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Effect of drug physicochemical properties on drug release and their relationship with drug skin permeation behaviors in hydroxyl pressure sensitive adhesive

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ABSTRACT

The aim of this study was to investigate the influence of drug physicochemical properties on drug release behaviors and their relationship with skin permeation behaviors, which provided transdermal enhancement strategies for the design of transdermal drug delivery system. Six model drugs with different physicochemical properties were selected and hydroxyl pressure sensitive adhesive (PSA) was synthesized. Horizontal diffusion cell was used to evaluate drug release and skin permeation behaviors. The relationship between physicochemical properties and release behaviors was conducted with regression analysis. Release behavior of 0.25% drug loading was linear related with polar surface area, which represented the hydrogen bond. Release behavior of 2.0% drug loading was dependent on the polarizability and log *P*, which represented dipole-dipole interaction and lipophilicity, respectively. According to the results of Fourier transform infrared spectroscopy, it was inferred that hydrogen bond was limited in controlling release of drug due to the limited quantity of bonding site, thus dipole-dipole interaction and log *P* became dominate control factors. Combining the drug release study and drug skin permeation study, it was concluded that drugs with different physicochemical properties should be applied with different transdermal enhancement strategies, which was useful for the design of transdermal drug delivery system.

1. Introduction

Over the past three decades, transdermal drug delivery system (TDDS) has been developed as one of the most successful drug delivery technologies. It provides many advantages such as stable plasma drug concentration, avoiding first-pass metabolism and good patient compliance. There are mainly two rate limiting steps in drug delivery of patch: the first one is drug releasing from the pressure sensitive adhesives (PSAs) and the second one is drug permeating into the skin, thus one or both of them will be the rate limiting step of transdermal drug delivery. The analyzing of the rate limiting step is extremely important for the TDDS development, which will provide information for the transdermal enhancement strategy. For the second step, restricted conditions of transdermal drug candidates are mentioned by many literatures that the drug should have relative molecular weight <500, a balanced lipophilicity value (log{octanol-water partition coefficient}), log *P* around 2 to 3 and a measurable solubility both in oil and water (Wiedersberg and Guy, 2014). Though these physicochemical parameters play significant role in the prediction of drug skin permeability, their influences are rarely mentioned in the evaluations of drug release behavior from PSA and rate limiting step of the whole transdermal drug delivery process in previous literature.

Drug release process is influenced by many factors. The first one is drug itself, including drug loading, molecular volume. The second one is the PSA, including polymer free volume or micro-viscosity. The third one is the environmental factor, including ambient temperature and hydration. And the fourth one, which is considered as the most important one, is the drug-PSA intermolecular interaction (Morimoto et al., 1992). On one hand, it has been demonstrated that there are interactions such as hydrogen bond, ionic bond and dipole-dipole interaction between functional groups of drug and polymer (Kothari et al., 2015), which could be revealed on physicochemical parameters of drugs and PSAs. Therefore, it is hypothesized that these interactions could be described by the drug physicochemical parameters in a fixed PSA. On the other hand, quantity of interaction sites in PSAs is limited, which may be saturated by drugs, thus it is also hypothesized that drug release and skin permeation behavior will be dependent on the drug loading. Combining these two points, it's inferred that drug release behaviors from patches with different drug loadings will exhibit different release profiles, which should be related with drug physicochemical parameters if there is intermolecular interaction between drug and PSA.

Guy and Hadgraft (1992) proposed an equation about the rate controlling step that comparison of the amount of drug released in a given period of time from the delivery system into aqueous sink, with the

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corresponding amount when the device was placed in contact with the skin would reveal the respective contributions of the device and the skin to the overall rate control. Finally, drug physicochemical properties are integrated with the release behaviors and skin penetration behaviors to predict the rate limiting step of transdermal drug delivery, and then accurate enhancement strategy will be chosen and targeted TDDS prescription will be designed from the view of drug.

Hydroxyl PSAs have been widely used in TDDS because numbers of drugs are obtained satisfactory skin permeation amount in this type of PSAs (Soler et al., 2012; Subedi et al., 2011; Rhee et al., 2008). Therefore, a representative hydroxyl PSA was synthesized as model adhesive matrix in this study. Similar molecular volume of six model drugs including diclofenac (DIC), etodolac (ETO), ketoprofen (KET), propranolol (PRO), zaltoprofen (ZAL), zolmitriptan (ZOL) with different physicochemical properties were selected to eliminate the influence of molecular size on drug release behavior (Kokubo et al., 1991; Kokubo et al., 1994). Their molecular structures were shown in Fig. 1. Drug release study was performed with horizontal diffusion cell. Physicochemical parameters including molecular volume (M.V.), polar surface area, polarizability, log *P* and melting point (M.P.) were chosen to investigate their relationship with drug release behaviors. Fourier transform infrared spectroscopy (FT-IR) study was carried out to investigate the drug-PSA interactions. Skin permeation study was also conducted with rat skin. The aim of this study was to clarify the effect of drug physicochemical parameters on drug release and their relationship with drug skin permeation behaviors.

2. Materials and methods

2.1. Materials

DIC was purchased from Hotai pharmaceutical Co., Ltd. (Wuhan, China). ETO and PRO were purchased from Wuhan DKY Technology Co., Ltd. (Wuhan, China). KET was purchased from Hubei Xunda Pharmaceutical Co., Ltd. (Wuhan, China). ZAL was purchased from Hubei KangBaoTai Fine-Chemicals Co., Ltd. (Wuhan, China). ZOL was purchased from Wuhan GPC-China Chemistry Co., Ltd. (Wuhan, China). 2-Ethylhexyl acrylate (EHA), Methyl acrylate (MA), 2-Hydroxyethyl acrylate (HEA) and 2, 2-Azobis (AIBN) were purchased from Aladdin Industrial Inc. (Shanghai, China). Isopropyl palmitate (IPP) was supplied by Shanghai Qianwei Oil Science&technology Co., Ltd. (Shanghai, China). All the other reagents used were chromatographic grade and obtained commercially.

2.2. Methods

2.2.1. Synthesis of hydroxyl PSA

Hydroxyl PSA composed of EHA, MA and HEA was synthesized by a free radical-initiated solution polymerization. The synthesis procedure was summarized as follows: the monomers and ethyl acetate were poured into four-neck bottle and heated with water bath keeping at 70 °C, and the mixture was stirred using a mechanical Teflon agitator blade with the protection of nitrogen. Then the initiator AIBN dissolved in ethyl acetate was added into the mixture when the system temperature became stable. The reaction was maintained about 10 h and the resulting PSA was detected with gas chromatography (Agilent Technologies, Inc., California, USA) to make sure that the residual monomer was <0.5%. The solid content of the resulting PSA was about 40%.

2.2.2. Drug solubility in phosphate buffer solution (PBS)

Drug solubility in PBS (pH 7.4, 2.0 mL) was determined to make sure the sink condition for drug release and skin permeation study. Excess drug was added into PBS in a glass tube which was set in thermostat maintained at 32 °C for 24 h. After the sample was centrifuged at 32 °C, drug solution was diluted with PBS then analyzed with HPLC (Pump L-2130, Auto Sampler L-2200 and UV Detector L-2420, Hitachi, Ltd., Tokyo, Japan) and Diamonsil C18 reversed-phase column (200 × 4.6 mm id., 5 μm; Dikma Technologies, Beijing, China). Mobile phase and wavelength of each model drug were modified from previous literatures (Secilmis-Canbay et al., 2012; Shojaee et al., 2016; Abd-Elbary et al., 2013; Cui et al., 2015; Liu and Fang, 2015) and they were listed as follows: DIC (Methanol: water: phosphoric acid: triethylamine = 85: 15: 0.1: 0.1, 280 nm), ETO (Methanol: water: phosphoric acid: triethylamine = 85: 15: 0.1: 0.1, 280 nm), KET (Methanol: water: phosphoric acid: triethylamine = 78: 22: 0.1: 0.1, 260 nm), PRO (Methanol: water: phosphoric acid: triethylamine = 50: 50: 0.1: 0.1, 288 nm), ZAL (Methanol: water: phosphoric acid: triethylamine = 85: 15: 0.1: 0.1, 330 nm) and ZOL (Methanol: water: phosphoric acid: triethylamine = 18: 82: 0.1: 0.1, 225 nm).

2.2.3. Patch preparation

Drug-in-adhesive patches with different drug loadings (0.25%, 0.5%, 1.0% and 2.0%) were prepared by the solvent evaporation technique (Liu and fang, 2015). After model drug was dissolved in a minimum amount of ethanol (50 mg/mL) completely, the hydroxyl PSA was added. The obtained mixture was stirred with magnetic bar for 1 h until it became

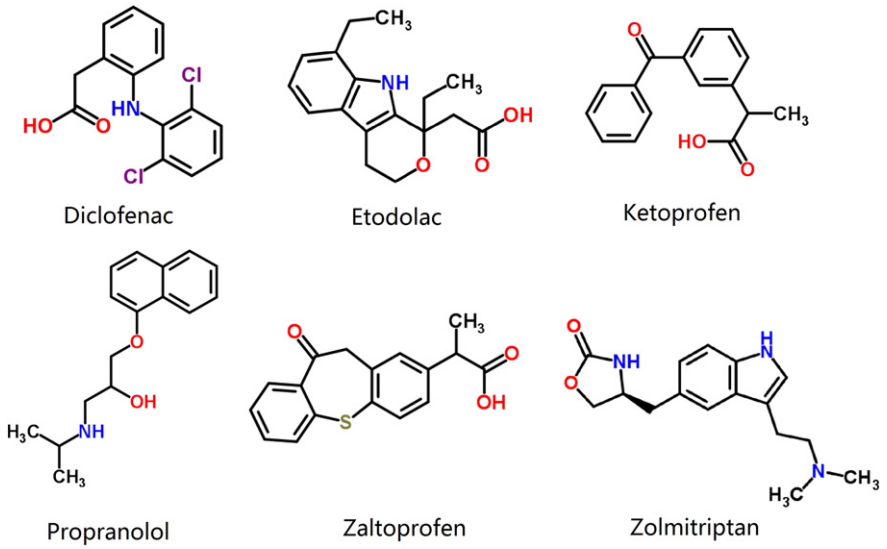

Fig. 1. Molecular structures of model drugs.