

# EVALUATION OF A SINGLE USE MIXING SYSTEM FOR USE IN A MULTIPURPOSE BIOPHARMACEUTICAL ENVIRONMENT

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**INTRODUCTION**

Single use technologies are being used by many biopharmaceutical manufacturers to improve facility throughputs by significantly reducing downtime between campaigns. Adoption of disposables also promotes the development of a multipurpose plant design because of the inherent flexibility of disposable systems.

The target objective of this evaluation was to determine if disposable mixing systems could be implemented for buffer preparation at Innogenetics to both reduce costs and increase plant operational flexibility. The choice of the correct system is important for the implementation of new projects, and especially important for contract manufacturing activities.

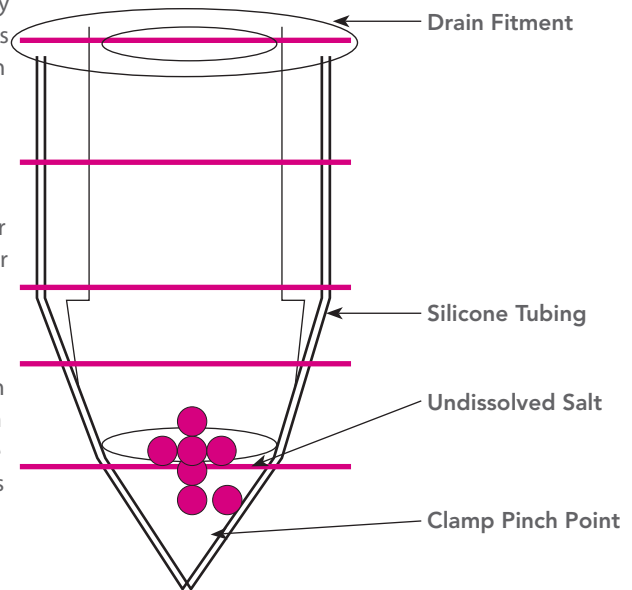
A new non-invasive, single use, disposable, liquid/liquid and liquid/powder mixing system was evaluated that potentially circumvents the time consuming and costly cleaning, sterilization and validation steps identified earlier. Initially the mixing system was tested to determine its suitability and effectiveness for the scalable and homogeneous mixing of sodium chloride which was used to simulate salt based buffers. The description of the test protocols and results obtained are detailed below.

**SECTION 1**

**MATERIALS AND METHODS**

ATMI's Newmix Pad-Drive 1000 mixing system was used in combination with a 200L circular holding tank fitted with a standard 200L Newmix-C disposable mixing bag. The C-mix bag contains an integrated mixing paddle which is sheathed in the same film used in the construction of the bag to maintain a continuous and homogeneous fluid contact layer. The mix system operates by oscillating the paddle within the liquid column in an action similar to that demonstrated when a coffee spoon is used to stir a cup of coffee. Thus,

**TABLE 1 DESIGN OF DRAIN AND COLLECTION OF SALT PARTICLES IN THE DRAIN**



**Scalability**

Sodium chloride (292g/L NaCl) was dissolved and mixed at 50 (14.6Kg NaCl) and 200L (58.4 Kg NaCl). Mixing efficiency was determined by measurement of conductivity at the top of the bag until the conductivity stabilized.

**Homogeneity**

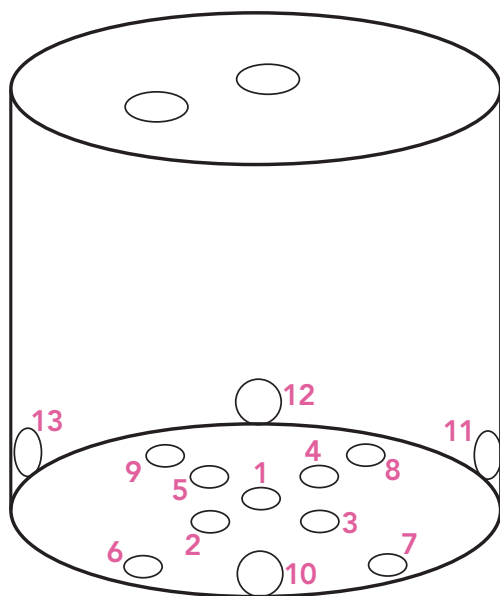
The bag was prefilled with 170L WFI, then 60Kg of sodium chloride (353g/L) was added to give a final concentration of 6.55M NaCl. Homogeneity of mixing was determined by measuring the conductivity of the solution at the top, middle and bottom of the bag until the conductivity measurements stabilized.

**THE TARGET OBJECTIVE OF THIS EVALUATION WAS TO DETERMINE IF DISPOSABLE MIXING SYSTEMS COULD BE IMPLEMENTED FOR BUFFER PREPARATION AT INNOGENETICS TO BOTH REDUCE COSTS AND INCREASE PLANT OPERATIONAL FLEXIBILITY**

the paddle revolves within the liquid column, but the paddle and its associated shaft do not rotate. This design provides a highly efficient, low shear mixing system with no integrated bearings.

The bags used in the scalability and homogeneity trials were standard 200L bags supplied by ATMI with integral filling lines, a 6-inch diameter powder transfer port, air supply line and bottom drain line.

**FIGURE 2** THE LOCATIONS OF THE TEST DRAINS ON THE 200L C-MIX TEST BAG



**TABLE 1** RESULTS OF VISUAL INSPECTION OF SALT ACCUMULATION IN EACH DRAIN

DRAIN #	TEST 1	TEST 2
1	6	6
2	2	1
3	3	2
4	5	3
5	2	4
6	2	4
7	2	4
8	5	5
9	2	2
10	1	0/1
11	0	1
12	0	1
13	0	1

**INITIAL SUMMARY**

The Pad-Drive 1000 unit with the 200L Newmix-C bag was simple and easy to use, gave excellent mixing characteristics and very quickly produced a homogeneous solution, determined by measurement of the conductivity of high molarity sodium chloride.

However, during mixing operations it became apparent that there was a significant accumulation of undissolved salt particles in the drain port at the bottom of the mixing bag, between the top of the drain connector and the pinch clamp used to seal the discharge tubing. No matter how vigorous the mixing cycle was, these salt particles remained in the drain port.

Therefore, a second series of experiments were entered into with the equipment manufacturer to both attempt to identify the root cause of the problem and to develop suitable solutions.

positioning of the drain ports as a possible, simple and inexpensive solution to the problem of particle accumulation in the drain port. To quickly determine if this was actually a viable option, Innogenetics worked with the manufacturer to produce a 200L C-Mix bag with 13 different drain connectors in various positions. See Figure 2.

Visual inspection was carried out on the drain connectors and tubing, during and after mixing, to see if salt was completely washed out of the drain connector inlets. If salt had accumulated in the drain connector, the amount was recorded visually and scored between 0 and 6, with 0 being no salt observed and 6 being salt filled to the top of the drain port. The same operator was used in all experiments to eliminate personal variability in determination of particulate accumulation. The same design drain port was fitted to each test location.

**SECTION 2**

**DRAIN PORT POSITIONING**

In conjunction with the manufacturer of the bags we looked at offsetments. In terms of average indication grades, the salt accumulation

**RESULTS**

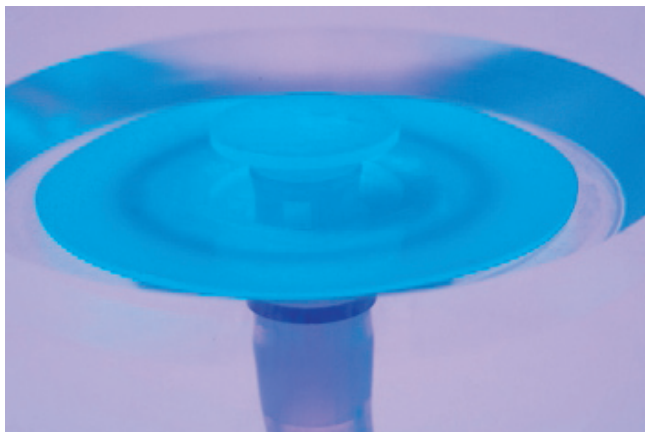
As shown in Table 1, considerable differences in the amounts of undissolved salt were observed depending on the position of the drain-fit

**TABLE 2** PRODUCT FAMILY VS. END-ITEM LEVEL EVALUATION

LOCATION	RESULTS	# OF DATA POINTS	AVERAGE VALUE
Bottom Center	6, 6	2	6
Bottom Middle	2, 3, 5, 2, 1, 3, 2, 4	8	2.75
Bottom Side	2, 2, 5, 2, 4, 4, 5, 2	8	3.25
Vertical Side	1, 0, 0, 0, 1, 0, 0, 1	8	0.375



**FIGURE 3** THE NEW DESIGN OF DRAIN PORT IN THE CLOSED POSITION AS USED DURING THE FILING, LOADING AND MIXING CYCLES



**FIGURE 4** THE DRAIN PORT IN OPEN POSITION

at the drains placed on the side of the bag were minimal compared to those drains located at the bottom center, (drain 1) bottom middle (drains 2 to 5) and bottom side (drains 6 to 9) of the bag.

This data reflects a higher salt accumulation in those ports located at the bottom side of the vessel than those located at the bottom middle. This may be due to the presence of the side wall of the vessel acting as a baffle, slowing horizontal flow and allowing undissolved particles to drop from suspension closer to the wall than can occur in the center of the bag.

#### DRAIN PORT DESIGN

From the results shown in Tables 1 and 2, it would appear that incorporating the drain into the side wall of the mixing bags would be a simple solution that would eliminate almost all particulate deposition and accumulation during mixing. However, positioning

the current design. The newly designed drain port is manufactured from LLDPE and works by closing the entrance to the drain port during the filling and mixing cycles (see Figure 3), thus preventing the accumulation of salt or other undissolved particles in the port entrance before the dissolution step of the mixing cycle is completed. A smooth surface is created at the bottom of the bag during the mixing cycle so that mixing efficiency is not compromised.

Following mixing, the center sealing plug in the drain is easily raised via a simple lever on the side of the mixing station to allow the mixed liquid to drain thoroughly from the bag (see Figure 4).

#### CONCLUSIONS

- The Newmix Pad-Drive 1000 with 200L bag option is a single use, disposable mixing system that provides a practical and cost effective solution for homogeneous, scalable,

**THE NEW MIXING PAD-DRIVE 1000 WITH 200L BAG OPTION IS A SINGLE USE DISPOSABLE MIXING SYSTEM THAT PROVIDES A PRACTICAL AND COST EFFECTIVE SOLUTION FOR HOMOGENEOUS, SCALABLE, HIGH EFFICIENCY MIXING**

the drain on the sidewall could potentially create other problems.

First, a side wall drain may increase the volume of liquid retained in, and unrecoverable from, the mixing vessel. For buffer mixing applications this may not be a problem, but for mixing intermediates or product, this additional loss is undesirable. Second, a side wall drain would require re-engineering of the mixing tank, specifically stainless steel jacketed tanks used for temperature control. Third, a fixed drain location means that the bag can only be positioned in one orientation within the mixing tank, therefore eliminating the flexibility of location of the powder addition port that the operators enjoy with the current design.

The manufacturer of the bags has developed a new drain port that would potentially overcome the issue of particulate accumulation in the old ports, and would be easy to use, cost-effective to manufacture and install while maintaining the inherent flexibility of

high efficiency mixing – eliminating the need for cleaning, sterilization and validation of following a mixing run.

- The mixing system was determined to be efficient and easy to use during preparation of chromatography and TFF buffers in a cGMP biopharmaceutical manufacturing environment.
- Optimization of the drain valve has eliminated the major issue noted in the original bag design, and in all other bag designs evaluated.
- The adoption of a disposable mixing step significantly reduced the turn around time required to transition between operating configurations.
- The ability to utilize the Pad-Drive mixing system with other tank volumes larger than the currently used 200L system will allow future scale up to be achieved with minimal additional capital investment. **FP**