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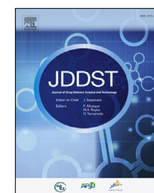

Research paper

Fluconazole-loaded niosomal gels as a topical ocular drug delivery system for corneal fungal infections

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A R T I C L E I N F O

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Non-ionic surfactant vesicles containing fluconazole (FLZ) were prepared using, span 60 or span 80 and cholesterol in weight ratios of 1:1, 2:1 and 1:2. The prepared vesicles were characterized for size, entrapment efficiency, and *in vitro* drug release. The drug encapsulation efficiencies varied from 40.0% to 84.35%. The particle size ranged from 140 to 280 nm. Higher encapsulation was obtained by the span 60: cholesterol ratio of 2:1, which showed the best drug release. The selected niosomal formulations were incorporated into poloxamer 407 and chitosan gel formulations. Drug release from niosomal dispersions and niosomal gels, permeation of drug from niosomal gels through goat cornea and its antifungal activity were evaluated. Results showed that the surfactant: cholesterol ratio had a significant effect on the encapsulation efficiency and the size of vesicles. The niosomes prepared with 2:1 surfactant: cholesterol showed superior release over the other niosomal formulations. The drug release and permeation from poloxamer gel were higher than that from chitosan gel. Permeation study showed that, the flux of drug was dependent on the viscosity of the gel. The selected niosomal gels had excellent antifungal activity where the poloxamer niosomal gel was more effective compared to chitosan niosomal gel.

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1. Introduction

Fungal keratitis is a serious disease that can lead to loss of vision if not diagnosed and treated promptly and effectively [1]. Previous ocular surface disease and trauma are the leading causes of fungal infection in the cornea [2]. Oral therapy requires high doses of an antifungal agent to reach therapeutic concentrations at the site of action, which may cause unwanted side effects. Fluconazole (FLZ) is an antifungal drug used in fungal infections caused by the pathogenic fungi, including *C. albicans*, which is a major contributory factor for cutaneous candidiasis [3]. It is commercially available as parental and oral dosage forms, which are largely confronted with well-known adverse effects including taste disturbances and GI irritation.

Topical ocular treatment is not effective due to protective mechanisms of the human eye. For example, lacrimal secretion and the blinking reflex cause rapid drainage of the formulation. The short pre-corneal contact time combined with corneal impermeability results in low bioavailability, and as a result, frequent dosing is usually needed [4]. In order to overcome the problems of conventional ocular therapy, numerous nanocarriers have been developed. Many of the ocular drug delivery systems (e.g., liposomes, micelles, solid lipid, and polymer-based nanoparticles) have reached the late stages of development, and some of them were approved but due to blurred vision or lack of patient compliance, they have not been universally accepted. So, the introduction of non-ionic surfactant vesicles (niosomes) which improved both permeability and bioavailability of poorly water soluble drugs, holds great promise for tremendous improvements in topical ocular drug delivery [5]. Ocular delivery using niosomes aims to achieve localized drug action since their size and low penetrability through epithelium keeps the drug localized at the site of administration and increases precorneal residence time. Many studies reported the value of niosomes in topical ocular drug delivery. Saettone et al. reported that niosomes increased the transcorneal permeation and bioavailability of cyclopentolate at ocular site [6]. Aggarwal et al. reported an enhanced ocular bioavailability of acetazolemide when dosed in niosomal dosage form (almost twice) as compared to free drug solution [7]. Ocular niosomal gentamicin sulphate showed a high retention as compared to the free drug solution [8]. Another study reported that tacrolimus niosomes coated with hyaluronic acid showed 2.3-fold and 1.2-fold increase in corneal permeability as that of suspension and non-coated

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niosomes, respectively [9]. Zubairu et al. proposed a chitosan coated niosomal formulation of gatifloxain which showed increased transcorneal permeation of the drug more than two fold than simple drug solution and a longer retention time on eyes and subsequent reduction in dosing frequency [10]. A recent study by Shukr who developed in situ gelling ocular inserts loaded with voriconazole niosomal suspension, showed significantly increased bioavailability of the drug in rabbits [11]. Niosomes are formed from the self-assembly of non ionic amphiphiles in aqueous media resulting in closed bilayer structures. These structures are analogous to liposomes and are able to encapsulate solutes, which are osmotically active and stable [12]. The low cost, greater stability and resultant ease of storage of non-ionic surfactants had offered them many advantages over liposomes [13]. Additionally, to avoid the rapid dilution, formulations with an increased viscosity have been evaluated. Among them, the in situ gel-forming formulations, which undergo phase transition from liquid to semisolid gel upon exposure to physiological environments, seem to be a promising tool. These formulations should be a free-flowing liquid at room temperature to allow easily reproducible administration into the eye as a drop. They also should undergo in situ phase transition to form a strong gel that is capable of withstanding shear forces in the cul de-sac and of sustaining drug release at physiological conditions [14].

The aim of the present work was to obtain an ophthalmic delivery system with improved properties and improved retention time with enhanced permeability for the treatment of ocular fungal diseases. To achieve this, FLZ was encapsulated in niosomal vesicles which were then incorporated into poloxamer in-situ forming gel and chitosan gel formulations. These formulations were then compared through characterization of their in-vitro and in-vivo performance.

2. Material and methods

2.1. Materials

FLZ was kindly provided by SEDICO Pharmaceutical Co. (Cairo, Egypt). Span 60, Span 80 and cholesterol were purchased from Sigma–Aldrich, Inc. (St. Louis, Mo, USA), Poloxamer 407 was from (BF Goodrich, USA), Chitosan was from (Fluka Chemie AG Buchs, Switzerland), Triethanolamine and sodium dihydrogen orthophosphate were purchased from El-Naser Chemical Co. (Cairo, Egypt). Semi permeable membrane cellulose acetate with cutoff 1000 Da was purchased from Sigma diagnostics (St. Louis, MO, USA). All other chemicals and components for buffer solutions were of analytical grade.

2.2. Preparation of drug-loaded niosomes

Film hydration method was used to prepare niosomes as reported by Bayindir, and Yuksel [15] with some modification. 0.5% w/w of FLZ was dissolved in organic solvent; surfactant and cholesterol were added in different ratios 1:1, 1:2, 2:1 (Table 1). The organic solvent was removed under vacuum at 60 °C by rotary evaporator (Buchi 200, BUCHI Labortechnik AG, Flawil, Switzerland) till the formation of a thin film. Extra vacuum was applied to remove residual organic solvents. This film was hydrated with 10 ml of ultrapure water at 60 °C. The resulting niosomal suspension was mixed by vortex mixing for 10 min and sonicated for 20 min. The niosomal suspension was left overnight at 4 °C and stored at refrigerator temperature (4–8 °C) for further study.

2.3. Characterization of niosomes

2.3.1. Determination of entrapment efficiency (EE %)

Niosomes containing FLZ was separated from un-entrapped drug by cooling centrifugation at 25000 rpm for 60 min at 4 °C. The niosomal pellets were suspended in distilled water and centrifuged again. The washing procedure was repeated two times as reported by Mokhtar et al. [16]. The supernatant was separated each time and assayed spectrophotometrically at λ_{max} 260 nm [17,18]. The amount of entrapped drug was obtained by subtracting amount of un-entrapped drug from the total drug incorporated [7]. The percent of encapsulation efficiency (EE %) was then calculated according to the following equation:

$$EE\% = \{\text{amount of entrapped drug}/\text{total drug added}\} \times 100 \quad (1)$$

Results are the mean of three separate experiments.

2.3.2. Measurement of niosomes particle size

The mean size and polydispersity index (PI) of the prepared niosomes were measured by photon correlation spectroscopy using 90 Plus Particle Size Analyzer (Brookhaven Instruments Corporation, New York, USA). The measurements were made from a 90 angle at room temperature and the average of three measurements was calculated. The corresponding zeta potentials (mv) were determined by Photon correlation spectroscopy (PCS) using the same instrument.

2.3.3. Scanning electron microscopy (SEM)

The surface characteristics of the prepared niosomes were examined with a scanning electron microscope (Joel, JSM-5400 LV, Japan) operated at an acceleration voltage of 15 kV. Dried niosomal samples were coated with gold palladium foil (54 nm) by sputter coater unit (SPI, sputter, USA) prior to examination.

2.4. Preparation of FLZ niosomal gels

Hydrogels containing FLZ-loaded niosomes equivalent to 0.5% w/w of the drug were prepared by different methods according to

Table 1
Composition and characterization of FLZ niosomal dispersions.

Formulation code	Surfactant type	Surfactant: cholesterol ratio	Particle size (nm)	PI	Zeta potential (mv)	EE (%)
F1	Span 60	1:1	170 ± 5.5	0.10	−45.6 ± 3.2	71.05 ± 2.5
F2	Span 60	2:1	190 ± 8.5	0.25	−60.9 ± 1.2	85.35 ± 6.8
F3	Span 60	1:2	265 ± 6.8	0.20	−38.7 ± 3.3	60.15 ± 2.8
F4	Span 80	1:1	140 ± 5.0	0.15	−35.8 ± 1.2	60.00 ± 2.5
F5	Span 80	2:1	180 ± 5.5	0.20	−40.6 ± 0.9	50.50 ± 5.5
F6	Span 80	1:2	280 ± 2.5	0.30	−30.1 ± 1.1	42.50 ± 2.5

Mean ± SD, n = 3.
PI: Polydispersity index.
EE: Entrapment efficiency.

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