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Microwave-assisted drying of pharmaceutical granules and its impact on drug stability

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ABSTRACT

The advent of microwave technology has intensified the search for pharmaceuticals amenable to microwave processing. This study investigated the influences of powder load, diluent particle size and amount of granulating liquid employed on the microwave-assisted drying and stability of acetylsalicylic acid (ASA)-loaded granules in a single pot high shear processor. Powder load affected the profiles, rate and extent of drying. Drying was more dependent on the size and structural properties of granules rather than their surface areas as heat was generated volumetrically. Increased granule size brought about by increasing the size of diluent particles and amount of granulating liquid resulted in higher drying rates. Drug stability was negatively correlated to the drying time of granules.

1. Introduction

Microwaves span the 300 MHz to 300 GHz frequency range of the electromagnetic spectrum (Schiffmann, 1995). The growing interest in microwave technology over recent years stemmed from its unique wave properties and superiority over conventional modes of heating. Attempts have been made to study microwaves for the extraction of natural products (Eskilsson and Björklund, 2000), organic syntheses of chemical compounds (De la Hoz et al., 2005) and the design of pharmaceutical dosage forms for purposes of controlling the release of drug (Teng and Groves, 1990; Wong et al., 2002, 2005; Vandelli et al., 2004; Nurjaya and Wong, 2005) or improving its dissolution properties (Kerč et al., 1998; Bergese et al., 2003).

Dielectric properties describe the fundamental electrical properties of materials and they govern the extent to which materials interact and absorb microwave energy (Metaxas and Meredith, 1988). Understanding the mechanisms involved in material-microwave interactions is critical for the optimization of microwave-assisted processes, prevention of unwanted effects induced by microwaves and efficient utilization of microwave energy (Thostenson and Chou, 1999). The microwave power absorbed by a unit volume of material, P_v, is governed by both equipment and material-related factors as seen in the equation (McLoughlin et al., 2003):

$$P_v = \omega\varepsilon_0\varepsilon'' E^2 = 2\pi f\varepsilon_0\varepsilon' \tan\delta E^2 \tag{1}$$

where P_v refers to the microwave power absorbed per unit volume of material ($\mathrm{W\,m^{-3}}$), ω is the angular frequency, E is the electric field strength ($\mathrm{V\,m^{-1}}$) and f is the frequency of the applied field (Hz). ε'' refers to the dielectric loss factor, $\tan\delta$, the loss tangent or dissipation factor, and ε', the dielectric constant or permittivity of the material. ε_0 is the dielectric constant or permittivity of vacuum. Under a constant frequency and electric field strength, P_v depends on the dielectric constant, loss tangent and dielectric loss of the material. These three parameters are inter-related in the following manner: dielectric loss is a measure of the amount of heat generated in a material per unit time (heating capability) under the influence of microwaves. This heating capability of the material, in turn, depends on how well the electric field can build up within the material (dielectric constant or permittivity) resulting in rotational movements of the dipolar molecules present. The resistance imposed on the rotational movements of these dipoles by their environment is reflected by the loss tangent of the material (Gabriel et al., 1998; McLoughlin et al., 2003).

Dielectric properties are dependent on the temperature, conductivity, heat capacity, molecular structure, moisture content, density, size, crystallinity and many other physical properties of the material (Nelson, 1994; Schiffmann, 1995; Gabriel et al., 1998; Thostenson and Chou, 1999; McLoughlin et al., 2003). Moisture

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content plays a critical role in influencing the dielectric properties of hygroscopic materials (İçier and Baysal, 2004). This can be attributed to the high dielectric constant of water. Under the influence of microwaves, the highly polarizable water molecules rotate rapidly in an attempt to align themselves with the alternating field. The frictional heat generated as a result of these rapid molecular rotations promotes evaporation of water. This forms the basis of microwave drying.

The efficiency of microwave drying is material-dependent (Vromans, 1994), with a heavy reliance on the moisture content and physical properties of the moistened material. This distinguishes microwave drying from conventional drying methods such as vacuum, conductive or convective modes of drying where the exposed surface area of the wet material remains the overriding factor affecting the efficiency of heat transfer and drying performance (Stahl and Van Vaerenbergh, 2005). When drying is carried out under microwave-assisted conditions, materials with higher moisture contents interact more readily with the waves as they possess higher dielectric constants and losses (Jones and Rowley, 1996; Sanga et al., 2000). As a result, these materials may potentially experience greater heating and drying rates than those which are comparatively drier. Such moisture-targeting effects are beneficial when drying products of large volumes since moisture is seldom uniformly distributed within the product load undergoing drying. This selective nature of microwave energy enables moisture levelling and maintenance of overall product quality (Jansen and Van der Wekken, 1991).

To date, application of the principles of dielectric theory to the development and optimization of pharmaceutical drying processes had directed attention to the dielectric heating capabilities of common pharmaceutical materials and how they influenced process outcomes (Kelen et al., 2006a,b). Considerable effort had been focused on developing and improving the design of microwave-related equipment (Doelling et al., 1992; Doelling and Nash, 1992; White, 1994) as well as comparing microwave and conventional drying in terms of their drying efficiencies and end product qualities (Bataille et al., 1993; Duschler et al., 1995; Mandal, 1995; Killeen, 1999; Prlić et al., 2001; Hegedűs and Pintye-Hódi, 2007).

The superiority of microwave drying in a single pot high shear processor over conventional hot air oven and fluidized bed drying for pharmaceutical granules had been demonstrated (Chee et al., 2005). There remained a need to examine the factors affecting the efficiency of microwave drying and its impact on the stability of moisture-sensitive drugs. In this study, the same processor was used to granulate a typical tablet formulation comprising lactose as the diluent at four powder loads. Granules formed were dried '*in situ*' under microwave-assisted conditions. The primary objective of the study was to investigate the influences of formulation variables, namely, powder load, size of diluent particles and amount of granulating liquid employed on the microwave-assisted drying of resultant granules. The impact of drying on the stability of acetylsalicylic acid (ASA) incorporated in the formulation was also studied.

2. Materials and methods

2.1. Materials

The materials used were lactose (Pharmatose 450 M or 200 M, DMV, the Netherlands), cross-linked polyvinylpyrrolidone (Crospovidone XL-10, ISP, USA), polyvinylpyrrolidone-vinyl acetate copolymer (Plasdone S630, ISP, USA), and ASA (Sintor, Romania). These represented the diluent, disintegrant, binder and moisture-sensitive drug, respectively. ASA was pre-sieved using a 355 μm aperture sieve and the undersize fraction was used for granulation. Deionized water was employed as the granulating liquid to moisten the powders and activate the binder to facilitate the agglomeration process.

Acetonitrile (HPLC grade, Merck, Germany) and phosphate buffer (pH 2.8), prepared using ortho-phosphoric acid (85%, Merck, Germany) and potassium dihydrogen phosphate (Merck, Germany), were used as the mobile phase for the analyses by high performance liquid chromatography (HPLC).

2.2. Methods

2.2.1. Material characterization

2.2.1.1. Moisture content. The moisture contents of the starting materials were determined by thermogravimetric analysis (DTG 60H, Shimadzu, Japan). An aluminium pan was filled with a thin layer of material and heated from 28 to 105 °C at a rate of 5 °C/min under a nitrogen environment. Depending on the bulk density, the quantity of material used each time ranged from 6 mg to 10 mg. The moisture content was calculated from the loss in weight of the sample upon heating and drying. All tests were repeated at least thrice.

2.2.1.2. Micromeritic properties. The median diameters (D_{50}) of the starting materials were determined by laser diffraction (LS230 with dry powder feeder, Coulter, USA). Their true densities were determined using a pycnometer (Pentapycnometer, Quantachrome, USA) under helium purge. Apart from ASA, materials were dried for 2 h in a convection oven preheated to 100 °C (Memmert, Germany) prior to the commencement of the test. ASA was dried overnight in a vacuum oven (450 mbar) at 60 °C (Gallenkamp, UK). True density measurements were carried out in triplicates for each material. The moisture contents, particle sizes and true densities of the materials are presented in Table 1.

2.2.2. Granulation and microwave-assisted drying of granules in a single pot high shear processor

The formulations of granules are shown in Table 2. Granulation and microwave-assisted drying of resultant granules were carried out in a 25 l single pot high shear processor (UltimaPro^{TM}25L, Collette, Belgium). The processor was equipped with multiple drying functions allowing the use of microwaves, bowl-jacketed heat, gas assistance (Transflo®) and vacuum for drying. These are depicted in a schematic in Fig. 1.

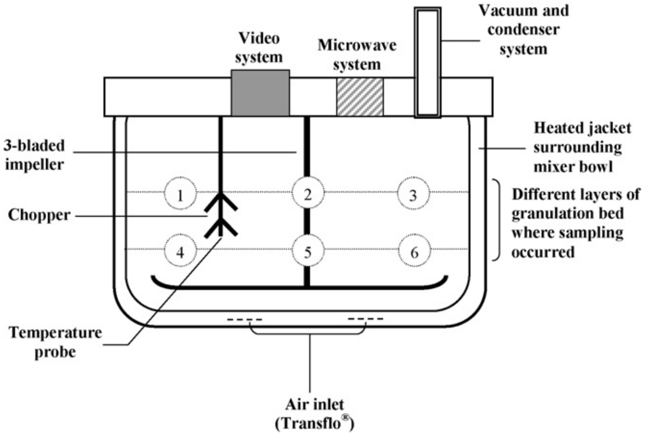

Fig. 1. Schematic of the cross-section of the single pot high shear processor (not to scale). 1–6 refer to the six sampling locations for the determination of the residual moisture contents of granules during drying.

Table 1
Moisture contents, particle sizes and true densities of materials used

Material	Moisture content[a] (%, w/w)	D_{50}[a] (μm)	True density (g/ml)
Lactose 200 M	0.236 (0.046)	36.83 (1.19)	1.535
Lactose 450 M	0.234 (0.075)	27.15 (0.53)	1.531
Cross-linked polyvinyl pyrrolidone	13.302 (0.669)	31.97 (0.51)	1.196
Polyvinylpyrrolidone-vinyl acetate copolymer	4.675 (0.123)	58.12 (5.03)	1.197
ASA	0.156 (0.041)	185.74 (7.13)	1.392

[a] Standard deviations are indicated in parentheses.

2.2.2.1. Granulation. Accurately weighed powders were first dry mixed for 5 min using a three-bladed impeller operating at a speed of 280 rpm. Thereafter, the required amount of granulating liquid was pumped into the mixer bowl with the aid of a pressurized vessel set at 0.4 bar. The same pressure was used for all experiments to ensure that the rate of liquid addition was consistent. During liquid addition, the impeller speed was maintained with the addition of the chopper operating at a speed of 600 rpm. Subsequent granulation was carried out for a total of 14 min at an impeller speed of 425 rpm for 10 min and 180 rpm for the remaining 4 min. The speed of the chopper was set at 2870 rpm throughout the entire granulation phase (Chee et al., 2005). Based on preliminary trials conducted, the amount of granulating liquid employed for each lactose type was different. Lactose 200 M granules were prepared with 8 and 11 % (w/w) of granulating liquid whereas lactose 450 M granules were prepared with 11 and 14% (w/w) of granulating liquid (Table 2). The different liquid requirements arose from disparities in specific surface areas of the powders (Kibbe and Weller, 2005). Four different batch sizes of lactose 200 M and 450 M granules were prepared using powder loads of 2.5 kg, 4 kg, 6.5 kg and 7.5 kg (Table 2).

2.2.2.2. Microwave-assisted drying of granules. For granules dried under microwave-assisted conditions, a microwave power output of 300 W, together with a jacketed bowl maintained at 55 °C provided the main sources of energy. A vacuum was created in the mixer bowl by lowering the internal bowl pressure to 50 mbar. This was based on manufacturer specifications which restricted the use of microwaves to a pressure range of 30–100 mbar. A small stream of purified air introduced at the base of the mixer bowl (Transflo®) minimized product adhesion and also facilitated the transport of moisture from the interior of the product bed to its surface during drying. To prevent the formation of hotspots as a result of non-uniformity in electric field distribution, intermittent agitation of granules was effected during drying with the impeller and chopper operating at the lowest speed of 44 rpm. This was performed only for the first 15 min of drying when the granules were still wet. Wetter granules were found to be more resilient to attrition and breakage than their drier counterparts in the presence of shearing stress (Nieuwmeyer et al., 2007). This was because there was a greater tendency for granule growth than breakage or attrition when the moisture contents of granules were still high, resulting in a net size increase at high moisture contents. A bowl swinging function which caused the mixer bowl to tilt to an inclination of 75° was also activated during drying, providing mild agitation to the granules. Due to its ability to encourage gentle mixing action, the swinging function was maintained throughout the entire duration of drying. This greatly minimized the attrition and sticking of granules undergoing the end stages of drying. The process settings during dry mixing, granulation and microwave-assisted drying were kept constant in all experiments. Each run was repeated at least twice.

2.2.2.3. Conventional drying of granules. Additional batches of lactose 200 M and 450 M granules were prepared at powder loads of 7.5 kg with 11 % (w/w) of granulating liquid. These were however, dried without microwave-assistance (control granules).

2.2.2.4. Drying profiles of granules. Drying profiles were charted by determining the residual moisture contents of granules sampled at 0 min, 5 min, 10 min, 15 min, 25 min, 35 min, 45 min and 60 min into the drying process. Due to the likelihood of non-uniform moisture distribution in the product load during drying, samples of granules, each weighing 6–10 g, were retrieved from six different locations in the mixer bowl at each sampling time point (Fig. 1). The mean residual moisture contents of these six samples provided a more accurate representation of the moisture present in the whole batch of granules. If granules were deemed insufficiently dried at the end of 60 min, further drying and sampling were carried out at 15 min intervals.

The weights of the freshly retrieved granules were accurately determined with a four decimal place electronic balance (A200S, Sartorius, Germany). Subsequently, they were dried for 1 h in a convection oven preheated to 105 °C (D06062 Model 600, Memmert GmbH, Germany). The residual moisture contents of granules were calculated by subtracting the final weights of the dried and cooled granules from their initial weights and expressing this difference as a % of the final dry weight of granules. The drying profiles were obtained by plotting the mean residual moisture content of granules (%, w/w) against drying time (min).

2.2.2.5. Computation of drying parameters. The drying profiles were subjected to regression analysis (SigmaPlot® 8.0, Systat Software Inc., USA). Goodness-of-fit of the experimental curves to model

Table 2
Formulation of granules

Material	Lactose 200 M granules	Lactose 450 M granules
Lactose 200 M	88%	–
Lactose 450 M	–	88%
Cross-linked polyvinyl pyrrolidone	2%	2%
Polyvinylpyrrolidone-vinyl acetate copolymer	5%	5%
ASA	5%	5%
Total dry weight (kg)	2.5, 4, 6.5, 7.5	2.5, 4, 6.5, 7.5
Granulating liquid (%, w/w)[a]	8, 11	11, 14

[a] Expressed as % total dry weight of powder.

equations were assessed by R^2 values. Drying rate parameters were derived from the first derivatives of the model equations and compared between the various batches of granules.

2.2.3. *Physical characterization of granules*

2.2.3.1. Size analyses of wet granules. A sample of wet granules was retrieved immediately after granulation was completed. These were observed under a stereomicroscope (Olympus, SZH, Japan) and sized using image analysis software (Micro Image, Media Cybernetics, USA). One hundred and twenty wet granules were sized and their mean equivalent circle diameters computed.

2.2.3.2. Size analyses of resultant granules. After drying was completed, granules were sieved through a 4 mm aperture sieve (Endecotts Ltd., UK) to remove the lumps. The proportion of lumps was calculated by expressing the weight of the oversize fraction (>4 mm) as a % of the initial weight of granules subjected to sieving. Granules smaller than 4 mm were divided by means of a spinning riffler (PT, Retsch, Germany) to obtain representative samples for size analysis.

One hundred grams of granules were sieved through a stack of sieves (Endecotts Ltd., UK) with aperture sizes ranging from 90 μm to 2800 μm arranged in a $\sqrt{2}$ progression. Sieving was carried out for 10 min at an amplitude of 1 mm using a vibratory mechanical sieve shaker (Endecotts Ltd., UK) and the weight of granules retained on each sieve was recorded. The mass median diameter, D_{50}, referred to the size of granules at the 50th percentile of the cumulative undersize plot. The modal fraction represented the size fraction in which majority of granules were found.

2.2.3.3. Bulk densities of granules. Bulk density determinations were carried out by allowing representative samples of granules from each batch to flow freely, with the aid of a funnel, into a 100 ml graduated cylinder. The weight of granules occupying 100 ml, w (g), was determined. Four replicated experiments were conducted and results averaged. Bulk density was defined as

$$\text{Bulk density}\,(\text{g/ml}) = \frac{w}{100}. \tag{2}$$

2.2.3.4. Crushing strengths and friability studies of granules. The mechanical strengths of lactose 200 M and 450 M granules prepared using 11% (w/w) granulating liquid were determined by crushing and friability tests. Representative samples of granules from each batch were sieved through a nest of sieves with aperture sizes ranging from 355 μm to 1000 μm in diameter. Those that were retained exactly within the apertures of 500 μm, 710 μm and 1000 μm sieves were retrieved and individually crushed by a platen moving at a velocity of 5 mm/min (EZ Tester-100N, Shimadzu, Japan). The maximum load (mN) required to crush individual granules was recorded. A minimum of 25 granules were crushed for each size fraction and the results averaged to represent their crushing strengths.

Granules 355–500 μm in size were subjected to friability tests as they were physically too small to crush. Accurately weighed 7 g samples of granules together with 25 steel balls, each weighing 0.88 g and measuring 6 mm in diameter, were subjected to 100 revolutions in a friabilator (TA20, Erweka GmbH, Germany). The steel balls acted as attrition agents during the test. Fine particles produced as a result of attrition were sieved through a 250 μm sieve (Endecotts Ltd., UK) and the weight of granules retained on the sieve was recorded. Each experiment was repeated thrice and the results averaged. Friability index was calculated in the following manner:

$$\text{Friability index}\,(\%) = \frac{\text{Initial weight of granules}\,(\text{g}) - \text{Weight of granules retained on 250}\,\mu\text{m sieve}\,(\text{g})}{\text{Initial weight of granules}\,(\text{g})} \times 100. \tag{3}$$

2.2.4. *Volume of void space*

The volume of void space in the mixer bowl during drying was calculated by subtracting the volume occupied by granules in the mixer bowl from the total capacity of the bowl. The volume of granules was derived from their bulk densities determined in Section 2.2.3.3:

$$\text{Volume of void space}\,(\text{ml}) = 25,000 - \text{Total volume of granules in the mixer bowl}. \tag{4}$$

2.2.5. *Degradation of ASA*

The % degradation of ASA during granulation and drying was determined by HPLC (LC 2010A, Shimadzu, Japan) in accordance to a method previously established (Chee et al., 2005). Analyses were carried out on the powder mixtures after the dry mixing stage, wet granules prior to drying and final dried granules prepared from 2.5 kg to 7.5 kg powder loads. These were annotated by 'powder', 'wet' and 'dried', respectively. The % degradation of ASA obtained for 'powder' was largely the amount of degradation of the ASA during storage, prior to its use for granulation. It should be taken as the baseline for the amount of ASA degraded.

A reversed phase C-18 column (Hypersil® BDS-C18, 5 μm, 4.6 mm × 150 mm, Agilent, USA) was employed as the stationary phase whereas the mobile phase consisted of phosphate buffer (pH 2.8) and acetonitrile in a ratio of 4:1. The powders and granules were pulverized before analyses. An accurately weighed amount of the pulverized material (approximately 150 mg) was dissolved and made up to a final volume of 20 ml with the mobile phase. The suspension was then ultrasonicated (LC60H, Fisher Scientific, Germany) for 10 min before being filtered through a 0.45 μm membrane filter (RC, Sartorius, Germany). Ten microliters of the filtrate were used for the assay. The column was maintained at 40 °C throughout the analyses, and the detection wavelength employed was 254 nm.

The areas under the curves of the degradation product, salicylic acid, and remaining ASA were determined and their corresponding concentrations calculated according to standard calibration curves. Four replicated assays were carried out. The % degradation of ASA was calculated in the following manner:

$$\text{Degradation of ASA}\,(\%) = \frac{\text{Concentration}\,(\text{g/ml})\,\text{of degraded ASA}}{\text{Concentration}\,(\text{g/ml})\,\text{of degraded ASA} + \text{Concentration}\,(\text{g/ml})\,\text{of remaining ASA}} \times 100. \tag{5}$$

3. Results and discussion

3.1. *Influence of powder load on the microwave-assisted drying of granules*

It could be observed from Fig. 2a–d that powder load affected the drying profiles of granules. As powder load increased to 6.5 kg

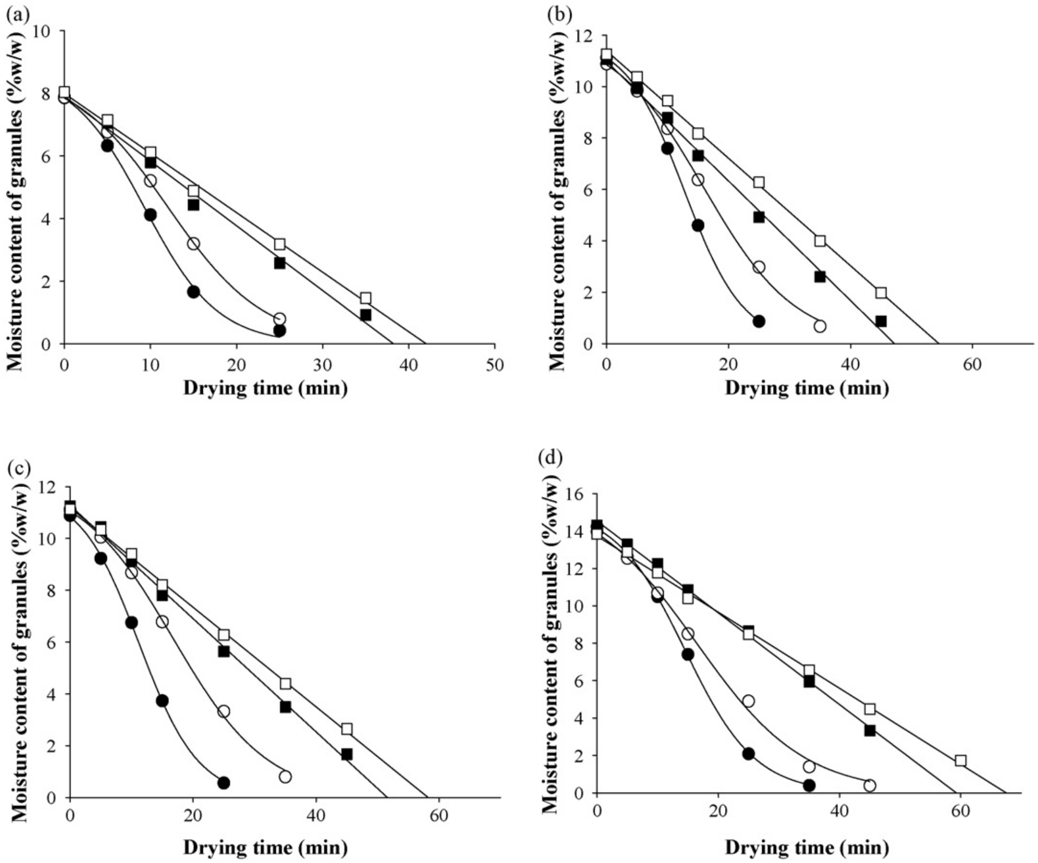

Fig. 2. (a–d) Drying profiles of granules prepared from powder loads of (●) 2.5 kg, (○) 4 kg, (■) 6.5 kg and (□) 7.5 kg. Symbols: experimental data, —: regression line/curve. Goodness of fit: $0.991 > R^2 > 1.000$. (a) Lactose 200 M/8% (w/w) granulating liquid, (b) lactose 200 M/11% (w/w) granulating liquid, (c) lactose 450 M/11% (w/w) granulating liquid and (d) lactose 450 M/14% (w/w) granulating liquid.

and 7.5 kg, moisture removal tended towards a constant rate as reflected by the increasing linearity of the drying profiles. The drying rate however, varied with time for granules prepared from smaller powder loads (2.5 kg and 4 kg), increasing in the initial phases to a maximum then falling towards the end of the drying process. The various drying parameters of granules are shown in Table 3. The maximum drying rate, R_m (g/min) and rate constant, k (g/min), were derived from the drying profiles of granules prepared from the smaller (2.5 kg and 4 kg) and larger powder loads (6.5 kg and 7.5 kg), respectively. $T_{50\%}$ (min) referred to the time required for the removal of 50% of the initial moisture content of granules.

Table 3
Volume of void space and drying parameters of granules

Lactose/amount of granulating liquid	Powder load (kg)	Void space (ml)	$T_{50\%}$ (min)	R_m (g/min)	k (g/min)
200 M/8% (w/w)	2.5	21200.6	10.15	12.92	–
	4	18907.1	13.15	15.68	–
	6.5	15377.5	19.12	–	13.42
	7.5	13776.7	21.02	–	14.25
200 M/11% (w/w)	2.5	21796.5	13.37	15.48	–
	4	19441.4	17.54	16.17	–
	6.5	15798.4	23.62	–	15.12
	7.5	13919.0	27.25	–	15.67
450 M/11% (w/w)	2.5	21452.6	13.04	15.73	–
	4	19215.5	18.30	16.04	–
	6.5	15313.0	25.86	–	14.20
	7.5	13938.1	29.12	–	14.41
450 M/14% (w/w)	2.5	21614.8	15.39	16.50	–
	4	19386.0	18.81	18.11	–
	6.5	15497.1	29.64	–	15.93
	7.5	14102.8	33.79	–	15.26
Control granules					
200 M/11% (w/w)	7.5	13872.4	43.21	–	9.37
450 M/11% (w/w)	7.5	13649.3	41.42	–	9.66

$T_{50\%}$ refers to the time required for the removal of 50% of the initial moisture content of granules. R_m and k refer to the maximum drying rate and rate constant, respectively.

The changing volume of void space as a result of varying powder loads (Table 3) could account for the observed differences in drying profiles. During drying, the void space in the mixer bowl formed the receptacle for moisture and vapour evaporating from the surfaces of granules and influenced the concentration gradient established at the liquid–gas interface for moisture and vapour diffusion. Relative to the larger powder loads, granules prepared from smaller powder loads of 2.5 kg and 4 kg experienced increasing drying rates due to the greater volume of void space which translated to higher moisture-holding capacities. As powder load increased, higher quantities of moisture needed to be removed. This, however, did not commensurate with the concomitant decrease in the volume of void space which became limiting for evaporation and vapour escape. Consequently, moisture removal tended towards a constant rate when granules prepared from larger powder loads were dried.

Expectedly, drying progressed at a slower rate from granules prepared from larger powder loads, as evident from the increase in $T_{50\%}$ with powder load (Table 3). Larger loads contain higher quantities of moisture and the energy supplied under the prescribed conditions was inadequate for moisture to be removed at a rate comparable to their smaller counterparts. The limited void space available at larger powder loads further impaired their drying efficiencies. This was confirmed by the negative correlation between the volume of void space and $T_{50\%}$ of granules (Pearson correlation coefficient, $-0.994 < R < -1.000$, $p < 0.01$, 2-tailed). For both lactose 200 M and 450 M granules, an increase in powder load from 2.5 kg to 7.5 kg resulted in an approximately two times increase in $T_{50\%}$. Irrespective of the amount of granulating liquid used, the extent of increase in $T_{50\%}$ was marginally lower for lactose 200 M granules. This indicated that lactose 200 M granules possessed specific physical properties which were more favorable for drying such that the impact of increasing powder load on the efficiency of moisture removal was diminished. This would be further discussed in the sections that follow.

3.2. Influence of diluent particle size and amount of granulating liquid on microwave-assisted drying of granules

From the mean equivalent circle diameters (Fig. 3) and D_{50} (Table 4) of the wet and resultant dried lactose granules, respectively, it could be observed that when identical amounts of granulating liquid (11%, w/w) and powder loads were used, lactose 200 M granules were generally larger in size than corresponding lactose 450 M granules. Lactose 200 M granules also exhibited higher drying rates at majority of the powder loads (4 kg, 6.5 kg and 7.5 kg) as evidenced by their shorter $T_{50\%}$ and higher R_m and k values. These results were surprising as typically, higher drying rates were expected from finer lactose 450 M granules due to the availability of a larger exposed surface area for moisture diffusion. This was supported by the control experiments that clearly showed that when drying was performed without microwave-assistance, finer lactose 450 M granules possessed comparatively shorter $T_{50\%}$ (41.42 min) and higher k (9.66 g/min) values than corresponding lactose 200 M granules (control granules, Table 3).

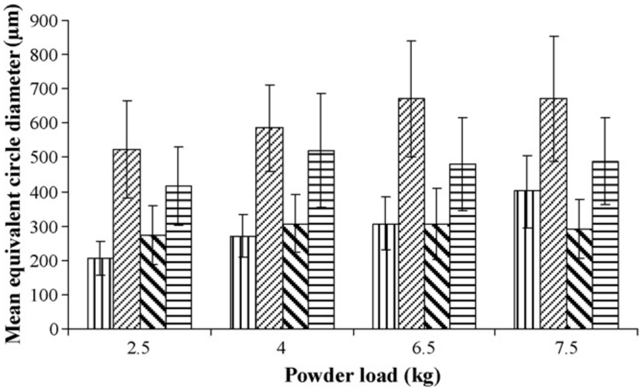

Fig. 3. Mean equivalent circle diameters of wet lactose 200 M and 450 M granules prepared with different amounts of granulating liquid: (▥) 200 M/8% (w/w), (▨) 200 M/11% (w/w), (▧) 450 M/11% (w/w) and (▤) 450 M/14% (w/w).

Such discrepancies arose from the different heat generative mechanisms under the influence of microwaves and conventional heating. Due to the penetrative and volumetric heating nature of microwaves, drying under microwave-assisted conditions is not restricted to the surfaces of wet granules. Studies on microwave-induced heating (Chamchong and Datta, 1999; Araszkiewicz et al., 2004, 2006; De la Hoz et al., 2005) have demonstrated that heat was generated internally within the irradiated objects resulting in the establishment of thermal gradients 'inside out' and opposite from that encountered under conventional heating. Applied in the current context, higher temperatures may have been achieved within the interior of granules resulting in the generation of pressure gradients for the outward movement of moisture and vapour from the granule cores. The structural properties of granules thus played a critical role in drying as they affected the migration of water from within the granules to their surfaces.

The mechanical strengths of granules corroborated with the above argument. From Table 5, it could be observed that the different sized lactose 200 M granules generally possessed lower crushing strengths and higher friability indices than their lactose 450 M counterparts at 6.5 kg and 7.5 kg powder loads. It could be inferred that these weaker lactose 200 M granules were structurally more porous and this facilitated the migration of water and vapour from the granule cores resulting in overall higher drying rates (shorter $T_{50\%}$ and higher k) than lactose 450 M granules. The reverse was observed at lower loads, in particular 2.5 kg, where all lactose 200 M granules were mechanically stronger. Since mechanically stronger granules are denser and less porous due to the greater number of inter-particulate contact points established between primary particles during granulation (Gokhale et al., 2005), a lower drying rate (longer $T_{50\%}$ and lower R_m) was observed for lactose 200 M granules compared to lactose 450 M granules at 2.5 kg powder load. These results clearly demonstrated the importance of the structural properties of granules in affecting the efficiency of moisture removal under microwave-assisted conditions.

McLoughlin et al. (2003) observed that the particle sizes of pharmaceutical materials exerted certain influences on their heat generative potential under the influence of microwaves. Larger particles were observed to heat better due to their improved heat entrapment and retention capabilities. Studies (Araszkiewicz et al., 2004, 2006) carried out on porous gypsum spheres heated by microwaves have also shown that temperatures at the core of spheres were higher than those at their surfaces. Higher core and surface temperatures were demonstrated for larger spheres as compared to smaller ones at identical liquid saturations. Based on these reported findings, it was possible that apart from their porous structures, the larger physical sizes of lactose 200 M granules enabled greater internal heat entrapment, resulting in generally higher drying rates relative to corresponding lactose 450 M granules.

The effects of granule size on drying could further be evaluated by comparing the drying rates of granules prepared using different amounts of granulating liquid. When the amounts of granulating liquid were increased from 8 to 11% (w/w) and 11 to 14% (w/w) for lactose 200 M and 450 M granules, respectively, resultant granules

Table 4
Size analyses of dried granules

Lactose/amount of granulating liquid	Powder load (kg)	D_{50} (μm)	Modal size fraction (μm)	Lumps (%)
200 M/8% (w/w)	2.5	226.3	250–355	2.8
	4	263.8	355–500	7.5
	6.5	327.5	355–500	12.5
	7.5	340.0	355–500	13.9
200 M/11% (w/w)	2.5	533.0	500–710	2.7
	4	527.0	500–710	5.3
	6.5	336.0	710–1000	7.7
	7.5	360.0	710–1000	11.7
450 M/11% (w/w)	2.5	305.0	250–355	5.8
	4	370.0	355–500	4.6
	6.5	327.5	355–500	12.0
	7.5	338.8	355–500	11.9
450 M/14% (w/w)	2.5	611.3	500–710	7.7
	4	582.5	500–710	16.2
	6.5	530.0	500–710	17.0
	7.5	510.0	500–710	15.9
Control granules				
200 M/11% (w/w)	7.5	428.8	710–1000	12.1
450 M/11% (w/w)	7.5	366.7	355–500	12.6

were larger and these possessed higher R_m and k values (Table 3). Fig. 4 shows the relationships between the sizes of all wet lactose 200 M and 450 M granules prepared at the smaller and larger powders loads and their respective R_m and k values. There were two distinct outliers at the lower loads where wet granules approximately 523 μm and 586 μm in size exhibited lower than expected R_m values. Incidentally, these corresponded to lactose 200 M granules prepared at 2.5 kg and 4 kg powder loads using 11% (w/w) of granulating liquid. As mentioned earlier, these granules were found to be denser and structurally less porous than their lactose 450 M counterparts (Table 5). Hence, despite their larger sizes which translated to improved heat retention capabilities, the movement of water and vapour within these lactose 200 M granules were impeded due to their dense structures, resulting in a net decrease in their R_m values. For the remaining wet lactose 200 M and 450 M granules, a positive correlation was observed between wet granule size and R_m (Pearson correlation coefficient $R = 0.890$, $p < 0.05$) as well as k (Pearson correlation coefficient $R = 0.744$, $p < 0.05$). These results reinforced the findings of the cited studies that larger particles heat better under microwave-assisted conditions and in the current context, dry at a faster rate than their smaller counterparts.

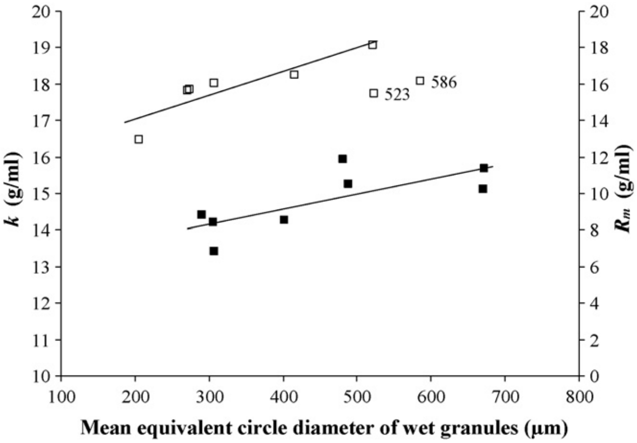

Fig. 4. Correlations between the sizes of all wet lactose 200 M and 450 M granules and their (□) maximum drying rates, R_m, as well as (■) rate constants, k.

Apart from granule size, microwave-specific moisture levelling effects could also account for the observed drying rates. Evaporation involves the escape of water molecules which have gained sufficient kinetic energy to overcome the surface tension forces holding them back at the liquid–gas interface. The number of gas molecules vaporized per unit time is given by the following equation (Giry et al., 2006):

$$M = \frac{KS(F-h)}{Pt} \tag{6}$$

where M is the number of gas molecules vaporized per unit time, K is a constant, S is the surface area of material in contact with the drying environment, F is the saturated vapour pressure, h is the vapour pressure in the ambient atmosphere, P is the pressure and t is the drying time. Under identical drying conditions, the rate of evaporation is governed primarily by the exposed surface area of wet granules (S) and the difference in vapour pressure of water above the surfaces of granules and the surrounding environment ($F - h$). Under normal heating conditions, it is unlikely that the rate of evaporation from granules would be enhanced when higher amounts of granulating liquid were used as the larger granules formed possessed smaller exposed surface areas. When microwaves were used however, the higher moisture contents of granules increased

Table 5
Mechanical strengths of lactose 200 M and 450 M granules prepared with 11% (w/w) of granulating liquid

Test	Size of granules (μm)	2.5 kg		4 kg		6.5 kg		7.5 kg	
		200 M	450 M	200 M	450 M	200 M	450 M	200 M	450 M
Crushing Strength mN	500	3269	2922	3050	3275	2920	3236	3003	3136
	710	5557	4915	5704	5527	5495	5757	5606	5670
	1000	8360	6932	8409	7161	8340	8565	8799	9010
Friability index (%)	355–500	2.78	4.95	3.58	4.78	4.74	4.72	6.10	3.89

their dielectric losses such that they became more susceptible to microwave-induced heating. The higher temperatures attained by granules as a result increased the saturated vapour pressure of water above the surfaces of the granules with the consequence of an increased vapour pressure differential between them and the surrounding environment. The increased diffusion gradient enhanced the efficiency of vapour diffusion and moisture loss from granules prepared using higher amounts of granulating liquid.

3.3. Arc detection as the end point of drying

The absorption of microwaves by wet granules was highly dependent on their moisture contents. Once their residual moisture contents had been reduced to a sufficiently low level, they ceased to absorb microwave energy resulting in a rise in electric field strength within the bowl. This culminated to an arcing phenomenon which automatically deactivated the magnetron, preventing further input of microwave energy. The times of arc detection and residual moisture content of granules at those time points are presented in Table 6. The latter were determined from the drying profiles of granules shown earlier (Fig. 2a–d).

Clearly, the increase in quantity of moisture brought about by increasing powder loads delayed the time of arcing and resulted in a concomitant increase in the final residual moisture content of granules. This was 0.1–0.5% (w/w) for granules prepared from 2.5 kg to 4 kg powder loads and greater than 0.5% (w/w) for those at larger powder loads of 6.5 kg and 7.5 kg. From these observations, it could be inferred that powder load exerted an impact on the extent of drying experienced by the wet granules. Under a constant microwave power output, a smaller powder load experienced greater microwave energy intensities and this facilitated a greater extent of drying with the consequence of lower residual moisture content in the end product. The energy supplied for the larger loads of granules (6.5 kg and 7.5 kg) was however insufficient and this diminished the extent of drying.

From the size analysis data shown previously in Table 4, there was a general tendency for the proportion of lumps to increase as powder load increased. As big lumps were inherently harder to dry uniformly, there was a possibility that nearing the end of the drying process where majority of the granules had been adequately dried, residual moisture locked in the interior of these wet lumps resulted in the continuous absorption of microwave energy without the occurrence of any arcs. These were indeed observed in some batches of granules as indicated by ‘–’. An earlier study by Duschler et al. (1995) reported similar findings where the localized accumulation and sticking of wet granules on the bowl wall during drying caused the continuous absorption of microwave energy and the persistence of a constant electric field strength within the drying cavity despite the fact that the remaining granules were dried sufficiently. This disrupted the auto-regulation of the magnetron which inadvertently resulted in the over-exposure of granules to microwaves. Undoubtedly, the arcing phenomenon could potentially serve as an ‘*in situ*’ drying end point to minimize the danger of overheating and provide an accurate control of the final moisture content in the product (Aulton, 2002). However such end points are useful only when optimal conditions for agglomerate growth exist for greater uniformity in microwave absorption.

3.4. Influence of microwave-assisted drying on % degradation of ASA

The % degradation values of ASA at various stages of processing are depicted in Fig. 5a–d. Generally, drug degradation was minimal during granulation as could be inferred from the small differences

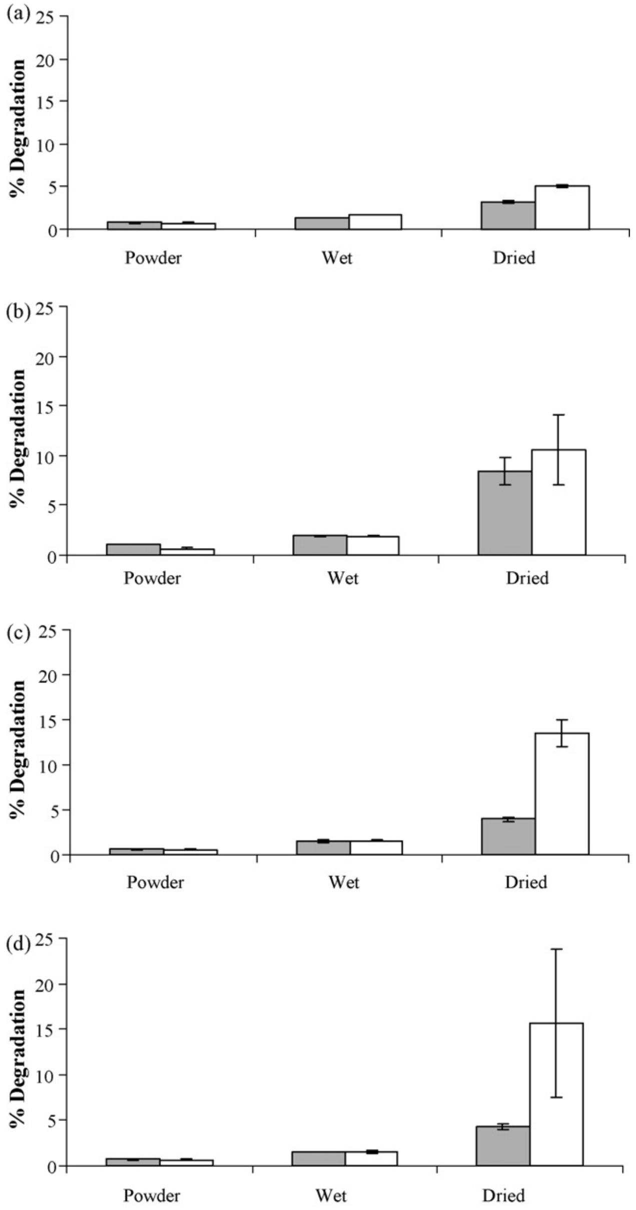

Fig. 5. (a–d) % degradation of ASA at various stages of processing for granules prepared from powder loads of (■) 2.5 kg and (□) 7.5 kg. (a) Lactose 200 M/8% (w/w) granulating liquid, (b) lactose 200 M/11% (w/w) granulating liquid, (c) lactose 450 M/11% (w/w) granulating liquid and (d) lactose 450 M/14% (w/w) granulating liquid.

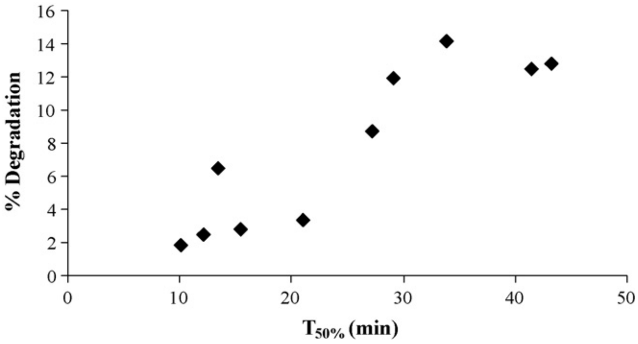

Fig. 6. Correlation between % degradation of ASA and $T_{50\%}$ of granules.

Table 6
Times of arc detection and corresponding residual moisture content of granules

Lactose/amount of granulating liquid	Powder load (kg)	Time of arc detection (min)	Moisture content of granules at time of arc detection (%, w/w)
200 M/8% (w/w)	2.5	17.0	0.249
	4	26.0	0.388
	6.5	–	–
	7.5	46.5	0.513
200 M/11% (w/w)	2.5	23.5	0.439
	4	34.5	0.117
	6.5	47.7	0.677
	7.5	55.0	1.000
450 M/11% (w/w)	2.5	25.5	0.268
	4	34.5	0.127
	6.5	51.5	0.925
	7.5	–	–
450 M/14% (w/w)	2.5	26.5	0.263
	4	43.5	0.079
	6.5	55.5	1.650
	7.5	69.5	0.589

–, means no arcs were detected.

in % degradation of ASA between the powders and wet granules. Drying *per se* resulted in a 1.84–14.18% degradation of ASA. Fig. 6 shows the correlation (Pearson correlation coefficient, $R = 0.898$, $p < 0.01$) between the extents of drug degradation in the granules as a result of drying and their corresponding $T_{50\%}$. It could be concluded that regardless of the formulation, powder load, energy source or drying rate, drying time was the most critical parameter influencing the stability of ASA. Longer drying times resulted in greater extents of drug degradation. This was due to the prolonged exposure of drug to moisture and heat during drying.

4. Conclusions

Granules prepared from different powder loads exhibited dissimilar drying profiles and drying rates which were related to the changing volume of void space in the mixer bowl. Under identical drying conditions, granules prepared from smaller powder loads experienced greater extents of drying with the consequence of lower residual moisture content in the resultant granules as compared to their larger counterparts. Owing to the unique penetrative and volumetric heating properties of microwaves, higher drying rates were generally observed for lactose 200 M granules as compared to their finer lactose 450 M counterparts prepared using identical amounts of granulating liquid and powder loads. This was due to the larger physical sizes of lactose 200 M granules which were conducive for heat retention, as well as their generally higher porosities. When higher amounts of granulating liquid were used, the rates of moisture removal from both lactose 200 M and 450 M granules were enhanced due to increased granule size and possibly microwave-specific moisture levelling effects. Degradation of ASA was considerably more pronounced during drying as compared to the granulation phase. The extent of drug degradation was found to be significantly correlated to the $T_{50\%}$ of granules. Longer $T_{50\%}$ brought about greater extents of drug degradation due to the prolonged exposure of drug to moisture and heat during drying.

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