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Centrifugal air-assisted melt agglomeration for fast-release "granulet" design

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ABSTRACT

Conventional melt pelletization and granulation processes produce round and dense, and irregularly shaped but porous agglomerates respectively. This study aimed to design centrifugal air-assisted melt agglomeration technology for manufacture of spherical and yet porous "granulets" for ease of downstream manufacturing and enhancing drug release. A bladeless agglomerator, which utilized shear-free air stream to mass the powder mixture of lactose filler, polyethylene glycol binder and poorly water-soluble tolbutamide drug into "granulets", was developed. The inclination angle and number of vane, air-impermeable surface area of air guide, processing temperature, binder content and molecular weight were investigated with reference to "granulet" size, shape, texture and drug release properties. Unlike fluid-bed melt agglomeration with vertical processing air flow, the air stream in the present technology moved centrifugally to roll the processing mass into spherical but porous "granulets" with a drug release propensity higher than physical powder mixture, unprocessed drug and dense pellets prepared using high shear mixer. The fast-release attribute of "granulets" was ascribed to porous matrix formed with a high level of polyethylene glycol as solubilizer. The agglomeration and drug release outcomes of centrifugal air-assisted technology are unmet by the existing high shear and fluid-bed melt agglomeration techniques.

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1. Introduction

Agglomerates are an assembly of solid particles in the form of a multi-particulate system, commonly bound by one or more binding agents. In comparison to single-unit solid dosage form namely tablets, agglomerates offer numerous advantages as an oral drug carrier. The agglomerates primarily undergo a widespread distribution in gastrointestinal tract (Aulton, 1988; Wong and Heng, in press). This reduces risks of dose dumping at a focus site of mucosa and variations in plasma drug levels. Agglomerates can be produced by various wet techniques such as extrusion–spheronization, fluid-bed, low shear and high shear agglomeration methods (Hausman, 2004; Wong and Heng, in press; Wong et al., 2005; Zakaria and Wong, 2009). Melt agglomeration is one of the recent techniques where binding of solid particles is brought about by molten binding liquid or solid binder which melts during the process by frictional heat generated from high shear mixing of processing materials (Nurulaini and Wong, 2011; Walker et al., 2006; Wong et al., 2005; Wong and Nurulaini, in press). Unlike conventional approaches, melt agglomeration runs without the need for aqueous or organic solvents by means of a one-pot, one-step technique. The drying phase, flame-proof facilities and solvent recovery equipment are not needed thereby reducing time and cost of a manufacturing operation.

The melt agglomerates are available as pellets or granules (Schæfer, 1997; Wong et al., 2005). Melt pellets are usually produced using high shear mixer. The high speed, high shearing action of impeller rotation can shape the cluster of solid particles, bound by molten binding liquid, into round and dense pellets through imposing a centrifugal motion on processing materials against the inner wall of mixer bowl. Melt granules are porous and have an irregular shape. Fluid-bed melt granulator is the typical processor used in production of these agglomerates. In comparison to high shear mixer, the fluid-bed technique processed with vertical air flow exerts a low level of shear and densification forces on the forming agglomerates, and with no centrifugal rounding action onto the processing mass.

Since 1960, there have been more than 500 publications investigating the formulation, processing and equipment aspects of technology employed in the preparation of fast-release solid matrices to improve the dissolution and bioavailability profiles of poorly water-soluble drugs (Craig, 2002). Melt pelletization is the latest processing technique employed where meltable hydrophilic binder such as polyethylene glycol, which has the highest pelletization capacity with reference to size, shape and density of the formed agglomerates, can act as solubilizer or wetting agent

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for poorly water-soluble drugs (Gupta et al., 2001; Schæfer, 1997; Vasconcelos et al., 2007; Vilhelmsen et al., 2005).

Drug release of a matrix can be promoted by reducing its dense microstructure and/or increasing its polyethylene glycol content (Iveson et al., 2001; Le et al., 2011; Leonardi et al., 2007; Newa et al., 2008). Spherical agglomerates exhibit a good flow property ideal for industrial processing and packaging (Passerini et al., 2010). Using high shear technique, the round agglomerates are nonetheless having low levels of porosity due to consolidation process (Le et al., 2011). The high shearing, high impact forces likewise do not allow the use of high polyethylene glycol fractions in a pellet formulation as an alternative measure since this will result in over-wetting and uncontrollable agglomerate growth (Schæfer, 1997; Thies and Kleinebudde, 1999). As such, this study aims to develop a processing technique, which can produce "granulets": round agglomerates with porous core, for use in design of fast-release solid multi-particulate system. In the present investigation, centrifugal shear-free moving air stream is utilized as a replacement of impeller blade to agitate processing materials. It is hypothesized that turbulent air flow can intersperse and loosen the assembly of solid particles bound in clusters by molten binding liquid, but allow agglomerates to roll over the wall of processing bowl thereby rounding into porous "granulets" with fast drug release attributes.

2. Materials and methods

2.1. Materials

Solid α-D-lactose monohydrate (Granulac 200 and Sorbolac 400, Meggle, Germany) was used as a non-meltable filler with polyethylene glycol (PEG) 3000, 6000, 10,000, 20,000 and 35,000 (Merck, Germany) as meltable binders and tolbutamide (D.K. Pharma Chem Pvt. Ltd., India) as a model poorly water-soluble drug. Hydrochloric acid and potassium chloride (Merck, Germany) were chemicals employed to prepare USP pH 2.2 dissolution buffer.

2.2. Methods

The study focused on development of centrifugal air-assisted melt agglomerator, and test of its feasibility to produce agglomerates and fast-release "granulets".

2.2.1. Development of centrifugal air-assisted melt agglomerator

Fig. 1a shows the schematic diagram of the assembly of a novel melt agglomerator (Laison Engineering Sdn. Bhd., Malaysia). The agglomerator was made of a processing bowl, an air guide, an electrical heating element and a fan system. The processing bowl was constituted of a cylindrical chamber with a height of 0.4 m and an internal diameter of 0.2 m. It was made of transparent glass in order to allow in-process observation and was equipped with a filter mesh (mesh aperture size: 0.24 ± 0.03 mm) at the top exit of bowl to prevent loss of processing materials via the circulating air flow. The air guide was a stainless steel bowl with a height of 0.1 m and an internal diameter of 0.2 m. It had multiple units of rectangularly shaped vane (average height: 24.56 ± 1.00 mm, average width: 74.11 ± 0.80 mm) aligned at a specific angle of inclination with respect to the horizontal plane. These vanes were constructed using a centrally radiating pattern with one end attached to the internal peripheral surfaces of air guide and the other end located at the midpoint of air guide interconnecting with the rest of the vane units. The vanes functioned to transform the vertically traveled air flow generated by the fan system beneath into centrifugal air stream in processing bowl fitted above the air guide (Fig. 1b). The attachment of air guide to processing bowl was supported by a stainless steel mesh (mesh aperture size: 0.10 ± 0.04 mm) placed immediately before the fan system in avoidance of processing material loss due to weight-induced sedimentation or force field effect of air stream.

A powder feeder (internal diameter of feeding tube: 16.08 ± 0.23 mm) was installed at the base of processing bowl to allow immediate contact of processing materials with air flow passing through the air guide and suspension of particles during agglomeration process. The introduction of powder materials through feeder was aided by compressed air (HP2 ORIMAS®, Sin Yuan Machinery Sdn. Bhd., Malaysia) to ensure minimal losses via adhesion onto the internal surfaces of feeding tube. The temperature of air and processing materials in bowl was modulated by an electrical heating element (MALTEC-H finned heater, dpstar Holdings Sdn. Bhd., Malaysia). Both air flow velocity and temperature were measured using velometer (ALNOR, Shoreview, USA) and thermocouple with stainless steel probe (MALTEC-T thermocouple, dpstar Holdings Sdn. Bhd, Malaysia) respectively. The air flow velocity and temperature were accordingly modulated by means of frequency inverter (TECO FM50 fluxmaster, TECO Westinghouse Motors Inc., Canada) and temperature controller (Shimaden SR92, OneTemp Pty. Ltd., Australia).

2.2.2. General operation of centrifugal air-assisted melt agglomerator

The processing bowl was first flushed with an air flow at a predetermined velocity and temperature for a specific duration. An appropriately weighed amount of processing materials was then introduced through feeder with the aid of an external compressed air into the processing bowl within 4 min. The air flow velocity was subsequently raised in a step-wise manner to maintain the dispersion of particles in the moving air stream during agglomeration. The agglomeration proceeded through binding of non-meltable solid particles by meltable binder which transformed from solid to liquid upon contacting with heated air flow. At intervals of 5 min, the filter mesh at the top compartment of bowl was subjected to air purging for 30 s to return the powder deposit into the processing mass. The agglomeration run was ended by terminating the air flow. The product was collected in an aluminum tray and cooled to ambient temperature in thin layers.

2.2.3. Optimization study

Equipment parameters, namely air-impermeable surface area of air guide and its angle of inclination and number of vanes, were optimized with respect to length of massing duration and deposition pattern of the processing materials at filter mesh (Fig. 1c). Five different air guides were designed: 3 air guides with 12 vanes positioned at 30, 50 and 70° angles of inclination with respect to the horizontal plane, and 2 air guides with 50° angle of inclination but made of 6 and 24 vanes respectively. All air guides had an air-impermeable surface area of 1.96×10^{-3} m^2 ascribing to central stainless steel holder of vanes. When necessary, the air-impermeable surface area was increased to 6.36×10^{-3}, 0.01 or 0.02 m^2 by installing a circular stainless steel plate at the central region of air guide.

One hundred grams of Granulac 200 lactose were used as the processing material. The study was carried out at 25 ± 1 °C in the absence of PEG. PEG was omitted to avoid the complication of agglomeration in the first phase of evaluation. The air velocity and powder deposition at top filter mesh at the respective air flow condition of empty as well as lactose loaded bowl were determined with reference to changes in inclination angle of vane, when applicable. Using vane with an optimal inclination angle, the effects of vane number and air-impermeable surface area of air guide on air velocity, powder massing time and deposition were examined. The massing of processing material was sustained through increasing the air flow velocity by variable frequency modulation of the fan

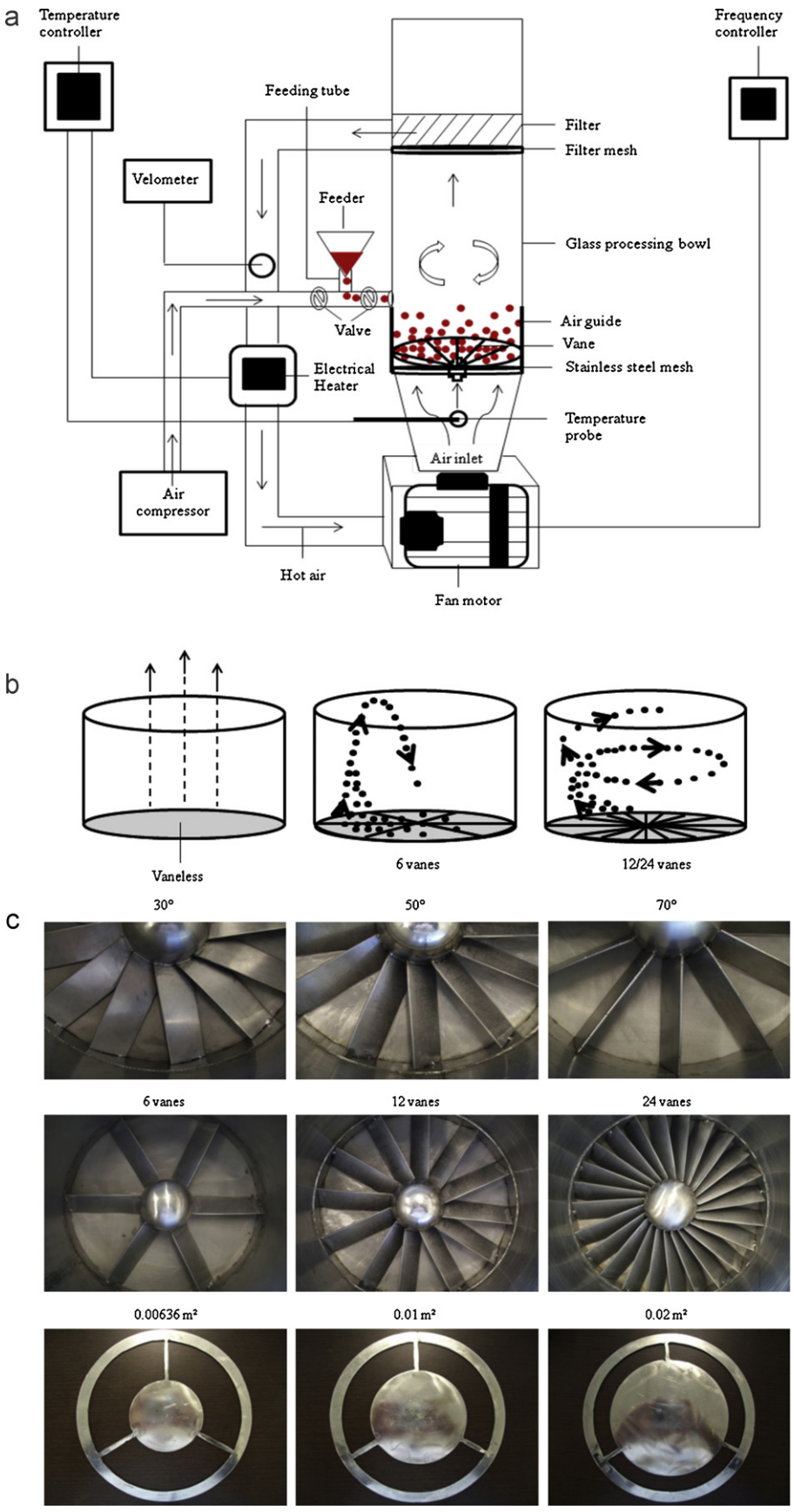

Fig. 1. Schematic diagram of (a) centrifugal air-assisted melt agglomerator, (b) air flow pattern in agglomerator and (c) photographs of vanes with different angles of inclination and unit numbers, and air guide with different air-impermeable surface areas.

system (10–60 Hz) within 5 s when a drop in height of the revolving powder mass was noted through the glass window of processing bowl. The massing time of a process was defined as duration taken for all processing materials to stop fluidizing under the current of air flow at its highest velocity limit, as determined by fan system set-up. The corresponding percent powder deposition at top filter mesh was calculated with reference to the initial processing material load at the end of each run. At least triplicates were conducted for each experiment and the results averaged.

2.2.4. Agglomeration feasibility study

A 100 g powder mixture of Granulac 200 lactose and PEG was used to assess the feasibility of centrifugal air-assisted melt agglomerator in agglomeration of solid lactose particles by in situ melting of PEG binder. PEG flakes were micronised by milling (Waring commercial blender, Torrington, USA) and sieve fraction of particle sizes below 830 μm (Retsch GmbH, Germany) was used in agglomeration feasibility study. PEG molecular weight and its weight ratio to lactose were varied in examination of possible agglomeration through evaluating product size, morphology and yield as well as powder deposition characteristics.

An air guide with 12 vanes at 50° angle of inclination and an air-impermeable surface area of 0.01 m^2 was used throughout the study. The processing bowl was air flushed for 10 min at the melting temperature of PEG (PEG 3000: 57.90 ± 0.47 °C, PEG 6000: 60.99 ± 1.03 °C, PEG 10000: 61.81 ± 0.34 °C, PEG 20000: 63.32 ± 0.19 °C, PEG 35000: 64.70 ± 0.64 °C) as determined previously by differential scanning calorimetry technique (Jade DSC, Perkin Elmer, USA). Air flushing was required to stabilize the air temperature and flow velocity within ± 3 °C and ± 5 m/s respectively. The air temperature was kept at the melting point of PEG as lower temperature ranges failed to soften or melt the PEG for agglomeration whereas higher temperature ranges induced rapid and uncontrollable agglomeration in preliminary trials. The solid lactose and PEG were manually mixed in an air bag for 5 min prior conveying into processing bowl through feeder. The process of agglomeration began with a low air flow velocity corresponding to 10 Hz and increased accordingly by a multiplication of 10 Hz

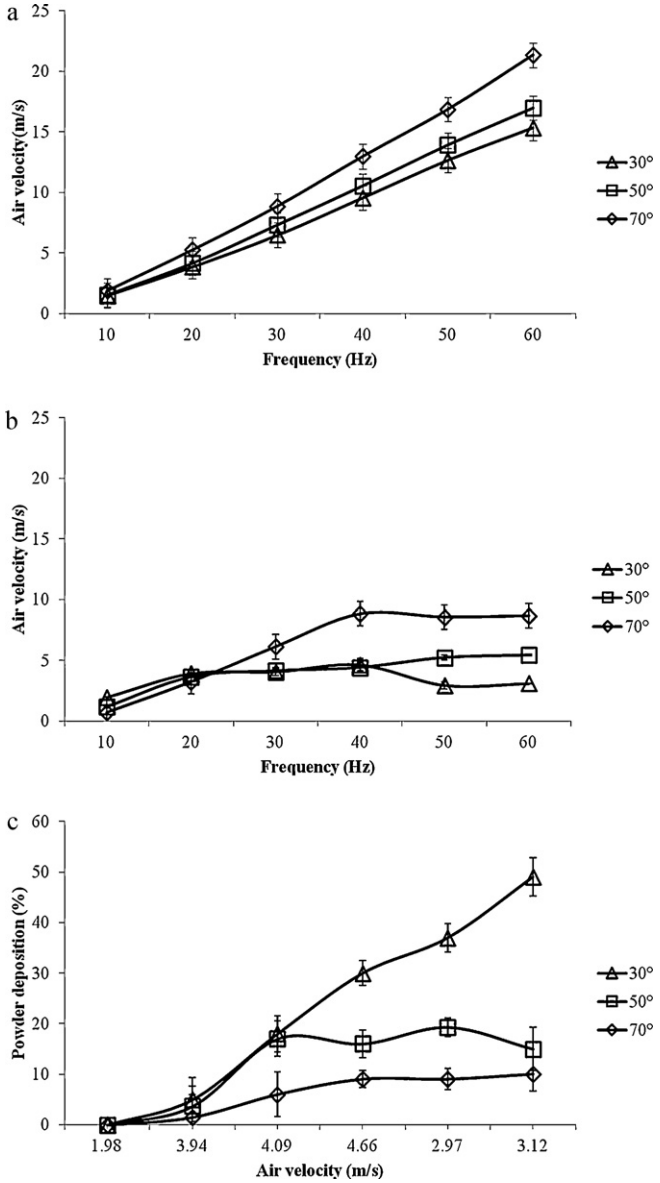

Fig. 2. Profiles of air velocity in (a) empty and (b) lactose loaded processing bowls, and (c) powder deposition on top filter mesh and (d) powder sedimentation on top surfaces of air guide with vanes at different angles of inclination.

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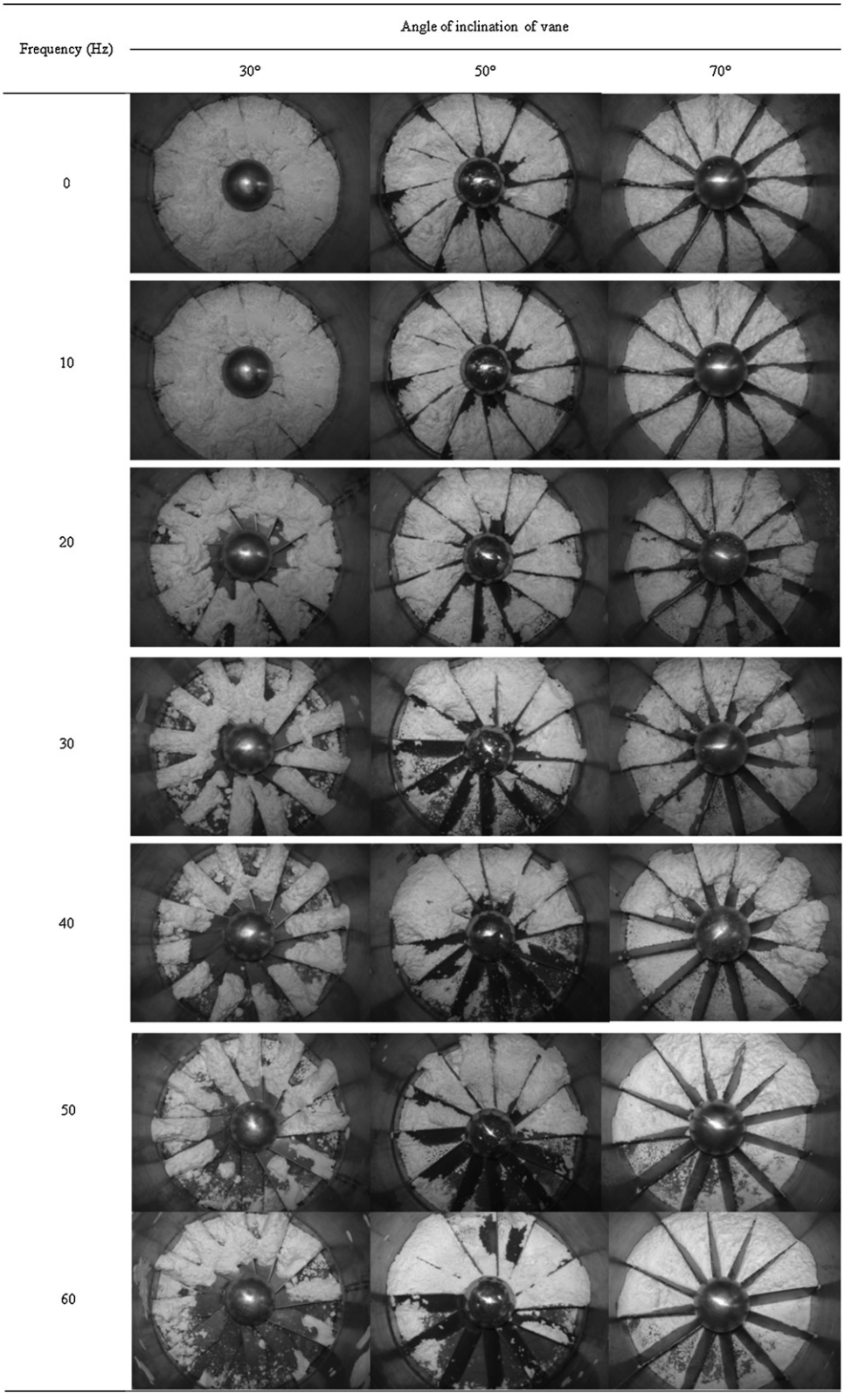

Fig. 2. (*Continued*).

when a drop in height of the revolving mass was noted through the glass window of processing bowl. Unless otherwise stated, the massing time was fixed at 20 min from the moment when powder mixture was introduced into processing bowl. At the end of each run, the agglomerates were spread out in thin layers on aluminum tray and allowed to cool at $25 \pm 1\,^{\circ}C$. The powder deposition on top filter mesh was calculated from the difference between initial processing material load and amount of collected product. At least triplicates were conducted for each formulation and the results averaged.

2.2.5. Fast-release agglomerate design potential

A 100 g powder mixture containing 50% PEG 3000, 40% Sorbolac 400 lactose and 10% tolbutamide was subjected to centrifugal air-assisted melt agglomeration using the same equipment and process parameters as agglomeration feasibility study, unless otherwise stated. Blank agglomerates with no drug incorporated were similarly prepared. The formed product was subjected to size, surface and cross-sectional morphology, drug release, drug content and physicochemical characterization at molecular scale using differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) analysis.

2.2.6. Physicochemical characterization of agglomerates

2.2.6.1. Size. The size distribution of melt agglomerates was determined using a sieve apparatus (Retsch GmbH, Germany) with a progression of nine standard sieves of mesh aperture sizes ranging from 0.1 to 3.0 mm. Each batch of agglomerates was placed in sieves and vibrated at the amplitude of 1 mm for 10 min. The mass median diameter and span were calculated.

2.2.6.2. Morphology. The shape of melt agglomerates was determined using a digimetric vernier caliper system (Mitutoyo, Japan). The length and breadth were measured from each agglomerate, and its shape was represented by aspect ratio which is the quotient of its length to breadth. An aspect ratio of value unity represents a perfect sphere, whereas higher values represent greater elongation. For each formulation, 20 agglomerates were randomly selected for measurement and the results averaged.

The cross-sectional morphology of melt agglomerates was examined using the field emission scanning electron microscopy technique (FESEM, JSM-6701F, Jeol, Japan). The samples were fixed with a carbon tape onto studs and coated with a thin gold–palladium layer (JFC-1600, Jeol, Japan). They were then viewed directly under a scanning electron microscope at an accelerating voltage of 5 kV. The surface morphology of agglomerates was examined using a stereomicroscope (Leica DMLP, Leica Microsystems Witzlar GmbH, Germany) which consisted of a computer system connected to a digital camera (Nikon E8400, Nikon Corp., Japan). Representative sections were photographed. At least triplicates were carried out for each batch of agglomerates.

2.2.6.3. Drug release and drug content. The drug release profile of melt agglomerates (size fraction $\geq$1.0 to <1.4 mm) was determined at 37.0 ± 0.2 °C under a sink condition using USP buffer pH 2.2 as dissolution medium simulating the gastric fluid which represented the first entry site of agglomerates upon oral administration. An accurately weighed amount of sample at 100 mg was placed in 500 ml of dissolution medium and was agitated at 50 strokes/min in a shaker bath (ST402, Nuve, Turkey). Aliquots were withdrawn at specific intervals up to 6 h and subjected to spectrophotometric assay using UV–Vis spectrophotometer (Cary 50 Conc, Varian Australia Pty. Ltd., Australia) at the wavelength maxima of 230 nm for drug. The percentage of drug release was calculated with respect to the drug content of agglomerates. The drug content was expressed as the percentage of drug encapsulated in a unit weight of agglomerates. The drug content was determined by subjecting the same sample of agglomerates from the drug dissolution study for an additional 24 h of magnetic stirring followed by ultrasonication for at least three consecutive periods of 10 min each before assaying for tolbutamide. Each experiment was carried out in triplicates and

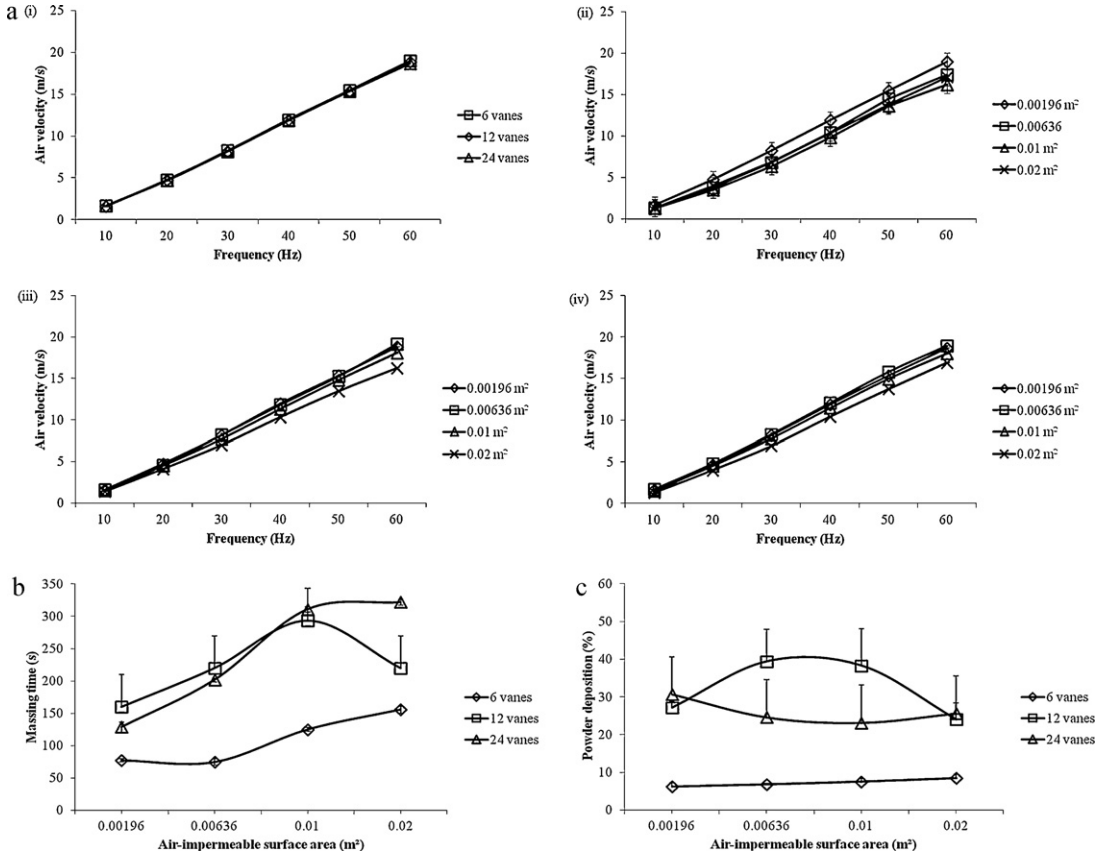

Fig. 3. Profiles of (a) air flow velocity in an empty processing bowl with (i) 0.00196 m^2 air-impermeable surface area, (ii) 6, (iii) 12 and (iv) 24 vanes, (b) powder massing time, (c) powder deposition on top filter mesh and (d) powder sedimentation on top surfaces of air guide as a function of vane number and air-impermeable surface area.

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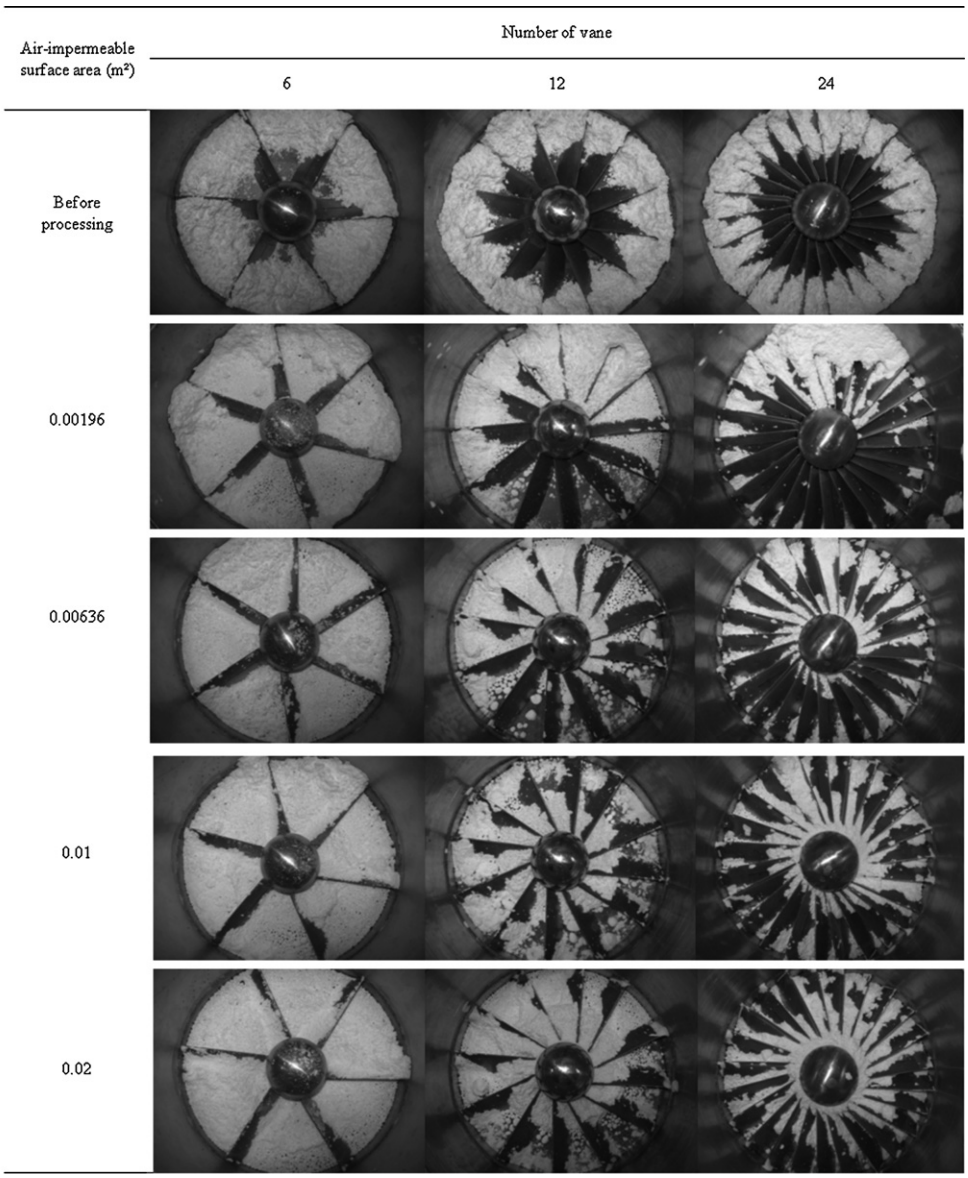


Fig. 3. (*Continued*).

the results averaged. Blank agglomerates were taken as a control sample.

The drug release profile of agglomerates was compared against a physical mixture prepared using the same chemical composition where percents lactose, PEG 3000 and tolbutamide were calculated with reference to drug and PEG 3000 contents of agglomerates derived from dissolution and DSC tests respectively. The PEG 3000 content of agglomerates was inferred from its enthalpy value of DSC endotherm at melting range between 55 and 58 °C. The content of lactose was deduced from weight difference of agglomerates from their calculated contents of drug and PEG 3000. Blank physical mixture was prepared as a control sample.

The drug release profile of the same agglomerates was also analyzed against agglomerates prepared from high shear melt pelletization technique (size fraction ≥1.0 to <1.4 mm) which had been commonly used to prepare fast-release solid matrix. In the latter, the contents of drug, PEG3000 and lactose were 5.0, 17.6 and 77.4% respectively. A lower PEG 3000 content was employed in high shear melt pelletization than centrifugal air-assisted technique due to high risks of agglomerate wetting and uncontrolled agglomeration in the former. Five percent of drug was used with the aim to reduce drug content heterogeneity in pellets which can possibly take place when a lower drug load was employed. The melt pelletization was conducted in a high shear mixer using a two-bladed impeller (ThermoMix, Laison Engineering Sdn. Bhd., Malaysia). The agglomeration was characterized by binding of non-meltable substances by molten PEG 3000 formed from solid meltable binder as a result of its exposure to frictional heat generated from high shear mixing. The water-jacket temperature was fixed at 60 °C for the entire pelletization process. The pre-melt phase began with mixing of drug, PEG 3000 and lactose at an impeller rotational speed of 450 rpm after pre-heating the mixture to the temperature of 30 °C. The impeller rotational speed was increased to 500 rpm at the product temperature of 46 °C, 600 rpm at 49 °C, 1000 rpm at 51 °C and 1200 rpm at 53 °C. A stepwise increment in impeller rotational speed was needed to avoid uncontrolled powder mixture circulation. The post-melt phase was initiated upon PEG 3000 melting at about 56 °C and binding of non-meltable powder mixture into agglomerates. The duration of post-melt phase was 18.5 min and the total agglomeration duration was 42 min. The formed product

was collected and spread out in thin layers on aluminum tray to cool at 25 ± 1 °C. Blank pellets with no drug incorporated were similarly prepared.

2.2.6.4. XRD. The crystallinity state of a sample was evaluated using X-ray diffractometer (Ultima IV, Rigaku Corporation, Japan) with Cu Kα radiation generated at 30 kV and 15 mA. The X-ray diffraction was operated at a scanning speed of 3°/min, ranging from 3 to 90° (2θ). At least triplicates were carried out for each batch of sample and the results averaged.

2.2.6.5. DSC. DSC thermograms were obtained using a differential scanning calorimeter (Jade DSC, Perkin Elmer, USA). Three milligrams of sample were crimped in a standard aluminum pan and heated from 30 to 380 °C at a heating rate of 10 °C/min under constant purging of nitrogen at 40 ml/min. The characteristic peak and enthalpy of the melting endotherm and exotherm were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

3. Results and discussion

The present study designed a pioneering agglomeration technology which made use of centrifugal air current to mix, rotate and bind the non-meltable solid particles into spherical or near spherical porous "granulets" by means of hydrophilic molten binding liquid, instead of high-speed, high-shear impeller blades. Unlike dense pellets produced by high shear melt agglomeration

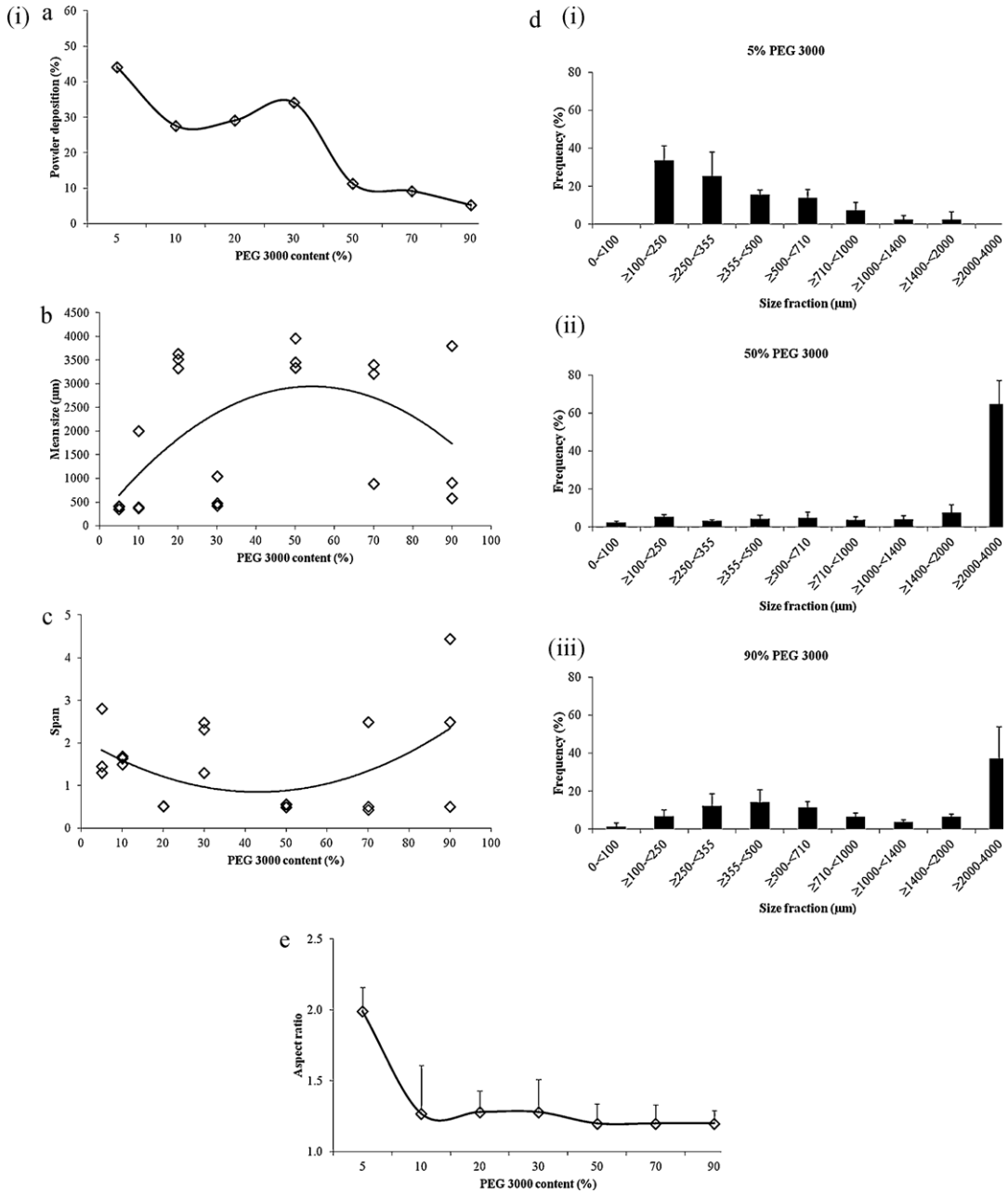


Fig. 4. Profiles of (I) (a) powder deposition on top filter mesh, (b) mean size, (c) span, (d) size distribution-frequency, (e) aspect ratio and (f) physical appearance of agglomerates obtained using different contents of PEG 3000. (II) (a) Powder deposition on top filter mesh, (b) mean size, (c) span, (d) aspect ratio and (e) physical appearance of agglomerates obtained using PEG of different molecular weights.

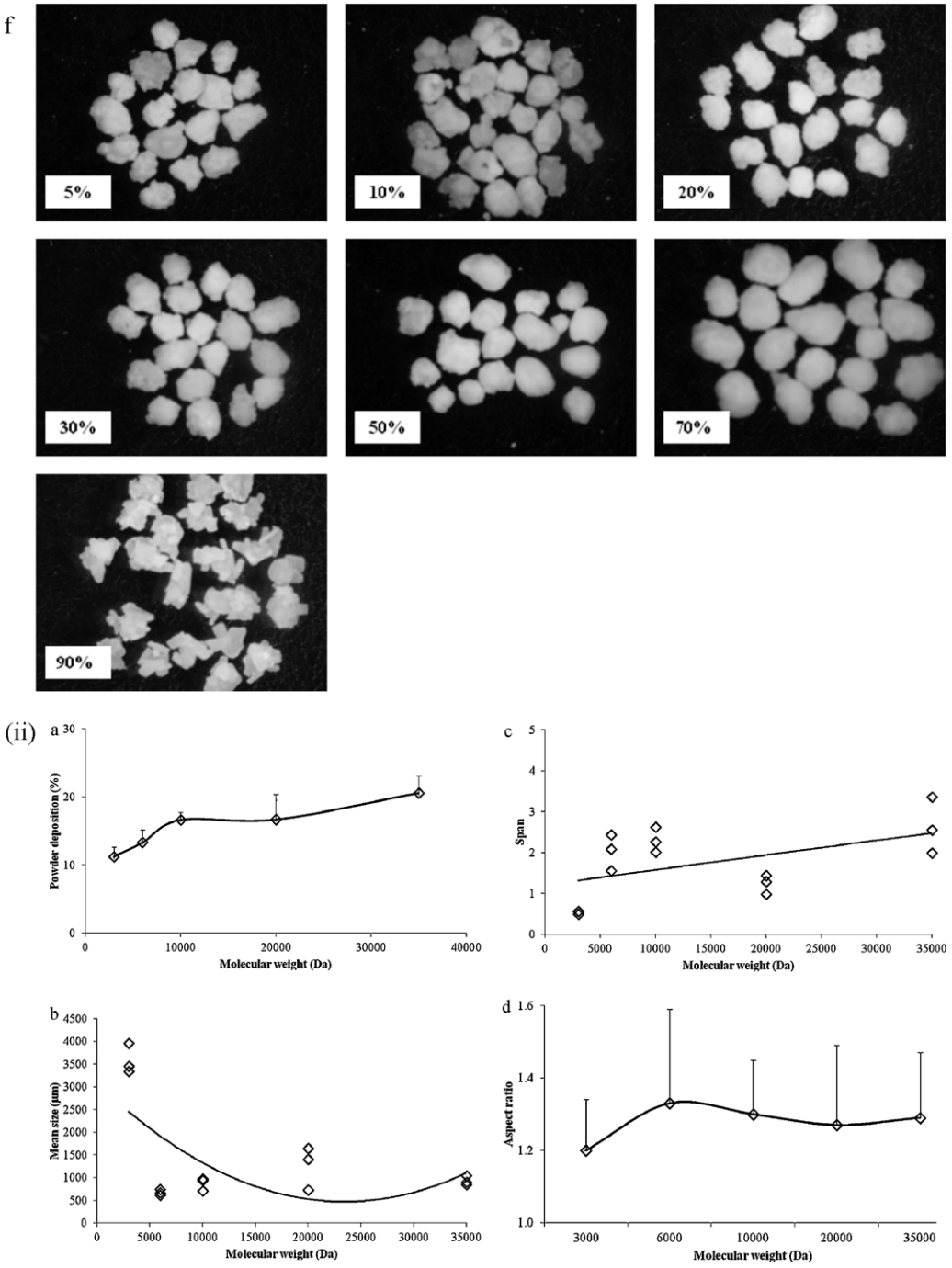


Fig. 4. (*Continued*)

technique, these "granulets" are porous agglomerates with the spherical attribute of pellets. They were envisaged to be able to promote the release of poorly water-soluble drug from matrix core to exterior medium at a greater propensity than pellets.

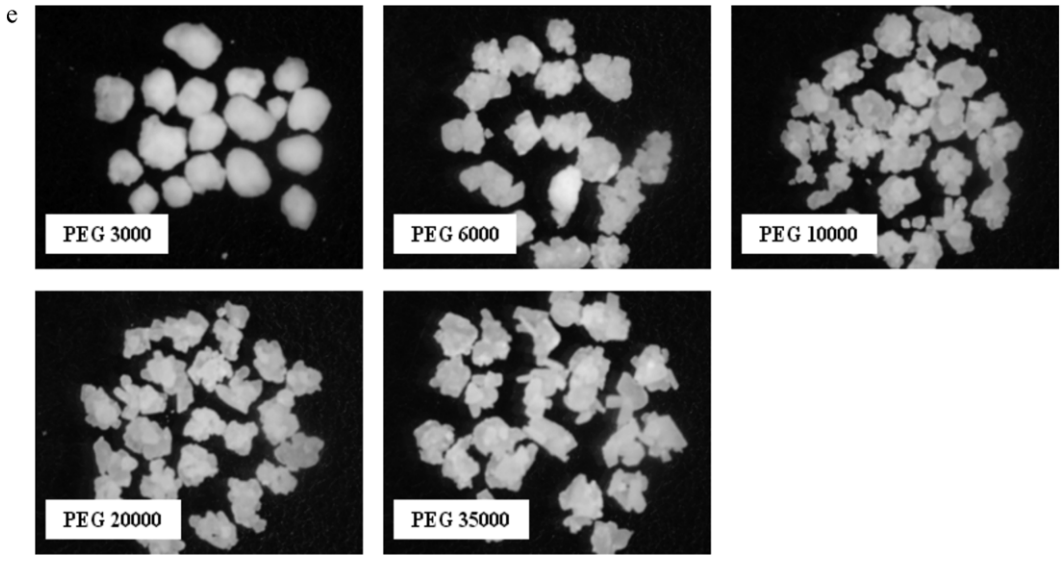
Three levels of experiments were conducted, namely equipment optimization, agglomeration feasibility assessment and fast-release agglomerate design. These experiments were conducted using the newly developed prototype centrifugal air-assisted melt agglomerator. The existing research aimed to provide an overall idea on the functionality of centrifugal air-assisted melt agglomeration technology and seek its potential for future engineering development for controlled-release applications.

3.1. Equipment optimization

3.1.1. Angle of inclination of vane

Using an empty processing bowl, the air flow velocity decreased with a reduction in the inclination angle of vane owing to a greater surface area of vane was placed in the direction of air flow (Fig. 2a). Loading of processing bowl with lactose further reduced the air flow velocity due to resistance across the powder bed and interruption of air flow by powder deposited on the top filter mesh installed before the velometer (Fig. 2a–c).

The use of vane with a higher angle of inclination was translated to a higher air flow velocity across the powder bed, with reduced powder deposition due to sweeping action of air current over the



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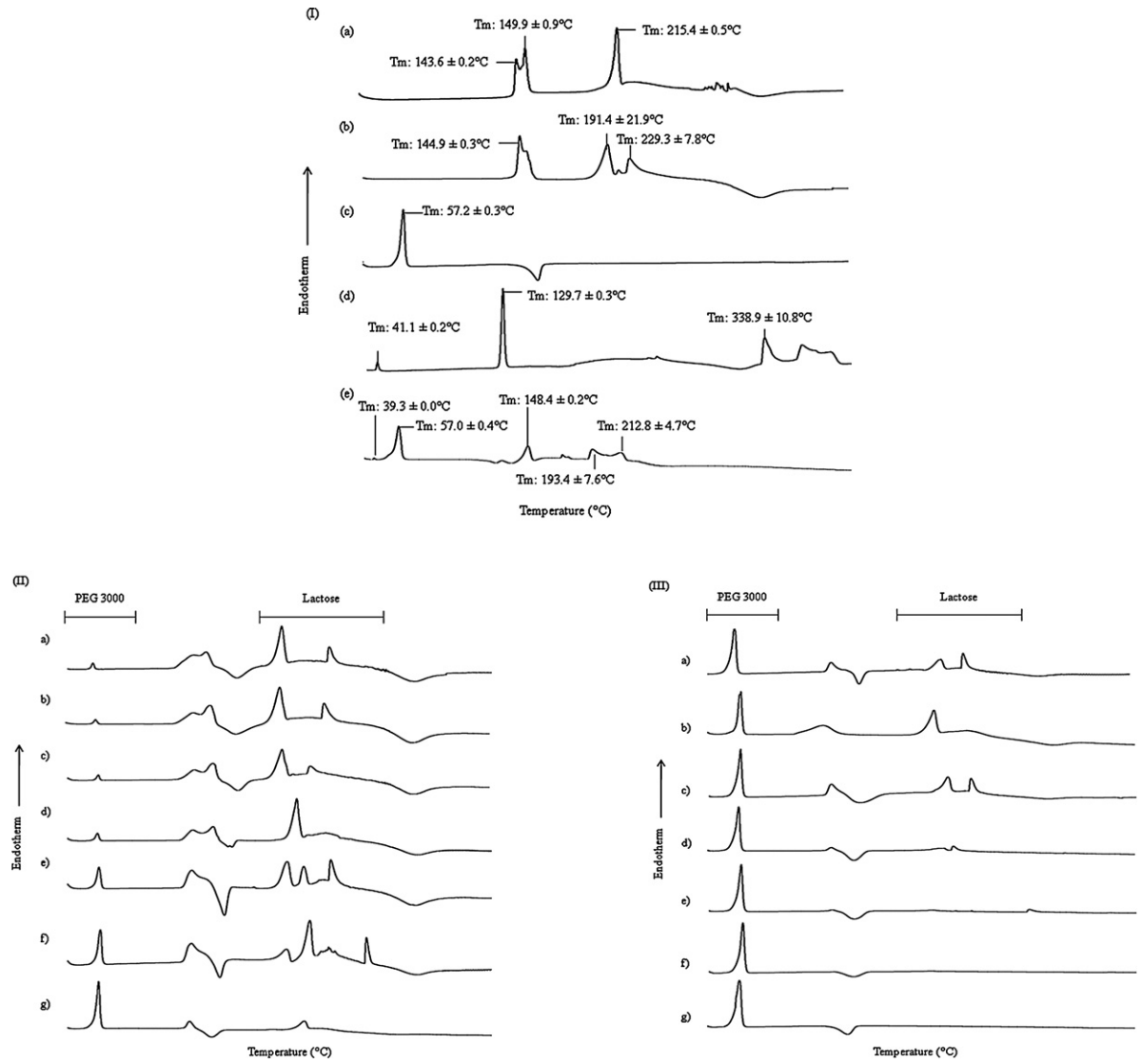

Fig. 5. DSC thermograms of (I) (a) Granulac 200, (b) Sorbolac 400, (c) PEG 3000, (d) tolbutamide and (e) agglomerate produced using 50% PEG 3000, 40% lactose and 10% tolbutamide. (II) Powder deposition on top filter mesh. PEG 3000 content: (a) 5, (b) 10, (c) 20, (d) 30, (e) 50, (f) 70 and (g) 90%. (III) Powder sedimentation on top surfaces of air guide. PEG 3000 content: (a) 5, (b) 10, (c) 20, (d) 30, (e) 50, (f) 70 and (g) 90%.

lower surfaces of top filter mesh (Fig. 2b and c). On the other hand, an excessively low inclination angle of vane brought about a remarkably high level of powder deposition on top filter mesh and this had interrupted the air flow outwards from processing bowl to velometer thereby leading to a reduction in the measurement of air velocity. The air flow in processing bowl had a higher tendency to circulate in the centrifugal mode when vanes of 30 and 50° angle of inclination were used. This was indicated by the disruptive pattern of powder sediment on top surfaces of air guide (Fig. 2d). Similar powder sedimentation profiles were not found with the use of vane characterized by a high inclination angle. At 70° inclination angle, the air flow tended to travel vertically upwards with a lower component of centrifugal kinetics. Gravitational settling of powder at the end of each run was characterized by a consistent presence of lactose particles throughout the surfaces of air guide.

3.1.2. Number of vane

The influences of vane number installed in a unit of air guide on powder massing time and its deposition on top filter mesh were examined. Air guides with vanes inclined at 50° were used as such tilt position provided centrifugal air flow with a high air flow velocity and a low powder deposition level on the top filter mesh, referring to previous investigation. The number of vane in an air guide was varied in view of a greater vane number was accompanied by a greater number of openings for incoming air to flow at regular intervals across two adjacent vanes. This was envisaged to be able to "cushion" the powder mass and aided its centrifugal rotation against the wall of processing bowl (Fig. 1b).

The 12- and 24-vaned air guide gave rise to a longer powder massing duration than the 6-vaned counterpart (Fig. 3b). The prolonged duration of massing was accompanied by a tendency to have a higher powder deposition on top filter mesh in the former (Fig. 3c). From the preliminary tests, it was noted that there was no substantial difference in the air flow velocity with a change in the vane number of air guide in an empty processing bowl (Fig. 3ai). Prolonged powder massing with 12- and 24-vane set up could probably ascribe to the availability of centrifugal air cushion. This was inferred from the powder sedimentation profiles on air guide at the end of massing where a disruptive powder deposition characteristic was attained (Fig. 3d). In the case of 6-vane design, vertical upwards air flow with a low centrifugal component had its turbulence sweeping clean the powder deposits on top filter mesh (Fig. 3c). Vertical settling of lactose particles at the end of massing gave rise to a complete coverage of top surfaces of air guide by powder (Fig. 3d).

3.1.3. Air-impermeable surface area of air guide

An increase in air-impermeable surface area of a 6-vaned air guide from 1.96×10^{-3} m^2 to 6.36×10^{-3}, 0.01 and 0.02 m^2 reduced the air flow velocity across the processing bowl (Fig. 3aii). In the cases of 12- and 24-vaned air guides, the air flow velocity decreased when the air-impermeable surface area was extended to 0.02 m^2 (Fig. 3aiii and iv). Apparently, a reduction in air flow velocity in relation to changes in air-impermeable surface area of air guide did not decrease the massing duration of powder. Instead, it led to a prolongation of powder massing (Fig. 3b). Examination of powder sedimentation profiles on air guide at the end of massing indicated that the turbulence degree of air flow increased with an increase in air-impermeable surface area particularly when the air guide was installed with 12 and 24 vanes (Fig. 3d). This could lead to the consequence of prolonged massing.

In comparison to 12-vaned air guide, system with 24 vanes provided a lower powder deposition on top filter mesh with air-impermeable surface areas kept beyond 1.96×10^{-3} m^2 and a longer massing duration when air-impermeable surface had an area of 0.02 m^2 (Fig. 3b and c). The apparent advantage of 24-vaned air guide was an artifact of the experiment. Using 24 vanes, it was observed that a greater fraction of lactose powder was trapped between the gaps of vanes during massing, and prolonged massing only involved a small quantity of lactose particles which resulted in a low level of powder deposition on top filter mesh. Thus, air guide equipped with 12 vanes was considered ideal relative to other models tested in the present study.

3.2. Agglomeration feasibility

3.2.1. PEG 3000 content

An air guide with 12 vanes tilted at 50° and had an air-impermeable surface area of 0.01 m^2 was used to test the possibility of using centrifugal air flow to assist melt agglomeration as a function of PEG contents and PEG molecular weights. Unlike runs using lactose powder per se, the addition of PEG 3000 meltable binder induced agglomeration. This led to reduced powder deposition on top filter mesh and interruption to air flow, and allowed massing for more than 15 min (Fig. 4Ia). Different from high shear agglomeration, high PEG 3000 contents beyond 30% of total powder mass

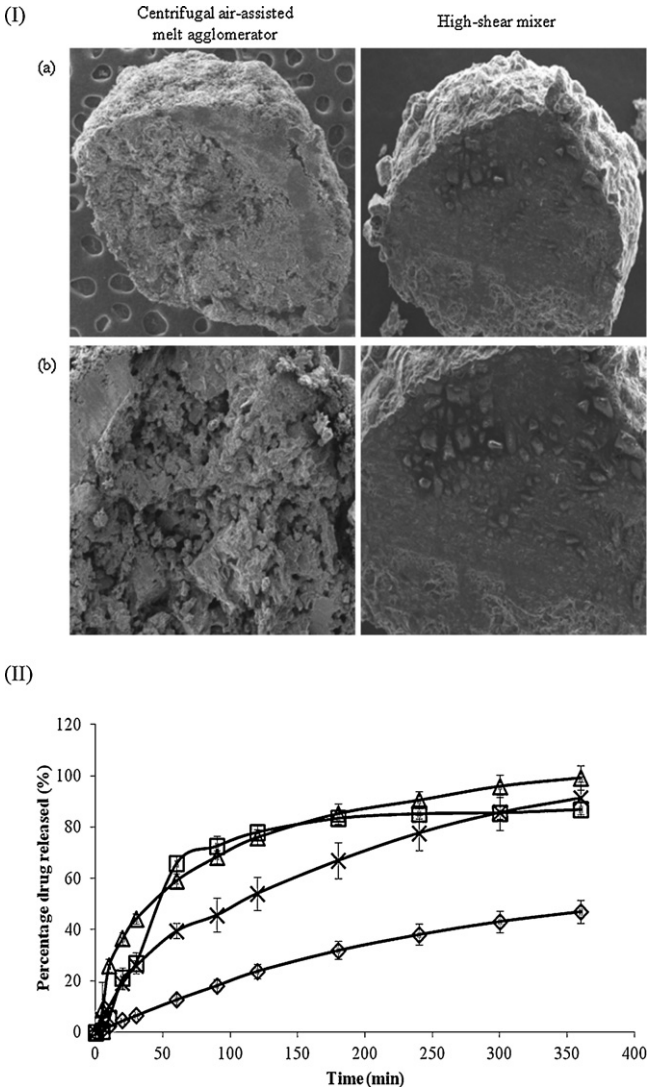

Fig. 6. Profiles of (I) cross-sectional scanning electron microscopy images of agglomerates prepared using centrifugal air-assisted melt agglomerator and high-shear mixer. (a) Magnification factor = 30 × and (b) magnification factor = 100×. (II) Drug dissolution of (◊) unprocessed drug, (×) physical mixture, agglomerates prepared using (□) high-shear mixer and (△) centrifugal air-assisted melt agglomerator.

can be used to bind lactose particles in air-assisted centrifugal melt agglomeration process. This was attributed to air exerted low impact forces on the formed nuclei and aggregates did not experience an excessive rise in liquid saturation due to matrix densification.

The size of agglomerates increased with a rise in PEG 3000 content from 5 to 50%, beyond which a tendency to fall in size of agglomerates took place (Fig. 4Ib). Using PEG 3000 contents lower than 50%, small agglomerates with a wide size distribution were produced (Fig. 4Ib and c). These agglomerates were formed from binding of nuclei into aggregates with partial coalescence as suggested by their "grape bunch" appearance (Fig. 4If). Low degrees of coalescence were a resultant effect of low binder content and impact forces acting onto aggregates thereby rendering low levels of plastic deformability were available for induction of coalescence growth. Using high contents of PEG 3000, agglomerates with irreproducible size and size distribution profiles were obtained (Fig. 4Ib and c). The agglomerates produced from 90% PEG 3000 had a flaky appearance of binder (Fig. 4If). The size of these agglomerates exhibited a bimodal distribution profile unlike those produced from lower PEG 3000 contents (Fig. 4Id). The air-assisted centrifugal agglomeration might be mediated via thermoplastic particle binding instead of complete PEG 3000 melting which was expected to deform the flaky geometry of binder (Fig. 4If). Agglomeration could have proceeded by immersion mechanism where dislodgement of loosely bound lactose particles from PEG 3000 gave rise to an additional population of particles at low size ranges (Fig. 4Idiii).

Agglomerates produced from 50% PEG 3000 were characterized by reproducible size and size distribution profiles, low powder deposition propensities at top filter mesh and a relatively high degree of sphericity as well as a smooth surface texture (Fig. 4I). DSC analysis of such agglomerates indicated that the matrix composed of both lactose and PEG 3000 (Fig. 5I). A comparison of thermograms of powder deposit on top filter mesh against powder sediment on surfaces of air guide indicated that a PEG 3000 content of at least 30% was required to agglomerate all lactose particles without them being removed as sediment (Fig. 5II and III). This was supported by the loss of endotherms ascribing lactose in the thermograms of powder sediment when 30% or more PEG 3000 were employed as a binder.

3.2.2. PEG molecular weight

Keeping PEG content at 50%, an increase in binder molecular weight from 3000 Da to 6000, 10,000, 20,000 and 35,000 Da was accompanied by a reduction in agglomerate size, and an increase in agglomerate size distribution, geometry irregularity, and powder deposition on top filter mesh (Fig. 4IIa–d). Examination of agglomerate surface morphology showed that the matrix formed from binder with a molecular weight higher than 3000 Da had flaky as well as "grape bunch" appearances (Fig. 4IIe). High molecular weight PEGs were more viscous and less plastically deformable. The aggregates made of these binders were less susceptible to coalescence growth. They took the shape of PEG flakes possibly due to thermoplastic growth and undergoing a low extent of rounding as a result of viscous binder resisting particle rearrangement into spherical agglomerates (Fig. 4IId and e).

3.3. Fast-release agglomerate design

Adopting air guide with 12 vanes tilted at 50° and had an air-impermeable surface area of 0.01 m^2, further studies were conducted to formulate fast-release agglomerates using tolbutamide as model poorly water-soluble drug. In this investigation, a finer lactose grade was used as it had a larger specific surface area and rendered the formation of smaller agglomerates at 50% PEG 3000 content (lactose particle size: Granulac 200: 31.45 ± 0.26 μm; Sorbolac 400: 9.98 ± 0.03 μm). In comparison to melt pellets prepared

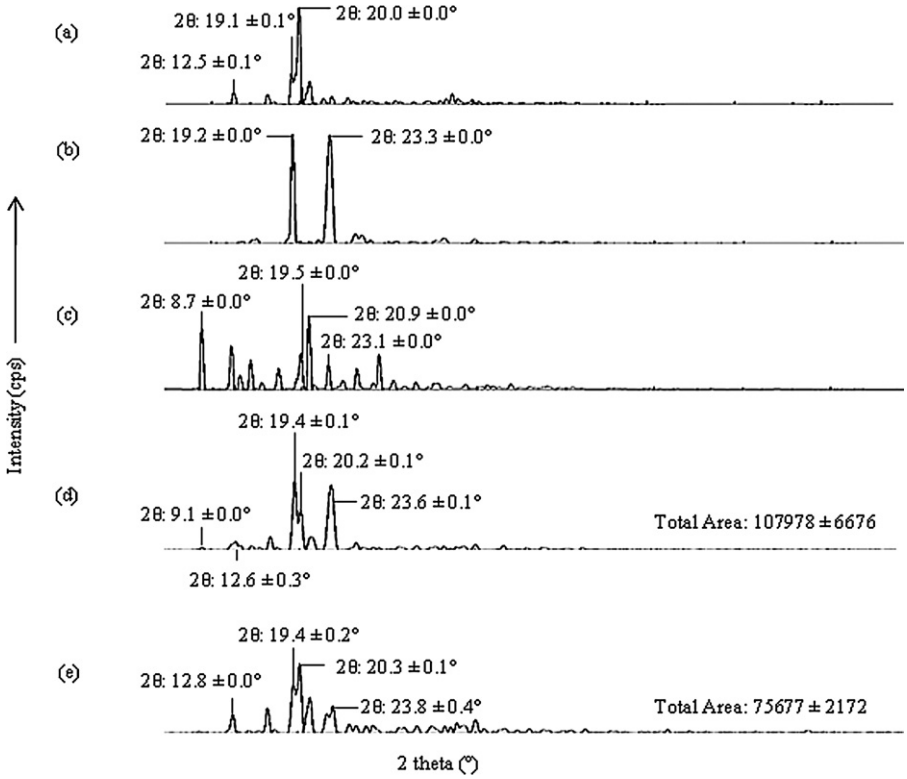

Fig. 7. XRD diffractograms of (a) Sorbolac 400, (b) PEG 3000, (c) tolbutamide, (d) granulets and (e) pellets prepared using centrifugal air-assisted melt agglomerator and high shear mixer respectively.

using high shear mixer, the agglomerates formed using air-assisted centrifugal melt agglomeration technique had a comparable degree of sphericity, but were characterized by a higher extent of porosity (Fig. 6I). These agglomerates can be termed as "granulets" which represented a matrix having the physical characteristics of both pellets and granules.

Formulation of tolbutamide into "granulets" provided a faster drug release propensity than unprocessed drug and physical mixture of tolbutamide, PEG 3000 and lactose respectively throughout the dissolution (Fig. 6II; ANOVA, $p < 0.05$). In addition, the "granulets" exhibited faster drug release at initial dissolution phase and complete drug release at late dissolution phase when compared to pellets produced using the high shear mixer (ANOVA, $p < 0.05$). In spite of the "granulets" had a more crystalline matrix than high shear pellets as proposed by XRD study (Fig. 7), the process of drug release from "granulets" could be aided by their porous nature and high weight ratio of PEG 3000 to drug (granulets: 5.00; pellets: 3.52) which promoted fast and complete drug dissolution.

3.4. Air-assisted centrifugal and fluid-bed melt agglomeration

Similarly to fluid-bed technique, air-assisted centrifugal melt agglomeration operates with a shorter process time than high shear pelletization technique (Passerini et al., 2010) and a higher agglomerate growth was attained using low viscosity instead of highly viscous binders (Tan et al., 2006). In the latter, low levels of agglomeration took place as a result of low probability of viscous binder being forced from core to surface for collision (Walker et al., 2006). The shear forces incurred by air were inadequate to induce agglomerate deformation and binder migration needed for binary growth.

Unlike fluid-bed melt agglomeration, PEG contents higher than 20–22.5% can be used in air-assisted centrifugal melt agglomeration without overwetting and defluidizing the processing mass (Walker et al., 2005, 2006). The formed agglomerates were able to be rounded through centrifugal movement of processing mass against the inner wall surfaces of bowl. Using 50% PEG 3000, these agglomerates could have a more deformable structure than fluid-bed granules for lactose and drug particles to rearrange into "granulets".

4. Conclusion

The pioneering design of centrifugal air-assisted melt agglomeration technology indicated the possibility of using air as a replacement of high-speed, high-shear impeller blades to produce "granulets". Porous and near spherical "granulets" were formed as a result of the absence of high shear forces and the presence of a high content of polyethylene glycol in matrix during the melt agglomeration process, thereby rendering agglomerates being plastically deformable and exhibited a greater ease of rounding without undergoing intense densification. The formed "granulets" promoted a faster drug release than physical powder mixture, unprocessed drug and pellets prepared from high shear mixer. The fast drug release attribute of "granulets" was ascribed to porous matrix formed with a high level of polyethylene glycol, a well known solubilizer. This is unmet by high shear and fluid-bed melt agglomeration techniques. The current investigation denotes the potential of using centrifugal air-assisted melt agglomeration technology as an alternative to the existing agglomeration methods. Future study will continue to shape its equipment parameters in order to improve the existing drug product yield which was lower than 80%.

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