Diffusion Cell Apparatus: Scientific Principles and Practical Challenges: I

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Center for Drug Research and Evaluation
U.S. Food and Drug Administration

Virtual Public Workshop
In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods
August 20th, 2021

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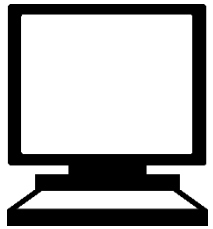
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.


It is what gives patients confidence
in their *next* dose of medicine.

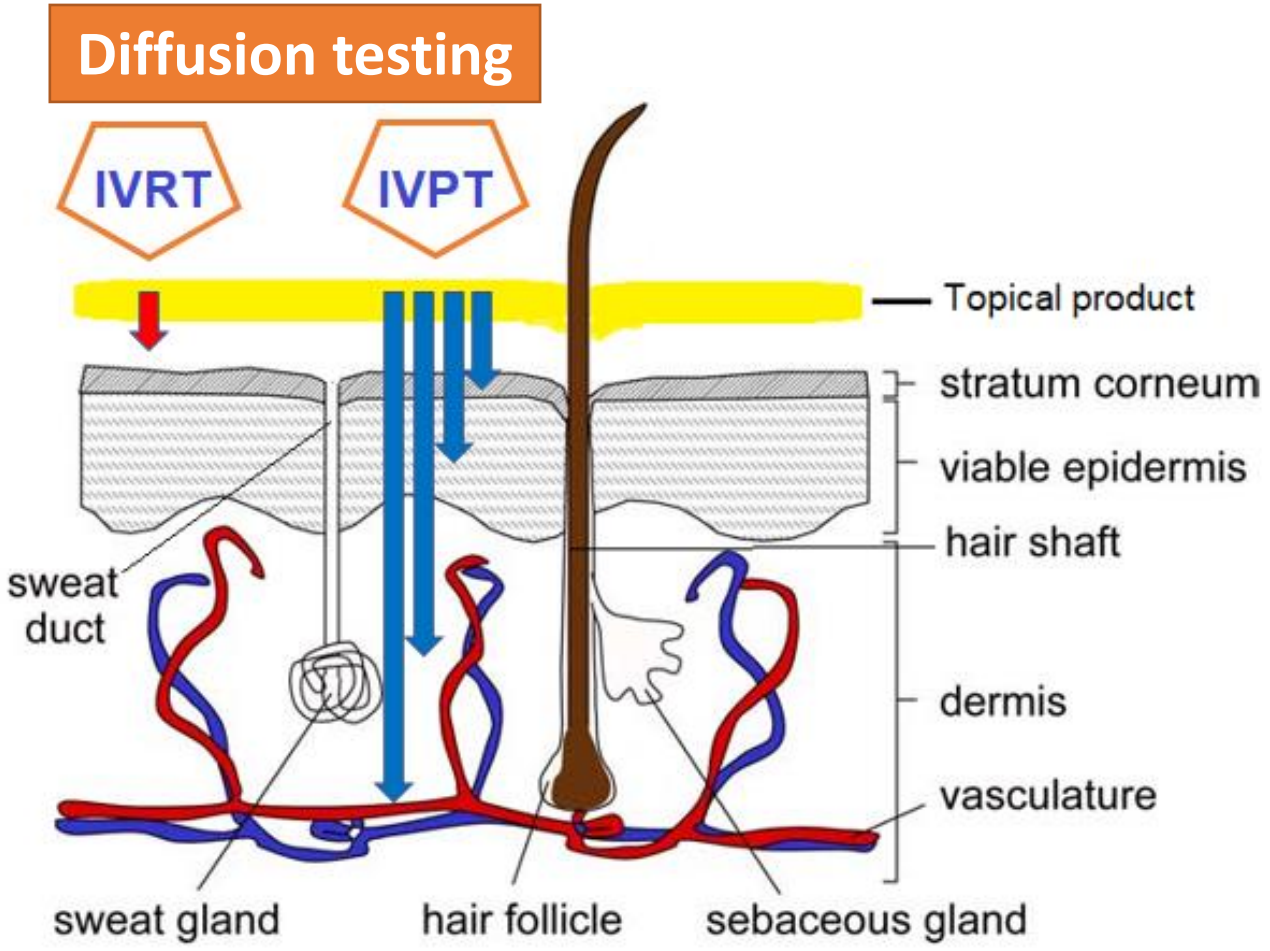
Outline

- Diffusion of topical drugs
- Diffusion cell testing
- Diffusion apparatus
- Technical challenges
- Optimization of diffusion test parameters
- Apparatus qualification parameters
- Key takeaways

Diffusion of topical drugs

Performance testing of topical products:

- **IVRT:** Drug diffusion from the product matrix to skin surface.
- **IVPT:** Drug diffusion from product matrix to various layers of skin and systemic circulation.
  - Physicochemical properties of the drug substance and the matrix.
  - Diffusion test parameters
  - Biological factors of skin (IVPT)



Diffusion of topical drugs

Diffusion parameters and kinetics:

❑ Katz & Poulsen, 1971 (Fick's Law of Diffusion)

$$J = \frac{P \times D \times \Delta C}{I}$$

J = Flux (µg/cm²/hour)
C = Concentration gradient
P = Partition Coefficient
D = Diffusion Coefficient
l = Length of Travel

- It considers a simple passive diffusion where molecules move by random motion from the matrix through the membrane/skin to the receiver media in the direction of decreasing concentration.

❑ Takeru and William Higuchi (1961 and 1962)

- Describes the "rate of release of solid drugs suspended in ointment bases into perfect sinks"

$$Q = (2A - C_s)\sqrt{D_t \Big/ 1 + \frac{2(A - C_s)}{C_s}}$$

- Describes the "the amount of drug released from a layer of ointment in which the drug is initially uniformly dissolved"

$$Q = hC_o\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\alpha}\frac{1}{(2m+1)^2}\, exp\left(-\frac{D(2m+1)^2\pi^2 t}{4h^2}\right)\right]$$

Q = Amount released at time t per unit area of application
h = The thickness of the diffusion layer
C_0 = initial concentration of the drug in the ointment
D = Diffusion constant of the drug in the ointment
m = An integer with a value between 0 and infinity
A = drug concentration (units/cm3)
Cs = drug solubility in external phase of ointment (units/cm³)
D = drug diffusion constant in external phase of ointment

Diffusion of topical drugs

Diffusion parameters and kinetics:

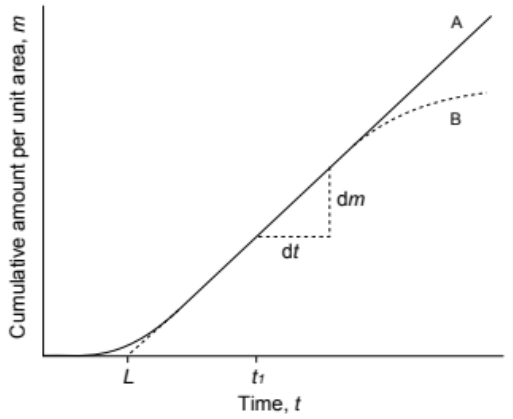
- **Franz & Lehman, 1995 (Finite Dose Equation)**

$$J = {}^{2P^2DC_0}/_{\nu} \sum_{n=1}^{\infty} \frac{\alpha_n e^{-D\alpha_n^2 t}}{sin\ \alpha_n i[i(\alpha_n^2 + h^2) + \nu]}$$

J = Flux (µg/cm2/hour)
P = Partition Coefficient
l = Stratum corneum thickness
α_n= Roots of [α i tan α i] = P/v i
C_0 = Concentration at t = 0
D = Diffusion Coefficient
v = Thickness of applied formulation

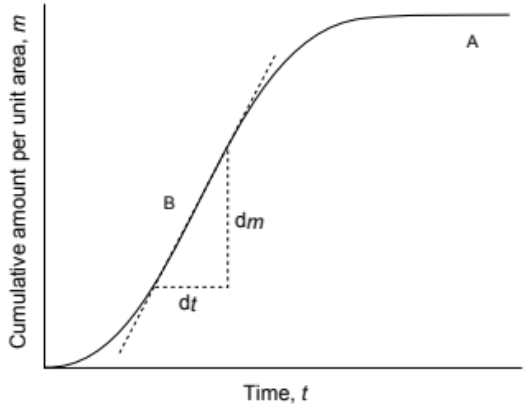
- Accounts for the thickness of the applied dose as well as dose depletion over time.
- It is used to predict permeant concentration at a given position inside the stratum corneum and at a given time.
- More relevant to clinically applied thin film doses to skin; however, very few studies have used this mathematical model.

Infinite dose regimen



- Graph A (solid line) represents a typical permeation profile for an infinite dose regimen.
- Graph B shows an alternate situation where a plateau is reached following prolonged incubation, indicating deviation from infinite dose conditions, due possibly to donor depletion or non-sink conditions

Finite dose regimen



- Graph A (solid line) represents a typical permeation profile for a finite-dose regimen.
- Given that steady-state flux may not be obtained before donor depletion becomes significant, the maximum flux may not represent steady-state flux.

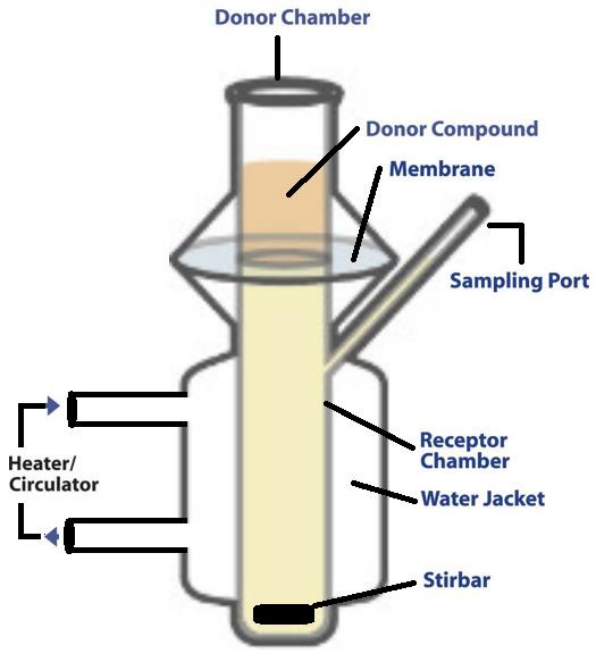
Diffusion testing

USP General Chapter <1724>: Semisolid Drug Products - Performance Tests

- Describes diffusion cell models.
- Provides technical methodology for the use of each model.
- Provides recommendations and guidelines for the test parameters.

Dermatomed skin

Membranes



Vertical diffusion cells (VDC)

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⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

General Chapters

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* ⟨724⟩ provides procedures and details for testing drug release from transdermal systems, and this chapter ⟨1724⟩ provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter ⟨3⟩. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP *Apparatus 4*. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug

Diffusion testing

USP General Chapter <1724>: Semisolid Drug Products - Performance Tests

- In vitro performance tests for semisolid products do not directly predict the in vivo performance of drugs.
- In vitro performance tests may be used to detect in vitro changes that may alter the in vivo performance of the dosage form.
- These in vitro changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.


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Diffusion testing

USP General Chapter <1724>: Semisolid Drug Products - Performance Tests

- Several apparatus may be used to assess drug diffusion, including the vertical diffusion cells, immersion cells, and a special cell used with USP Apparatus 4.
- The primary use of in vitro drug release testing is comparison testing in which any difference in delivery rate is undesirable.
- Drug release testing is most suitable for evaluation of slight variation in formulation composition and process changes, manufacturing site, and stability testing.
- Significant formulation changes may result in unmeaningful results, unless extensive validation is performed to select test parameters that ensure that the sensitivity of the test is meaningfully correlated with in vivo performance.

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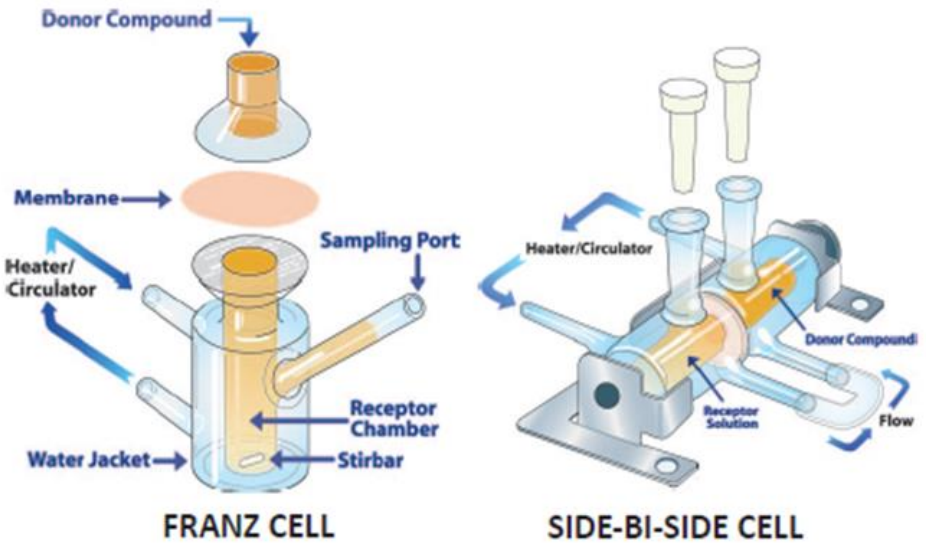
Official from December 1, 2016

Diffusion apparatus

❑ Static cells (Vertical or Side-bi-Side)

- Vertical cells or Side-bi-Side cells uses fixed volume receptor chamber, controlled temperature, port to sample receptor fluid, and stirred receptor fluid.
- Side-Bi-Side cells allow stirring of both the donor and receptor chambers.
- **Technical considerations:**
  1. Sink conditions are maintained for a highly permeable compound with a large volume receptor chamber.
  2. Non-sink conditions result for a highly permeable compound with a small receptor chamber; therefore, slows the flux of the compound.
  3. Analytical detectability could be a problem for a low permeability compound with large volume receptor chamber.



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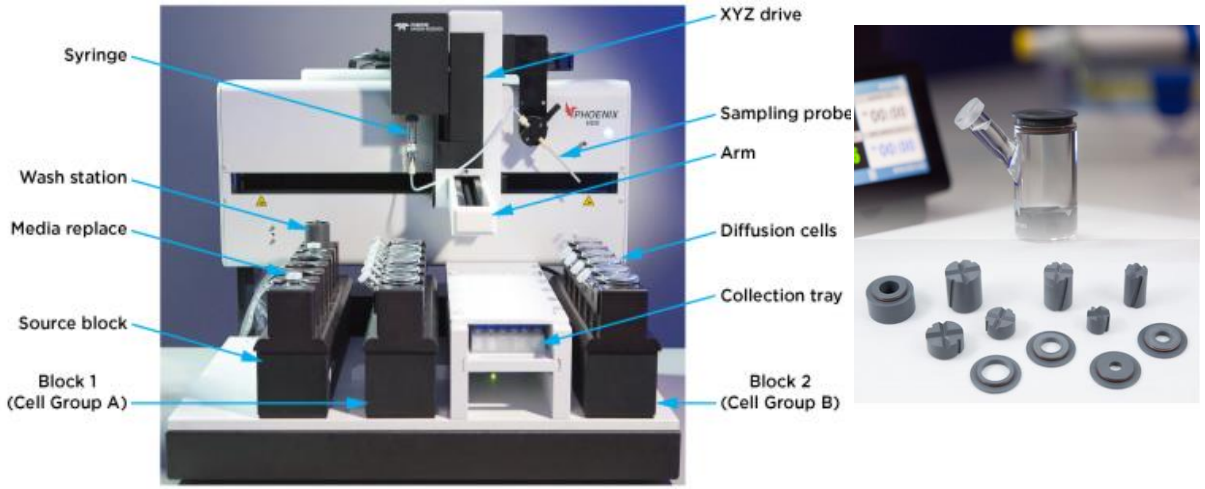


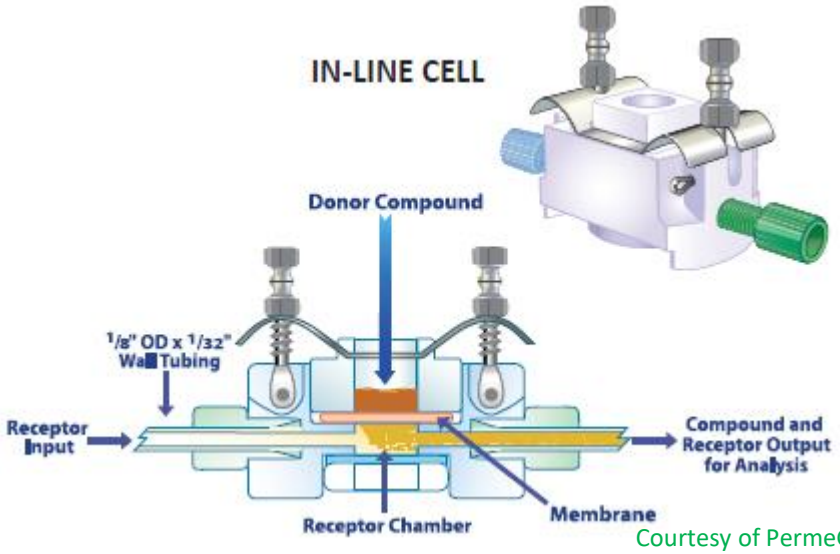
Teledyne Hanson Automated Diffusion System

Diffusion apparatus

❑ Continuous flow cell or flow-through cells

- In-Line cells (Type 1) have a continuous flow of the receiver media which causes turbulence in the receptor chamber and simulates stirring.
- Flow-through cells (Type 2) use a fixed volume of receptor chamber, controlled temperature, and adjustable flow rate.
- **Technical considerations:**

1. For a highly permeable compound with high flow rate necessary to clear the receptor chamber to maintain gradient, a large volume of permeant to analyze results in.
2. For a low permeability compound with high flow rate necessary, a large volume of permeant may result in challenges in drug detection.
3. Low flow rate in a smaller receptor chamber may result in smaller permeant volumes thus better detection.



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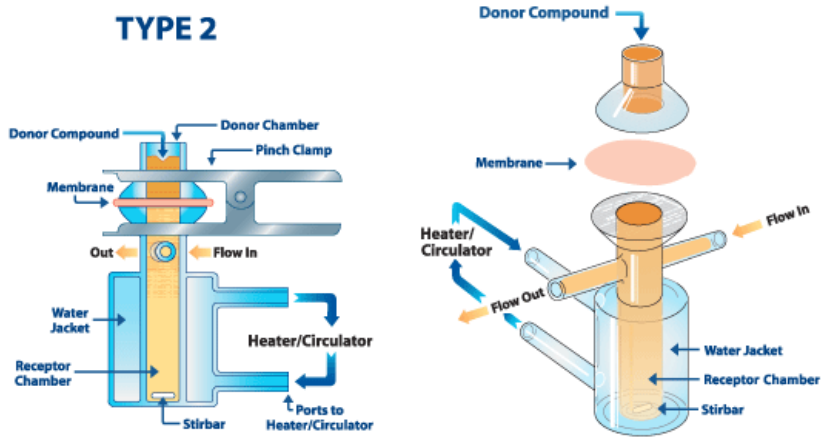


Courtesy of PermeGear, Inc.

Technical challenges

Selection of membrane type or permeation barriers

1. Human tissues (ex-vivo) **2. Animal tissues (small or large)**
3. Polymeric artificial membranes **4. Engineered 3D skin constructs**

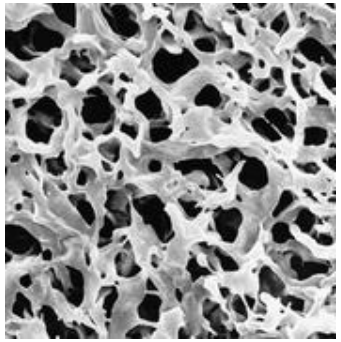
Dermatomed skin

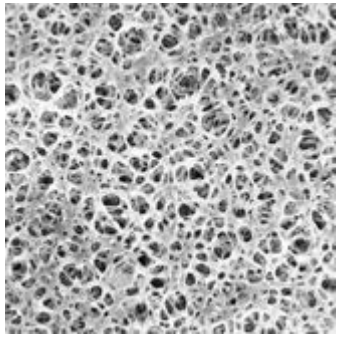
Membranes

- For IVRT, diffusion occurs across an inert, highly permeable support membrane. The membrane is intended to keep the product and the receptor medium separate and distinct. Membranes should offer the least possible diffusional resistance and should not be rate controlling.

- **Identification of the candidate membranes is based upon the following:**
  - Pore size (~0.5 µm ± 0.3 µm is often suitable; e.g., 0.45µm)
  - Consider pore size relative to the viscosity of the formulation
  - Potential for receptor solution back-diffusion (and stirring rate)
  - Typical binding/inertness characteristics of the material
  - Hydrophobic vs. hydrophilic material of the membrane
  - Chemical compatibility of material with the receptor solution
  - Consistent commercial availability

Examples of membranes
- Cellulose Acetate
- Cellulose Nitrate
- Mixed Cellulose Esters
- Nylon
- Teflon
- PTFE
- Durapore
- PVDF
- Versapor acrylic copolymer
- Polyethersulfone
- Tuffryn polysulfone





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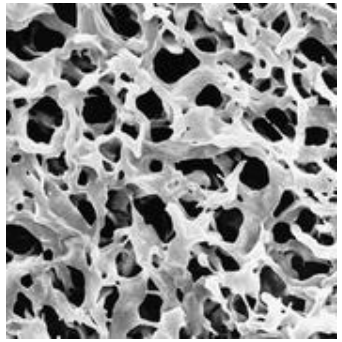
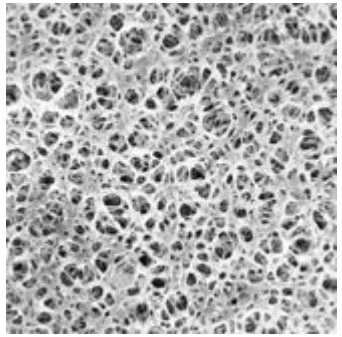
Dermatomed skin

Membranes

For IVPT:

- Excised skin is the main barrier for drug diffusion.
- Evaluation of the stratum corneum barrier integrity.
- Barrier integrity tests may be based upon tritiated water permeation, trans-epidermal water loss (TEWL), or electrical impedance/conductance measured across the skin.
- The test parameters and acceptance criteria utilized for the skin barrier integrity test.
- The skin thickness should be relatively consistent for all donors.
- The assignment of replicate skin sections from a donor to each treatment group should be randomized, as feasible.
- The ethical and legal considerations for using skin samples.



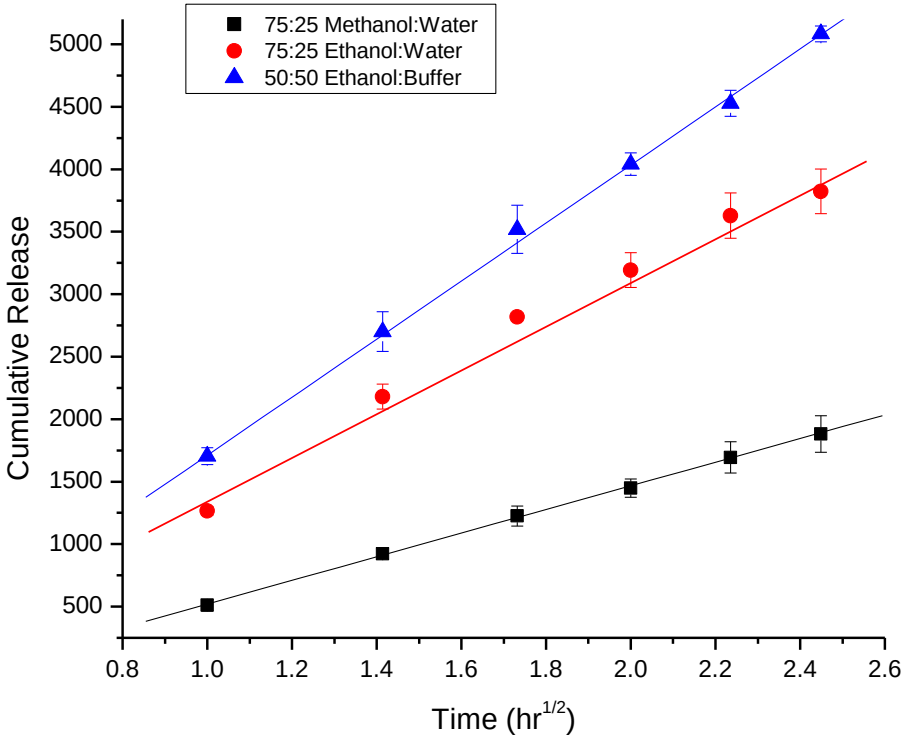


Technical challenges

Identification of receptor solution

For IVRT:

- Solubility and stability of the active ingredients
- Maintenance of sink conditions (use of solubilizer such as surfactants, BSA, lipids, polymers, etc.)
- Aqueous miscibility and suitability for chromatographic analysis.
- Effect of salt species, concentration and pH on diffusion kinetics.



For IVPT:

- Same as IVRT, plus ..
- Compatibility with skin (alcohol and detergent effects)
- Inclusion of antimicrobial agent (e.g., ~0.1% sodium azide or ~ 0.01% gentamicin sulfate) to mitigate potential bacterial decomposition of the dermis and/or epidermis of skin samples through the study duration.

Technical challenges

Dose application

- Dosage dispensing device
- Dosage application techniques
- Finite dose vs In-finite dosing
- Occlusion vs non-occlusion (IVPT)
- **Control of procedures related to the dose:**
  - Area of dose application
  - Dose amount
  - Dosing technique
  - Dose duration
  - Blinding and randomization procedures
  - Differences in dosing technique may alter the metamorphosis of the dose
  - Inconsistencies in the diameter of the area dosed may results in errors in the flux.

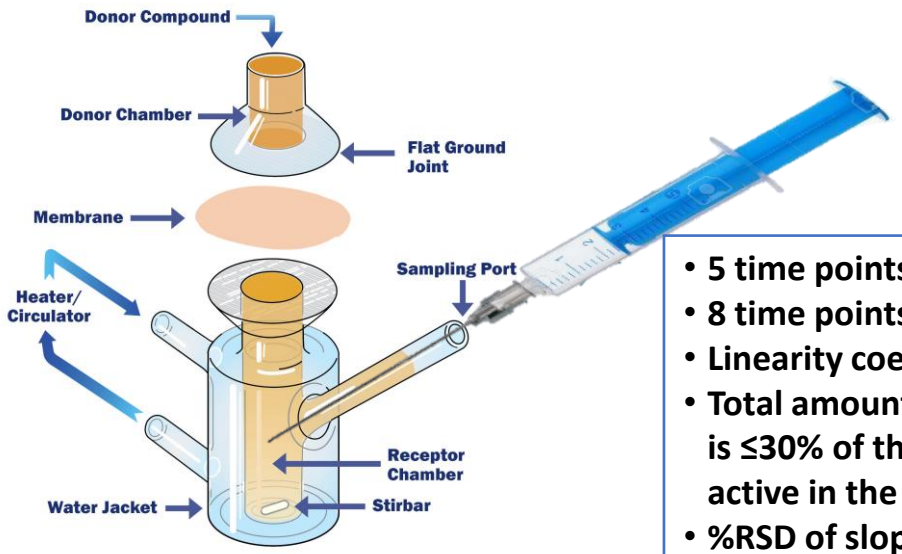
Dosage forms	Volume or quantity	Application method	Removal method
Liquid	Minimal volume: 5 µL	Micropipette, spread w/ inoculating loop	Micropipette, rinse with solvent
	100 µL		
Oils	Minimal volume: 1 µL	Positive displacement pipette, spread w/inoculating loop or closed-end round-bottom capillary tube	Q-tips w/ known volume of extraction solvent
Semisolids	1 µL to 4 µL		
	5 µL or more		
Solids (Powder)	According to protocol	Syringe and spread w/ inoculating loop	Water/solvent, micropipette
TDS	According to protocol	Cut to proper size, apply to skin surface with pressure	Forceps, rinse w/ known volume of extraction solvent
Microneedles	According to protocol	Apply to skin surface with pressure	Forceps, rinse w/ known volume of extraction solvent

Courtesy of OTR training course to OGD reviewers, Dr Yang Yang

Technical challenges

Sample collection

- Fine needle with long stock and 1 mL syringe

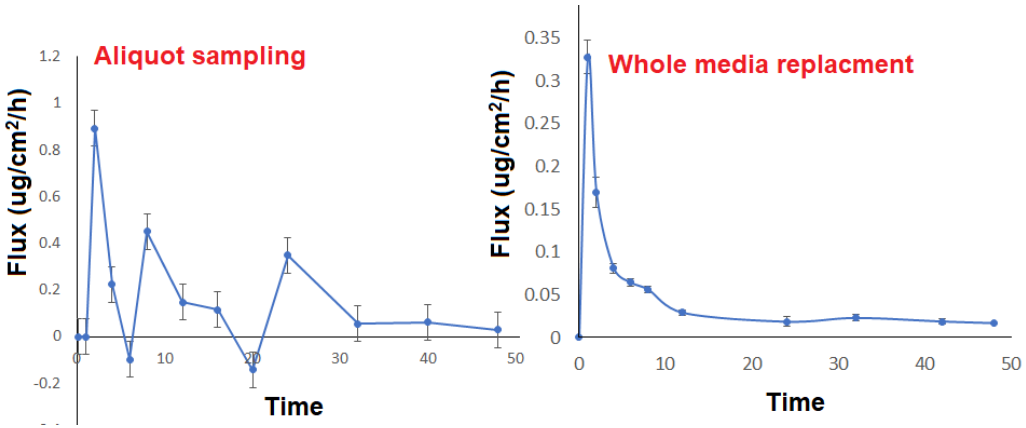


- **5 time points minimum (IVRT)**
- **8 time points minimum (IVPT)**
- **Linearity coefficient (R^2) ≥ 0.90**
- **Total amount of drug diffused is ≤30% of the total amount of active in the applied dose**
- **%RSD of slope ≤ 20%**

- Fraction collector – for flow through cells
- Automated sampling – collect in HPLC vials
- Handling and retention of Testing Samples. Ref to 21 CFR 320.38, 320.63 and FDA guidance.

Sampling method and schedule

- Identification of adequate sampling time intervals, frequency, and volume.
- For IVPT, loss of skin contact with the receiver media during whole media replacement. Effect of positive pressure in automated sampling on skin integrity should be considered.
- Changes in the release/permeation flux curve by changing from aliquots to whole media replacement.



Optimization of diffusion test parameters

Selection of the best receptor solution and test parameters is based upon:

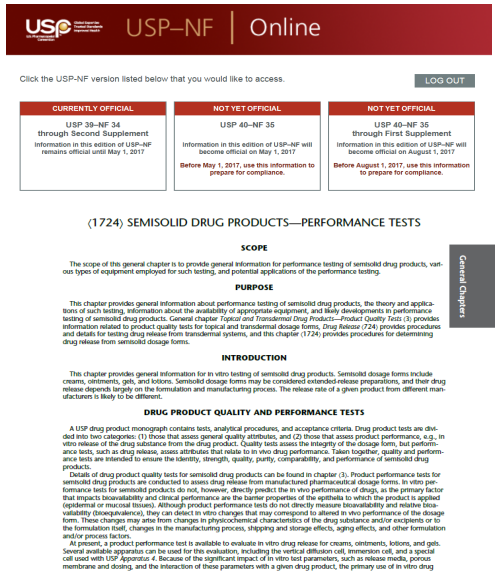
- Top-end drop off (adjust sampling schedule as appropriate)
- Bottom-end lag (adjust sampling schedule as appropriate)
- Linearity of release (r^2)
- Coefficient of Variation for linearity among replicate diffusion cells (%CV)
- Magnitude of Release/permeation (Slope)
- Coefficient of Variation for slope among replicate diffusion cells (%CV)
- Identify a cutoff for acceptability of Slope %CV (e.g., < 10%)
- Prefer higher ratios of excess solubility capacity in the receptor solution relative to the average and minimum API solubility in the receptor solution
- Prefer lesser extent of API depletion from the applied dose
- Consider matrix compatibility with the HPLC sample analysis method

Apparatus qualification parameters

- For IVRT or IVPT method, the apparatus utilized should be appropriately validated
- Qualification of the IVRT apparatus is described in USP <1724>
- Unless the method specifies otherwise, the qualification of the apparatus has been verified when
- Analysts determine that the test temperature and stirring rate are within their specified requirements and
- A satisfactory performance verification test results.
- Supporting documentation (e.g., certificates of conformance)
- Guidelines for installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) of VDC apparatus and accessories
- Recommended schedules for maintenance and re-qualification

Qualification Parameters

- Cell orifice diameter
- Receptor medium
- Membrane temp
- Sampling volume
- Stirring speed
- Environmental conditions
- Cell capacity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⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

General Chapters

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* ⟨724⟩ provides procedures and details for testing drug release from transdermal systems, and this chapter ⟨1724⟩ provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that asses general quality attributes, and (2) those that asses product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter ⟨3⟩. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP *Apparatus 4*. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug

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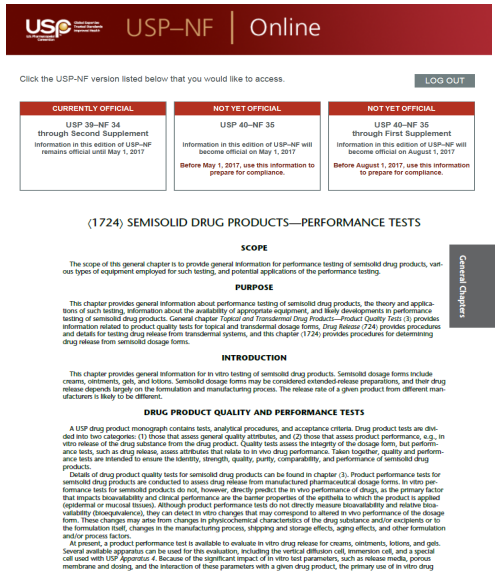
Apparatus qualification parameters

USP <1724> Independently specifies that

- The diameters of the orifices of the donor chamber and receptor chamber, which define the dosage delivery surface area for the test, should be sized within ±5% of the specified diameter.
- The diameter of the donor and receptor chamber orifices may vary depending on the application.
- The receptor chamber orifice should never be smaller than the orifice of the donor chamber.
- The design of the VDC should facilitate proper alignment of the donor chamber and the receptor orifice.
- The receptor chamber should be manufactured consistently with uniform height and geometry.
- All the cells should have the same nominal value, and the true volume should be measured for each individual cell.

Qualification Parameters

- Cell orifice diameter
- Receptor medium
- Membrane temp
- Sampling volume
- Stirring speed
- Environmental conditions
- Cell capacity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Apparatus qualification parameters

Control Parameter	Description	Target Specification	Average Value	Precision	Result
Manufacturing Specification - Flat Ground Joint	11.28mm Diameter Donor Orifice	11.28mm ± 5%	11.37mm	0.09% CV	PASS
Manufacturing Specification - Flat Ground Joint	11.28mm Diameter Receptor Orifice	11.28mm ± 5%	11.38mm	0.20% CV	PASS
Manufacturing Specification - O-Ring Joint	11.28mm Diameter Donor Orifice	11.28mm ± 5%	11.28mm	0.49% CV	PASS
Manufacturing Specification - O-Ring Joint	11.28mm Diameter Receptor Orifice	11.28mm ± 5%	11.42mm	0.59%CV	PASS
Manufacturing Specification - Flat Ground Joint	15.00mm Diameter Donor Orifice	15.00mm ± 5%	15.04mm	0.36% CV	PASS
Manufacturing Specification - Flat Ground Joint	15.00mm Diameter Receptor Orifice	15.00mm ± 5%	14.94mm	0.43% CV	PASS
Manufacturing Specification - O-Ring Joint	15.00mm Diameter Donor Orifice	15.00mm ± 5%	15.01mm	0.38% CV	PASS
Manufacturing Specification - O-Ring Joint	15.00mm Diameter Receptor Orifice	15.00mm ± 5%	14.99mm	0.24% CV	PASS
Dose Area - 1cm^2 O-Ring Joint	Actual Area of 1% HC Cream dose	Dose Area Precision of ± 5%	1.34 cm^2 Dose Area	2.48% CV	PASS
Dose Area - 1cm^2 Flat Ground Joint	Actual Area of 1% HC Cream dose	Dose Area Precision of ± 5%	1.08 cm^2 Dose Area	2.22% CV	PASS
Manufacturing Specification - Magnetic Impeller	Stirring at 600 rpm	600 rpm ± 10%	601.5 rpm	0.54% CV	PASS
Manufacturing Specification - Stir Bar (1cm^2)	Stirring at 600 rpm	600 rpm ± 10%	598.5 rpm	0.29% CV	PASS
Manufacturing Specification - Stir Bar (2cm^2)	Stirring at 600 rpm	600 rpm ± 10%	599.6 rpm	0.25% CV	PASS
Manufacturing Specification - 1 cm^2 Flat Ground Joint	Receptor Volume Control	5.5mL ± 5%	5.5mL	1.69% CV	PASS
Manufacturing Specification - 1 cm^2 O-Ring Joint	Receptor Volume Control	6.0mL ± 5%	5.9mL	3.59% CV	PASS
Manufacturing Specification - 2 cm^2 O-Ring Joint	Receptor Volume Control	7.0mL ± 5%	6.9mL	2.50% CV	PASS
Manufacturing Specification - 2 cm^2 Flat Ground Joint	Receptor Volume Control	7.0mL ± 5%	7.0mL	0.58% CV	PASS
Membrane Temperature - 1 cm^2 Flat Ground Joint	Temperature Control over 6 hr duration	32°C ± 1°C	32.3°C	± 0.32°C	PASS
Membrane Temperature - 1 cm^2 O-Ring Joint	Temperature Control over 6 hr duration	32°C ± 1°C	32.5°C	± 0.14°C	PASS
Membrane Temperature - 2 cm^2 O-Ring Joint	Temperature Control over 6 hr duration	32°C ± 1°C	32.5°C	± 0.12°C	PASS
Membrane Temperature - 2 cm^2 Flat Ground Joint	Temperature Control over 6 hr duration	32°C ± 1°C	32.2°C	± 0.14°C	PASS
Membrane Temperature - 1 cm^2 Flat Ground Joint	Linear drug release over 6 hr duration	Mean $r^2 > 0.90$	$r^2 > 0.99$	All Cells	PASS
Membrane Temperature - 1 cm^2 O-Ring Joint	Linear drug release over 6 hr duration	Mean $r^2 > 0.90$	$r^2 > 0.99$	All Cells	PASS
Membrane Temperature - 2 cm^2 O-Ring Joint	Linear drug release over 6 hr duration	Mean $r^2 > 0.90$	$r^2 > 0.99$	All Cells	PASS
Membrane Temperature - 2 cm^2 Flat Ground Joint	Linear drug release over 6 hr duration	Mean $r^2 > 0.90$	$r^2 > 0.99$	All Cells	PASS

Qualification Parameters

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- Receptor medium
- Membrane temp
- Sampling volume
- Stirring speed
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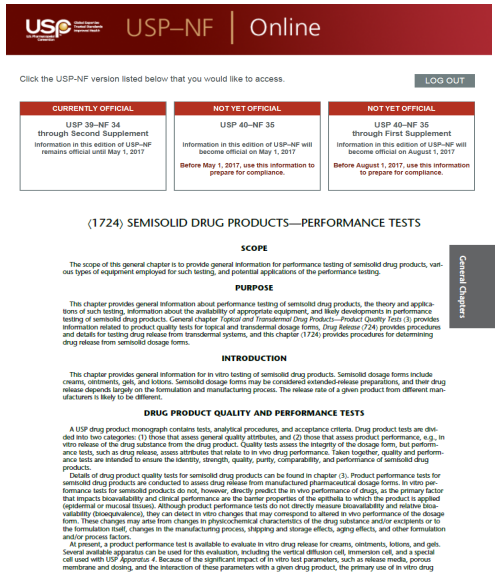
- Cell capacity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⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

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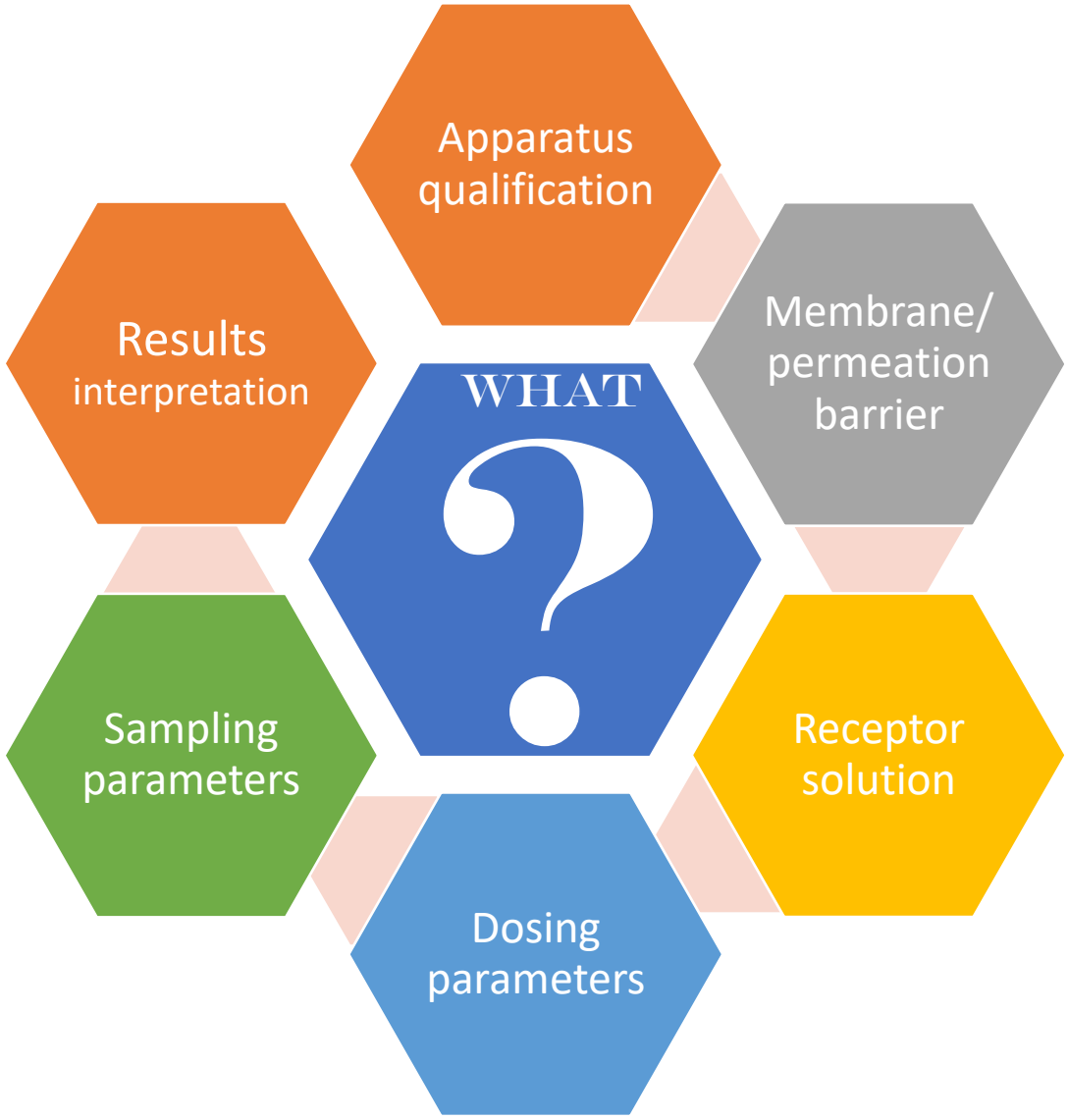
Key takeaways

- Adequate diffusion testing of topical product may be achieved by coupling an appropriate diffusion apparatus with a well-planned experimental protocol with clear objectives.
- Adequate control over the instrumental and test parameters beforehand will reduce the number of failed attempts and produce consistency between experiments that is crucial when comparing results.

- **Questions to be answered before attempting any diffusion experiments:**

1. What are the critical physicochemical characteristics of API(s)?
2. What are the expected diffusion kinetics?
3. What is the appropriate diffusion apparatus?
4. What is the critical diffusion test conditions ……



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