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Development and *in-vitro* characterization of sorbitan monolaurate and poloxamer 184 based niosomes for oral delivery of diacerein

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ABSTRACT

The aim of the study was to develop a niosomal drug delivery system for poorly soluble drugs with sorbitan monolaurate, poloxamer 184 and their mixture (sorbitan monolaurate and poloxamer 184) forming the niosomal surfactant system. Diacerein, a highly lipophilic antiosteoarthritic drug, was used as a model drug: it has variable oral bioavailability due to its poor aqueous solubility. The diacerein loaded niosomes were prepared with 1:1, 6:4 and 7:3 surfactant to cholesterol ratios at constant levels of dicetyl phosphate (2.5%) as a negative charge imparting agent. All studied ratios of surfactant to cholesterol produced diacerein loaded niosomes sized from 350 to 1000 nm and with PDI values below 0.5. The transmission electron microscope images revealed well defined spherical vesicles. Mixed system formulations showed better entrapment efficiencies, with the best composition the entrapment efficiency being 90.5%, with smaller particle sizes and lower PDI values in comparison to formulations prepared with pure surfactant systems. With increasing cholesterol amount the niosomes were smaller, with more drug entrapped and better long term stability. Drug release studies showed improved dissolution profiles of all the niosomal formulations compared to pure diacerein.

1. Introduction

Niosomes, also called non-ionic liposomes, have high potential to act as carriers for poorly soluble drugs (Kumar et al., 2013; Bragagni et al., 2014). Niosomes are self-assembling non-ionic vesicle systems formed from nonionic surfactants in an aqueous environment (Lo et al., 2010). They are biodegradable and biocompatible, relatively nontoxic and capable of loading both hydrophilic and lipophilic drugs (Bendas et al., 2013; Li et al., 2014). Hydrophilic drugs are entrapped inside of vesicular aqueous core or adsorbed on bilayer surfaces while lipophilic substances are encapsulated by partitioning into the lipophilic domain of the bilayers (Moghassemi and Hadjizadeh, 2014).

Niosomes are structurally similar to liposomes (Moghassemi et al., 2015), but due to the better stability of niosomes combined with their lower cost, they are a real alternative to liposomes in drug delivery (Kazi et al., 2010; Marzio et al., 2011). A number of nonionic amphiphilic surfactant materials, such as alkyl ethers, alkyl esters, polysorbates and alkyl amides are typically used for formulation of niosomes and in most studies single surfactant systems are utilized (Escudero et al., 2014; Marzio et al., 2011; Moghassemi and Hadjizadeh, 2014). However, using more than one amphiphiles can improve wettability as compared to single surfactants as well as drug release and permeation profiles

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(Kamel et al., 2013; Shi et al., 2013). The nature of the surfactant is not the only factor controlling the self-assembly of amphiphilic molecules into niosomes; membrane additives, properties of entrapped drug and preparation method also matter (Uchegbu and Vyas, 1998). Utilization of niosomes for different drug delivery purposes, including oral, ocular, intramuscular, intravenous, pulmonary and transdermal applications, as well as for diagnostic imaging has been studied (Uchegbu and Vyas, 1998; Junyaprasert et al., 2012).

Diacerein is sparingly soluble in water with low oral bioavailability. It is classified as a Biopharmaceutics Classification System (BCS) class II drug with low solubility and high permeability (El-laithy et al., 2015). Numerous formulation strategies have been adopted to increase its solubility, dissolution profile and therapeutic index including the use of surfactants, solid dispersions, nanotechnology, polymeric conjugates, and water soluble carriers (Hong et al., 2006). For example, solid dispersions of diacerein have been prepared with poloxamer 407 by a simple melting technique (Patil et al., 2010). An inclusion complex of diacerein/cyclodextrin was designed in an effort to investigate the effect of cyclodextrin on its aqueous solubility (Petralito et al., 2011). In the same context, nanosuspensions of diacerein were prepared by using a combined bottom-up/top-down technique (Elsayed et al., 2014). Self-nanoemulsifying nanosuspension systems were developed by homogenization using diacerein as a model poorly soluble drug (El-laithy et al., 2015). Despite this significant research with respect to formulation approaches, diacerein could not present itself as an attractive drug candidate for management of osteoarthritis in the medical field. Little information is available in the literature describing the improvement of the biopharmaceutical characteristics of diacerein using nonionic surfactant vesicles *i.e.* niosomes.

Sorbitan monolaurate is a sorbitan ester surfactant, which is considered safe and is widely used in both food and pharmaceuticals (Yoshioka et al., 1994). Poloxamers are block copolymers consisting of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) groups (Bayindir et al., 2015). These polymers sterically stabilize vesicular carriers and prolong their half-life (Tavano et al., 2010). In addition to this, they have particular abilities to interact with body membranes and lipophilic surfaces, thus increasing the drug transport across intestinal epithelial cells (Tavano et al., 2013).

Motivated by the advantages associated with niosomal drug delivery systems, the aim of this study was to formulate niosomal carriers in order to improve the drug release of the poorly soluble model drug, diacerein. Further, diacerein loaded niosomes were produced by rarely used technique, *e.g.* formation of niosomes using more than one amphiphiles. The effects of surfactant selection as well as membrane additives were covered. Diacerein-loaded niosomal formulations based on pure sorbitan monolaurate, poloxamer 184, as well as a mixture of the two, with different amounts of cholesterol in the composition were produced and a thorough physicochemical analysis of the formulations was performed.

2. Materials and methods

2.1. Materials

Diacerein was a gift sample from Global Pharmaceuticals (Islamabad, Pakistan). Sorbitan monolaurate was from Fluka Chemica (Germany), poloxamer 184 (poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol)) from Sigma-Aldrich (USA), cholesterol from Sigma-Aldrich (The Netherlands), dicetyl phosphate from Sigma Aldrich (USA), methanol from Fluka (Switzerland), chloroform from Rathburn Chemicals Ltd. Walkerburn (Scotland), potassium dihydrogen phosphate from VWR Prolab Chemicals (Belgium), disodium hydrogen phosphate from Sigma-Aldrich (USA), sodium chloride from Sigma-Aldrich (Germany), potassium chloride from Sigma Aldrich (USA), hydrochloric acid from VWR Prolab Chemicals (France). Water used was Milli Q-water (Millipore, Merckmillipore, USA).

2.2. Preparation of niosomes

Niosomes were prepared using the thin film hydration method as described previously (Pardakhtay et al., 2007). Briefly, 400 μmol of surfactant/cholesterol in different molar ratios (1:1, 6:4, 7:3) was dissolved in 15 ml of an organic mixture of chloroform and methanol (2:1.). A constant amount of dicetyl phosphate (2.5%) was added to each formulation as a negative charge imparting agent. The organic solvents were removed at 57 °C, under reduced pressure, in a rotary evaporator (Buchi, Switzerland). The resulting surfactant film was dried overnight in a desiccator under vacuum. The dried lipid film was then hydrated with 20 ml PBS containing diacerein (200 μmol ~ 73 mg) by gentle rotation in water bath at 57 °C. The obtained niosomal formulations were left aside at room temperature overnight to mature, after which they were stored at 4 °C for further characterization. The composition of the niosomal formulations is presented in Table 1.

2.3. Interaction studies

2.3.1. ATR-FTIR

The possible interactions between niosome ingredients was studied by attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. The ATR-FTIR spectra of individual niosomal components, physical mixtures and niosomes (F_{Mixed}), as F_{Mixed} contains both surfactants, were taken using a Bruker VERTEX Series FTIR spectrometer (Bruker Optics, Germany) with a horizontal ATR accessory (MIRacle, Pike Technology, Inc., Germany) for sample placement. The ATR-FTIR spectra were recorded in the wavenumber range (4000–650 cm^{-1}) with a resolution of 4 cm^{-1} at ambient temperature using OPUS software (OPUS 5.5).

2.3.2. Thermal analysis

The physical state of diacerein in selected formulation F_{Mixed} (containing both surfactants) was investigated using differential scanning calorimetry (DSC) (Mettler Toledo, PTD 2007-2555). Pure diacerein, niosomes constituents, the physical mixture and formulation (F_{Mixed}) were accurately weighed in aluminium pans (3–5 mg) and covered with an aluminium lid. The thermograms were recorded at scan rate of 10 °C min^{-1} by heating samples from 10 °C to 250 °C. These scans were recorded in an atmosphere of nitrogen at purging rate of 50 ml min^{-1}.

2.4. Drug entrapment studies

The niosomal formulations were subjected to ultracentrifugation at 28,000 rpm for 1 h at 4 °C by using ultracentrifuge (Beckman Coulter, Optima LE-80K, USA). The isolated pellet obtained at the bottom of centrifuge tube was washed with PBS twice and centrifuged again for 1 h. The percent entrapment efficiency (% EE) was determined according

Table 1
Composition of niosomal formulations. In all the batches the amount of diacerein was 73 mg and the total volume of the formulations 20 ml.

Nonionic surfactant system	Batch	Surfactant-cholesterol ratio (mol/mol)	Amount (mg)	
			Surf	CHO
Sorbitan monolaurate	F_1-SP	1:1	69.29	77.33
	F_2-SP	6:4	83.15	61.86
	F_3-SP	7:3	97.00	46.39
Poloxamer 184	F_1-PL	1:1	580.00	77.33
	F_2-PL	6:4	696.00	61.86
	F_3-PL	7:3	812.00	46.39
Sorbitan monolaurate and poloxamer 184	F_1-Mixed	1:1	273.00	77.33
	F_2-Mixed	6:4	389.57	61.86
	F_3-Mixed	7:3	526.00	46.39