DEVELOPING AN *IN VITRO* RELEASE TESTING (IVRT) METHOD FOR THE VALIDATION OF SEMI-SOLID TOPICAL FORMULATIONS

EXECUTIVE SUMMARY

The effective measurement of drug release of an active pharmaceutical ingredient (API) from a dosage form plays a critical role in both formulation design and control of finished pharmaceutical products. The evaluation method used is determined by a variety of factors, including the dosage form itself and the intended route of delivery. As semi-solid topical formulations become more prevalent, *in vitro* release testing (IVRT) has shown great potential as a means to evaluate release properties through the combined effect of several physical and chemical parameters, including solubility and particle size of an API and the rheological properties of the dosage form.

IVRT FOR SEMI-SOLID TOPICAL FORMULATIONS

In formulation design, novel or complex dosage forms can exhibit significant variability. This creates challenges in establishing a single testing system that can evaluate the drug release profiles of varying dosage forms. Traditionally, different equipment, procedures, and techniques have been employed on a case-by-case basis, while methods selected have often been specific to the dosage form category, formulation type or even an individual product.

For topical dermatological preparations, quality control testing has generally relied on identification, assay, homogeneity, rheological properties, specific gravity, and particle size distribution. However, these tests have proven to be limited in their use due to their inability to provide conclusive information about drug release properties or the effect of processing and manufacturing variables on the performance of the finished product.

IVRT has drawn much attention as it can be used as a research and development tool to optimise formulations, and as a quality control tool to assess manufacturing quality and consistency over time. The technique, which allows for appropriate selection of a clinical candidate with Quality by Design (QbD) principles, is recommended by the FDA's Nonsterile Semisolid Dosage Forms for Scale-up and Post-Approval Changes (SUPAC-SS) guideline. The guidance states, "*in vitro* release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s)."[1]

The mandate recommends that IVRT be performed to compare equivalency between pre- and post-change batches. It is now feasible that agencies may request that these tests are included for the following regulatory filings:

- new drug applications (NDAs)
- abbreviated new drug applications (ANDAs)
- abbreviated antibiotic drug applications (AADAs)[1]

> *In vitro release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s).*[1]

Recipharm offers expertise in the development and validation of IVRT methods for topical formulations. The dosage forms we study include:

CREAMS

GELS

OINTMENTS

LOTIONS

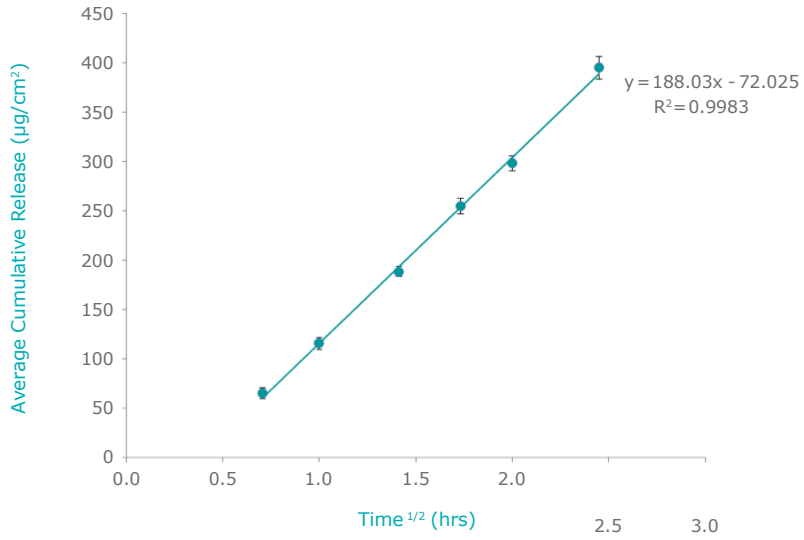
FOAMS

IVRT PRINCIPLE AND THEORY

Drug release from semi-solid dosage forms follows the simplified Higuchi equation (see Equation 1).[2] This equation is applicable when the drug is solubilised in the formulation matrix and the amount of drug released at the end of the experiment is less than 30%.

The amount of drug released is proportional to the square root of time; therefore, a plot of average cumulative release vs. time$^{1/2}$ should yield a straight line, the slope of which is used to calculate flux (amount released/cm^2/hr). Release of the drug is studied over a period of four to six hours, which is the typical duration of application for a topical product.

FIGURE 1.
Linear plot of average cumulative drug released versus square root of time.



Equation 1

$Q = 2\ C_0\ (D\ t / n)^{1/2}$

where,

Q = amount of drug released per unit area of application

C_0 = initial concentration of drug

D = diffusion coefficient of drug

T = time

Figure 1 demonstrates a typical release profile that abides by Equation 1. Exceptions to this rule may be encountered with novel formulation approaches that have altered release profiles.

Successful IVRT is reliant on adequate drug transport from a test material through a membrane and into a receiving medium. 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.

Today, the industry's increased focus on the development of semi-solid formulations has fuelled demand for more reliable and reproducible IVRT methods, which has called for greater exploration into how the technique can be further optimised.

METHOD DEVELOPMENT

IVRT method development generally consists of the following steps:

1. Solubility screening to develop a receptor medium that prevents saturation and maintains sink conditions.
2. Selection of a membrane that has no leachables, minimises drug binding and has no rate limiting effect on release.
3. Selection of appropriate equipment for testing. The Franz diffusion cell assembly which is commonly used for testing semi-solid topical dosage forms (USP <1724>) is shown in Figure 2.
4. Determination of the dose of formulation mounted to mimic infinite dosing conditions.
5. Selection of time points to evaluate the release profile of drug from the product (SUPAC-SS recommends a minimum of five time points).
6. Other parameters such as sample volume, stirring speed, method of formulation addition, and temperature of the receptor solution are also evaluated.

The IVRT team at Recipharm is supported by experienced analytical scientists that have expertise in developing and validating high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-MS) methods for high throughput sample analysis.

FIGURE 2.
Schematic of Franz Diffusion Cell Model used by Recipharm for IVRT.

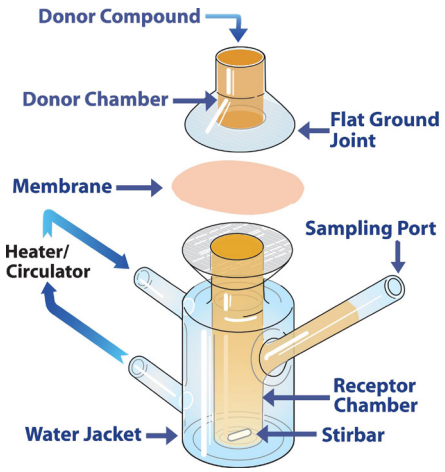


Image courtesy of Permegear

Figure 2 shows the IVRT method we use, which employs an open chamber design, called the Franz diffusion cell system .

The developed IVRT method can be used for the comparison of formulation prototypes to aid in product development and the comparison of generic formulation prototypes with a Reference Listed Drug (RLD) or a comparator.

FIGURE 3.
Comparison of RLD versus two prototype formulations (n=6 cells used for each experiment).

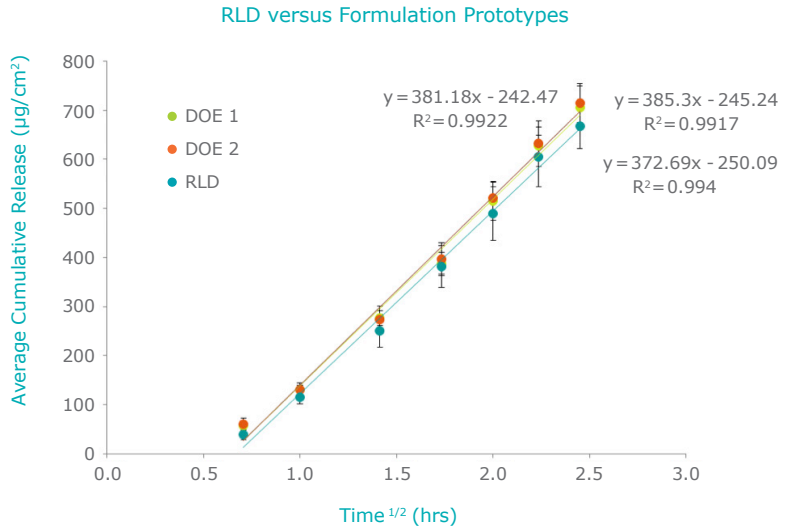


Figure 3 demonstrates typical results for comparisons of prototype formulations with the RLD. The Wilcoxon Rank Sum/Mann-Whitney rank test was used for comparison as described in the SUPAC-SS. Release from the prototypes is comparable to release from the RLD i.e. within the confidence interval of 75%-133.33%.

FIGURE 4.
Multi-station Franz diffusion cell system – stirrers pictured here.

METHOD VALIDATION

IVRT has been used for batch-to-batch uniformity testing, product certification and validation for several decades. More recently, it has been used to optimise formulations during product development.

The IVRT method validation process assesses a number of parameters, including precision (repeatability, intermediate precision, robustness), accuracy and method discrimination. Parameters for validation should be selected based on product requirements..

FIGURE 5.
Validation of the IVRT method to assess for inter-day precision (n=6 cells used for each experiment). The release profiles of the two experiments are not significantly different.

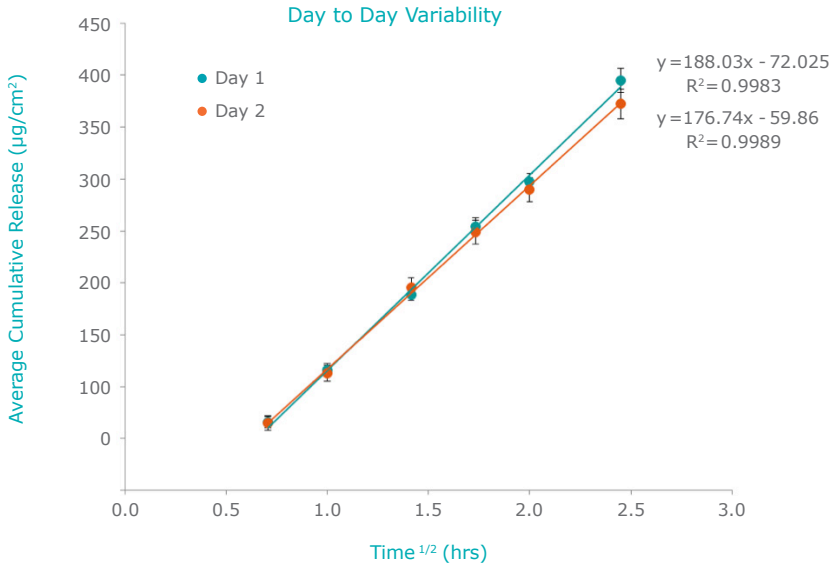


Figure 5 demonstrates typical examples of intermediate precision analysis on two separate days.

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.

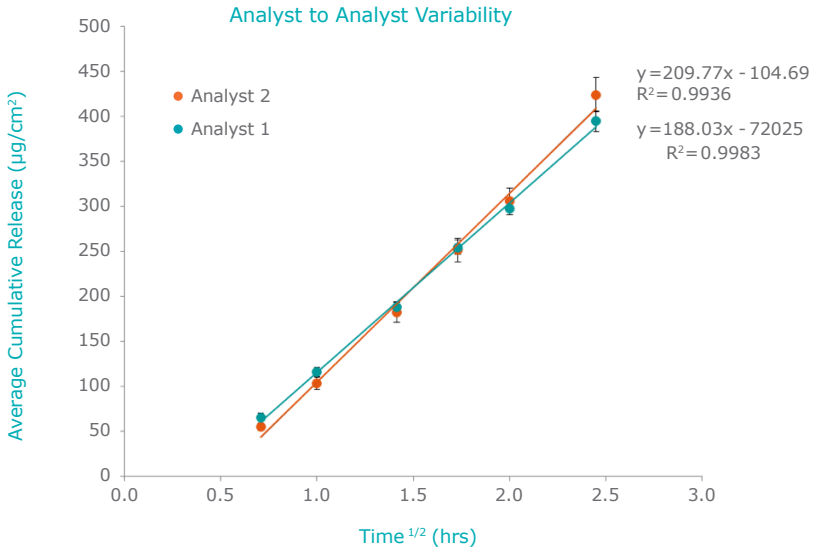


Figure 5 shows examples by two different analysts.

FIGURE 7.
Validation of IVRT method to assess the effect of change in drug concentration (n=6 cells used for each experiment). Release from the original formulation (100% drug) is significantly higher compared to a formulation containing 50% drug.

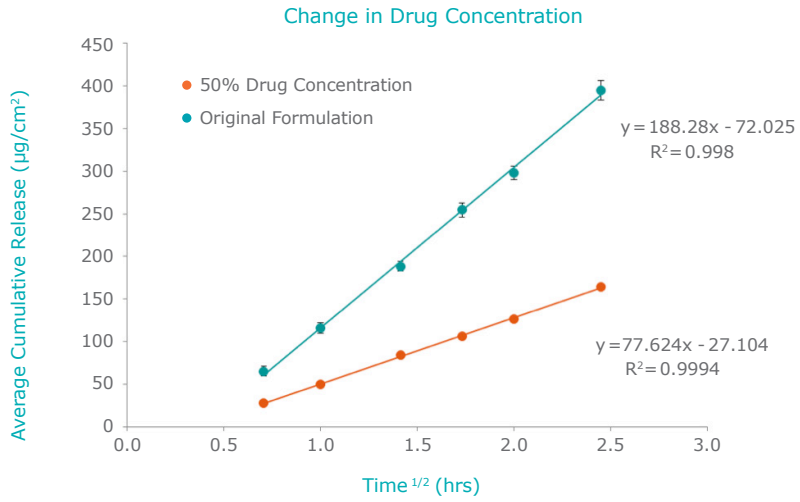
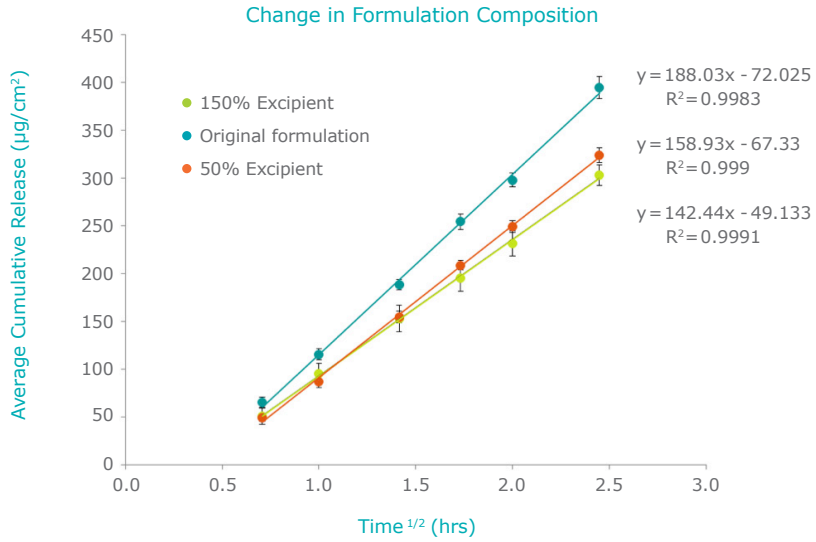


Figure 7 and Figure 8 show the ability of the IVRT method to discriminate between formulations that have different drug concentrations and different excipient compositions, respectively.

FIGURE 8.
Validation of the IVRT to assess the effect of change in formulation composition (n=6 cells used for each experiment). The release from 50% excipient and 150% excipient formulations is significantly different compared to the original formulation.



The validated IVRT method can be used to establish the sameness of registration batches produced by different manufacturing procedures or at different manufacturing sites (as per the SUPAC-SS guidelines). Parameters for validation should be selected based on product requirements.

BENEFITS OF THE IVRT METHODOLOGY

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

SUMMARY

Recipharm's IVRT methodology provides an efficient method for the evaluation of drug release from semi-solid topical formulations, with the technique's use increasing as both a development tool and means of setting product specifications. With IVRT likely to become a regulatory expectation, use of a suitable system will be critical in achieving a properly validated method that can ensure strict control of variables and assess manufacturing quality over time. The methodology can not only help to minimise risk when it comes to the regulatory scrutiny of new formulations, but can contribute considerable savings in both time and cost for manufacturers.

ABOUT RECIPHARM

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 5,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way.

REFERENCES

1. FDA Guidance for Industry: Nonsterile Semisolid Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, May 1997, SUPAC-SS CMC 7
2. Active Compounds Release from Semisolid Dosage Forms; J Pharm Sci. 2012 Nov;101(11):4032-45; Anna Olejnik*, Joanna Goscianska andIzabela Nowak; Adam Mickiewicz University in Poznan, Faculty of Chemistry, ul. Umultowska 89b, 61-714 Poznań, Poland

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