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Self-nanoemulsifying drug delivery systems of tamoxifen citrate: Design and optimization

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ABSTRACT

Tamoxifen citrate is an antiestrogen for peroral breast cancer treatment. The drug delivery encounters problems of poor water solubility and vulnerability to enzymatic degradation in both intestine and liver. In the current study, tamoxifen citrate self-nanoemulsifying drug delivery systems (SNEDDS) were prepared in an attempt to circumvent such obstacles. Preliminary screening was carried out to select proper ingredient combinations. All surfactants screened were recognized for their bioactive aspects. Ternary phase diagrams were then constructed and an optimum system was designated. Three tamoxifen SNEDDS were then compared for optimization. The systems were assessed for robustness to dilution, globule size, cloud point, surface morphology and drug release. An optimum system composed of tamoxifen citrate (1.6%), Maisine 35-1 (16.4%), Caproyl 90 (32.8%), Cremophor RH40 (32.8%) and propylene glycol (16.4%) was selected. The system was robust to different dilution volumes and types. It possessed a mean globule size of 150 nm and a cloud point of 80 °C. Transmission electron microscopy demonstrated spherical particle morphology. The drug release from the selected formulation was significantly higher than other SNEDDS and drug suspension, as well. Realizing drug incorporation into an optimized nano-sized SNEDD system that encompasses a bioactive surfactant, our results proposed that the prepared system could be promising to improve oral efficacy of the tamoxifen citrate.

1. Introduction

Tamoxifen citrate has been the clinical choice for the antiestrogen treatment of advanced or metastatic breast cancer for more than 20 years (Memisoglu-Bilensoya et al., 2005). Tamoxifen belongs to a class of non-steroidal triphenylethylene derivatives (Fig. 1) and is considered the first selective estrogen receptor modulator. Tamoxifen has a relatively low toxicity and is less harmful than most chemotherapeutics (Shin et al., 2006).

Tamoxifen citrate is a highly lipophilic drug of poor water solubility (Gao and Singh, 1998). Furthermore, its oral bioavailability is mainly affected by the first-pass metabolism and P-glycoprotein (P-gp) pump efflux in the liver and intestine. Tamoxifen is a substrate for the efflux of P-gp, breast cancer resistance protein (BCRP) and multidrug resistance-associated protein (MRP), the members of ATP binding cassette (ABC). The ABC family of transport proteins plays a central role in the defense of organisms against toxic compounds. P-gp, MRP2 and BCRP located within the polarized apical membrane of the intestine, liver and kidney mediate the efflux of xenobiotics and toxins into the intestinal lumen, bile and urine (Shin et al., 2006). The only attempt to improve tamoxifen oral bioavailability encompassed co-administration of tamoxifen with quercetin. The study was based on quercetin dual inhibitory effect on CYP3A4 and P-gp (Shin et al., 2006). In spite of the marked role of the drug in the cancer therapy, no other trials were so far adopted to enhance its oral therapeutic effect.

In recent years, much attention has been focused on lipid-based formulations to improve oral bioavailability of lipophilic drugs. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions (Nielsen et al., 2008), liposomes (Schwendener and Schott, 1996), microemulsions, nanoemulsions, with particular emphasis on self-emulsifying and self-nanoemulsifying drug delivery systems (SNEDDS) (Gursoya and Benita, 2004). The latter systems comprise isotropic mixtures of natural or synthetic oils with surfactants and co-surfactants. These systems spontaneously emulsify when exposed to GIT fluids to form oil in water nanoemulsion with nanometric droplet size, in the range of 20–200 nm (Mou et al., 2008; Porter et al., 2008). SNEDDS exhibited privileges over other delivery systems. They are characterized by excellent stability, circumventing the stability problem of solid lipid nanoparticles (Mueller et al., 2000) and liposomes (Sharma and Sharma, 1997). Furthermore, SNEDDS would be an efficient, convenient and more patient compliant approach in comparison to o/w nanoemulsion as SNEDDS can be filled in hard gelatin capsules due to their anhydrous nature enabling its administration as unit dosage form (Date

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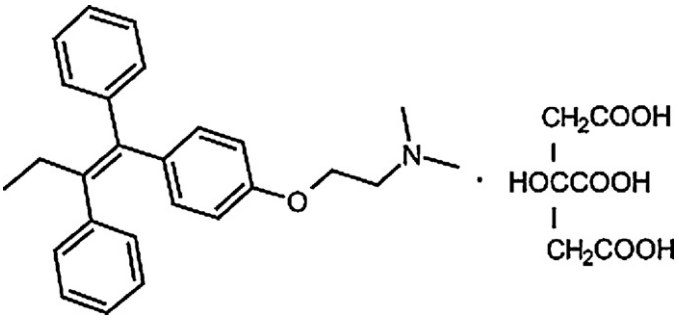

Fig. 1. Chemical structure of tamoxifen citrate.

and Nagarsenker, 2007; Rao and Shao, 2008). Bioavailability from SNEDDS was higher than oils and surfactant dispersions (Nielsen et al., 2008).

SNEDDS are characterized by high solvent capacity, small particle size and excellent stability. In addition, they can enhance permeation across the intestinal membrane, reduce or eliminate food effect and enhance drug bioavailability (Rane and Anderson, 2008; Wasan et al., 2009). Improved drug bioavailability induced by SNEDDS is not merely a matter of solubilization or particle size reduction. The interplay between certain excipients and enzymes or transporters has raised much concern about effect of such systems on drug absorption and metabolism. Reported bioactive excipients encompass Cremophor, Solutol HS-15, Tween 20 and 80, Labrasol, Sucrose monolaurate, Vitamin E-TPGS and Pluronic block copolymers (Chen, 2008). In addition, the drug can be loaded in the inner-phase of SNEDDS and therefore be protected against enzymatic hydrolysis in the gastrointestinal tract. Cefpodoxime proxetil (Date and Nagarsenker, 2007) and proteins (Rao and Shao, 2008) are candidates for drugs that have been successfully protected from presystemic clearance when incorporated in SNEDDS. Furthermore, the drug can be delivered by lymphatic bypass share, restraining hepatic first-pass metabolism of vulnerable drugs (Porter and Charman, 2001). This was apparent in enhanced bioavailability of atorvastatin when incorporated into a self-nanoemulsifying system containing Cremophor RH40. The system was proposed to reduce hepatic clearance of the drug, in addition to increasing its solubility (Shen and Zhong, 2006).

The efficiency of oral absorption of the drug compound from the self-emulsifying formulation depends on many formulation related parameters, such as surfactant concentration, oil/surfactant ratio and droplet size, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as self-emulsifying formulation, confirming the difficulty of formulating hydrophobic drug compounds into such formulations. At present, there are four drug products, Sandimmune® and Sandimmun Neoral® (cyclosporin A), Norvir® (ritonavir), and Fortovase® (saquinavir) on the pharmaceutical market, the active compounds of which have been formulated into specific self-emulsifying formulations. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case (Porter et al., 2008; Gursoya and Benita, 2004).

Under the aforementioned circumstances, the current work endeavors to design an optimal SNEDD system of tamoxifen citrate. Formula optimization was based on in vitro assessments. The formulation was tailored to compromise between drug solubility in excipients, ease of emulsification and globule size of the dispersion. The system components used were reported for bioactive effects. Selected formulation exhibiting promising in vitro characters is anticipated to improve oral delivery of the drug. The in vivo characteristics of the optimal formulation are currently under investigation.

2. Materials and methods

2.1. Chemicals and reagents

Tamoxifen citrate was obtained from Chemische Fabrikberg, Germany. Glycerol monolinoleate (Maisine 35-1®), propylene glycol monocaprylate (Caproyl 90®), isopropyl myristate (IPM), medium chain triglycerides (Labrafac lipophile® WL 1349), PEG-8 caprylic/capric glycerides (Labrasol®), oleoyl macrogol 6-glycerides (Labrafil® M1944CS) and diethylene glycol monoethyl ether (Transcutol HP®) were kindly donated by Gattefosse Co. (Lyon, France). Apricot kernel oil PEG-6 esters (DUB GPE AB) was a kind gift from Stearinerie Dubois Co. (France). Polyoxy 40 hydrogenated castor oil (Cremophor RH40®) and polyoxy 35 castor oil (Cremophor EL®) were obtained from BASF Co. (Germany). Propylene glycol and Tween 80 were obtained from Al-Nasr Pharmaceutical Co. (Egypt). All other chemicals used were of analytical grade.

2.2. Solubility studies

The solubility of tamoxifen citrate in various buffers, oils, surfactants, and co-surfactants was measured using shake flask method. An excess amount of tamoxifen citrate was added into each vehicle followed by vortex mixing for 30 s (GEMMY vortex mixer; VM-300, Germany). Mixtures were shaken for 48 h at 30 °C in a thermostatically controlled shaking water bath (Kottermann, type 3047, Hanigsen, Germany), followed by equilibrium for 24 h. Mixtures were then centrifuged at 3000 rpm for 10 min and the supernatant was filtered through a Millipore membrane filter (0.45 μl). Samples were suitably diluted with methanol and drug concentration was obtained via UV validated method at 270 nm using methanol as a blank (R^2 = .99057, % Er = 1.5, CV = 2%). The experiment was repeated in triplicates. Results were represented as mean value (mg/ml) ± SEM.

2.3. Preliminary screening of surfactants

Different surfactants for the peroral use were screened for emulsification ability according to the method described by Date and Nagarsenker (2007). Briefly, 300 mg of the surfactants (including Labrasol, Cremophor RH40, Cremophor EL, and Tween 80) were added to 300 mg of the oily phase. The mixtures were gently heated at 50 °C for homogenization of the components. Each mixture, 50 mg, was then diluted with distilled water to 50 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2 h and their % transmittance was evaluated at 638.2 nm by UV-160A double beam spectrophotometer (Shimadzu, Japan) using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation.

2.4. Preliminary screening of co-surfactants

The selected oily phase and surfactant were used for further screening of the different co-surfactants (Labrafil, Transcutol HP, DUB GPE AB, and propylene glycol) for their emulsification ability. Mixtures of 100 mg of co-surfactant, 200 mg surfactant, and 300 mg oil were prepared and evaluated in a similar fashion as described in Section 2.3.