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Original Research Paper

Design and evaluation of a novel transdermal patch containing diclofenac and teriflunomide for rheumatoid arthritis therapy

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ABSTRACT

The aim of this study was to design a compound transdermal patch containing diclofenac (DA) and teriflunomide (TEF) for the treatment of rheumatoid arthritis (RA). The various organic amines salts of DA were prepared and their forming was confirmed using DSC and FTIR. The percutaneous permeation of organic amines salt of DA was investigated *in vitro* using a two-chamber diffusion cell with excised rabbit skin as transdermal barrier. The formulation of the patch was optimized in terms of the concentration of percutaneous permeation enhancer and the loading dose of drugs. The pharmacokinetic behavior of the optimal formulation was studies in rabbits and the anti-inflammatory and analgesic effects of the optimal patch were evaluated with the adjuvant arthritis model in rats and the pain model in mice, respectively. The result showed that skin penetration of diclofenac-triethylamine (DA-TEtA) salt was better than other organic amine salts. Based on previous study of our laboratory, teriflunomide-triethylamine (TEF-TEtA) significantly enhanced the skin permeation of TEF. 10% of azone (AZ) was the best enhancer for the two drugs. The optimal patch formulation was composed of 2% of TEF-TEtA, 6% of DA-TEtA and 10% of AZ. The cumulative permeated amount of DA-TEtA *in vitro* was comparable with that of the commercial diclofenac-diethylamine (DA-DEtA) patch. The absolute bioavailability of TEF-TEtA was 42%, which could achieve the therapeutic drug levels. In animal study, the optimized compound patch containing DA-TEtA and TEF-TEtA displayed significant anti-inflammatory and analgesic effect, which indicated the potential of the compound patch.

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1. Introduction

Rheumatoid arthritis (RA) is a long-term and chronic inflammatory disease caused by the immune system attacking joints, which is characterized by symmetrical distribution [1]. Chronic synovitis attacks cartilage articularis, ligament and muscle tendon, leading to joint deformity and functional disorder. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of musculoskeletal disorders such as osteoarthritis and rheumatoid arthritis [2]. However, there is no evidence to show that NSAIDs can delay the progression of RA [3]. On the other hand, disease-modifying antirheumatic drugs (DMARDs) could prevent the pathological process of RA and avoid the joint damage but could not relieve the pain immediately [4]. Considering that monotherapies and fixed-dose can not meet the needs of different patients, NSAIDs and DMARDs are always used in combination for RA treatment clinically since 1950s [5].

Diclofenac(2-[2-(2,6 dichlorophenyl amino) phenyl]acetic acid) is one of the most prospective and commercially successful drug in the family of NSAIDs [6,7] and has an annual turnover over 1 billion US dollars [8]. It is used for the treatment of rheumatoid arthritis, osteoarthritis and relief the pain of varying origin treatment [9]. The main mechanism of action is to inhibit the activity of cyclooxygenase (COX) by interdicting the prostaglandin (PG) synthesis [10]. However the main disadvantage of oral administrated diclofenac dosage form is the serious adverse effects such as gastrointestinal disturbances, nausea, vomiting and stomach pain, etc [11].

Leflunomide (LEF) is one of DMARDs, which has been recommended for RA therapy by the American College of Rheumatology [12]. The LEF is transferred into its active metabolite teriflunomide (TEF) and TEF plays the major role for therapy [13,14]. It was shown TEF could inhibit the production of PGE_2 and the activity of cyclooxygenase-2 (COX-2) [15]. However, up to 50% of patients showed intolerability to this drug after oral administration, especially suffering from some gastrointestinal adverse effects [16]. With regarding to this, another administrating route avoiding the severe adverse effects is desired for delivering of the combination of DA and TEF into the body.

Transdermal drug delivery system (TDDS) is a promising alternative way of drug delivery which can maintain a uniform plasma concentration, reduce dosing frequency associated with improved the patient compliance, and avoid the gastrointestinal action. The compound transdermal patch containing DA and TEF will not only avoid the gastrointestinal irritation, but also provide double response of controlling RA activity. It has been reported that the skin permeation of weak acidic DA and TEF (Table 1) is unsatisfactory, but the addition of organic amines can significantly increase the percutaneous permeability of TEF [12] and DA [17,18]. Therefore, the experiment firstly prepared the different origin amine salts of DA and screened the salt with the optimal permeation. Based on previous study of our laboratory [12], TEF-TEtA significantly enhanced the skin permeation of TEF and the effect of different chemical enhancers had been investigated. The best concentration of enhancer for two drugs and the loading dose of drugs were chosen. There is no commercial transdermal product of TEF, so the pharmacokinetics study of TEF is used to confirm whether the loading dose of TEF-TEtA is reasonable or not. To investigate the anti-inflammatory and analgesic effects of the compound patch, the pharmacodynamic study was carried out finally.

2. Materials and methods

2.1. Chemisty and materials

DA, diclofenac-sodium (DA-Na), diclofenac-potassium (DA-K), and diclofenac-diethylamine (DA-DEtA) were purchased from Tiande Pharmaceutical Co. Ltd (Tieling, China). TEF and TEF-TEtA were synthesized in our laboratory [12]. Pressure sensitive adhesive (PSA) was supplied by Henkel Corp., (New Jersey, USA). Korean commercial DA-DEtA patch was obtained from Samyang. Corp., (Korea). Complete Freund's adjuvant (CFA) was purchased from Sigma–Aldrich Co. LLC., (Missouri, USA). Propylparaben was obtained from Bodi Chemical Holding Co. Ltd., (Tianjin, China). Diethanolamine (DEA), triethanolamine (TEA), triethylamine (TEtA), propylparaben were all obtained from Bodi Chemical Holding Co. Ltd., (Tianjin, China). 1-(2-Hydroxyethyl) pyrrolidine (NL) was purchased from Tianjin Heowns Biochem LLC, N-(2-Hydroxyethyl) piperidine (NP) was supplied by Alfa Aesar (Massachusetts, USA). N-methyl pyrrolidone (NMP), azone (AZ), isopropyl myristate (IPM), Transcutol® P (TP), oleic acid (OA), Span 80, propylene glycol (PG) and L-menthol (MT) were obtained from International Specialty Products Inc., (New Jersey, USA), Tianmen Kejie Pharmacy Co. Ltd., (Hubei China), China National Medicines Co. Ltd., (Shanghai, China), Beijing Chemical Co. Ltd., (Beijing, China), Tianjin Bio Chemical Co. Ltd., (Tianjin, China), Tianjin Bio Chemical Co. Ltd., (Tianjin, China), Nanjing chemical reagent Co. Ltd., (Nanjing, China) and Suzhou Healthytech Bio-Pharmaceutical Co. Ltd., (Jiangsu, China), respectively. All other chemicals and solvents were analytical reagent grade.

2.2. Animals

Rabbits (male, 1.8–2.2 kg), Wistar rats (male, 180–220 g) and KM mice (male, 18–22 g) used all in the experiments were purchased from the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). The experiments were performed in accordance with the guidelines for animal use published by the Life Science Research Center of Shenyang Pharmaceutical University.

2.3. Synthesis of organic amine salts of DA

DA was completely dissolved in acetone and then equimolar of organic amines was added. After the mixture of DA and organic amine was subjected to ultrasound for 1 h at room temperature, the solvents were removed by using rotary evaporator. The obtained solid product was further dried in a vacuum oven for 24 h at room temperature. The synthesis of organic amine salt was confirmed by DSC (DSC1 STAR^e System, Mettler-Toledo International Inc., Schwerzenbach, Switzerland) and FTIR (Spectrum 100, PerkinElmer Inc., Massachusetts, USA) respectively.