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Release Rate Determination of Various Dapsone Gels Using an IVRT Method Performed on the Phoenix RDS Automated Diffusion Tester

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Introduction

Many pharmaceutical companies have shown interest in developing generic versions of Aczone® 7.5%. Aczone is a Reference Listed drug product of Dapsone topical gel. A few of them have been filed with the US FDA for approval, and some are approved. Teledyne Hanson has developed and validated an in vitro release testing (IVRT) method for Aczone using the Phoenix RDS, an automated diffusion tester.

A validated IVRT method can be used to support a demonstration of bioequivalence (BE) of generic drug product to the reference listed drug (RLD). The use of the IVRT method is recommended by the United States Food and Drug Administration (US FDA) to assess the drug product sameness in the SUPAC SS guidance [1, 2]. IVRT is also established as a compendial procedure in the United States Pharmacopeia (USP), under General Chapter <1724>. In this chapter the test procedure, apparatus and statistical methods are described to prove the product's similarity or sameness [3]. For certain types of products, the FDA's regulations generally require that the generic products be qualitatively (Q1) and quantitatively (Q2) the same as for the RLD [4]. FDA also provides the recommendations for physicochemical and structural (collectively, Q3) characterizations that can be used (1) to identify the dosage form of a proposed generic (test) topical product and (2) to describe properties of the drug product that may be critical to its performance to support a demonstration of bioequivalence (BE) when comparing the Q3 attributes of two topical products [5].

Recently, a huge interest has been growing for the use of IVRT method as an additional measure to prove the product similarity in an Abbreviated New Drug Application (ANDA). The US FDA has published a product-specific draft guidance for Dapsone gel 7.5% [6]. The European Medical Agency (EMA) has also published a guidance document for use of an IVRT procedure to access product quality and support for equivalence of topical products [7].

Chemicals and Formulations

Dapsone Certified Reference Standard was purchased from Sigma Aldrich. High-performance liquid Chromatography (HPLC) grade acetonitrile and ethanol (95%) were purchased from Cole Parmer. Generic Dapsone Gel, 7.5%, lot number AC64371 and expiry dated March 2024, was manufactured by Taro Pharmaceuticals and is an approved, commercially available product. Innovator ACZONE® (Dapsone) Gel, 7.5% was purchased from a local pharmacy, lot number TFAK and expiry dated June 2024, and was manufactured by Almirall, LLC. Topical products containing Dapsone gel (7.5%) were specially manufactured in a laboratory for use as test products and were identified as Dapsone Gel (7.5%). These gels were manufactured by a well-trained scientist under the supervision of an experienced professor of Pharmacy in a laboratory at the Swami Vivekananda Education Society (VES) School of Pharmacy, Mumbai India. Part of the analysis of this research work has been conducted in the same facility.

The Phoenix RDS diffusion apparatus

Formulation details and comparison				
Sr No	Name of Excipients	Aczone	Generic (TARO)	In-house Gel
1	Dapsone	√	√	√
2	Diethylene glycol monoethyl ether	√	√	√
3	Methyl Paraben	√	√	√
4	Acrylamide/Sodium acryloyldimethyl taurate copolymer, Isohexadecane, Polysorbate 80	√	×	√
5	Carbomer homopolymer type C	×	√	×
6	Sorbitan monooleate	×	√	×
7	Sodium Hydroxide	×	√	×
8	Polysorbate 80	×	√	×
9	Light mineral oil	×	√	×
10	Purified water	√	√	√

Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC)

The Dapsone concentration in the IVRT samples were determined by an in-house qualified HPLC system (Shimadzu Scientific, model LC-2010). It contained a photo diode array (PDA) detector and was recalibrated in February of 2023. An ACE® Equivalence™ C18 chromatographic column (4.6 x 250 mm, 5 µ) was used for the entire study. The mobile phase consisting of water: acetonitrile in the ratio of 70:30 pumped at a flow rate of 1.0 ml/min following a 10 µL sample injection. The eluate was monitored at a wavelength 230 nm.

Method development of the IVRT method

The IVRT method was developed and validated by assessing membrane inertness, the solubility of Dapsone in the receptor medium, and the linearity, precision, reproducibility, sensitivity, specificity, and selectivity of the method. A detailed method description is mentioned in Teledyne Hanson's Application Note 012 [8].

In Vitro Release Test of Gel Containing Dapsone

The study was completed per the guidance provided in the US FDA's Scale-Up and Post Approval Changes Semisolids (SUPAC-SS). The receptor compartments of Vertical Diffusion Cells (VDC) were filled with 10 mL of ethanol-water solution (60:40 V/V) and maintained at 32 ±0.5°C. PVDF membranes were mounted on each cell. Approximately 30 minutes later, when the cells were equilibrated, about 400 mg of Dapsone Gels, 7.5% were applied to the membrane. To prevent evaporation and to maintain product integrity, the donor compartments were covered using glass discs. The steering speed was set at 400 RPM to keep the receptor solution continuously mixed throughout the test period using magnetic stirrers.

Diffusion Parameters	
Cell Size	Small, 10 mL volume
Mixer Size	30 mm
Cell Cap	11.3 mm orifice x 4 mm
Temperature	32.0 ± 1 °C
Stirring Speed	400 rpm
Membrane	PVDF, 0.45 µ
Sampling Time Points	0.5, 1, 2, 3, 4, and 6 hours
Sample Volume	400 µL
Replacement volume	400 µL
Average Diffusional Surface Area	1.0 cm2

Calculation of Release Rates

The release rate was calculated using the Higuchi model, which assumes the perfect conditions for test. Obvious dilutions of the receptor media due to replacement were considered and the concentration at each time point were determined using an RP-HPLC with a PDA detector. The concentration of Dapsone in the receptor medium at different sampling times and the cumulative amount of drug released were calculated using an in-house validated Excel spreadsheet.

The release rate corresponds to the slope of the regression line for the plot of the amount of drug released (µg/cm2) versus the square root of time (√t) and is affected by sample volume, cell volume, and the cell orifice diameter. Consequently, these parameters were verified during the process of apparatus qualification.

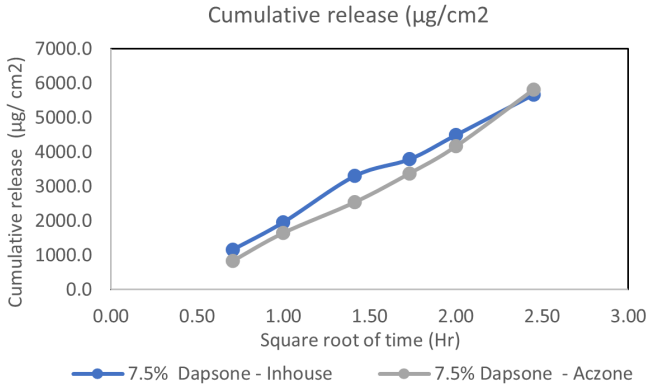

Figure 1. ACZONE® vs In-house gel.

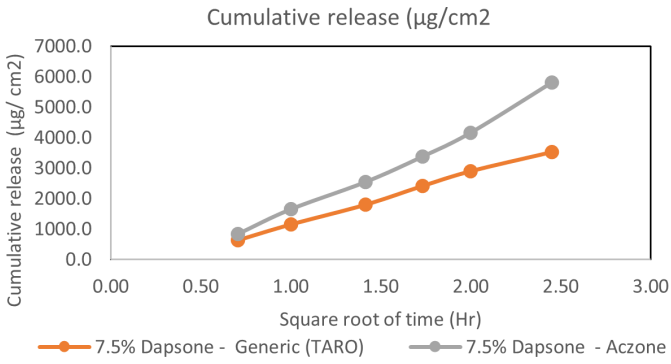

Figure 2. ACZONE® vs Marketed Generic gel (TARO).

Statistical Analysis

As mentioned in the USP General Chapter <1724>, the statistical approach was used to calculate the release rates of the generic formulation ("marketed"), and each of the Dapsone gel test formulations ("in-house") were used to calculate the Test/Reference (T/R) ratios. 6 diffusion cells were used to test both products, hence a total of 36 T/R ratios were obtained and placed numerically in order of lowest to highest. As required, the 90% confidence Interval (CI) was determined from the listed T/R ratios in which the 8th and the 29th ratio are the lower and upper limit, respectively. When the 90% CI is within the range of 75%–133.33%, the products considered to be equivalent. The IVRT studies were conducted in accordance with the FDA's SUPAC-SS guidance [1]. The test products—i.e., approved marketed generic formulations Dapsone gel (7.5%) (TARO) and in-house Dapsone gel (7.5%)—were compared against the reference product, ACZONE® (Dapsone) Gel, 7.5% as shown in Figure 1.

The samples were placed randomly on VDCs as test (T) and reference (R) products in accordance with the SUPAC-SS guidance [1]. The individual cumulative amounts of drug released from R and T were plotted versus the square root of time. Because common testing artifacts such as air bubbles, membrane defects, and yield measurements that are not normally distributed, a nonparametric statistical technique is used to evaluate the test results. Since a few outliers are expected to occur during IVRT (e.g., due to air bubble formation), a nonparametric method that tends to be resistant to the presence of such outliers was used. As suggested in the USP general Chapter 1724, the Mann-Whitney U test was used to calculate the 90% confidence interval (CI) for the ratio of slopes between Reference and Test products.

Comparative IVRT of Two Topical Gel Products

The results obtained when RLD of Dapsone Gel known as ACZONE® (Dapsone) Gel (7.5%) was compared against an in-house Dapsone gel (7.5%) (Figure 1). The Confidence Interval (CI) of 90.5%–93.91% is a clear indication of the sameness of two products. Comparison of the release rates of ACZONE® (Dapsone) Gel (7.5%) and marketed generic gel is indicating inequivalence between these two products (Figure 2). Although all products contained 7.5% Dapsone, the difference in formulation in terms of the excipient types and quantities as well as Q3 factors may have impacted the study results.

Product Name	Computed 90% CI		Sameness Confirmed
	Lower Limit	Upper limit	
ACZONE® vs In-house gel	90.5	93.91	Yes
ACZONE® vs Generic gel (TARO)	59.6	61.7	No

Conclusions

In vitro release tests (IVRT) of an in-house manufactured gel, an approved RLD, and marketed generic topical products of Dapsone gels were conducted according to recommendations of the US FDA Draft Guidance for Dapsone gel as well as the SUPAC SS Guidance for non-sterile semisolid dosage forms and the USP General Chapter <1724>. An in-house Dapsone Gel (7.5%) showed "sameness" to the reference listed drug product ACZONE® (Dapsone) Gel, 7.5%, whereas the release rate of another generic Dapsone gel (TARO) did not meet the acceptance criteria of 75–133.33%. The comparison between the generic gels indicated that these were not equivalent in terms of release rate per the analytical test method used. This inequivalence may be because generic gel formulation is not Q1/Q2 with RLD; possibly the main reason is that a different grade of polymer was used in formulation.

It can be concluded that the IVRT method is very useful to accurately discriminate release rates, which could reflect the difference or similarity in product performance. Furthermore, the results indicate that the developed IVRT method and the tools used have an incredible ability to detect changes in a formulation. The results obtained in the study provide the evidence that Phoenix RDS equipment and the validated test method have the capability to accurately determine the release rate of Dapsone from topical gel products. The combination of the IVRT method and the Phoenix RDS system can be relied on to provide compelling data for use in biowaiver applications.

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