Evaluation of the compression properties of co-processed paracetamol, gelatin and microcrystalline cellulose formulation prepared via melt-in agglomeration

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Abstract

Co-processing techniques have been used to modify the properties of dosage forms. The aim of this study is to evaluate the granules and tablet properties of co-processed paracetamol, gelatin and microcrystalline cellulose. Batches of co-processed paracetamol granules (A-E) were prepared by melt-in agglomeration process using paracetamol with varying amounts of gelatin (1.0, 2.0, 3.0 or 4.0 % w/w) or starch (3.0 % w/w) and microcrystalline cellulose. A control batch (F) of conventional granules was also prepared by wet granulation method with starch mucilage (4.0 % w/w). The granules were subjected to micromeritic, compaction and differential scanning calorimetric analyses. The granules were compressed into tablets and their tablet properties evaluated. Granules of batches A-D had higher percent maximum volume reduction of 12.25-16.13 % compared to the percent maximum volume-reduction (9.52 and 11.81) of granules from batches E and F respectively. Differential scanning result indicates amorphous solidification of co-processed paracetamol. Tablets formulated from batches A-D showed improve tensile strength (3.63 - 8.26 Nm^{-2}) and faster disintegration time (1.32- 1.12 min) compared to the tensile strengths (5.09 & 5.01 Nm^{-2}) and disintegration times (2.54 & 4.43 min) of tablets from batches E and F respectively. There were no significant difference ($P \geq 0.05$) in their maximum amounts (>70 %) of drug released after 40 min. Melt-in agglomeration of paracetamol and gelatin with microcrystalline cellulose created amorphous dispersion that improved tabletability parameters of granules and disintegration time and dissolution properties of tablets.

Keywords: Co-processed, compaction, maximum volume-reduction, amorphous solidification, tabletability.

1. Introduction

Physical properties of excipients significantly affect their flow-ability, packing, compaction, compressibility and ability to transform into coherent solid dosage forms (1-3). Processing techniques such as solid-solid dispersion, solid-suspension, milling to micro or nanoparticle size, co-solvency, supercritical fluid, cryogenic and complexation have been used to modify excipients for better dosage formulation and drug delivery (4). Solid-solid dispersion technique is used to disperse micronized drug particle in another solid dissolution medium (5-7). The micronization and dispersion of solid-solid particles may be achieved using fusion, solvation, solvation and fusion, electrospinning and sonocrystallization. Fusion technique uses thermal energy and mechanical force

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to increase the surface area and energy for interaction and mixing of solids in their liquid or semi-solid states, and cooling to produce high energy metastable form. Fusion technique can be carried out through hot-melt, hot-melt extrusion or melt agglomeration processes. Melt agglomeration process can be prepared by melt-in or spray-on procedure. Melt-in agglomeration procedure is by heating mixture of binder, drug and stabilizer excipient to a temperature above the melting point of the binder. Melt agglomeration spray-on procedure is by spraying dispersion of molten drug-polymer mixture on a heated stabilizer excipient in a high shear mixer. Melt-in agglomeration procedure produces a metastable and homogenous solid dispersion with a higher dissolution rates than spray-on procedure (8). But the metastable dispersion is unstable and may reverts to low energy stable crystalline form (9). To prevent reversion of metastable to crystal forms, melt-in agglomeration applies rapid cooling of molten drug-polymer mix and addition of intermediary stabilizer - polymer carrier (10).

This work will co-process paracetamol powder using melt-in agglomeration process in different concentration of gelatin slurry dispersion stabilized with microcrystalline cellulose. Paracetamol is a fluffy and dusty powder that is difficult to pack or compress without processing. Processing of high drug-loaded paracetamol tablets and capsules allows little alteration in bulk size by using only small amount, about 10 %, of co-former adjunct such as starch, gelatin and polyvinylpyrrolidone as binders (11-13). Starch gel, though not as intense a binder as povidone, is widely used because of its biocompatible and biodegradable bio-properties (13, 14). Gelatin, a bio-sourced material like starch, with higher binding property is gaining consideration in drug formulation. Gelatin has the advantage of stability, short retention time, and non-accumulation in the body. Gelatin can absorb four times its weight, is thermo-reversible, melts at body temperature, and can have similar biocompatible viscosity to blood plasma (14). The combination of melt-in agglomeration technique, bio-adhesive gelatin and intermediary microcrystalline cellulose is a way of harnessing the blending efficacy of melt-in agglomeration, the high granules and tablet binding properties of gelatin

slurry and the improvement of drug bioavailability by carriers such as microcrystalline cellulose in ternary systems.

Hence, the aim of this study was to co-process paracetamol powder using melt-in agglomeration procedure to enhance the pre-compression properties of paracetamol granules and post-compression properties of its tablets.

2. Materials & methods

Paracetamol powder (Dizpharm Nigeria Limited), gelatin powder, Type A (Jiangsu Guo Tai International Group Huatai Import and Export Company Limited, China), microcrystalline cellulose (Vijlak Pharma Limited, India), maize starch BP (Norbright Industry Limited, China), lactose monohydrate, USP-NF (Danone GmBH, Germany) and magnesium stearate (Xllong Chemical Company Limited, Guangdang Province, China). The other reagents used were of analytical grade.

2.1. Preparation of paracetamol granules

Using the formula in Table 1, various batches of granules were prepared using calculated quantities of ingredients required to produce sufficient granules for 100 tablets. Batches A-E were prepared by co-processing paracetamol with varying amounts of gelatin (1.0-4.0 % w/w) or starch (3.0 % w/w) and microcrystalline cellulose. The gelatin or starch were dispersed in sufficient water and heated over a hot water bath at 40 °C with constant stirring to produce slurries. Using the melt-in agglomeration procedure of Vilhelmsen *et al*. (8), the required quantities of paracetamol and microcrystalline cellulose powders were added to the slurries and heated to 70 °C (above the melting point of gelatin and gelatinization temperature of thermoplastic starch) with constant stirring. The resultant semi-solid mass was allowed to cool for 2 h and forced through a 2.0 mm stainless steel sieve. The resultant granules were dried in a hot air oven for 5 h at 40 °C and then pass through 750 μm mesh sieve.

While for batch F, conventional paracetamol granules were prepared by wet massing paracetamol and microcrystalline powders with sufficient quantities of starch (4.0%w/w) mucilage. The wet mass was forced through a 2.0

Table 1. Formula used in the preparation of paracetamol granules and tablets.

Ingredients (g)	Batches					
	A	B	C	D	E	F
Paracetamol	50.0	50.0	50.0	50.0	50.0	50.0
Gelatin (%w/w)	0.53	1.05	1.58	2.10	-	-
Starch (%w/w)	-	-	-	-	1.58	2.10
Microcrystalline cellulose	0.53	0.53	0.53	0.00	0.53	0.53
Lactose	1.18	0.66	0.13	0.13	0.13	0.13
Magnesium stearate	0.26	0.26	0.26	0.26	0.26	0.26
Total	52.50	52.50	52.50	52.50	52.50	52.50

mm stainless steel sieve and the wet granules were dried in a hot air oven for 5 h at 40 °C and then pass through a 750 μm mesh size sieve.

Lactose of varying amounts and 0.5 %w/w of magnesium were added to all the batches of granules and mixed thoroughly. The dried granules were stored in a desiccator until analysis and compression.

2.2. Micromeritic analysis of granules
2.2.1. Bulk and tapped densities

About 10 g of granules was poured through a funnel into a 50 ml measuring cylinder. The volume occupied by the granules was recorded as the bulk volume. The weight of the granules divided by the bulk volume was recorded as the bulk density. The cylinder was tapped on a padded wooden base from a height of 2.5 cm until a fixed tapped volume was obtained. Tapped density was calculated from the powder weight divided by the tapped volume.

2.2.2. Carr's index and Hausner's ratio

The difference between the tapped and bulk densities of the granules, divided by the tapped density and expressed as a percentage were recorded as their Carr's indices while the ratio of the tapped to bulk densities of the granules were recorded as their Hausner's ratios.

2.2.3. Angle of repose

A glass funnel was clamped to a retort stand at 5.0 cm from a horizontal surface with a clean white paper. Thirty (30) grams of the granules was poured into the funnel with its opening closed. Then the granules were allowed to fall freely under the influence of gravity, forming a heap on the white paper. The height and base diameter of the heap of granules was measured and used in calculating the angle of repose employing Equation 1.

$$\theta = tan^{-1}(h/r) \qquad \text{(Eq. 1)}$$

Where h is the height of the heap of granules and r is the radius of the circular base.

2.2.4. True/particle density

Using the solvent displacement method of Persson et al (15), a 25 ml glass pycnometer (specific gravity bottle) was filled with acetone and weighed (a). The bottle was emptied and dried. About 0.5 g (b) of the granules was poured into the dried bottle, filled with acetone and weighed (c) after cleaning off the excess acetone from the bottle. The weights recorded were used to calculate the true density of the granules using Equation 2.

$$\rho = \frac{b}{[(a+b)-c]} \times S \qquad \text{(Eq. 2)}$$

Where ρ is the particle density and S is the specific gravity of acetone

2.2.5. Granule porosity

The porosity of the paracetamol granules was calculated using the Equation 3.

$$Powder\ porosity = 1 - \frac{Bulk\ density}{True\ density} \qquad \text{(Eq. 3)}$$

2.3. Compaction properties
2.3.1. Granule consolidation analysis

Using the method of Ilic et al., (1), 30 g

of the paracetamol granules was poured through a funnel into 100 ml cylinder of 11.1 mm diameter to mark. The cylinder was tapped on a padded wooden base from a height of 2.5 cm at the rate of 20 taps per minute in steps of 10 to 1000 taps. The tapped volumes of the granules were recorded at 20, 40, 60, 80 and 100 steps. The tapped densities after N taps and bulk density were used to determine the rate of powder consolidation (K) and consolidation index (C) using Equation 4 (16).

$$Log \frac{Tapped\ density - Bulk\ density}{Tapped\ density} = K\ Log\ N + C \quad \text{(Eq. 4)}$$

2.3.2. Kawakita analysis

The compactibility and cohesiveness of the paracetamol granules were assess using the Kawakita analysis. About 10 g of granules was gently poured into a 50 ml measuring cylinder and its volume (Vo) recorded. The cylinder was gently tapped ten times on a wooden horizontal surface and the resultant volume (VN) recorded. Tapping was continued with the granule volume recorded after every ten taps until a constant volume was obtained. The data obtained were fitted into the Kawakita Equation 5 and a plot of N/C against N with a slope (1/a) and intercept (1/ab).

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \quad \text{(Eq. 5)}$$

Where N = number of taps, C= degree of granule volume reduction (Vo-VN/Vo), a and b are constants, where a= compactibility of granule (maximum degree of compression) and 1/b=cohesiveness of granule (yield strength or pressure needed for powder to reach half of maximum volume reduction) (17, 18).

2.3.3. Differential scanning calorimetry (DSC) analysis

DSC characterization of pure paracetamol powder and the formulated granules was carried out to investigate any drug excipient interaction using a differential scanning calorimeter (DSC 60, Schimadzu, Japan) with DuPoint 9900 thermal analyser. About 5.0 mg of the sample was sealed in a flat-bottom aluminium pan and heated over a temperature range of 30-300 °C while nitrogen

was used as the purge gas and at a flow rate of 70 ml/min at a constant increasing rate of 10 °C/min. The thermogram obtained for the pure drug was compared with that of the granule formulation.

2.4. Compression of granules

The granules were compressed using a six station rotary tablet press (Taizhou Quanta Machinery Equipment Co. Ltd) set at 35 KN and to compress granules weighing 525 mg. The compressed tablets were stored in a desiccator at room temperature for 7 days prior to analysis.

2.5. Tablet evaluations
2.5.1. Weight variation

Twenty tablets were randomly selected from each batch and weighed individually using an electronic balance (Mettler, Switzerland). Their individual weights were recorded and used in calculating the average weight and standard deviation.

2.5.2. Friability test

The friability of 10 tablets from each batch was determined using a single drum friabilator (PTF 10E, Pharma Test Instruments India Pvt. Limited, India). The tablets were collectively weighed and place in the drum of the friabilitor set to rotate at 25 rpm for 4 min. Thereafter, the tablets were removed, dusted and weighed again. The percentage loss in weight was calculated and recorded as the friability of the tablets.

2.5.3. Crushing and tensile strengths

Ten (10) tablets were selected at random from each batch and the compression force required to crack the tablets was determined using a motorised tablet hardness tester (Campbell Electronics, Model HT- 30/50, India). The mean crushing strength and standard deviation were calculated using the compression force values from the tablets. Also, the tensile strength of the tablets were calculated using Equation 6.

$$\delta = \frac{2F}{\pi dT} \quad \text{(Eq. 6)}$$

Where δ = tensile strength in Nm-2, F = force in Newton required to cause fracture, d =

Table 2. Micromeritic properties of the paracetamol granules.

Batch	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Particle density (g/cm^3)	Hausner's Ratio	Carr's index	Porosity	Angle of repose (°)
A	0.48±0.02	0.53±0.02	5.36±0.12	1.11±0.02	9.56±0.09	0.92±0.01	31.39±1.95
B	0.42 ±0.18	0.44±0.03	3.57±0.08	1.06±0.03	5.45±0.08	0.87±0.01	25.84±2.97
C	0.41±0.05	0.43±0.03	2.05±0.03	1.04±0.02	4.03±0.04	0.77±0.04	29.97±3.01
D	0.38±0.03	0.42±0.02	3.21±0.12	1.08±0.01	7.69±0.98	0.85±0.03	34.55±2.80
E	0.71±0.03	0.82±0.01	1.07±0.08	1.16±0.02	13.00±1.12	0.34±0.02	30.29±2.02
F	0.58±0.04	0.66±0.01	2.23±0.10	1.14±0.01	12.12±1.09	0.73±0.01	32.06±2.75

tablet diameter in m and T = tablet thickness in m.

2.5.4. Disintegration time

Disintegration test was performed on six tablets from each batch using a disintegration tester (Model MK4, Manesty Machine Limited, England) operated at 30 cycles/min with 1 L of 0.1 N HCl at 37±1.0 °C. The time taken for fragments of the tablets to completely pass through all the tubes meshes was recorded and the mean disintegration time and standard deviation calculated.

2.5.5. Dissolution profile

The dissolution profiles of tablets from the various batches of the paracetamol formulations were determined using a USP Type II Dissolution Apparatus (Caleva Company Limited, England) containing 900 ml of 0.1 N HCl at 37±1.0 °C and paddle speed of 100 rpm. The experiment was ran for 60 min and 5.0 ml samples were withdrawn at time intervals and replaced with fresh dissolution medium kept at the same temperature of 37±1.0 °C. Withdrawn samples were subjected to a two-fold dilution and their absorbances read at 243 nm in a UV spectrophotometer (Model 23D, Uniscope, England). Amounts of drugs in the samples were computed from the equation derived from the calibration plot of pure paracetamol.

2.6. Statistical analysis

Experiments were carried out in triplicates and data presented as mean ± standard deviation (SD). Differences between means were analyzed by one way analysis of variance (ANOVA) ($p<0.5$) using Microsoft Excel 2007.

3. Results
3.1. Micromeritic properties

The results from the micromeritic evaluation are presented in Table 2. Batches of the paracetamol granules (A-D) containing co-processed gelatin and microcrystalline cellulose exhibited bulk (0.38-0.48 g/cm^3) and tapped (0.42-0.53 g/cm^3) densities that decreased with increased concentration of gelatin used in their co-processing. The conventional granules (F) and those of the co-processed starch and microcrystalline cellulose (E) showed significantly higher bulk (0.58, 0.71 g/cm^3) and tapped (0.66, 0.82 g/cm^3) density values, respectively. Granule's particle densities ranged from 2.05-1.07 g/cm^3) with batch E granules exhibiting significantly higher values. The Hausner's ratios (1.04-1.16) and Carr's indices (4.04-13.00) of the granules were lower for the co-processed gelatin and microcrystalline cellulose batches (A-D) while their porosities and angles of repose ranged from 0.34-0.92 and 25.84-34.55°, respectively.

3.2. Compaction properties

The results from the consolidation and Kawakita analyses of the paracetamol granules are shown in Table 3 and Figures 1 and 2. Co-processed gelatin granules showed decrease in percent maximum volume reduction (12.25-16.13%) though higher in values when compared to the 9.52% and 11.81% of the co-processed starch and conventional granules, respectively. All the batches of granules showed a linear correlation in their consolidation with the number of taps at the start of experimentation (Figure 1) and deviated as the number of taps increased. The rate of
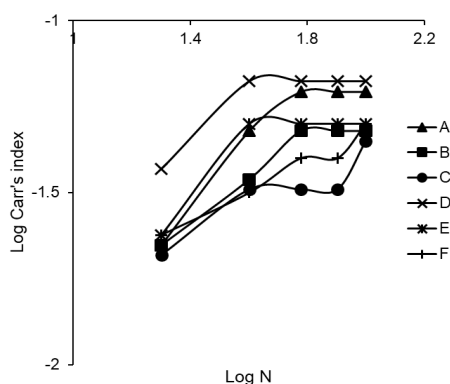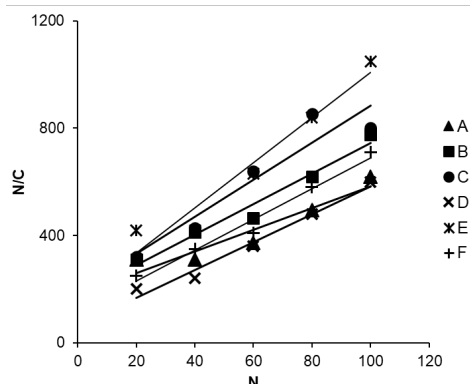
Figure 1. Consolidation plots of the paracetamol granules.

Figure 2. Kawakita plots of the paracetamol granules.

consolidation of the co-processed gelatin granules (0.34-0.65) and their consolidation indices ranging from -1.8253 to -2.4359 decreased with increased amounts of gelatin.

The constants of the Kawakita equation (Table 3) gotten from the slope and the intercept of the line from graphs N/C versus N (Figure 2) showed the compactibility (a) values of the granules ranging from 4.63 to 7.69 for the co-processed gelatin granules with the values of the co-processed maize and conventional granules being lower. Cohesiveness (1/b) of the co-processed granules ranged from 12.31 to 44.62 and decreased with increased amounts of gelatin.

3.3. Drug-excipient interaction

The thermographs from the DSC analysis of pure paracetamol powder (a) and paracetamol granules prepared with co-processed microcrystalline cellulose and gelatin (b) or starch (c) are presented in Figure 3. The characteristic trough of the paracetamol powder was evident in the thermographs of the granules, indicative of no interaction or complex formation between paracetamol and excipients during the co-processing.

3.4. Tablet parameters

The tablet parameters are shown in Table 4. The weights of tablets range from 525-528 mg. The hardness or crushing strengths of the tablets increased from 3.25 to 6.25 kgf with increase in the gelatin concentration used in the co-processing. The same is applicable to the tensile strengths of the tablets, ranging from 3.63-8.26 Nm-2 as against 5.09 and 5.01 of the co-processed starch and conventional tablets, respectively. The friability of all the tablets were below 1.0 % while their disintegration times ranged from 1.12 to 1.32 min.

The tablets exhibited variable dissolution profiles (Figure 4) and different per cent dissolution (78-89 %) after 60 min dissolution testing. There were not significant difference ($p \geq 0.05$) in their maximum amounts of drug released at the end of the experiment. All the tablets released over 70 % of their drug content in less than 40 min.

4. Discussion

Results from the micromeritics and com-

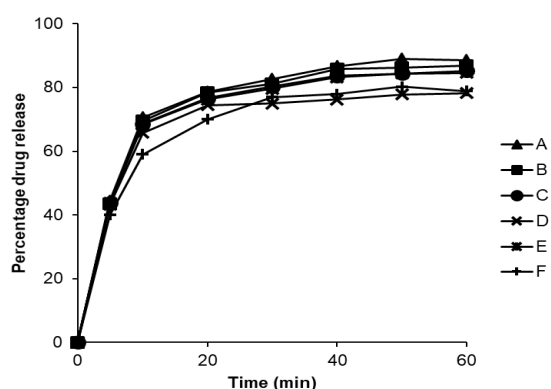Table 3. Consolidation and compression parameters of granules.

Batch	Consolidation plot				Kawakita plot			
	a (%)	K	C	1/a	1/ab	1/b	a	b
A	16.13	0.6505	-2.4359	0.13	5.80	44.62	7.69	0.02
B	12.90	0.5062	-2.2843	0.18	5.67	30.91	5.46	0.03
C	12.25	0.3907	-2.1713	0.22	6.00	27.78	4.63	0.04
D	16.67	0.3484	-1.8253	0.17	2.13	12.31	5.77	0.08
E	9.52	0.4412	-2.1221	0.40	8.00	20.00	2.50	0.05
F	11.81	0.5023	-2.4100	0.25	8.27	33.34	4.03	0.03
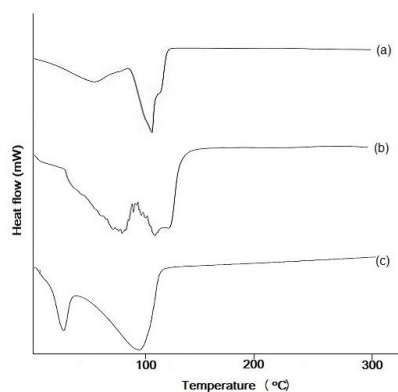
Figure 3. DSC thermograms of paracetamol (a) and granules of co-processed microcrystalline cellulose with gelatin (b) and starch (c).

Figure 4. Drug release profile of the different batches of paracetamol tablets.

paction evaluations of the batches of granules showed improved flow properties tabletability properties such as compaction (a), rate of compression (K) and compression index (Cl), with increase in gelatin concentration used in co-processing. These improvements may be attributed to agglomeration and particle re-arrangement of paracetamol powders due to cohesiveness of gelatin slurry. This result is consistent with results of agglomeration and powder size on powder behaviour as reported by researchers such as Castellanus (19), Nordstrom *et al.* (20), Nordstrom *et al.* (21) and Persson *et al.*, (12).

   The batches A-D, E, and F paracetamol tablets containing co-processed gelatin, co-processed starch, and conventional granules respectively, had passable physicochemical properties of hardness >4 Kgf, <1.0 % friability, and <15 minutes disintegration time. In comparison with batches E and F tablets, batches A-D tablets had higher hardness and tensile strength and low fria-

bility. These result agrees with other studies on impact of gelatin on tablet properties such as Okoye et al (14). The disintegration time for batches A-D tablets were shorter, in comparison with the disintegration times of batches E and F tablets. The improvement in disintegration of the tablets can be attributed to the influence of co-processed microcrystalline cellulose in the solid dispersion. This result is consistent with reports by researchers such as Bejaoui *et al.* (22) on the effect of ternary co-former additives such as polymer carriers and surfactants that serves as intermediary stabilizer in drug-solid dispersion to prevent crystallization and improve solubility. For all the tablets, about 80 % paracetamol dissolved after 60 minutes in 0.1 N HCl dissolution medium. Paracetamol is a bio-classification system's Class I drug, appropriate for biowaver, and its physicochemical and release properties of paracetamol from dosage form can be used to extrapolate the paracetamol bioavailability (13, 23).

   The DSC thermogram of co-processed

Table 4. Physicochemical properties of tablets.

Batch	Weight (mg)	Crushing strength (kgf)	Tensile strength (Nm-2)	Density (g/cm3)	Friability (%)	Disintegration time (min)	Dissolution (%) in 60 min
A	525.20±2.10	3.25±0.54	3.63±0.04	0.94±0.12	0.35±0.03	2.41±0.12	89.00
B	525.00±1.40	5.50±0.21	6.12±0.13	0.94±0.31	0.35±0.01	1.12±0.13	87.00
C	527.20±1.12	6.00±0.09	6.68±0.20	0.98±0.22	0.22±0.16	1.28±0.11	85.00
D	528.60±0.12	6.25±0.17	8.26±0.15	1.12±0.06	0.17±0.07	1.32±0.09	78.00
E	525.40±0.83	4.56±0.13	5.09±0.10	0.94±0.11	0.35±0.03	2.54±0.08	85.00
F	525.00±0.43	4.00±0.12	5.01±0.16	0.92±0.08	0.85±0.14	4.43±0.08	79.00

paracetamol granules showed a shift in baseline, expanded halo and widening of not too noticeable peak (concave) in thermographic spectrum of paracetamol in the presence of gelatin and microcrystalline. This result demonstrates amorphous or semi-crystalline solidification of co-processed paracetamol mixture. The earlier disadvantage of crystallization and increase in tablet disintegration time from using high binding gelatin in tablet formulation is not seen in this gelatin slurry ternary mixture with paracetamol and microcrystalline cellulose.

5. Conclusion

Melt-in agglomeration procedure with paracetamol and gelatin in the presence of microcrystalline cellulose produced ternary produced granules with improved particle flow, compaction, compression, porosity, filling and tabletability properties, and produced tablets with good compact size and hardness, faster disintegration and improved dissolution rate.

Acknowledgement

Conflict of Interest

None declared.

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