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Functionality of chitin as a direct compression excipient: An acetaminophen comparative study

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ABSTRACT

The particle and tableting properties of chitin extracted from shrimp exoskeletons were evaluated and compared with common excipients used for the preparation of tablets. Chitin offered more benefits in terms of functionality than calcium diphosphate, lactose monohydrate and pregelatinized starch. Further, highly plastic deforming materials such as sorbitol and PVP K30 and microcrystalline cellulose showed the best compactibility and dilution potential, whereas brittle deforming materials such as lactose monohydrate and calcium diphosphate were poorly compactable. Chitin had better compactibility than pregelatinized starch, calcium diphosphate and lactose monohydrate. Further, along with calcium diphosphate, chitin was the least sensitive material to compaction speed due to a combination of a plastic and brittle behavior. Moreover, chitin was less sensitive to magnesium stearate and possessed better acetaminophen loading capacity than pregelatinized starch, calcium diphosphate and lactose monohydrate. Chitin showed potential for use as a direct compression excipient.

1. Introduction

Chitin is a natural macromolecule which belongs to the class of polysaccharides. It is the (1-4)-2-acetamido-2-deoxy-β-D-glucan, industrially produced from marine resources with a limited degree of deacetylation (Kurita, 2006; Muzzarelli, 2012; Muzzarelli et al., 2012). Chitin as well as chitosan, is biodegradable and nontoxic and particularly recommended as a drug carrier (Mir-Garcia et al., 2010; Ravi Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004).

Currently, more than 80% of all dosage forms in the market are comprised of tablets because (i) they are easy to dispense, (ii) they offer accuracy in the dose, (iii) they present low likelihood of toxicity compared to parenteral dosage forms, (iv) they are tamper resistant compared to capsules, and (v) they offer better stability to heat and moisture compared to liquid and semi-solid formulations (Jivraj, Martini, & Thomson, 2000). These dosage forms are composed of active ingredients and excipients. Excipients are non-active ingredients which are contained in a finished pharmaceutical dosage form and are classified as carbohydrates (i.e., cellulose, starch, etc.), inorganic salts (i.e., calcium diphosphate) and as synthetic (i.e., polyvinyl pirrolidone). Cellulose, starch, polyvinyl pirrolidone, lactose, sorbitol, and calcium diphosphate are some of the most common excipients employed for tableting. Direct compression, wet granulation and dry granulation are the processes that allow for the preparation of a blend of the active pharmaceutical ingredient (API) and the selected excipient(s) before tableting or capsule filling take place. Direct compression is a simple and economic process by which compacts are made directly from a powder blend of API and appropriate excipients. In wet granulation, the API is mixed with a wet binder and other excipients and then passed through sieves to achieve granules which are later either milled or sifted before tableting (Allen, Popocich, & Ansel, 1999, Chap. 1; Hedden et al., 2006). The dry granulation process involves the preparation of a dry blend of the API and excipients, followed by precompression of the powder in high pressure rollers employing from 1 to 6 tons of pressure to form ribbons which are then milled and sized. Typically, those processes require the addition of several specialized excipients, such a binder (compact forming material), filler (diluent), disintegrant (allows for rapid compact disintegration) and glidant/lubricant (eases powder flow and reduces punch and die friction). In this study, the particle and mechanical properties of chitin were evaluated and compared with those of commercial tableting excipients, namely: microcrystalline cellulose, pregelatinized starch, lactose monohydrate, sorbitol, polyvinyl pirrolidone and calcium diphosphate.

2. Materials and methods

2.1. Materials

Chitin was obtained from shrimp exoskeletons (Comerpes SA, Cartagena, Colombia). Microcystalline cellulose (Avicel® PH-101,

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lot 2339), pregelatinized starch (Starch 1500®, lot IN504089) and lactose monohydrate (lot 01-20-187-2) were obtained from FMC Biopolymers (Newark, DE), Colorcon (Indianapolis, IN) and DmV international (Veghel, Netherlands), respectively. Concentrated hydrochloric acid (37%; lot 2612KLHV) and magnesium stearate (Powder Hyqual®, lot #2256KXDS) were purchased from Mallinckrodt Specialty Chemicals Co. (St. Louis, MO). Sorbitol (lot 024M0118), PVP-K30 (lot 0911106, MW 40000) and calcium diphosphate (lot 02733) were obtained from Bell Chem Corp. (Longwood, USA). Sodium hydroxide (lot B064398119) and acetaminophen (lot G0H0A01) were obtained from Merck (Darmstadt, Germany) and Sigma–Aldrich (St. Lois, USA), respectively. Sodium hypochlorite (lot 1791) was purchased from JM Chemicals (Medellin, Colombia).

2.2. Preparation of chitin from shrimp exoskeletons

Approximately, 20 g of dry exoskeletons were milled on a cutting mill (Model 3, Willey, Arthur Thomas Co., Philadelphia, USA), passed through a # 16 mesh sieve and hydrolyzed at the conditions shown in Table 1 using a heating mantle (P&P, Medellin, Colombia) coupled with a round bottom flask and a two-decked condenser. The solid-to-HCl solution ratio was (1:10). The dispersion was then neutralized with a 3 M sodium hydroxyde solution, filtered and dried in an oven (U50, Memmert, Schawabach, Germany) at 100 °C for 3 h. The dry material was then hydrolyzed with a 3 M sodium hydroxyde at 100 °C for 4 h to decompose proteins, fats and pigments. This dispersion was then neutralized with an 8% HCl solution, vacuum filtered and treated with a 15% w/v sodium hypochlorite for 24 h at a 1:2 solid-to-NaClO ratio for bleaching at room temperature. The resulting material was then washed until a conductivity of <20 μS/cm was reached and filtered. The cake product was dried at 60 °C for 24 h and passed through a #100 mesh sieve. The resulting degree of acetylation and molecular weight of the product were 58% and 70 kDa, respectively.

2.3. Particle size analysis

Excipients were fractionated on a ROTAP sieve shaker (Model, RX29, W.S. Tyler Company, Mentor, OH) using stainless steel 180, 150, 125, 106, 75, 44 and 38 μm size sieves, stacked together in the order written (Fisher Scientific Co., Pittsburgh, PA). Approximately, 20 g of the sample was shaken for 15 min. The geometric mean diameter, d_g, was determined from the log-normal distribution plot constructed between the sieve mean diameter and cumulative percent frequency using the Minitab software (v.16, Minitab, Inc, State College, PA).

2.4. Particle properties

The moisture content was obtained by the gravimetric method by heating at 100 °C for 4 h in a mechanical convection oven (U50, Memmert, Germany). True density was determined using a helium displacement micropycnometer (AccupycII 13340, Micromeritics, USA). Approximately, 2 g of a dry sample was used for the analysis. The test was carried out in triplicates. Bulk density (ρ_{bulk}) was determined on 20 g of material. Tap density was measured on a tap density analyzer (AT2, Quantachrome instruments, USA) for 500 taps. Testing was carried out in triplicate. Porosity (ε) was calculated as reported previously (Rojas, Hernandez, & Giraldo, 2013). Flow rate was obtained from ~20 g of material that passed through a glass funnel having a 13 mm diameter orifice and its weight was recorded as a function of time. The test was conducted in triplicate.

2.5. Compressibility analysis

Compacts of ~500 mg were made on a single punch tablet machine (060804 Compac, Indemec, Itagui, Colombia) coupled with a load cell (LCGD-10K, Omega Engineering, Inc., Stamford, CT) at 1 and 30 s using a flat-faced 13 mm punches and die tooling. Pressures ranged from ~10 MPa to 205 MPa. Pressures were measured on a strain gauge (LCGD-10K, Omega Engineering, Inc., Stamford, CT). Compacts were analyzed immediately after ejected. The natural logarithm of the inverse of compact porosity, $\ln(1/\varepsilon)$, was plotted against compression pressure (σ) to construct the Heckel plots given by (Heckel, 1961):

$$\ln \frac{1}{\varepsilon} = m\sigma + A$$

where A is the intercept obtained by extrapolating the linear region to zero pressure. The slope (m) is inversely related to the material yield pressure (P_y), which is a measure of its plasticity (Alderborn & Nyström, 1996, Chap. 2). Thus, a low P_y (usually values <100 MPa) indicates a high ductile deformation mechanism upon compression. Other parameters are D_o, D_a, and D_b, which are related to initial powder packing/densification, total compact densification and particle rearrangement/fragmentation at the initial compaction stage, respectively (York, 1992). D_o was calculated by dividing the bulk density with the true density (Chowhan & Chow, 1980). D_a and D_b were obtained by the expressions:

$$D_a = 1 - \exp^{-A}$$

$$D_b = D_A - D_o$$

2.6. Compactibility analysis

Compacts were made as described under "compressibility analysis". The analysis was performed using a tablet hardness tester (UK 200, Vankel, Manasquan, NJ) and the compact tensile strength (MPa), was then recorded. The crosshead speed of the left moving platen was 3.5 mm/s. The area under the tensile strength curve (AUTSC) obtained from the Leuenberger model was used to determine the compactibility of the materials (Leuenberger & Rohera, 1986):

$$\mathrm{TS} = T_{\max} \times (1 - e^{-\gamma_c * \mathrm{P} * \rho\gamma})$$

where TS is the radial tensile strength (MPa), T_{max} is the theoretical tensile strength at infinite compression pressure, γ_c is the compression susceptibility parameter (MPa^{-1}), ρ_r is the relative density and P is the compression pressure (MPa).

2.7. Dilution potential (DP)

Acetaminophen was used as model drug for direct compression due to its poor compaction properties. Tablets of ~500 mg in weight containing different levels of acetaminophen (0, 25, 50, 70%), a poorly compressible drug, were prepared and their tensile strength was determined. Acetaminophen and the test excipient mixtures (50 g total) were mixed in a 150 cm^3 V-Blender (Rhiddi Pharma, India) for 15 min at 15 rpm and then compressed on a single punch tablet press at 40, 80 and 120 MPa and a dwell time of 1 s. The DP was obtained from the area ratios vs composition plots as reported previously (Minchom & Armstrong, 1987).

2.8. Lubricant sensitivity

Lubricant sensitivity was assessed by mixing powders with magnesium stearate, talc and stearic acid in 99:1 weight ratio in a V-blender (Rhiddi Pharma, India) for 5 min. Tablets were prepared

Table 1
Powder Properties.

Sample		CD[b]	Chitin	LM[c]	MCC PH-101[d]	PS[e]	PVP-K30	Sorbitol
D_g (μm)[a]	$n=3$	181.7 ± 9.7	90.0 ± 10.7	104 ± 9.4	86.4 ± 14	54.8 ± 15	96.1 ± 9.2	190.7 ± 9.3
MC (%)	$n=3$	0.7 ± 0.0	5.8 ± 1.2	2.7 ± 0.1	6.4 ± 1.1	4.6 ± 1.3	5.0 ± 0.1	1.4 ± 0.1
True density (g/cc)	$n=3$	2.88 ± 0.02	1.74 ± 0.00	1.52 ± 0.00	1.56 ± 0.02	1.49 ± 0.01	1.19 ± 0.02	1.46 ± 0.01
Bulk density (g/cc)	$n=3$	1.02 ± 0.04	0.33 ± 0.02	0.61 ± 0.01	0.36 ± 0.05	0.66 ± 0.01	0.33 ± 0.02	0.44 ± 0.05
Tapped density (g/cc)	$n=3$	1.34 ± 0.01	0.44 ± 0.01	0.98 ± 0.06	0.50 ± 0.02	0.82 ± 0.07	0.49 ± 0.01	0.57 ± 0.05
Porosity (%)	$n=1$	65	81	67	77	56	72	70
Flow rate (g/s)	$n=3$	19.1 ± 0.0	1.9 ± 1.4	6.0 ± 0.3	11.9 ± 0.0	3.8 ± 0.1	4.8 ± 0.0	13.7 ± 0.0

[a] Geometric mean diameter.
[b] Calcium diphosphate.
[c] Lactose monohydrate.
[d] Microcrystalline cellulose.
[e] Pregelatinized starch.

using a single punch tablet press at a dwell time of 1 s. The lubricant sensitivity was expressed as the lubricant sensitivity ratio (Bolhuis & Zuurman, 1995).

2.9. Reprocessing susceptibility

About 10 g of an acetaminophen:excipient (50:50) mixture was passed freely on a 250 μm sieve and prepared using a V-blender for 10 min. Round compacts of 10% porosity, each weighing about 1 g and measuring 13 mm in diameter were made using a single punch press. This means that compact heights of 5.2, 5.9, 6.4, 6.9, 7.0, 7.5 and 6.5 mm were obtained for calcium diphosphate, chitin, lactose, starch, PVP, sorbitol and MCC PH101, respectively. Compact hardness was measured and tablet pieces were milled and passed through a 150 μm sieve, then compressed and analyzed by a hardness tester.

2.10. Elastic recovery (ER)

Compacts of ~500 mg were made on a single punch tablet press equipped with a fat-faced 13 mm diameter tooling at 10% porosity. This means that compact heights of 2.1, 3.3, 3.1, 3.2, 3.6, 2.8 and 3.1 mm were obtained for calcium diphosphate, chitin, lactose, starch, PVP, sorbitol and MCC PH101, respectively. Tablet thickness was measured immediately after ejected (0.01 mm sensitivity) and after 5 days of storage. The ER was calculated as reported previously (Armstrong & Haines-Nutt, 1972).

2.11. Compact disintegration

Tablets, each weighing 500 mg, were made on a single punch tablet press using a 13 mm round, flat-faced punches and die set at 10–210 MPa and a residence time of 1 s. It was performed in triplicate in 1000 mL of distilled water at 37 °C employing an Erweka GmbH disintegration apparatus (39-133-115, Hanson Research Corporation, Northridge, CA, USA) at 30 strokes/min.

3. Results and discussion

3.1. Powder properties

The powder and tableting properties of chitin and commercial excipients are shown in Table 1. Chitin exhibited irregular particles with a 90 μm in diameter and was comparable in size to PVP K30, LM and MCC PH101. In contrast, sorbitol and CD had the largest particle size (182–190 μm) and PS showed the smallest size (55.8 μm). Further, the true density of chitin was the second highest after CD due to the high arrangement of the chains, whereas, PVP K30 had the smallest true density. All other materials showed values in-between. Chitin, MCC PH101 and PVP K30 presented the lowest bulk (0.33–0.36 g/cc) and tap densities (0.44–0.50 g/cc), whereas CD had the largest one (1.02 and 1.34 g/cc, respectively). Moreover, since PS, LM and CD presented the largest densities, they also exhibited the smallest porosities (56–67%). On the other hand, chitin and MCC PH101 had the largest porosity, but at the same time the smallest densities. Since in all cases the moisture content was <7% the effect of moisture on particle properties can be considered as negligible. Further, sorbitol and CD had the largest flow rate due to their high particle size and more regularity in shape. Conversely, chitin showed the slowest flow rate. This is mainly attributed to its small densities, particle size, high porosity and irregular particle shape.

3.2. Tableting properties

In order to assess the compressibility of materials the Heckel analysis was employed and the Heckel curves are shown in Fig. 1. The yield pressure value, P_y, refers to the pressure at which the material begins to deform plastically. In general, the lower the P_y value, the higher the ductility of the material. In this case, PVP K30 (~36 MPa) and sorbitol (48 MPa) had the lowest values; whereas, CD and LM had the highest P_y values (~150–218 MPa). Chitin, MCC PH101 and PS presented the intermediate P_y values (~62–122 MPa). Reported values from the literature are 70, 72, 149 and 261 MPa for PS, Avicel PH101, LM, and CD, respectively (Martinez-Pacheco, Gomez Amoza, & Vil-Jato, 1987; Rojas et al., 2013; Wong & Pilpel, 1990). Thus, from the P_y values, it is deduced that PVP K30 and sorbitol were the most plastic deforming materials upon compression, while LM and CD were the most brittle deforming materials. In this scenario, chitin was less ductile than MCC PH101, sorbitol, PVP K30, and PS, but more ductile than CD and LM. Based on the area under the Heckel curve (AUHC) it is deducted that powder compressibility was the largest for sorbitol and the lowest for CD. Usually, plastic materials had a high densification, whereas those with a low P_y were less compressible. Therefore, the decreasing trend to plastic deformation upon consolidation followed the order: sorbitol >PVP K30 > MCC PH101 > PS > LM > chitin > CD.

The D_o, D_a and D_b parameters, calculated from the Heckel plots, represent the initial packing of the material upon die filling, total packing at low pressures, and degree of powder bed arrangement due to fragmentation at low pressures, respectively. Sorbitol had the largest densification by die filling (D_o) and MCC PH101 along with chitin had the lowest values. On the other hand, PVP K30 and sorbitol, presented the largest total particle densification (D_a) and the largest rearrangement (D_b) upon densification. Conversely, PS and CD presented the lowest rearrangement at initial compression pressures ($D_b \sim 0.13$–0.15). This is attributed to their initial large bulk densities and low porosity causing a small volume reduction at low pressures.

Highly plastic materials such as PVP K30 and sorbitol had the largest strain rate sensitivity (37–40.5%). Conversely, CD which was the most brittle deforming material was not affected by the change

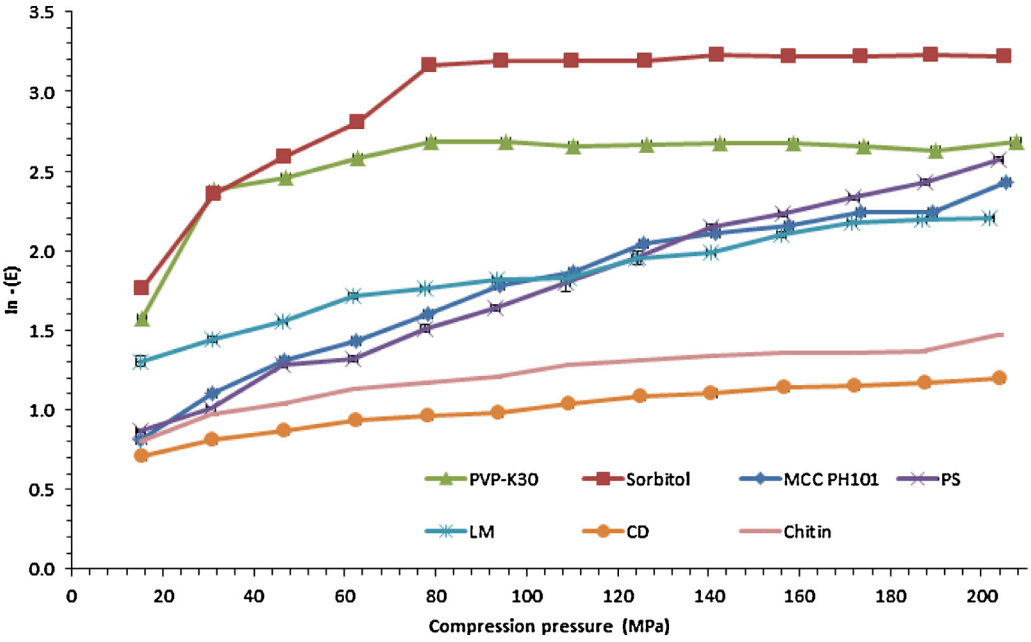

Fig. 1. Out-of-die Heckel plots of chitin and commercial excipients.

in compaction speed. This indicates that for plastic materials a consolidation time had a large effect on the amount of contact points formed by sliding of crystal planes. Therefore, magnitude of the change in P_y is increased with increase in plasticity.

Fig. 2 depicts the relationship between the radial tensile strength, and the product of pressure and relative density according to the Leuenberger equation (Leuenberger & Rohera, 1986). The fitting parameters are listed in Table 2. Chitin formed compacts that were stronger than CD, LM and PS tablets. The magnitude of difference in compact tensile strength increased with increasing pressures. This change was very small for CD and LM. The compressibility parameter (γ_c) is inversely related to the powder yield pressure and so does the Heckel slope. For instance, sorbitol and PVP K30 had high γ_c values of 4.84 and 4.80 MPa, respectively. This indicates that they were highly plastic deforming materials. The comparable tensile strength for highly plastic deforming materials such as sorbitol and PVP K30 suggests that they are related due to their comparable yield pressure (γ), T_{max} and compactibility (AUTSC). The area under the curve of tensile strength (AUTSC) was used to rank materials according to their compactibility. The trend was: PVP K30 > sorbitol > MCC PH101 > chitin > PS > CD > LM.

The elastic recovery (ER) for all materials was small (<2.5%) except for PS indicating that it was independent of the deformation mechanism upon consolidation and hence, they had a low free energy stored upon compression and their particles behave less elastically. It is possible that the high ER of PS is due to its rubbery state at room temperature.

In order to assess the effect of a poorly compressible substance on the compactibility of chitin and other materials, compacts containing different weight ratios of the test material and acetaminophen were prepared and their dilution potential (DP)

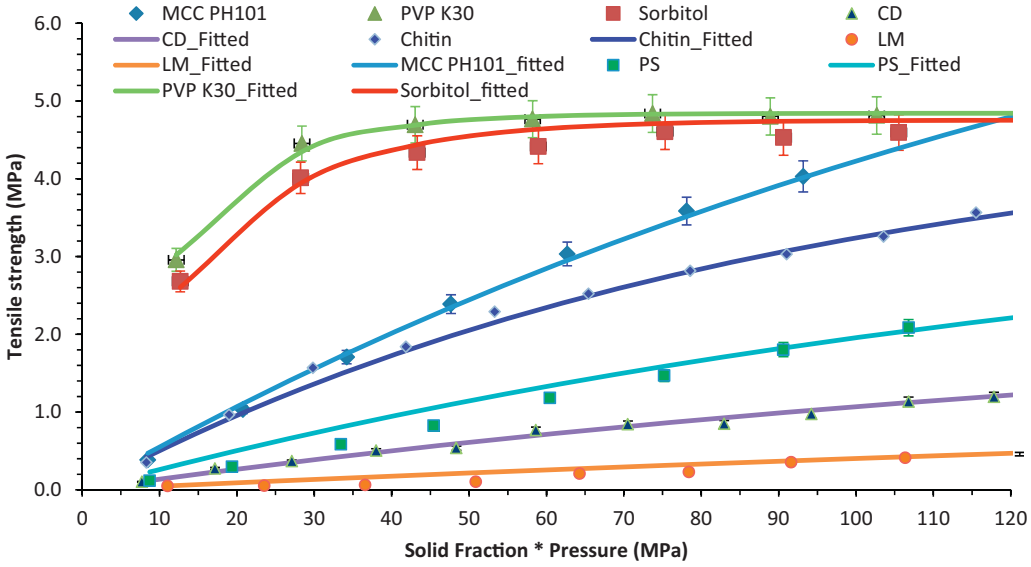

Fig. 2. Compact tensile strength of chitin and commercial excipients according to the Leuenberger model.

Table 2
Tableting properties.

Parameter/test	CD[a]	Chitin	LM[b]	MCC PH-101[c]	PS[d]	PVP-K30	Sorbitol
P_y [e] (MPa^{-1})	250.1	173.6	115.8	62.5	75.1	35.7	48.4
D_o [f]	0.36	0.20	0.38	0.23	0.33	0.27	0.39
D_a [g]	0.49	0.52	0.69	0.44	0.48	0.72	0.79
D_b [h]	0.13	0.31	0.31	0.21	0.15	0.46	0.40
AUHC[i]	192.4	230.7	346.2	341.6	336.5	494.5	566.6
r^2	0.9747	0.9719	0.9976	0.9952	0.9851	0.9056	0.9808
T_{max} (MPa)[j]	2.45	4.87	1.56	6.25	3.96	4.84	4.80
γ (MPa^{-1})[k]	0.006	0.011	0.003	0.006	0.007	0.08	0.062
AUTSC[l]	78.7	248.2	28.9	312.1	145	469.7	451.1
r^2	0.9789	0.9987	0.9041	0.9981	0.9770	0.9940	0.9935
SRS[m] (%)	0.0	3.7	6.4	32.1	23.2	40.5	37
DP[n] (%)	>80	50	>80	43	68	20	15
ER[o] (%)	0.5 ± 0.1	1.9 ± 0.7	0.7 ± 0.2	2.4 ± 0.8	13.7 ± 0.8	2.5 ± 1.0	0.1 ± 0.1

[a] Calcium diphosphate.
[b] Lactose monohydrate.
[c] Microcrystalline cellulose.
[d] Pregelatinized starch.
[e] Yield pressure.
[f] Initial rearrangement as a result of die filling.
[g] Total powder packing at low pressures.
[h] Particle rearrangement/fragmentation at early compression stages.
[i] Area under the Heckel curve.
[j] Theoretical maximal tensile strength.
[k] Pressure susceptibility.
[l] Area under the tensile strength curve.
[m] Strain rate sensitivity.
[n] Dilution potential.
[o] Elastic recovery.

determined. Results are presented in Table 2. Sorbitol and PVP K30 had the best DP (~15–20%) followed by MCC PH101, chitin and PG. Further, the level of CD and LM has to exceed 80% so coherent compacts can be successfully produced. Therefore, these two materials are not recommended for direct compression of poorly compressible drugs due to their inability to form sufficient hydrogen bonding. These characteristics might limit the mechanical interlocking and formation of contact points needed for consolidation and particle binding under pressure which is required to make strong compacts. The above results indicate that compactibility was related to DP since it followed the same decreasing order: PVP K30 ≅ sorbitol > MCC PH101 > chitin > PS > CD > LM.

3.3. Lubricant sensitivity

The lubricant sensitivity was tested with magnesium stearate, stearic acid and talc at 1.0% w/w concentration. They are commonly used in tablet formulations to reduce friction between an excipient and the punches-and-die set. The results depicted in Fig. 3 showed that most materials were susceptible to magnesium stearate and stearic acid rather than talc. This means that hydrophobic lubricants were more efficient to coat the surface of particles and prevented the formation of hard compacts. This effect was more pronounced in highly plastic materials that had a smooth surface such as PS. Therefore, for materials such as PS the negative effect of lubricants on crushing strength was more intense since the formation of new surfaces, free of lubricants is partially prevented during compaction. Thus, the lubricant covers the surface of the particles and thereby, restricts the contact between particles rendering compacts of low strength and hence, a high lubricant sensitivity. On the contrary, in most materials the lubricant film coating the particle surface is not complete especially for highly irregular in which the lubricant is trapped in the particle cavities (Bolhuis & Zuurman, 1995).

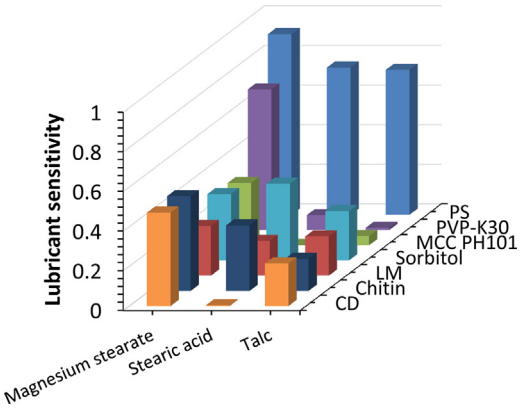

Fig. 3. Lubricant sensitivity of chitin and commercial excipients.

3.4. Reprocessing susceptibility

Fig. 4 shows the tensile strength of round compacts before and upon reprocessing or double compression. In general, reprocessing had a negative impact on the mechanical properties of excipients except for highly plastic materials such as PVP K30 and sorbitol which became more plastic. It has been reported that the loss of compactibility is due to the increase in the yield pressure, which in turn is reflected in a less plasticity after the first compression and milling (Kochhar, 1994). The loss of compactibility was less intense for CD and LM which were the most brittle deforming materials. Some studies suggested that the work of hardening which is generated after dry granulation might be the cause for the loss of compactibility (Herting & Kleinebudde, 2008). The work hardening implies that after recompression a great amount of defects in the particles and entanglement of new dislocations occurs while being deformed plastically. These defects harden particles and makes plastic deformation more difficult for a subsequent compaction process (He, Secreast, & Amidon, 2007).

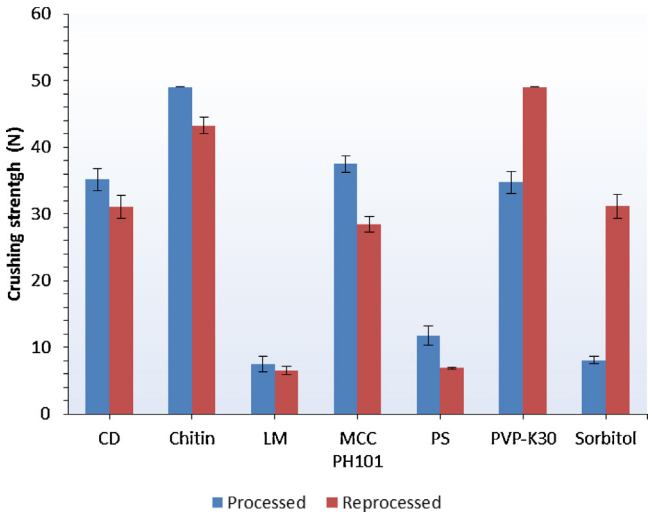

Fig. 4. Reprocessing susceptibility of chitin and commercial excipients.

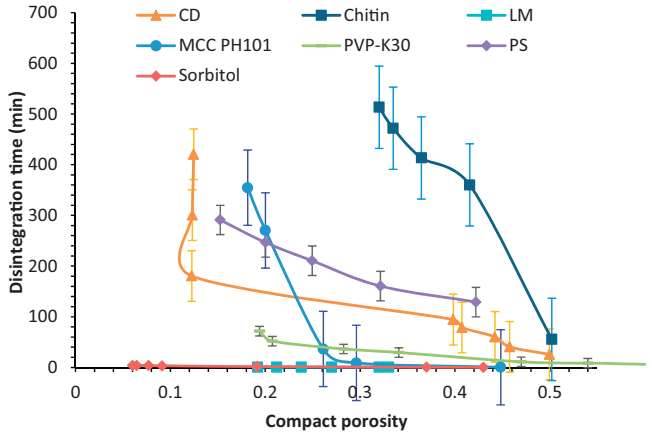

Fig. 5. Compact disintegration time of chitin and commercial excipients.

3.5. Compact disintegration

The disintegration time of compacts as a function of porosity is illustrated in Fig. 5. Compact disintegration time decreased as porosity increased. Further, materials with a very low compactibility such as CD and LM presented a fast disintegration. This effect was more pronounced if the excipients were highly soluble in water such as sorbitol and PVP K30. PS and chitin had a more delayed disintegration due to the swelling and less hydrophillic character, respectively.

4. Conclusions

The tableting properties of chitin were studied and compared to those of CD, LM, MCC PH101, PS, PVP K30 and sorbitol. Chitin had a better compactibility and better acetaminophen dilution potential than PS, CD and LM. However, along with CD were the least compressible materials and had a slow disintegration time and small sensibility to compaction speed. Further, chitin had a close compressibility to that of CD. Chitin was found to be less friable, less sensitive to magnesium stearate, and possessed better acetaminophen loading capacity than CD, LM and PS, but lower compactibility than highly plastic deforming materials such as PVP K30, sorbitol and MCC PH101. The above result shows that chitin can be used as an excipient for the preparation of solid dosage forms with a poorly compressible drug such as acetaminophen.

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