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# Investigation of microemulsion system for transdermal delivery of meloxicam

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**Abstract**

A new oil-in-water microemulsion containing 0.375% meloxicam was developed in order to improve the skin permeability of meloxicam. Among various surfactants and cosurfactants investigated in the microemulsion system, polyoxyethylene sorbitan trioleate (Tween 85) showed excellent solubility and ethanol expressed skin permeation enhancing effect for meloxicam. The microemulsion existence ranges were defined through the construction of the pseudo-ternary phase diagram. The effect of the content of isopropyl myristate (IPM) and the effect of the mass ratio of the surfactant/cosurfactant (Km) on skin permeation of meloxicam were evaluated with excised rat skins. The optimum formulation with the highest skin permeation rate (5.40 μg/cm$^2$/h) consisted of 0.375% meloxicam, 5% IPM, 50% Tween 85/ethanol (1:1) and water.


*Keywords:* Meloxicam; Microemulsion; Transdermal; IPM; Phase diagram; Skin permeability

## 1. Introduction

Meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (Fig. 1), is a potent non-steroidal anti-inflammatory drug (NSAIDs) of the enolic acid class of oxicam derivatives which shows preferential inhibition of cyclo-oxygenase-2 (COX-2) and inhibits prostaglandin synthesis. Turck et al. (1997) reported that the usual oral dosage of meloxicam in clinical treatment was 7.5–30 mg/day, the elimination half life period of meloxicam in plasma was approximately 20 h, and Cmax was 0.993 μg/ml after oral administration of 15 mg meloxicam to 24 healthy male volunteers. It is very efficient for the treatment of rheumatoid arthritis, osteoarthritis, and other joint diseases. Its therapeutic benefits combined with a good gastrointestinal tolerability are well-documented in comparision with other NSAIDs, however, its oral administration can produce some side effects such as bellyache and indigestion, so meloxicam is not suitable for the treatment of rheumatological patients with gastric ulcer (Davies and Skjodt, 1999). In order to avoid the irritation of gastrointestinal tract, minimize systemic toxicity and achieve a better therapeutic effect, one promising method is to administer the drug via skin (McNeill and Potts, 1992). Transdermal dosage forms such as patch (Ji et al., 2005) and gels (Gupta et al., 2002) has been tested for this purpose. In this study a new microemulsion system for transdermal delivery of meloxicam was developed to improve the skin permeation of meloxicam.

Microemulsion typically consist of oil, surfactant, cosurfactant and aqueous phase, which is transparent, thermodynamically stable and has a droplet size <0.15 nm and does not have the tendency to coalesce (Kreilgaard, 2002). Microemulsion has several advantages such as enhanced drug solubility, good thermodynamic stability, ease of manufacturing and enhancement effect on transdermal delivery over conventional formulation (Lawrence and Rees, 2000; Gasco, 1997). Recently, more attention has focused on microemulsions for transdermal delivery of drugs. The transdermal delivery of aceclofenac (Lee et al., 2005), diclofenac diethylamine (Djordjevic et al., 2004), triptolide (Chen et al., 2004), using microemulsion has been reported. In transdermal delivery, the key point of dosage design

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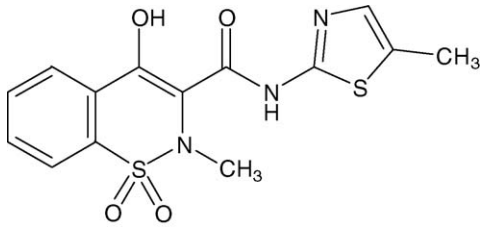


Fig. 1. The structure of meloxicam.

was to solubilize the drug in microemulsion and improved the permeability.

There are two basic types of microemulsion systems: oil-in-water (O/W) and water in oil (W/O), while the O/W microemulsion was important to improve the solubility of poorly water-soluble drugs. The traditional way was dissolve the drug in oils firstly and then incorporated into microemulsion, this method can be applied for most drugs such as triptolide (Chen et al., 2004), aceclofenac (Lee et al., 2005), and diclofenac diethylamine (Djordjevic et al., 2004). In this study, due to the higher solubility of meloxicam in surfactants than that in oils, another way was adopted to dissolve poorly water-soluble drugs into O/W microemulsion, which was dissolve the drug in hydrocarbon chain of surfactants firstly and then miroemulsified (Ye et al., 2003). The aim of this work was to formulate a new O/W microemulsion system for transdermal delivery of meloxicam using polyoxyethylene sorbitan trioleate as surfactant, which had low content of surfactants and high skin permeability.

## 2. Materials and methods

### 2.1. Materials

Meloxicam (99% purity) was obtained from Taiyang Pharmaceutical Co., Ltd. (Beijing, China). PEG-8 caprylic/capric glycerides (Labrasol®), diethylene glycol monoethyl ether (Transcutol® P) were kindly donated by Gattefosse, France. Isopropyl myristate (IPM), Cremophor® EL (EL) were supplied by Sigma Chemical Co., USA. Oleic acid, ethyl oleate, polyoxyethylene sorbitan trioleate (Tween 85), polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monooleate (Span 80), polyoxyethylene (10) isooctylphenyl ether (Triton X-100; OP) were purchased from Shanghai Chemical Co., China. Water was purified by double distillation in a glass apparatus. All other chemicals and solvents were of analytical reagent grade.

### 2.2. Determination of the solubility of meloxicam in oils and surfactants

In order to find out appropriate solvents with good solubilizing capacity of meloxicam, the solubility of meloxicam was investigated in some oils such as oleic acid, ethyl oleate and isopropyl myristate, and some surfactants including Tween 80, Tween 85, Tween 20, Cremophor® EL, Labrasol® and OP. An excess amount of meloxicam was added to 5 ml of each selected solvent and was shaken at 20 °C for 72 h. The suspension was filtered through a membrane filter (0.45 μm), and the concentration of meloxicam in the filtrate was determined by HPLC.

### 2.3. Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams were constructed by instillation of homogenous liquid mixtures of oil, surfactant, and cosurfactant, with water at ambient temperature (Djordjevic et al., 2004). At desired Km (3:1, 1:1 and 1:3), oily mixtures of oil, surfactant and cosurfactant were prepared. The ratio of oil to the mixture of surfactant and cosurfactant was varied from 9:1 to 1:9. Water was added drop by drop under gentle stirring to each oily mixture. The compositions of microemulsion at which phase seperation from homogeneous microemulsion to heterogenous phases occurred were recorded. The phase inversion of the microemulsion from O/W to W/O was determined based on the change of conductivity (Baroli et al., 2000) which was measured using a conductance meter (Analytical equipment mill, Tianjin, China, model DDS-11C) at 20 ± 0.5 °C. Based on these results, appropriate oil, surfactant and cosurfactant were selected and used in the preparation of microemulsions containing 0.375% meloxicam. The effect of the contents of the oil and the mixture of surfactant and cosurfactant on the permeation of meloxicam through excised rat skins was evaluated.

### 2.4. Measurement of droplet size

The average droplet size of the microemulsions were measured by dynamic light scattering (DLS) using a Zetasizer Nano-ZS (Malvern Instruments, England). The measurement by backscatter at a fixed angle was 173° at 20 °C.

### 2.5. Skin permeation study

The skin permeation rates of meloxicam from various microemulsions were determined to evaluate the effect of the formulation factors. The abdominal skins were obtained from male Wistar rats weighing 220 ± 20 g. After hair was shaved carefully with an electric clipper (Oster, USA), the skin was excised from the abdominal region of each sacrificed rat and the subcutaneous fat and other extraneous tissues were trimmed. The excised rat skins were washed, then stored at 4 °C and used within 24 h after the skin harvest.

The permeation experiments were performed using Franz diffusion cells fitted with excised rat skins at 37 °C. The effective diffusion area was 2.27 $cm^2$ (17 mm diameter orifice), and the receptor compartment was filled with 13.5 ml of 20% ethanol in pH 7.4 phosphate buffer. It was constantly stirred at 600 rpm throughout the experiment. After meloxicam-loaded microemulsion (2 g) was applied on the epidermal surface of the skin, the receptor medium was withdrawn every hour for up to 10 h after the application. An equal volume of the fresh phosphate buffer was immediately replenished after each sampling. Collected samples were filtered through 0.45 mm polyvinyl