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Original Research Paper

A new self-emulsifying formulation of mefenamic acid with enhanced drug dissolution

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ARTICLE INFO

Article history:
Received 16 August 2014
Received in revised form
29 September 2014
Accepted 11 October 2014
Available online 20 December 2014

Keywords:
Self-emulsifying formulation
Poorly water-soluble drug
Mefenamic acid
Drug dissolution

ABSTRACT

To enhance the dissolution of poorly soluble mefenamic acid, self-emulsifying formulation (SEF), composing of oil, surfactant and co-surfactant, was formulated. Among the oils and surfactants studied, Imwitor® 742, Tween® 60, Cremophore® EL and Transcutol® HP were selected as they showed maximal solubility to mefenamic acid. The ternary phase diagram was constructed to find optimal concentration that provided the highest drug loading. The droplet size after dispersion and drug dissolution of selected formulations were investigated. The results showed that the formulation containing Imwitor® 742, Tween® 60 and Transcutol® HP (10:30:60) can encapsulate high amount of mefenamic acid. The dissolution study demonstrated that, in the medium containing surfactant, nearly 100% of mefenamic acid were dissolved from SEF within 5 min while 80% of drugs were dissolved from the commercial product in 45 min. In phosphate buffer (without surfactant), 80% of drug were dissolved from the developed SEF within 5 min while only about 13% of drug were dissolved in 45 min, from the commercial product. The results suggested that the SEF can enhance the dissolution of poorly soluble drug and has a potential to enhance drug absorption and improve bioavailability of drug.

1. Introduction

Mefenamic acid, a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, is widely used in mild to moderate pain including headache, dental pain, dysmenorrheal, rheumatoid arthritis, osteoarthritis and other joint disorders. The solubility of mefenamic acid in water is 0.04 mg/ml [1]. Mefenamic acid is rapidly absorbed after oral

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Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2014.10.003

administration. Following a single 1-g oral dose, mean peak plasma levels ranging from 10 to 20 mg/ml have been reported. Peak plasma levels are attained in 2–4 h and the elimination half-life approximates 2 h [2,3]. Mefenamic acid belongs to class II category under the biopharmaceutical classification system (BCS), i.e., it is inherently highly permeable through biological membranes, but exhibits low aqueous solubility. Rate of absorption and/or extent of bioavailability for such insoluble hydrophobic drug are controlled by rate of dissolution in gastro-intestinal fluids. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate [1–3].

Various approaches for improving drug dissolution rate have been reported in literature, including reducing the particle size, solid dispersion, inclusion complex formation, solubilization in surfactant system, using prodrugs and drug derivatization, lipid-based formulation, and self-emulsifying drug delivery system [4]. Among these approaches, self-emulsifying drug delivery system (SEDDS) is found to be a prominent approach to improve solubility and drug dissolution. SEDDS is an isotropic mixture of oil, surfactant, co-surfactant and drug, which spontaneously forms thermodynamically stable oil-in-water emulsions when introduced into aqueous phase under gentle agitation conditions, similar to those which would be encountered in the GI tract [5–7].

Poorly water-soluble drugs can be dissolved in SEDDS, allowing them to be encapsulated as dosage form for oral administration. Upon contact with aqueous phase of GI tract, the SEDDS formulations are self-emulsifying and very fine dispersions are then formed spontaneously with the aid of GI motility [8] because the free energy required to form the emulsion is either low and positive or negative. Therefore, the drug remains in solution in the GI lumen, avoiding the dissolution step which often limits the rate of absorption of poorly water-soluble drugs from the crystalline state [9]. SEDDS appears to be an attractive choice of formulation as it requires simple manufacturing equipment. This is because it is physically stable lipid-based solution and omits the need of high energy emulsification process, and thus reduces the manufacturing cost. Moreover, greater dissolution rate of SEDDS reveals the reduction in drug dose and possibly reduce the dose-related side effects.

In this study, we developed a new self-emulsifying formulation (SEF) of mefenamic acid to enhance the dissolution rate of mefenamic acid. Physical properties and dissolution profiles of SEF were evaluated in comparison to mefenamic acid powders and commercial capsules.

2. Materials and methods

2.1. Materials

Mefenamic acid, clove oil, olive oil and rice bran oil were purchased from P.C. Drug Center (Thailand). Caprylic/capric triglycerides (Miglyol® 812) and caprylic/capric glyceride (Imwitor® 742) were purchased form Sasol (Germany). Oleic acid was purchased from Sigma–Aldrich (USA). Polyoxyethylene 20 sorbitan monolaurate (Tween® 20), Polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene 20 sorbitan monooleate (Tween® 80), sorbitan monolaurate (Span® 20) and sorbitan monostearate (Span® 60) were purchased from Fluka (USA). Polyoxyl 40 hydrogenated castor oil (Cremophor® RH40) and polyoxyl 35 castor oil (Cremophor® EL) were a gift form BASF (Thai) Co., Ltd. (Thailand). Diethylene glycolmonoethyl ether (Transcutol® HP) was supported by Gattefosse (Saint-Priest Cedex, France). Other chemicals were of reagent or analytical grade and used without further purification. Distilled water was used in all preparations.

2.2. Determination of drug solubility in various vehicles

Solubility of mefenamic acid was determined in various vehicles by adding excess amount of mefenamic acid (500 mg) in 10 mL of a pure vehicle in glass tubes. The drug suspension was equilibrated at 25 °C in a thermostatically controlled bath for 72 h. After equilibration, the tubes were centrifuged at 12,000 rpm for 20 min and the clear supernatants were analyzed for mefenamic acid with a high performance liquid chromatography (HPLC, model JASCO PU-2089 plus quaternary gradient inert pump, and a JASCO UV-2070plus multi-wavelength UV–vis detector, Jasco, Japan) using Luna 5u C18 column (5 μm, 4.6 nm × 25 cm) (Phenomenex, USA). The mobile phase composing of acetonitrile, pH 5.0 phosphate buffer and tetrahydrofuran (23:20:7) was filtered through a 0.22-μm membrane filter, and degassed in a sonicator bath before use. The flow rate of mobile phase was 1 mL/min, and the UV detection wavelength was 254 nm.

2.3. Construction of ternary phase diagram and preparation of SEF

Based on the solubility studies, the oil (Imwitor® 742), surfactant (Tween® 60 or Cremophor® EL) and co-surfactant (Transcutol® HP) were chosen for the construction of ternary phase diagram. A series of SEF were prepared using various concentrations (10–80% v/v) of oil, surfactant and co-surfactant. The oil, surfactant and co-surfactant were mixed at ambient temperature (25 °C), until clear solution was obtained. Then, excess amount of mefenamic acid (500 mg) was added to the mixtures and mixed thoroughly. The resultant formulations were shaken at ambient temperature (25 °C) for 72 h, in the same manner as mentioned above, before further analysis of mefenamic acid content, as described above.

2.4. Physical characterization

Visual observation of self-emulsification: Evaluation of the self-emulsifying properties of SEF was visually observed (i.e., until a clear homogenous system was obtained).

Droplet size analysis: The droplet size of emulsion formed after reconstitution of SEF in water (200 times) was determined by static laser light scattering (model LA-950, Horiba, Japan). Reconstituted samples were withdrawn and diluted to a final concentration of approximately 0.05% (w/w) with distilled water. A relative refractive index of 1.2 (ratio of the indices between the oil and water phase) was used. All measurements were repeated 3 times and the values of mean diameter were reported. The span, which is the width of the