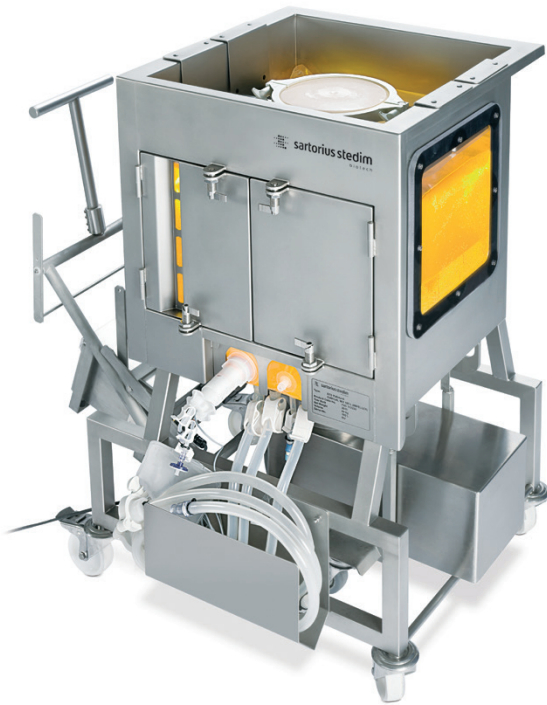




Mixing performance study of the Flexel[®] for LevMixer[®]



Application
Note

#11

#12

#13

#14

#15

Mixing studies and tests performed by Franziska Jonas and Markus Bollmann – Sartorius Stedim Biotech in Goettingen

Executive Summary

The new Flexel[®] for LevMixer^{®1} allows rapid, efficient and robust mixing for solid | liquid and liquid | liquid mixing applications.

Introduction

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

Mixing studies have been performed on 50L to 1,000L 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.

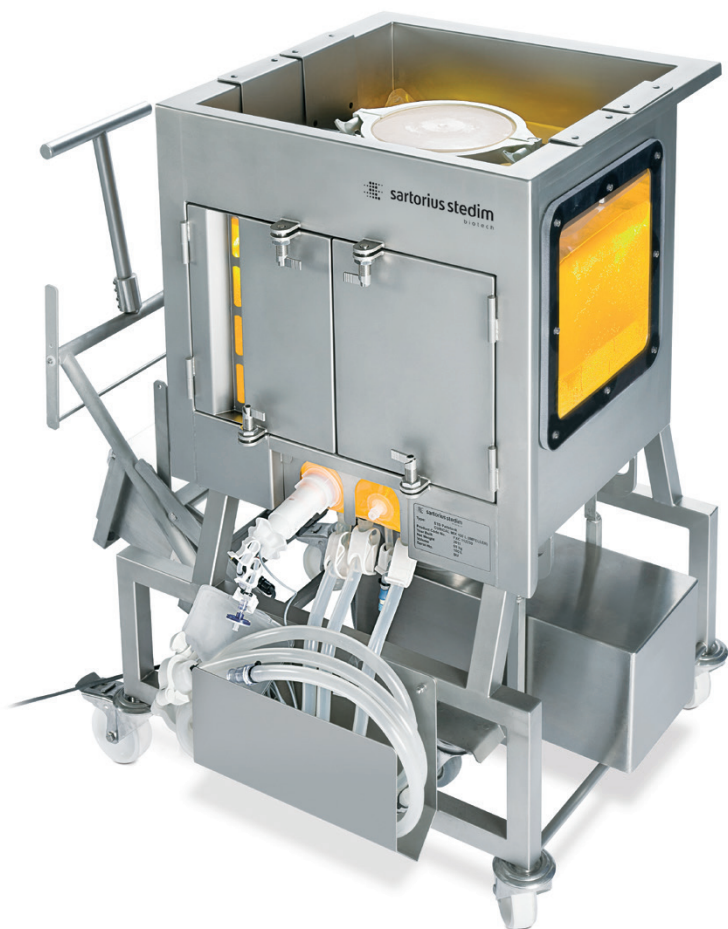


Figure 1: Flexel[®] for LevMixer[®]

Materials

Mixing System:

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

Equipments:

- Pump: WM 520 – Watson Marlow
- Scale: Combits (1 to 50kg) –
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 μ Quant – 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

¹ LevMixer[®] is a trademark of Pall Corporation and this product uses Pall patented LevMixer[®] technology.

² All information on patents can be found at Pall.com/patents

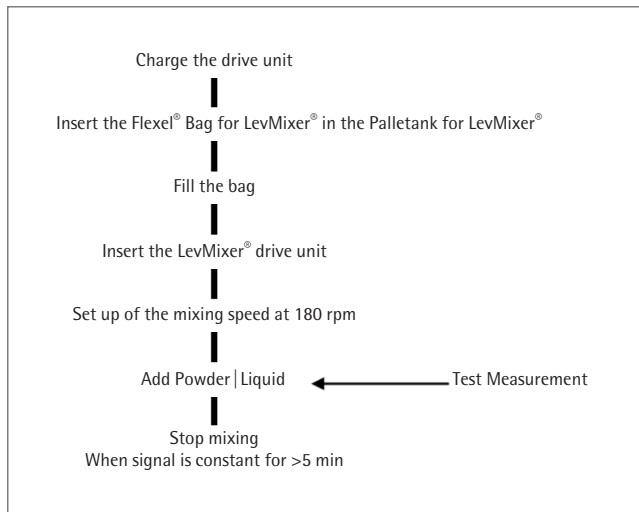


Figure 2: General mixing protocol

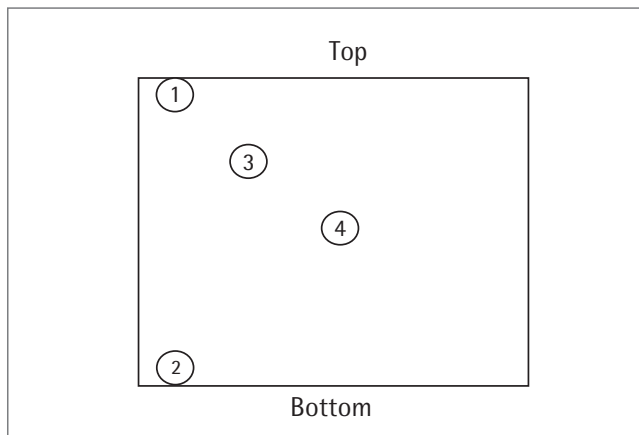


Figure 3: Pallettank for LevMixer® – Lateral face

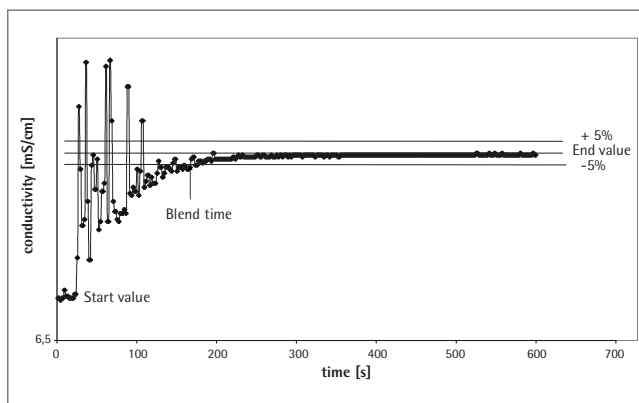


Figure 4: Blend time determination

Methods

General mixing protocol

Figure 2 illustrates the general protocol for mixing experiments according to the instructions for use of the Flexel® for LevMixer® (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 part of the Flexel® Bags for LevMixer®. 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 Pallettank 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.

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						Measurement performed
		50L	100L	200L	400L	650L	1,000L	
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 ₃ COONa			×				IR (20°C)
	5g/L Yeastolate powder			×				UV (300 nm) Conductivity
	5g/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 LevMixer[®] 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 200L than the lower volumes. This is due to the impeller size: the 4-magnet impeller assembled into the bags from 200L to 1000L are larger than the 6-magnet impeller assembled into the 50L and 100L bags.

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

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	200L	T < 1 min	
		1M NaCl	50L	T < 2 min
			100L	T < 3 min
			200L	T < 1 min
			400L	T < 4 min
			650L	T < 6 min
			1,000L	T < 11 min
		3M NaCl	200L	T < 2 min
		0.1M NaOH*	200L	T < 4 min
		1M NaOH*	200L	T < 5 min
		6M Urea	200L	T < 27 min
		1M NaOH* and 1M NaCl	200L	T < 4 min
		20% Sorbitol and 1M CH ₃ COONa	200L	T < 4 min
		5g/L Yeastolate powder	200L	T < 6 min
		5g/L Yeastolate granulate	200L	T < 2 min
		0.5% Pluronic acid	50L	T < 2 h
			100L	T < 2,5 h
	200L		T < 2 h	
	400L		T < 5 h	
	650L		T < 6 h	
	1,000L		T < 6,5 h	
Liquid Liquid	0.1M HCl	50L	T < 1 min	
		100L	T < 1 min	
		200L	T < 1 min	
		400L	T < 1 min	
		650L	T < 1 min	
		1,000L	T < 3 min	
		1M HCl	200L	T < 2 min

Table 2: Blend time results overview

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

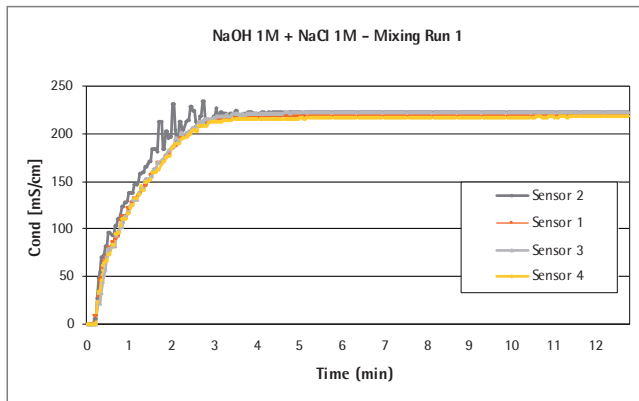


Figure 5:
Measurement mapping – NaOH 1M + NaCl 1M in 200L of RO water

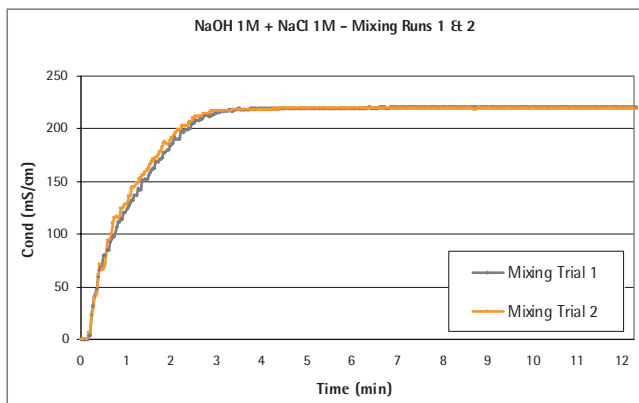


Figure 6:
System reproducibility - NaOH 1M + NaCl 1M in 200L of RO water

Measurement mapping

Figure 5 shows the mixing trial of NaOH 1M and NaCl 1M in 200L 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 200L 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 LevMixer[®].

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 LevMixer[®].

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

Table 3: System reproducibility - Blend time comparison

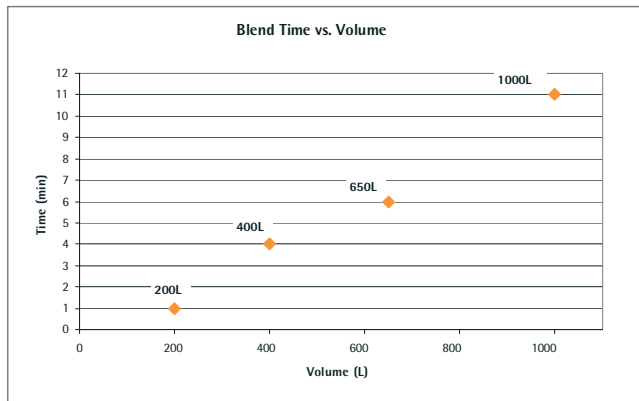


Figure 7: Mixing time vs. volume (4 magnets – 200L to 1000L)

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.

Conclusion

The Flexel[®] for LevMixer[®] 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 LevMixer[®]. The new Flexel[®] for LevMixer[®] allows rapid, efficient and robust mixing for solid | liquid and liquid | liquid mixing application.

In conclusion, the Flexel[®] for LevMixer[®] 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

Sales and Service Contacts

For further contacts, visit www.sartorius-stedim.com

Europe

Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49.551.308.0

Sartorius Stedim Systems GmbH
Robert-Bosch-Strasse 5-7
34302 Guxhagen
Phone +49.5665.407.0

France
Sartorius Stedim FMT S.A.S.
ZI des Paluds
Avenue de Jouques - CS 91051
13781 Aubagne Cedex
Phone +33.442.845600

Sartorius Stedim France SAS
ZI des Paluds
Avenue de Jouques - CS 71058
13781 Aubagne Cedex
Phone +33.442.845600

Austria
Sartorius Stedim Austria GmbH
Modecenterstrasse 22
1030 Vienna
Phone +43.1.7965763.18

Belgium
Sartorius Stedim Belgium N.V.
Rue Colonel Bourg 105
1030 Bruxelles
Phone +32.2.756.06.80

Hungary
Sartorius Stedim Hungária Kft.
Kagyló u. 5
2092 Budakeszi
Phone +36.23.457.227

Italy
Sartorius Stedim Italy S.r.l.
Via dell'Antella, 76/A
50012 Antella-Bagno a Ripoli (FI)
Phone +39.055.63.40.41

Netherlands
Sartorius Stedim Netherlands B.V.
Phone +31.30.60.25.080
filtratie.nederland@sartorius-stedim.com

Poland
Sartorius Stedim Poland Sp. z o.o.
ul. Wrzesinska 70
62-025 Kostrzyn
Phone +48.61.647.38.40

Russian Federation
LLC "Sartorius Stedim RUS"
Vasilyevsky Island
5th line 70, Lit. A
199178 St. Petersburg
Phone +7.812.327.53.27

Spain
Sartorius Stedim Spain, S.A.U.
Avda. de la Industria, 32
Edificio PAYMA
28108 Alcobendas (Madrid)
Phone +34.913.586.098

Switzerland
Sartorius Stedim Switzerland AG
Ringstrasse 24 a
8317 Tagelswangen
Phone +41.52.354.36.36

U.K.
Sartorius Stedim UK Ltd.
Longmead Business Centre
Blenheim Road, Epsom
Surrey KT19 9 QQ
Phone +44.1372.737159

Ukraine
LLC "Sartorius Stedim RUS"
Post Box 440 "B"
01001 Kiev, Ukraine
Phone +380.44.411.4918

Americas

USA
Sartorius Stedim North America Inc.
5 Orville Drive, Suite 200
Bohemia, NY 11716
Toll-Free +1.800.368.7178

Argentina
Sartorius Argentina S.A.
Int. A. Ávalos 4251
B1605ECS Munro
Buenos Aires
Phone +54.11.4721.0505

Brazil
Sartorius do Brasil Ltda
Avenida Senador Vergueiro 2962
São Bernardo do Campo
CEP 09600-000 - SP- Brasil
Phone +55.11.4362.8900

Mexico
Sartorius de México, S.A. de C.V.
Libramiento Norte de Tepetzotlan s/n,
Colonia Barrio Tlacateco,
Municipio de Tepetzotlan,
Estado de México,
C.P. 54605
Phone +52.55.5562.1102
leadsmex@sartorius.com

Peru
Sartorius Peru S.A.C.
Avenue Alberto del Campo 411
Floor 12 - The Office
15076 - San Isidro, Lima
Phone +51.1.441 0158

Asia | Pacific

Australia
Sartorius Stedim Australia Pty. Ltd.
Unit 5, 7-11 Rodeo Drive
Dandenong South Vic 3175
Phone +61.3.8762.1800

China
Sartorius Stedim (Shanghai)
Trading Co., Ltd.
3rd Floor, North Wing, Tower 1
No. 4560 Jinke Road
Zhangjiang Hi-Tech Park
Pudong District
Shanghai 201210, P.R. China
Phone +86.21.6878.2300

Sartorius Stedim (Shanghai)
Trading Co., Ltd.
Beijing Branch Office
No. 33 Yu'an Road
Airport Industrial Park Zone B
Shunyi District, Beijing 101300
Phone +86.10.8042.6501

Sartorius Stedim (Shanghai)
Trading Co., Ltd.
Guangzhou Branch Office
Room 1105
Xing Guang Ying Jing Building
No. 119, Shui Yin Road
Yue Xiu District, Guangzhou 510075
Phone +86.20.3836.4193

India
Sartorius Stedim India Pvt. Ltd.
#69/2-69/3, NH 48, Jakkasandra
Nelamangala Tq
562 123 Bangalore, India
Phone +91.80.4350.5250

Japan
Sartorius Stedim Japan K.K.
4th Fl., Daiwa Shinagawa North Bldg.
8-11, Kita-Shinagawa 1-chome
Shinagawa-ku, Tokyo, 140-0001 Japan
Phone +81.3.4331.4300

Malaysia
Sartorius Stedim Malaysia Sdn. Bhd.
Lot L3-E-3B, Enterprise 4
Technology Park Malaysia
Bukit Jalil
57000 Kuala Lumpur, Malaysia
Phone +60.3.8996.0622

Singapore
Sartorius Stedim Singapore Pte. Ltd.
10 Science Park Rd
The Alpha #02-13/14
Singapore Science Park II
Singapore 117684
Phone +65.6872.3966

South Korea
Sartorius Korea Biotech Co., Ltd.
8th Floor, Solid Space B/D,
PanGyoYeok-Ro 220, BunDang-Gu
SeongNam-Si, GyeongGi-Do, 463-400
Phone +82.31.622.5700



▶ www.sartorius-stedim.com