doi.org/10.36721/PJPS.2023.36.5.REG.1515-1526.1

Compressibility behavior of pioglitazone hydrochloride in mannitol-based formulations: An investigation using compaction simulator and QbD approach

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Abstract: This study aimed to investigate the compressibility properties of Pioglitazone Hydrochloride (PGZ) oral dispersible tablets using a compaction simulator. The tablets were prepared and formulated by direct compression method with varying particle sizes of PGZ in mannitol-based formulations, containing Ludiflash® and its corresponding physical mixture. All formulations were compressed at different compaction forces (5kN-20kN). Powders were evaluated for their tablet properties, such as hardness, friability, disintegration time, and dissolution rate. Results showed that all formulations exhibited good compressibility properties. The compaction force and choice of excipient played a vital role in formulation performance and drug release profile. With the use of Minitab 19™ an optimized formulation was derived, and all predicted outputs was seen to be within range after evaluations. In conclusion, the combined use of the compaction simulator and Minitab 19™ were found to be useful tools in predicting the compressibility properties of PGZ and therefore developing a robust oral dispersible tablet. These findings suggest that the compressibility properties of PGZ oral dispersible tablets can be effectively modified by adjusting the critical process parameters (CPP). Hence, providing valuable insights into the compressibility behavior of PGZ oral dispersible tablets and also aiding in the development of optimized tablet formulations.

Keywords: Pioglitazone, compaction simulator, oral dispersible tablets, quality by design, compressibility.

INTRODUCTION

One of the major issues arising when formulating a solid dosage form such as tablets is the flowability, compressibility, and tabletability of the powder drug (Hausner, 1981). These powder characteristics are solely responsible for the design, tableting method, and choice of the excipients used in the formulation.

Pioglitazone HCl (PGZ) is a drug from the thiazolidinedione class that is intended to treat type 2 (non-insulin-dependent) diabetes mellitus, a condition marked by a number of metabolic abnormalities such as decreased insulin production and insulin resistance (Gillies and Dunn, 2000). It is a peroxisome proliferator-activated receptor (PPAR-γ) agonist, it has been demonstrated to lower blood sugar levels in people with type 2 diabetes mellitus (Tang *et al*., 2018). The drug is not soluble in aqueous media and has a relatively low bioavailability. It belongs to Class II of the BCS classification (Tang *et al*., 2018; Taupitz *et al.*, 2013).

PGZ has poor powder flow, as well as a poorly compressible powder. The poor compressibility is similar to other antidiabetic drugs, just like metformin hydrochloride, which is usually formulated in combination with PGZ. With these challenges, it is imperative to improve the powder flow properties of these drugs or improve the formulation's compressibility through the addition of excipients (Satheesh kumar *et al*, 2014). The selection of tableting process is dependent on the amount as well as the physicochemical properties of the drug.

The use of the direct compression method is always a challenge for poorly compressible powders. However, with the support of direct-compressible co-processed excipients, these challenges can be tackled and solved with less effort. Co-processed excipients are created by combining the benefits of two or more excipients to create a superior excipient that is ready for use (Barot *et al.*, 2010). Ludiflash is one of those novel co-processed excipients which possess good tableting characteristics and is suitable for direct compression (Lura *et al.*, 2017). The benefits of co-processed excipients are to simplify the tableting process by using fewer excipients while maintaining the unique properties of each excipient and its tableting characteristics (Chadhary *et al.*, 2010).

In recent years, there has been a rise in the formulation of oral dispersible tablets (ODTs) available for commercial use. The need for these tablets is attached to their importance in patient compliance, not only for geriatrics but also for younger patients who may take their medications on the go without the need for the liquid to swallow. ODTs are usually designed with medications that disintegrate in the mouth without water within 180 seconds or less (Jacob *et al.*, 2017).

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ODTs are frequently produced using the direct compression method because it uses the simplest technology and typically does not require changing the standard tableting equipment (Aguilar-Diaz *et al.*, 2009).

Compaction simulators are defined as devices capable of simulating the exact cycle of any tablet press in real time and recording the parameters (Brniak *et al.*, 2013). Compaction simulators have potential applications in pharmaceutical research and development in terms of studying basic compaction mechanisms, troubleshooting, various process variables, compaction data library creation, scale-up parameters, and fingerprinting of new active pharmaceutical ingredients (APIs) or excipients. A compaction simulator also helps in the characterization of powder compressibility by use of sophisticated software which is capable of performing complex mathematical equations from acquired compression data.

The characterization of powders can be achieved using various compression equations that have been derived by many researchers (Jiwa *et al.*, 2021; Denny, 2002; Nordström *et al.*, 2009; Sonnergaard, 2001). The complexity of the systems being compressed makes it challenging to conduct a thorough analysis of the observed changes in volume, despite the fact that several methodologies have been used to try to characterize the compressional process (Chow *et al.*, 2008). Several mathematical equations, such as the F-D curve, the Heckel plot, and the ejection force, to name a few, have been used to characterize the tableting of a pharmaceutical powder formulation.

Quality by Design (QbD) is a systematic process for developing pharmaceutical dosage forms, supported by the International Conference on Harmonization (ICH) guidelines. Studies on the effectiveness of QbD are numerous, and it has been found to be effective in influencing formulation development by way of excipient or process performance, which has a positive impact on the final product. This is achieved through the evaluation of critical quality attributes (CQA). To create a suitable and dependable final quality product, QbD analyzes various parameters within the formulation based on various factors (powder compactibility, excipient amount, compaction force, etc.). This careful analysis, selection of formulation, and process dynamics help create a robust design, which has a positive influence on the sustainable quality of the final product (Kushner *et al*., 2014).

The aim of this study was to understand as well as optimize the compressibility of PGZ with the help of direct-compressible excipients. Using the application of the QbD approach to give a better understanding of the role of excipient on compaction parameters for the best possible outcome.

MATERIALS AND METHODS

Materials

Pioglitazone hydrochloride regular powder (Merck Millipore, Germany) was our model drug. Ludiflash® (BASF, Germany) was used as our co-processed direct compressible excipient. Mannitol (Roquette, France), Kollidon® CL SF (BASF, Germany), and Kollidon® 30 (BASF, Germany) as a combination, Sodium Stearyl Fumarate (SSF), were used. For dissolution studies, potassium chloride (Emprove, Germany), hydrochloric acid (Sigma-Aldrich, USA), and sodium hydroxide (Emprove, Germany) were used.

Methods

Powder Characterization

Micromeritics properties of powder

True density of all formulations was measured using a Helium pycnometer (Quantachrome Ultrapyc 1200e). Formulation compositions were also measured for bulk density and tapped density by weighing 20 g of the sample and putting it into a graduated cylinder measuring 50ml. A tapping machine (Ewerka, Germany) was used in this study. The procedure was done in accordance with USP monograph. The angle of repose was determined using the fixed funnel method. Powder flow properties were determined by Carr's index (CI), Hausner ratio (HR), and angle of repose (AR). Equations 1 and 2 were used to calculate the results.

$$\text{Carr}'s\ \text{index} = \frac{\text{Bulk density} - \text{Tap density}}{\text{Bulk density}} \text{ x } 100 \quad (1)$$

$$\text{Hausner ratio} = \frac{\text{Tap density}}{\text{Bulk density}} \quad (2)$$

Scanning electron microscopy

Scanning electron microscopy (SEM), was performed on PGZ for regular grade and micronized powders. EVO LS 10 was used to capture SEM pictures. (Zeiss, Germany). SEM images of pioglitazone micronized crystals. Mag. 1.00 K X and 2.00 K X respectively.

Blending

The powder blend has a total mass of 200mg per tablet for each formulation, as seen in table 1. The powder blend for each formulation was done by hand in an amber jar, due to the powder bulk of the formulation. The active ingredient and excipients were mixed for 15 minutes; the sodium stearyl fumarate was added and mixed for 2 minutes.

Tableting

All formulations were pressed at two compaction forces of 5, 10, 15, and 20kN respectively. Tablets were pressed using a flat-faced Euro B punch of 8mm diameter on a compaction simulator (Stylcam 200R, Medelpharm) equipped with data acquisition software (Analis, version 2.01, Medelpharm).

Post-compression tablet control tests

Determination of tablet hardness

Tablet mechanical strength was determined by randomly selecting six tablets and crushing them using a hardness tester (Erweka TBH 325, Germany). The results for all formulations and forces were recorded.

In vitro disintegration test

A disintegration tester (Erweka ZT 322, Germany) was used for the test. For each formulation, six tablets were randomly chosen. Tablets were put in the tubes of the disintegration apparatus and submerged in distilled water at a temperature of 37±2ºC. Following each tablet's complete disintegration, the disintegration time for each one was noted.

Friability test

A friability test was conducted using an Erweka TA 220 (Germany) friability tester. Using a random selection process, 20 tablets were picked, dusted, and precisely weighed. The friability of tablets was tested by rotating them 100 times (4 minutes, 25rpm) in a machine. After carefully removing dust, the tablets were reweighed. Equation 2 was used to determine the weight loss percentage of the tablets.

$$\text{Friability \%} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \boldsymbol{x\ 100} \quad (4)$$

In vitro dissolution test

The dissolution tester (Erweka DT 720, Germany) was used to conduct an *in vitro* drug release study for all compressed formulations in accordance with the USP Paddle Method (Apparatus II). As the dissolution medium, 900ml of pH 2.0 potassium chloride buffer solution was kept at 37±0.5°C, at 75rpm paddle speed. Samples were taken at intervals of 1, 3, 5, 10, 15, and 30 minutes. Using a UV spectrophotometer (UV- 1800 Shimadzu spectrophotometer, Tokyo, Japan), the absorbance of the extracted samples was measured at 269nm after being diluted with the buffer solution. Calculated drug release percentages were plotted against time (n=6).

Compaction data analysis

F-D Curve analysis

To evaluate the compaction behavior of the formulation and determine the work required during tablet compaction, compression force vs. punch displacement curves (F-D curves) can be obtained from compaction simulator. The area under the curve was calculated and used to determine the deformation characteristics of each formulation in regard to compression force (Özalp and Jiwa, 2021).

Heckel analysis

To understand the compaction behavior of various formulations during compression, compaction data generated by the data acquisition software was collected. Using this data, the mean yield pressure of the formulations was assessed to determine the dominant deformation mechanism of the tablets.

$$-\ln(P) = 1/P_y\,(P+A) \quad (5)$$

Where P is given as pressure, P_y is given as the corresponding mean yield pressure derived from a linear regression, and constant A represents the sum of two densification terms.

Ejection force

Ejection force analysis is a critical process in pharmaceutical tablet manufacturing, where the force required to eject a tablet from a die is measured and analyzed. Ejection force was derived from compaction simulator data. Using the tracking cam and sensors, the ejection force was measured and recorded by the Analis software and graphs were generated for individual formulations and forces. Ejection force was plotted against compaction force and was evaluated.

Mathematical and statistical results analysis

The resulting data are shown as the mean standard deviation (SD) of a set of measurements. The 'MS Excel Data Analysis Tool' (Windows 10) was used to do a one-way analysis of variance (ANOVA) on the data to determine significant differences. When the p-value was derived at $p<0.05$, a difference was deemed statistically significant.

Evaluation of the data and optimization of post-compression parameters using minitab

The response is described as a function of these independent variables using Minitab 19™ software, which looks into the multivariate impacts between these variables throughout the formulation and procedure. From the evaluation of experimental data, an optimized formulation was determined.

Response Surface Methodology model is one of the most used statistical approaches (Mahapatra *et al*., 2020). This model was used to evaluate the influence of independent variables (X1: PGZ types, X2: excipient types and X3: compaction force) on dependent variables (i.e., response) variables of Y1 (hardness), Y2 (friability), Y3 (Disintegration), Y4 (Dissolution 1 min.), Y4 (Dissolution 3 min.), Y4 (Dissolution 5 min.), Y4 (Dissolution 10 min.), Y4 (Dissolution 15 min.), and Y4 (Dissolution 30 min.).

RESULTS

Powder Characteristics

Micromeritics results

The powder flow properties of the binary mixtures of all PGZ formulations were evaluated by CI, HR, and AR. The results show the similarity in the flow characteristics of PGZ regular powder in comparison to the micronized

powder. Formulations containing Ludiflash® suggested that the powder exhibited fair flow with both CI and HR data range (17.1%;17.4%, and 1.24;1.27) respectively. For physical mixture formulations, CI and HR results were recorded as good flow (15.6;15.3, and 1.18;1.16) respectively. However, AR indicated that all formulations had excellent flow having and angle less than 25°.

Scanning electron microscope

SEM images oregular crystals. Mag. 1.00 K X and 2.00 K X respectively.
SEM images of pioglitazone regular crystals. Mag. 1.00 K X and 2.00 K X respectivel

Fig. 1a and b show SEM at a fixed magnification of 1000X. The images of PGZ regular and micronized crystals respectively, are seen. The SEM photos show the particle packing of the individual powders. The space between particles and the powder particle clustering.

Post-Compression evaluation of tablets

Results of the quality control tests for all formulations at different forces were obtained and are presented in table 2. The data presented clearly illustrates the excipient's role in the formulation's quality output. Formulations containing a similar composition (Pi-MKK and Pi-MKK-M) as Ludiflash® (Pi-LFS and Pi-LFS-M) recorded harder tablet results in accordance with the target outcomes. The effect of PGZ micronized powder on hardness was also seen.

Hardness

Results of the tablet hardness test were derived from data that was recorded during the mechanical strength valuation of the tablets (n=6). The data shows the relationship between tablet hardness and compaction force. An increase in compaction force gave a proportional increase in tablet hardness. This is the same for all formulations.

In vitro disintegration

Formulations containing physical mixture (Pi-MKK and Pi-MKK-M) at different compaction forces (5kN - 15kN) showed only a slight change in disintegration time (with disintegration time between 32 to 41 secs) collectively. The effect of compaction force on tablet disintegration time can be seen in formulations containing Ludiflash®.

In vitro dissolution

Table 3 depicts the dissolution profile for Ludiflash® containing formulations and formulations containing physical mixture. PGZ should have a release profile of at least 80% at 15 mins according to USP recommendations (USP-NF, 2021).

F-D curve

Fig. 4a and b show the upper punch force plotted against the upper punch displacement. The graphs illustrate the total work of compaction done in relation to tablet composition. The graph illustrates the closeness in total work done with no obvious differences between formulations of similar compositions in respect to compaction force.

Ejection force

All formulations at different compaction forces were pressed at a fixed compaction speed. Hence, the average in-die dwelling time for all formulations at different compaction forces was 20ms. Taking into consideration that SSF lubrication concentration was kept at a constant (1%), ejection force was plotted against time to understand formulation ejection behavior at different forces.

Heckel analysis

The yield pressure results were calculated using the Analis software. Results showed the same trend for all formulations for 5kn and 10kN. The R^2 value for all given formulations was recorded at >0.995 to indicate that the variance of independent variable for all linear regression is a good fit. Ludiflash® containing formulations had yield pressures of 89.6Mpa; 74.2Mpa, and 100.5Mpa; 100.5Mpa at 5kN and 10kN respectively. For formulations containing physical mixtures, there was little change in yield pressure from 5kN to 10kN which was recorded as 91.3Mpa; 93.1Mpa, and 93.2Mpa; 96.8Mpa respectively.

Optimization of post-compression parameters using minitab19™.

The graphical interaction plot in fig. 6 depicts the responses for all formulation and their effects in post-compression outputs. The differences in PGZ type (regular and micronized) did not have an effect on formulation responses for all outputs. Physical mixtures showed better results than Ludiflash® for all responses with exception of friability where there were no significant differences recorded ($p>0.05$).

The results from the Pareto charts are shown in fig. 7. Statistical evaluations were used to input the formulations CMA and CPP. Furthermore, the impact of input variables on outputs was assessed. The pareto chart data also shows the effect of CMA and CPP on the critical quality attributes (CQA). From the chart, it is observed that the type of PGZ grade used in the formulations had no significant effect on any of the outputs (friability %, disintegration time, hardness, and dissolution at 15 mins).

Optimized formulation parameters and fixed points

The prediction for responses showing the probability of success is depicted in table 4. Through computations of set values to achieve the target profile, the Minitab 19™ software was used to derive an optimized set of inputs as variables. Analysis obtained from post-compression

results were used as input and output variables. Hence, an illustration of the set points was analyzed to predict suitable parameters which will have a lower chance of failure and higher probability of success rate.

All responses were derived in accordance with set parameters as seen in table 5. The optimized formulation was measured for Dissolution (1 min, 3 min, 5 min, 10 min, 15 min, and 30 min), Disintegration, Friability, and Hardness. The result shows that all predicted outcomes did fall within the set of given ranges for all set points. All QTTP-determined limits were confirmed.

DISCUSSION

Micromeritics results

The results obtained provide insights into the potential compressibility of the proposed formulations. Given that physical mixture formulations exhibited lower values for evaluated methods (i.e., CI, and HR), it is comprehensive to suggest superior flow characteristics compared to the other formulations. This can be attributed to the composition of the binary mixtures, given that the bulk majority is made up of Ludiflash® and Mannitol in each respective formulation. Taking into considerations that one of the key factors affecting how powder flows is particle size and shape (Thalberg *et al*., 2004).

Scanning electron microscope

Powder particle size and shape play an important role in the compactibility of the powder. The SEM images show a difference in particle size between micronized and regular PGZ, with micronized having smaller particles. The compactibility of a powder during tableting is dependent on a variety of factors, including surface area, crystallinity, morphology, surface energy, and bulk structure (Edge *et al*., 2002). The images show micronized powder packing (agglomerate) and indicate that PGZ micronized powder has a larger surface area, enhancing its compactibility in comparison to regular powder. This result is supported by the hardness test in table 2.

Post-Compression evaluation of tablets

The data illustrates that the micronization of PGZ did not have a significant effect on hardness. This could be as a result of API ratio to excipient, given that PGZ is a low dose therapeutic drug. It is evidently known from literature that in predicting the compressibility of a formulation, there is a proportional relationship with the powder flow characteristics, thereby affecting the tabletability of the powder (Nalluri and Kuentz, 2010; Fassihi and Kanfer, 1986; Nagel and Peck, 2003). Theoretically, the amount of the active ingredient in a binary mixture is vital to the tablet properties of the formulation output (Celik, 1992), however, because of the amount of the drug in the binary mixture this is not applicable in this case. Friability for all formulation passed the test according to USP specifications, with all formulations having a friability percentage below 1%.

Hardness

The effect of compaction force on tablet strength is evident, showing the relationship between the parameter and output. An increase in compaction force is directly proportional to tablet strength increase, which is affected by particle bonding and volume reduction (tablet thickness) (Celik, 1992). As compaction force increases, the powder compact becomes more closely bonded resulting in harder tablets (May *et al*., 2013). As expected, there was an increase in the tablet hardness from 5kN to 15kN. However, the tablet hardness between 15kN and 20kN do not present wide difference in range for individual formulations. The linear relationship between hardness and compression force exists until an optimum threshold is met, resulting in little or no increase in tablet hardness (Higuchi *et al*., 1953).

In literature, the difference in particle size has been seen to have either a positive or negative effect on tablet strength (Higuchi *et al*., 1953; Zhao *et al*., 2018). From data obtained shows that micronized PGZ powder result in harder tablets at similar formulation and forces, however, the differences are not significant. The PGZ ratio in the formulation mixture is a determining factor, considering that most of the powder bulk of the formulation is made up of excipients. Variation in hardness can be attributed to formulation composition rather than the particle size of the active ingredient. The broader particle size distribution of the physical mixture to Ludiflash® could be considered. Given that the in-die particle packing of the physical mixture after compression resulted in higher tablet hardness. This can be seen from data illustration in comparison of formulations with physical mixture to Ludiflash® at all compaction forces, having harder tablets.

In vitro disintegration

As compaction force increases, disintegration time increases (Desai *et al*., 2016). There is a correlation between the mechanical tablet strength and disintegration time, which are directly proportional (Bolhuis *et al*., 2009). The relationship sometimes may not be significant or existent at a selected range of forces. This scenario is seen with formulations containing physical mixture at 5kN and 10kN compaction forces.

From data obtained, it was obvious that formulations containing Ludiflash® were more affected by increase in compaction force than formulations containing the physical mixture. Formulations containing physical mixture gave complete disintegration, however, formulations containing Ludiflash® were observed to have shown erosion behavior rather than disintegration at higher compaction forces (15kN and 20kN).

Table 1: Formulation composition for PGZ ODTs

Formulation Code	PGZ (mg)	Ludiflash® (mg)	Mannitol (mg)	Kollidon® CL-SF (mg)	Kollidon® 30 (mg)	SSF (mg)	Total Weight (mg)
Pi-LFS	15	183	-	-	-	2	200
Pi-LFS-M	15	183	-	-	-	2	200
Pi-MKK	15	-	168.4	8.24	6.41	2	200
Pi-MKK-M	15	-	168.4	8.24	6.41	2	200

Formulation codes and abbreviations: PGZ: Pioglitazone hydrochloride, SSF: Sodium stearyl fumarate, LFS: formulations containing Ludiflash®, LFS-M: formulations containing Ludiflash® and micronized PGZ powder, MKK: formulations containing mannitol physical mixture, MKK-M: formulations containing mannitol physical mixture and micronized PGZ powder.

Table 2: Post-compression results for all compressed formulation tablets

Formulations	Compaction Force (kN)	Disintegration (sec)	St dev.	Hardness (N)	St dev.
Pi-LFS	5	24	6.976	75	5.636
	10	82	4.119	135	9.621
	15	193	2.875	175	13.33
	20	268	7.148	180	24.7
Pi-LFS-M	5	28	6.091	84	4.131
	10	81	4.817	143	7.062
	15	182	1.643	182	1.643
	20	257	5.75	185	11.39
Pi-MKK	5	33	1.966	85	8.854
	10	33	14.45	151	8.377
	15	38	7.278	216	4.546
	20	51	11.22	226	2.608
Pi-MKK-M	5	32	7.789	92	6.442
	10	34	6.919	168	9.745
	15	41	3.266	222	5.61
	20	58	6.626	230	4.215

Table 3: Dissolution (drug percentage release) results for all formulation at different compaction forces. (n=6)

Code	(Compaction Force)	1 min	3 min	5 min	10 min	15 min	30 min
Pi-LFS	5	35	35	36	34	39	44
	10	17	19	21	25	24	24
	15	30	24	24	26	29	29
	20	23	25	26	26	32	30
Pi-LFS-M	5	29	36	32	38	44	51
	10	19	18	18	20	20	23
	15	29	24	25	26	26	30
	20	25	25	27	28	29	31
Pi-MKK	5	50	71	76	83	82	83
	10	49	70	78	83	88	88
	15	37	60	73	78	83	83
	20	46	67	74	81	82	84
Pi-MKK-M	5	41	63	69	74	75	75
	10	45	66	77	82	82	85
	15	34	57	69	73	78	83
	20	34	60	71	82	79	79

Table 4: Yield pressure results from Heckel analysis for all formulations at 5kN and 10kN.

Code	Yield Pressure (Mpa)			
	5kN	R^2	10kN	R^2
Pi-LFS	89.6	0.998	111.5	0.998
Pi-LFS-M	74.2	0.996	100.5	0.997
Pi-MKK	91.3	0.998	93.2	0.997
Pi-MKK-M	93.1	0.998	96.8	0.999

Table 5: Multiple response predictions for optimized formulation output by Minitab 19™.

Variables	Setting			
Tb Pres. Force (kN)	7.7991			
PGZ	A			
EXCP	M			
Response	Fit	SE Fit	95% CI	95% PI
Dis. 30 min	83.48	4.75	(72.53; 94.42)	(62.83; 104.13)
Dis. 15 min	82.43	3.99	(73.22; 91.64)	(65.06; 99.80)
Dis. 10 min	80.59	2.91	(73.89; 87.29)	(67.95; 93.23)
Dis. 5 min	75.78	3.16	(68.49; 83.06)	(62.04; 89.51)
Dis. 3 min	67.89	3.09	(60.74; 74.98)	(54.43; 81.29)
Dis. 1 min	48.02	3.96	(38.89; 57.15)	(30.80; 65.24)
Disintegration (Secs)	29.65	6.18	(15.39; 43.91)	(2.75; 56.54)
Friability (%)	0.5637	0.0297	(0.4953; 0.6321)	(0.4347; 0.6927)
Hardness (N)	129.04	3.28	(121.47; 136.60)	(114.77; 143.30)

Table 6: Optimized formulation results for Minitab 19™ prediction set points.

Response	Output
Dis. 30 min	92
Dis. 15 min	94
Dis. 10 min	89
Dis. 5 min	81
Dis. 3 min	76
Dis. 1 min	57
Disintegration (Secs)	46
Friability (%)	0.65
Hardness (N)	118

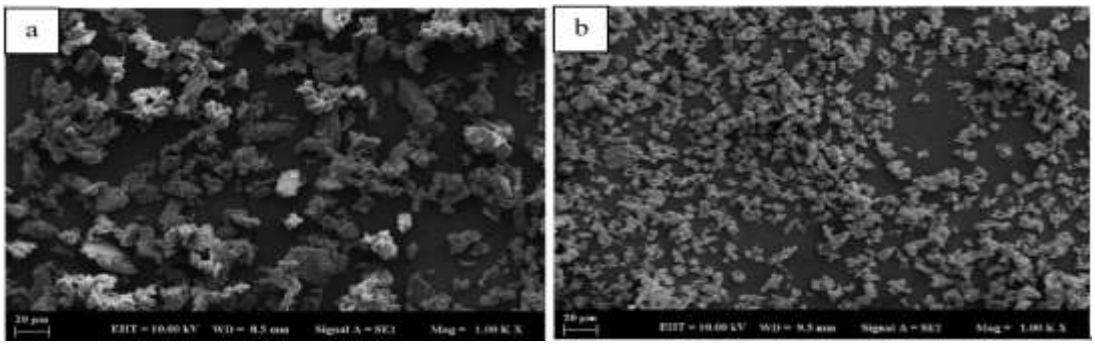

Fig. 1(a-b): SEM images for PGZ powder (regular and micronized respectively) at a fixed magnification of 1000X.

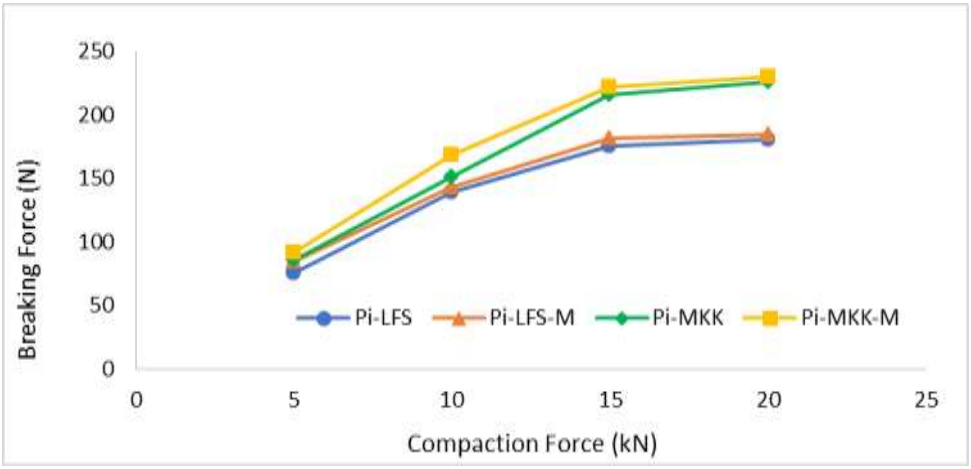

Fig. 2: Tablet hardness comparison of all formulations from 5kN to 20kN compaction forces (n=6).

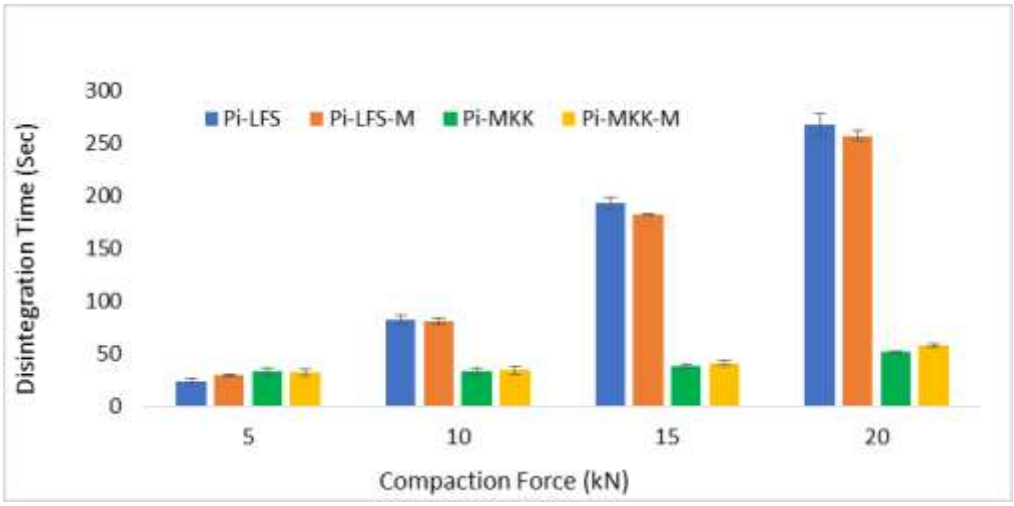

Fig. 3: Disintegration time for all formulations from 5kN to 20kN compaction forces (n=6).

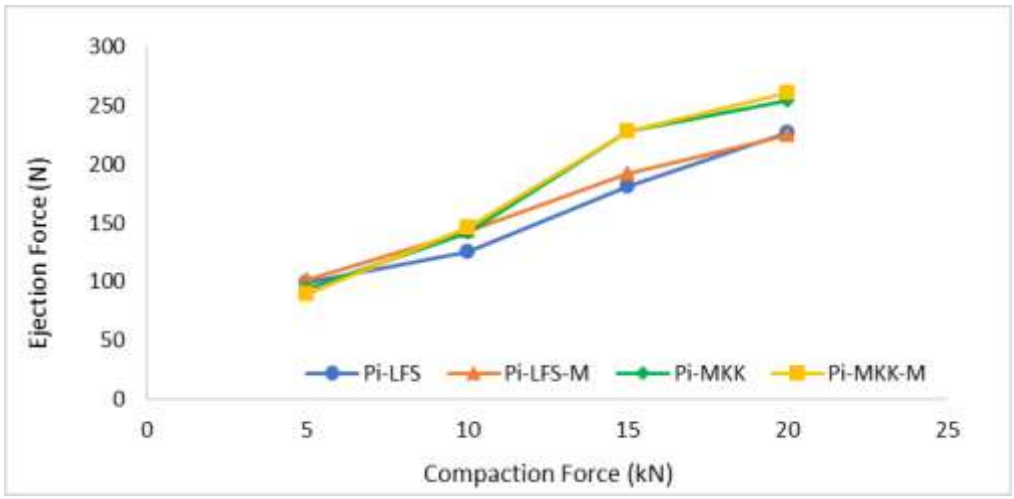

Fig. 4: Ejection force vs compaction force graph for all formulations from 5kN to 20kN.

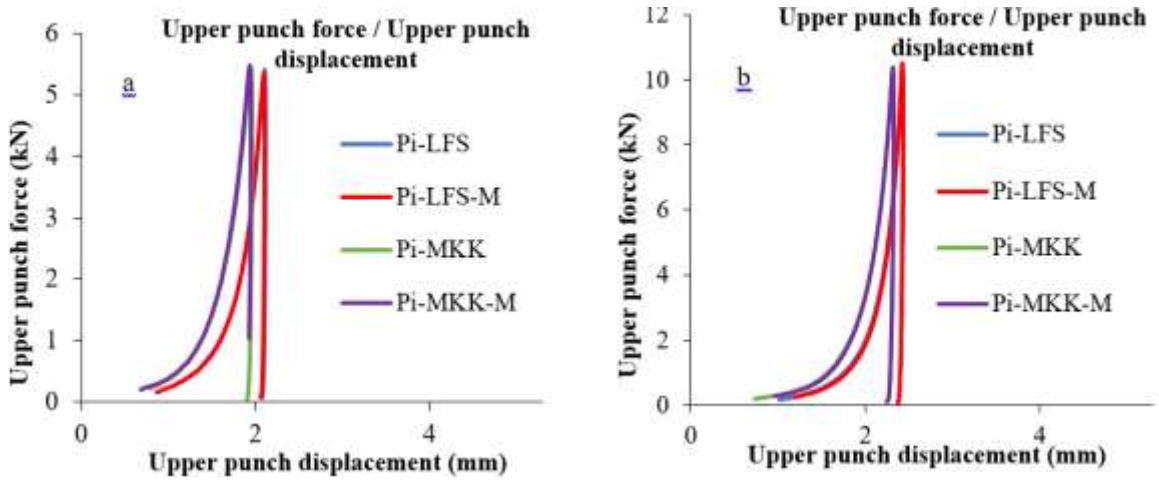

Fig. 5(a-b): F-D curve for formulation compressed at 5 and 10kN respectively (Analis, version 2.01, Medelpharm).

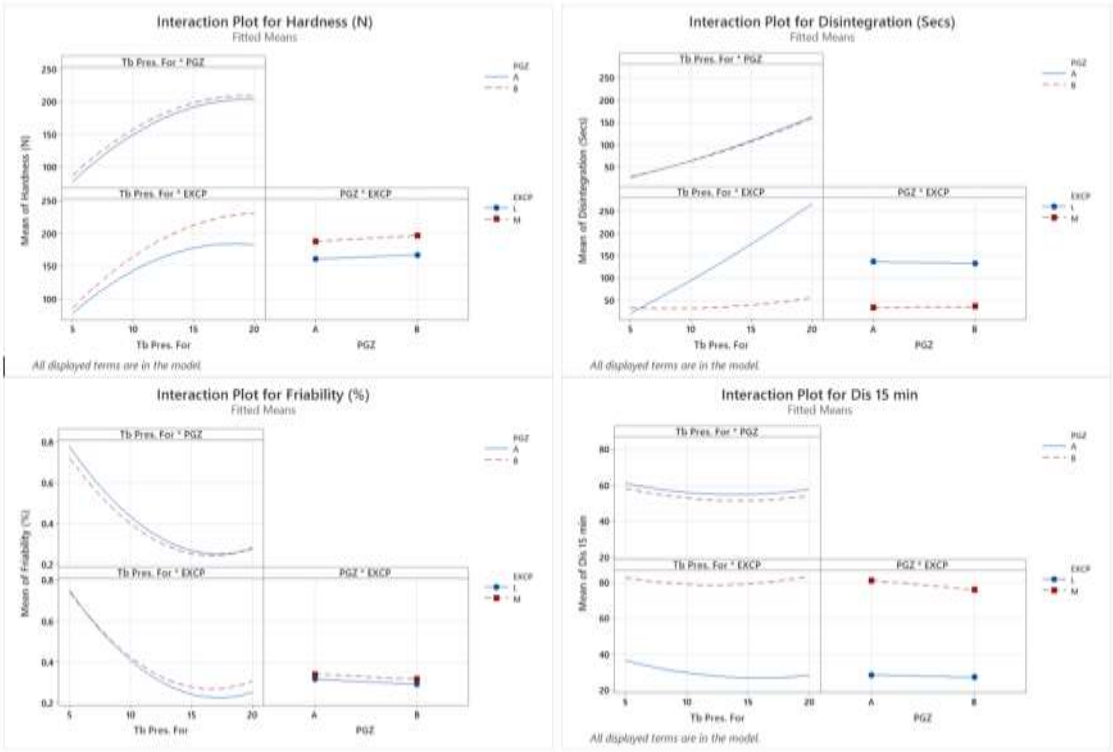

Fig. 6: Graphical interaction plot for Minitab 19™, for all formulations; Hardness, disintegration, friability, and dissolution (at 15 mins) tests.

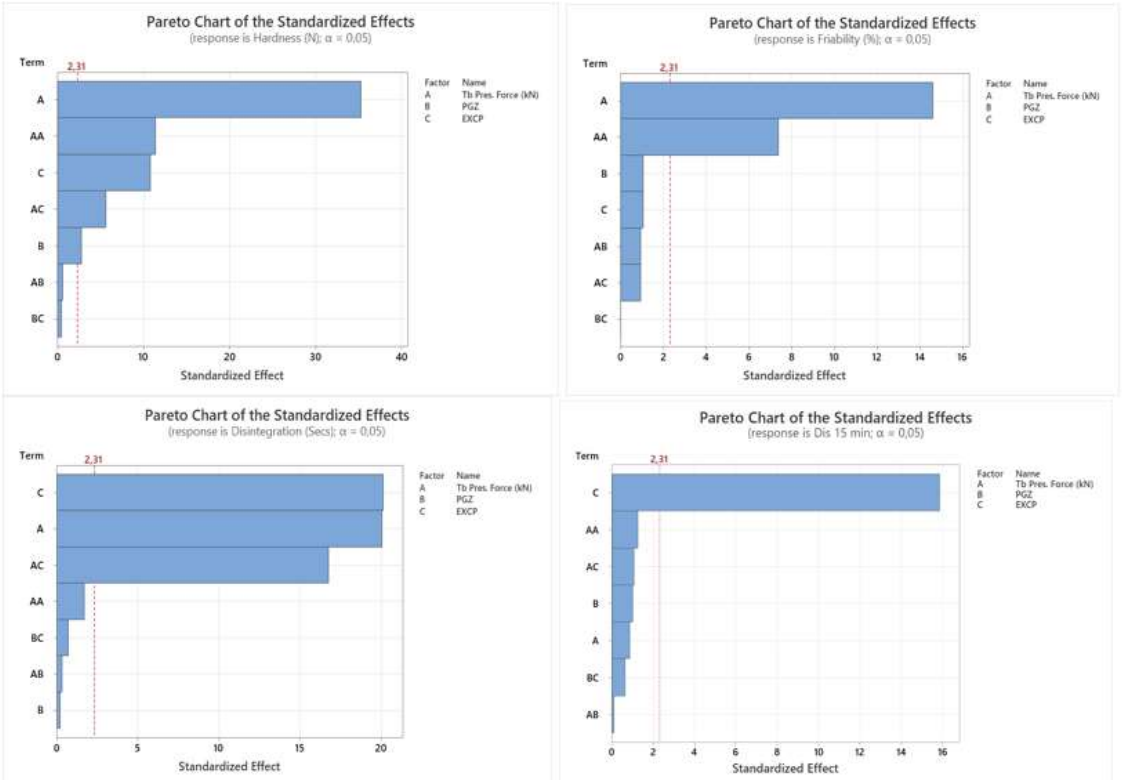

Fig. 7: Pareto chart for input responses; friability (%), disintegration (secs), hardness (N), and dissolution at 15 mins (mins).

In vitro dissolution

At all compaction forces (5kN to 20kN) formulations containing physical mixture and PGZ regular powder grade were seen to have released over 80% of the drug at the stipulated time as seen in table 3. It was observed that all PGZ micronized powder formulations containing either physical mixture or Ludiflash® failed to reach this release profile with the exception of Pi-MKK-M at 10kN. According to the literature, Ludiflash® exhibits a tendency to exhibit swelling behavior during dissolution testing, leading to an alteration of the drug release rate (Lura *et al*., 2019). This phenomenon was observed across all formulations containing Ludiflash® at varying compaction forces. Therefore, physical mixture formulations demonstrated superior drug release properties in comparison.

F-D curve

Compaction data derived from fig. 4a, and b show a comparison of total work of compaction as compression force changes. Volume reduction and particle bonding are expressed through total work of compaction (Fell and Newton, 1970). These factors are suggesting that the total work of compaction can be used to understand our formulation tablet properties.

Formulations containing micronized PGZ have lesser work done on compaction of powder mass than formulations containing PGZ regular powder. As a result of particle size difference, lesser particle surface area will require more energy for particle bonding (Edge *et al*., 2002). An increase in energy signifies an increase in work done needed for better particle bonding. This outcome shows a repeated pattern for all compaction forces and formulations. Formulations containing physical mixture of powder show a higher work done on compaction in comparison to formulations containing Ludiflash®. The increase in work done on compaction for formulations with physical mixture is observed because of a broader particle size distribution (PSD) than that of co-processed Ludiflash®. Due to friction during compaction, and particle packing, there is an increase in energy for consolidation (Lee *et al*., 2021).

Ejection force

From results seen in fig. 5, formulations containing physical mixtures (Pi-MKK and Pi-MKK-M) exhibited more sensitivity at higher compaction forces than formulation containing Ludiflash®. (Uzondu *et al.*, 2018) suggested that an increase in compaction force is subsequently proportional to an increase in ejection force. This behavior can be seen for all formulation at different compaction forces. The high sensitivity of physical mixture on ejection force can be attributed to particle size. A decrease in particle size increase ejection force due to increase surface area which gives an increase contact area with the die wall (Shotton and Ganderton, 1961).

Heckel analysis

As known from literature, the higher the yield pressure (P_y) values, the more brittle fragmentation is observed in the powder bed (Roberts and Rowe, 1985). The results show that all formulations are seen to have more brittle fragmentation tendencies, which is expected given that mannitol is the major component for all formulations (Zhang *et al*., 2017; Souihi *et al*., 2013).

The Heckel analysis derived showed that an increase in compaction force gave an increase in P_y value. As derived from literature findings, it is acknowledged that the P_y value is directly proportional to compaction force (Patel *et al*., 2007). While all formulations displayed an increase in P_y value, formulations that contained physical mixtures did not show a statistically significant increase. This observation may be attributed to the sensitivity of particle size variation of excipients during the direct compression method (Lee *et al*., 2021). Ascertaining that Heckel plots exhibit dependence on compaction force, particle size, and powder density is a well-established scientific observation (Patel *et al*., 2010; McKenna and McCafferty, 1982).

CONCLUSION

The study found that the compressibility properties of PGZ Oral Dispersible Tablet were influenced by compaction force and excipient type, but not differences in PGZ particle size. The tablet exhibited good compressibility and appropriate drug release characteristics, providing valuable insights into its mechanical properties and behavior during the compaction process. The Heckel results of the analysis also revealed that tablets had good compressibility properties and can withstand high compaction pressures without undergoing plastic deformation. With the combination of compaction simulator and Minitab 19™ the optimization of oral dispersible tablet through tablet manufacturing processes was achieved. The PGZ regular powder and physical mixture were identified as the optimized formulation at 7.8kN compaction force, meeting all set points and QTPP. The findings can improve existing products and guide the development of new formulations, ultimately benefiting patients.

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