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Advances in Product Quality and Performance Tests for Topical and Transdermal Products: View of the USP Expert Panel

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ABSTRACT

Quality and performance testing of topical and transdermal products encompasses a broad set of product types, test equipment, and unique considerations. This *Stimuli* article is one in a series of such articles on product testing methods that explore the relevant considerations and identify opportunities for standardization with different types of quality and performance tests. The objective of this *Stimuli* article is to highlight current knowledge gaps and potential challenges associated with quality and performance tests for certain topical and transdermal products, and to stimulate public input from product testing labs, product developers, regulators, and others. The input received may inform the development or revision of USP general chapters.

INTRODUCTION

Quality and performance testing is a key part of formulation and product development. Appropriately developed test methods can facilitate an enhanced understanding of a product, and of the manner in which manufacturing process parameters alter the attributes and behavior of that product. These insights can help product developers mitigate the risks associated with inconsistent performance or unexpected failures during clinical development and manufacturing.

For topical and transdermal products, established performance tests described in the USP general chapter *Semisolid Drug ProductsPerformance Tests <1724>* (*1*) are routinely utilized to evaluate the rate of drug release, using an in vitro release test (IVRT), and the rate and extent of drug permeation into and through the skin, using an in vitro permeation test (IVPT). Best practices have been established for the development, validation, conduct, and analysis of IVRT and IVPT methods, and as a result, these tests are routinely used to guide the formulation, reformulation, process development, and control of topical semisolid dosage forms.

A detailed discussion of IVRT or IVPT methods, which are already well established, is beyond the scope of this article. Readers are referred to the following resources where the IVRT and IVPT methods are discussed in detail:

- Proceedings from the public workshop co-sponsored by the US Food and Drug Administration and the Center for Research on Complex Generics, titled: *In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions*" available at complexgenerics.org/IVRTIVPT (*2*).
- Proposed revision of <1724> in *PF* 48 (*3*). The proposed revision discusses the experimental design and method development considerations for IVRT and IVPT methods. Also, appropriate contexts for use of IVRT and IVPT studies are discussed, providing a guide for selecting which test method is appropriate based on the goals of the study.
- FDA Draft Guidance for Industry: *In Vitro*

Permeation Test Studies for Topical Drug Products Submitted in ANDAs (October 2022) (*3*)

- FDA Draft Guidance for Industry: *In Vitro Release Tests Studies for Topical Drug Products Submitted in ANDAs* (October 2022) (*4*)

This *Stimuli* article focuses on novel dosage forms that utilize microneedles and novel product quality tests such as those which characterize the arrangement of matter in dosage forms. The development and assessment of these topical and transdermal dosage forms necessitates the identification and standardization of suitable practices, technologies, equipment, test methods, and data analysis procedures. In addition, certain existing test methods may have limitations, and may benefit from these improvements. This *Stimuli* article discusses current challenges and opportunities related to quality and performance testing in these areas, with the intent to stimulate public comments about how USP can contribute to the establishment of best practices and standards for such tests. This *Stimuli* article will specifically focus on the following novel product quality and performance test considerations for topical and transdermal dosage forms:

- In vitro adhesion tests for transdermal and topical delivery systems (collectively called TDS)
- In vitro quality and performance tests for microneedle array systems
- Physicochemical and structural (Q3) characterization tests for topical drug products

IN VITRO TDS ADHESION PERFORMANCE TESTS

The surface area of a TDS that is dosed upon the skin and remains adhered to the skin can modulate the amount of drug delivered into, and through the skin at any point in time. The entire contact surface area of a TDS should ideally remain consistently and uniformly adhered to the patient's skin throughout the duration of wear. When a TDS loses its adherence during wear, the amount of drug delivered to the patient may be reduced. Therefore, the adhesive properties and adhesion performance of a TDS product is routinely evaluated with tests that assess peel adhesion, release liner peel, and tack, as outlined within *Topical and Transdermal Drug Products-Product Quality Tests* <3> (*5*).

Each of these tests measures the force required to separate the TDS from another surface. In addition to characterizing the adhesive properties, cold flow and shear tests also measure the cohesive properties of a TDS formulation based on the resistance to flow of the adhesive matrix. Although useful to monitor batch-to-batch consistency, these tests have limitations, that make it challenging to correlate the test results with the in vivo adhesion performance of TDS. Thus, it is difficult to assess whether or not variations in manufacturing parameters that alter the results of these tests might also impact the clinical performance of the product.

A fundamental issue is that the current compendia! methods to evaluate the adhesive properties and adhesion performance of a TDS product are not designed to be biorelevant. However, such tests could be designed in a manner that systematically consider the influence on adhesion performance of intrinsic TDS attributes such as size, shape, adhesive type, adhesive system, adhesive formulation, TDS design, and the flexibility, stretchability, and occlusivity of the backing membrane. In addition, to help provide test results that relate to the real-world performance of a TDS on a patient, the tests may need to emulate extrinsic factors that have the potential to impact TDS adhesion, including the anatomically relevant temperature, curvature, torsion/flexion, softness, micro-topographical features, moisture, and flaking (micro-delamination) of the surface substrate.

Therefore, public input is sought from investigators who work with TDS products to clarify what intrinsic properties and extrinsic factors are most likely to influence in vivo adhesion performance, and to conceive novel test methods that are intentionally designed to monitor the performance of TDS products under biorelevant conditions. It may also be important to assess adhesion performance over time scales that are relevant to the wear period of the product, because the surface area of a TDS may progressively detach to greater degrees at longer time points. Also, in order to correlate in vitro adhesion test results with in vivo observations, it would be important to harmonize in vitro and in vivo study designs and control parameters.

PRODUCT PERFORMANCE TESTS FOR MICRONEEDLE ARRAY SYSTEMS

There are a variety of microneedle array systems being studied and/or under development, and there is a need for an in vitro performance test that would correlate with and be predictive of the in vivo performance of these products. Each microneedle variant may have unique aspects to characterize, whether it involves drug coated microneedles, dissolvable microneedles with drug formulated into the microneedles themselves, or larger capacity hydrogel dissolvable microneedles (Avcil et al.,

2021) (*6*). A focus on the commonalities of the variants and the fundamental drug product attributes that are critical for microneedle drug product performance can help guide the development of a predictive in vitro performance test. There are two fundamental aspects relevant to clinical performance that are common to all microneedle variants: 1) microneedle insertion, and 2) dissolution/drug release of the active ingredient.

The product quality attributes and related considerations that may impact product performance (e.g., microneedle insertion) can include, but are not limited to, microneedle geometry (including length and spacing), tip sharpness, application velocity, force, and duration, as well as the impact of drug loading on microneedle strength for both coated and dissolving microneedles. Some of the mechanical testing related to microneedle insertion has been discussed by Lutton et al., 2015 (*7*); however, the most important aspect of product performance is to measure the microneedle penetration and the deposition of drug below the stratum corneum when a clinically relevant application force is used.

In relation to drug release/deposition below the stratum corneum, several product quality attributes can impact the product performance, such as the solubility of the drug, the formulation, the location of the drug in or on the microneedles, and the uniformity across the microneedle array with regard to location and duration of insertion. While the duration of microneedle application evaluated in many pre-clinical microneedle studies can be up to 24 h, it is preferable to minimize the application time in the clinical setting. An ideal performance test would ideally also identify a target duration of application (as well as a minimum time and maximum time, to guide human factors studies) that would provide consistent clinical performance while minimizing the application time.

Examples of performance test methods for a microneedle array system that combines assessments of microneedle insertion and in vitro drug release have been described by Larrañeta et al., 2015 (*8*). In one implementation of this methodology, dissolving microneedle arrays containing 196 needles (600 mm needle height) were inserted into a single layer of Parafilm M (PF), and a hermetic "pouch" was created including the array inside (Fig. 1A). The hermetic "pouch" containing the microneedle array system was placed in a dissolution bath and the rate of drug release was evaluated (Fig. 1B). Different microneedle formulations were tested using this methodology, releasing between 40 and 180 mg of a drug after 6 h. In another implementation of this methodology, the microneedle penetration through a PF membrane was tested using a vertical diffusion cell (Fig. 1C) yielding comparable release curves. Microscopy was used in order to characterize the insertion of the different microneedle arrays in the PF membrane.

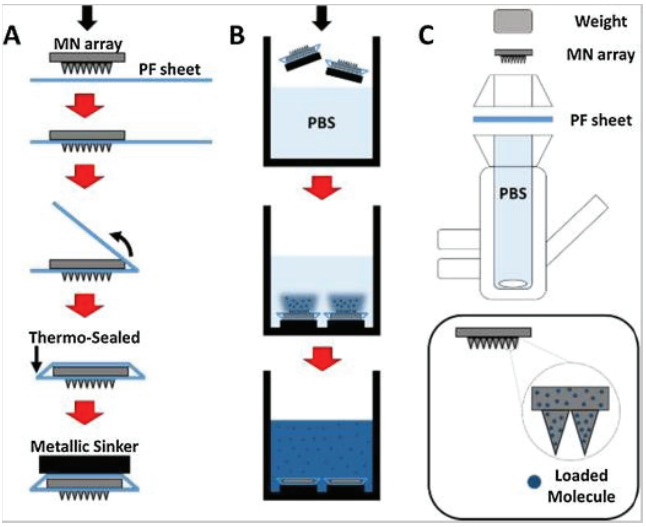

*Figure 1. (**A**) Diagram illustrating the insertion and preparation of a microneedle pierced through a PF membrane and enclosed in a hermetic "pouch". (**B**) Diagram illustrating an in vitro release test in which the hermetic "pouch" is immersed in a dissolution vessel. (**C**) Diagram illustrating an in vitro release test in which the microneedle array system penetrates through a PF membrane mounted in a vertical diffusion cell. [Image courtesy of Larrañeta et al., 2015, (8)].*

The performance tests described by Larrañeta et al., 2015 (*8*) illustrate how interdependent performance attributes may need to be considered in the design of suitable test methods. Ideally, pre-clinical and/or clinical data should be used as a basis for validating the test in order to assess an in vitro-in vivo correlation (IVIVC). For example, Tekko et al., 2022 (*9*) conducted a preclinical in vivo study using Sprague Dawley rats to evaluate a microneedle array system containing cabotegravir. Examples of such clinical studies with microneedles are limited. However, there is clinical data as well as pre-clinical data available for abaloparatide, including different formulations of coated microneedles (Bahar et al., 2015 (*10*); Hattersley et al., 2017 (*11*); Miller et al., 2021 (*12*). Such information could potentially provide a basis to validate a testing approach using an appropriate application force, velocity, and duration, as well as to provide additional validation to assess whether the aforementioned PF membrane (or another membrane that may serve as a mechanical surrogate for human skin) has the appropriate thickness, resistance to penetration, and elasticity to suitably represent how human skin influences the clinical performance of microneedle array systems. For example, the clinical performance of a microneedle array system may be influenced by the coating on the solid microneedles; if the drug was predominantly coated

on regions close to the baseplate that do not penetrate below the stratum corneum to deliver the full dose, or if the coating on the needles had a tendency to be physically displaced from the tip to the baseplate upon microneedle insertion, then the drug delivery may be significantly impacted. An in vitro performance test that could discern such effects would be ideal.

The development of an in vitro performance test for microneedle array systems would ideally include optimization of the membrane that mechanically emulates relevant attributes of human skin, potentially leveraging ideas from performance tests developed for other complex dosage forms, such as the use of hydrophobized alginate hydrogels for the vessel-simulating flow-through cell described by Semmling et al., 2013 (*13*) for biorelevant drug-eluting stent testing. Alternatively, if the human skin is determined to be the optimal membrane to utilize in the test, it may be appropriate to evaluate whether a standardized test system may be utilized, such as commercially available preparations of ex vivo human skin in transwell systems described by Larson et al., 2021 (*14*) and developing a microneedle testing system based on such a model. One potential advantage of such a test system with viable human skin, is that it may also be able to assess certain skin responses to the application of a microneedle array system, and possibly the rate and extent of drug permeation through the deeper epidermal and dermal layers of the skin.

Therefore, public input is sought from investigators who work with microneedle array systems to comment on the current needs and uses for in vitro quality and performance test methods for these dosage forms, particularly relating to microneedle insertion performance testing and in vitro release testing. It would be helpful to receive comments relating to any considerations that may be unique to different types of microneedle array systems (coated, dissolvable, etc.) and to receive comments on the potential development of any preferred test system or testing methods currently utilized or proposed, including but not limited to those described above, which should be further developed to establish as a new USP compendia! test.

PHYSICOCHEMICAL AND STRUCTURAL (Q3) CHARACTERIZATION TESTS

When considering the critical quality attributes that modulate the performance of most liquid-based and other semisolid dosage forms (e.g., topical lotions, transdermal gels, vaginal creams), it is helpful to think about these within a conceptual framework that describes the type, amount, and arrangement of matter in the dosage form. The type of matter in a dosage form is routinely described by its ingredients, typically specified further in terms of a particular grade of that ingredient-this is a description of its qualitative components (i.e., Q1). The amount of each type of matter in a dosage form is routinely described by a formula that defines the relative proportion of each of the ingredients in the formulation-this is a description of its quantitative composition (i.e., Q2). Every batch of a pharmaceutical product is designed to have the same Q1 and Q2 attributes (within specified tolerances) because significant differences in the components or composition of a product may alter its performance from batch to batch.

In addition, manufacturing process parameters are also controlled within specified limits, because they can influence the arrangement of matter in the dosage form. This is very important, because the resulting physicochemical and structural (Q3) attributes are analogous to the molecular machinery within a dosage form that modulates numerous aspects of its performance. Thus, ensuring consistency in the Q1, Q2, and Q3 attributes of a product helps ensure consistent product performance. Regulatory concepts relating to Q3 characterization are described in FDA's Draft Guidance for *Physicochemical and Structural (Q3) Characterization of Topical Drug Products* (*15*).

There are established compendial standards to characterize the type, grade, and purity/potency of many ingredients which are routinely utilized in topical and transdermal products, so describing the Q1 and Q2 attributes of a product is relatively straightforward. Characterizing the Q3 attributes of a product typically involves a collection of specific tests that individually describe specific product attributes, and collectively describe the arrangement of matter in ways that are useful. However, different test methods can sometimes be used to characterize a particular Q3 attribute of a product, and the different methods may not provide the same information, so identifying and optimizing appropriate, standardized test methods for Q3 characterization is exceptionally useful.

Perhaps the simplest of the Q3 tests characterizes the appearance and texture of a product and may also describe attributes like odor. This test is frequently performed using human sensory assessments that describe the look and feel of a product as well as its smell, if relevant. Microscopic examination of the product can

help to characterize the number and type of phase states, describing features like globules and suspended particles. This can help to characterize the structural organization of matter in the dosage form, potentially defining whether it is an emulsion, what the globule size distribution or particle size distribution is, as well as identifying features like polymer matrices or crystal habits of any suspended drug.

These tests help us to understand the architecture and potential interactions among the molecular machinery of the system. For example, differences in globule size distributions would correspond to various factors such as differences in the surface area across which dissolved drug may partition from the globules to the continuous phase, and differences in the proportion of total interfacial surface area with the skin that may be occupied by the cross section of a globule, from which drug partitioning from a globule into the skin may be different than the same drug partitioning from the continuous phase into the skin.

The Q3 characterization of topical dosage forms is particularly important because their physicochemical and structural features may not be evident from their dosage form nomenclature. For example, a lotion may actually be a viscous single-phase solution, a gel may be an emulsion, a cream may not have globules, an ointment may or may not contain any petrolatum, and any of these may contain fully dissolved or partially suspended drug. If there is suspended drug, it would be appropriate to characterize the polymorph(s), and to characterize them within the drug product. If different polymorphic forms of the drug exist, then the control of these polymorphs in the product may be determined based on considerations outlined in decision tree #4 within the International Council for Harmonisation (ICH) specifications (*16*).

It is particularly important to recognize that the performance of topical and transdermal dosage forms may be modulated by their metamorphosis following their application on the skin, and potentially even by the metamorphosis during product dispense and dose administration. For example, many semisolid dosage forms are shear thinning, and differences in apparent viscosity may have the potential to alter the drug diffusion within the dosage form, flow properties on the microtopography and into the appendages of the skin, retention at the site of application, transfer to an unintended recipient, and other considerations.

The rheological behavior of a product reflects how the components interact within the molecular machinery, and how the system responds to stress. This typically involves using a rheometer that is appropriate for monitoring the potentially non-Newtonian flow behavior of liquid and semisolid dosage forms. Whenever it is feasible, it is ideal to characterize the flow curves across a range of attainable shear rates, typically until low- or high-shear plateaus are identified; at a minimum, it is important to characterize the apparent viscosity at low-, medium-, and high-shear rates. The best way to visualize comparative rheology data for a test and reference product is by plotting the data for both, shear stress versus shear rate, and viscosity versus shear rate. Also, if the product exhibits plastic flow behavior, then the yield stress should be characterized, and if it is relevant, the linear viscoelastic response can also be very informative; a good way to visualize this, is by plotting the storage and loss moduli versus frequency.

Another phenomenon that occurs during the metamorphosis of topical and transdermal dosage forms is evaporation of volatile components, including water. As these components evaporate, the composition of the product formulation changes, and this can lead to changes in drug solubility that alter the drug concentration as well as the amount of dissolved drug available for partitioning into the skin, along with alterations in the thermodynamic activity of the drug in the product (residue) on the skin. Therefore, it may be important to characterize the solvent (water) activity using an appropriate device, or to measure the drying rate gravimetrically, at relevant temperatures.

It is well understood that physicochemical properties like the pH of a product can have a substantial impact on a variety of potentially critical quality attributes, such as the viscosity of a gel or the ionization state of the drug, and the pH of the product following application upon the skin may be dependent upon how well the product is buffered. So, it may also be important to characterize the pH of products with aqueous formulations, and to characterize any buffer systems as well.

By contrast, for products comprised of more than 70% oleaginous contents (like many petrolatum-based ointments), it is typically feasible to characterize the product using the tests listed in the *USP* monograph for petrolatum, recording quantitative test results such as the actual pH of the pooled washings during an alkalinity test with a calibrated pH meter, or recording the result for a drop point test (described in *USP* general chapter <741>) as the average observed melting temperature. In addition to the quantitative tests, qualitative characterization of the relative proportions of different hydrocarbons

in petrolatum-based ointments may be particularly important since petrolatum is comprised of a mixture of hydrocarbon species, and differences in the proportions of hydrocarbons in that mixture may also alter the drug delivery from the ointment to the skin.

Different manufacturing process parameters (e.g., mixing rate and duration) may have the potential to alter the amount of entrapped air in a product formulation, which may in turn impact the delivered dose, so it may be considered prudent to characterize the specific gravity of a topical or transdermal semisolid product. Also, different packaging configurations may influence the shear forces exerted on the dosage form during dispensing (e.g., from a tube vs. a pump), so it may be important to characterize the influence of the container closure system on the Q3 attributes of the dispensed product. Additionally, product metamorphosis may occur as a function of aging, so it may be important to characterize Q3 attributes at different points in time across the shelf life of the product; the corollary is that, when characterizing multiple batches of a product, it is prudent to monitor trends where Q3 attributes may progressively change as a function of age.

Suffice it to say that characterization of the Q3 attributes of a topical or transdermal dosage form can be exceptionally informative, because these attributes can modulate how the product will perform under clinical use conditions, and because these Q3 characteristics enable us to systematically compare different aspects of the arrangement of matter between batch to batch of a product, between a reference and test batch of a product that may experience a post-approval change, and between a reference standard product and a generic product. The challenge is that compendia! test methods do not yet exist for many of the tests that may be utilized to facilitate Q3 characterization. For example, there are different methods, equipment, and test conditions that may be utilized to characterize Q3 attributes as simple as pH, or as complex as rheological behavior. Particle size distribution may be characterized in the dosage form by using optical microscopy or morphologically directed Raman spectroscopy. Similarly, the polymorphic form(s) of suspended drug in the dosage form may be characterized by X-Ray diffraction or by Raman spectroscopy.

Therefore, public input is sought from investigators who work with topical and transdermal products to clarify whether it is challenging to identify appropriate test methods, equipment, and conditions, and to determine the appropriate number of replicate measurements or the relevant data analysis and reporting considerations. It would be exceptionally valuable to ascertain from public comments to this *Stimuli* article whether USP should establish compendia! tests that represent a comprehensive tool kit of methods that can be utilized for Q3 characterizations of topical and transdermal products.

CONCLUSION

This article was written to raise awareness of the diversity and challenges to develop product performance tests methods for topical and transdermal drug products. It is the authors hope that the topics noted in this article will stimulate collaborative and harmonized research to develop test methodologies to become standards which can be incorporated into future compendia! chapters.

DISCLAIMER

The views presented in this article do not necessarily reflect those of the FDA. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

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