Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 288 (2005) 169–175
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Oral evaluation in rabbits of cyclosporin-loaded Eudragit RS or RL nanoparticles

N. Ubrich[a,*], C. Schmidt[b], R. Bodmeier[b], M. Hoffman[a], P. Maincent[a]

[a] *Laboratoire de Pharmacie Galénique, EA 3452, Faculté de Pharmacie, 5, rue Albert Lebrun, B.P. 403, 54001 Nancy Cedex, France*
[b] *College of Pharmacy, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany*

Received 28 April 2004; received in revised form 7 September 2004; accepted 10 September 2004

Abstract

The hydrophobic cyclic undecapeptide cyclosporin A (CyA) used in the prevention of graft rejection and in the treatment of autoimmune diseases was encapsulated by nanoprecipitation within non-biodegradable polymeric nanoparticles. The effect of polymers (Eudragit® RS or RL) and additives within the alcoholic phase (fatty acid esters and polyoxyethylated castor oil) on the size, zeta potential and the encapsulation efficiency of the nanoparticles was investigated. The mean diameter of the various CyA nanoparticles ranged from 170 to 310 nm. The size as well as the zeta potential increased by adding fatty acid ester and polyoxyethylated castor oil within the organic phase. No significant differences in surface potential were observed for all formulations tested. Probably due to the very low water solubility of the drug, high encapsulation efficiencies were observed in a range from 70 to 85%. The oral absorption of CyA from these polymeric nanoparticles was studied in rabbits and compared to that of Neoral® capsule. Based on comparison of the area under the blood concentration–time curve values, the relative bioavailability of CyA from each nanoparticulate formulation ranged from 20 to 35%.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Nanoparticle; Cyclosporin; Oral administration; Eudragit®

1. Introduction

Cyclosporin A (CyA), a potent immunosuppressive agent, is widely used for the prevention of graft rejection in transplanted patients (Matzke and Luke, 1988) as well as in the treatment of autoimmune diseases (Richardson and Emery, 1995).

CyA was first marketed as an oil-based oral solution, or an injectable solution containing polyoxyethylated castor oil. However, the oral bioavailability of CyA from these conventional preparations displayed considerable inter- and intra-individual variability (Fahr, 1993; Molpeceres et al., 1998, 2000), probably because of poor drug absorption and intestinal metabolism.

* Corresponding author. Tel.: +33 3 83 68 22 97; fax: +33 3 83 68 23 01.
E-mail address: ubrich@pharma.uhp-nancy.fr (N. Ubrich).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.09.019

Moreover, CyA exhibits a broad toxicity profile, including nephrotoxicity and hepatotoxicity. The marketing of a pre-microemulsion of CyA allows a better reproducibility of the absorption, but the bioavailability, although improved, is still low (Klyashcchitsky and Owen, 1998).

Various dosage forms have been studied to reduce the toxicity and to increase the absorption of CyA. Particulate polymeric drug delivery systems such as micro- and nano-particles have been studied extensively. CyA has been associated to poly(isohexylcyanoacrylate) nanospheres (Bonduelle et al., 1992), or encapsulated within poly(isobutylcyanoacrylate) or poly-ε-caprolactone nanoparticles (Guzman et al., 1993). Sanchez et al. (1993) demonstrated the feasability of efficiently encapsulating CyA into poly(DL-lactide-co-glycolide) micro- and nano-spheres allowing a controlled release of the drug. CyA loaded nanocapsules composed of an oily core (mygliol®) and a poly-ε-caprolactone coat were interesting carriers for ocular delivery; this dosage form resulted in a better absorption of the drug through the cornea (Calvo et al., 1996). Poly(acrylic acid) polymeric gels and poly(isobutylcyanoacrylate) nanocapsules of CyA also showed, ex vivo, an increased absorption of the drug in the bovine cornea model (Le Bourlais et al., 1997). More recently, CyA loaded poly(DL-lactic acid) microspheres prepared in the presence of fatty acid esters as additives exhibited a significant inhibitory effect on the edema after subcutaneous administration in rats with adjuvant-induced arthritis (Urata et al., 1999).

CyA delivery systems were also prepared without particle-forming polymers. CyA nanospheres were prepared by precipitation in an aqueous surfactant solution; however, after oral administration in dogs, the absorption of CyA and the relative bioavailability were poor when compared to the Neoral® microemulsion (Ford et al., 1999). On the contrary, liposomes and mixed micelles containing CyA (Lee et al., 1999) as well as lecithin micelles (Guo et al., 2000) and CyA loaded stearic acid nanoparticles (Zhang et al., 2000) showed that CyA was available after topical, intravenous or oral administration. However, these formulations were not stable enough and the bioavailability was lower than the currently available marketed dosage forms of CyA.

In this study, CyA nanoparticles were prepared by nanoprecipitation with non-biodegradable positively-charged polymers (Eudragit® RS and RL), with or without fatty acid esters (Maisine®) and polyoxyethylated castor oil (Cremophor®). Maisine and Cremophor are excipients already used in the marketed dosage form Neoral®. The association of colloidal particles and polycationic polymers was supposed to improve the interaction with the negatively-charged mucus of the gastro-intestinal tract. The formulations were characterized in vitro with regard to encapsulation efficiency, size and surface potential and were evaluated in vivo after oral administration to rabbits, in comparison to both, a Neoral® capsule administered orally and a marketed CyA solution administered intravenously.

2. Materials and methods

2.1. Materials

Eudragit® RS 100 and RL 100 as well as Maisine® (glyceryl monolinoleate), Cremophor® RH40 (polyoxyethylated castor oil) and Pluronic® F68 were kindly supplied, respectively, by Röhm GmbH (Darmstadt, Germany) and BASF (Ludwigshafen, Germany). Cyclosporin A powder and absolute ethanol were purchased from Sigma (St. Louis, MO, USA). Marketed cyclosporin (injectable solution, Sandimmum®) and Neoral® capsules (25 mg) were obtained from commercial sources. The standard kit (Emit®) used for the assay of free cyclosporin recovered in the aqueous solution for the determination of the encapsulation efficiency, as well as the absorbed cyclosporin recovered in blood for the pharmacokinetic study was provided by Dade Behring (Paris, France). All other chemical reagents were of analytical grade and used as supplied.

2.2. Preparation of nanoparticles

The preparation of the nanoparticles was carried out by the nanoprecipitation method previously described by Fessi et al. (1989) and Bodmeier et al. (1991) and adapted as follows: Eudragit® RS or RL (0.2 g) and cyclosporin A powder (50 mg) were dissolved in a sealed vial containing ethanol (1 ml) in an ultrasound bath for 10 min. Then, an aqueous solution (9 ml) of Pluronic® F68 (0.5% m/V) was added to this organic solution under magnetic stirring (500 rpm) for 2 min.

Download English Version:

https://daneshyari.com/en/article/9919028

Download Persian Version:

https://daneshyari.com/article/9919028

Daneshyari.com