International Journal of Pharmaceutics 454 (2013) 641–648

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Development of oil-in-water microemulsions for the oral delivery of amphotericin B

Acarília Eduardo Silva[a,b], Gillian Barratt[b], Monique Chéron[c], E. Sócrates T. Egito[a,*]

[a] Universidade Federal do Rio Grande do Norte, Faculdade Farmácia, Laboratório de Sistemas Dispersos (LASID), Rua Gal. Cordeiro de Farias, S/N, Petrópolis, Zip Code 59010-180 Natal, RN, Brazil
[b] Université Paris Sud XI, Institut Galien Paris Sud, 5 rue Jean-Baptiste Clément, Zip Code 92296 Châtenay-Malabry, France
[c] ANBiophy, FRE 3207 CNRS, Université Pierre et Marie Curie, 75252 Paris, France

ARTICLE INFO

Article history:
Received 17 February 2013
Received in revised form 12 May 2013
Accepted 16 May 2013
Available online 31 May 2013

Keywords:
Amphotericin B
Lipids
Microemulsions
Surfactants
Rheology
In vitro toxicity

ABSTRACT

Amphotericin B (AmB) is a very efficient drug against serious diseases such as leishmaniasis and systemic fungal infections. However, its oral bioavailability is limited due to its poor solubility in water. Nevertheless, it is marketed as high-cost lipid parenteral formulations that may induce serious infusion-related side effects. In this study, oil-in-water (O/W) microemulsions (MEs) were developed and characterized with a view to their use as solubility enhancers and oral delivery systems for AmB. Therefore, different nonionic surfactants from the Tween® and Span® series were tested for their solubilization capacity in combination with several oils. Based on pseudoternary phase diagrams, AmB-loaded MEs with mean droplet sizes about 120 nm were successfully produced. They were able to improve the drug solubility up to 1000-fold. Rheological studies showed the MEs to be low-viscosity formulations with Newtonian behavior. Circular dichroism and absorption spectra revealed that part of the AmB in the MEs was aggregated as an AmB reservoir carrier. Cytotoxicity studies revealed limited toxicity to macrophage-like cells that may allow the formulations to be considered as suitable carriers for AmB.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

Amphotericin B (AmB) is a polyene antibiotic with potent antifungal and leishmanicidal activities (Hartsel and Bolard, 1996; Ibrahim et al., 2012). Its chemical structure is characterized by a glycosylated lactone with an amphiphilic polyhydroxyl region, a conjugated heptane chromophore and an amphoteric ion pair (Fig. 1). As a consequence of both apolar and polar sides of its lactone ring and due to the presence of ionizable carboxyl and amine groups, AmB molecule presents both amphoteric and amphiphilic behavior (Damasceno et al., 2012). As a result, AmB is poorly soluble in aqueous media and in many organic solvents (Torrado et al., 2008). This low solubility leads to limited bioavailability and membrane permeability, which hinder the development of formulations for the oral route that is the most convenient and acceptable route for patients.

On the other hand, effective lipid parenteral formulations of AmB have been developed and marketed, but they have some serious limitations such as the inconvenience and complexity of the intravenous administration, the incidence of serious acute infusional side effects and the high cost that poses an important barrier for patients in developing countries (Wasan et al., 2009).

Recently, lipid-based formulations have been extensively investigated as a suitable approach to improve the bioavailability of poorly soluble drugs after oral administration (Han et al., 2009). When incorporated into these systems, the active molecule is believed to remain in solution throughout its period in the gastrointestinal tract (Pouton, 2006). Additionally, the absorption of the drug could be enhanced by the presence of lipids as a result of stimulation of biliary and pancreatic secretions by the gallbladder, an increase in the gastric residence time and others (Dahan and Hoffman, 2008).

Since microemulsions (MEs) are able to incorporate a wide range of drug molecules, increase their solubilization and bioavailability, and reduce their toxicity, they are promising delivery systems for oral administration of lipophilic molecules, such as AmB (Fanun, 2012; Pestana et al., 2008). Therefore, the aim of this work was to develop oil-in-water (O/W) MEs based on long- and medium-chain triglycerides in order to increase the solubility of AmB and enable its use by the oral route.

* Corresponding author at: UFRN, CCS, Departamento de Farmácia, Rua Praia de Areia Branca, 8948, 59094-450 Natal, RN, Brazil. Tel.: +55 84 9431 8816; fax: +55 84 3342 9817.
E-mail addresses: acariliasilva@gmail.com (A.E. Silva), gillian.barratt@u-psud.fr (G. Barratt), monique.cheron@u-psud.fr (M. Chéron), socratesegito@gmail.com, socrates@ufrnet.br (E.S.T. Egito).

0378-5173/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.05.044

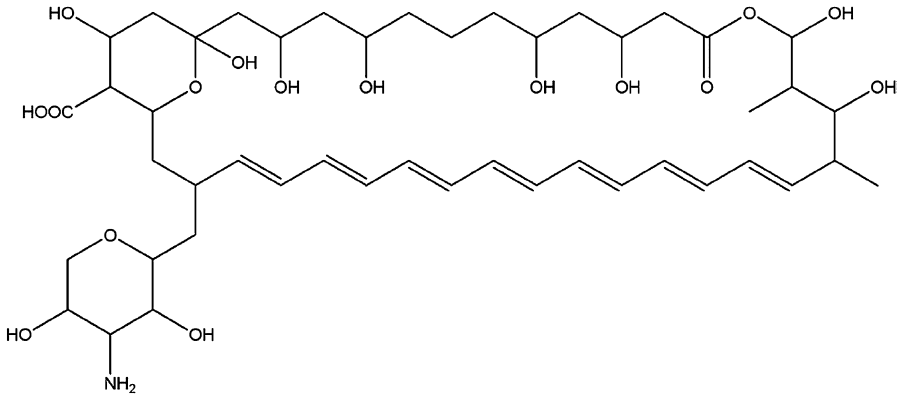

Fig. 1. Chemical structure of AmB (Santos et al., 2012).

2. Materials and methods

2.1. Materials

2.1.1. Chemicals

Sodium hydroxide (NaOH), chloride acid (HCl), amphotericin B (AmB) and HPLC grade methanol were purchased from Sigma–Aldrich (Saint Quentin Fallavier, France).

2.1.2. Surfactants

Span® 20, Span® 80, Span® 85, Tween® 20, Tween® 80 and Tween® 85 were purchased from Sigma–Aldrich (Saint Quentin Fallavier, France).

2.1.3. Lipids

Capryol® 90 (C90), Capryol® PGMC (CPGMC), Lauroglycol® 90 (L90), Labrafac® lipophile WL 1349 (LWL), Labrafac® PG (LPG) and Peceol® (Pec) were kindly supplied by Gattefossé S.A. (Saint-Priest, France). Corn oil and olive oil were obtained from Sigma–Aldrich (Saint Quentin Fallavier, France).

2.2. Methods

2.2.1. Selection of oil and hydrophilic surfactant

Nonionic surfactants of the Tween® series (Tween® 20, 80 and 85) and the lipids mentioned in Section 2.1.3 were weighed and put into a series of screwcap test tubes in the ratios of 0.1:0.9, 0.2:0.8, 0.3:0.7, 0.4:0.6, and 0.5:0.5 (w/w) g of 1 g per batch, mixed together, and vortexed thoroughly. Afterwards, 100 μL of distilled water was added to each oil–surfactant mixture in 20–25 μL drops using a micropipette. After each drop of water was added, the system was vortexed for 15 s at room temperature.

Visual observations were made, and the clarity or turbidity of each sample was recorded. The isotropy of each system was also observed by light polarized microscopy through a Nikon E600 Eclipse direct microscope (Champigny/Marne, France) equipped with a long focus objective (LWD 40 × 0.55; 0–2 mm). A Nikon Coolpix 950 camera was used to record the images with a resolution of 1600 × 1200 pixels. The surfactant forming most clear systems was selected as the hydrophilic surfactant that best matched the tested lipid.

2.2.2. Selection of surfactant blends

The individual nonionic hydrophilic surfactant chosen in Section 2.2.1 was blended with the lipophilic surfactants of the Span® series (Span® 20, 80 and 85) in ratios of 3:2, 7:3, 4:1, and 9:1 (w/w) to produce blends of surfactants with various hydrophilic-lipophilic balances (HLBs) in the range of 9.7–14.4 (Table 1). The solubilization capacities of the blends of surfactants were studied using the same method as that used to study the other surfactants individually. The blend of surfactants forming a clear system at most of the ratios was selected as the blend that best matched the HLB of the tested lipid.

Table 1
Composition of the surfactant blends and their final HLB values.

Surfactant blend	Surfactants		Weight ratio	HLB
M1	Tween® 80	Span® 20	3:2	12.4
M2	Tween® 80	Span® 20	7:3	13.1
M3	Tween® 80	Span® 20	4:1	13.7
M4	Tween® 80	Span® 20	9:1	14.4
M5	Tween® 80	Span® 80	3:2	10.7
M6	Tween® 80	Span® 80	7:3	11.8
M7	Tween® 80	Span® 80	4:1	12.9
M8	Tween® 80	Span® 80	9:1	13.9
M9	Tween® 80	Span® 85	3:2	9.7
M10	Tween® 80	Span® 85	7:3	11.0
M11	Tween® 80	Span® 85	4:1	12.4
M12	Tween® 80	Span® 85	9:1	13.7

M, mixture; HLB, hydrophilic LIPOPHILIC balance, mixture; HLB, hydrophilic lipophilic balance.

2.2.3. Construction of pseudoternary phase diagrams

After selection of the most suitable surfactant blend, pseudoternary phase diagrams were constructed based on the types of systems formed when the mixtures of lipids and surfactant blend were serially titrated by water followed by sonication. The systems were characterized by visual observation as described by Mahdi et al. (2011) (Table 2). The systems were also assessed regarding their isotropy by polarized light microscopy as described in Section 2.2.1.

2.2.4. Preparation of microemulsions

Based on the pseudoternary phase diagrams, the most suitable ratios of oil, surfactant blend and water for the production of O/W microemulsions were selected. The lipid was mixed with the

Table 2
Classification of the systems generated on the pseudoternary diagrams.

Category	Description
Microemulsions (ME)	Transparent or translucent and can flow easily
Liquid crystal (LC)	Transparent or translucent nonflowable when inverted 90°
Emulsion (EM)	Milky or cloudy and can flow easily
Emollient gel or cream (EG or EC)	Milky or cloudy non flowable when inverted 90°
Bicontinuous phase (BP)	More than one type of dispersion existing in the mixture, as indicated by the presence of more than one abbreviation of dispersions

Download English Version:

https://daneshyari.com/en/article/5820173

Download Persian Version:

https://daneshyari.com/article/5820173

Daneshyari.com