

Baxa Corporation

EM2400 Valve Set Flush Analysis

Technical Paper

An investigation and analysis of the Exacta-Mix™ 2400's ability to flush ingredients from the Valve Set.



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Introduction

Baxa Corporation designs, builds, markets and supports state-of-the-art automated compounders and software for mixing multi-ingredient parenteral solutions. The Exacta-Mix 2400 Compounder (EM2400), introduced in December 2001, represents the most advanced technology for automated compounding and medication safety in the industry.

This paper describes the EM2400's ability to flush ingredients from the valve set and how the compounder's performance was measured and tested.

Verification Test

1.1 Test Description

This test verified the ability of the valve system to rinse ingredients from the flow path. Solutions containing calcium and phosphate were pumped sequentially; separated by a flushing rinse. The two ingredients form an insoluble precipitate if allowed to mix, unless separated by an effective rinse. The precipitate is easily detected through the use of a particle counter and provides an easy, reliable method to confirm the effectiveness of the rinse separating the two incompatible ingredients. This scenario would exist when compounding a TPN solution with both calcium- and phosphate-containing ingredients. During this test, precipitate-forming solutions were positioned and sequenced on the valve to produce worst-case rinsing conditions.

Worst-case rinsing conditions occur when precipitating ingredients are positioned at opposite ends of the valve. The ingredient furthest from the valve outlet (position 23 or 24) is pumped first, and the ingredient closest to the valve outlet (position 1 or 2) is pumped last. The two ingredients are separated by a 30 mL flush using deionized ultra-filtered water (DIUF water). The final volume used for collecting precipitates is 100 mL. Note: this is minimal dilution compared to actual use. The volume of the second precipitating ingredient is 7 mL, which is less than the volume of the outlet tube (about 10 mL). Therefore, any precipitate caused by the interaction of the two ingredients will remain in the outlet tube and be captured by the subsequent sample purge. See figure 1 for a diagram of the rinsing sequence used for this test.

1.2 Acceptance Criteria

All samples must not exceed the levels allowed by USP 788 for large-volume injectables (LVI) at 99% confidence and 99% reliability. The average particle concentration plus 5.075 standard deviations must be less than the allowable limit for that particle size range.

USP maximum allowable particles per ml	
10-25 microns	>25 microns
Avg load + 5.075 std dev ≤ 25 particles/mL	Avg load + 5.075 std dev ≤ 3 particles/mL

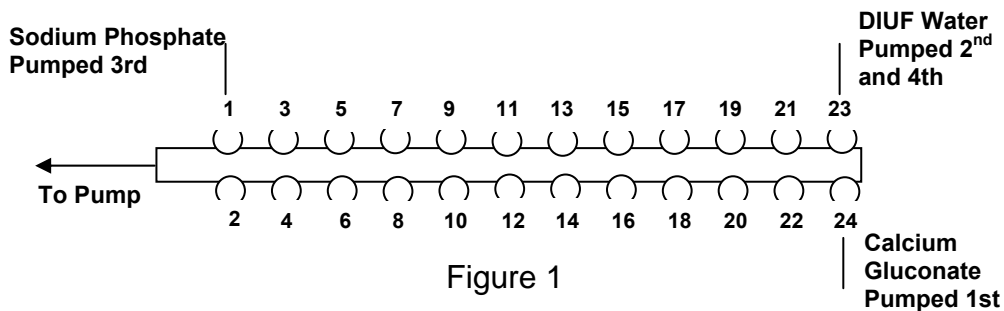
1.2.1 Statistical Rationale

The severity of particulates has been established in the hazard analysis for the valve. In accordance with the hazard analysis, this aspect of valve performance will be tested as a major concern (N=10) (K=5.075).

1.3 Test Method

Rinsing Behavior of Valve Assembly

1. Set up the valve set as shown below.



2. Confirm that the calcium gluconate and sodium phosphate ingredients do not contain visible levels of particulate (sometimes saturated solutions of salts auto-precipitate on standing).
3. Connect DIUF water to port 23, calcium gluconate to port 24, and sodium phosphate to port 1 using appropriate inlets, as shown above.
4. Prime each inlet to eliminate air. Do not allow the calcium gluconate and sodium phosphate solutions to contact as a heavy precipitate will result.

1.4 Control Samples

A control sample must be collected to determine the background particle level present in the sodium phosphate and DIUF water. It is not necessary to include effects from the calcium gluconate since this ingredient is rinsed from the valve before collection of the actual sample (see method below). Each sample collected for testing will contain approximately 7 mL of sodium phosphate and 93 mL of DIUF water (final volume is 100 mL). Prepare control samples by pumping these volumes of solutions into a low-particle sample bottle.

1. Pump 30 mL of DIUF water followed by 7 mL of sodium phosphate. Discard both solutions to waste. Use normal pumping speeds.
2. Pump 100 mL of DIUF water at about 800 mL/min and collect in a low-particle pre-cleaned bottle. This control contains approximately 7 mL of sodium phosphate and 93 mL of DIUF water.
3. Collect one control sample for each lot number combination of DIUF water and sodium phosphate. Each time a new lot of either ingredient is used, collect a new control.

4. Add 0.9-1.1 mL of 70% (v/v) isopropyl alcohol to each control to inhibit bacterial growth.
5. Before proceeding to collection of actual sample; open valve 23 and flush the valve set with 100 mL of DIUF water. Discard pump output.

1.5 Test Samples

For each valve tested, perform the procedure below.

1. Pump 20 mL of calcium gluconate from port 24 at 160 mL/min. Discard to waste. Close the port.
2. Pump 30 mL of DIUF water from port 23 at 345 mL/min. Discard to waste. Close the port.
3. Pump 7 mL of sodium phosphate from port 1 at 160 mL/min. Discard to waste. Close the port.
4. Pump 100 mL of DIUF water from port 23 into a clean, low-particle bottle at 345 mL/min. Retain this sample for analysis. Add 0.9-1.1 mL of 70% (v/v) isopropyl alcohol to inhibit bacterial growth.
5. Submit all control and actual samples to an outside Good Laboratory Practice (GLP) certified lab for analysis by USP method 788 for large-volume injectables.
6. Transcribe the lab results to Table 6 of Appendix B. Subtract the particulate level found in the control samples from the particle level found in the test samples and record in the last column of Table 3.
7. Calculate the average, standard deviation, and upper confidence limit for the sample data at the bottom of Table 6 (use $K=5.075$).

Test Results

The results show that the rinsing behavior for the valve is acceptable. A summary of the test results compared to the acceptance criteria is shown below.

	Acceptance Criteria	Test Results
9-Month Aged Valve	n/a	n/a
10-25 microns	≤ 25 particles/mL	18.4 particles/mL
>25 microns	≤ 3 particles/mL	1.1 particles/mL
Non-Aged Valve	n/a	n/a
10-25 microns	≤ 25 particles/mL	13.1 particles/mL
>25 microns	≤ 3 particles/mL	2.3 particles/mL