On the surface...

Tony Copley, Copley Scientific, outlines testing strategies for topical semi-solids

Model answer: Vertical diffusion cell test system model HDT 1000 from Copley Scientific

The skin is an important and commonly used route of administration for pharmaceutical products, for both topical and systemic action. Associated test methods are defined on the basis of the intended action, with new specifications being released for topical products as recently as 2013, in the form of United States Pharmacopeia (USP) Chapter <1724>. This article provides a brief introduction to transdermal and topical drug product testing and the associated regulatory landscape, focusing on methods for semisolids.

Using the skin for drug delivery

For certain drugs for systemic action, such as nicotine and hormones, the skin offers a delivery route with high patient acceptability that avoids first pass metabolism. The resulting transdermal systems or transdermal drug products are typically patches, of varying design, that release an active ingredient into the blood stream, over time.

Topical drug products are, in contrast, designed to treat a localised skin condition, and may be foams, sprays or aerosols, or semisolids; the focus of this article. Semisolids include creams, gels, ointments, pastes, suspensions and lotions. These topical drugs enable the delivery of high loadings of active ingredients, directly to the site of action, with a significantly reduced risk of any systemic impact.

The testing applied to transdermal and topical products reflects their different modes of action, and includes both product quality and product performance tests. Product quality tests assess general quality attributes, while product performance tests focus specifically on drug substance release, from the formulation matrix.

Regulatory guidance and compendial methods for semisolids

Until relatively recently there were no compendial methods specifically for semisolid testing but chapters are now in place for both product quality and product performance testing, USP Chapter <3> and USP Chapter <1724> respectively[1,2]. Product quality tests for semisolids include the measurement of apparent viscosity and product uniformity over the assigned shelf life. Performance testing involves the measurement of drug release rate, and three different apparatuses are specified: Vertical Diffusion (or Franz) Cell (VDC); Immersion Cell; and Flow-Through Cell (USP Apparatus 4). Food and Drug Administration (FDA) Guidance for "Non-sterile Semisolid Dosage Forms SUPAC-SS CMC 7"[3], which provides guidance for scale-up and post-approval changes, similarly references the Franz cell.

At the time of writing, the European Medicines Agency (EMA) does not offer specific guidance for semisolids and though transdermal products are covered in the European Pharmacopoeia (EP Chapter 2.9.4)[4], there is, as yet no equivalent chapter to USP <1724>.

The practicalities of drug release testing

As stated in USP <1724> semisolids performance testing is "conducted to assess drug release from manufactured pharmaceutical dosage forms." This includes measurement of the total amount of drug released as well as release rate. In practice drug release testing is achieved by placing a sample in contact with a reservoir of receptor medium and measuring the changing concentration of drug substance in the receptor medium, as a function of time.

The VDC is rapidly emerging as the apparatus of choice for this application, with three different cell designs referenced in USP <1724> (see figure 1).

Although better suited to automation, the double port arrangement employed on the Cell Type A design is widely acknowledged to be less than ideal from a practical perspective because of its propensity to cell leakage and/or back diffusion. The simpler design of Cell Types B and C, which have a single arm for sample withdrawal and media replacement largely eliminates these problems. These latter two cells differ only in terms of size, with Cell Type – C enabling higher volume testing.

All three cells essentially comprise of two main parts: the donor chamber which contains the sample, and the receptor chamber. These two parts are separated by a membrane which holds the sample in contact with the receptor medium. Testing is typically conducted over a period of six hours with samples taken at regular intervals and media levels subsequently topped up to maintain a full cell. Holding the receptor medium at 32°C mimics normal skin conditions.

The introduction of USP <1724> has focused attention on semisolids testing and equipment manufacturers have, in response, refreshed their offering to meet evolving needs. For example, the latest cells are designed for use with heating blocks, as oppose to being water-jacketed. This saves bench space and also eliminates the "spaghetti" of pipework associated with jacketed systems. Accessories such as the Vacuum Deaerating Apparatus Model VDA, from Copley Scientific, can also be helpful in routine testing, which requires a degassed receptor medium to avoid bubble collection beneath the membrane and a consequent reduction in diffusion rate.

In conclusion

The testing procedures and regulatory framework for drug products applied to the skin differs depending on whether they deliver topical or systemic treatments. The latest revisions to the USP provide welcome specifications for topical semisolid testing, to complement methods already in place for transdermal delivery systems. Associated equipment developments make it easier for drug developers to test semisolids efficiently, in line with the new specifications, supporting faster progress towards a successful submission.

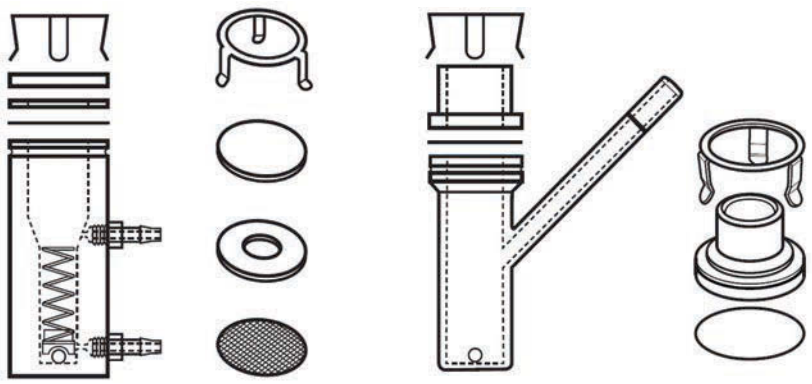

Figure 1: Line Drawings showing the construction of the VDCs described in USP <1724> as Model A (left) and Models B and C (right)

References:

1 USP37-NF32 Chapter <3> Topical and transdermal drug products – product quality tests.

2 USP38-NF33 Chapter <1724> Semisolid drug products – performance tests

3 FDA Guidance for Industry. Nonsterile Semisolid Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation.

4 Ph. Eur. 8th Edition, Chapter 2.9.4, Dissolution Test for Transdermal Patches.