Stereomicroscopic Imaging Technique for the Quantification of Cold Flow in Drug-in-Adhesive Type of Transdermal Drug Delivery Systems

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ABSTRACT: Cold flow is a phenomenon occurring in drug-in-adhesive type of transdermal drug delivery systems (DIA-TDDS) because of the migration of DIA coat beyond the edge. Excessive cold flow can affect their therapeutic effectiveness, make removal of DIA-TDDS difficult from the pouch, and potentially decrease available dose if any drug remains adhered to pouch. There are no compendial or noncompendial methods available for quantification of this critical quality attribute. The objective was to develop a method for quantification of cold flow using stereomicroscopic imaging technique. Cold flow was induced by applying 1 kg force on punched-out samples of marketed estradiol DIA-TDDS (model product) stored at 25°C, 32°C, and 40°C/60% relative humidity (RH) for 1, 2, or 3 days. At the end of testing period, dimensional change in the area of DIA-TDDS samples was measured using image analysis software, and expressed as percent of cold flow. The percent of cold flow significantly decreased ($p < 0.001$) with increase in size of punched-out DIA-TDDS samples and increased ($p < 0.001$) with increase in cold flow induction temperature and time. This first ever report suggests that dimensional change in the area of punched-out samples stored at 32°C/60%RH for 2 days applied with 1 kg force could be used for quantification of cold flow in DIA-TDDS.
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INTRODUCTION

Many of the adverse events associated with transdermal drug delivery systems (TDDS) are attributed to adhesion/cohesion failures such as poor skin adhesion, drug leakage from reservoir type TDDS, and excessive cold flow occurring in drug-in-adhesive type TDDS (DIA-TDDS).[1] For example, TDDS lift reduces contact area of skin, and thereby reduces dose delivered to patient.[2,3] The scientists from American Association of Pharmaceutical Scientists, United States Food and Drug Administration (US FDA), and United States Pharmacopeia (USP) conducted several meetings and workshops, and recently published a white paper for the benefit of those in the industry involved in the development of such products in presenting comprehensive chemistry, manufacturing, and controls information to the USA and international regulatory bodies involved in the review of the TDDS dossier.[3] This white paper has emphasized the importance of developing new tools in testing and control of TDDS. In this context, the US FDA has published a guidance document on residual drug in TDDS at the end of labeled period of application[4] because of its high potential to impact the product quality, safety, and efficacy.

Cold flow resulting from adhesive oozing out from under the backing beyond the edge of DIA-TDDS forms a dark ring on application to the skin. The dark ring is formed because of the mix of adhesive with lint and dust. It is not only a cosmetic blemish, but may also alter the contact area between the drug-loaded matrix and the skin, affecting the therapeutic effectiveness of the DIA-TDDS[3,5,6] as well as increasing the risk of drug transfer from patients to nonpatients.[7,8] It can also lead to DIA-TDDS adhering to the inside of the pouch (primary container) making its removal and application difficult, and potentially decreasing the available dose if any drug remains adhered to the pouch. Thus, cold flow is considered as one of the critical quality attributes for product quality, efficacy, and safety of TDDS.[1,3,5,9] The recently published USP and white paper on TDDS have highlighted the importance of cold flow in transdermal drug products.[3,10] There have been neither compendial nor noncompendial methods published in the literature for quantifying this critical quality attribute, that is, cold flow of DIA-TDDS. In the light of this information, studies were carried out to develop a method for quantification of cold flow in DIA-TDDS. In this first ever report, dimensional change in the area of a sample punched out of the DIA-TDDS after inducing cold flow was measured using a stereomicroscopic imaging technique. This research paper describes the suggested testing conditions of the method developed for the quantification of cold flow in DIA-TDDS.

MATERIALS AND METHODS

Materials

Estradiol transdermal systems, ScotchPak® 9744 (Fluoropolymer Coated Polyester Film Release Liner), and extra thick microscope slides (3"X2") were purchased from M/s Bradley Drugs

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This scientific contribution is intended to support regulatory policy development. The views presented in this article have not been adopted as regulatory policies by the United States Food and Drug Administration at this time.

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(Bethesda, Maryland), M/s 3M Drug Delivery Systems Division (St. Paul, Minnesota), and Fisher Scientific (Pittsburgh, Pennsylvania), respectively.

Preparation of Punched-Out Samples of Estradiol TDDS

Drug-in-adhesive type of estradiol TDDS, obtained from the market (labeled *in vivo* delivery rate of 0.1 mg/24 h) with the same lot number, were used in the present study. Circle-shaped samples with selected diameters (11, 14.3, and 17.8 mm) were punched out using a Swing Arm Sample Die Cutter (Model DC-500; ChemInstruments, Fairfield, Ohio) fitted with cutting dies (circle shaped nominal diameter 11 ± 0.127, 14.3 ± 0.127, or 17.8 ± 0.127 mm; Fremont Cutting Dies, Inc., Fremont, Ohio). The estradiol TDDS with the release liner intact was placed on the lower platen cutting pad of the die cutter. The respective cutting die (circle shaped with diameter 11, 14.3, or 17.8 mm) was placed on estradiol TDDS and the upper platen was pressed down with the swing arm to punch out circular samples.

Induction of Cold Flow

A minimum of 10 samples punched out from 10 different estradiol TDDS were 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 stuck at the center of a clean extra thick microscope glass slide (3"X2") without wrinkles. A fluoropolymer-coated polyester release liner (ScotchPak® 9744) film with the coating-side down and in size approximately covering the glass slide was placed over the TDDS sample stuck on the glass slide. Cold flow was induced by placing a load of 1 kg force (1 kg Class F Stainless Steel Weight; Scales Galore, Brooklyn, New York) on the TDDS sample stuck onto the glass slide. In order to study the influence of temperature and time on the induction of cold flow, these samples were stored at 25°C/60% relative humidity (RH), 32°C/60%RH, and 40 °C/60%RH for 1, 2, or 3 days.

Quantification of Cold Flow Using Stereomicroscopic Imaging

At the end of cold flow induction period, the stainless steel weights were removed from the surface of the glass slides. The release liner sheet (ScotchPak® 9744) covering the glass slide was carefully peeled off to minimize the transfer of DIA migrated beyond the edge of TDDS sample due to cold flow. The degree of cold flow due to the migration of DIA beyond the edge of TDDS on the glass slide was quantified by stereomicroscopic imaging technique. The glass slide with the induced cold flow of DIA-TDDS sample was placed on the stage of a stereomicroscope (SMZ-745T Zoom Stereo Photo Microscope; Nikon Instruments Corporation, Melville, New York), zoomed initially to 5×, and focused to see the clear edge of TDDS sample, using episcopic illumination source of light-emitting diode (LED) lamp attached to stereomicroscope stand, if necessary. The sample was then zoomed to 0.67× to see the entire DIA-TDDS punched-out sample with cold flow region under a large field view. At this stage, the LED lamp was not used as the room light was sufficient to illuminate the sample under study. The stereomicroscope, used in this study, was attached with a digital camera (DS Fi2; Nikon Instruments Corporation) and incorporated an optical path-switching lever that enables easy switchover between eyepiece and camera. The digital camera was connected to a computer through a camera control unit (DS-U3; Nikon Instruments Corporation).

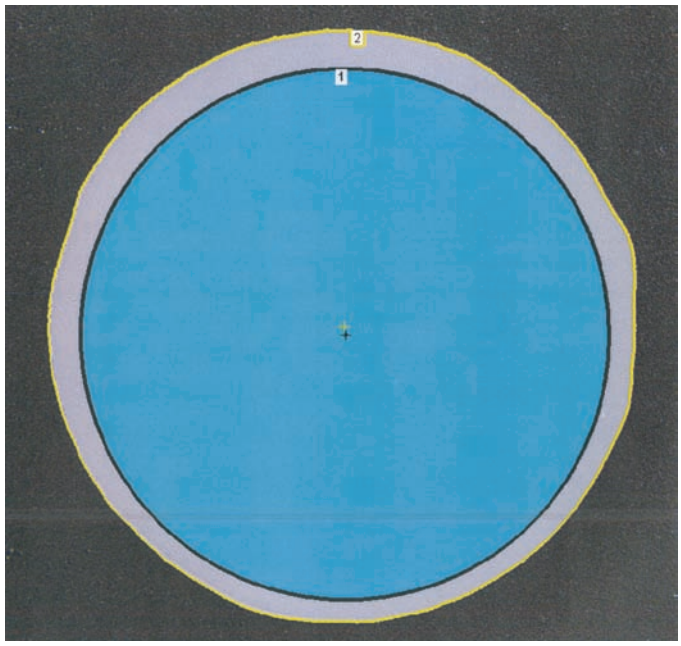

Figure 1. Image showing the area of (1) punched-out circular marketed estradiol DIA-TDDS sample without cold flow region and (2) punched out circular marketed estradiol DIA-TDDS sample with cold flow region (image surface of the TDDS sample was redacted to hide identification of the product).

After a fine focus of TDDS sample from the eyepiece with 0.67× 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). A representative captured image of DIA-TDDS punched-out sample with induced cold flow is shown in Figure 1 (surface of the TDDS was redacted to hide identification of the product). The region of interest (ROI) around the perimeter of the TDDS sample was marked with n-point circle (ROI-1), and ROI along the cold flow region (ROI-2) was marked with either autodetection mode or polygon mode. The area of ROI-1 measured the area of the circular TDDS sample up to the edge 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 (dimensional change in the area of circular TDDS sample due to cold flow) was the area of DIA migrated from under the bottom of backing membrane of TDDS due to cold flow. The ratio of change in dimension 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.

Statistical Analysis

The significance of the observed differences in the percent of cold flow of estradiol TDDS samples showing the effect of sample size and cold flow induction temperature after 1, 2, and 3 days of study (cold flow induction time) was tested by two way analysis of variance (ANOVA) (SigmaPlot for Windows Version 12.5; Systat Software, Inc., San Jose, CA, USA). Similarly, the significance of the observed differences in the percent of cold flow of estradiol TDDS samples showing the effect of cold flow