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Twin product/process approach for pellet preparation by extrusion/spheronisation Part I: Hydro-textural aspects

S. Galland [a], T. Ruiz [a,*], M. Delalonde [b]

[a] *Laboratoire de Génie des Procédés et d'Elaboration de Bioproduits, UMR, CIRAD 016, Université Montpellier II, CC 05, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France*
[b] *Laboratoire de Génie des Procédés et d'Elaboration de Bioproduits, UMR, CIRAD 016, Université Montpellier1, 15 Avenue Charles Flahault, B.P. 14491, 34093 Montpellier Cedex 5, France*

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Abstract

The extrusion/spheronisation technique has made a notable contribution to the existing range of pharmaceutical forms especially in the area of modified-release products. The twin product/process approach adopted in this work is based on the on-line monitoring of the hydro-textural characteristics of the product up to its final form. The objective is to balance the influence of the operating parameters for each successive stage against the influence of product characteristics. A coherent "representational framework" is proposed for insoluble substances through a diagram locating intergranular porosity value depending on water content. The wetting/kneading operation brings the material to a state in which porosity is linked to water content. The extrusion operation densifies the material to saturation point, while spheronisation is only a shaping process which maintains hydro-textural state. The drying operation finalises the textural characteristics of the product by densifying the medium through induced shrinkage.

Keywords: Wet granulation; Pellets; Texturation; Extrusion/spheronisation; Hydro-textural diagram

1. Introduction

Among the different ways of drug administration, the oral route is the most commonly used. Any innovation in the area of solid dosage forms is thus very important and their optimization and the development of new forms are of great interest for formulators. In this context, the present work focuses on the development of spherical multiparticulate systems, pellets, by the extrusion/spheronisation process (Newton, 1998; Bianchini and Vecchio, 1989). The morphology of these microsystems, their low particle size distribution as well as their texture and porosity, directly connected to the subsequent availability of active compounds, are important parameters to control (Sousa et al., 2002).

The extrusion/spheronisation technique is a complex process made up of four successive unit operations. During the wetting/kneading stage, the addition of a fluid, characterized by its binding properties, will ensure particles agglomeration and impart the properties of flow, cohesion and deformability that are necessary for shaping. The extrusion and spheronisation stages are mechanical processes that shape the wet heterogeneous medium thus modifying the organisation of the different phases. Drying, which involves mass and energy transfers, finalises the textural characteristics of the product by densifying the medium through mechanical shrinkage induced by extracting the liquid phase.

The properties of the raw materials are an important factor in the quality of the final product, but are not sufficient to ensure the required characteristics of the pellets. Predicting the quality of the final product requires the taking into account the technological elements involved in the process and actions of the various process parameters. So, quality control depends both the material aptitudes (component of a formulation) and process capacities (modes, process parameters). The literature indicates the existence of a liquid/solid ratio optimizing this feasibility.

* Corresponding author. Tel.: +33 4 67 14 46 17; fax: +33 4 67 14 47 87.
E-mail address: truiz@univ-montp2.fr (T. Ruiz).

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Several studies have focused on finding a methodology to identify this optimum. The work of Bier et al. (1979) may be cited in this instance, dealing with the wetting operation by measuring power consumption of the mixer to characterize wet powder consistency as a function of water content. Other authors measured torque evolution (Soh et al., 2006; Baërt et al., 1991; Goldszal and Bousquet, 2001). Consistency or rheological behaviour can also be measured using a cone penetrometer or by recording the curves of wet mass flow in capillary rheometry tests (Delalonde et al., 2000).

Extrusion/spheronisation is a process which shapes and textures wetted powders. The objective is to analyse the process as a whole by quantifying the role of the most influential parameters on obtaining a given texture, in order to propose an optimization approach. To do so, an approach is proposed to monitor the hydro-textural characteristics of the product at the end of each unit operation in the extrusion/spheronisation process. Various transformation paths appear, resulting of product/process coupling effects and allowing to quantify the influence of the specific process parameters in each unit operation. This approach is applied to insoluble products in the wetting liquid used. Entirely developed in the case of the CMC, the introduction of Ibuprofen (insoluble drug) makes it possible to validate and extend this approach. Its provides a "representational framework" for the analysis of extrusion/spheronisation process.

2. Theoretical background

A hydro-textural diagram is needed to understand and model the different phenomena involved in each operation. It then becomes possible to integrate each aspect, whether linked to the material or to the process. It provides a visual support for monitoring of the transformations in the initial product up to its final form in the course of 4 unit operations.

2.1. Hydro-textural aspects

The mass and volume states of an elementary volume of a three phase porous medium (solid–liquid–gas) are defined as a function of the standard variables used in the science of porous media: mass water content (w), intergranular porosity (n) and saturation degree (S_w). These three variables represent the hydro-textural characteristics selected to characterize the material at the various stages of the shaping process:

$$w = \frac{m_w}{m_s} \tag{1}$$

$$n = \frac{V - V_s}{V} = 1 - \frac{\rho_s}{\rho_s^*} = 1 - \frac{m_s}{V d_s^*} \tag{2}$$

$$S_w = \frac{V_w}{V - V_s} = \frac{m_w / d_w^*}{V - m_s / d_s^*} \tag{3}$$

m_s and m_w the masses of solid and water phases, V_s, V_w the volumes of solid and water phases and V the apparent volume of the mixture; $\rho_s = m_s/V$ the apparent volumic mass of the solid phase, $\rho_s^* = m_s/V_s$ the true volumic mass of the solid, d_s^* the true density of solid ($d_s^* = \rho_s^*/\rho_w^*$) with ρ_w^* the true volumic mass of the liquid equal to 1 g cm^{-3} for water. For a binary mixture of solids, the true volumic mass $\rho_{s,M}^*$ is given by a mixture law:

$$\rho_{s,M}^* = \frac{1 + m_I/m_{CMC}}{1/\rho_{s,CMC}^* + (m_I/m_{CMC})(1/\rho_{s,I}^*)} \tag{4}$$

with m_I and m_{CMC}, respectively the masses of Ibuprofen and CMC. Volume deformation to monitor isotropic pellet shrinkage is defined as:

$$\varepsilon = \frac{V_0 - V}{V_0} \tag{5}$$

where V_0 is the initial apparent volume of the mixture.

2.2. Hydro-textural diagram

This diagram is used to locate the potential states of the mixture at the various stages of preparation. The evolution of the material can thus be followed, from its pasty state after wetting up to its final form of dry pellets. Parameters of texture and intergranular porosity, versus water content are followed to define and construct the hydro-textural diagram proposed in this study.

The first stage consists in strictly defining the surface combining all the hydro-textural states that can be reached at the different stages of product engineering. The saturation curve represents the porosity value for which the interstitial fluid saturates all the pores for a given wetting and constitutes the lower limit of the diagram. This curve corresponds to relationship:

$$n(w_{sat}) = \frac{d_s^* w_{sat}}{1 + d_s^* w_{sat}} \tag{6}$$

The different states reached during preparation will necessarily be above this saturation curve showing the minimum intergranular porosity for a given water content to be reached by the material during its preparation.

The experimental results are shown on this diagram, establishing a processing path to follow the hydro-textural evolution of the material at each stage of transformation. These paths depend on the material and the process conditions imposed and represent the possible various paths during preparation to assess the influence of the product and that of the process.

3. Materials and methods

3.1. Materials

The pharmaceutical excipient, Macrocrystalline Cellulose (CMC, Celpac50®-Penwest) is chosen for this study. Currently used in pellet formulation, this excipient is studied alone or mixed with a drug, Ibuprofen (Intsel Chimos) in proportion $m_I/m_{CMC} = 60/40$ (m/m). The Ibuprofen/CMC mixture is carried out in a Turbula T2A mixer for obtain a homogeneous dry powder mixture. These two substances are practically insoluble in the wetting liquid used in this study. The true densities evaluated by Multivolum Pycnometer 1305-Micromeretics helium pycnometer are respectively $\rho_{s,CMC}^* = 1.55$ g cm^{-3} for CMC

and $\rho^*_{s,I} = 1.12$ g cm^{-3} for Ibuprofen. From mass mixture law, given by the relationship (4), the true density of mixture is $\rho^*_{s,M} = 1.26$ g cm^{-3}.

The mean sizes measured by a Malvern Instrument Southboutough-MA laser granulator are $d_{50} = 60$ μm for CMC and 100 μm for Ibuprofen.

The wetting liquid is distilled water, used with CMC and with the mixture Ibuprofen/CMC in different proportions with dry material. The various ratios tested are between 85 and 135% (m/m) for CMC and between 40 and 100% for Ibuprofen/CMC mixture.

Wetting is carried out in a planetary mixer (Kenwood major) at a fixed speed of 65 rpm. The water is steadily added to 200 g of powder for 3 min and the wetted mass was homogenised in terms of water content for a further 3 min. The wet mass is immediately extruded using a single screw axial extruder (Gabler Machinenbau, model Pharmex 35T) through a 1 mm diameter screen. For CMC, the extruder screw rotation speeds (Ω) are 30, 55, 80 or 110 rpm. A load of 50, 100 or 200 g of extrudates is then spheronised (Gabler Machinenbau-modèle Sphaeromat SPH 250 MA spheroniser) at fixed rotation speeds of 620, 760, 1180 or 1600 rpm for 1, 2 or 4 min. The pellets of CMC obtained are then dried in a ventilated oven at 50 or 60 °C for 24 h (Ecocell).

In the case of Ibuprofen/CMC mixing, operating parameters are fixed: (i) the extruder screw rotation speed at 55 rpm; (ii) for spheronisation: load 100 g, speed 1180 rpm, time 2 min; (iii) the drying conditions: 60 °C for 24 h.

3.2. Method

Water mass and dry solid mass, required to evaluate the distribution of two or three phases present in the granular medium during preparation, are measured by loss through desiccation (weighting of samples before and after drying at 105 °C up to constant mass for CMC and 60 °C for Ibuprofen). Apparent sample volumes (V) are evaluated, in the case of the wet mass, by taking a core sample of the agglomerate using a cylindrical metal ring and, in the case of extrudates and pellets, by immediately reading the displaced volume after placing them in graduated tests-tubes containing a known and perfectly defined volume of paraffin oil. This measurement is validated by ensuring that the paraffin oil does not penetrate through the porous network during the experimental contact period (less than 1 min).

4. Results and discussions

4.1. Wetting/kneading

For all formulations (CMC and Ibuprofen/CMC), saturation degrees of wet masses evolve with water content according to a sigmoid form (Fig. 1a and b). For weak wetting, the saturation degrees does not vary much with wetting. The liquid is distributed on the surface of the powder particles and leads to the agglomeration by dispersed capillary meniscus, disrupted at the medium scale. For higher wetting levels, a zone is observed, where saturation degree varies strongly with water content (quasi-linear dependence). The liquid bridges are more numerous and more uniformly distributed, generating better cohesion. Saturation is then reached asymptotically.

The intergranular porosity of these unsaturated states depends on water content (Fig. 2a and b). Experimental points define a kneading curve. In the range of water contents studied and for fixed processing parameters, porosity progressively decrease with wetting to a minimal value. The water content, which corresponds to this minimal porosity, is situated closely 115% for CMC and closely 65% for the mixing (Ibuprofen/CMC). These water contents define a densification optimum. With higher wetting levels, porosity increase asymptomatically to the saturation curve given by Eq. (5). For wettings over 180% for CMC and 100% for the mixing, porosity is assumed to correspond to that of the saturated product.

The relations between porosity or saturation degree and water content reveal a phenomenon linking the texture of the material to its water content. This kneading curve (Fig. 1a and b) is described in a study (Ruiz et al., 2005):

$$S_w = 1 - \frac{1}{1 + e^{(w - w_m)/d}} \quad (7)$$

with w_m and d two parameters depending of the product and process conditions with d linked to the slope of the linear part: $1/d$ corresponds to the slope of the function $\mathrm{Ln}(1/(1 - S_w(w)) - 1)$, and w_m is the water content corresponding to $S_w = 0.5$ (Fig. 1a and b). For the range of water content tested, Ruiz et al. (2005)

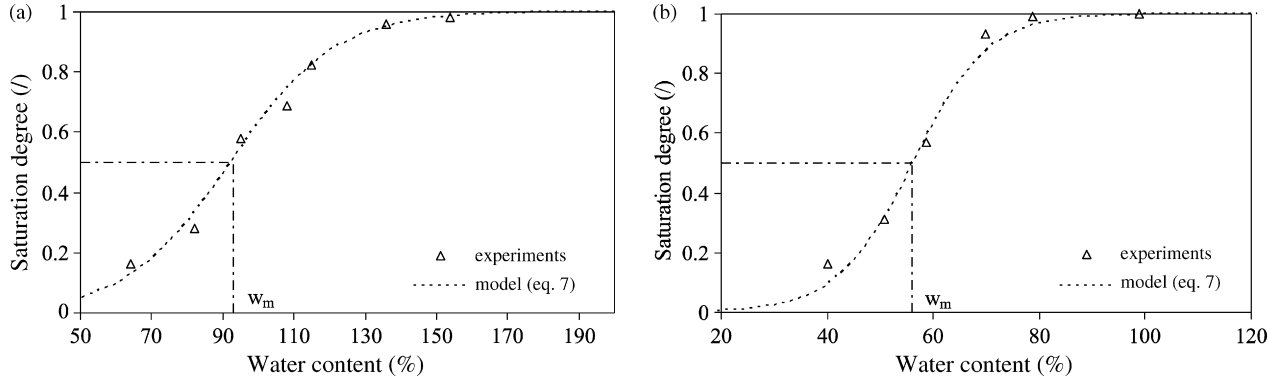

Fig. 1. (a) Variation in saturation degree vs. water content for wetting mass for CMC. (b) Variation in saturation degree vs. water content for wetting mass for Ibuprofen/CMC mixture.

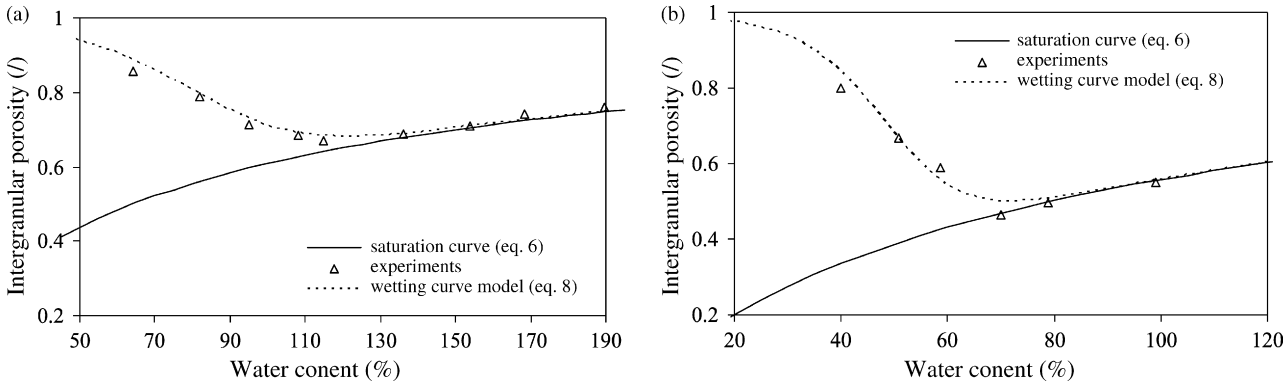

Fig. 2. (a) Variation in intergranular porosity vs. water content for wetting mass for CMC. (b) Variation in intergranular porosity vs. water content for wetting mass for Ibuprofen/CMC mixture.

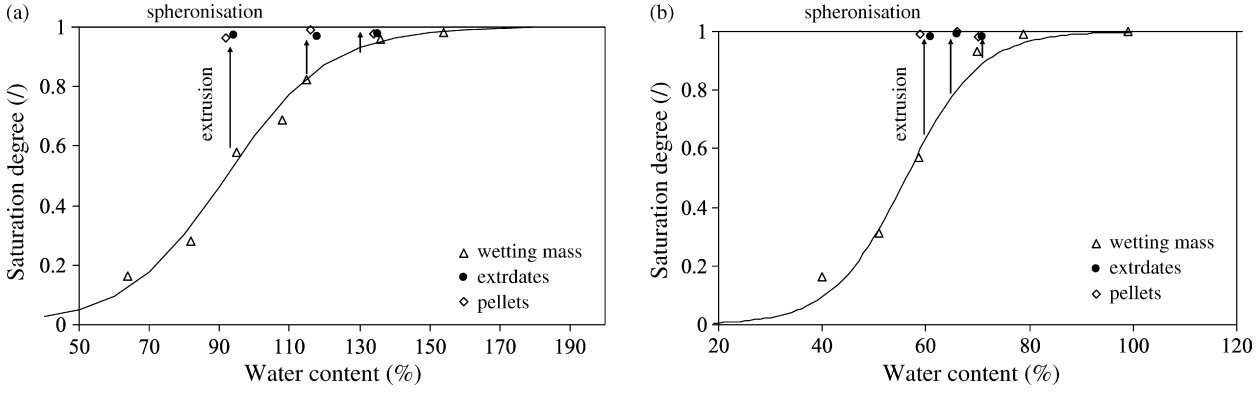

Fig. 3. (a) Variation in saturation degree vs. water content for wetting mass, extrudates and pellets for CMC. (b) Variation in saturation degree vs. water content for wetting mass, extrudates and pellets for Ibuprofen/CMC mixture.

show that the relation between porosity and water content is interpolated with a very good agreement by the following relation:

$$n = 1 - \frac{\rho_s}{\rho_s^*} = \frac{d_s^* w(1 + e^{-(w-w_m)/d})}{1 + d_s^* w(1 + e^{-(w-w_m)/d})} \quad (8)$$

This relation depends on the true densities of the solid(s) and the liquid phases as well as two adjustment parameters: w_m and d resulting from the analysis of the curve $S_w(w)$ (Eq. (7)). The wetting curve, composed of different hydro-textural states of the wet mass after kneading, fixes the upper limit of the hydro-textural diagram for the given mixing operation conditions.

4.2. Extrusion/spheronisation

For each initial water content, extrudates and pellets are close to saturation (Fig. 3a and b). These findings confirm the observations of Jerwanska et al. (1995). Extrusion thus ensures compaction allowing total drainage of the interstitial gaseous

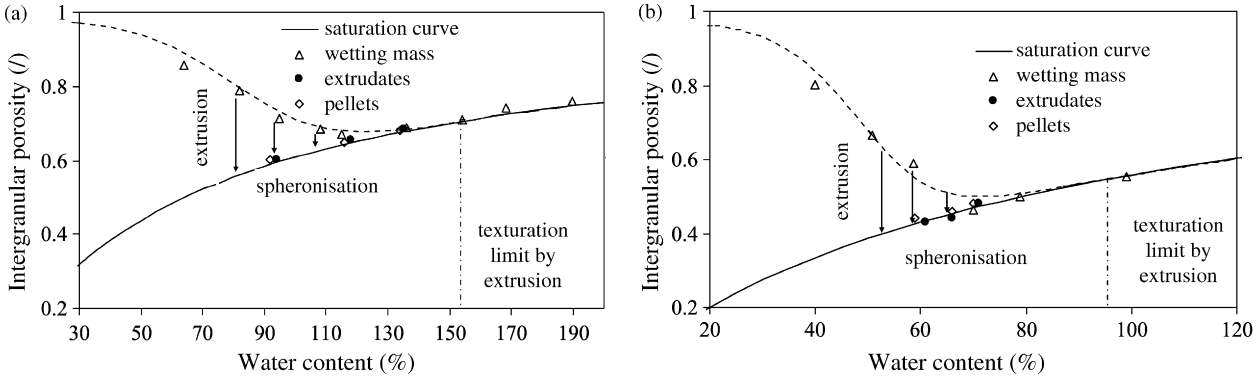

Fig. 4. (a) Variation in intergranular porosity vs. water content for wetting mass, extrudates and pellets for CMC. (b) Variation in intergranular porosity vs. water content for wetting mass, extrudates and pellets for Ibuprofen/CMC mixture.

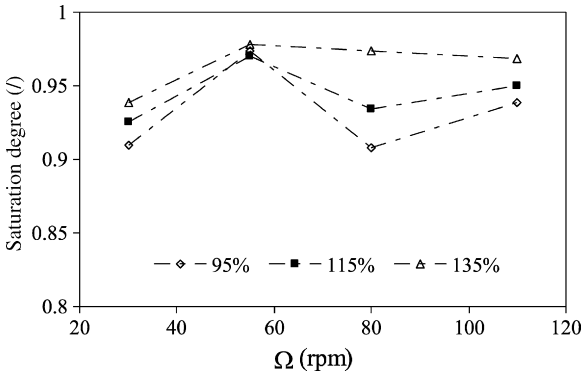

Fig. 5. Saturation degree values of extrudates at different extrusion speeds for CMC.

phase. The material is thus biphasic (solid/liquid). The higher the wet mass porosity, the higher the compaction, ensured by extrusion (Fig. 4a and b). Thus, the wet mass is textured by this process as long as initial water content remains below a value ensuring its saturation. Indeed, beyond this value, extrusion is merely a shaping process. Wet masses and extrudates porosity values are identical. A limit is highlighted in texturation capacity by extrusion. This corresponds to the intersection of the wetting and saturation curves.

In the case of CMC, these observations are generalized at different extruder screw rotation speeds. For each water content and whatever the speed of extrusion tested, the porosity of the extrudates is always in a zone close to porosity at saturation (Fig. 5). The initial water content value is noted to condition the porosity of wet extrudates and pellets regardless of the speeds (Ω) tested. Obtaining the desired porosity can thus be approximated by fixing the initial water content at a value deduced from relationship (6). For extrudates saturation degree—values around 0.95 ($\pm$0.02), the weak influence of extruder screw rotation speed is noted (Fig. 6).

A more complete study of the influence of extruder screw rotation is given in (Galland et al., 2003).

At the spheronisation stage, for all the trials realised with CMC and the operating conditions presented (different loads, speeds and times), the hydro-textural state of extrudates is not modified, the porosity and saturation degree of extrudates and pellets are the same (Figs. 3 and 4). This result confers on the spheronisation stage the exclusive role of a shaping process (Galland et al., 2005). Whatever the values of the three operating parameters selected (speed, load and time of spheronisation), their respective and mutual influences do not appear significantly through the hydro-textural characteristics of pellets. Just before drying, pellets are in the same relative hydro-textural state located on the curve of saturation.

4.3. Drying

This operation finalises the textural characteristics of the product by densifying the medium. Indeed, for these water contents, the wet pellets behaves like a strongly deformable medium and presents mechanical shrinkage during the water transfer.

Drying kinetics are analysed for CMC using characteristic drying curves (Fig. 7), i.e. drying flux/water content graphs (Nadeau and Puiggali, 1995), where drying flux is defined:

$$F = \frac{1}{S_{\text{pellets}}} \left| \frac{\mathrm{d}w}{\mathrm{d}t} \right| \tag{9}$$

At saturation, the interfacial area between liquid and solid pellets (S_{pellets}) is likened to the external area of each pellet. This mode of representation reveals four distinct periods (Fig. 7).

Drying starts directly with an initial period in which water evaporation flux is constant and maximal. The critical water content corresponding to the end of the constant rate period was, for all trials, situated around 65% (w_{c1}). A model adapted to pellet geometry and taking account of shrinkage has been proposed by Ruiz et al. (2006) to determine critical water content. The drying rate then undergoes a first period of decreasing. Water content corresponding to the end of this period is systematically located around 25% (w_{c2}) (Ruiz et al., 2006). Drying continues with an even greater decrease in flux, with the end of this period corresponding to water content near to 5% (w_{c3}) for all tests. Drying finishes with stabilisation at equilibrium water content noted as w_{eq}.

For all tests, temperature influences the rate of the phenomena but does not appear to affect their transitions (Galland, 2005). It should also be noted that the initial water content does not influence the periods referred to.

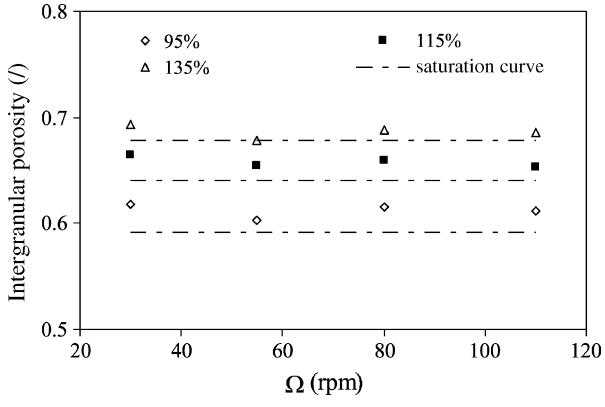

Fig. 6. Intergranular porosity values of extrudates at different extrusion speeds for CMC.

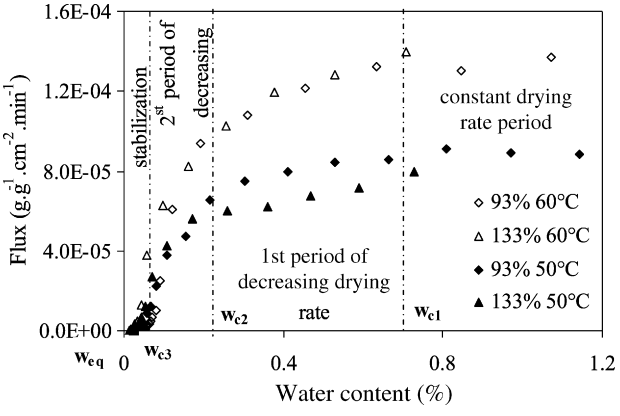

Fig. 7. Characteristic drying curves for CMC.

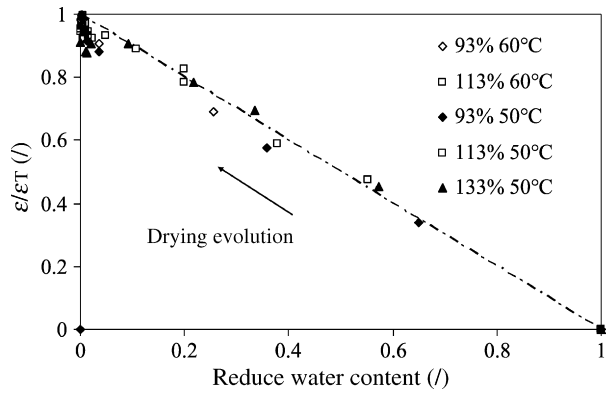

Fig. 8. Ideal shrinkage during drying for all trials for CMC.

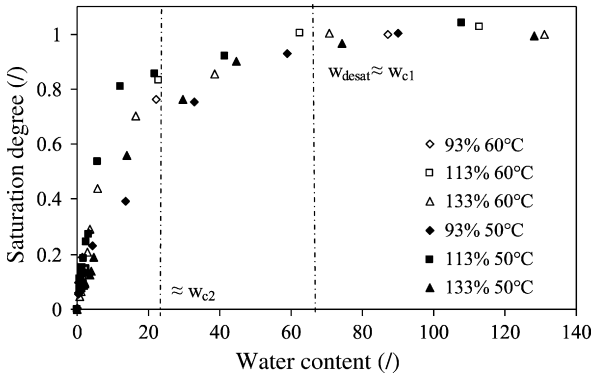

Fig. 10. Variation in saturation degree vs. water content for all CMC trials.

The mechanical shrinkage of the material during drying, due to the stresses induced by capillary pressure, has a repercussion on volume and porosity. The shape remains unchanged and sphericity is preserved.

Volume variations are measured and represented by the changes in volume deformation. Fig. 8 shows volume deformation divided by the final deformation reached at the end of drying (ε_T), versus reduced water content for all tests. The reduced water content provides a comparison between different wettings as a function of relationship:

$$w_r = \frac{w - w_{eq}}{w_0 - w_{eq}} \tag{10}$$

Total volume deformation is independent of process conditions and initial conditions. Its value was the same for all the tests carried out $\varepsilon_T \approx 55\%$. The material appears to deform practically throughout the drying process and in an ideal shrinkage situation. This demonstrates how pellet volume variation exactly compensates evaporated water volume. This situation shows that the drying and deformation periods correspond: no dephasing exists between the evaporation phenomenon and induced shrinkage.

During drying, variations in water content and intergranular porosity induced by the consolidation of the medium are shown in the hydro-textural diagram (Fig. 9). These experimental points plot the path followed by the material during drying and identify three distinct periods. Texture variation begins with an initial period in which the hydro-textural state of the pellets follows the saturation curve. This period coincides with the constant evaporation flux period described previously for which the biphasic medium also deforms at a constant rate. The water content, w_{desat}, marking the end of this period corresponds to the desaturation of the medium (Fig. 9) and appears little affected by the initial wetting (Fig. 10). For all tests, w_{desat}, was very close to critical water content w_{c1}, confirming the absence of dephasing between the evaporation and shrinkage phenomena.

In the second period that follows, the medium becomes triphasic (presence of air), and continues to consolidate with slower kinetics that nevertheless lead to strong porosity variation. The saturation degree slowly decreases to a value close to 80% (Fig. 10). The pellets maintain a hydro-textural state close to saturation with no possibility of discriminating the transformation paths specific to each case. A third period is identified when the water content attains value w_{c2}. This slowing is due to the limitation in water transfer in the sample. Saturation degree reduces greatly with water content, and differentiation appears between the transformation paths, showing that the medium is now consolidating differently depending on its initial water content. At w_{c3}, the material has now reached total rigidity. Porosity remains unchanged, while water content remains constant around its hygroscopic equilibrium value.

The final porosities are shown versus initial wettings in Fig. 11. They confirm that weaker porosities were obtained for a cellulose powder that was less wetted initially. This result thus

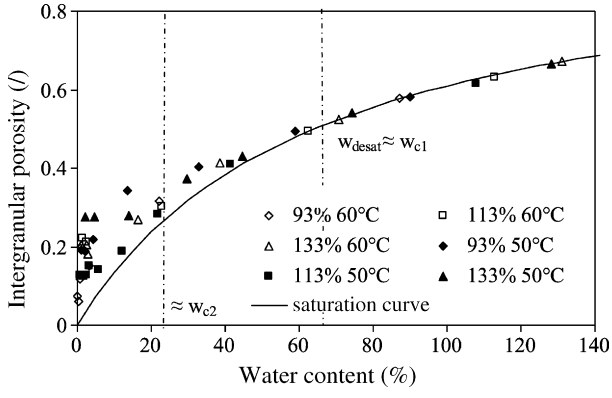

Fig. 9. Transformation paths for all tests on the hydro-textural diagram for CMC.

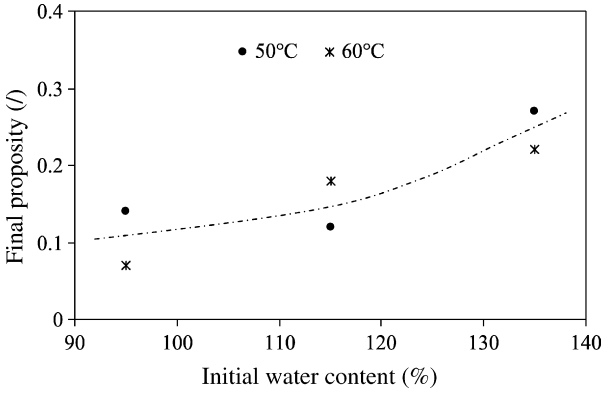

Fig. 11. Final porosity vs. initial water content for two drying temperatures for CMC.

indicates a means of controlling this essential variable for drug release.

5. Conclusion

The approach suggested in this study provides a dynamic analysis of elaboration by extrusion/spheronisation by monitoring the hydro-textural characteristics of the product at each stage of the process. The hydro-textural diagram reveals the major implication of the wetting/kneading operation (so the formulation: solid/liquid ratio) and of the drying stage to obtain pellets of controlled texture. With oven drying, final porosity increases with initial water content. Another study will interest specifically to analyse and quantify water content influence on the morpho-granulometric aspects.

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