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Full Length Research Article

2×3 Factorial Analysis to Study Lubrication and Mixing Variables' Impact on Orodispersible Composite Tensile Strength

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ABSTRACT
This study hypothesized that the tensile strength of placebo tablets produced from newly engineered α-lactose-starch orodispersible composite using a single-punch tablet press was dependent on the combined effects of magnesium stearate concentration, tumbling speed of a double cone mixer, and the duration of mixing. A 2x3 full factorial experiment was designed to: (i) understand the main effects associated with each of the factors, and (ii) to understand the interactions between the factors using main effect, interaction, pareto, cube, response surface plots, and regression modelling tools of Minitab® 19 (Minitab Limited, United Kingdom). The main effects plots indicated that the tensile strength of the novel α-lactose-starch orodispersible composite increases at low factor settings of magnesium stearate concentration, and low tumbling speed, but diminishes at low settings of mixing time. Conversely, for mixing time the effect on tensile strength was greater at the high setting. Conclusively, the magnesium stearate concentration, tumbling speed of a double cone mixer, and the duration of mixing are critical factors affecting the tensile strength of the α-lactose-starch orodispersible composite, suggesting further optimization in future formulation design.
Keywords: Orodispersible excipients; Full factorial design; Process analytical technology; Tensile strength; Material science

INTRODUCTION
Orodispersible excipients are tablet formulation additives for manufacturing specialized tablets with rapid disintegration (Aguilar *et al.,* 2013; Comoglu and Ozyilmaz, 2019). Such excipients are significantly scanty to satisfy the demand of the pharmaceutical manufacturing industry (Kozarewicz and Loftsson, 2018). Consequently, particle engineering technologies leverage material science to develop composites from two or more existing single-component excipients such as lactose monohydrate and starch (Kolter and Guth, 2016; Bhatia *et al.,* 2022). In early phases of development, the critical material attributes of the novel orodispersible composites such as tensile strength, young modulus, yield stress, viscoelasticity, plastic deformation, brittle fracture index in conjunction with numerous other physicomechanical parameters need to be thoroughly investigated (Mohammed *et al*., 2005; Aguilar *et al*. 2013; Shang *et al*., 2013; Salim *et al*., 2018; Salim *et al.*, 2022).

Lubricants are critical formulation excipients that function at interparticle and powder-metal interfaces to reduce friction, thus enhancing efficient fluidity, mixing, and facilitating smooth ejection of compacted masses from die cavities during the decompression phase of the tablet formation cycle (Alderborn and Frenning, 2017; Li and Wu, 2014). In high-speed multi-station powder compaction presses, the resultant effect of lubricants is increased efficiency of compression cycles. The role of lubricants in the reduction of failure modes attributable to tablet mechanical problems such as capping, picking, or lamination points to their delineation as critical formulation additives (Hiremath *et al.,* 2019). Moreover, in critical unit operations such as coating and pharmaceutical packaging, the kinetics of sliding friction strongly influence the response of the finished tablets to any form of applied stress such as gravity (Hancock *et al.,* 2010).

Magnesium stearate ($Mg(C_{18}H_{35}O_2)_2$) synthesized from the reaction of stearic acid with magnesium salt, is a highly acting tableting lubricant that forms a hydrophobic interfacial film at interparticulate contact points resulting in net reduction of coefficient of friction at such points (Li and Wu, 2014; Hiremath *et al.,* 2019). However, like most organic lubricants, magnesium stearate has a deleterious effect on the compression and compaction dynamics of certain powder systems affecting other critical quality attributes such as tensile strength, disintegration, and dissolution (Li and Wu, 2014).

The function of a lubricant is influenced by formulation and process variables (Hiremath *et al.,* 2019). The chemical constitution of the formulation ingredient determines the degree of physical interaction at interfaces and the extent of modification of the surface and interfacial characteristics (Li and Wu, 2014). Mechanistically, the function of lubricant is affected by the rate and extent of dispersive, convective, and shear forces arising from the mechanics of mixing operation (Twitchell, 2018; Wang *et al.,* 2010). Tumbling mixers are low-shear mixers for blending lubricants and free-flowing powder ingredients just prior to compression unit operation (Twitchell, 2018). The degree of mixing is jointly influenced by the tumbling mixer design, rotational speed, blending time, and spatial orientation (angle of inclination) on the rotating gear. To understand the interrelationship between these Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Critical Quality Attributes (CQAs), the traditional One-Variable-At- a Time (OVAT) analysis is not only non-economic and inefficient but rather lacks the statistical robustness to furnish reliable results (Antony, 2003c). OVAT research design often leads to false optimum factor settings (Bowden *et al.,* 2019).

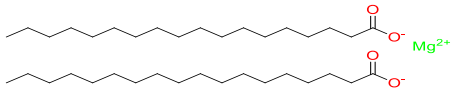

Figure 1: Chemical structure of magnesium stearate.

Given the integrated applications of Quality-by-Design principles in pharmaceutical solid dosage form design and manufacture (Yu, 2008; Yu *et al.,* 2014; Apeji *et al.,* 2018; Badawy *et al.,* 2019), this study embraced a 2x3 full factorial analysis for preformulation studies of newly engineered tabletting composites developed from α-lactose monohydrate, starch, and sodium starch glycolate. The effect of shape factors and dilution potential of the novel composite have been extensively studied in a previously published study (Salim *et al.,* 2022). However, the impact of magnesium stearate lubrication and mixer type has not yet been investigated.

We therefore hypothesized that the tensile strength of the newly engineered α-lactose-starch orodispersible composite was dependent on the combined action of magnesium stearate concentration, the tumbling speed of a double cone mixer, and the duration of mixing. The goals of the DoE were to (i) understand the main effects associated with each of the factors in the experiment, and (ii) to understand the interactions between the factors.

MATERIALS AND METHODS

Materials

FlowLac90® (Lot L101534118) and MicroceLac100® (Lot No: L103153918) are commercial brands of directly compressible spray-dried agglomerate donated by Meggle Wasserburg GmbH & Co. KG, Germany. FlowLac90® is a single-component excipient comprising of α-lactose monohydrate only. MicroceLac100® is a coprocessed excipient derived from microcrystalline cellulose (25%) and α-lactose monohydrate (75%). Explotab® (Sodium starch glycolate) was donated by JRS Pharma, Rosenberg, Germany. All excipients were of pharmacopoeial standards. Starch, and magnesium stearate (Batch No: 010112) were commercially obtained from Central Drug House, New Delhi, India. The experimental coprocessed composite consists of α-lactose monohydrate, corn starch, and sodium starch glycolate (SSG) at 80.75%, 14.25%, and 5% proportions. The protocol for the design and engineering of the experimental α-lactose-starch orodispersible composite has been reported in a previous study (Salim *et al.,* 2022).

Methods

Design of Experiment

The factors included in the study are presented in Table 1. The coded design matrix for the two-level three-factor experiment was created using Minitab 19 (Table 2). Magnesium stearate was incorporated into the coprocessed diluent at 0.5% and 5%. The mixing process was conducted at 5 and 30 min using a 150 x 250 mm double cone tumbling mixer mounted on the universal gearbox of R &D All Purpose Machine (model: AP-01 Plus, Orchid Scientific, India). The mixing speed was automatically operated at 50 and 200 rpm (Figure 2). Die filling was volumetrically adjusted using a blended diluent-lubricant sample of 140±5 mg corresponding to the target tablet weight. Compression proceeds at a constant compaction force of ~10 kN in a single station tablet press (model SSP-12 Shakti Pharmatech, PVT. LTD, India) equipped with 8x4 mm elongated convex-faced punches. The ejected tablets were dedusted, packaged, and sealed in polyethylene dispensing envelopes, and stored under ambient conditions for 48 h to allow for equilibration and prevent false tensile strength measurement (Salim *et al.,* 2022). The experimental runs were fully randomized by the Minitab® 19 to ensure that the factor levels had the same chances of being influenced by noise. However, the entire run consisted entirely of a single block with zero centre point. To obtain reasonable estimates of the experimental error, the tensile strength of ten randomly selected tablets was measured for each run.

Table 1: Factors and their levels included in the design of experiment.

FACTORS	LEVELS	
	Low (-)	High (+)
Lubricant Concentration (A) (%)	0.5	5
Tumbling Speed (B) (rpm)	50	200
Mixing Time (C) (min)	5	30

rpm: revolution per minute

Tensile Strength Measurement

The response of interest for the factorial design is the tensile strength of the formed tablets. The protocol for tensile strength measurement of the experimental α-lactose-starch-SSG coprocessed diluent has been previously reported by the authors. Taking into consideration the geometry of the tablets (Figure 1), the tensile strength (σ) was computed from the modified Pitt's equation (Pitt & Heasley, 2013).

$$\sigma_t = \frac{2}{3}\left(\frac{10P}{\pi D^2\left(2.84\frac{t}{d} - 0.126\frac{t}{w} + 3.15\frac{w}{d} + 0.01\right)}\right) \quad \textit{Equation 1}$$

Where, P is the force required to cause compact fracture measured using a pre-calibrated digital tablet tester (Type THT-2, Biobase, India). The compacts were oriented with their scoring parallel to the two metallic platens of the tester. The dimensions *t, d,* and *w* were the compact total axial thickness, tablet wall height, and diameter as defined in Figure 3 (Pitt *et al.,* 2011; Pitt and Heasley, 2013; Yohannes and Abebe, 2021; Salim *et al.*, 2022)

Table 2: Coded design matrix for the 2^3 factorial experiments.

RUN	LUBRICANT CONCENTRATION (A)	TUMBLING SPEED (B)	MIXING TIME (C)	RUN LABEL	TENSILE STRENGTH, σ (MPa)
1	+	+	+	*abc*	σ_1
2	+	+	-	*ab*	σ_2
3	+	-	+	*ac*	σ_3
4	+	-	-	*a*	σ_4
5	-	+	+	*bc*	σ_5
6	-	+	-	*b*	σ_6
7	-	-	+	*c*	σ_7
8	-	-	-	*1*	σ_8

Low level: -, High: +

Figure 2: Experimental set-up for mixing operation.
Double cone mixer [a], All-purpose equipment [b]. Mounting shaft [I], digital speed indicator [II], digital speed regulator [III], digital timer [IV], timer control [V].

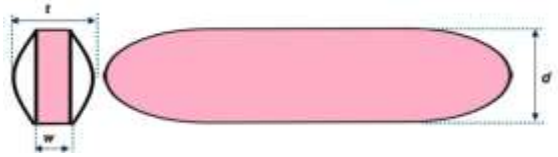

Figure 3: Elongated convex-faced tablet.
t: overall axial thickness, w: tablet wall height, d: diameter. 2-D flipped side view [left], 2-D resting position top view.

Calculation of Factor Effects

To estimate the effect of a factor, the difference between the sum of the responses of the experiments conducted at a high level (positive runs) and the sum of the responses obtained at a low level of the factors (negative runs) was considered. For an experiment consisting of *k* number of factors conducted at 2 levels, the effect of a factor, *E* is given by:

$$E = \frac{(\sum Postive\ runs - \sum Negative\ runs)}{2^{k-1}}$$ Equation 2

$$E = Mean\ of\ positive\ runs - Mean\ of\ negative\ runs$$
Equation 3

Taking the effects of *A* as an example, the factor effect was simply derived as:

$A_{B_-C_-} = [a - (1)]/n$ Equation 4

$A_{B_+C_-} = [ab - b]/n$ Equation 5

$A_{B_-C_+} = [ac - c]/n$ Equation 6

$A_{B_+C_+} = [abc - bc]/n$Equation 7

where:

$A_{B_-C_-}$: effect of *A* at low levels of *B* and *C*

$A_{B_+C_-}$: effect of *A* at high level of *B* and low level of *C*

$A_{B_-C_+}$: effect of *A* at low level of *B* and high level of *C*

$A_{B_+C_+}$: effect of *A* at high levels of *B* and *C*

The average effect of *A* is given by as the average of Equation 19, 20, 21 & 22 (Antony, 2003b, 2003d).

$$A = \frac{1}{4n}[(a - (1)) + (ab - b) + (ac - c) + (abc - bc)]$$
Equation 8

By rearranging the terms, the effect of all factors was calculated as:

$$A = [a + ab + ac + abc - (1) - b - c - ac]/4n$$
Equation 9

$$B = [b + ab + bc + abc - (1) - a - c - ac]/4n$$
Equation 10

$$C = [c + ac + bc + abc - (1) - a - b - ac]/4n$$E quation 11

Statistical Analysis

The DoE analytical tools to understand the main effects and interaction effects of the studied factors include the main effect, interaction, pareto, cube, normal probability, residual, and response surface plots as well as the building of regression models using the DoE software, Minitab® 19 (Minitab Limited, United Kingdom) (Antony, 2003a, 2003b, 2003d).

RESULTS AND DISCUSSION

The Quality-by-Design (Q-b-D) framework for innovative pharmaceutical development forms the integral component of Process Analytical Technology initiative of the Food and Drug Administration (FDA) and International Council of Harmonization (ICH) for the technical requirement of medicines for human use (ICH Q8, 2009). Under the context of the current regulations, understanding the complex interactions of Critical Material Attributes, Critical Process Parameters, and Critical Quality Attributes are important in the chemical engineering of novel excipients and formulation development of pharmaceutical dosage forms (ICH Q8, 2009; Yu *et al.,* 2014; Badawy *et al.,*2019).In this study, a

2x3 full factorial design was applied to understand the impact of material and process parameters affecting the tensile strength of newly engineered coprocessed diluents intended for direct compression manufacturing.

Main Effect Plots

The main effects plots provide the sign and magnitude of the mean tensile strength at each level of the studied factors. The sign (low or high) tells the direction of the mean response. Based on factor effects (Figure 4), tensile strength increases at low concentrations of magnesium stearate, and low tumbling speed, but diminished at low setting of mixing time. Conversely, for mixing time the effect was greater at the high setting.

Interaction Plots

The various interaction plots (Figure 5), depicted the mean response of two factors at all possible combinations. This is a useful plot that tells the synergism or antagonism of a combination of two factors. The non-parallel lines between lubricant concentration and tumbling speed as well as tumbling speed versus mixing time indicated antagonistic interaction between the subset of factors. Synergistic interaction occurred where the line plots appeared in parallel. This corresponds to lubricant concentration versus mixing time, and tumbling speed versus lubricant concentration.

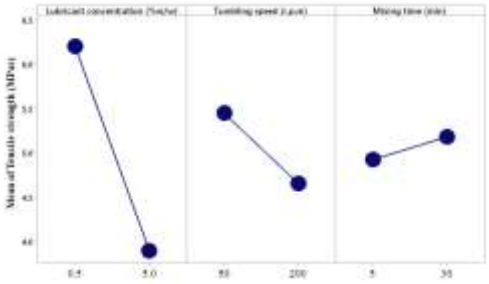

Figure 4: Main effects plots for tensile strength.

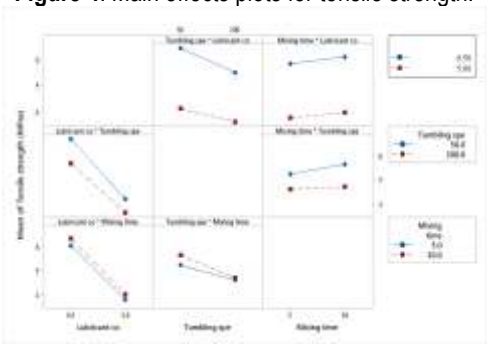

Figure 5: Interaction plots of factors.

Cube Plot

Cube plot shows the mean tensile strength at all possible combinations of process parameters. The fitted means shown in the cube plot were derived from the predicted values of the fitted model. From the design matrix, the order of mean tensile strength can be ranked as $\sigma_7 > \sigma_8 > \sigma_5 > \sigma > \sigma_3 > \sigma_4 > \sigma_2 > \sigma_1$ (Figure 6). This result has shown that the maximal tensile strength was attained when magnesium stearate and tumbling speed were kept at low levels while mixing time was set at a high level. The lowest tensile strength was obtained at high level of all factors. The cube plot is represented in Table 3 for simplicity.

Table 3: Mean tensile strength at each experimental run.

RUN	RUN LABEL	MEAN TENSILE STRENGTH, σ *(MPa)*
1	*abc*	$\sigma_1 = 3.60129$
2	*ab*	$\sigma_2 = 3.64470$
3	*ac*	$\sigma_3 = 4.42008$
4	*a*	$\sigma_4 = 3.92883$
5	*bc*	$\sigma_5 = 5.81006$
6	*b*	$\sigma_6 = 5.56781$
7	*c*	$\sigma_7 = 6.88873$
8	*1*	$\sigma_8 = 6.55315$

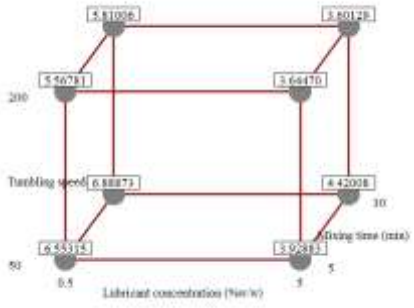

Figure 6: Cube plot for tensile strength (in MNm^{-2}).

Pareto Plot

The pareto chart is a useful tool that indicates the factors or their combinations that are critical to the studied response. Figure 7 indicated that lubricant concentration and tumbling speed were the most important factors determining tensile strength.

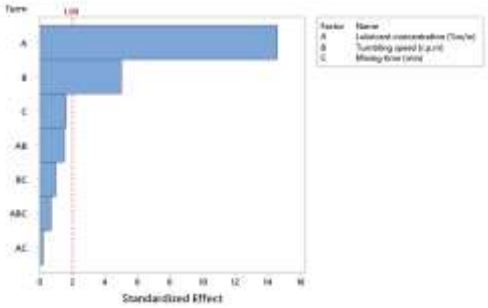

Figure 7: Pareto chart of the standardized effects (response is tensile strength in MNm^{-2}), α = 0.05).

Contour Plots

The contour plots are response surface plots that are used for establishing desirable response values and processing conditions. The contour plot shows the response surface as a 2-D plane where all interconnected points possess constant tensile strength (Figure 8-10). The shape and linearity of the contour plot are determined by the order of the regression model and

the terms in the model. For the first-order regression model, the contour lines appeared straight when it only contained the main effects (with no interactions). Curved contour lines are obtained when interaction effects are present in the model. Second-order regression model furnishes elliptical contour lines.

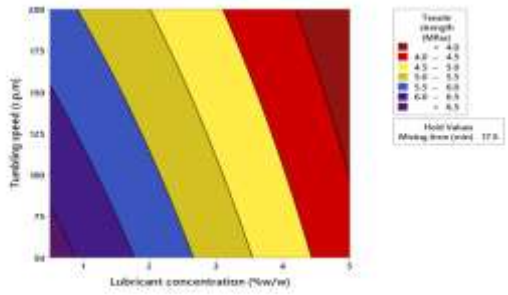

Figure 8: Contour plot of tensile strength vs tumbling speed, and lubricant concentration

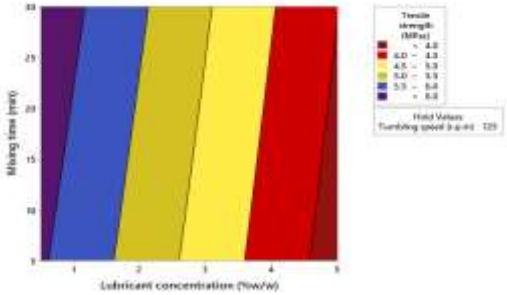

Figure 9: Contour plot of tensile strength vs mixing time, lubricant concentration.

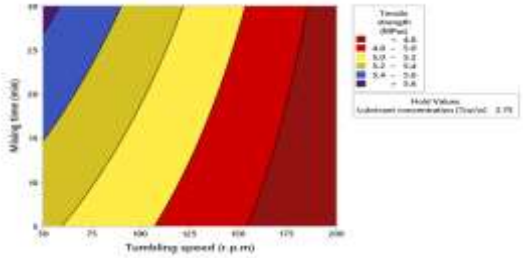

Figure 10: Contour plot of tensile strength vs mixing time, tumbling speed.

In direct compaction tablet manufacturing ingredients are blended with lubricants to facilitate smooth ejection of tablets from the die cavity of multi-station tablet presses. However, the rate and extent of the mixing process with alkaline stearate lubricants are impactful variables on the downstream CQAs such as the tensile strength of the tablets. For novel coprocessed diluents, lubricant sensitivity is a critical preformulation parameter that must be critically evaluated. The novel coprocessed excipient has been designed with required mechanical functions to suit the direct compression of tablets (Salim *et al*., 2022), there was no study yet to critically evaluate its lubrication properties. Consequently, the multidimensional interaction between CMAs, CPPs, and CQAs calls for a carefully designed and executed DoE to aid understanding of the criticality and interaction pattern of the parameters to furnish optimal conditions for successful tableting (Hebbink *et al.*, 2023). The sensitivity of powder systems to alkaline stearate lubricants has been shown to significantly lower the tensile strength of tablets. This study integrated multivariate factor settings to understand their impact on the tensile strength of the novel coprocessed diluent.

The model describing the tensile strength from the multidimensional interaction of the factors is given from the regression model for two-level factors in Eq. 12.

$$\sigma = \sigma_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 + \in$$

Equation 12

where, σ_0 is the mean tensile strength, $\beta_1, \beta_2, \beta_3 \ldots \ldots \beta_{23}$ are regression coefficients, and $\in$ is an error term. Substituting, the coded units, the generated regression equation was of the form:

$$\sigma = 7.133 - 0.649(A) - 0.00703\ (B) + 0.0133\ (C) + 0.001170\ (A) * (B) + 0.00269\ (A) * (C) - 0.000012\ (B) * (C) - 0.000026\ (A) * (B) * (C)$$

Equation 13

where *A, B,* and *C* are the lubricant concentration, tumbling speed of the double cone mixer, and mixing time, respectively.

From the observed cube plot (Figure 6), the novel co-processed excipient demonstrated optimal tensile strength ranging from 3.60 to 6.89 MPa. We can understand that in the current study, the main significant single-factor effect was determined by lubricant concentration followed by tumbling speed. The mixing time did not cross the standardized effect line (1.99) beyond which a significant effect is recognized at α=0.05. This study therefore indicated that the observed reduction in tensile strength was non-time dependent but significantly dependent on oscillations in lubricant concentration and tumbling speed.

The deleterious effect of magnesium stearate on plastic-deforming materials manifests as diminished tensile strength due to the formation of monomolecular films of hydrophobic surfaces which form weak bonds during compaction and consolidation (Wang *et al.,*2010; Li and Wu, 2014). This inherent material property can be linked to the composition of the coprocessed diluent. Up to 80.75% of the coprocessed composite was dominated by α-lactose monohydrate which deforms by fragmentation creating clean surfaces for bonding with other structural components of the composite during compaction cycles (Özalp *et al.,* 2020). The ability of the coprocessed composite to exhibit high tensile strength could also be linked to the synergistic impact of coprocessing which is a particle engineering strategy for amplifying the mechanical performance of tablet manufacturing excipients (Li *et al.,* 2017; Salim *et al.,* 2018, 2021).

It should be noted that, while the tensile strength of the novel coprocessed excipient could be considered moderately stable to the deleterious effect of the hydrophobic alkaline stearate, this generalization should be cautiously implemented given the stochastic behaviour of pharmaceutical powder systems. The current study is limited to placebo compacts of the novel α-lactose-starch orodispersible composite. Further investigations are recommended using model active pharmaceutical ingredients with divergent fragmentation and deformation physics to corroborate existing findings and to simulate the potential industrial tablet manufacturing applications of the diluent.

CONCLUSIONS

The tensile strength of placebo tablets produced from the novel engineered α-lactose-starch composite using Single-Punch Tablet Press was dependent on the combined effects of magnesium stearate concentration, tumbling speed of a double cone mixer, and the duration of mixing. Hence, these factor settings should be well optimised in future tablet formulation designs to manufacture tablets with optimal tensile strength.

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