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INFLUENCE OF THE PARAMETERS MOLECULAR STRUCTURE AND GRANULARITY ON THE COMPACTIBILITY OF A POWDER

C. Andrès, A. Ndiaye, C. Thomas, A. Tromelin, B. Chaillot and Y. Pourcelot
Physico-chemical and technology group on pharmaceutical powders
School of Pharmacy - University of Burgundy
7 boulevard Jeanne d'Arc
21033 Dijon, France

ABSTRACT

The aim of this study was to determine whether it is possible to obtain better characterization of materials in order to find out if these one are suitable in Quality Assurance for direct tableting. We tried to show that a methodological approach combining chemical, physical and technological aspects could control the direct compression process. We chose orthoboric acid as a study model for the direct compression. From a chemical point of view, our findings show only one crystalline molecular structure (RX, DSC and Pycnometry) which means an homogeneous chemical system. Concerning the particular state (Sieving and Microscopic approach), granularity is very different between the two forms, "crystalline" ABC and "powder" ABP.

Technological studies show a rheological and mechanical difference, as it is demonstrated, on the one hand by the behaviour of the bulk powder (Volumenometer), on the other hand by the feasibility on the machine (Alternative EKO). We explain this difference of behaviour by only the granularity aspect. Consequently, we think that in this case, controling the granularity means controling this direct tableting process.

INTRODUCTION

Tablets remain the most commonly used pharmaceutical formulation. The successful formulation and manufacture of this form depend mainly on the aspects of physical stability, technological suitability and therapeutic aspects of a better understanding of the particle state, "the fourth state of matter". In addition, although particulate materials are very common, their physical properties are still poorly defined and poorly understood (1). It is difficult to forecast the quality of the tablet by characterising the particles since there are difficulties in characterising and measuring these particles.

The purpose of this study was to demonstrate the importance of a systematic approach which includes both microscopic and macroscopic aspects, ranging from the molecular structure to the particulate state and to the "bulk" state "bulk powder", which has the properties associated with a set of particles (2, 3), in

order to predict the rheological and mechanical behaviour of a powder and therefore its suitability for direct compression.

The importance of the size, size distribution and morphology of particles has been discussed in several publications (4, 5, 6). In particular, various methods have been developed for measuring these parameters which involve a variety of physical principles: optical, electrical, mechanical etc., to mention only those most commonly used for pharmaceuticals (7).

For a given population of particles, the results obtained using these methods can be expressed either in the form of a physical variable of differing dimensions or a geometric variable (length, area, volume) or weight (mass). In recent years, new analytical techniques have emerged which clearly reflect the limitations of each approach: it is only by combining the results obtained by several such methods, which show varying degrees of complementarity, that we can obtain any real knowledge of the powder (8-9).

The present study involved a single chemical compound, orthoboric acid, which is manufactured commercially in "crystalline" and "powder" forms, referred to as "ABC" and "ABP" respectively. The aim was to determine whether it is possible to obtain better characterisation of these materials in order to find out whether they are suitable for direct tableting, by comparing the data obtained using these various methods concerning:

- molecular structure,
- particulate state (size and shape),
- the behaviour of the bulk,
- feasibility on the tableting machine.

MATERIALS AND METHODS

Materials

The two commercial grades available (Merck) correspond to the following trade reference codes:

- "crystalline orthoboric acid", batch 299 K 1795 7560, code: ABC
- "powdered orthoboric acid", batch 234 K 180 38762, code: ABP.

The selection of these two forms was based on several criteria:

- chemical criteria: orthoboric acid crystallizes as two established systems: one of these is a stable form (triclinic) and the other metastable (orthorombic) (10);
- therapeutic criteria: the substance must have bactericidal activity;
- formulation technology: a substance with plastic properties, chosen in order to minimise the impact of the parameters of the tableting process and to facilitate the demonstration of the influence of the molecular structure and granularity parameters on machining feasibility.

Methods

- Study of molecular structure: this was done by means of X-ray diffraction (Inel Diffraction system fitted with a localization curve counter - Cu- anti cathode), differential scanning calorimetry (DSC 92 - Setaram) and helium pycnometry (Quantachrome Multipycnometer). The mean of three readings was used for the last two methods.

- Study of particulate state

-Morphological analysis: scanning electron microscopy was used (Cambridge Stereoscan 250 MHz).

-Particle size analysis: after examining various samples under an optical microscope we were able to select (7 screens: 710, 500, 355, 250, 180, 125 and 90 µm) and operate an appropriate mechanical sieving process (Retsch KS1 plane sieve).

Each powder was analysed in triplicate, under the following operating conditions: number of horizontal rotations of the sieving plane: 250 rpm, rotation time: 10 min, test sample: 100 g.

- Behaviour of the "bulk": this was investigated using packing volumetry (STAV 2003 Stampfvolumeter - J. Engelsman) and the results reported as the mean of tests carried out on five different samples. The parameters usually deduced were the apparent density, the Hausner index and compressibility index and the porosity measured before and after n jolts, where n was equal to 500 (11).

- Machining feasibility test: this was carried out on a an alternating machine fitted with instruments -Korsch Eko). The tablets were produced by an automated procedure, running at 20 cycles per minute at three pressure levels (50, 100 and 150 MPa) in a fixed-volume compression chamber (h=10 mm, d=10 mm). The compressibility was determined during tableting by measuring the distance covered by the upper punch from the surface of the powder to its maximum descent. One hour after tableting the following parameters were measured on a sample of 20 tablets: mass (using a Mettler H2OT), resistance to crushing (Schleuniger Tablet Tester 60) and dimensions of the finished tablet.

The temperature and ambient relative humidity were monitored throughout the tests.

RESULTS

Study of molecular structure

- X-Ray Diffraction

Two crystalline states of orthoboric acid are known to exist (10): one is a triclinic structure and one an orthorombic structure. Analysis of the diffractograms obtained (Figure 1) shows that the crystalline states of the two starting materials are similar: both contain the triclinical form alone and both contain traces of dibasic sodium tetraborate decahydrate or borax.

- Differential scanning calorimetry

This method confirmed the similarity of the two starting materials; their thermograms are similar in all respects: each shift occurs at the same temperature. The specific heat, measured at 70°C, was found to be 1.544 J/g/°C for ABC and 1.546 J/g/°C for ABP.

- Helium pycnometry

The reproducibility of the particle density determination was very good: the value found was 1.507 g/cm3 for ABC and 1.505 g/cm3 for ABP. These values are not significantly different, which confirms the chemical identity of ABC and ABP.

Study of the particulate state

The particulate state is characterised by the morphological properties and size of the particles.

Morphological properties of the particles

Scans of several samples of the starting materials taken using a scanning electron microscope (SEM) make it possible to define the form and size of the

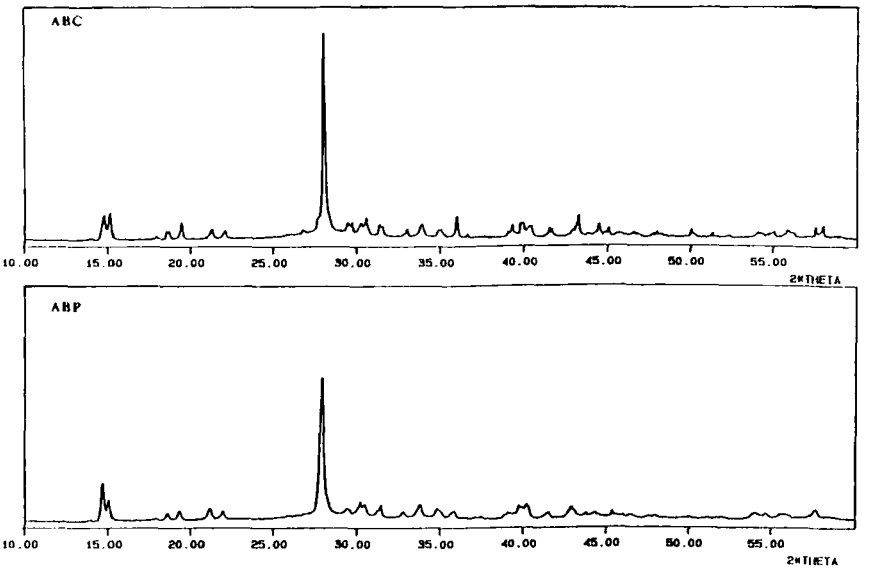

FIGURE 1

Diffractogram of "crystalline" orthoboric acid (ABC) and "powder" orthoboric acid (ABP).

particles. Different magnifications were used for ABC (x230, Figure 2) and for ABP (x330, Figure 3) in order to obtain an appropriate field of observation.

- In the case of ABC, the particles on all the scans can be seen to have a similar appearance (Figures 2, 4), but extend over a relatively wide range of sizes, reaching particle sizes of 500 μm and more.

- In the case of ABP, there is a wide variety of sizes, ranging from a few tenths to a few hundredths of a micrometer (Figure 3).

The surfaces are stratified and irregular (Figure 4). With regard to shape, the smaller particles tend to be more lamellar, whereas those over 100 μm are equidimensional.

Size characteristics of the particles

Particle size analysis, performed in order to detect any differences in particle size distribution in the two compounds, was carried out in this instance by sieving.

In the case of ABC (Figure 5), the median diameter was found to be 220 μm, with a wide range of particle sizes. The particle size category representing the greatest mass, 180 to 250 μm, contained to 20.9±0.1% of the mass of the powder bed. More than 90.0±0.1% of the mass of the powder consisted of particles with a diameter of less than 500 μm.

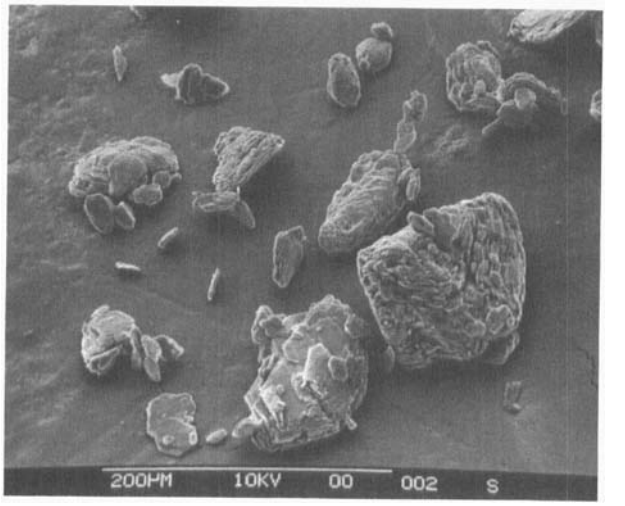

FIGURE 2

Particles of "crystalline" orthoboric acid (ABC) from the bulk powder, magnification: x 230.

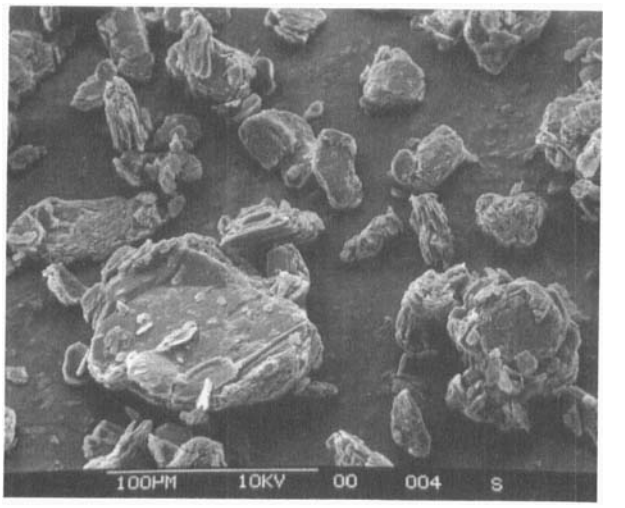

FIGURE 3

Particles of "powder" orthoboric acid (ABP) from the bulk powder, magnification: x 330.

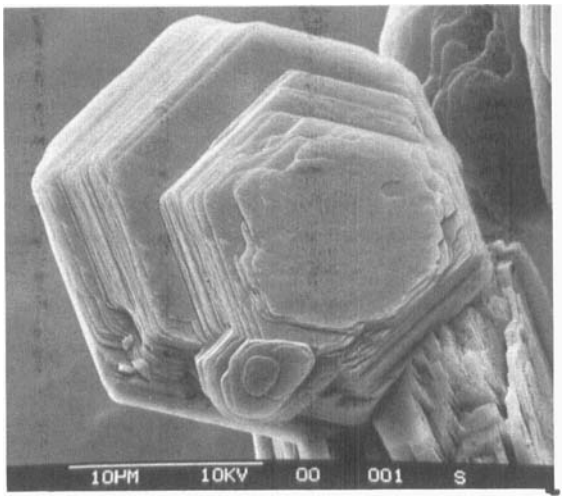

FIGURE 4

Particles of "crystalline" orthoboric acid (ABC) from the bulk powder, magnification: x 3000.

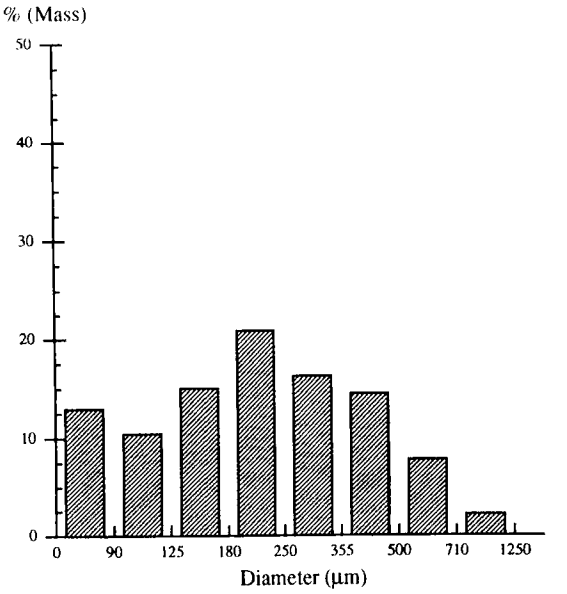

FIGURE 5

Differential histogram of the particle size distribution of "crystalline" orthoboric acid (ABC) powder.

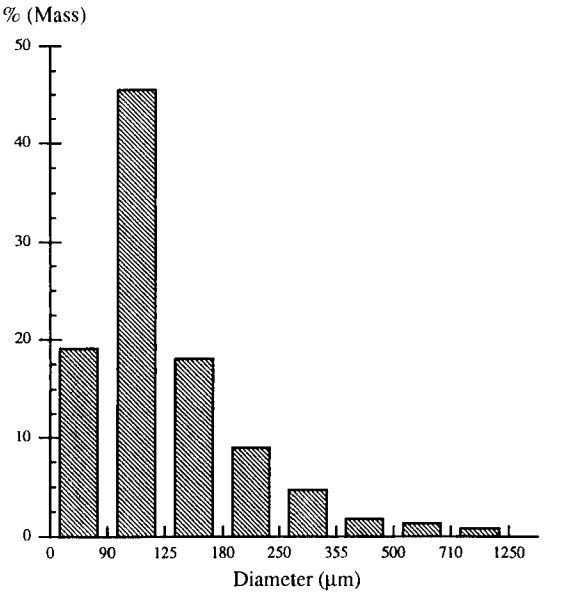

FIGURE 6

Differential histogram of the particle size distribution of "powder" orthoboric acid (ABP) powder.

In the case of ABP (Figure 6), the median diameter was found to be 115 µm, with a narrower range of particle sizes. The particle size category containing the greatest mass was the 90 to 125 µm fraction, which accounted for 45.4±5.2 % of the mass of the powder bed. More than 96.2±0.3 % of the mass of the powder consisted of particles with a diameter of less than 250 µm.

Investigation of the behaviour of the bulk

Packing volumetry is a well defined method which is relatively easy to use. This is a useful method which can be used to evaluate the behaviour during flow and during the rearrangement of powders (11) and is also predictive. The results are shown in Table 1.

These two starting materials, which have the same crystalline structure and the same particle density, demonstrate differing packing capacities.

Machining feasibility study

A powder suitable for tableting must have a capacity for flow combined with compressibility and cohesion.

Flow capacity

The flow phase is of primordial importance in tablet production. The powder must flow regularly and uniformly and this flow determines the nature of the particle

TABLE 1
Synthesis of Various Forms of Expression of the Results Obtained using a Packing Volumeter.

	ABC	ABP
ρ_0 (g cm^{-3})	0.78	0.60
ρ_n (g cm^{-3})	0.96	0.82
I_H	1.23	1.37
I_C (%)	19	27
ε_0 (%)	48	60
ε_n (%)	36	46

ρ_0: density before packing, ρ_n: density after packing,
$I_H = \rho_n / o$: Hausner index, $I_C = (\rho_n - o) / \rho_n$: compressibility index,
$\varepsilon_0 = 1 - \rho_0 / \rho_v$: initial porosity, $\varepsilon_n = 1 - \rho_n / \rho_v$: final porosity,
where ρ_v is the particle density measured using a helium pycnometer.

rearrangement which occurs in the tableting chamber. This can be investigated:

- either, indirectly during manufacture by monitoring the pressure reading;
- or, after manufacture, by an analysis of the mass uniformity of the tablets for a given filling volume. This is method we adopted. The results found are shown in Table 2.

Compressibility

This can be estimated during manufacture by measuring the distance covered by the upper punch from the surface of the powder to its maximum descent or, after manufacture, by measuring the thickness of the tablets. However, in the latter method the elastic rebound of the material has also to be taken into account, and so we opted for the former method. The results obtained are shown in Table 3.

Cohesiveness

This was investigated here by measuring the mechanical resistance of the tablets in the diametrical breaking test. The tensile strength (σx) is determined by applying Newton's equation (Table 4): $\sigma x = 2 F / (e D_t)$

where F is the force applied at breaking point, D_t the diameter of the tablet and e its thickness (12).

DISCUSSION

Investigation of the molecular structure of the two starting materials, carried out using several methods (13): X-ray diffraction, DSC and helium pycnometry, demonstrates that they have the same molecular structure (Figure 1). This is an important finding, since it makes it possible to relate any behavioural differences subsequently detected to particle characteristics alone.

Investigation of the particulate state, and therefore of the individual and collective characteristics of the particles, was carried by by means of scanning electron microscopy (qualitative aspects) and also by dry sieving (quantitative

TABLE 2
Mean Mass (in grams) of the Tablets of "Crystalline" Orthoboric Acid (ABC) and "Powder" Orthoboric Acid (ABP) Obtained at Various Tableting Pressures.

	Mean mass (in grams) of tablets produced at a pressure of 50 MPa (CV)	Mean mass (in grams) of tablets produced at a pressure of 100 MPa (CV)	Mean mass (in grams) of tablets produced at a pressure of 150 MPa (CV)
ABC	0.6269 (0.5%)	0.6257 (0.3%)	0.6194 (0.6%)
ABP	0.4110 (1.4%)	0.4060 (1.5%)	0.4068 (1.5%)

TABLE 3
Apparent Density of the Powder Before (ρ_{min}) and After (ρ_{max}) Compression Found for "Crystalline" Orthoboric Acid (ABC) and "Powder" Orthoboric Acid (ABP).

	Tablets produced at a pressure of 50 MPa	Tablets produced at a pressure of 100 MPa	Tablets produced at a pressure of 150 MPa
ABC	ρ_{min}=0.80 ρ_{max}=1.45 I_C=45%	ρ_{min}=0.80 ρ_{max}=1.53 I_C=48%	ρ_{min}=0.80 ρ_{max}=1.58 I_C=50%
ABP	ρ_{min}=0.52 ρ_{max}=1.41 I_C=63%	ρ_{min}=0.52 ρ_{max}=1.49 I_C=65%	ρ_{min}=0.52 ρ_{max}=1.57 I_C=68%

ρ_{min}: apparent density of the powder bed in the punch, in g/cm^3 before compression,
ρ_{max}: apparent density of the powder bed in the punch, in g/cm^3 after compression,
$I_C = (\rho_n - \rho_0)/\rho_n$: compressibility index on the machine or the relative reduction in the volume of the powder bed during the compression phase.

TABLE 4
Tensile Strength (in MPa) of the Tablets of "Crystalline" Orthoboric Acid (ABC) and "Powder" Orthoboric Acid (ABP).

	Tensile strength of the tablets produced at a pressure of 50 MPa (CV)	Tensile strength of the tablets produced at a pressure of 100 MPa (CV)	Tensile strength of the tablets produced at a pressure of 150 MPa (CV)
ABC	0.30 (10%)	0.68 (9%)	0.88 (6%)
ABP	0.66 (27%)	1.59 (15%)	2.15 (10%)

aspects). The latter method provides both an analysis and a mechanical separation of the powder. The results obtained demonstrate:

- qualitative aspects: virtually equidimensional particles for the 180-250 µm category of both powders, but more lamellar forms for particles measuring less than 100 µm. Irregular surfaces, consisting of strata, were also observed and probably reflected stratified crystallisation of the orthoboric acid (Figures 2, 3 and 4).

- quantitative aspects: considerable differences were found between the two starting materials with regard to median diameter, range and distribution of sizes. ABP contained 64% fine particles with a diameter of less than 125 µm and 3% of large particles with a diameter of more than 500 µm, whereas ABC had only 23% of fine particles and 12% of large particles (see Figures 5 and 6).

Investigation of the behaviour of the bulk or the collective behaviour of the particles using the volumeter, demonstrated that the flow capacity of ABC was greater than that of ABP (Table 1). The interparticular friction was greater in the case of ABP (Hausner index of ABP 1.37 *versus* 1.23 for ABC). A difference was also found between the powders with regard to the apparent density before and after packing, which reflects differing particle arrangements. These behavioural differences are related to the differences in particle size distribution referred to above. Tests carried out with the volumeter using specified central particle size ranges (180-250µm) of ABC and ABP resulted in very similar behaviours (Hausner index of 1.07 and 1.10 respectively). As Hausner pointed out (14), the flow of a powder, its apparent density and its ability to mix are all behavioural characteristics influenced by interparticular friction.

The machining feasibility study, which involved investigating the flow capacity, compressibility and cohesiveness, was performed in order to allow for product-process interaction and to investigate the influence of granularity.

The flow of the powders on the machine (Table 2) was tested by investigating the mass uniformity of the tablets and demonstrated greater uniformity for ABC (CV 0.3% to 0.6%) than for ABP (CV 1.4% to 1.5%). This provided further confirmation of the findings obtained on the packing volumeter. It was also found that the apparent densities obtained for the two substances were very different.

The compressibility of the powders on the machine was determined by calculating the compressibility index which showed that ABP was more compressible than ABC (Table 3). Within the particle size distributions, the incidences and size ratios between the particles resulted in differing initial particle arrangements and, hence differing initial densities and interparticle contacts, which are key aspects during the early stages of compression.

The cohesiveness of the powders on the machine was tested by calculating the tensile strength at breaking point of the tablets (Table 4). Both starting materials showed an increase in this strength with pressure at the three pressure levels tested. For any given pressure, the strength was always greater for ABP. ABP therefore demonstrated greater cohesiveness than ABC, and this can be accounted for by the fact that it contains a higher proportion of fine particles, as we have already seen (ABP: 64% *versus*. ABC : 23%).

CONCLUSION

We chose orthoboric acid as a study model. This substance is available in two commercial form, the "'crystalline" and the "powder" forms. Our findings show that these are forms of a single type of orthoboric acid and constitute a

homogenous chemical system. However, the different reference codes are justified when the micrographs and particle size analysis data obtained by sieving are examined. The results reported demonstrate that despite having the same molecular structure, the "powder" and "crystalline" forms of the two substances have differing particle size distributions and a different percentage of fine particles. "Crystalline" orthoboric acid has better flow characteristics whereas the "powder" acid demonstrates better cohesiveness.

Although tablets are the most commonly used pharmaceutical form, this study shows that control of the direct tableting process requires a methodological approach combining chemical, physical and technological aspects ranging from the molecular structure to the tablet, which must include an investigation of the particulate state and the collective behaviour of particles. The formulator must constantly keep this aspect in mind when dealing with either bio-active substances or adjuvants.

We are continuing this work in order to obtain differing granularities on the basis of size and morphology, by investigating the dissolution profiles of powders and tablets in order to determine the role of various factors in determining the bio-availability of the drug.

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