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Drug in adhesive patch of palonosetron: Effect of pressure sensitive adhesive on drug skin permeation and *in vitro-in vivo* correlation

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ABSTRACT

Palonosetron (PAL) is recommended for the prevention of chemotherapy-induced nausea and vomiting. The aim of this study was to develop a long-acting PAL transdermal patch to improve patient compliance. We were particularly concerned about the effect of pressure sensitive adhesives (PSAs) on PAL skin permeability. Formulation factors including PSAs, backing films and drug loadings were investigated in the *in vitro* skin permeation study using rabbit skin. Fourier transform infrared spectrometer study and thermal analysis were conducted to investigate the drug-PSA interaction and thermodynamic activity of PSAs, respectively. The results indicated that high drug skin permeation amount was obtained in PSA DURO-TAK®87-2516, which had low interaction potential with PAL and high thermodynamic activity. The optimized patch was composed of PAL of 8 %, DURO-TAK®87-2516 as PSA, CoTran™ 9700 as backing film and Scotchpak™ 9744 as release liner. The *in vitro* skin permeation amount of the optimized patch was $734.0 \pm 55.8\ \mu g/cm^2$ during 3-day administration. The absolute bioavailability of the optimized patch was 43 % in rabbit and a good *in vitro-in vivo* correlation coefficient was obtained ($R^2 = 0.989$). These results indicated the feasibility of PAL transdermal patch in the prevention of chemotherapy-induced nausea and vomiting.

1. Introduction

Palonosetron (PAL) is a second-generation 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist, which is recommended for prevention of chemotherapy-induced nausea and vomiting (CINV) (Walton, 2000; Celio et al., 2015). Nausea and vomiting are the common side effects of chemotherapy (Viale, 2005). According to MASCC/ESMO Antiemetic Guidelines, 30–90 % of the patients suffer from CINV after chemotherapy. Nausea and vomiting may lead to dehydration, malnutrition or electrolyte imbalance, which affect the quality of life, the willingness for therapy even the hope of survival (ASHP, 1999; Hesketh, 2000). According to its onset time, CINV is divided into three categories: Acute CINV occurs within 24 h after chemotherapy, delayed CINV starts at 24–48 h after chemotherapy and anticipation CINV appears before chemotherapy (Gregory and Ettinger, 1998).

PAL hydrochloride (Fig. 1) is one of the drugs approved by FDA for the treatment of delayed CINV. At present, oral and injection preparations of PAL hydrochloride are available in market. It is suggested that patients who receive multiple-day cisplatin should take PAL on day 1, 3 and 5 according to MASCC/ESMO Antiemetic Guidelines. However, the invasive and apprehensive nature of injection will decrease patient compliance. Besides, those who are suffering from nausea and vomiting are not suitable for oral drug delivery, which will worsen the symptoms. Therefore, transdermal drug delivery system (TDDS) is a promising alternative due to the advantages such as the convenience of administration, sustained release of drug and the possibility of termination immediately after side effect. The only transdermal drug delivery product for the treatment of CINV is granisetron patch (SANCUSO®), which is approved by FDA in 2008 (Duggan and Curran, 2009). Meanwhile, the physicochemical properties of PAL (Fig. 1) are suitable for TDDS, such as its relative molecular weight is 296.4, log*P* is 2.7 and melting point is 91 °C. So PAL transdermal patch has a potential to relief the CINV thus benefits the patients as well.

Single layer patch is simple and stable, which is a widely used design in TDDS. Pressure sensitive adhesives (PSAs) not only provide adhesion force for the patches but also play a significant role in controlled drug release (Wokovich et al., 2006). In the patch formulation optimization, the selection of PSAs is largely based on

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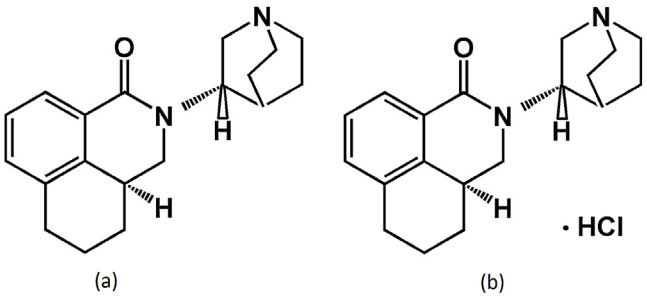

Fig. 1. Chemical structures of (a) PAL and (b) PAL hydrochloride.

trials and errors due to the lack of theories about the influence factors of PSAs on drug release. Hence, the investigation of the influence of PSAs will provide references for the research and development of TDDS. At the same time, it will give insight into drug-PSA binary system and provide theory basis for the drug-in-adhesive patch design (Cui and Frank, 2006).

In this study, a long-acting drug-in-adhesive patch of PAL was designed and prepared. Fourier transform infrared spectrometer (FT-IR) and thermal analysis (DSC) were conducted to illustrate the differences of three commercial PSAs. The pharmacokinetic study of the optimized patch was conducted in rabbit model; meanwhile *in vitro-in vivo* correlation was built up using deconvolution method.

2. Materials and methods

2.1. Materials

PAL hydrochloride was purchased from Hangzhou Rongda Pharm & Chem Co., Ltd. (Hangzhou, China). Three acrylic PSAs including DURO-TAK®87-4098 (DT 4098), DURO-TAK®87-2677 (DT 2677) and DURO-TAK®87-2516 (DT 2516) were purchased from Henkel AG&Co. (Germany). Sodium hydroxide, ethyl acetate, sodium chloride, anhydrous sodium sulfate, sodium azide, acetic acid, triethylamine, propyl paraben, normal saline, ammonium acetate and formic acid were purchased from Yuwang Pharmaceutical Co., Ltd. (Shandong, China). Tropisetron was purchased from Zhongshan Hengsheng Pharmaceutical Co., Ltd. (Guangdong, China). All the other chemicals were reagent grade and purchased commercially.

2.2. Animals

Rabbits (male, 2.0 ± 0.2 kg) were purchased from the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). All animal experiments were performed in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised in 1978) and also with the guidelines for animal use published by the Life Science Research Center of Shenyang Pharmaceutical University. All efforts were made to limit the amount of animals used.

2.3. Preparation of PAL free base

PAL hydrochloride dissolved in distilled water was titrated to pH 11 with sodium hydroxide solution of 4 % (w/v). Then the solution was extracted three times with ethyl acetate. Subsequently, the collected ethyl acetate fraction was washed once with saturated NaCl slolution and dried with anhydrous sodium sulfate for 12 h, and then the ethyl acetate fractions were filtered and evaporated using a rotary evaporator (EYELA N-1000, AiLang Co. Ltd., Shanghai, China) at 40 °C. The obtained crystal of PAL free base was stored in a vacuum drying oven to eliminate residual water. PAL free base was finally confirmed by DSC (Mettler-Toledo AG, Schwerzenbach, Switzerland) and mass spectrum (Bruker solariX, USA).

2.4. Preparation of patch

The drug-in-adhesive patch was prepared by dissolving PAL free base (78 mg, drug loading of 8 %) in ethyl acetate of 0.5 mL and then stirred thoroughly with PSA (2 g, solid content of 45 %, DT 4098, DT 2677 or DT 2516) to obtain a homogeneously drug-PSA mixture. The obtained mixture was coated onto a fluoropolymer-treated polyester release liner (ScotchPak™ 9744; 3M, St. Paul, Minnesota, USA) with a laboratory coating unit (0.8 mm, TB-1, KaiKai Co. Ltd., Shanghai, China). The drug-PSA film was allowed to stand 10 min in the room temperature to prevent the form of bubble, and then followed by oven drying at 50 °C for 10 min to remove the residual solvent. A backing film (CoTran™ 9700, 9720, 9726 or Scotchpak™ 9680, 3M, St. Paul, Minnesota, USA) was laminated on it. The residue of solvent in the patch was determined to make sure little ethyl acetate was left according to the previous literature (Liu et al., 2012). The final thickness of the PSA layer was 120–130 μm. Crystallization study was conducted according the previous literature (Liu and Fang, 2015), which was used to confirm the saturated state of drug in PSA using microscopic observation method with a microscope (XSP-2CA, Shanghai optical Instrument Factory, China).

2.5. Determination of drug content in patch

The patch ($4.52\ cm^2$, $n = 4$) was immersed into methanol (20 mL) followed a sonication process for 20 min. Then the methanol was transferred into a volumetric flask (50.0 mL) diluted with methanol to volume. After filtration, the concentration of PAL was determined with Hitachi HPLC system (pump L-2130, UV detector L-2420, autosampler L-2200, T-2000L workstation) and a Diamonsil ODS (5 μm, 200×4.6 mm) with temperature maintained at 40 °C. The mobile phase consisted of 0.5 % acetic acid in water-methanol mixture (35:65), adjusted to pH 7.0 with triethylamine. The flow rate was 1.0 mL/min and the wavelength was 242 nm. Propyl paraben was used as the internal standard.

2.6. Drug release study

Drug release study was in accordance with the skin permeation test, but skin was replaced by the cellophane membrane (Agilent, Germany). The cellophane membrane was added in the front of the patch instead of skin, which was made of natural raw material cotton with the molecular weight cut off of 3500 and it acted as the upholder in drug release study.

2.7. Thermal analysis

Glass transition temperature (T_g) measurement was performed using a Mettler-Toledo thermal analyzer (DSC 1, Mettler-Toledo AG, Schwerzenbach, Switzerland). Before the measurement, pure PSA and drug-loaded PSA with drug loading of 4.0 % were dissolved in ethyl acetate and added in the aluminum DSC pans. The DSC pans were allowed to stand in the room temperature for 12 h followed oven drying for 0.5 h at 50 °C to evaporate the organic solvent. The weight of sample was determined after the drying procedure. The sample was heated from −70 °C to 20 °C at the rate of 5 °C/min in the thermal analysis and the phase transition midpoint was determined as glass transition temperature (T_g).