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RESEARCH PAPER

A Process to Produce Effervescent Tablets: Fluidized Bed Dryer Melt Granulation

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ABSTRACT

The purpose of the present study was to apply melt granulation in a fluidized bed dryer (fluidized bed dryer melt granulation) to manufacture one-step effervescent granules composed of anhydrous citric acid and sodium bicarbonate to make tablets. This study permitted us to establish that such process parameters as concentrations of polyethylene glycol (PEG) 6000, residence times in the fluidized bed dryer, fineness of PEG6000, fineness of initial mixture effervescent systems, and efficiency of two lubricants markedly affect some granule and tablet characteristics. It is a dry process that is simple, rapid, effective, economical, reproducible, and particularly adapted to produce effervescent granules that are easily compressed into effervescent tablets.

Key Words: *Anhydrous citric acid; Effervescent granules; Effervescent tablets; Fluidized bed dryer; Melt granulation; PEG6000; Sodium bicarbonate.*

INTRODUCTION

To solve the problems caused by the manufacture of effervescent granules with the traditional process of granulation (1,2), defective flowability and cohesiveness in dry methods (3–5), loss of carbon dioxide, time and energy consumed in the wet method (6–9), in this work we studied a one-step process without solvent called fluidized bed dryer melt granulation (10–14) to produce effervescent granules of anhydrous citric acid and sodium bi-

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carbonate. Anhydrous citric acid–sodium bicarbonate, an effervescent system that is more efficient for the production of carbon dioxide than other potential effervescent systems, is the stem for which the one-stage process is the must difficult. Nevertheless, according to the results of our study, fluidized bed dryer melt granulation is an easy process for very rapid (35 min) production of effervescent granules that can be compressed into white, smooth, and bright tablets with sufficient strength and without such processing problems as sticking, capping, and friction.

EXPERIMENTAL

Materials

Anhydrous citric acid as moderately coarse powder (ACAmcp) and anhydrous citric acid as very fine powder (ACAvfp) were obtained from Roche (Tienen, Belgium). Sodium bicarbonate as moderately coarse powder (SBCmcp) and sodium bicarbonate as very fine powder (SBCvfp) came from Solvay (Brussels, Belgium). Contensio Chemicals (Marl, Germany) was the manufacturer of the polyethylene glycol 6000 as very fine powder (PEGvfp). Polyethylene glycol 6000 as flake (PEGf) came from Hoechst (Hohenbrunn, Germany). Sodium benzoate as very fine powder (SBvfp) was obtained from Mallinckrodt (St. Louis, MO), and silicone (Silbione) came from Rhone Poulenc (Paris). We made siliconed sodium benzoate as very fine powder (SSBvfp).

Moderately coarse powder (mcp) and very fine powder (vfp) were classified according to USP 23.

Manufacturing Methods

The process temperature of 55°C was imposed by the physicochemical constraints of the components; PEG6000 melts between 55°C and 63°C (15), and sodium bicarbonate becomes unstable when heated to about 50°C (16).

The formulas were made up with 1 kg of a stoichiometric effervescent system (ES) formed of anhydrous citric acid (43.2%)/sodium bicarbonate (56.8%) as moderately coarse powder or very fine powder, and a melt material was added (PEGvfp or PEGf). After mixing in a Turbula mixer (T2A, Basel, Switzerland) at 28 rpm for 10 min, the effervescent mixtures were put in a vertical fluidized bed dryer (Uni-Glatt, Binzen, Germany), adjusted first to 55°C ± 1°C and 123 m^3/hr. The granules were obtained by the linking of particles by melting PEG6000 for 5 min, 15 min, or 30 min. After cooling at 30% ± 3% relative humidity (RH) at 22°C ± 1°C for 30 min, the granules were screened with an oscillating granulator (Erweka FGS, Frankfurt, Germany) fixed at a moderate speed (II) and fitted with a 800-μm screen.

Formulations

The experimental formulas are given in Table 1. The proportions of PEG and sodium benzoate were calculated relative to 100 g of the effervescent system (e.g., formula A was PEGvfp = 1% of 100 g ES; SBvfp = 3% of 100 g of ES; total of formula A = 100 + 1 + 3 = 104).

Table 1

Formulations Used

Components	A	B	C	D	E
ACAmcp	43.2	43.2	43.2	43.2	—
ACAvfp	—	—	—	—	43.2
SBCmcp	56.8	56.8	56.8	56.8	—
SBCvfp	—	—	—	—	56.8
PEGvfp	1	3	5	—	6
PEGf	—	—	—	3	—

	A1	A2	B1	B2	C1	C2	D1	D2	E1	E2
SBvfp	3	—	3	—	3	—	3	—	3	—
SSBvfp	—	3	—	3	—	3	—	3	—	3

ACAmcp = anhydrous citric acid as moderately coarse powder; ACAvfp = anhydrous citric acid as very fine powder; SBCmcp = sodium bicarbonate as moderately coarse powder; SBCvfp = sodium bicarbonate as very fine powder; PEGvfp = polyethylene glycol 6000 as very fine powder; PEGf = polyethylene glycol 6000 as flake; SBvfp = sodium benzoate as very fine powder; SSBvfp = siliconed sodium benzoate as very fine powder.

Study Methods

The study methods permitted us to characterize the granules and tablets to choose the experimental formulas that had a satisfying technological quality: granule flowability of 10 s or less; granule ability to settle ($V_{10} - V_{500}$) of 20 ml or less; mean granule size between 400 μm and 520 μm; granule water content of 0.5% or less; white, smooth, and bright tablet aspect; tablet resistance to crushing of 70 to 120 N; tablet water content of 0.5% or less; tablet effervescence time of 180 s or less; limpid tablet solution aspect; tablet pH solution of 6 or less; tablet weight more than 2 g; tablet weight variation ±5%; and absence of such processing problems as sticking, capping, and sliding friction during compression.

Pharmaceutical Technical Procedures

Granule Flowability and Densities

Granule flowability and density were measured using 100 g of sample accurately weighed. The granule flowability was measured with a flow meter that consisted of a standardized funnel (EP, 3rd ed.) and a chronometer. Tapped densities d_{10} and d_{500} and ability to settle $d_{10} - d_{500}$ were determined using a volume meter (Jel/Stav 2003A, Ludwigshafen, Germany).

Granule Size Distribution

The granule size distribution was analyzed employing 100 g of granule and a vibrating Siever Retsch (Haan, Germany) (amplitude 1.5; 10 min) fitted with a European Pharmocopeial (3rd ed.) series of sieves (710, 500, 355, 250, 180, 125 μm). Mean granule size was determined graphically with a log-normal chart (15).

Granule Friability

The granule friability was determined with a 25 g sample accurately weighed of a fraction of granules from a Turbula mixer (28 rpm, 10 min) and a 180-μm sieve. The percentage of weight lost after mixing and sieving was calculated:

$$\frac{(\text{Weight before mixing and sieving} - \text{Weight after mixing and sieving})}{\text{Weight before mixing and sieving}} \times 100$$

Effervescence Time

The effervescence time was determined with 3 g of granules accurately weighed in a beaker containing 200 ml of distilled water at 20°C ± 1°C. The effervescence time was measured with a chronometer; the end of effervescence was reached when the solution became limpid and was without any particles.

Tableting

The granule property of forming tablets with a resistance to crushing between 70 N and 120 N when compressed in a single-punch press was studied. After mixing in a Turbula mixer at 28 rpm for 10 min, 700 g of effervescent granules with sodium benzoate or siliconed sodium benzoate, we obtained granule mixtures ready to be compressed into tablets.

Siliconed sodium benzoate was manufactured by mixing 600 g of very fine powder of sodium benzoate with 40 g of Silbione (silicone) for 30 min in a Kenwood planetary mixer at low speed (II). The mixture was screened with a 125-μm sieve. Silbione is an oil lubricant that could act to enhance the efficiency of sodium benzoate.

Tablets were manufactured with a single-punch press (Frogerais OA, Evry Lisses, France) equipped with chromed punches 24 mm in diameter in a workroom in which air conditioning was adjusted to 30% ± 3% RH and 22°C ± 1°C. Tablet weight, resistance to crushing (Erweka TBH 28, Heusenstamm, Germany), friability (Pharma Test PTF 1E, Haiberg, Germany), and effervescence time were evaluated using European Pharmacopeial methods (3rd ed.). Tablet water content, carbon dioxide content, pH solution, tablets, and solution aspects were evaluated with the same methods for the granule. Sticking to the punch faces and die wall, capping, and sliding friction at the die wall were also evaluated visually.

All formulas were compressed in constant conditions (depth of lower punch within the die was 6.98 mm, and the distance at which the upper punch penetrated the die was 6.04 mm) to select those tablets with weight above 2 g and resistance to crushing from 70 to 120 N without processing problems during compression.

Physicochemical Methods

Water Content

Water content was determined with 1 g of sample accurately weighed or with one pounded tablet; the material was dried in a desiccator containing activated silica gel. This method was used to avoid the alteration of sodium bicarbonate (16) and melting of PEG6000 (17). The loss on drying was calculated after a specified time of 4 hr:

$$\frac{(\text{Weight of sample before drying} - \text{Weight of sample after drying})}{\text{Weight of sample before drying}} \times 100$$

Solution Aspect and pH

Solution aspect and pH were determined with 3 g of granules or one tablet in 200 ml of distilled water at 20°C ± 1°C.The solution aspect of the sample was estimated organoleptically; the solution had to be limpid at the end of effervescence.

The pH was determined with an Aquadata APH 1000 pH meter.

Carbon Dioxide Content

The carbon dioxide content from 3 g of granules accurately weighed or one tablet in 100 ml of diluted sulfuric acid (R) was determined with a sensitive balance, Mettler PG 503 S (Viroflay, France) (18,19). The results were expressed as a loss of weight of the sample at the end of effervescence (mg CO_2 per gram of ES).

Granule Equilibrium Moisture Content

The granule equilibrium moisture content was made with samples of 3 g of granules in three microclimates containing a saturated salt solution of potassium nitrate (90% RH, 18°C), sodium chloride (71% RH, 18°C), and sodium nitrite (60% RH, 18°C). The first day and after 7 days in the microclimates, the percentage equilibrium moisture content (EMC%) (20) of the granules was measured with Aqualab CX2 (Paris) (Decagon).

RESULTS AND DISCUSSION

The results of the study are given in Tables 2 to 5 and Figs. 1 to 7. In the discussion, we investigate the influence of the following process parameters on the granule and tablet characteristics:

1. Concentrations of PEG6000 of two finenesses (very fine and flaked powder)
2. Three residence times in the fluidized bed dryer (5, 15, and 30 min)
3. Two finenesses of effervescent systems (moderately fine and very fine powder)
4. Two lubricants (sodium benzoate and siliconed sodium benzoate)

Particle Size Distribution and Water Content of Raw Materials

We determined the particle size distribution and water content of the raw materials. According to the results in Table 2, we can say that, for any raw material, the greater the subdivision of particles, the greater their surface area (21). For very fine powder and moderately coarse powder of the ES, the particle size distribution of the components was close; this allows homogeneous mixing. The low water content of the raw materials is in accordance with the manufacturing requirements for effervescent forms (22,23).

Table 2

Results of Particle Size Distribution and Water Content of Raw Materials

Raw Materials	Particle Size Distribution (% w/w)	Water Content (%w/w)
ACAmcp	Over 355 μm = 12	
	355 to 180 μm = 84	0.05
	Under 180 μm = 4	
ACAvfp	Under 125 μm = 100	0.09
SBCmcp	Over 355 μm = 17	
	355 to 180 μm = 60	0.03
	Under 180 μm = 23	
SBCvfp	Under 125 μm = 100	0.06
PEGvfp	Under 125 μm = 100	0.04
PEGf	Over 1 μm = 95	0.02
	Under 1 μm = 5	
SBvfp	Under 125 μm = 100	0.05
SSBvfp	Under 125 μm = 100	0.05

ACAmcp = anhydrous citric acid as moderately coarse powder; ACAvfp = anhydrous citric acid as very fine powder; SBCmcp = sodium benzoate as moderately coarse powder; SBCvfp = sodium bicarbonate as very fine powder; PEGvfp = polyethylene glycol 6000 as very fine powder; PEGf = polyethylene glycol 6000 as flake; SBvfp = sodium benzoate as very fine powder; SSBvfp = siliconed sodium benzoate as very fine powder.

Granules Made with Moderately Coarse Powder of Anhydrous Citric Acid and Sodium Bicarbonate

We have studied the influence of concentrations of PEGvfp (1%, 3%, and 5%) and PEGf (3%). For all concentrations of PEG6000, we studied the influence of residence time in the fluidized bed dryer (5 min, 15 min, and 30 min).

Influence of Process on Granule and Tablet Characteristics

According to the results, we distinguished three groups of granule and tablet characteristics: those not affected, those slowly affected, and those markedly affected. As shown in Table 3, physicochemical properties

Table 3

Granule and Tablet Characteristics Not Affected by the Process

Granule characteristics	
Flowability (s) ($n = 3$)	9 (1)[a]
Ability to settle ($V_{10} - V_{500}$) (ml) ($n = 3$)	7 (1)
Water content (%w/w) ($n = 3$)	0.02 (0.001)
Carbon dioxide content (mg CO_2/g granules) ($n = 5$)	292 (2)
pH ($n = 6$)	5.64 (0.06)
Solution aspect	Limpid
Characteristics of tablets compressed with 2.8% sodium benzoate	
Tablet aspects	Smooth and bright
Water content (%w/w) ($n = 3$)	0.02 (0.01)
Carbon dioxide content (mg CO_2/g tablet) ($n = 5$)	291 (3)
pH ($n = 6$)	5.64 (0.02)
Solution aspect	Limpid
Characteristics of tablets compressed with 2.8% siliconed sodium benzoate	
Tablet aspects	Smooth and bright
Water content (%w/w) ($n = 3$)	0.02 (0.02)
Carbon dioxide content (mg CO_2/g tablet) ($n = 5$)	292 (3)
pH ($n = 6$)	5.61 (0.04)
Solution aspect	Limpid

[a] Mean (standard deviation), n = number of determinations.

of granules and tablets such as water content, carbon dioxide content, solution pH, and solution aspect were not affected by the process since the values obtained were the same as those of initial effervescent mixture powders before granulation (water content 0.02%, carbon dioxide content 292 mg CO_2/g effervescent powder, solution pH 5.6, limpid solution aspect). As the physicochemical properties of granules never changed relative to the initial mixture powders before granulation, this is proof that the process did not deteriorate the initial components of the formulas. So, fluidized bed dryer melt granulation is a soft and more advantageous method compared with the wet methods.

As for the granule and tablet characteristics that were slowly affected, the granule effervescence time was less than that of the initial effervescent mixture powder before granulation (e.g., 181 s vs. 191 s). The granule flowability was increased over that of the initial effervescent mixture powder (e.g., 9 s vs. 7 s). However, the values of effervescence time, granule flowability, and tablet effervescence time (e.g., A1 = 71 s, A2 = 59 s) in formula A are the same for other formulas.

Figures 1 to 7 show that granule and tablet characteristics were markedly influenced by the concentrations of PEG6000, fineness of PEG6000, fineness of the ES, and residence times in the fluidized bed dryer.

Mean Granule Size

The increase of mean granule size (Fig. 3) followed the increase of concentrations of PEG6000, fineness of PEG6000, coarseness of initial mixture effervescent powder, and the residence times in the fluidized bed dryer.

The use of 3% flaked PEG6000 in moderately coarse effervescent powder (formula D) gave granules with a mean size that was less than that of granules made with 3% of very fine powder of PEG6000 in moderately coarse effervescent powder (formula B). This observation shows the influence of fineness of PEG6000 on the granulability of the ES. This can be explained by the proposed mechanism of melt granulation (Fig. 2): Since melt granulation is related to the linking of particles by melting PEG6000 through the bed of initial effervescent mixture to give

Table 4

Equilibrium Moisture Content (%) in the Initial Effervescent Mixing and in the Granules

	Initial Effervescent Mixing			Effervescent Granules		
Microclimates	1st Day	7th Day	Variation (%w/w)	1st Day	7th Day	Variation (%w/w)
90% RH, 18°C	0.24 (0.01)[a]	0.74 (0.02)	208	0.21 (0.02)	0.57 (0.01)	171
71% RH, 18°C	0.24 (0.01)	0.39 (0.01)	63	0.21 (0.02)	0.29 (0.02)	38
60% RH, 18°C	0.24 (0.01)	0.32 (0.01)	33	0.21 (0.02)	0.21 (0.01)	0

[a] Mean (standard deviation), $n = 3$.

Table 5

Results of the Process Reproducibility

Granule Characteristics	Batch 1	Batch 2	Batch 3
Flowability (s) ($n = 3$)	8 (1)[a]	9 (1)	8 (1)
Ability to settle ($V_{10} - V_{500}$) (ml) ($n = 3$)	7 (1)	6 (1)	7 (1)
Water content (%w/w) ($n = 3$)	0.02 (0.001)	0.02 (0.002)	0.02 (0.001)
Tapped density (d_{500}) ($n = 3$)	0.78 (0.02)	0.78 (0.01)	0.78 (0.01)
Mean granule size (μm)	510	510	510
Granule friability (%w/w) ($n = 3$)	0.5 (0.1)	0.6 (0.2)	0.6 (0.01)
CO_2 content (mg CO_2/g of granules) ($n = 5$)	291 (4)	292 (3)	292 (5)
Effervescence time (s) ($n = 6$)	180 (3)	180 (2)	181 (2)
pH ($n = 6$)	5.62 (0.02)	5.61 (0.03)	5.61 (0.02)
Solution aspect	Limpid	Limpid	Limpid
Characteristics tablets compressed with 2.8% siliconed sodium benzoate			
Tablet aspects	Smooth and bright	Smooth and bright	Smooth and bright
Weight (g) ($n = 20$)	2.33 (0.02)	2.32 (0.03)	2.32 (0.02)
Resistance to crushing (N) ($n = 10$)	113.4 (3.5)	112.6 (5)	113.1 (43)
Water content (% w/w) ($n = 3$)	0.02 (0.002)	0.02 (0.002)	0.02 (0.002)
Effervescence time (s) ($n = 6$)	71 (3)	72 (3)	72 (3)
CO_2 content (mg CO_2/g tablet) ($n = 5$)	281 (4)	283 (3)	283 (43)
Friability (%w/w)	0.4	0.4	0.5
pH ($n = 6$)	5.63 (0.04)	5.63 (0.04)	5.62 (0.04)
Solution aspect	Limpid	Limpid	Limpid

[a] Mean (standard deviation), n = number of determinations.

aggregates that form granules after cooling and screening, the finer the PEG6000, the greater the surface area it can cover.

Formulas containing very fine powder of ES (formula E) need more powdered PEG6000 to make a granule than formulas containing moderately coarse powder of ES (formula B) (e.g., 6% in formula E vs. 3% in formula B). This observation demonstrates the influence of fineness of ES on the growth of granules. The explanation can also refer to the proposed mechanism of melt granulation: Since the degree of subdivision of the particles of very fine powder of ES is greater than that of moderately coarse powder of ES, the surface area to cover by PEG is greater, and the consumption of PEG6000 is increased.

Granule Tapped Density

The decrease of tapped density (Fig. 3) followed the increase of concentrations of PEG6000, fineness of PEG6000, and fineness of the initial effervescent mixture. The effect of residence times was not constant. The decrease of tapped density can be explained by the increase of the mean granule size when the process parameters varied.

Granule Friability

The decrease of granule friability (Fig. 4) followed the increase of concentrations of PEG6000, fineness of PEG6000, and fineness of initial effervescent mixture. The effect of residence times was not constant (except

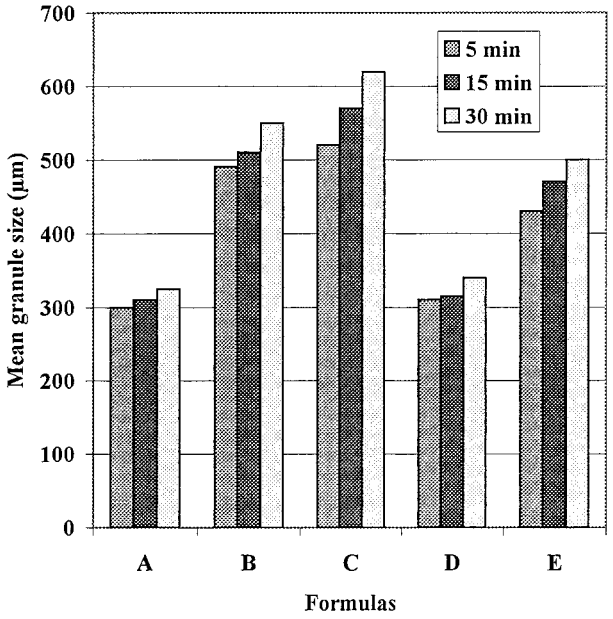

Figure 1. Influence of process on mean granule size.

with formula B, in which the decrease of granule friability followed the increase of residence time). As PEG6000 acts as a binder, the greater the concentrations of PEG6000 were, the greater the hardness of the granule was.

Tablet Weight

As shown in Fig. 5, the tablet weight decreased when the following process parameters increased: concentration of PEG6000, fineness of PEG6000, fineness of initial mixture ES, and residence time. This could be due to the fact that the granule size increased when the process parameters increased and induced the decrease of tapped density, which provoked the decrease of tablet weight.

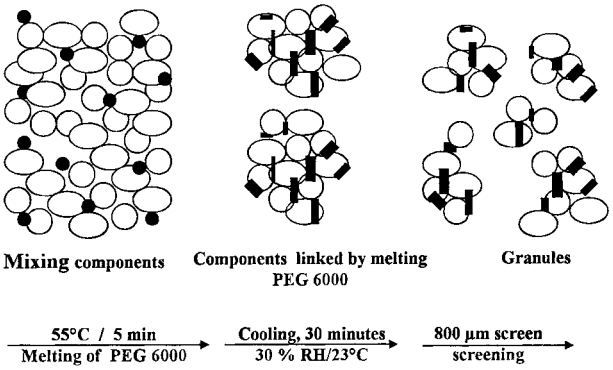

Figure 2. Mechanism of melt granulation: After mixing and putting components in fluidized bed dryer, PEG6000 melts and links the particles through the bed of the effervescent mixing to form aggregates that, after cooling and screening, give granules (○ anhydrous citric acid; ○ sodium bicarbonate; ● PEG6000).

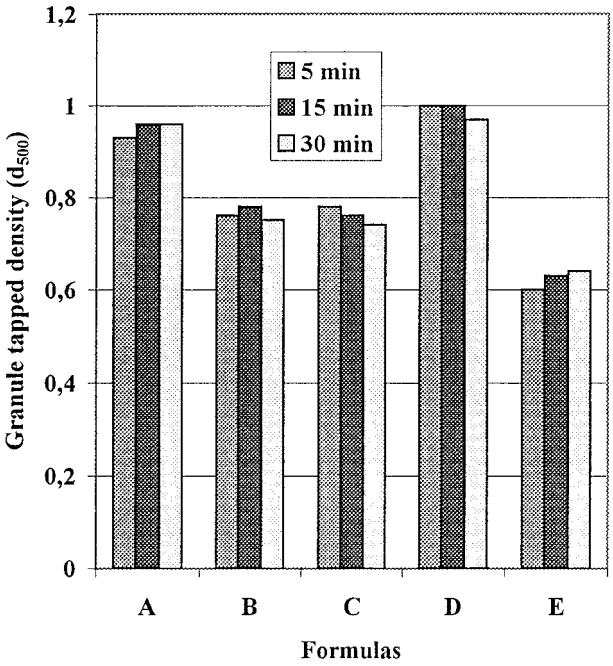

Figure 3. Influence of process on granule tapped density d_{500}.

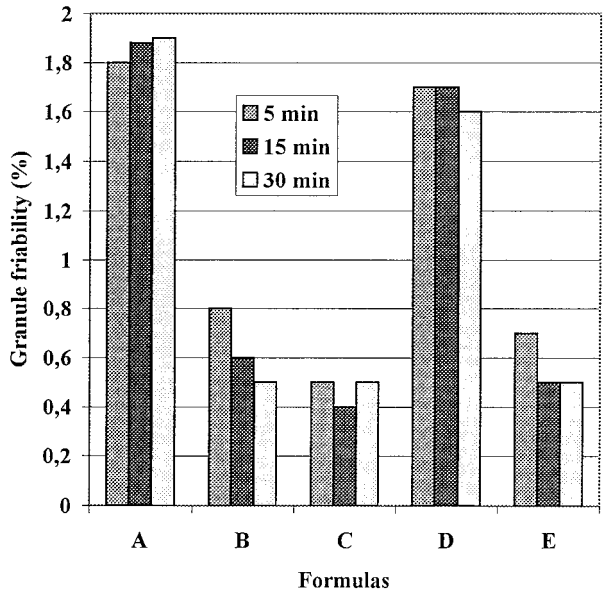

Figure 4. Influence of process on granule friability.

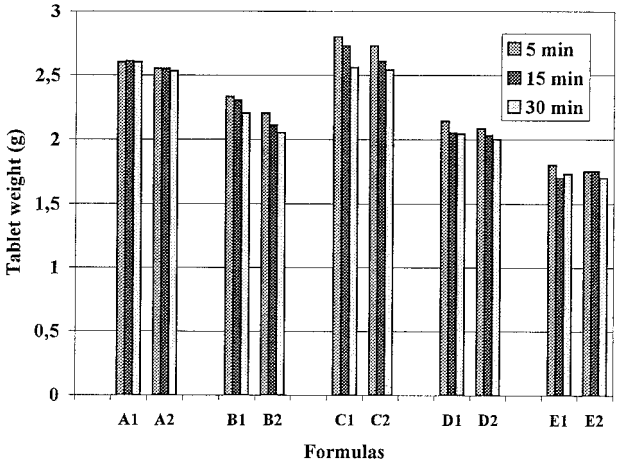

Figure 5. Influence of process on tablet weight.

The use of siliconed sodium benzoate instead of sodium benzoate avoided the sticking and friction, but slowly decreased the weight of the tablets.

In all formulas studied, the coefficient of variation (CV%) of tablet weight ranged from 0.45% to 1.15%. This can be explained by the fact that flowability and ability to settle ($V_{10} - V_{500}$) of granules ready to be compressed into tablets was good (7 s and 6 ml, respectively).

Tablet Resistance to Crushing

As shown in Fig. 6, it is possible to manufacture tablets with granules made with formulas A and B even if

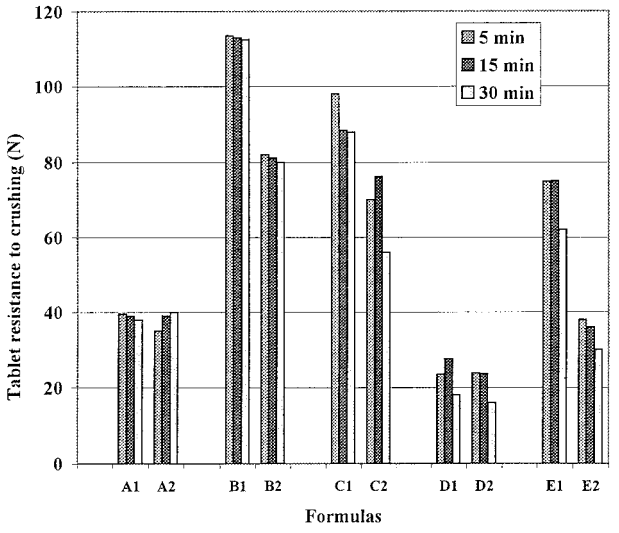

Figure 6. Influence of process on tablet resistance to crushing.

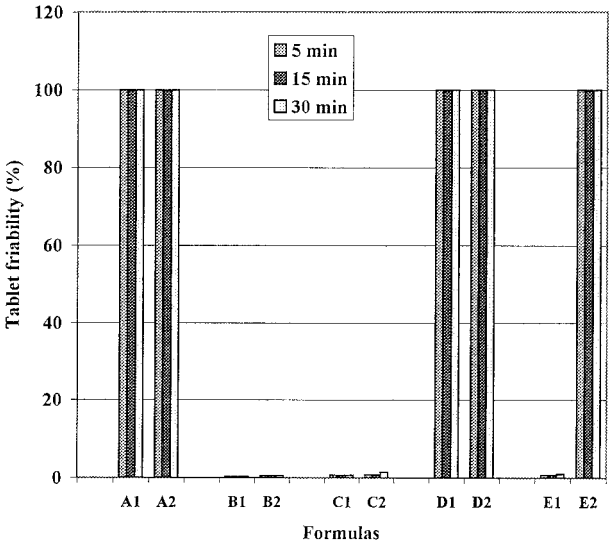

Figure 7. Influence of process on tablet friability.

their resistance to crushing is too poor and even when it is impossible with initial effervescent mixture before granulation because of sticking, capping, and friction. According to this observation, we can say that the process enhances the compressibility of the initial effervescent mixture.

The resistance to crushing reached the maximum (113 N) with B1 melt granulated for 5 min. The appearance of sticking required the use of a lubricant that is more efficient. The use of siliconed sodium benzoate avoided the sticking and friction, but decreased the resistance to crushing of the tablet (e.g., for formula B, 113 N vs. 82 N). This observation is a general characteristic of an efficient oil lubricant, which has the drawback of decreasing the resistance to crushing of the tablet (24). So, 5 minutes is a good residence time for the fluidized bed dryer melt granulation since 15 and 30 min did not increase the resistance to crushing. Siliconed sodium benzoate appeared to be a good lubricant since tablets had a resistance to crushing (82 N) that is sufficient to withstand mechanical handling and transport.

With formula C, the resistance to crushing of the tablet was inferior to that of tablets made with formula B, and the appearance of sticking was not avoided by using siliconed sodium benzoate. Therefore, the excess of PEG6000 in a moderately coarse ES provoked the sticking even if an efficient lubricant was used. This observation shows that 3% of very fine powder of PEG6000 was an efficient concentration in the moderately coarse powder ES.

Tablet Friability

As shown in Fig. 7, tablets made with formulas A, D, and E2 were totally friable (friability = 100%). Formulas B, C, and E2 had good friability, ranging from 0.3% to 1.5%.This observation was foreseeable according to the tablet resistance to crushing. Tablets made with formulas A and D were totally friable because of the lack of PEG, which acts as a binder. Tablets made with formula E2 were totally friable because of the presence of siliconed sodium benzoate.

Granules Made with Very Fine Powder of Anhydrous Citric Acid and Sodium Bicarbonate

In the very fine powder ESs, we studied the influence of concentrations of PEG6000 very fine powder (1%, 3%, 6%, 9%, 15%). For all concentrations, we studied the influence of residence times in the fluidized bed dryer (5 min, 15 min, and 30 min).

We checked if, with an ES of very fine powders of anhydrous citric acid and sodium bicarbonate, it was possible to manufacture a granule with a concentration of powdered PEG6000 at less than 6%. A very fine powder ES needs more very fine powder of PEG6000 than a moderately fine powder ES (e.g., 6 % versus 3%) (Fig. 2). With concentrations of 9% and 15% of very fine powder PEG6000, after cooling, we obtained a strong mass that could not be screened with our apparatus.

With 6% very fine powder PEG (formula E), granule characteristics to make tablets were better than those of the initial very fine powder ES; the modification of particle size distribution of the initial very fine powder ES induced the increase of mean granule size (e.g., 430 μm vs. 75 μm). The growth of particles induced the decrease of flowability (e.g., 8 s vs. infinite), ability to settle ($V_{10} - V_{500}$) (e.g., 10 ml versus 34 ml), tapped density (e.g., 0.61 versus 0.89), effervescence time (e.g., 176 s vs. 184 s). The use of sodium benzoate as a lubricant gave light tablets with an acceptable resistance to crushing (e.g., 75 N) (Fig. 6) and with sticking appearing during compression. The siliconed sodium benzoate eliminated sticking during compression, but the tablets became totally friable during the friability test (Fig. 7).

Hygroscopic Properties of Formulation

For study of the hygroscopic properties, we chose formula B2 melt granulated for 5 min; these tablets possessed a technological quality satisfactory for the evaluation of the equilibrium moisture of effervescent granules.

According to the results in Table 4, in all microclimates studied, the variation in percentage of equilibrium moisture content after 7 days for effervescent granules ready to be compressed into tablets was less than that of the initial effervescent mixture (e.g., at 90% RH and 18°C, 171% vs. 208%; at 71% RH and 18°C, 38% vs. 63%). At 60% HR and 18°C, the variation in percentage of equilibrium moisture content after 7 days was nothing, even when that of the initial mixture was 33%. So, effervescent granules ready to be compressed into tablets are nonhygroscopic up to 60%RH at 18°C. This observation can be explained as follows. Since granulation increases the particle size, the contact area of the particle with the atmosphere decreases. As PEG6000 is a nonhygroscopic material (class I hygroscopicity) (21–24), when it covers the granule, it reduces the contact area of the initial materials with the atmosphere. The hydrophobic property of siliconed sodium benzoate acts as a moisture repellent. Therefore, the studied effervescent granules ready to be compressed into tablets can be handled without moisture intake at an atmosphere up to 60% RH at 18°C.

Reproducibility of Fluidized Bed Dryer Melt Granulation

Three batches of formula B2 melt granulated for 5 min were manufactured to check the reproducibility of the process. According to the results in Table 5, the granule and tablet characteristics were almost the same for the three batches studied. Thus, the data established that the process is reproducible.

CONCLUSION

For all formulas studied, the increase of concentrations of PEG6000 and residence times in the fluidized bed dryer enhanced the compressibility of the initial effervescent mixture and induced the modification of the particle size distribution, characterized by the increase of mean granule size. Physicochemical properties of granules and tablets were not affected by the process.

The increase of PEG6000 concentration acted to increase the surface of the initial effervescent mixture able to be covered and to increase the resistance to crushing of the tablets. During compression with sodium benzoate as a lubricant, the higher the concentrations of PEG6000 were, the more precocious the appearance of sticking was. The appearance of capping during compression of formulas made with 1% powdered PEG6000 and 3% flaked PEG6000 was due to the lack of PEG6000, which

acts as a binder. The efficient concentrations of PEG6000 are related to the fineness of the initial effervescent mixture: The finer the effervescent mixture was, the greater the concentrations of PEG6000 were.

The efficiency of PEG6000 was related to its fineness: The greater the subdivision of particles of PEG6000 was, the greater its efficiency was.

The increase of residence times in the fluidized bed dryer increased the homogeneous particle linking by melting PEG6000 through the bed of the initial effervescent mixture for all concentrations of PEG6000 studied; the weight of tablets was related to the residence times in the fluidized bed dryer. When the time in the fluidized bed dryer increased, the weight of the tablet decreased because of the increase of particle size, which induced the decrease of tapped density.

In all cases, the effervescence time decreased from the initial mixture ES to the granule and tablet (190 s, 180 s, and 71 s, respectively). These data show the predominance of production of the effervescent tablet form on effervescent granule form and effervescent powder form.

The fact that, in all cases, the physicochemical properties of granules and tablets were not affected, is the proof that fluidized bed dryer melt granulation respects the stability of the initial components.

The latent period before screening (cooling) is very important because, when the screening is precocious (less than 30 min at 30% ± 3% RH and 22°C ± 2°C after removal from the fluidized bed dryer), the granules adhere to each other to form aggregates, which increase and make flowability discontinuous and act to increase the weight variation of the tablets. When tableting with granules precociously screened, the tablets were pasty instead of being breakable during the test for resistance to crushing test. Therefore, 30 min is the necessary time to make the melting PEG6000 in the granule become harder.

According to the formulas studied, only formula B2 gave tablets that satisfied the defined technological quality (i.e., good weight and good resistance to crushing, e.g., residence time 5 min = 2.2 g and 82 N; 15 minutes = 2.11 g and 81.1 N; 30 min = 2.05 and 80 N) without processing problems during compression. We can also say that fluidized bed dryer melt granulation is a simple and rapid process because, after 5 min of residence time in the fluidized bed dryer and 30 min of cooling (35 min total), the granules were ready to be compressed into tablets.

We next plan to investigate the application of fluidized bed dryer melt granulation for granulation of one-stage mixtures of effervescent system and active ingredients to make tablets.

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