Design and Evaluation of a Monolithic Drug-in-Adhesive Patch for Testosterone Based on Styrene–Isoprene–Styrene Block Copolymer

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ABSTRACT: The purpose of the present study was to design and evaluate a monolithic drug-in-adhesive patch with a novel pressure-sensitive adhesive (PSA) matrix based on styrene–isoprene-styrene (SIS) block copolymer. Testosterone was selected as the model drug. The orthogonal array design for ternary mixtures was employed to optimize the amounts of SIS, C-5 hydrocarbon resin, and liquid paraffin. The drug release percentage, water vapor permeability, adhesive properties were chosen as response variables. The patch formulation was optimized by investigating the effects of the drug loading capacity, the type, and amount of permeation enhancer on the adhesive properties and skin permeation. The compositions of the optimal matrix were: 120 g of SIS copolymer, 120 g of C-5 hydrocarbon resin, 60 g of liquid paraffin. An optimized formulation with maximum skin permeation and acceptable adhesive properties was developed incorporating 2% testosterone and 6% isopropyl myristate. No significant differences for *in vitro* release, skin permeation, and *in vivo* absorption were observed between the optimal formulation and Testopatch®. The stability evaluation showed that the patches were stable at 25°C/60% relative humidity for 6 months. The result indicated that SIS copolymer was a suitable and compatible polymer for the development of PSA. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2221–2234, 2013

Keywords: styrene–isoprene–styrene block copolymer; adhesive properties; pressure-sensitive adhesive; skin; transdermal drug delivery; permeability; pharmacokinetics; stability; testosterone

INTRODUCTION

The advantages of transdermal drug delivery system (TDDS) include the control of drug release, prolongation of steady-state plasma concentration with much less peak-and-trough variation, improving the safety and patient convenience. The drug-loaded adhesive patch in TDDS has attracted increasing attentions as an alternative delivery system. The monolithic drug-in-adhesive (DIA) matrix-type patches, which comprise a nonpermeable backing, an adhesive matrix, and a removable release liner are the most popular because of the thin, small, flexible, and comfortable properties.[1] The patches are based on pressure-sensitive adhesives (PSAs) such as polyisobutylenes, polysiloxanes (silicones), and polyacrylate copolymers (acrylics).[2] The PSA matrix provides several functions including skin adhesion, drug reservoir in which drugs are dissolved or dispersed, controlling drug release, and governing the drugs partitioning into the stratum corneum (SC).[2] Hence, PSA is regarded as one of the most critical components in fabricating a patch. It is important to choose an ideal PSA that can provide adequate adhesion to skin, good formulation compatibility with drug and other excipients, biocompatibility with skin and long-term stability.

Styrene–isoprene–styrene (SIS) block copolymer is a thermoplastic elastomer composed of the soft polyisoprene phase and the rigid polystyrene phase. Because of the viscoelastic property of SIS, it has the

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potential for the preparation of PSA when combined with tackifying resin and plasticizer after blending and coating process. The tackifying resins such as C-5 hydrocarbon resin can provide good biocompatibility, mechanical strength, and viscosity as adhesive matrix materials. To compensate the high T_g of SIS, small molecular plasticizers such as liquid paraffin are introduced into the matrix to improve the peel strength. The chemical and physical properties of SIS-based PSAs such as adhesiveness,[3] morphological,[4] rheological,[5] as well as thermodynamic properties[6] have been extensively investigated. The adhesive and cohesive properties of SIS-based PSAs could provide sufficient attachment to the skin and enable a residue-free removal after the intended wearing period.

Generally, the SIS-based PSAs are prepared and casted by hot melt or solution method.[7,8] As for solution method, the residual organic solvents in matrix may alter the properties including adhesive performance, drug release, and skin compatibility.[2] The hot melt process that can avoid skin irritation, drug stability problems, and nonvolatile impurities is becoming popular for the development of hot melt pressure-sensitive adhesive (HMPSA).[9–12] The PSAs are solid at room temperature and become liquid when heated to a relatively low temperature.[13] SIS-based HMPSAs are solvent-free, environmental friendly, and can be produced on a large industrial scale.[14] However, the applications of SIS-based HMPSAs in TDDS are rarely reported.

Drugs with low solubility could readily form crystals in PSAs, cause skin irritation, and decrease the skin permeation and adhesive force.[1] Additionally, the interactions between the functional groups of PSAs and drugs lead to the decrease of cumulative drug release and skin permeation.[15] However, SIS-based PSAs rarely interact with drugs due to the hydrocarbon nature and the lack of polar functional groups.[15] SIS-based PSAs perform excellent drug loading capacity and self crystallization inhibition effects, provide consistent and effective drug delivery to skin, especially for hydrophobic drugs with low permeability. Hence, testosterone (TS) was chosen as the model drug.

Testosterone is an androgen in the human body and used for male hypogonadism caused by the decrease in TS plasma concentration clinically. Various dosage forms of TS have been developed, including oral administration, intramuscular injections, and transdermal formulations. The transdermal preparations are considered to be safer and more effective than the conventional forms because they can avoid the first-pass metabolism in the liver and the wide fluctuations. Currently, transdermal systems such as gel (Fortesta™ or AndroGel®), spray (Axiron®), reservoir-type patch (Androderm®), and matrix-type patch (Testopatch®) are commercially available internationally. The monolithic DIA matrix-type patches are preferred in terms of patient compliance, production, manufacturing cost, and practical usability.[2]

Accordingly, the present study was designed to formulate a monolithic DIA matrix-type patch containing TS with SIS-based HMPSA for transdermal application. The experimental parameters were a composition of the matrix (including the amounts of SIS, C-5 hydrocarbon resin, and liquid paraffin), drug concentration and skin penetration enhancers. The formulation optimization of PSA matrix was conducted based on the L_9 orthogonal array design. The effects of drug loading capacity and penetration enhancers were studied. The formulations were evaluated by differential scanning calorimetry (DSC) for the compatibility between the drug and PSA. The adhesive properties and *in vitro* skin permeation of different formulations were characterized to optimize the formulation. For *in vivo* studies, the pharmacokinetics was evaluated by comparing the pharmacokinetic parameters of the optimal formulation with that of the commercial product, Testopatch®.

MATERIALS AND METHODS

Materials

SIS D1161 polymers were supplied by Kraton Polymers Trading Company Ltd. (Shanghai, China). The C-5 hydrocarbon resins as the tackifying resin were purchased from Nanjing Yangzi Eastman Chemical Company Ltd. (Nanjing, China). The pharmaceutical grade liquid paraffin as the plasticizer was purchased from Nanchang Baiyun Pharmaceutical Company Ltd. (Nanchang, China). Antioxidant 1010 as the thermal stabilizer was obtained from JiYi Chemical Company Ltd. (Beijing, China). Chp 2010 grade TS was kindly supplied by Zizhu Pharmaceutical Company Ltd. (Beijing, China) as gifts. Azone (AZO), isopropyl myristate (IPM), propylene glycol (PG), oleic acid (OA), lauryl lactate (LA), glyceryl triacetate (TA), 1-menthol (MEN), poly(ethylene glycol) (PEG) 200, and other chromatography grade solvents were purchased from Merck Chemicals Company Ltd. (Shanghai, China). N-methyl-2-pyrrolidone (NMP) was supplied by International Specialty Products Company Ltd. (Shanghai, China). All other organic solvents were of analytical grade or higher and used without further purification.

Release liner antistickiness film (silicone-coated polyethylene terephthalate film, thickness: 50 μm, YiDong Company, Shanghai, China) and backing layer nonwoven fabrics (thickness: 200 μm, medical grade, YiDong Company) were gifted from National Engineering Research Center for Traditional Chinese Medicine of China.