



Original research

Application of N-hexoyl chitosan derivatives with high degree of substitution in the preparation of super-disintegrating pharmaceutical matrices

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ABSTRACT

The present work investigated the utilization of degree of substitution in preparing N-hexoyl chitosan matrices with superdisintegration power. Different degrees of substitution of N-hexoyl chitosan (58, 67 and 75%) were prepared and evaluated. The study includes characterization of the derivatives using DSC, FTIR, surface tension, particle size, zeta potential, moisture uptake, powder flowability and powder porosity analysis. In addition, pressure-displacement, compact surface roughness using AFM, tensile strength, compact disintegration and dissolution studies. The studies indicated that the best super-disintegrant was due to the N-hexoyl chitosan with degree of substitution 57%. A compact of N-hexoyl chitosan with degree of substitution 57% showed water sorption more than 5 times increase of its initial weight. In addition, it showed a fast disintegration time i.e. less than 0.5 min. Such material could be a potential for the preparation of orodispersible tablets.

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1. Introduction

Chitosan (CS) is a natural safe, biocompatible and biodegradable polysaccharide obtained by partial deacetylation of chitin poly(N-acetylglucosamine) [32]. CS has many applications in food, biomedical, cosmetic and pharmaceutical fields [2,56,63]. In the pharmaceutical field, CS has been used as a drug delivery system for plenty of drugs including protein drugs due to its permeation enhancer effect and its protective effect against intestinal peptidases [11–13,58]. Another interesting application is the use of CS as a pharmaceutical tableting excipient [30,33,55]. CS has some favorable physico-mechanical properties over other traditionally known direct compressible excipients including microcrystalline cellulose regarding plastic deformation and compression behavior [45]. In addition, CS showed some tablet disintegration activity [30]. Furthermore, CS has the ability to interact with negatively charged excipients and resulted in modified release behavior in solid dosage forms [34]. However, CS still suffers from several shortcomings such as insolubility in water, poor bulk density and

hence poor flowability [24] besides to its erratic behavior which made it difficult to be used as a single component in preparation of solid dosage forms [41]. To overcome such weaknesses different approaches were adopted.

The first approach of modifying CS properties was through physical co-processing with other excipients. For example, in order to improve the mechanical properties of CS, it was co-processed with other inorganic materials such as silica or metal silicates [10]. The resultant co-excipient was found to have much higher compressibility and disintegrating power than CS itself [24,27,53,54]. Furthermore, in order to enhance CS controlled release activity, it was mixed with other polymers such as sodium alginate [8,28], xanthan gum [4,23], hydroxyethyl cellulose [7], carrageenan [40], and guar gum [9].

The second approach was through the formation of CS salts such as CS sulfate [5], CS citrate [1] and CS acetate [49]. Citrate and acetate salts improved the sustained release properties of CS polymer.

The third approach was through chemical structure modification such as partial N-substitution with phthalic and succinic acids. This modified CS was used for colon targeted delivery [3]. In addition, N-acyl thiolated CS was applied as a controlled release matrix system [62]. Another interesting chemical conjugation that

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remarkably affected CS physical properties was the N-acyl groups. It was reported that the degree of substitution (DS) with N-acyl groups was strongly affecting CS surface tension properties and water solubility [6,35,42]. N-acylated CS was previously described and evaluated for many applications such as film forming ability [46], drug carrying ability [20], papermaking [15], etc. One interesting N-acylated CS derivative with short chain fatty acid is the N-hexoyl CS. The short fatty acid chain (C6) induced little polymer hydrophobicity and at the same time decreased inter and intra hydrogen bonding. Consequently, it was demonstrated that N-hexoyl CS exhibited significant swelling property compared to other medium and long fatty acid chain N-acylated CS derivatives such as octanoyl, myristoyl and palmitoyl CS [37]. Such property is crucial for the preparation of rapid disintegrating compacts. It is known that swelling is the most widely accepted mechanism of action which explains tablet disintegration [14]. However, the effect of DS of N-hexoyl CS on mechanical, disintegration and dissolution properties has not been fully described in the literature. In this study, N-hexoyl CS derivatives with different degree of substitutions (DS) were prepared. The objective of this work was to study the effect of DS of N-hexoyl CS (HCS) on certain pharmaceutical properties. The physicochemical, disintegration and dissolution properties of HCS matrices were studied and compared to CS.

2. Experimental

2.1. Materials

CS polymer, with a viscosity average molecular weight of 150 kDa and degree of deacetylation (DDA) of 90% measured using UV spectrophotometer method [47], was obtained as a kind gift from the Jordanian Pharmaceutical Company, Naor, Jordan. Hexanoic anhydride (assay 97%, code 186752500, lot: A0300939) was purchased from Acros Organics, UK.

2.2. Methods

2.2.1. Preparation of HCS powder

Three HCS derivatives were prepared as described previously with some modifications [66]. CS (5 g) powder was dispersed in 200 mL distilled water, the pH was adjusted around 7.5, then hexanoic anhydride (3.5 mL, $d = 0.928 \text{ g/mL}$ at 20°C) was added gradually with magnetic stirring for 20 min. Similarly in separate experiments, two volumes (5.4 and 7.2 mL) of hexanoic anhydride were used to obtain various DS. In a preliminary work, the amount of hexanoic anhydride added to CS was determined based on compact disintegration time. The addition of very small volumes of hexanoic anhydride to CS produced compacts that have a disintegration time much similar to that of CS. Therefore, higher volumes of hexanoic anhydride were applied. The mixtures were homogenized using homogenizer (IKA® T29 digital Ultra turrax, Germany) for additional 20 min, afterward the dispersions were sonicated using Ultrasonicator (Branson Probe®, 102C (CE), EDP 101-135-066K supplied with Branson Sonifier® 450, duty cycle 100%, and microtip setting of 5 amplitude) for another 20 min. Then, the dispersions were put on a magnetic stirrer and 0.2 M sodium hydroxide solution was added until pH reached 8.5 to end the reaction. Finally, the fine powder was filtered using Whatsmann filter paper (Whatman International, Maidstone, England) and washed carefully for several times with water/ethanol (50:50 w/w) to remove excess impurities and placed in a mechanical convection oven (Memmert Model 100–800, Schwabach, Germany) at 65°C for 12 h. The dried samples were triturated by a mortar and pestle and the fine powder was passed through a stainless steel sieve with

aperture of $315 \mu\text{m}$ (Laboratory Test Sieve, Endecott Ltd, England) and put in screw capped bottles and stored in desiccators containing silica gel until needed.

2.2.2. Characterization of HCS

2.2.2.1. Chemical identification using FTIR and DSC. To study the change in chemical structure of CS after the reaction, the dry samples were placed in the micro-sample cup of Shimadzu diffuse reflectance infrared fourier transform spectroscopy (DRIFT) accessory using FTIR spectrometer (IR Prestige 21, Shimadzu, Japan). The transmittance mode for intensity measuring was applied in the spectrum ranging from 800 to 4000 cm^{-1} [65].

For DSC measurements, samples between 5 and 8 mg were placed in open aluminum pans and measurements were conducted using a previously calibrated differential scanning calorimeter (STA 449 F1 Jupiter® Netzsch, Germany). The thermograms were recorded from room temperature to 350°C . Samples were heated at a rate of 10°C/min . The samples were subjected to protective nitrogen flow with a rate of 20 mL/min during measurements.

2.2.2.2. Determination of DS. The FTIR spectrometer (IR Prestige 21, Shimadzu, Japan) data obtained as mentioned previously with the exception of using absorbance mode instead of transmittance.

DS was determined based on absorbance ratios A_{1560}/A_{2880} , the mostly recommended ratios since the amide band of the N-acyl CS appeared at 1560 cm^{-1} which can be used as probe band, and the 2880 cm^{-1} band is CH stretching band, being independent of carbon number in acyl group, so it was used as reference band [67]. The percent DS was determined based on the equation (1) [67].

$$\text{Absorbance ratio } (A_{1560}/A_{2880}) = 0.0121 \text{ DS } (\%) + 0.1805 \quad (1)$$

2.2.2.3. Particle size and zeta potential studies. Sample of 10 mg, for each CS derivative, was dispersed in 200 mL 0.1 M HCl. The sample was centrifuged using a centrifuge (Heraeus Labfuge 200 centrifuge, Thermo Fischer LED GmbH, Germany) at 5300 rpm for 10 min. A portion of 2 mL of the supernatant was withdrawn and the particle size distribution and zeta potential measurements were carried out using Zetasizer Nano-ZS (Malvern Instruments, UK) at 25°C .

2.2.2.4. Surface tension studies. Surface tension was determined using surface tensiometer (Kibron with KBN 315 sensor head, Finland) at ambient temperature (25°C). Distilled water (1 mL) was added to three Kibron plate wells, and then measurement of surface tension was started. After 300 s, 0.2 mL sample of each CS derivative with a concentration of 0.02 mg/mL (0.1 M HCl) was inserted via a syringe beneath 1 mL distilled water present in Kibron wells. The change in surface tension of distilled water after sample injection was monitored as a function of time.

2.2.2.5. Loss on drying. Loss on drying of CS and HCS samples were determined using a mechanical convection oven at 110°C for 3 h.

2.2.2.6. Moisture uptake studies. Samples of CS and HCS derivatives (initial weight of 1 g) were spread inside Petri dishes and subjected to different relative humidity (RH) conditions (33, 75 and 90%) resulted from saturated salt solutions [24]. The samples were kept inside the humidity chambers at ambient temperature (25°C) for 1 week until equilibrium was reached. The percentage change in weight from the original weight was recorded for each humidity conditions. Hygrometer (Highest II, Satokeiryoki Mfg Co., Japan)

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