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Mixing Performance Study Of the Flexel® for Lev Mixer

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Executive Summary

The new Flexel® for Lev Mixer[1] allows rapid, efficient and robust mixing for solid | liquid and liquid | liquid mixing applications.

Introduction

The Flexel® for Lev Mixer is a single-use mixing solution using the Lev Mixer impeller, Flexel® Bags for Lev Mixer[2] and Palletank®. Flexel® for Lev Mixer offers a single-use and sterile solution for a variety of liquid | liquid and solid | liquid mixing applications.

Mixing studies have been performed on 50 L to 1,000 L bag volumes to demonstrate mixing efficiency, reproducibility and scalability. The mixing process and test measurements are defined and described in this application note for each trial. The results are illustrated and analyzed in the report.

[1] Lev Mixer is a trademark of Pall Corporation and this product uses Pall patented Lev Mixer technology.
[2] All information on patents can be found at www.Pall.com/patents

Find out more: www.sartorius.com/en/products/fluid-management/mixing

Materials

Mixing System:
- Palletank® for Lev Mixer:
  50 L (FXC110820), 100 L (FXC112230),
  200 L (FXC110821), 400 L (FXC111135),
  650 L (FXC110822), 1,000 L (FXC113384)
- Flexel® Bags for Lev Mixer:
  50 L (FXB111567), 100 L (FXB111568),
  200 L (FXB111420), 400 L (FXB111421),
  650 L (FXB111565), 1,000 L (FXB111569)
- Lev Mixer drive unit,
  (6-magnet impeller for 50 L and 100 L and 4-magnet impeller for 200 L to 1,000 L)

Equipments:
Pump: WM 520 – Watson Marlow
Scale: Combics (1 to 50 kg) –
Sartorius Mechatronics

Sensors and monitoring:
- Conductivity transducer:
  InoLab Cond 740 - WTW
- Conductivity meter
  (4 probes, temperature compensated):
  TetraCond 325 - WTW
- pH meter (temperature compensated):
  portable pH meter Pt-10 – Sartorius Mechatronics
- RI measurement:
  Refractometer AN 72771 - Carl Zeiss
- UV measurement: Spectro-photometer UV µQuant –
  BioTek Instrument

Raw materials
- NaOH 99% Pellets [CAS: 1310-73-2] Fluka
- HCP 37%: [CAS: 7647-01-0] Fluka
- NaCl: [CAS: 7647-14-5] Fluka
- Urea: [CAS: 57-13-6] Fluka
- Pluronic acid: [CAS: 9003-11-6] Sigma life science
- Sorbitol: [CAS: 50-70-4] Carl Roth
- Reversed Osmosis water (RO water)
- Yestolate – granulate: [CAS: 8013-01-2] Merck
- Yestolate – powder: [CAS: 8013-01-2] Beckton Dickinson

Figure 1: Flexel® for Lev Mixer

Methods

General mixing protocol

Figure 2 illustrates the general protocol for mixing experiments according to the instructions for use of the Flexel® for Lev Mixer
(Ref SPT5717-p_85034-536-18).

Reagent addition and data measurement were started at the same time and each mixing trial was performed in duplicate.

Powders were continuously added through the top port of the Flexel® Bags for Lev Mixer. Liquid reagents were transferred into the bag with a peristaltic pump.

Sampling and measurement positions

1: Lateral face - Top corner
2: Lateral face - Bottom corner
3: Lateral face - Upper left area
4: Lateral face – Middle face

These positions are representative of the four Palletank® faces. Position 1 at the top corner is the furthest point from the impeller.

Conductivity was measured (with 4 separate sensors) at positions 1, 2, 3 and 4. UV, pH and RI were measured at positions 1 and 2.

Mixing time determination

The mixing process is considered complete when the signal is the same for all various sampling points and when the signal remains constant for a minimum of 5 min. The blend time corresponds to the time when 95% of the final value measurement is reached and when all next measurements stay within a 5% tolerance.

Figure 4 illustrates the blend time determination.

The complete mixing time corresponds to the time when the slope of the sensor profile reaches zero.

The mixings results will be based on the blend time.

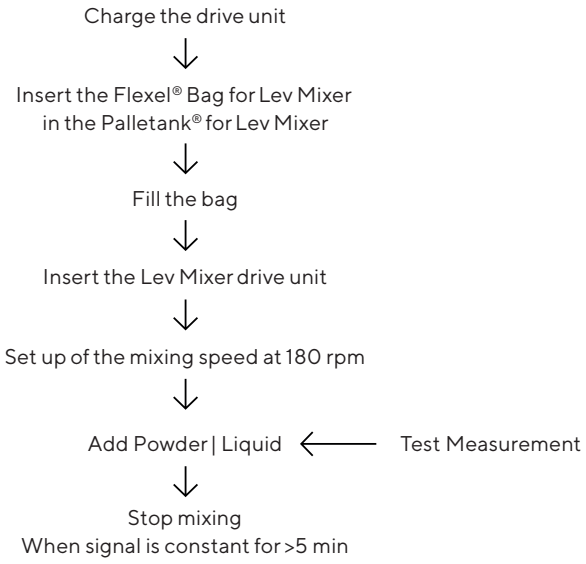

Figure 2: General mixing protocol

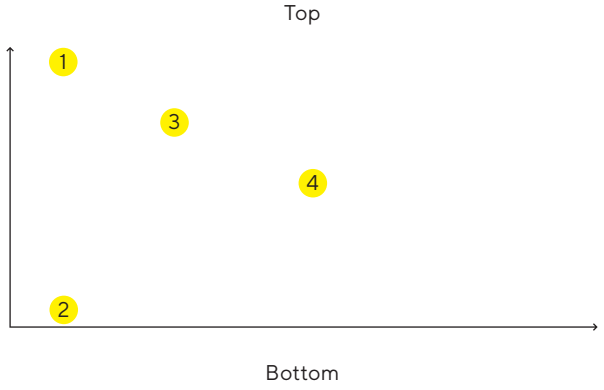

Figure 3: Palletank® for Lev Mixer – Lateral face

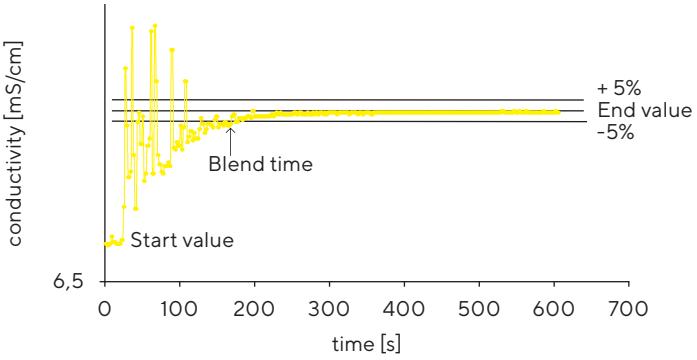

Figure 4: Blend time determination

Mixing study overview

Table 1 summarizes the mixing studies that have been performed.

The mixings studies are classified into:

- Solid | Liquid mixing application (powder hydration and dissolution)
- Liquid | Liquid mixing application (liquid homogenization)

Table 1 shows the solid or liquid application, the final target concentration, the final volume and the test measurement performed.

Mixing application	Product & final concentration in RO water	Mixing volume 50 L	100 L	200 L	400 L	650 L	1,000 L	Measurement performed
Solid | Liquid	0.1M NaCl			■				Conductivity | Visual check
	1M NaCl	■	■	■	■	■	■	Conductivity | Visual check
	3M NaCl			■				Conductivity | Visual check
	0.1M NaOH*			■				pH
	1M NaOH*			■				pH
	6M Urea			■				UV (230 nm)
	1M NaOH* and 1M NaCl			■				pH | Conductivity | Visual check
	20% Sorbitol and 1M CH_3COONa			■				IR (20 °C)
	5 g/L Yeastolate powder			■				UV (300 nm) | Conductivity
	5 g/L Yeastolate granulate			■				UV (300 nm) | Conductivity
	0.5% Pluronic acid	■	■	■	■	■	■	UV (202 nm)
Liquid | Liquid	0.1M HCl	■	■	■	■	■	■	pH | Conductivity
	1M HCl			■	■	■		pH | Conductivity

Table 1: Mixing study overview

* slow addition of NaOH pellets is required to avoid localized increase of temperature

Results & Discussion

Overview of results

Table 2 summarizes the results of the mixing studies:

Table 2 illustrates the mixing performances of the Flexel® for Lev Mixer for both solid | liquid mixing and liquid | liquid mixing applications. The mixing trials of 1 M NaCl and 0.5% Pluronic acid show better performances for the 200 L than the lower volumes. This is due to the impeller size: the 4-magnet impeller assembled into the bags from 200 L to 1000 L are larger than the 6-magnet impeller assembled into the 50 L and 100 L bags.

Fast dissolution and mixing times (less than 10 min) were achieved for multiples examples at large scale (up to 1,000 L).

Complete homogeneity was achieved in every mixing application. Every product nature, concentration and process conditions was successfully mixed.

Mixing application	Product & final concentration in RO water	Mixing volume	Blend time
Solid | Liquid	0.1M NaCl	200 L	T < 1 min
	1M NaCl	50 L	T < 2 min
		100 L	T < 3 min
		200 L	T < 1 min
		400 L	T < 4 min
		650 L	T < 6 min
		1,000 L	T < 11 min
	3M NaCl	200 L	T < 2 min
	0.1M NaOH*	200 L	T < 4 min
	1M NaOH*	200 L	T < 5 min
	6M Urea	200 L	T < 27 min
	1M NaOH* and 1M NaCl	200 L	T < 4 min
	20% Sorbitol and 1M CH_3COONa	200 L	T < 4 min
	5 g/L Yeastolate powder	200 L	T < 6 min
	5 g/L Yeastolate granulate	200 L	T < 2 min
	0.5% Pluronic acid	50 L	T < 2 h
		100 L	T < 2,5 h
		200 L	T < 2 h
		400 L	T < 5 h
		650 L	T < 6 h
		1,000 L	T < 6,5 h
Liquid | Liquid	0.1M HCl	50 L	T < 1 min
		100 L	T < 1 min
		200 L	T < 1 min
		400 L	T < 1 min
		650 L	T < 1 min
		1,000 L	T < 3 min
	1M HCl	200 L	T < 2 min

Table 2: Blend time results overview
* slow addition of NaOH pellets is required to avoid local increase of temperature

Measurement Mapping

Figure 5 shows the mixing trial of NaOH 1M and NaCl 1M in 200 L of RO water. The different curves show the conductivity measurement at the 4 sensor positions. In this case, the mixing profiles look similar at all 4 positions. The homogeneity is achieved in less than 4 minutes.

System reproducibility

Each mixing trial was performed in duplicate. Figure 6 shows the concentration profile for the two runs of NaOH 1M and NaCl 1M in 200 L of RO water.

For each run, the curve represents the median of the 4 conductivity's measurement.

Figure 6 demonstrates the excellent reproducibility of the Flexel® for Lev Mixer.

The reproducibility of the mixing performances was also assessed by comparing the blend time for different products and different mixing volumes. Table 3 illustrates the reproducibility performances obtained with the Flexel® for Lev Mixer.

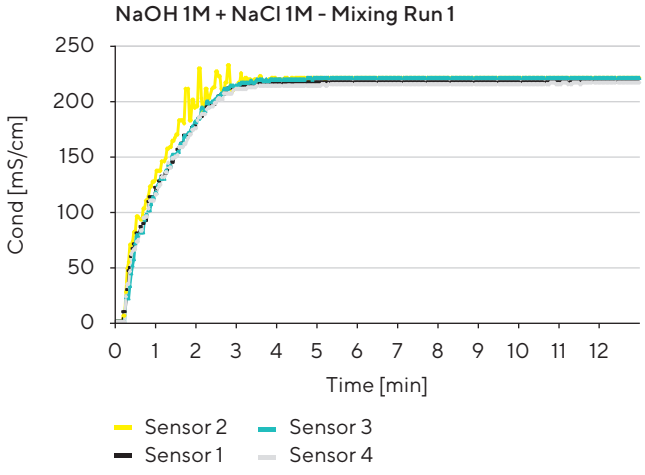

Figure 5: Measurement mapping – NaOH 1M + NaCl 1 M in 200 L of RO water

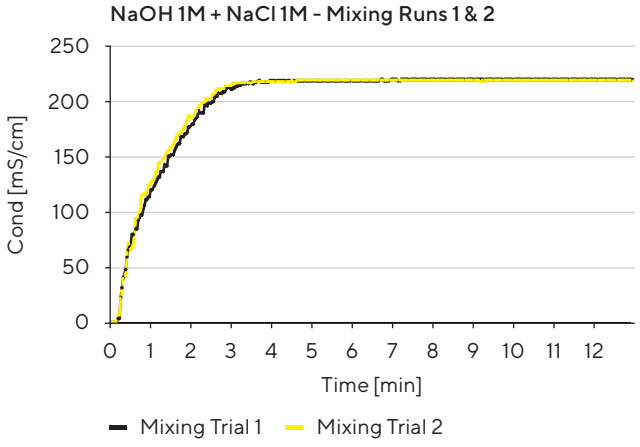

Figure 6: System reproducibility - NaOH 1M + NaCl 1 M in 200 L of RO water

Product & final concentration in RO water	Mixing volume	Blend time Run 1	Blend time Run 2
1M NaCl	400 L	174 s	198 s
0.1M NaOH	200 L	174 s	190 s
5 g/L Yeastolate granulate	200 L	78 s	106 s
0.5% Pluronic acid	200 L	2100 s	2040 s
1M HCl	200 L	84 s	64 s

Table 3: System reproducibility - Blend time comparison

Mixing time vs. volume
Figure 7 shows, the influence of the mixing volume on the blend time for preparation of 1M NaCl solution.

The results show the relationship and scalability between the blend time and the volume.

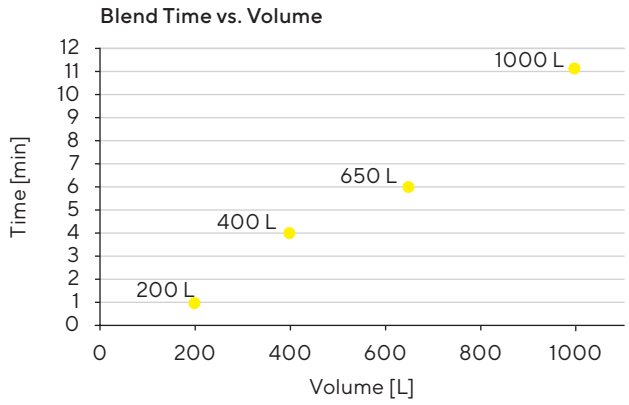

Figure 7: Mixing time vs. volume (4 magnets – 200 L to 1000 L)

Conclusion

The Flexel® for Lev Mixer has been successfully tested for several mixing applications (dissolution, homogenization) with various products and process conditions.

This application note summarizes all these mixing trials and the results show the high-performance and reproducibility of Flexel® for Lev Mixer. The new Flexel® for Lev Mixer allows rapid, efficient and robust mixing for solid | liquid and liquid | liquid mixing application.

In conclusion, the Flexel® for Lev Mixer can ideally be applied for liquid | liquid mixing and solid | liquid mixing applications that require moderate to high mixing intensity such as:

- Buffer & media preparation
- Product formulation | Reformulation
- Hydration | Dissolution of hydrophobic powders
- Bulk intermediate resuspension
- Viral inactivation
- Final formulation

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