Many drugs and bioactive molecules are very sensitive to temperature and to organic solvents; therefore, during encapsulation, they should be kept in aqueous solution at low temperatures.

Water-in-oil-in-water ($w_1/o/w_2$) solvent evaporation method is the most used technique for the encapsulation in microspheres of water soluble drugs or biologically active molecules [8,9]. The drug is dissolved in a low amount of water and the aqueous solution (w_1) is dispersed in a polymeric solution in organic solvents (o). The first emulsion is then dispersed in a second aqueous solution containing a stabilizer (w_2). During the evaporation of the volatile solvent and at the end of preparation the drug remain solubilized in water. Finally, the water is eliminated by lyophilization and the drug is encapsulated as free powder after the volatile solvent is completely removed. However, the most important drawback of this method is the diffusion of a large amount of the drug from the first to the second aqueous phase, thus resulting in low encapsulation efficiency [10,11]. In fact, the first emulsion, consisting of a huge number of small droplets (micro- or nano-dispersion) with a very large surface comes in contact with the second aqueous phase facilitating the diffusion of the water soluble drug. This phenomenon is emphasized when the ratio between the first aqueous phase and the amount of the polymer in the organic phase is high [12]. In fact, although the 1:10 ratio of the aqueous/organic phase (obtained dispersing 0.5 mL aqueous drug solution in 5 mL organic phase with 0.2 g dissolved polymer [12]) is acceptable, after complete evaporation of the volatile solvent, 0.2 g dried polymer should entrap ~0.5 g aqueous polymer solution. The final microcapsules should display a cellular structure with very thin walls similar with a honeycomb, facilitating a rapid diffusion of the drug towards the secondary aqueous phase during the preparation process as well as a high release rate in physiological fluids. Several water soluble bioactive molecules were encapsulated by

Abbreviations: ESEM, environmental scanning electron microscopy; PBS, phosphate buffer solution at pH = 7.4; PLGA, poly(lactide-co-glycolide); HPCD, 2-hydroxypropyl-β-cycodextrin; γ-CD, γ-cyclodextrin; PEI, polyethyleneimine; PVA, poly(vinyl alcohol); DCM, dichloromethane; DM, dexamethasone sodium phosphate.

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http://dx.doi.org/10.1016/j.reactfunctpolym.2016.08.008
1381-5148/