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

U.S. Food and Drug Administration

**Purpose**

Cold flow (CF) is a phenomenon occurs widely in drug-in-adhesive type of transdermal drug delivery systems (DIA-TDDS) due to migration of drug-in-adhesive coat beyond the edge. Excessive CF can affect their therapeutic effectiveness, make removal of TDDS difficult from the pouch and potentially decrease available dose if any drug remains adhered to pouch. The objective was to develop a method for quantification of CF in the absence of compendial/non-compendial method for this critical quality attribute.

**Methods**

CF was induced by applying 1-kg force on punched-out samples (11, 14.3 and 17.8 mm in diameter) of marketed estradiol DIA-TDDS (model products) stored at 25, 32 and 40°C/60%RH for 1, 2 or 3 days. At the end of testing period, CF samples were imaged using stereomicroscope, and the area of TDDS alone and TDDS with CF region was measured using image analysis software. CF was expressed as percent dimensional change. To find the relevance of this method, drug migration/drug loss in CF region of samples induced at 25/32°C was measured by HPLC.

**Results**

The percent of CF significantly decreased (P<0.001) with increase in size of punched-out TDDS samples (Fig. 1 and 2), suggesting that CF is more likely to happen in DIA-TDDS products with smaller sizes. It increased significantly (P<0.001) with increase in CF induction temperature (Fig. 1 and 2) and time (Fig. 3). Since 32 and 40°C/60%RH reflect skin surface and bathroom storage temperatures, respectively, this indicates longer wearing or storage at such conditions will result in greater CF. Drug migration to CF region of samples induced at 32°C was higher compared to those induced at 25°C (shelf storage), the values of which are consistent with dimensional change, indicating the relevance of CF quantification methods.

**Conclusion**

This systemic study suggests that dimensional change in the punched-out samples (11 mm in diameter) stored at 32°C/60%RH for 3 days applied with 1-kg force could be used for quantification of CF in DIA-TDDS.