

# Ibuprofen DC 85 W

## Powder characterization and tableting assessment to obtain high-strength ibuprofen tablets by a DoE approach

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## Introduction

Ibuprofen is a chiral propionic acid derivative belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and non-selective COX inhibitors used in the temporary treatment of mild-moderate pain, fever, and inflammation<sup>1</sup>. Although it is primarily administrated in tablets, this drug is challenging for direct compression. It presents punch sticking issues due to its low melting point and poor flow because of its needle-like particles shape. Because of these reasons, direct compression formulations with high content of ibuprofen are often avoided (maximum 60% w/w) (Giatt et al., 2019)<sup>2</sup>, and wet or dry granulation is preferred.

Ibuprofen DC 85 W is the BASF formulated ibuprofen designed for direct compression. It is produced by roller compaction and contains 84.66–85.34% of Ibuprofen 50, 6.59–6.67% of microcrystalline cellulose

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(MCC) as the filler/binder, 2.86–3.02% of croscarmellose sodium as the disintegrant and 5.34–5.52% of silicon dioxide as a glidant. Ibuprofen DC 85 W provides a substantial powder flow and engraving improvement, minimizing tablet mass variability and punches sticking problem, resulting in significant time and cost savings during production scale. In addition to that, being a densified product and containing low quantities of excipients, tablets produced by Ibuprofen DC 85 W are smaller than the wet-granulated ones, improving patient compliance and favoring drug combinations.

This study aimed to characterize Ibuprofen DC 85 W flow properties and produce high-strength ibuprofen tablets, evaluating the variables that affect tablet mechanical resistance using a design of experiments (DoE) approach.

## Materials and methods

Ibuprofen DC 85 W (BASF) and Ibuprofen 50 (BASF) materials were characterized by particle size distribution (PSD), flow properties (angle of repose, bulk density, tapped density) and scanning electronic microscopy (SEM). Tableting was performed in a Bosch (Syntengon) tablet press model TPR-200. Tablet hardness, weight, and thickness were measured by an Erweka GmbH with a sample number of 20 (N=20).

### Powder characterization of Ibuprofen DC 85 W

Tapped and bulk densities were measured by protocols outlined in the USP (<616> Bulk Density and Tapped Density of Powders)<sup>3</sup>. An FT4 powder rheometer was utilized to determine materials compressibility percentage (CPS%), cohesion and flow function (FF) using a 15 kPa pressure in all tests. An Erweka GTB was used to measure angle of repose.

### Design of experiment (DoE)

Tableting tests were defined based on a full factorial with center points to evaluate variability and curvature. The Design-Expert 13 software was used to design the study, considering the impact of tableting parameters (punch size, tableting speed and use of precompression) on the tablet mechanical properties

(hardness, tensile strength and friability). The full factorial design 2<sup>3</sup> with center points resulted in 12 experiments. The study is shown in the Table 1.

The evaluated factors were punch size: 19 x 9 mm and 22 x 10 mm oblong shape; tableting speed: 150, 550 (center point) and 950 tablets/minute (tab/min); use of precompression force: process with or without precompression.

All tests in this study were formulated with Ibuprofen DC 85 W only (no other excipient was included in the formulation) and then tableted by direct compression. Main compression force and tablet weight were kept constant during the processes; 20 kN of main compression force and a mass of 941,18 mg ± 5 %, aiming to obtain 800 mg of ibuprofen per tablet.

Normality and analysis of variance (ANOVA) tests were run with the Design-Expert 13 software, wherein p < 0.05 was established as a statistically significant difference.



**Table 1: Ibuprofen DC 85 W tableting test conditions**

Run	Tableting speed (tab/min)	Punch size (mm)	Precompression force (6 kN)
1	950	19 x 9	without
2	950	22 x 10	with
3	550	22 x 10	with
4	150	22 x 10	without
5	150	19 x 9	without
6	550	19 x 9	without
7	950	19 x 9	with
8	550	19 x 9	with
9	550	22 x 10	without
10	950	22 x 10	without
11	150	19 x 9	with
12	150	22 x 10	with

## Measurements

The DoE responses, tablet tensile strength and friability, are attributes associated to the tablet mechanical properties. The breaking force, or hardness, was determined with a tablet hardness tester, following the USP guidelines (<1217> Tablet Hardness)<sup>4</sup>.

The tensile strength provides a measure of the tablet strength (hardness) normalized by its dimensions. For oblong punches 19 x 9 mm and 22 x 10 mm, the equation used to calculate the tensile strength was:

$$\sigma_t = \frac{2}{3} \left( \frac{10P}{\pi D^2 \left( 2.84 \frac{t}{D} - 0.126 \frac{t}{W} + 3.15 \frac{W}{D} + 0.01 \right)} \right)$$

where  $\sigma$  is the tensile strength,  $10P$  is the breaking force (N) multiplied by 10,  $\pi$  is the Pi constant (3.14),  $D$  is the tablet diameter,  $W$  is the tablet belly band, and  $t$  is the tablet thickness (Pitt, K. & Heasley M., 2013)<sup>5</sup>.



The dimensions were determined by a micrometer and the belly band was calculated by the overall tablet thickness less the cup depth of the punches.

Tablet friability is a measure of the tablet's resistance to mechanical stress by tumbling them in a rotating cylinder. The percentage weight loss after tumbling is referred to as the "friability" of the tablet. Standardized methods and equipment for testing friability have been provided by the USP guidelines (<1216> Tablet Friability)<sup>6</sup>.

## Results and discussion

Particle size distribution (PSD) and scanning electronic microscopy (SEM) results for Ibuprofen DC 85 W and Ibuprofen 50 are shown in Figure 1, A and B, respectively. The dataset presents a median particle size of 850  $\mu\text{m}$  ( $d_{10} = 193 \mu\text{m}/d_{50} = 671 \mu\text{m}/d_{90} = 1620 \mu\text{m}$ ) for the Ibuprofen DC 85 W and 55  $\mu\text{m}$  for the Ibuprofen 50 ( $d_{10} = 15.6 \mu\text{m}/d_{50} = 50.4 \mu\text{m}/d_{90} = 120 \mu\text{m}$ ). The SEM image captures the densified granules of the Ibuprofen DC 85 W which result in its great flowability and the needle-like particle of a typical ibuprofen drug presented in the Ibuprofen 50.

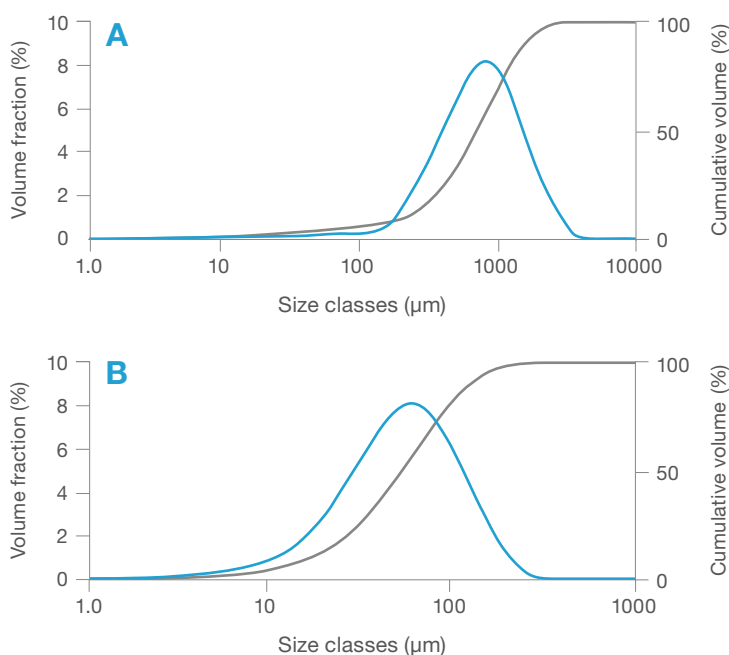
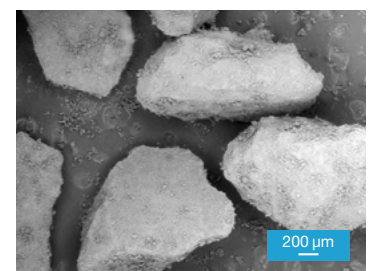
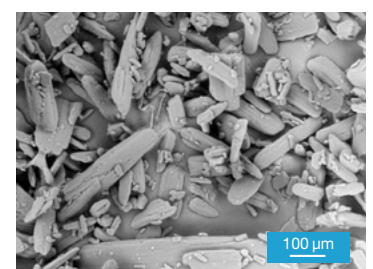


Figure 1: Typical PSD of BASF Ibuprofen DC 85 W (A) and Ibuprofen 50 (B).

■ Volume fraction (%) ■ Cumulative volume (%)



SEM of BASF Ibuprofen DC 85 W.



SEM of Ibuprofen 50.



**Ibuprofen DC 85 W displays enhanced free-flowing characteristics compared to the regular Ibuprofen 50.**

Based on the results of the FT4 powder rheometer, angle of repose, and Hausner ratio shown in Table 2, Ibuprofen DC 85 W presents good flow properties for a robust tableting process. Compared to regular Ibuprofen 50, Ibuprofen DC 85 W has much lower compressibility (%) (lower percentage in volume change with an applied normal pressure). It means when a force is applied, Ibuprofen 50 tends to compact more than Ibuprofen DC 85 W. Ibuprofen 50 also has a slightly higher cohesion value and lower flow function (FF). In this case, the material tends to agglomerate more and flow worse compared to Ibuprofen DC 85 W. Higher values of compressibility (%) and cohesion can translate to increased material compaction in the funnel or feeder hopper, leading

to bridging or rat hole issues and an inconsistent mass flow to fill the powder into the dies. Oppositely, Ibuprofen DC 85 W presents lower compressibility and lower cohesion due to its free-flowing characteristic.

This flow property is corroborated with the lower angle of repose and Hausner ratio results.

The tableting process had no unexpected stops. Tablets mass variability was low at (941.18 ± 28 mg). The average results (N=20) for tablet hardness and tensile strength, and the friability measurement are presented in Table 3. Tensile strength and friability results were evaluated by ANOVA to check the impact of the investigated tableting parameters.

**Table 2: FT4 powder rheology, bulk/tapped density, Hausner ratio and angle of repose results of Ibuprofen DC 85 W and Ibuprofen 50**

Material @ 15 kPa	Cohesion (kPa)	Flow function	CPS (%)	Bulk density (g/mL)	Tapped density (g/mL)	Hausner ratio (T/B)	Angle of repose (°)
Ibuprofen DC 85 W	0.7	13	4	0.58	0.68	1.17	36
Ibuprofen 50	0.9	8	23	0.39	0.59	1.50	49

**Table 3: Hardness, tensile strength and friability results**

Run	Tableting speed (tab/min)	Punch size (mm)	Pre-compression force (6 kN)	Average hardness (kP)	Average tensile strength (Mpa)	Friability (%)
1	950	19 x 9	without	19.3	1.39	1.44
2	950	22 x 10	with	15.0	1.35	0.29
3	550	22 x 10	with	15.9	1.45	0.22
4	150	22 x 10	without	15.9	1.45	0.37
5	150	19 x 9	without	19.0	1.39	0.29
6	550	19 x 9	without	19.6	1.44	0.48
7	950	19 x 9	with	20.3	1.48	0.32
8	550	19 x 9	with	20.6	1.51	0.34
9	550	22 x 10	without	13.6	1.24	0.28
10	950	22 x 10	without	12.9	1.17	1.10
11	150	19 x 9	with	21.7	1.60	0.41
12	150	22 x 10	with	16.1	1.48	0.29

The ANOVA results for tensile strength are shown in Table 4. These show an F-value of 12.34 and a p-value of 0.0143, implying that the model is significant. Furthermore, all individual factors' p-values were less than 0.05, indicating that tableting speed (A), punch size (B), and precompression (C) are relevant terms. No relevant cross factors interactions were reported (p-value above 0.05).

**Table 4: ANOVA results for tensile strength**

Source	Sum of squares	Degrees of freedom	Mean square	F-value	p-value
Model	0.1447	7	0.0207	12.34	0.0143
A-Tableting speed	0.0338	1	0.0338	20.18	0.0109
B-Punch size	0.0363	1	0.0363	21.67	0.0096
C-Precompression	0.0533	1	0.0533	31.84	0.0049
AB	0.0112	1	0.0112	6.72	0.0606
AC	0.0000	1	0.0000	0.0299	0.8712
BC	0.0001	1	0.0001	0.0796	0.7918
ABC	0.0098	1	0.0098	5.85	0.0729
Residual	0.0067	4	0.0017		
Cor total	0.1514	11			

Note: R<sup>2</sup> = 0.9557; Adjusted R<sup>2</sup> = 0.8783.

**Table 5: ANOVA results for the friability response**

Source	Sum of squares	Degrees of freedom	Mean square	F-value	p-value
Model	1.34	7	0.1919	6.07	0.0832
A-Tableting speed	0.4005	1	0.4005	12.67	0.0378
B-Punch size	0.0444	1	0.0444	1.41	0.3212
C-Precompression	0.3640	1	0.3640	11.52	0.0427
AB	0.0136	1	0.0136	0.4307	0.5585
AC	0.4851	1	0.4851	15.35	0.0296
BC	0.0030	1	0.0030	0.0952	0.7779
ABC	0.0325	1	0.0325	1.03	0.3851
Residual	0.0948	3	0.0316		
Cor total	1.58	11			

Note:  $R^2 = 0.9341$ ; Adjusted  $R^2 = 0.7802$ .

The ANOVA results for the friability test are presented in Table 5. The Model F-value was 6.07, and the p-value was 0.0832. The high adjusted  $R^2$  shows that 78 % of the friability data can be explained with the evaluated variables, tableting speed (A), punch size (B), and precompression (C). However, variables A and C and their first-order interaction AC have high statistical relevance in explaining the variance of the friability results. This is further demonstrated by the mean square errors. High mean square errors correlate to a more expressive contribution to the total variation of

the response, i.e., Friability. Thus, the factors AC, A, and C, affect the Friability response progressively in this order.

This Friability model can be optimized for quantitative predictions (higher adjusted  $R^2$ ) if the non-significant variables – punch size (B) and its interactions, are removed. The authors caution against this in this study due to the small sample size and, thus, the increased uncertainty that may arise at the tails of the t-distribution.





The Pareto diagrams shown in Figures 2 and 3 are another way to observe the significance of the evaluated terms. The graphs show the value of the effects, ranked from highest to lowest; wherein variables above the grey line (t-value limit) can be considered statistically significant. As observed in Figure 2, all individual tableting parameters studied significantly affected the tensile strength values, having precompression as the most significant one, followed by punch size and tableting speed.

This behavior is expected since ibuprofen and MCC undergo plastic and elastic deformation. Ibuprofen, as a plastically deforming ingredient, is more susceptible to the compaction rate, dwell time, and punch geometry (Peeters et al., 2018)<sup>7</sup>.

Moreover, it can be observed in Figure 3 that tableting speed, use of precompression force, and their interaction significantly influenced the friability. A lower friability can be translated into stronger tablets obtained by using an optimal compaction rate, which is directly correlated to an ideal adjust of the dwell time.

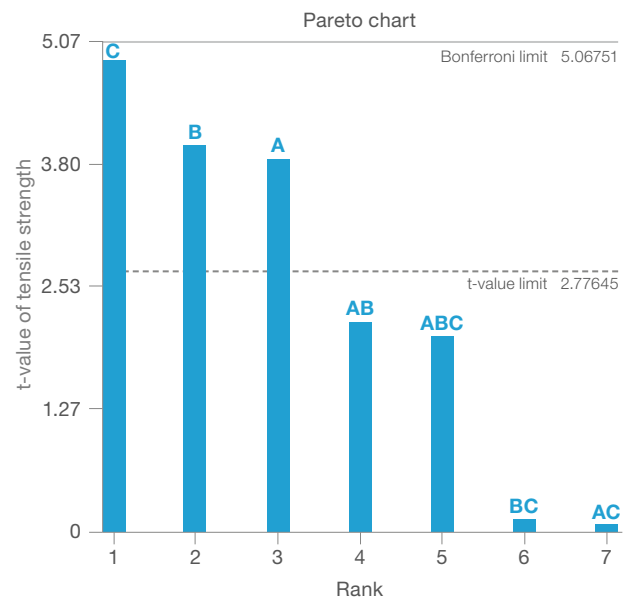


Figure 2: Pareto diagram: Tensile strength. Individual factors and their interactions.

A Tableting speed B Punch size C Precompression

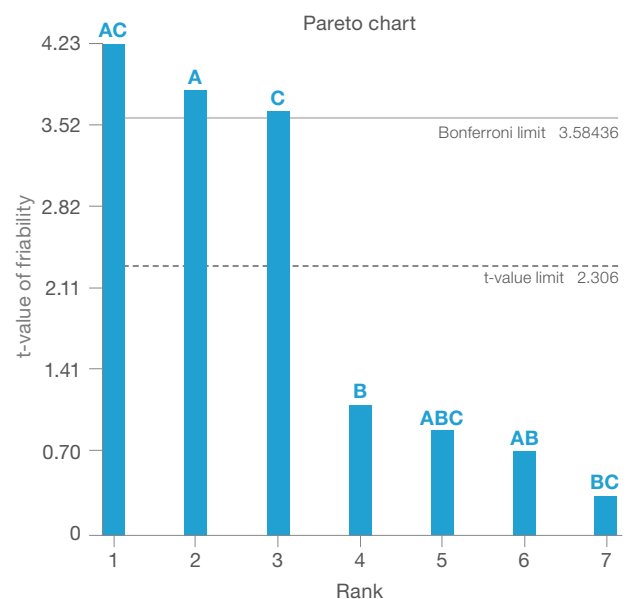


Figure 3: Pareto diagram: Friability. Individual factors and their interactions.

A Tableting speed B Punch size C Precompression



The evaluation of interaction cross factors presented on the charts in Figures 4, 5, and 6 helps to understand the correlation of the studied parameters (A, B, and C) and their effects on the mechanical resistance of 800 mg ibuprofen tablets obtained by the direct compression of the Ibuprofen DC 85 W.

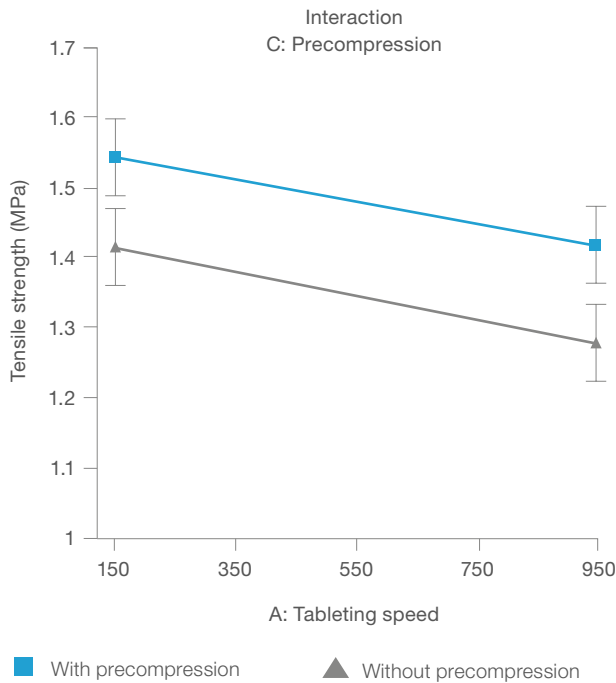


Figure 4: Tensile strength interaction graph: Precompression x tableting speed. Note: Punch size is represented by the average value.

Figure 4 illustrates how precompression force and tableting speed factors impacted the tablet tensile strength values. Regarding the compression speed, it is correlated to the residence time. The length of time the main compression pressure is applied to compact the powder and form the tablet is called dwell time. So, the faster the machine's rotation (tablet per minute), the reduced residence time (lower dwell time), which can impact the tablet's mechanical resistance. This

phenomenon explains the influence of the tableting speed on the Ibuprofen DC 85 W tablets.



Ibuprofen and MCC presented in Ibuprofen DC 85 W's formulation undergo mainly plastic deformation. Plastically deforming materials are considered residence-time dependent because they increase deformation and particle-particle bonding when a force is applied for a longer period. Besides that, tablet axial recovery (expansion) is lowered when the tableting speed is reduced by raising the plastic deformation over the elastic one, generating stronger compacts (P.V. Marshall et al., 1993)<sup>8</sup>. In a nutshell, the faster the equipment rotation, the lower the tensile strength of materials that undergo plastic deformation.

As part of the process parameters study, the highest tablet tensile strength was obtained using the pre-compression force and the lowest speed rotation (150 tab/min) parameters, presenting an average value of 1.54 MPa (1.48–1.59 MPa). Keeping the pre-compression force and increasing the speed rotation to 950 tab/min, the tensile strength values dropped to 1.41 MPa. Tablets compressed without precompression force showed an average tensile strength value of 1.40 MPa (1.35–1.46 MPa) at the lowest tableting speed; lesser values of 1.28 MPa were obtained when the tableting speed was increased.

The precompression force is relevant for particle arrangement and consolidation inside the dies, releasing entrapped air between the particles. This tableting step enables closer granules contact, contributing to their binding and densification when the main compression force is applied, leading to an improved tablet engraving. In addition, precompression acts like extending the dwell time by compacting the powder two times, driving an important influence on materials undergo plastic deformation<sup>7</sup>. Based on that, precompression can improve tablet's mechanical properties, such as hardness, tensile strength, and friability, by providing a better powder compaction (Perez-Gandarillas et al., 2016)<sup>9</sup>.

In conclusion, precompression minimizes the impact of machinery speed on tableting process of plastically deforming materials, like Ibuprofen DC 85 W by extending the dwell time, yielding stronger tablets.





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precompression. Moreover, it is important to highlight that the most significant reduction in the tensile strength value was changing from the 19 x 9 mm to the 22 x 10 mm punch, tableting without precompression at 950 tab/min speed.

Besides the equipment rotation and the use of precompression factors, punch sizes performed distinctly, showing interesting tensile strength differences in value, as illustrated in Figure 5 (a), (b), and (c), corresponding to 150, 550, and 950 tab/min, respectively. The charts show that the 19 x 9 mm punches provided a tensile strength value higher than the 22 x 10 mm with or without precompression and at all tableting speeds. However, a slight difference was observed for the 150 tab/min process without

Compression pressure (or compaction pressure) is calculated by dividing the applied force by the cross-sectional area of the punch ( $\text{Pressure} = \text{Force} / \text{Area}$ ). Since this study was performed using the same main compression force (20 kN) to the same material mass ( $941.18 \pm 28 \text{ mg}$ ), the only change to impact the pressure value was the punch surface area. Therefore, the smaller 19 x 9 mm punch has a lower area than the 22 x 10 mm and because of that, a higher pressure was applied to the Ibuprofen DC 85 W material, resulting in stronger tablets.

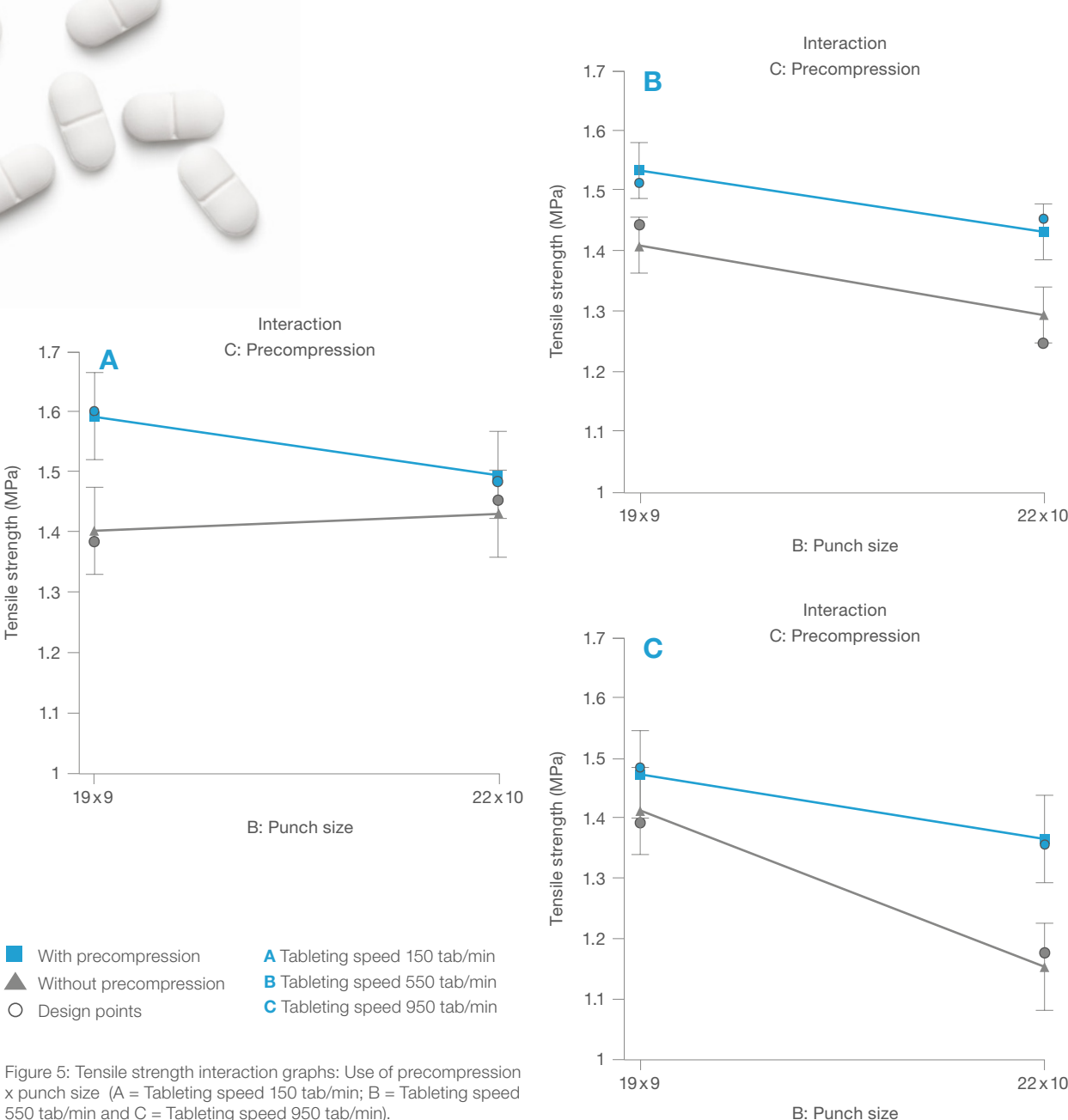
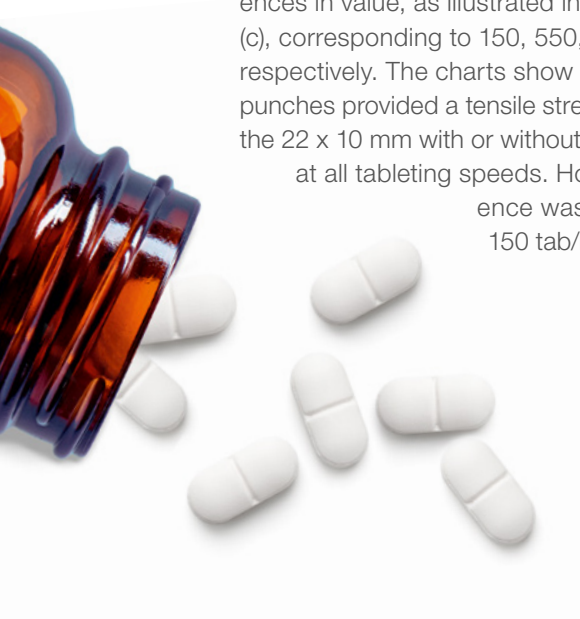


Figure 5: Tensile strength interaction graphs: Use of precompression x punch size (A = Tableting speed 150 tab/min; B = Tableting speed 550 tab/min and C = Tableting speed 950 tab/min).

Lastly, Figure 6 presents the results regarding friability, which were influenced mainly by precompression and tableting speed. The 950 tab/min test without precompression force had friability values around 1.0%. For all tests using the precompression force, the friability remained close to 0.3%, even at low and high tableting speeds. It emphasizes the impact of precompression force on the Ibuprofen DC 85 W particles consolidation and densification. So, it is possible to highlight that precompression plays an essential role in the final mechanical properties of plastically deforming materials such as ibuprofen and MCC, contributing to improve tablet integrity and reduce friability.

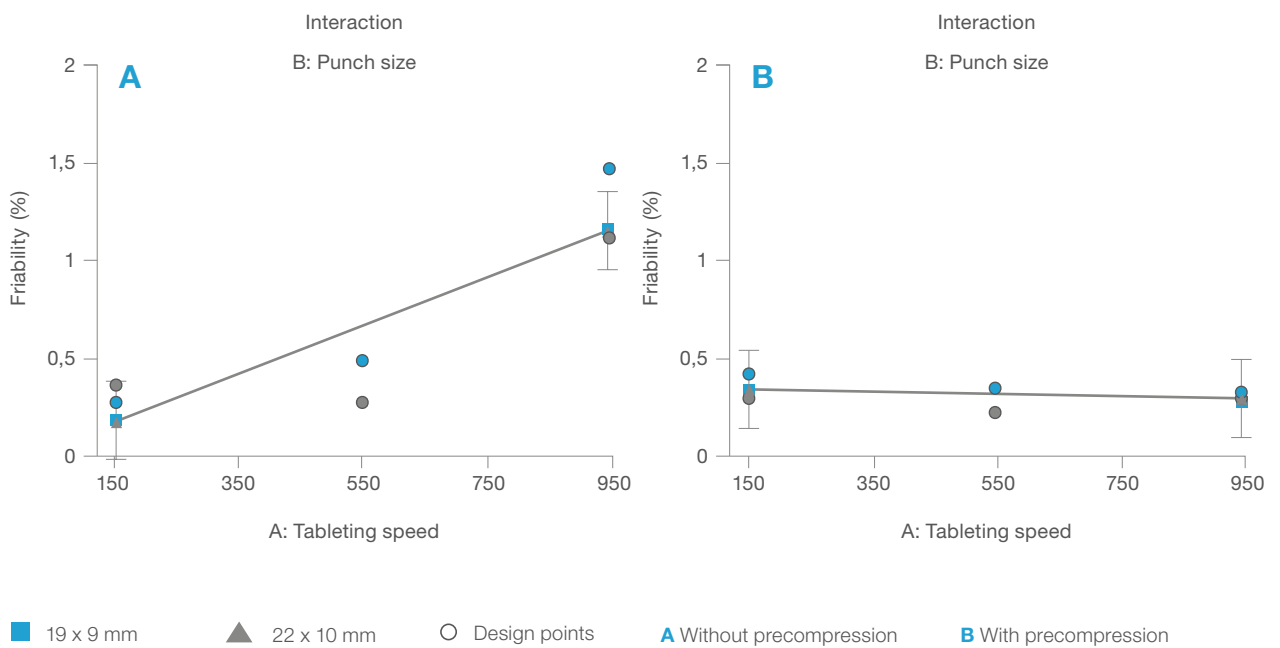


Figure 6: Friability interaction graphs: Punch size x tableting speed (A = without precompression and B = with precompression).

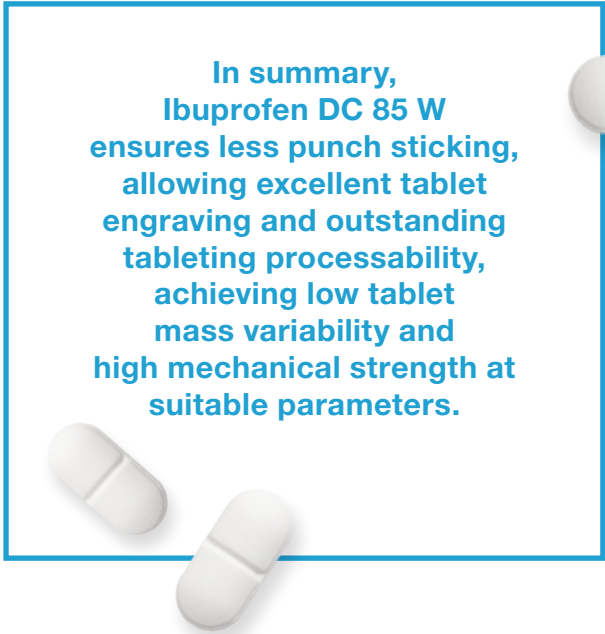
**Precompression plays an essential role in the final mechanical properties of plastically deforming materials, contributing to improve tablet integrity and reduce friability.**



## Conclusion

Ibuprofen DC 85 W is a formulated drug ideal for direct compression of diverse ibuprofen strengths, including the high 800 mg ibuprofen dose. This material has a lower cohesion, compressibility percentage, angle of repose and Hauser ratio value than the standard ibuprofen grade, emphasizing improved flowability to ensure a consistent tablet weight for a robust direct compression process.

The DoE provided relevant results and understanding about the Ibuprofen DC 85 W compressibility, where the precompression relevance was observed to improve tablet mechanical properties as well as the dwell time and punch size impact. The Pareto diagram showed that precompression has the largest effect on tablet tensile strength. Friability was dependent on the interaction between precompression and tableting speed.



**In summary,  
Ibuprofen DC 85 W  
ensures less punch sticking,  
allowing excellent tablet  
engraving and outstanding  
tableting processability,  
achieving low tablet  
mass variability and  
high mechanical strength at  
suitable parameters.**

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