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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