FDA Perspectives on Product Quality of Transdermal Drug Delivery Systems

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Disclaimer: Views expressed in this presentation are mine, and have not been adopted as regulatory policies by the Food and Drug Administration at this time.
Transdermal Drug Delivery Systems

- Provide continuous systemic drug delivery over the proposed wear period
- Avoid first-pass metabolism
- No dose dumping
- Unwanted effects can be terminated
- High patient compliance

Source: www.vivelledot.com
Increased number of TDDS- DIA type gaining popularity


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Some of the FDA approved TDDS

- Scopolamine (Scop®)
- Nitroglycerin (Nitro-Dur®)
- Testosterone (Androderm®)
- Estradiol (Climara®, Alora®, Vivel-Dot®)
- Estradiol/Norethindrone acetate (CombiPatch®)
- Estradiol/Levonorgestrel (Climara Pro®)
- Nicotine (Nicoderm®)
- Oxybutynin (Oxytrol®)
- Methylphenidate (Daytrana System®)
- Fentanyl (Duragesic®)
- Norelgestromin/Ethynyl Estradiol (Ortho Evra®)
- Selegeline (Emsam®)
Global sales for potent TDDS significantly high

Product Quality Defects of TDDS: Recalls and Warning Letters

- **Leakage** from reservoir systems
- E.g., fentanyl patches - led to Class I recalls
Adhesion failure modes
(Wokovich et al., EJPB, 64: 1-8, 2006)

Shire's Daytrana Patch Recall Is 8th So Far: Time to Pull the Plug?

Shire (SHEGY) has voluntarily recalled the Daytrana ADHD patch citing problems with patient removing the liner on the back. It is not a safety issue, the company says. Daytrana is for children with ADHD, it is the only patch product to treat the condition. "Sudden death" is one of the side effects of Daytrana, because ADHD products raise patients' blood pressure.
Adhesion lacking: Most widely reported Quality Defect of TDDS
(Source: FDA/Medwatch Reports)
Drug release faster than specified

Fentanyl Transdermal System Recall
Potential for Active Ingredient to Release Faster Than Specified

October 22, 2010

The Food and Drug Administration (FDA) notified healthcare professionals and patients that laboratory testing identified a patch in one lot of Fentanyl Transdermal System (Control/Lot # 30349) that released its active ingredient faster than the approved specification. An accelerated release of Fentanyl can lead to adverse events for at-risk patients, including excessive sedation, respiratory depression, hypoventilation (slow breathing), and apnea (temporary suspension of breathing). As a precautionary measure, in addition to the aforementioned lot, Actavis is recalling an additional 18 lots due to the possibility that additional patches may release Fentanyl more quickly than indicated.
Drug crystallization in TDDS

www.aan.com/neurologytoday

Crystallization in TDDS may lead to reduced flux, associated adhesion difficulties or other general product quality stability issues.
Drug-in-adhesive type of transdermal drug delivery systems (TDDS) associated product quality issues

Patients’ voice about that “sticky stuff’ and “permanent circles”

“Hated those patches, trying to remove the sticky stuff before adding new patches was the pits. There are still some of the circles from the patches on some of my clothes that I can't get out in the wash.”

“Yea the stickiness is ridiculous! I have permanent circles all over :)

“The patches ruined a pair of bed sheets for me! That sticky stuff was just impossible.”

“And if you have kids don't let them get ahold of them. Mine got into mine and stuck them all over their wall. I now have permanent circles all over. There is no washing those off, with out taking off the paint.”

TDDS Product quality issues

- Adhesion failures
- Leakage of reservoir-type TDDS
- Drug crystals on TDDS
- Excessive cold flow
- Variability in permeation (skin flux)
- Complex product designs/ manufacturing process (product and process variables)
- Warrants for understanding the scientific basis for product quality defects
Generic TDDS

• Demonstration of Bioequivalence (BE) requires establishment of:

(1) Pharmaceutical Equivalence (PE)-
  • Same active ingredient
  • Same dosage form
  • Same route of administration and same strength (designated as rate for TDDS)

(2) Comparable bioavailability (rate and extent of absorption)
Generic TDDS ….

• **To establish Therapeutic Equivalence (TE),** Generics
• (1) Must demonstrate PE and BE to the reference product
• (2) Must have adequate labeling and cGMP manufacturing
• (3) Generics rely on the safety and efficacy of the reference product
• Demonstrate for non-inferiority for adhesion, irritation and sensitization
• Minimal residual drug after labelled period of use (FDA guidance)
TDDS: Other Critical Quality considerations

- CQA of finished product - critical to quality and performance
- Maintain physical integrity during storage and application to skin
- Should be stable - no crystallization, no change in adhesion
- Potential for drug transfer where skin-to-skin contact with another person is possible
- Heat effects: Heat pad, electric blankets, sunbathing, heat or tanning lamps, sauna, hot tubs or hot baths
- Effect of sunscreen or moisturizing lotion on absorption
- Effect of showering and exercise
Development of Generic TDDS

• First step is to focus on Quality Target Product Profile (QTPP)/ Target Product Profile (TPP)-
  -Delivery rate, bioequivalence, stability, Critical Quality Attributes (CQA), labeling etc.
• Demands a thorough product and process understanding
• Several CMA/CPP impact the CQA
• Requires a scientifically-sound product development approach (e.g., QbD and DoE) along with a
  comprehensive control strategy (from starting to ending)
Guidance for Industry

• Residual drug in Transdermal and Related Drug Delivery System (August 2011, FDA)
• Estradiol TDDS (Draft, revised Sep 2015, FDA)
• Selegiline (final Oct 2011, FDA)
• Rivastigmine (Draft, revised Nov 2013, FDA)
• Scopolamine (Final, Oct 2011, FDA)
• Guideline on quality of transdermal patches (EMA, June 2015)
FDA Internal Research on cold flow of DIA-TDDS
Cold flow in Drug-in-adhesive type of TDDS

- Drug-in-adhesive oozes out from under the backing membrane beyond the edge of TDDS
Implications of excessive cold flow

• Can lead to TDDS adhering to inside of pouch
  → makes removal and application difficult
• Drug loss due to cold flow
  → decreases drug’s thermodynamic activity affecting delivery rate
• Increase in dimension
  → alters contact area between drug-loaded matrix & skin
  → affects therapeutic effectiveness
• Risk/ safety to patient
  → potential for continued drug absorption after TDDS removal
  → increase risk of drug transfer from patients to non-patients (e.g., highly potent Fentanyl TDDS)
Possible reasons for excessive cold flow

• Selection of PSA and other formulation ingredients is critical
• Dissolved drug/excipients in PSA influence PSA plasticization (cohesive/adhesive strength)
• Too high degree of PSA plasticization increases flow properties
• Too low degree of PSA plasticization may lead to loss of tack/peel properties
• DIA-TDDS formulations are to be designed with balanced adhesive and cohesive properties
• Balance in the degree of PSA plasticization (or low creep compliance) to prevent excessive cold flow
There are no compendial or non-compendial methods for quantification of cold flow in TDDS
To develop a method for quantification of cold flow

To quantify drug loss in cold flow region

To determine the influence of cold flow on drug flux and potential of drug transfer via interpersonal contact

Estradiol TDDS (used in HRT) selected as model drug product
Approach for cold flow quantification in DIA-TDDS

- May take long time to observe CF immediately after releasing the batch with well-designed TDDS products.
- CF may occur faster when DIA-TDDS are improperly exposed to high temperatures.
- Adopted test methods described for assessing CF resistance of bulk dry PSA.
- CF induced at accelerated conditions (by application of 1-kg force on punched out circular sample stuck to a glass slide stored at selected temperatures (e.g., 32 °C/60%RH) for 1-3 days.


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.


Keywords: transdermal; skin; drug delivery systems; microscopy; cold flow; stereomicroscopic; method development; imaging; drug-in-adhesive; physical characterization


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Quantification of cold flow

- Marketed estradiol TDDS (used in HRT) chosen as a model drug product
- Cold flow induced at accelerated testing conditions (25, 32 and 40 °C) with punched-out TDDS samples (e.g., 1 cm²) loaded with 1-kg force for 3 days.
- Measured as percent dimensional change in area
- Also measured as percent drug loss/migration to cold flow region of TDDS
Induction and Evaluation of Cold Flow in TDDS

[TDDS](http://www.unitronusa.com/products/stereo-microscopes/z850-photos-and-description)

**Cold Flow Induction**

(Top) Release liner-1

TDDS

Release liner-2 (bottom)

**Stereomicroscope Imaging**

Before

T., RH., Time

After

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Effect of **sample diameter** and **induction temperature** on cold flow development in circular estradiol DIA-TDDS

- *Percent of CF*
  - Decreases with increase of sample diameter
  - Increases as induction temperature increases

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**Percent of CF**

Effect of **sample diameter, induction time and temperature** on cold flow development in circular estradiol DIA-TDDS

<table>
<thead>
<tr>
<th>Sample Diameter (mm)</th>
<th>Percent of Cold Flow in Samples Stored at</th>
<th>25°C/60% RH</th>
<th>32°C/60% RH</th>
<th>40°C/60% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1-day</td>
<td>7.9 ± 1.4\textsuperscript{a}</td>
<td>12.8 ± 2.0\textsuperscript{b}</td>
<td>39.4 ± 5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0 ± 0.6\textsuperscript{c,d}</td>
<td>5.6 ± 0.8\textsuperscript{c,b}</td>
<td>12.8 ± 2.1\textsuperscript{c}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3 ± 0.3\textsuperscript{e,g,f}</td>
<td>3.7 ± 0.5\textsuperscript{c,g,b}</td>
<td>7.5 ± 0.5\textsuperscript{c,e}</td>
</tr>
<tr>
<td>14.3</td>
<td>2-day</td>
<td>9.9 ± 1.5\textsuperscript{a}</td>
<td>27.3 ± 6.8\textsuperscript{b}</td>
<td>61.4 ± 3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.9 ± 0.9\textsuperscript{c,a}</td>
<td>10.0 ± 1.2\textsuperscript{c,b}</td>
<td>19.8 ± 1.5\textsuperscript{c}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8 ± 0.3\textsuperscript{c,d,e}</td>
<td>6.3 ± 1.3\textsuperscript{c,f,g}</td>
<td>11.2 ± 1.7\textsuperscript{c,h,i}</td>
</tr>
<tr>
<td>17.8</td>
<td>3-day</td>
<td>13.2 ± 1.8\textsuperscript{a}</td>
<td>35.9 ± 5.8\textsuperscript{b}</td>
<td>60.8 ± 3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.3 ± 0.4\textsuperscript{c,a}</td>
<td>11.5 ± 2.6\textsuperscript{c,d,b}</td>
<td>25.2 ± 2.2\textsuperscript{c,d}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2 ± 0.5\textsuperscript{c,e,a}</td>
<td>7.4 ± 1.1\textsuperscript{c,b}</td>
<td>13.1 ± 0.8\textsuperscript{c}</td>
</tr>
</tbody>
</table>

**Conclusions:** Percent of CF

- Decreases with increase of sample diameter
- Increases as induction temperature increases
- Increases as induction time prolongs

Excessive CF alters contact area and drug concentration in TDDS

Punched-out circular samples loaded with 1-kg force and stored at 25°C/60%RH or 32°C/60%RH for 3 days

(Image surface of product-B was redacted to hide product identification)

<table>
<thead>
<tr>
<th>Cold flow measured as</th>
<th>Measurement method</th>
<th>Samples stored at</th>
<th>Product-A (86 µg/cm²)</th>
<th>Product-B (156 µg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent dimensional change in area</td>
<td>Spectroscopic Imaging</td>
<td>25°C/60%RH for 3 days</td>
<td>14.4 ± 2.5</td>
<td>6.5 ± 0.8**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32°C/60%RH for 3 days</td>
<td>32.0 ± 2.9##</td>
<td>39.1 ± 3.6##</td>
</tr>
<tr>
<td>Percent drug migration to CF region</td>
<td>HPLC</td>
<td>25°C/60%RH for 3 days</td>
<td>15.8 ± 3.2</td>
<td>8.8 ± 2.0**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32°C/60%RH for 3 days</td>
<td>32.6 ± 3.4##</td>
<td>41.9 ± 3.1##</td>
</tr>
</tbody>
</table>

**: Significant at P<0.01 when % dimensional change is compared to that of product-A

##: p<0.001 when compared to samples at 25°C/60%RH

Cold flow measurement tool

- Can be useful in selecting the best adhesive, excipient, drug substance ratios and formulations.
- Can assist in developing the appropriate product quality control method and potentially justifying acceptance criterion for cold flow
- Understanding the long term cold flow characteristics specific to each product is necessary to establish a quality product
- Cold flow should be included in stability protocol along with results at the time of submission for both ANDA and NDAs.
- Refer to *USP <Chapter 3> Topical and Transdermal Drug Products- Product Quality Tests*
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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Cold flow induction method for drug loss/ drug transfer studies

![Diagram of TDDS device with labels:](image)

- **11 mm TDDS w/ CF**
- **Punched-out 11 mm TDDS**
- **CF**

![Diagram of TDDS device with labels:](image)

- **Glass disk**
- **Dosage donor area**
- **Dosage wafer**
- **Sampling port**
- **Skin**
- **Water jacket**
- **Receptor solution**
- **Replace port w/ bubble trap**
- **Helix mixer & magnetic Stirrer**

**Hanson Vertical Diffusion Cells**

**Release liner-1**

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Automatic Franz Diffusion Cell System for in vitro drug permeation study

- **Source:** Cooperative Human Tissue Network (CHTN, Charlottesville, VA).
- **Type:** Surgically discarded human skin (after abdominoplasty) of living female subjects (age 20-55 years)
- **Sample:** Heat-separated human epidermis
- **Protocol:** Research Involving Human Subjects Committee (RIHSC #12-015-D)
Cold flow reduced drug flux


Mean (±S.D.) amount of drug permeated from estradiol TDDS product-A and product-B samples before cold flow induction (control) and after cold flow induction at 25°C and 32°C (excluding cold flow region) across human epidermis (n=6)
Cold flow also reduced the overall drug flux

Mean (±S.D.) amount of drug permeated from estradiol TDDS along with cold flow region of product-A and product-B samples induced with cold flow at 25°C and 32°C across human epidermis (n=6)

Drug transfer due to CF is far higher than that due to DRE after labeled period of use

Mean (±S.D.) *in vitro* amount of drug transferred from drug-containing human epidermis (DRE) pretreated with application of estradiol TDDS (Product-B) to the contacting human epidermis (n=6) at A) 8 h, B) 16 h and C) 24 h. The amount of drug transferred from cold flow (CF) region of estradiol TDDS (Products-B) across human epidermis at A) 8 h, B) 12 h and C) 24 h were also presented for comparison (n=6). CF was induced at 25 and 32 °C/60% RH for 3 days.  

_JrishiSah YSR, Yang Y, Khan MA (2014) / FDA internal data_
Conclusions

• Percent of cold flow (CF) decreased with increase of sample diameter
• Increased with increase in induction temperature
• Increased as induction time prolonged, but not beyond 3 days
• The method can be applied to discriminate differences in formulation designs of TDDS products
• *In vitro* skin permeation study showed that excessive cold flow decreased delivery rate of estradiol TDDS
• Drug transfer occurred from cold flow region of TDDS products
Further reading on various methods for cold flow

- Evaluated marketed TDDS for cold flow using wiping method, macroscopic observations and microscopic method (qualitative)

- Variable outcome in the three methods demonstrated the importance of understanding scientific product development throughout the TDDS lifecycle

Studies in Progress

• Understanding the scientific basis for excessive cold flow
• Development of science-based quality standards for cold flow in TDDS
• Model development for prediction of cold flow occurrence based on Rheology and real time CF measurement data
• Hyperspectral imaging for measurement of CF in TDDS at real-time storage conditions (i.e., without inducing cold flow)
• Hyperspectral imaging as a Process Analytical Tool (PAT) in the manufacture of TDDS
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