Microwave Drying of Granules Containing a Moisture-Sensitive Drug: A Promising Alternative to Fluid Bed and Hot Air Oven Drying

Sze Nam CHEE,[a] Anne Lene JOHANSEN,[b] Li GU,[a] Jan KARLSEN,[b] and Paul Wan Sia HENG*,[a]

[a] *Department of Pharmacy, Faculty of Science, National University of Singapore; 18 Science Drive 4 Singapore 117543: and* [b] *Department of Pharmacy, Faculty of Science, University of Oslo; Sem Saelandsvei 3, Postboks 1068 Blindern, N-0316 Oslo, Norway.* Received January 8, 2005; accepted April 15, 2005

The impact of microwave drying and binders (copolyvidone and povidone) on the degradation of acetylsalicylic acid (ASA) and physical properties of granules were compared with conventional drying methods. Moist granules containing ASA were prepared using a high shear granulator and dried with hot air oven, fluid bed or microwave (static or dynamic bed) dryers. Percent ASA degradation, size and size distribution, friability and flow properties of the granules were determined. Granules dried with the dynamic bed microwave dryer showed the least amount of ASA degradation, followed by fluid bed dryer, static bed microwave oven and hot air oven. The use of microwave drying with a static granular bed adversely affected ASA degradation and drying capability. Dynamic bed microwave dryer had the highest drying capability followed by fluid bed, static bed microwave dryer and conventional hot air oven. The intensity of microwave did not affect ASA degradation, size distribution, friability and flow properties of the granules. Mixing/agitating of granules during drying affected the granular physical properties studied. Copolyvidone resulted in lower amount of granular residual moisture content and ASA degradation on storage than povidone, especially for static bed microwave drying. In conclusion, microwave drying technology has been shown to be a promising alternative for drying granules containing a moisture-sensitive drug.

Key words microwave drying; fluid bed drying; hot air oven drying; acetylsalicylic acid; copolyvidone; povidone

Wet granulation technique is often employed in the preparation of free flowing agglomerates. It is essential that the agglomerates/granules produced were suitably dried prior to further processing such as tabletting, capsule or sachet filling. The drying process can have an impact on the final properties of granules and it has been reported that solute migration, overheating and structural damages of granules were not uncommon in conventional drying methods.[1,2] Often, the properties of the granules have been found to influence the quality of the final product.[3—5] Thus, it is crucial that the drying method be controlled to assure that it does not adversely affect the quality of the final product.

Common drying methods used in the pharmaceutical industry include hot air oven drying and fluid bed drying. These methods employ different modes of moisture removal and differ in drying capability. In recent years, microwave drying has gained greater interest. The moist material is subjected to the high frequency electromagnetic waves that selectively excite the polar molecules (dipoles) and ions causing them to align with the rapidly alternating electric field. Heat (dielectric heating) will be generated during the orientation of these dipoles and ions that in turn evaporates the moisture present in the material. Thus, a pressure gradient is created and it promotes the rapid removal of liquid water and water vapour towards the surface of the material.[6—9] Basically, the principle of dielectric heating involves the absorption of energy by dipoles and the energy absorbed is given by:

$$P = 2\pi f E^2 E_0 E_r \tan\delta \quad (1)$$

where P = energy absorbed
f = microwave frequency
E = electric field
E_0 = dielectric constant of vacuum
E_r = dielectric constant of material
$\tan\delta$ = loss tangent

$\tan\delta$ can be regarded as a measure of the molecular interaction. The product of the dielectric constant, E_r and $\tan\delta$ is the loss factor and it determines the energy absorbed and thus the heating rate. McLoughlin and other coworkers found that the moisture content variation within the material undergoing drying with microwave was lower than a conventionally dried product.[8] Thus, microwave drying is especially useful for moisture-sensitive materials.

In addition, the microwave drying technology is useful for production of very high potency dosage forms because it provides the possibility of drying in the same production container. Thus, it reduces the likelihood of cross contamination and human contact with the high potency drug. Furthermore, such a single-pot process also reduces the number of equipment used for production and its associated cleaning and validation activities.

Various authors have investigated the influence of equipment parameters and the effects of dielectric properties of materials in microwave drying.[8,10,11] It was reported that localised heating could arise in microwave drying and be overcome with bed agitation. With respect to the influence on granular properties, Mandal found that microwave radiation did not modify the surface properties and dissolution rates of sulphathiazole/lactose granules.[12] In contrast, the microwave power level was found to affect the granular size distribution in another study.[13] It has been reported that different materials have different ability to absorb the microwave radiation and generate heat during dielectric heating.[10,14] A typical formulation usually consists of several excipients other than the drug. Thus, product quality could be affected by the excipients, especially if excessive heat was generated.

Considering the potential usefulness of microwave technology in drying granules produced from wet granulation method and the limited information of microwave radiation on drug degradation, this study aimed to investigate the influ-

* To whom correspondence should be addressed. e-mail: phapaulh@nus.edu.sg

ence of microwave drying on the degradation of a moisture-sensitive model drug, acetylsalicylic acid, with respect to conventional drying methods, hot air oven and fluid bed drying. In addition, the effects of different microwave power levels/intensities (300, 600, 900 W) and binders on the degradation of drug were investigated. Lastly, the impact of these drying methods on the physical properties of the granules was also determined.

Experimental

Materials Acetylsalicylic acid (BP grade, China) was pre-sieved and size fraction of less than 355 μm was used as a moisture-sensitive model drug. Povidone (Plasdone® K 29—32) or copolyvidone (Plasdone® S-630) was employed as binder and crosprovidone (Polyplasdone® XL-10) as disintegrant in the formulations that were studied. Both binders and disintegrant were supplied by International Speciality Products (U.S.A.). α-Lactose monohydrate (Pharmatose® 200 M, De Melkindustrie Veghel, The Netherlands) was used as the filler and deionised water as the granulating liquid.

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 mobile phase for the HPLC analyses.

Preparation of Granules A high shear granulator (UltimaPro 25, Collette, Belgium) was used. The formulations are shown in Table 1. The disintegrant, binder and drug were pre-mixed in a plastic bag before introducing into the bowl of the granulator with the filler. Dry mixing of the materials was performed with an impeller speed of 280 rpm for 3 min. During the wet massing stage, the deionised water was sprayed into the granulation bowl within 1 min, with a pressure of 0.4 bar, at an impeller speed of 280 rpm and a chopper speed of 600 rpm. Amount of deionised water added was about 11% of the total dry powder blend. Granulation was then carried out with an impeller speed of 425 rpm for 8 min followed by 180 rpm for 2 min. The chopper speed was maintained at 2870 rpm throughout the granulation stage. The moist granules obtained were either used for dynamic bed microwave drying or collected and sub-divided into 3 portions for drying by other methods.

Drying Processes An arbitrary residual moisture content of 1% or less was selected as the end point for drying of the granules. Preliminary studies were conducted and the drying parameters selected. Formulation II was selected for the study on dynamic bed microwave drying using various power levels because of the higher amount of ASA degradation compared to Formulation I.

Hot Air Oven Drying Eight hundred grams of moist granules were spread over two metal trays, each with a dimension of 374 mm by 277 mm. The thickness of granular bed was about 7 mm. Drying of the granules was then carried out in a hot air oven (UL 40, Memmert, Germany) at 60 °C for 4 h.

Fluid Bed Drying Granules weighing about 800 g were dried in a fluid bed dryer (STREA-1, Aeromatic, Switzerland) for 30 min. The inlet air temperature was set at 60 °C and the airflow was adjusted to ensure sufficient fluidisation of the granular bed.

Static Bed Microwave Drying Drying was carried out in a microwave oven (ETHOS 900, Milestone Microwave Laboratory Systems, Italy) set at a power level of 200 W with a drying time of 30 min and a ventilation period of 10 min. The oven consisted of a single magnetron with static microwave diffuser for homogenous microwave distribution. In the drying studies, 400 g of granules were loaded onto a cylindrical microwave-compatible plastic container with a nylon-mesh base. The container had a base diameter of 225 mm and height of 45 mm. The thickness of granular bed was about 17 mm. The container was then placed in the polyethylene chamber. An air circulation of about 20 to 25 l/min through the granular bed was achieved within the chamber with the aid of a vacuum pump.

Dynamic Bed Microwave Drying About 3.3 kg of moist granules were dried in the high shear granulator (UltimaPro 25, Collette, Belgium) with microwave under vacuum. The temperature of the bowl and lid was maintained at 30 °C. The bowl was set to swing 75° to either side to facilitate the drying process. The impeller and chopper speeds were set at 44 and 600 rpm respectively, and were rotated for 5 s every fourth cycle on the left swing and every second cycle on the right swing. The pressure within the bowl was maintained at about 50 mbar. The microwave supply was automatically terminated when sparks were detected within the bowl. The microwave drying time ranged between 10 to 40 min, depending on the power level used (300, 600, 900 W). Further drying was carried out with air streaming through the granular bed (transflow) at 10 l/min.

Table 1. Formulas Used in the Study

	Formula I	Formula II
ASA	5%	5%
Copolyvidone (Plasdone S630)	5%	—
Povidone (Plasdone K29/32)	—	5%
Crospovidone (Polyplasdone XL-10)	2%	2%
Lactose 200M (Pharmatose 200M)	88%	88%
Total dry weight (kg)	3	3

Regranulation The products obtained from static bed microwave and hot air oven drying were re-granulated with an oscillating granulator (AR400, Erweka, Germany) lined with a 1 mm mesh sieve to break down any lumps or cakes present.

Evaluation of Granules The dried granules were randomly separated using a riffler (Retsch, Germany) and the samples collected were used for various evaluation tests. Two batches of granules were dried using each drying method and two determinations were carried out for each batch of granules.

Moisture Content Determination The residual moisture content of about 4 g of granules was determined with a moisture balance (EB-330 MOC, Shimadzu, Japan). The samples were heated at 90 °C for 30 min. Four determinations were carried out and the mean moisture content computed.

Drug Degradation Determination Determination of the amount of drug degradation was performed one day and two months after drying of granules. The granules were sealed in a plastic bag and stored at a temperature of 23±2 °C and relative humidity of 55±5%. Granules were pulverised with a pestle and mortar before analysis. One hundred and fifty grams of the pulverised material were accurately weighed, dissolved and made up to a final volume of 20 ml with the mobile phase. The suspension was then sonicated (LC60H, Fisher Scientific, Germany) for 10 min and the coarse insoluble materials were filtered off (Whatman No. 1). The filtrate was then pass through a 0.45 μm membrane filter (RC, Sartorious, Germany) prior to HPLC analysis. Assays of the ASA and salicylic acid (SA) in the filtrate were carried out within an hour after dissolution of the pulverised granules. Ten microlitres of the filtrate were used for the HPLC assay (LC 2010A, Shimadzu, Japan). A reversed phase C-18 column (Hypersil BD-C18, 4.6×100 mm, Agilent, U.S.A.) was employed as the stationary phase whereas the mobile phase consisted of phosphate buffer (pH 2.8) and acetonitrile in an 8 : 2 ratio. The column was maintained at 40 °C and the detection wavelength was set at 254 nm. Areas under curve of SA (AUC_{SA}) and remaining ASA (AUC_{ASA}) were determined and the percentage of ASA degradation was then calculated (Eq. 2).

$$\%\ \text{ASA degraded} = \frac{AUC_{SA}}{AUC_{ASA} + AUC_{SA}} \times 100\% \quad (2)$$

Size Analysis Size analysis by weight was performed using a nest of sieves (Endecotts, U.K.) of aperture sizes 0.18, 0.25, 0.355, 0.5, 0.71, 1, 1.4, 2 and 4 mm. About 60 to 90 g of granules were used and the sieve shaker (VS1000, Retsch, Germany) was vibrated at 1 mm amplitude for 10 min. The size and size distribution of the granules were defined by the mass median diameter and span respectively. Mass median diameter ($X_{50\%}$) of the granules was the granule diameter at the 50 percentile of the cumulative percent oversize plot and the span was calculated as shown in Eq. 3.

$$\text{span} = \frac{X_{90\%} - X_{10\%}}{X_{50\%}} \quad (3)$$

where $X_{90\%}$, $X_{10\%}$, and $X_{50\%}$ are the granule size at the 90, 10 and 50 percentile on the cumulative percent oversize plot respectively.

Friability About 10 g of the granules with size ranging from 0.355 to 2 mm were placed in a friabilator (TA20, Erweka®, Germany) and tumbled at 25 rpm for 10 min. Twenty five steel balls (diameter 6 mm, weighing 0.884 g each) were used as attrition agents. After friability testing, the granules were then passed through a 0.25 mm sieve and the percent friability (% F) was then calculated accordingly (Eq. 4).

$$\% F = \frac{Wi - Wr}{Wi} \times 100\% \quad (4)$$

where Wi was the initial weight of granules before friability testing, and Wr was the weight of granules retained on the sieve with 0.25 mm aperture size after friability testing.

Hausner Ratio and Carr Index Granules were poured gently into a pre-weighed graduated cylinder cut exactly to 25 ml with the aid of a glass funnel. Excess granules were removed using a spatula and the weight of the cylinder with granules was determined. The cylinder was then tapped (STAV 2003, Stampfvolumeter, JEL Engelsmann, Germany) according to USP method until the difference between two consecutive measurements was less than 2%.[15] Bulk density (ρ_b) was calculated as the quotient of the weight of the granules and the volume of the cylinder used. Tapped density (ρ_t) was calculated as the quotient of the weight of the granules and its final volume after tapping. Hausner ratio (H_R) and Carr index (I_C) were calculated according to Eqs. 5 and 6.[16,17]

$$H_R = \frac{\rho_t}{\rho_b} \quad (5)$$

$$I_C = \frac{\rho_t - \rho_b}{\rho_t} \quad (6)$$

Results and Discussion

Drying Capability. Comparison of Static Bed Microwave Method and Conventional Drying Methods For comparison of the effects of drying methods on granules, a residual moisture level of 1% or less was selected as the end point for drying of the granules. The residual moisture levels of the dried granules are shown in Table 2. The granules dried with fluid bed dryer possessed the lowest residual moisture level, followed by those dried with hot air oven and static bed microwave oven. The quotient of the average amount of moisture removed by the drying method and its drying time, R_e, was used as an indicator of drying capability. A higher R_e value is reflective of higher moisture removal capability. Fluid bed drying has the highest R_e value, followed by static bed microwave and hot air oven drying. Clearly, the fluidisation of the granular bed promoted efficient heat exchange between particles and drying air, as well as rapid removal of the evaporated water vapour. Since a static granular bed impacted negatively on drying capability, we would then expect a lower drying capability when a thicker granular bed was employed. However, static bed microwave drying was more efficient than hot air oven drying despite the presence of a thicker granular bed. The pressure gradient created by the rapid evaporation of water during microwave drying provided the additional driving force to keep the granular bed reasonably porous thereby aiding the removal of water vapour.

Some caking of the product was observed for the granules dried with static bed microwave oven and hot air oven whereas none was seen for those dried with fluid bed dryer. The continuous movement of the granules in the fluid bed dryer not only limit the duration of direct contact between particles during the drying process, it also served as an attrition force which could greatly reduce the caking of product. Upon removal of moisture from the granules, solutes in the granulating liquid re-crystallised out and formed solid bridges between the particles. In both static bed microwave and hot air ovens, the granular bed remained stationary throughout the drying process and there were no attrition forces to break any resultant solid bridges, if formed, between adjoining granules. Thus, it may lead to possible formation of cakes or clumps in the dried product.

Effect of Intensity of Microwave on Drying Capability From the static bed microwave studies described earlier, it was found that formulation II resulted in comparatively higher level of ASA degradation than formulation I. Therefore, formulation II was selected for the study on the influence of microwave intensity on the amount of ASA degradation to avoid protective effect, if any, exerted by the binder. As it is our interest to study the impact of microwave on moisture removal and drug degradation, the R_e value was derived from the amount of moisture removed till the point of spark detection and the duration when the microwave radiation was in operation. It was apparent that a higher microwave power level greatly enhanced the drying capability (Table 2). The R_e value at 600 W was almost 2 fold higher than the R_e value at 300 W. Interestingly, at 900 W, the R_e value was smaller in magnitude compared to the value at 600 W. However, it was still greater than the R_e value at 300 W. In spite of the higher drying capability effected by the higher microwave power level employed, the probability of spark generation was also increased. Thus, it resulted in an early termination of the microwave radiation before substantial amount of moisture could be removed. It appeared that an optimal microwave power level exists for efficient drying using microwave. In this case, 600 W seemed to be the optimal or near optimal microwave power level for drying. In spite of a smaller role in drying, mixing of the granular bed

Table 2. Residual Moisture Content and Percent ASA Degradation of Granules Dried with Fluid Bed Dryer, Hot Air Oven and Microwave (μw) Dryers

Binder	Drying method	Moisture content (%)	R_e[a] (g/min)	ASA degradation (%)	
				One day	Two months
Copolyvidone (Formulation I)	Fluid bed	0.53±0.23	2.37	0.24±0.06	2.84±0.04
	Hot air oven	0.57±0.15	0.29	1.04±0.13	6.47±0.68
	SB[b] μw oven	0.65±0.03	1.17	0.96±0.22	7.03±0.37
Povidone (Formulation II)	Fluid bed	0.68±0.02	2.33	0.66±0.05	3.90±0.59
	Hot air oven	0.73±0.07	0.29	1.78±0.17	7.77±0.84
	SB[b] μw oven	0.93±0.11	1.13	1.77±0.03	10.08±1.26
	DB[c] μw with power level				
	300 W	0.56±0.02	4.60	0.51±0.10	—
	600 W	0.45±0.08	10.35	0.55±0.06	—
	900 W	0.42±0.16	8.67	0.50±0.13	—

a) Quotient of the average amount of moisture removed by the drying method and its drying time. *b*) Static bed. *c*) Dynamic bed.

and the application of vacuum, in combination with microwave resulted in considerably low residual moisture level of about 0.5%.

Effect of Binders on Drying Capability When the effect of the binder was compared, it was found that dried granules containing povidone had higher residual moisture content than those containing copolyvidone as a binder. Copolyvidone, with its vinyl acetate moiety, is more hydrophobic and binds less tightly with the water molecules than povidone. Thus, a comparatively more stringent drying condition would be required by granules containing povidone to achieve similar residual moisture level as those granules containing copolyvidone.

Degradation of ASA. Comparison of Static Bed Microwave Method and Conventional Drying Methods The percent degradation of ASA present in granules dried with fluid bed dryer, hot air oven and static bed microwave oven after one day and two months of storage are shown in Table 2. As all samples were subjected to identical sonication process for the assay of drug degradation, any effect exert by the sonication process would be present for all assays. Thus, differences in ASA degradation would be due to the drying methods employed. Static bed microwave oven drying resulted in significantly higher amounts of ASA degradation than fluid bed drying (ANOVA, $p<0.05$, SPSS) for both binders. The differences were significant for both one day and two months of storage. Fluid bed-dried granules were in continuous motion during drying and all surfaces of the moist granules were exposed to a blanket of hot air that facilitated drying and moisture removal. As such, the granules were exposed to heat and moisture for a shorter period of time as compared to those dried by static bed microwave oven and hot air oven. Furthermore, the moist granules undergoing fluid bed drying were continuously cooled by the endothermic condition brought about by the evaporation of moisture that ensured a low product temperature, just above the wet bulb temperature. The temperature of the fluid bed granules would only rise when the granules were dried, thus exposing the granules to higher temperature only briefly. In addition, at the terminal drying stage, the lower moisture content in the granules would also limit the extent of degradation of a moisture-sensitive substance.

However, granules dried with the static bed microwave oven and hot air oven were not significantly different when the ASA degradation levels were compared (ANOVA, $p<0.05$, SPSS). It is likely that ASA degradation is not only dependent on the time at which the drug is exposed to heat during drying but also by the amount of moisture present. For the static bed microwave oven drying, the circulating air had to stream through a relatively thicker granular bed. It was necessary for the moisture vapours to travel a longer and more tortuous path before it could be removed. Thus, moisture dissipation was not efficient and the product was subjected to moisture continuously during the period of drying. In addition, heat dissipation was also not efficient with a thicker granular bed and bed temperature could be elevated. As a result, the extent of ASA degradation was similar to that of the hot air oven drying despite the higher drying capability of static bed microwave drying. The negative impact of a thicker granular bed on drying capability and ASA degradation was confirmed when the moist granules were dried in the hot air oven using the microwave-compatible container (Table 3). Despite a lower wet granular load, it was found that a thicker static granular bed during drying resulted in a lower R_e and higher amount of ASA degradation when the granules were dried to the predetermined end point.

Table 3. Effect of Granular Bed Thickness on Degradation of ASA Using Hot Air Oven Drying

Drying container	Microwave-compatible container	Tray
ASA degradation (%)	2.51±0.38	1.78±0.17
R_e [a] (g/min)	0.09	0.29
Thickness of granular bed (mm)	17	7

a) Quotient of the average amount of moisture removed by the drying method and its drying time.

Interestingly, in comparison with granules dried using other methods, static bed microwave-dried granules had a higher rate of ASA degradation, determined after two months of storage. It was believed that the higher amount of initial residual moisture content of the static bed microwave-dried granules contributed to higher rate of ASA degradation.

Effect of Microwave Power Level/Intensity and Mixing on the Degradation of ASA The percent ASA degradation at various power levels/intensities of microwave after one day of storage is shown in Table 2. The amount of ASA degradation was not determined after two months of storage because our intent was to ascertain the impact of microwave intensity on degradation of ASA. The results showed that granules exposed to microwaves displayed no significant increase in degradation with various levels of microwave radiation used. Thus, it could be concluded that microwaves per se did not have any direct detrimental effect on ASA. Furthermore, the lack of difference in the amount of ASA degradation when the granules were immediately analysed after production supported this finding. The percent of ASA degradation was 0.23 and 0.26% for microwave power level of 300 and 900 W respectively.

In comparison with other drying methods, dynamic bed microwave drying resulted in significantly lower percent of ASA degradation, determined 24 h after drying, with the exception of the nominal difference between dynamic bed microwave drying and fluid bed drying. Unlike static bed microwave drying, the swinging motion of the product bowl and mixing of the granules during drying turn around the moist granules at the base of the bowl thereby facilitating the diffusion of vapours and its removal. The improved moisture removal efficiency resulted in a rapid reduction in the residual moisture and thus lowered the percent degradation of ASA. In addition, mixing of the granules prevented the build up of hot spots, thus limiting the rise in temperature of the granular bed undergoing drying. The active vacuum also improved moisture removal and hence minimising two detrimental factors, moisture and heat, associated with the degradation of ASA.

Effect of Binders on Degradation of ASA The ASA degradation was significantly higher in granules containing povidone compared to those containing copolyvidone for the drying methods investigated (Table 2). It was found that granules containing copolyvidone consistently possessed

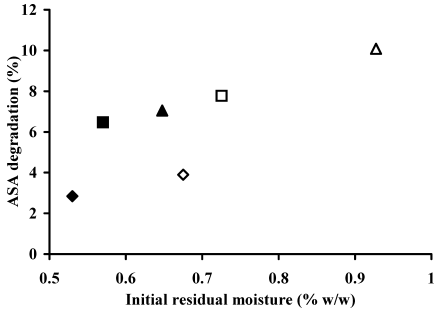

Fig. 1. Percent of ASA Degradation after Two Months of Storage with Respect to the Residual Moisture Content of Dried Granules

Fluid bed dryer (◆), hot air oven (■) and static bed microwave oven (▲); (closed symbol represents copolyvidone, open symbol represents povidone).

lower residual moisture content than granules containing povidone after drying. Thus, it could be inferred that the higher amount of ASA degradation in granules containing povidone was due to the higher residual moisture content. The effect of residual moisture content on the extent of ASA degradation after two months of storage was depicted in Fig. 1. Generally, it showed the trend of higher amount of ASA degradation with increasing residual moisture content. It was believed that the residual water molecules could migrate within the granular matrices and degrade the ASA.[18] It was also observed that the increment in ASA degradation after two months of storage with respect to one-day measurements was larger for granules containing povidone. This could be attributed to the formation of complexes between povidone and salicylic acid and the removal of salicylic acid could have favoured the degradation of ASA. Plaizier-Vercammen and De Nève believed that both the pyrrolidine ring and paraffin backbone of povidone were involved in the complexation with salicylic acid.[19] The vinyl acetate moiety of copolyvidone found along the paraffin backbone could have interferred with its bonding with salicylic acid. Thus, resulting in a lower degradation of the moisture-sensitive components.

Effects of Various Drying Processes and Microwave Power Levels on the Physical Characteristics of Granules

The size and size distribution of granules dried with fluid bed dryer, hot air oven and static bed microwave oven are shown in Fig. 2. The mass median diameters of the microwave-dried granules were comparable to the mass median diameters of granules (of the same formulation) dried with the common methods studied. They ranged from 0.583 to 0.633 mm for Formulation I and 0.689 to 0.719 mm for Formulation II.

Various amounts of microwave radiation did not significantly influence the granular mass median diameter and span (Fig. 3). However, in comparison with other methods, dynamic bed microwave drying produced significantly wider granular size distribution. The combined attrition forces contributed by the transflow, swinging motion of the bowl, mixing action of impeller and chopper probably caused a greater extent of granular breakdown and resulted in the wider size distribution.

The percent friability of the granules after fluid bed, hot air oven and static bed microwave oven drying are presented in Fig. 4. Granules dried with static bed microwave oven were not markedly different from those dried with hot air oven. However, the microwave-dried granules were significantly

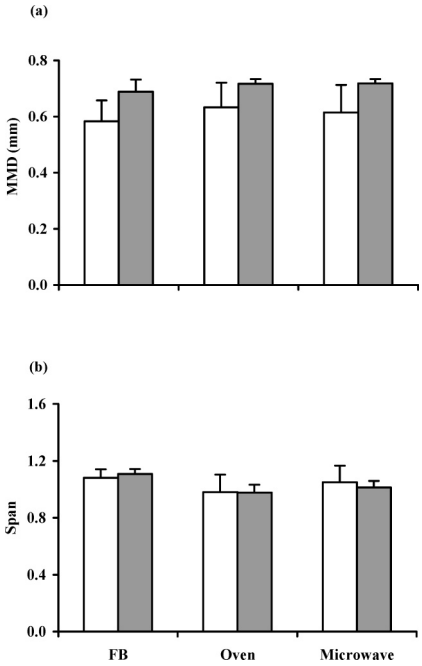

Fig. 2. (a) Size and (b) Size Distribution of Granules Dried with Fluid Bed Dryer (FB), Hot Air Oven (Oven) and Static Bed Microwave Oven (Microwave)

Shaded bar represents povidone, unshaded bar represents copolyvidone.

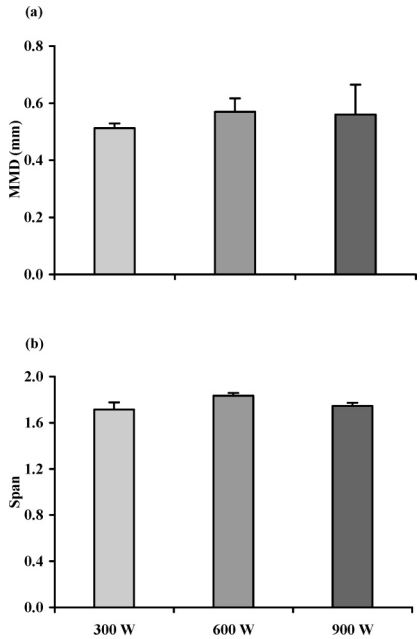

Fig. 3. (a) Size and (b) Size Distribution of Granules Dried with Dynamic Bed Microwave Dryer at Various Power Levels

weaker compared to those dried with fluid bed dryer. The rougher treatment of the granules during fluid bed drying would have broken down the weaker granules, thus leaving the stronger and less friable granules intact.

The power level of microwave radiation did not markedly influence the friability of granules. Dynamic bed microwave drying also resulted in less friable granules compared to the other methods.

The various drying methods and microwave radiation levels did not adversely affect the flow properties of the gran-

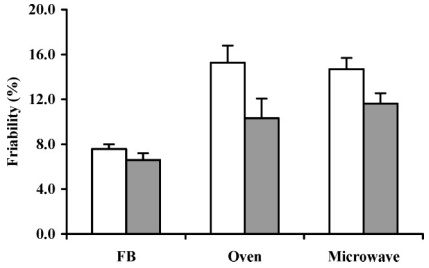

Fig. 4. Percent Friability of Granules Dried with Fluid Bed Dryer (FB), Hot Air Oven (Oven) and Static Bed Microwave Oven (Microwave)

Shaded bar represents povidone, unshaded bar represents copolyvidone.

Table 4. Flow Properties of Granules Dried with Various Methods and Microwave (μw) Power Levels

Binder	Drying method	Hausner ratio	Carr's index (%)
Copolyvidone (Formulation I)	Fluid bed	1.07±0.02	6.39±1.58
	Hot air oven	1.11±0.01	9.73±0.64
	SB[a] μw oven	1.11±0.03	9.72±2.88
Povidone (Formulation II)	Fluid bed	1.11±0.02	9.81±1.54
	Hot air oven	1.09±0.02	8.00±1.73
	SB[a] μw oven	1.12±0.02	10.47±1.75
	DB[b] μw with power level		
	300 W	1.15±0.04	12.55±2.72
	600 W	1.18±0.02	14.99±1.63
	900 W	1.15±0.03	12.96±2.38

a) Static bed. *b*) Dynamic bed.

ules as indicated by the Hausner ratio and Carr's index values (Table 4). Both flow indicators showed that all batches of the granules produced had good/excellent flow properties.[16] Though it may not be significant, the granules dried with dynamic bed microwave dryer had relatively poorer flow properties as indicated by the flow indicators. This could be attributed to the larger amount of fines that was produced during the drying process.

Effects of Binder on the Physical Characteristics of Granules It was found that copolyvidone produced smaller-sized granules than povidone regardless of the drying methods (Fig. 2). The relatively more hydrophobic nature of copolyvidone produced weaker inter-particulate bonds. Being more hydrophobic, the binding potential of copolyvidone in a relatively hydrophilic granular mass of lactose and aspirin is not strong.

Copolyvidone also produced more friable granules than povidone, though the difference was only significant for hot air oven and static microwave oven drying (Fig. 4). The weaker inter-particulate bonds probably played a role in granular friability. Generally, granules containing copolyvidone possessed comparable or slightly better flow properties than those containing povidone.

Conclusions

A static granular bed adversely affected heat and moisture dissipation during microwave drying that in turn influenced the drying capability and extent of ASA degradation. Static bed microwave drying was less effective than fluid bed drying whereas the former was better than hot air oven drying based on drying capability and percent of ASA degraded. However, when the dissipation of heat and moisture was improved through mixing (dynamic bed microwave drying), the drying capability and stability of ASA were greatly enhanced. The amount of ASA degradation on storage was dependent on the initial residual moisture level of the granules and was in turn influenced by the drying methods employed. The power level/intensity of the microwave radiation per se did not affect the degradation of ASA, size and size distribution, friability and flow properties of the dried granules. Mixing of granules during fluid bed and dynamic bed microwave drying resulted in the production of more fines leaving the stronger granules intact. Thus, the size distribution, flow properties and friability of the granules were affected. Mixing should be maintained at a level to achieve acceptable drying capability and minimal fines production. Copolyvidone was believed to bind less tightly to water and resulted in lower initial residual moisture level which led to a reduction in percent of ASA degradation. This effect was more apparent in static bed microwave-dried granules compared to granules dried with other methods. The mechanism of ASA degradation is not within the scope of this paper. However, a better understanding of the ASA degradation mechanism can be achieved through further studies. In conclusion, microwave drying technology offers a promising alternative with high capability for drying granules containing a moisture-sensitive drug without adverse impact on drug degradation.

References

1) Allan G. B., *J. Microwave Power*, **3**, 21—28 (1968).
2) Rubinstein M. H., Ridgway K., *J. Pharm. Pharmacol.*, **26**, 24P—29P (1974).
3) Selkirk A. B., Ganderton D., *J. Pharm. Pharmacol.*, **22**, 79S—85S (1970).
4) Selkirk A. B., Ganderton D., *J. Pharm. Pharmacol.*, **22**, 86S—94S (1970).
5) Wikberg M., Alderborn G., *Pharm. Res.*, **10**, 88—94 (1993).
6) Doyle C., Cliff M. J., *Manufact. Chem.*, **58**, 23—32 (1987).
7) Van Scoik K. G., Zoglio M. A., Carstensen J. T., "Encyclopedia of Pharmaceutical Technology," Vol. 4, Drying and Driers, ed. by Swarbric J., Boylan J. C., Marcel Dekker, New York, 1991, pp. 485—515.
8) McLoughlin C. M., McMinn W. A., Magee T. R. A., *Food Bioprod. Process*, **78**, 90—96 (2000).
9) Reh C. T., Gerber A., *Food Chem.*, **82**, 125—131 (2003).
10) Vromans H., *Eur. J. Pharm. Biopharm.*, **40**, 333—336 (1994).
11) Duschler G., Carius W., Bauer K. H., *Drug Dev. Ind. Pharm.*, **21**, 1599—1610 (1995).
12) Mandal T. K., *Drug Dev. Ind. Pharm.*, **21**, 1683—1688 (1995).
13) Kiekens F., Córdoba-Díaz M., Remon J. P., *Drug Dev. Ind. Pharm.*, **25**, 1289—1293 (1999).
14) Cheng W. Z., Ye Y. H., Chen Z. Z., *Microwave Opt. Technol. Lett.*, **22**, 205—207 (1999).
15) U.S. Pharmacopeial Convention, "US Pharmacopeia XXV," U.S. Pharmacopeial Convention Inc., Maryland, 2002, pp. 1981—1982.
16) Carr R. L., *Chem. Eng.*, **72**, 163—168 (1965).
17) Hausner H. H., *Int. J. Powder Metall.*, **3**, 7—13 (1967).
18) Patel N. K., Patel I. J., Cutie A. J., Wadke D. A., Monkhouse D. C., Reier G. E., *Drug Dev. Ind. Pharm.*, **14**, 77—98 (1988).
19) Plaizier-Vercammen J. A., De Nève R. E., *J. Pharm. Sci.*, **71**, 552—556 (1982).