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RESEARCH PAPER

Influence of Manufacturing Process on Tabletting Ability of Powder: Comparison Between Blending, Grinding, and Spray Drying of Two Formulations Made of Theophylline and Lactose/Cellulose or Cellactose®

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ABSTRACT

Three manufacturing processes were applied to two formulations composed of 20% anhydrous theophylline associated with either 20% microcrystalline cellulose and 60% lactose or 80% Cellactose®. The processing method (dry blending, grinding, or spray drying) and the formulation were investigated through the comparison of the physical and flow characteristics and the compactibility of the end products. The results demonstrated that the formulation had a major effect on the mechanical properties, with binary blends exhibiting a higher resistance than ternary ones, whereas flow properties and densification depended on the process. Nevertheless, it was also observed that spray drying decreased the difference between the mechanical properties of the two formulations, probably by modifying the texture of the Cellactose® in suspension.

Key Words: *Anhydrous theophylline; Cellactose®; Cellulose/lactose mixture; Compaction; Manufacturing process*

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INTRODUCTION

Processing of primary particles into secondary particles or aggregates—depending on the process applied—is commonly performed in order to modify the properties of the products (size adjustment, flowability improvement, compactibility enhancement). It is documented in the literature that granulations of one specific formulation might show different compactibility when the granulations have been processed differently (1–9). Also direct compression excipients are available, increasingly composed of several components with differing properties. This is the case for Cellactose®, that combines lactose and cellulose by co-processing. Such integrated excipients may offer advantages such as stability against demixing, limited ingredients in the formulation, and easier packing of the particles in the early stages of compaction. The possibilities available for the production of tablets are then numerous, leading to products with varying characteristics. Thus, a better knowledge of how the parameters of the manufacturing process modify the tabletting behavior is important.

The objective of this study was to elucidate the influence of the manufacturing process on the physical, rheological, and mechanical properties of the resulting products; the incidence on the lyoavailability of the drug has been discussed in a previous work (10). Two mixtures were compared: a ternary blend composed of cellulose (20%), α-lactose monohydrate (60%), and anhydrous theophylline (20%); and a binary blend consisting of 80% Cellactose® and 20% anhydrous theophylline. The two formulations have the same chemical composition but different technological properties due to the presence of the co-processed excipient in the binary mixture. Several manufacturing techniques were applied (dry blending, grinding, and spray drying) that permitted us to analyze the effect of parameters such as particle size (dry blending/grinding) and excipient characteristics (binary vs. ternary blend) and to compare dry and wet processes (grinding/spray drying).

EXPERIMENTAL

Materials

Anhydrous theophylline was obtained from Boehringer-Ingelheim, Ingelheim, Germany. It is a well-characterized active ingredient used as a bronchiodilatator in breath affections. Lactose and microcrystalline cellulose are two common pharmaceutical excipients: Pharma 200/70 α-lactose monohydrate was obtained from S.A. du Sucre de Lait, Sains du Nord, France and Avicel PH 101 microcrystalline cellulose was obtained from FMC Corporation, Newark, DE. Cellactose® was supplied by Meggle Milchindustrie GmbH & Co., Germany. Physical characteristics of the materials are highlighted in Table 1.

If lactose and cellulose are currently used in compression after dry or wet granulation, Avicel PH 101 and Cellactose® are specially designed for direct compression.

Two formulations were analyzed:

- A *ternary mixture* composed of 20% anhydrous theophylline, 20% microcrystalline cellulose, and 60% α-lactose monohydrate.
- A *binary mixture* composed of 20% anhydrous theophylline and 80% Cellactose®.

For each formulation, three manufacturing processes were compared:

- *Direct blending* of raw materials, using a Turbula Type T2C (Bachofen AG, Uster, Switzerland) reciprocating tumble mixer set at 70 rpm for 5 min.

Table 1

Physical Characteristics of the Raw Materials

	Anhydrous Theophylline	Pharma 200/70	Avicel PH 101	Cellactose®
Specific surface area (m^2/g)	0.722	0.171	1.166	0.500
Pycnometric density (g/cc)	1.493	1.534	1.534	1.529
Bulk density (g/cc)	0.267	0.844	0.303	0.399
Median diameter (μm)	17	236	71	113

- *Grinding* after blending, using a planet grinder Fritsch Pulverisette S (Roucaire Society, France).
- *Spray drying* of a 15% aqueous suspension of dry blends. The spray-drying apparatus employed was a laboratory type (Büchi 190 Mini Spray Dryer, Büchi, Switzerland).

Compositions and processes with their notations are given in Table 2.

Methods

Physico-Chemical Characteristics

- *Particle morphology and texture* of the products were observed using scanning electron microscopy (SEM) (Hitachi S 2500, Hitachi, Tokyo, Japan).
- *Particle size distribution* was assessed by laser diffraction (Malvern Mastersizer, Malvern Instruments, Malvern, UK).
- *Specific surface area* of the powders and compacts was determined by the gas adsorption technique using nitrogen as condensable gas (Gemini 2360, Micromeritics Instruments Inc., Norcross, GA). The samples were first degassed under vacuum for 24 hr at 50°C (VacPrep 61, Micromeritics Instruments Inc., Norcross, GA).
- *Porosity* was investigated by mercury porosimetry measurements (Micromeritics 9300 Porosimeter, Micromeritics Instruments Inc., Norcross, GA). The samples were first degassed at room temperature under a pressure of 5 Pa. The limiting pore size for mercury penetration was calculated from the penetration pressure assuming circular pore openings, a surface tension for mercury of 485 mN/m, and a contact angle between mercury and the material of 130°. Penetration pressures between 0.001 and 40 MPa were used.
- Powder *pycnometric density* was determined using a helium pycnometer (AccuPyc 1330, Micromeritics Instruments Inc., Norcross, GA), after degassing under vacuum for 24 hr at room temperature.
- *Bulk density*, d (g/cc), was calculated from the volume V (cc) occupied by a known mass of powder m (g): $d = m/V$. The volume of the powder was measured using a volumetric cylinder.

Flow Characteristics

The evolution of the apparent density of a powder bed in a volumetric cylinder subjected to successive vertical shocks (taps) was followed utilizing the Erweka Model SVM2 unit (Erweka GmbH, Heusenstamm, Germany). The reduction in powder volume, estimated by the parameters described as follows, is indicative of packing ability and flowability:

- A difference between the volumes after 10 and 500 taps ($V_{10} - V_{500}$) larger than 20 cc indicates the presence of air between the particles and consequently a high compressibility which compromises the quality of flowability.
- The packing kinetic, represented as $\log(V_0/V) = f(\text{taps})$, where V_0 is the initial powder volume and V the volume after tapping, indicates good rheological properties when the curve levels off rapidly.

Uniaxial Compression and Axial Compressive Strength

The materials were compacted in a die with flat-faced punches, at pressures varying from 10 to 160 MPa using a uniaxial press controlled by a

Table 2

Summary of the Products Under Study

	Dry Mixtures (%)		Ground Mixtures (%)		Spray-Dried Mixtures (%)	
	Binary 1D	Ternary 2D	Binary 1G	Ternary 2G	Binary 1S	Ternary 2S
Anhydrous theophylline	20	20	20	20	20	20
α-Lactose monohydrate		60		60		60
Microcrystalline cellulose		20		20		20
Cellactose®	80		80		80	

computer (Lloyd Instruments 6000R, Lloyd Instruments Ltd., Segensworth East, UK). The die (15 mm in diameter and 45 mm in height) was manually filled with an accurate mass of powder, calculated from the bulk density, so as to correspond to the cell volume of 7.95 cc. Magnesium stearate was used as the external lubricant. The application of the force was kept constant at 1.14 mm/min.

Mechanical properties of the resulting compacts were determined directly after compaction, by axial compressive strength. Measurements were performed using the uniaxial Lloyd press and consisted of applying a force F (N), at a rate of 0.38 mm/min, in the same direction as the consolidation pressure until rupture occurred. The apparent resistance, R (MPa), was calculated according to:

$$R = \frac{4F}{\pi D^2}$$

where D is the compact surface diameter (mm). The given values are the means of three measurements.

RESULTS AND DISCUSSION

Powder and Agglomerate Characteristics

Physical Properties

The observation of particles and agglomerates issued from the different manufacturing processes reveals a number of differences with respect to shape, surface texture, and geometry, as noted in Fig. 1:

- The dry mixtures exhibit heterogeneous particles with varying shapes and sizes corresponding to the different constituents: particles of lactose are angular in shape, those of Avicel are acicular, and theophylline appears to be platelike.
- The ground powders consist of agglomerated particles (40 to 80 μm) mixed with fines (0.1 to 1 μm).
- The spray-dried products are constituted of spherical particles stuck together to form agglomerates. The particle sizes vary between 0.5 and 7 μm.

Physical parameters are presented in Table 3. The ground mixtures develop a specific surface area significantly higher than that of the other products due to the small size of their particles and their irregular surface (Fig. 1). By contrast the round spray-dried particles appear to be very smooth and free of defects.

The median diameters are given as indicative parameters since bimodal populations were evidenced by the granulometric distributions. Furthermore, SEM observations revealed the presence of agglomerates; this indicates that these results have to be considered as an overestimation of the particle sizes.

Flow Properties

All packing kinetic curves (Fig. 2) are characterized by a quite similar initial slope. Dry mixtures appear to be less compressible products as they have the lowest plateau. Products can be identified according to their manufacturing process, but no difference was evidenced between formulations. The process effect appears to be the prevailing factor.

The values of $V_{10} - V_{500}$ complete this observation (Table 3.). The spray-dried mixtures have the worst flow properties with a value of $(V_{10} - V_{500})$ that indicates a high compressibility. The spherical shape of the spray-dried particles permits a fast packing of particles in the powder bed (high initial slope), but their small size contributes to the poor flow. The dry mixtures have good flow properties but, as expected, a reduction in particle size by grinding degrades the flow behavior of particles.

Densification

Analysis of the evolution of relative density in the powder bed as a function of the compression stress was assessed by the application of Heckel's empirical equation (11):

$$\ln\left(\frac{1}{1-\rho_r}\right) = K + BP$$

where ρ_r is the relative density of the compact and the constants K and B are determined by the intercept and slope of the linear region. The reciprocal of B corresponds to the yield pressure P_y that is used to determine the dominating deformation mechanisms of the powder.

As shown in Fig. 3, the Heckel plots indicate that the densification mechanism of the materials is more sensitive to the manufacturing process than to the formulation, with plastic deformation prevailing

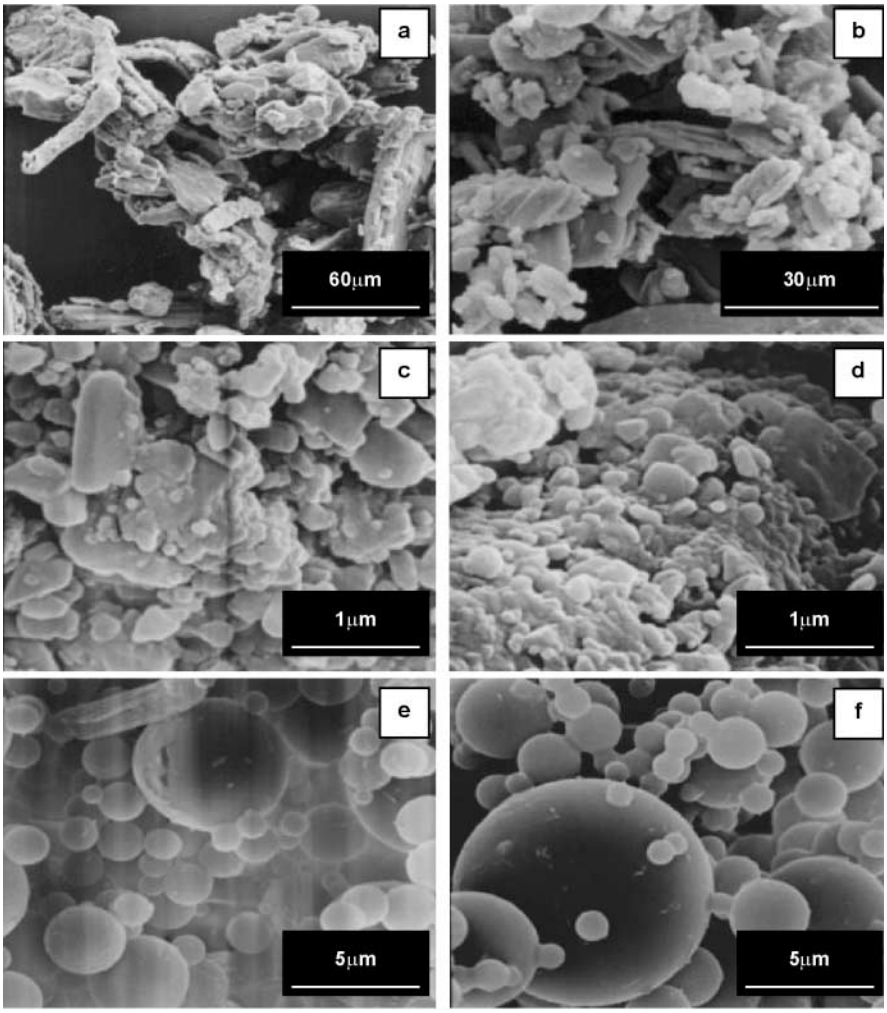

Figure 1. Scanning electron micrographs of the products: (a) binary dry mixture; (b) ternary dry mixture; (c) binary ground mixture; (d) ternary ground mixture; (e) binary spray-dried mixture; (f) ternary spray-dried mixture.

Table 3

Physical Characteristics of the Products

	Dry Mixtures		Ground Mixtures		Spray-Dried Mixtures	
	1D	2D	1G	2G	1S	2S
Specific surface area (m^2/g)	0.462	0.468	3.307	3.604	0.716	0.821
Median porous diameter (μm)	20.38	15.15	2.43	1.35	9.21	14.48
Total porous volume (cc/g)	1.416	1.012	0.834	0.650	1.335	1.235
Pycnometric density (g/cc)	1.522	1.523	1.579	1.585	1.485	1.459
Bulk density (g/cc)	0.406	0.483	0.399	0.413	0.249	0.247
Median diameter (μm)	79	162	26	17	25	20
$V_{10} - V_{500}$ (cc)	15	15	24	24	54	54

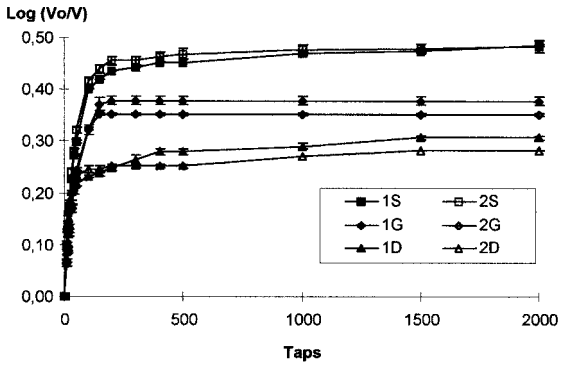

Figure 2. Packing kinetics of the different products.

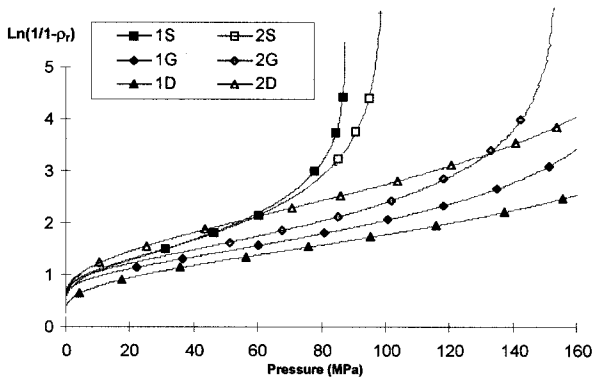

Figure 3. Heckel plot of the densification step of materials subjected to compression stress.

for spray-dried products. A similar result was obtained by Fell and Newton (12), when they studied spray-dried and crystalline α-lactose monohydrate and Sebhatu and Alderborn (13), leading to the hypothesis that decreasing the crystallinity could favor plastic deformation during compaction. Indeed, complementary work (10) and a study by Yonemochi et al. (14) have demonstrated that spray-dried products have poor crystallinity.

The ground products present a decreased fragmentation tendency compared with the dry mixtures due to the decreased particle size (15,16).

Although the Heckel relationship is extremely sensitive to operating conditions and accurate determination of the true density of the material (17), it seems that the dry binary mixture is likely to consolidate by brittle fracture more than the ternary one, as indicated by its lower Heckel plot slope, due to the propensity of Cellactose® to undergo fragmentation (18). In contrast, Belda and Mielck (19) did not observe any difference in the Heckel parameter when comparing Cellactose® and a mixture of lactose and cellulose. However, it must be highlighted that in their work only pure materials were analyzed and no active ingredient was included in the formulation. Furthermore, compacts were prepared using an eccentric tabletting machine and densification behavior was studied over a more limited pressure range. All these differences can explain the divergent observations.

Compact Characteristics

Specific Surface Area

The incidence of the process on the texture is clearly shown by the difference in the initial specific surface area between the spray-dried and the ground products, as illustrated in Fig. 4. Nevertheless, in both cases the general tendency is for a decrease in the specific surface area with compaction pressure after a small increase up to 25–50 MPa, due to the fragmentation of particles and agglomerates (20–22). The decrease in specific area can be explained by the rearrangement of particles and the formation of bonds between particles under pressure. The similarity of the curve profiles corresponding to binary and ternary blends of ground and spray-dried products indicates that the process dominates the formulation.

In contrast, for the dry blends constituted of primary particles, the evolution of the specific surface area is more sensitive to the formulation. The binary blend gives a curve with a more marked increase in the specific surface area with pressure than the ternary blend, suggesting a more fragmenting behavior. This observation is supported by the greater fragmenting propensity of the binary blend, that was noticed in the densification analysis.

Porosity

The general trend is for a decrease in total porous volume (Fig. 5) and median porous diameter of the different compositions with pressure (Fig. 6).

For the processes that lead to small particle size (spray drying and grinding) the porous volume decreases sharply up to 15 MPa, then stabilizes and decreases slightly up to 160 MPa (Fig. 5). In the case of the dry ternary and binary blends the diminution extends over a larger range (up to 50 MPa) but the final total porous volume reaches

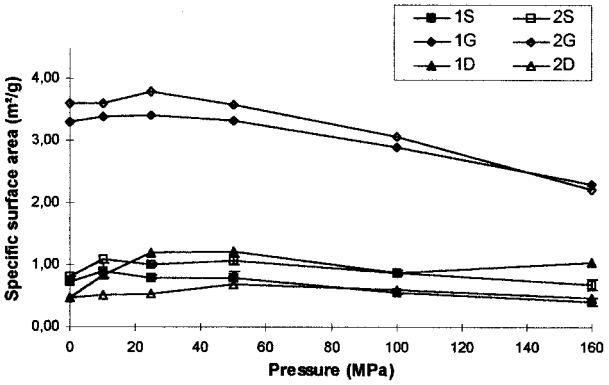

Figure 4. Evolution of the specific surface area with the compaction pressure.

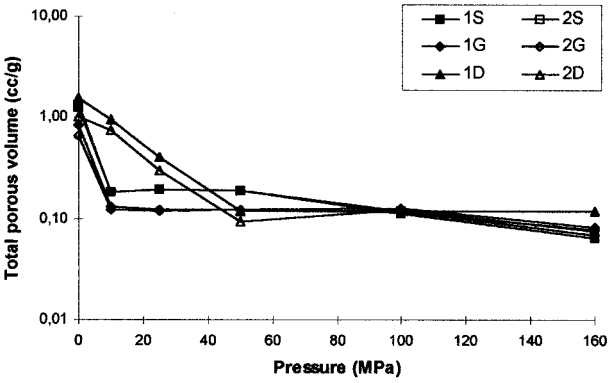

Figure 5. Evolution of the total porous volume of the different compositions with the compaction pressure.

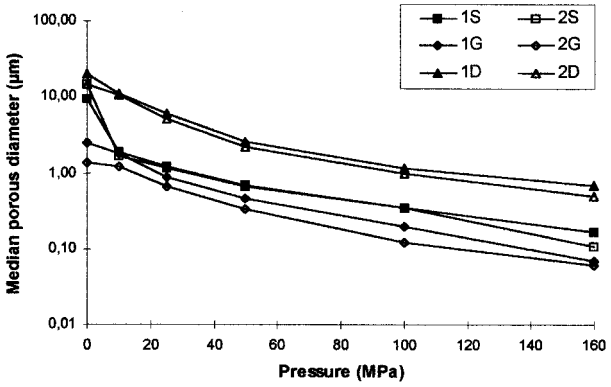

Figure 6. Evolution of the median porous diameter of the different compositions with the compaction pressure.

the same value as for the other products. This difference in the first step of densification probably results from the rupture of the particles that occurs to a larger extent in the case of coarse particles. Concerning the evolution of the median porous diameter, the spray-drying process differs from the other processes through a more important decrease at the beginning of the compression. For the blends and the ground materials the reduction of the pore size is regular over the whole pressure range.

It is interesting to notice the prevailing influence of the process over the formulation: no significant difference between the ternary and the binary formulations is observed, whatever the process.

Compact Strength

The mechanical characteristics examined in this study appear in Fig. 7. For all products the compact strength increases with the compaction pressure. Binary blends exhibit a higher resistance than ternary ones, even after grinding, making evident the cohesive performance of Cellactose® claimed by its suppliers and also observed by Belda and Mielck (19) and Schmidt and Rubensdörfer (23). Not only does the intimate contact of the lactose and the cellulose in the co-processed product facilitate the bond formation during compaction, but also the higher degree of fragmentation (24) of the binary blend will contribute to the enhanced strength of the dry binary mixture compacts.

When comparing the mechanical properties of spray-dried and ground products, spray drying appears to improve the mechanical characteristics of the ternary blend, probably by modifying the

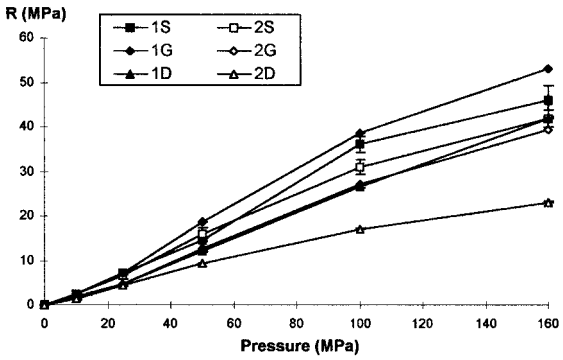

Figure 7. Evolution of the axial compressive strength with the compaction pressure.

texture of the product. On the contrary, in the case of the binary product this process seems to create new particles having lower cohesive properties. In addition it seems that spray drying induces a specific texture that lowers the effect of the formulation on the mechanical properties, as evidenced by the similarity of the curves corresponding to the two spray-dried products in Fig. 7. It may be argued that spray drying leads to an intimate contact between the components in suspension, almost like in the case of co-processing of Cellactose®.

For both formulations, decreasing the particle size by grinding or spray drying results in stronger compacts, as observed by McKenna and McCafferty (25), who argued that increased frictional forces were associated with smaller sizes while fragmentation of coarser particles did not occur in a regular manner in the compact, leading to a heterogeneous structure. The increase in tablet strength with a reduction in particle size has also been evidenced by Sebhatu and Alderborn (13).

CONCLUSION

The aim was to investigate the incidence, respectively, of the formulation and manufacturing process on the physico-mechanical properties of materials and their ability to compress. From the observations made in this study, the mechanical properties were shown to depend essentially on the formulation, whereas the process imposes its effect on flow properties and densification of materials.

However, the differences due to the formulation seem to be reduced by spray drying. The variations linked to the raw materials are covered up by the wet process, whereas in the dry processes (mixing and grinding) the properties of each material are retained.

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