Colloids and Surfaces A: Physicochem. Eng. Aspects 516 (2017) 63–71

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

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

Research Paper

Impact of detergents on the physiochemical behavior of itraconazole loaded nanostructured lipid carriers

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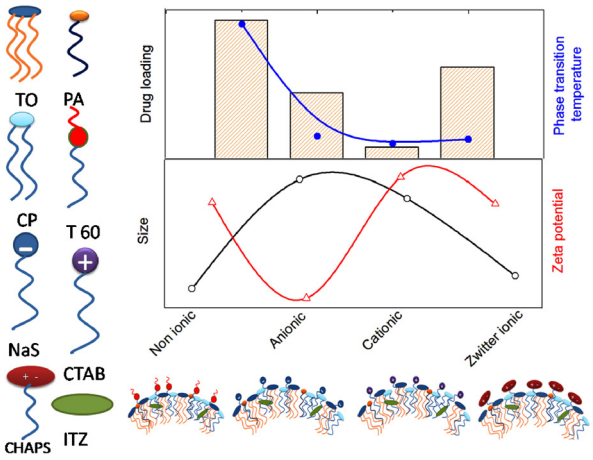
HIGHLIGHTS

- NLCs were prepared with triolein, cetyl palmitate and palmitic acid.
- Cationic, anionic, zwitterionic and nonionic surfactants were used as stabilizers.
- Antifungal drug, itraconazole was loaded into NLC.
- Physicochemical characterizations of drug loaded NLCs were done.
- Drug loaded NLCs showed superior antifungul activities.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 September 2016
Received in revised form
25 November 2016
Accepted 8 December 2016
Available online 9 December 2016

Keywords:
NLC
ITZ
DLS
DSC
Drug release
Antifungul activity

ABSTRACT

Effect of different surfactants (nonionic, anionic, cationic and zwitterionic) as stabilizer on the physicochemical properties of the nanostructured lipid carriers (NLC) comprising cetyl palmitate, triolein and palmitic acid were explored in the absence and presence of a potent antifungal drug, itraconazole. The blank and drug loaded NLC formulations were prepared by way of hot homogenization and ultrasonication technique. Combined dynamic light scattering, electron microscopy, atomic force microscopy, differential scanning calorimetry, UV–vis absorption spectroscopy and method of dialysis were adopted in characterizing the formulations. NLCs were stable up to 100 days irrespective of the surfactant. While the ionic surfactant comprising NLCs were electrostatically stable, the nonionic surfactants imparted better steric stabilization as revealed from the decreased size and polydispersity index values. Up shift in the phase transition temperature, changes in enthalpy and heat capacity in case of nonionic surfactant comprising systems substantiated its superior stabilization effect over the ionic surfactants. NLC formulations, stabilized by nonionic surfactants, exhibited superior drug incorporation, loading capacity and sustained release for itraconazole. Itraconazole loaded NLC formulations exhibited substantial antifungal

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http://dx.doi.org/10.1016/j.colsurfa.2016.12.009

activity against the fungal strain *Aspergillusniger* MTCC 3323. Such a comprehensive set of studies could assess the NLC formulation as potential drug delivery system for itraconazole.

1. Introduction

Since last few decades efforts have been made in developing lipid based colloidal drug delivery systems in order to enhance the bioavailability of poorly water soluble drugs [1–4]. Conventional liposome, emulsion, polymeric and solid lipid nanoparticles, although initially showed promising behavior [5–10], however, those formulations were found to suffer serious limitations like poor encapsulation, poor drug loading, drug leakage and unrestrained release of the incorporated drugs [7–10]. Nanostructured lipid carriers (NLC) are capable of overcoming these serious limitations whereby enhanced bioavailability of the lipophilic drugs and sustained release could be achieved. Solid lipids, in combination with the liquid lipids, are used for the development of NLCs [8,9]. Liquid lipids can enhance drug encapsulation and loading, thus promoting the bioavailability and providing long circulating effect of the incorporated drugs [10].

Itraconazole (ITZ) is a well known antifungal agent which belongs to the triazole group of drugs. It is an active pharmaceutical agent having potent activity against *Candida*, *Aspergillus* and dermatophyte species. ITZ shows promising result in the treatment of deep fungal infections like histoplasmosis and aspergillosis. It is also effective in the treatment of superficial fungal infections such as dermatomycosis. ITZ was found to give positive response in the treatment of vaginal candidacies [4,11–14]. In order to improve the poor bioavailability issue of ITZ, several delivery systems have been designed, *e.g.*, microemulsion, nanosuspension, liposomes, to mention a few. However, the formulations largely failed to improve the ITZ encapsulation and its bioavailability. Attempts were, therefore, made to develop ITZ loaded NLC formulations to overcome the limitations. But studies related to the enhancement of the bioavailability of itraconazole (ITZ) involving a suitable NLC system are not so common in literature [3,4,11]. Hence, further investigations are warranted in developing suitable NLC formulations by modifying the lipid composition and using suitable dispersion medium. In the present set of work, the effort has been given in developing stable NLC formulations for ITZ and in investigating the effect of different types (nonionic, anionic, cationic and zwitterionic) of surfactants as dispersion medium on the physicochemical stability, drug encapsulation as well as release of ITZ.

In general, different types of monoglycerides, diglycerides, triglycerides, waxes, phospholipids and fatty acids, both saturated (solid) as well as unsaturated (liquid) components are used in developing NLC. In the present series of works, triolein (TO), cetyl palmitate (CP) and palmitic acid (PA) have been chosen for the NLC formulation which are not so common in literature. Nonionic surfactants with relatively larger hydrophilic moieties are usually employed in formulating NLCs, which can tender steric stabilization. However, the use of ionic surfactants as stabilizers for the NLC formulations are less explored. It is expected that the biocompatible ionic surfactants can also act as promising stabilizers, through electrostatic repulsion. In order to address this issue, comprehensive studies were carried out through the physicochemical characterization of NLCs stabilized by a variety of surfactants bearing different head groups. The different surfactants that were used as stabilizers include nonionic: Tweeen 60, Tween 40 and Tween 20; anionic: sodium dodecyl sarcosinate (NaS) and sodium deoxycholate (NaDC); cationic: hexadecyltrimethylammonium bromide (CTAB) and zwitterionic: 3-[(3-cholamidopropyl) dimethyl ammonio]-1-propanesulfonate (CHAPS). The surfactants have been used separately as the dispersion medium to understand its impact on the physicochemistry and pharmacological behavior of different NLC formulations. NLC formulations stabilized with the different category of surfactants have been subjected for the determination of hydrodynamic diameter, polydispersity index and zeta potential to gather information regarding the solution phase stability. Morphology of the NLC formulations were studied by transmission electron microscopy and atomic force microscopy. Influence of the dispersion medium on the thermal behavior and the different thermodynamic parameters have also been evaluated by differential scanning calorimetry. Drug (ITZ) entrapment, loading and release kinetics of were investigated by the method of centrifugation and the dialysis bag approach respectively. Antifungal activity of the ITZ loaded NLC formulations were also assessed on *Aspergillusniger* MTCC 3323 strain. It is believed that such a comprehensive set of studies would help in developing novel drug delivery systems, besides shedding further light on the fundamental understanding on NLCs.

2. Materials and methods

2.1. Materials

Glyceryltrioleate/triolein (TO) and CHAPS hydrate were purchased from Sigma Aldrich, USA. Palmitic acid (PA), Tween 20, Tween 40 and Tween 60 were obtained from Sisco Research Laboratory, India. Cetyl palmitate (CP), sodium N-lauryl sarcosinate (NaS) were procured from TCI Chemicals, Japan. Hexadecyl/cetyl trimethylammonium bromide (CTAB) and sodium deoxycholate (NaDC) were obtained from RFCL Ltd., New Delhi, India and SD fine-chemicals Limited, Mumbai, India respectively. Itraconazole (ITZ) was a kind gift from Vyome Bioscience, New Delhi, India. All the chemicals used were stated to be ≥99% pure and were used as received. HPLC grade solvents and double distilled water having conductance of 2–4 μS (at 25 °C) were used throughout the study.

2.2. Preparation of NLC and ITZ loaded NLC

NLCs were prepared by hot homogenization followed by ultrasonication method [15,16]. TO, CP and PA, in the molar ratio 2:2:1, was dissolved in chloroform – methanol mixture (3:1, V/V) and the solvent was removed using a rotary evaporator. The thin film thus obtained was melted at 65 °C followed by the addition of the preheated aqueous surfactant solution. Concentration of the surfactant was fixed at 2 mM. The coarse emulsion obtained was then exposed to high speed dispersion for 1 h. The obtained pre-emulsion was sonicated with a probe sonicator (Takashi U250, Takashi Electric, Japan) at 150 W/(20–25 kHz) maintaining the same temperature for a period of another 1 h to produce nanoemulsion. The obtained nanoemulsion was allowed to cool down at room temperature to obtain the NLC and stored at 4 °C. In case of drug loaded formulation, the concentration of ITZ was fixed at 0.1 mM in all the cases. ITZ and the lipid mixture was melted altogether and the drug – lipid melt was subjected for the preparation of ITZ loaded NLC formulation.