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Effects of moisture on tablet compression of chitin

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ABSTRACT

Direct compression of chitin was studied with special reference to the effects of moisture content on tablet formation and properties. Two cellulosic direct compression materials, microcrystalline cellulose (MCC) and spray-dried lactose-cellulose (SDLC, (Cellactose®) were used as reference materials. The compaction studies were carried out using an instrumented single-punch tablet machine. For physical material characterisation, water sorption isotherms were determined gravimetrically and the effects of moisture on the solid-state properties were studied by means of FT-NIR spectroscopy and X-ray powder diffractometry (XRPD). The sorption isotherms showed that the moisture sorption capacity of chitin is clearly higher than that of SDLC and only slightly higher than that of MCC, especially in the high humidity range. The maximum crushing strength for the chitin tablets was obtained at the moisture content ranging from 7% to 9%, approximately double the corresponding monolayer moisture content (m_o). Lower and higher humidity levels clearly reduced the mechanical strength of the tablets. It was also found that the elasticity and plasticity factors of chitin, MCC and SDLC were strongly dependent on the level of moisture present during compaction.

1. Introduction

Chitin is a high-molecular-weight linear polymer (polysaccharide) of N-acetyl-D- glucosamine units linked by β(1–4) bonds. It is a naturally occurring structural polysaccharide abundant in crab, shrimp and lobster shells and the second most common biopolymer after cellulose (Synowiecki & Al-Khateeb, 2003). Several reports describe the successful use of chitin and chitosan in tablets as disintegrants (Bruscato & Danti, 1978; Ritthidy, Chomto, Pummangura, & Menasveta, 1994; Wang, Yang, Hu, & Hu, 1997) and preferably as a direct compression diluent (Garcia, Orozco, Bilbao, & Nieto, 2002; García Mir et al., 2008; Garzon, Romero, James, & Ramos, 1998; Knapczyk, 1993; Rege, Shukla, & Block, 1999; Sawayanagi, Nambu, & Nagay, 1982a, 1982b). To date, however, fairly little is known about the applications of these excipients as direct compression filler binders in tabletting applied either as a pure material or combined with established direct-compression diluents.

Many factors can affect the compaction behaviour of the pharmaceutical excipients. Moisture is one of the most important external factors that can play a significant role in the consolidation and compaction properties of pharmaceutical powders (Garr & Rubinstein, 1992; Khan & Pilpel, 1986; Malamataris, Goidas, & Dimitriou, 1991; Nokhodchi, Rubinstein, Larhrib, & Guyot 1995; Shukla & Price, 1991). The presence and distribution of moisture in different forms will depend on the chemical nature of the particle material, its physical properties and the ambient relative humidity. Water can plasticize the polymer matrix or form stable bridges through hydrogen bonding, resulting in an anti-plasticizing effect (Ahlneck & Alderborn, 1989). These changes are obviously due to the combined effect of moisture on the interparticle and intermolecular forces (Malamataris et al., 1991). The behaviour of water can be transformed in the presence of a polymer, depending on the degree of chemical or physical association between water and polymer phases (Agrawal, Manek, Kolling, & Neau, 2004; Hatakeyama & Hatakeyama, 1998). Conflicting evidence is reported as to both the optimum amount of moisture to be included in a tablet formulation and how this moisture affects the tablet strength (Nokhodchi et al., 1995).

The purpose of the present study was to investigate the direct compression of chitin with special reference to the effects of

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moisture content on the compaction properties and final tablet properties. Microcrystalline cellulose (MCC) and spray-dried lactose cellulose (SDLC) were used as direct compression reference materials.

2. Experimental

2.1. Materials

The materials studied were milled and fractionated native chitin (125–250 μm; extracted from lobster shell; Laboratories Mario Muñoz, Cuba), microcrystalline cellulose, MCC (Avicel® PH 102, FMC International, Cork, Ireland) and spray-dried lactose-cellulose, SDLC (Cellactose®, Meggle, Germany). Magnesium stearate (Ph.Eur.) was used as a lubricant for direct compression.

2.2. Water sorption measurements

The direct compression materials were dried in the oven (Heraeus Vacutherm, Heraues, Germany) at 45 °C and 70 mbar for 24 h. The water sorption of the powders was determined gravimetrically before and after storage at controlled room temperature (22 °C) under 0%, 11%, 23%, 33%, 45%, 54%, 58%, 75%, 85% and 95% relative humidity (RH) conditions.

These RH conditions were achieved in desiccators by using proper saturated salt solutions. The relative humidities were 0% RH (silica gel), 11% RH (lithium chloride), 23% RH (potassium acetate), 33% RH (magnesium nitrate), 43% RH (potassium carbonate), 52% RH (magnesium nitrate), 59% RH (sodium bromide), 75% RH (sodium chloride), 85% RH (potassium chloride) and 95% RH (disodium hydrogen phosphate). All the salts were of reagent grade. Samples in triplicate were stored in open glass vials during 2, 4, 6, 8, 10 and 25 days. The water sorption behaviour was evaluated from the average weight increase at each storage time.

Moisture sorption isotherms were calculated as the equilibrium of moisture sorption (EMC) and experimental monolayer water values were determined from the adsorption isotherm using a BET equation (Eq. (1)) (Brunauer, Emmett, & Teller, 1938) and a GAB equation (Eq. (2)) (Guggenheim, Andersen, & de Boer, Monolayer sorption theory for modelling moisture sorption isotherms) (Van der Berg, 1981).

$$\frac{a_w}{(1-a_w)\ m} = \frac{1}{m_o C} + \frac{a_w\ (C-1)}{m_o\ C} \tag{1}$$

$$m = \frac{C_1\, k\, m_o\, a_w}{(1-ka_w)(1-k\,a_w + C_1\, k\, a_w)} \tag{2}$$

where m = moisture content, a_w = water activity, m_0 = monolayer moisture content, C = constant related to excess enthalpy of sorption, C_1 and k = constants.

2.3. Near infrared spectroscopy

Near infrared (NIR) spectra were measured with a Fourier transform FT-NIR spectrometer (Bomem MD-160 DX, Hartmann & Braun, Quebec, Canada) using Bomem-GRAMS software (v. 4.04, Galactic Industries Inc., Salem, NH, USA) and Teflon as reference (99% reflective Spectralon, Labsphere Inc., North Sutton, NH, USA). The spectra were measured through the bottom of the glass vial containing the sample. The measurements were carried out in triplicate. The spectra were recorded over a range of 10,000–4000 cm^{-1} with a resolution of 8 cm^{-1} and averaged over 32 scans. Second derivative transformations of absorbance, log (1/R), were performed with 11-point Savitzky-Golay smoothing using Matlab software (v. 5.3, MathWorks Inc., Natick, MA, USA).

2.4. X-ray powder diffractometry

The samples were measured using an X-ray powder diffractometer (Bruker axs D8, Germany). The X-ray powder diffraction (XRPD) experiments were performed in a symmetrical reflection mode with CuK radiation (1.54 Å) using Göbel Mirror bent gradient multilayer optics. The scattered intensities were measured with a scintillation counter. The angular range was from 5° to 30° with steps of 0.1° and a measuring time of 5 s/step.

The estimation of the crystallinity was based on the assumption that the experimental XRPD intensity curve is a linear combination of intensity of a crystalline and of an amorphous component. The crystallinities of the samples were estimated by fitting the intensities of the crystalline and the amorphous component to the experimental intensity curve. The diffraction patterns of the samples where the Bragg peaks were subtracted were used as the amorphous model intensity curve and the crystalline one consisted only of the diffraction peaks.

2.5. Tablet compression

Prior to compression studies the powders were kept at temperature and humidity conditions identical to those used in the sorption study (in desiccators with different humidity conditions). The total amount of water in the samples was determined in a Sartorius moisture analyser (Model MA 50, Goettingen, Germany) just before the compression. For tablet compression, the excipients were individually weighed out and poured into a pre-lubricated die (acetone solution of magnesium stearate 5% w/w). Tablets were manually compressed with an instrumented single-punch tabletting machine (Korsch EK-O, Berlin, Germany) using 9-mm flat-faced punches. The tablet height under load was held constant at 3.0 mm. Therefore, the upper punch was adjusted to the lowest position and the lower punch was adjusted using a calibration plate (3.00 mm thick). The tabletting machine was operated at a fixed speed of 36 rpm and compression pressure of 87.8 ± 6.6 MPa at controlled humidity conditions (21 °C and 50% RH).

The plasticity and elasticity of the materials under compression were measured from the force-distance curve near the maximum force by a method described by Antikainen and Yliruusi (2003). The plasticity factor (PF) determines the extent of plastic flow at a certain compression force level and gives a comparable numerical value (Eq. (3)).

$$\mathrm{PF} = \left(\frac{W1}{W1+W2}\right) \times 100\% \tag{3}$$

$W1$ and $W2$ can be calculated from the force–displacement curve according to Antikainen and Yliruusi (2003). The elasticity factor (EF) was calculated using Eq. (4)

$$\mathrm{EF} = \left(\frac{S_{\max} - S_{od}}{S_{\max} - S_o} \times 100\%\right) \tag{4}$$

where $S_{\max}$ is the maximum upper punch displacement, S_o is the displacement of the upper punch when force is first detected and S_{od} is the displacement of the upper punch in the decompression phase (Antikainen & Yliruusi, 2003).

2.6. Evaluation of tablets

The weight and the height of each tablet were measured with an analytical balance (Sartorius CP 2245, Raute, Goettingen, Germany) and a digital micrometer (Sony DZ 521, Tokyo, Japan), respectively. The crushing strength of the tablets (the force required to fracture a tablet across its diameter) was determined immediately after compression with a tablet hardness tester (Schleuniger 2E, Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland).

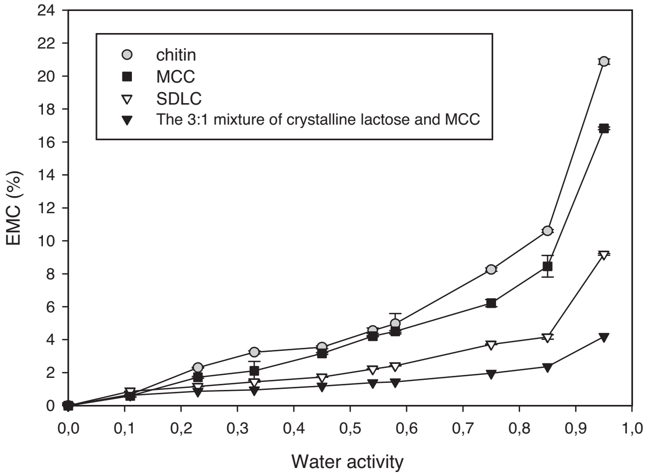

Fig. 1. Moisture sorption isotherms of chitin, microcrystalline cellulose (MCC) and spray-dried lactose-cellulose (SDLC, Cellactose®) (n = 3), and the modeled isotherm for the 3:1 mixture of crystalline lactose (75%) and microcrystalline cellulose, MCC (25%).

3. Results and discussion

3.1. Moisture sorption

For all materials, the sorption isotherms show a typical S shape or a type II behaviour (Fig. 1) commonly reported for water-insoluble hydrophilic polymers (Agrawal et al., 2004; Airaksinen et al., 2005). The total moisture uptake by these materials in decreasing order was chitin 20.8% (w/w), MCC 16.8% (w/w) and SDLC 9.2% (w/w). These materials presented a relatively high moisture uptake in the high humidity range, especially in a relative humidity higher than 85%.

The parameters for the BET and GAB models obtained from the sorption data by regression are listed in Table 1. The correlation coefficients of these polynomial regression analyses showed good fit of the experimental data to the BET and GAB equation, except for MCC and SDLC in the GAB equation (0.919 and 0.926, respectively). The BET monolayer values (m_o) for chitin and MCC were close to each other (2.6 and 2.3, respectively) in the range of a_w from 0.05 to 0.5, suggesting a similar chemical affinity of these polymers for water at low water content. This could be related to the similarity of chemical structures of both polymers, where the main difference is that the hydroxyl group at carbon-2 in MCC is replaced by an acetamido or amino group depending on the degree of deacetylation in chitin. These results are in accordance with previous studies which demonstrated no significant difference in the ability to tightly bind the water molecule between MCC and chitosans with different degrees of deacetylation (50–100%) at low water content (Agrawal et al., 2004).

Table 1
Computed parameters in the GAB and BET equation and fit of moisture sorption data ($n = 3$).

Parameter	m_o (g H_2O/100 g d.m.)	K	C	R^2
BET				
Chitin	2.63		8.43	0.994
MCC	2.28		4.12	0.962
SDLC	1.05		20.07	0.996
GAB				
Chitin	4.30	0.927	2.19	0.980
MCC	2.98	0.849	2.93	0.919
SDLC	1.17	0.902	16.54	0.926

The values of the monomolecular water parameter (m_o) obtained from the GAB equation ($0.05 < a_w < 0.9$) indicate that the monolayer coverage by water in chitin is higher than that in MCC and SDLC. As seen in Fig. 1, both excipients show an evident increment of their moisture content at relative humidities above of 85%. This effect was found to be higher for chitin than for MCC. In general, water sorption in polyamides depends on the degree of crystallisation of the polymer and on the chemical nature of the binding sites. Likewise, impurities such as mineral elements (calcium) and proteins can affect the sorption capacity of chitin of different sources (Pääkkönen & Plit, 1991).

SDLC exhibited the lowest BET and GAB monolayer values. SDLC is a co-processed composition of a spray-dried mixture of α-lactose monohydrate (75% w/w) and cellulose powder (25% w/w). Therefore the water sorption of SDLC was different from that of chitin and MCC. In comparison with MCC and chitin, α-lactose monohydrate is a crystal hydrate-forming solid whose external surfaces can absorb small amounts of water (Airaksinen et al., 2003).

The sorption isotherm for the 3:1 mixture of lactose–cellulose (a ratio respective to composition of SDLC) was also predicted using the moisture sorption isotherm data of MCC and the respective data for crystalline lactose obtained from the literature (Bronlund & Paterson, 2004). As seen in Fig. 1, the experimental sorption isotherm for SDLC obtained in our study differs from the modelled isotherm of the 3:1 mixture of crystalline lactose and MCC. The higher moisture sorption values for SDLC are obviously due to the presence of higher amount of amorphous lactose in SDLC compared to the theoretical mixture of crystalline lactose and MCC. Amorphous lactose absorbs approximately 100 times more water than crystalline lactose in the same conditions (Bronlund & Paterson, 2004). SDLC is a spray-dried excipient and thin layers of amorphous lactose are formed on the surface of the powder during flash drying and milling operations.

3.2. Effects of humidity conditions on the state of water and degree of crystallinity

A series of NIR spectra for chitin, MCC and SDLC stored for 25 days in desiccators with saturated salt solution are shown in Fig. 2. Since carbohydrates (cellulose, chitin and lactose) mainly include CH and OH bonds, their NIR spectra were similar. In addition, chitin exhibited bands of free and acetylated NH groups. As seen in Fig. 2, the presence of water affects the overall spectrum since the scattering depends on the ratio of the refractive index of the particles to that of the surrounding medium. Water bands in 1450 and 1930 nm increased with increase in relative humidity, and this increment was higher with chitin than with MCC and SDLC.

Second derivative NIR spectra of the log 1/R in the region of 1800–2050 nm (combination water band) of chitin (a), MCC (b) and SDLC (c) stored for 25 days, are presented in Fig. 3. With the increment of moisture content, the water band of chitin and MCC shifted gradually from 1920 to 1909 nm. This effect has been described previously by Luukkonen et al. (2001) as a change of energetic state of water due to the change from bound to bulk water. A band of free water can be seen at around 1910 nm with both materials. However, the intensity of the water band was higher in chitin than in MCC. These results evidence the presence of free water in chitin and MCC when the moisture content in these materials is above 10.6% (w/w) and 8.5% (w/w), respectively. With SDLC, two bands were detected at 1906 nm (related to increased moisture content) and at 1935 nm (related to the lactose monohydrate band) in agreement with the results of Luukkonen et al. (2001). The high amount of lactose in SDLC determines how water interacts with this excipient.

Fig. 4 presents measured XRPD diffraction patterns of chitin, MCC and SDLC samples stored under conditions of different RH (0%, 54% and 95% RH). Taking into account the XRPD diffraction

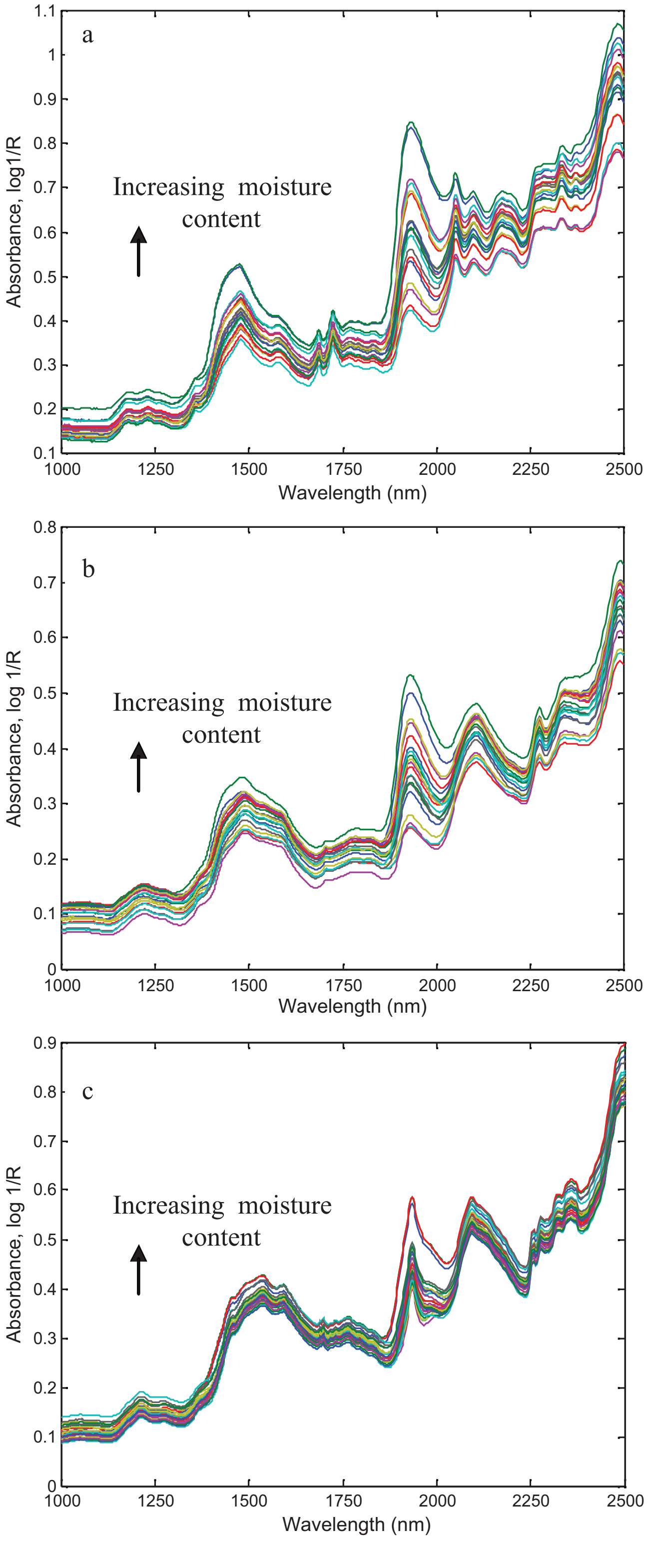

Fig. 2. NIR absorbance spectra (log 1/R) of (a) chitin, (b) microcrystalline cellulose (MCC) and (c) spray-dried lactose-cellulose (SDLC, Cellactose®) after 25 days in different relative humidities.

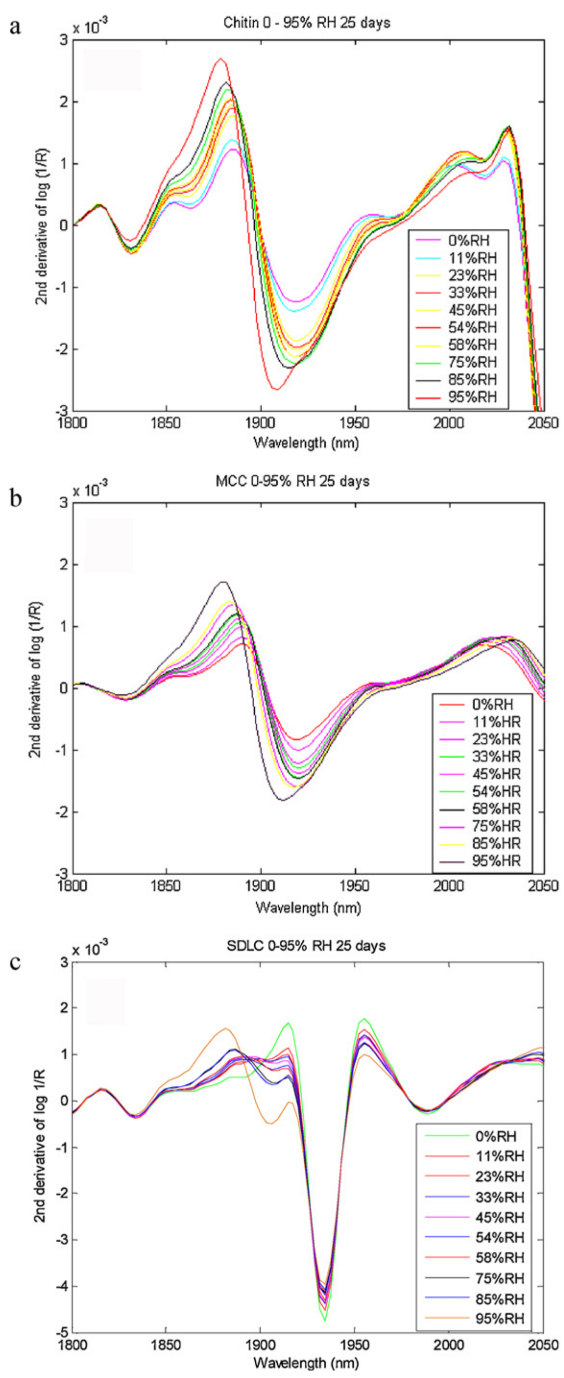

Fig. 3. Second derivative NIR spectra of log 1/R 1800-2050 nm of (a) chitin, (b) microcrystalline cellulose (MCC) and (c) spray-dried lactose-cellulose (SDLC, Cellactose®) after 25 days in different relative humidities.

patterns and the sorption isotherm data it is obvious that the lower water adsorption for SDLC (compared to that observed with chitin and MCC) is due to the presence of higher levels of crystalline lactose monohydrate which will adsorb very little water at low to moderate relative humidities. The estimated crystallinities for chitin, MCC and SDLC after storage at 0–54–95% RH were 49–49–49%, 50–48–47%, and 55–55–64%, respectively. The crystallinity of MCC diminished slightly and the estimated crystallinity of SDLC increased at 95% RH. A similar effect was described previously by Airaksinen et al. (2005) for α-lactose monohydrate, the major component (75% w/w) of SDLC.

3.3. *Effect of moisture content on tablet compression*

The presence of water in the powder has been reported as an important factor in the formation of solid bridges in tablets (Higuchi, Arnold, Turker, & Busse, 1952). The critical humidity at which this takes place is characteristic of each solid material. Chitin

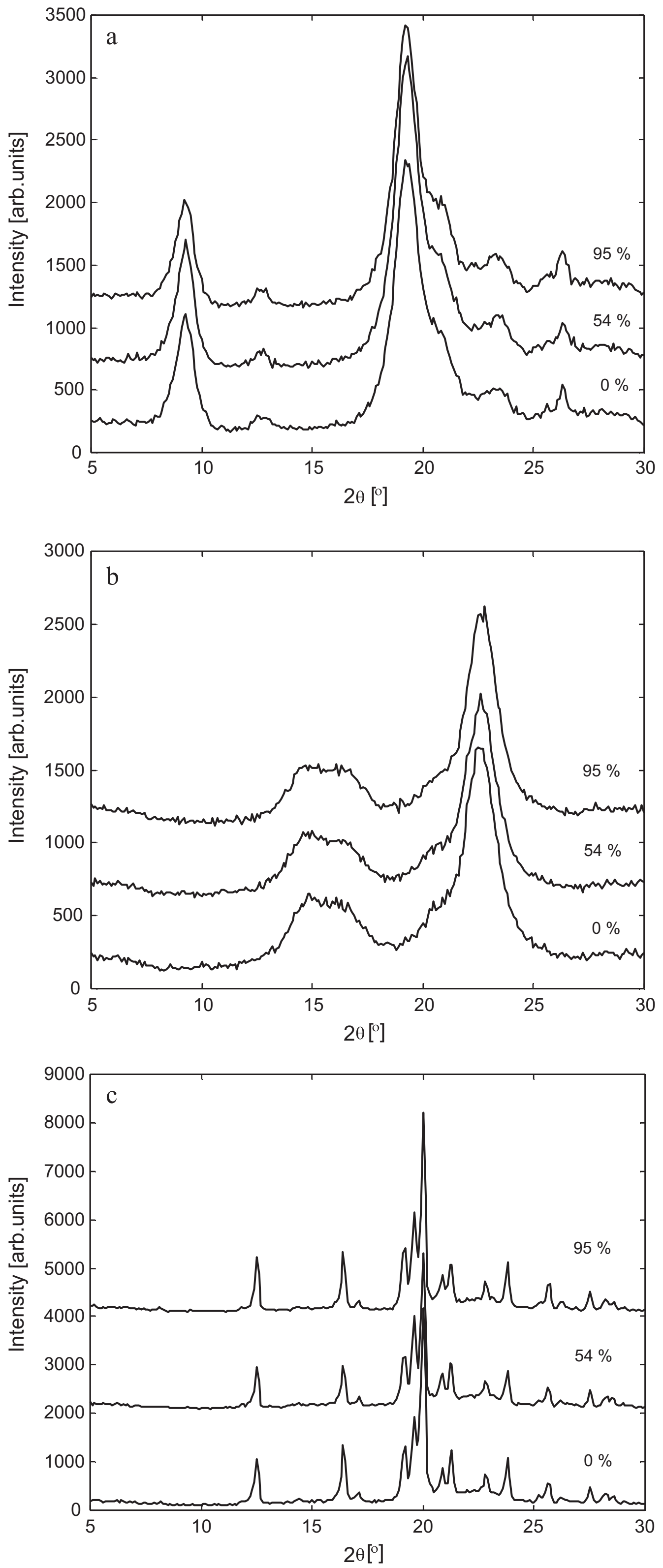

Fig. 4. XRPD diffraction patterns of (a) chitin, (b) MCC and (c) SDLC samples (0%, 54% and 95% RH).

and MCC have the ability to hold a relatively large amount of water in their internal structure (as shown in Fig. 1). For this reason, it would be reasonable to measure the magnitude of this effect on the compression and friction properties.

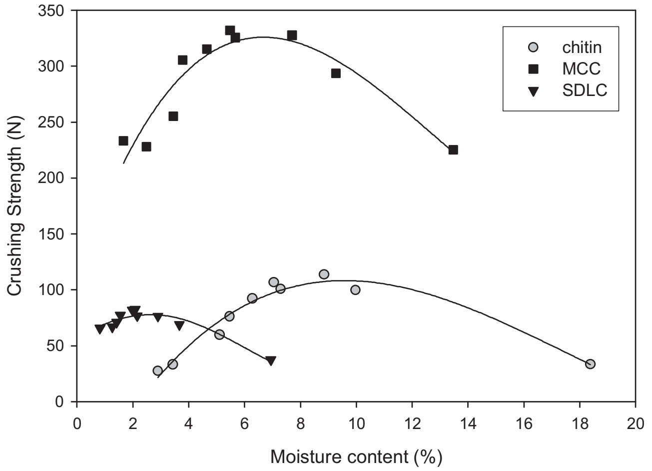

Fig. 5. Effects of moisture content on crushing strength of tablets compressed from chitin, microcrystalline cellulose (MCC and spray-dried lactose-cellulose (SDLC, Cellactose®).

The results of the compression studies with different moisture contents of materials are shown in Fig. 5. The maximum crushing strength for chitin tablets was obtained at a moisture contents range of 7–9% and for MCC at around 5–8%. These values are almost double the mean of the corresponding m_0 in Table 1. SDLC with the lowest water sorption ability exhibited a similar behaviour, and the maximum crushing strength for the SDLC tablets was obtained at the moisture level ranging from 1.5% to 2.9%.

It is evident that the present increase in crushing strength due to moisture content is caused by externally adsorbed monomolecular water (m_0), and this is in accordance with earlier reports (Khan & Pilpel, 1986; Malamataris et al., 1991; Nokhodchi et al., 1995). Tightly bound water makes it easier for the formation of hydrogen bondings between particles (thus preventing elastic recovery) and/or increases the van der Waal's forces. This, in turn, smooths out the surface microirregularities and reduces interparticle separation. The subsequent decrease in crushing strength with the moisture content ($\gg m_0$) has been attributed to an excessive moisture that provokes a disruption on the force between the molecules, especially in the tablet surface due to high absorbed water within the particle or condensed water in the surface (Malamataris et al., 1991).

The plasto-elasticity behaviour of these materials was quantified from the force distance curve by Antikainen and Yliruusi's method (2003). According to the literature, MCC and chitin mainly undergo plastic deformation during compression (Antikainen & Yliruusi, 2003; García Mir et al., 2008; Roberts & Rowe, 1987). With SDLC, in spite of the low cellulose proportion, the binding between the majority of the lactose particles is mediated by cellulose (Belda & Mielck, 1996; Roberts & Rowe, 1987). As seen in Fig. 6a, the values for the plasticity factor (PF) initially increased for SDLC and chitin, reaching maximum values at moisture contents of 1.5–2.5% and 7–10%, respectively. The highest values of PF (4.4%) were obtained with MCC. The PF of MCC was clearly decreased as the moisture content was increased up to 14% (at 95% RH) as a consequence of the effect of free water. The PF values of chitin were at this compression pressure (approximately 88 MPa) between 0.1% and 1.5% lower than those of MCC and SDLC (Fig. 6a). The crushing strength and PF curves of chitin were similar in shape and relative position (Figs. 5 and 6a). The maximum PF values and maximum crushing strength for each material were found at similar intervals of moisture content.

The elasticity factor (EF) initially decreased, reached the minimum and then increased inversely to plasticity factor and crushing

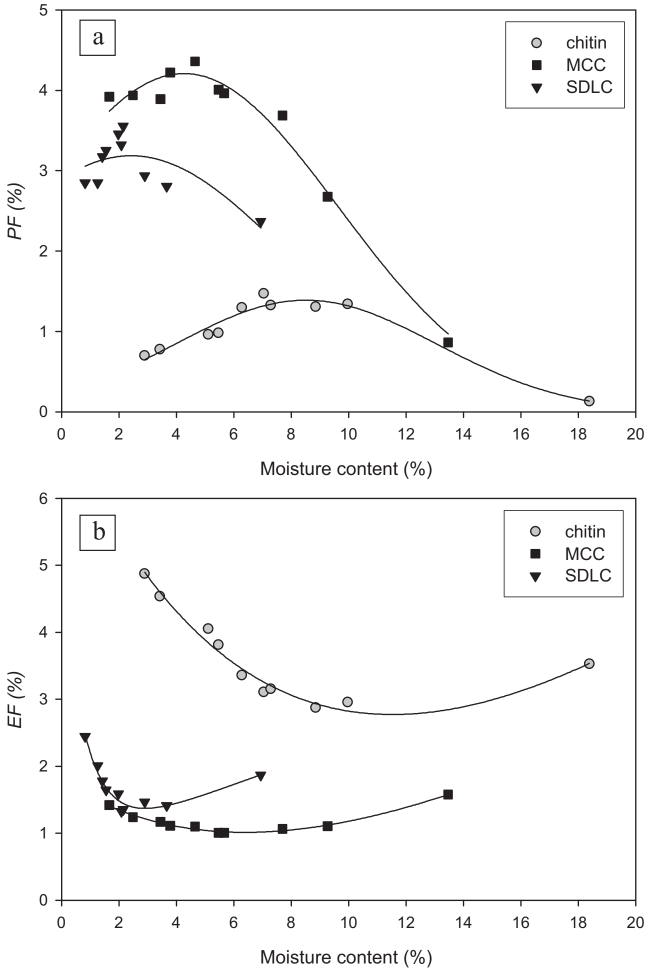

Fig. 6. Effects of moisture content of direct compression materials on the values for (a) plasticity factor (PF) and (b) elasticity factor (EF).

strength. MCC and SDLC presented quite similar EF values at the same moisture content (1.5–4%). The highest values of EF (4.9%) were obtained with chitin at the lowest moisture content (2.9%).

An interesting future extension on the evaluation of mechanical properties of tablets containing biopolymers would be the dependence of water content of biopolymer, glass transition temperature and mechanical properties of tablets. For example, it is well known that for starch there is a clear change in mechanical properties of films at around 9% water content whereas the water content where the glass transition temperature is ambient, is around 20%. Relating the mechanical properties with water content to anti-plasticization at low water contents and a brittle to ductile transition at higher water contents (which has been earlier discussed by e.g., Roudaut, Dacremonta, Vallès Pàmies, Colas, & Le Mestea, 2002), would be the relevant topic for future tablet compression studies on chitin and other biopolymers.

4. Conclusions

Compression of chitin is very sensitive to the presence of moisture, and this should be taken into account in formulating chitin-containing tablets. In particular, the moisture greatly affects the plasticity and elasticity of chitin powder under compression, thus affecting the mechanical properties of the tablets. The optimal moisture content of chitin for preparing tablets with a satisfactory mechanical strength would range from 7% to 9%. The humidity room conditions should be carefully controlled in compression of chitin tablets.

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