

# Semi-solid in vitro release testing — are you prepared?

## Introduction

In the pharmaceutical industry, in vitro release testing (IVRT) has played an important role in both formulation design and quality control of finished products. Used originally for solid oral dosage forms, this form of testing is now being applied to a variety of “novel” or “complex” dosage forms as drug delivery becomes more complex. As these formulations, including semi-solids, have become more prevalent, there has been an increase in development of this testing method to determine the release performance of various dosage forms.

For orally administered solid drug products, this test is commonly referred to as a dissolution test, since the intention is that the drug dissolves rapidly in a test medium. For non-oral dosage forms such as topical and transdermal delivery systems, the test is commonly referred to as an in vitro release test, since the drug must diffuse and be released by its vehicle before penetrating the skin.

Because novel and complex dosage forms exhibit significant variability in formulation design, it has been difficult to devise a single test system that can be used to study the drug release properties of each dosage form. Different apparatus, procedures, and techniques have been employed on a case-by-case basis, and the methods are often specific to the dosage form category, formulation type, or even an individual product.

Recent updates to the U.S. Pharmacopeia now provide guidance for in vitro testing of semi-solid dosage forms. These published guidelines create a change in

regulatory perspective — a change that will likely result in requests for in vitro test results. The good news is that in vitro release testing is an alternative that can save both time and cost compared to bioequivalence studies.

This paper examines in vitro release testing for semi-solid topical dosage forms and discusses the recent changes in published testing standards, the subsequent increase in interest by regulators, and how to navigate this new environment to give your drug development project the best chance to clear regulatory scrutiny.

## The Value of IVRT in Semi-Solid Topical Formulation Development

For a topical semi-solid dosage form, the release rate of the active pharmaceutical ingredient (API) can be influenced by both its physical and structural properties; therefore, it is imperative to understand the API’s release rate throughout drug product development and life cycle management. To gauge the effectiveness of a semi-solid topical formulation, conducting in vitro release testing is critical in determining the release rate of the API in the topical drug products.

In vitro release testing characterizes the rate of API release. This method is also used to compare the underlying sameness in product quality characteristics in a range of semi-solid dosage forms, such as topical creams, ointments, aerosols, lotions, and gels. As such, it is very important to understand the API release throughout the development of the semi-solid drug product and understand the potential for any physical changes.

IVRT methods are responsive to physicochemical changes in semi-solid drug products and serve in demonstrating API release rates as well as comparing test and reference listed drug products (for abbreviated new drug applications). The FDA has provided product specific guidances for semi-solid topical products to outline effective approaches for demonstrating bioequivalence (BE).

An example of the FDA's expectation for demonstrating BE, the Product Specific Guidance for Acyclovir Cream – In Vitro Options includes the following testing recommendations:

- Formulation Q1/Q2 Sameness: The test and Reference Listed Drug (RLD) products are qualitatively and quantitatively same.
- Q3 Similarity: The physicochemical properties of test and RLD products are similar.
- In Vitro Release Test (IVRT) Studies: The test and RLD products have equivalent rates of acyclovir release.
- In Vitro Permeation Test (IVPT) Studies: The rate and extent of acyclovir permeation through excised human skin from test and reference products are comparable.

In May 1997, the FDA released the (now updated) guidance Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation for NonSterile Semisolid Dosage Forms (SUPAC-SS), dedicated to semi-solid forms such as creams, gels, lotions, and ointments.

and particle size determination. However, these tests provide little information about the drug release properties of the product or the effect of processing and manufacturing variables on the performance of the finished product.

The value of in vitro release testing has been realized over time through customized usage. Although applied sparingly, it has been essential in determining product sameness, particularly during any change in formulation, excipients, or manufacturing process or site. This has been the predominant use of in vitro release testing, but other applications and methods have evolved over time. In vitro release testing can also optimize formulation during the early stages of development.

### How IVRT Helps With Post Approval and Development

As stated above, in vitro release testing yields tremendous benefit and can fulfill certain requirements during two stages of drug development:

- Post-approval — ensures quality of production and supports site changes or other alterations to the product
- Development — optimizes formulation development

Current quality control tests provide limited information about the drug release properties or the effect of process/manufacturing changes on the performance of the finished dosage forms. Since the in vitro release rate can reflect the combined effects of several physical and chemical parameters, it represents an essential tool in quality control to assess product "sameness" after certain scale-up and post-approval changes for semi-solid products.

In development, drug release testing serves a different purpose. The vehicle composition and design strongly influence the product performance and how rapidly the drug substance may be released.

Animal skin or ex vivo human skin can be employed as an approach to assess a dermatological formulation's performance. However, given the wide variation in

### The Context for Today's In Vitro Release Testing

Since this release of SUPAC-SS, the most commonly used quality control tests for topical dermatological preparations have included identification, assay, homogeneity, rheological properties, specific gravity,



The following questions can help you determine when your semi-solid drug development project may require or benefit from in vitro release testing:

#### Post-Approval Changes:

1. Did your formulation undergo post-approval change that requires a regulatory filing?
2. Do you plan to change excipients in your formulation and need to explain the impact of this change on release performance?
3. Do you plan to change manufacturing sites and need to assess the sameness between the batches produced in one site compared to a different site?
4. Did you change a manufacturing procedure or equipment and need to assess the variance in formulations manufactured with one process/equipment and the new process/equipment?

#### Formulation Screening:

1. Would you like to have predictive estimates with respect to in vivo performance of a drug product before proceeding to biopharmaceutical characterization?
2. Would you like to have cost-saving formulation screening, reducing the number of candidates for subsequent development phases?
3. Are you developing a new dermatological drug product and need to compare its release performance with currently marketed formulations?
4. Are you developing a generic product and need to compare its release rate with a reference-listed drug formulation?
5. Would you like to investigate the effect of time, temperature, and humidity in the release performance of your test formulation?
6. Would you like to optimize or reformulate the vehicle of your drug product and determine the effect on drug substance release? early stages of development.

donor-to-donor skin samples — when compared to a synthetically manufactured membrane — test results will be less predictive. Additionally, a wide range of experimental formulations is necessary in the early screening phase of a drug product, requiring the use and/or sacrifice of many animals.

In vitro release testing, on the other hand, is a cost-effective alternative providing some predictive estimates in respect to the in vivo performance of a drug product. This helps a team narrow the selection of test product candidates for subsequent biopharmaceutical characterization, enabling a rational strategy within the screening process.

#### How to Determine If IVRT Will Facilitate Your Semi-Solid Formulation Project

Pharmaceutical companies can benefit from a validated in vitro release method — primarily with post-approval changes and formulation screening.

#### Should I Really Be Using In Vitro Release Testing?

The infrequent use of in vitro release testing is due, in part, to limited guidance published on the topic. Until recently, no compendial apparatus, procedures, or requirements for in vitro release testing of semi-solid topical dosage forms had been described in relevant pharmacopeias. Standard practice dictates that in instances where a compendial (e.g., European Pharmacopoeia [Ph. Eur.] or United States Pharmacopeia [USP]) method exists, it should be employed.

The FDA's SUPAC-SS guidance for nonsterile semi-solid dosage forms describes release rate studies using the vertical diffusion cell (Franz cell) procedure and recommends in vitro release rate comparison between pre-change and post-change products for approval of SUPAC-SS-related changes. As in vitro release testing methods have evolved, the use of the Franz cell diffusion system engineered specifically for semi-solid dosage forms was suggested at the USP Pharmacopeial Forum. This method was recently published in the USP General Chapter 1724 and is aligned with the



FDA's SUPAC-SS. As a result, regulatory agencies may now request that these tests be included in filings and applications.

Considering the new regulatory perspective, in vitro release testing is an alternative that can save both time and cost compared to bioequivalence studies for assessing product sameness after post-approval changes. Knowing what the agencies expect, and providing it to them, gives your drug development project the best chance to clear regulatory scrutiny. As the saying goes, you can "pay now, or pay later." Any perceived savings of time and money in the near term will be lost as the cost of a regulatory inquiry or outright rejection halts your project.

### You Need a Partner With Proven Excellence in Semi-Solid Forms

In vitro release testing can serve multiple functions in a drug's life cycle. Recently, the U.S. Pharmacopeia adopted General Chapter 1724 to define and standardize in vitro release testing standards for semi-solid formulations. As a result, regulatory agencies may now request that companies perform these tests and include them as part of a filing package.

Regulatory agencies continue to demand that drug companies demonstrate deep understanding of each drug's formulation, performance, and consistency. In vitro release testing is simply another way to demonstrate such understanding — and now that a standard has been published by USP, regulatory agencies may move toward an implicit mandate.

Working with a partner like DPT will give you access to experts on the leading edge of in vitro performance testing. Because of our relationships with thought leaders and key influencers in the industry, our experts can quickly provide development and validation of in vitro release tests — from initial screening of experimental formulations in the product development phase to assessment of batch-to-batch sameness for products undergoing post-approval changes.

When it comes to developing and manufacturing semi-solids and liquids, DPT offers expertise that simplifies the complexities of in vitro release testing.

## ABOUT DPT

DPT, a Viatris company, is a contract development and manufacturing organization (CDMO) recognized for our expertise in semi-solid and liquid dosage forms, with an established legacy of excellence dating back more than 80 years. More than any other CDMO, we understand how scale-up will be interwoven from your research and development project into full-scale commercialization, offering close consultation throughout your product's life cycle. From pre-formulation to commercial manufacturing, you only need one partner to streamline your path from lab to market: DPT does it all.

