ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES 11 (2016) 751–759

HOSTED BY

Available online at www.sciencedirect.com

ScienceDirect

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

Original Research Paper

Loading of tacrolimus containing lipid based drug delivery systems into mesoporous silica for extended release

Li Liu [a], *Jia Li* [a], *Mei-hui Zhao* [a], *Hui Xu* [a,*], *Lin-sen Li* [b], *Shao-ning Wang* [c]

[a] *School of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China*
[b] *Department of Biochemistry, Shenyang Medical College, Shenyang 110034, China*
[c] *School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China*

ARTICLE INFO

Article history:
Received 15 April 2016
Received in revised form 22 June 2016
Accepted 20 July 2016
Available online 4 August 2016

Keywords:
Tacrolimus
Lipid-based drug delivery system
Mesoporous silica
Silica-lipid hybrid
Sustained-release

ABSTRACT

Many studies had been focused on designing tacrolimus sustained release preparations based on solid dispersion technique, but no one had tried to employ mesoporous silica as the carrier material to realize this goal. The purpose of this study was to develop a novel, simple and environmental friendly drug loading method with mesoporous silica to obtain tacrolimus sustained-release preparation. Tacrolimus was firstly dissolved in the molten mixed lipid composed of Compritol 888 ATO and Gelucire 50/13 to prepare a drug loaded lipid-based drug delivery systems (LBDDS), then the liquid LBDDS was adsorbed by mesoporous silica to transfer the liquid into solid powder, ie. the tacrolimus sustained release silica-lipid hybrid (SLH). The SLH was characterized by SEM, CLSM, XRPD and DSC, and the *in vitro* drug release was tested using a paddle method. SEM and CLSM observation showed that the LBDDS was efficiently distributed throughout the pores of the silica. The results of DSC and XRPD illustrated that the lipid existed inside the silica at amorphous state. The drug-loaded SLH showed good flowability, compressibility, compactibilty and two-phase *in vitro* drug release process within 24 hours, which did not change obviously even after storage at 40 °C for 10 d. The present study provided a novel and simple method to prepare tacrolimus sustained release powder, which provided a feasible solution to solidify the liquid LBDDS of not only extended drug release behavior, but also improved stability and micromeritic properties.

* *Corresponding author.* School of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China. Fax: 024-23986356.
E-mail address: xuhui_lab@163.com (H. Xu).

Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2016.07.005

1. Introduction

Tacrolimus, previously known as FK506, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Due to its potent immunosuppressive activity, low dosage, high organ survival rate and low incidence of acute rejection rate, tacrolimus is clinically used in the prophylaxis of organ rejection after hepatic and renal transplantation procedures [1]. As a BCS class II drug, the poor water solubility of tacrolimus greatly limited its oral bioavailability. Thus, increasing the solubility or dissolution of tacrolimus was one of the key problems in improving oral bioavailability, and many studies have been devoted to the modification of various drug delivery systems, including solid dispersion [2,3], nanoparticles [4–6], liposome [7,8], and self-emulsification [9]. Tacrolimus extended release preparations attracted great attention in both clinical practice and drug development due to its superior therapeutic profits, such as decreased ratio of peak/trough blood drug level, improved oral bioavailability and eliminated need for frequent dosing. There were already two modified release products of tacrolimus approved and marketed worldwide. A once-daily tacrolimus sustained release capsule supplied by *Astellas Pharma Inc* was approved in Europe (Advagraf®) and Japan (Graceptor®) in 2007 [10,11]. After that, tacrolimus sustained-release tablet produced by *Veloxis Pharmaceuticals* was approved both in Europe and USA with the brand names Envarsus® and Envarsus®XR, respectively. In addition, there was an explosion of interest in developing tacrolimus extended release preparations in recent years. *Cho* et al. had focused on the development of novel fast-dissolving tacrolimus solid dispersion-loaded prolonged release tablet. *Wang* et al. reported a novel gastro-retentive sustained-release tablet of tacrolimus based on self-microemulsifying mixture [12].

Lipid excipients aroused great interest from drug formulation researchers owing to their ability of providing solutions to drug delivery challenges, such as low drug solubility and dissolution rate, poor oral absorption of water-insoluble drugs, as well as the simplified and safety manufacturing processes, and so on [13–15]. For poorly water-soluble drugs, lipid-based drug delivery systems (LBDDS) unveiled distinguish prospects as it can mimic the food effect via creating a lipophilic microenvironment within the gastrointestinal tract, thus enhancing the solubilization of poorly water-soluble drug molecules and providing a concentration gradient that drive the absorption of drug molecules in the intestinal tract [16–20]. One of the major disadvantages of LBDDS lies in its liquid or low melting-point semi-solid state (eg. lipid solutions, suspensions, and emulsions) at ambient environment, which may result in physicochemical instability during storage, thus greatly limited applications of LBDDS [21,22].

Mesoporous materials with tunable pore size of 2 nm to 50 nm, large surface area and porosity, and high adsorbing capacity have been selected as ideal carriers for both fast and extend drug release. Mesoporous silica was widely investigated as drug delivery systems since *Vallet-Regi* firstly used it for loading of drug in 2001 [23–27]. The use of mesoporous silica in drug delivery systems is mainly due to its excellent adsorptive properties. In previous reports, organic solvent solution soaking method was often used to load poorly water-soluble drugs for fast drug release. *Wang* et al. achieved sustained release of drug by employing supercritical fluid technique to load poorly water-soluble drug deep into the pore channels of mesoporous silica [25]. It is the physical interaction between silica and adsorbed guest molecules that delays drug release [28]. Mesoporous silica can also be used as a carrier of LBDDS via physical adsorption to convert the liquid or semi-solid state LBDDS into solid powder and formed silica-lipid hybrid (SLH) with improved the flowability, compressibility and compactibility. The powdered SLH combined the well-known advantages of LBDDS with those of solid dosage forms, and what's more, it bore the ability to greatly improve the physicochemical stability of LBDDS [29].

Till now, there is no report on the use of lipid excipients and mesoporous silica as the organic/inorganic hybrid carrier to achieve solidified LBDDS for sustained tacrolimus release. In this study, tacrolimus was dissolved in a mixture of molten lipids composed of glyceryl behenate and stearoyl polyoxyl-32 glycerides to obtain drug loaded LBDDS, and then mesoporous silica was used to adsorb the liquid LBDDS to obtain SLH powder. The physicochemical properties of SLH powder and its *in vitro* drug release were studied. It is desirable to achieve a novel, simple and solvent-free technique to fabricate tacrolimus sustained release preparations with this method.

2. Materials and methods

2.1. Materials

Tacrolimus (Chinese Pharmacopeia) was a gift from Zhejiang Hisun Pharmaceutical Co. Ltd (Jiangsu, China); glyceryl behenate (Compritol 888 ATO) and stearoyl polyoxyl-32 glycerides (Gelucire 50/13) were kindly donated by Gattefossé (France); mesoporous silica (Parteck SLC) was provided by Merck & Co. Inc (Germany). Tacrolimus capsules: brand name Prograf; standard 1 mg/capsule; batch number 1E2201A. All other chemicals used were of chemical or analytical grades and used as received.

2.2. Preparation of tacrolimus loaded LBDDS and SLH

Tacrolimus loaded SLH was prepared in a process of two-steps, ie., preparation of drug-loaded LBDDS and the solidification of LBDDS to form the drug-loaded SLH as described below. (1) tacrolimus, and/or Compritol 888 ATO and Gelucire 50/13 were accurately weighed according to the formulations listed in Table 1, and placed into a glass round bottom flask and heated at 80 °C with constant stirring until all the excipients were melted; then tacrolimus was added into the molten mixture at 70 °C with stirring to form a homogenous mixture. (2) The mesoporous silica was mixed with the above molten mixture, and the molten mixture was adsorbed into the pores inside the silica under decreased pressure. The mixture was stirred for another half an hour at 70 °C and then cooled down to room temperature to form the final solid hybrid mixture. The lipid free, tacrolimus loaded mesoporous silica was prepared with similar method using ethanol as the solvent and fabricated at room temperature.