The Development of a Microwave Fluid-Bed Processor. II. Drying Performance and Physical Characteristics of Typical Pharmaceutical Granulations

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Four typical pharmaceutical granulations were used to measure the enhanced drying performance of a laboratory-sized microwave fluid-bed processor, the design and construction of which were presented in Part I of this work (preceding paper). Results demonstrate improvements in observed drying rates by as much as sixfold depending upon the granulation type and drying conditions. At a low inlet temperature (30°C), drying was achieved with microwave power inputs of 100–125 W/liter of working capacity, whereas similar targeted moisture levels were unattainable using conventional fluid-bed drying. Microwave energy available for heating and drying was 68 to 86% of the total microwave energy inputted.

KEY WORDS: microwave dryer; fluid-bed dryer; process equipment validation.

INTRODUCTION

The construction, design features, and validation of a 1-kg, laboratory-size microwave-assisted fluid-bed processor (MFBP) was presented in Part I of this work (1). MFBP combines the superior evaporative characteristics of conventional fluid-bed drying with the direct and selective heating properties of microwave propagated energy in a single integrated unit.

In Part II of this work (present paper), the drying performance of the MFBP was measured for three aqueous granulations and one nonaqueous granulation. In addition to calculating the observed drying rate constant (k_{obs}), the microwave energy efficiency of the drying process was determined. Thermal effects of microwave energy to the physical properties of the dried granulations were determined by measuring particle size distribution, loose and tapped bulk density, granule morphology, and granulation compaction.

MATERIALS AND METHODS

Materials

All excipients listed in Table I were used in the preparation of four placebo granulations.

Granulation Models

Experiments were designed to determine the drying capabilities of the MFBP. In order to evaluate drying performance accurately, four significantly different placebo granulations were prepared. The formulations were comprised of commonly used pharmaceutical excipients and were designed to represent "typical" pharmaceutical granulations but with significantly different drying times when subjected to conventional fluid-bed drying. The latter criterion was accomplished by selecting excipients that were known either to dry quickly (give up superficial moisture readily) or to dry slowly (retain unbound moisture). The excipients chosen to typify fast-drying behavior (high-drying efficiency) and slow-drying behavior (low-drying efficiency) were dicalcium phosphate dihydrate and pregelatinized starch, respectively (2). Drying behavior was supported by the observed drying times as illustrated in Figs. 1–4. In an effort to demonstrate a drying continuum in the aqueous mode, an intermediary formulation possessing an equal mixture of dicalcium phosphate and pregelatinized starch was prepared to represent medium-drying efficiency. The fourth and final formula was simply the starch formulation, where isopropyl alcohol was used as the granulating agent in place of purified water. All four (4) granulation formulas are presented in Table II.

In addition to satisfying these two major criteria, each formulation was to possess reasonable compressional characteristics so as to produce pharmaceutically useful tablets. (The term pharmaceutically useful connotes acceptable tablet appearance, hardness, and friability.)

Granulation Procedure

All granulations were prepared in a 10-qt planetary mixer. The following steps were used to manufacture all four formulations.

a. One-half (½) of the largest percentage (w/w) component was placed into the bowl. This was either dicalcium phosphate, starch, or an equal mixture of both.
b. Microcrystalline cellulose was then added.
c. The other half of item a. was then added.
d. Material was dry-mixed for 5 min at approximately 26 rpm.
e. The granulating solution was prepared with 25°C purified water or isopropyl alcohol and povidone. The povidone was slowly added to the granulating solvent using moderate agitation.
f. Once the povidone was dissolved, the solution was added to the mixed powders at 26 rpm over a 3- to 4-min period.
g. The wetted powders were then mixed for an additional 15 min at the same speed. More granulating solution was added at this point to achieve the final wet granulation.
h. The granulation was then forced through a No. 8 mesh (2360-μm opening) hand screen and collected in a stainless-steel (SS) container. The moisture content of the granulation was immediately determined thermogravimetrically using a Compu-Trac moisture

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Table I. Excipients Used to Formulate Placebo Granulations

Ingredient	Lot no.	Source
Pregelatinized starch NF (Starch 1500)	903022	Colorcon Corp. West Point, PA 19846
Dicalcium phosphate, dihydrate unmilled USP (Di-Tab)	3223	Stauffer Chemical Shelton, CT 06484
Microcrystalline cellulose NF (Avicel, pH 101)	1850	FMC Corp. Newark, DE 19711
Povidone USP (Plasdone k29-32)	11720512385	GAF Corp. Wayne, NJ 07470
Isopropyl alcohol	A-5204	J. T. Baker, Inc. Phillipsburg, NJ 08865

analyzer (Motorola Corp.) at a setting of 100°C. The screened, wet granulation was covered with a polyethylene sheet to minimize moisture loss between drying experiments.

Description of Drying Experiments

Two experiments were performed for each of the four previously described granulations (A–D): at a constant inlet air temperature of 30°C, five drying curves were developed using microwave power inputs of 0, 250, 500, 750, and 1000 W, and the same experiment was then repeated at an inlet air temperature of 60°C. Although no attempts were made purposely to randomize the drying trials, typically at each inlet air temperature drying curves were generated in the sequence of 0, 1000, 250, 750, and 500 W of inputted power.

Drying Procedures

Following a 5-min warm-up period, the product bowl was removed and charged with screened wet granulation to approximately 90–95% of its volume. The granulation weight varied with the density of each formulation. Formula A, having the highest density, had a load weight of 1000 g, while Formula C, being the lowest, was 800 g. Formulas B and D had charge weights of 900 and 850 g, respectively.

At the end of each drying interval, the fluid-bed dryer and microwave generator were turned off, the filter bag shaker was activated for approximately 15 sec, and the product bowl was removed. The granulation was then gently mixed by hand to obtain a representative sample prior to withdrawing a 10-g aliquot for moisture analysis. In order to eliminate the influence of repeated product loss due to moisture testing, a fresh granulation was charged into the product bowl after *every other* moisture determination or drying interval. The drying was then allowed to proceed past previous time intervals until a new, unsampled, time interval was reached. This moisture sampling and granulation replenishing procedure continued until the desired moisture level was reached. In other words, at the start of a drying experiment, fresh granulation was loaded and dried for 5 min. After a sample was taken for moisture content, the drying process resumed until the 10-min time point. The second sample was then taken and the granulation discarded. Another fresh granulation was introduced and dried to the 15-min time point without interruption. A sample was withdrawn and the granulation was dried for another 5 min or until the 20-min time point. This second granulation was then discarded after the sample was taken. This procedure continued until the desired moisture level was reached. These moisture levels were 1.5–2.5, 2–3, 4–5, and 4–5% for formulas A, B, C, and D, respectively.

At the end of each drying interval, the following parameters were recorded: total drying time, inlet air temperature,

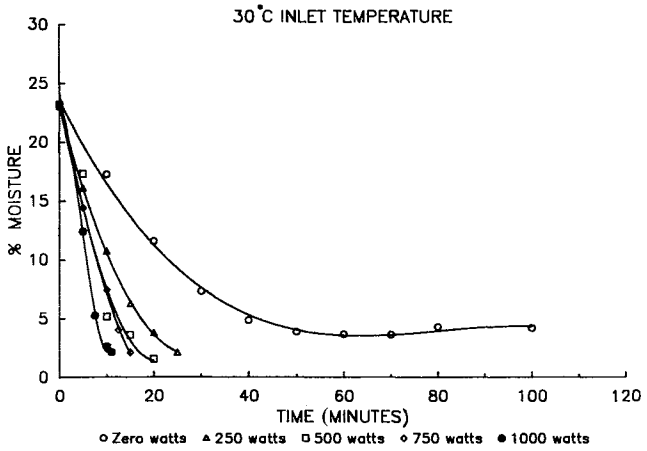

Fig. 1. Drying curves for aqueous dicalcium phosphate granulation at various microwave power inputs.

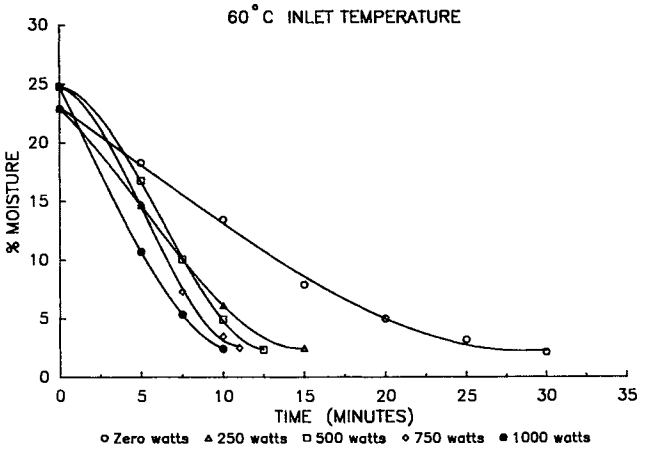

Fig. 2. Drying curves for aqueous dicalcium phosphate granulation at various microwave power inputs.

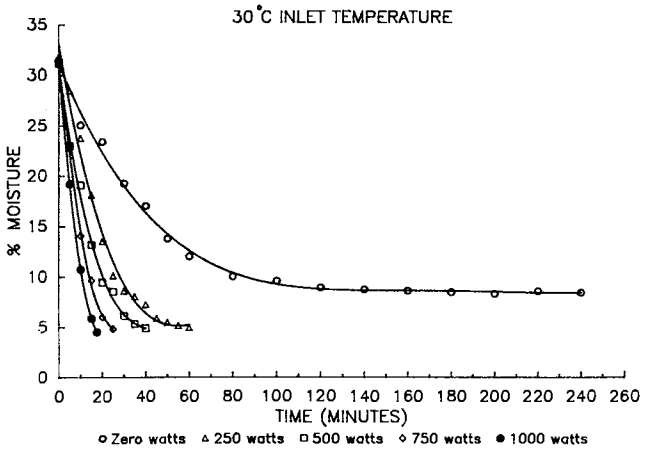

Fig. 3. Drying curves for aqueous starch granulation at various microwave power inputs.

expansion chamber air temperature, outlet air temperature, reflected microwave power, and granulation moisture.

The last drying parameter to be controlled was the inlet air volume. Due to differences in product densities, the air velocity was adjusted for each formulation in order to maintain a consistent fluidization pattern. The air velocities were 2.0, 1.9, 1.7, and 1.8 m/sec for formulas A, B, C, and D, respectively.

Physical Testing of Dried Granulations

In order to characterize and assess any changes in the physical properties of the dried granulations, the following test procedures were employed.

Particle Size Analysis

A particle size analysis was performed on all dried granulations using an Allen-Bradley Sonic Sifter Model L-3 (ATM Corporation, Milwaukee, WI). The screen sizes used were 20, 60, 80, 100, and 120 mesh. The average particle diameters were then calculated using the method described by Parrot (4).

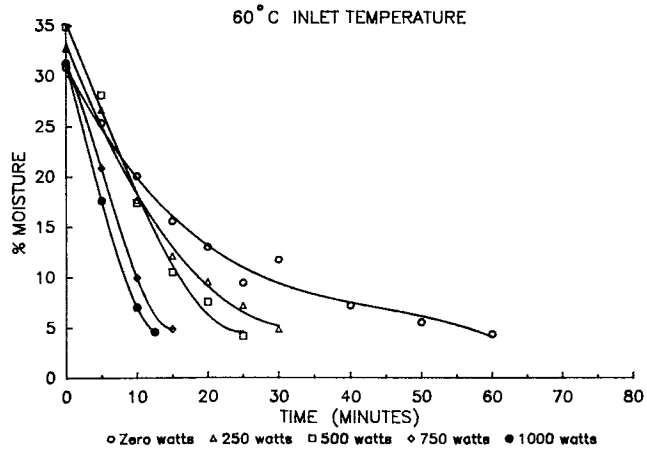

Fig. 4. Drying curves for aqueous starch granulation at various microwave power units.

Loose and Tapped Bulk Densities

Both the loose and the tapped bulk densities were measured in a glass 50-ml graduated cylinder and the sample weights were maintained at between 20 and 30 g. For loose bulk density measurement, the sample was placed into the graduated cylinder and the sides were tapped slightly to achieve a uniform horizontal powder level. The same sample received 1000 taps prior to tap density measurement.

Granule Morphology

Scanning electron microscopy was used to study the effect of microwaves on granule morphology for aqueous dicalcium phosphate and starch granulations treated with 0 and 1000 W of microwave power and a constant 60°C inlet air temperature.

Compression Profiles

The applied and transmitted forces needed to compress granulations A–D were recorded using an instrumented single-station Stokes-F compression machine (Pennwalt Corp., Warminster, PA). The drying conditions tested were 0 and 1000 W of microwave power input at a constant 60°C inlet air temperature. Target specifications were a 600-mg tablet weight and 5–7 kp in hardness using 7/16-in. standard round concave tooling.

RESULTS AND DISCUSSION

Drying Performance of the Microwave Fluid-Bed Processor

In order to assess the drying performance of the MFBP accurately, two evaluations were carried out. The first focused on the basic drying curves and observed drying rates, which were calculated with the aid of a computer by the method of least squares from the natural logarithm of percentage moisture remaining versus time plots. The second measured the microwave energy utilization of the MFBP. An "energy balance equation" was developed to express the inputted, reflected and available microwave energy during the drying process. Drying rate data and microwave utilization are discussed separately.

Drying Curves and Drying Rate Data

The design of the drying experiments permitted a direct comparison of drying curves and hence observed drying rate constants of conventional hot air fluid bed drying versus those produced with microwave assistance. Figures 1 through 4 depict the dramatic improvements microwave energy had on reducing the total drying time for aqueous dicalcium phosphate (fast-drying) and aqueous starch (slow-drying) granulations at both 30 and 60°C inlet air temperatures. Similar drying curves (not shown in this report) were also observed for granulations B and D. These basic drying curves demonstrate that the desired moisture ranges for every granulation type and every drying condition were obtained with the exception of a 30°C inlet air temperature and 0-W microwave power input. The inability to meet the targeted moisture range at this particular drying condition was expected, due to the very low energy (heat) input that was

Table II. Formulations[a]

Excipient	Loss[3] factor value[b]	(A) High-drying efficiency (%, w/w)	(B) Medium-drying efficiency (%, w/w)	(C) Low-drying efficiency (%, w/w)	(D) Nonaqueous (%, w/w)
Pregelatinized starch NF	0.41	0	37.5	75	75
Calcium phosphate, dihydrate, unmilled USP	0.01	75	37.5	0	0
Microcrystalline cellulose NF	0.10	20	20	20	20
Povidone USP	Unknown	5	5	5	5
Purified water[c]	6.1	25	25.8	33.3	—
Isopropyl alcohol[c]	2.9	—	—	—	30
Total		100	100	100	100

[a] For convenience, high-, medium-, and low-drying efficiency formulas are referred to as Formulas A, B, and C, respectively. Formula D identifies the nonaqueous granulation.
[b] The relative loss of energy from the applied electrical field due to the interaction (absorption) of the dielectric materials. Reported values are for the frequency of 2450 MHz.
[c] As a percentage of dry powder, not found in final product.

presented to the fluidized granulation. For this reason an equipment scale-up approximation was made at 100–125 W/liter of working capacity. However, recent work has shown that laboratory equipment is typically less efficient with respect to microwave usage because of its smaller cavity to product volume ratio (5). This would suggest that during scale-up of the MFBP, even lower microwave power inputs may be used effectively.

Table III summarizes the drying rate data collected for all four pharmaceutical granulations. The reported values for k_{obs} were all calculated using a first-order kinetic treatment (6). Review of the data presented in Table II shows remarkable similarity among the drying rates for either those granulations that were dried under the processing parameters of 60°C inlet air temperature and no microwave power input or those that received 30°C air inlet and a 250-W microwave power input. To explore this more fully, a comparison of energy usage was made between the two drying conditions (7). If we assume adiabatic conditions and a heat-limited (constant rate) drying mechanism, then the energy for evaporation must come from the inlet air (E_{air}) or the microwave energy contribution (E_{mw}). Taking the data for 30°C inlet air + 0 W as a base or "reference" state, we can express the additional drying capacity (DC) as

$$DC = E_{air} + E_{mw} \quad (1)$$

The experimental observation is that DC for 60°C + 0 W is approximately equal to 30°C + 250 W. Rewriting Eq. (1) gives

$$E_{air_{60}} + E_{mw_0} = DC = E_{mw_{250}} + E_{air_{30}} \quad (2)$$

By definition, the reference state $E_{air_{30}}$ equals 0, which simplifies Eq. (2) to give

$$E_{air_{60}} = E_{mw_{250}} \quad (3)$$

Table III. Comparison of Observed and Calculated Drying Rates at Various Inlet Air Temperatures and Microwave Power Inputs for Aqueous Dicalcium Phosphate, Dicalcium Phosphate/Starch, Starch, and Nonaqueous Starch Granulations (Formulations A–D, Respectively)[a]

	Formula A, DCP ($k = 0.0002P + 0.0012T$)		Formula B, DCP/starch ($k = 0.00012P + 0.0008T$)		Formula C, starch ($k = 0.0001P + 0.0006T$)		Formula D, starch/IPA ($k = 0.0003P + 0.0009T$)	
Watts	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}
				30°C				
0	0.019	0.036	0.013	0.024	0.008	0.018	0.016	0.027
250	0.096	0.086	0.044	0.054	0.034	0.043	0.087	0.102
500	0.140	0.136	0.083	0.084	0.048	0.068	0.148	0.177
750	0.157	0.186	0.107	0.114	0.078	0.096	0.257	0.252
1000	0.226	0.236	0.139	0.124	0.112	0.118	0.305	0.327
				60°C				
0	0.084	0.072	0.041	0.048	0.032	0.036	0.069	0.054
250	0.152	0.122	0.080	0.078	0.064	0.061	0.130	0.129
500	0.190	0.172	0.104	0.108	0.086	0.086	0.207	0.204
750	0.212	0.222	0.122	0.138	0.131	0.111	0.363	0.279
1000	0.233	0.272	0.165	0.168	0.156	0.136	0.389	0.354

[a] k values are reported as reciprocal minutes. P = constant microwave power input (Watts); T = constant inlet air temperature (°C).

The microwave (MW) contribution is available by using data for MW energy input (E_i) and reflected power (E_l) in Eq. (4) including a conversion factor (K) for changing watts to kilojoules per minute.

$$E_{mw} = (E_i - E_l) * K \quad (4)$$

The energy contribution from inlet air can be calculated by comparing the specific enthalpy (H) of the inlet air with the reference condition (30°C + 0 W) and multiplying by the mass flow rate (M) of air to get an energy term expressed as kilojoules per minute.

$$E_{air} = (H_i - H_{30}) * M \quad (5)$$

Taking a data point (15 min) from the constant-rate section of the aqueous starch granulation experiments, use of Eqs. (4) and (5) gives

$$E_{air_{60}} = 15.2 \text{ KJ/min}$$
$$E_{mw_{250}} = 13.3 \text{ KJ/min}$$

The difference in the calculated values of $E_{air_{60}}$ and $E_{mw_{250}}$ was approximately 12.5%.

It is recognized that this simple comparison is only a "snapshot" of the drying process, but in light of the similarities between the observed drying rate constants, it does provide additional support of the phenomenon, and the cited difference between $E_{air_{60}}$ and $E_{mw_{250}}$ may be within experimental error. It should be noted that a critical analysis of the drying thermodynamics was beyond the scope of the presented work; however, such studies are recommended in order to sequence and characterize correctly the multiple energy components and pathways which make up the total energy balance of microwave fluid-bed drying.

For example, it is suggested by the authors that microwave energy is absorbed not only by the granulation but also by the fluidizing air and the moisture it contains. This gives possibilities of improved moisture capacity of the inlet air and additional convective heat transfer to the granulation by the elevated fluidizing gas temperature within the product loading bowl and expansion chamber. Loss of microwave energy would occur through a simple exhaust of fluidizing gas and vapor which has absorbed microwave energy or through heat loss to the "system."

A plot of the observed drying rate constant (k_{obs}) versus microwave power input was constructed in order to understand the relationship which exists between these two drying variables. Figure 5 illustrates that a linear relationship exists between the observed drying rate constant and the microwave power input for the aqueous starch granulation at an inlet air temperature of 30 and 60°C. Plots for the other three granulation types at both inlet air temperatures produced similar results.

Drying rate equations were also developed for each of the four granulation types. The variables subject to this particular analysis were the constant microwave power input and inlet air temperature. The results of this particular analysis are also reported in Table III. Review of the equations reported in Table III strongly indicates that inlet air temperature and microwave power input have near-equal influence on the observed drying rates. For example, when k_{calc} is

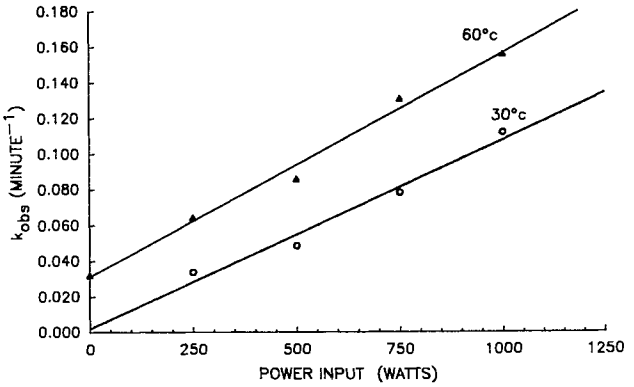

Fig. 5. Observed first-order drying rate constants vs microwave power input for aqueous starch granulation.

calculated for the aqueous dicalcium phosphate/starch granulation which was dried using a 250-W microwave power input and 30°C inlet air temperature, one obtains

$$k_{calc} = 0.00012P = 0.0008T = 0.00012(250) + 0.008(30) = 0.054 \text{ min}^{-1} \quad (6)$$

The k_{obs} was determined to be 0.044 min^{-1}. These drying rate equations make use of a basic engineering principle, namely, that the total energy inputted into the system is the sum of its partial energies expressed as either work, power, or heat energy. The energy received by the system may be expressed as the observed drying rate constant where

energy output (observed drying rate constant, k_{obs}) = microwave input energy, P + thermal input energy, T + energy that is lost to the system (7)

Our analysis showed that the change in drying rate constants (or slopes) is related to the nature of the granulating liquid (aqueous vs nonaqueous), the basic materials being dried (dicalcium phosphate vs starch), and the composition of matter (75%, w/w, dicalcium phosphate—Formula B vs 37.5%, w/w, dicalcium phosphate, 37.5%, w/w, starch—Formula C vs 75%, w/w, starch—Formula D).

Microwave Utilization

An important characteristic of the MFBP is its ability to direct, localize, and contain the inputted microwave energy within the drying areas of the unit, namely, the expansion chamber and product bowl. If successfully designed, the MFBP should promote microwave absorption (by the drying granulation) through microwave energy localization and maximize energy efficiencies by containing the energy and restricting the flow of free or reflected microwave energy from the drying chamber. Drying efficiency is dependent upon several factors such as the loss factor of the granulation excipients and granulating liquid, the microwave frequency, and the dryer design.

In order to characterize the drying efficiency of the MFBP, it was necessary to compare the total amount of microwave energy (kW * hr) which was inputted during drying to the amount of microwave energy that was reflected from the drying chambers back through the waveguide assembly to the magnetron. (As a reminder, the reflected

power was measured by the reverse coupler and power meter located adjacent to the generator.) The amount of microwave energy available for drying was determined indirectly by subtraction of total energy reflected (E_r) from total energy inputted (E_t). The following energy balance equation was derived for these calculations:

$$E_t = E_d + E_r \quad (8)$$

where E_t equals total microwave energy input (kW * hr), E_d equals total microwave energy available for drying (kW * hr), and E_r equals total amount of reflected microwave energy (kW * hr).

The value for E_t was obtained by multiplying the constant microwave power input by the observed drying time required to meet the targeted moisture range specified for a given formulation. The total loss of microwave energy through reflection (E_r) was calculated based upon the following assumptions: First, there was a linear increase in power loss between and within drying intervals; and second, there was no reflected power at time zero.

Determining the value of E_d, the microwave energy available for drying, was carried out by substituting the values of E_r and E_t into Eq. (8) and solving for E_d. The E_t, E_r, and E_d values for all four granulations (A, B, C, and D) that were dried using inputs of 250, 500, 750, and 1000 W and constant inlet air temperatures of 30 and 60°C are reported in Table IV.

Based upon the data reported in Table IV, the following general observations were made.

1. As the constant microwave power input was in-

Table IV. Comparison of Inputted, Reflected, and Available Microwave Energy for Aqueous Dicalcium Phosphate, Dicalcium Phosphate/Starch, Starch, and Nonaqueous Starch Granulations[a]

Inlet air temperature (°C)	Constant power input (W)	Observed drying time (hr)	Total energy input (kW * hr)	Total reflected energy (kW * hr)	Total energy available (kW * hr)	Efficiency (available/input) * 100%
Formula A						
30	250	0.417	0.104	0.028	0.076	73.6
30	500	0.333	0.167	0.049	0.116	70.0
30	750	0.250	0.188	0.042	0.146	77.8
30	1000	0.183	0.183	0.042	0.141	77.0
60	250	0.250	0.062	0.012	0.048	75.3
60	500	0.208	0.104	0.017	0.088	84.1
60	750	0.183	0.138	0.025	0.113	82.2
60	1000	0.167	0.167	0.031	0.135	81.5
Formula B						
30	250	1.000	0.250	0.068	0.183	73.0
30	500	0.583	0.292	0.119	0.173	59.2[b]
30	750	0.417	0.313	0.099	0.214	68.4
30	1000	0.333	0.333	0.106	0.227	68.1
60	250	0.500	0.125	0.035	0.091	71.7
60	500	0.417	0.208	0.063	0.146	70.0
60	750	0.333	0.250	0.071	0.179	71.7
60	1000	0.250	0.250	0.037	0.213	85.1
Formula C						
30	250	1.000	0.250	0.072	0.173	69.3
30	500	0.667	0.333	0.071	0.262	78.9
30	750	0.417	0.313	0.055	0.258	82.5
30	1000	0.292	0.292	0.074	0.218	74.7
60	250	0.500	0.125	0.026	0.099	79.1
60	500	0.417	0.208	0.057	0.152	72.8
60	750	0.250	0.188	0.028	0.159	84.9
60	1000	0.208	0.208	0.031	0.177	85.3
Formula D						
30	250	0.417	0.083	0.024	0.059	70.6
30	500	0.208	0.104	0.025	0.079	76.0
30	750	0.125	0.094	0.015	0.079	84.0
30	1000	0.100	0.100	0.013	0.087	87.0
60	250	0.250	0.063	0.018	0.045	71.4
60	500	0.167	0.083	0.017	0.066	79.5
60	750	0.125	0.094	0.018	0.076	80.4
60	1000	0.083	0.083	0.014	0.072	86.8

[a] Each granulation received various microwave power inputs at fixed inlet air temperatures of 30 and 60°C.
[b] Statistical outlier.

creased, the total amount of microwave energy (E_t) also increased.
2. As the value for E_t increased, the total amount of reflected microwave energy (E_r) increased.
3. As the value of E_t increased, the amount of microwave energy which was available for drying (E_d) also increased.
4. The efficiency of the dryer to utilize microwave energy was relatively constant both within and among formulations. Comparison of the means within each formula for 30 and 60°C air inlet air temperatures proved statistically insignificant ($P = 0.05$) as well as among formulations for the same inlet air temperature. In addition, the mean of all efficiency values at 30°C inlet air temperature ($X = 16$) was compared to the mean generated for 60°C, and again, no statistical significance was observed (at $P = 0.05$). A range of 68 to 86% ($X = 77\%$) of the total microwave energy inputted was available for heating or drying.

The first two observations were anticipated due to the constant microwave power input throughout the drying process. No attempts were made to "step down" the microwave power input as the moisture levels of the granulations decreased and the reflective microwave energy increased. The general upward trend in E_d values at higher microwave power inputs was suspected to be the result of microwave absorption by the vapor in the fluidizing gas. Exhaust air temperatures did increase as higher microwave power inputs were recorded; however, the design did not permit the recording of exhaust dew-point temperatures to confirm an increase in moisture capacity.

Influence of Microwave Energy on the Physical Characteristics of Fluid-Bed Dried Granulations

Particle/Granule Size Analysis

Particular attention was given to the aqueous dicalcium phosphate and starch granulations, as it was assumed that if no significant differences were noted in these formulations, then the 50:50 mixture of dicalcium phosphate and starch (Formula B) and the change to a nonaqueous medium (Formula D) would exhibit similar results. The average granule diameter values for the dried granulations (Formulas A and C) were statistically similar at both temperatures and all microwave power inputs and varied from a low of 331 to a high of 458 μm.

Loose and Tapped Bulk Densities

Comparison of the loose and tapped bulk densities of the dried aqueous starch and dicalcium phosphate granulations were examined and are reported in Table V. Although there were slight differences found within each formulation, these differences were considered within normal processing expectations. In addition, there were no observable trends, which further substantiates the negligible effect microwaves had on granule size and morphology in this study.

Granule Morphology

Like granule size, consistent and predictable granule morphology is a critical parameter to be considered when developing a reproducible process for the manufacture of solid oral dosage forms. Scanning electron micrographs (SEM) of the aqueous dicalcium phosphate and starch granulations showed no effect in granule morphology with the addition of microwave energy during the fluid bed drying process (see Figs. 6A and B). The SEMs lacked evidence of enlarged intragranular channels or surface pores within each formulation. The gross distribution and morphology of the excipients located on the granule surface were examined for evidence of thermal damage. Again, all the granulations tested resulted in no observations of thermal damage or localized fractures on the granule surface.

Table V. Loose and Tapped Bulk Densities at Various Microwave Inputs for Aqueous Dicalcium Phosphate (Formula A) and Starch (Formula C) Granulations at 30 and 60°C Inlet Air Temperatures

Microwave power (W)	Loose bulk density value (g/cm³)		Tapped bulk density value (g/cm³)		Percentage compressibility[a]	
	30°C	60°C	30°C	60°C	30°C	60°C
Formula A						
0	0.698	0.782	0.814	0.918	14.2	14.8
500	0.727	0.769	0.915	0.917	20.5	16.1
1000	0.707	0.780	0.919	0.910	23.1	14.3
Formula C						
0	0.603	0.515	0.769	0.655	21.6	21.4
500	0.526	0.595	0.666	0.721	21.0	17.5
1000	0.599	0.576	0.727	0.729	17.6	21.0

[a] [(Tap − Loose)/Tap] 100%.

Table Compression Characterization

Compression profiles were generated for both the aqueous dicalcium phosphate and the starch granulations. Peak applied (F_a) and transmitted (F_t) forces were extracted from these profiles and are reported in Table VI.

Review of the data demonstrates remarkable consistency within each formula and no identifiable trends between the F_a and the F_t forces among the various drying conditions. These observations strongly suggest that microwaves had little or no effect on the compression characteristics of Formulas A and C.

CONCLUSIONS

Drying Performance

The ability of the MFBP to combine the superior evaporative characteristics of fluidized drying with the direct and selective heating of microwave energy was demonstrated by improvements in observed drying rates for each formulation studied. At an inlet air temperature of 60°C, the observed drying rates increased by 3-, 4-, 5-, and 6-fold for Formulations A, B, C, and D, respectively, when 1000 W of microwave power was inputted. With conventional fluid-bed drying, at a low temperature of 30°C, the target moisture range was unattainable regardless of the type of granulation dried. When a microwave power input of 250 W or greater was

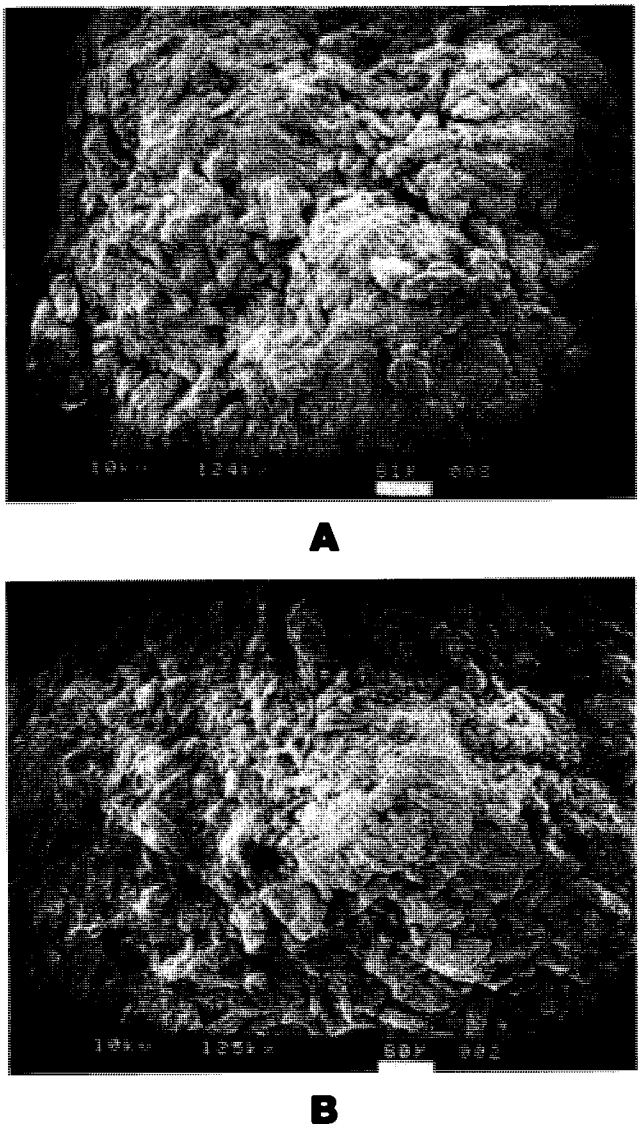

Fig. 6. Scanning election micrograph of an 850-μm aqueous starch granule (Formula C) dried in a fluid bed under the following conditions: (A) 60°C air inlet temperature and microwave power of 0 W and (B) 60°C air inlet temperature and microwave power of 1000 W. 125×; reduced to 75% for reproduction.

used, the targeted moisture range was easily achieved regardless of the inlet air temperature. For this reason, microwave power required for commercial scale-up of a MFBP unit is estimated to be 100–125 W/liter of working capacity.

In addition to producing significant improvements in drying rates, it was determined that a strong linear relationship existed between the observed drying rate constant (k_{obs} min^{-1}) and the constant microwave power input (W) at a prescribed constant inlet air temperature. This linear relationship enabled predictions to be made with respect to the microwave power requirements for selected drying rates.

Microwave Energy Performance

Microwave energy performance studies showed that a range of 68 to 86% of the total microwave energy (E_t) was available for heating and drying (E_d). As anticipated, at higher constant microwave power inputs, values for total energy (E_t) and total reflected energy (E_r) also increased since no attempts were made to attenuate the incoming microwave power as the moisture content of the granulation decreased. The phenomenon of E_d increasing as the incoming microwave power was increased may be the result of the fluidizing gas and vapor absorbing microwave energy. The heat energy can either be transferred to the granulation or lost to the "system" via the walls of the expansion chamber, product, etc., or exhaust air.

Table VI. Compression Characteristics of Aqueous Starch and Dicalcium Phosphate Granulations Dried Under Various Microwave and Inlet Air Conditions

Drying conditions	F_a[a] (kN)	F_t[b] (kN)
Formula A		
30°C air/1000 W	13.5	8.9
60°C air/0 W	13.8	8.9
60°C air/1000 W	10.2	6.9
Formula C		
30°C air/1000 W	84.9	38.7
60°C air/0 W	87.9	39.9
60°C air/1000 W	93.3	41.8

[a] F_a, applied force kilonewton = 224.8 lb.
[b] F_t, transmitted force kilonewton = 224.8 lb.

Physical Testing

Physical parameters such as particle size, loose and tapped bulk densities, granule morphology, and compressibility were evaluated for all dried granulations receiving microwave energy during the fluid-bed drying process. Particle size distribution and average particle diameters showed consistency within each formulation regardless of microwave power input. Also there were no differences in loose and tapped bulk densities. Scanning electron micrographs of granulations exposed to microwaves showed no evidence of morphological changes or thermal damage to the granule surface or interior. Compressibility profiles and the shape of their curves for each of the formulations exhibited remarkable consistency in the amount of both applied and transmitted forces (KN) required to compress a tablet. Effects on granulations compressibility were not found at exposure levels of 1000 W/800 g of wet granulation.

In summary, the present microwave fluid-bed processor design successfully combined the technologies of fluid-bed processing and microwave heating. The new equipment takes advantage of the fast evaporation rates, random particle travel, and multiprocessing capabilities of fluid-bed drying. Moreover, the disadvantages of the slower initial drying rates and nonuniform moisture distributions that are typically associated with fluid-bed drying are eliminated by the introduction of microwave energy. The MFBP also presents a safe and uncomplicated design for the introduction of microwaves to a conventional, laboratory-sized fluid-bed pro-

cessor. In addition, the use of a single-slotted tuner in the MFBP results in reduced energy losses and enhanced drying performance. The development and performance of the microwave-assisted fluid bed processor represent a significant advance in the drying of pharmaceutical materials.

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