Characterization of Xcellerex XDM and XDUO 100 single-use mixers

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This application note describes mixing and heating-cooling characterization data for the Xcellerex XDM/XDUO 100 single-use mixer. A design of experiments (DoE) approach to liquid-liquid mixing was successfully used to establish a statistical model to predict the mixing time throughout the working range. Liquid-liquid mixing times as low as 13 s were observed at the nominal volume (100 L) and highest viscosity tested (20 cP). Further, mixing of two different solids, PBS and saline, was tested. Mixing to 95% homogeneity (t_{m95}) of both solids was reached within 50 s. Heating of liquid from 5°C to 20°C and 20°C to 37°C was achieved within 1.4 h for all tested volumes (30, 65, and 100 L). Cooling from 37°C to 20°C and 20°C to 5°C was achieved within 1.5 h except cooling from 20°C to 5°C at 30 L, which took 2.0 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 100 in terms of mixing and heating-cooling. The mixing properties of XDM/XDUO 100 were investigated regarding 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 (30, 65, and 100 L).

The characterization data presented in this application note is essential for optimizing the mixing or heating-cooling protocol of XDM/XDUO 100 for bioprocess applications, and for effective scale-up.

Materials and methods

System setup

The mixer was equipped with an XDM 100 Plus bag and an Xcellerex temperature probe. A temperature control unit (TCU) was used to control the temperature of the liquid (Polyscience, 3 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 (30, 65, and 100 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 100 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. The software MODDE (version 11.0.0.1717, MKS Umetrics AB) was used to create a statistical model.

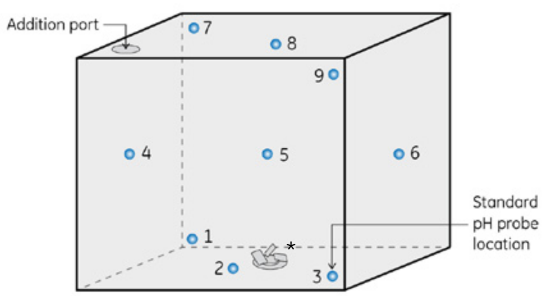

Fig 1. pH probe distribution in XDM/XDUO 100 at 100 L. Probes 4 to 9 were lowered for tests at 65 L. At 30 L, probes 4 to 6 were lowered additionally and probes 7 to 9 were disconnected. *Note that the impeller is welded to the bag.

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, 90 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 100 were tested at three different volumes: 30, 65, and 100 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 100 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 30, 65, and 100 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.

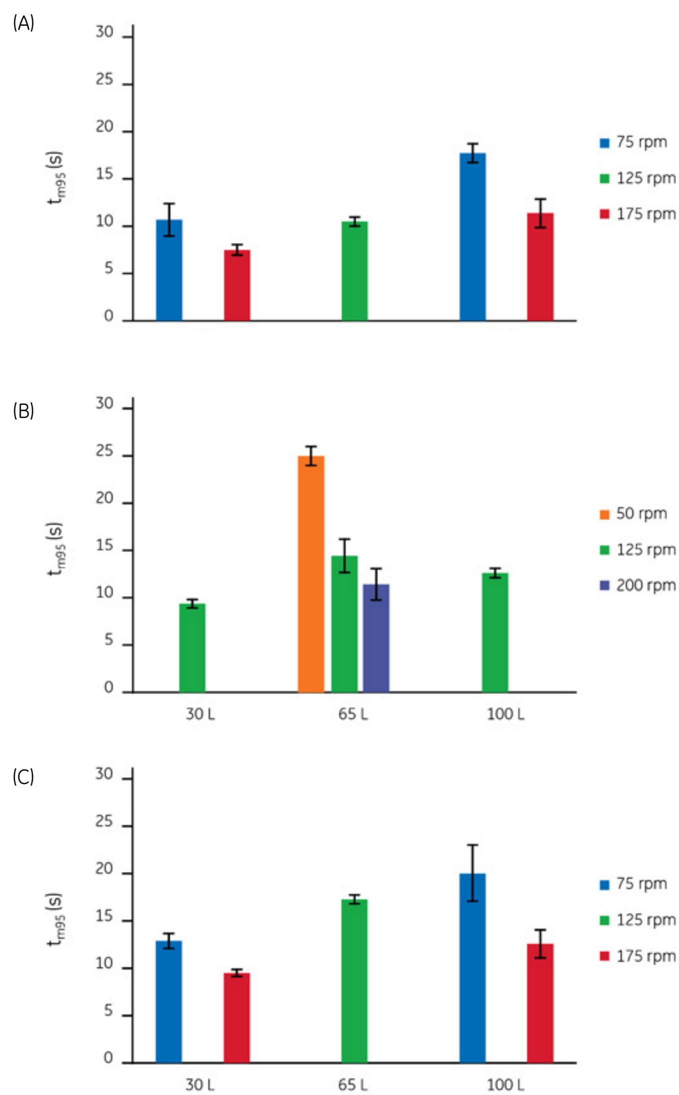

Fig 2. t_{m95} results from the liquid-liquid mixing study at (A) 1 cP, (B) 10 cP, and (C) 20 cP viscosities. Error bars display one standard deviation.

The t_{m95} varied between 8 and 25 s for the tested conditions (Fig 2). The mixing time decreased with decreasing volume and increasing impeller speed. Mixing was generally faster at the lower viscosities.

The average difference in t_{m95} for the fastest and slowest probe position for each run was 6 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)	0.83
Q^2 (Model fit prediction)	0.75
RSD (Residual standard deviation)	1.90

The model showed a good fit with high R^2 and Q^2 and a residual standard deviation (RSD) of 1.90 (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, volume, and viscosity as significant factors affecting the mixing time.

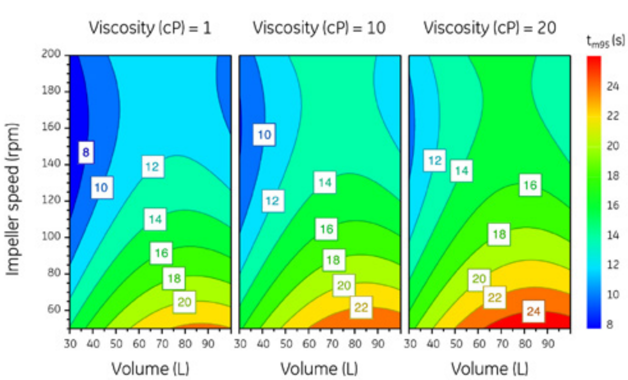

Fig 3. t_{m95} for liquid-liquid mixing. Contour plot of the statistical model, produced in MODDE software.

Solid-liquid mixing

Mixing to 95% homogeneity was achieved in less than 50 s for both solutions and both impeller directions (Fig 4). The difference in mixing time between CW and CCW impeller direction was insignificant (p_{NaCl} = 0.25, p_{PBS} = 0.29).

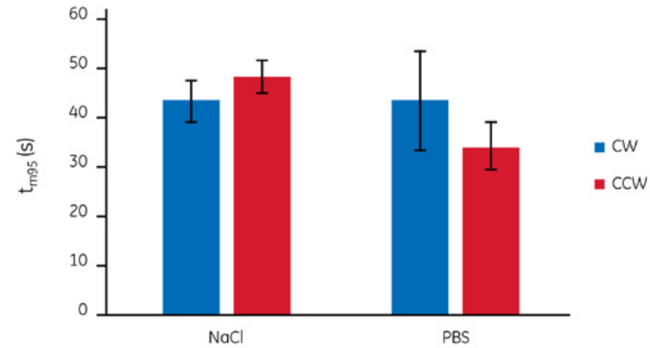

Fig 4. t_{m95} results from the solid-liquid mixing tests. Error bars display one standard deviation.

Heating-cooling

The manual temperature control showed fast heating and cooling times and the intended set point was reached with little or no overshoot/undershoot in temperature (Fig 5). The t_{95} for the heating and cooling intervals was less than 1.5 h for all tested conditions, except for cooling from 20°C to 5°C at 30 L, which had a t_{95} of 2 h (Fig 6). Heating and cooling times were generally longer at 30 L compared to the other volumes, however, for heating from 5°C to 20°C the 30 L volume was fastest with a t_{95} of only 1.1 h.

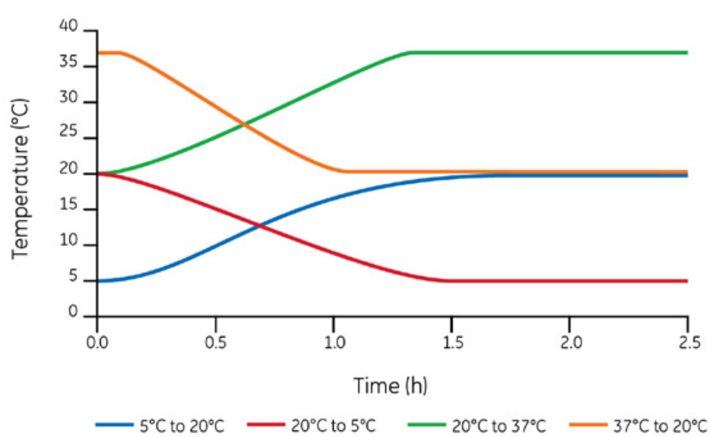

Fig 5. Heating and cooling curves at 100 L.

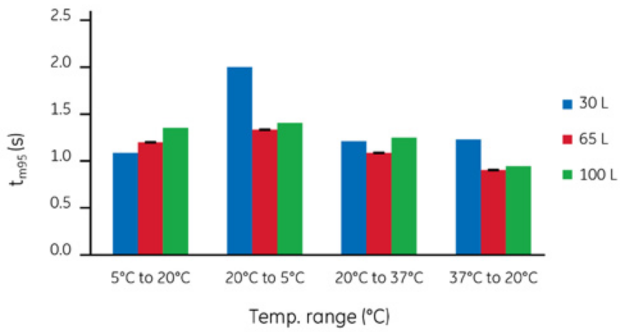

Fig 6. t_{95} results from the heating-cooling tests for different temperature ranges. The error bars display one standard deviation.

Conclusions

This characterization study demonstrates the ability of Xcellerex XDM/XDUO 100 single-use mixers in the preparation and handling of solutions in multiple applications and conditions. Robust liquid-liquid mixing times as low as 13 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 t_{m95} mixing of PBS and NaCl was achieved within only 50 s at 150 rpm impeller speed. Heating and cooling of liquid was generally achieved within 1.5 h except for cooling from 20°C to 5°C at 30 L which was somewhat longer (2.0 h). The results of these studies are of use to users intending to invest in an XDM/XDUO system or when scale-up and transfer of processes are required.

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 100 Plus bag	888-0154-C

Related documents	Product code
Performance guide: 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 200 single-use mixers	29242788
Application note: Characterization of Xcellerex XDM and XDUO 500 single-use mixers	29242789
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.

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