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The Physico-Technical Properties of a Multicomponent *Lentinus tuber regium* Based Co-processed Excipient (*fizlent*)

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Abstract

A study of the physico-technical properties of a novel co-processed multicomponent *Lentinus tuber regium* (LTR) based excipient (*fizlent*) designed to improve flowability and compressibility of LTR was carried out. A wet mass obtained by solvent evaporation of alcoholic dispersions of LTR, sodium bicarbonate, tartaric and citric acids in proportions of 80, 10, 6.5, 3.5 % w/w respectively was granulated, dried at 60º C and classified with 250µm sieve. Densities (bulk, tapped and particle), flow properties (flow rate, angle of repose, Carr's index, Hausner's ratio), swelling index, hydration capacity, differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and pH were determined for the natural, processed LTR and *fizlent*. *Fizlent* appeared as a compactable, tasteless, off-white powder without distinct odour. Aqueous dispersion of it has pH of 6.92 ± 0.13. Results show that a new pharmaceutical grade co-processed excipient, *fizlent* with enhanced flow, compressibility and dilution potential of 70-80% (paracetamol) and ≤ 30% for metronidazole, ascorbic acid and ibuprofen respectively was developed by particle engineering of *Lentinus tuber regium,* citric acid, tartaric acid and sodium hydrogen carbonate. *Fizlent* may be a useful filler-binder with potentials as directly compressible powder especially for most low dose drugs and may possibly serve as superdisintegrant.

1. Introduction

Researches in pharmaceutical technology are often directed towards introducing improved excipients, formulations and equipment [1]. Excipients with enhanced characteristics can be attained by developing new ingredients through combination of existing materials [2]. This approach has provided extensive platform for the manipulation of excipient functionality to generate innovative raw materials and is known as co-processing or particle engineering of two or more existing excipients [3]. It has been the most successful strategy for the development of better-quality production ingredients [4]. The co-processed multicomponent-based excipients are introduced to achieve better features and tableting properties than a single substance or the physical mixtures [5]. Several of such excipients are commercially available and include ludipress (lactose, polyvinylpyrollidone and crosspovidone), cellactose and microlac (lactose and cellulose), starLac (starch and lactose), prosolv (microcrystalline cellulose and silicon dioxide) etc. [6, 7]. Development of co-processed adjuvant starts with the selection of the

materials to be combined, their targeted proportion, selection of preparation method such as co-drying to get optimized product with desired physico-chemical considerations. An excipient of reasonable price has to be combined with the optimal quantity of a functional material in order to obtain integrated product with superior functionality than the simple mixture of components. In co-processing, the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within mini-granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in-process control easy and reliable [5]. Co-processing of excipient offers an interesting tool to alter these physico-technical properties. The primary feature of these excipients is that often no chemical change occurs during co-processing and all the reflected changes mostly show up in the physical properties of the excipient particles [8]. Another advantage achieved with co-processing is improved flow properties due to controlled optimal particle size and particle-size distribution [9]. Co-processed excipients have been used mainly in direct-compression tableting because there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler-binder. The compressibility performance of excipients such as cellactose [10] and ludipress [11] have been reported to be superior to the simple physical mixtures of their constituent excipients. Co-processed powders enjoy better dilution potential, fill weight variation and reduced lubricant sensitivity. Major limitations of co-processed excipient is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the active pharmaceutical ingredient and dose per tablet under development [12]. In the pharmaceutical industry, several natural products have been useful as binding, disintegrating, thickening, gelling agents, etc. [13]. Modified starch has been used as a new pregelatinized starch product in directly compressible controlled-release matrix system [14]. Cellulose has excellent disintegrant properties, good physicochemical characteristics with pronounced binding, swelling, lubricant properties, excellent diluent properties and simplified tablet manufacture as a result of its direct compressibility properties [15]. Processed *Lentinus tuber-regium* (LTR) powder has been studied as tablet disintegrant and could be a substitute for maize starch BP [16].

Lentinus tuber-regium (LTR) is an edible mushroom (basidiomycete) occurring in both tropical and subtropical regions of the world [17]. In the southern part of Nigeria, it is considered as luxury food and important table delicacy especially among rural dwellers [18]. The sclerotium is often dark brown on the surface and white inside. These are usually harvested from decaying logs, the dark brown exterior is peeled off and the white compact mycelial tissue is used for nutrition or nutraceutical. One of the most common dietary applications of LTR in Nigeria is as soup thickener. The white tissue is blended into fine powder and when added to soup, it swells and bulks up the soup [19]. LTR contains potassium, calcium, protein, trace amount of vitamin E, lipid, alkaloids and tannins [20]. It is palatable, with slight aroma and fairly succulent in nature [21]. A study of the disintegrant and drug release rate enhancing effects of admixture of maize starch BP and LTR powders in wet granulated paracetamol tablet has been documented [22]. A particle engineered novel powder containing LTR and polyvinylpyrollidone was documented to have potential as filler-binder and disintegrant [23].

There is rising search for new excipients to achieve desired set of functionalities due to the increasing number of new drug moieties with varying physico-chemical and stability properties. Other factors driving the search for new excipients are the growing popularity of the direct-compression technology and a demand for an ideal filler-binder that can substitute two or more excipients, tableting machinery's increasing speed capabilities, which require excipients to maintain good compressibility and low weight variation even at short dwell times, shortcomings of existing excipients such as loss of compaction of microcrystalline cellulose (MCC) upon wet granulation, high moisture sensitivity and poor die filling as a result of agglomeration, etc. [8].

This continual drive for new pharmaceutical grade excipients gave rise to this study. The objective was to develop by co-processing and characterizing a new multi-component powder containing a processed edible mushroom, *Lentinus tuber-regium* (LTR), sodium hydrogen carbonate, citric and tartaric acids. The design was to enhance the compressibility and flow properties of *Lentinus tuber-regium* powder which hitherto lacked in these qualities.

2. Materials and Methods

2.1. Materials

All reagents were used as received and includes hypo® (sodium hypochlorite solution) (Multipro, Nigeria), ethanol (Fischer Scientific, UK), n-hexane (Sigma-Aldrich, U.S.A), sodium hydrogen carbonate, lactose (Surechem, England), citric acid, tartaric acid (Loba Chemie, India), *Lentinus tuber-regium* tubers (purchased from *Ahia-ohuru* market, Aba, Nigeria).

2.2. Identification of Sample

The sample used for this study was identified by a Taxonomist, Dr. N. L. Edwin-Wosu, University of Port Harcourt reference herbarium as *Lentinus tuber-regium* (fr.) (family: Polyporaceae); Syn. *Pleurotus tuber-regium* (fr.). A voucher number OG-Acc-001. UPH. No. C-058 was assigned to it as it was deposited in the University of Port Harcourt, Port Harcourt, Nigeria region herbarium.

2.3. Processing of Pulverized *Lentinus tuber-regium*

The method of Iwuagwu and Onyekweli was adopted [16]. The dark brown skin of the sclerotia was removed and the white tissue were cut into small bits. The pieces were powdered and bleached with sodium hypochlorite solution with continuous stirring for 30 min. The whitened powder was washed severally with deionized water and later slurred with ethanol in a stainless steel vessel, then left to stand in a water bath at 60 ^{o} C, stirring for 60 min. The slurry was pressed using a fine muslin cloth. The material was dried in the oven (New Life, DHG-9023A, China) at 60 ^{o}C for 23h. The resulting powder was passed through 250µm stainless steel sieve (Endecott, England) and kept for further procedures.

2.4. Preparation of Co-processed Excipient (*fizlent*)

A novel excipient containing processed LTR (80% w/w), sodium hydrogen carbonate (10% w/w), tartaric acid (6.5% w/w) and citric acid (3.5% w/w) was developed by co-processing. Solvent evaporation method was adopted [24]. Citric and tartaric acids was blended in their dry form and dispersed in sufficient alcohol. Sodium hydrogen carbonate and the processed LTR was mixed and dispersed in enough alcohol too. Both alcoholic dispersions was homogenized and stirred till alcohol evaporated. The thick paste obtained was granulated with sieve 10 mesh size and dried to constant weight in an oven at 60º C. It was classified with 250µm stainless steel sieve and stored in an air-tight amber coloured glass container. The co-processed powder was referred to in this work as *fizlent*.

2.5. Determination of Physico-Technical Properties of Powders

The following parameters were determined for co-processed powder along the natural and processed forms of LTR for comparison.

2.6. Bulk, Tapped and Particle Densities

A 20 g quantities of the respective powders was employed in the determination of bulk and tapped densities using Stampfvolumeter (STAV 2003JEF, Germany). Three replicate determinations were carried out for each powder. The bulk and tapped densities were calculated using the following equation:

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume,Vo}} \quad \text{.....(1)}$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume,Vf}} \quad \text{.....(2)}$$

The particle density of the respective powders was determined by solvent displacement method using n-hexane as non-solvent [25]. An empty 25ml pycnometer was weighed (W). It was filled with n-hexane and weighed (W_1). The difference between this (W_1) and W was calculated as W_2. A 0.5g quantity of the powder was weighed (W_3) and carefully transferred into the pycnometer. The excess fluid was wiped off and the bottle was weighed again (W_4). Three determinations were carried out. Particle density, P_t (g/ml) was calculated according to the equation:

$$Pt = W2 \times W3/V\,(W3 - W4 + W2 + W) \quad \text{.....(3)}$$

where: v is the volume of pycnometer, 25 ml

2.7. Flow Properties

2.7.1. Flow Rate and Angle of Repose

A 50 g each of the respective powders was used to determine flow rate using the funnel method reported by Carstensen and Chan [26]. The angle of repose for the natural powder of LTR was determined by pouring 50 g of powder into a cylindrical paper roll fixed on to a flat base whose diameter is known and the same as the internal diameter of the cylinder. The cylinder was slowly pulled out vertically so as to form a cone of powder on the base. The height of the cone was measured. This is a modification of the method of Jones and Pilpel [27]. For the processed and co-processed powders of LTR, their respective angle of reposes was determined as follows. A clean glass funnel was clamped on a retort stand such that a constant perpendicular height of the tip of the funnel was 3 cm from a horizontal flat base with a clean graph sheet of paper. Each of the powders was in turn poured into the funnel until the powder heap formed touched the funnel tip and stopped further outflow of powder from the funnel orifice [28]. The diameter of the circumference of the heap was measured. Three determinations were carried out.

Calculations were made as follows:

$$\text{Flow rate} = \text{Mass of powder} / \text{Time} \quad \text{.....(4)}$$

$$\text{Angle of repose}, \theta = \tan - 1\ \frac{2h}{d} \quad \text{.....(5)}$$

where θ is the angle of repose, *h* is the height of heap of powder, *d* is the diameter of heap of powder.

2.7.2. Hausner's Ratio [29]

This was calculated as the ratio of tapped density to bulk density of the powder.

$$\text{Hausner quotient} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{.....(6)}$$

2.7.3. Carr's Index (CI) [30]

This was calculated using bulk and tap densities data when fitted into the equation:

$$\text{Carr's Index} = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 10 \quad \text{.....(7)}$$

2.7.4. Powder Porosity

The porosity of the powder was calculated using the respective values of the bulk and particle density determined for the powder. This was calculated using the formula:

$$\text{Porosity} = \{1 - [\text{Bulk density}/\text{True density}]\} \times 100 \quad \text{..(8)}$$

2.8. Hydration Capacity

The hydration (water retention) capacity of the respective powders was determined by the method of Ring [31]. A 1g quantity of powder was placed in a 15ml plastic centrifuge tube and 10ml of water was added. The tube was shaken intermittently over a 2 h period and left to stand for 30 min. This was then centrifuged for 10 min at 3000 rpm. The supernatant was decanted and the weight of the powder after water uptake and centrifugation, x was determined. Triplicate determination were carried out and mean values were determined.

$$\text{Hydration capacity} = \frac{x}{y} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (9)$$

where x is the weight of moist powder after centrifugation and y is the weight of dry powder.

2.9. Swelling Capacity

The swelling capacity of the respective powders was determined by the modification of the methods of Bowen and Vadino [32]; Iwuagwu and Okoli [33]. The tapped volume occupied by 5g of the powder Vx, was noted. The powder was then dispersed in 85ml of water and the volume made up to 100ml with water. After 24 hours of standing, the volume of the sediment, Vv, was estimated. Triplicate determinations were carried out. The swelling capacity was computed as follows:

$$\text{Swelling capacity} = \frac{Vv}{Vx} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (10)$$

where Vv is the volume of sediment and Vx is the tapped volume occupied by powder.

2.10. pH Measurement

The pH of 2 % w/v aqueous dispersion of powder was determined using a pH meter (Corning, model 10, England).

2.11. Differential Scanning Calorimetry (DSC)

DSC studies were carried out using a DSC – 204F1 (NETZSCH, Germany) using aluminum pan pierced lid in atmosphere of liquid nitrogen at the rate of 20 ml/min within the temperature range of 27- 400 ^{0}C at 10 ^{0} C rise/min incremental rate to generate the thermograms for the natural, processed LTR powders and the coprocessed excipient, *fizlent*.

2.12. Scanning Electron Microscopy (SEM)

The scanning electron microscopy was carried out using JEOL-SEM, Instrument 7500F, Japan to obtain the scanning electron micrographs of the natural and processed LTR powders as well as that for co-processed excipient, *fizlent.*

2.13. Determination of Compressibility and Dilution Potential

The compressibility and dilution potential of the natural, processed powders of LTR and *fizlent* was determined using paracetamol, metronidazole, ascorbic acid and ibuprofen. Each of these drugs and the respective test materials was blended in proportions of 1:9 - 9:1 respectively. Each admixture was lubricated with 0.1% (w/w) magnesium stearate prior to compression. A single punch table top tableting machine (Erweka, EP1, Germany) was used, applying a maximum compression force of 1.5 tons. The hardness of the respective batches of compressions was determined using a digital hardness tester (Erweka TBH 100, Germany).

3. Results and Discussion

3.1. Physico-Technical Properties

The physico-technical properties of *fizlent* are shown in Table 1. *Fizlent* was an off-white powder without characteristic odour or taste. Its aqueous dispersion was cloudy and had pH close to neutral when compared to those of the natural and processed LTR. There was insignificant difference in the bulk and tapped densities for the natural, processed LTR and the co-processed powders ($p>0.05$), though a significant difference was observed within the particle density ($p<0.05$). Ugoeze and Okpara [23] obtained similar results from studies of the properties of co-processed LTR and polyvinylpyrollidone. Since the interparticulate interactions influencing the bulk properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison as the compressibility index or the Hausner's ratio is often used as an index of the ability of the powder to flow. These two parameters are measures of the propensity of a powder to be compressed. As such, they are measures of the powder ability to settle and they permit an assessment of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. The difference in the value of bulk and tapped densities for *fizlent* was insignificant ($p>0.05$). This shows the enhancement in flowability of *fizlent* with reference to the natural or processed LTR. The values of angle of repose, Carr's index and Hausner's ratio which decreased from the natural LTR to the co-processed excipient ($p<0.05$) were further indication of improvement in flow properties.

The angle of repose has been applied in characterizing the flow properties of solids and is also related to interparticulate friction or resistance to movement between particles. In as much as some variation in the qualitative description of powder flow may exist while applying the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification of Carr [30, 34, 35]. Neumann

noted that angle of repose above 40^o are indicative of very cohesive powder [36]. Pilpel also reported that angle of repose less than or equal to 40^o suggest a poorly flowing material [37]. It has been observed that as particles becomes more irregular, angle of repose increases. In recent years the Carr's index (CI) and the closely related Hausner's ratio (HR) became the simple, fast and popular methods of predicting powder flow characteristics [29, 30]. The values obtained for flow rate, angle of repose, Carr's index and Hausner's ratio showed consistent improvement in flowability and compressibility of the co-processed excipient in comparison with the natural or processed LTR ($p<0.05$). The results obtained for swelling index showed that the procedures adopted in processing LTR and co-processing it with micro-particulate composites caused a significant reduction in the swellability of the material of LTR. The natural form retained higher value of swelling index followed by the processed and then, the *fizlent* ($p<0.05$) in the order: natural LTR powder > processed powder > *fizlent*. Though, there appear to be a continual decease in hydration capacities from the natural LTR to *fizlent*, statistical evaluation showed these to be insignificant ($p>0.05$).

Table 1. *Physico-technical properties of the natural, processed LTR and fizlent.*

Parameter	Natural powder	Processed powder	Co-processed excipient
Colour	Off-white	white	Off white
Taste	Tasteless	Tasteless	Tasteless
Odour	Slight sweet smell	No characteristic odour	No characteristic odour
pH	6.05	5.07	6.92 ± 0.13
Particle density (g/ml)	1.21 ± 0.06	1.47 ± 0.09	1.56 ± 0.14
Bulk density (g/cm3)	0.31±0.12	0.41 ±0.13	0.47 ± 0.01
Tapped density (g/cm3)	0.48±0.14	0.56±0.16	0.61 ± 0.01
Flow rate (g/sec)	No flow	12.37±0.52	18.55 ± 0.49
Angle of repose (θ)	53.9˚± 2.00	32.30˚±1.00	29.28^o ± 3.63
Carr's index (%)	34.2±0.11	26.79±0.14	22.95 ± 1.69
Hausner's ratio	1.55±0.12	1.37±0.13	1.23 ± 0.03
Porosity (%)	74.38±0.15	72.11±0.12	69.87 ± 0.12
Swelling index	3.50±0.15	2.93±0.12	2.60 ± 0.16
Hydration capacity	3.50 ± 0.04	3.43 ± 0.12	3.30 ± 0.11
Compressibility	Very poorly compressible	Poorly compressible	Compressible

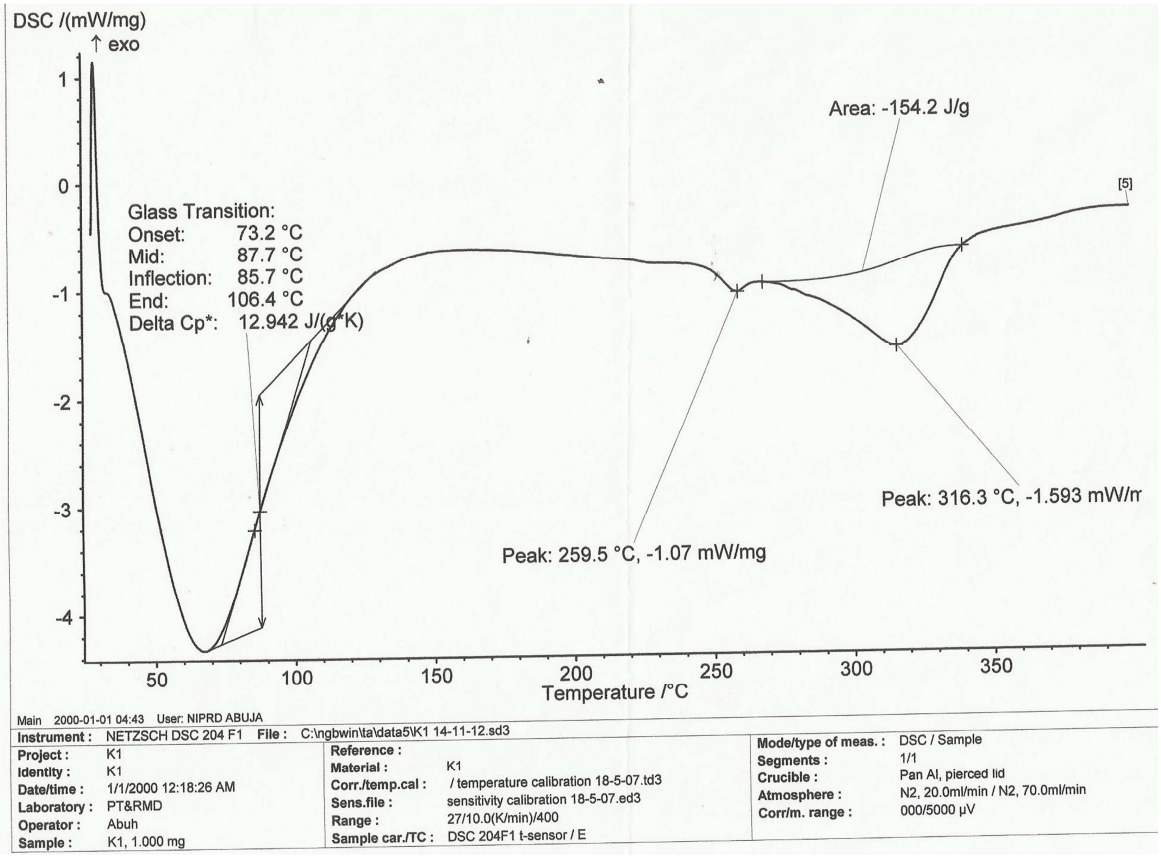

Fig. 1. *DSC thermogram of the natural LTR powder.*

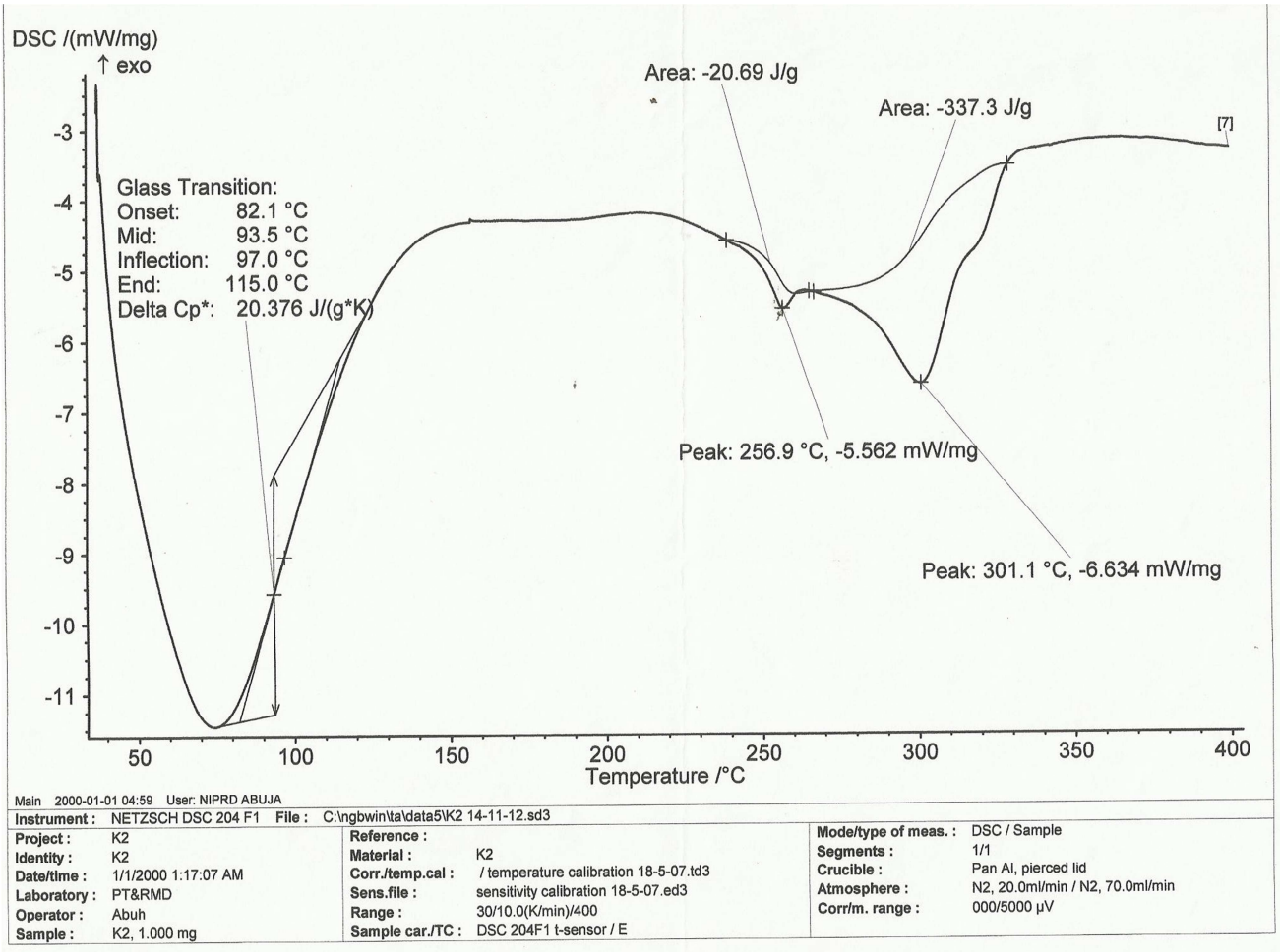

Fig. 2. *DSC thermogram of the processed LTR powder.*

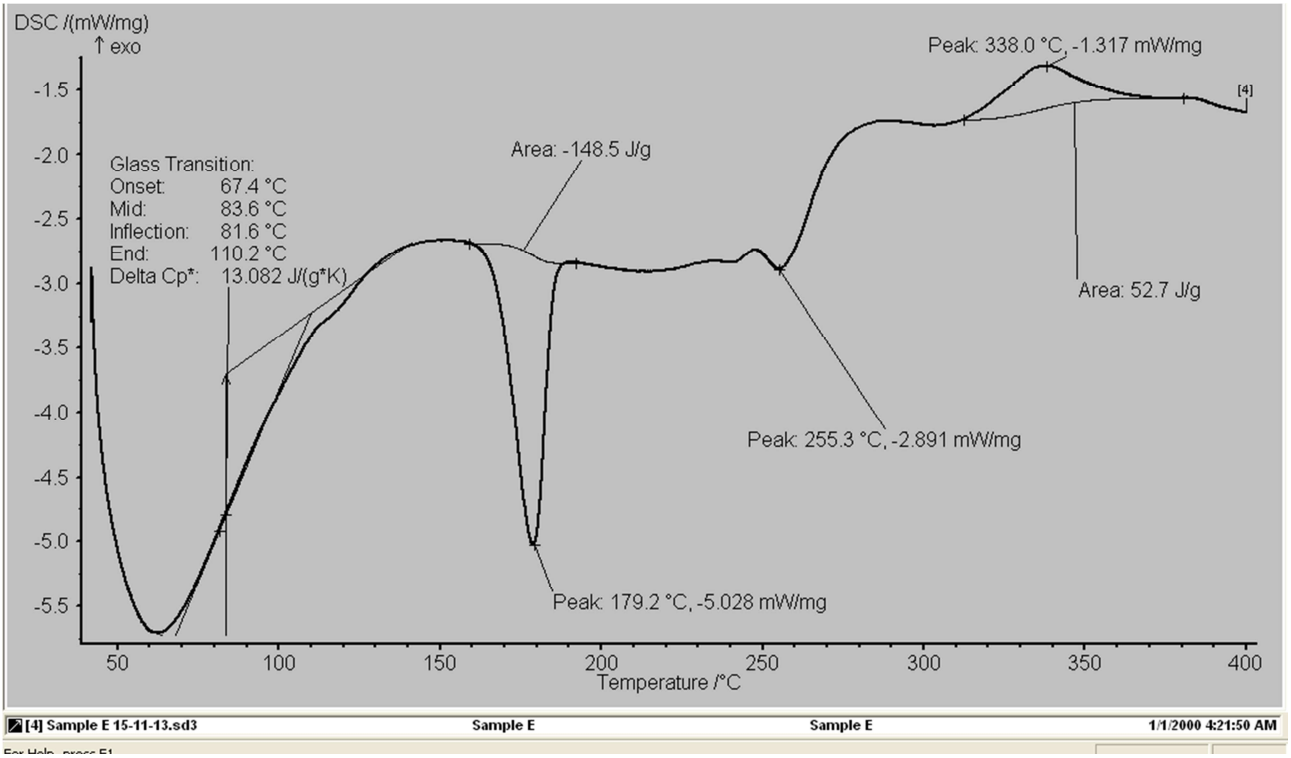

Fig. 3. *DSC thermogram of the co-processed excipient.*

The DSC thermograms are presented in Figures 1-3. Two melting peaks each were observed in the thermogram of both the natural and processed LTR powders. This may be possible since the powder is a biomaterial which have been reported to contain some minerals, protein, alkaloids, tannins, carbohydrate[20], etc. The thermogram of the processed LTR powder in addition to showing two melting peaks, also reveal lower melting temperatures than those for the natural powder. This lowering in melting temperature may be attributed to the processing method adopted in this work. However, after co-processing the processed form of LTR with citric acid, tartaric acid and sodium hydrogen carbonate, the thermogram for *fizlent* rather showed three melting peaks, the third peak being exothermic with the previous first two melting temperatures much lower than those in the natural and processed powders of LTR respectively. This observation could still be due to the introduction of more material into LTR powder. The occurrence of an exothermic peak on the thermogram of *fizlent* may indicate a trace of crystalline substance emerging as a result of the particle engineering of the multicomponent microparticles with processed LTR. The suggestion that *fizlent* contains some crystalline material may be traced to the scanning electron micrographs of the natural, processed LTR and *fizlent* (Figures 4-6) respectively. These showed that the method of coprocessing adopted to obtain *fizlent* appears to have increased the densification and possibly the crystallinity.

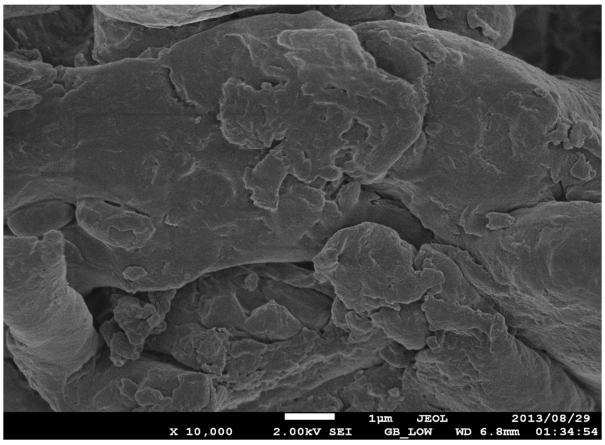

Fig. 4. *Scanning electron micrograph of the natural LTR powder.*

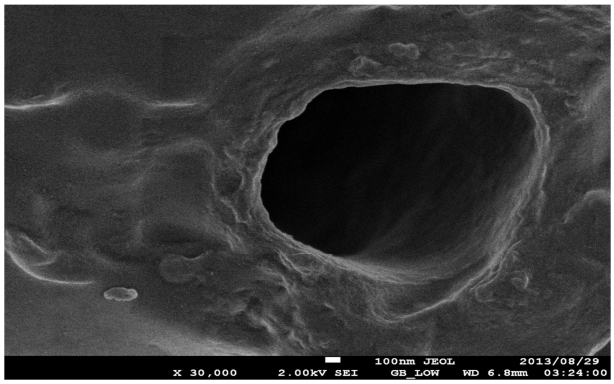

Fig. 5. *Scanning electron micrograph of the processed LTR powder.*

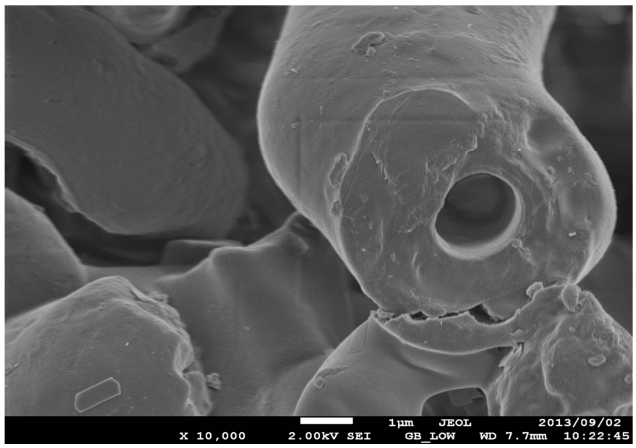

Fig. 6. *Scanning electron micrograph of the co-processed excipient.*

These results show that there were changes in the physical properties of the processed powder as a result of co-processing it with citric acid, tartaric acid and sodium hydrogen carbonate. There was increased densification and crystallinity which could have led to the improvement in flowability of *fizlent* as revealed in the results of angle of repose, Carr's index and Hauser's ratio (Table 1). The compacts compressed from *fizlent* showed crushing strength up to 3.5N as against the compacts obtained from the natural or processed forms of LTR which were highly friable. Furthermore, the dilution potential for *fizlent* was 70-80% (paracetamol) and ≤ 30% for metronidazole, ascorbic acid and ibuprofen respectively. These show that the compressibility of natural or processed LTR has been improved by co-processing method adopted in this study.

3.2. Conclusion

A new pharmaceutical grade co-processed excipient, *fizlent* with improved flow properties, compressibility and dilution potential of 70-80% (paracetamol) and ≤ 30% for metronidazole, ascorbic acid and ibuprofen respectively was developed from *Lentinus tuber regium,* citric acid, tartaric acid and sodium hydrogen carbonate. Results show that *fizlent* may be a useful filler-binder and superdisintegrant especially in direct compression solid dosage form formulation.

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