Salim *et al.*
Bulletin of the National Research Centre (2022) 46:173
https://doi.org/10.1186/s42269-022-00860-7

Bulletin of the National Research Centre

RESEARCH Open Access

A study on the effect of biconvex compact shape factors on prediction of dilution potential from tensile strength–compaction force data of coprocessed diluents

Ilyasu Salim[1*], Adeniji Kehinde Olowosulu[2] and Abdulrahman Abdulsamad[2]

Abstract

Background: The purpose of this research was to compare the effect of shape factors of biconvex compacts on prediction of dilution potential from polynomial regression models of area ratio-mass fraction data of novel α-lactose monohydrate-starch orodispersible diluent (α-LSOD) and StarLac®. Ibuprofen-diluent blends were compacted between 4.98 and 29.89 kN. Given the biconvex round compact dimensions (t = axial thickness, w = central cylinder thickness, and d = diameter), tensile strength was computed as $\sigma_{\text{biconvex}} = \Phi\frac{F}{\pi dt}$, where F is the breaking force. The shape factor (Φ) was defined as $\left[\frac{t}{2d}\right]^{-1}$, $\left[\frac{0.14t}{d}+\frac{0.36w}{d}\right]^{-1}$, $\left[10/\left[\left(\frac{2.84t}{d}\right)-\left(\frac{0.126t}{w}\right)+\left(\frac{3.15w}{d}\right)+0.01\right]\right]$ for Podczeck (Φ_{Pz}), Shang (Φ_{Sh}), and Pitt (Φ_{Pt}) models, respectively. Area under the curve (AUC) was obtained by second-order polynomial fitting of the tensile strength–compaction force curve followed by integration of the quadratic regression equation between the two compaction force limits. The AUC of each powder system was normalised with the AUC of ibuprofen-free powder to obtain area ratio (AR). The AR was plotted against mass fraction of ibuprofen, and the curvilinear data was fitted by third-order polynomial fitting. Dilution potential was obtained from the regression equation by back extrapolation to zero area ratio.

Results: Tukey's multiple comparison test indicated statistically significant differences between the three shape factors ($p < 0.001$). The shape factors Φ_{Sh} and Φ_{Pt} were higher than Φ_{Pz} by a factor of 2.4 and 1.2, respectively. The quadratic regression model sufficiently explained the observed relationship between tensile strength and compaction force as indicated by the coefficient of determination whose values ranged between 0.9344 and 0.99843 and 0.93725 and 0.99812 for α-LSOD and Starlac®, respectively. Dilution potential was predicted as $AR = B_3x^3 + B_2x^2 + B_1x + c$, where x and its coefficients are ibuprofen mass fraction and regression constants, respectively. The predicted dilution potential of the three tensile strength models were within a close range of $\approx 110.93 \pm 1.02$ and $\approx 116.02 \pm 0.62$ for both α-LSOD and StarLac®.

Conclusions: This study suggests the adoption of the simplest Podczeck model given a biconvex round punch tooling and highlights the suitability of polynomial regression to predict dilution capacity from nonlinear area ratio-mass fraction data.

*Correspondence: silyasu.pht@buk.edu.ng

[1] Department of Pharmaceutics and Pharmaceutical Technology, College of Natural and Pharmaceutical Sciences, Bayero University, PMB 3011, Kano, Nigeria
Full list of author information is available at the end of the article

Keywords: Coprocessed diluents, Dilution potential, Mechanical strength, Tensile strength, Shape factors, Biconvex tablets, Polynomial regression

Background

Tablets are versatile solid drug delivery systems obtained by compacting blends of therapeutic principles and excipients into compacts of defined geometry (Armstrong 2007). Depending on the type of punch and die tooling, tablets can be manufactured in compaction presses into various shapes including oval, capsule (oblong), flat round, biconvex round, bullet, barrel, arrow, triangle, modified triangle, square, pentagon, pillow, rhomb, heart, half moon, and so forth (Bauer-Brandl 2007; Pitt and Heasley 2013; Osamura et al. 2017; Yohannes and Abebe 2021). Tablet shape is an important tool for product differentiation and identification (Notenboom et al. 2017). Shaping of tablets to ease swallowing is also clinically meritorious to geriatric, paediatric, and dysphagic patients (Wan et al. 2015; Fields et al. 2015).

The mechanical strength of tablets is a critical quality attribute (CQA) that defines the success of tablet formation and use (Thoorens et al. 2014). Additionally, mechanically stronger tablets are necessary for downstream manufacturing operations such as coating, polishing, and packaging. Throughout its shelf life, tablets are required to be sufficiently strong to withstand transportation and patient handling (Alderborn and Frenning 2017; Yohannes and Abebe 2021). For pharmaceutical manufacturing in-process quality control, tensile strength is used as a measure of mechanical strength of compacts. Tensile strength is defined as the maximum bearable stress prior to fracture and is computed from the tablet dimension and breaking force (Pitt and Heasley 2013; Sabri et al. 2018).

Practically, a tablet is a heterogeneous mixture of several blends of powders in a compressed state. Accordingly, the mechanical strength of tableting diluents (pharmaceutical powders for tablet manufacturing) can be accurately expressed in terms of dilution potential. Dilution potential, or dilution capacity, is a property that measures the ability of a diluent to retain optimal mechanical strength when blended with other powder ingredients (Habib et al. 1996). In designing novel diluents for direct compaction application, dilution potential analysis constitutes a critical preformulation study aimed at validating direct compression propensity (Jivraj et al. 2000; Mirani et al. 2011; Thoorens et al. 2014). More precisely, the dilution propensity quantitatively expresses the maximum amount of active pharmaceutical ingredient that can be incorporated in a given tablet formulation to retain optimal tensile strength (Kuentz and Leuenberger 2000; Haruna et al. 2020).

Experimental determination of dilution potential involves tensile strength measurement as a function of applied compaction forces. The compaction profile of a given powder system in binary blends of a diluent and poorly compactible active pharmaceutical ingredient is analysed (Minchom and Armstrong 1987; Habib et al. 1996). Measurement of tensile strength of tablets with simple shapes such as cylinder (round flat faced) is quite simple and straight forward. In pharmaceutical technology, the Brazilian compression test is commonly used to measure the tensile strength of round flat-faced compacts (Mohammed et al. 2006). Newton and Fell 1970 has defined tensile strength of this type of tablets as:

$$\sigma = \frac{2F}{\pi d t} \tag{1}$$

where σ—tensile strength of round flat-faced tablets; F—diametral breaking force; d—compact diameter; t—compact thickness.

Equation 1 is quite applied in early formulation development where simple round flat-faced punch tooling is often utilised to study dilution potential. However, as the punch and die tooling deviate from round flat-faced shapes during technology transfer, the complexity to compute tensile strength increases (Yohannes and Abebe 2021). The true mechanical behaviour of shaped tablets calls for consideration of their divergent dimensions. For biconvex tablets, such as those produced in this experiment (Fig. 1a), the general expression for computation of tensile strength takes into account the shape factor (Φ) of the tablet as given by Eq. 2 (Razavi et al. 2015).

$$\sigma_{\text{biconvex}} = \Phi \frac{F}{\pi d t} \tag{2}$$

At least four experimentally determined equations for the estimation of Φ was independently derived in order to describe the relationship between compact dimension and tensile strength (Pitt et al. 2011; Shang et al. 2013; Podczeck et al. 2013; Razavi et al. 2015). The complexity to compute tensile strength of biconvex tablets would be better appreciated considering the shape factors expressed in Eqs. 3, 4, and 5.

Coprocessed diluents are combinations of two or more pharmaceutical excipients specially designed to offer superior compaction performance relative to the

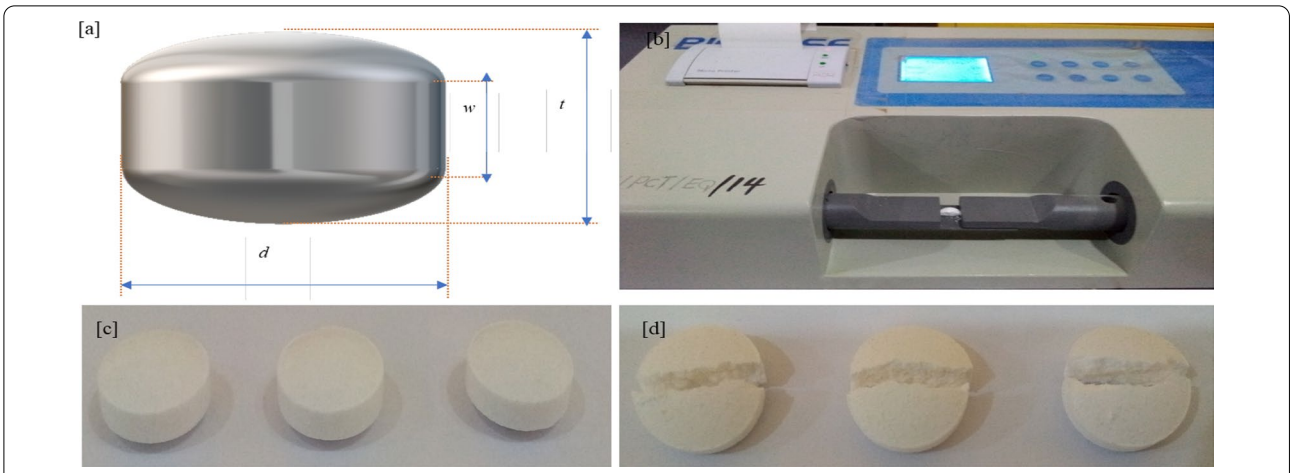

Fig. 1 Schematic presentation of biconvex tablet dimensions (**a**). *d*: compact diameter, *t*: total axial thickness, *w*: compact wall height (central cylinder thickness). Digital tablet hardness tester (Model THT-2, Biobase, India) (**b**). Samples of experimental biconvex compacts (**c**). Diametral fracture pattern of orodispersible α-lactose-starch diluent compacts (**d**)

individual parent constituents or their physical blends (Gohel and Jogani 2005; Li et al. 2017; Salim et al. 2018, 2021). In addition, orodispersible coprocessed diluents have extended applications in formulation of orally disintegrating tablets for enhancing buccal dispersion and facilitating swallowing in dysphagic patients (Aguilar-Díaz et al. 2012; Chinwala 2020). For these newer-generation excipients, it is critically important to have sound understanding of their mechanical properties. Moreover, given the recent recorded advances in elucidation of microstructural and mechanical properties of composite materials for metallurgical engineering applications (Farag et al. 2016; Reda et al. 2018, 2022; Zohdy et al. 2021), continuous and complimentary efforts are needed in critical analysis of mechanical behaviour of novel composite particles engineered for pharmaceutical product manufacturing applications.

The purpose of this research was therefore to critically analyse the dilution potential of newly engineered directly compactible α-lactose-starch orodispersible coprocessed diluent (α-LSOD) from tensile strength–compaction force profiles generated using biconvex round-shaped punch tooling. Firstly, the research was aimed at comparing the complexity of computing tensile strength of biconvex compacts according to the three independent equations postulated by Shang et al. 2013; Pitt and Heasley 2013; Podczeck et al. 2013. The second goal was geared towards application of a modified Minchom and Armstrong technique to estimate the dilution capacity from integrated area under the tensile strength–compaction force curves of the α-LSOD diluent relative to a reference coprocessed diluent for direct compression (StarLac®). This was followed by third-order polynomial modelling of area ratio-mass fraction curvilinear data and back-extrapolation to zero area ratio using the generated regression equation to predict dilution capacity. The ultimate goal was to arrive at the simplest tensile strength computation model to predict the dilution capacity of the coprocessed diluents given a complicated biconvex punch tooling.

Materials

StarLac® (75% α-lactose monohydrate, 15% Maize starch), α-lactose monohydrate (Tablettose 100®, Lot No: L104292618, Meggle GmbH & Co. KG, Germany), ibuprofen, maize starch (CDH Chemicals, India), and sodium starch glycolate (Batch No: 41110174119, JRS Pharma, Rosenberg, Germany). All excipients are of pharmaceutical grade.

Methods

Engineering of the new directly compactible orodispersible α-lactose-starch orodispersible diluent (α-LSOD)

The coprocessing formula comprises of sodium starch glycolate (SSG) (5%), α-lactose monohydrate (80.75%), and maize starch (14.25%). SSG was cold hydrated in 200-mL distilled water and mixed with partially pregelatinized starch paste in a plastic drum. α-lactose monohydrate was mechanically incorporated into the SSG-starch paste mixture using geometric dilution. The α-LSOD wet mass was screened through 1-mm sieve aperture followed by convective drying at 60–70 °C for 18 h. The dried coprocessed composite was comminuted using ball mill operated on All Purpose Equipment ™ (Orchid Scientific, India) at 200 r.p.m for 10 min. The size reduced powder was fractionated using nest of sieves vibrated for 10 min over Ro-Tap® test sieve shaker (W.S Tyler Mentor, Ohio, USA). Coarser

particle dimensions (>500 μm) and fines (<50 μm) were separated from the particle size distribution by mechanical sieving.

Compaction of powders to form biconvex compacts

Homogeneous binary powder blends of α-LSOD at 0%w/w, 20%w/w, 30%w/w, 40%w/w, and 100%w/w ibuprofen mass fractions were achieved using rotating cube blender operated on All Purpose Equipment (AP-01 Plus, Orchid Scientific, India) at 100 r.p.m for 10 min. Biconvex round compacts were formed by compressing 500 ± 5 mg powder samples in manually operated single station tablet press (model NP-RD10, Natoli Engineering Company, Missouri, USA) equipped with 12-mm upper and lower convex (cup)-shaped punch tooling. Each powder sample was compressed at 4.98, 9.96, 14.95, 19.92, 24.91, and 29.89 kN at a dwell time of 30 s. The punch and die surfaces were sufficiently lubricated with 2% w/v magnesium stearate in acetone. Ejected compacts were stored for 24 h prior to evaluation to allow for sufficient elastic recovery and prevent false tensile strength values. The same procedure was adopted for generation of compaction data using StarLac® as diluent.

Measurement of tensile strength of biconvex tablets

Tensile strength of the biconvex compact ($\sigma_{biconvex}$) was determined according to the protocol described in the United States Pharmacopoeia (USP 41-NF 36 2018). Digital tablet dimension tester was used for the measurement of the compact dimensions *d*, *w*, and *t* (Fig. 1a). Diametral breaking force (*F*) was measured as the load required to trigger diametral fracture determined by stationing a compact between two parallel platens of a digital hardness tester (Model THT-2, Biobase, India) (Fig. 1b). $\sigma_{biconvex}$ was calculated according to Eq. 2. The value of Φ was computed according to the three models described independently from previous works as given by Eqs. 3, 4, and 5, respectively (Shang et al. 2013; Pitt and Heasley 2013; Podczeck et al. 2013).

$$\Phi_{Pz} = \left[\frac{1}{\left(\frac{t}{2d}\right)}\right] \tag{3}$$

$$\Phi_{Sh} = \left[\frac{1}{\left[\left(\frac{0.14t}{d}\right) + \left(\frac{0.36w}{d}\right)\right]}\right] \tag{4}$$

$$\Phi_{Pt} = 10\left[\frac{1}{\left[\left(\frac{2.84t}{d}\right) - \left(\frac{0.126t}{w}\right) + \left(\frac{3.15w}{d}\right) + 0.01\right]}\right] \tag{5}$$

where Φ_{Pz}, Φ_{Sh}, and Φ_{Pt} denote the compact shape factors computed according to the described models. As shown in Fig. 1a, d is the compact diameter, *t* is the overall axial thickness, while *w* is the central cylinder thickness. Measurements were conducted on five randomly selected compacts from each compacted powder blends, and the mean tensile strength value was used for AUC calculations. Shape factors and tensile strength calculations were performed using Microsoft Excel Spreadsheet.

Computation of dilution potential from compaction data

The values of tensile strength were plotted against the range of applied compaction forces for each powder system. The tensile strength–compaction force data was fitted using second-degree polynomial fitting. The quadratic regression equation was integrated between the limits of 4.98 and 29.89 kN to calculate the AUC. The AUC of each of the powder system was normalised with that of 0% ibuprofen (100% coprocessed diluent) to obtain the area ratio. The area ratio was plotted against ibuprofen mass fraction (Minchom and Armstrong 1987; Habib et al. 1996; Kuentz and Leuenberger 2000). The area ratio-mass fraction curvilinear data was fitted by third-order polynomial fitting. Both integration and polynomial fittings were conducted using OriginPro, Version 2021b, OriginLab Corporation, Northampton, MA, USA. Using the generated polynomial regression equation, dilution capacity was obtained by back extrapolation to zero area ratio.

Shape factor variation at variable compaction forces within each ibuprofen mass fraction was analysed through one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test using GraphPad Prism version 5.01 for Windows, GraphPad Software, California, USA. Statistical significance was set at alpha level of 5%.

Results

Analysing the effect of Podzeck, Shang, and Pitt shape factors on magnitude of tensile strength

The sample data shown in Table 1 reflects drug-diluent binary mixture compacted at variable compaction forces but with the same punch tooling. The tested validity of Pitts model has shown a $w/d \geq 2.0$ which was above the theoretical minimum acceptable value of 1.0. The shape factors decrease with increasing values of *d*, *t*, and *w*. Previous studies found only slight differences between the shape factors, however with Φ_{Sh} being slightly higher (Yohannes and Abebe 2021). Comparing the shape factors for the three models in this study, it was observed

Table 1 Sample data indicating trend of shape factors in the experiment

Compaction force (kN)	*d* (m)	*t* (m)	*w* (m)	Φ_{Pz}	Φ_{Sh}	Φ_{Pt}	$\frac{\Phi_{Sh}}{\Phi_{Pz}}$	$\frac{\Phi_{Pt}}{\Phi_{Pz}}$
4.98	0.0122	0.00463	0.00263	5.253	12.413	6.448	2.363	1.227
9.96	0.0123	0.00485	0.00277	5.068	11.955	6.172	2.359	1.218
14.95	0.0121	0.00491	0.00274	4.929	11.718	6.061	2.377	1.230
19.92	0.0121	0.00488	0.00254	4.967	12.081	6.363	2.432	1.281
29.89	0.0121	0.00481	0.00259	5.031	12.103	6.332	2.406	1.259
Mean	0.0122	0.00482	0.00265	5.050	12.054	6.275	2.387	1.243
SD	8.94E−05	1.10E−04	9.81E−05	1.26E−01	2.52E−01	1.56E−01	3.10E−02	2.62E−02

Φ_{Pz}, Φ_{Sh}, Φ_{Pt}: Shape factors according to Podczeck et al. (2013), Shang et al. (2013), Pitt and Heasley (2013), respectively. *d* diameter, *t* axial tablet thickness, central cylinder thickness, *SD* standard deviation

that Φ_{Pt} was slightly higher than Φ_{Pz}, but Φ_{Sh} differ significantly to as twice their values. Tukey's multiple comparison test indicated statistically significant differences between the three shape factors ($p < 0.05$) (Table 2). The variability can be appreciated when both Φ_{Sh} and Φ_{Pt} were normalized with Φ_{Pz}. The shape factors Φ_{Sh} and Φ_{Pt} were higher than Φ_{Pz} by a factor of 2.4 and 1.2, respectively. Similar trend holds for all other compaction data.

Based on Eq. 2, the tensile strength was directly proportional to the shape factor (Φ). It then follows that the term $(\frac{F}{\pi d^2})$ was constant in all the three models, hence the shape factor was regarded as the main determinant of variability in the values of the tensile strength measured at each compaction force. Given a biconvex compact with the experimentally determined dimensions (Table 1), it can be deduced that the shape factors were of the order $\Phi_{Sh} > \Phi_{Pt} > \Phi_{Pz}$. Consequently, for all experimental runs, the magnitude of the calculated tensile strength was of the order Shang > Pitt > Podzeck, respectively. Accordingly, the tensile strength calculated using the model by Shang et al. 2013 was approximately twice that obtained via Pitt and Heasley 2013 and Podczeck et al. 2013. Similar trend was observed from compaction data of StarLac®. However, the values of the tensile strength of compacts from StarLac®-ibuprofen blends were similar indicating equivalent tabletability compared to α-LSOD diluent.

It is noteworthy that although the magnitude of the calculated tensile strength, AUCs, and area ratios varies considerably between Podzeck, Shang, and Pitt models, the predicted dilution capacities were similar as presented subsequently.

Quadratic regression models and Integrated Area Under the Curve

The tensile strength–compaction force profiles and fitted quadratic regression models for each set of powder system are presented in Figs. 2, 3, 4, 5, 6 and 7 for α-LSOD and Starlac®, respectively. Since the tensile strength varied appreciably with ibuprofen loading and compaction forces, the curves were not superimposable. Lower compaction forces generally resulted in lower tensile strength. To predict the response variable, which is the tensile strength of the biconvex tablets ($y = \sigma_{biconvex}$), the quadratic regression model was described by the general expression:

$$y = B_1 x^2 + B_2 + c \tag{6}$$

where x variable is the compaction force, while the coefficients B_1, B_2, and c are regression constants.

The quadratic regression models sufficiently explained the observed relationship between the tensile strength and compaction forces as indicated by the coefficient of determination (R-squared), whose values ranged between 0.9344 and 0.99843 and 0.93725 and 0.99812 for α-LSOD diluent and Starlac®, respectively. By integrating between the limits of the compaction forces (4.98 to 29.89 kN), the AUC of each powder system was described by:

Table 2 Multiple comparison test for a sample compaction data

Tukey's multiple comparison test	Mean difference	Level of significance at $p < 0.05$	95% Confidence interval of difference
Podczeck versus Shang	−7.004	Yes	−7.318 to −6.690
Podczeck versus Pit	−0.9500	Yes	−1.264 to −0.6360
Shang versus Pit	6.054	Yes	5.740 to 6.368

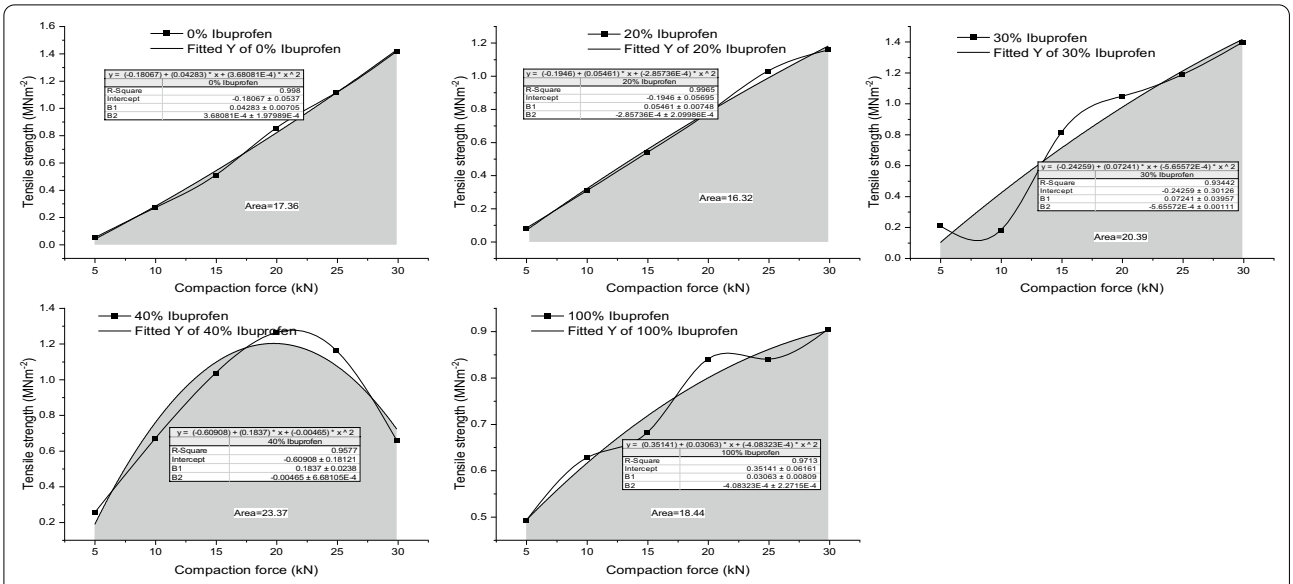

Fig. 2 Area under the tensile strength–compaction force curve for α-lactose-starch orodispersible diluent. Tensile strength computed by Podczeck et al. (2013) model

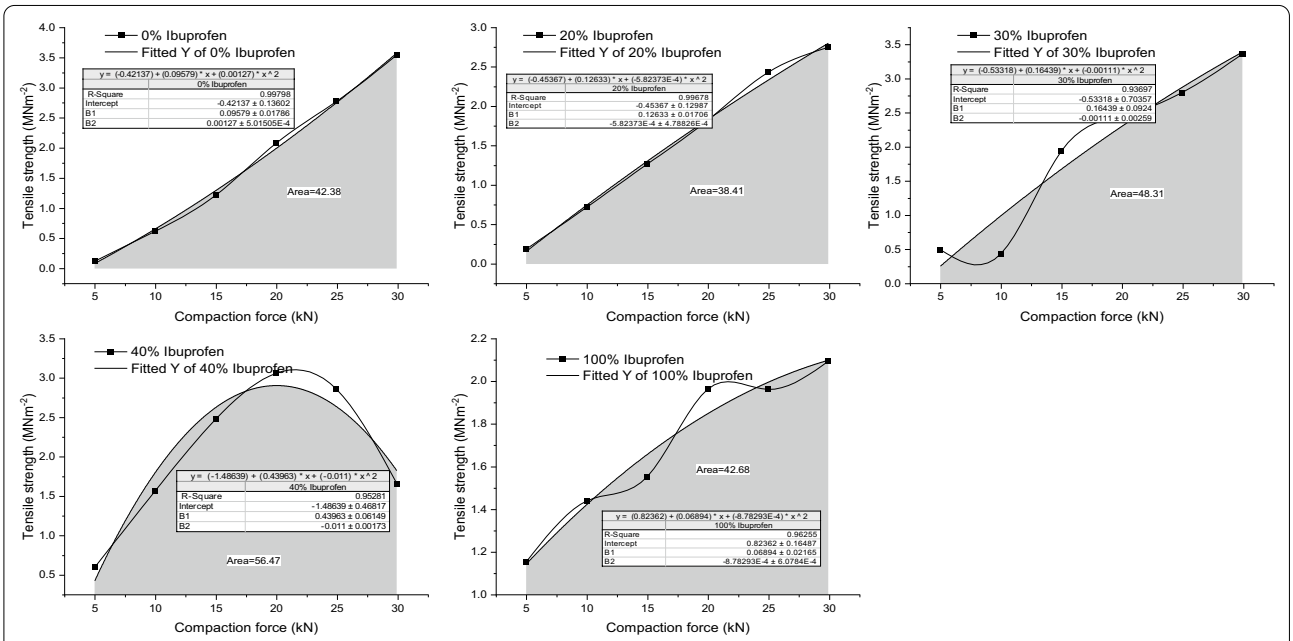

Fig. 3 Area under the tensile strength–compaction force curve for α-lactose-starch orodispersible diluent. Tensile strength computed according to the Shang et al. (2013) model

$$\mathrm{AUC} = \int_{4.98}^{29.89} \left(B_1 x^2 + B_2 x + c\right) \mathrm{d}x \tag{7}$$

The magnitude of this area reflects the extent of densification and formation of coherent mass as result of interparticle bonds. Like the tensile strength values, the AUCs increased in the order Shang > Pitt > Podczeck. The observations summarized in Table 3 compared the mechanical properties of the two coprocessed excipients. From the integrated AUC for Podczeck, Shang and Pitt models, it can be inferred that both diluents possess similar deformation physics. The observed trends in the AUCs have explained the following mechanical performance of the diluents.

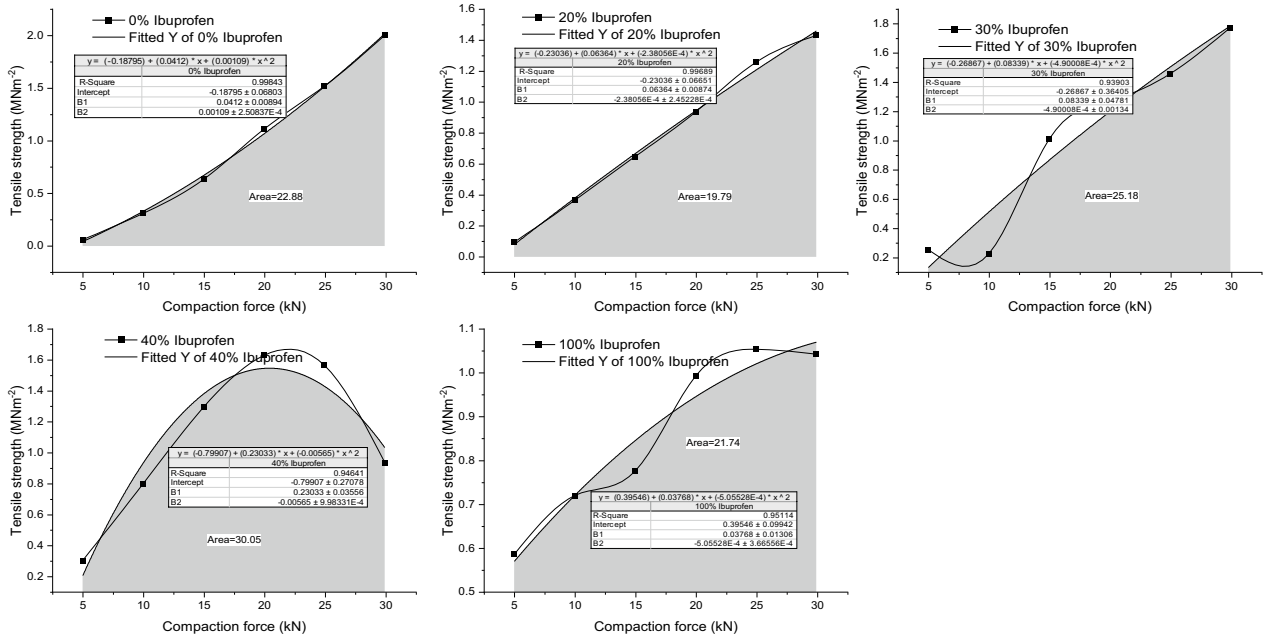

Fig. 4 Area under the tensile strength–compaction force curve for orodispersible α-lactose-starch diluent. Tensile strength computed according to the Pitt and Heasley (2013) model

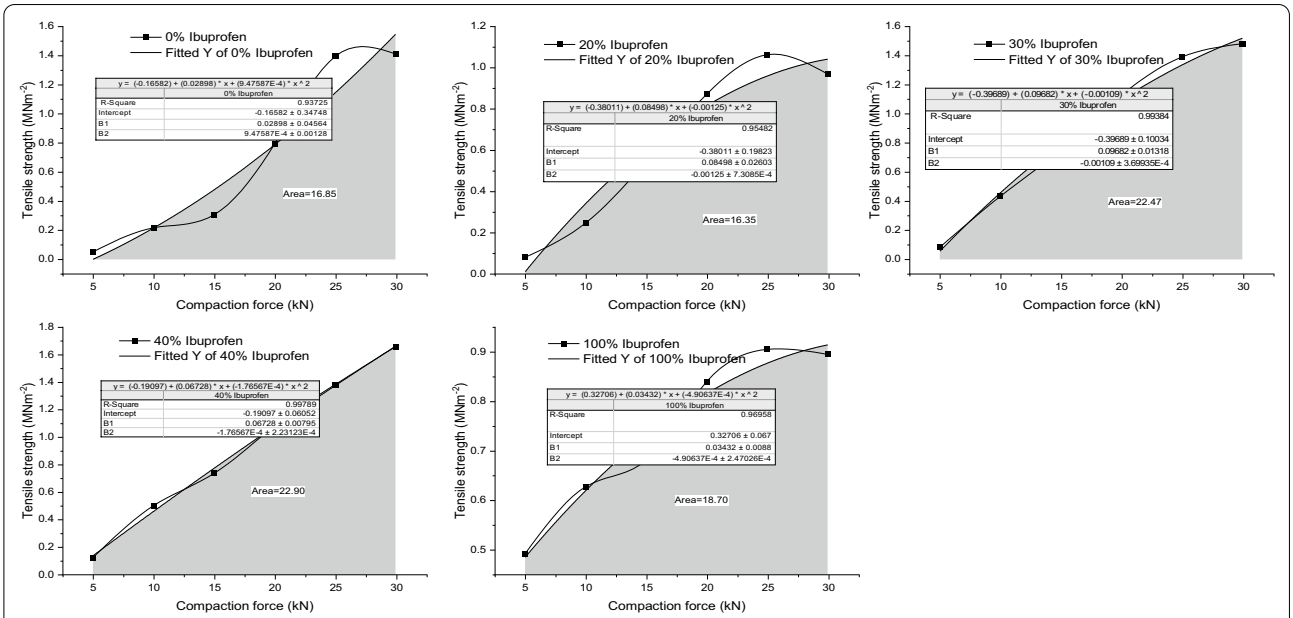

Fig. 5 Area under the tensile strength–compaction force curve for StarLac®. Tensile strength computed according to the Podczeck et al. (2013) model

(i) $AUC_{100} > AUC_0$

AUC_{100} and AUC_0 describe the mechanical strength of pure ibuprofen particles and pure coprocessed diluents, respectively. This signifies that pure ibuprofen is mechanically stronger than the pure coprocessed diluents.

(ii) $AUC_{20} < AUC_0 < AUC_{100}$.

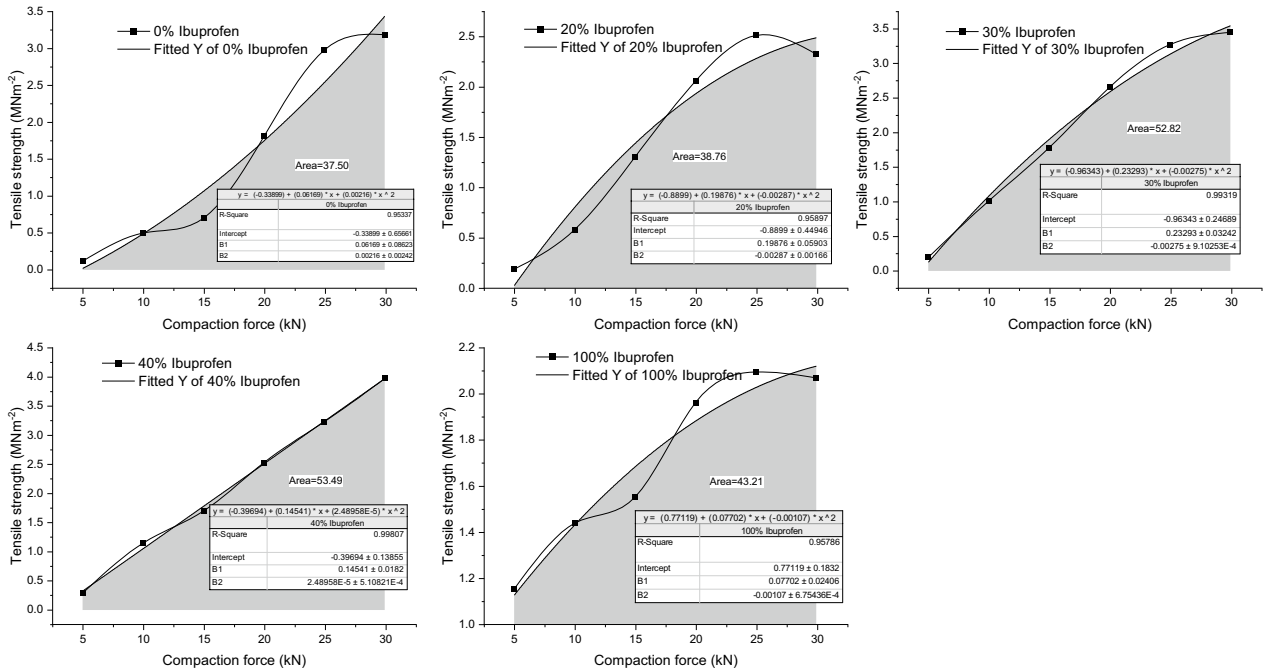

Fig. 6 Area under the tensile strength–compaction force curve for StarLac®. Tensile strength computed according to the Shang et al. (2013) model

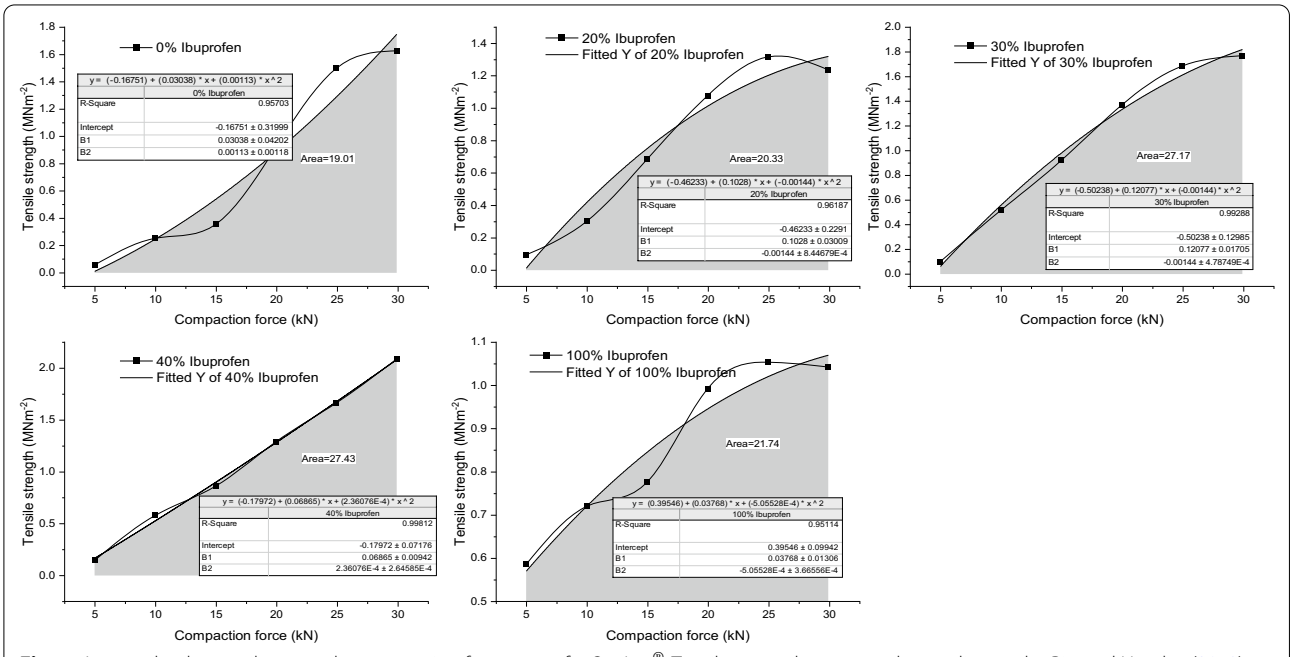

Fig. 7 Area under the tensile strength–compaction force curve for StarLac®. Tensile strength computed according to the Pitt and Heasley (2013) model

Table 3 Area under the tensile strength–compaction force profiles of the powder systems

Mass fraction (%w/w ibuprofen)	AUC code	AUC of α-LSOD (MPa/kN)			AUC of StarLac® (MPa/kN)		
		Podczeck model	Shang model	Pitt model	Podczeck model	Shang model	Pitt model
0	AUC_0	17.36	42.38	22.88	16.85	37.5	19.01
20	AUC_{20}	16.32	38.41	19.79	16.35	38.76	20.33
30	AUC_{30}	20.39	48.31	25.18	22.47	52.82	27.17
40	AUC_{40}	23.37	56.47	30.05	22.9	53.49	27.43
100	AUC_{100}	18.44	42.68	21.74	18.7	43.21	21.74

Pure coprocessed excipients were more compactible than binary blends at 20% ibuprofen, but less compactible than pure ibuprofen.

(iii) $AUC_{40} > AUC_{30} > AUC_{20}$

This implied that compaction strength increased as ibuprofen was increased suggestive of constructive (synergistic) compaction up to 40%.

(iv) $AUC_{100} < AUC_{40}$

Constructive compaction occurs where all ingredients contribute to the tensile strength of the compact. In contrast, destructive compaction infers significant depreciation of tensile strength in the presence of another component. At 40% ibuprofen mass fraction constructive compaction of the powder blends predominates over destructive compaction.

Discussion

The concept of powder dilution capacity can best be viewed as the dilution of the tensile strength of a given powder in the presence of another material of inferior, equivalent, or superior mechanical strength. In this research we focused on critical analysis of dilution capacity of novel diluent (α-LSOD) in the presence of ibuprofen powder.

Plotting the normalized AUC values (area ratio) as a function of ibuprofen mass fraction formed the basis of prediction of dilution capacity from nonlinear compaction data. The concept described by Minchom and Armstrong 1987 and later modified by Habib et al. 1996 was based on simple linear regression analysis of area ratio-mass fraction data followed by back extrapolation to zero area ratio.

In contrast, this study utilised third-order polynomial regression to predict the drug loading capacity. Polynomial regression is a special form of multiple linear regression that is employed to explain nonlinear relationship between an independent variable and a dependent variable (Ostertagová 2012; Angelini 2019). The polynomial regression model was applied to describe the curvilinear compaction pattern of the studied diluents. From the fitted data (Figs. 8 and 9), the following form of polynomial regression equations was derived for prediction of dilution potential.

$$y = B_3x^3 + B_2x^2 + B_1x + c \quad (8)$$

where y is area ratio, while all x coefficients and c are regression coefficients, with x being the mass fraction of ibuprofen.

The R-squared (R^2) shown in Figs. 8 and 9 indicates the appreciable robustness of the regression model in explaining the relationship between area ratio and mass fraction. Conventionally, $0 \leq R^2 \leq 1$ with $R^2 \geq 0.9$ indicating a very good explanation (Ostertagová 2012; Cheng and Shalabh 2014; Chicco et al. 2021). Conclusively, back-extrapolation to zero area ratio yields average predicted ibuprofen mass fractions of $\approx 110.93 \pm 1.02$ and $\approx 116.02 \pm 0.62$ for α-LSOD and StarLac®, respectively (Table 4).

In summary, the dilution capacities of both experimental (α-LSOD) and reference (StarLac®) coprocessed diluents have suggested appreciable ibuprofen loading capacities. Ibuprofen and the coprocessed excipients were compactible at all dilution ratios. This suggested that in the presence of ibuprofen, both substances synergistically contributed in interparticle bond formation. The observed mechanical profile of the compacts produced from these diluents could be attributed to multifunctional synergy imparted by coprocessed excipients (Bhatia et al. 2022). Constitutional similarities of α-LSOD and StarLac® contributed to similarities in their deformation physics and hence similar dilution capacities. Despite being a lactose-based coprocessed excipient, Starlac is less brittle (Özalp et al. 2020). In fact, earlier studies have shown that Starlac® deforms plastically with minimal elasticity, which implies high mechanical profile (Hauschild and Picker-Freyer 2004).

Conclusions

Quantification of drug loading capacities of pharmaceutical diluents as conceptualized by Minchom and Armstrong was derived from area under the curve of tensile strength–compaction force data. Unlike compaction simulators, non-automated acquisition of such data is

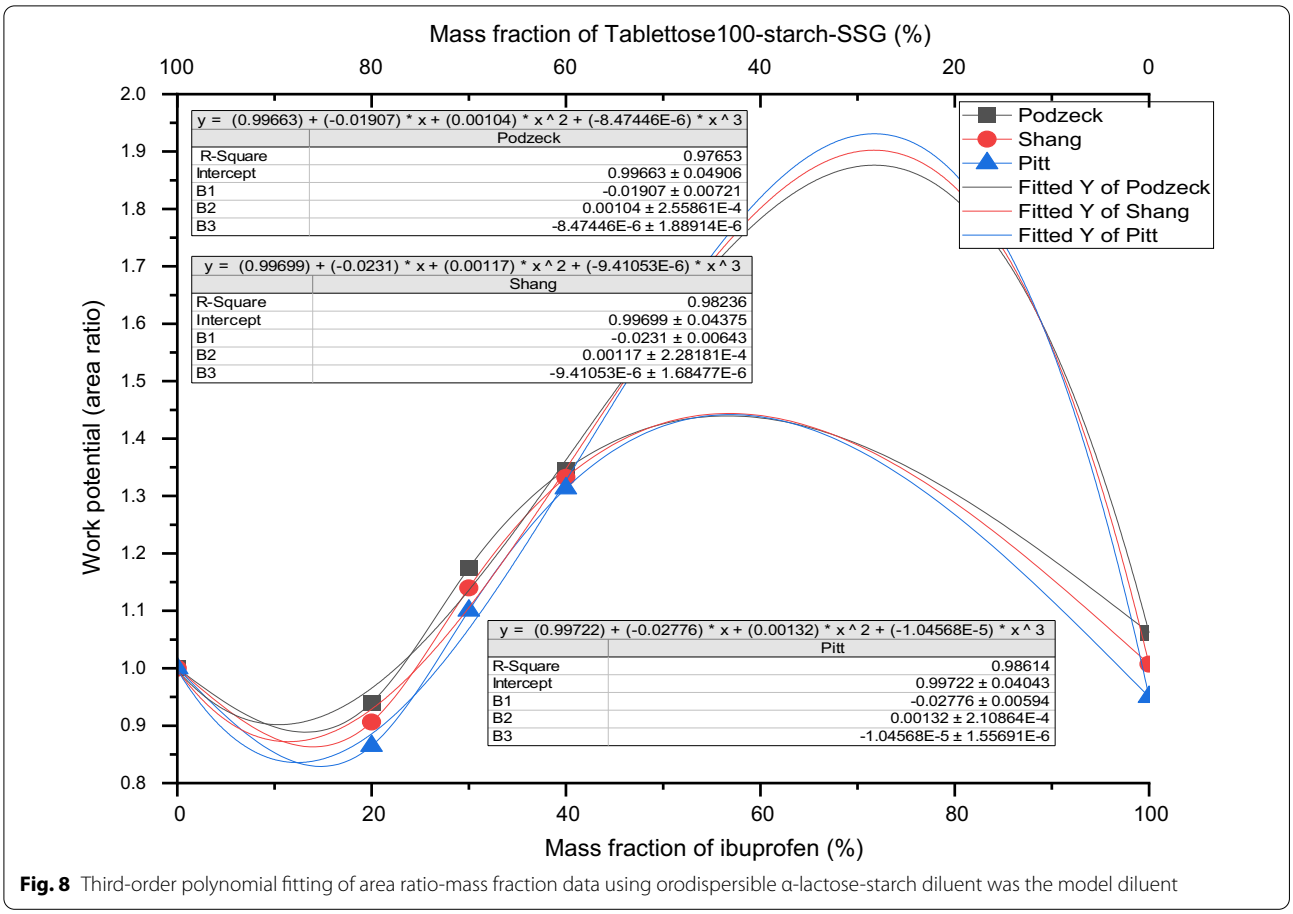

Fig. 8 Third-order polynomial fitting of area ratio-mass fraction data using orodispersible α-lactose-starch diluent was the model diluent

tedious and time-consuming. In scenarios where more complex punch shapes other than the more common round flat-faced tooling are used, tensile strength measurement is complicated given the intricacies of accounting for compact diameter (d), central cylinder thickness (w), and overall axial thickness (t). Accordingly, prediction of dilution potential from the tensile strength–compaction force data would be time-consuming. From simplistic view point, this study suggests the adoption of the simplest Podzeck model compared to the Shang and Pitt models given a biconvex round punch tooling.

This study further introduced polynomial regression analysis to model curvilinear data as complimentary to the original technique where simple linear regression was used to model linear association between area ratio-mass fraction data. Using the fitted third-order regression model, the average predicted dilution capacities of α-lactose-starch orodispersible coprocessed diluent (α-LSOD) and StarLac® obtained by extrapolation to zero area ratio were $\approx 110.93 \pm 1.02$ and $\approx 116.02 \pm 0.62$ ($R^2 > 0.9$). However, this study is limited to ibuprofen. Since pharmaceutical powder systems demonstrate broad-ranged anisotropic behaviours, we recommend similar studies using other moderately compressible model drugs and diluents to validate the current postulations.

Table 4 Estimated dilution potential of coprocessed excipients based on back extrapolation using polynomial regression equations shown in Figs. 8 and 9

Coprocessed excipient type	Tensile strength model	Dilution potential (%w/w ibuprofen)
α-LSOD	Podczeck	112.01
	Shang	110.80
	Pitt	109.98
StarLac®	Podczeck	115.39
	Shang	116.05
	Pitt	116.62

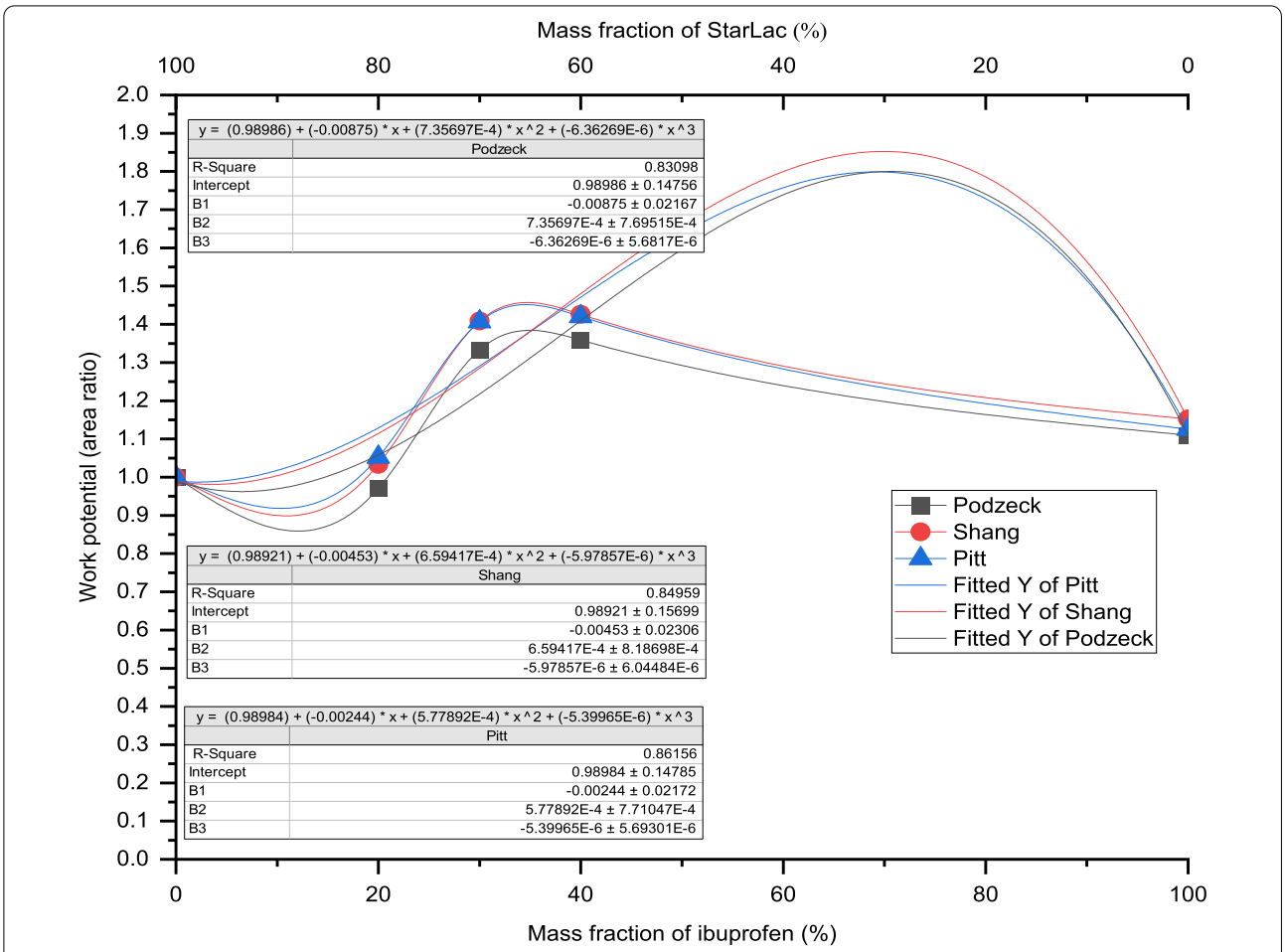

Fig. 9 Third-order polynomial fitting of area ratio-mass fraction data. StarLac® was the reference diluent

Abbreviations

α-LSOD: α-Lactose Monohydrate-Starch Orodispersible Diluent; ANOVA: Analysis of variance; AR: Area ratio; AUC: Area under the curve; CQA: Critical quality attribute; r.p.m: Revolution per minute.

Acknowledgements

The authors wish to sincerely appreciate the technical support offered during compaction experimentations by Mamuda Bappah Aliyu of the Department of Pharmaceutics and Pharmaceutical Technology, Gombe State University, Nigeria. We sincerely appreciate Meggle GmbH & Co. KG, Germany, for the gift of StarLac® and Tablettose100®. The gracious donation of Explotab® by JRS Pharma, Rosenberg, Germany, is equally appreciated.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SI, AKO, and AA. The first draft of the manuscript was written by SI, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded through the Academic Staff Training and Development of the Tertiary Education Trust Fund (2018 intervention), Federal Ministry of Education, Nigeria.

Availability of data and materials

The raw and processed data associated with this research can be obtained from the corresponding author on special request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author details

[1]Department of Pharmaceutics and Pharmaceutical Technology, College of Natural and Pharmaceutical Sciences, Bayero University, PMB 3011, Kano, Nigeria. [2]Department of Pharmaceutics and Industrial Pharmacy, Ahmadu Bello University, Zaria, Nigeria.

Received: 19 May 2022 Accepted: 5 June 2022
Published online: 15 June 2022

References

Aguilar-Díaz JE, García-Montoya E, Suñe-Negre JM et al (2012) Predicting orally disintegrating tablets formulations of ibuprophen tablets: an application of the new SeDeM-ODT expert system. Eur J Pharm Biopharm 80:638–648. https://doi.org/10.1016/j.ejpb.2011.12.012

Alderborn G, Frenning G (2017) Tablets and compaction. In: Aulton M, Taylor KMG (eds) Aulton's pharmaceutics: the design and manufacture of medicines, 5th edn. Elsevier, London, pp 517–563

Angelini C (2019) Regression analysis. Encycl Bioinform Comput Biol ABC Bioinform 1–3:722–730. https://doi.org/10.1016/B978-0-12-809633-8.20360-9

Armstrong NA (2007) Tablet manufacture by direct compression. Encycl Pharm Technol 6:3673–3683

Bauer-Brandl A (2007) Tooling for Tableting. In: Swarbrick J (ed) Encyclopedia of pharmaceutical technology, 3rd edn. Informa Healthcare, New York, pp 3782–3796

Bhatia V, Dhingra A, Chopra B, Guarve K (2022) Co-processed excipients: recent advances and future perspective. J Drug Deliv Sci Technol 71:103316. https://doi.org/10.1016/J.JDDST.2022.103316

Cheng CL, Shalabh GG (2014) Coefficient of determination for multiple measurement error models. J Multivar Anal 126:137–152. https://doi.org/10.1016/J.JMVA.2014.01.006

Chicco D, Warrens MJ, Jurman G (2021) The coefficient of determination R-squared is more informative than SMAPE, MAE, MAPE, MSE and RMSE in regression analysis evaluation. PeerJ Comput Sci 7:1–24. https://doi.org/10.7717/PEERJ-CS.623/SUPP-1

Chinwala M (2020) Recent formulation advances and therapeutic usefulness of orally disintegrating tablets (ODTs). Pharm J Pharm Educ Pract 8:186. https://doi.org/10.3390/PHARMACY8040186

Farag HK, El-Shamy AM, Sherif EM, Zein El Abedin S (2016) Sonochemical synthesis of nanostructured ZnO/Ag composites in an ionic liquid. Zeitschrift Fur Physikalische Chemie 230:1733–1744. https://doi.org/10.1515/ZPCH-2016-0777/MACHINEREADABLECITATION/RIS

Fields J, Go JT, Schulze KS (2015) Pill properties that cause dysphagia and treatment failure. Curr Ther Res 77:79–82. https://doi.org/10.1016/J.CURTHERES.2015.08.002

Gohel MC, Jogani PD (2005) A review of co-processed directly compressible excipients

Habib Y, Augsburger L, Reier G et al (1996) Dilution potential: a new perspective. Pharm Dev Technol 1:205–212. https://doi.org/10.3109/10837459609029895

Haruna F, Apeji YE, Oparaeche C et al (2020) Compaction and tableting properties of composite particles of microcrystalline cellulose and crospovidone engineered for direct compression. Future J Pharm Sci 6:1–9. https://doi.org/10.1186/S43094-020-00055-9

Hauschild K, Picker-Freyer KM (2004) Evaluation of a new coprocessed compound based on lactose and maize starch for tablet formulation. AAPS PharmSci 6:27. https://doi.org/10.1208/PS060216

Jivraj M, Martini LG, Thomson CM (2000) An overview of the different excipients useful for the direct compression of tablets. Pharm Sci Technol Today 3:58–63. https://doi.org/10.1016/S1461-5347(99)00237-0

Kuentz M, Leuenberger H (2000) A new theoretical approach to tablet strength of a binary mixture consisting of a well and a poorly compactable substance. Eur J Pharm Biopharm 49:151–159. https://doi.org/10.1016/S0939-6411(99)00078-8

Li Z, Lin X, Shen L et al (2017) Composite particles based on particle engineering for direct compaction. Int J Pharm 519:272–286

Minchom CM, Armstrong NA (1987) A proposed technique for expressing the capacity of directly compressible diluents. In: British pharmaceutical conference. p 69

Mirani AG, Patankar SP, Borole VS et al (2011) Direct compression high functionality excipient using coprocessing technique: a brief review. Curr Drug Deliv 8:426–435. https://doi.org/10.2174/156720111795767960

Mohammed H, Briscoe BJ, Pitt KG (2006) A study on the coherence of compacted binary composites of microcrystalline cellulose and paracetamol. Eur J Pharm Biopharm 63:19–25. https://doi.org/10.1016/J.EJPB.2005.10.001

Newton J, Fell J (1970) Determination of tablet strength by the diametral-compression test. J Pharm Sci 59:688–691

Notenboom K, Leufkens HG, Vromans H, Bouvy ML (2017) Learning from patients: identifying design features of medicines that cause medication use problems. Int J Pharm 517:128–134. https://doi.org/10.1016/J.IJPHARM.2016.12.004

Osamura T, Takeuchi Y, Onodera R et al (2017) Prediction of effects of punch shapes on tableting failure by using a multi-functional single-punch tablet press. Asian J Pharm Sci 12:412–417. https://doi.org/10.1016/J.AJPS.2017.05.001

Ostertagová E (2012) Modelling using polynomial regression. Procedia Eng 48:500–506. https://doi.org/10.1016/J.PROENG.2012.09.545

Özalp Y, Onayo MM, Jiwa N (2020) Evaluation of lactose-based direct tableting agents' compressibility behavior using a compaction simulator. Turk J Pharm Sci 17:367. https://doi.org/10.4274/TJPS.GALENOS.2019.94840

Pitt KG, Heasley MG (2013) Determination of the tensile strength of elongated tablets. Powder Technol 238:169–175. https://doi.org/10.1016/J.POWTEC.2011.12.060

Pitt KG, Newton JM, Richardson R, Stanley P (2011) The material tensile strength of convex-faced aspirin tablets. J Pharm Pharmacol 41:289–292. https://doi.org/10.1111/J.2042-7158.1989.TB06458.X

Podczeck F, Drake KR, Newton JM (2013) Investigations into the tensile failure of doubly-convex cylindrical tablets under diametral loading using finite element methodology. Int J Pharm 454:412–424. https://doi.org/10.1016/J.IJPHARM.2013.06.069

Razavi SM, Gonzalez M, Cuitiño AM (2015) General and mechanistic optimal relationships for tensile strength of doubly convex tablets under diametrical compression. Int J Pharm 484:29–37. https://doi.org/10.1016/J.IJPHARM.2015.02.030

Reda Y, El-Shamy AM, Eessaa AK (2018) Effect of hydrogen embrittlement on the microstructures of electroplated steel alloy 4130. Ain Shams Eng J 9:2973–2982. https://doi.org/10.1016/J.ASEJ.2018.08.004

Reda Y, Yehia HM, El-Shamy AM (2022) Microstructural and mechanical properties of Al–Zn alloy 7075 during RRA and triple aging. Egypt J Pet 31:9–13. https://doi.org/10.1016/J.EJPE.2021.12.001

Sabri AH, Hallam CN, Baker NA et al (2018) Understanding tablet defects in commercial manufacture and transfer. J Drug Deliv Sci Technol 46:1–6. https://doi.org/10.1016/J.JDDST.2018.04.020

Salim I, Kehinde OA, Abdulsamad A et al (2018) Physicomechanical behaviour of novel directly compressible starch-MCC-povidone composites and their application in ascorbic acid tablet formulation. Brit J Pharm 3:527. https://doi.org/10.5920/BJPHARM.2018.03

Salim I, Olowosulu AK, Abdulsamad A et al (2021) Application of SeDeM Expert System in the development of novel directly compressible co-processed excipients via co-processing. Future J Pharm Sci 7:1–12. https://doi.org/10.1186/S43094-021-00253-Z

Shang C, Sinka IC, Jayaraman B, Pan J (2013) Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. Int J Pharm 442:57–64. https://doi.org/10.1016/J.IJPHARM.2012.09.005

Thoorens G, Krier F, Leclercq B et al (2014) Microcrystalline cellulose, a direct compression binder in a quality by design environment—a review. Int J Pharm 473:64–72

USP 41-NF 36 (2018) General information. United States Pharmacopoeia-National Formulary 7637–7639

Wan X, Woods AT, Salgado-Montejo A et al (2015) Assessing the expectations associated with pharmaceutical pill colour and shape. Food Qual Prefer 45:171–182. https://doi.org/10.1016/J.FOODQUAL.2015.06.009

Yohannes B, Abebe A (2021) Determination of tensile strength of shaped tablets. Powder Technol 383:11–18. https://doi.org/10.1016/J.POWTEC.2021.01.014

Zohdy KM, El-Sherif RM, El-Shamy AM (2021) Corrosion and passivation behaviors of tin in aqueous solutions of different pH. J Bio- and Tribo-Corrosion 7:1–7. https://doi.org/10.1007/S40735-021-00515-6

Publisher's Note