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The Effects of Relative Humidity and Super-Disintegrant Concentrations on the Mechanical Properties of Pharmaceutical Compacts

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The influence of the composition and the relative humidity on the properties of pharmaceutical compacts prepared from mixtures of three excipients and three super-disintegrants was evaluated. Various amounts of super-disintegrant and different conditions of relative humidity during the storage were used to study mechanistically the disintegration process and to connect it to compact's mechanical properties. Three point single beam test was used to measure tensile strength and Young's modulus of compacts containing various amount of disintegrant and stored under various relative humidity. The presence of moisture within pharmaceutical compacts containing a disintegrant influences drastically their mechanical properties. Then, the results are related to micro-cracks visualized by MEB.

Keywords super-disintegrant; mechanical properties; Young's modulus; tensile strength; relative humidity; moisture content

INTRODUCTION

A drug given in orally administered tablets must dissolve before the absorption and the transport into the systemic circulation. Before the dissolution, it is necessary to overcome the cohesive strength obtained by compaction to observe the disintegration of the tablet (Roche-Johnson Wang, Gordon, & Chowhan, 1991). Super disintegrants are usually included in pharmaceutical tablets formulation to induce this process. Their purpose is to facilitate the break-up of compact when it is placed in an aqueous environment (i.e., after administration to ensure rapid availability of the active ingredient for absorption) (Visavarungroj & Remon, 1990). Different theories dealing with mechanisms of action of disintegrant have been proposed in the literature: wicking (Curlin, 1955), heat of wetting (Matsumaru, 1958; Matsumaru, 1959), deforming recovery (Hess, 1978), particle-particle repulsion (Guyot-Hermann & Ringard, 1981), and swelling (Bolhuis, Van Kamp, Lerk, & Sessink, 1982; Caramella, Colombo, Conte & La Manna, 1983; Couvreur, Gillard, Van den Schrieck, & Rolland, 1974), which may be the main mechanism in the disintegration process. It seems that no single mechanism of disintegrant action is applicable to all disintegrants but in many cases, a combination of mechanisms may be operative. Whatever the mechanism may be, to obtain a rapid disintegration, a disintegrant force must be developed inside the tablet to weak and to break interparticle bonds (Caramella, Colombo, Conte & La Manna, 1987). Disintegrant agents are able to draw large amounts of water into the porous network of compact and simultaneously to swell. Therefore, it is also of interest to evaluate the effect of the storage at various relative humidity on compacts containing super-disintegrant in their formulation because the following water uptake is likely to affect their mechanical properties. Then, for a successful formulation, equilibrium between excipients and disintegrant concentrations must be reached to obtain mixtures easily compressed, tablets with adequate strength and stability that finally disintegrate after reaching an aqueous medium (Chebli & Cartilier, 1998).

In this study, the effects of mixtures composition on compaction behavior of the tablets and moisture uptake were first examined. Secondly, the effects of type and amount of disintegrant and storage humidity on compact's mechanical properties were examined. Tensile strength (σ_r) and Young's modulus (E) of compacts compressed from binary mixtures of three representative direct compression excipients and three super-disintegrants were evaluated using three point single beam test with a micropress prototype. A lubricant was added in standardized and unchanged conditions, in each mixture.

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MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel PH101®, SEPPIC, batch no 6512), dibasic calcium phosphate dihydrate (Ditab®, Aventis Pharma, batch no 057741) and lactose spray dried (Lactose Fast Flo®, SEPPIC, batch no 8597122562) were used as tableting excipient. They present very different deformation mechanisms under pressure (ductile, brittle, and intermediate, respectively [Busignies, Tchoreloff, Leclerc, Besnard & Couarraze, 2004; Doelker, 1993; Doldan, Souto, Concheiro, Martinez-Pacheco & Gomez-Amoza, 1995] and different solubility (hygroscopic, hydrophilic, and insoluble, water soluble [Cartilier & Tawashi, 1993; Doelker, 1993; Doldan et al., 1995]. Croscarmellose sodium (AcDiSol®, SEPPIC, batch no T533C), sodium starch glycolate (Explotab®, SPCI, batch no 8359), and crospovidone (Kollidon CL®, BASF, batch no 59–1641) were used as disintegrant. These disintegrants exhibit different swelling properties (Gissinder & Stamm, 1980). Indeed, Explotab® and AcDiSol® present high swelling forces and high swelling volumes, since Kollidon CL® is characterized by high swelling force despite a moderate swelling volume (Caramella, Colombo, Conte, Ferrari, & La Manna, 1986). Magnesium stearate (Akcros Chemicals, batch no NF-BP-MF2 039445) was used as internal lubricant.

Powder Characterization

The particle size distributions of materials were studied by laser diffraction (Coulter LS 230, λ = 750 nm) in conditions of validity of Fraunhofer's theory. Dry condition measurements were used for the tableting excipients: cellulose, dibasic calcium phosphate dihydrate, and lactose. Since, the disintegrants are cohesive powders; the measurements were performed in wet conditions using dispersions in silicon oil to avoid the swelling. The apparent particular densities ($\rho_{particular}$) of the materials were determined by helium-pycnometry (Accupyc 1330, Micromeritics Instruments. Inc, Atlanta, GA). The apparent particular densities of the mixtures (ρ_m) were evaluated by using the following equation:

$$\frac{100}{\rho_m} = \frac{x_1}{\rho_{particular1}} + \frac{x_2}{\rho_{particular2}} + \frac{x_3}{\rho_{particular3}} \qquad (1)$$

where x_i and $\rho_{particular-i}$ are respectively the mass fraction (%) and the apparent particular density of each component.

The surface area of the powders was determined by gas adsorption (Coulter SA 3100) based on the BET monolayer adsorption theory of a gas (nitrogen) on a solid surface at reduced temperature. Table 1 summarizes the main characteristics of the materials. All of these measurements were performed in triplicate.

Blends Preparation

A series of ternary powder blended mixtures comprising tableting excipient (Avicel PH101®, Lactose Fast Flo® or Ditab®), different amount of disintegrant (AcDiSol® or Explotab® or Kollidon CL®, from 0 to 8% by weight) and lubricant (Magnesium stearate, 1% by weight) were prepared using a Turbula blender (type T2C, Willy A Bachofen, Basel, Switzerland) at 50 rpm for 5 min for each stages (i.e., the excipients were added to the disintegrant by three stages and the lubricant was last added).

Nine different sorts of mixtures were studied and their notations are illustrated in Table 2. For each of these mixtures, seven different compositions with various disintegrants ratios (0, 1, 2, 3, 4, 5, and 8% by weight) were prepared.

Powder Compaction

Two geometries of compacts were used: parallelepipedical compacts and cylindrical compacts. The parallelepipedical geometry is more adapted to perform the measurement of mechanical properties such as Young's modulus and tensile strength obtained with three point single beam tests. On the other hand, it is easier to obtain a number of cylindrical tablets

TABLE 1
Physicochemical Properties of Materials Used (n = 3).

Sample	Particle Diameter 50% Volume	Particle Diameter 90% Volume	Particles Shape	$\rho_{particular}$ (g.cm^{-3})	Surface Area (m^2.g^{-1})
Avicel PH101®	< 65 µm	< 143 µm	elongated	1.5433 ± 0.0003	1.094 ± 0.006
Lactose Fast Flo®	< 122 µm	< 192 µm	± round	1.5314 ± 0.0004	0.454 ± 0.023
DiTab®	< 182 µm	< 255 µm	± round	2.5022 ± 0.0007	1.736 ± 0.064
AcDiSol®	< 48 µm	< 116 µm	elongated	1.5943 ± 0.0004	0.489 ± 0.015
Explotab®	< 50 µm	< 80 µm	± round	1.4196 ± 0.0009	0.232 ± 0.008
Kollidon CL®	< 110 µm	< 206 µm	± round	1.2003 ± 0.0002	0.643 ± 0.010

TABLE 2
Mixtures Contains Notation

	AcDiSol®	Explotab®	Kollidon CL®
Avicel PH101®	AA	EA	KA
Lactose Fast Flo®	AL	EL	KL
DiTab®	AD	ED	KD

with the help of an instrumented eccentric press, and then, to modelize the raw data to perform the Heckel plots.

Parallelepipedical Compacts

Parallelepipedical compacts were prepared by direct compaction on an instrumented hydraulic press (Perrier Labotest®, Perrier, France) with a constant compaction speed of 0.1 mm.s^{-1}. Beams were made by compaction in rectangular dies of about 40 mm length and 6 mm breadth. The amount of material required to give a 5 mm height beam at zero theoretical porosity was calculated from their particular densities to allow direct comparison of all materials (Busignies et al., 2004). To obtain each compact, the powder mixture was individually weighted and manually poured into the die cavity, ensuring uniform distribution of the powder and the compaction was then performed. Compacts were prepared at various compression pressure (about 40, 85, 130, and 170 MPa) to achieve compacts of varying porosities. Three beams were prepared for each load, and each storage condition.

Cylindrical Compacts

Cylindrical compacts were produced using an instrumented Frogerais OA eccentric press (Frogerais, France) with a compaction speed of about 80 mm. s^{-1}. The volume of the die was maintained constant (punch diameter of 11.28 mm and die depth of 10 mm, i.e., a volume of 1 cm^3) and filled manually. Applied forces and punch displacements were recorded using Pecamec 4.1® software (J2P Instrumentation, Vitry/Seine, France) (Busignies et al., 2004). The pressures applied were 85 MPa and those necessary to obtain the Heckel plots (Heckel 1961a,b) of the mixtures.

Storage Conditions

The parallelepipedical compacts and cylindrical compacts were then conserved in a closed chamber, for at least 10 days, over four different relative humidity conditions (RH): 2% (± 2%) prepared using a desiccant, silicagel®, 30, 50, and 80% RH (± 4%) prepared using saturated aqueous solutions of $CaCl_2$, $Na_2Cr_2O_7$ $2H_2O$, and KBr, respectively. Compacts dimensions were then measured with an electronic micrometer (Mitutuyo 500-161U, Japan) and weighted on an analytical balance (Sartorius BP221S, Germany). The porosities (ε) of the resultant compacts (i.e., after full relaxation under different RH) were then determined from their dimensions and weights according to:

$$\varepsilon = 1 - \frac{apparent\ \ density}{particular\ \ density} \qquad (2)$$

Moisture Sorption

Moisture uptake was determined gravimetrically with cylindrical compacts obtained under 85 MPa (Nokhodchi, Rubinstein, Larhrib & Guyot, 1995). The compact moisture content may be expressed by weight as the ratio of the mass of water present to the theoretical dry weight of the compact. The compacts were successively stored in the different RH conditions (2, 30, 50, and 80% RH). Compacts were taken out periodically and accurately weighted on an analytical balance (Sartorius BP 2215, Germany, with a resolution of 0.1 mg) until a constant weight was obtained (about 10–15 days). The moisture content percentage (MC (%)) of the compact was defined as:

$$MC = \frac{W_{compact} - W_{dry\ compact}}{W_{dry\ compact}} \times 100 \qquad (3)$$

with $W_{compact}$ and $W_{dry\ compact}$, respectively the compact weight and the theoretical dry compact weight (RH = 2%).

Heckel Plots

Major consolidation mechanisms in pharmaceutical powders are plastic deformation and/or brittle fracture. The study of Heckel plots obtained using the Frogerais OA press is used to distinguish between these two compaction behaviors. Mean yield pressure (P_y expressed in MPa) of all the materials (cylindrical compacts) were measured according to Heckel equation (Heckel, 1961a; Heckel 1961b):

$$\ln \frac{1}{1-D} = kP + A \qquad (4)$$

where $D = 1 - \varepsilon$ is the relative density of the powder bed at the pressure P, k, and A are constants obtained respectively from the slope and the intercept of the curve $\ln[1/(1-D)] = f(P)$. k is classically related by its reciprocal value ($1/k = P_y$) to the mean yield pressure of the material.

Measurement of Mechanical Properties

Tensile strength is commonly used to describe compact degree of cohesion (strength). Young's modulus, defined as the ratio of stress versus strain, is used to describe material stiffness. Tensile strength (σ_r) and Young's modulus (E) of the compact were measured using a three point single beam test

(Busignies et al., 2004b) with a micropress prototype (Digipharm, MCC0300-01, France). A parallelepipedical beam is subjected to transverse loads and its central deflection due to bending is determined. The test was performed at a constant speed of 0.060 mm.min^{-1}. Forces applied and displacements were recorded (with a frequency of 0.1 s^{-1}) using DIGITEST V1.0.04® software (Digipharm, France). Force-displacement profiles were obtained.

By considering the geometrical conditions under which the tests are performed, Young's modulus (E expressed in GPa) was determined from the slope of the linear portion of the force-displacement curves using the following equation (Beaudoin & Sereda, 1976):

$$E = \frac{F\, L^3}{4\, \delta\, t^3\, w} \tag{5}$$

where F is the dynamic applied load (N), δ is the vertical deflexion of the mid point of the beam (mm), L is the distance between supports (mm), t is the sample thickness (mm) and w the sample width (mm).

A definite number of loading-unloading cycles were completed (4, 3, and 2, respectively for compact containing Avicel PH101®, Lactose Fast Flo®, and Ditab®) in order to reach the stability of the studied samples and to obtain only the elastic response of the compact. These cycles avoid possible errors caused by incomplete contact between the beams under test and allow to only considering the elastic response (reversible deformation) of the beam. The applied load that is required to perform such cycles must be lower than the loading which cause compact fracture (Busignies, Tchoreloff, Leclerc, Hersen, et al., 2004).

Secondly, the tensile strength (σ_r expressed in MPa) was determined, on the same beam, from the force required to fracture the beam, according to the formula (Fell & Newton, 1970):

$$\sigma_r = \frac{3\, F_r\, L}{2\, w\, t^2} \tag{6}$$

where F_r is the fracture loading (N), L is the distance between supports (mm), w is the sample width (mm) and t the sample thickness (mm).

RESULTS AND DISCUSSION

Compression Behavior

The material's deformation mechanisms were evaluated during compression of cylindrical compacts from the Heckel plots (Heckel, 1961a,b). The mean yield pressure of the three excipients show the difference in their compaction behavior (P_y = 62 +/– 1 MPa for Avicel PH101®, P_y = 145 +/– 1 MPa for Fast Flo® and P_y = 400 +/– 6 for DiTab®). P_y values (MPa) versus disintegrant concentrations (% by weight) are presented in Figure 1. As expected, compacts containing Ditab®, Avicel PH101®, and Fast Flo® were respectively highly brittle (high mean yield pressure), ductile (low mean yield pressure), and intermediate. The mean yield pressure (P_y) values, calculated from the linear part of the Heckel profile, for cylindrical compact containing a high proportion of Ditab®, Fast Flo®, and Avicel PH101® varied respectively from 400 to 304 MPa, from 145 to 126 MPa, and from 66 to 58 MPa according to disintegrant nature and concentration. Results point out that compression behavior of powder mixture was dictated by the filler which represent in this study at least 91% (weight/total weight of the compact). Other authors show a similar trend for binary mixtures containing one component with a proportion lower than 10% w/w (Busignies, Leclerc, Couarraze, & Tchoreloff, 2006; Humber-Droz. Mordier & Doelker, 1983; Ilkka & Paronen, 1993; Sheikh-Salem & Fell, 1981; Van Veen, Van der Voort Maarschalk, Bahuis, Zuurman & Frijlink, 2000).

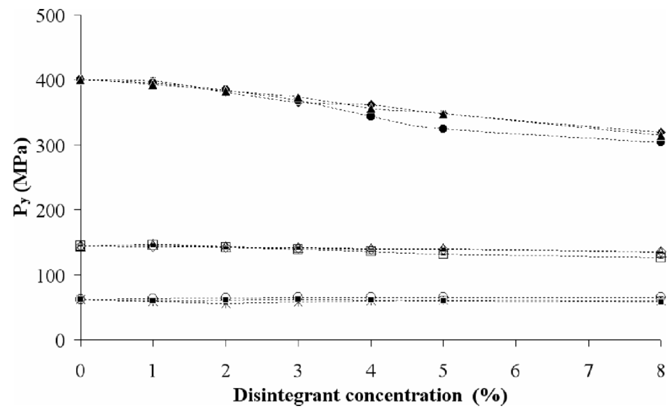

FIGURE 1. Mean yield pressure (P_y) versus disintegrant concentrations (the standard deviations are confused with experimental points, n = 3). Key: ❍, AA; ■, EA; ✶, KA; ✧, AL; □, EL; Δ;, KL; ♦, AD; •, ED; ▲, KD.

The mean yield pressures of the studied mixtures show a poor dependence upon the type and concentration of disintegrant concerning the compacts obtained from Avicel PH101® or Fast Flo®. On the other hand, for compacts with Ditab® as tableting agent, P_y values seem more influenced by disintegrant concentration. The mean yield pressure decreases with increasing disintegrant concentration. Nevertheless, this result is to be taken with precaution because the pressures used for the determination of P_y (σ_c = 250MPa) are weak compared to P_y (400MPa), and the obtained values of P_y of the DiTab® cannot thus be regarded as absolute values. Then, the addition of a super-disintegrant leads to a slight variation of the deformation mechanism of mixture during compaction in regard to pure Ditab®.

Moisture Uptake Studies

Measurements of moisture uptake, under equilibrium conditions, were carried out with cylindrical compacts compressed at 85 MPa. This compression pressure corresponds to compact of about 20% porosity in the case of compacts with pure Fast Flo® and Avicel PH101®, and 30% porosity for compact with pure DiTab®. These porosities are in the middle of the range of porosities obtained with tablets of pure tableting excipients (Rowe, Sheskey, & Owen, 2005).

Moisture contents under equilibrium conditions versus relative humidities for the nine sorts of mixtures (AA, EA, KA, AL, EL, KL, AD, ED, KD), either with 8% of disintegrant or without disintegrant, are presented in Figure 2. In all cases, except for compacts containing DiTab® without disintegrant, moisture content of mixed powders increases with RH. The moisture uptake values, for compacts consisting of DiTab® without disintegrant, are not affected by RH increase (i.e., 0.02% moisture content at 80% RH); however, compacts consisting of Fast Flo® and above all of Avicel PH101®, without disintegrant are respectively, slightly (0.3% moisture content at 80% RH) and highly (6% moisture content at 80% RH), affected by the relative humidity. This indicates that in the case of tablets containing DiTab®, water is uptaken only by the disintegrant particles. The high moisture content of compacts with Avicel PH101®, even without disintegrant, may be explained by the hygroscopic properties of Avicel PH101® which promote moisture penetration into the compacts.

Concerning compacts with Avicel PH101®, the amount of moisture uptake increases markedly with RH (Figure 2a). Nevertheless, pure Avicel PH101® compacts, sorb significant amounts of moisture (6% water at 80% RH) whereas the addition of disintegrant only leads to a limited additional increase of sorbed moisture (2.5% more water content at 80% RH for compact with 8% Kollidon CL® compared to pure Avicel PH101®). The amounts of moisture uptaken by compact containing Avicel PH101® and AcDiSol® in their formulations are only slightly affected by the disintegrant concentration except for the 80% RH. For this later, a constant increase in moisture content with increasing concentration of disintegrant was noted. For compacts with Avicel PH101® and Explotab® or Kollidon CL®, moisture uptake was similar and higher than those of AcDiSol®. For 30 and 50% RH, there is significant moisture content increase (0.7%) when disintegrant is added (1%). For a disintegrant concentration higher than 1% there is no more water uptake increase. At 80% RH, a constant increase in moisture uptake with disintegrant concentration was noted. Avicel PH101® compacts were characterized by a strong hydration capacity (it demonstrates both properties, being binder and disintegrant (Chebli & Cartilier, 1998)) and water uptake profiles depend on both disintegrant and relative humidity. Other authors (Gordon & Chowhan, 1987; Roche-Johnson et al., 1991) illustrated the relationship between increasing hygroscopicity of the tablet material and minimizing superdisintegrant efficiency.

Concerning compacts with Lactose Fast Flo®, the increase in disintegrant concentration and RH lead to moisture uptake increase (Figure 2b). The moisture content evolutions, in the case of compacts with Explotab® or AcDiSol® as disintegrating agent, are similar for 30% and 50% RH. For 80% RH, the amount of water uptake in the case of compacts containing Explotab® (2.7% of water for compact with 8% of Explotab®) is clearly more important than in the case of those containing

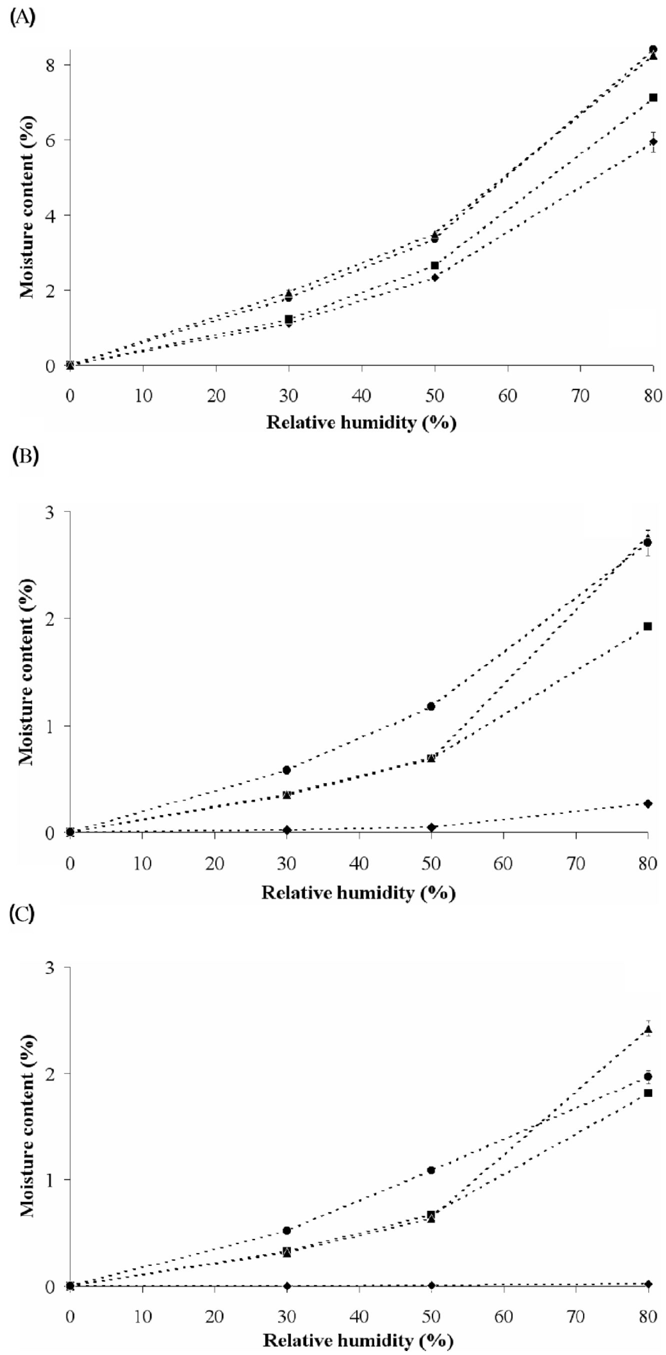

FIGURE 2. Moisture content versus relative humidity for compacts of pure material and containing 8% of disintegrant; (A) compacts with Avicel PH101®, (B) compacts with Fast Flo®, (C) compacts with DiTab®. The data points and error bars represent the $M \pm SD$ of three replicates. Key: ♦, pure filler; ■, filler with AcDiSol®; ▲, filler with Explotab®; ●, filler with Kollidon CL®.

AcDiSol® (1.9% of water for compact with 8% of AcDiSol®) and reach the same moisture content than compacts with Kollidon CL® (2.7%), whereas these later compacts show higher moisture content at 30 and 50% RH (respectively 0.6 and 1.2% of water for compacts with 8% of disintegrant) than compacts with AcDiSol® (respectively 0.3 and 0.7%) or Explotab® (respectively 0.4 and 0.7%). The more the relative humidity increases and the more important the influence of disintegrant concentration on the moisture content is.

Concerning compacts with Ditab®, moisture content increases both when relative humidy and/or disintegrant amount increases (Figure 2c), with a marked effect, for compacts with Kollidon CL®, when disintegrant concentration is higher than 3%. The evolutions of moisture content versus relative humidity are parallels to those with lactose Fast Flo®. But, knowing that DiTab® is insoluble filler, the water uptake is only due to the addition of disintegrant in the formulation. The moisture content evolution in the case of compacts with Explotab® or AcDiSol® as disintegrating agent is similar for relative humidities of 30 and 50% (respectively 0.3 and 0.6% for compact with 8% of disintegrant). For a relative humidity of 80% the amount of water uptake by compacts containing Explotab® (2.4% for compact with 8% of disintegrant) is clearly more important than in the case of the AcDiSol® (1.8%). The same trend was observed on the moisture sorption isotherm performed on these three disintegrants (Chang et al., 1998). These results are similar to those obtained with lactose Fast Flo® compacts since, the more the relative humidity increases and the more important the influence of disintegrant concentration on the moisture content is.

Moisture uptakes of compacts containing Ditab® or lactose Fast Flo® are very similar and these results suggest that in both cases the water is mainly uptaken by disintegrant particles. The comparison of the obtained results for our various systems, by disregarding moisture uptake by the tableting excipient (Avicel PH101®, lactose Fast Flo®, and Ditab®) shows that the effect of disintegrant is identical whatever the tableting excipient is. Moreover, compacts containing AcDiSol® in their formulations sorb less moisture than those containing Explotab® or Kollidon CL®. In other terms, tablet disintegration depends on hygroscopicity of the filler and other ingredients as well as the water uptake of the disintegrating agent.

Mechanical Properties

As reported previously (Rowe & Roberts, 1995), when the porosity is reduced by increasing compaction pressure, the Young's modulus, and tensile strength of compacts increase. The trend was preserved at each relative humidity of storage and each composition. Both porosities were chosen to study and compare mechanical properties of compressed materials in a range of porosity corresponding to experimental data. The Young's modulus and tensile strength at 20% of porosity (Avicel PH101®, lactose Fast Flo®) or 30% of porosity (DiTab®) were subsequently determined by interpolation using the Ryschkewitch-Duckworth relationship (Ryshkewitch, 1953).

$$A = A_0 \, . \, e^{-k\,\varepsilon} \tag{7}$$

where A is the material property at porosity ε, A_0 is the material property at zero porosity, and k is a constant.

Mixtures with Avicel PH101®. The tensile strength and Young's modulus values are only slightly affected by concentration and nature of disintegrants (Figures 3 and 4). The two mechanical properties decrease when a little proportion of

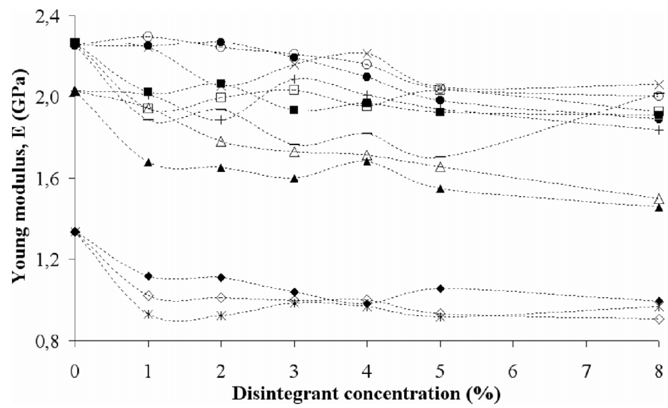

FIGURE 3. Effect of disintegrant concentration and relative humidity on the Young's modulus of compacts (20% porosity) containing Avicel PH101® in their formulations. Key: ●, EA with RH = 2%; ■, EA with RH = 30%; ▲, EA with RH = 50%; ♦, EA with RH = 80%; ❍, KA with RH = 2%; □, KA with RH = 30%; Δ, KA with RH = 50%; ✧, KA with RH = 80%; –, AA with RH = 2%; ×, AA with RH = 30%; +, AA with RH = 50%; ✶, AA with RH = 80%.

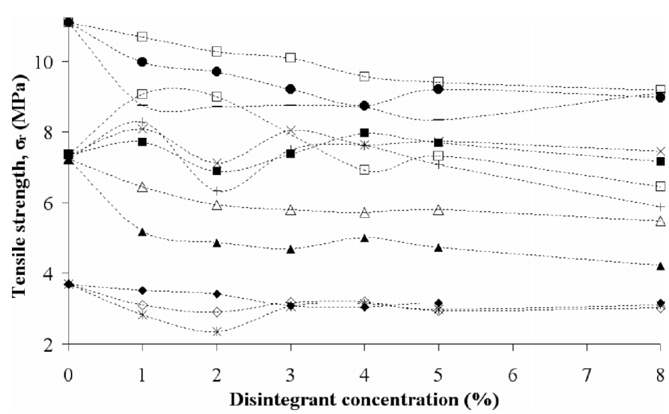

FIGURE 4. Effect of disintegrant concentration and relative humidity on the tensile strength of compacts (20% porosity) containing Avicel PH101® in their formulations. Key: ●, EA with RH = 2%; ■, EA with RH = 30%; ▲, EA with RH = 50%; ♦, EA with RH = 80%; ❍, KA with RH = 2%; □, KA with RH = 30%; Δ, KA with RH = 50%; ✧, KA with RH = 80%; –, AA with RH = 2%; ×, AA with RH = 30%; +, AA with RH = 50%; ✶, AA with RH = 80%.

disintegrant is added. But, an increase in the amount of disintegrant above 1% does not have any additional effect. Relative humidity had a marked effect on tensile strength and Young's modulus, which both decrease when storage relative humidity increases. Indeed, from 30 to 80% of relative humidity, the Young's modulus of pure Avicel PH101® decreases from 2.26 and 1.34 GPa and the tensile strength decreases from 7.4 to 3.7 MPa. These results agree with the moisture content study: high moisture content (high RH) leads to low tensile strength and Young's modulus. For disintegrant proportions lower than 1%, Young's modulus is more sensitive to the addition of disintegrant than tensile strength. On contrary, results are only slightly affected by disintegrant concentration above 1% for 30 and 50% RH. Nevertheless, at 80% RH, moisture content increases regularly when disintegrant concentration increases from 0 to 8%, whereas, σ_r stays unchanged (3 MPa). Moreover E decreases when 1% of disintegrant was added but rapidly reach an asymptotic value (1 GPa).

Mixtures with Fast Flo®. Relative humidity influences the compact mechanical properties but in a way clearly less important than in the case of compacts with Avicel PH101®. More, in the case of tablets with Kollidon CL®, stored at 80% RH, it was impossible to measure the Young's modulus and tensile strength because of a lack of cohesion of the beams. Disintegrant concentration has a significant effect on compact mechanical properties (Figures 5 and 6). Young's modulus and tensile strength decrease when disintegrant concentration increases. These results are consistent with moisture content data. Indeed, an increase in moisture content (when RH and disintegrant concentration increase) leads to a Young's modulus and tensile strength decrease. Nevertheless, when disintegrant concentration increases from 0 to 8%, moisture content increases regularly, whereas, E and σ_r decrease to reach an asymptotic value for a particular proportion of disintegrant. This observation is similar to those of Chebli and Cartilier

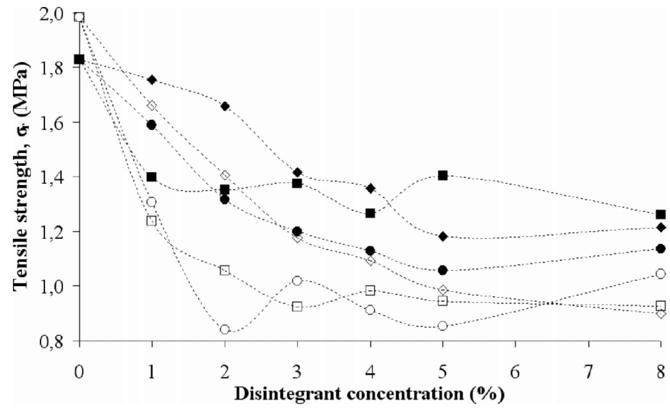

FIGURE 6. Effect of disintegrant concentration and relative humidity on the tensile strength of compacts (20% porosity) containing lactose Fast Flo® in their formulations. Key: ●, KL with RH = 2%; ■, EL with RH = 2%; ♦, AL with RH = 2%; ❍, KL with RH = 50%; □, EL with RH = 50%; ✧, AL with RH = 50%.

(1998) concerning tensile strength of tablets composed of a spray dried lactose and 2 to 10% of Ac Di Sol® or Explotab®. As shown in Figures 5 and 6, Young's modulus and tensile strength are not highly affected by relative humidity in the case of compacts with Explotab®, AcDiSol® or without disintegrant. For disintegrant concentration which does not exceeds 2%, Young's modulus data (Figure 5) are quite similar in the case of 50% RH and 2% RH. Concerning beams with lactose Fast Flo® and Kollidon CL®, results are markedly influenced by relative humidity and by disintegrant concentration. Indeed, at 2% RH, there is a slow and regular decrease in E when Kollidon CL® concentration increases, whereas for a relative humidity of 50%, a concentration equal to 2% is sufficient to reach a constant and low Young's modulus value (about 0.45 GPa). Compacts with Kollidon CL® exhibit the lowest E and σ_r and, as it was shown during moisture content studies, these beams uptake the larger amount of water when RH and disintegrant concentration increase. Nevertheless, when disintegrant concentration increases above 2% (RH = 50%) or 5% (RH = 2%), the moisture content increases and the mechanical properties stay constant.

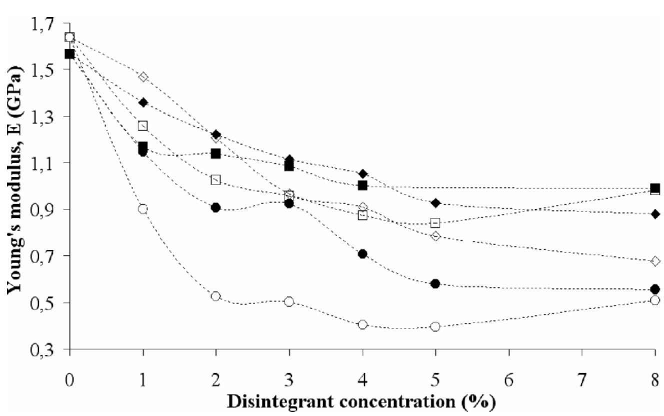

FIGURE 5. Effect of disintegrant concentration and relative humidity on the Young's modulus of compacts (20% porosity) containing lactose Fast Flo® in their formulations. Key: ●, KL with RH = 2%; ■, EL with RH = 2%; ♦, AL with RH = 2%; ❍, KL with RH = 50%; □, EL with RH = 50%; ✧, AL with RH = 50%.

Mixtures with DiTab®. Concerning compacts with DiTab® and AcDiSol® or Explotab® as disintegrating agents (Figure 7), the obtained results, in terms of Young's modulus for 2, 30, and 50% RH are very similar. Yet, for 80% RH, a marked decrease of Young's modulus values is observed, which is more important with compacts containing AcDiSol®. The Young's modulus for pure DiTab® compacts stays almost unchanged (between 1.2 and 1.4 GPa) when relative humidity increases. It supposes that the decrease of Young modulus for all the tested samples only depends on the disintegrant. Nevertheless, this decrease in Young's modulus values also depends on disintegrating agent. In the case of Kollidon CL®, Young's modulus values are lower than those obtained for compacts

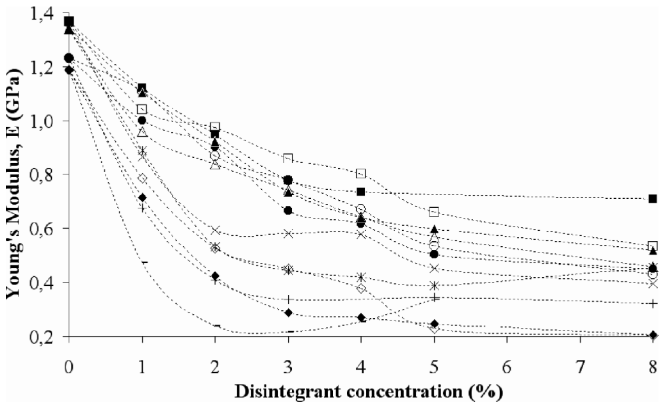

FIGURE 7. Effect of disintegrant concentration and relative humidity on the Young's modulus of compacts (30% porosity) containing DiTab® in their formulations. Key: •, AD with RH = 2%; ■, AD with RH = 30%; ▲, AD with RH = 50%; ♦, AD with RH = 80%; ❍, ED with RH = 2%; □, ED with RH = 30%; Δ, ED with RH = 50%; ✧, ED with RH = 80%; +, KD with RH = 2%; ×, KD with RH = 30%; ✶, KD with RH = 50%; –, KD with RH = 80%.

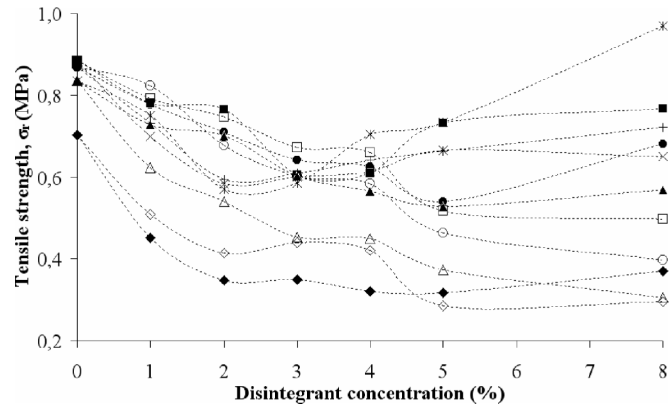

FIGURE 8. Effect of disintegrant concentration and relative humidity on the tensile strength of compacts (30% porosity) containing DiTab® in their formulations. Key: •, AD with RH = 2%; ■, AD with RH = 30%; ▲, AD with RH = 50%; ♦, AD with RH = 80%; ❍, ED with RH = 2%; □, ED with RH = 30%; Δ with RH = 50%; ✧, ED with RH = 80%; +, KD with RH = 2%; ×, KD with RH = 30%; ✶, KD with RH = 50%.

with Explotab® or AcDiSol®. There is an important decrease of Young's modulus when disintegrant concentration increases from 0 to 2% for Kollidon®, 0 to 5% for Explotab®, and 0 to 3% for AcDiSol® (e.g., E decreases from about 1.2 to 0.24 GPa at 80% RH). Up to this concentration, values remain stable. At 80% RH, the constant value of Young's modulus is quite similar for the three formulations.

Different results were obtained in terms of tensile strength. In all the cases, tensile strength of compacts containing AcDiSol® or Kollidon® decreases when disintegrant concentration increases. But, σ_r is slightly affected up to 50% RH, whereas above 50% and for disintegrant proportion ranged from 0 to 4%, varying the RH conditions has no impact on tensile strength. A similar trend was also observed in previous work (Chebli & Cartilier, 1998) with tensile strength of tablet of Emcompress® containing 2 to 10% of AcDiSol®. In the case of mixtures with Kollidon CL® at a concentration higher than 4% and stored at 80% RH, it was impossible to measure the Young's modulus and tensile strength because of a lack of cohesion of the beams. With compacts with Explotab®, RH influences tensile strength (Figure 8). Tensile strength decreases when both RH and disintegrant concentration increase.

There is a general trend towards decreasing the measured mechanical properties (E and σ_r) when increasing RH, that means moisture content increase. These data agree with the hypothesis that disintegrant particles are very hydrophilic and swell when they are brought in contact with water. Disintegrants swell against compacts structure and this obviously leads to the development of a swelling force. This swelling force will modify the stress distribution within the beam and will lead micro-cracks to appear in the whole compact structure. This assumption was confirmed by surface scanning electron microscopy (SEM) for example Fast Flo® compacts containing in their formulations super-disintegrants at a proportion of 8%. These later were initially stored for 2 weeks at 50% RH and then at 2% RH during 48 h in order to carry out the SEM. The photographs (Figure 9) show cracks resulting from the super-disintegrant particles and being propagated to the whole compact surface. The development of micro-cracks might weaken the interparticle interactions. The stress concentration near the new cracks allows beams to break up when they were submitted to stress during the loading test. Indeed, the stress concentration due to the presence of such cracks modify the elastic strain response of the porous beam to the applied stress and result in lower Young's modulus and tensile strength. The compact strength reduction could be considered as the result of reduction in interparticle bonding (Van Veen et al., 2000). As defined by Hancock, Clas, & Christensen (2000), it seems that water uptaken by a compact will exert its major influence by disrupting and weakening the interparticle interaction. Indeed, when a compact breaks up it is most likely to fail at these interparticle contacts since they will include some of the weakest links between particles. The SEM photographs of compacts containing Kollidon® show wider cracks than on the surface of tablets with Explotab® and AcDiSol® as disintegrants. Then, despite a moderate swelling volume, Kollidon® particles should generate a higher swelling force than particles of Explotab® and AcDiSol®. This should also explain that tablets become weaker with Kollidon® as a disintegrant.

According to the observed data, compacts that contained Fast Flo® or DiTab® were more affected by disintegrant concentration than compacts composed of Avicel PH101®. At a constant relative humidity, it could be explained by the mechanism of deformation of the three excipients under pressure. Recent results of other authors (Busignies, Leclerc, Porion, et al., 2006; Kuentz & Leuenberger, 2000; Van Veen et al.,

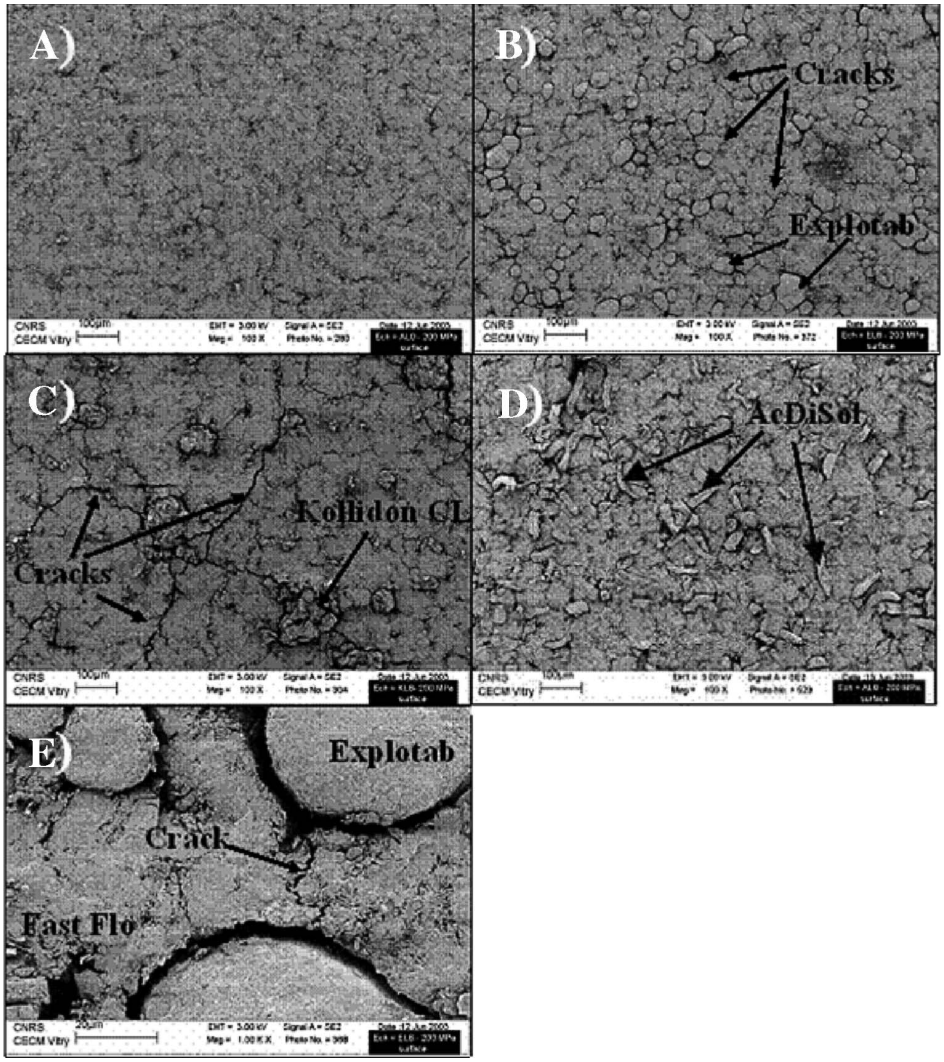

FIGURE 9. Scanning electron micrographs of surface of lactose Fast Flo® compacts containing 8% of super-disintegrant in their formulations and compressed at a compaction load of 200 MPa, (A) pure lactose Fast Flo® compact (Magnification 100×), (B) Fast Flo® compact containing Explotab® (Magnification 100×), (C) Fast Flo® compact containing Kollidon CL® (Magnification 100×), (D) Fast Flo® compact containing AcDiSol® (Magnification 100×), (E) Fast Flo® compact containing Explotab® (Magnification 1000×).

2000) pointed out that a plastic material (such as Avicel PH101®) are less affected by low proportions of other excipients than brittle materials (such as Fast Flo® and DiTab®). Kanig and Rudnic (1984) explained that as particle swell, there must be little or no accommodation by the tablet matrix of that swelling; if the matrix yields elastically to the swelling, little or no force will be expended on the system. A consistent explanation for the lack of correlation between disintegrant concentration and mechanical property evolution is not easy to emphasize. Indeed, no significant relationship was observed between changes in compacts mechanical properties and moisture contents after storage. With regard to the formulated compacts with Fast Flo® or DiTab® (high P_y, low E, and σ_r), the increase in disintegrant concentration leads to a regular increase in the amount of moisture content, whereas the decreases in E or σ_r are not regular. These results are of importance for the low disintegrant amount. Kollidon CL®, which is well known to provide a high swelling pressure in spite of a moderate swelling volume (Bolhuis et al., 1982; Bolhuis, Zuurman & Wierik, 1997), is the disintegrant that leads to the lowest Young's modulus. Moreover, compacts with Fast Flo® or DiTab® at 80% RH, were very weak and changes of the compact surface were observed as the result of humidity and swelling of Kollidon CL® particles, whereas it was not the case for compacts with Avicel PH101® (low P_y, high E, and σ_r). These results agree with Leblanc, Ducatteau, and Guyot-Hermann (1983), who reported that Crospovidone leads to a decrease of compact's strength when its concentration increases and particularly when relative humidity increases.

CONCLUSION

Young's modulus and tensile strength comparison of the different specimens allow to obtain several information on the effect of relative humidity and disintegrant/filler proportions on the compacts mechanical properties. Densification behavior, moisture uptake, and mechanical properties of the different mixtures containing super-disintegrants in their formulations were examined and compared. At macroscopic level, tensile strength and Young's modulus decrease with increasing relative humidity. At microscopic level, it seems that internal structure degenerates and micro-defects (cracks) develop because of the disintegrant particle swelling. This swelling acts in disrupting and weakening interparticle contacts. To conclude, for a successful formulation, equilibrium must be found to optimize the disagregation and the mechanical properties. Due to the hygroscopic properties of Avicel PH101®, moisture uptake is important even without disintegrant. Then, with this filler, a super-disintegrant is not absolutely necessary. But, if a disintegrant is used in the formulation, to limit the effect of humidity, AcDiSol® seems the most appropriate. A proportion higher than 1% is not necessary. On the contrary, Fast Flo® and DiTab® are not affected by the relative humidity. Then, the disintegration must be obtained using a disintegrant. This supposes to find a balance between the cohesion and the moisture sorption. To this end, it is preferable to use Explotab® or AcDiSol® rather than Kollidon®.

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NOMENCLATURE

AA	Avicel PH101®/AcDiSol® mixtures
EA	Avicel PH101®/Explotab® mixtures
KA	Avicel PH101®/Kollidon CL® mixtures
AL	Fast Flo®/AcDiSol® mixtures
EL	Fast Flo®/Explotab® mixtures
KL	Fast Flo®/Kollidon CL® mixtures
AD	DiTab®/AcDiSol® mixtures
ED	DiTab®/Explotab® mixtures
KD	DiTab®/Kollidon CL® mixtures
MC	Moisture content (%)
RH	relative humidity (%)
P_y	mean yield pressure obtained from Heckel plots (MPa)
ε	porosity of the compact
E	Young's modulus (GPa)
σ_r	Tensile strength (MPa)

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