Starch 1500®
Partially Pregelatinized Maize Starch

Colorcon®

Effect of Mixing Time and Mixing Process on Lubricant Sensitivity of Excipients with Different Deformation Characteristics

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Introduction

Lubricants are commonly used in tablet formulations to reduce die wall friction during tablet compression and ejection. In pharmaceutical applications, magnesium stearate, stearic acid, and sodium stearyl fumarate are predominantly used. Some commonly used excipients for tablet formulations are modified starch (Starch 1500), microcrystalline cellulose (MCC), and lactose monohydrate. Starch 1500 is partially pregelatinized maize starch, commonly used in tablet and capsule formulations. It can be considered as a plastically deforming material with less strain rate sensitivity and high elastic energy in comparison to MCC (**Table 1**) [1]. Our previous study demonstrated that combination of starch and MCC is beneficial for direct compression (DC) of tablets [1]. Along with that, lactose is utilized in DC due to its high-flow and less lubricant sensitivity. The purpose of this study is to select lubricant/s which has low lubricant sensitivities for selected diluents at various operating conditions.

Objectives

- To determine impact of mixing times and shear on tabletability for blends containing microcrystalline cellulose (MCC), lactose, and modified starch (Starch 1500) along with different lubricants.
- To determine most suitable lubricant for a blend containing MCC and Starch 1500.
- To provide optimum blend with better compression and less lubricant sensitivity to prepare immediate release tablets.

Methods

Blend Preparation: Formulation composition is shown in **Table 2**. MCC and colloidal silicon dioxide were mixed and passed through #18 mesh sieve, and lubricant was passed through #30 mesh sieve prior to blending. All excipients were blended using V-blender (Patterson Kelley, USA) with and without shear using intensifier bar for 2, 5, 10, and 15 minutes.

Tablet Preparation: Tablets were prepared using a rotary tablet press (Piccola, Riva, Argentina) at 100 to 250 MPa compaction pressures using 10 mm round standard concave tooling at tablet weight of 400 mg. Turret speed was 25 rpm; feeder speed was kept at minimum (<10 rpm) to prevent over blending of lubricant.

Starch 1500: Starch 1500 has low water activity and strain rate sensitivity (%SRS) to that of MCC as shown in Table 1.

Table 1: Mean yield pressure and strain rate sensitivity values (from Ref.1)

Excipient	Mean Yield Pressure (Py)		%SRS
	At Low Speed (Py1)	At High Speed (Py2)	
Starch 1500	129.5	146.6	**11.7**
Microcrystalline Cellulose	83.0	106.9	22.3

Table 2: Formulation composition using different lubricants (Batch size: 2.0 kg)

Excipients	Composition (%w/w)			
	Plastic Diluents			Brittle-Plastic Diluents
	A	B	C	D
Starch 1500	33.0	33.0	33.0	-
Microcrystalline Cellulose (MCC)	65.5	65.5	65.5	33.5
Lactose Monohydrate	-	-	-	65.0
Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5
Magnesium Stearate	1.0	-	-	-
Stearic Acid	-	1.0	-	1.0
Sodium Stearyl Fumarate	-	-	1.0	-
Total	100.0	100.0	100.0	100.0

Results

Impact of Mixing time on Tensile Strength: No Shear (MCC-Starch 1500)

Figure 1. Impact of mixing time (without shear) with different lubricant using MCC-Starch 1500 as diluents. Data represents n=70 for ejection force profile and n=20 for tensile strength profile.

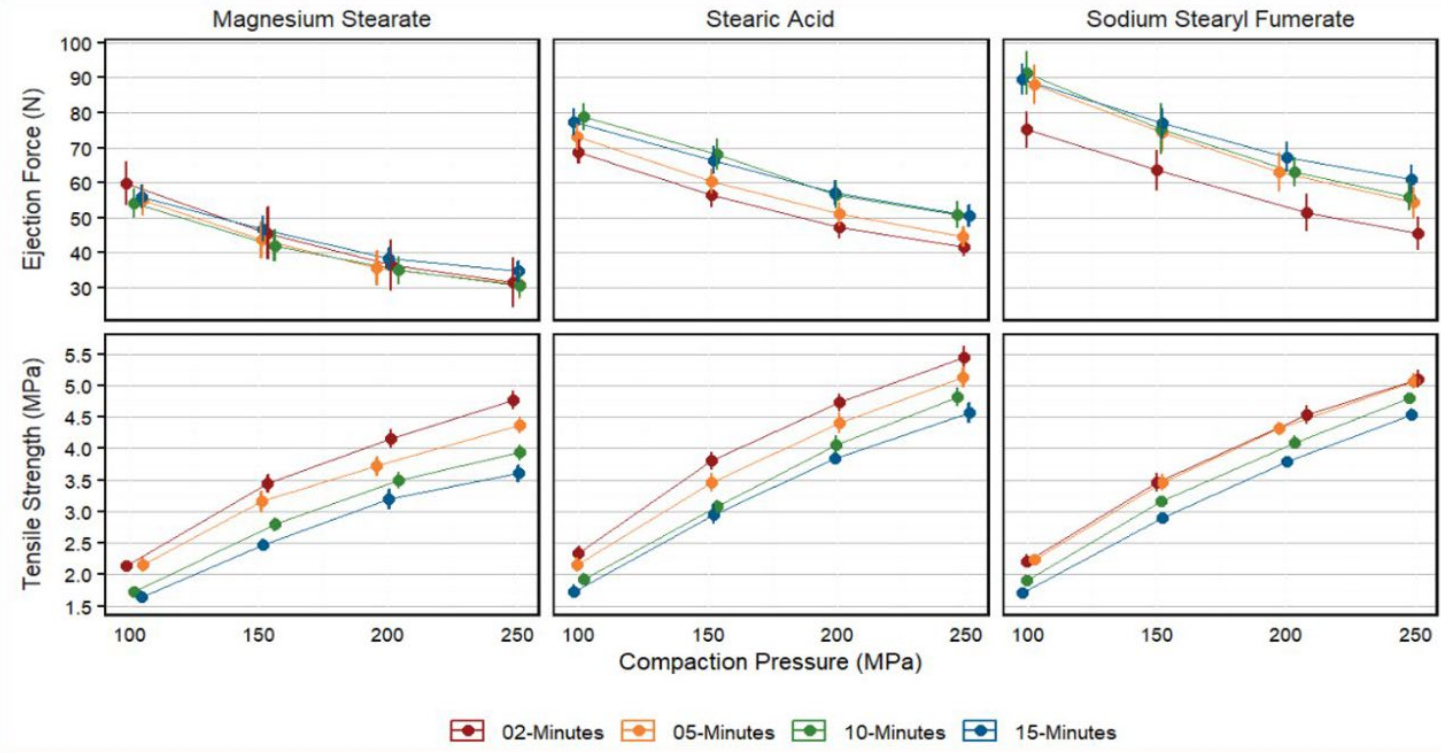
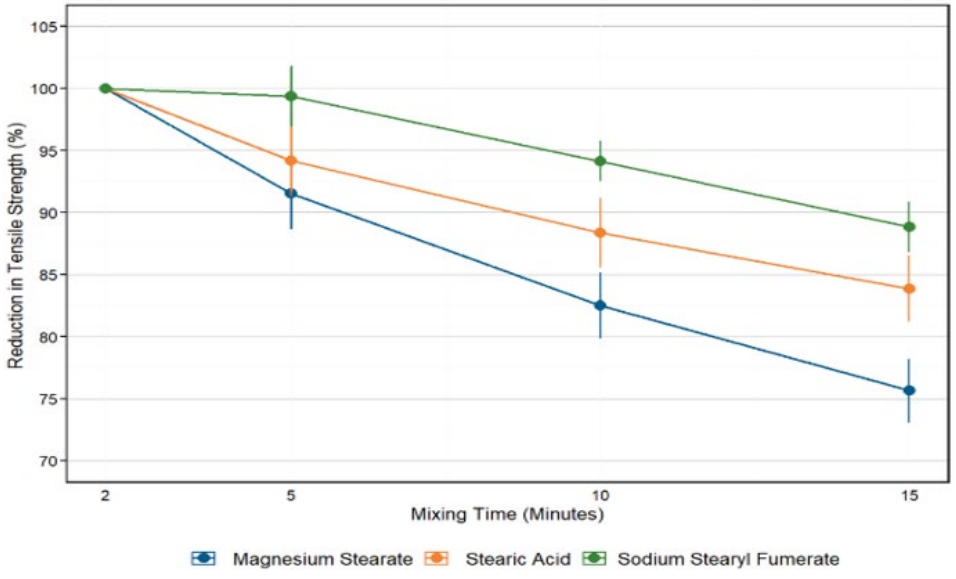


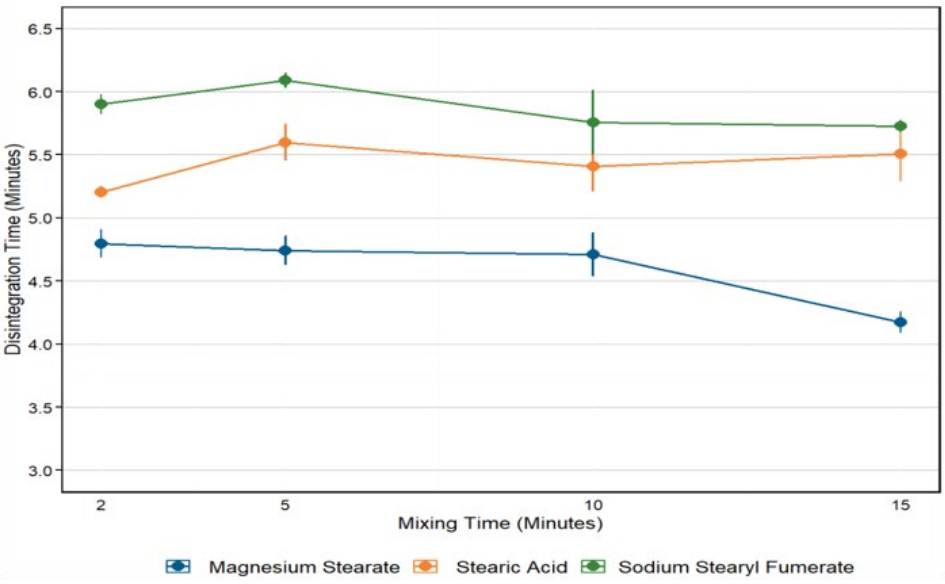
Figure 2. Impact of mixing time (without shear) on:

A) Percent reduction in tensile strength.

B) Disintegration time with use of different lubricant using MCC-Starch 1500 as diluents at 250 MPa Compaction Pressure

* Statistical Difference Using One Way Anova P <0.01.





- Over lubrication observed for all the lubricants.
- With increase in blending time did not affect disintegration time of tablets.
- Magnesium stearate is highly sensitive to lubricant mixing time when blended with plastic and elastic materials. Hence it was excluded from further studies.
- Both stearic acid and sodium stearyl fumarate can be choice of lubricant based on the results.

Impact of Mixing time on Tensile Strength: Shear (MCC-Starch 1500)

Figure 3: Impact of mixing time (with shear) with selected lubricants using MCC-Starch 1500 as diluents.

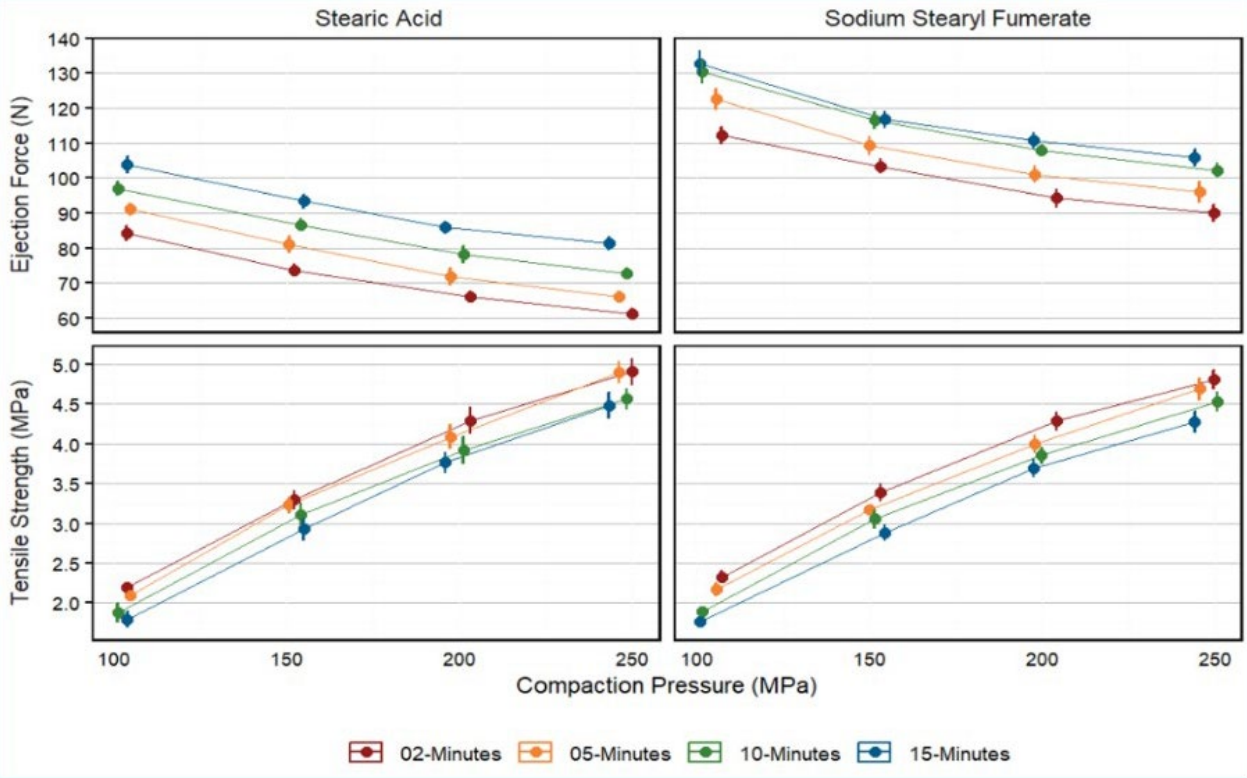
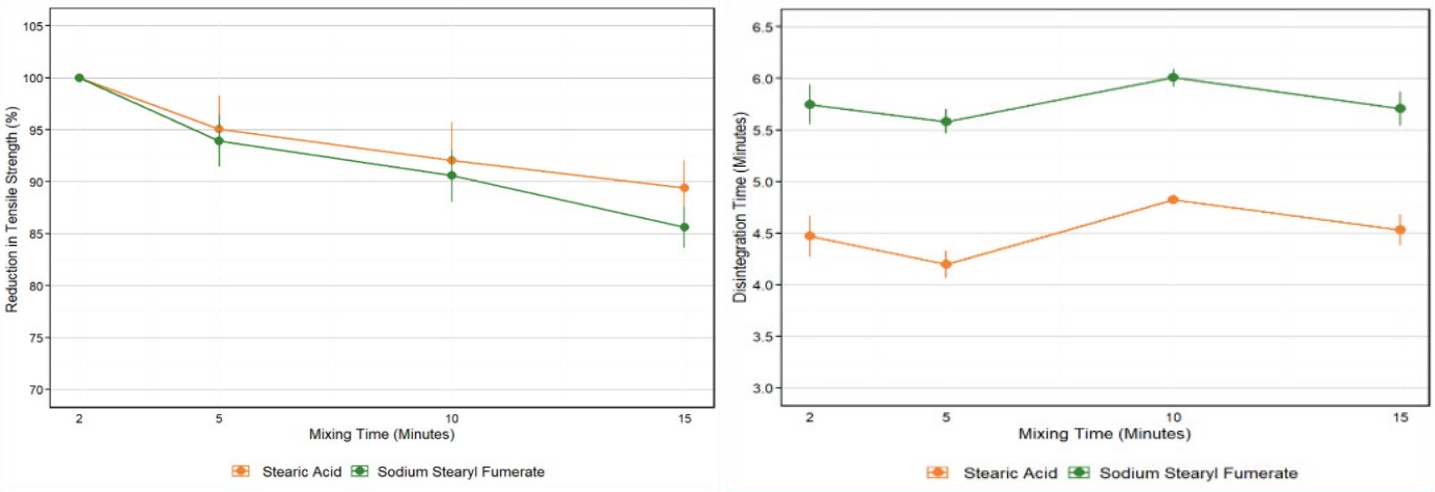


Figure 4: Impact of mixing time (with shear) on:

Percent reduction in tensile strength; B) Disintegration time (DT)

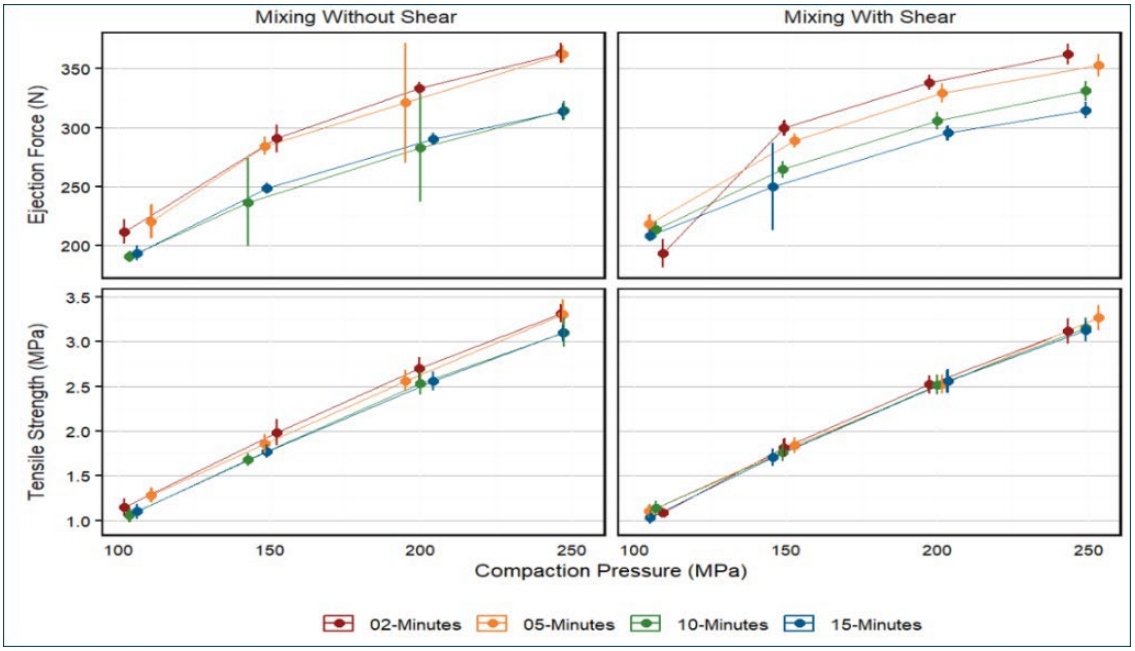
* Statistical Difference Using One Way Anova P <0.01v



- Tablets with both stearic acid and sodium stearyl fumarate showed similar tabletability, better DT observed for tablets with stearic acid.
- Based on the results, stearic acid was selected for further studies.

Impact of Mixing time on Tensile Strength: MCC-Lactose

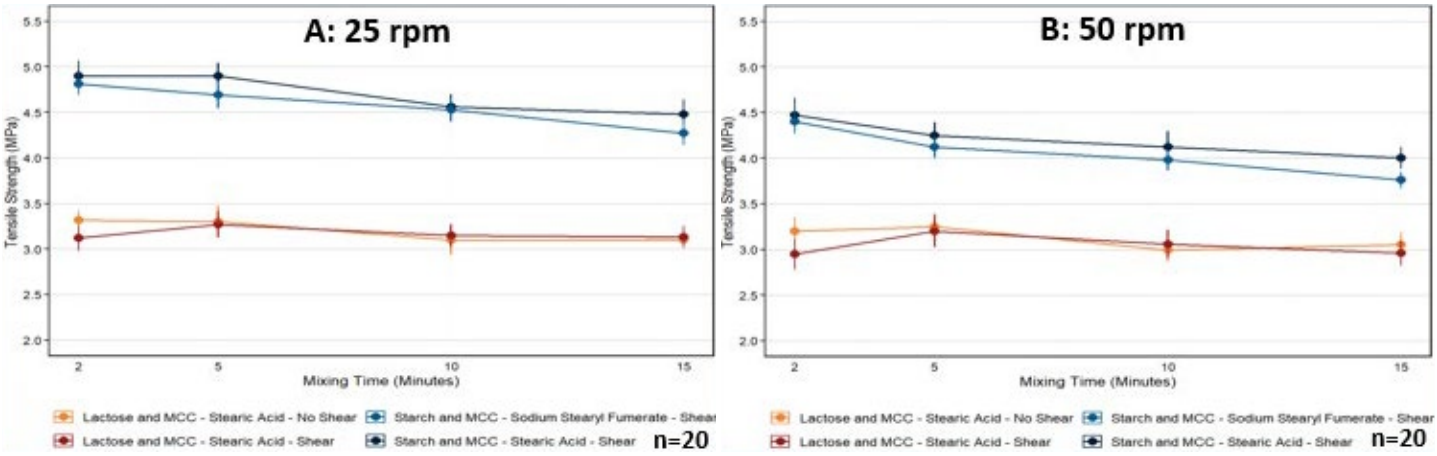
Figure 5: Impact of mixing time (with and without shear) with stearic acid as a lubricant using brittle-plastic (Lactose-MCC) diluents.



Similar tabletability observed with higher inclusion of lactose. Higher ejection observed with use of lactose as brittle material.

Impact of Turret Speed on Tensile Strength: 25 vs 50 rpm

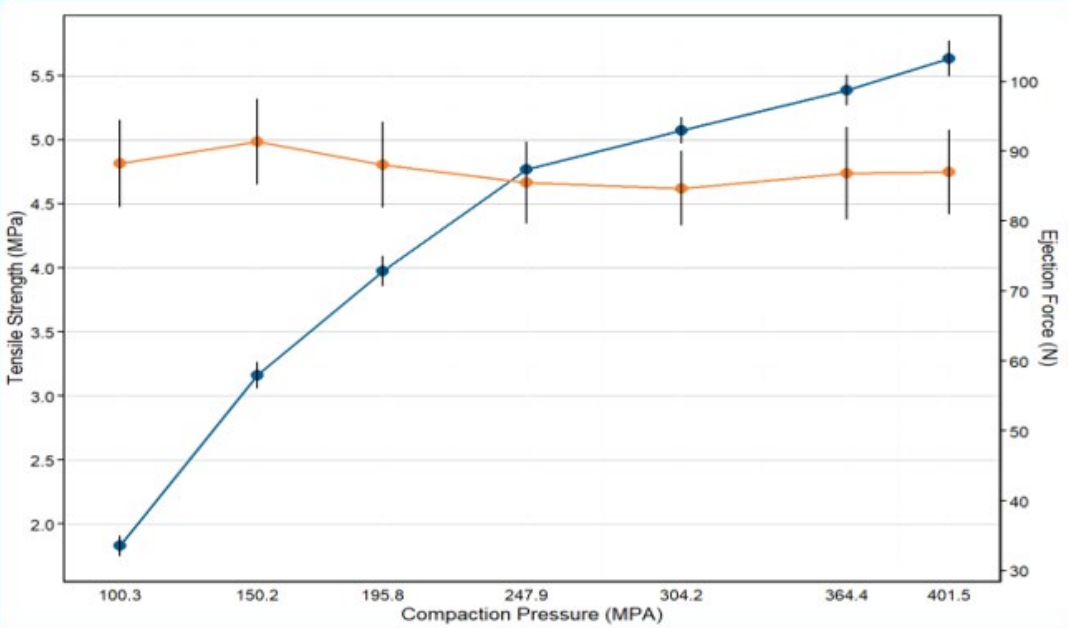
Figure 6: Impact of Turret Speed on MCC-Starch and Lactose-MCC Diluents with A) 25 rpm turret speed vs. B) 50 rpm turret speed.



With change in turret speed, diluents with plastic deforming characteristics showed reduction in tensile strength; whereas no change observed for diluents with brittle/plastic deforming diluents.

Robust Formulation Recommendation with Use of Starch-1500

Figure 7: Tabletability Study of Optimized Formulation with MCC, lactose, and Starch 1500



- Optimum formulation developed with use of **Starch 1500, MCC, and Lactose** with better compressibility, lower ejection force at different compaction pressure.
- Prepared formulation showed minimum impact in tensile strength at different turret speed **(Table 3)**.

Table 3: Impact of turret speed at different compaction pressure on tensile strength

Turret Speed	Tensile Strength (Mpa)	
	At 150 MPa Compaction Pressure	At 200 MPa Compaction Pressure
25 rpm	3.16 ± 0.10	3.97 ± 0.12
50 rpm	2.73 ± 0.13	3.78 ± 0.12

Conclusions

The presence of stearic acid or sodium stearyl fumarate as lubricant in tablet formulations containing either Starch 1500 or MCC, reduced lubricant sensitivity and maintained tablet tensile strength with different lubricant mixing time.

Use of Starch 1500 along with lactose-MCC can help minimize lubricant sensitivity/ strain rate sensitivity while maintaining excellent compressibility.

References

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2. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment - A review. Int J Pharm. 2014.
3. Paul S, Sun CC. Systematic evaluation of common lubricants for optimal use in tablet formulation. European Journal of Pharmaceutical Sciences. 2018;117.