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Understanding the implication of Kawakita model parameters using in-die force-displacement curve analysis for compacted and non-compacted API powders

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Abstract

The aim of this study was to investigate powder mechanics upon compression using data obtained from force-displacement (F-D) curves. The Kawakita model of powder compression analysis was adopted in order to compare the pressure-volume reduction relationship of the drug powders in relation to the F-D curves. Experiments were carried out on six model drugs (metronidazole, metformin, secnidazole, ciprofloxacin, norfloxacin, and mebeverine). The drugs were compressed at different pressures in the non-processed or processed (using a roller compactor) forms. Results indicate the similarity between the F-D curves and a rearranged form of the Kawakita model. The foregoing enables the calculation of two important powder parameters, "*a*" (maximum powder volume reduction) and "P_k" (pressure required to achieve half of the maximum volume reduction) from the F-D curves without the need, as in the case of the conventional Kawakita model, to compress powders into tablets at different compression forces.

Keywords: Compacted powders, Compression analysis, Elastic recovery, Force-displacement curve, Kawakita equation, Mathematical manipulation

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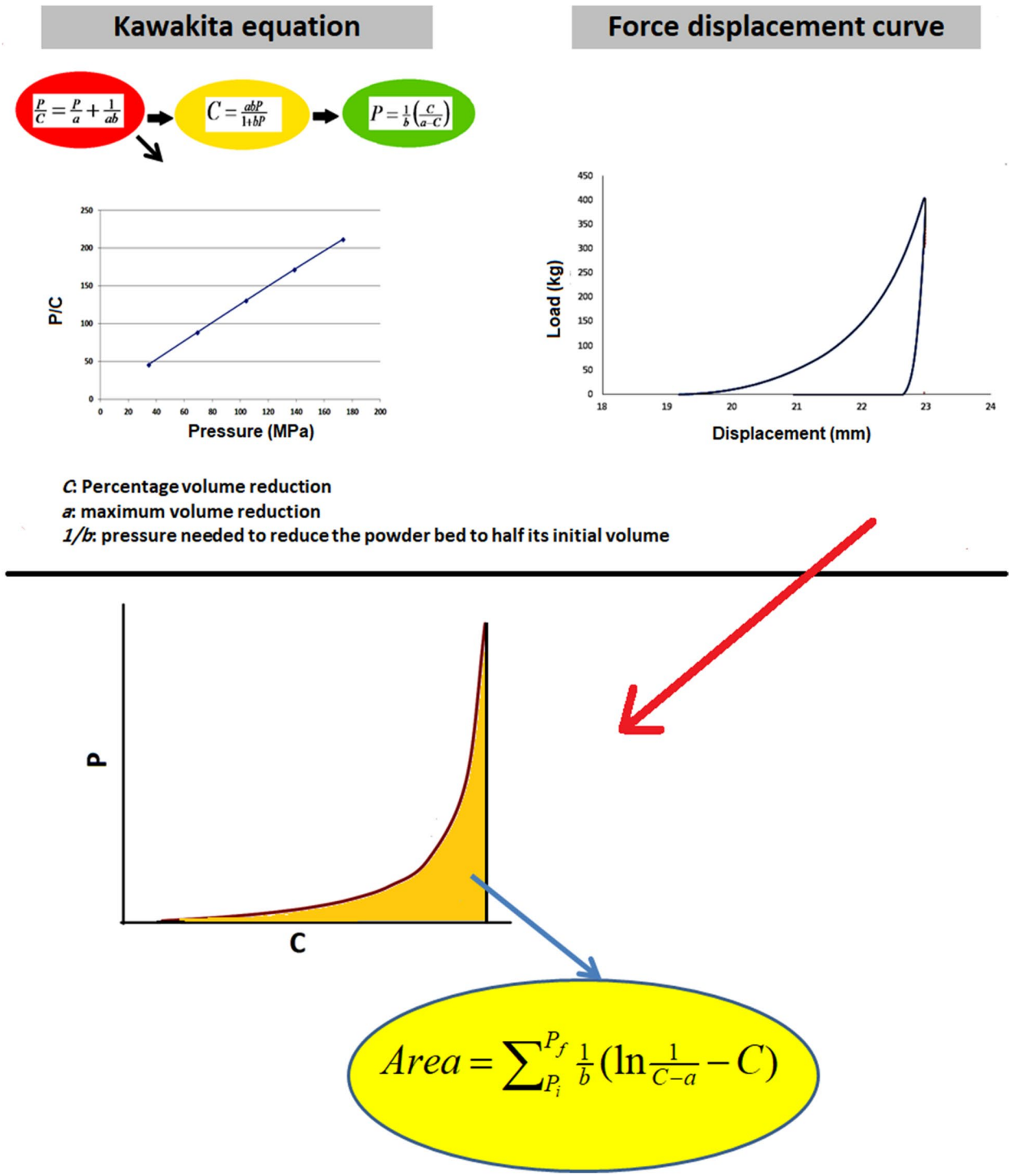
Graphical abstract



Introduction

Powder compression has been investigated to understand the behavior of powders under various mechanical loads (Jonsson et al., 2017; Worku et al., 2017; Chung et al., 2016; Roopwani & Buckner, 2011; Almaya & Aburub, 2008; Busignies et al., 2006). The intrinsic material properties of drug powders, i.e., plasticity, elasticity, brittle-fracture, and powder densification are usually theoretically estimated by means of a number of mathematical models (Ilkka & Paronen, 1993; Shivanand & Sprockel, 1992; Lin & Cham, 1995; Nordstrom et al., 2009; Pasha et al., 2013; Tomas, 2004; Russell et al., 2014; Rathbone et al., 2015). Such models are mainly based upon the change in powder bed size when a material of a specific density is subjected to a mechanical load. Heckel and Kawakita equations are the most common mathematical models used to characterize powders of specific true or bulk densities, respectively (Ilkka & Paronen, 1993; Shivanand & Sprockel, 1992; Lin & Cham, 1995; Nordstrom et al., 2009; Heckel, 1961; Krycer et al., 1982). Once a specific load is applied to compress a powder bed into a tablet, the new bed dimensions are measured. Compression profiles obtained from such data are used to deduce parameters that can be interpreted in relation to the nature of the plasticity/brittleness of the powder and the extent to which the powder particles can undergo rearrangement and compression (Ilkka & Paronen, 1993).

Another common method used to describe the behavior of a powder subjected to a specific load is the force-displacement (F-D) curve. When the applied load of a tablet press is plotted against displacement of the upper punch, a curve with increasing slope is obtained. Moreover, when the applied load is removed the powder bed expands corresponding to the elastic recovery of the powder which causes displacement of the punch in the opposite direction. The path drawn in the form of two intercepting curves—resulting from recording such displacement using force transducers—correlates to the compression mechanics of powders (Gharaibeh & Aburub, 2013; Pawar et al., 2016). From the area under these curves (i.e., the F-D curve), the compression and decompression energies can be deduced and, theoretically, attributed to the deformation mechanics of the powders (Dwivedi et al., 1991; Oates & Mitchell, 1989). However, the area under the F-D curve is regarded as an indication of the plastic and elastic behavior of the powder under investigation. Likewise, this area does not provide numerical parameters which can be used to quantify the extent of plastic/elastic/brittle behavior or powder compressibility. Nevertheless, Antikainena and Yliruusia have determined the plasticity of powders by correlating the areas under the curve confined to the difference between the maximum compression pressure and the maximum displacement (Antikainen & Yliruusi, 2003). Despite their finding, the area under the F-D curve itself was not included in their correlations to express powder mechanics data. The aforementioned problem continued until Roopwani and Buckner attempted to establish a statistical model to correlate the F-D curve with powder mechanics using principal component analysis (Roopwani & Buckner, 2011). In this technique, solid fraction parameters, in addition to a mechanical work parameter, were statistically processed to predict the deformation behavior of powder mixtures. The solid fraction parameters were composed of the mass, true density, and bed dimensions of the powders examined. However, there was no clear mathematical outcome that related the properties of the materials with their energy upon compression (or area under the F-D curve). This lack of information necessitates a different approach to be adopted in an attempt to gain a better understanding of the implications and significance of the area under the F-D curve.

The two compression models, Heckel and Kawakita, and the F-D curve are commonly used to describe powder characterization upon compression whereby an applied force causes a reduction in volume (Heckel and Kawakita models) or displacement (F-D curve) of the powder bed. However, the difference between the two models and the F-D curve is only manifested in the measurement of powder bed dimensions. With regard to the Kawakita equation, bed dimensions are considered based upon tablet thickness after completion of powder compression at each applied force (Nordstrom et al., 2009). While in the case of F-D curves, bed dimensions are considered throughout the movement of the upper punch which takes place when the applied load increases gradually up to the maximum value assigned to the instrumental tablet press (Patel et al., 2006). Therefore, the applied load/pressure-volume reduction relationship estimated using the Kawakita model should be intrinsically similar to the applied load/powder displacement outcome from the F-D curve. Accordingly, when the concept of Kawakita model is re-evaluated, it is suggested in this work that the F-D curve is made up of a series of "Kawakita points" each representing the compression of an in-die tablet. Such an approach renders compression analysis simpler and more time saving than that manifested by classical Kawakita analysis. The later requires tablet ejection and measurement of its thickness after each compression force (Alakayleh et al., 2016). In contrast, the applied load can be considered to be composed of increasing successive loads. Thus, one applied load is practically sufficient to provide the same powder mechanics and, thereby, powder compression and tablet properties can all be determined using the F-D curve. The higher the

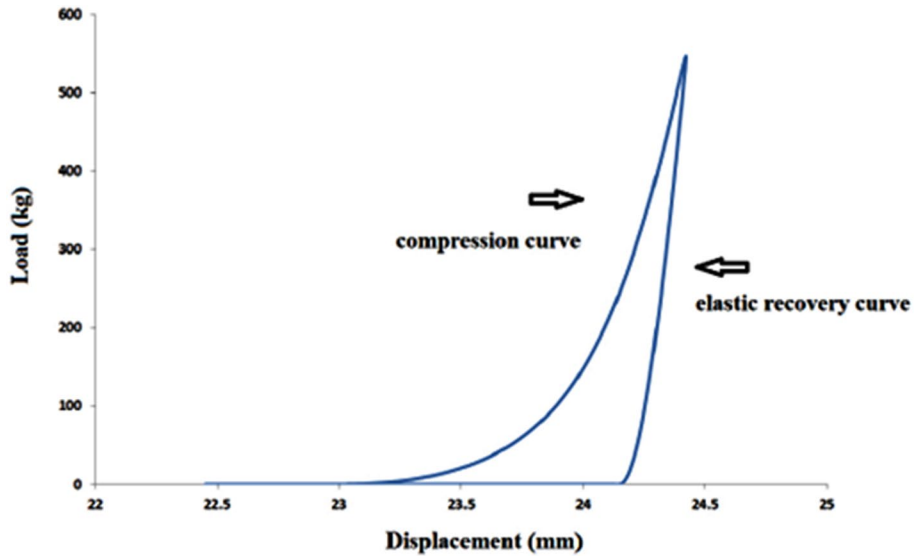


Fig. 1 Typical F-D curve plot representing compression process using GTP

value of the applied load used, the better the description of the aforementioned correlations to the compression behavior.

Force-displacement analysis has already been utilized to perform in-die Heckel analysis whereby first derivative plots of displacement–force profiles were found to determine deformation behavior of powders (Gharaibeh & Aburub, 2013). However, the principle of the F-D curves is technically similar to the Kawakita model since both principles describe pressure-powder displacement relationship. This is in contrast to Heckel analysis which describes a porosity-pressure relationship. Such model (Heckel) assumes a linear relationship between the logarithmic inverse of powder porosity and the applied pressure. For pharmaceutical powders, these plots are generally not linear on the whole pressure range which corresponds to rearrangement and/or fragmentation (Busignies et al., 2006). Moreover, determining the type of deformation (plastic/elastic or brittle) using the Heckel equation was found to be highly sensitive to small errors in true density measurement. The later may result in up to, for example, a 14% difference in yield pressure determination for a true density error of 0.5% (Rojas & Hernandez, 2014). Accordingly, the F-D was not considered in this work to calculate Heckel parameters.

The work reported herein was conducted in order to evaluate any similarities in the correlation between Kawakita plots and F-D curves upon powder compression. Six APIs (metronidazole, metformin, secnidazole, ciprofloxacin, norfloxacin, and mebeverine) that are commonly processed through wet granulation and used at high mass content in tablet dosage forms (or high strength tablets) were used in compacted and non-compacted forms. These APIs were chosen on the basis of their poor flowability and poor compression properties, in addition to their high dose, all of which create formulation problems (Odunayo et al., 2021; Mady et al., 2021; Raval et al., 2013; Azad et al., 2021a; Bawuah et al., 2020; Sharaf et al., 2006; Siddiqui et al., 2021). Such problems are commonly attributed to the API's particle size and shape, to the materials low bulk density, and to the mode of deformation upon powder compression which, the latter, creates lower surface areas available for particle-particle bonding (Casian et al., 2022). The compression behavior of these AIPs was assessed using the two techniques (Kawakita plots and F-D curves) for non-compacted and compacted API powders. The latter, i.e., compaction of APIs, was thought to present major changes in particles size and shape, in powder bulk density and somehow in powder's mode of compression (plastic or brittle-fracture deformation). Furthermore, the Kawakita equation was rearranged in order to show that the parameters (a and P_k) used in this equation can be deduced directly from force (pressure)-displacement curves. The approach was validated by investigating the compression behavior of the APIs with and without roller compaction of the drug powders. Such technique has demonstrated its ability to manifest variations in powder bulk density and particle morphology, surface area, and crystallography. All these properties are major variables which determine the two main Kawakita parameters (a and P_k) (Abu Fara et al., 2020).

Materials and methods

Materials

The following pharmaceutical grade API(s) were investigated: metronidazole (Shreeji Pharma International, Gujarat, India) of D90 = 54 μm, metformin (Zhuhai Tianjian Chemical Co., Ltd., Zhuhai, China) of D90 = 60.4 μm, secnidazole (Wuhan Shu Ou Technology Co., Ltd., Wh City, China) of D90 = 48 μm, ciprofloxacin (Wuhan Dong Kang Yuan Technology Co., Ltd., Hubei, China) of D90 = 55.6 μm, norfloxacin (Zhejiang Neo-Dankong Pharmaceutical Co., Ltd., Yantou Industry Zone, China) of D90 = 61 μm and mebeverine (RA Chem Pharma, Hyderabad) of D90 = 38 μm. The D90 particle size for all materials was measured using a laser diffraction Malvern particle size analyzer (Malvern Panalytical Ltd, Malvern, UK). The instrument uses the Mastersizer 2000 (version 5.6) software to display the results.

Methods

Bulk density and roller compaction of drug powder

The bulk densities of the non-compacted ($n = 5$) and compacted drug powders ($n = 5$) was determined by pouring 20 g of the powders into a 50-mL graduated cylinder. The volume attained by the added powder was recorded and the bulk density was calculated by dividing the drug weight (g) over the volume (mL). In total, 500 g of each drug powder was processed using a roller compactor (TFC-LAB Micro, Vector Corporation, USA) equipped with serrated surface rollers. The compactor parameters were fixed at a roll speed of 3 rpm, screw speed of 25 to 30 rpm, and roll pressure of 6 MPa, and the gap width was controlled via hydraulic pressure and fixed at 2 mm between the rollers. The compacted sheets produced were ground and sieved using an oscillating granulator (AR-401 Erweka model, ERWEKA GmbH, Heusenstamm, Germany) with a mesh size of 700 μm.

Compression of powders using the Gamlen Tablet Press

A total of 200 mg of each drug under investigation was weighed and added into the 6-mm die of a Gamlen Tablet Press (GTP; Gamlen Tableting Ltd., Biocity Nottingham, Nottingham, UK). Manual addition of the powders was gradually carried out without tapping as the Kawakita compression model, used herein, is dependent upon the bulk densities of the powders examined. Compression was then carried out using the 6-mm circular punch of the GTP at a set speed for all samples of 60 mm/min. Compression data were statistically tested for reproducibility of three times repetition of compression of the powder. The applied loads used were 100, 200, 300, 400, and 500 kg. Lubricants were not added to the powders in order not to disrupt the arrangement of particles prior to compression (Rashid et al., 2010).

Two types of data were deduced from the GTP upon compression of the powders; namely, the work exerted on the powder during compression and the pressure-volume reduction relationship corresponding to the Kawakita equation. A typical F-D plot representing compression carried out by the GTP is presented in Fig. 1. The area under the F-D curve—corresponding to the work of compression and elastic recovery—was numerically calculated by the summation of areas of the rectangles having a width comprising the difference between two successive displacement points and a height comprising the average force of the two successive points. Following compression, ejection of the tablets was carried out using the GTP ejection mode. The thickness of the tablets, which was used in the Kawakita analysis, was immediately measured using a caliper. Tablet hardness was measured in Newtons (N) units using a hardness tester (Copley, Nottm Ltd., Therwil, Switzerland).

Mathematical rearrangement of Kawakita equation

The Kawakita equation, which describes the volume reduction in the drug powder bed when subjected to compression, is given in Eq. 1:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \tag{1}$$

Whereby P is the applied pressure, C is the degree of reduction in powder volume (or relative volume reduction), "a" and "b" are constants where a represents the maximum degree of compression and "$1/b$" (P_k) is the pressure needed for the powder to reach half of the maximum volume reduction or $a/2$. The Kawakita equation can be rearranged to give Eq. 2 (Nordström et al., 2009; Nordström et al., 2008):

$$P = \frac{1}{b}\left(\frac{C}{a - C}\right) \tag{2}$$

The rearranged Kawakita equation can be used to plot the relation between pressure and degree of volume reduction carried out on powders compressed into tablets over a specific pressure range. These plots are suggested, herein, to be a typical F-D curve relationship which is carried out on powders at a specific applied pressure. This analogy was based on the fact that both the F-D curve and the Kawakita model describe the effect of an applied force on the axial movement of a powder in a die of the compression machine. Consequently, the area under the curve of

Table 1 Kawakita parameters (P_k and a) and tablet hardness values measured upon compression of non-compacted (BC) and compacted (AC) drug powders using the Gamlen Tablet Press. Bulk density was measured for BC and AC powders prior to compression

Drug	P_k, BC	P_k, AC	% Change in P_k	a, BC	a, AC	% Change in a	Hardness, N, BC	Hardness, N, AC	Bulk density, g/mL, BC	Bulk density, g/mL, AC
Mebeverine	4.78±0.042	10.02±0.13	+ 109.6	0.771±0.01	0.561±0.01	− 27.2	29.1±2	58±4	0.273±0.05	0.517±0.06
Metronidazole	5.608±0.057	8.687±0.09	+54.9	0.504±0.06	0.492±0.01	− 2.4	10±3	10±2	0.681±0.07	0.685±0.08
Norfloxacin	15.584±0.011	14.031±0.32	− 9.96	0.581±0.03	0.515±0.04	− 11.4	64.8±5	52.15±3	0.584±0.03	0.658±0.07
Metformin	15.047±0.012	8.061±0.13	− 46.42	0.629±0.01	0.546±0.01	− 13.2	51±3	43±2	0.509±0.04	0.542±0.04
Ciprofloxacin	4.842±0.018	9.566±0.20	+97.56	0.838±0.04	0.569±0.03	− 32.1	47.5±5	145±4	0.239±0.06	0.559±0.03
Secnidazole	2.476±0.032	6.182±0.08	+123.0	0.665±0.02	0.532±0.02	− 20.0	37±3	25.7±2	0.428±0.07	0.617±0.04

P_k, a, hardness, and bulk density data are shown as a mean of 3 repetitions, 3 repetitions, 10 tablets, and 5 repetitions, respectively, ± the standard deviation

BC before compaction, *AC* after compaction

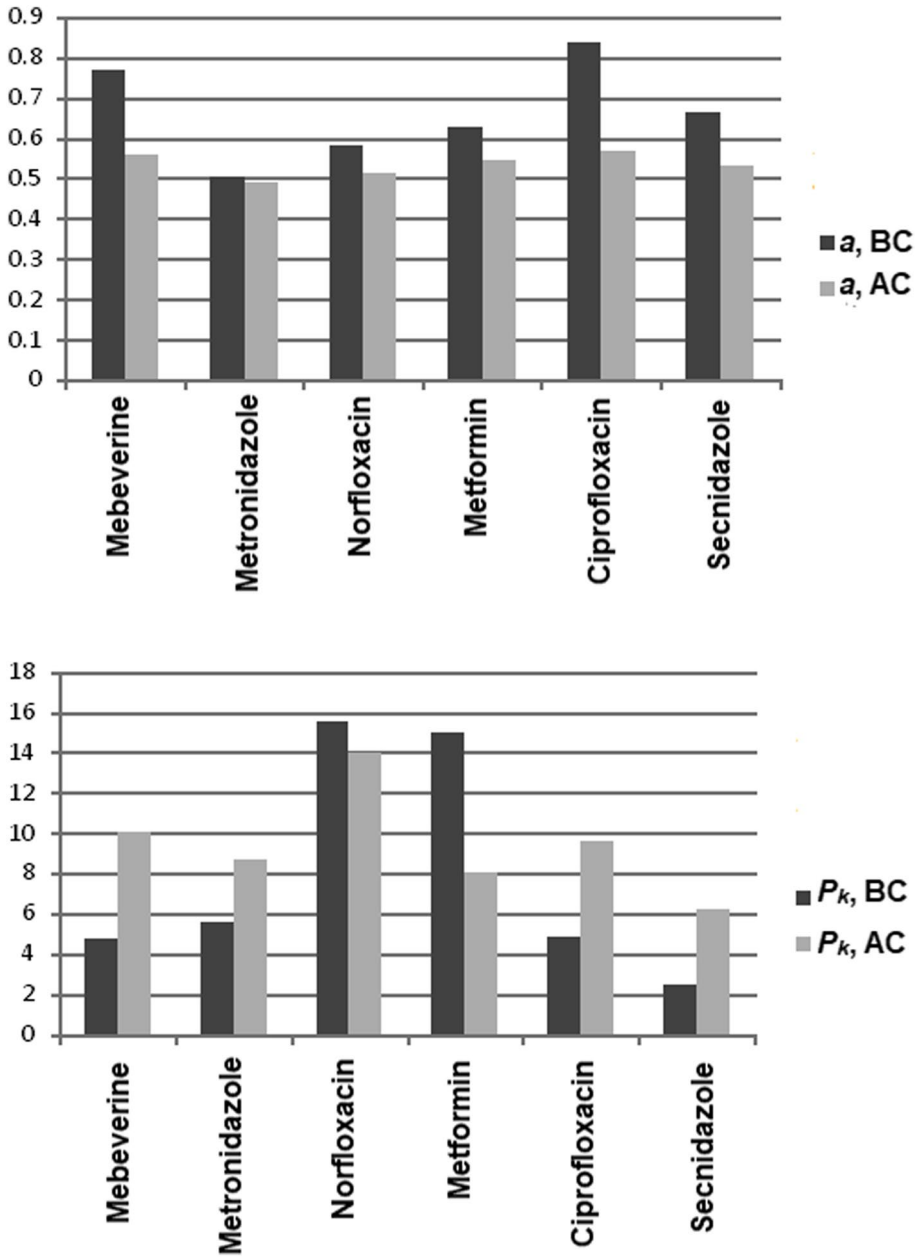


Fig. 2 Kawakita parameters

the rearranged Kawakita equation correlates to the work of compression, but instead of having a force in units of Newtons to cause a displacement in "m" unit, the relation will describe a pressure in MPa to cause a displacement in "m." It is important to note that the force and displacement presented by the GTP machine are in kilograms and millimeters, respectively for a punch size of 6 mm diameter.

It was suggested that the F-D curve was made up of a series of increasing compression pressures, whereby at a given pressure a rearranged Kawakita analysis can be applied. Accordingly, the area under the rearranged Kawakita equation is the summation of the areas over the whole pressure range under which the powders were compressed using the GTP, i.e., from an initial compression pressure (P_i) = 34.67 MPa to a final pressure (P_f) = 173.35 MPa. A mathematical representation of the aforementioned area is given in Eq. 3, the solution to this equation is presented in Eq. 4.

$$Area = \sum_{P_i}^{P_f} \int \frac{1}{b} \times \frac{C}{a - C}\, dC \tag{3}$$

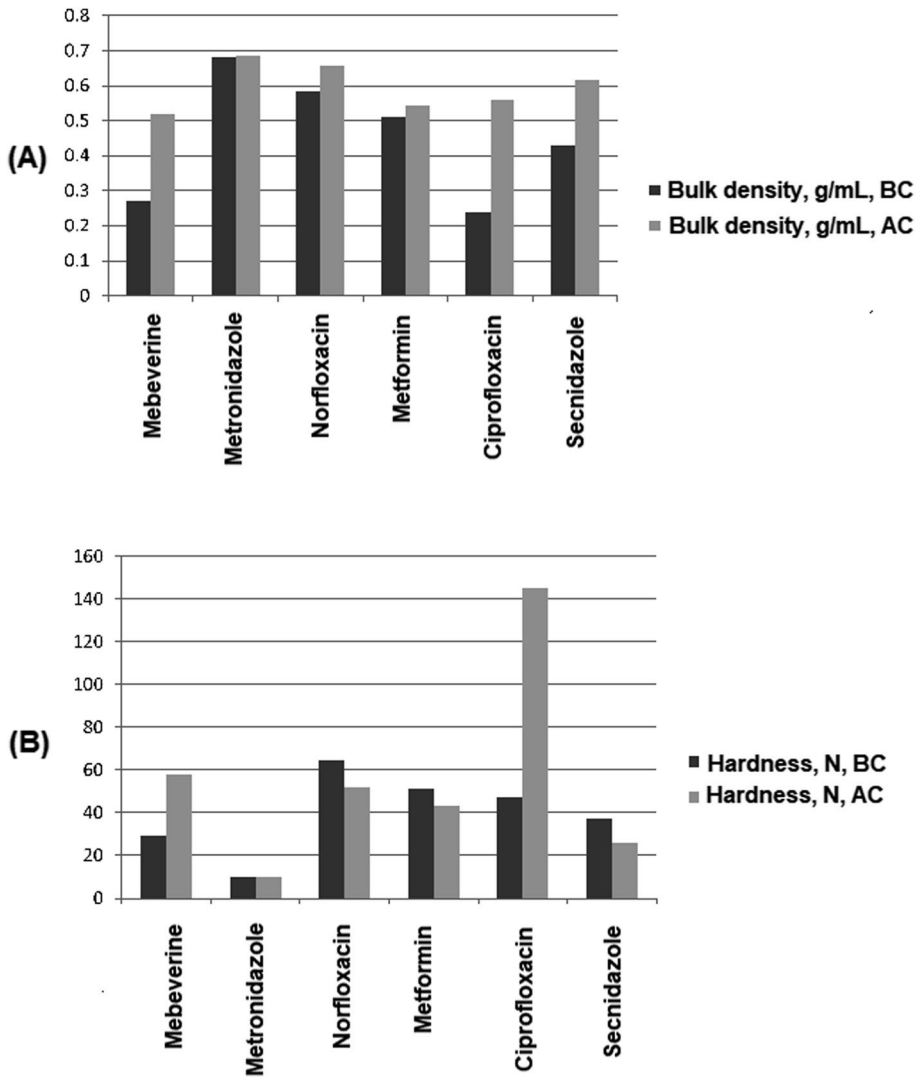


Fig. 3 Bulk density and hardness

$$Area = \sum_{P_i}^{P_f} \frac{1}{b}\left(\ln \frac{1}{C-a} - C\right) \quad (4)$$

Statistical analysis

A *t*-test was carried out to determine if there is a significant difference between the means of two groups of data. In the current work, data represent the measured and calculated compression work/ or energy measurements. The *t*-test assumes a null hypothesis that the two means are equal or—in other words—the test assumes no statistical significance (p value > 0.05) between the two sets of data.

Results

Kawakita plots were generated for the investigated drug powders (compacted and non-compacted). Kawakita data are presented in Table 1 and Fig. 2. The deduced Kawakita parameters and powder and tablet properties were statistically reproducible. Initially, it is clear from the results that the values of "a" have decreased for all compacted drugs compared to that of non-compacted forms. The decrease was obvious for ciprofloxacin (32%), mebeverine (27%), and secnidazole (20%). As "a" is a physical characteristic of the powder which represents the maximum attained volume reduction when being compressed, this implies that roller compaction resulted in densified granules of lower porosity that consequently led to smaller reduction in the powder volume (Al-Asady et al., 2015).

With regard to the "P_k" values, all compacted drug powders—except norfloxacin and metformin—showed an increase when compared to non-compacted drugs. This means, as implied from the definition of "P_k," that compacted powders required a higher compression pressure to produce the same volume reduction, i.e., "$a/2$"

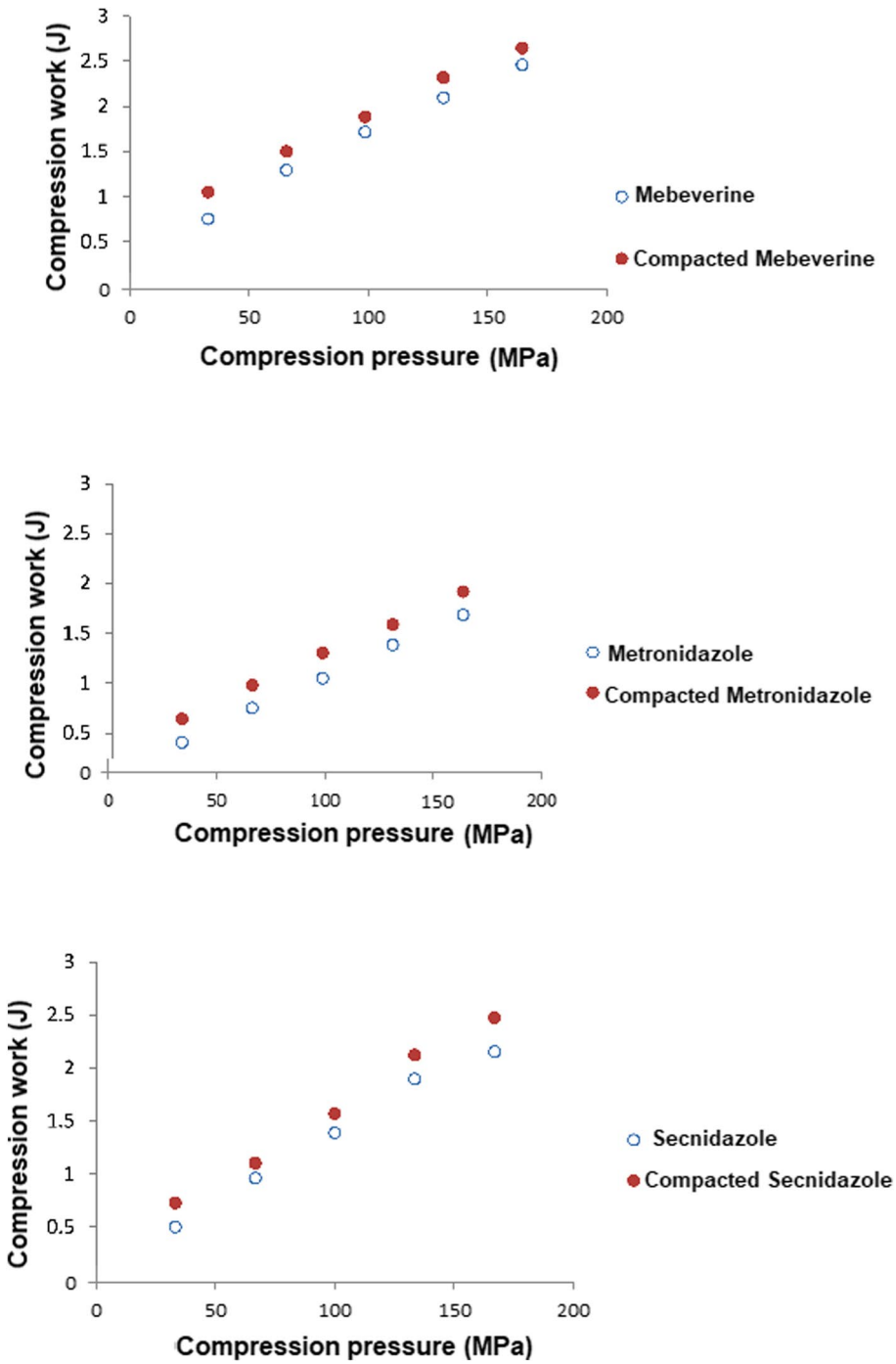


Fig. 4 The compression work, calculated based on the F-D curves, for non-compacted and compacted drugs comprising mebeverine, metronidazole, and secnidazole at different compression pressures

(Rashid et al., 2010). Obviously, such higher compression pressures reflect the higher resistance of the compacted powders to volume reduction when a compression force is applied. This might be attributed to lower granule porosity and the more regular shape of particle surfaces of compacted powders compared to their non-compacted forms (Patel et al., 2006; Kazemi et al., 2017; Freeman et al., 2016).

The data in Table 1 also presents the measured bulk densities of compacted and non-compacted powders in

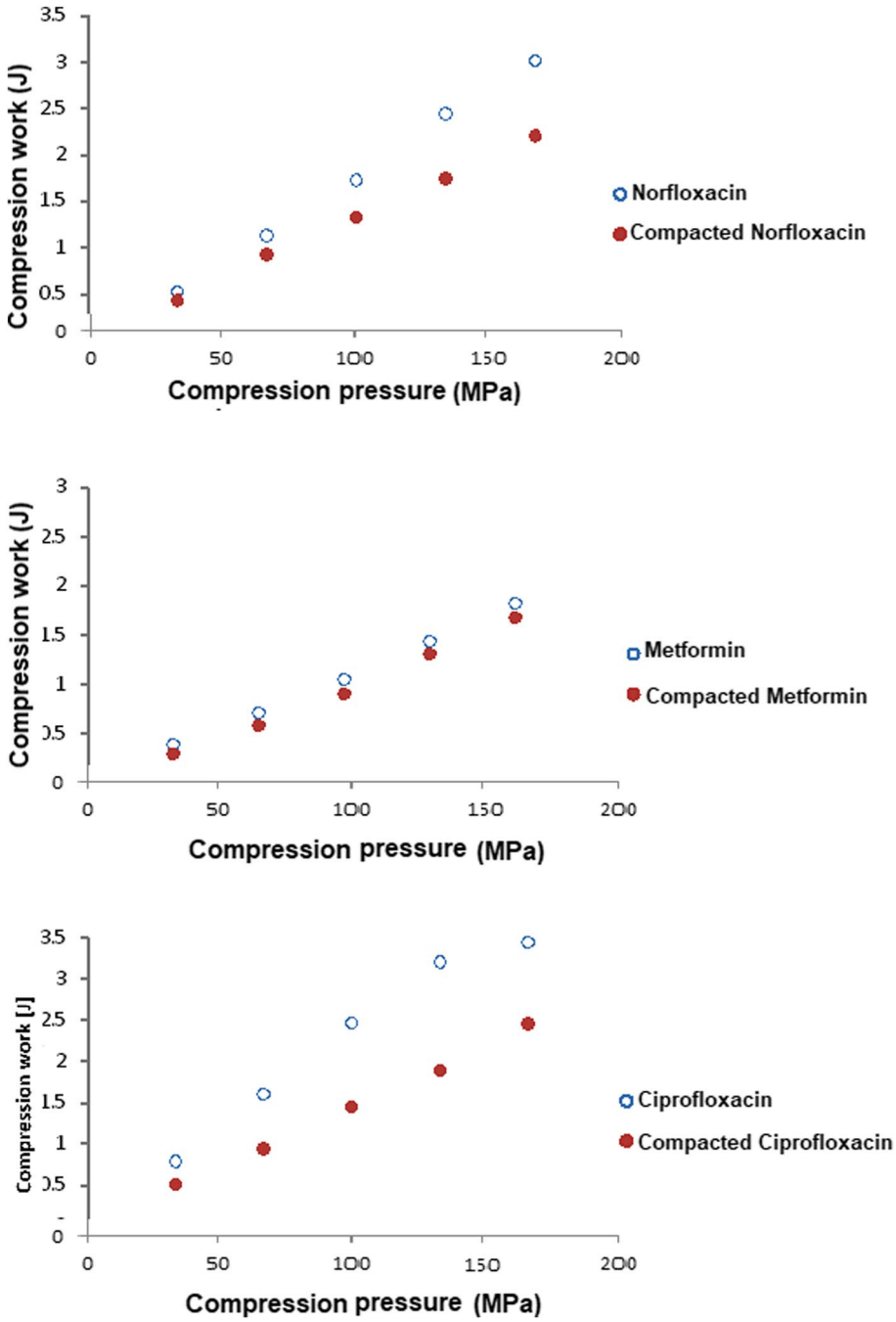


Fig. 5 The compression work, calculated based on the F-D curves, for non-compacted and compacted drugs comprising norfloxacin, metformin, and ciprofloxacin at different compression pressures

addition to the hardness of tablets produced by the GTP. The results are depicted in Fig. 3A,B. It can be noted that there is some consistency and inconsistency between the change in bulk density of powders and hardness of tablets. This behavior is addressed in the "Discussion" section through compilation of Kawakita and F-D curve analysis.

The compression work, based on "in-die" measurement of the displacement of powder bed, was calculated as (force × displacement) which is represented by the area under the F-D curve typically depicted in Fig. 1. Results of the work as function of the applied compression force are presented in Figs. 4 and 5 for the different

Table 2 Compression work and elastic recoveries calculated from the F-D curves of non-compacted (BC) and compacted (AC) drug powders at a GTP compression force of 500 kg (equivalent to a compression pressure of 173.3 MPa)

Drug	Comp W (BC) [kg. mm]	Comp W (AC) [kg. mm]	Elastic W (BC) [kg. mm]	Elastic W (AC) [kg. mm]
Mebeverine	250.6795	269.6996	52.1892	51.8949
Metronidazole	171.85	195.4405	60.822	59.7429
Secnidazole	219.6429	252.3599	50.1291	53.1702
Norfloxacin	307.04	224.5843	56.7999	57.879
Metformin	184.8549	170	46.4013	47.8728
Ciprofloxacin	351.4964	249.9241	54.6417	55.917

drugs (non-compacted and compacted). Figure 4 shows the compression work for mebeverine, metronidazole, and secnidazole, where the compacted powders showed higher compression work than the non-compacted corresponding ones. A reverse trend in work is observed for the drugs norfloxacin, metformin, and ciprofloxacin, as shown in Fig. 5. Table 2 shows the compression work and elastic recovery work for the investigated drug powders at compression pressure of 173.3 MPa (equivalent to a GTP compression load of 500 kg).

The rearranged Kawakita equation in the form of Eq. 2 which relates the out-die calculated relative volume reduction (C) to the compression pressure (P) is used to elucidate how (C) is varying with (P) for non-compacted and compacted drug powders as shown in Figs. 6 and 7.

The compression work as a function of the compression pressure was calculated using the F-D profiles and Eq. 4 which is the integrated form of Kawakita equation. Results are shown in Figs. 8 and 9.

The p values for the measured and calculated compression work/ or energy of Figs. 8 and 9 were 0.95, 0.70, 0.97, 0.97, 0.71, and 0.91 for mebeverine, metronidazole, norfloxacin, metformin, ciprofloxacin, and secnidazole, respectively. Accordingly, the rearranged Kawakita model was in close proximity to the measured compression work/ or energy from the F-D curves of the Gamlen Tablet Press.

Discussion

Dominance of 1/b and "a" in controlling pressure variations of the Kawakita model and the F-D curve

Kawakita and F-D curve analysis were performed on compacted and non-compacted powders upon compression of 6 APIs. Based upon the similarity of pressure-volume reduction relation of the Kawakita model with the F-D curve, variations in the P values for compacted (P_c) compared to non-compacted (P_{nc}) powders are dependent on variations in parameters "$1/b$ or P_k" and "a" of the rearranged Kawakita equation (Eq. 2). According to the sketch in Fig. 10, these variations can be outlined as follows:

$P_c > P_{nc}$, if $(1/b)_c > (1/b)_{nc}$ and $a_c < a_{nc}$ (condition 1)

$P_c < P_{nc}$, if $(1/b)_c < (1/b)_{nc}$ and $a_c > a_{nc}$ (condition 2)

This implies that the effect of the change in ($1/b$) on P (either P or P_c) is opposite to that in "a." Accordingly, the net change in P will depend on the dominant effect of these parameters (i.e., $1/b$ or "a").

Deviations of Eq. 2

The aforementioned conditions (1 and 2) are valid when the final displacements/or maximum Kawakita volume reductions (i.e., "a") for non-compacted and compacted APIs are in close proximity to each other as in the case of all drugs (except ciprofloxacin and mebeverine) whereby the sketch of Fig. 11 applies. Bearing in mind that the displacement parameter is technically correlated to the Kawakita "a" parameter, a different scenario can be presented by the sketch of Fig. 12 (unlike Fig. 11) whereby differences in "a" or in final displacement are remarkably large. In other words, there is a considerable difference in displacement between compacted (d_1) and non-compacted (d_2) drugs at a fixed compression force. In this regard, considering the "a" value of non-compacted drugs as a reference, compacted ciprofloxacin showed the greatest decrease in the value of "a" when compared to the other compacted drugs. It is suggested that large differences in "a" are responsible for deviations of Eq. 2, whereby ciprofloxacin represents a typical example. This exception may justify the decrease in compression work for compacted ciprofloxacin although the value of "P_k" is increased. Such a decrease contradicts the trend of Eq. 2 which indicates that higher compression work is accompanied by an increase in "P_k" and a decrease in the "a" values. The needle shaped ciprofloxacin particles together with their high aspect ratio are more likely responsible for the lowest recorded bulk density and highest compressibility (or volume reduction) of the fluffy powder compared to the other APIs tested in the current work (Azad et al., 2021b).

Relating F-D work to P_k and "a" parameters of the Kawakita model

In order to facilitate the discussion and thereby the comparison between the two techniques (Kawakita and F-D curves), the data in Figs. 4 and 5 as well as Table 1 presented in Table 3 in "+" and "−" formats. The "+" sign of each parameter indicates an increase in value when the drug powder is compacted, the "−" sign indicates a decrease in the value. Initially, all

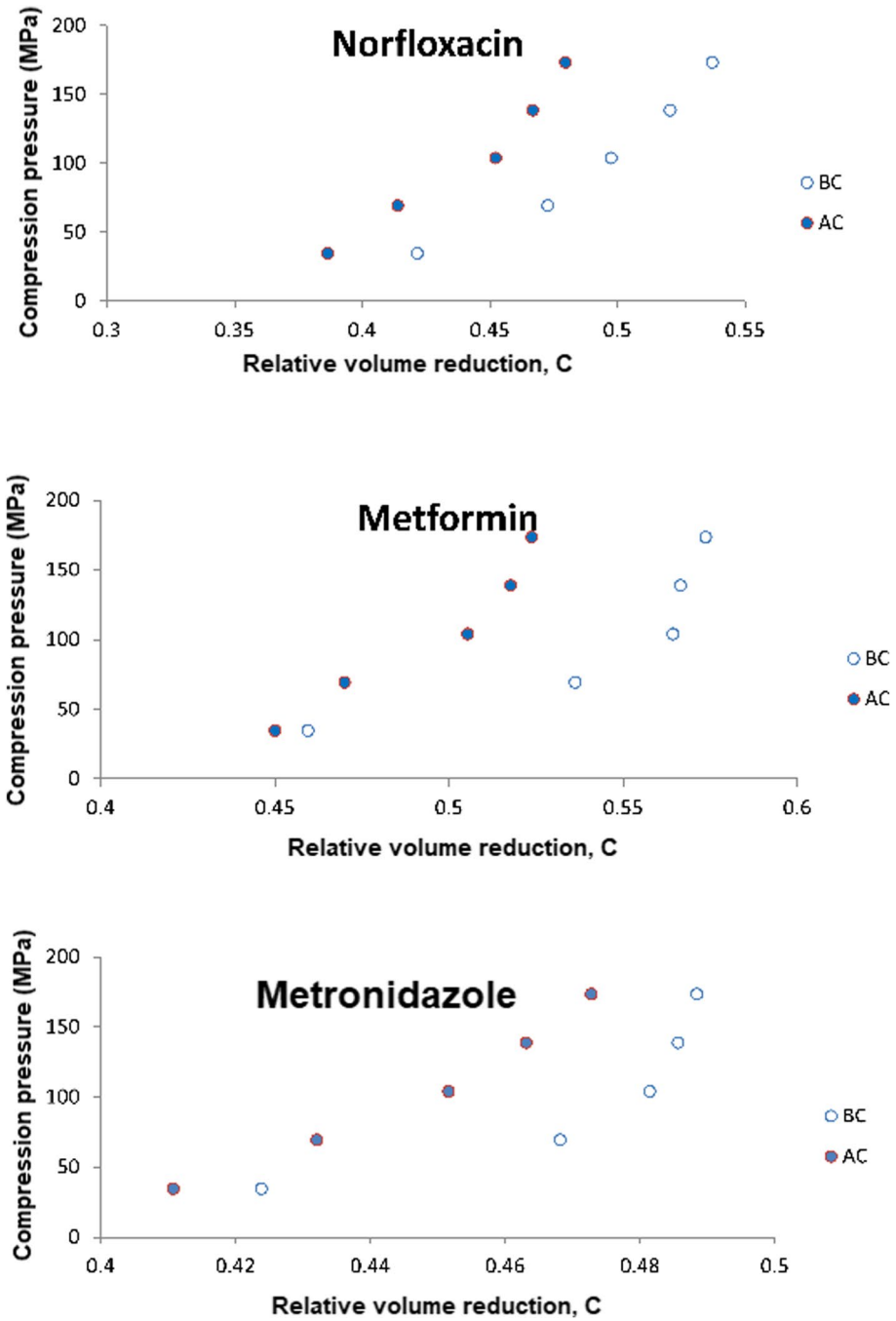


Fig. 6 The compression pressure-relative volume reduction relationship according to Eq. 2 applied to all non-compacted (BC) and compacted (AC) drugs comprising norfloxacin, metformin, and metronidazole

compacted drugs showed lower relative volume reduction compared to non-compacted drugs (Figs. 6 and 7). For drugs representing the P_k data in Tables 1 and 3 (mebeverine, metronidazole, and secnidazole), the force required to cause half of the maximum volume reduction was higher ($+P_k$) for compacted powders. For the work of compression (Table 2), values were higher indicating higher energy upon compression. Thus, ideally, the work of compression for these powders was influenced by the higher P_k ($+P_k$) and lower a values ($-a$), which is in agreement with the expected results obtained by Eq. 2.

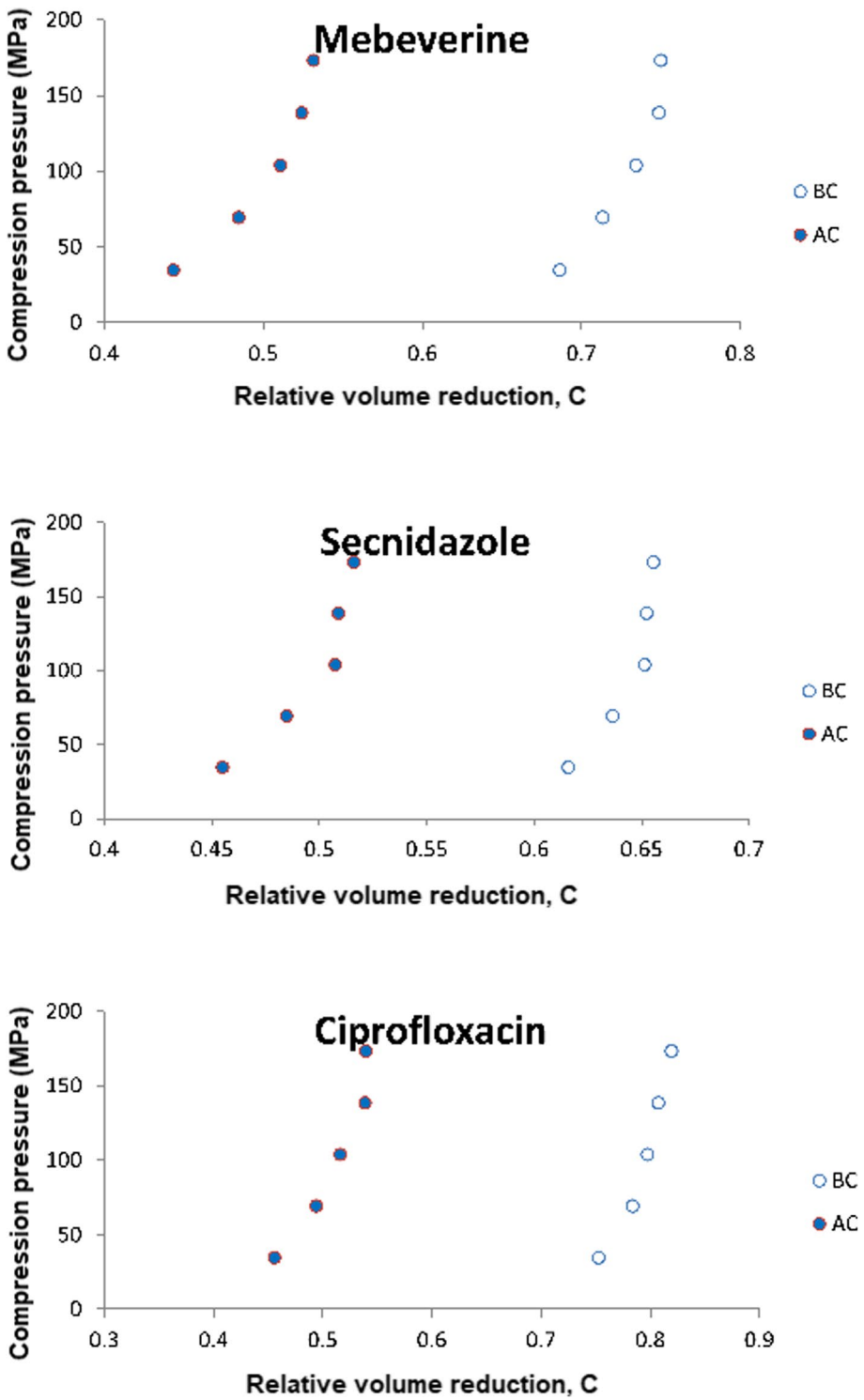


Fig. 7 The compression pressure-relative volume reduction relationship according to Eq. 2 applied to all non-compacted (BC) and compacted (AC) drugs comprising mebeverine, secnidazole, and ciprofloxacin

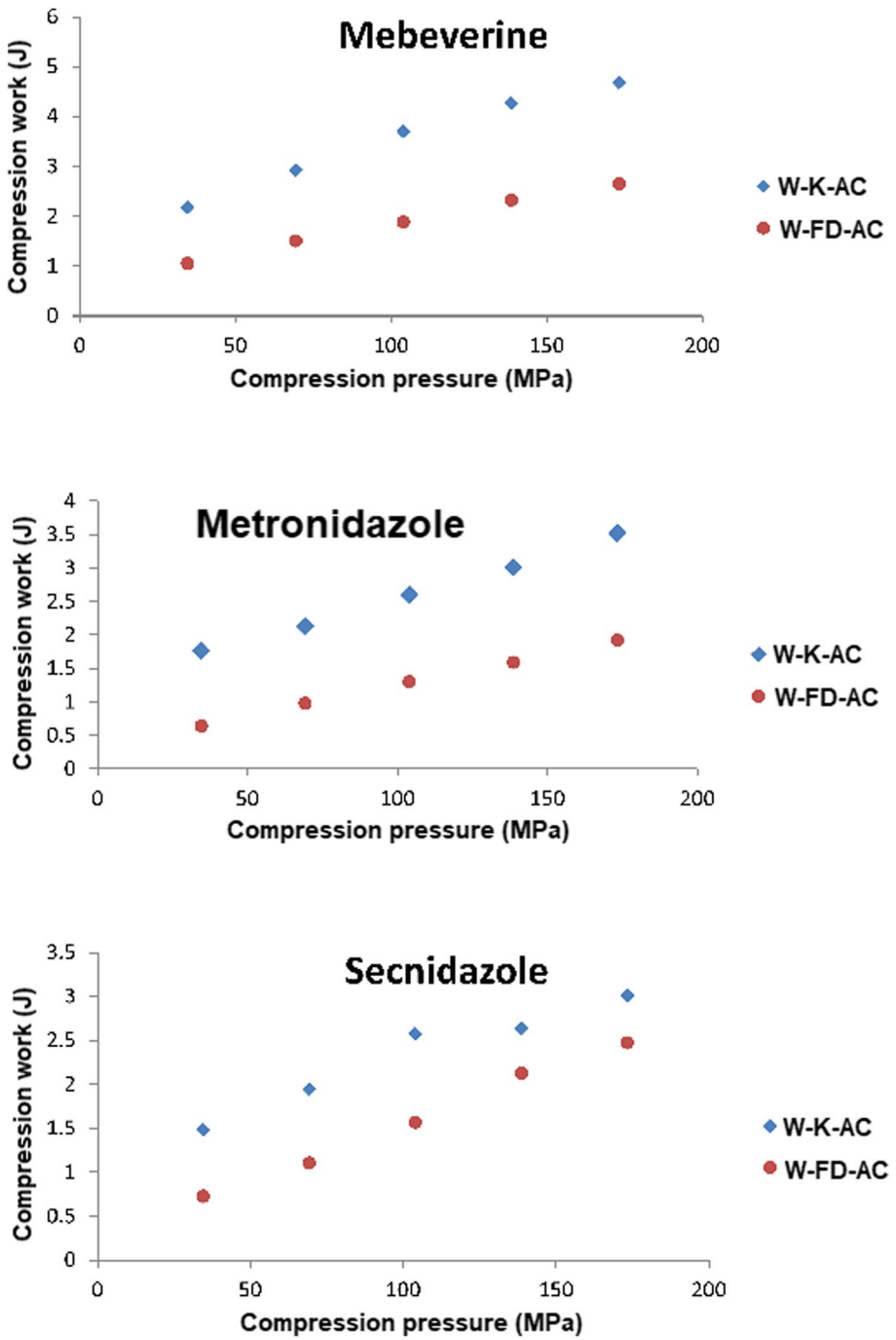


Fig. 8 Work of compression calculated using the integrated form of Kawakita equation (Eq. 4) and the F-D curve for the drugs comprising compacted mebeverine, metronidazole, and secnidazole all compressed at compression pressures 34–173 MPa

On the other hand, in case of norfloxacin and metformin, the reduction in compression work was accompanied with lower value of "*a*" which implies that the P_k has the dominant effect (Tables 1 and 3 and Fig. 10). Accordingly, the $(-a)$ had no significance in the change in work of compression. In other words, there is a difference in the interpretation between the calculated compressibility from the Kawakita equation and the measured distance displayed for each unit force from the F-D curve. The two aforementioned parameters

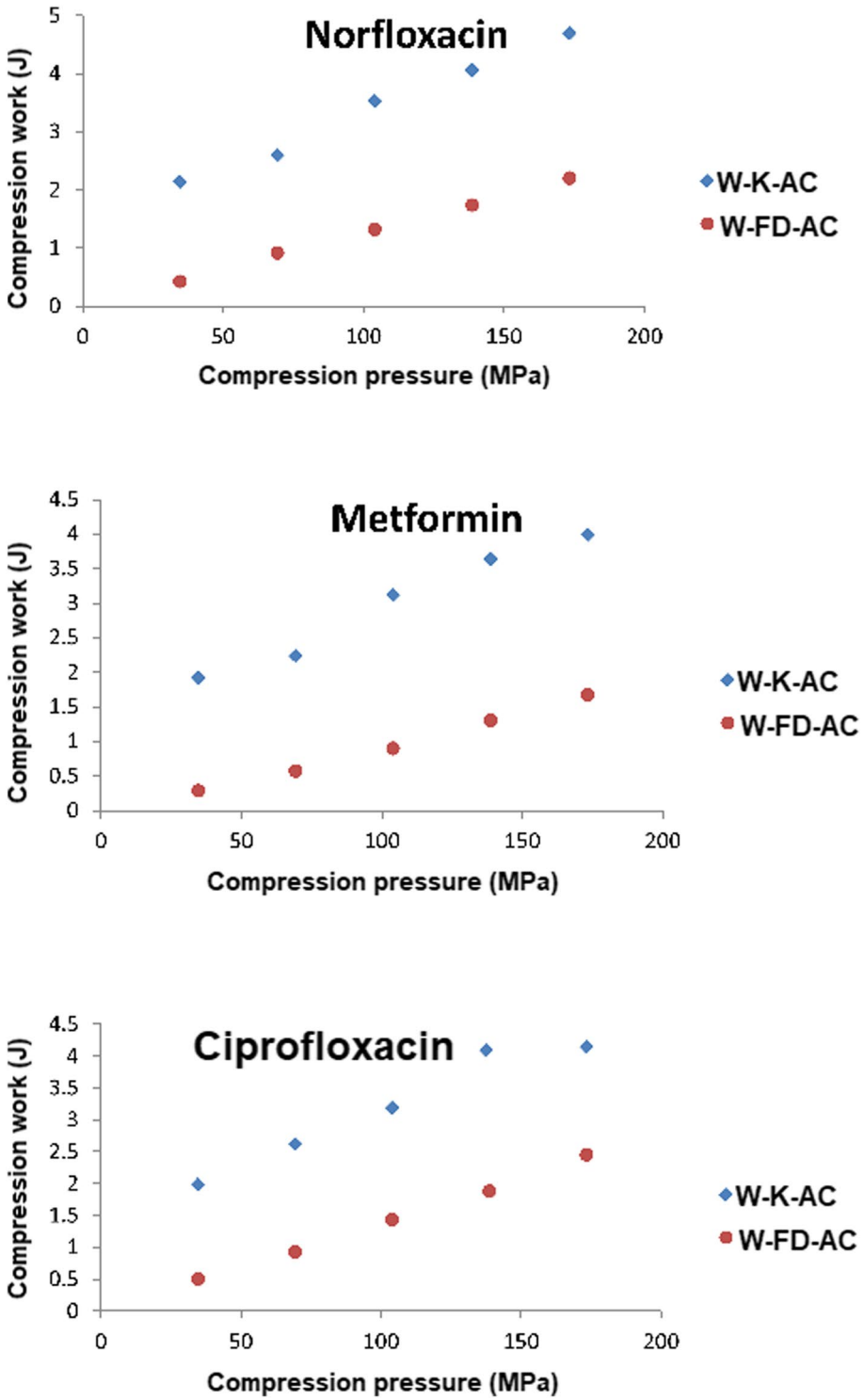


Fig. 9 Work of compression calculated using the integrated form of Kawakita equation (Eq. 4) and the F-D curve for the drugs comprising compacted norfloxacin, metformin, and ciprofloxacin all compressed at compression pressures 34–173 MPa

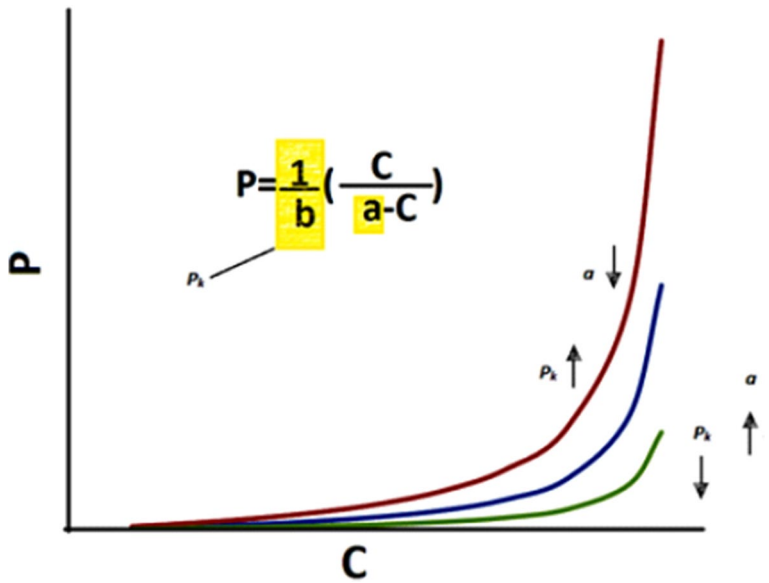


Fig. 10 A sketch representing the effect of changing Kawakita parameters (P_k and a) on the position of the F-D curve in accord with Eq. 2 when there is no remarkable difference in maximum volume reduction values between non-compacted and compacted powders

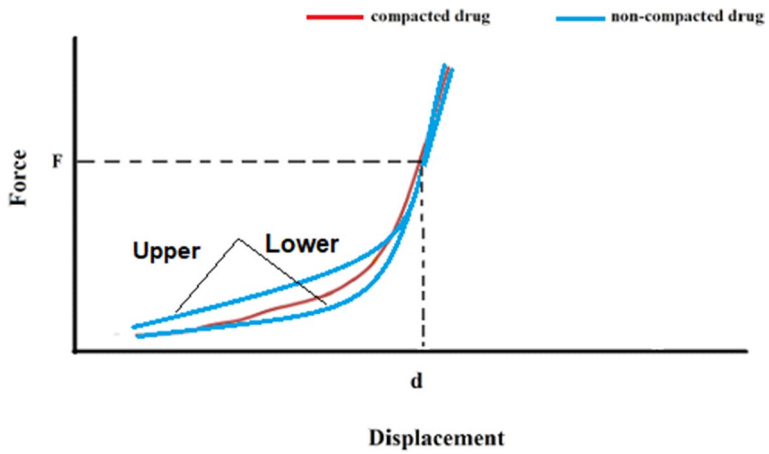


Fig. 11 A sketch representing the effect of changing Kawakita parameters (P_k and a) on the position of the F-D curve in accord with Eq. 2 when there is no remarkable difference in the maximum volume reduction for both higher and lower initial F-D profiles of compacted than non-compacted powders

may, in some cases, not be linked to the actual volume reduction. In fact it will be shown later, on ciprofloxacin, that both the compressibility of the powder and the value of P_k dictate the displacement distance covered by the upper punch of the GTP.

Dominance of "a" parameter on F-D work

Despite the apparent contradiction, the change in the "*a*" values is better correlated to the compressibility or porosity of the powders. This can be justified by the high increase in bulk density and tablet hardness of mebeverine compared to metronidazole after compaction of both. In this context, mebeverine displayed lower "*a*" values (a decrease by 27.2%) than metronidazole (a decrease by 2.4%) after compaction. This is, more likely, attributed to lower porosity of the harder compacted mebeverine granules compared to metronidazole. The decrease in the drug porosity for mebeverine is justified by 89% increase (before and after compaction) in its bulk

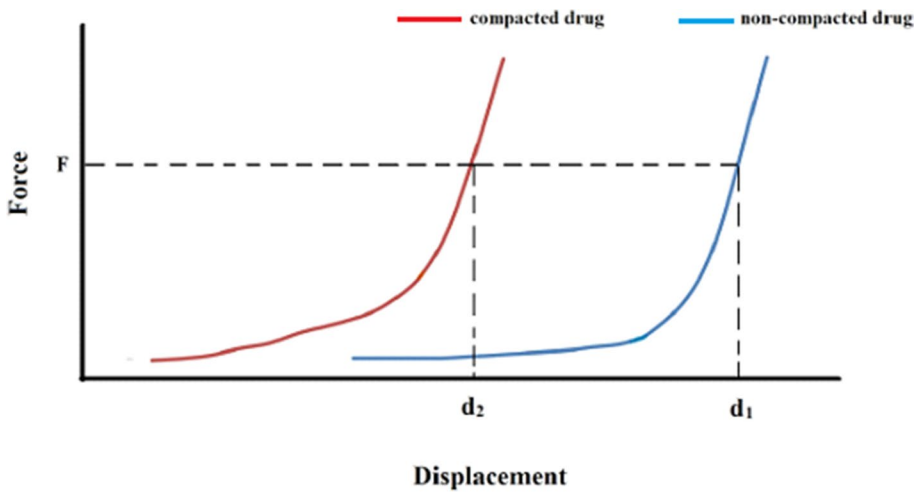


Fig. 12 A sketch representing the effect of changing Kawakita parameters (P_k and a) on the position of the F-D curve in accord with Eq. 2 when there is a remarkable difference in the maximum volume reduction values between non-compacted and compacted powders

density compared to 0.6% for metronidazole (Table 1). It should be noted that the lower Kawakita compressibility of compacted mebeverine was in agreement with the F-D increase in work which, the later, indicated a lower displacement for each unit force. On the other hand, there is almost no change in compressibility between compacted and non-compacted metronidazole powder. In other words, compaction of metronidazole did not affect the Kawakita "a" values, the bulk densities, and the recorded displacement displayed for each unit force.

Dominance of P_k on F-D work

For norfloxacin and metformin, the force required to cause half of the maximum volume reduction was lower ($-P_k$) for compacted powders causing a higher displacement for each unit force (i.e., lower energy for deformation; −W). However, the "a" values of both drugs underwent a decrease. Accordingly, the lower work of compression of both drugs, after compaction, was greatly influenced by the decrease in P_k ($-P_k$) rather than the decrease in the "a" ($-a$) parameters which, the latter, tends to increase the work of compression (Fig. 10) when its "a" value decreases. Similar to mebeverine, the change in the "a" parameter (11% and 13% decrease for norfloxacin and metformin, respectively) was manifested more in the decrease of powder bulk density and hardness of compacts when "a" is correlated to porosity.

Table 3 Notations of the increase or decrease of the compression work, Kawakita parameters (P_k and a), bulk density and tablet hardness before and after compaction marked by the "+" and the "–" signs. The "++" indicates large increase, "−−" indicates large decrease. "0" indicates no change

	Compression work	P_k	a	Bulk density	Tablet density
Mebeverine	+	+	−−	++	+
Metronidazole	+	+	−	+	0
Norfloxacin	−	−	−	+	−
Metformin	−	−	−	+	−
Ciprofloxacin	−	+	−−	++	++
Secnidazole	+	+	−−	++	−

"a" from the Kawakita equation and the F-D distance displayed are different

For ciprofloxacin, the force required to cause half the maximum volume reduction was higher ($+P_k$) for compacted powders with lower energy of compression (−W) and further manifested a much lower compressibility "a." The foregoing corresponds to a lower granular porosity and thus justifies the high increase in its bulk density when the drug underwent compaction. In other words, the high forces needed to compress compacted ciprofloxacin resulted in highly packed granules which produced the highest crushing force tablets among all the drugs investigated. However, the decrease in the value of "a" for ciprofloxacin was the highest recorded among all drugs tested in this work. This had the greatest impact on lowering the granule porosity ($--a$) to the extent that the highest bulk density and compact hardness was exhibited by ciprofloxacin. However, according to such a high drop in "a" values, the

treatment of changes in ciprofloxacin F-D curve before and after compaction is suggested to follow the trend illustrated in the sketch shown in Fig. 12. The foregoing is justified by the fact that after compaction, P_k undergoes an increase whereas "*a*" shows a remarkable decrease; however, the work of compression underwent a decrease. Such a trend gives more impact to the physical shift of the F-D curve to be relocated to an extreme position away from its original position. Again, this gives more emphasis to what has been earlier addressed, that there exists a difference in the interpretation between the calculated compressibility from the Kawakita equation and the actual distance displayed for each unit force from the F-D curve.

For secnidazole, the force required to cause half of the maximum volume reduction was higher ($+P_k$) for compacted powders with a lower displacement displayed for each unit force. The drug underwent lower compressibility "*a*"—due to lower porosity—and thereby increased bulk density; however, the tablet hardness was lower. The same aforementioned change in compressibility was further manifested by the plot of the rearranged Kawakita equation (Figs. 6 and 7) as the relative volume reduction of all drugs underwent a decrease at a fixed compression pressure.

Dependence of the F-D curve on Kawakita parameters

Analysis of the data in Table 3 affords further insight on the dependence of the F-D curve on Kawakita parameters. When both "P_k" and "*a*" have the same sign as in the case of norfloxacin and metformin, the sign of work F-D parameter follows the sign of the two Kawakita parameters. In other words, when "P_k" and "*a*" are "+" or "−", work values from F-D follow their sign that is "+" or "−", respectively. This is in accord with the previous finding that the increase or decrease in "P_k" and "*a*" values pushes the rearranged Kawakita standard curve upwards or downwards, respectively. On the other hand, when "P_k" and "*a*" signs are opposite to each other (which are manifested by mebeverine, metronidazole, ciprofloxacin, and secnidazole), the work values calculated from the F-D curve follow the "P_k" sign of the aforementioned drugs except for ciprofloxacin. The later drug had a "−" F-D work sign which was similar to that of "*a*". This means that in the case of ciprofloxacin, the Kawakita parameter "*a*" is a dominant factor in decreasing the F-D work values. Such a finding is equivalent to the early interpretation discussed herein whereby the response of the rearranged Kawakita curve is dependent upon "P_k" and "*a*" (Fig. 10).

Up to this stage of the findings, the main conclusion that can be drawn is the fact that the F-D curve generated by powder compression is dependent on the Kawakita parameters. Accordingly, changes in the energy needed for compression is largely associated with changes in the "P_k" and "*a*" values of the Kawakita parameters. Based upon the foregoing, Eq. 4 illustrates a possible correlation of the estimated energy of compression in being used to calculate the area under the curve of the rearranged Kawakita model, or Eq. 2. This implies that the work of compression is a function of "P_k" and "*a*," or the energy of compression is directly proportional to "P_k" and "*a*" or more princely to *1/b* and $\ln[1/(C-a)]$, respectively.

Validation of Eq. 4 was verified in Figs. 8 and 9 by comparing the results calculated using Eq. 4 for each drug with the work of compression generated by the Gamlen Tablet Press. Initially, the data representing the measured work have some degree of linearity, the extent of which differs from one drug to another and according to the pressure applied. Therefore, the rearranged Kawakita data chosen for investigation, of compression pressures from 34.7 to 173.3 MPa, had almost a linear relation work of compression profile against the pressure applied. The linearity is more likely to be attributed to the insignificant change in the elastic recovery work/energy (Table 2) between compacted and non-compacted powdered drugs (Almaya & Aburub, 2008). On the other hand, the no statistical significance ($p > 0.05$) between the measured and calculated data, Figs. 8 and 9, verified the assumption of similarity between the area under the curve of the rearranged Kawakita model and compression work/energy from the F-D curves of the Gamlen Tablet Press.

Conclusions

The work reported herein supports the concept of a new method for data treatment of powder compression mechanics using F-D curves. The foregoing is based on the finding that F-D curve follow a rearranged form of the Kawakita model of compression. Consequently, changes in the energy needed for powder compression is largely associated with changes in "P_k" and "*a*" values of the Kawakita parameters. Therefore, Kawakita parameters of compression analysis can be estimated from the F-D curve. Strong emphasis should be given to calculate Heckel parameters using the F-D curve. In this context, careful consideration should be given to the range of applied pressures since Heckel parameters are dependent on the linear portion of this pressure range.

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Authors' contributions
IR is the corresponding author. He came up with the article's idea. He contributed to the calculations presented in the manuscript. RRH and AAA supplied most of the lab work data using the instrumental compression machine. RNA and RMA assisted in applying Kawakita analysis on the compression data. All author(s) read and approved the final manuscript.

Declarations

Competing interests
The authors declare that they have no competing interests.

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