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*Review Article*

# A Review on *In-Vitro* Release Testing Methods for Topical Dosage Forms

**Seelam Jayadev[1] , Ismail. Y[2*]**

[1]*Research Scholar, Crescent School of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and Technology, GST Road, Vandalur, Chennai, Tamil Nadu, India*

[2]*Associate Professor, Crescent School of Pharmacy, B.S Abdur Rahman Crescent Institute of Science and Technology, GST Road, Vandalur, Chennai, Tamil Nadu, India*

[*]*Address Correspondence to Ismail. Y, Associate Professor, E-mail: ismailcsp@crescent.education*

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**Abstract**

IVRT is an *in-vitro* release testing parameter which determines release of drug from the topical dosage form. By using this IVRT tool we can determine the product similarity between the 2 similar semisolid dosage forms (reference and test products). The similarity between the 2 formulations should be in the limit of 75%-133.33% as per the FDA-SUPAC-SS guidance. To check the similarity among the reference and test product we have to validate the test product. To initiate the IVRT method validation performing laboratories should be certified, equipped and chartered, maintenance and control of the study facility environment and systems. Qualification and calibration of the instruments used for the validation activity shall be certified as per the USP semi solid drug products-performance tests. To check release of API released from a dosage form a validated quantification method is required.

**Keywords:** IVRT; Validation; Semisolid dosage form; Reference product; Test product

## Introduction

## IVRT guidance and applications

The below graphical representation summarises the principle of IVRT methodology used in the rate and extent of drug release from the semisolid dosage form (Figure 1).

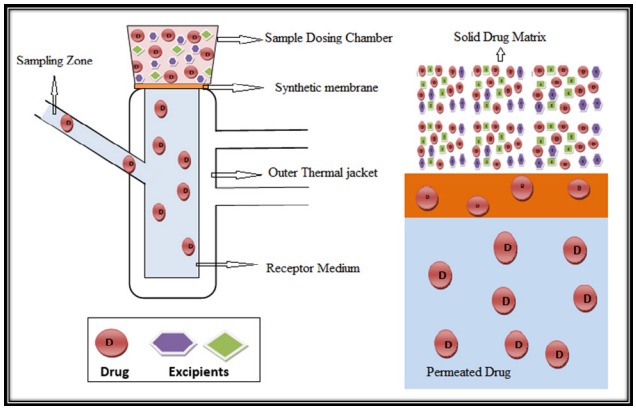


**Figure 1:** The principle of IVRT methodology used in the rate and extent of drug release from the semisolid dosage form

IVRT is used as one of the representative performance testing tools for few semisolid formulations [1-3]. IVRT is a sensitively grounded procedure for characterization of drug product performance especially when the release of API released from a dosage form is controlled by means of excipients and drug thermodynamic properties [4-6]. This release testing tool has been widely accepted for use to obtain a disclaimer of pharmacokinetic sessions after the post approval changes to a dosage form [6].

This article is a comprehensive review of IVRT guidance, applications, methodology, apparatus, and validation parameters used along with published results of this technique in a few semisolid formulations.

## Importance of IVRT method

The API release rate in a semi-solid topical product can be greatly affected by its properties [7]. It is, therefore, necessary to evaluate *in-vitro* drug release properties of topical formulations to simulate and analyze their in-vivo performance [7-10]. The IVRT technique is a very discriminative and sensitive process which is reactive to physicochemical alterations in a topical dosage form such as partition coefficient, solubility/melting point, molecular size, Ionization, and several others. An IVRT method can be developed to analyze the drug release of a wide range of topical/semi-solid dosage forms as mentioned below:

- Ointments
- Creams and Lotions
- Hydrogels
- Topical aerosols
- Topical patches
- Suspensions

- Microencapsulation formulations
- Liposomes/Ethosomes

The physicochemical properties and analytes release processes in topical/semi-solid dosage forms, often necessitating multiple types of IVRT testing machines [8-12].

**Applications of IVRT technique**

FDA first recommended IVRT/in-vivo tests to support of non-sterile semi-solid formulations with topical routes of administration (SUPAC-SS) in May 1997 [1]. More recently, several guidelines specific to *in-vitro* release and permeation methodologies has been published by FDA not only to overcome barriers to the development of topical and generic products, but also to improve patient-care [13].

Some current applications of IVRT are listed below:

- Development of generics products and ANDA submissions [14].
- Manufacturing, screening, and scale-up of complex topical formulations including microbicide gels and films [15].
- Comparative assessment with RLD for ANDA submissions [14].
- Evaluation of numerous physical characteristics of potential topical products during stability testing and to screen the API rate of release from formulations [16].
- To support claims of extended pharmaceutical/ therapeutic equivalence [17-19].

Other potential applications:

- Drug release consistency from batch-to-batch [17-19].
- Characterization of physicochemical properties of the API [1].
- Effective time and cost-saving method when compared to bioequivalence studies [1,18,19].

**IVRT in comparative assessment of various topical formulations**

A copious amount of literature is available on *in-vitro* release testing parameter in topical/semi-solid dosage forms [4]. Higuchi et al. (1961) first published the theoretical analysis of drug diffusion from ointment bases of topical/semi-solid dosage forms. In this derivation, the drug was assumed to diffuse into a perfect sink [20]. Later in 1970, Roseman and Higuchi developed a silicone rubber matrix model to explain impact of other constraints on the release rate [21]. Matrix boundary layer models were used in several other studies later to describe the change in drug release through a diffusion-layer into receptor fluid [22-26].

Several conventional and non-conventional methods of IVRT for semisolid dosage have been developed and tested. Table 1 provides a comparative assessment of some release testing studies along with the various active components, study design/apparatus, dissolution medium, membrane, and receptor medium used for the studies [27-35].

**Table 1:** Comparison of various release studies and their study characteristics

| Product name | Apparatus used | Selected membrane | Receptor medium | Active compound | References |
|---|---|---|---|---|---|
| Acyclovir cream, 5% | Vertical diffusion cell | Polysulfone | 0.9% NaCl solution | Acyclovir | Tiffnera et al. (2018) |
| Zovirax cream | USP type-II with immersion cell | Polysulfone | Alkaline borate buffer, pH 9.2 | Acyclovir | Krishnaiah et al. (2014) |
| Acyclovir ointment | USP type-II with immersion cell | Nylon | Ph 7.4 phosphate buffered saline | Acyclovir | Xu et al. (2015) |
| Betamethasone dipropionate ointment | Franz diffusion cell | Polysulfone | Ethanol, IPA, acetonitrile, hexane | Betamethasone dipropionate | Zatz et al. (1996) |
| Acyclovir cream | Vertical diffusion cell | Nylon, Tuffryn, Durapore and Nitrocellulose | Normal saline (0.9%w/v NaCl) | Acyclovir | Nallagundla et al. (2014) |
| Metronidazole cream | Vertical diffusion cell | Tuffryn | 0.9% NaCl solution | Metronidazole | Rath et al. (2020) |
| Nitroglycerine patches | USP paddle method | NA | DE aerated water | Nitroglycerine | Shah et al. (1986) |
| Hydrocortisone acetate cream | Vertical diffusion cell | Tuffryn | Ethanol and water | Hydrocortisone acetate | Mudyahoto et al. (2020) |
| Cyclosporine ophthalmic ointment | Franz diffusion cells | Polyethersulfone | pH 7.4 PBS+0.5% SDS+20% ethanol | Cyclosporine | Dong et al. (2018) |

Despite of the wide research done on IVRT techniques in different formulations, there are still several products mentioned in the FDA (not limited to creams, ointments, gels and lotions) that require the IVRT Study profiling as mentioned in the draft guidance published [36-40].

**Methodology of IVRT**

The IVRT method quantifies the amount of API released from a dosage form and determines its rate of release [41]. In semisolid dosage forms, the drug release greatly depends on its permeability through human skin. In order to mimic skin permeation kinetics, the IVRT method for semisolids is designed to measure the drug released from a vehicle/donor into a receptor medium, separated by an inert membrane [42].

**Principle**

The analyte diffusion rate from topical/semi-solid dosage forms was elucidated in the Higuchi theory of Equation [41]:

Where

Q represents the amount of analyte released per unit area of application

C0 represents the preliminary Concentration of analyte

D represents diffusion coefficient of the analyte

t represents time.

The drug release is usually studied during a 4 hour–6 hour period. The amount of Analyte released from the topical/ semi-solid dosage form is straight comparative to time square root. Hence a linear plot of average cumulative drug released (vs) square root of time (Figure 2). Obtained slope values can be capable to conclude the flux values [41]. This equation might not be relevant to formulations which are novel and dosage forms with altered release profiles [41].

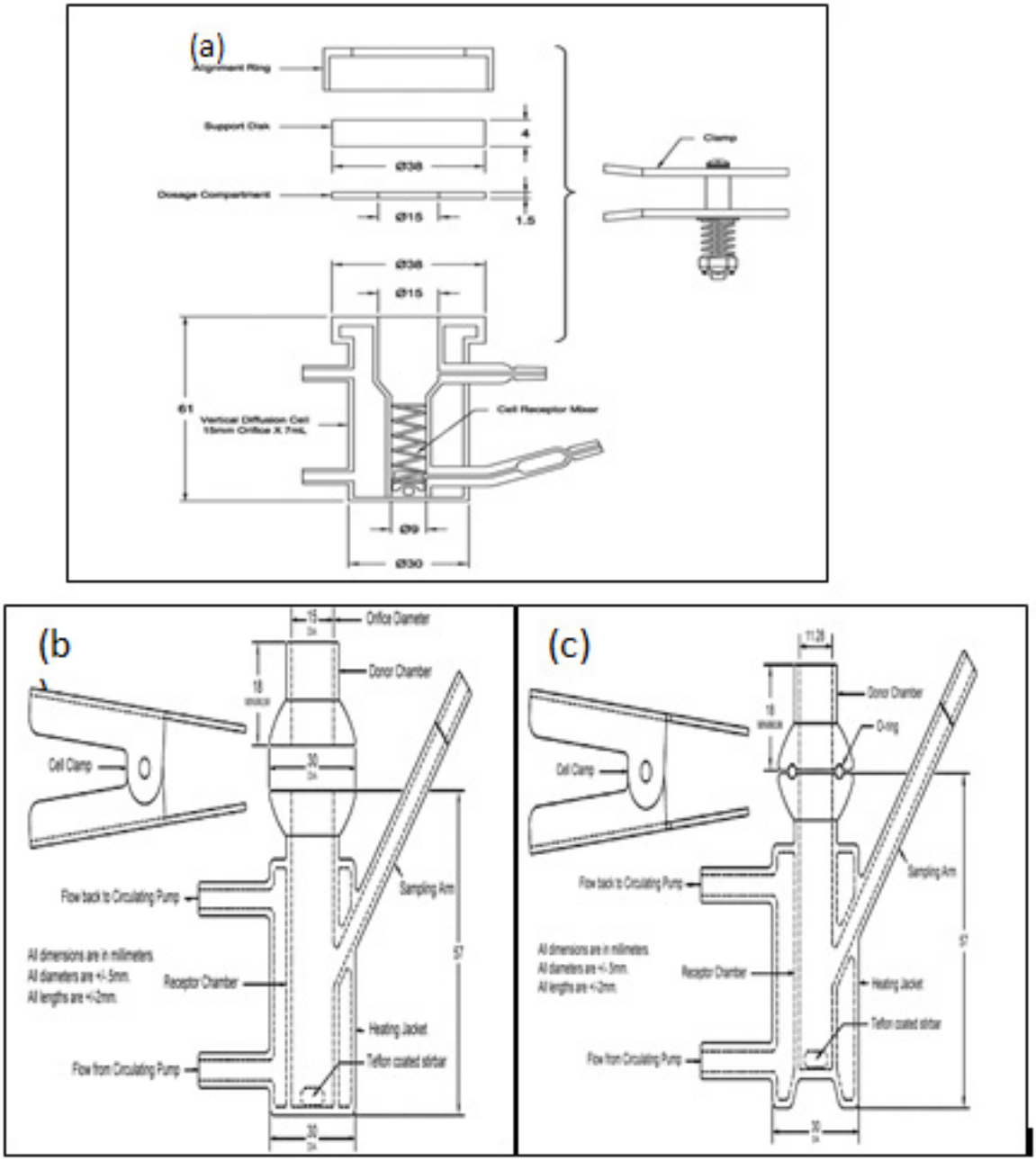


**Figure 3:** Schematic diagram of the 3 models of vertical diffusion cell: (a) Model A, (b) Model B, (c) Model C

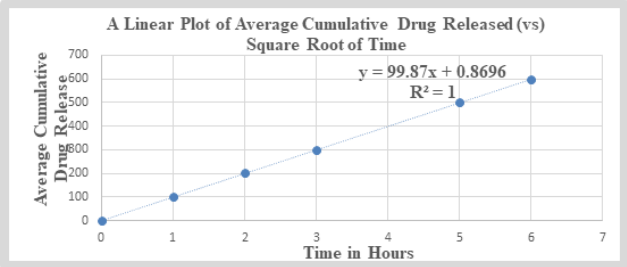


**Figure 2:** Demonstration of release profile using the Higuchi theory of equation

The success of an IVRT technique depends on the reliable drug transport from the drug product into the receptor medium, through a membrane. Therefore, it is important to choose appropriate quantities of API, suitable synthetic membrane, optimized receptor medium, and external thermal environments for the profile releasing proportion [7,17].

Until now, there are no standard and effective directives established to determine drug release. Therefore, many researchers have designed different apparatus and methods to carry out the IVRT procedure. The reliability of the results, however, depends on the study design employed, quantities of API and other components, appropriate membrane, receptor, and temperature for the release testing [41,42].

## Apparatus for IVRT

The IVRT apparatus are classified into 3 categories as per the United States Pharmacopeia (USP chapter 1724). Table 2 provides a comparison table of different types of IVRT machine used for Diffusion of API or analytes from various semisolid/topical dosage forms [7,43,44].

**Table 2:** Comparison of 3 IVRT apparatus

| Comparison parameters | VDC apparatus (Franz cell diffusion) | Immersion cell instrument | Flow through cell instrument |
|---|---|---|---|
| Construction of instrument | Cylindric structure with 38 mm cell orifice | Cylindric structure vessel that can be used with USP apparatus 1 or 2 | Cone structure with 22.6 mm diameter of cell |
| Cell volume capability | 3 mL, 7 mL and 12 mL | 150 mL-200 mL | Cell volume flow can be adjusted to 8 mL/min, 16 mL/min and 24 mL/min |
| RPM | at 400 RPM, 500 RPM or 600 RPM | at 25 RPM-100 RPM | Flow rate is estimated instead of RPM |
| Temperature | at 32°C or 37°C | at 32°C or 37°C | at 32°C or 37°C |
| Sample amount | Application of optimized product not less than 200 mg | Application of optimized product ranging from 300 mg to 2 gm | Application of optimized product ranging from 400 mg to 1200 mg |
| Sensitivity | Advanced complex method | Conventional and insensitive technique | Advanced sensitive technique |

The most often utilized apparatus to approve and validate IVRT technique is the vertical diffusion cell (Figure 3). Several studies reviewed the reproducibility and applications of vertical diffusion cell apparatus in non-sterile semisolid formulations to the most recent Topical Drug Classification System (TCS). It is considered the most compatible (for very low/high dosage strengths) and sensitive among other acceptable IVRT methodologies. It is a robust and rugged method with multiple cell volumes and is feasible even for micro sample collection [43-46].

## Selection of sample amount

During the Study profile not limited to development, validation, pilot and pivotal study at least 0.3 gram of formulation sample shall be applied onto the heightened membrane [4,10]. The extent of diffusion of the drug molecule from formulation sample through the synthetic membrane intends to encounter the principles of the Higuchi's Law [21–24].

## Selection of an appropriate membrane

Appropriate receptor medium should be selected that simulates good rate of sink varied conditions. Water soluble drugs generally require an aqueous buffer as the receptor. A hydroalcoholic receptor medium is suitable for sparingly water-soluble dosage forms. The medium pH should remain constant throughout the study period. Back diffusion should be minimal for the medium to avoid drug transformation [1,7,17].

## Sampling time and temperature

The sampling time usually depends on the type of dosage form. In general, a study for duration of about 6 hours with a minimum of 5 sampling times (at 30 mins, 1 h, 2 h, 4 h and 6 h) is suggested to regulate the analyte diffusion study by generating an adequate release profile. At each sampling interval, it is recommended that a aliquot of sample shall be withdrawn and fresh Optimized receptor media shall be replaced, so that during the duration of the study, the lower surface of the membrane is in touch with the receptor phase [1,7,17].

## Analyte sample analysis

To determine the sample concentrations the diffused samples, bioanalytical procedures must be applied [1,7,17].

## Comparison study plan for the test molecule and reference molecule

A representative IVRT Instrument has 6 cells. Each time you run the device, you need to assign the 2 products in the following manner (Figure 4).

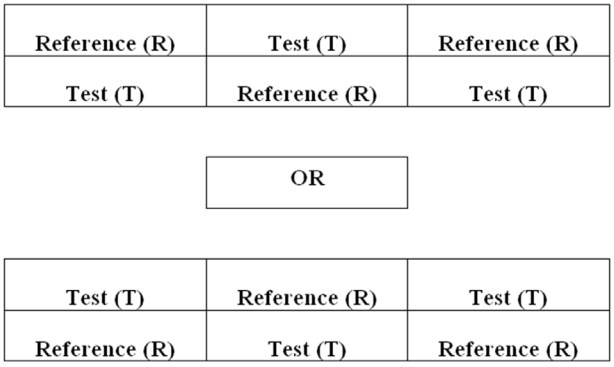


**Figure 4:** A representative IVRT instrument

If there are systemic differences between runs, this strategy of utilising both items in each run of the in vitro device helps to assure an objective comparison runs [7,17].

## Discussion

### *In-vitro* method validation parameters

According to the draft FDA guidance the following parameters shall be considered on the validation of IVRT technique shall be based on the draft guidance on acyclovir cream USP 5% [40] (Table 3).

### *In-vitro* bio-analytical method validation parameters

The following parameters shall be considered for the bio-analytical method validation for IVRT Quantification by analytical method [47,48] (Table 4).

**Table 3:** Acceptance criteria for in vitro method validation parameters

| Parameters | Evaluation parameters | Acceptance criteria |
|---|---|---|
| **IVRT apparatus qualification** | Temperature at membrane | Must be within ± 1.0°C of Temperature of 32.0°C |
| | Cell volume | Must be 5% of the Certified Cell Volume |
| | RPM | Must be within ± 2% of set Value |
| **Cell to cell variability and linearity** | % RSD for slopes of 6 cells | NMT 15% |
| | Regression coefficient (r2) | ≥ 0.90 |
| **Recovery, mass balance and dose depletion** | Mass balance | In the range of 70.0% to 130% |
| | Dose depletion/recovery | % Report |
| **Intra-run precision** | % RSD for Average slopes of 6 cells | NMT 15% |
| | Regression coefficient (r2) | ≥ 0.90 |
| **Inter-run precision** | % RSD for slopes of 6 cells for intra run | RSD of slope must be within 15% |
| | % RSD for slopes of 6 cells for inter run | |
| | % RSD for slopes of 12 cells (intra and inter run) | |
| | Regression coefficient (r2) of 6 cells for inter run | ≥ 0.90 |
| | Regression coefficient (r2) of 12 cells (Intra and inter run) | |
| **Inter analyst reproducibility** | % RSD for slopes of 6 cells (Analyst-1) | % RSD of slope must be within 15% |
| | % RSD for slopes of 6 cells (Analyst-2) | |
| | % RSD for slopes of 12 cells (Analyst-1 and Analyst-2) | |
| | Regression coefficient (r2) for slopes of the 6 cells (Analyst-2) | ≥ 0.90 |
| | Regression coefficient (r2) of the 12 cells (analyst-1 and analyst-2) | |
| **Average slopes of IVRT precision and reproducibility** | % RSD for 18 slopes from 3 independent IVRT runs (intra-run precision, inter-run precision and inter analyst reproducibility | % RSD of slope must be within 15% |
| **Receptor medium variations** | % RSD of slopes for altered condition of receptor media | % RSD of slope must be within 15% |
| | % Difference between average slopes of IVRT precision and reproducibility and altered condition of receptor media | NMT 15% |
| **Dose amount variations** | % RSD of slopes for altered condition of dose amount | % RSD of slope must be within 15% |
| | % Difference between average slopes of IVRT precision and reproducibility and altered condition of dose amount | NMT 15% |
| **Temperature conditions** | % RSD of slopes for altered condition of temperature | % RSD of slope must be within 15% |
| | % Difference between average slopes of IVRT precision and reproducibility and altered condition of temperature | NMT 15% |
| **Mixing rate variations** | % RSD of slopes for altered condition of Mixing rate | % RSD of slope must be within 15% |
| | % Difference between average slopes of IVRT precision and reproducibility and altered condition of mixing rate | NMT 15% |
| **Receptor solution sampling qualification** | % RSD should not be more than 5.0 | % RSD at all sampling points (6 replicates) should be NMT 5.0% |
| | % Accuracy of observed value should be within 90.0%–110.0% of nominal volume | % Accuracy at all sampling point (6 replicates) should be within 90.0%-110.0% of nominal value |

**Table 4:** Acceptance criteria for in vitro method validation parameters

| Parameters | Evaluation parameters | Acceptance criteria |
|---|---|---|
| **System suitability** | USP tailing factor | Must be not greater than 2.0 |
| | USP theoretical plates | Must be not less than 2.0 |
| | Blank carry over | Must be greater than 20.0% of CS-1 |
| | Analyte MQC 6 replicate injections | Must be not greater than 2.0% |
| | Correlation coefficient from the Calibration Curve | Must be not greater than or equal to 0.98 |
| | % Y Intercept against CS-1 | Must be not greater than 20.0% |
| | % RSD for Response factor | Must be not greater than 10.0% |
| | Calibration Curve Standard (CS-1) | Deviation not greater than ± 15% of the actual or nominal concentrations |
| | Calibration Curve Standards (CS-2 to CS-8) | No deviation more than ± 20%. |
| **Calibration curve standards** | Regression coefficient (r2) | Must be not greater than or equal to 0.98 |
| | % Y intercept against CS-1 | Must be not greater than 20.0% |
| | % RSD for response factor | Must be not greater than 10.0% |
| | Calibration standard concentration-response | Deviation not greater than ± 15% of the actual or nominal concentrations |
| | | Out of 8 calibration standards, 6 calibration standards including CS-1 and CS-8 should meet the above acceptance criteria. |
| **Quality control standards** | % Accuracy for QCs | 85.0% to 115.0% |
| | | At least 67% of QCs should attain the range of 85.0% to 115.0% |
| | | At least 50% of QCs at each level should attain the range of 85.0% to 115.0% |
| **LOD and LOQ** | S/N ratio for LOD for API | Must be not greater than or equal to 3.0 |
| | S/N ratio for LOD for API | Must be not greater than or equal to 10 |
| | The percentage RSD of response for API from 6 injections (LOQ level) | Must be not greater than 20.0% |
| **Precision** | For method precision | System should meet the system suitability criteria |
| | | % RSD for retention time of API should not be more than 5.0% |
| | For intermediate precision | System should meet the system suitability criteria. |
| | | % RSD for retention time of API should not be more than 5.0% |
| **Accuracy and recovery** | For LQC, MQC and HQC | System should meet system suitability criteria |
| | | Individual and mean % recovery for LQC, MQC and HQC for API at each level should be between 85.0 to 115.0. |
| | | % RSD for LQC, MQC and HQC for API should be NMT 15.0. |
| **Robustness** | Column oven temperature | System should meet system suitability criteria. |
| | Flow rate | |
| | Composition of the mobile phase | |

## Conclusion

*In-Vitro* Release Testing (IVRT) plays a critical role in evaluating the performance of topical semisolid dosage forms. IVRT is not only a valuable tool for assessing drug release from these formulations but also for ensuring the similarity between reference and test products, in compliance with FDA guidelines. The IVRT method is highly sensitive and responsive to various physicochemical alterations in topical dosage forms, making it an indispensable tool in the pharmaceutical industry. The importance of IVRT is further underscored by its wide range of applications, spanning different topical dosage forms, including ointments, creams, hydrogels, patches, and more. Its utility extends to the development of generic products, manufacturing, screening, and scale-up of complex formulations, as well as comparative assessments with reference listed drugs. The methodology of IVRT, including the principles it's based on, apparatus selection, sample amounts, membranes, receptor media, sampling times, and temperature conditions, is crucial to the accurate determination of drug release. Furthermore, the validation parameters for IVRT and the bio-analytical method are vital to ensure the reliability and robustness of this technique.

## Acknowledgement

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**Conflict of Interest**

Authors declares that no conflict of interest.

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