Characterization of Xcellerex XDM and XDUO 500 single-use mixers

Intellectual Property Notice: The Biopharma business of GE Healthcare was acquired by Danaher on 31 March 2020 and now operates under the Cytiva™ brand. Certain collateral materials (such as application notes, scientific posters, and white papers) were created prior to the Danaher acquisition and contain various GE owned trademarks and font designs. In order to maintain the familiarity of those materials for long-serving customers and to preserve the integrity of those scientific documents, those GE owned trademarks and font designs remain in place, it being specifically acknowledged by Danaher and the Cytiva business that GE owns such GE trademarks and font designs.

cytiva.com

CY13916-27May20-AN

Characterization of Xcellerex™ XDM and XDUO 500 single-use mixers

This application note describes mixing and heating-cooling characterization data for the Xcellerex XDM/XDUO 500 single-use mixer. A design of experiments (DoE) approach to liquid-liquid mixing was successfully applied to establish a statistical model to predict the mixing time throughout the working range. Liquid-liquid mixing times as low as 17 s were observed at the nominal volume (500 L) and highest viscosity tested (20 cP). Further, mixing of two different solids, PBS and NaCl, was tested. Mixing to 95% homogeneity (t_{m95}) of both solids was reached within 4 min at 150 rpm. Heating of liquid from 5°C to 20°C and 20°C to 37°C was achieved within 2 h for all tested volumes (110, 305, and 500 L). Cooling from 37°C to 20°C and 20°C to 5°C was achieved within 4 h.

Introduction

Xcellerex single-use mixers (XDM and XDUO) are available in several different configurations. In terms of mixing capability, the XDM and XDUO are identical. XDUO, however, offers more powerful automation capabilities than XDM. The XDM mixers range in size from 50 to 1000 L, while XDUO mixers are available from 100 to 2500 L. In common for all configurations is the robust mixing performance and ease of use. The mixers are designed for process development, commercial and clinical production of biopharmaceuticals, vaccines, and other biologics. Xcellerex mixers support upstream and downstream applications for preparation of buffer, media, product and intermediates, as well as other process fluids.

The aim of this study is to give a detailed description of the physical characteristics of XDM/XDUO 500 in terms of mixing and heating and cooling. The mixing properties of XDM/XDUO 500 have been investigated with regard to both liquids and different types of solids. For mixing of liquids, a DoE approach was applied where liquid volume, viscosity, and impeller speed were varied to create a statistical model predicting the mixing time across the working range. In addition to liquid mixing, mixing of solids was investigated by preparation of two model solutions; PBS and saline, to show the mixer's ability to handle solids. Heating and cooling times for different temperature intervals were investigated for minimum, middle, and nominal liquid volumes (110, 305, and 500 L).

The characterization data presented in this application note is essential for optimizing the mixing or heating-cooling protocol of XDM/XDUO 500 for bioprocess applications, and for effective scale-up.

Materials and methods

System setup

The mixer was equipped with an XDM 500 Plus bag and an Xcellerex temperature probe. A temperature control unit (TCU) was used to control the temperature of the liquid (Polyscience, 9 kW). External pH (ProMinent), temperature, and conductivity probes (Ahlborn) were used for logging of data via a data logger (Ahlborn).

Liquid-liquid mixing

The liquid-liquid mixing time was assessed by adding pulses of acid and measuring the pH change at different positions in the mixer (Fig 1). The tests were performed according to DoE where impeller speed, volume, and viscosity were varied simultaneously. The factorial design was a central composite design.

The mixer bag was filled with liquid to the volume to be tested (110, 305, and 500 L). For the tests at 1 cP viscosity, the liquid consisted of 0.1 M NaCl in purified water. For tests at 10 and 20 cP, sucrose and NaCl were dissolved in water to generate a viscous liquid with a final NaCl concentration of 0.1 M. The impeller was set to rotate in a counterclockwise (CCW) direction giving an upward pumping mixing pattern. The temperature was controlled at 20°C. For pH change, acid (0.2 M HCl in purified water, 10 or 20 cP sucrose) was added at a ratio of 1:2667 for 1 cP and 1:1000 for 20 cP of the liquid volume in the mixer. The ratios were chosen to induce a pH step change of approximately 1 pH unit. The pH was recorded at nine positions in the mixer at 500 L (Fig 1). The probes were arranged to cover all areas where poor mixing could be expected to occur. The pH probes were connected to an external data logger for logging of data. The number of probes was reduced as the liquid volume was lowered. The mixing time was assessed by calculating the time to reach 95% of the pH step change (t_{m95}). The slowest t_{m95} from each run was used for model calculations in the software MODDE (version 11.0.0.1717, MKS Umetrics AB).

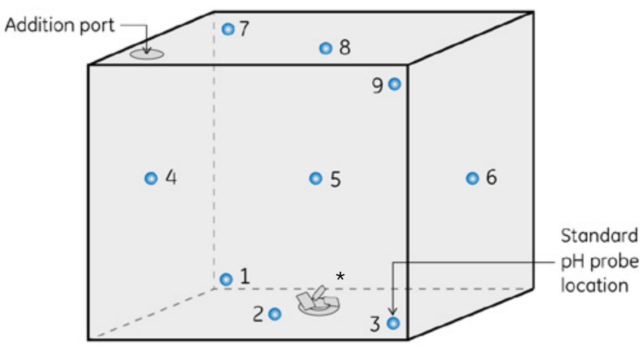

Fig 1. pH probe distribution in XDM/XDUO 500 at 500 L. Probes 4 to 9 were lowered for tests at 305 L. At 110 L, probes 4, 5, and 7 to 9 were disconnected. *Note that the impeller is welded to the bag.

Solid-liquid mixing

Mixing of solids was tested by preparing two different standard solutions with salts: 1 M NaCl and 20 mM PBS (pH 7.4) with 150 mM NaCl. The concentrations were chosen in the higher range to represent demanding conditions. The mixer bag was filled with purified water to 90% of the nominal volume, that is, 450 L. The impeller speed was set to 150 rpm. Both clockwise (CW) and counterclockwise (CCW) impeller directions were tested. As opposed to CCW, CW impeller direction creates a downward pumping mixing pattern. The temperature was controlled at 20°C. The salts were added through a funnel connected to the powder port on top of the mixer bag. The mixing time was assessed by calculating t_{m95} on the conductivity step change. The conductivity probe was placed in position 9 (Fig 1).

Heating-cooling

The heating-cooling properties of XDM/XDUO 500 was tested at three different volumes: 110, 305, and 500 L. The mixer bag was filled with 6 g/L NaCl in purified water to the volume to be tested and the impeller speed was set to 125 rpm (CCW). The heating and cooling properties of XDM/XDUO 500 were assessed by measuring the time to reach 95% of the temperature step change (t_{95}) for four different temperature intervals: 5°C to 20°C, 20°C to 5°C, 20°C to 37°C, and 37°C to 20°C. If using an XDUO mixer connected to an X-Station mobile control console, automatic temperature control with PID regulation is possible. However, for the results to be applicable for both XDM and XDUO mixers, a manual approach was used. The temperature setting on the TCU was controlled manually by setting the temperature to 10°C above (for heating) or below (for cooling) the intended set point and adjusting it to the intended set point when 95% of the step change had been reached. Temperature logging continued until it could be verified that the temperature stabilized at the intended set point. The temperature was logged using an external temperature probe and data logger.

Results and discussion

Liquid-liquid mixing

Liquid-liquid mixing was tested at 110, 305, and 500 L at three different viscosities: 1, 10, and 20 cP. The impeller speed was varied from 50 to 200 rpm. In Figure 2, results are shown from the probe position with the longest t_{m95} determined for each run, that is, the worst-case scenario.

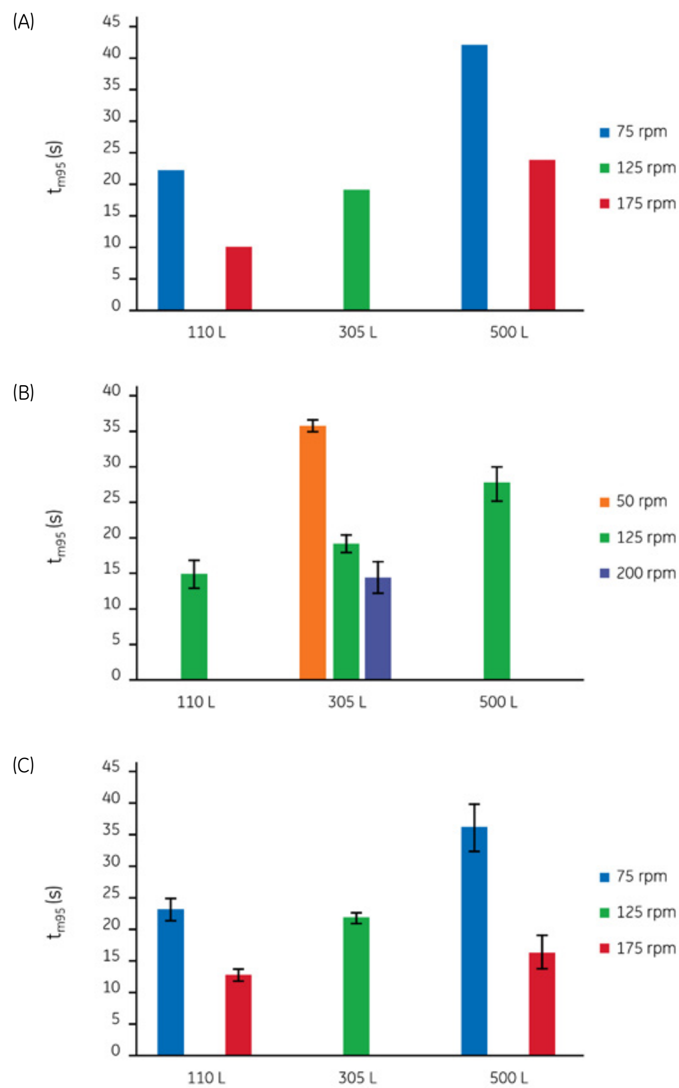

Fig 2. t_{m95} results from the liquid-liquid mixing study at (A) 1 cP, (B) 10 cP, and (C) 20 cP viscosities. Error bars display one standard deviation.

The t_{m95} varied between 10 and 42 s for the tested conditions (Fig 2). The mixing time decreased with decreasing volume and increasing impeller speed.

The average difference in t_{m95} for the fastest and slowest probe position for each run was 9 s, indicating that mixing is fast and efficient throughout the whole mixer volume.

The resulting t_{m95} from the slowest probe position were evaluated using the statistical software MODDE. A multiple linear regression (MLR) model was created from the central composite test design. The investigated factors: liquid volume, impeller speed, and viscosity were evaluated at a 95% significance level. The model fit was judged by the fraction of variation of the response explained by the model (R^2) and the fraction of variation of the response that can be predicted by the model (Q^2, Table 1). Values close to 1.0 for both R^2 and Q^2 indicate a good model with excellent prediction power. Q^2 values greater than 0.1 indicate a significant model.

Table 1. The liquid-liquid mixing t_{m95} model's statistical parameters

Statistical parameter	Value
R^2 (Model fit)	0.92
Q^2 (Model fit prediction)	0.88
RSD (Residual standard deviation)	2.48

The model showed a good fit with high R^2 and Q^2 and a residual standard deviation (RSD) of 2.48 (Fig 3 and Table 1). Altogether this means that the model is adequate and can be used for predictions of t_{m95} within the design space.

The model for liquid-liquid mixing t_{m95} is visualized as a contour plot in Figure 3. The model predicts impeller speed and volume as significant factors affecting the mixing time.

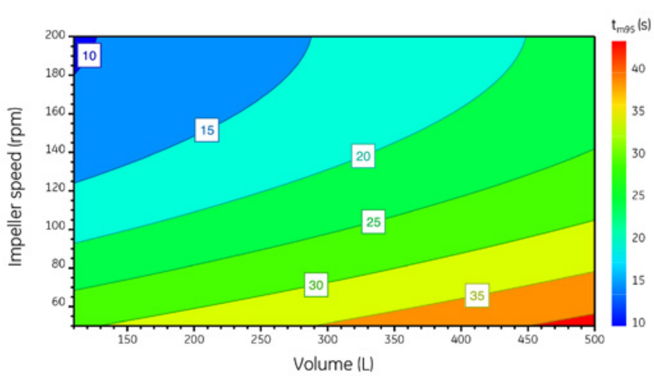

Fig 3. t_{m95} for liquid-liquid mixing. Contour plot of the statistical model, produced in MODDE software.

Solid-liquid mixing

The mixing times were similar for NaCl at both impeller directions and PBS at CCW impeller direction with t_{m95} values around 4 min (Fig 4). Mixing of PBS at CW impeller directions was significantly faster with a t_{m95} of 130 s.

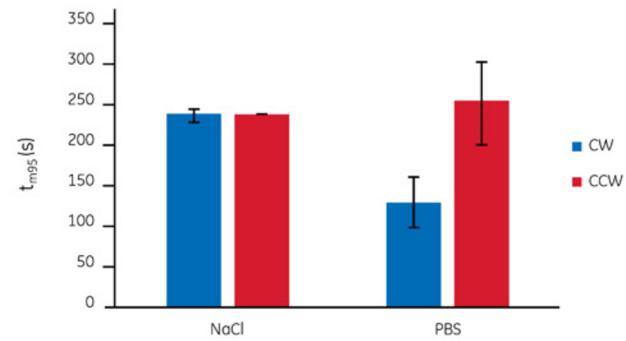

Fig 4. t_{m95} results from the solid-liquid mixing tests. Error bars display one standard deviation.

Heating-cooling

The manual temperature control was efficient and the intended set point was reached as depicted (Fig 5). t_{95} for the heating intervals, 5°C to 20°C and 20°C to 37°C, was 2 h or less for all tested volumes (Fig 6). t_{95} for cooling from 20°C to 5°C varied between 1.9 and 2.8 h while cooling times for the 37°C to 20°C temperature interval varied between 3.0 and 3.8 h.

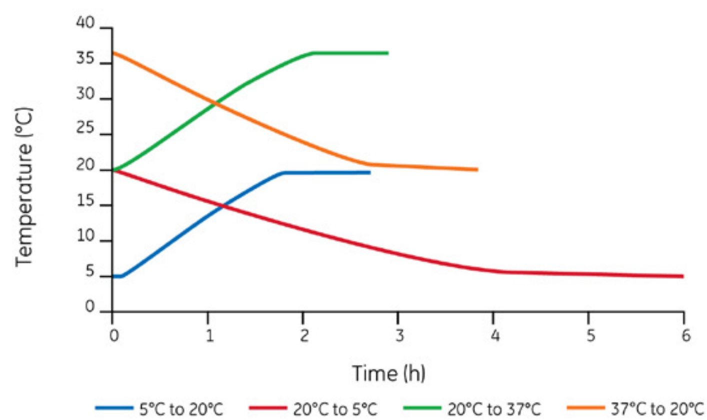

Fig 5. Heating and cooling curves at 500 L.

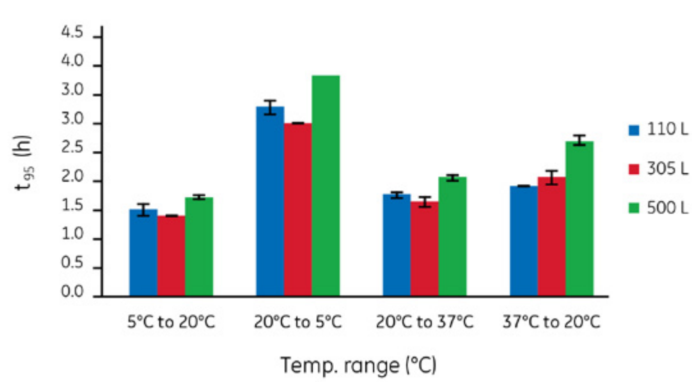

Fig 6. t_{95} results from the heating-cooling tests for different temperature ranges. The error bars display one standard deviation.

Conclusions

This characterization study demonstrates the ability of Xcellerex XDM and XDUO 500 single-use mixers in the preparation and handling of solutions in multiple applications and conditions. Robust liquid-liquid mixing times as low as 17 s were observed at the maximum volume and viscosity tested. The mixing was efficient throughout the complete mixer volume. We successfully used a DoE approach to liquid-liquid mixing and created a model to predict the mixing time within the operating range. In the solid-liquid mixing, effective mixing to 95% homogenity of PBS and NaCl was achieved within 4 min at 150 rpm impeller speed. Heating of liquid was achieved within 2 h for all tested volumes and temperature intervals whilst cooling times varied between 1.9 and 3.8 h.

The results of these studies should aid in the implementation of single-use mixers in new facilities and help in process optimization and scale-up.

Ordering information

Product	Product code
Xcellerex XDM-T Jacketed Stainless Steel Mixing System	29054862
Xcellerex XDUO-T Jacketed Stainless Steel Mixing System	29054863
XDM 500 Plus Bag	888-0156-C

Related documents	Product code
Performance guide: Mixing and heating-cooling characterization of Xcellerex XDM and XDUO single-use mixers	29237251
Application note: Characterization of Xcellerex XDM 50 single-use mixer	29237878
Application note: Characterization of Xcellerex XDM and XDUO 100 single-use mixers	29242783
Application note: Characterization of Xcellerex XDM and XDUO 200 single-use mixers	29242788
Data file: Xcellerex XDM Mixer	29048367
Data file: Xcellerex XDUO Mixer	29048366
Data file: Xcellerex XDUO 2500 Mixer	29153543

For more information on Xcellerex XDM and XDUO mixing systems, please contact your local sales representative.

GE Healthcare Bio-Sciences AB
Björkgatan 30
751 84 Uppsala
Sweden

gelifesciences.com/xcellerex

GE Healthcare UK Ltd., Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, UK
GE Healthcare Europe GmbH, Munzinger Strasse 5, D-79111 Freiburg, Germany
GE Healthcare Dharmacon Inc., 2650 Crescent Dr, Lafayette, CO 80026, USA
GE Healthcare Bio-Sciences Corp.,100 Results Way, Marlborough, MA 01752, USA.
HyClone Laboratories Inc., 925 W 1800 S, Logan, UT 84321, USA
GE Healthcare Japan Corp., Sanken Bldg., 3-25-1, Hyakunincho Shinjuku-ku, Tokyo 169-0073, Japan
For local office contact information, visit gelifesciences.com/contact

29242789 AB 02/2017