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Development of a fast dissolving sublingual film containing meloxicam nanocrystals for enhanced dissolution and earlier absorption

Qing Song[a], Chengying Shen[a], Baode Shen[a,b], Wangquan Lian[a,b], Xiao Liu[a,c], Bo Dai[a], Hailong Yuan[a,*]

[a] Department of Pharmacy, Air Force General Hospital, PLA, Beijing 100142, China
[b] Key Lab of Modern Preparation of TCM, Ministry of Education, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China
[c] Pharmacy College, Chengdu University of Traditional Chinese Medicine, Chengdu 100039, China

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ABSTRACT

The objective of this work was to prepare and evaluate fast dissolving sublingual films containing meloxicam nanocrystals (MLX-NS-FDSFs). Nanocrystals (NS) were utilized to allow for improved dissolution of the drug, whereas the films were used to shorten the onset of action via the sublingual route. Meloxicam nanocrystals (MLX-NS) were prepared by nanoprecipitation based on acid-base neutralization method and then encapsulated into the films by solvent casting method. The obtained FDSFs exhibited uniform thickness of 82 ± 8 μm and drug content of 7.38 ± 0.011 mg/film (4 cm^2) and disintegrated rapidly in 23.08 ± 1.76 s. The MLX-NS-FDSFs with reconstituted particle size of 196.4 ± 6.3 nm showed faster dissolution rate in vitro than the MLX coarse suspension based films (MLX-CS-FDSFs). The SEM images and XRD indicated that MLX nanocrystals were highly dispersed into the films. After administrated to rats, T_{max} of MLX was significantly shortened following sublingual administration of MLX-NS-FDSFs. The absorption of MLX from MLX-NS-FDSFs resulted in 3.00 fold increased in bioavailability as compared to MLX-CS-FDSFs and 4.34 times with reference to the MLX-CS. These results indicated that the NS-FDSFs could be a promising delivery system to enhance the dissolution and shorten the onset time of MLX.

1. Introduction

Meloxicam (MLX) is a cyclo-oxygenase-2 preferential nonsteroidal anti-inflammatory drug originally developed by Boehringer Ingleheim and prescribed for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis [1]. Although used mainly as an antirheumatic drug, it is also an effective analgesic for various conditions [2–7]. MLX can be classified as a Class II drug according to the Biopharmaceutics Classification System (i.e. exhibits low water solubility and high permeability). MLX is a weakly acidic drug with pH dependent solubility related to its multiple ionization states [8], which lead to dissolve of MLX in upper gastrointestinal tract is especially poor [9]. Oral dosage forms of MLX have a T_{max} (time to reach maximum concentration) of 4–6 h in the human body and they require approximately 2–3 h to reach the therapeutic serum concentration that enable the onset of action [1,10]. Such a slow onset limits MLX from its full potential for the application of situations requiring rapid onset of action (such as acute pain, sciatica, exacerbations of rheumatism and acute flares of osteoarthritis) [11]. Moreover, it is known that pain or its associated trauma would decrease gastric fluid secretion and motility, these changes have direct impact on disintegration and dissolution rate of oral formulations, and then impair the oral absorption of drugs [12]. Masanori Ochi et al. [13] have reported that there was 18-fold reduction of AUC_{0-4} for orally crystalline MLX in rats treated with propantheline for the suppression of gastric motility compared with that in normal rats. Although the intramuscular injection of MLX is available in the market, problems of the potential local tissue irritation and necrosis have restricted its clinical benefit [14]. Therefore, this parenteral route is not recommended for the chronic use and should be switched to oral formulation as soon as the rapid onset of action is achieved.

This can be achieved by development of fast dissolving sublingual films (FDSFs) which contains a hydrophilic polymer that allows the dosage form to disintegrate or dissolve within minute in sublingual part of oral cavity after contact with saliva without drinking or chewing [15]. FDSFs can be available for the treatment of a generalized oral condition or absorbed through the sublingual mucosa for systemic therapy [16]. Rapid drug absorption and instant bioavailability is possible since relatively less thickness and the higher blood flow of

* Corresponding author.
E-mail address: yhlpharm@126.com (H. Yuan).

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sublingual area, and this leads to quick-onset of drug action [17,18]. In some cases, the sublingual route provides an alternative to invasive intravenous dosing if rapid delivery to the systemic circulation is required [17]. However, FDSFs have some disadvantages: i) high dose cannot be incorporated into the film [19]; ii) they are not suitable for the delivery of water insoluble drugs [20,21]. Since the oral daily dose of MLX is 7.5–15 mg, which makes the administration of MLX via sublingual route suitable [11].

To maximize the potential of MLX sublingual mucosa absorption and accordingly faster onset of action, we attempted to improve dissolution rate of MLX via fabrication of MLX nanocrystals (MLX-NS) before integration into FDSFs. Nanocrystals (NS) are drug crystals with a particle size ranging from dozens to hundreds of nanometers and have become one of the most effective and simple methods for improving the dissolution behavior and bioavailability of poorly water-soluble drugs [22–24]. Moreover, NS have some other advantages such as relatively lower cost, higher drug loading and none or fewer carrier-associated side effects compared with carrier nanoparticles [25]. NS are typically prepared by either top-down process (breaking of large drug particles through mechanical forces generated by milling or homogenization) or bottom-up process (building nanoparticles up from drug molecules generally via precipitation induced by anti-solvent), as well as a combination of the two methods [26]. Bottom up process exhibits better control on particle size distribution and requires lower energy input compared with top-down technology. However, since organic solvent is used in this process, the solvent residue may arise safety concerns [27]. Inspired by pH dependent solubility related to its multiple ionization states of MLX, it is rational to prepare MLX-NS with the acid-base neutralization based nanoprecipitation.

In the present study, MLX-NS was prepared by nanoprecipitation based on acid-base neutralization and then transformed into FDSFs using casting method with a view to improve the dissolution properties and shorten the onset of pharmacological effects of MLX. Box–Behnken design (BBD) is a rotatable second-order design based on three-level incomplete factorial designs and mainly advantageous in less experimental trials needed to evaluate multiple parameters and their interactions [28,29]. To reduce the number of trials and attain the most information on properties of the FDSFs containing MLX nanocrystals (MLX-NS-FDSFs), a three-level, three-factorial BBD was employed systematically to evaluate and optimize the formulation variables of the MLX-NS-FDSFs. The physicochemical properties were characterized by particle size distribution analysis, morphology, X-ray powder diffraction (XRPD) before and after film formation. The appearance, thickness, drug content, and disintegration time were also tested. To verify the advantages of the MLX-NS-FDSFs, the dissolution behavior and the pharmacokinetic profiles were investigated.

2. Material and methods

2.1. Materials

Meloxicam (MLX, the purity is up to 99.9%) was purchased from Wuhan Jing Chu Chen Pharmaceutical Chemical Co., Ltd. (Hubei, China). Tween 80 (T80), Poloxamer 188 (P188), Poloxamer 407 (P407), D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Polyvinylpyrrolidone k30 (PVP k30), Sodium dodecyl sulfonate (SDS) were obtained from Beijing Fengli Jingqiu Pharmaceutical Co., Ltd. (Beijing, China). Hydroxypropylmethylcellulose E5, E30 (HPMC E5, HPMC E30) were gifted from Anhui Shanhe Pharmaceutical Accessories Co., Ltd. (Anhui, China). Polyethylene glycol 400 (PEG 400) was obtained from Tianjin Fuchen Chemical Reagent Factory (Tianjin, China). NaOH, HCl and other reagents were of at least analytical grade and purchased from local distributors.

2.2. Preparation of MLX-NS

The MLX-NS was prepared by nanoprecipitation based on acid-base neutralization. In brief, 0.825 g MLX and stabilizers were firstly solubilized in 50 mL NaOH aqueous solution (0.1 M), and then 5 mL HCl aqueous solution (1 M) was poured into the solution quickly. Simultaneously, high speed shearing (B25, B.R.T Equipment Co., Ltd., China) was included to control the particle size distribution. The MLX-NS was obtained within several minutes.

Based on the single-factor method, an optimized formulation was obtained by screening several main formulation and process factors, including the type of stabilizers (T80, P188, P407, TPGS, PVP k30, SDS, HPMC E5), the ratio of the mass concentration of MLX/stabilizer (10:1, 10:2, 10:3, 10:4, 10:5, 10:6), the speed (1000 rpm, 13,000 rpm, 16,000 rpm) and time (1 min, 2min, 3 min, 4 min, 5 min) of high speed shearing. Each experiment was run in triplicate.

2.3. Preparation of MLX coarse suspensions

MLX coarse suspensions (MLX-CS) were prepared by dispersing MLX in a stabilizer solution and then stirred by a magnetic stirrer (SH-2, Beijing Jinbeide Industrial And Trading Co., Ltd., China) to obtain a uniform suspension. The composition of MLX-CS was the same as that of MLX-NS.

2.4. Particle size and size distribution analyses

The MLX-NS was analyzed for the average particle size (PS) and polydispersity index (PDI) by a laser particle size analyzer (Winner 801, Jinan Winner Particle Instrument Stock Co., Ltd., China). Prior to measurement, a suitable concentration of MLX-NS for analysis was achieved by diluting with double-distilled water. The samples were measured at a fixed angle of 90 °C at 25 °C. The measurement was performed in triplicate and the average value was used.

The PS and PDI of reconstituted MLX nanocrystals from FDSFs were measured as follows: a piece of films (2 × 2 cm^2) was placed into an appropriate amount of distilled water followed by sonication for 2 min. The obtained suspension was analyzed for PS and PDI by the same methods.

2.5. Stability index

The stability of MLX-NS was evaluated by stability index (SI), as follows:

$$SI_{PS} = \frac{PS_{0d}}{PS_{7d}} \quad (1)$$

$$SI_{PDI} = \frac{PDI_{0d}}{PDI_{7d}} \quad (2)$$

In which PS_{0d} is the average particle size value of the MLX-NS on day 0, and PS_{7d} is the corresponding average value of MLX-NS on day 7; PDI_{0d} is the PDI value of the MLX-NS on day 0, and PS_{7d} is the corresponding value of MLX-NS on day 7. An SI value of near 100% usually means that MLX-NS is more stable.

2.6. Preparation of MLX-NS-FDSFs

The films were prepared using solvent casting method [21]. HPMC E30 was used as film-forming polymers and PEG 400 was used as a plasticizer according to preliminary experiments. Specified weight of film-forming polymers was first soaked in water for swelling and then mixed with PEG-400 to obtain a polymeric dispersion. A specified volume of the selected MLX-NS was added and mixed gently with the polymeric solution under magnetic stirring. The mixture was cast onto a previously cleaned glass plate to prepare thin film and then dried at