Diffusion Method Transfer Guide from Microette to Phoenix™ Diffusion Test Systems.

TELEDYNE HANSON
Everywhereyoulook™

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Ashvin Patel, Ph.D.

Introduction

Diffusion or permeation testing measures the release or permeation rate at which an active pharmaceutical ingredient diffuses from a semisolid preparation; it is a very good quality control tool to measure the critical performance data of semisolid formulation.

Diffusion testing using diffusion cells has become the industry standard due to the pioneering work of Dr. T. J. Franz, who developed the "Franz cell." The use of Franz cells is a widely used methodology to evaluate in vitro drug permeation or in vitro drug release. This device consists of a small-volume, water-jacketed cell (receptor compartment), and a donor compartment containing a chamber for drug application. A membrane is placed between the donor and receptor compartments. The drug may diffuse through this membrane into the receptor chamber. Samples may later be extracted from the chamber at a desired time point and analyzed for drug release. Later developments include non-water-jacketed, dry-heat cells such as Teledyne Hanson's Phoenix line of diffusion testers.

A traditional diffusion testing system typically has a group of six cells for simultaneous testing of six specimens. A magnetic cell drive controls the mixing of each cell receptor chamber throughout the test, and a circulating bath provides heated water to the jacketed cells to maintain a constant temperature. With the innovations in our newer systems, the receptor media — also known as a dry-heat cell — is heated directly to achieve a precise temperature. Samples are taken from the receptor chamber, and the same amount of media is then replaced to maintain a constant media-membrane interface.

Sampling of the receptor medium can be performed manually or automatically. Teledyne Hanson's manual diffusion testing systems consist of six cells, a cell drive, a speed control, and a manual sampling syringe. The analyst removes samples using the syringe and then replaces the medium. The automated system provides automated sampling, collection, and media replacement.

Background

Historically Teledyne Hanson manufactured and sold the Microette Diffusion system. Recent new requirements from industry and regulators have inspired Teledyne Hanson to redesign the diffusion system. To accomplish this, a non-water-jacketed, dry heat system, compliant with 21 CFR part 11, has been developed. This system maintains data integrity and keeps track of all the events that occur while using the system.

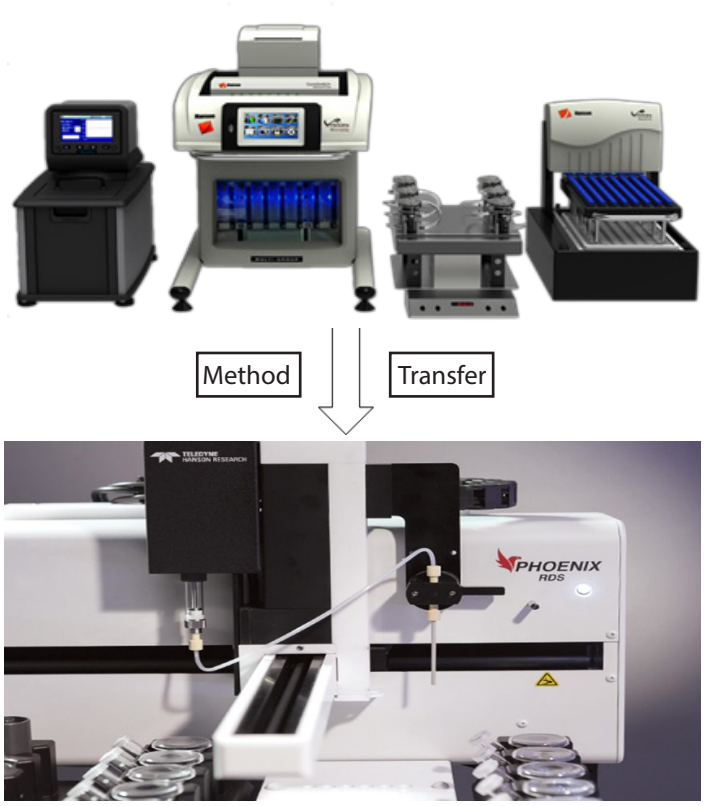

Figure 1: Image of the discontinued Microette diffusion system and the current Phoenix RDS

As is well known, when the process or a critical part of an analytical methodology gets changed, the analytical methods must be evaluated thoroughly to access the impact of those changes on product quality and, if needed, the method must be revalidated or verified per guidance provided by regulatory agencies and/or the United States Pharmacopeia. With the introduction of the new Phoenix system, the same approach is required for users who are upgrading to the newly developed Phoenix system from the Microette system. There are many guidance documents available for these users regarding method transfer. This document suggests a general approach to proceeding with method transfer from an older system (Microette) to the new system (Phoenix).

Procedure

The process used is the Method Transfer procedure[1]. This starts by evalutating the parameters that will be changed when changing the apparatus. Do not change the duration of the test (test length), HPLC test parameters, the orifice size of the donor chamber, and the dosing amount. Instead, list the main factors affected by the change, such as cell volume, stirring speed, etc. Also, evaluate the HPLC analytical test procedure for LOD/LOQ/ injection volume linearity, because the sample concentration in the receptor chamber may change. Cell volume and orifice size differences for the Microette and Phoenix system are listed in Table 1 below.

System	Cell Volume, mL	Orifice Size, mm
Vision Microette Diffusion	4	9
	7	15
	12	15
Phoenix Diffusion Manual DB-6 and Robotic Diffusion System	10	9 and 11.3
	14	
	16	11.3 and 15
	22	
	21	15 and 20
	31	

Table 1: Difference in cell volume and orifice size.

The most common factor affecting diffusion is the orifice size; method transfer is easier if the orifice size isn't changed. In addition, a change to the volume may impact solubility and sink condition. Normally the amount of Active Pharmaceutical Ingredient (API) available in the donor compartment is significantly higher than the concentration of API obtained in the receptor chamber at the end of the diffusion test. However, this factor should also be evaluated in the pre-transfer evaluation study.

The HPLC analytical procedure should not be changed except for the injection volume. Evaluate the HPLC test procedure for changes to the Limit of Detection (LOD) and Limit of Quantitation (LOQ). If the orifice size for the new system remains unchanged, then only the injection volume should be changed, based on the cell volume. The recommended injection volume factor based on the cell volume is listed in Table 2 below. For example, if an injection volume is 25 µL using a Microette system, then increase the injection volume by multiplying 25 µL by the factor provided in the table below and injecting to the nearest full microliter possible volume.

Microette		Phoenix Diffusion Platform			
Orifice Size, mm	Cell Volume, mL	Orifice Size, mm	Cell Volume, mL	Mixer Height, mm	*Multiply by the Injection Volume Factor for the Phoenix System
15	7	15	16	30	2.3
		15	22	13	3.1
		15	21	30	3.0
		15	31	13	4.4
15	12	15	16	30	1.3
		15	22	13	1.8
		15	21	30	2.5
		15	31	13	2.6

Table 2: Injection volume factor based on the cell volume.

**If increasing the injection volume is not possible, then it is necessary to perform the entire method validation[2, 3].*

Comparative Testing

The study objective of a procedure comparison is to demonstrate that a new procedure performs equivalent to, or better than, an old procedure. Based on an initial examination of a test procedure, do a comparative test for method verification[4] using one batch of product on both instruments three times; then a data analysis should be performed to access the impact of change. A risk-based evaluation of the changes should be performed and evaluated against the draft guidance provided by the U.S. FDA in its Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry (April 2016)[5].

Such analysis shall be conducted based on a preapproved study protocol that stipulates the details of the procedure, the samples that will be used, and the predetermined acceptance criteria, including acceptable variability. Meeting the predetermined acceptance criteria is necessary to assure that the method is adequately suitable to perform the test on a new instrument. It is often necessary to compare two analytical procedures to determine if differences in accuracy and precision are less than an amount deemed practically important. A change in a procedure includes a change in technology, a change in laboratory or a change in the reference standard in the procedure. Procedures with differences less than the practically important criterion are said to be equivalent or better. Perform the comparison based on SUPAC SS guidance[6] for product similarity, and if it meets the requirements, the new system can be easily used for future testing.

Study Report

When the study is successfully completed, produce a report that describes the results obtained in relation to the acceptance criteria, along with conclusions with confirmation that the new instrument is qualified to run the procedure. Any deviations should be thoroughly documented and justified. If the acceptance criteria are met, the study is successful, and the new instrument is qualified to run the procedure; otherwise, the procedure cannot be considered transferred until effective remedial steps are adopted to meet the acceptance criteria. An investigation may provide guidance about the nature and extent of the remedial steps, which include training and clarification to more complex approaches, or revalidation depending on the procedure.

References

1. United States Pharmacopeia (2022). *General Chapter, <1224> Transfer of Analytical Procedures*. USP-NF. Rockville, MD: United States Pharmacopeia.
2. United States Pharmacopeia (2022). *General Chapter, <1225> Validation of Compendial Procedures*. USP-NF. Rockville, MD: United States Pharmacopeia.
3. U.S. Food and Drug Administration. Analytical Procedures and Method Validation for Drugs and Biologics: Guidance for Industry. July 2015.
4. United States Pharmacopeia (2022). *General Chapter, <1226> Verification of Compendial Procedures*. USP-NF. Rockville, MD: United States Pharmacopeia.
5. U.S. Food and Drug Administration. Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing and Controls Information, Draft Guidance. April 2016, Revision 1.
6. U.S. Food and Drug Administration. SUPAC SS: 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.

Note: This document is prepared as a general guidance; users must contact the relevant regulatory agency to confirm the approach regarding method transfer from an older system to a new system to decide and act accordingly.

Teledyne Hanson
9810 Variel Ave, Chatsworth, California,91311 USA
Phone: (818) 882-7266

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