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Cold flow of estradiol transdermal systems: Influence of drug loss on the *in vitro* flux and drug transfer across human epidermis

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ABSTRACT

The objective was to quantify drug loss due to cold flow (CF) in marketed estradiol transdermal drug delivery systems (TDDS), and study its influence on the *in vitro* flux and drug transfer across contacting skin. TDDS samples (products-*A* and *B*) were induced with CF at 25 and 32 °C/60% RH by applying 1-kg force for 72 h. CF was measured as percent dimensional change and amount of drug loss/migration in CF region. *In vitro* drug permeation studies were conducted across human epidermis from TDDS excluding CF region, and CF region alone against control (without CF). In both products, significantly higher percentage of CF (dimensional change and drug migration) was observed at 32 °C compared to 25 °C. *In vitro* flux from both products excluding CF region either at 25 or 32 °C was the same, but significantly lower compared to control. Drug transferred from CF region of product-*A* after 8 h was the same at 25 and 32 °C, but significantly higher in product-*B*. Flux from both products together with CF region at 32 °C was significantly lower than that observed at 25 °C. Results showed that excessive CF at storage (25 °C) and clinical usage (32 °C) conditions may have implications on product performance and safety of estradiol TDDS.

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1. Introduction

A phenomenon called "cold flow" (CF) analogous to drug leakage from the edge of membrane-controlled transdermal drug delivery systems (TDDS) is one of the product quality defects (Cilurzo et al., 2012; EMA, 2012) associated with drug-in-adhesive (DIA) type of TDDS. The liquid excipient(s) and drug(s) plasticize pressure-sensitive adhesives (PSA) of DIA-TDDS to varying degree depending on their physicochemical properties and composition (Cilurzo et al., 2012). Imbalance in the degree of PSA plasticization may result in oozing out (creeping) of DIA from under the backing membrane beyond the edge of TDDS (cold flow) leading to storage problems, adhesion failures and formation of dark ring on application to skin (Van Buskirk et al., 2012).

The dried drug-in-adhesive PSA formulations are evaluated for the tendency of cold flow during pharmaceutical product development (Benedek, 2004). As there were no standard methods for the evaluation of cold flow in DIA-TDDS, a simple method has been developed (Krishnaiah et al., 2014). Cold flow has been induced at accelerated testing conditions (25, 32 and 40 °C) with punched-out TDDS samples (*e.g.*, 1 cm^2) loaded with 1-kg force for 3 days. The dimensional change in punched-out TDDS samples was measured using a stereomicroscopic imaging technique and expressed as percent of cold flow. Study results suggested that this is a potential method to evaluate (i) the possibility of dark ring formation on multiday application to patient skin by inducing CF at 32 °C, and (ii) possible effect of cold flow on long-term storage and usage problems related to unwinding of DIA coated rolls during production and removal of DIA-TDDS from pouch by inducing CF at 25 °C. In both cases, quantification of drug migration/loss into the cold flow region of DIA-TDDS is important to evaluate its impact on storage and usage problems. For example the loss of drug due to cold flow may decrease the drug flux across the skin due to decreased thermodynamic activity (Allen et al., 2005). The increased dimension in TDDS due to CF may alter the contact area between the drug-loaded matrix and the skin affecting the therapeutic effectiveness of the DIA-TDDS (Gutschke et al., 2010; Schulz et al., 2010; Van Buskirk et al., 2012). Furthermore, the dark ring formed on patient skin due to cold flow may increase the risk of drug transfer from patients to non-patients (Woolf et al., 1997; Yerasi et al., 1997). Therefore the present study was carried out to

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quantify drug loss to cold flow region of two marketed estradiol DIA-TDDS (model products with varying formulation designs) exposed to accelerated testing conditions simulating storage (25 °C) and clinical usage (32 °C). *In vitro* skin permeation studies were also carried out across human epidermis to determine the influence of cold flow on drug flux and potential of drug transfer *via* inter-personal contact.

2. Materials and methods

2.1. Materials

Estradiol transdermal systems were purchased from M/s Bradley Drugs (Bethesda, MD, USA). Estradiol USP reference standard was obtained from US Pharmacopeial Convention (Rockville, MD, USA). ScotchPak® 9744 (Fluoropolymer Coated Polyester Film Release Liner) and CoTran® 9720 (Polyethylene backing membrane) were purchased from M/s 3M Drug Delivery Systems Division (St. Paul, MN, USA). Acetonitrile (HPLC grade) and methanol (HPLC grade) were obtained from Fischer Scientific (Pittsburgh, PA, USA). Nylon membrane filters (0.22 μm) were purchased from Millipore Corporation (Bedford, MA, USA). Deionized water was supplied in house by a Millipore Milli-Q System (Bedford, MA, USA).

2.2. Induction of cold flow in estradiol TDDS

Two products (Product-*A* and *B*) of drug-in-adhesive type of estradiol TDDS with labeled *in vivo* delivery rate of 0.1 mg/24 h, used for hormone replacement therapy, were obtained from the market. Each of the products from the same lot number was used in the present study. Circular samples with 11 mm diameter were punched out using a Swing Arm Sample Die Cutter (Model DC-500, ChemInstruments, Fairfield, OH, USA) fitted with a cutting die (circle shaped nominal diameter 11.00 ± 0.13 mm; Fremont Cutting Dies, Inc., Fremont, OH, USA).

For each of the products (Products-*A* and *B*), 25 samples were punched out and used in the study. The release liner of the punched-out sample of estradiol TDDS was peeled off, and the adhesive-coated side of TDDS applied at the center of a fluoropolymer-coated polyester release liner film (approx. size of 6 cm × 6 cm; ScotchPak® 9744) without wrinkles. The sample was then covered with equal sized polyethylene backing membrane (CoTran® 9720). All the samples were subjected to cold flow induction at 25 °C/60% RH (simulating to shelf-storage temperature) and 32 °C/60% RH (simulating to skin temperature) by applying 1-kg force (1-kg Class F Stainless Steel Weight; Scales Galore, Brooklyn, NY, USA) for 3 days. At the end of 3 days, samples were removed from the chambers, and quantified for cold flow response by (a) stereomicroscopic imaging and (b) determination of estradiol concentration in cold flow region. Cold flow samples were also subjected to *in vitro* drug permeation studies across human epidermis to find the flux against control (TDDS samples without cold flow). Furthermore, the amount of drug transfer from the cold flow region of TDDS samples was also determined.

2.3. Quantification of cold flow as percent dimensional change

At the end of the cold flow induction period, the stainless steel weights were removed from the surface of all samples. Samples sandwiched between the release liner film (ScotchPak® 9744) and the backing membrane (CoTran® 9720) were subjected to stereomicroscopic imaging to quantify the degree of cold flow as described in previous report (Krishnaiah et al., 2014). Briefly, sandwiched sample was placed on the stage of a stereomicroscope (SMZ-745 T Zoom Stereo Photo Microscope, Nikon Instruments Corporation, Melville, NY, USA) with the backing membrane facing the object lens. The sample was zoomed initially to 5x and focused to see the clear edge of the TDDS sample using episcopic illumination source from light-emitting diode (LED) lamp attached to stereomicroscope stand, if necessary. The sample was then zoomed to 0.67x to see the entire DIA-TDDS punched-out sample with cold flow region under a large field view. After a fine focus of TDDS sample from the eyepiece with 0.67x zooming, the optical path switching lever was then switched over to the digital camera for monitoring and digital imaging of TDDS samples with induced cold flow. The image was captured, saved and analyzed using an image acquisition and analysis software (NIS Elements Advanced Research software Version 4.12.01, 1991–2013; Nikon Instruments Corporation, Melville, NY, USA). The region of interest (ROI) around the perimeter of the TDDS sample was marked with *n*-point circle (ROI-1) tool, and ROI along the cold flow region (ROI-2) marked with either autodetection mode or polygon mode. The area of ROI-1 measured the area of the circular TDDS sample along its perimeter only, and that of ROI-2 measured the area of circular TDDS sample along with cold flow region. The difference in the areas of ROI-1 and ROI-2 gave the dimensional change in the area of circular TDDS sample due to cold flow. The ratio of change in dimensional area of TDDS sample due to cold flow to that of TDDS sample without cold flow was calculated, and expressed as percent of cold flow.

2.4. HPLC analysis of estradiol

An Agilent 1200–4 series high-performance liquid chromatography (HPLC) system equipped with binary solvent pump, autosampler, photodiode array detector, thermostated column compartment and Chemstation chromatographic software was used for estimating concentration of estradiol. The methods described elsewhere in the literature were used with a few modifications (Havlikova et al., 2006; Medendorp et al., 2007). Waters X-Select™ C18 column (3.5 μm, 4.6 × 150 mm) maintained at 35 °C was used to elute estradiol. The mobile phase used was an isocratic mixture of acetonitrile, methanol and water in the ratio of 45:5:50. The flow rate was 0.8 ml/min. Standard solutions (100 μl) of estradiol containing 0.05 to 10 μg/ml were injected into the HPLC column, and the eluting estradiol solutions were detected at 225 nm. The peak areas were obtained and subjected to regression analysis. A good linear relationship was observed between the peak area of estradiol standard solutions and their concentration with a high correlation coefficient ($r = 1.0$). The HPLC analytical method was validated according to USP Validation of Compendial Methods (USP36-NF31, 2013a). The method was precise (intra- and inter-day variation was <1.0%) and accurate (mean recovery 99.8%). The standard curve, constructed as described above, was used for determining the estradiol quantity in the samples of drug assay and cold flow studies.

2.5. Assay of estradiol in TDDS products

Circular samples (0.95 cm^2) of estradiol TDDS (products-*A* and *B*) were punched-out ($n = 12$) using a cutting die (11 mm in diameter) and assayed for determining the estradiol quantity. The TDDS sample was added to a polypropylene conical tube (Becton Dickinson Labware, Franklin Lanes, NJ, USA) containing 50 ml of solvent (acetonitrile, methanol and water in the ratio of 45:5:50), screw-capped and sonicated in a bath sonicator (Branson 8210, Branson Ultrasonics, Danbury, CT, USA) for 99 min at 35 °C. At the end of the sonication cycle, samples were withdrawn, filtered through syringe filter (0.22 μm) and injected into HPLC for determining the concentration of estradiol. The values of estradiol concentration were used to calculate the estradiol quantity in

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