Master's Thesis Engineering Technology

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High-Shear Wet Milling of API's

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INTRODUCTION

Reducing the specific surface area of API's has been a popular method for increasing solubility for a long time. Therefore, the traditionally dry milling units are used. Currently, the popularity of wet milling is increasing due to its efficiency. First of all, the production cycle can be reduced with one step. On top of that, because dust explosions are not a possibility during wet milling, the technique is safer. Unfortunately, the available literature is currently limited, and the mechanism of action is still indistinct. Therefore, different solids with respectively different starting size, hardness, solid loading… were tested to gain an insight on the working principle. Next to the different solids, two set-ups were compared to determine the influence of possible segregation. Finally, various HSWM configurations were tested and the tip-speed was varied.

SET-UP

Traditionally, the setup in lab scale and production differ. Lab scale uses the suction from above, Figure 4, while production uses the bottom valve for suction, Figure 3. During this study, the difference between the two set-ups is explored. As show in Figure 3, the end point of both set-ups is approximately the same, the big difference is the amount of turnovers necessary to achieve the endpoint decreases. This influence is amplified by using bigger starting material.

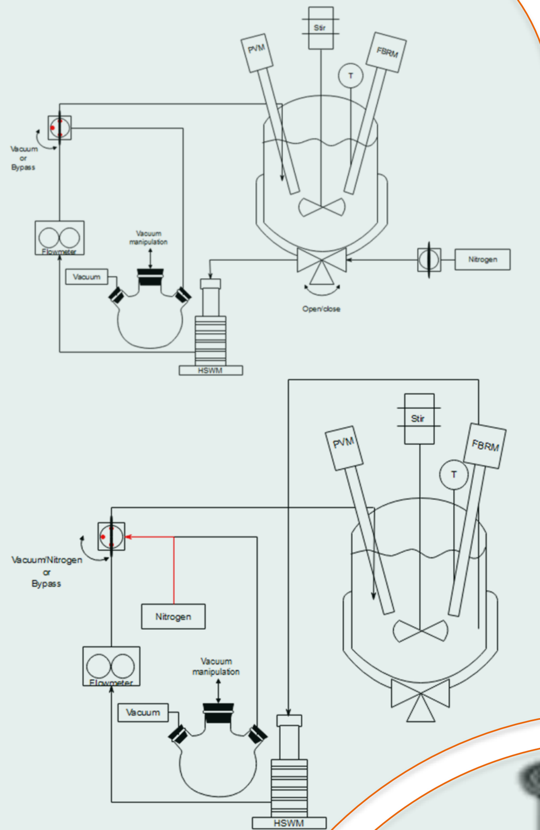


Figure 1: Set-up

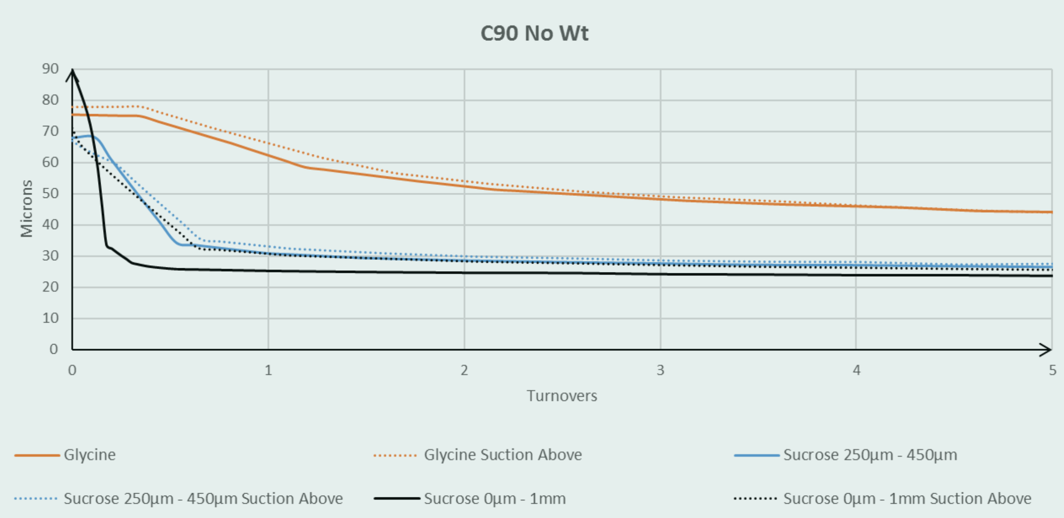


Figure 2: C90 different set-ups

HSWM CONFIGURATION

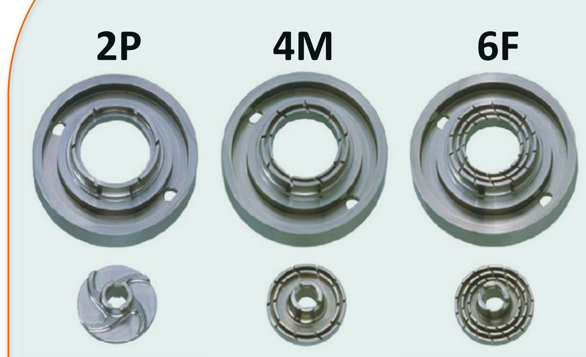


Figure 5: Rotor-stator

The influence of different High-Shear Wet Mill configurations is tested. Various combination of roto-stator disks, illustrated in Figure 5, are used. The shear, delivered by the disks, should increase proportional to the number of tooth in the disks [1]. It was expected that the final size off the crystals would be smaller proportional to this delivered shear, but the differences remained small.

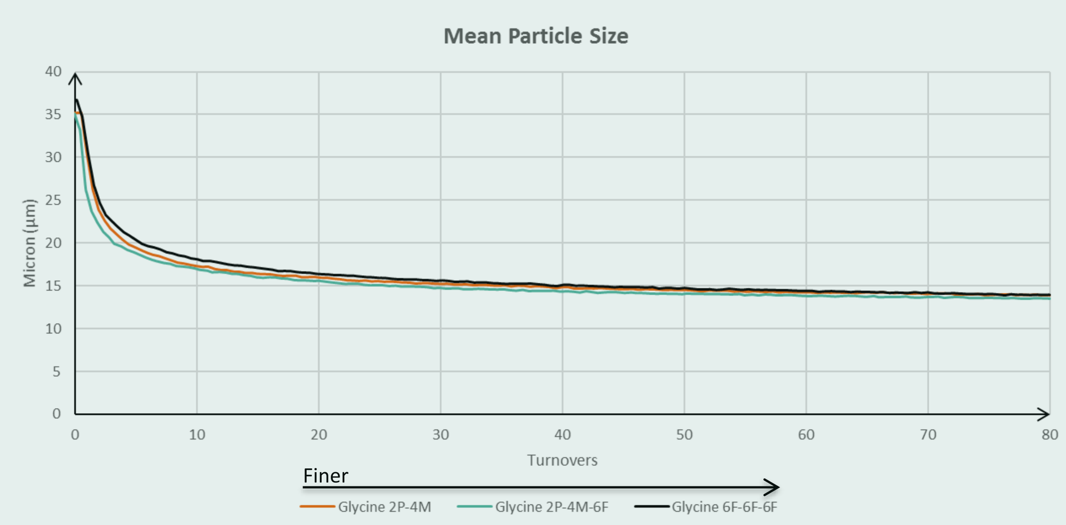
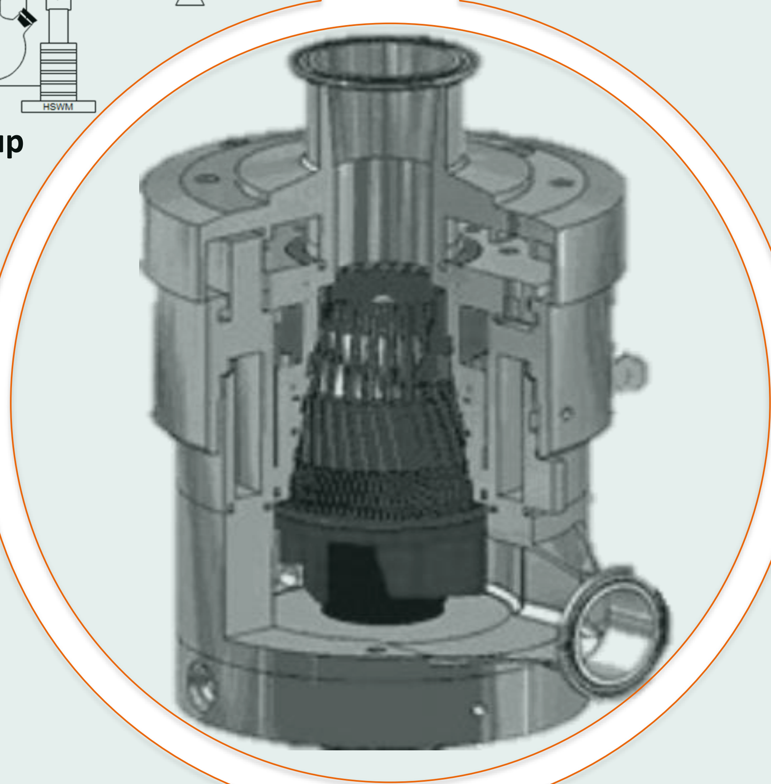


Figure 6: C90 different set-ups



BRITTLENESS

The brittleness of a component, described by the brittleness index (BI), depends on the hardness, fracture toughness and elasticity. The theory is that more brittle compounds, fracture easier and less brittle compounds suffer more attrition.

- ↓BI = ↑C90, ↓C10 [2]

To confirm this theory, four compounds with respectively a lower BI: sucrose, ascorbic acid, glycine and NaCl

Figure 3: influence BI

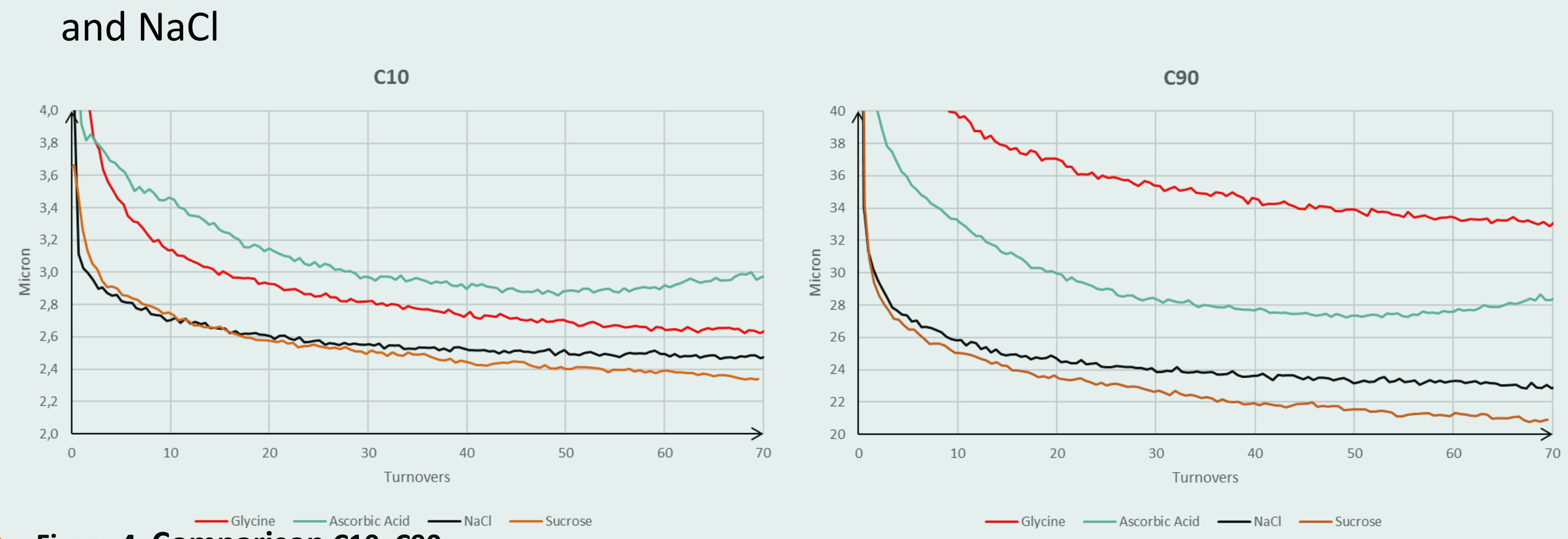


Figure 4: Comparison C10, C90

ROTATING SPEED ROTOR

The shear force is proportional to the rotation speed of the rotor. As shown in Figure 7, a higher tip-speed can result in a lower C90. This means that 90% of the particles in the vessel are smaller with a higher tip-speed.

The effect of tip-speed appears to be linear with the C90 distribution of the particles.[3]

Figure 8: HSWM panel to set RPM

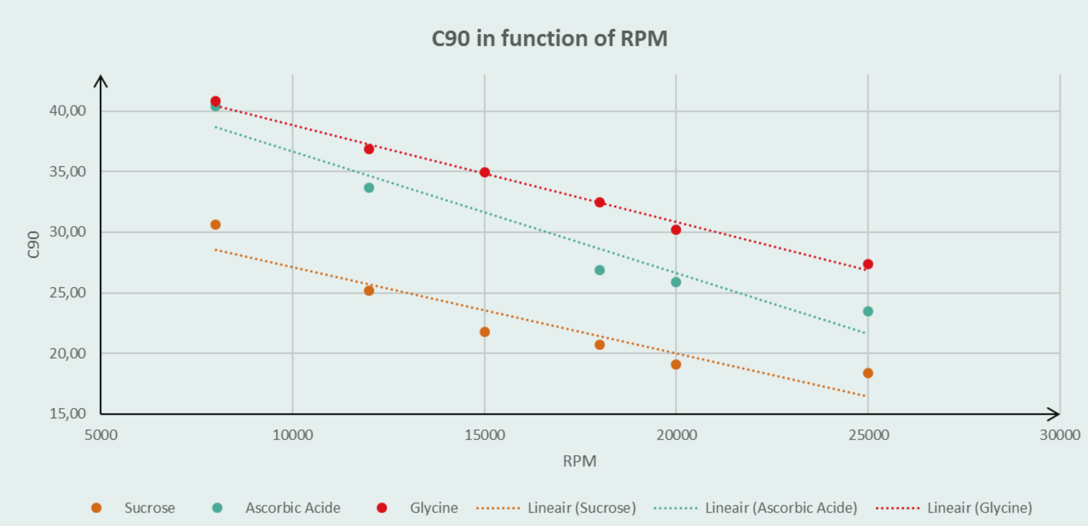


Figure 7: Comparison C10, C90

CONCLUSION

The wet milling of crystals is a complicated process. During the research, the influence of set-up and the high-shear wet mill configuration are proven to be insignificant during the milling process. On the other hand, the influence of compound dependent properties (e.g. hardness, elasticity, fracture toughness) turn out to determine the breaking mechanism of the substances. Experientially was experienced that Sodium Chloride (NaCl) was harder too break, nonetheless it didn't follow the theoretical rule off breakage. Because infinite small particles off NaCl were detected in a wet sample, this deviation can be explained by the attrition of really small parts off the sodium chloride crystal, that was not detected by the FBRM, causing its measurements too increase the actual size, and slipped through the filter. The greatest influence was obtained by increasing the tip-speed of the stator.

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[1] R. Buergelin, "Janssen Pharmaceutica N . V . Welcome to our seminar /// Scale up - Training," 2018, p. 105.
[2] K. Ghaderzadeh and R. V Calabrese, "Crystal Wet Milling and Particle Attrition in High Shear Mixers," no. September, 2017.
[3] R. O. Williams III, A. B. Watts, and D. A. Miller, Formulating Poorly Water Soluble Drugs, 2nd ed., vol. 22. 2012.

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