Application Note

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Flexsafe® Pro Mixer

The Fast, Flexible and Intelligent Solution for Heat Transfer Applications

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Abstract

Flexsafe® Pro Mixer is a unique single-use technology fitting all mixing applications from buffer and media preparations, downstream processes to final formulation. Flexsafe® Pro Mixer ergonomic design enables intuitive, modular and agile use to achieve fast installation and mixing operations. Additionally, the Flexsafe® film offers high standard quality attributes such as biocompatibility, integrity and robust supply chain.

This application study presents heat transfer performance data of the Flexsafe® Pro Mixer from 50 L to 2,000 L.

Heating or cooling in mixing bags is required in several biomanufacturing steps such as cooling or temperature holding in downstream or heating in media and buffer applications. Efficient mixing also allow better heat transfer performance for larger volumes.

4 different Flexsafe® Pro Mixer volumes have been tested with water in heating phase from 4°C to 37°C and in cooling phase from 37°C to 4°C with different variables values. A total of 189 experiments have been performed in order to model the heat transfer coefficient U by multiple linear regression and to populate a specific calculation sheet to automatically generate heating and cooling curves. The performance of the system is characterized by the time needed to achieve the temperature set point. Moreover, the impact of parameters such as impeller speed and jacket flow rate on heat transfer efficiency is evaluated.

Find out more: www.sartorius.com/flexsafe-pro-mixer

Introduction

The purpose of this application study is to assess the heating and cooling performance of the Flexsafe® Pro Mixer featuring the Palletank® for Mixing jacketed. The heat transfer performance have been demonstrated at 50 L, 200 L, 1,000 L and 2,000 L.

Heating or cooling in mixing bags is required in numerous biopharmaceutical applications. For example, in downstream processes, several steps require cooling or temperature holding and in buffer and media preparation, WFI can be heated up to accelerate the dissolution and thereby optimize the process. For large volume Palletank®, the jacket surface is often not sufficient for large heat transfer needs and requires a strong agitation to increase heat transfer and reduce time to reach temperature target.

The heating or cooling rate depends on how the heat is supplied or removed, the mixing intensity, which is influenced by the type of agitator and its rotation rate, and many other parameters e.g. the geometry, the agitated liquid properties, etc. Good knowledge of all these parameters is important for the design of the process. The influence of most of these parameters can be represented by the overall heat transfer coefficient U.

We have designed an experimental plan in order to model U (W/m^2K) as a function of process variables so that heating and cooling curves can be readily generated. For this purpose, we have generated a large number of experiments with various combinations of impeller speed N (rpm), jacket flowrate F_j (L/min), jacket supply temperature T_j (°C) and available heating | cooling power (%) for 4 different Palletank® sizes (50 L, 200 L, 1000 L and 2000 L) in heating phase from 4°C to 37°C and for 3 different Palletank® sizes (200 L, 1000 L and 2000 L) in cooling phase from 37°C down to 4°C to cover the broader panel of temperature usually requested.

This led us to conducting 189 experiments. For each experiment, U was estimated by linear regression on time versus log mean temperature difference (LMTD) during the interval for which jacket temperature T_j was constant according to the following equation:

$$\ln\left(\frac{T_j - T_o}{T_j - T}\right) = \frac{A_j U}{mC_p} t$$

where the parameters are defined as follows:

Table 1: Description of parameters involved in overall heat transfer coefficient calculation

Parameters	Units	Description
T_j	°C	Jacket supply temperature (assumed constant)
T_o	°C	Initial bulk liquid temperature
T	°C	Bulk liquid temperature
Aj	m^2	Active surface area of the jacket in contact with the liquid-filled region of the bag
U	W/m^2K	Overall heat transfer coefficient
m	kg	Mass of liquid in the bag
Cp	J/kgK	Specific heat capacity of liquid in the bag
t	s	Time

This equation is obtained from the heat removal rate definition:

$$Q = UA\Delta T_m = mc_p \frac{\delta T}{\delta t}$$

where m is the batch of mass to heat or cool and where

$$\frac{\delta T}{\delta t} = \frac{UA}{mc_p} (T_s - T)$$

for a constant supply temperature T_s. This equation is then rearranged and integrated to provide the equation used for the calculation.

Materials and Methods

Materials

Consumable
- Standard Flexsafe® Pro Mixer bags (50 L, 200 L, 1,000 L and 2,000 L)
- Deionized water
- Jacket fluid: 40% propylene glycol

Equipment
- Palletank® for Mixing jacketed with weighing - PED (± 0.01 kg accuracy)
- Flexsafe® Pro Mixer drive unit
- Sensors (all calibrated to NIST traceable standards):
  - 4 temperature sensors, Pt100 (RTD) Resistance Temperature Detectors (± 0.5°C accuracy)
  - 1 flow meter, Coriolis type (± 0.01 L/min accuracy)
  - 2 pressure transmitters (± 0.5 psi accuracy)
- Chiller
- SCADA (Supervisory Control And Data Acquisition) system configured for process control and real-time remote data acquisition of several parameters including for example glycol supply and return pressures (psig), glycol differential pressure (psig), glycol flow and glycol flow setpoint (Lpm), glycol supply and glycol return temperatures (°C), mixer speed actual and setpoint (rpm), bag wall and bag thermowell temperature (°C).

Method

1. Install Flexsafe® Pro Mixer bag in the Palletank® for Mixing jacketed. Install one RTD between the wall and the bag at the center location of the wall. Fill up the bag with deionized water to 100% of the nominal volume. Couple the drive unit to the Palletank®. Install the other RTD through the bag thermowell. Position the insulated lid onto the jacketed Palletank®.
2. The glycol supply is connected to the Palletank® and is circulating through the jacket.
3. Set the glycol flow rate. Set the chiller to the appropriate heating | cooling power. Set the jacket supply temperature set point. Set mixer speed. Impeller speed values have been adjusted depending on bag nominal volume to reflect customers' application set-up. Each of the parameters have been variated with different values according to table 2. The combination of the parameters' setting for each volume means that 189 experiments have been conducted to perform this study.

Table 2: Values tested for each parameter

Process variables		Value 1	Value 2	Value 3
Impeller speeds (rpm) depend on bag nominal volume	Volume (L)	Speed 1	Speed 2	Speed 3
	50	74	187	300
	200	108	304	500
	1000	185	468	750
	2000	200	475	750
Jacket flowrates (L/min)		20	35	50
Heating | cooling power (%)		30	65	100
Jacket supply temperature (°C)		40° C for heating 1° C for cooling		

4. Start mixing, start chiller and run the test.
   - The target for the heating cycle is to heat bag content from 4°C up to 37°C and the test is run until the Thermowell RTD temperature reading reaches 38°C ± 0.5°C.
   - The target for the cooling cycle is to cool bag content from 37°C down to 4°C and the test is run until the Thermowell RTD temperature reading reaches 3°C ± 0.5°C.

Results

1. Multiple Linear Regression (MLR) to model Flexsafe® Pro Mixer performance – Example of 200 L system

MLR model is used to estimate U for a given impeller speed (N) and jacket flowrate (F_j). The experiment with 200 L system gave 54 transients. With the data, response contour plot have been generated in MODDE software (figure 1) to predict U values with R^2>0.953 for all U curve fits.

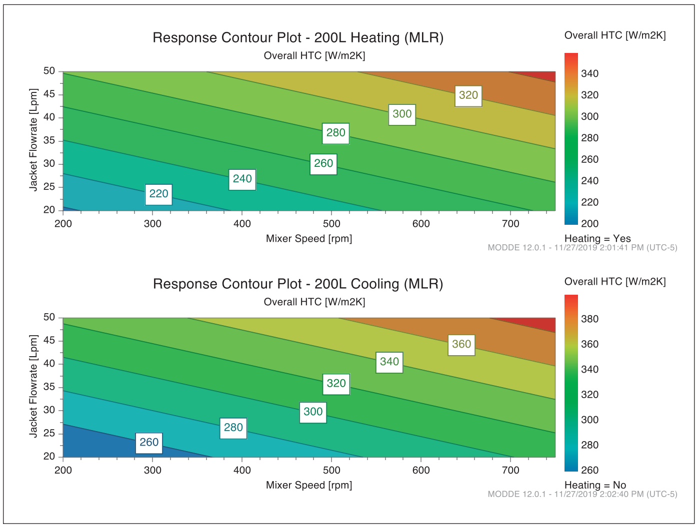

Figure 1: Response contour plot for 200 L heating and 200 L cooling

We have plotted observed U obtained during our experiments versus predicted U values (figure 2). Overall results fitted to MLR model with R^2=0.878.

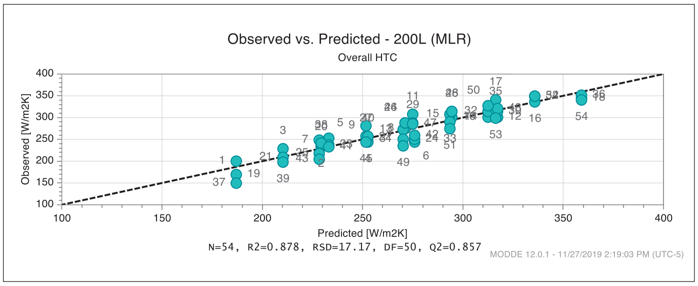

Figure 2: Observed U values compared to Predicted U values for 200 L MLR

For all the different volumes, R^2 was always found above 0.75.

We were able to define the following equations where N is the impeller speed and F_j the jacket flowrate:
$U = 119 + 0.12N + 2.8F_j$ for 200 L heating
$U = 161 + 0.12N + 2.8F_j$ for 200 L cooling

The chiller power is not included in these U equations because it only determines how long it takes to change the jacket temperature from its initial to its target temperature and we do not include this time in the calculation for U.

2. Heat transfer coefficient for all the volumes tested.

The same method was applied for the other volumes tested and conducted to different MLR values and equation for U (table 3):

Table 3: U (W/m²K) calculation for 50 L, 200 L, 1,000 L and 2,000 L in heating or cooling experiments

Palletank® volume	U equation for heating (W/m²K)	U equation for cooling (W/m²K)
50 L	$156 + 0.19N + 2.0F_j$	–
200 L	$119 + 0.12N + 2.8F_j$	$161 + 0.12N + 2.8F_j$
1000 L	$96 + 0.034N + 2.3F_j$	$90 + 0.034N + 2.3F_j$
2000 L	$76 + 0.046N + 2.3F_j$	$61 + 0.046N + 2.3F_j$

3. Time calculation

The U values are used to determine time required for step change from initial temperature T_0 to target temperature T_t for an assumed constant jacket supply temperature T_j. A chart showing temperature evolution and thermal power is generated. The maximum power value will help defining chiller size. Smaller chiller can be used but with longer time to achieve target temperature. For this calculation, the active heat transfer area A_j of the Palletank® is also needed (table 4).

Table 4: Active heat transfer area A_j for the different Palletank® tested

Palletank® volume	Surface area of jacket in contact with liquid filled area of the bag at nominal volume (A_j)
50L	0.355 m²
200L	0.81 m²
1000L	2.796 m²
2000L	3.836 m²

a. Example with 200 L heating curve:
To heat a volume of 200 L of water from 4°C to 20°C with a constant jacket supply at 23°C , knowing that for the 200 L Palletank®, the active heat transfer area A_j = 0.81 m² (table 4) and that the specific heat capacity of liquid water Cp= 4184 J/kgK.

If we set the mixer speed N at 500 rpm and the jacket flowrate F_j at 50 Lpm, the U value obtained is U=319 W/m^{2}K and the chart is generated (figure 3).

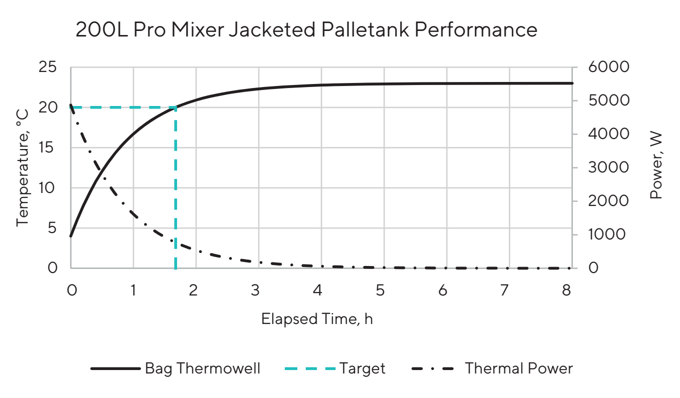

Figure 3: 200 L heating curve from 4°C to 20°C

The result obtained is 1.6 hour and the maximum heating power needed is 5000W.

b. Example with 200 L cooling curve:
To cool a volume of 200 L of water from 20°C to 4°C with a constant jacket supply at 1°C, with a mixer speed N at 500 rpm and a jacket flowrate F_j at 50 Lpm, the U value obtained is U=361 W/m^{2}K and the following curve is obtained (figure 4):

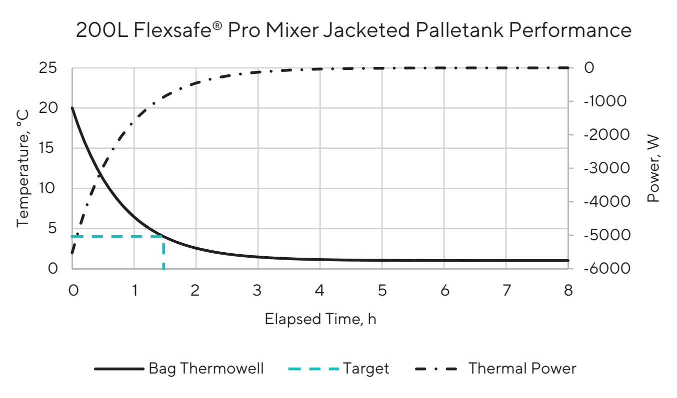

Figure 4: 200 L cooling curve from 20°C to 4°C

The result obtained is 1.4 hour and the maximum cooling power needed is about 5800W.

4. Time obtained for the different volume tested in heating and cooling

Taking the higher mixer speed tested for each volume (speed 3 from table 2) and the jacket flowrate F_j at 50 Lpm, and assuming that the jacket supply temperature will each time be 3°C above target temperature for heating and be 3°C below target temperature for cooling, the results obtained for the 4 different volume tested either in heating from 4°C to 20°C and from 20°C to 37°C or in cooling from 37°C to 20°C and from 20°C to 4°C are available in figure 5.

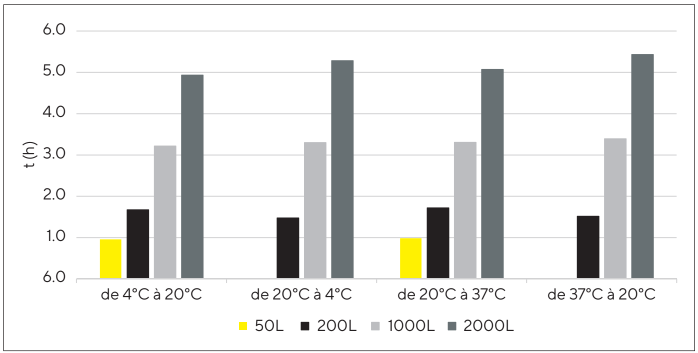

Figure 5: Heating and cooling time for the 50 L, 200 L, 1,000 L and 2,000 L Flexsafe® Pro Mixer system

Basically, any of these steps can be achieved in average in 1 hour for the 50L, in 1.6 hour for the 200L, in 3.3 hours for the 1,000 L and between 4.9 and 5.4 hours for the larger volume of 2,000 L.

Average heating and cooling rates are calculated and provided in table 5:

Table 5: Average heating and cooling rates for the 50 L, 200 L, 1,000 L and 2,000 L Flexsafe® Pro Mixer system

Palletank® volume	**Average heating rate (°C/h)**		**Average cooling rate (°C/h)**	
	4°C to 20°C	20°C to 37°C	37°C to 20°C	20°C to 4°C
50L	16.68	17.24	–	–
200L	9.56	9.89	11.21	10.85
1000L	4.98	5.14	5.01	4.85
2000L	3.24	3.35	3.13	3.03

5. Influence of different parameters variations on final result.

a. Impact of jacket flowrate on pressure drop:
The pressure drop is measured for the 4 different volumes in heating and cooling phases with the 3 different jacket flowrates at 20, 35 and 50 Lpm. The values are shown on figure 6.

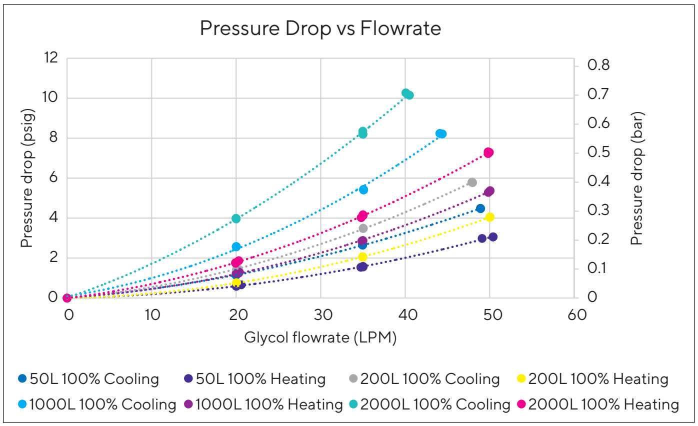

Figure 6: Pressure drop versus jacket flowrate for the 50 L, 200 L, 1,000 L and 2,000 L Flexsafe® Pro Mixer system.
Note: For 1,000 L & 2,000 L cooling steps, the pump size used during the test was only able to generate 40-45LPM due to the higher pressure drop.

The pressure drop is increasing with the jacket flow rate and with the Palletank® volume. For the same volume, the pressure drop is bigger during cooling than heating phase. The pressure drop is changing due to the impact of temperature on viscosity of the 40% glycol solution. For cooling the solution is more viscous and has a higher pressure drop; for heating the solution is less viscous and has a lower pressure drop.

b. Impact of jacket flow rate on time to achieve target temperature:
The 200 L system is tested during heating phase from 20°C to 37°C with different jacket flowrates at 20, 35 and 50 Lpm. The mixer speed is kept at 500 rpm and the jacket supply temperature at 40°C. The resulting curves are shown on figure 7, heating times and associated pressure drops are summarized in table 6.

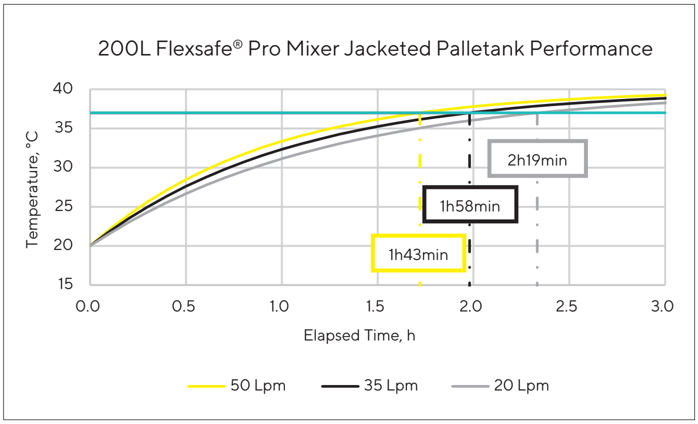

Figure 7: Comparison of the time needed to achieve a heating step from 20°C to 37°C at 3 different jacket flowrates inside a 200 L Flexsafe® Pro Mixer bag.

Table 6: Overview of heating time between 20 and 37°C at 3 different jacket flowrates and resulting pressure drop in a 200 L system.

Jacket flowrate (L/min)	Time needed to reach target temperature	Pressure drop (psig)
20	2H19	0.76
35	1H58	2
50	1H43	4.1

The fastest time is obtained with the highest jacket flowrate that correspond to the highest pressure drop. The time difference between the run at 20 Lpm and the run at 50 Lpm is 37 min.

In this case, increasing the flow rate by 2.5 times leads to a reduction of 26% in time.

c. Impact of impeller speed on time to achieve target temperature:

The 200 L system is tested during heating phase from 20°C to 37°C with different impeller speed at 108, 304 and 500 rpm. The jacket flowrates is kept at 50 Lpm and the jacket supply temperature at 40°C. The resulting curves are shown on figure 8.

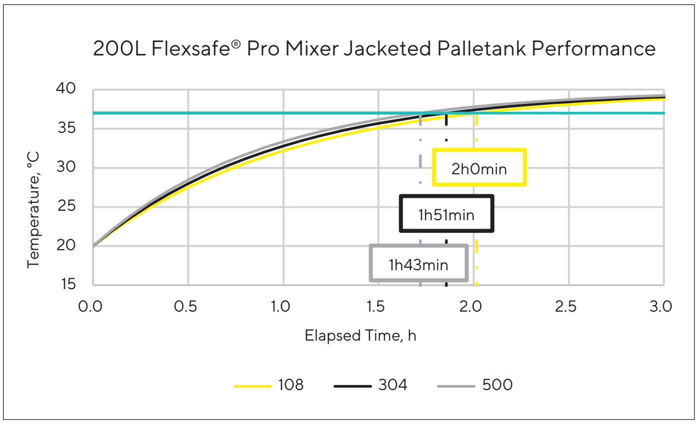

Figure 8: Comparison of the time needed to achieve a heating step from 20°C to 37°C at 3 different impeller speed inside a 200 L Flexsafe® Pro Mixer bag.

The fastest time is obtained with the highest impeller speed. The time difference between the run at 108 rpm and the run at 500 rpm is 17 min.

In this case, increasing the impeller speed by 4.6 times leads to a reduction of 14% in time.

d. Other parameters to be taken into account:

i. The range between target and HTF temperature

The 200 L system is tested during heating phase from 4°C to 20°C at 500 rpm impeller speed, 50 Lpm jacket flowrate and with different jacket supply temperature at +1°C ,+3°C and +5°C from target temperature. The result is shown on figure 9.

The fastest time is obtained with the biggest temperature difference between target temperature and HTF temperature. The time difference between the run with +1°C difference and the run with +5°C difference is 1H16min, it represents a reduction of 50% in time.

In all the experiments described in this application note, a +3°C have been applied.

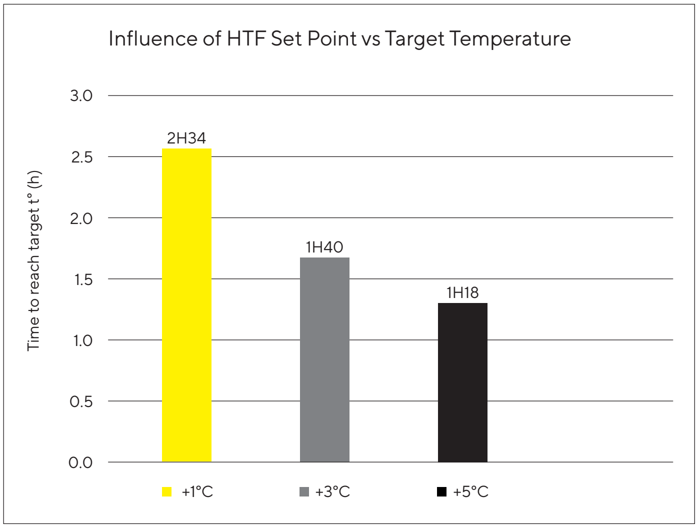

Figure 9: Influence of the difference between HTF and target temperature in a 200 L Flexsafe® for Pro Mixer system

ii. The type of liquid

Liquids have specific heat capacity Cp. The specific heat capacity of a substance is the amount of energy that must be added, in the form of heat, to one unit of mass of the substance in order to cause an increase of one unit in its temperature. Most biopharmaceutical fluids are close to water properties and can use the Cp for water (4184 J/kgK) in calculations. However, in the case that the heat capacity of the solution is significantly different from that of water then we can expect that the overall process time will change.

6. Efficiency of mixing on temperature homogeneity

The temperature homogeneity throughout the bag during heat transfer can be associated to a simple liquid-liquid mixing application for which Flexsafe® Pro Mixer have proven high efficiency. The data are available in other application notes as well through a technical note on CFD.

Indeed, Computational Fluid Dynamics proved mixing efficiency throughout the entire volume with specific key features: a radial flow generated at the bottom of the bag which becomes an axial flow when reaching the walls and generating recirculation loop above the impeller combined with the cubical design of Flexsafe® Pro Mixer system which creates a partial baffle effect and generates ascending and descending flows. This ensures that high mixing efficiency is obtained throughout the bag.

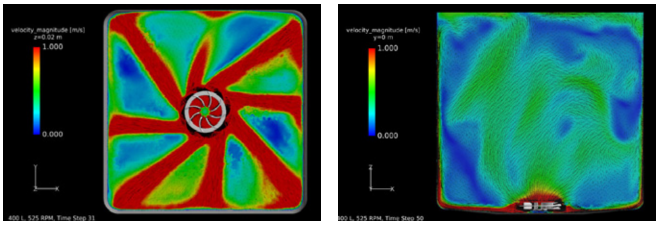

Figure 10: Top and side views extracted from Computational Fluid Dynamic analysis

Discussion

The MLR model allowed us to predict U values for different impeller speed and different jacket flow rate with a good coefficient of determination R2 always above 0.75 for the 4 volumes tested which indicates a strong level of prediction, thus a good model to use.

Good heating and cooling performance was obtained for each volume with 1 hour for the 50 L, less than 2 hours for the 200 L and for the large volumes, approximately 3 hours for the 1,000 L and 5 hours for the 2,000 L and with resulting heating and cooling rates between 18°C/h and 3°C/h.

The "pressure drop versus jacket flowrate" information is useful to define the pressure drop needed in order to pump the 40% glycol solution into the jacket depending on the jacket flowrate required to achieve expected performance. The experiment did not highlight any influence of the heating | cooling power on the final time result in our test conditions.

However, this study shows that a lot of parameters can influence thermoregulation process and should be carefully defined during process design phases in order to maximize efficiency.

Jacket flow rate shows more influence than impeller speed within the range of tested values during our study. HTF temperature should be chosen carefully as it can significantly influence the result as in our test where going from +1°C to +5°C led to a reduction by half on the final time.

The experiments have been run with bags filled up to nominal volume before starting the heating | cooling process. The possibility to start the heating | cooling process during the bag filling will allow to save time on the overall operation and should also be considered during process design.

Moreover, in our study, jacket supply temperature have been assumed constant. Normally, additional time will be observed as the temperature of the jacket supply is not at the set point from the very start. To ensure better heating or cooling times, customers may decide to run a pre-heating or pre-cooling step of the internal tank of the chiller to ensure that the temperature of the HTF entering the jacket would already be at the set point value allowing a better efficiency of the heat transfer from the very beginning.

Conclusion

The Flexsafe® Pro Mixer technology, which combines the proven design of the Palletank® for Mixing jacketed together with the power and low shear of the Flexsafe® Pro Mixer drive unit and Flexsafe® bag, features excellent heat exchange for heating and cooling applications.

This application study demonstrates its efficiency up to 2000 L and gives tools to determine performance in specific conditions.

Flexsafe® Pro Mixer is a unique single-use technology fitting all mixing steps from buffer and media preparations, downstream steps to final formulation requiring thermo-regulation.

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