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Mechanical energies associated with compaction of form I and form II paracetamol powder

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ABSTRACT

Paracetamol solid state has three known polymorphic forms; monoclinic form (Form I), orthorhombic form (Form II) and Form III. In this work Form II was successfully produced in appreciable quantities by controlled crystallization of melted Form I. The moisture content of both forms stored for 3 weeks at 25 °C at different relative humidity conditions was investigated. It was found that neither form acquires any significant amount of moisture in any of the storage conditions. The results showed that Form II is stable for 3 weeks of storage at relative humidities of 23%, 43%, and 58%. Work of compression, work of decompression, plasticity index (ψ), and elastic energy/plastic energy (EE/PE) ratio associated with the compaction of both forms were determined at maximum applied compression forces of 35 kN, 27 kN, 18 kN, 11 kN, and 5 kN. It was found that both forms have high magnitude of elastic energy recovery during decompression. Moreover, it was found that for generating compacts of equal volumes of the two forms the plasticity index is larger for Form II and the EE/PE ratio is larger for Form I.

1. Introduction

Paracetamol exists in three polymorphic forms, the monoclinic form (I), the orthorhombic form (II), and a third form (III) [1–3]. Form I, which is the commercially used form, is stable at ambient temperature and pressure. However, it is characterized by poor pharmaceutical and industrial properties in terms of compactability [4,5]. This makes it unsuitable for direct compression into tablets. Form I is proposed to have a crystal structure that lacks slip planes. The presence of such slip planes in the crystal structure of a powder is a prerequisite for plastic deformation upon compaction. Consequently, Form I has to be mixed with binding agents before tableting. Form II has been suggested to have slip planes in its crystal structure. Therefore, From II could undergo plastic deformation upon compaction [6]. Di Martino et al. prepared paracetamol polymorph Form III [7]. However, it was found to be highly unstable at ambient conditions.

Despite considerable efforts to crystallize Form II by slow evaporation of an ethanol solution, as described by Haisa et al. [1], this method has eluded subsequent researchers [7,8]. The method that has been reported for consistent bulk production of pure Form II is by crystallization from melted Form I [8]. It has been reported that rapid cooling of the melt would lead preferably to the crystallization of Form I. However, when low regular cooling rates are allowed Form II can be obtained.

Joiris et al. found that Form II exhibits better compaction properties than Form I [6]. Its ability to reduce in volume as a result of applied pressure is accompanied by lower elastic recovery. It was suggested that there is a great tendency of Form II particles to undergo brittle fracture at low compression pressures and undergo plastic deformation at higher compression pressures. Thus, particles come into closer proximity with each other such that interparticulate bonds are formed. Garekani et al. studied the elastic recovery, elastic energy and elastic energy/plastic energy ratio of untreated paracetamol powder and of crystallized paracetamol in the presence of polyvinylpyrrolidone (PVP) [9]. The results suggested that particles crystallized in the presence of PVP exhibited much less elastic behavior under pressure when compared to untreated paracetamol particles.

In this work and for the first time, we estimated the work of compression, work of decompression, plasticity index, and elastic energy/plastic energy (EE/PE) ratio associated with the compaction of Form I and Form II paracetamol powder compacted at different compression forces. We then compared the estimated results to elucidate mechanical energy differences between both forms.

2. Theory

Force vs. displacement curves are used for mechanical energy (work) estimation [10]. Area under the curve during compression and during decompression is used to estimate the work of compression,

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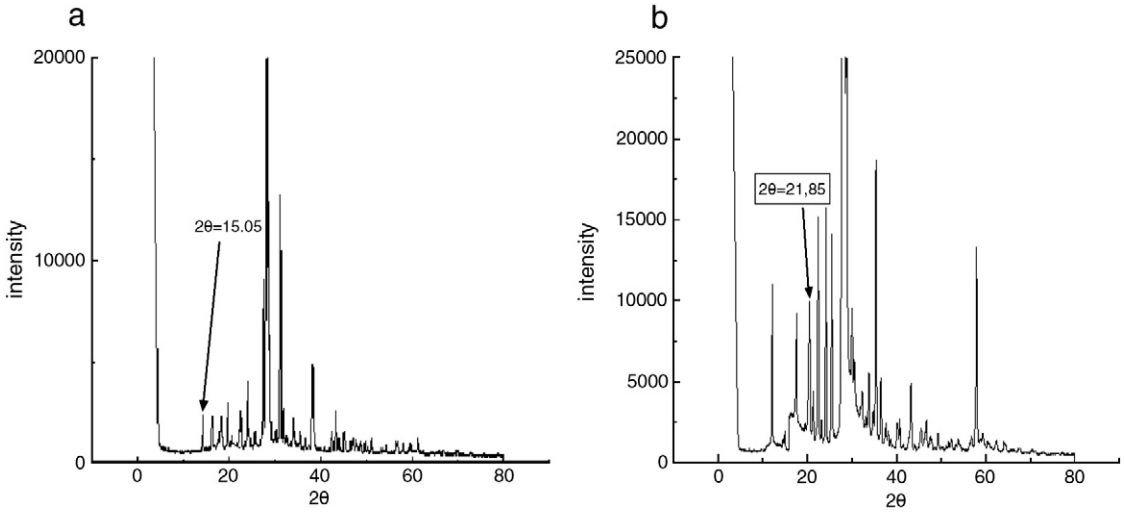

Fig. 1. XRPD pattern of paracetamol powder; (a) Form I, (b) Form II.

Wc, and the work of decompression, Wd, respectively according to the following equations:

$$Wc = \int_0^{D\ max} F.dD \tag{1}$$

$$Wd = \int_{D\ max}^0 F.dD \tag{2}$$

Where D_{max} is the displacement at maximum compression force, F is the force, *dD* is the increment change in displacement.

The plasticity index (ψ) was used as an indicator for the magnitude of net work accommodated by the compacted powder and can be calculated using the following equation [11]:

$$\Psi = \frac{Wc - Wd'}{Wc} \tag{3}$$

Where Wd′ is the absolute value of Wd. In addition, the elastic energy/plastic energy (irrecoverable work) ratio (EE/PE) is used as an indicator for the magnitude of compression energy that is utilized during decompression and is calculated using the following equation [12]:

$$EE/PE = \frac{Wd'}{Wc - Wd'}. \tag{4}$$

3. Materials and method

3.1. Materials

Highly pure (99%) paracetamol (Form I) was purchased from SIGMA CHEMICAL CO. (St. Louis, MO, USA), potassium acetate from s.d.fine-CHEM Ltd. (Boisar, India), potassium carbonate from AppliChem Gmbh (Darmstadt, Germany), sodium bromide, sodium chloride and potassium nitrate from Scharlau Chemie S.A. (Sentmenat, Spain). Form I paracetamol was used in compaction experiments as received.

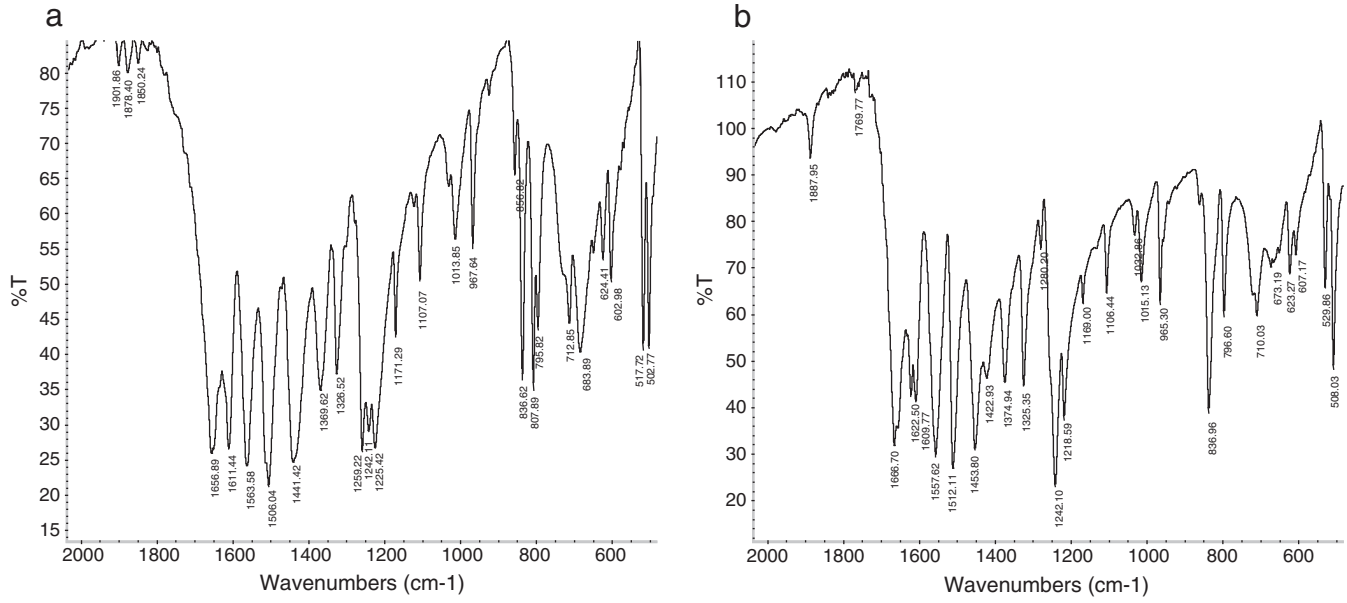

Fig. 2. FT-IR spectrum of paracetamol powder; (a) Form I, (b) Form II.

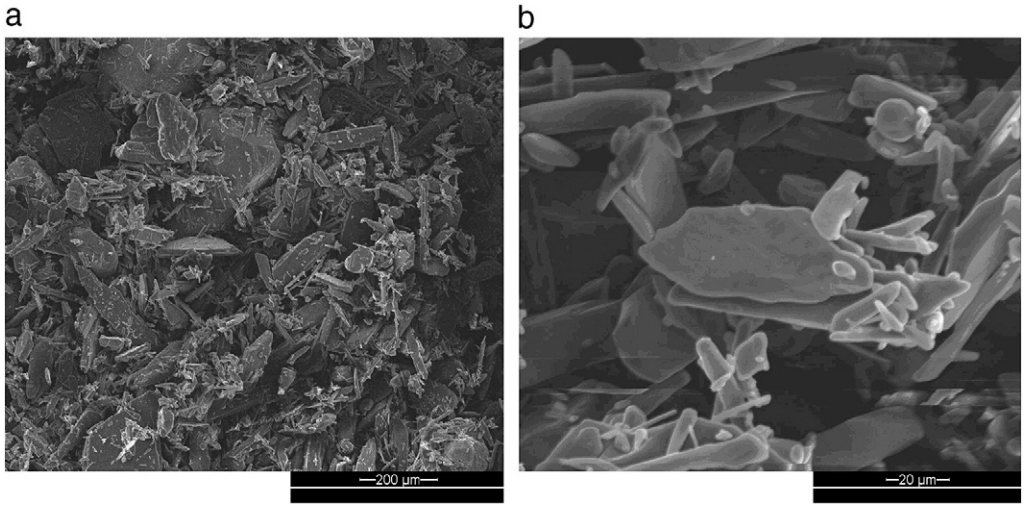

Fig. 3. Scanning electron micrographs of Form I paracetamol powder at different magnifications; (a) 200×, (b) 1500×.

3.2. Preparation of Form II

4.0 g of paracetamol powder (Form I) were weighed and placed in a clean test tube. The wall of the test tube was then wiped with acetone to remove any traces of powder. The test tube was placed in paraffin oil bath (500 ml beaker) and heated on a hot plate to 170–180 °C. After complete melting of paracetamol the test tube was immediately removed and placed in a water bath (500 ml beaker) at a temperature of 60–75 °C. After complete solidification of the melt, the test tube was placed in ice for one minute. The solidified mass was then removed from the test tube using a small spatula. Large aggregations were reduced in size by gently pressing against them with a spatula. The collected powder was then analyzed.

3.3. Preparation of desiccators with different relative humidities

Saturated solutions of pure salts of potassium acetate, potassium carbonate, sodium bromide, sodium chloride and potassium nitrate were prepared separately and each of the solutions was placed in a desiccator. The saturated solutions of these salts are reported to give relative humidity values of 23%, 43%, 58%, 75%, and 94% respectively at 25 °C [13]. Form I and prepared Form II paracetamol powder were placed in these tightly sealed desiccators for 3 weeks at 25 °C.

3.4. Characterization of powder

3.4.1. Determination of melting point

The melting points (maximum melting temperature) of Form I and Form II were determined using a differential scanning calorimeter (DSC-50, Shimadzu, Japan). Approximately 3 mg of each form was filled in an open pan. The sample was then heated at 10 °C/min. from room temperature to 200 °C. The internal atmosphere was maintained by purging nitrogen gas at a flow rate of 100 ml/min. The DSC was calibrated with indium (melting point, 156.6 °C; $\Delta Hm = 28.54\ J\ g^{-1}$).

3.4.2. Determination of moisture content

Approximately 2–8 mg of each sample was filled in an open pan and analyzed using a thermogravimetric analyzer (TGA-50, Shimadzu, Japan). Each sample was heated at 10 °C/min. from room temperature to 180 °C. The internal atmosphere was maintained by purging nitrogen at a flow rate of 100 ml/min. Mass calibration was performed with a 100 mg calibration weight. Temperature calibration was performed with alumel (magnetic transition temperature, 163.0 °C) and nickel (magnetic transition temperature, 354.0 °C).

3.4.3. Electron microscopy imaging

The particle shape was obtained using a scanning electron microscope (Quanta 200, FEI company, Netherlands). Samples were

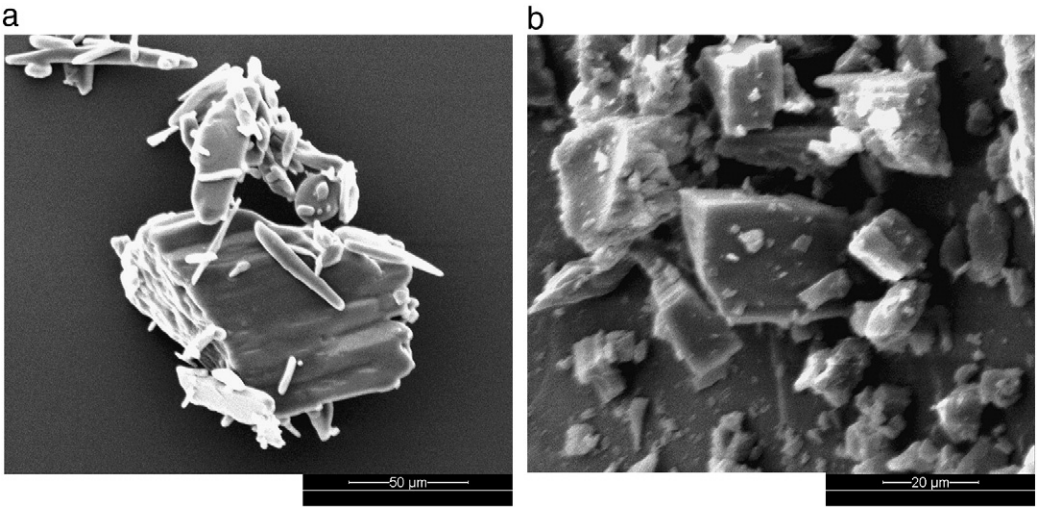

Fig. 4. Scanning electron micrograph of the prepared Form II paracetamol powder at different magnifications; (a) 1200×, (b) 2400×.

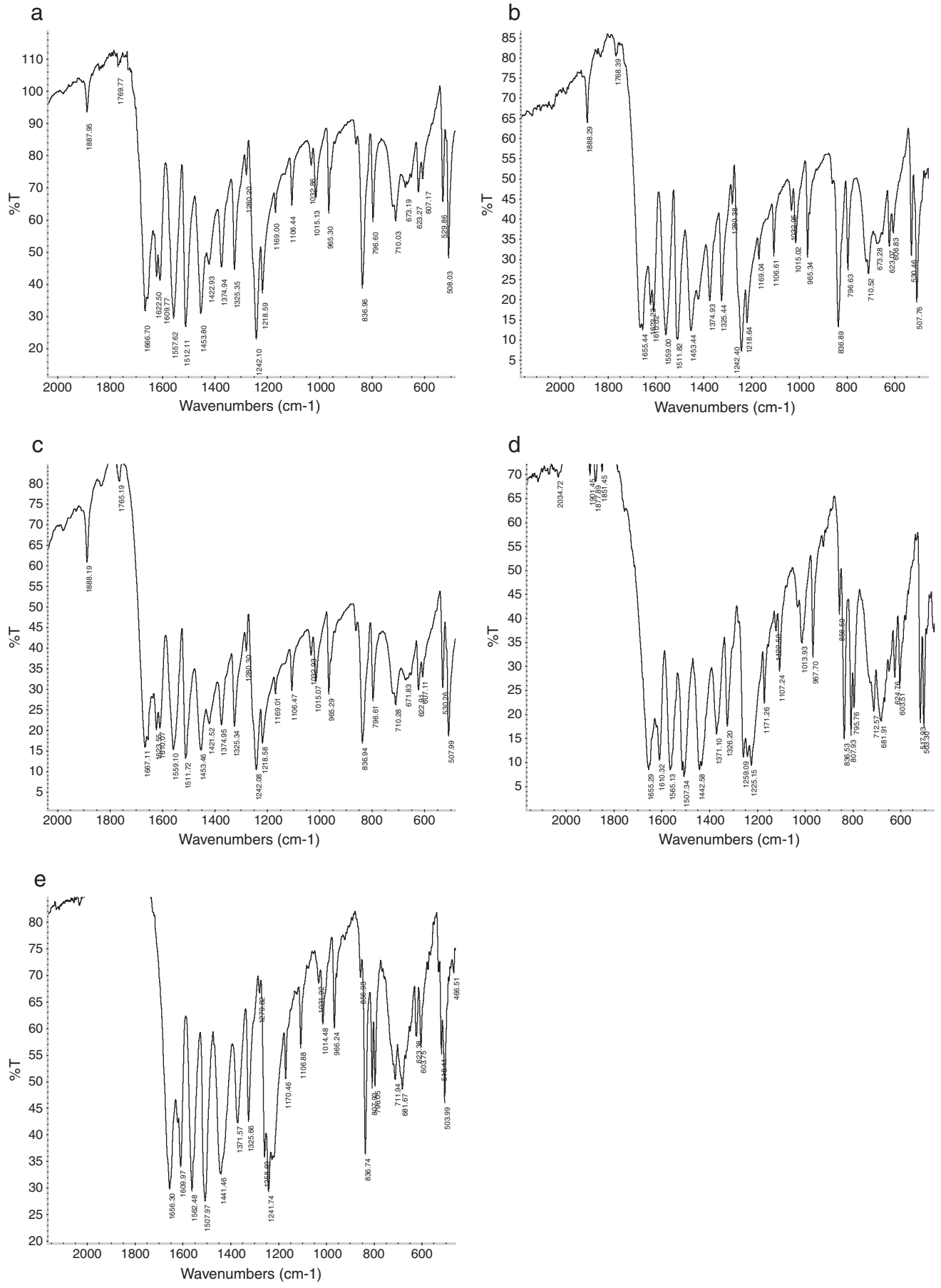

Fig. 5. FT-IR Spectra of the prepared Form II paracetamol powder after 3 weeks of storage at (a) 23%, (b) 43%, (c) 58%, (d) 75%, and (e) 94% relative humidity.

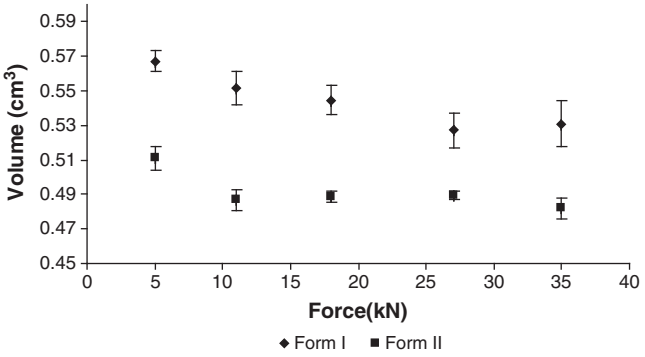

Fig. 6. Relation between volume of compacted tablets of both forms and applied compression force.

mounted on aluminum stubs by double-sided sticky disks of conductive carbon then gold coated by sputtering method at 1200 V and 20 mA using a vacuum coater (Polaron E6100, Polaron,UK).

3.4.4. X-ray powder diffraction (XRPD) analysis

XRPD patterns were recorded at room temperature (25 °C) on an X-ray diffractometer (PW 1729, Philips, Netherlands). Cu anode operated at 35 kV and 40 mA. The samples were scanned from 5 to 80° two theta at a rate of 1.5° min.$^{-1}$.

3.4.5. FT-IR analysis

Fourier transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Nicolet Impact 410, Thermo Nicolet, USA). Each form was scanned as KBr disk (1% w/w). Spectra were obtained in the transmission mode. Two milligrams of each sample were mixed with 200 mg of KBr and ground gently with an agate pestle and mortar then pressed into a 13-mm disk by applying 10 tons of force using a manual hydraulic tablet press (Specac, UK).

3.5. Powder compaction

Compaction was performed using a compression machine (RKM 50, Roell- Korthaus, Germany). 500 mg of each sample were separately placed in a die cavity with a diameter of 13.8 mm and compressed at different forces. The die cavity and punches were lubricated with a suspension of magnesium stearate in ethanol (5% w/v). The maximum applied compression forces were 35 kN, 27 kN, 18 kN, 11 kN, and 5 kN. The force and displacement data were collected by the integrator during the compression and decompression cycles. Rate of compression and rate of decompression were set at (1.5 mm/s.). Force displacement data for 5 replicates of each form compressed at a given maximum applied compression force were recorded on coordinate charts. A developed computer software was then used to transform the scanned charts into data points that were utilized for area under the curve calculations. Area under the curve was calculated by implementation of the trapezoide rule. The estimated work values were corrected for the deformation of the punches.

4. Results and discussion

4.1. Characterization of paracetamol polymorphs

The melting points of both Form I and the prepared Form II were determined using Differential Scanning Calorimetry (DSC). The melting point of Form I was determined to be 169 °C and that of Form II 157 °C. Fig. 1 shows the XRPD patterns that were acquired for both forms. The characteristic peaks for the crystal structure were noted at $2\theta = 15.05$ for Form I and at $2\theta = 21.85$ for Form II which are in accordance with what is reported by Di Martino et al. [7]. In addition, the FT-IR spectra of both forms show differences in the stretching peaks (Fig. 2). The most distinct difference between the two spectra is the presence of an additional peak at 808 cm^{-1} in the spectrum of Form I [14].

Figs. 3 and 4 show the SEM of Form I and Form II, respectively. The graphs indicate that there is no uniform shape for Form I or Form II particles. In addition it can be seen that differences in particle size exist between the forms. Particle size and particle shape are known to affect compaction behavior of powders. However, it is reported that differences in these properties result in slight variations in the compaction behavior of materials that deform predominantly by brittle fracture such as paracetamol Form I [15–17]. Moreover, Joiris et al. reported that the compaction of smaller particle size fractions of partacetamol Form II results in a slightly reduced densification processes. The aforementioned is consistent with a plastic deformation mechanism [6]. However, processing such as grinding of the prepared Form II paracetamol was avoided due to the inherent possibility of phase transition to the more stable Form I [18].

4.2. Effect of relative humidity storage conditions on the physical stability of Form II

Analysis of TGA thermograms of both forms shows that neither form gains any appreciable amount of moisture (<0.1% weight change) when stored at the studied relative humidity conditions. In addition, form II was characterized using FT-IR spectrometry immediately after preparation and following 3 weeks of storage at each relative humidity condition. Fig. 5 shows the FT-IR spectra of Form II after 3 weeks of storage at different relative humidity conditions. The spectra of the samples stored at 23%, 43%, and 58% relative humidity conditions do not have the distinct Form I peak at 808 cm^{-1} indicating that Form II is stable. However, the spectra of the samples stored at 75% and 94% relative humidity conditions show an absorption peak at 808 cm^{-1} indicating transformation into Form I. Form II paracetamol powder does not appear to gain any appreciable amount of moisture during storage at high relative humidity conditions. However, the presence of high concentration of water vapor around Form II particles seems to facilitate polymorphic transition into Form I. Any amount of Form I that is formed can act as a nuclei (seed) that facilitates further transformation [18].

4.3. Determination of compaction energies

The compaction behavior of both Form I and Form II paracetamol powder stored at 58% relative humidity were studied. Fig. 6 shows the change in the volume of equal weight tablets compacted at different forces. It shows that compacted samples of Form II have lower volume when compared to those of Form I at each applied compression force. This finding suggests that Form II particles undergo deformation that leads to closer interparticulate distances. Compression of Form I paracetamol powder at all compression forces produced weak compacts that required gentle handling. However, Form II showed tendency to form stronger compacts. Nevertheless, all compacts that were formed had crushing strengths below 10 N.

Fig. 7 shows force vs. displacement profiles obtained from the compaction of both forms of paracetamol powder at different compression forces. The travel of the upper punch at low forces is due to particle rearrangement in the powder bed. However, at higher forces the particles undergo deformation which leads to further volume reduction. During decompression, the compact exerts force on the upper punch due to elastic deformation (elastic recovery). It can be seen for almost all force vs. displacement profiles that there is a large backwards travel of the upper punch with a recorded force. This indicates a large degree of elasticity in the compressed material.

Tables 1 and 2 list the work obtained from compaction of equal weights of both Form I and Form II paracetamol powder at different

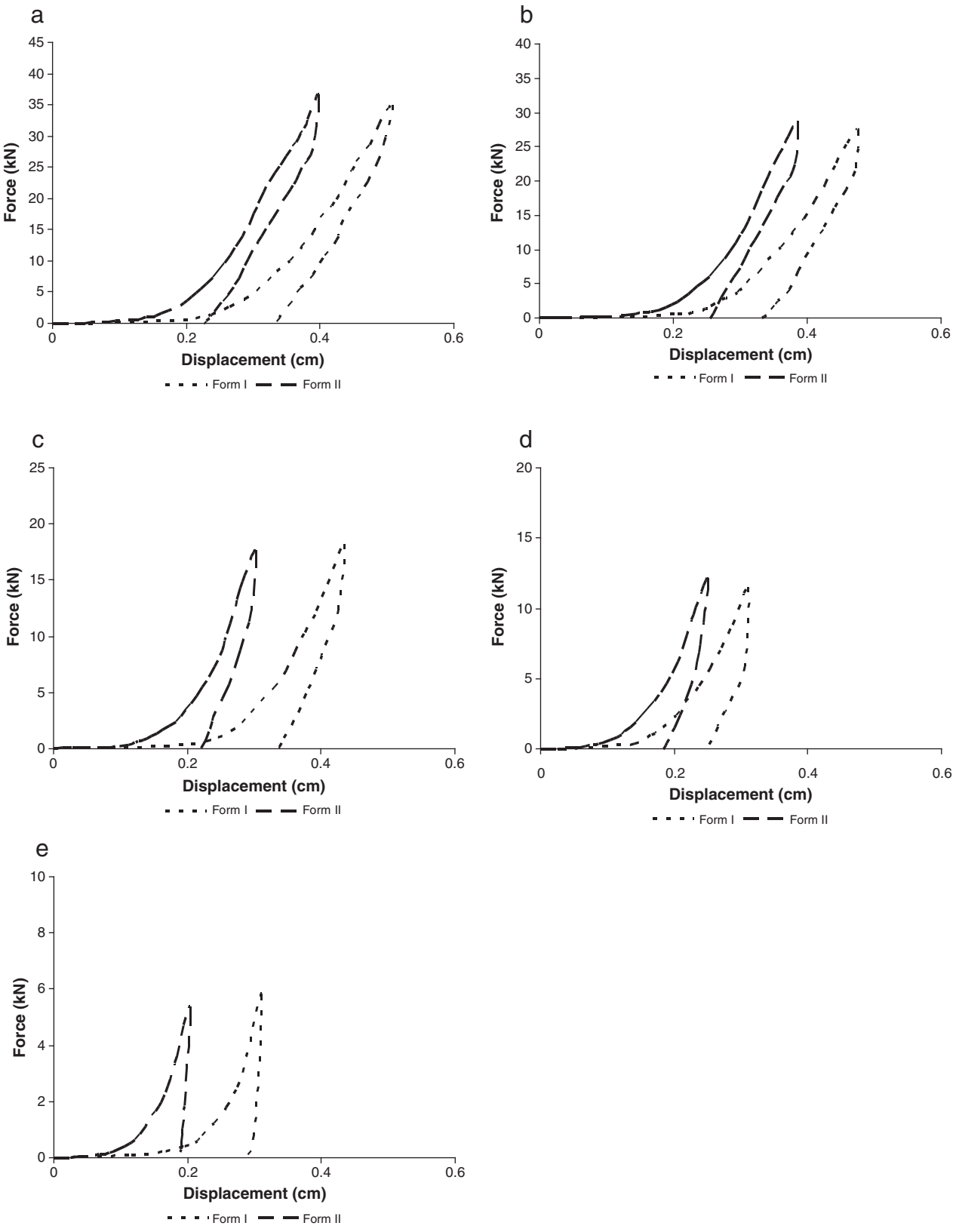

Fig. 7. Compaction profiles of both forms compacted to a maximum force of (a) 35 kN, (b) 27 kN, (c) 18 kN, (d) 11 kN, and (e) 5 kN.

compression forces. The tables show that for both forms, the work of compression increases markedly as the applied compression force increases. The absolute value of the work of decompression of compacted Form I powder increased from 0.34 ± 0.16 J to 22.89 ± 1.89 J when the applied compression force increased from 5 kN to 35 kN. Similarly, the absolute value of the work of decompression of compacted Form II powder increased from 0.32 ± 0.09 J to 23.62 ± 1.86 J when the applied compression force increased from 5 kN to 35 kN.

Table 1
Compaction parameters associated with compaction of Form I paracetamol powder (n = 5).

Compression force (kN)	Average work of compression, Wc (J)	Standard deviation	Average work of decompression, Wd (J)	Standard deviation	Average plasticity index (Ψ)	Standard deviation	Average EE/PE ratio	Standard deviation
35	39.00	2.20	−22.89	1.89	0.41	0.033	1.43	0.19
27	27.69	1.43	−15.12	0.64	0.45	0.012	1.20	0.06
18	14.86	0.50	−6.48	0.38	0.56	0.019	0.77	0.06
11	8.00	0.45	−2.44	0.53	0.69	0.048	0.44	0.10
5	2.63	0.41	−0.34	0.16	0.88	0.049	0.14	0.06

Table 2
Compaction parameters associated with compaction of Form II paracetamol powder (n = 5).

Compression force (kN)	Average work of compression, Wc (J)	Standard deviation	Average work of decompression, Wd (J)	Standard deviation	Average plasticity index (Ψ)	Standard deviation	Average EE/PE ratio	Standard deviation
35	38.89	1.67	−23.62	1.86	0.39	0.058	1.6	0.41
27	25.13	1.28	−15.65	0.92	0.38	0.010	1.65	0.07
18	11.75	0.96	−5.55	0.74	0.53	0.027	0.89	0.09
11	6.79	0.35	−2.34	0.37	0.66	0.038	0.53	0.09
5	2.35	0.20	−0.32	0.09	0.87	0.035	0.16	0.05

This marked increase in the work of decompression with maximum applied force indicates that both forms of paracetamol exhibit a marked increase in the magnitude of elastic recovery as the compression force increases. This is in agreement with immediate elastic recovery results obtained by Joiris et al. for both forms of paracetamol [6]. Moreover, the compact volume of Form II is lower than that of Form I. Therefore, it is expected that for generating equal compact volumes of the two forms a larger work of compression and a larger absolute value of the work of decompression would be associated with the compaction of Form I (Figs. 8 and 9).

Tables 1 and 2 also list the calculated values of the plasticity index at each compression force for both forms of paracetamol. It can be seen that there is a decrease in the magnitude of plasticity index as the compression force increases. This finding suggests that the net work (irrecoverable work) accommodated by the compacted powders decreases when the compression force increases. This is mostly due to a large increase in the work of decompression with increasing applied compression force. Thus, a large percent of the work associated with particle deformation is recovered during decompression. Fig. 10 shows the relation between the plasticity index and compact volumes obtained at different applied compression forces for both forms. Accordingly, it would be expected that for generating equal compact volumes, Form II would have a larger plasticity index compared to Form I.

Tables 1 and 2 also list the calculated elastic energy/plastic energy (EE/PE) ratio at each compression force for both forms of paracetamol. The results show that there is an increase in the EE/PE ratio as the compression force increases. A large EE/PE ratio is an indication of a large magnitude of compression energy utilized as elastic energy during decompression. The results suggest that both forms of paracetamol have a large magnitude of elastic component which increases significantly as the compression force increases. Fig. 11 shows the relation between the EE/PE ratio and compact volume. Accordingly, it would be expected that for generating equal compact volumes, Form I would have a larger EE/PE ratio.

5. Conclusions

It was possible to produce paracetamol Form II powder in quantities of several grams by melting Form I in a test tube immersed in a heated paraffin oil bath followed by controlled cooling. FT-IR analysis indicates that Form II paracetamol is physically stable when stored at 25 °C for 3 weeks at relative humidity conditions of 23%, 43%, and 58%. However, it undergoes polymorphic transition to the more stable Form I when stored at 75% and 94% relative humidity conditions. From mechanical energy estimations, results indicate that both forms have a large absolute value of work of decompression (elastic recovery) especially at high compression forces. However, generating equal compact volumes of both forms is associated with a plasticity index that is larger for Form II and an EE/PE ratio that is larger for Form I.

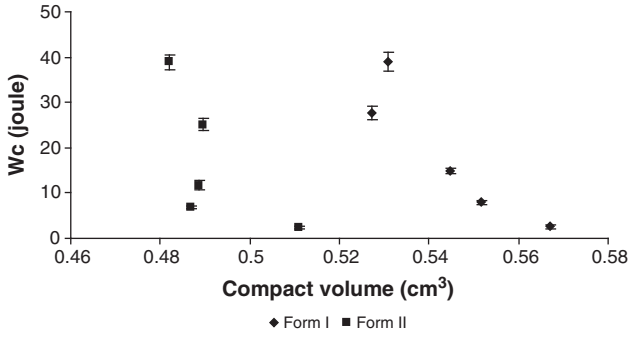

Fig. 8. Relation between work of compression (Wc) and compact volume for both forms of paracetamol.

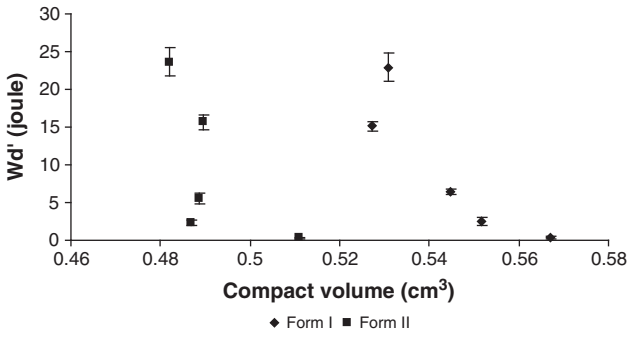

Fig. 9. Relation between the absolute value of work of decompression (Wd′) and compact volume for both forms of paracetamol.

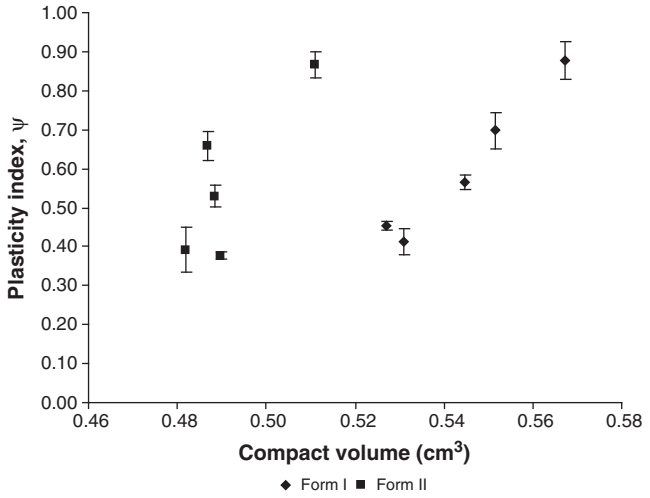

Fig. 10. Relation between plasticity index and compact volume for both forms of paracetamol.

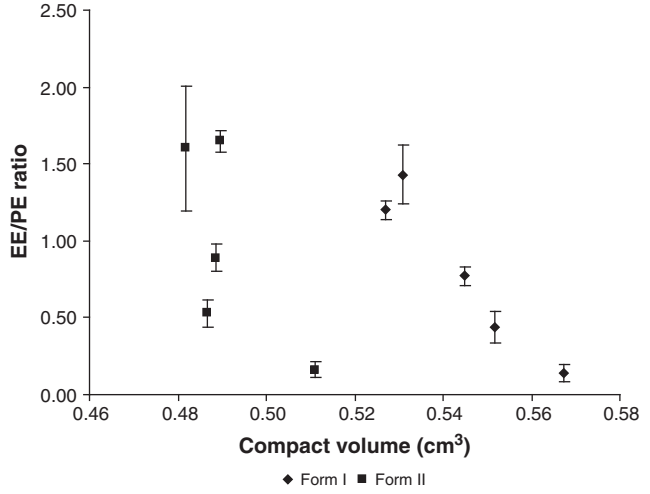

Fig. 11. Relation between EE/PE ratio and compact volume for both forms of paracetamol.

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