An *In Vitro* Release Test for Ketoprofen in Semisolids using Immersion Cells with USP Apparatus 2

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INTRODUCTION

Semisolid drug products are used for topical and systemic delivery of Active Pharmaceutical Ingredients (API). As stated in USP 40, General Chapter <1724>, semisolids (creams, ointment, gels, lotions, etc.) "may be considered extended-release drug preparations, and their drug release depends largely on the formulation and manufacturing process." As a consequence, different excipients with differing physicochemical properties, and different production processes allow semisolids to be designed to achieve optimal, and commercially reproducible drug release characteristics.

In order to develop, formulate, and reproducibly-manufacture semisolid drug products, drug product quality and performance tests are required. In vitro release tests (IVRT) serve to characterize the rate of drug released from a semisolid product, and between different semisolid to discern differences in release rate formulations or deviations from drug release specifications of an approved product suggestive of formulation and process changes, errors in manufacturing, change of manufacturing site, or physical and/or chemical instability of the drug product. IVRT are required to verify acceptability of a formula/process change, batch scaling, and change in manufacturing site.

IVRT do not measure systemic absorption, bioavailability, or bioequivalence though changes in measured release-rate could correlate with these in vivo parameters since, for example, skin absorption or permeation would depend upon the API released from the drug product in a solubilized form.

USP describes several approaches to IVRT, including the vertical diffusion cell (Franz cell), immersion cell, and a modified USP Apparatus 4 (flow-through cell). This study describes the development and preliminary evaluation of drug release from topical ketoprofen formulations using the Hanson Research, Immersion Cell.

METHODS

Lipoderm® and pleuronic lecithin organogel (PLO) formulations containing 10%, 20%, and 30% ketoprofen were prepared as outlined in Table 1. For each comparative drug release test, samples of equivalent strength Lipoderm® and PLO formulations were loaded into three of the six immersion cells used (immersion cell prep and experimental details in Fig. 1 and Table 2.). Ketoprofen concentrations in receiver media samples were determined by HPLC (Table 3.). Cumulative ug ketoprofen per cm^2 released over six hours was plotted versus square root of time.

Table 1. Test Formulations*

5, 10, 20% Ketoprofen Lipoderm® Formula (30 g)		5, 10, 20% Ketoprofen Pleuronic Lecithin Organogel (PLO) (30 g)	
Ketoprofen USP, PCCA Special Micronized	5, 10, or 20% w/w	Ketoprofen USP, PCCA Special Micronized	5, 10, or 20% w/w
Diethylene glycol monoethyl ether NF	2% w/w	Diethylene glycol monoethyl ether NF	2% w/w
Propylene glycol USP	8% w/w	Propylene glycol USP	8% w/w
PCCA Lipoderm®	q.s. to 100%	Lecithin isopropyl palmitate solution	22% w/w
		Poloxamer 407, NF Gel 20%	q.s to 100%

Mixed two minutes with an Unguator® e/s electronic morter & pestle. Gako International.

*All materials were purchased from Professional Compounding Centers of America, South Wilcrest Drive, Houston, TX 77099.

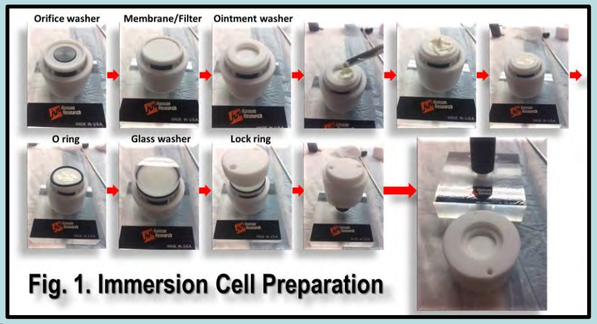


Fig. 1. Immersion Cell Preparation

Table 2. Release Test

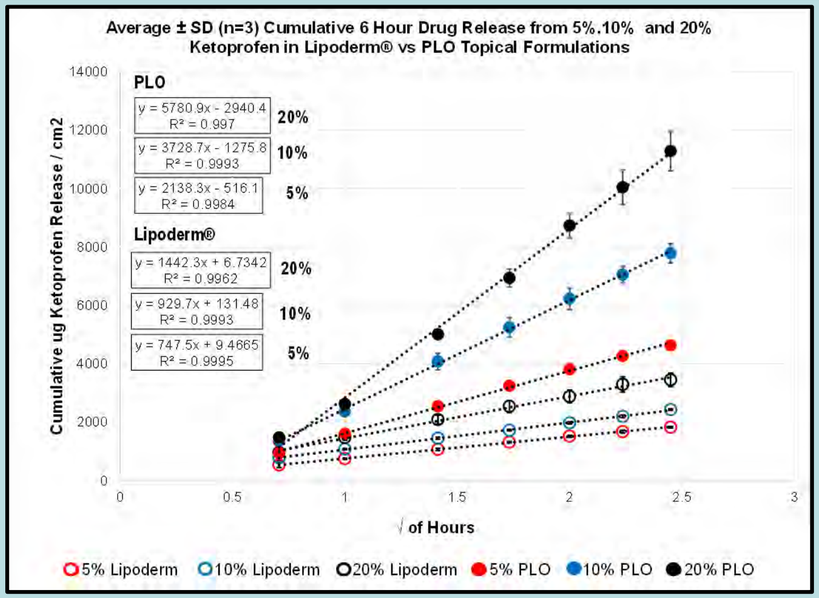
- Hanson / Teledyne Immersion Cells (0.53 mL sample compartment)
- Tuffryn® polysulfone membrane disc filter; 0.45 um, 25 mm
- 150 mL flat-bottomed dissolution flasks
- Modified Hanson SR6, USP 1 & 2 dissolution tester
- Receiver Media – 100 mL Phosphate Buffered Saline, pH 7.4 (PBS)
- Stirring – Paddles @ 100 rpm
- Test Temperature 32° C
- 1 mL samples @ 0.5, 1, 2, 3, 4, 5, 6 hours

Table 3. HPLC (modified USP)

- Shimadzu HPLC system
- Column - ODS Hypersil 5 um; 250 x 4.6 mm
- Mobile Phase – Acetonitrile:Acetic Acid:H_2O; 90:1:110
- Flow Rate -1.3 mL/min
- Analyte Detection – U.V. 250 nm
- Sample volume – 20 uL

Fig. 2. Immersion Cell in USP 2

RESULTS



Ketoprofen release from the tested formulations was linear with the square root of time and proportional to drug concentration in the test samples. Results demonstrate that at all ketoprofen concentrations, drug release was notably faster from the pleuronic lecithin organogel (PLO) than the Lipoderm®-based cream.

What Defines Acceptable IVRT Data?

1. NMT than 30% of the sample API released at last sample

Formulation	Sample Wt	API	Total API Released in 6 hours	% API Released in 6 hours
20%	577.3 ± 0.6 mg	115.5 mg	19.9 ± 1.2 mg	17.2%
10%	571.7 ± 7.5 mg	57.2 mg	13.7 ± 0.6 mg	23.9%
5%	563.0 ± 6.2 mg	28.2 mg	8.2 ± 0.1 mg	29.0%

2. Data is linear when plotted against √t (an R^2 value > 0.90 acceptable) NLT 0.9962
3. Slopes are consistent
   a. < 15% CV acceptable
   b. < 5% very good
4. No significant lag time to linearity

What Defines Acceptable IVRT Data?

5. Slopes (flux) proportional to API concentration.

Base	% ketoprofen	Regression Slope
PLO	20	5781
	10	3729
	5	2183
Lipoderm®	20	1442
	10	930
	5	748

Consideration of Sink Conditions for IVRT

- At a minimum:
  - "Receiver solution must accommodate more that the amount of material released at the last sample point."
- Ideally:
  - "Receiver solution should be able to dissolve 10 x the amount of material released during the test."

Solubility in PBS, pH 7.4	Receiver Volume	Theoretical Solution Capacity	20%		10%		5%	
			≈ ketoprofen in sample	Sink	≈ ketoprofen in sample	Sink	≈ ketoprofen in sample	Sink
1.68 mg/mL	100 mL	168 mg	115 mg	x 1.5	58 mg	x 2.9	29 mg	x 5.8
			30% of ketoprofen	Sink	30% of ketoprofen	Sink	30% of ketoprofen	Sink
			35 mg	x 4.8	17 mg	x 10	9 mg	x 18.7

CONCLUSION

Preliminary evaluation of the described IVRT for Ketoprofen topical drug products suggest it may be suitable for determining differences in drug release from different formulations and identifying changes in drug release related to variability in manufacturing processes and materials.

Under the conditions of test, ketoprofen is released from PLO at a faster rate than Lipoderm®-based formulations.

Reference: *Diffusion Method Development Guidelines White Pater. John Heaney. May 22, 2014. Hanson Research, Chatsworth, CA.;* USP 40, <1724>.

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