Optimising In Vitro Release Testing For Topically Applied Products

Dr. Upendra Bhatnagar & Sasidhar Pasumarthi

upendra.bhatnagar@vimta.com

Vimta
Driven by Quality. Inspired by Science.

Table of Contents

Executive Summary

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. Growing experience confirms the value of in vitro release test (IVRT) in the measurement of drug release properties in topical semisolid dosage forms. The assay has 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. 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 formulation;

A robust and reproducible IVRT method that is adequately sensitive to highlight the differences in physicochemical and rheological characteristics of the formulation and stress conditions should be developed and properly validated. A validated method should possess the attributes like precision; accuracy/sameness; dose proportionality; sensitivity to changes in excipient type, the amount of excipient, the size of the batch, and the method of manufacture. As there are limited standard approaches for ensuring the quality, reliability, and reproducibility of in vitro release data, this paper outlines IVRT methods and discusses key design considerations to ensure reliable results.

Introduction

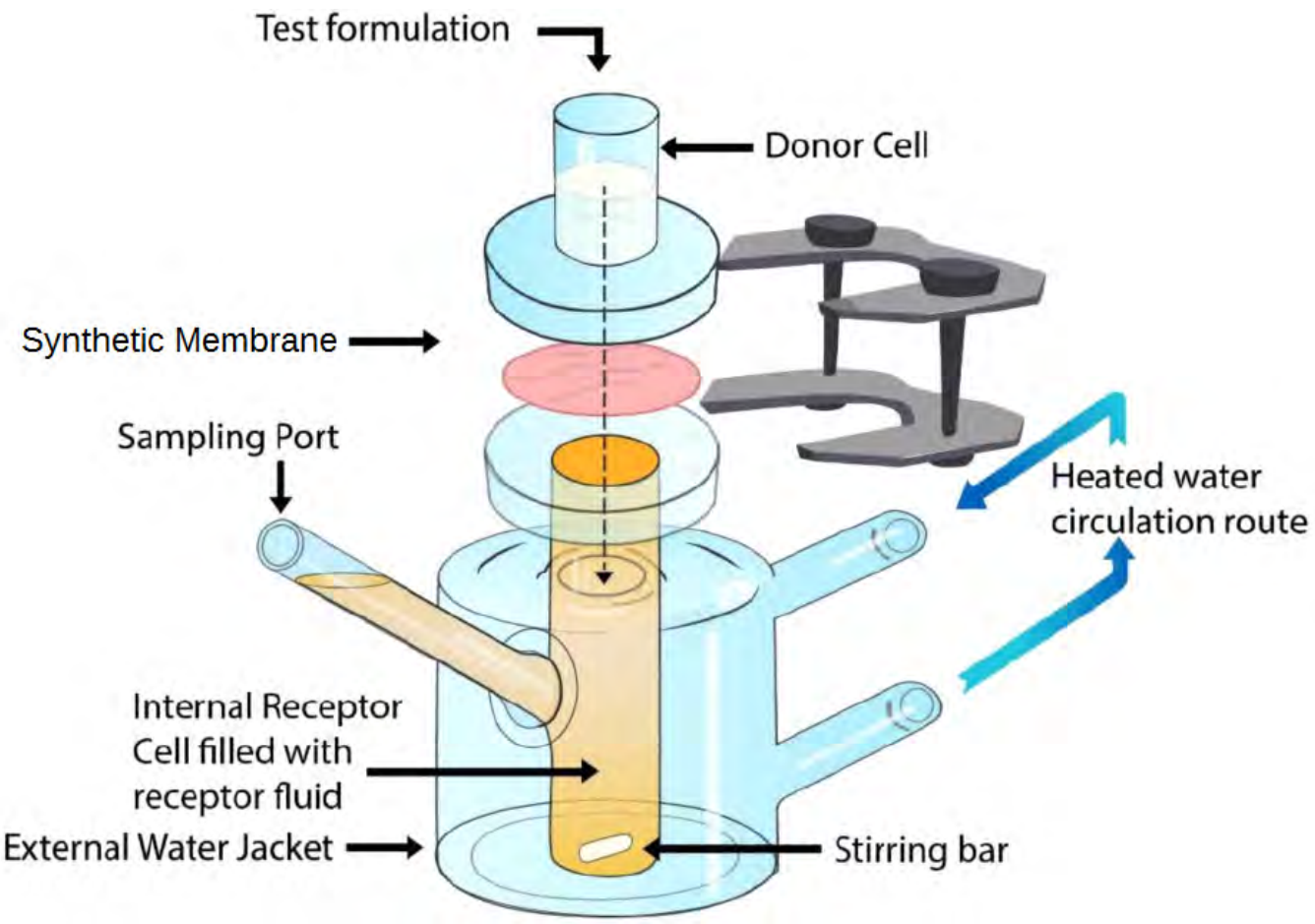
The FDA SUPAC-SS guidance recognizes the value of in vitro surrogate tests to assure maintenance of product quality and performance over time and in the course of changes, since clinical trial evaluation is unfeasible due to time cost. In abbreviated new drug applications (ANDAs) for generic approval, bioequivalence may be demonstrated using pharmacokinetic and pharmacodynamic studies, clinical trials, and in vitro tests. 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.The central task in generic product development is demonstrating the bioequivalence of a generic with the innovator reference listed drug (RLD). Current regulatory trends suggest that IVRT as a surrogate for clinical evaluation may provide a viable alternative to costly, time consuming clinical trials.

Much interest has also been shown relating to the use of IVRT data as a surrogate procedure for use as a waiver of bioequivalence. 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.

The Franz Diffusion Cell is the industry standard for IVRT studies. 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. The two chambers are separated by a synthetic membranes (cellulose acetate/ nitrate/mixed ester, polysulfone, polytetrafluoroethylene, nylon, polycarbonate etc.). Specific volumes of samples are withdrawn from the receptor chamber at predetermined time intervals and analysed to evaluate the drug release properties in topical semisolid dosage forms. In order to ensure that an IVRT method is reproducible and reliable, it is important to establish a robust and reproducible IVRT method that is adequately sensitive to highlight the differences in physicochemical and rheological characteristics of the formulation and stress conditions. However, there are limited standard approaches for ensuring the quality, reliability, and reproducibility of in vitro release data.

Figure 1

Schematic of Franz Diffusion Cell Model used by Vimta for IVRT.



Principle of IVRT

Drug release from semi-solid dosage forms follows the Higuchi model. This model is applicable when no more than 30% of the total amount of the dose applied is released into the medium at the end of the experiment.

During release from semisolid formulation, the diffusion of molecules occurs from a region of higher concentration to a region of lower concentration. The amount of drug released per unit area (µg/cm2) is proportional to the square root of time; therefore, a plot of average cumulative release vs. square root of time should yield a straight line (as required by SUPAC-SS2), the slope of which is used to calculate flux (amount released/cm2/hr-1/2). Release of the drug is studied over a period of six hours, which is the typical duration of application for a topical product.

Amount released at each time point (t) is calculated using the following equation:

$$t_1AR_1 = (A_{U1}/A_S) \times C_S \times 1000 \times (V_C/A_0)$$

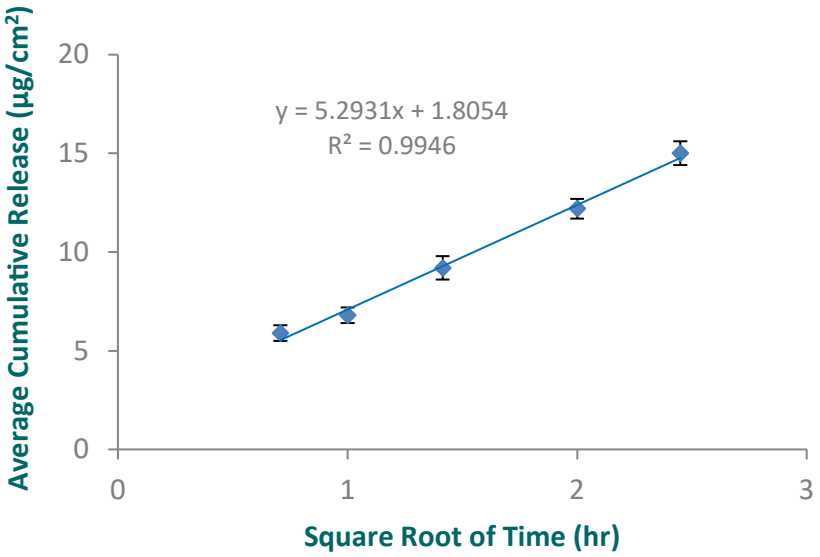
$$t_2AR_2 = (A_{U2}/A_S) \times C_S \times 1000 \times (V_C/A_0) + [AR_1 \times (V_S/V_C)]$$

AR = amount of drug released (µg/cm2)
A_U = response (e.g., peak area, or peak height or absorbance) from the Sample solution
A_S = average response (e.g., peak area, or peak height or absorbance) from the Standard solution
C_S = concentration of the Standard solution (mg/mL)
V_C = volume of the diffusion cell (mL)
A_0 = area of the orifice (cm2)
V_S = volume of sample taken (mL)

.

Figure 2

Typical IVRT Release Profile.



Method Development

The success of an IVRT method relies on the reliable drug transport from the test material through a membrane and into the receiving medium. Therefore the identification of optimal experimental parameters focuses on an API's physiochemical properties and is aimed at the selection of the proper membrane, receiving medium and sampling schedule. IVRT method development generally consists of the following steps:

1. Solubility screening to develop a receptor medium that prevents saturation and maintains sink conditions. Sink conditions exist when a receptor medium has a relatively "high capacity to dissolve or carry away the drug" and the receptor media "exceeds 10% of Cs (drug solubility in the releasing matrix) at the end of the test". For a reasonable starting point, as per the SUPACSS FDA guidance an "Appropriate receptor medium such as aqueous buffer for water soluble drugs or a hydro-alcoholic medium for sparingly water-soluble drugs" can be used.

2. Selection of a membrane that has no leachables, compatible with the test material and receptor medium, minimizes drug binding, has no rate limiting effect on drug release and reproducible. There are many choices in synthetic membranes which vary controllably in pore size, thickness and hydrophilicity. Since the major constituent of many semisolid products is water, hydrophilic/ hydrophilized synthetic membranes are typically used.

3. Selection of appropriate diffusion cell will dictate other parameters such as the membrane diameter, test product application amount, and sample aliquot removed from the receptor chamber. As described in USP General Chapter 1724, for testing of semi-solid topical dosage forms vertical Franz diffusion cell assembly is used.

4. Number of samples: Although systems with three cells have been used, a minimum of 6 cells is recommended (SUPAC-SS) for characterising release rate (profile) of an API from semi-solid products.

5. Temperature of the receptor medium is generally set to 32 ± 1 °C in an attempt to approximate the natural surface temperature of the skin. In the case of vaginal drug products, the temperature is set to 37 ± 1 °C.

6. Sample application: Depending on the method used to interpret the release data, either a finite or pseudo-infinite dose will be applied to the donor compartment of the test system. An pseudo-infinite dose is preferred over a finite dose for following reason:
    - Simplifies diffusion kinetics.
    - Reduces the variability due to slight mass variations in finite dosing.
    - Maintains "30% rule".
    - Makes application of dose easier.

    Typically for pseudo-infinite dose, semisolid sample NLT 200 mg is placed uniformly on the membrane and kept occluded to prevent solvent evaporation and compositional changes

7. Selection of time points to evaluate the release profile of drug from the product (SUPAC-SS recommends a 6-hour study period with minimum of five time points, i.e., at 30 minutes, 1, 2, 4 and 6 hours). Depending on the formulation's burst effect and the time for release to reach a plateau, the sampling times may have to be adjusted. The "burst" is a common phenomenon where a high initial release is observed. For most of the fast release matrix type (gels and ointments), earlier sampling times (between 0 to 2 hours) were found to be more discriminative. Therefore, IVRT duration and sampling times may be varied depending on the formulation matrix.

8. Sample analysis: Appropriate validated specific and sensitive analytical procedure will be used to analyse the samples and to determine the drug concentration and the amount of drug released.

Figure 3

Multi-station Automated Franz Diffusion Cell System at Vimta

Method Validation

Validation of IVRT method provides assurance that the test method is capable to demonstrate change in drug release rates upon changes in formulation composition, batches or sources of ingredients and/or method of manufacture.

The IVRT method validation process assesses a number of parameters, including sensitivity, specificity, selectivity, precision (repeatability, intermediate precision, robustness), accuracy, recovery, mass balance and dose depletion. Parameters for validation should be selected based on product requirements.

Figure 4

Validation of the IVRT method to assess for sensitivity, specificity, selectivity (n=6 cells used for each concentration).The release profiles of different strength formulations are significantly different and the change in release rates are proportional as a function of drug strength.

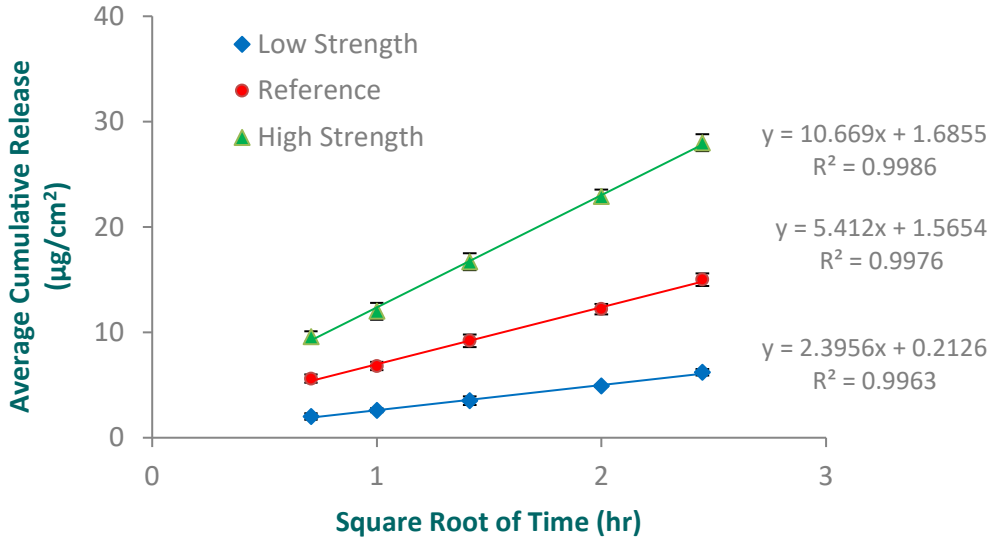


Figure 5

Validation of IVRT method to assess for inter-analyst precision (n=6 cells used for each experiment). The release profiles from two experiments are not significantly different.

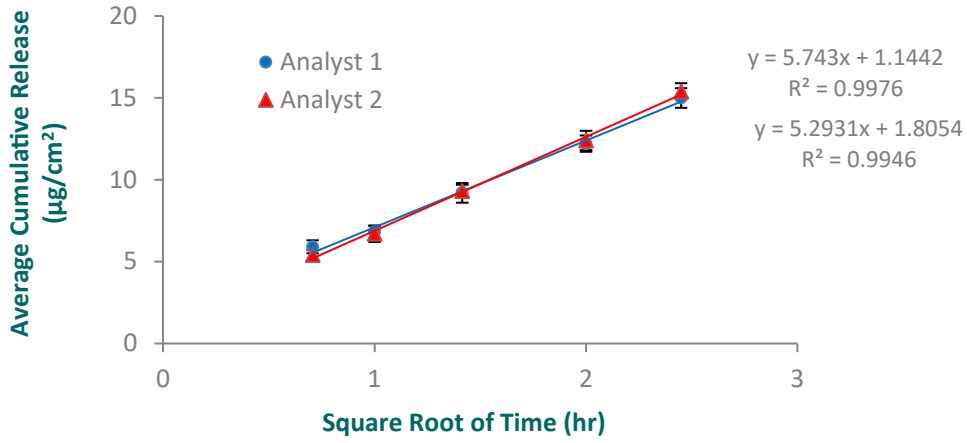
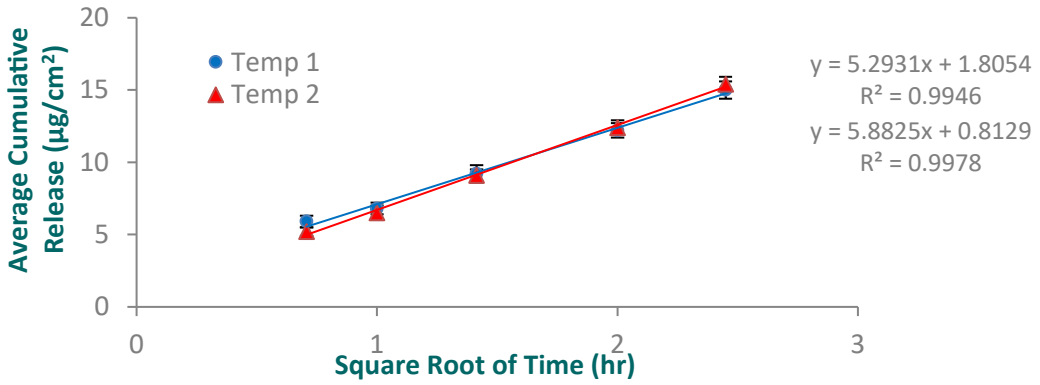


Figure 6

Validation of IVRT method to assess for robustness (n=6 cells used for each experiment). The release profiles from minor variations of IVRT method parameters are not significantly different.

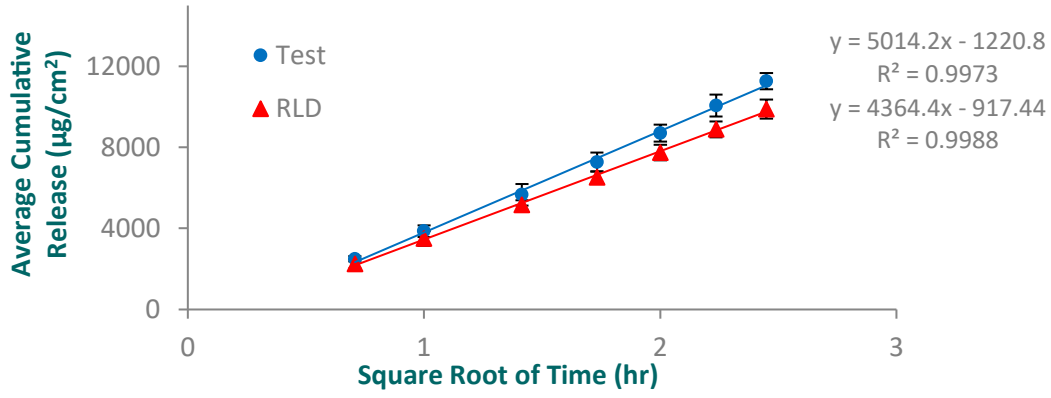


In Vitro Release Rate Comparison Test

Sample position within the blank of Franz cells should be randomised to ensure an unbiased comparison test. The analysis involves non-parametric assessment of release rate by statistical means and is based on the calculation of an appropriate 90% confidence interval (CI) on the Wilcoxon Rank Sum/Mann-Whitney rank test.

Figure 7

Pivotal Study to assess the equivalent release rate of drug from Test and RLD.



Statistics of IVRT

According to SUPAC-SS, comparison of two IVRT runs is carried out in two-stages.

Stage 1: Six slopes for each run will be obtained and a 90% CI for the ratio of the median *in vitro* release rate for one run over the median *in vitro* release rate of another run will be computed and expressed in percentage terms. If this 90% CI falls within 75% to 133.33%, no further testing is required.

Stage 2: If the test is not passed in the first stage, 2 additional runs (each six cells) for each product will be carried out. The 90% CI will be computed using all 18 runs for each product and it should fall within 75% to 133.33%.

As per EMA, 90% CI should be within 90% to 111%.

Advantages of IVRT

The IVRT method offers an effective and easy-to-use evaluation tool to measure the *in vitro* release profiles of topical formulations. As well as ensuring optimal thermodynamic activity and batch-to-batch performance, it provides evidence that product quality remains uniform throughout a formulation's shelf-life, which is a critical component of regulatory submissions.

Following regulatory approval, the IVRT method can prove useful in ensuring the quality of on-going production, while supporting site and other changes to a product, such as:

I. Changes in the component or composition, between 5 and 10% of excipients, with the total additive effect of all excipients changes being no more than 10%.
II. Changes in the equipment (different design or principle).
III. Changes in the manufacturing process, such as the rate of mixing, the rate of cooling, operating speeds and holding times.
IV. Changes in the scale-up/scale-down of manufacture, more specifically changes in batchsize beyond a factor of 10

The method also contributes time and cost savings in predictive estimates of the in vivo performance of a drug. From a regulatory perspective, it can also ensure agencies are readily provided with the information that they require.

Conclusion

VIMTA Lab's provides an effective method for the evaluation of release rate of topical semi-solid formulations. This method can be substituted for a clinical trial in certain cases where changes are likely to have impact on formulation quality and performance such as change in manufacturing process, changes in manufacturing site and batch size. IVRT helps to minimize the risk during regulatory scrutiny of new formulations. IVRT has been established as a proficient method by the USP, for the tests are described in the USP General Chapter 1724. The right formulation and delivery method in topical pharmaceuticals plays a vital role and thus evaluating by the right method will cut the cost and time for the manufacturing industry.

REFERENCE

- 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, May 1997, SUPAC-SS CMC 7.
- Draft Guidance on Acyclovir. U.S. Department of Health and Human Services, Food and Drug Administration, Office of Generic Drugs, September 2019.
- USP General Information 1724, Semisolid Drug Products-Performance Tests.
- European Medicines Agency: Draft Guideline on Quality and Equivalence of Topical Products, October 2018.
- The Topical/Transdermal Ad Hoc Advisory Panel for the USP Performance Tests of Topical and Transdermal Dosage Forms, Stimulus Article: Topical and Transdermal Drug Products, Pharmaceutical Forum, 2009: 35 (3): 750.