DURABILITY OF EPINEPHRINE SUBLINGUAL FILM UNDER REAL-WORLD USE

Steve Wargacki, PhD[1], Vincent Buono[1], Gregory Tsodikov[1], Nils Confer, PhD[1]

[1]Aquestive Therapeutics, Inc.

INTRODUCTION

- Epinephrine, administered intramuscularly into the anterolateral thigh via manual injection or auto-injector (e.g., EpiPen®, Auvi-Q®), is the first-line treatment for anaphylaxis.1
- Currently, all approved therapies involve delivery of an aqueous-based solution containing the needed epinephrine. Aqueous environments have known limitations when considering extreme temperatures.
- Therefore, an ideal epinephrine rescue medication for anaphylaxis should possess physiochemical properties that aid in withstanding environmental conditions that may occur during normal patient carriage, while not sacrificing shelf-life. For example, the product should retain sufficient chemical stability after exposure to a variety of real-world scenarios, such as the environmental conditions that can occur in a car, a pocket, a wallet, and when storing in a phone case.
- Anaphylm (AQST-109, DESF), is a sublingual film containing a prodrug of epinephrine, in development as a non-device, minimal water containing alternative to address the limitations associated with all currently approved therapies.

OBJECTIVES

- To assess the durability of Anaphylm against real-world use conditions such as refrigeration, accidental laundering, rain exposure, product folding, and premature removal from packaging before administration readiness.
- To determine the impact of extreme environmental conditions on drug potency and release properties.
- To assess the physical integrity and functionality of Anaphylm after repeated stress exposure.

METHODS

STUDY DESIGN

- Anaphylm 12 mg was subjected to the excursion cycles and samples were tested against current finished product specifications:

Freeze Thaw Cycles

- Replicate sample sets were frozen at -20°C for 24 hours, then thawed for 24 hours at 25°C ± 2°C, 40°C ± 2°C, and 60°C ± 2°C. This cycle was repeated three times. Afterward, samples were stored at 25°C/60% RH and tested at various time intervals.

Water Submersion

- Anaphylm samples in pouches were submerged in 60°C water for 30 and 60 minutes, then stored at 25°C/60% RH for 24 hours and submerged in 25°C water for 1 and 7 days before testing.

Period After Opening

- Individual Anaphylm strips were removed from their packaging and exposed to controlled 25°C/60% RH storage for a period of 3-, 6-, 9-, and 12-hours.

Fold Endurance

- Anaphylm samples were tested for durability after repeated 180° folds.

Film Durability

- Anaphylm samples were conditioned to temperatures ranging from -80°C to 70°C to assess temperature-dependent film integrity and performance (dissolution).

Anaphylm demonstrates novel durability properties for an epinephrine rescue medication in extreme real-world conditions.

CONCLUSIONS

Anaphylm maintained stability and performance in extreme conditions (also see Poster 305). Performance attributes demonstrated that Anaphylm is the sole epinephrine rescue candidate proven effective under sub-freezing temperatures where liquid formulations freeze.

Durability Beyond Expectations:
Anaphylm's potency remained unchanged after all freeze-thaw cycles, even when exposed to temperatures beyond typical freeze-thaw conditions to effectively mimic real-world lifestyle conditions.

Water Resilience:
Anaphylm remained effective even after prolonged submersion at various time points, demonstrating its reliability for daily use.

Fold Endurance:
Anaphylm retained its physical integrity after repeated folding over 12 months, ensuring usability even after being stored in a pocket or bag.

Consistent Dissolution:
Anaphylm performs consistently independent of exposure to environmental temperatures. The data suggest that equilibration time is not required.

RESULTS

- All stability results comply with the applicable proposed 40°C and 60°C) beyond standard freeze-thaw specifications:

Freeze Thaw Cycles

- Potency remained unchanged compared to non-frozen samples for up to 12 months (**Table 1**).
- Results remained consistency at extreme temperatures (conditions (25°C).

Water Submersion

- Minimal impact on dissolution rates, confirming usability under such conditions (**Table 2**).

Period After Opening

- Anaphylm retained 95.6% potency up to 12 hours after opening the package (**Table 3**).

Fold Endurance

- Repeated folding over 12 months had no impact on physical integrity or potency (**Table 4**).

Dissolution

- Dissolution rates remained consistent after exposure to extreme conditions (**Figure 1**).
- Anaphylm can be utilized at extreme temperatures, such as frozen or hot (70°C).

Table 1: Freeze-Thaw Cycle Results

	25°C Thaw	40°C Thaw	60°C Thaw
Time Point	25°/60%RH	25°/60%RH	25°/60%RH
Initial	101.5	102.2	100.8
3 Months	98.6	99.7	97.4
6 Months	98.8	98.5	97.7
9 Months	97.8	99.5	97.1
12 Months	98.0	100.7	99.0

Table 2: Water Submersion Results

60°C Submersion		25°C Submersion	
Time Point	Water Content	Time Point	Water Content
30 Minutes	3.1	1 Day	3.2
60 Minutes	3.1	7 Days	3.1

RESULTS (cont'd)

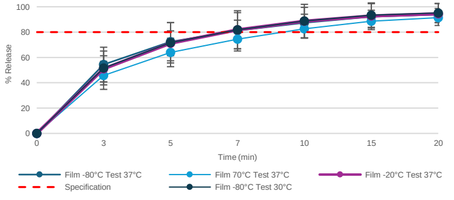
Table 3: Period After Opening Results

25°/60%RH Exposure	
Time Point	Potency (%LC)
3 Hours	98.1
6 Hours	100.0
9 Hours	97.0
12 Hours	95.6

Table 4: Fold Endurance Results

Excursion/Storage Conditions	Folding Endurance (average n=3 replicates)
Control	>100
Freeze/Thaw @ 25°C - 12M @ 25°C/60% RH	>100
Freeze/Thaw @ 40°C - 12M @ 25°C/60% RH	>100
Freeze/Thaw @ 60°C - 12M @ 25°C/60% RH	>100
28 days @ 50°C - 12M @ 25°C/60% RH	>100
21 days @ 60°C - 12M @ 25°C/60% RH	>100
7 days @ 70°C - 12M @ 25°C/60% RH	>100

Figure 1: Anaphylm Release After Extreme Temperature Exposure



REFERENCES

1. Shaker MS, Wallace DV, Golden DBK, et al. *J Allergy Clin Immunol.* 2020;145(4):1082-1123.

ACKNOWLEDGMENTS

This study was sponsored by Aquestive Therapeutics, Inc.

DISCLOSURES

All authors are employees of Aquestive Therapeutics Inc.