Performance Testing for Topical and Transdermal Drug Delivery

The recent revision of US Pharmacopoeia (USP) Chapter <1724> brings clarity to the testing of semisolids - topical products for the relief of dermatological conditions - mirroring the framework already in place for transdermal drug products (TDPs). In this article we survey the regulatory framework for topical and transdermal drug delivery, focusing particularly on the in vitro tests specified for the performance testing for semisolids.

The skin is a commonly used route of administration for pharmaceutical products for both systemic and topical action. Systemic therapies are delivered via transdermal drug products (TDPs) which release an active ingredient through the skin into the bloodstream. TDPs have high patient acceptability, enable steady, controlled delivery over a prolonged period and offer the additional benefit of avoiding first-pass metabolism in the gastrointestinal tract, which can damage the efficacy of certain drugs. As a result TDPs - which are often patches - are commonly used for the sustained delivery of, for example, hormones and treatments for smoking cessation.

Topical products, in contrast, are intended for localized action and offer immediate relief for dermatological conditions. They are easy to use, have a high degree of patient acceptance and enable the delivery of relatively high concentrations of drug directly to the site of action, substantially reducing the risk of systemic exposure and any associated side effects. Topical formulations include foams, sprays or aerosols, but the majority can be classified as semisolids, a product grouping that encompasses gels, ointments, pastes, suspensions and lotions. These are often formulated to deliver a moisturizing effect, which can further enhance efficacy as well as offering immediate patient relief.

In vitro tests routinely applied to topical products and TDPs quantify both product quality and product performance. Product quality tests assess general physical attributes while product performance testing focuses specifically on release of the pharmacologically active drug substance from the formulation matrix. The specific tests for each product type are defined by their intended mode of action, and the compendial methods are therefore different in each case. Those for TDPs have been in place for some time and are well-established, but the test methods for semisolids are comparatively new.

A Revised Regulatory Landscape

USP Chapter <3> specifies product quality tests for both TDPs and topical products. For TDPs these include methods for assessing tack and adhesion, while for semisolids the measurement of apparent viscosity and product uniformity over the assigned shelf life is recommended. With regards to performance testing - measurements of the rate of drug release from a patch - TDPs are covered by USP Chapter <724>. The protocols used are closely similar to those applied for the dissolution testing of oral solid dosage forms with the release characteristics of the active substance tested via suitable dissolution method such as Paddle over Disk (Method 5) or Rotating Cylinder (Method 6).

For many years there were no compendial methods specifically for semisolid performance testing but this situation changed with the introduction of USP Chapter <1724>. Measurement of drug release rate, as well as the total amount of drug released, using one of three different apparatuses: Vertical Diffusion Cell (VDC); Immersion Cell; and/or Flow-Through Cell (USP Apparatus 4).

Semisolids are typically hydrocarbon-based systems or oil in water emulsions, incorporating additional ingredients such as emulsifiers, stabilizers, pH buffers and preservatives. The test methods and apparatuses specified are designed to produce meaningful and
relevant data for these physical forms and generate a release profile for the drug as a function of time. These products often have complex compositions and release mechanisms, making multi-point release essential for robust characterization. The resulting data enable the assessment of different formulations and shelf-life consistency, the evaluation of the impact of process changes, and quality control where they are routinely applied to test for batch-to-batch consistency.

Focusing on In Vitro Performance Testing for Semisolids

Of the three apparatuses specified in USP Chapter <1724>, the VDC is rapidly emerging as the preferred choice because of its simplicity and reproducibility, but the Immersion Cell also remains widely used. The Flow-Through Cell is the least routinely deployed of the three, and consequently not covered in detail in this article. It does, however, have certain claimed advantages when used in combination with an automatic fraction collector, especially for testing formulations with rapid permeation characteristics. Understanding how the two most popular apparatuses work aids choice and effective testing.

The Vertical Diffusion Cell

USP Chapter <1724> references three different designs of VDC, but in each case the basic principle of operation is the same; all three designs can be assembled with either an open or closed cell top (see Figure 1). A closed cell configuration is used for fixed volume testing, while an open cell enables larger/infinite volume measurements, or conversely, testing with just a minimal smear of product. An open configuration may be more suitable for less solid preparations such as certain gels and lotions.

In an open configuration, the sample is held in a donor chamber in the cell top, and separated from the receptor media by an artificial membrane (or skin). The cell top and membrane are then clipped to the main body of the cell as shown in Figure 2. A closed configuration is closely similar but consists of: a clear sample support disc, which occludes the sample during testing and prevents air ingress; a PTFE sample chamber ring of fixed volume in which the sample is initially placed; and the artificial membrane. This ‘sandwich’ is clipped on to the cell body as with an open configuration, so that the membrane is covered in the receptor medium (see Figure 2).

The receptor chamber of compendial Model A (see Figure 3, left) has two ports while those of Models B and C (Figure 3, right), have one. With the two port configuration sample is withdrawn from the upper port, during testing, by introducing replacement media into the lower port to displace the sample from the upper port. This design is well-suited to automation, but the upward pressure associated with ‘forcing’ the sample out of the upper port has a tendency to result in cell leakage and/or back diffusion in the sample holding assembly. The simpler design of Models B and C largely eliminates these problems and is increasingly preferred. These latter two cells differ only in terms of size, with Model C enabling higher volume testing where this is helpful because of the drug concentration/dosage form concerned.

Testing is typically conducted over a period of six hours. During this time, receptor medium samples are periodically removed via a side arm for analysis/assay, with fresh medium added to keep the sample constantly bathed in the receptor fluid. A magnetic stirring bar inserted into the cell ensures even temperature distribution and mixing of the cell contents. Test temperatures are normally 32°C, skin temperature, or 37°C for vaginal preparations. With a jacketed cell...
design, temperature is maintained using a water circulation system but a more modern, efficient approach is to use a compact heated block (see Figure 4) which simplifies the test set-up and eliminates the ‘spaghetti’ of tubing associated with water circulation. Data can be compromised by any air in the receptor medium collecting at the membrane interface and affecting diffusion so accessories that degas the receptor medium ahead of testing can also be helpful in improving the ease and accuracy of routine testing.

**Immersion Cell**

An Immersion Cell test set-up uses the conventional USP apparatus 2 for oral solid dosage dissolution testing with a smaller volume dissolution vessel; 200 mL rather than the 1 L used in standard testing. The Immersion Cell itself (as shown in Figure 5) consists of the cell body, the membrane, and a washer/retaining ring assembly to hold the membrane securely in contact with the sample. The sample is held within the cell body, a variable volume compartment that can be adjusted to meet testing requirements.

The testing process itself is carried out in an analogous way to testing with the VDC, over a comparable period of time. Once the sample has been loaded, the entire cell is immersed in receptor medium by placing it on the base of the dissolution vessel. Samples of receptor medium are then extracted periodically for assay to generate a release profile, with preheated, degassed medium added to maintain a constant volume in the dissolution vessel.

Maximizing the Relevance of Test Data

As with all *in vitro* testing there are limitations as to the extent to which the results of semisolids performance testing can fully capture and reflect product behavior. This is why such testing is generally complementary to, rather than a complete replacement for, bioavailability and/or clinical studies. However, there are steps that can be taken to enhance the relevance of testing and make the data as representative of *in vivo* performance as possible. Choosing test equipment and experimental conditions with careful consideration of the physiological conditions at the site of drug administration, and so as to ensure sufficient sensitivity to detect clinical significant difference is vital.

For example, an underlying premise of drug release testing is that it is carried out under ‘sink conditions’. The maintenance of ‘sink conditions’ requires that the concentration of drug dissolved in the receptor medium is kept at such a low level that it does not inhibit the diffusional process. This approach eliminates the confounding influence of localized drug build-up, which can be dependent on experimental set-up, but may require a modification to sample volume, or in extreme cases the apparatus used. Beyond this the two issues that require most consideration in semisolids testing are medium and membrane choice.

**Medium Choice**

Diffusion processes are influenced by the balance of intermolecular forces between the solvate and solute. This means that the properties/composition of the receptor medium can directly influence the dissolution characteristics of the drug molecule, from the semisoloid matrix. The following points provide some general guidance for receptor medium optimization:

- ‘Like dissolves like’ so choose a medium that is compatible with the chemical characteristics of the drug substance to achieve high drug solubility.
• Reflect the physiology of the skin: the pH of the medium is usually adjusted to lie in the range 5 – 6 for this reason.1
• Keep viscosity low to enhance the permeability of the membrane within the test set-up and reduce diffusional resistance.
• Choose a medium that does not impact the integrity of either the product or the membrane.

Membrane Choice
The membrane acts as a support for a sample but more specifically provides an in vitro representation of the skin. This may suggest natural/real skins as an ideal choice for testing but these can be subject to a high degree of variability, difficult to wet, and present safety and storage issues. Synthetic membranes are the alternative and there are many to choose from. Conventional options may be made from materials such as cellulose acetate, polycarbonate, nylon, polysulfone and Teflon, but newer test materials such as Strat-M can offer important advantages, delivering data that are highly predictive of in vivo diffusion while avoiding the limitations associated with real skin. When choosing a membrane it is important to select one that is:
• Chemically inert to both the receptor and the product
• Wets easily
• Has high permeability, such that the rate limiting process is diffusion of the drug product from the formulation, rather than through the membrane

Going Forward
The testing procedures and regulatory framework for drug products applied to the skin differs depending on whether they deliver topical or systemic therapies. The introduction of USP Chapter <1724> provides welcome specifications for topical semisolid testing, to complement methods already in place for TDPs. 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 and effective QC.

References
1. USP38-NF33 Chapter <1724> Semisolid drug products – performance tests
2. USP38-NF33 Chapter <3> Topical and transdermal drug products – product quality tests.
3. USP38-NF33 Chapter <724> Drug Release

For more information
Copley Scientific Limited
Tel: +44 (0)115 961 6229; Fax: +44 (0)115 961 7637
www.copleyscientific.com