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The role of carboxyl group of pressure sensitive adhesive in controlled release of propranolol in transdermal patch: Quantitative determination of ionic interaction and molecular mechanism characterization

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ABSTRACT

Acrylic pressure sensitive adhesives (PSAs) are widely used in transdermal drug delivery system (TDDS). However, there was little research about the quantitative relationship between drug release and drug-PSAs interaction. In this study, five acrylic PSAs with different molar fraction of carboxyl group were designed and synthesized. Propranolol (PRO) was used as model drug to evaluate release profiles in the PSAs *in vitro* and *in vivo*. The drug release percent in the PSAs were 81.66, 78.22, 51.66, 21.81 and 11.73%, and their release behaviors were decreased with carboxyl group content of PSAs. Furthermore, it was found that quantity of carboxyl group of PSAs was equal to residual drug by the quantitative determination. In addition, the ionic interaction between PRO and PSAs was confirmed by FT-IR and MDSC results qualitatively. Using the FT-IR, MDSC, Flory-Huggins interaction parameters and molecular dynamic simulation, interaction strength between drug and PSAs was determined quantitatively, which demonstrated that the drug release amount decreased linearly with interaction strength. Based on above results, we proposed that the PRO was possibly binding to the carboxyl group of PSAs one-by-one, which provided references for the accurate design of TDDS.

1. Introduction

Transdermal drug delivery systems (TDDS) offers a number of advantages, which provides a prolonged period of administration and maintains drug levels within the therapeutic window (Wiedersberg and Guy, 2014). Transdermal drug delivery is known as a successful controlled release technology, which is a kind of dosage form designed to deliver a therapeutically effective amount of drug into the systemic circulation across skin (Ghosh et al., 2015). Acrylic pressure sensitive adhesives (PSAs) have been introduced into TDDS for decades and play a significant role in the TDDS development to attain the desired drug release profile in drug-in-adhesive patch (Tan and Pfister, 1999). The controlled release of drugs from PSAs is a key point that should be focused. An approach to control drug release from polymer is to design chemical bonds between the drug and the polymer chains, which controls the drug release rates (Li and Mooney, 2016).

For transdermal patches, PSAs serve as a pivotal excipient on which different interactions with drug control drug release profile. Commonly, PSAs are modified with carboxyl and hydroxyl functional groups. Previous reports (Kim et al., 2000; Liu et al., 2016b; Weng et al., 2016) revealed that PSAs containing hydroxyl group had a slight effect on drug release and acceptable miscibility for basic drug. However, PSAs containing carboxyl group had strong interaction with basic drug, which hindered the drug release (Naruse et al., 2012; Jung et al., 2015; Park et al., 2012). Hence, carboxyl group is the key functional group for controlled release of basic drug in the PSAs. Moreover, effect of various commercial PSAs on drug release and skin permeation was investigated, which was a vital part of formulation optimization (Subedi et al., 2011; Nalluri et al., 2008; Liu et al., 2016a). The observed diffusion behavior was only interpreted by the interaction between the drug and PSAs in the study (Yasunori et al., 1992). Previous studies about interaction between drug and PSAs were qualitative, mainly including ionic bond and hydrogen bond (Liu et al., 2017; Li et al., 2017). There is little research about the quantitative relationship between drug release and drug-PSAs interaction due to the lack of understanding about the components of commercial PSAs, which hinders the investigation of structure-activity relationship of the PSAs and results in a limitation of accurate design of the TDDS. As a result, we utilize drug–PSAs interactions to design and synthesize PSAs to entail an accurate control of drug release from the transdermal patch. In addition, it is an urgent need to illustrate molecular interactions between PSAs and drug for better understanding and design of the TDDS.

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The aim of present study is to establish a quantitative relationship between carboxyl group content of PSAs and drug release amount, in addition, characterize their molecular mechanism for the accurate design of the TDDS. In this study, five acrylic PSAs with different molar fraction of carboxyl group were designed and synthesized. Hydroxyl groups were added to improve the mechanical properties of the PSAs. Propranolol (PRO) was chosen as model drug to evaluate the influences of carboxyl groups on drug release *in vitro* and *in vivo*. Moreover, the quantitative determinations of drug release mainly include drug content in the patch after the release experiments and the carboxyl group content of the PSAs. The FT-IR spectroscopy and modulated differential scanning calorimetry (MDSC) were used to investigate the interaction between drug and the PSAs qualitatively. In addition, the interaction strength between drug and the PSAs was determined by FT-IR, MDSC, Flory-Huggins interaction parameters, and molecular dynamics (MD) simulation, quantitatively.

2. Materials and methods

2.1. Chemicals and animals

The materials used for the synthesis of the pressure sensitive adhesive include methyl acrylate (MA), 2-ethylhexyl acrylate (2-EHA), 2-hydroxyethyl acrylate (HEA), acrylic acid (AA), initiator of 2, 2-Azobis (AIBN) and ethyl acetate, all of which were purchased from Aladdin Industrial Corporation (Shanghai, China). Propranolol was purchased from Wuhan DKY Technology Co., Ltd. (Wuhan, China). The backing film (Scotchpak™ 9680) and the release liner (Scotchpak™ 9744) were purchased from 3 M Co. (St. Paul, USA). All other chemicals and solvent were reagent grade and obtained commercially.

Male Wistar rats (180–220 g) were supplied by the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). All the procedures were performed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals, and were approved by the Animal Ethics Committee of Shenyang Pharmaceutical University. (No·SYPU-IACUC-C2016-1228-206).

2.2. Synthesis and characterization of PSAs

2.2.1. Synthesis of PSAs

Acrylic PSAs were synthesized by copolymerization of monomers in ethyl acetate and AIBN was used as a free radical initiator. 2-EHA was soft monomer and MA was hard monomer. HEA and AA were used as functional monomers containing hydroxyl and carboxyl group, respectively. The initial percentages monomers of five PSAs are presented in Table 1. The free-radical initiated polymerization process was summarized as follows: the monomers and ethyl acetate were mixed in the 1000 mL four-neck bottle under the protection of nitrogen and heated with water bath of 80 °C. Then the initiator (dissolved in ethyl acetate) was added when it reached the temperature. The reaction was maintained about 12 h to reduce residual monomer.

2.2.2. Molecular weight characterization

Gel permeation chromatography (GPC) was used to determine the molecular weights of acrylic PSAs. GPC analysis was performed on the Water Alliance e2695, which equipped with refractive index detector (Water 2414). Tetrahydrofuran (THF) was used as the eluent at a flow rate of 1 mL/min, and the sample solutions (dissolved in THF) of 20 μL were injected for each analysis. The column temperature was set at 35 °C.

Table 1
The initial monomers percentages of PSAs.

Sample	2-EHA (mol%)	MA (mol%)	HEA (mol%)	AA (mol%)
PSA-1	45.4	48.6	6.0	0
PSA-2	45.3	48.5	6.0	0.2
PSA-3	45.1	48.4	6.0	0.5
PSA-4	44.3	47.7	6.0	2.0
PSA-5	44.0	47.0	6.0	3.0

2.2.3. Determination of carboxyl group content

The acid-base titration was used to determinate carboxyl content of the PSAs (Ai et al., 2017). Sample of 4.0 g was dissolved in 10 mL pyridine in N_2 atmosphere, and thymolphthalein as indicator was added. The solution was titrated with 0.02 mol/L KOH in ethanol, until the blue color could be remained unchanged. The carboxyl content was calculated from amount of the titer.

2.3. Preparation of PRO patch

The patch was prepared by dissolving PRO free base (drug loading of 1%), adhesive in ethanol of 0.5 mL and agitated thoroughly to obtain a homogeneous drug-PSA solution. The resulting solution was coated onto release liner by using film applicator (0.45 mm, SLT200, Kaikai Co., Ltd., Shanghai, China). The drug-PSA film was dried at room temperature for 10 min and oven-dried at 50 °C for 5 min to remove the residual solvent. Then, the coated release liner was laminated with backing film. The final thickness of the PSA layer was 85 μm and drug content was 90 μg/cm^2.

2.4. In vitro drug release and mass balance study

The patch (1.13 cm^2, $n = 4$) was attached to semipermeable membrane (Cellophane®), instead of skin. The other experimental procedures were in accordance with the skin permeation test.

After the release experiment, the residual drug content in patch was determined. The patch was removed and immersed into methanol (10 mL), followed a sonication process for 15 min. Then, the methanol was transferred into a volumetric flask (50.0 mL) and diluted with methanol to volume. The resultant solution was filtered and determined with Hitachi HPLC system (pump L-2130, UV detector L-2420, autosampler L-2200, T-2000L workstation) and a Diamonsil ODS (5 mm, 200 × 4.6 mm). The mobile phase was methanol: water: phosphoric acid: triethylamine (50: 50: 0.1: 0.1, v/v) with a flow rate of 1 mL/min. The column temperature was kept at 40 °C and the wavelength was 288 nm.

2.5. In vitro skin permeation study

Skin permeation experiments were performed according to the method of Xi et al. (2012). The permeability study was performed with horizontal diffusion cell. The patch was adhered on stratum corneum of skin. The cell was fixed with a clip and put into the multi-functional transdermal diffusion instrument at 32 °C. PBS (pH 7.4) was used as the acceptor fluid to ensure sink conditions. The receptor fluid was stirred using a magnetic bar at 600 rpm. Acceptor solution (2.0 mL) has been sampled after 2, 4, 6, 8, 10, 12, 24 h of incubation and then replaced with an equal volume of fresh medium. The quantitative measurement of drug was same as the Section 2.4.

2.6. Pharmacokinetic study and IVIVC

Male Wistar rats (200 ± 10 g) were used for pharmacokinetic study. The abdominal hair was removed using an electric clipper. After 1 week, a total of 24 male Wistar rats were randomly divided into 4 groups for transdermal pharmacokinetics study of representative PSA-1, PSA-3 and PSA-5 and drug intravenous injection study. The patch (80 cm^2) were applied to the shaven dorsal skin with an overlay using gauze and removed 24 h later and propranolol (5 mg/kg) was used for intravenous injection.