International Journal of Pharmaceutics 495 (2015) 393–403

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Prediction of dexamethasone release from PLGA microspheres prepared with polymer blends using a design of experiment approach

Bing Gu, Diane J. Burgess*

University of Connecticut, School of Pharmacy, Storrs, CT 06269, United States

ARTICLE INFO

Article history:
Received 17 July 2015
Received in revised form 25 August 2015
Accepted 26 August 2015
Available online 15 September 2015

Keywords:
Design of experiment
Mathematical model
PLGA
Polymer blends
Release profile
Microspheres

ABSTRACT

Hydrophobic drug release from poly (lactic-co-glycolic acid) (PLGA) microspheres typically exhibits a tri-phasic profile with a burst release phase followed by a lag phase and a secondary release phase. High burst release can be associated with adverse effects and the efficacy of the formulation cannot be ensured during a long lag phase. Accordingly, the development of a long-acting microsphere product requires optimization of all drug release phases. The purpose of the current study was to investigate whether a blend of low and high molecular weight polymers can be used to reduce the burst release and eliminate/minimize the lag phase. A single emulsion solvent evaporation method was used to prepare microspheres using blends of two PLGA polymers (PLGA5050 (25 kDa) and PLGA9010 (113 kDa)). A central composite design approach was applied to investigate the effect of formulation composition on dexamethasone release from these microspheres. Mathematical models obtained from this design of experiments study were utilized to generate a design space with maximized microsphere drug loading and reduced burst release. Specifically, a drug loading close to 15% can be achieved and a burst release less than 10% when a composition of 80% PLGA9010 and 90 mg of dexamethasone is used. In order to better describe the lag phase, a heat map was generated based on dexamethasone release from the PLGA microsphere/PVA hydrogel composite coatings. Using the heat map an optimized formulation with minimum lag phase was selected. The microspheres were also characterized for particle size/size distribution, thermal properties and morphology. The particle size was demonstrated to be related to the polymer concentration and the ratio of the two polymers but not to the dexamethasone concentration.

1. Introduction

Diabetes mellitus is a chronic metabolic disease affecting about 387 million people globally (2014 data) according to International Diabetes Federation (Cho, 2014). Fluctuation in blood glucose levels is a typical symptom of diabetic patients due to underproduction or underutilization of insulin. It is critical for diabetic patients to closely monitor their blood glucose levels in order to control disease progression and prevent severe complications (Fowler, 2008). At present, most diabetic patients rely on glucose strips along with hand held glucose meters to measure blood glucose levels *via* finger pricking (Samuelson and Gerber, 2009). Continuous glucose monitoring provides the advantage of accurately monitoring the blood glucose trend for precise calculation of the insulin dose, therefore eliminating the possibility of hypo/hyperglycemic conditions (Lodwig et al., 2014). Currently, commercially available continuous glucose monitoring devices can only function for up to 7 days with a glucose oxidase based transcutaneous amperometric sensor (Henning, 2009). These sensors lose functionality after one week due to the foreign body reaction (FBR) which is a series of sequential events that ultimately rejects the implanted biomaterials (Morais et al., 2010). The initial biofouling and sequential inflammatory cell attack can affect enzyme stability and reduce sensor sensitivity. Fibrous encapsulation, the final event of FBR, deprives the senor of adequate analyte supply leading to a loss in sensor signal. Inhibition of local FBR is one of the most promising strategies to extend sensor lifetime (Vaddiraju et al., 2010).

In order to achieve long-term continuous glucose monitoring, biocompatible coatings composed of poly (lactic-co-glycolic acid) (PLGA) microspheres embedded in a polyvinyl alcohol (PVA)

Abbreviations: PLGA, poly (lactic-co-glycolic acid); FBR, foreign body reaction; PVA, polyvinyl alcohol; QbD, quality by design; DoE, design of experiment; DMSO, dimethyl sulfoxide; DCM, methylene chloride; ACN, acetonitrile; THF, tetrahydrofuran; DSC, differential scanning calorimeter; T_g, glass transition temperature; SEM, scanning electron microscopy; EE, encapsulation efficiency; ANOVA, analysis of variance.

* Corresponding author.
E-mail address: d.burgess@uconn.edu (D.J. Burgess).

http://dx.doi.org/10.1016/j.ijpharm.2015.08.089
0378-5173/