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Efficiency of NaCMC Powder Dissolution Using the Flexsafe® Pro Mixer

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Abstract

This application study presents performance data of the Pro Mixer at 625 L scale for Sodium Carboxymethylcellulose (NaCMC) dissolution.

NaCMC is used in several pharmaceutical applications among others and is known for its difficulty to dissolve in water at ambient temperature even with a high shear homogenizer. As the expected time to achieve homogenization is long, a well-established single-use mixer has been used as reference to compare results and draw conclusion on Flexsafe® Pro Mixer efficiency.

The performance of the single-use mixing systems was assessed by visual inspection.

Flexsafe® Pro Mixer achieved complete dissolution of NaCMC in less than half the time when compared with the reference single-use mixer.

Flexsafe® Pro Mixer is a unique single-use technology that fits all mixing applications from buffer and media preparations, downstream processes to final formulation.
Its technology combines speed and efficiency to deliver high performance mixing during powder dissolution and a levitating impeller to preserve the drug during low shear blending applications. Additionally, the Flexsafe® film offers high standard quality attributes such as Biocompatibility, Integrity and Supply network.

For More Information, Visit
www.sartorius.com/en/products/fluid-management/mixing/flexsafe-pro-mixer

Introduction

The purpose of this application study is to assess the performance of the single-use Pro Mixer used for the dissolution of Sodium Carboxymethylcellulose (NaCMC).

NaCMC is widely utilized in several types of industries. In the pharmaceutical industry, it is used in vaccine manufacturing and more broadly as a stabilizing and suspending agent in pharmaceutical formulations, and as a lubricant in artificial tears to name a few examples. It is also used in other industries as an additive in Food products and Fast-Moving Consumer Goods (FMCG).

NaCMC is known for its difficulty to dissolve directly in water, even with a high shear homogenizer, and is prone to clump formation, which further complicates dissolution. Various strategies can be introduced into the process to facilitate the mixing operation, for example the suspension of the NaCMC powder in a volatile organic solvent such as acetone prior to adding the required amount of water while the suspension is aggressively agitated. In this case, the acetone must be removed through evaporation by gentle heating afterwards. These additional steps increase the complexity and length of the process and were not incorporated into this study. Therefore, NaCMC dissolution in water constitutes an absolute worst case.

This application study presents performance data of the Pro Mixer at 625 L scale using only NaCMC and water to obtain a 1% (w/v) solution. A well-established single-use mixer was used as reference to compare results and draw conclusion on Flexsafe® Pro Mixer efficiency. The trial was performed in triplicate with both Flexsafe® Pro Mixer and the reference mixing system to ensure consistency of the results. The performance of the single-use mixing systems was assessed by visual inspection.

The procedure for NaCMC solution preparation includes the slow incorporation of powder in the bag partially filled to 70% of the nominal volume with water.

650 L Palletank® for Mixing

The powder is sifted directly into the installed vortex generated by the Flexsafe® Pro Mixer drive unit operating at 700 rpm or by the reference single-use mixer motor operating at its maximum speed. The final step of the process required the addition of water to 100% of the nominal volume to aid in the dissolution of the remaining clumps and obtain the correct dilution.

The magnetic coupling of the impeller with the Flexsafe® Pro Mixer drive unit enables a rotation speed up to 750 rpm, providing a powerful mixing. The strong vertical vortex combined with the baffle effect of the cubical design of the Palletank® allows instant downward movement and good fluid dispersion throughout the entire bag volume for a highly efficient dissolution of powders.

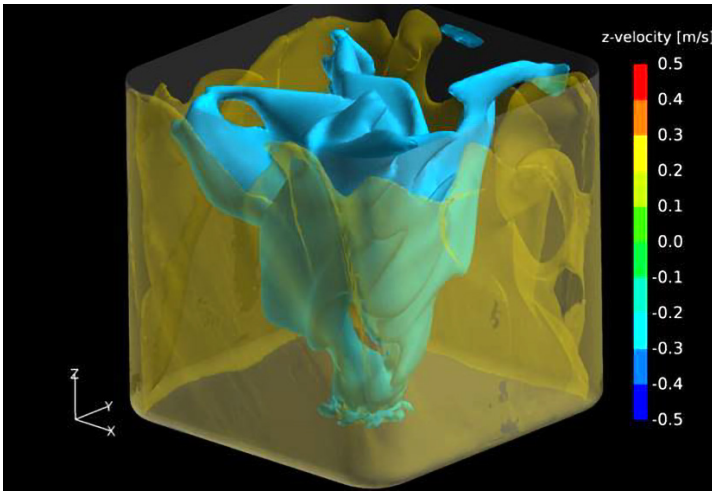


Figure 1: 3D view - simulation of vertical velocity in Pro Mixer 1.000 L at 750 rpm

Computational Fluid Dynamics analysis, a numerical simulation of fluid motion, shows the existence of ascending and descending flows without any stagnant areas as well as the formation of a recirculation loop above the impeller for an efficient mixing process. The data are available in a specific technical note "Flexsafe® Pro Mixer Computational Fluid Dynamic studies" published in 2019.

Materials

Consumables

- 3×650 L Standard Flexsafe® bags for Pro Mixer
- 3×650 L Reference Single-Use Mixer bags
- Sodium Carboxymethylcellulose (concentration at 1% (w/v), i.e. 6 kg 250 NaCMC in 625 L final volume)
- Tap water

Equipment

- 650 L Palletank® for Mixing
- Flexsafe® Pro Mixer drive unit
- 650 L Reference Single-Use Mixer system
- Temperature probe
- Camera

Flexsafe® Pro Mixer drive unit

Method

1. Install the Flexsafe® Pro Mixer according to associated instructions for use and fill the bag with water to 70% (437.5 L) of final volume (625 L).
2. Measure and record water | solution temperature at initial, during and end of the process.
3. Set impeller speed at 700 rpm to get strong vortex.
4. Start timer and slowly sift the Sodium Carboxymethylcellulose powder through the top port into the vortex of vigorously agitated water. The rate of addition should be slow enough for the particles to separate in the water without lump formation, but not so slow that the solution thickens appreciably before all the solid is added.
5. Fill the remaining 30% (187.5 L) of water into the bag once all the powder is added and continue agitation until all the swollen gelatinized particles are dissolved to yield a smooth solution.
6. Perform a final visual check to ensure that all the Sodium Carboxymethylcellulose had dissolved into solution.
7. Stop timer and record mixing time.
8. Repeat the same process 3 times.
9. Install the Reference Single-Use Mixer according to associated instructions for use and repeat the same process as described above 3 times (step 1 to 7).
   The impeller speed is set at the maximum speed allowed by the reference system to ensure strong vortex presence and best efficiency possible for this application.

Mixing time is monitored and determined by visual inspection. It corresponds to the time when the powder has gone into solution and all suspended particles are visually dissolved. Mixing time includes NaCMC powder's addition. The mixing process is recorded by video to confirm powder dissolution.

Results & Discussion

The process temperature was stable from start to end at around 26°C + | - 1°C for each of the 6 experiments.

In all experiments, the powder was added in intervals by powder additions of 1.5-2.5 kg, sifted into the vortex to allow for the slow and even distribution into the bag and to increase mixing efficiency. Despite this requirement, many clumps were observed to form each time during the initial addition.

The mixing times presented in this application note include the weighing and transfer of multiple containers of powder into the mixing bags but do not include the time it takes for equipment set up or water filling to 70%. Thanks to the ergonomic design of the Flexsafe® Pro Mixer, the complete set-up and bag installation takes approximately 5-10 minutes for a 650 L.

1. 650 L Flexsafe® Pro Mixer result

Three experiments were run with this system. Final visual inspection confirmed that Sodium Carboxymethylcellulose had completely dissolved into solution in the 3 experiments.

Run	Impeller speed	Mixing time confirmed by visual inspection	Observation
1	700 rpm	1 h 30	NaCMC in solution with no remaining clumps prior to final water addition
2	700 rpm	1 h 50	Few clumps still observed after 1 h 35 when the filling to 100% started
3	400 rpm (for 1 h 30) then 700 rpm	2 h 12	Still great number of clumps observed after 1 h 30 at 400 rpm. Impeller speed raised to 700 rpm. Only a few clumps visible after 1 h 45 when the filling to 100% started

Table 1: Summary of testing time, impeller speed and dissolution status with the 650 L Flexsafe® Pro Mixer

For the two experiments run at 700 rpm, the dissolution times obtained are 1 h 30 and 1 h 50. The powder was added more gradually in the first run, resulting in a more rapid dissolution that occurred before final water addition.

As the two first experiments were successful, allowing a full dissolution in less than 2 h, a run at 400 rpm was tested to determine whether complete dissolution could be achieved at a lower speed. After 1 h 30, the time recorded for final dissolution in the first experiment, many clumps were still observed and the agitation obtained was not sufficient to mix NaCMC into solution, so the impeller speed was raised to 700 rpm for 42 additional minutes, after which complete dissolution was achieved.

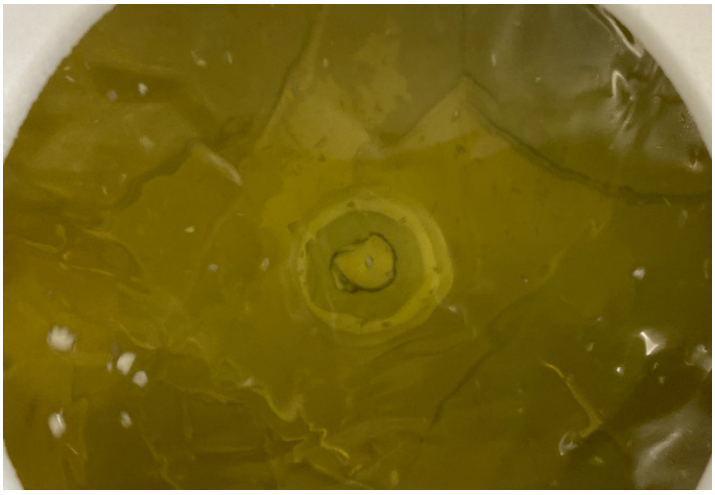
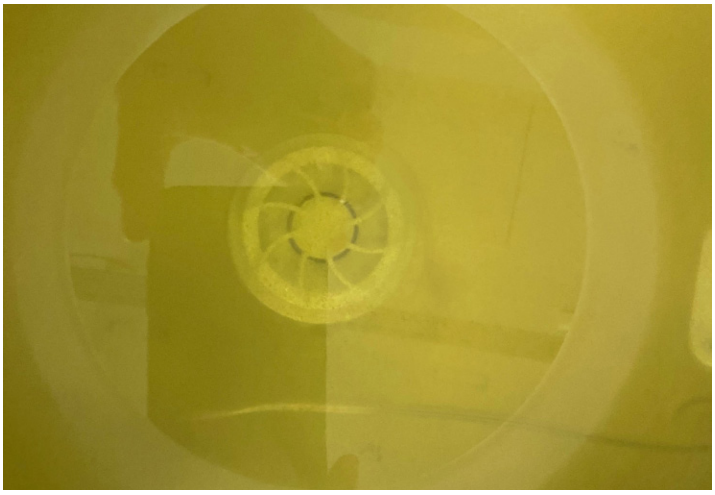


Figure 2: Clumps observed prior to final dissolution



Complete dissolution of NaCMC

2. 650 L reference single-use mixer result

Three experiments were run with this system. Only one experiment out of the three led to full dissolution of the Sodium Carboxymethylcellulose after 3 h 50.

Run	Impeller speed	Testing time	Mixing status after visual inspection	Observation
1	Max speed	3 h 03	Few clumps left	Clumps still observed after 2 h 30 when the filling to 100% started
2	Max speed	3 h 50	Full dissolution confirmed	Few clumps still observed after 2 h 45 when the filling to 100% started
3	Max speed	4 h	Few clumps left	Clumps still observed after 3 h when the filling to 100% started

Table 2: Summary of testing time and dissolution status with the 650 L reference single-use mixer

In the first experiment, significant clumping was observed at 2 h 30, despite this, the remaining volume was filled to 100% to aid in the dissolution of the remaining clumps. After 3 h, a smaller number of clumps were observed but no more improvement in clump reduction could be achieved, so mixing was stopped.

In the second experiment, significant clumping was observed during powder addition, but mixing was continued. At 2 h 45, a few clumps were still observed, and the remaining volume was filled to 100%. After 3 h 50, complete dissolution of Sodium Carboxymethylcellulose was confirmed.

In the third experiment, significant clumping was still observed at 3 h, the remaining volume was filled to 100% to aid in the dissolution of the remaining clumps. After 3 h 30, a few clumps were observed, so mixing continued to 4 h, but no improvement was observed, so mixing was stopped.

Conclusion

Flexsafe® Pro Mixer is a unique single-use technology platform suitable for all mixing applications from buffer and media preparations, downstream process intermediates to final formulation from 50 L up to 3,000 L volumes.

This application note demonstrates the efficiency of the Flexsafe® Pro Mixer to mix worst case powders. Flexsafe® Pro Mixer can achieve complete dissolution of 1% NaCMC at 625 L scale in 1 h 30 at 700 rpm. As a comparison, under the same conditions, the reference single-use mixer, when operating at its maximum speed, showed poor efficiency for this type of application. Indeed, the reference mixer led to complete dissolution in only one experiment out of the three trials, and after a much longer period of 3 h 50, more than twice as much as the Flexsafe® Pro Mixer, which represents a 52% improvement in mixing efficiency over the reference mixing system.

The technical note on Flexsafe® Pro Mixer Computational Fluid Dynamic provides additional information to characterize mixing performance and provides characteristic parameters for it. This study that has been performed on each Flexsafe® Pro Mixer volume from 50 L to 1,000 L at 750 rpm, its maximum speed. It includes, among others, information about flow patterns, dimensionless numbers and specific power consumption as well as an analysis of speed profile evolution and vortex formation.

Flexsafe® Pro Mixer allows for quick set-up, efficient mixing and fast changeover to save time at all the mixing steps during biomanufacturing.

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