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Sorbitol based powder precursor of cubosomes as an oral delivery system for improved bioavailability of poorly water soluble drugs

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ABSTRACT

The objective of this study was to develop sorbitol based powder precursor of cubosomes loaded with tamoxifen citrate (TC), as a model of poorly water soluble drug, aimed at enhancing its oral bioavailability. TC-loaded powder precursor formulations were prepared by sequential spraying of TC/glycerol monooleate (GMO)/poloxamer 407 solution onto the surface of sorbitol powder. Four formulations (F1, F2, F3 and F4) were prepared at four GMO: sorbitol ratios of 1:2.5, 1:5, 1:7.5 and 1:10 w/w, respectively. The prepared powder precursors were subjected to *in vitro* and *in vivo* characterization. *In vitro*, direct correlations were observed between GMO: sorbitol ratio and % yield, drug content, flowability and dissolution efficiency of TC-loaded powder precursors. TC-loaded cubosomes, derived from the prepared powder precursors, exhibited a size range of 67.34 ± 4.40–102.01 ± 4.86 nm and entrapped more than 95% TC. *In vivo* absorption study in rats showed improved rate and extent of TC absorption from drug-loaded powder precursor (F4) compared to those of plain TC powder, with evidence of a relative bioavailability of 152.50 ± 32.67%. In conclusion, sorbitol based powder precursor of cubosomes may be a promising oral delivery system for enhancing the bioavailability of poorly water soluble drugs.

1. Introduction

Glycerol monooleate (GMO) is known to spontaneously form liquid crystalline cubic phases in excess water, consisting of bicontinuous lipid bilayers extending in three dimensions, separating two networks of water channels [1]. Cubic liquid crystals are transparent and isotropic phases that are physically stable in excess water [2,3]. The emulsification of cubic lipid phases in water results in the production of cubosomes that can be defined as nanoparticulate disperse systems characterized by high biocompatibility and bioadhesivity [4].

One of the promising approaches for enhancing the oral bioavailability of poorly soluble drugs is the incorporation of these drugs in cubosomes. Because of their lyotropic and bioadhesive properties [5–7], cubosomes have been used as an oral drug delivery system for enhancement of the oral bioavailability of poorly water soluble drugs [8–12].

Several techniques have been described for preparation of aqueous cubosomal dispersions including fragmentation of the cubic phase using high-energy devices [13–15], solvent dilution method [16] and dry powdered precursors [17].

The dry powder precursor, which spontaneously forms cubic phases upon hydration in situ, is more advantageous than liquid phase product and can overcome the problem of sticky and waxy nature of GMO when oral solid dosage forms are required. Different preparation techniques and carrier materials have been used to prepare powdered precursors of drug-loaded cubosomes. For example, diclofenac sodium-loaded powder precursor have been prepared by spray-drying a solution of GMO in isopropanol containing dispersed diclofenac sodium and the adsorbent/carrier material magnesium trisilicate [18]. Bovine serum albumin-loaded powders were prepared by spray-drying, freeze-drying and/or spray-freezing using different types of carrier materials, including mannitol, polyvinyl pyrrolidone and polyethylene glycols [19].

The objective of the present study was to develop a powder precursor of cubosomes as an oral delivery system for enhancing bioavailability of a poorly water soluble drug by using sorbitol as a solid hydrophilic carrier. Tamoxifen citrate (TC) was selected as a model of poorly water soluble drug and the prepared TC-loaded powder precursors were characterized to evaluate their influence on the *in vitro* and *in vivo* performance of the drug.

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2. Materials and methods

2.1. Materials

TC was kindly supplied by Medical Union Pharmaceutical Company, Egypt. Myverol® 18–99 K, as a source of monoolein, was a gift from Kerry Ingredients & Flavours (Zwijndrecht, The Netherlands). Poloxamer 407 was purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI, USA). Sorbitol was obtained from Fluka Biochemika Company, Sigma Germany. Acetonitrile, Chloroform and Methanol (HPLC grade) were from Merck, Darmstadt, Germany. Sodium lauryl sulfate (SLS) was purchased from El-Nasr pharmaceutical Chemical Co., Egypt. All other chemicals were of analytical grade and were used as received.

2.2. Preparation of TC-loaded powder precursor formulations

TC-loaded powder precursor formulations were prepared by dissolving GMO (500 mg), poloxamer 407 (50 mg), and TC (50 mg) in 5 ml methanol/chloroform (1:2 v/v). Aliquots (0.5 ml) of the obtained solution were sprayed in a stepwise manner onto the surface of sorbitol powder in a 100 ml rounded bottom flask. The flask was attached to a rotary evaporator (RV 10 basic, IKA®, Staufen, Germany) to evaporate the solvent under reduced pressure at 70 rpm and at room temperature until sorbitol appeared to be dry, then, the next aliquot was sprayed. This process was repeated until all solution had been applied. Evaporation was continued until the content in the flask had become a completely dry and freely flowing product. Solvent traces were completely removed by vacuum for 12 h. The obtained dry powder product was stored in a refrigerator (8 °C) in a tightly closed container for further evaluation. Four formulations (F1, F2, F3 and F4) were prepared at four GMO: sorbitol weight ratios of 1:2.5, 1:5, 1:7.5 and 1:10 respectively.

2.3. Preparation of TC-loaded cubosomal dispersions

To prepare the cubosomal dispersions, powder precursor formulations were dispersed with 37 °C deionized water by vortex for 2 min. The resulting cubosomal dispersions of all formulations were containing 5% w/v GMO, 0.5% w/v poloxamer 407 and the final TC concentration was 5 mg/ml. The cubosomal dispersions were used for the determination of the entrapment efficiency, particle size analysis and morphological studies.

2.4. Characterization of TC-loaded powder precursor formulations

2.4.1. % Yield and drug content

The % yield of the prepared formulations was calculated from the ratio of the recovered powder precursor weight to the sum of the initial weight of starting materials. For determination of drug content, powder precursor equivalent to 10 mg of TC were weighed accurately and dissolved completely in methanol. The solution was filtered through a 0.45 μm membrane filter, suitably diluted and analyzed for TC content spectrophotometrically at $\lambda_{max} = 276$ nm. Each sample was tested in triplicate.

2.4.2. Powder flowability

Flow properties of the prepared powder precursor formulations were evaluated by determining their angle of repose using fixed funnel method [20]. In brief, a glass funnel was fixed at a height of 2.5 cm above a graph paper placed on horizontal surface. The powder (10 g of sample) was poured carefully through the funnel to form a cone on the surface. The angle of repose was then calculated by measuring the height of the cone (h) and the diameter of its base (d). The angle of repose (θ) was calculated as follows:

$$\tan\theta = 2h/d$$

2.4.3. Differential scanning calorimetry (DSC)

To detect any possible change in the physical state of TC in the prepared powder precursors, DSC was performed on pure TC, F1 (a representative TC-loaded powder precursor), sorbitol, poloxamer 407 and GMO using a thermal analysis system (DSC-60, Shimadzu, Japan). The samples (5 mg) were heated at a constant rate of 10 °C/min, in an aluminum pan under a nitrogen atmosphere. A similar empty pan was used as the reference.

2.4.4. X-ray diffraction

X-ray diffraction patterns of pure TC, F1, sorbitol, poloxamer 407 and GMO were obtained using the X-ray diffractometer (X'Pert-PRO Diffractometer, PANalytical, The Netherlands) with Cu as tube anode. The diffractograms were recoded under the following conditions: voltage was 45 kV, the current was 30 mA, steps were 0.02° of (°2θ) and the counting rate was 0.5 s/step at room temperature. Data were collected using scattering angle (2θ) ranged from 4° to 40°.

F1 was selected for DSC and XRD studies based on its higher concentrations of cubosomal components (GMO, poloxamer 407 and TC) relative to sorbitol concentration in comparison to the other formulations.

2.5. Characterization of TC-loaded cubosomal dispersions

2.5.1. Particle size analysis

The particle size distribution (Z-average) and polydispersity index (PDI) of cubosomal dispersions were determined by dynamic light scattering, using Zeta Sizer Nano-series (Nano ZS), Malvern, Worcestershire, UK. Samples were diluted with deionized water and measured at 25 ± 0.5 °C in triplicate.

2.5.2. Morphology of cubosomes

Morphological examination of cubosomal nanoparticles was carried out using atomic force microscopy (AFM) and transmission electron microscope (TEM). AFM analysis was performed on Wet – SPM Scanning Probe microscope (Shimadzu, Japan). A drop of TC-loaded cubosomal dispersion was adsorbed on freshly cleaved muscovite mica squares and removing excess water by air-drying. Subsequently, the sample was mounted in a microscope scanner for viewing and imaging in the non-contact mode at a frequency of 312 kHz and a scan speed of 2 Hz. The TEM investigation was carried out using a Tecani-G20 microscope (FEI, The Netherlands) equipped with super twin lens, a LaB6 electron source and operated at 60 kV. A droplet of TC-loaded cubosomal dispersion was placed on a 200 mesh carbon-coated copper grid, and the excess fluid was removed by an absorbent filter paper. The samples were stained with 1% sodium phosphotungstate solution and were viewed using magnification up to 1000000 x.

2.5.3. Identification of liquid crystalline phase

To identify the nature of the formed liquid crystals either isotropic or anisotropic, a drop of the cubosomal dispersion (F4) was placed on a glass slide and examined under the polarizing microscope (Tech Optics, Germany) with and without crossed polarizer at 400 x magnification. Images were recorded using a Canon Power shot A 630 digital camera (Canon, Japan).