

EVALUATION OF A SINGLE USE MIXING SYSTEM FOR USE IN A MULTIPURPOSE BIPHARMACEUTICAL ENVIRONMENT

By Rutger Vandiest ¹
and Derek Pendlebury ²



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.

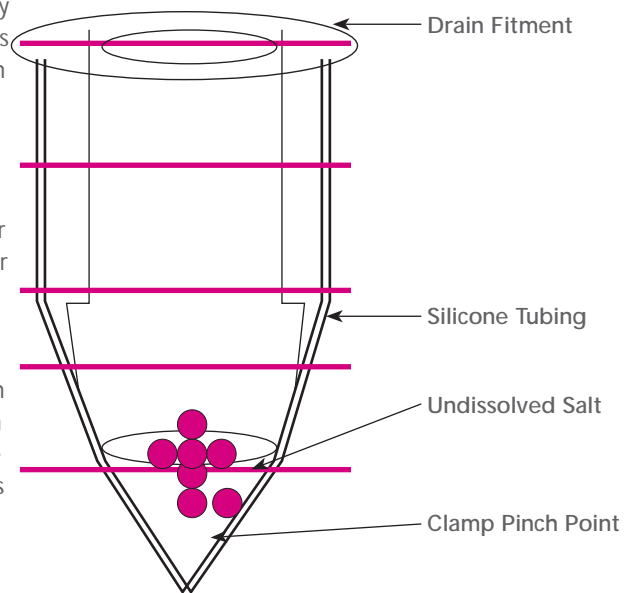
A new non-invasive, single use, disposable, liquid/liquid and liquid/powder mixing system was evaluated that potentially circumvents the time consuming and costly cleaning, sterilization and validation steps identified earlier. Initially the mixing system was tested to determine its suitability and effectiveness 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 liquid 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 pre-filled 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

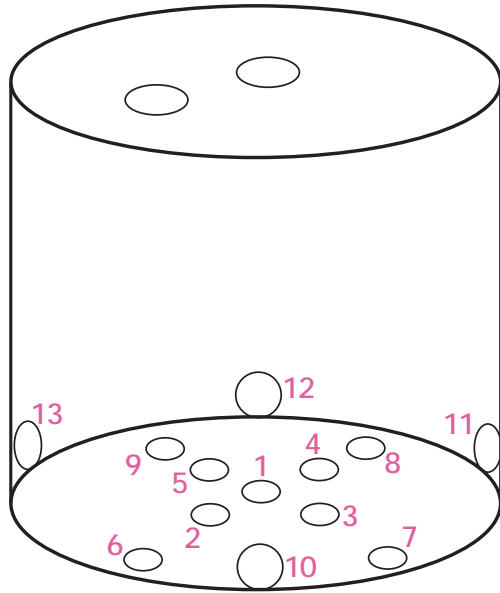


TABLE 1 RESULTS OF VISUAL INSPECTION OF SALT ACCUMULATION IN EACH DRAIN

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 piled 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.

RESULTS

As shown in Table 1, considerable differences in the amounts of undissolved salt were observed depending on the position of the drain- test locations. In terms of average indication grades, the salt accumulation

SECTION 2

DRAIN PORT POSITIONING

In conjunction with the manufacturer of the bags we looked at o

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

