



DPT Thought Leadership Issue 16

SEMI-SOLID *IN VITRO* RELEASE TESTING (IVRT) – ARE YOU READY?

INTRODUCTION

In the pharmaceutical industry, *in vitro* release testing has played an important role in both formulation design and quality control of finished products. Used primarily for solid oral dosage forms, this test has expanded to a variety of “novel” or “complex” dosage forms as drug delivery becomes more complex. Because 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, in the vehicle, must diffuse and be released by the vehicle, becoming available to penetrate into skin.

Because novel or 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 US 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, discusses the recent changes in published testing standards, 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.

IN VITRO RELEASE TESTING – THE LAST 15 YEARS

In May 1997, the FDA released a guideline entitled Scale-up and Post Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Release Testing and *In vivo* Bioequivalence Documentation for Non-Sterile Semi-solid





Dosage Form (SUPAC-SS). The guideline was dedicated to semi-solid forms such as creams, gels, lotions, and ointments.

During the time since the SUPAC-SS guideline was released, the most commonly used quality control tests for topical dermatological preparations have included identification, assay, homogeneity, rheological properties, specific gravity 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 used sparingly – primarily in quality control – it has been essential in determining product sameness, particularly during any change in formulation, excipients, or manufacturing process/site.

Although this has been the predominant use of *in vitro* release testing, other applications and methods have evolved over time. In addition to its use in quality control, *in vitro* release testing can also optimize formulation during the early stages of development.

IN VITRO RELEASE TESTING – HOW DOES IT HELP?

As stated above, *in vitro* release testing yields tremendous benefit during two stages of drug development:

- **Post approval – ensures quality of production and supports site or other changes to 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 effect of several physical and chemical parameters, it represents an essential tool in quality control to assess product “sameness” under certain scale-up and post approval changes for semi-solid products.

In development, the focus of 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.

The use of animal skin or *ex vivo* human skin can be employed as an approach to assess a dermatological formulation’s performance. Given the wide variation in 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 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 to the subsequent biopharmaceutical characterization phase, enabling a rational strategy in the screening process.

BENEFITS OF IN VITRO RELEASE TESTING

Pharmaceutical companies can benefit from a validated *in vitro* release method – primarily for post approval changes and formulation screening.

The following questions can help you determine when your drug development project can 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 to release performance?**



3. Do you plan to change manufacturing sites and 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?
5. Would you like to implement a quality control method that gives more information regarding product performance than a prior quality control method?

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?

DO I NEED TO USE *IN VITRO* RELEASE TESTING TODAY?

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.), United States Pharmacopeia (USP)) method exists, it should be employed.

The FDA's SUPAC-SS guidance for dosage forms describes release rate studies using the vertical diffusion cell (Franz cell) procedure and requires *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, use of the Franz cell diffusion system for semi-solid dosage forms was suggested in 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 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.



CONCLUSION

In vitro release testing serves multiple functions in a drug's life cycle. Recently, the US 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 companies to perform these tests and include them as part of a filing package. As cited in our previous Quality by Design (QbD) series, regulatory agencies continue to demand that drug companies demonstrate deep understanding of their 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 in the USP– regulatory agencies may move toward an implicit mandate.

Working with a partner like DPT Labs 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 assessing batch-to-batch sameness for products undergoing post-approval changes.

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

To discuss your *in vitro* release testing needs and how DPT Labs can help, contact us at <http://www.dptlbs.com/contact-us> or call 1.866.CALL.DPT.

ABOUT DPT LABORATORIES:

DPT is a contract development and manufacturing organization (CDMO) helping pharmaceutical companies achieve clinical and commercial success. Through our specialized Centers of Excellence, we're tenacious about discovering solutions. We ask the right questions and thoroughly investigate your options. Our experts give you the answers you need from development through commercialization. We bring vast experience in resolving development and manufacturing challenges in sterile and non-sterile semi-solids & liquids. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

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