



100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

MES HYDRATE 2021 VALIDATION LOT
LONG TERM STABILITY REPORT:
ME3200-232-0221-PV

The information contained herein is the confidential property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.

Page 1 of 10

Controlled Copy Number: 1, Controlled Copy Location: Website
Printed By: VIRGINIA.PENA, on 17 Jul 2024

TABLE OF CONTENTS

| | |
|---|----|
| 1. OVERVIEW:..... | 3 |
| 2. REFERENCES: | 3 |
| 3. SAMPLE DESIGNATION: | 3 |
| TABLE 1: PACKAGING DETAILS | 4 |
| 4. STORAGE:..... | 4 |
| 5. INVESTIGATIONS:..... | 4 |
| 6. LOT EVALUATION:..... | 5 |
| TABLE 2: LONG TERM STABILITY RESULTS FOR ME3200-232-0221-PV P/P | 5 |
| GRAPH 1: ABSORBANCE @ 280NM..... | 6 |
| GRAPH 2: ABSORBANCE @ 260NM..... | 7 |
| GRAPH 3: ASSAY (AS IS) | 8 |
| GRAPH 4: LOSS ON DRYING..... | 9 |
| 7. CONCLUSION:..... | 10 |
| 8. STATEMENT OF COMMITMENT: | 10 |

The information contained herein is the confidential property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.

1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the long-term stability study of MES Hydrate (MES). Testing intervals are designated by T_n , where n = the number of months on stability. Testing is performed every three months for the first year, every six months for the second year, and annually for each subsequent year in order to maintain that the manufactured product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may also aid in a re-evaluation of the retest date for the finished good product.

This long-term analysis will assess the stability data of MES validation lot ME3200-232-0221-PV that completed 36-months of real time stability in February 2024. This study includes the following analyses: Absorbance (1M) @ 280nm, Absorbance (1M) @ 260nm, Assay (As Is), Appearance and Color, Identification (IR), and Loss on Drying (LOD). Results from all analyses are summarized in Table 2. The data was analyzed utilizing a Shelf-Life Plot, which determines the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Shelf Life. This allows BioSpectra to ensure that the product is stable over the time period in which it is part of the stability program. All quantitative data was analyzed using these methods.

The stability program is designed to analyze for the stability indicating analyses established for a product in accordance with the Stability Testing Program BSI-SOP-0136. The specifications for the stability indicating analyses are established in accordance with the Stability Indication Protocol BSI-SOP-0289 when a new product is manufactured. The study is used to trend the data to determine if there is any significant change over the course of the study to establish the shelf life of the product. This study will be used to establish shelf life for all product codes of MES, Hydrate. The following Product Codes are commercially available.

- MESH-3250

2. REFERENCES:

- 2.1. BSI-SOP-0136, Stability Testing Program
- 2.2. BSI-SOP-0146, Stability Inventory
- 2.3. BSI-SOP-0289, Stability Indication Protocol
- 2.4. Current USP
- 2.5. ICH Q1E

3. SAMPLE DESIGNATION:

- 3.1. Samples initially placed on the stability program for real time testing consisted of one validation lot of MES. Stability samples from this lot were put into P/P packaging configuration. The samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

TABLE 1: PACKAGING DETAILS

| Packaging Configuration | Packaging Description |
|-------------------------|--|
| Poly/Poly (P/P) | Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a poly pail and sealed. |

4. STORAGE:

- 4.1. The packaging and storage requirements for MES are to be in a tightly closed container and stored in a dry, well-ventilated area. For this real time study, samples were stored in the Real Time Stability Chamber, H03SC01, at the Bangor, PA facility. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature ($25^{\circ}\text{C} \pm 2$), relative humidity ($60\%\text{RH} \pm 5$) and mean kinetic temperature (monitor). For the time period of February 2021 to February 2024 the samples were located in the Real Time Stability Chamber. The maximum temperature recorded was 27.80°C , the minimum temperature was 22.63°C , the average temperature was 25.45°C , and the average Mean Kinetic Temperature was 25.45°C . The maximum relative humidity recorded was 80.5%, the minimum relative humidity was 31.3%, and the average relative humidity was 61.4%. Maximum and minimum values that are outside limits for temperature and humidity are due to opening the door of the chamber as explained in Temperature and Humidity Monitoring Assessments. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

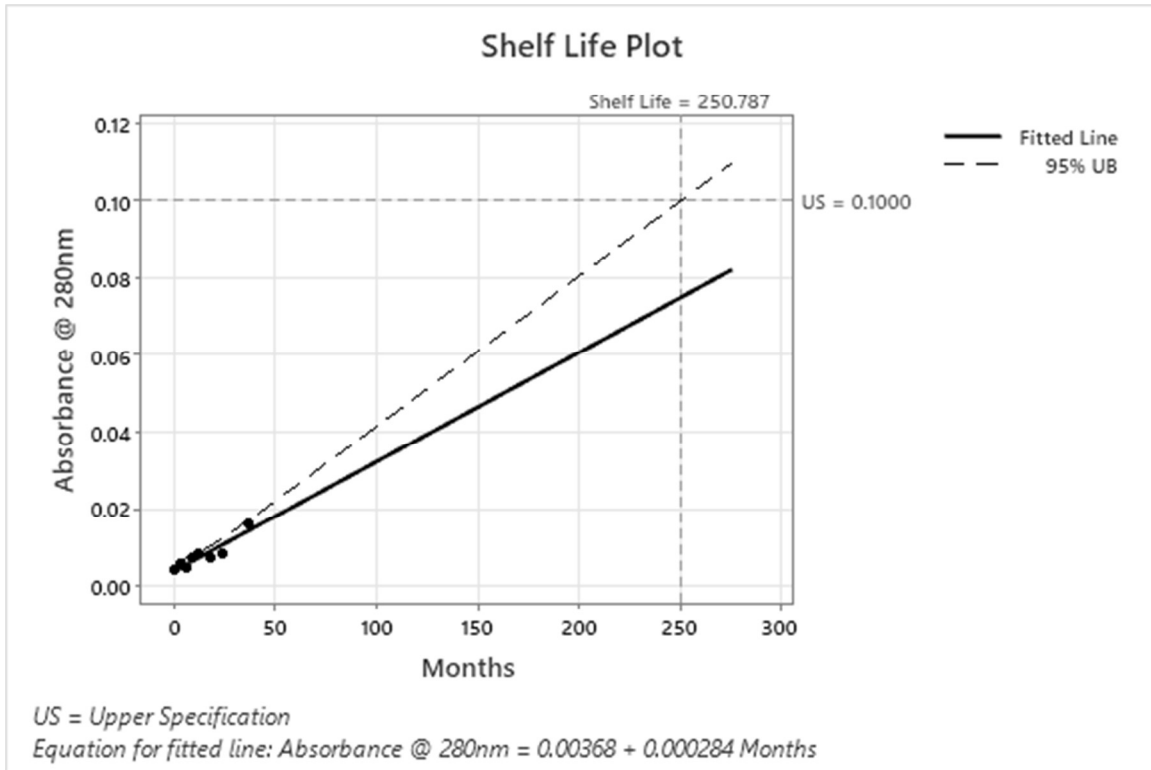
- 5.1. **BDI22-61:** This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Real Time Stability Chamber from 01/28/22 until 02/09/22. The loggers were reset on 02/09/22, and functioned normally for the rest of the monitoring period. The backup Analog chart recorders were inspected, and it was determined that there were no temperature and humidity excursion outside the specification ranges for that time.
- 5.2. **BDI22-138:** This discrepancy documents an out of specification humidity readings. The out of specification humidity result was 50.8% and lasted for over 4 hours. This was due to a valve that regulates the humidity being turned off. There is no impact to the stability samples because the excursion was brief and lasted less than 5 hours.
- 5.3. **BDI22-143:** This discrepancy investigation covers missing data points for the MadgeTech data loggers located in the Real Time Stability Chamber from 11/20/21 until 12/03/21, which was the end of this data collection time period. The backup Analog chart recorders were inspected, and it was determined that there were no temperature and humidity excursion outside the specification ranges for that time.
- 5.4. **BDI24-13:** Out of range humidity for the Real Time Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. The issue was found to be a faulty pump and later repaired. There was no impact to the current list of materials in the stability chamber.

6. LOT EVALUATION:**TABLE 2: LONG TERM STABILITY RESULTS FOR ME3200-232-0221-PV P/P**

| Analysis | Specification | T₀ | T₃ | T₆ | T₉ | T₁₂ | T₁₈ | T₂₄ | T₃₆ |
|--------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Absorbance (1M) @ 280 nm | 0.1000 a.u. max. | 0.0041 a.u. | 0.0053 a.u. | 0.0047 a.u. | 0.0071 a.u. | 0.0080 a.u. | 0.0069 a.u. | 0.0079 a.u. | 0.0161 a.u. |
| Absorbance (1M) @ 260 nm | 0.1000 a.u. max. | 0.0051 a.u. | 0.0054 a.u. | 0.0042 a.u. | 0.0069 a.u. | 0.0085 a.u. | 0.0068 a.u. | 0.0074 a.u. | 0.0172 a.u. |
| Assay (As Is) | 99.0% min. | 100.20% | 100.22% | 99.95% | 99.77% | 99.71% | 100.41% | 100.06% | 100.38% |
| Appearance and Color | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals | White/ Crystals |
| Identification (IR) | Passes Test | Passes Test | Passes Test | Passes Test | Passes Test | Passes Test | Passes Test | Passes Test | Passes Test |
| Loss on Drying (105°C) | 7.0 – 10.0% | 8.5846% | 8.4651% | 8.4299% | 8.4606% | 8.5032% | 8.4635% | 8.4687% | 8.4776% |

- Future pull dates
 - T = 48: Scheduled for February 15, 2025
 - T = 60: Scheduled for February 15, 2026

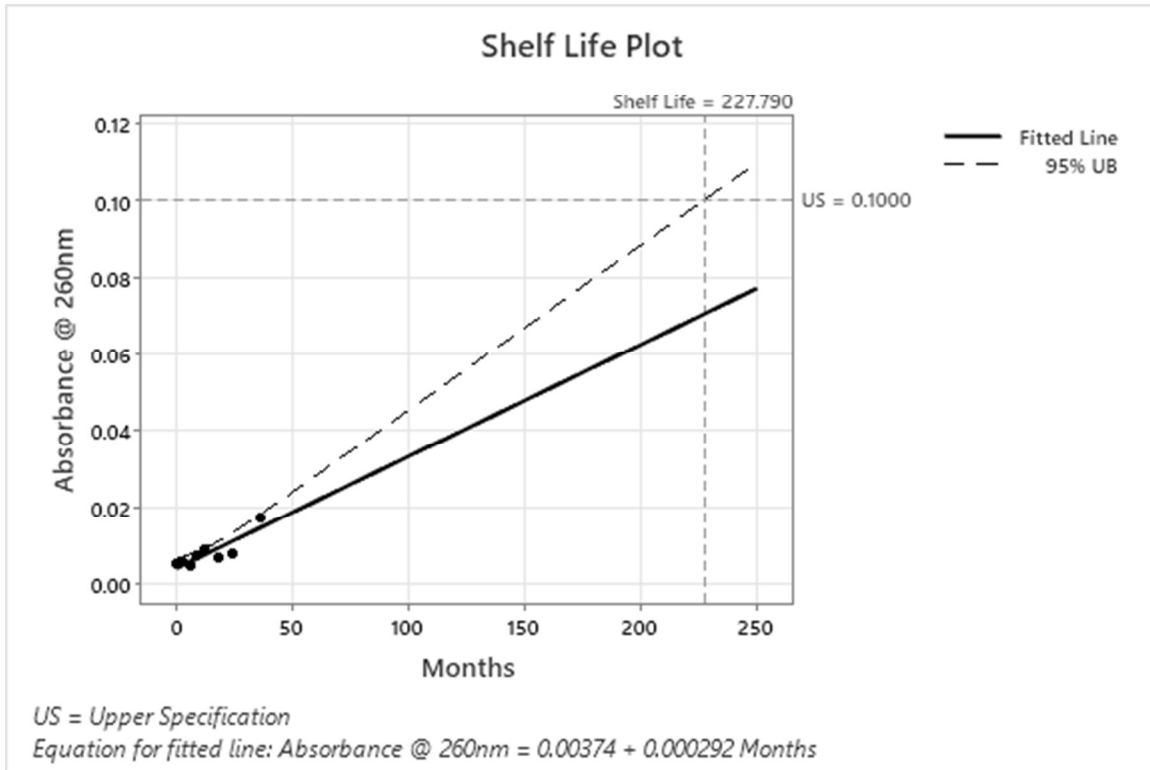
The information contained herein is the confidential property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.



GRAPH 1: ABSORBANCE @ 280NM

The predicted Shelf-Life for ME3200-232-0221-PV Absorbance @ 280 nm was determined to be 250.787 months at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.

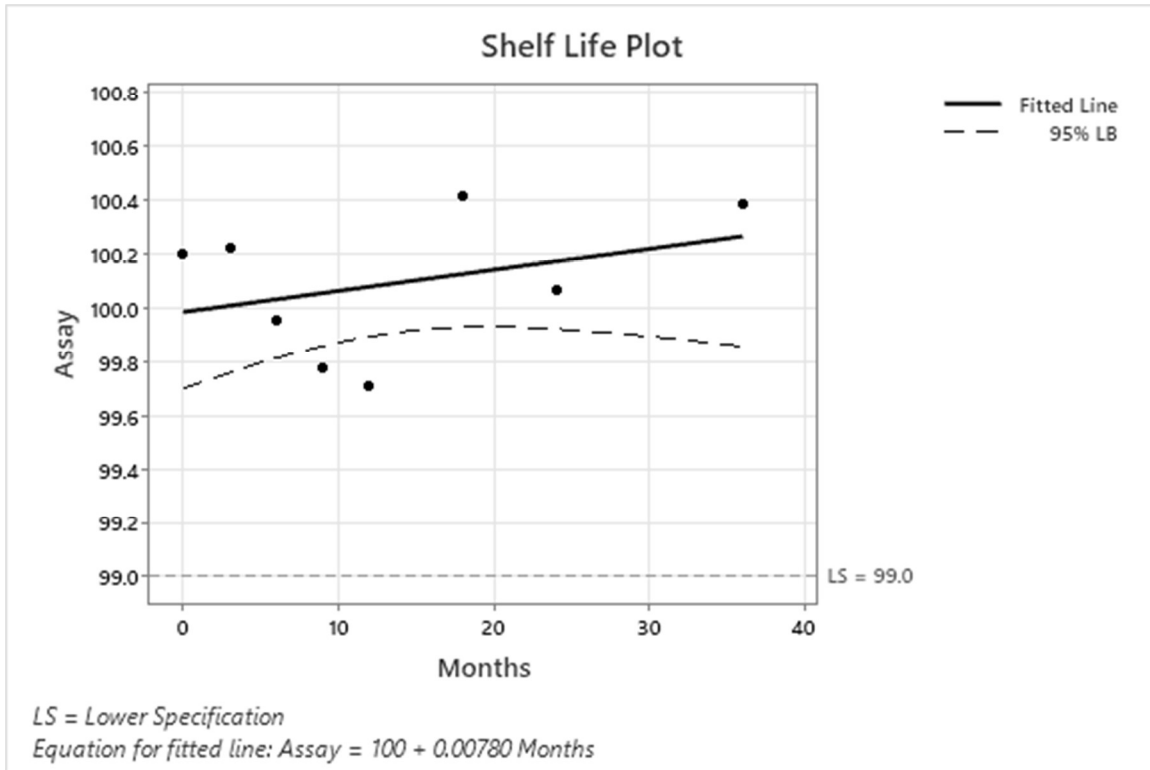
The information contained herein is the confidential property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.



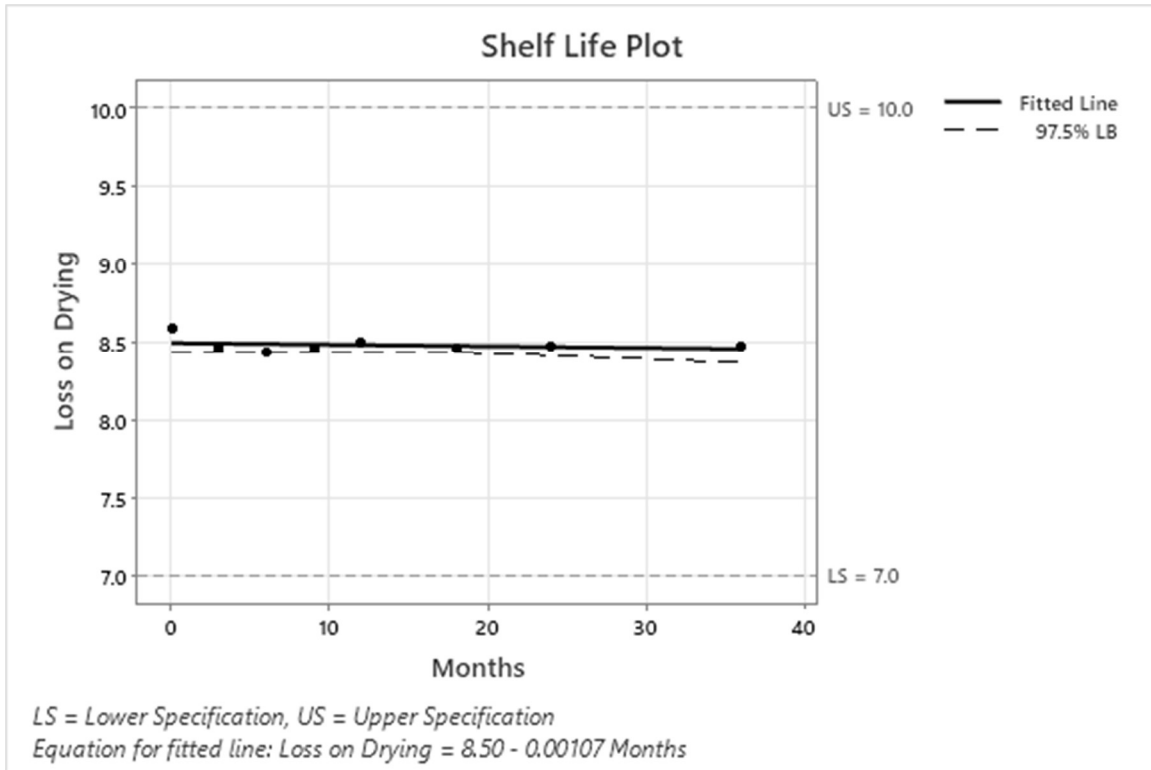
GRAPH 2: ABSORBANCE @ 260NM

The predicted Shelf-Life for ME3200-232-0221-PV Absorbance @ 260 nm was determined to be 227.790 months at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.

The information contained herein is the confidential property of BioSpectra. The recipient is responsible for its safe-keeping and the prevention of unauthorized appropriation, use, disclosure and copying.

**GRAPH 3: ASSAY (AS IS)**

No Shelf-Life was able to be determined for ME3200-232-0221-PV Assay (As Is), as the mean response slope is not significantly different from zero using 95% confidence at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.



GRAPH 4: LOSS ON DRYING

No Shelf-Life was able to be determined for ME3200-232-0221-PV Loss on Drying, as the mean response slope is not significantly different from zero using 95% confidence at the T=36-month time interval. There is no impact to the product or currently assigned retest period of this material.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E, the retest date may be proposed for up to 2x, where x is the period covered by long-term stability data, but should be no more than 12 months beyond for real time conditions. In regards to the Long-Term Stability Study for MES, Hydrate (MES), all data met the specifications set forth in the Stability Testing Program for the lot stored at the recommended long-term condition. The Long-Term Stability Study data, along with the predicted shelf-life plots, supports a retest date of 24 months and expiration date of 36 months for MES, Hydrate (MES), manufactured at BioSpectra in the Bangor, PA facility.

8. STATEMENT OF COMMITMENT:

- 8.1. BioSpectra is responsible for the following regarding Stability Data in this report:
 - 8.1.1. In the event that any long-term stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.
 - 8.1.2. This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.
 - 8.1.3. If a stability analysis is found to be out of specification and the product has an established shelf life, the batch will be withdrawn from the market through communication with any customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.
 - 8.1.4. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.