Development of Directly Compressible Metformin Hydrochloride Using Size Reduction Technique

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ABSTRACT

Solid dosage forms have factually been related to conventional formulations such as tablets due to the ease of manufacturing, administration, and economic feasibility. Metformin hydrochloride shows poor compressibility during compaction, frequently resulting in soft and unacceptable tablets with a high tendency to cap. The present study was aimed to develop directly compressible metformin HCL by the ball milling technique. Powder of metformin was thoroughly examined using the angle of repose for flowability, laser diffraction particle size analyzer, scanning electron microscopy, differential scanning calorimetry, and Fourier transform infrared spectroscopy. Differential scanning calorimetry and Fourier transform infrared spectroscopy experiments displayed that the milled drug did not undergo any chemical or physical modifications. Tablets were compacted using a direct compression method, followed by evaluations of mechanical properties and disintegration testing. The results of milled metformin HCL showed a good compressibility profile and produced harder tablets compared to un-milled. It was concluded that milled metformin provides a good balance between tablet hardness and disintegration time.

Key Words: *Solid dosage forms, Flowability, Ball milling, Metformin HCL, Hardness.*

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INTRODUCTION

Direct compression is a preferred tableting technique due to the ease of manufacturability, use of conventional equipment and excipients, reduced time and energy consumption, as well as improved product stability [1, 2]. For certain APIs, faster dissolution rates may be generated from tablets prepared by direct compression compared to wet granulation [3]. Though, the selection of direct compression technique is highly prejudiced by material physical properties such as compressibility, flowability, powder segregation, and dilution potential [4-6]. The process may not be applicable for materials possessing low bulk density as the produced tablets could be too thin. Similarly, static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing [7]. Additionally, certain APIs have poor compressibility/compactibility and hence are difficult to formulate using direct compression producing tablets that have low mechanical strength [8].

Material compressibility is its ability to exhibit a reduction in volume under pressure, while compactibility is the ability of the consolidated powder bed to achieve desired strength [9]. Tablets are produced upon the application of pressure on powder bed resulting in the formation of coherent compacts. Bonds between particles are established conferring a degree of mechanical strength to the tablet [10]. The volume reduction occurs through one of the three broadly classified processes that are used to classify materials namely plastic elastic and/or fragmentation [11]. The basic principle of milling is to reduce the size of particles which may have a diversity of chemical, mechanical، and physical features. Milling technique reduces the size of particles through the transfer of energy from the miller to the powder resulting in blending and dispersing the powder. The particle size is reduced due to the breakage of bonds within the particle which changes the shape and results in the loss of energy

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in the particles. So, there is a larger surface area produced compared to the original powder as the particles are finer. In this study, ball milling can be a method of modifying API to optimize them for use in tablet dosage forms. API such as metformin can be individually milled to enhance its compressibility.

The main aim of this study was to employ milling as a method of energy input into the particles. The use of milling for flowability and compressibility/compactibility improvement was investigated. This paper dealt with charting the development, testing, and optimization of the applications. In this study, a model high dose poorly compressible API (metformin) was selected to investigate the impact of size reduction on metformin powder properties as well as its mechanical properties such as hardness and friability. The morphology and powder characteristics of the control and milled powders were evaluated using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and Fourier transform infrared (FTIR).

MATERIALS AND METHODS

Materials

Magnesium stearate was obtained from Sigma-Aldrich Company (New York, USA. Metformin hydrochloride was donated from Riyadh Pharma (Riyadh, Saudi Arabia).

Methods

- **Preparation of Milled Powders**

Milled samples of metformin HCL were prepared using a Fritsch Pulverisette ball miller. The powder blends were prepared using a cube mixer for 10 minutes at 500 rpm. Non-milled metformin (F0) was used as control. The formulations and parameters are listed in (Table 1) below.

Table 1: Formulations content and the milling parameters used to prepare 3different powders of metformin HCL in this study.

Code of Formulation	Milling Time (min)	Metformin HCL%, w/w	Mg.st %,w/w	Batch size gm
F0	0	99	1	50
F1	10	99	1	50
F2	20	99	1	50
F3	30	99	1	50
F4	40	99	1	50

- **Powder flowability (angle of repose method)**

Powder flowability was evaluated using the angle of repose technique [12]. 5g of powders were poured through a funnel onto a flat surface. The funnel was placed 10 cm above the horizontal surface, and the powders were permitted to flow freely until the development of a symmetrical cone. Both the base (b) and height (h) of the generated cone were assessed and recorded. The equation below was utilized to estimate the angle of repose ($\boldsymbol{\theta}$). Values were represented as the mean ± standard deviation (n=3).

$$\boldsymbol{\theta = \tan^{-1}(h/0.5b)}$$

The findings of the angle of repose were related to flowability. An angle of less than 30° reveals excellent flowability, the angle between 31-35° is for good flowability, while angles above 45° are an indication of poor flowable powder [13].

- **Particle size analysis**

Powder particle size analysis was performed using Mastersizer 2000, sample dispersion/laser (Malvern, United Kingdom). An R3 lens with a functioning range between 0 and 175 µm was used for this study. The instrument allows the powder to circulate constantly through the system during the measurements through the sample dispersing system dry disperser. Powder sample (0.5 g) was spread over the feeding tray of the VIBRI that transfers the sample into the dispenser. Plots of particle size distribution were achieved covering the range from 0.5-175 µm. Parameters like the volume mean diameter (VMD), X10, X50 (median, 50% volume percentile), and X90 were obtained. All the measurements were carried out in triplicate.

- **Scanning Electron Microscopy (SEM)**

SEM technique was carried out to assess the morphological structure of particles. Samples were distributed by sprinkling on a double adhesive carbon tape placed over an aluminum stub. Then, samples were coated twice with gold in a sputter auto fine coater Jeol JFC-1600 (Jeol Equipment, Tokyo, Japan) at 30mA for 5 minutes and then examined by the SEM before imaging to enable sample conductivity. The sample imaging was performed on a field emission scanning electron microscope.

- **Differential scanning Calorimetric Studies (DSC)**

Thermal analysis was carried out using the DSC technique. Q-200 DSC system (TA instruments–Waters New Castle, DE, USA) was employed to determine melting point temperatures of the excipients and formulations in their powder form. About 3 mg of the samples were loaded into aluminum pans and heated to 300°C at 10°C/min with a nitrogen purge. An empty aluminum pan was used as a reference for all measurements. The resulting graphs were analyzed by TA manager software. Melting point values were measured from the intersection of relative tangents to the baseline.

- **Fourier Transform Infrared (FTIR)**

Fourier transform infrared (FTIR) spectra were recorded on solid samples utilizing the Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer (Hertfordshire, UK), coupled with Thermo Scientific OMNIC software that is used to operate and analyze FTIR spectra. A sample of approximately 10-20 mg was loaded on the iD5 ATR Diamond sample holder above a laser lens and held in place by screwing down the relevant pressure screw till the clutch mechanism provided maximum surface contact with the sample. For each sample's IR spectrum, scans were obtained over the range of 500–4000 cm^{-1} with a resolution of 2 cm^{-1}.

- **Tablet characterization**

Powder mixes were compacted into 860 mg tablets under a compression force of 3 tones, with a dwell time of 10s before the compression force was released. The tablet press applied for preparing the tablets was a bench-top semi-automatic hydraulic press from Specac Ltd. (Slough, UK) equipped with flat-faced dies of 13 mm diameter. Tablets were characterized for hardness, disintegration time, and friability.

- **Tablet hardness**

A tablet hardness tester (TBH 425) from Erweka (Heusenstamm, Germany) was used to investigate the hardness of three tablets of each formulation. All measurements were carried out in triplicate and were measured in Newtons (N) for this study. The values were reported as mean ± standard deviation.

- **Tablet friability**

Friability was measured using a Roche friabilator from J. Engelsmann AG (Ludwigshafen, Germany). 6 tablets were rotated at 25 rpm for 100 revolutions. Tablets were de-dusted before and after the test, and friability was presented as the percentage loss in weight. The percentage loss in weight (% Friability) was determined by utilizing the following equation.

$$\%\ Friability = \frac{Initial\ Weight - Final\ weight}{Initial\ weight} \times 100$$

- **Tablet disintegration**

A disintegration tester (D-63150) from Erweka (Heusenstamm, Germany) was utilized. A tablet was situated in the disintegration basket (without using a disk) which was raised and lowered at a constant frequency of 30 cycles/min in the disintegration medium. Distilled water (800 mL) maintained at 37°C was utilized as the disintegration medium while disintegration time was recorded for one tablet at a time to improve the accuracy of recording. Time of disintegration was recorded when all the disintegrated fractions of the tablet passed through the mesh at the base of the disintegration basket.

- **Statistical Analysis**

Statistical analysis studies were carried out utilizing Graph Pad Prism software (Version 6.01, CA, USA). As applicable, t-test, one-way analysis of variance (ANOVA), and pair-wise multiple comparisons method (Tukey's test) were utilized to compare data groups by utilizing mean values and standard deviation (SD). The significant difference was measured utilizing the probability value of 95% ($P<0.05$).

RESULTS AND DISCUSSION

Metformin is a known poorly compressible API [14]. It is highly water-soluble, hygroscopic, and suffers from poor stability. Using a size reduction technique, the aim was to produce directly compressible material (metformin) allowing high load while retaining its stability [15].

Flow property and particle size analysis

An important requirement for excipients in direct compression is good flow properties as it has an impact on uniformity [16]. Characterizing flow properties of unmilled metformin (F0) and milled metformin (F1-F4) were performed through the measurement of the angle of repose. The morphology of the particles as well as their particle size distribution may also impact flow properties. Metformin flowability diverse between passable to poor or very poor flows based on the angle of repose. Unmilled metformin is a powder that has passable flowability (angle of repose 42.46±2.5º); improvement of this property will enhance the quality of the final dosage form pertinent to weight uniformity [17]. Additionally, the irregular shape of powder flow might entrap excess air in tablets during compaction which will result in tablet capping and lamination [18]. The addition of MCC as a binder with an excellent flow property (angle of repose 44.24±2.34º) deteriorated the flow properties of metformin with a reduction in the particle size from 83.11 to 11.16. Therefore, reduction in the size of metformin resulted in a statistically significant increase in the angle of repose and hence poor flow properties (t-test, $p<0.05$). The analysis of particle size measurements is depicted in Table 2. The X90 of F0, F1, F2, F3, and F4 of metformin is expected a very cohesive fine powder. Additionally, particle shape also contributes to the flow properties (see figure 1).

Table 2: Flow properties of unmilled metformin (F0) compared to milled metformin HCL mannitol (F1-F4) and the particle size analysis parameter (X90), angle of repose (°) and the corresponding flow property.

Product	X90	θ (°)	Flow property*

F0	83.11±3.03	44.24±2.34	Passable
F1	60.26±0.14	46.05±0.97	Poor
F2	41.37±0.23	48.11±1.23	Poor
F3	19.88±2.17	53.39±0.34	Poor
F4	11.16±2.17	55.17±3.11	Poor

*Excellent flow when the angle of repose (θ): 25-30°; Good: 31-35°; Fair: 36-40°; Passable: 41-45°; Poor: 46-55° [19].

Scanning Electron Microscope (SEM)

Particle shape donates to flow properties of powders where the spherical shape has minimal inter-particulate contact and particles which are shaped liked flakes and dendrites tend to have low flowability due to the increase in surface/volume ratio [20]. SEM micrographs of unmilled and milled metformin HCL are shown in Figure 1 (a-b) and (c-d) respectively. The preliminary screening of the morphology of metformin HCL exhibited that where the particles showed needle, rod-shaped particles with surface holes and fragmentations, support both poor flowability and compressibility despite the large particle size of the powder as shown in Figure 1. The needle-like shape contributes to the poor flow properties and low compressibility of metformin. Also, it was noted that metformin HCL particles are agglomerated possibly owing to its cohesive property [21]. It was also observed that milling metformin had modified most of the needle-like/longitudinal structure of the original crystal to more globular structures with size reduction to 15 µm as seen in F4.

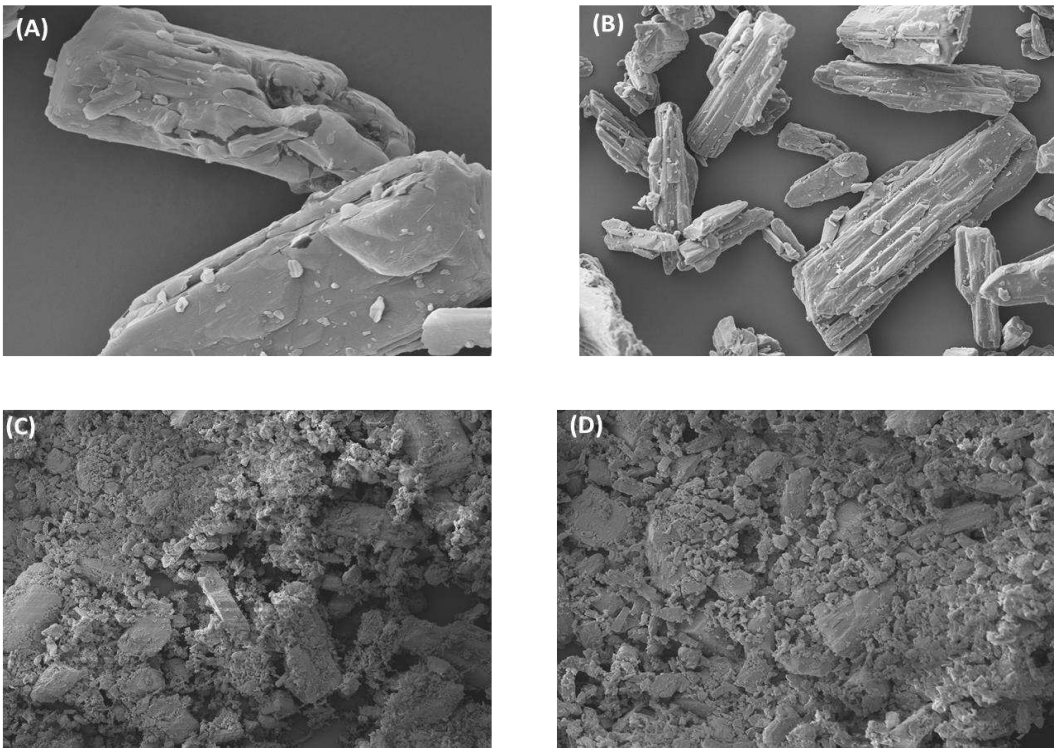
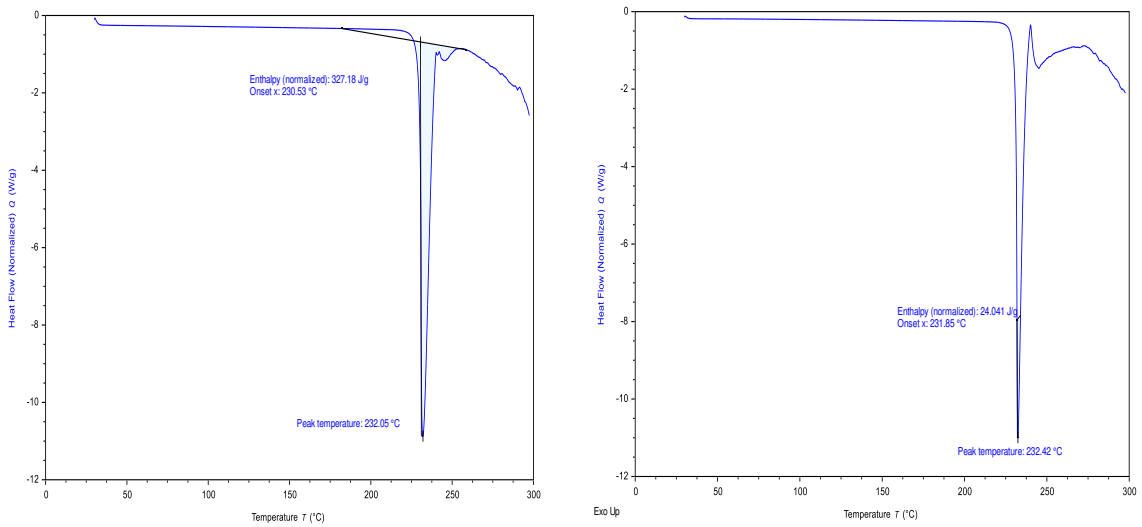


Figure 1: Scanning electron micrograph with different magnifications of (a and b) un-milled metformin HCL, and (c and d) milled metformin HCL (F4) powders.

- **Differential Scanning Calorimetric (DSC) and FTIR Studies**

Metformin powders were tested for melting point using DSC to establish crystal state alongside FTIR analysis. Finally, to ensure compatibility of MCC with metformin and the ability of a dry coating to retain the innate characteristics of the actives, FTIR and DSC were performed. Based on DSC analysis, no other transition or melting points were observed. The milled metformin was chemically stable and there were no reactions to the material. Furthermore, DSC thermal profiling as shown in figure 2 indicated that there was no difference in the crystal state post-milling as the thermal profile had remained very similar to unmilled metformin (F0). This proposed that there were no amorphous regions in the milled powders. Thermal analysis of the powders (both unmilled and milled) showed the endothermic peak at 232°C followed by the decomposition peak starting at 253.4°C. Similar results were reported by Santos *et al.* (2008) [22].



(a) (b)

Figure 2: DSC heating curves showing the melting point event as a function of temperature for (a) unmilled metformin powder (F0) and (b) milled metformin HCL (F4).

FTIR spectrum for metformin powders (unmilled or milled) as depicted in figure 3 (a and b respectively) exposed the two characteristic bands at 3368 and 3151 cm^{-1} attributed to primary stretching of N-H, whereas the secondary stretching band was shown at 3148 cm^{-1}. Additional troughs representing C=N stretching appeared at 1564 cm^{-1} [23]. There was no shift or change in any of the characteristic troughs indicating the ability of the milling process to retain the distinctive properties of metformin powders.

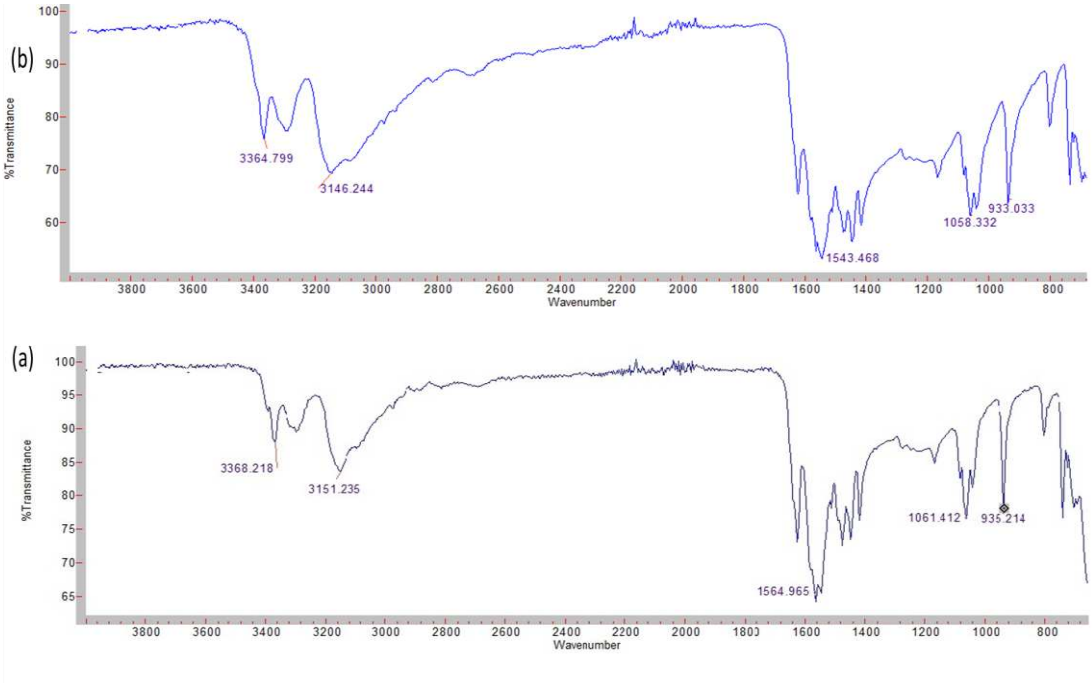


Figure 3: FTIR spectra of (a) unmilled powder metformin HCL and (b) milled metformin (F4).

- **Mechanical properties of tablets**

Tablet dosage forms are exposed to various mechanical forces during the manufacturing steps and transportation. Consequently, a successful tablet formulation must have sufficient mechanical strength [24]. The results for the hardness of tablets made from unmilled or milled metformin and 1% w/w magnesium stearate showed a significant hardness for all formulations ($p<0.05$) (Figure 4). Tablets' hardness showed significant enhancement for the four milled formulations upon the decrease in particle size. The improvement of friability, though not statistically significant, displayed a drastic decrease in friability upon size reduction by up to 45%. These results imply the

superiority of milling in improving the compactibility of metformin compared to un-milled metformin.

A brittle fragmenting for unmilled metformin which indicated that the material was densifying particle rearrangement through fragmentation. On the other hand, milled metformin showed an improvement in the compressibility of the powder and its mechanical properties perhaps due to the lower degree of fragmentation under compression and more plastic deformation profile [25]. Furthermore, SEM results showed that longitudinal particles of metformin that resulted in the very poor hardness of tablets [26].

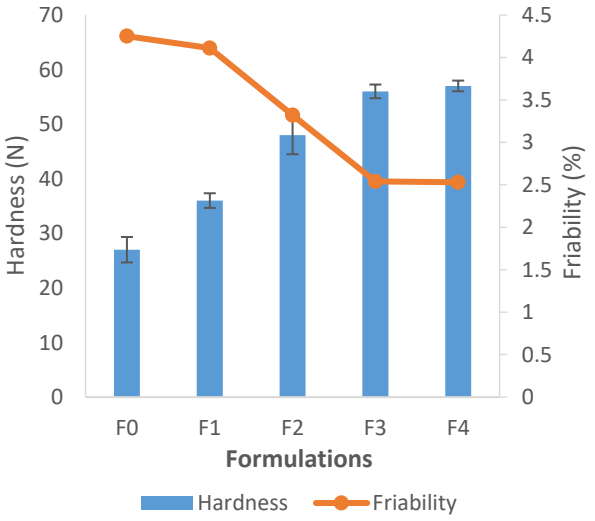


Figure 4: Hardness and friability profile of control (F0) and milled metformin (F1-F4) tablets. Tablets were compressed at 3 tonnes compression force. Results of hardness were reported as mean±SD (n=3).

Disintegration time

The disintegration time of metformin HCL tablets prepared from different milled powders was evaluated (figure 5). Disintegration time of compacts varied according to the type and concentration of pharmaceutical materials, with a remarkable reduction in disintegration time with increasing concentration of super-disintegrants suggesting that it swells upon contact with water through wicking which provides the basis of fast disintegration properties [27]. The results showed that disintegration time tended to increase alongside the enhancement of hardness of tablets, this was expected as the harder tablets resulted in less water being able to wick into the metformin tablet [28]. The disintegration time was observed generally lower than the control formulation (F0) which may indicate that the tablets had an enhanced wetting time and had a higher affinity for water due to the small particle size of the metformin [29]. Statistically, F0, F2, F3, and F4 showed a significant difference in disintegration time (ANOVA, $P<0.05$).

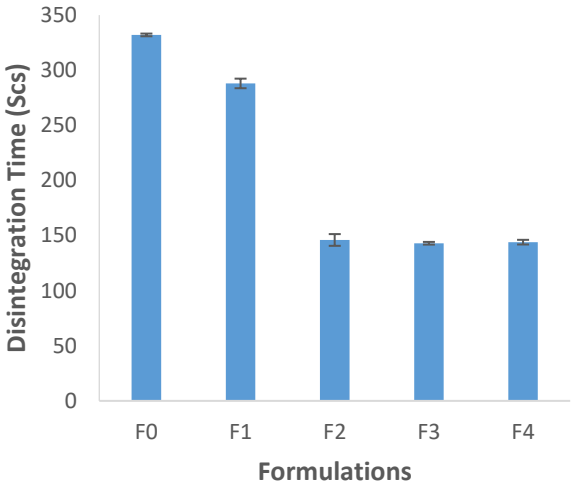


Figure 5: Disintegration time profile of control (F0) and milled metformin (F1-F4) tablets. Tablets were compressed at 3 tonnes compression force. Results were reported as mean±SD (n=3).

CONCLUSION

The application of a size reduction technique using ball milling in the compressibility of poorly compressible drugs such as metformin HCL improvement is a step forward in the pharmaceutical industry. The ability of the technique to enhance the mechanical properties and disintegration time using milling provides a multitude of advantages. The process is solvent-free and does not involve any drying step or use of any organic solvents. The stability of the metformin HCL was not exposed as evident from FTIR and DSC results. Due to the high friability and low hardness of metformin HCL based tablets, reduction of particle size of metformin powder was achieved to enhance mechanical strength and friability of tablets due to reduced fragmentation during compression and improved compressibility. Accordingly, milled metformin (F3) will be taken forward to the next stage to design and develop a fixed-dose combination (FDCs) of type 2 diabetes oral solid dosage forms.

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Conflict of interest

There were no conflicts of interest.

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