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Compression profiles of different molecular weight chitosans

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ABSTRACT

The compression behavior of hydrophilic chitosan has been investigated as a function of molecular weight (MW), ranging from 8 to 100 kDa. Powder packing, plasticity, elasticity, brittle-fracture nature were evaluated using force displacement curves and Heckel/Kawakita analysis upon compression of different MW chitosan powders. The compacts produced were subjected to ejection work determination and tensile strengths analysis, the later using Leuenberger equation. Molecular modeling was used to correlate the MW-binding energy dependence on the physical strength of the chitosan compacts. The high work of compression of the low MW (≤30 kDa) chitosans is accounted for their brittle nature upon compression. At high compression forces (>3 kN), the low MW chitosan compacts exhibited slightly lower tensile strength due to their increasing extents of elastic recovery and ejection work. Lower particle size of chitosan enhances lower fragmentation, packing, and frictional tendency that can be related to an increase in plastic deformation and compacts tensile strength. In molecular modeling, the calculated higher binding energies of the high MW chitosan (88 kDa) than that of the low MW chitosan (8 kDa) may further explain its rigid, complex nature when compared to low MW chitosan. Upon compression, increasing MW of chitosan is manifested as higher energies for densification which in turn determines the extent of helical packing from intermingled molecular to open structure as the MW is decreased. Such changes in structural configuration are suggested to contribute to the transfer from plastic to brittle-fracture nature with high packing extent of chitosan upon compression when the MW is reduced. The foregoing may justify the slow diclofenac Na drug release upon dissolution testing when low MW chitosan is used in tablet preparation.

1. Introduction

Chitosan powders have been the subject of various investigations as matrices for immediate/controlled release solid dosage forms [1–9]. Since chitosan is prepared from chitin [10,11], the final molecular weight (MW) of chitosan depends on the source or initial MW of chitin and the deacetylation time and temperature [12]. However, Hwang KT et al. [13] demonstrated the complexity of variables, e.g. temperature and time, involved to control the depolymerization and/or the deacetylation of chitosan. Many of these variables were found to manipulate the effective surface charge, electrokinetic mobility, and colloidal stability of chitosan especially upon interfacial interaction inside an aqueous environment [14,15]. Unfortunately, the literature itself lacks sufficient handling of the physicochemical investigations as a function of chitosan MW. Investigations were mostly concerned with applications with few justifications, if present, on the role of chitosan MW at the molecular and morphological level [16–25]. These justifications were confined to structure-MW dependence and supported by the fact that the MW is equivalent to the number of repeating units of D-glucosamine. Onto each of these units, interactive amine groups (NH_2) are bonded. The general observation conclusively illustrates that the longer the chain length of chitosan, the more NH_2 binding sites are available. Consequently chitosan binding affinity, uptake capacity, rheological properties, particle morphology and subsequently surface area, are all strongly dependent on the number of NH_2 groups in a specific polymer mixture, i.e. average MW.

The scientific inputs become even shallower when chitosan is present in the powder state. In this context, the compression behavior of chitosan powder was not understood to be MW related [1,5,6,26–27]. In order to correlate such compression dependency, the particle morphology and density have to be introduced for analysis when the MW of chitosan is varied. These two parameters play a significant role in the packing and arrangement upon powder compression [28]. Fortunately, some attention has been given to try to understand the complex relationship between the MW of chitosan and the structural changes and consequently the powder physical properties, all as a function of chain

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length (or MW). For example, Goycoolea et al. pointed out that chitosan of longer chain lengths tends to form 'loops' giving rise to the creation of more expanded structures and to a denser packing [7]. Ofori-Kwakye et al. related the change in the intrinsic viscosity of different MW chitosans to the change in particle shape and size [29]. Aggarwal et al. highlighted the dependence of chitosan molecular architecture and MW on the mechanical strength of branched chitosans synthesized by grafting low MW chitosan chains [30]. Furthermore, bulk density and flow of powders were found to be dependent on the MW of chitosan when the later is spray-dried with lactose [31]. In this regard, it was noted that the lower the MW of chitosan the higher the bulk density and better flow of their processed mixture. However, the poor powder flow and thereby compressibility have never been investigated as a function of chitosan MW. Consequently, an insight into the behavior of different MW chitosan powders upon compression is of significant interest.

In light of the foregoing remarks which are important parameters in characterizing powder compression properties for direct compression pharmaceutical applications, the work reported herein addresses the mechanistic densification behavior of depolymerized chitosan powders. The properties of the compressed tablets were assessed in the context of testing tablet mechanical properties as a function of MW.

2. Materials and methods

2.1. Materials

Chitosan (Hong Ju Ginseng Co., Ltd., Dalian Liaoning, China), particle size <150 μm, MW 100 kDa, (93% degree of deacetylation) of 100 kDa MW was supplied as pharmaceutical grade. The 8, 13, 18, and 30 MW chitosan powders were prepared by the Jordanian Pharmaceutical Manufacturing Company (JPM, Naor, Jordan) using the acid hydrolysis of the 100 kDa chitosan. This technique was described in details by Qandil et al. [32], who illustrated the de-polymerization of chitosan by acid hydrolysis, the determination of viscosity average molecular weight using the relative and reduced viscosities of the Mark-Houwink technique, and finally the determination of the degree of deacetylation which was approximately 100% for all chitosan samples according to the first derivative UV spectroscopic method [33]. Diclofenac sodium was supplied by CHEM. Co., Ltd. (CCS. Xiaoshan Hangzhou, China).

2.2. Methods

2.2.1. Compression of chitosan samples

Prior to compression the chitosan samples were grinded and sieved using an oscillating granulator with a mesh size 250 μm and collected on a 90 μm mesh. 100 mg of each MW (8, 13, 18, 30, 100 kDa) chitosan sample was compressed using a Gamlen Tablet Press (Gamlen Tableting Ltd. Biocity Nottingham, UK). Initially, the powders were compressed at a punch size of 6.0 mm diameter, enough to accommodate the chitosan samples. The die was manually filled and the machine operated under an automatic compression force or displacement control. Ejection was carried out in the same direction as compression i.e., the tablets were pushed through the bottom of the die into a tablet holder which was removed from the machine. The test speed was set at 60 mm/min. The applied loads used were; 100, 200, 300, 400, and 500 kg equivalent to 098–4.9 kN compression force or to 34.6–173.2 MPa compression pressure (compression force/punch surface area) applied on a 6 mm diameter circular punch. The Gamlen Tablet Press (GTP) software displayed a full data capture of the work of compression and work elastic recovery on a PC screen. After ejection the thickness of the tablets were immediately measured using a caliber. Other tablets produced in the same manner were directly subjected to tensile strength tests using a hardness tester (Copley, Nottm Ltd., Therwil,Switzerland). The average tensile strength of 10 tablets was recorded at each compression force for each MW chitosan. From the measured tablet hardness, the tensile strength was calculated according to the equation [34]:

$$\sigma = 2F/(\pi Dh) \quad (1)$$

where σ is the tensile strength (Pa), F is the tablet hardness (N), D the tablet diameter (m), and h the tablet thickness (m).

2.2.2. Work of compression, elastic recovery and tablet ejection, and extent of powder packing

A typical illustration of the force displacement curve is presented in Fig. 1 for the 100 kDa chitosan (100 mg) whereby the input load was set at 100 kg (4.91 kN). The upper punch, at a distance of 27.379 cm from the base, displays an automatic displacement starting from the zero position (point A), followed by point B where the upper punch makes the first contact with the powder. The powder then undergoes compression whereby the recorded curve represents an increase in the amount of force as a function of the upper punch displacement. The maximum recorded force terminates the punch movement in the downward direction and is presented by point C of the displacement value D. However, the powder's elasticity exerts an upward force to the punch in the form of a decreasing force profile until it reaches zero at point E.

From Fig. 1, the area under the curve BCD is the work of compression in J (N · m). On the other hand, the area under the curve ECD represents the work of elastic recovery. In both cases, the data are tabulated by the software of the GTP into two columns, one for the position of the upper punch (mm) and the other for the load applied (kg). The total area was numerically calculated by approximation using areas of rectangles. The width and height of such rectangles were taken as the difference between two successive displacement points and their corresponding 'load value' length respectively. The summation of all rectangles areas represents the area under the curve (AUC).

The packing extent can be estimated from the final volume of the powder after being compressed compared to its initial bed volume before compression. Empirically, the packing extent can be estimated from Fig. 1 using the following equation;

$$\text{Packing extent} = \left(\frac{D-B}{27.379-B}\right) \times 100\% \quad (2)$$

where (D − B) and (27.329 − B) represent the final (after compression) and initial (before compression) heights of the powder bed respectively, mm.

Generally, the die-wall friction can be usually estimated by either of the following methods; by calculating the difference in the work of compression of unlubricated and lubricated granules [35], or by calculating the difference in the work of compression for the upper punch forces and that for the lower punch [36]. However, both methods were not adopted in this work as lubricants, in the first case, may disrupt the arrangement of particles through agglomeration [37]. The extent of such disruption may vary between different MW of chitosans. In the second case, the GTP does not provide a lower punch for compression, it can, however, measure the work for tablet ejection by the upper punch from within the die. A typical force-displacement profile for the ejection of the 100 kDa chitosan tablets compressed at the input load of 500 kg (4.9 kN) is presented in Fig. 2. The AUC, which represents the work for tablet ejection, was calculated for all force-displacement curves for each MW of chitosan and then plotted at each compression force. Accordingly, after the powder was being compressed into a tablet, the GTP setting was turned into the ejection mode using the same upper punch and inverting the closed die base position into an open position.

2.2.3. Analysis of compression data

Heckel, Kawakita, and Leuenberger analysis were used to characterize the compression properties of different MW chitosan samples. The