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

BioSpectra Validation External Report

Validation Report for the Manufacture of:

2-(N-Morpholinio) Ethanesulfonic Acid

To be Manufactured as the Following Codes:

MES, Monohydrate & MES, Hydrate Bio Excipient Grade
MESM-32XX & MESH-32XX or Below Compliance Grade

To be Manufactured at:

BioSpectra, Inc., 100 Majestic Way, Bangor,
Pennsylvania, 18013

In Compliance with the Standards of:

The Joint IPEC – PQG Good Manufacturing Practices
Guide for Pharmaceutical Excipients
ICH Q7 Good Manufacturing Practice Guide

Manufactured to be Suitable for Use as:

An Excipient

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1. INTRODUCTION:

The validation of a manufacturing process used to produce process chemicals is a requirement under IPEC-PQG Joint Good Manufacturing Practice Guide and ICH Q7 guidelines. The objective of this validation study was to assure that the manufacturing process at BioSpectra's Bangor, PA facility for MES, Monohydrate, product code MESM-32XX and MES, Hydrate, product code MESH-32XX or below grades, is a controlled and validated process capable of consistently producing material that meets pre-established specifications and critical quality attributes. The validation was conducted as a MES, Monohydrate Bio Excipient Validation, however upon completion, three lots of MES, Monohydrate were analyzed to MES Hydrate, MESH-3250, specifications and all batches met the finished product specifications, with the exception of Cytotoxicity which was not tested. This validation was initiated by change control BCC20-43, MES Agitation Speed Range Change, an increased rate for agitation during cooling and BCC21-21, MES, Monohydrate in E05, validation of manufacturing in API Suite 1, E05 and a longer sifting time during drying.

This MES, Monohydrate Bio Excipient Grade validation study consisted of one concurrent validation batch to ensure that the MES, Monohydrate Bio Excipient Grade manufacturing process conforms to the pre-established critical process parameters established using tools such as process mapping, Failure Modes Effect Analysis (FMEA) and Cause & Effect matrix, the development study, and historical manufacturing data. A concurrent validation is a validation study in which the batches can be released for commercial distribution based on the monitoring and analysis of the lot. The lot must conform to finished goods specifications before commercial distribution.

2. OBJECTIVE:

The objective of this validation report is to verify and assure that the manufacturing process for MES, Monohydrate & MES, Hydrate Bio Excipient Grade in API Suite 2, Room E05 of BioSpectra's Bangor, PA facility consistently produces material that meets a set of pre-determined specifications as listed in Table 1 and quality attributes.

The validation batch of MES, Monohydrate Bio Excipient Grade was manufactured according to the current revision of the batch record. Once the manufacture of the validation batch was completed, representative samples were submitted to the QC laboratory and were tested against finished good specifications. This was conducted to verify that the process is capable of consistently producing material that meets finished good specifications.

3. SCOPE:

This report applies to the manufacturing process for MES, Monohydrate & MES, Hydrate Bio Excipient Grade, which includes the following process steps: charging mother liquor creation or mother liquor verification, raw material charge, 2-stage purification, recrystallization, wet crystal separation, tray drying and final packaging of the final product. Specifications and approval requirements for all raw materials (RM) and components have been created; therefore, these RM and components are not covered by this report except that only approved RM and components were used.

4. REFERENCES:

4.1. BSI-ATM-0009, MES Monohydrate Testing Methods

4.2. BSI-MPR-0017, MES Monohydrate Bio Excipient Grade Batch Record

4.3. BSI-PRL-0112, Degradation and Impurity Profile Protocol: MES, Monohydrate

4.4. BSI-PRL-0387, MES Monohydrate Bio Excipient Grade Validation Protocol 2021

4.5. BSI-RPT-0782, Degradation and Impurity Profile Report: MES, Monohydrate 2021

4.6. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

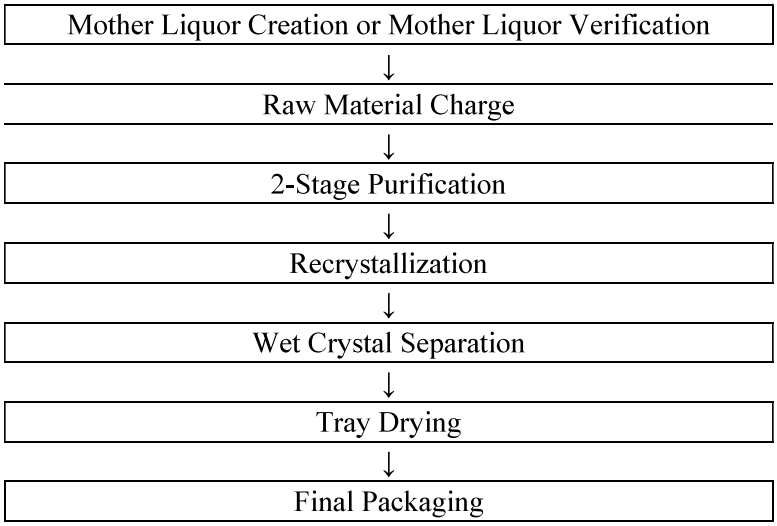
4.7. The Joint IPEC-PQG Good Manufacturing Practice Guide

5. EXECUTIVE SUMMARY:

The MES, Monohydrate & MES, Hydrate Bio Excipient Grade manufacturing process is a manufacturing process with critical process parameters as detailed in the validation protocol. The CPP's that were developed prior to the validation study were found to be in accordance with BioSpectra's Manufacturing Process Validation Master Plan. The utilities and process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The validation batch manufactured for this validation was manufactured following the current MES, Monohydrate Bio Excipient Grade Batch Record and CPP parameter values detailed in the validation protocol. The manufacturing process for MES, Monohydrate & MES, Hydrate Bio Excipient Grade consistently produces material that meets a set of pre-determined specifications and attributes, passing batch uniformity and finished good specification testing.

6. PROCESS FLOW DIAGRAM:

MES, MONOHYDRATE & MES, HYDRATE PROCESS FLOW DIAGRAM



7. ANALYSIS:

The MES, Monohydrate Bio Excipient Grade validation batch that was manufactured in accordance with the current MES, Monohydrate Bio Excipient Grade Batch Record has met the BioSpectra critical quality attributes associated with product code MESM-32XX and MESH-32XX. The analytical results for the critical quality attributes (CQA) of the validation batch can be found in Table 1. All in-process and finished goods analyses were met as required in the validation study and for finished good release.

TABLE 1: CRITICAL QUALITY ATTRIBUTES RESULTS

CQA		Specification	ME3200-232-0221-PV Result
Absorbance	260 nm	≤ 0.0300 a.u.	0.0051 a.u.
	280 nm	≤ 0.0300 a.u.	0.0041 a.u.
Appearance and Color		White / Crystals	White/Crystals
Assay		≥ 99.0 %	100.2%
Identification (IR)		Passes Test	Passes Test
Loss on Drying @ 105 °C		7 - 10%	9%
pH (0.5M)		2.5 - 4.5	3.2
pH (5% Solution)		3.0 - 3.5	3.4
pKa		5.9 - 6.3	6.1

8. ADDITIONAL INFORMATION:

8.1. Degradation and Impurity Profile

8.1.1. A degradation and impurity profile were performed for this validation in accordance with the Degradation and Impurity Profile Protocol: MES, Monohydrate, BSI-PRL-0112. The results were reported in the Degradation and Impurity Profile Report: MES, Monohydrate 2021, BSI-RPT-0782.

8.2. Stability Study

8.2.1. The stability analysis for MES, Monohydrate & MES, Hydrate Bio Excipient Grade consists of an evaluation of the following analyses and associated specifications detailed in Table 2. These analyses were selected based on a combination of incoming raw material specifications, finished goods requirements and known process information and the specifications were set based on this same information. Each batch placed on the real time stability program will undergo stability analysis at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60-month intervals.

TABLE 2: STABILITY ANALYSIS

Analysis	Specification
Absorbance (1M) @ 280 nm	≤ 0.1000 a.u.
Absorbance (1M) @ 260 nm	≤ 0.1000 a.u.
Assay (As-is)	≥ 99.0%
Appearance and Color	White/Crystals
Identification (IR)	Passes Test
Loss on Drying	7.0 - 10.0%

9. CONCLUSION:

BioSpectra has successfully manufactured one batch of MES, Monohydrate / MES, Hydrate to be compliant with key compliance grades up to and including the Bio Excipient grade. The results reported in this external validation report deem MES, Monohydrate / MES, Hydrate manufactured using this process to be acceptable. The utilities and process equipment utilized in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. All Raw Materials used for the processing of MES, Monohydrate / MES, Hydrate were approved before use in accordance with RM specifications. The validation samples of MES, Monohydrate / MES, Hydrate have been placed into Real Time Stability. The Stability Study will be utilized to continuously evaluate the established retest date . All Finished Goods samples analyzed for the batch of this validation study, met Finished Good Specifications for Bio Excipient MES product codes: MESM-3220, MESM-3221, MESM-3222, MESM-3223, and MESM-3250. Additionally, three lots of MES, Monohydrate were analyzed to MES Hydrate MESH-3250 specifications and met the finished product specifications, with the exception of Cytotoxicity which was not tested.