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IVRT INSIGHTS FROM CMC EXPERTS OF FRONTAGE LABS

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Synopsis

Growing experience confirms the value of in vitro release test (IVRT) in the measurement of drug release properties in topical semisolid dosage forms. IVRT is increasingly used to profile drug performance characteristics in the development of both innovator and generic drug products. For generics, IVRT is fast becoming the standard method for comparison to a reference product. Recent Food and Drug Administration guidance offers an option to use IVRT data to demonstrate bioequivalence in some drug products rather than conduct long, costly clinical trials for a topical antiviral formulation; proposals are emerging to apply similar approaches to evaluation of other topical formulations. While clearly the way forward for topical semisolid dosage forms, IVRT programs are complex and demand specific expertise and operational components to succeed. This paper outlines IVRT methods and benefit, discusses key design considerations to ensure reliable results. A companion case study to illustrate IVRT method development.

Introduction

Topical semisolid dosage forms, which are normally presented in the form of ointments, creams, lotions, and gels, are widely used delivery systems for both systemic therapies delivered through the skin, and therapies that treat the skin itself. The measurement of active pharmaceutical ingredient (API) release—a critical assessment in drug development—is accomplished for solid formulations using dissolution testing. For semisolids, however, accurate, reliable measurement of drug release across the skin barrier is more problematic. Neither animal models nor mathematical simulations yield consistent, accurate predictions of dermal absorption or product performance in humans.[1]

Historically, a variety of physical and chemical tests such as solubility, particle size, viscosity, and form of active ingredient have been used to assure product performance for a semisolid dosage form. More recently, the development of the in vitro release test (IVRT) has provided a comprehensive, more direct means to assure product performance based on reliable and reproducible measurement of drug release from semisolid dosage forms.

IVRT is widely used to compare product performance as a function of the rate of release of the active ingredient. These studies typically are conducted using vertical diffusion cells (e.g., Franz Cells). Diffusion cell IVRT systems have demonstrated capability to detect altered product performance that may arise from changes in manufacturing locations, sources of excipients, or manufacturing processes that may cause a product to perform differently than a reference product. IVRT can also detect in vitro changes that may correspond to altered in vivo performance of the dosage form.

The U.S. Food and Drug Administration's 1997 Guidance on scale-up and post-approval changes for non-sterile semisolid dosage forms (SUPAC-SS) requires IVRT studies to demonstrate continuing product quality and performance characteristics related to specific changes in chemistry and manufacturing processes.[2] In generic product development, IVRT offers drug developers a potential alternative to costly and time-consuming clinical efficacy trials. In innovator drug development, IVRT is an invaluable screening tool to help identify an optimal formulation for use in clinical evaluation.

The utility and benefits of IVRT have been clearly established and applications continue to expand. But IVRT programs are complex and require specific expertise and operational components to generate reliable, reproducible results. This paper details IVRT methods pertaining to generic and innovator products and discusses their potential benefits in terms of quality, time and cost. An associated case study illustrates key design and formulation considerations and ways to avoid common pitfalls.

Diffusion Cells in IVRT: Vertical and Horizontal Systems

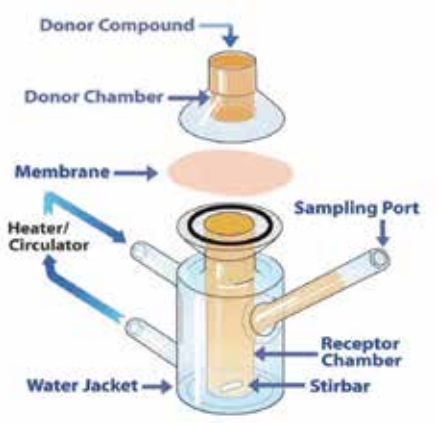
The Franz Diffusion Cell is the industry standard for IVRT studies. Developed over the past 40 years by Dr. Thomas J. Franz, the diffusion cell dramatically advanced development of topical formulations and remains the single most powerful tool to accurately predict a drug's topical delivery and pharmacokinetic profile. Diffusion cells may be vertical or horizontal (Side-Bi-Side) systems.

Vertical Diffusion Cell (VDC)

The vertical cell comprises two parts: a donor chamber above, which holds the test product; and a receptor chamber below, which holds a receptor medium (see Figure 1). The two chambers are separated by a membrane. The membrane may be excised animal or human skin for in vitro permeation test (IVPT), or one of a number of synthetic (polymeric) membranes for IVRT. The product is placed

in the upper donor chamber and diffused across the membrane into the receptor medium in the receptor chamber below. A stir bar ensures that the sample is homogenous. Samples of the receptor medium are collected at predetermined time points and analyzed for drug content, usually by HPLC. After each sampling, each receptor sampling aliquot removed was replaced with stock receptor medium or the receptor chamber is stocked with fresh medium.

Figure 1: Vertical Diffusion Cell (VDC): The Franz Cell



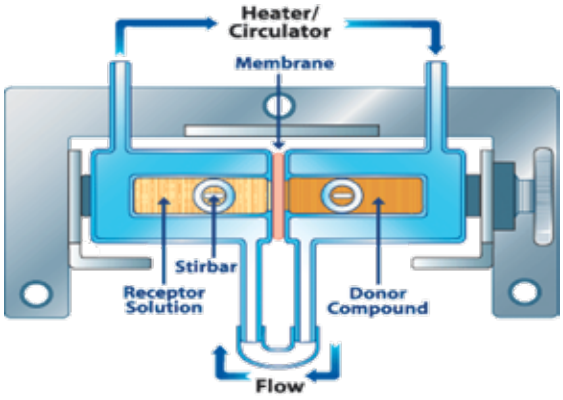
Source: S Raney, P. Lehman, T Franz, "30th Anniversary of the Franz Cell Finite Dose Model: The Crystal Ball of Topical Drug Development".[1]

Compared to horizontal systems, VDC more closely simulates real-world performance of topical drugs. The disadvantage of VDC, especially when utilizing skin as a membrane, is that the receptor chamber requires large volumes (typically 6 to 8 mL or greater) which can make detection challenging and can result in high error rates. This may impact detection methods because very small quantities of compound can go undetected or under-detected. Another disadvantage is that the temperature of the donor compartment is not thermostated and therefore is subject to variations in environmental temperature.

Horizontal Side-Bi-Side Diffusion Cell (SBS)

Horizontal systems require measurements from two separate but experimentally identical compartments (e.g., fluid type, volume, constant stirring, etc.) to assess skin penetration. Horizontal systems can be configured in numerous ways. A basic set-up is illustrated in Figure 2, with the donor chamber on the right and the receptor chamber on the left, as viewed from above. The membrane is place between the cell halves and a clamp is placed around them to hold the glass halves and membrane together. The assembly is situated over magnetic stir bars and water is heated and circulated around the chambers. Either side can be used as donor or receptor chamber.

Figure 2: Horizontal Side-Bi-Side (SBS) Diffusion Cell



Source: PermeGear Inc. (http://www.permegear.com/sbs.htm)

The main advantage of SBS is easy sampling because sampling ports are big enough to allow samples to be taken directly using regular pipettes. A disadvantage is that SBS requires large dosing volumes (typically from 1 to 3 mL) compared to approximately 10 µL/cm² for skin conduct utilizing VDC. This may be an issue if the amount of available product is limited. Compound must also be homogenous and stirring is more difficult in SBS systems

IVRT Method Development and Validation Phases

The typical method development and validation phases for IVRT are shown in Table 1. Development and validation pose and number of challenges. Decisions regarding the choice of membrane and receptor medium will impact the validity and reproducibility of IVRT results.

Table 1. IVRT Method Development and Validation Phases

• Select an appropriate receptor medium for assessing release of the drug of interest from the formulation of interest.
• Select an appropriate membrane for assessing release of the drug of interest from the formulation of interest.
• Determine intra- and inter-day reproducibility of the in vitro release method.
• Determine the in vitro release method's ability to discriminate between formulations containing different concentrations of the drug of interest.
• Determine the in vitro release method's ability to discriminate between intentionally altered formulations.
• Evaluate IVRT method robustness.

Choice of Receptor Medium

The solubility of the active ingredient in the receptor medium is an important factor. Receptor medium should provide a "diffusional sink" for active ingredient released from the semisolid formulation. To characterize solubility, literature searches and prior experience with a compound can supply information on its chemical properties. For new compounds, solubility can be determined by testing the active ingredient against various reagents. The type of compound, that is, whether it is a small- or large-molecule compound, may be a factor. Other considerations include stability and light sensitivity, which pose questions concerning degradation.

Choice of Membrane: Cadaver Skin vs. Synthetic

For IVRT, the membrane must keep the test product and the receptor medium separate and distinct. It should offer the least possible diffusional resistance and should not be rate controlling. The membrane selected should provide an inert holding surface for the test product, but not a barrier, allowing the active ingredient should diffuse readily into the receiving medium as it is "released" from the test product. It is important to confirm that there is no interaction—physical or chemical—between membrane and test product. The excipients present in the test product may affect the physical integrity of the membrane.

For IVPT, cadaver skin, surgical skin and animal skin are commonly used. It introduces additional factors, such as the age and health of the skin, the ethnicity of the donor, and the anatomical source (e.g., trunk, leg). Cadaver skin or surgical skin more closely mimics drug performance in real-world product use. Diffusion testing can evaluate drug performance across skin layers—the outer stratum corneum, epidermis and dermis. This information, which is not obtainable using synthetic membranes, may be important depending on whether the drug target is the skin itself or if passage through the dermis is necessary to deliver drug into the blood stream. Collecting and analyzing samples from each layer adds complexity and time. In addition, skin may not be readily available and is more expensive compared to synthetic membrane. Using synthetic membrane (IVRT) typically takes four to six hours; using skin (IVPT), it can take from 24 to 72 hours. However, IVPT can be used to create a drug penetration profile, which is a ratio of the absorption of the product across the skin as a function of time. The absorption or penetration profile can be compared to measurements of API in the blood plasma of clinical trial subjects. The results obtained from IVPT and clinical trial can be used to create in vitro-in vivo correlations. Several comparison evaluations have shown strong in vitro-in vivo correlations. [3, 4, 5]

Validation

Validation requires evaluation of the IVRT method's ability to discriminate rates of release of the active ingredient from test product formulations with altered concentrations or altered product composition. Validation may involve precision and accuracy, reproducibility, sensitivity, selectivity, recovery, and robustness. Developers must be in compliance with the FDA's 1997 guidance on scale-up and post approval changes (SUPAC-SS) for nonsterile semisolid dosage forms.

IVRT Applications in Drug Development

Formulation Profiling and Optimization. In drug development, the primary role of IVRT is to characterize dosage forms in order to select appropriate candidates for clinical evaluation. Appropriate candidates must demonstrate effective delivery of the active ingredient to the target site to achieve therapeutic response. Delivery will depend on the effective of the formulation, the chemistry of the active ingredient, the target site (the skin itself or another tissue/organ) and the disease for which the drug is indicated.

IVRT is used to determine the release rate of the active pharmaceutical ingredient (API) across the synthetic membrane. Candidate profiles characterize release of active drug from the formulation, penetration of the drug into the synthetic membrane, and duration of drug effect. Key parameters are but not limited to active ingredients, formulation components, dose strength, particle size, and viscosity.

After candidate profiling and selection, IVRT can be used during clinical trials to monitor drug performance and to optimize the final dosage form. In these applications, an in vitro rate of release profile is established.

Demonstrating Bioequivalence in Generic Development. The central task in generic product development is demonstrating the bioequivalence of a generic with the innovator reference listed drug (RLD). IVRT is playing an increasingly important role in bioequivalence evaluation.

In abbreviated new drug applications (ANDAs) for generic approval, bioequivalence may be demonstrated using pharmacokinetic and pharmacodynamic studies, clinical trials, and in vitro tests. Regulators use three classifications—Q1, Q2, and Q3—to characterize the comparison between a generic and RLD. Q1 indicates similar quality regarding composition of individual ingredients; Q2 indicates similar quantities of each ingredient; and Q3 indicates a product that has Q1 and Q2 similarities and, in addition, exhibits structural similarities to the RLD, with the same arrangement of matter and state of aggregation.

Semisolids pose special challenges for bioequivalence evaluation because most produce non to very low amounts of drug in blood or plasma. Comparative clinical trials have been required to establish bioequivalence for most topical generic formulations. Current regulatory trends suggest that IVRT may provide a viable alternative to costly, time consuming clinical trials.

A 2000 FDA Guidance waived the requirement for in vivo bioequivalence studies for immediate-release solid oral dosage forms, based on the Biopharmaceutics Classification System. According to the 2014 proceedings of a scientific workshop convened to consider challenges and solutions for establishing bioavailability for topical dermatologics, this waiver represents a precedent that might be extended to topical formulations.

The proceedings note that since FDA's 1997 SUPAC-SS guidance, IVRT has been an accepted measure of semisolid product performance, used to compare pre-and post-change product release rates: "An IVRT is thus a performance verification test for test and reference semisolid dosage forms." Under carefully prescribed circumstances, might clinical comparison be waived and IVRT used to demonstrate bioequivalence of semisolid dosage forms? A decision-making process was proposed, beginning with Q1, Q2, and Q3 evaluation of the generic and RLD products. As an example, if the generic were Q1/Q2 equivalent with the RLD, in vitro testing might be sufficient to show bioequivalence.[7]

Although such an approach remains in the proposal stage, the urgent need to reduce escalating costs and time of clinical trials argues for adopting more cost-effective methods to demonstrative bioequivalence. In 2012, the FDA took a significant step toward acceptance of IVRT as a surrogate for clinical evaluation in a draft guidance that outlines two options—in vitro or in vivo studies—to demonstrate bioequivalence for topical ointment formulations of an antiviral drug. To qualify for the in vitro option, the generic and RLD forms must be Q1/Q2 equivalent; physiochemistry must be comparable; and IVRT release rates must be comparable.[8]

IVRT Requirements for FDA SUPAC-SS Compliance

The FDA SUPAC-SS guidance recognizes the value of in vitro surrogate tests to assure maintenance of product quality and performance over time and in the course of changes, since clinical trial evaluation is unfeasible due to time cost. Regarding the role of IVRT, the guidance notes, "...in vitro release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s) from semisolid products. In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products."[5] However, FDA does not consider IVRT alone as a surrogate test for in vivo bioavailability or bioequivalence, and does not accept use of in vitro release rates to compare formulations across manufacturers. In generic development, SUPAC-SS compliance requires testing and documentation to support Q1 and Q2 changes in generic products

The SUPAC-SS guidance details requirements for in vitro release tests and/or in vivo bioequivalence tests to demonstrate that changes do no compromise product quality or performance.2 These include changes in: 1) product components or composition; 2) manufacturing processes; 3) manufacturing scale-up or scale-down; and 4) the manufacturing site during the post-approval period.

Requirements vary according to the level of change: Level 1 changes are those unlikely to have any detectable impact on formulation quality and performance; Level 2 changes are those that could have a significant impact; Level 3 changes are those that are likely to have a significant impact. The guidance stipulates testing procedures, including the diffusion cell system to be used, appropriate types of synthetic membrane, and appropriate types of receptor medium.

Components and Composition Requirements. SUPAC-SS requirements for IVRT testing in the development phase pertain to Level 2 changes in components and composition: changes of >5% and ≤10% in the approved amount of an individual excipient; change in supplier of a structure forming excipient; change in the technical grade of a structure forming excipient; and change in particle size distribution of the drug substance for drugs that are in suspension. IVRT documentation is required to demonstrate the release rate of the novel drug formulation, or of the modified formulation, compared to a pre-change formulation of comparable age. For Level 3 changes (those likely to have significant impact), in vitro release rate of the new or modified formulation is not required, but developers are encouraged to establish release rate as a point of reference for use in documenting later changes.[2]

Manufacturing Requirements. SUPAC-SS requires documentation for manufacturing changes that impact both the manufacturing processes and equipment. IVRT documentation is required for Level 2 changes in equipment to a different design or operating principle, such as changes in type of mixing equipment from high shear to low shear. The in vitro release rate of a lot of the dosage form prepared in new equipment must be compared with that of a recent lot of prepared in the original equipment. The two formulation s should be demonstrated to be within acceptable limits using test procedures described in the guidance. IVRT documentation is also required for Level 2 process changes, such as: mixing rate and time; cooling rate; operating speed; holding times outside of approved application ranges; and any changes in the process of combining the phases. In vitro release rates must be compared for product pre- and postchange.[2]

Batch Size (Scale-up/Scale-down) Requirements. For the NDA pivotal clinical trial batch, or for the abbreviated new drug applications (ANDA) or abbreviated antibiotic drug application (AADA) biobatch, be at least 100 kg or 10% of a production batch, whichever or larger. Scale changes must be properly validated. IVRT is required for Level 2 changes, which are changes in batch size beyond a factor of 10 times the size of the pivotal clinical trial or biobatch, where the equipment, operating procedures, formulation and manufacturing procedures are the same.

In vitro release rate of the scaled up batch must be compared to that of the prechange scale. The median rates for the lots of the two scales should be within acceptable limits using the guidance-prescribed testing procedure.[2]

Manufacturing Site Requirements. IVRT documentation is required for Level 3 site changes, which consist of a manufacturing site change to a different location that is not the same original, contiguous or adjacent site. The in vitro release rate of a lot of the dosage form prepared at the new site must be compared with that of form manufactured at the former site. Median rates must be comparable within acceptable limits, according to the guidance-prescribed testing procedure.[2]

IVRT's Expanding Role in Advancing Drug Development

Advances in in vitro approaches promise dramatic reductions in the time and cost of drug evaluation. IVRT offers methods to improve development of topical semisolid dosage forms by informing candidate selection. Regulatory trends suggest that IVRT is on the threshold of providing new pathways to faster, more efficient market approval for semisolid generic products. The increasing number and complexity of ANDA submissions, together with the need to inspect the increasing number of international generic manufacturing facilities, pose additional pressures on the need to streamline generic evaluation. Greater reliance on predictive, non-clinical tools such as IVRT offers important solutions.

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