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Understanding the quality of protein loaded PLGA nanoparticles variability by Plackett–Burman design

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ABSTRACT

The aim of this investigation was to screen and understand the product variability due to important factors affecting the characteristics CyA-PLGA nanoparticles prepared by O/W emulsification-solvent evaporation method. Independent variables studied were cyclosporine A (CyA) (X_1), PLGA (X_2), and emulsifier concentration namely SLS (X_3), stirring rate (X_4), type of organic solvent employed (chloroform or dichloromethane, X_5) and organic to aqueous phase ratio (X_6). The nanoparticles properties considered were encapsulation efficiency (Y_1), mean particle size (Y_2), zeta potential (Y_3), burst effect (Y_4) and dissolution efficiency (Y_5). The statistical analysis of the results allowed determining the most influent factors. The nanoparticles were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) and Fourier transform infrared (FTIR) spectroscopy. The factors combination showed variability of entrapment efficiency (Y_1), mean particle size (Y_2) and zeta potential (Y_3) from 10.17% to 93.01%, 41.60 to 372.80 nm and 29.60 to 34.90 mV, respectively. Initially, nanoparticles showed burst effect followed by sustained release during the 7-day in vitro release study period. The dissolution efficiency (Y_5) varied from 52.67% to 84.11%. The nanoparticles revealed Higuchi release pattern and release occurred by coupling of diffusion and erosion. In conclusion, this study revealed the potential of QbD in understanding the effect of formulation and process variables on the characteristics on CyA-PLGA nanoparticles.

1. Introduction

Cyclosporine (CyA) is a cyclic neutral undecapeptide produced by fungus *Tolypocladium inflatum* which contains mainly D-amino acid, with a potent immunosuppressive activity that has been used to prevent allograft rejection in various organ transplantation such as kidney, liver, heart, lung and pancreas (Matzke and Luke, 1988; Lemley and Katz, 1988), in psoriasis (Costanzo et al., 2009) and atopic dermatitis (Akhavan and Rudikoff, 2008). It has been explored in the treatment of autoimmune disorders such as rheumatoid arthritis (Richardson and Emery, 1995) and Behçet's uveitis disease (Akman-Demir et al., 2008). New evidences are emerging its role in controlling ulcerative colitis (Yadav and Liu, 2009), and as a neuroprotective agent (Hatton et al., 2008).

Despite its promising pharmacological profile and great therapeutic value, the bioavailability after oral administration is low with high inter-patient variability (20–50%) (Lindholm et al., 1988; Fahr, 1993). The low oral bioavailability is due to its poor aqueous solubility (0.02 mg/ml) (Miyake et al., 2000) and furthermore, it is a substrate of p-glycoprotein (Charuk et al., 1995).

Many formulation strategies were investigated to improve solubility and bioavailability of CyA such as complexation with cyclodextrin (Matilainen et al., 2006), and particulate delivery system including microspheres (Yeung and Chaw, 2009) and liposome (Czogalla, 2009). The formulation of CyA in nanoparticles dosage has received much attention in the last few years mainly due to its ability to improve bioavailability and could be a better alternative to current delivery system. Biodegradable materials investigated for nanoparticles of CyA are chitosan (El-Shabouri, 2002) polycaprolactone (Varela et al., 2001), PLGA (Italia et al., 2007) and hydroxypropylmethyl cellulose phthalate (Wang et al., 2004). Investigators claimed 1.8-fold increase in bioavailability of CyA by chitosan based nanoparticles when compared with neoral microemulsion in Beagle dogs (El-Shabouri, 2002). Similarly, PLGA nanoparticles of CyA showed 119.2% relative bioavailability, low toxicity and prolonged release when compared with Sandimmune neoral dosage (Italia et al., 2007). PLGA based nanoparticles have distinct advantage of being FDA

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