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Research Article

In Vitro Evaluation of Native Taro Boloso-I Starch as a Disintegrant in Tablet Formulations

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Introduction. In drug delivery, solid dosage forms, of which tablet is the commonest, are still the leading preferences. An area of research focus in tablet drug delivery is the search for tablet excipients. This study was aimed at evaluating and optimizing native Taro Boloso-I starch as a tablet disintegrant. *Methods*. The response surface method with central composite design (CCD-RSM) was used for the analysis and optimization of the concentration of native Taro Boloso-I starch and compression force. Wet granulation method was used for the preparation of paracetamol tablets. The response variables considered were tablet crushing strength, friability, and disintegration time. *Results and Discussion*. Both the native Taro Boloso-I starch concentration and compression force had increasing effect on the tablet breaking force. The friability of the tablets was shown to decrease with increasing levels of the disintegrant concentration. On the other hand, compression force had a decreasing effect on friability in the investigated range. The disintegration time of the tablets was found to decrease with the concentration of the starch. The paracetamol tablets prepared with the optimized levels of native Taro Boloso-I starch and compression force showed tablet breaking force of 116.24 N, friability of 0.153%, disintegration time of 1.36 min, disintegration efficiency ratio of 562.3 N/(%Min), and comparative disintegration efficiency ratio of 13.6 with respect to commercial potato starch. *Conclusions*. The tablets exhibited improved crushing strength, friability, *in vitro* disintegration time, and disintegration efficiency ratio which suggest the novel applicability of the native Taro Boloso-I starch as an efficient pharmaceutical tablet disintegrant.

1. Introduction

Among solid dosage forms, tablets are the commonest and thus the search for suitable tableting excipients is a continuing research endeavor. For oral solid dosage forms, starch is a multipurpose excipient applied as binder, diluent, and disintegrant [1, 2]. Disintegrants are incorporated to ensure the disaggregation of tablets so as to achieve maximum pharmaceutical availability and acceptable drug bioavailability to guarantee the projected performance of the dosage form [3]. This is an essential biopharmaceutical functionality which qualifies disintegrants among the principal tablet excipients.

The claimed mechanisms of action for tablet disintegrants include swelling, wicking, strain recovery, interruption of particle-particle bonds, heat of interactions, or a combination of these mechanisms. However, the disintegrant property of starch is, more importantly, due to its swelling properties attributable to its amylopectin content [4–6]. According to a previous study [7], native Taro Boloso-I starch (NTBIS) was shown to have higher swelling power than potato starch® at temperatures of 20, 37, 65, 75, and 85°C. On the other hand, it showed lower moisture content and sorption properties than potato starch. Further, the granules of NTBIS have an average particle size of $2.45 \pm 0.11\,\mu$m exhibiting an A-type polymorphism which is

quite diminutive compared to other tuber starches. Based on these findings, the current study hypothesized that NTBIS would have a potential application as a tablet disintegrant. Accordingly, in the current study, the suitability of NTBIS as a disintegrant in tablet formulations was evaluated *in vitro* using paracetamol as a model drug.

Central composite design response surface method was applied for optimization of the tablet formulations. The concentration of NTBIS (NTBISC) and compression force were used as factors while tablet breaking force (TBF), friability, and disintegration time (DT) were the response variables. Moreover, the disintegration efficiency ratio (DER) of the tablets prepared using NTBIS was compared with that of tablets prepared using commercial potato starch®. In addition, the dimensionless quantity, the comparative disintegration efficiency ratio (DERc), which depicts the disintegrant efficiency of a disintegrant against standard disintegrants at the same concentration level, was evaluated using a method established elsewhere [8].

2. Materials and Methods

2.1. Materials. Taro Boloso-I was obtained from Areka Agricultural Research Institute, Wolaitta, Ethiopia. Pure paracetamol (China Associate Co. Ltd, China) was donated by the Ethiopian Pharmaceutical Manufacturing Share Company (EPHARM). Sodium hydroxide, magnesium stearate, potassium monobasic phosphate, and sodium chloride (Sörensen, Leuren, Denmark), potassium bromide (Research Lab Fine Industries, India), and PVP-K30 were used as obtained.

2.2. Methods

2.2.1. Isolation of Native Starch. NTBIS was extracted from the tubers of Taro Boloso-I as per the method described by Balcha et al. [7]. Accordingly, fresh Taro Boloso-I tuber was washed, cleaned, peeled, and trimmed into pieces and then crushed with 1% (w/v) $NaCl_{(aq)}$ solution using Blender-888A, Germany. This was then washed with the same saline solution containing 0.03 N NaOH to facilitate sedimentation. The sediment was dried, ground, and sieved.

2.2.2. Preparation and Characterization of Granules. According to the quantities in Table 1, an aqueous solution of PVP-K30 was applied to paracetamol powder at 3% (w/w) concentration and the mixture was blended in a laboratory kneader (Erweka D-63150 LK5, Germany) for 20 min. The wet mass was screened through 1.6 mm sieve and dried overnight in an oven (KOTTERMANN® 2711, Germany) at 40°C. The dried granules were further screened through a 1 mm sieve to control their particle size. Bulk density was determined as a ratio of weight (g) of granules to its volume (ml) measured in a 0.5 ml graduated 250 ml measuring cylinder. Tapped density was determined employing a fixed drop of one-half inch at a rate of 250 taps/min for 2 min in a tapped densitometer (Erweka, type SVM, Germany). Carr's index and Hausner ratio were calculated from the tapped and bulk densities. The static angle of repose was determined employing funnel without stem with its tip fixed at 10 cm height [9]. To determine the size distribution, 30 g of granules were shaken in a set of sieves (ISO 3310-1) for 2 min using an Erweka universal drive unit (Type AR 401, Germany). The sizes of the granules in each sieve and the overall mean size were computed using averages of the mean sizes of the sieves. To perform the friability test, 10 g of granules (>315 μm) was used in a friability tester (Erweka®, GmbH Heusenstamm, Germany) which was rotated for 4 min at 25 rpm dropping the granules a distance of 6 inches. The weight loss was calculated as percent friability. This was performed in triplicate and reported as mean ± SD.

2.2.3. Compression and Characterization of Tablets. The formulations shown in Table 1 were prepared through blending the paracetamol granules with NTBIS as disintegrant in a tumble mixer (Willy A. Bachofen AG, Turbula® 2 TF, Basel, Switzerland) at 49 rpm for 10 min. The mixture was further mixed with 0.5%w/w of magnesium stearate for 5 min in the same mixer and compressed using instrumented tablet machine (Korsch AG XP1 K0010288, Germany) using 10 mm flat-faced punches (Table 1). From each batch, 10 tablets were evaluated for TBF employing a tablet hardness tester (CALEVA, G.B., Caleva Ltd., UK) and the average force was reported as the TBF. To evaluate the friability, 20 tablets were placed into the friability tester and rotated for 4 min at 25 rpm falling a distance of 6 inches. The tablets were dusted and the weight loss was calculated as percent friability. The thicknesses of 10 tablets were measured using a sliding caliper scale (Nippon, Sokutei, Japan). The porosity (ϵ) was calculated as $\varepsilon = (1 - P_f) \times 100\%$ where the packing fraction P_f is the ratio of bulk density of the tablet to its true density (1.56 ± 0.2 gm/cm^3) [7]. The tablet bulk density was determined from the weight, thickness, and diameter data using the methods used elsewhere [10]. The disintegration test was carried out as per USP-NF [9] on a disintegration tester (Erweka ZT504, Germany). The disintegration efficiency ratio (DER) was calculated as a quotient of TBF/friability to DT. The comparative disintegration efficiency ratio (DER_c) was determined as the ratio of DER of tablets prepared using NTBIS as a disintegrant to that of the DER of tablets prepared using the commercial disintegrant, potato starch, using the method described elsewhere [8].

2.2.4. Experimental Design. Circumscribed central composite design (CCD) was applied for optimization [11] with 13 experimental runs (4 factorial points, 4 axial points, and 5 central points) (Table 1). While the concentration of NTBIS and compression force were factors, TBF, friability, and DT were used as the responses. To validate the optimization process and compare the NTBIS with a standard disintegrant, tablet formulations at optimum levels of the factors were prepared with both NTBIS and potato starch separately. These tablets were evaluated and compared with the predicted values by determining residuals. Also, the

Table 1: Formulations and compression forces of tablets (central composite design).

No.	Factor 1				Factor 2		
	Code X1	Actual NTBISC [g (%)]	Granules [g (%)]	Mg stearate [g (%)]	Code X2	Actual CF (kN)	
F1	−1	17.5 (5)	330.75 (94.5)	1.75 (0.5)	−1	15	Factorial design points
F2	+1	52.5 (15)	295.75 (84.5)	1.75 (0.5)	−1	15	
F3	−1	17.5 (5)	330.75 (94.5)	1.75 (0.5)	+1	25	
F4	+1	52.5 (15)	295.75 (84.5)	1.75 (0.5)	+1	25	
F5	−1.414	10.5 (3)	337.75 (96.5)	1.75 (0.5)	0	20	Axial design points
F6	+1.414	59.5 (17)	288.75 (82.5)	1.75 (0.5)	0	20	
F7	0	35.0 (10)	313.25 (89.5)	1.75 (0.5)	−1.414	13	
F8	0	35.0 (10)	313.25 (89.5)	1.75 (0.5)	+1.414	27	
F9-13	0	35.0 (10)	313.25 (89.5)	1.75 (0.5)	0	20	Central points

NTBISC: NTBIS concentration; CF: compression force.

efficiency of tablets prepared with the NTBIS as disintegrant was compared with that of potato starch.

2.2.5. Fourier Transform Infrared Spectroscopy. The FTIR spectra of pure paracetamol, NTBIS, and paracetamol-starch physical mixture (1 : 1) were obtained with an infrared spectrophotometer (Tensor II FTIR Spectrometer, Bruker Optics, USA) in transmittance mode using KBr method. For each run, 16 scans were performed in the range of wave number of 4000–500 cm^{-1} at a resolution of 4 cm^{-1}. For data presentation, Origin version 7 (Origin LabTM Corporation, USA) was applied.

2.2.6. Differential Scanning Calorimetry (DSC). DSC was performed using a thermal analyzer (NETZSCH, Selb, Germany) in which 3 mg samples were hermetically sealed in flat bottom aluminum pans. It was operated at ramps of 10°C/min from 20°C to 200°C and scanned parallel to an empty sealed reference pan under nitrogen flow.

2.2.7. Statistical Analyses. Response surface methodology and contour plots were used for the analysis of effects of factors on the responses. All the results of direct measurements were presented as arithmetic mean ± standard deviation of at least three measurements. Some data obtained from literature for comparative evaluations were used directly. The responses were expressed in polynomial models in terms of compression force and concentration. Statistical analyses including one-way ANOVA were performed. The software including Design Expert 8.0.7.1 and 13 software (Stat-ease, Corp. Australia) and Origin version 7 (Origin LabTM Corporation, USA) was used. The level of significance of statistical data was such that p-value <0.05.

3. Results and Discussion

3.1. Precompression Properties of Tablet Formulations

3.1.1. Size Distribution of Granules. The size distribution of the paracetamol granules was as depicted in Figure 1. The size distribution was reasonably close to normal distribution with a mean size of 480.3 ± 13.68 μm.

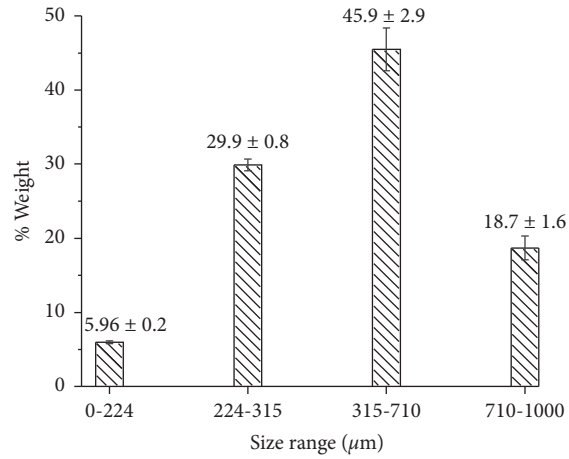

Figure 1: Size distribution of paracetamol granules.

3.1.2. Granule Friability. Granule friability was measured to estimate relative magnitudes of attractive forces conserving the primary particles together. The friability was found to be 0.63 ± 0.04% which is acceptable (<1%) [9].

Flowability and Compressibility Indicators: Density, flow properties, compressibility indexes, and Hausner ratios of the granules were as depicted in Table 2. This supports that the granules did not have flow problems (USP-NF, 2020).

3.2. Properties of Compressed Tablets. The weight, thickness, TBF, friability, and DT profiles of the tablets were as shown in Table 3. The tablet formulations with 5% NTBISC at compression force of 25 kN had acceptable TBF (110.75 ± 8.8 N) but significantly higher friability (4.000 ± 0.60%) and extremely longer disintegration time (43.00 ± 0.6 min). With 3% NTBISC compressed at 20 kN, the tablets had acceptable TBF (107.00 ± 11.2 N) and friability (0.600 ± 0.17%) but significantly longer disintegration time (42.50 ± 0.3 min). However, with 10% NTBISC compressed at 27 kN, the tablets had acceptable TBF (107.00 ± 11.2 N) and DT (10.20 ± 0.3 min) but higher friability (2.880 ± 0.47%). In terms of weight variation tests, tablet formulations of the study were all within ±5% which is acceptable for tablets weighing >250 mg [12]. The tablet

Table 2: Bulk density, tapped density, Carr's index, and Hausner ratio of compression mixtures.

	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (°)	Flow rate (g/sec)
F1	0.53 ± 0.06	0.57 ± 0.06	7.02 ± 0.71	1.18 ± 0.01	31.0 ± 2.8	6.65 ± 0.4
F2	0.53 ± 0.04	0.58 ± 0.05	9.48 ± 0.76	1.03 ± 0.01	26.6 ± 2.1	6.03 ± 0.6
F3	0.52 ± 0.05	0.56 ± 0.04	7.14 ± 0.66	1.14 ± 0.01	30.5 ± 2.9	6.65 ± 0.5
F4	0.52 ± 0.04	0.57 ± 0.03	9.65 ± 0.54	1.03 ± 0.01	26.6 ± 2.0	6.04 ± 0.2
F5	0.54 ± 0.04	0.59 ± 0.05	8.47 ± 0.79	1.14 ± 0.02	31.5 ± 2.9	6.66 ± 0.7
F6	0.53 ± 0.03	0.59 ± 0.02	10.2 ± 0.74	1.14 ± 0.01	27.0 ± 2.4	6.00 ± 0.8
F7	0.50 ± 0.05	0.55 ± 0.05	9.09 ± 0.67	1.02 ± 0.01	25.0 ± 2.0	8.05 ± 0.9
F8	0.50 ± 0.06	0.54 ± 0.03	7.41 ± 0.60	1.18 ± 0.00	23.9 ± 2.0	8.06 ± 0.0
F9	0.50 ± 0.04	0.55 ± 0.05	9.09 ± 0.78	1.09 ± 0.01	24.7 ± 2.3	8.04 ± 0.6
F10	0.51 ± 0.04	0.56 ± 0.06	8.93 ± 0.64	1.03 ± 0.01	21.2 ± 2.0	8.03 ± 0.7
F11	0.50 ± 0.05	0.55 ± 0.04	9.09 ± 0.69	1.02 ± 0.01	23.9 ± 1.7	8.03 ± 0.8
F12	0.51 ± 0.03	0.56 ± 0.05	8.65 ± 0.73	1.02 ± 0.01	24.8 ± 2.0	8.05 ± 0.9
F13	0.50 ± 0.04	0.55 ± 0.05	9.09 ± 0.65	1.03 ± 0.01	24.9 ± 2.0	8.04 ± 0.8

Table 3: Weight, thickness, TBF, friability, and DT values of paracetamol tablets prepared with NTBIS as disintegrant.

	Weight (mg)	Thickness (mm)	TBF (N)	Friability (%)	DT (min)
F1	351.7 ± 3.5	3.96 ± 0.05	97.30 ± 6.0	0.150 ± 0.10	14.10 ± 0.9
F2	350.3 ± 4.9	3.91 ± 0.04	131.00 ± 5.9	0.200 ± 0.02	2.65 ± 0.0
F3	349.0 ± 3.8	3.94 ± 0.07	110.75 ± 8.8	4.000 ± 0.60	43.00 ± 0.6
F4	349.5 ± 4.1	3.90 ± 0.04	161.32 ± 5.7	0.200 ± 0.02	3.00 ± 0.3
F5	350.2 ± 2.9	3.95 ± 0.05	107.00 ± 11.2	0.600 ± 0.17	42.50 ± 0.3
F6	349.8 ± 6.0	3.89 ± 0.04	153.43 ± 6.8	0.100 ± 0.02	2.08 ± 0.1
F7	350.0 ± 3.0	3.94 ± 0.08	99.20 ± 3.4	0.175 ± 0.08	3.02 ± 0.5
F8	350.1 ± 3.1	3.93 ± 0.06	143.00 ± 6.1	2.880 ± 0.47	10.20 ± 0.3
F9	350.0 ± 2.8	3.93 ± 0.05	141.50 ± 5.6	0.233 ± 0.01	6.40 ± 0.4
F10	351.8 ± 3.0	3.94 ± 0.06	138.25 ± 6.3	0.200 ± 0.04	6.30 ± 0.3
F11	351.0 ± 4.5	3.93 ± 0.05	141.50 ± 5.1	0.195 ± 0.03	6.30 ± 0.1
F12	350.5 ± 4.5	3.94 ± 0.06	138.00 ± 3.5	0.217 ± 0.04	2.40 ± 0.3
F13	350.0 ± 3.0	3.93 ± 0.04	137.10 ± 5.7	0.198 ± 0.03	2.60 ± 0.6

thickness was found to decrease slightly with increasing CF probably because higher compression force brings the granules into more cohesive form and hence decreases the thickness and porosity [9].

3.3. Mathematical Models and Factor Response Relationships. To graphically and mathematically demonstrate trends of levels of the responses across changing levels of the factors, respective best-fitting models had to be selected using the Design Expert software into which the arithmetic means of TBF, friability, and DT values of the tablets (Table 3) were fed. Using the software output, the linear, two-factor interaction (2FI), quadratic, and cubic models were compared in terms of R2, adjusted R2, predicted R2, and predicted residual sum of square (PRESS) values for each of the responses. All the three response variables were found to best satisfy the quadratic polynomial model. The quadratic polynomial models had greater R2 values (0.9797, 0.9941, and 0.9720), adjusted R2 values (0.9653, 0.9898, and 0.9520) closer to 1 and in more reasonable agreement with the predicted R2 values (0.8749, 0.9661 and 0.0.8398), and smaller predicted residual sum of square (PRESS) values (632.92, 0.098, and 402.52) than any other nonaliased model [13]. The adequacy of these models for predicting influences of the factors on the responses was verified employing the ANOVA test. The model significance tests were such that $p < 0.05$ and lack-of-fit tests (mean errors) were insignificant ($p > 0.05$) for all three responses. In the same fashion, signal to noise ratios (adequate precision values) of 24.583 for TBF, 49.677 for friability, and 19.881 for DT demonstrated the signal was adequate and quadratic models are quite valid.

Two extra tests proved the validity of the regression models. The first was the normal probability plots of residuals versus predicted values which reasonably approximated the normal plot of predicted values. The second was the internally studentized residuals in which values were <3 units away from zero and also randomly scattered. Thus, the quadratic polynomial models were found to desirably reveal the relationships existing between the variables within 95% CI and applied to elucidate the types and trends of influences [13]. Then, equivalent mathematical equations were generated to summarize trends of TBF, friability and DT with changing levels of disintegrant concentration and compression force. Moreover, the response surface and contour plots were constructed. Using these mathematical and diagrammatic approaches, the individual and interaction effects of the factors on the responses were demonstrated. In this regard, equation (1) and Figures 2(a) and 2(b) demonstrate the trend of TBF of tablets with varying levels of the two factors.

$$H = 139.27 + 18.74X_1 + 13.21X_2 - 4.67X_1^2 - 9.23X_2^2, \quad (1)$$

where H, X_1, and X_2 stand for the levels of TBF, NTBIS concentration, and compression force, respectively. Figure 2

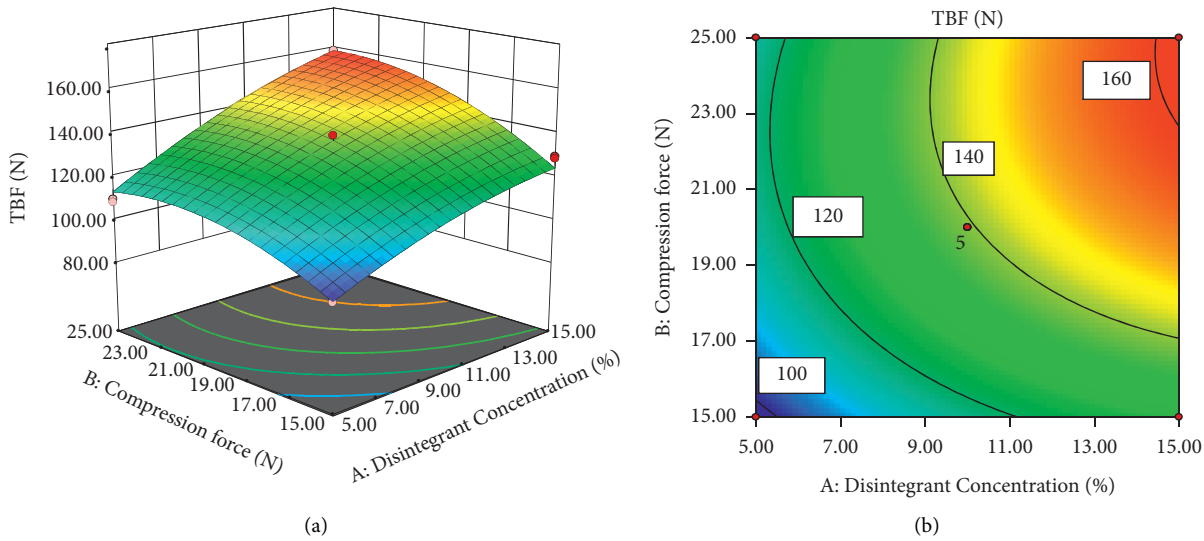

Figure 2: Response surface (a) and contour plots (b) of TBF as a function of compression pressure and NTBISC.

and equation (1) demonstrate the overall trend of TBF with the disintegrant concentration (coefficient = 18.74, $p < 0.0001$) and compression force (coefficient = 13.21, $p < 0.0001$). As shown in Figure 2, with increasing CF, TBF was found to increase and then decrease after reaching a maximum. On the other hand, TBF was found to increase with increasing disintegrant concentration. TBF increased with compression force probably because of the good compactability nature of NTBIS which in turn might presumably be due to its fine particle size [14]. Both NTBISC and compression force had convex quadratic effects on TBF of the tablets with coefficients of −4.67 ($p < 0.0147$) and −9.23 ($p < 0.001$), respectively. This is probably due to the poor compressibility and bonding of pure paracetamol powder leading to a high tendency for capping at higher CFs. In contrast, the NTBISC had a stronger positive influence on TBF than CF as the term X1 has a greater coefficient (18.74) than that of X2 (13.21).

Similarly, the trend of friability of tablets with varying levels of concentration of NTBIS and compression force was as depicted in equation (2) and Figures 3(a) and 3(b).

$$\log \mathrm{Fr} = -0.68 - 0.28X_1 + 0.39X_2 - 0.36X_1X_2 + 0.26X_2^2, \quad (2)$$

where logFr, X_1, and X_2 stand for the levels of log-transformed friability, NTBIS concentration, and the compression force, respectively.

Figure 3 and equation (2) suggest that friability of the tablets decreases with increasing disintegrant concentration (coefficient = −0.28, $p < 0.0001$). The reason for the observed effect of starch concentration on TBF and friability, respectively, is probably due to the increased arrangement of the particles in closer contact which brings about more interparticular bonding. At high compression force, the small particle size of NTBIS granules might experience interparticular adhesive forces to increase and result in an improved transmission of axial pressure. The subsequent stronger stresses at particles' contact points result in an increase in contact area due to deformation and allow the particles to approach each other forming stronger compacts [15]. Rice starch which has similar morphology to that of NTBIS is claimed to be the most compressible native starch [16]. The reason for the strong compactability could also be the mechanical interlocking due to the shapes of granules [17, 18]. On the other hand, compression force (coefficient = 0.39, $p < 0.0001$) showed an increasing effect on friability. The interaction of the NTBISC and CF antagonizes log friability of tablet (coefficient = −0.36, $p < 0.0001$). CF had a positive quadratic effect on the log-transformed friability of the tablets with a coefficient of 0.26 ($p < 0.0001$).

In the same way, equation (3) and Figures 4(a) and 4(b) demonstrate a trend of DT of tablets with varying levels of concentration of NTBIS and compression force.

$$\mathrm{DT} = 4.8 - 13.58X_1 + 4.93X_2 - 7.14X_1X_2 + 9.05X_1^2, \quad (3)$$

where DT, X_1, and X_2 stand for the levels of DT, NTBIS concentration, and the compression force, respectively.

Figure 4 and equation (3) demonstrate that the DT of the tablets is negatively affected by the concentration of the disintegrant starch (coefficient = −13.58, $p < 0.0001$). However, it was positively affected by compression force (coefficient = 4.93, $p = 0.0032$). Depending on the mechanism of disintegrant action, the reason for decreasing effect of NTBIS on the disintegration might be higher swelling behavior. Conceivably, the increase in the DT with increasing compression force is due to the reduction of porosity and hence liquid penetration at higher compaction resulting in lower swelling [19, 20]. The interaction of the NTBISC and compression force favors faster DT of the tablets as distinguished by the sign of the term X1X2, −7.14 ($p = 0.0028$). It is observable that the NTBISC has a positive (concave) quadratic effect on the DT of the tablets with a coefficient of 9.05 ($p = 0.0001$). NTBISC has a stronger negative influence on tablet DT than the positive influence of CF as the magnitude of

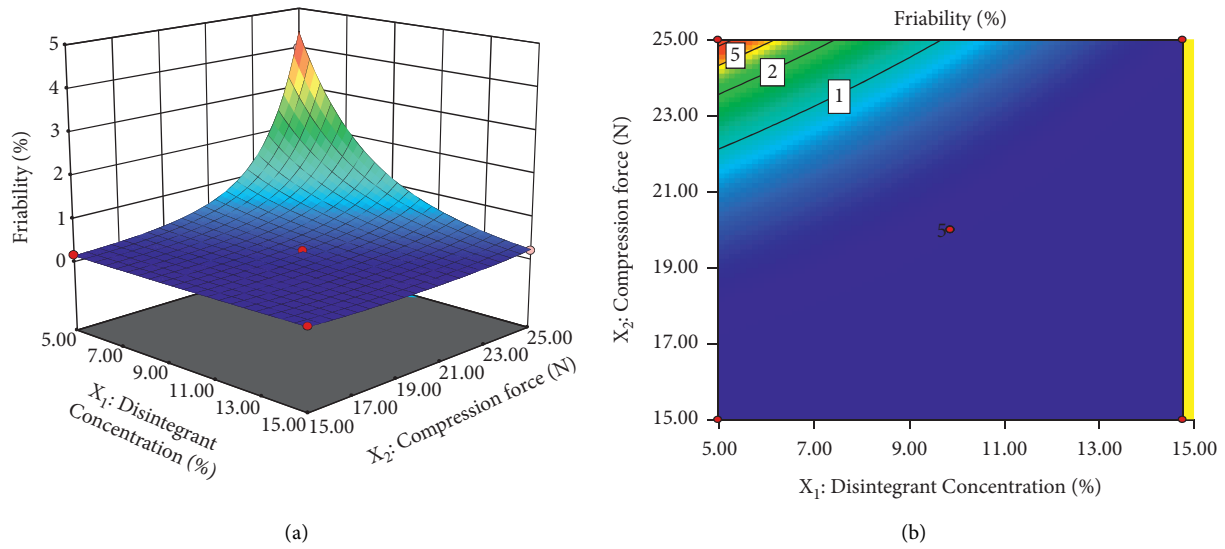

Figure 3: Surface response (a) and contour plot (b) of friability as a function of compression pressure and NTBISC.

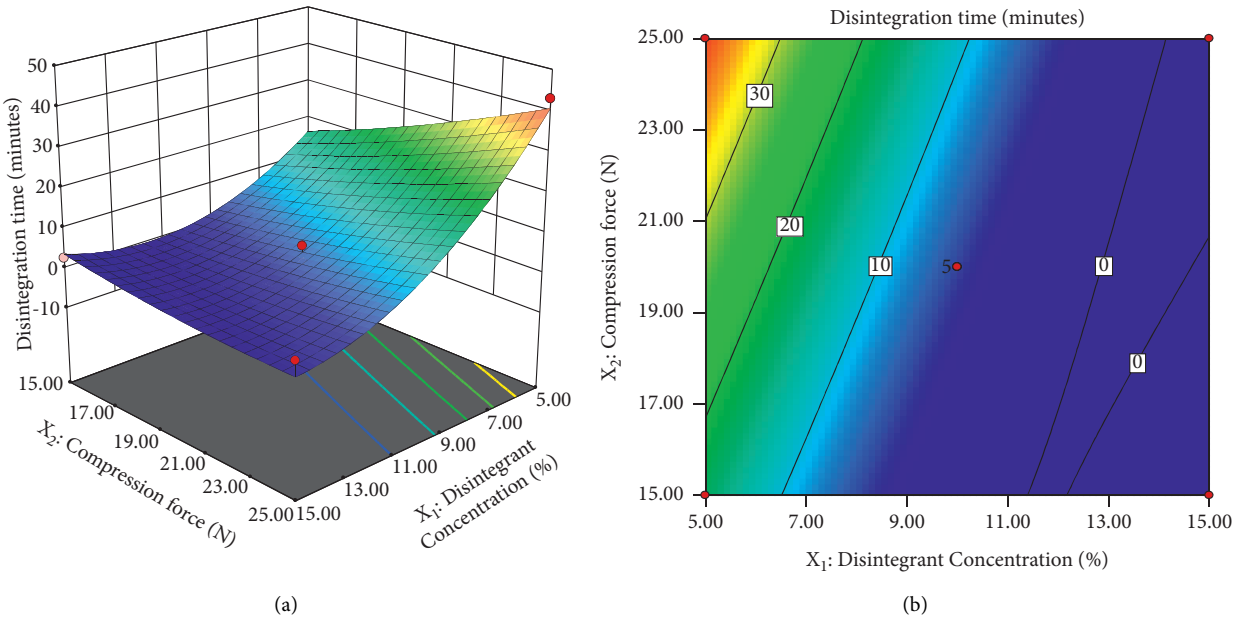

Figure 4: Surface response (a) and contour plot (b) of DT as a function of compression pressure and NTBISC.

the coefficient of X1 (−13.58) is greater than that of X2 (4.93). Therefore, the TBF and DT of tablets are affected more by the concentration of NTBIS than compression force whereas friability is affected more by compression force.

3.4. Optimization and Validation. In this study, numerical (desirability-based) (Figures 5(a) and 5(b)) optimization and graphical (overlaying/superimposing contours) (Figure 6) optimization methods were applied [13].

As a result, optimum starch concentration was 9.80% while compression force was 15 kN resulting in values of TBF, friability, and DT of 116.24 N, 0.153%, and 1.36 min, respectively, with desirability 0.728. For validation of the optimization and evaluation of the NTBIS as disintegrant with standard potato starch, the properties of paracetamol tablets prepared with 9.80% (w/w) NTBIS as a disintegrant and CF of 15 kN and those of potato starch with the same concentration and CF values, respectively, were determined in Tables 4 and 5. The results demonstrate the tablet preparations did not have significant weight and thickness variations [9].

All the 3 batches of the tablets demonstrated acceptable average TBF (116.8 ± 7.5 N), i.e., in between 50 N and 150 N, and reasonably agree with the predicted value (116.2 N) (Table 5). Similarly, the average friability value of the three

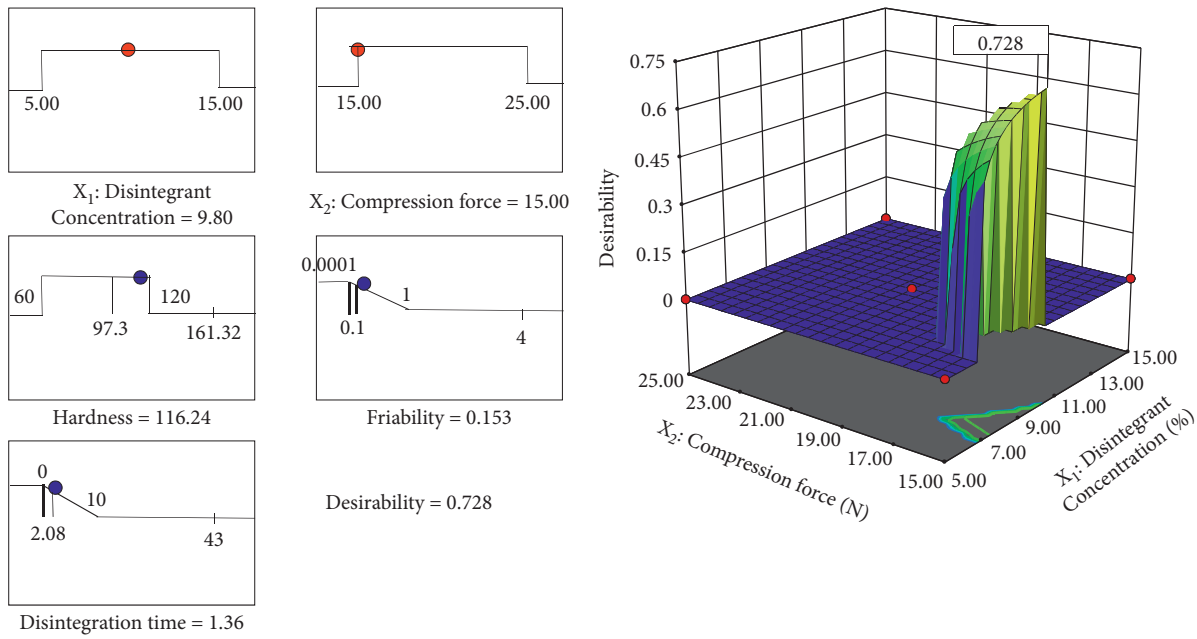

Figure 5: The ramps of optimization (a) and the overall desirability function (b).

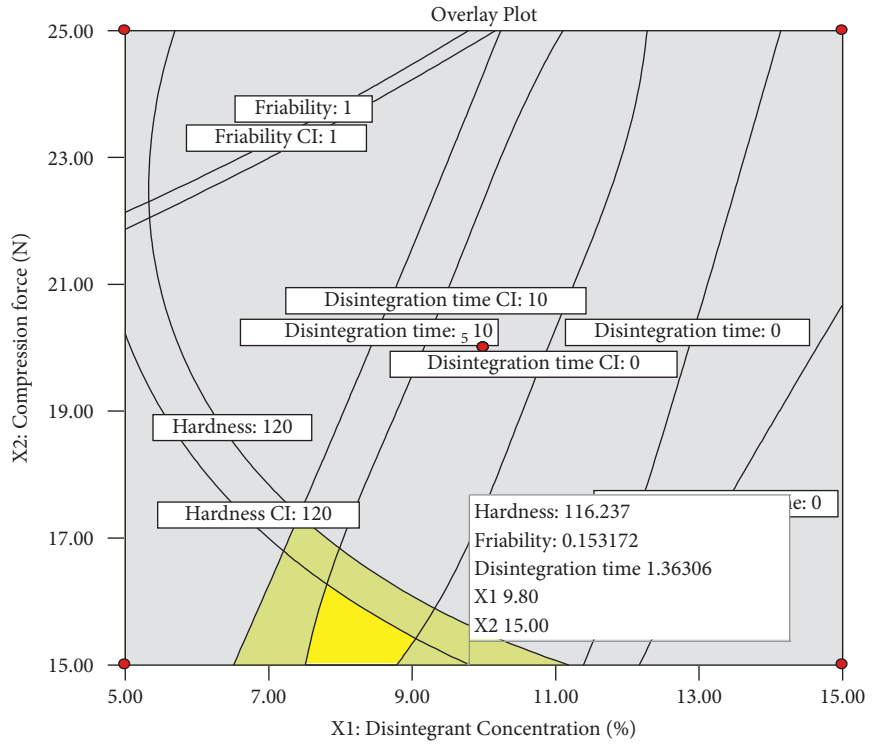

Figure 6: Superimposed contour plots of the responses of the tablets as a function of the factors.

batches was 0.157 ± 0.03% which is far below 1% sensibly agreeing with the predicted value (0.152) and hence acceptable. The equivalent tablets prepared with the same concentration of potato starch compressed at the same compression force did not have acceptable mechanical strength (54.8 ± 6.4 N TBF and 1.01 ± 0.18% friability). The findings suggest that the tablets prepared at the optimum levels of the factors, i.e., 9.80% of disintegrant NTBIS and 15 kN of compression force, maintain improved mechanical strength compared to the report by Adane et al. on a variant of Godare starch with corresponding optimum levels of 7% Godare starch and 19 kN of compression force with mean

Table 4: The weight, thickness, and porosity of tablets prepared with NTBIS and potato starch at optimum levels of factors.

		Weight (mg)	Thickness (mm)	ϵ (%)7
NTBIS	B1	350.0 ± 8.0	4.0	9.8
	B2	350.0 ± 4.0	3.9	9.1
	B3	351.0 ± 7.0	4.0	7.0
	$\mu \pm$ SD	350.3 ± 6.3	4.0	8.6 ± 1.5
	PV	350.0	—	
	ε	0.09		
Potato starch	B1	349.8 ± 10.9	4.1	8.1
	B2	350.9 ± 8.1	4.0	10
	B3	350.5 ± 3.0	4.0	9.2
	$\mu \pm$ SD	350.4 ± 7.8	4.0	9.1 ± 0.9

*B, ∈, PV, and ε stand for batch number, disintegration efficiency ratio, porosity, predicted value, and percent error, respectively.

Table 5: The TBF, friability, disintegration time, and DER of tablets prepared with NTBIS and potato starch at optimum levels of factors.

		TBF (N)	Friability (%)	DT (min)	DER $(N/(\%Min)^{-1}$	DER_c
NTBIS	B1	112.3 ± 6.5	0.190 ± 0.02	1.31 ± 0.17	476.0	9.3
	B2	116.0 ± 6.1	0.15 ± 0.02	1.35 ± 0.19	582.7	15.2
	B3	122.2 ± 6.8	0.13 ± 0.02	1.39 ± 0.11	685.9	16.3
	$\mu \pm$ SD	116.8 ± 7.5	0.157 ± 0.03	1.35 ± 0.16	581.6	13.6
	PV	116.2	0.153	1.36	562.3	
	ε	0.52	2.61	−0.74	3.43	
Potato starch	B1	58.5 ± 6.0	0.96 ± 0.02	1.20 ± 0.06	50.8	—
	B2	50.4 ± 5.8	1.08 ± 0.30	1.23 ± 0.06	40.0	—
	B3	54.7 ± 4.8	1.01 ± 0.07	1.3 ± 0.04	42.1	—
	$\mu \pm$ SD	54.8 ± 6.4	1.01 ± 0.18	1.24 ± 0.07	44.3	—

*B, DER, DER_c, PV, and ε stand for batch number, disintegration efficiency ratio, relative disintegration efficiency ratio, predicted value, and percent error, respectively.

friability of 0.86 ± 0.1% and mean DT of 3.18 ± 0.13 min [21]. The porosity of the 3 batches of the optimized paracetamol tablets using NTBIS was found to be 8.6 ± 1.5%. The mean DT of the optimum tablets (1.35 ± 0.16 min) was comparable with the predicted value (1.36 min) ($p > 0.05$).

It is worth studying the mechanical properties of tablets together with the DT using the disintegration efficiency ratio (DER) which is a good indicator of tablet quality. This is because TBF of the tablets is a factor of physical nature of granules such as mechanical strength and deformation under load and binders and above all the compression force and the TBF per se influences disintegration [22, 23]. The DER correlates DT with TBF and friability hence weighing the cumulative impacts of strength and weakness of tablets simultaneously on the DT. The DER of the test tablets, in this case, was found to be 562.3 N (%Min)−1 which is significantly higher than that of the tablets prepared using potato starch 44.3 N (%Min)−1. Moreover, DERc with respect to commercial potato starch of the optimized tablets was observed to be 13.6. This indicates that NTBIS would be a more efficient disintegrant with a greater ability to enhance the balance between the mechanical and disintegration properties of the tablets [8].

3.5. Drug-Excipient Compatibility. To verify the drug-excipient compatibility, peaks of the finger print region and the other characteristic vibrational bands of paracetamol including –NH–, –OH, –CO, $-CH_3$, benzene ring, and phenyl-OH were considered. This was performed considering the corresponding absorbance peaks in the spectra of a mixture of 1 : 1 drug to excipient ratio and critically comparing with the spectrum of pure paracetamol (Figure 7).

The sharp absorption bands at 3325.73 cm^{-1} and 1610.29 cm^{-1} are attributable to the symmetric stretching and out-of-plane (OOP) bending bands of –NH–bonds, respectively. The broad background absorption around 3450–3110.29 cm^{-1} (OH-stretches) and the presence of bands near 1600 cm^{-1} indicate the presence of the phenolic –OH group. The presence of aromatic ring was evidenced from the doublet at 1563.71 cm^{-1} and 1506.64 cm^{-1}, possible weak overtone, and combination bands between 2000 cm^{-1} and 1600 cm^{-1}. The presence of the acetyl group was supported as there are strong bands at 2884.9 cm^{-1} and 1369.67 cm^{-1} of the methyl C-H bonds and by the presence of a strong peak at 1655.02 cm^{-1} suggesting CO stretching vibration. The presence of the peaks at 1258.39 cm^{-1} and 1225.57 cm^{-1} is common to C-O/C-N stretching vibrations [24, 25]. The presence of the vibrational absorbance bands which possibly qualify the structural groups of paracetamol implies that chemical interaction of paracetamol with NTBIS is unlikely [26].

Moreover, the DSC curves of pure components and their 1 : 1 (w/w) physical mixtures were compared (Figure 8). In the DSC thermograms, there occurred neither appearance of strange peak nor disappearance of existing characteristic

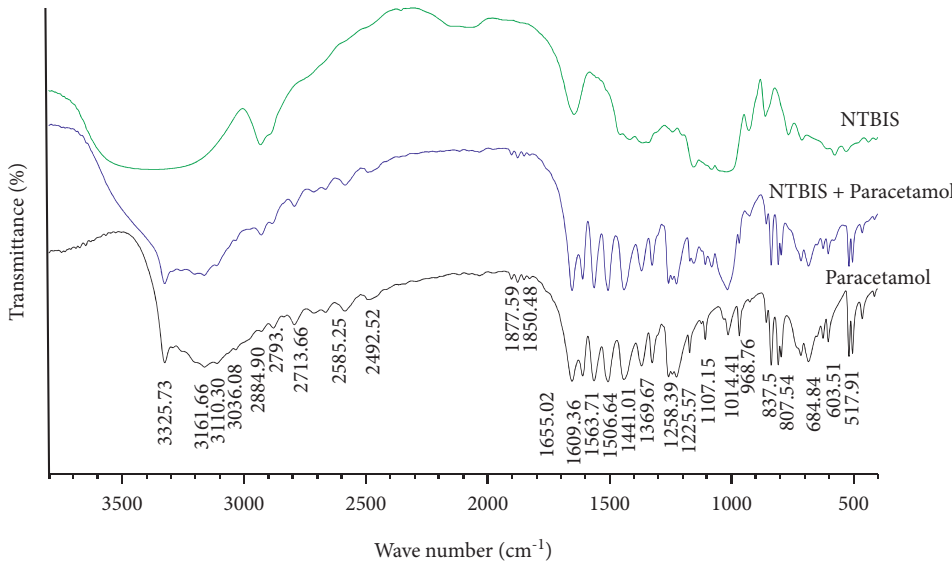

Figure 7: Overlay FTIR spectra of paracetamol, paracetamol mixed with NTBIS (at 1 : 1 ratio), and NTBIS.

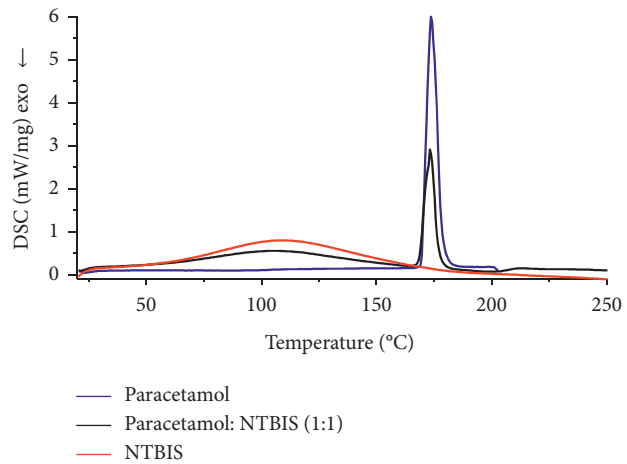

Figure 8: DSC thermogram of drug-excipient compatibility study.

peaks up to 200°C. The broad endothermic peak observed in the graph is presumably due to the moisture content whereas the sharp peak indicates the melting point of paracetamol. Moreover, there was no significant shift in the existing peaks. These facts suggest that the interaction between paracetamol and NTBIS is unlikely in the range of temperature investigated [25, 26].

4. Conclusions

Evaluation of the native Taro Boloso-I starch as tablet disintegrant was performed successfully. As a result of optimization of the concentration of NTBIS as a disintegrant and compression force using CCD-RSM design and paracetamol model drug, 9.80% NTBIS concentration and 15 kN compression force were the optimized values. At these values of the factors, TBF of 116.2 N, friability of 0.153%, and DT of 1.36 min were achieved fulfilling the DT requirement of even potential orodispersible tablet formulations, i.e., <3 min. Moreover, NTBIS resulted in tablets of high balance between binding and disintegration effects as DER of 562.3 N%$^{-1}$ Min^{-1} and DER$_c$ of 13.6 with respect to potato starch indicate. The findings revealed that the tablets could comply with the pharmacopeial disintegration time requirements for orodispersible tablets.

Data Availability

The authors confirm that all the data associated with this paper are available upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

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References

[1] J. Swarbrick, *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare, New York, US, 2007.

[2] C. R. Raymond, J. S. Paul, and E. Q. Marian, *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, UK and USA, 6th ed edition, 2009.

[3] J. van der Merwe, J. Steenekamp, D. Steyn, and J. Hamman, "The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and bioavailability," *Pharmaceutics*, vol. 12, no. 5, pp. 393–409, 2020.

[4] M. D. Parind, V. L. Celine, and W. S. H. Paul, "Review of disintegrants and the disintegration phenomena," *J Pharm Sci*, vol. 105, no. 9, pp. 2545–2555, 2016.

[5] O. Kunle, "Starch source and its impact on pharmaceutical applications," in *Chemical Properties of Starch*, M. Emeje, Ed., Intech Open, London, England, 2019.

[6] P. M. Desai, C. V. Liew, and P. W. S. Heng, "Review of disintegrants and the disintegration phenomena," *Journal of Pharmaceutical Sciences*, vol. 105, no. 9, pp. 2545–2555, 2016.

[7] T. Balcha, N. Mary Joseph, and A. Belete, "Isolation and physicochemical characterization of starch from Taro Boloso-I tubers," *Indian Drugs*, vol. 55, no. 7, pp. 20–27, 2018.

[8] O. D. Akin-Ajani, O. A. Itiola, and O. A. Odeku, "Evaluation of the disintegrant properties of native and modified forms of fonio and sweet potato starches," *Starch - Stärke*, vol. 68, no. 1-2, pp. 169–174, 2016.

[9] The United States Pharmacopeia and National Formulary (USP-NF), "The United States Pharmacopeial Convention, inc." Rockville, Maryland, 2020, https://online.uspnf.com/uspnf/document/GUID-AC788D41-90A2-4F36-A6E7-769954A9ED09_1_en-US.

[10] T. Riyanto and H. Aziz, "Compression and mechanical properties of directly compressible pregelatinized sago starches," *Powder Technology*, vol. 269, pp. 15–21, 2015.

[11] M. Ritesh and Z. Pabari, "Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets," *Int J Pharm*, vol. 430, no. 1-2, pp. 18–25, 2012.

[12] British Pharmacopoeia Commission, *British Pharmacopoeia*, The Stationery, London, England, 2020.

[13] G. A. Lewis, D. Mathieu, and R. Phan-Tan-luu, *Pharmaceutical Experimental Design*, Marcel Dekker, New York, US, 1999.

[14] A. Almaya and A. Aburub, "Effect of particle size on compaction of materials with different deformation mechanisms with and without lubricants," *AAPS PharmSciTech*, vol. 9, no. 2, pp. 414–418, 2008.

[15] S. Abdel-Hamid, F. Alshihabi, and G. Betz, "Investigating the effect of particle size and shape on high speed tableting through radial die-wall pressure monitoring," *International Journal of Pharmaceutics*, vol. 413, no. 1-2, pp. 29–35, 2011.

[16] O. S. Kittipongpatana and N. Kittipongpatana, "Preparation and physicomechanical properties of co-precipitated rice starch-colloidal silicon dioxide," *Powder Technology*, vol. 217, pp. 377–382, 2012.

[17] A. ElShaer, P. Hanson, and A. R. Mohammed, "A systematic and mechanistic evaluation of aspartic acid as filler for directly compressed tablets containing trimethoprim and trimethoprim aspartate," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 83, no. 3, pp. 468–476, 2013.

[18] M. Santl, I. Ilic, F. Vrecer, and S. Baumgartner, "A compressibility and compactibility study of real tableting mixtures: the impact of wet and dry granulation versus a direct tableting mixture," *Int J Pharm*, vol. 414, pp. 131–139, 2011.

[19] M. Riippi, O. Antikainen, T. Niskanen, and J. Yliruusi, "The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 46, no. 3, pp. 339–345, 1998.

[20] I. C. Sinka, F. Motazedian, A. C. F. Cocks, and K. G. Pitt, "The effect of processing parameters on pharmaceutical tablet properties," *Powder Technology*, vol. 189, no. 2, pp. 276–284, 2009.

[21] M. Adane, M. G. Abdel-Mohsen, and T. Gebre-Mariam, "Evaluation and optimization of Godare starch as a binder and disintegrant in tablet formulations," *Ethiopian Pharmaceutical Journal*, vol. 24, pp. 106–115, 2006.

[22] G. Alebiowu and O. A. Itiola, "Effects of starches on the mechanical properties of paracetamol tablet formulations. II. Sorghum and plantain starches as disintegrants," *Acta Pharmaceutica*, vol. 53, no. 4, pp. 313–320, 2003.

[23] O. A. Adeleye, M. N. Femi-Oyewo, and M. A. Odeniyi, "Effect of compression pressure on mechanical and release properties of tramadol matrix tablets," *Current Issues in Pharmacy and Medical Sciences*, vol. 28, no. 2, pp. 120–125, 2015.

[24] J. Coats, "Interpretation of infrared spectra: a practical approach," in *Encyclopedia of Analytical Chemistry*, R. A. Meyers, Ed., pp. 10815–10837, John Wiley & Sons, Chinchister, 2000.

[25] Y. Sakata, E. Tanabe, T. Sumikawa, S. Shiraishi, Y. Tokudome, and M. Otsuka, "Effects of solid-state reaction between paracetamol and cloperastine hydrochloride on the pharmaceutical properties of their preparations," *International Journal of Pharmaceutics*, vol. 335, no. 1-2, pp. 12–19, 2007.

[26] R. Chadha and S. Bhandari, "Drug-excipient compatibility screening-Role of thermoanalytical and spectroscopic techniques," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 87, pp. 82–97, 2014.