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Ultra-fine self nanoemulsifying drug delivery system for transdermal delivery of meloxicam: Dependency on the type of surfactants

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ABSTRACT

The aim of this study was to develop and evaluate ultra-fine selfnanoemulsifying drug delivery system (UF-SNEDDS) of meloxicam (MLX) to enhance its transdermal delivery. The preliminary screening was carried out to select SNEDDS components according to type IV lipid based formulations using surfactant and co-surfactant. The prepared SNEDDS formulations were subjected to different thermodynamic stability tests. The droplet size, polydispersity index (PDI), zeta potential, turbidity, transmission electron microscopy (TEM) and in vitro MLX release studies were investigated. Finally, the influence of UF-SNEDDS on the MLX transdermal delivery was assessed. These UF-SNEDDS showed droplet size range of 14.41 ± 2.50 nm to 25.58 ± 2.33 nm, PDI less than 0.3, zeta potential with negative charge and turbidity range of 1.92–3.47 NTU. TEM of reconstituted SNEDDS-F5 demonstrated dark smaller droplet with spherical shape. The in vitro MLX release from SNEDDS was found to be higher in comparison to saturated solution (control). An in vitro permeation study was achieved in rat skin, the permeated amount of MLX was increased up to 11.89-fold as compared to control. Then, the presence of surfactant and its type can influence on both the drug release and the transdermal delivery of MLX. These results indicated that UF-SNEDDS developed for transdermal delivery may be a promising delivery system for MLX, with high solubility and improved skin permeation.

1. Introduction

MLX (MLX) is an effective lipophilic nonsteroidal anti-inflammatory drug (NSAID) which has been used for the treatment of rheumatoid arthritis, osteoarthritis and other various kinds of pain [1]. It was described that the usual oral dose of MLX in clinical effect was 7.5–30 mg/day. Nowadays, many routes of administration like oral, topical and parenteral are used for the treatment of these diseases. Similar to other NSAID, MLX produces gastrointestinal disturbance upon frequent/chronic administration [2]. So, transdermal administration is a promising route of MLX to avoid this disturbance [3]. However, the main restriction of this route is the permeation difficulty of the drug to pass through the skin due to the presence of stratum corneum (SC) [4]. Alternative approaches have been employed to overcome the permeation difficulty. These include chemical penetration enhancer [5], physical penetration enhancement e.g., iontophoresis [6], electroporation [7] and sonophoresis [8] and encapsulating the drug in nanoparticle delivery systems [9]. Microemulsion has been reported as another positive approach for transdermal delivery of hydrophilic and lipophilic drugs [10]. Microemulsion has several benefits such as thermodynamic stability, simplicity of preparation, high ability of solubilization and small droplet size [10]. Due to these benefits, microemulsion is considered as a perfect liquid carrier for drug delivery [9]. The small droplet size of microemulsion provides adhering effect to biological membranes, which enhance the transdermal drug delivery [11].

Recently, self nanoemulsifying drug delivery systems (SNEDDS) comprise lipid and surfactant, in combination with cosurfactant or cosolvent and can form microemulsions upon mixing with aqueous phase [12]. There are few drug products on the pharmaceutical market formulated as SNEDDS 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 [13]. Due to high potency and poor water solubility of MLX, it is considered as a good candidate in the preparation of lipid based formulation like SNEDDS [14,15]. The possible application of SNEDDS for transdermal drug delivery has been investigated [11]. The main advantage of this system is the highest stability of hydrolysable drug. It was observed that SNEDDS may also convert into nanoemulsion after mixing with aqueous phase coming up from the skin following occlusive topical application. As a result of this dilution, supersaturated system was obtained. Therefore, higher driving force for transdermal drug delivery was achieved [9–11]. Newly, ultra-fine SNEDDS (UF-SNEDDS) were developed, which are clear, transparent, isotropic system of drug, oil,

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surfactant and cosurfactant, which forms ultra-fine nanoemulsions (usually less than 50 nm in size) upon slight agitation, followed by dilution with an aqueous medium [16,17]. UF-SNEDDS have not been studied as nanocarrier for transdermal delivery of the drugs. When ultra-UF-SNEDDS formulations are applied topically, they spread easily into the skin surface following mixing with transepidermal water loss providing the drug in nanometer size range, which enhance the drug dissolution and skin permeation. Therefore, the main objective of the current study was to develop, characterize and evaluate new UF-SNEDDS for transdermal delivery of MLX. Also, this system is used to enhance the solubility as well as dissolution rate of MLX and reduce its side effects related to the oral therapy. In this study, due to the higher solubility of the MLX in surfactants than that in oils [18], type IV lipid based formulations was adopted to dissolve poorly water soluble into nanoemulsion. The MLX was dissolved in the hydrocarbon chain of surfactants and then nanoemulsified without using oils [19]. The significant advantage of the present study is that UF-SNEDDS were prepared by using surfactants only and providing necessary data about the ability of this system in transdermal delivery. Also, the effect of different surfactants on the transdermal drug delivery from SNEDDS is considered. The materials used in the preparation of this system are pharmaceutically acceptable and falls under generally regarded as safe category.

2. Experimental

2.1. Materials

MLX was obtained from Riyadh Pharma, Riyadh, KSA. Oleic acid and ethyl oleate were obtained from Riedel-de Haan, Germany. Peanut oil was obtained from Uni-Chem, England. Sesame oil propylene glycol and polyethylene glycol 400 (PEG 400) were obtained from Fluka, Switzerland. Linseed oil was obtained from Winlab, UK. Capmul GMO-50, Capmul MCM C8, Capmul MCM EP, Capmul MCM, and Capmul MCML were kindly supplied by ABITEC, USA. Tween 40, Tween 60, Tween 80 and Tween 85 were obtained from Sigma, USA. Cremophor RH 40 was kindly supplied by BASF, Ludwigshafen, Germany. Methanol (HPLC grade) was purchased from BDH, Poole, England. All other chemicals were of analytical grade. Water was double distilled.

2.2. Chromatography

MLX was determined using a validate reverse-HPLC method with modification [1]. The HPLC system (Waters™ 600 controller, USA) is equipped with a wavelength detector (Waters™ 2487 a Dual λ_{max} Absorbance detector, USA), a pump (Waters™ 1252 a Binary pump, USA), and an automating sampling system (Waters™ 717 plus Autosampler, USA). The column used was a reversed-phase C18 column (μBondapak™, 4.6 × 150 mm, 10 μm particle size, Waters). The mobile phase consisted of methanol: 0.1 M potassium dihydrogen phosphate (40:60 v/v), the pH was adjusted to 6 by addition of 1 M potassium hydroxide. The flow rate was1.2 ml/min, injection volume was 20 μl. The column effluent was monitored at 356 nm and the chromatographic data analysis was performed with the Empower™ Program (Waters, USA). All the operations were carried out at an ambient temperature.

2.3. Equilibrium solubility study of MLX

To develop SNEDDS formulations, the solubility of drug in their components is very important to obtain nano-emulsion. Therefore, the appropriate oils, surfactants and cosurfactants were selected according to the high solubility of the drug to maintain the drug in solubilized form [17]. The solubility of MLX was determined by adding an excess amount of drug in 2 g of selected oils (oleic acid, ethyl oleate, castor oil, peanut oil, olive oil, sesame oil, linseed oil), surfactants (Capmul GMO-50, Capmul MCM C8, Capmul MCM EP, Capmul MCM, Capmul MCML, Tween 40, Tween 60, Tween 80, Tween 85 Cremophor RH 40) and co-surfactant (propylene glycol and PEG 400) in 5 ml capacity stopper vials. The mixtures were mixed using vortex (Fisons Whirlimixer™ England). The vials were then kept at 32 °C in an isothermal shaker for 72 h. The equilibrated samples were removed and centrifuged at 9000 rpm for 30 min. The supernatant was filtered through a 0.45 μm membrane filter. The concentration of meloxicam was determined using HPLC method.

2.4. Preparation of the tested formulations

According to the solubility study, highest solubility of MLX was obtained in Cremophor RH 40, Tween 60, Capmul MCM C8 (as surfactants) and PEG 400 (as cosurfactant). Cremophor RH 40 (HLB, 13–14) was chosen as the main hydrophilic surfactant. Therefore, a series of SNEDDS formulations were prepared to investigate the effect of kind and mixture of surfactants on the transdermal delivery of MLX. SNEDD-F1: Cremophor RH 40 only. SNEDDS-F2: mixture of Cremophor RH 40 and Tween 60. SNEDDS-F3: mixture of Cremophor RH 40 and Capmul MCM C8. SNEDDS-F4: mixture of Cremophor RH 40 and PEG400. SNEDDS-F5: mixture of Cremophor RH 40, Tween 60, Capmul MCM C8 and PEG 400. The various components were weighed in beakers and mixtures were heated to 50 °C in water bath until all components were liquefied. Then, the MLX was added under gentle mixing to obtain a clear solution. The mixtures were visually examined for the homogeneity.

2.5. Characterization of the prepared formulations

2.5.1. Visual observations

The homogeneous mixtures were evaluated for their self-emulsification properties by visual inspection. The formulations (60 mg) were introduced into 100 ml of water in a glass Erlenmeyer flask at 25 °C and gentle stirring was applied. The tendency to spontaneously form mono-phasic transparent system was considered a good SNEDDS. Contrary, it was considered a bad SNEDDS, when poor or no emulsion was formed [20]. Phase diagram was constructed to identify the good self-nanoemulsifying region (Fig. 1). All studies were repeated in triplicates and the formulation composition is shown in Table 2.

2.5.2. Thermodynamic stability test

In order to confirm the good self nanoemulsion character of these SNEDDS formulations, thermodynamic stability tests were performed [21]. The investigated formulations were exposed to two thermodynamic stability tests, centrifugation and freeze-thaw cycles as mentioned in previous article [22]. The prepared formulations were centrifuged at 50,000 rpm for 30 min. Also, these formulations were subjected to three freeze-thaw cycles between −20 °C and +22 °C with placing in each temperature for 48 h. It was observed that all the prepared formulations did not show any phase separation, which referred to a good stable SNEDDS.

2.5.3. Turbidity measurement

The formulation (1 g) of meloxicam SNEDDS was diluted with 25 ml water in a stopper tube and gently mixed by inverted the tube. The resultant of nanoemulsions was evaluated for its turbidity. Turbidity was measured by using Turbidity meter (MARTINI 415 instruments, Romania) using nephlometric turbidity units (NTU). Turbidity measurements were performed on 10 ml of nanoemulsion stored in clear screw-capped vials [20].

2.5.4. The droplet size and zeta potential measurement

The formulation (1 g) was dispersed in 25 ml of water in a stopper tube and gently mixed by inverting the tube to convert the SNEDDS to nanoemulsion. The droplet size, poly dispersity index (PDI) and zeta potential of the nanoemulsion was measured by photon correlation spectroscopy. These measurements were employed by using a Zetasizer Nano ZS (Malvern Instruments, UK). Light scattering was monitored at