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Self-stabilized chitosan and its complexes with carboxymethyl starch as excipients in drug delivery

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ABSTRACT

This study focuses on the behavior of chitosan (**CHI**) and its polyelectrolyte complexes with carboxymethyl starch (**CMS**) used as monolithic matrices with acetaminophen as drug tracer. Two different chitosan grades were tested alone or associated in various ratios with CMS as excipients for tablets obtained by direct compression. The degree of deacetylation (DDA) of CHI, estimated from ^{1}H NMR and FTIR data, was correlated with X-ray diffraction and scanning electron microscopy (SEM) to evaluate structural organization of the monolithic matrices. *In vitro* drug dissolution assays showed major differences in CHI kinetic profiles between tablets exposed to acidic medium for 2h (to mimick gastric passage) prior to dissolution in simulated intestinal fluid (**SIF**), and those administered directly to SIF. Prior exposure to acidic SGF conducted to longer dissolution profiles (release completed after 16 h) and preservation of tablet shape, whereas tablets directly incubated in SIF were rapidly disintegrated. The improved properties of chitosan matrices exposed to SGF may be related to an outer compact coating layer (visible in SEM). The effect of self-stabilization of chitosan in acidic medium was compared to that due to formation of polyelectrolyte complexes (PEC) in co-processed polymeric systems (CHI:CMS). The self-formed membrane following exposure to gastric acidity appears to help maintaining tablet integrity and allows higher drug loading, recommending CHI and its complexes with CMS as excipients for drug delivery.

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1. Introduction

The number of biocompatible polymers (natural or synthetic) proposed as excipients for the drug formulations by the pharmaceutical industry recorded a huge increase during the last decades.

Chitosan [poly β-(1,4)-2-amino-2-deoxy-D-glucopyranose, CHI] can be obtained by the deacetylation and partial depolymerization of chitin, the most abundant polysaccharide in nature [1]. Until recently, only marine sources (shrimp, prawn, crab) have been used to provide the starting chitin. Chitosans obtained following this difficult to control process [2] contain chains with 2-amino-glucose and with N-acetyl-2-amino-glucose units, in variable ratios. They are obtained in different molecular weights. Recently, new commercial chitosans, better characterized by manufacturers and with enhanced safety characteristics for certain pharmaceutical, cosmetic, and biomedical applications have been produced at lower costs [3–5]. Not affected by seasonal variations, different fungi have also been studied in recent years as a competitive source of chitin/chitosan [6,7].

The interest for chitosan-based materials for pharmaceutics and biomedical applications continues to increase [8–17]. Chitin, the natural source of chitosan, not being of plant origin, generated a certain delay in acceptance by the pharmaceutical industry in many countries. However, the fact that chitosan is nontoxic,

Abbreviations: CHI, Chitosan; CMS, Carboxymethylstarch; DDA, degree of deacetylation; FTIR, Fourier transformed Infra-Red; GIT, Gastrointestinal tract; ^{1}H NMR, proton nuclear magnetic resonance; HAS, Gelatinized High Amylose Starch; PEC, polyelectrolyte complex; SIF, simulated intestinal fluid; SGF, simulated gastric fluid.

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biocompatible, biodegradable, antimicrobial, and easy to obtain makes it a good candidate for many applications. There are reports of chitosan used in dietary foods [1,9,10], as films for food packaging and for biomedical applications [11,12], as matrix for immobilization of bacterial cells [13], as implantable delivery systems [14], in bandages [15] and as excipient for oral medication [2,16,17]. Chitosan is considered Generally Recognized As Safe (GRAS) and approved for specific applications [18–20]. Another attractive feature of chitosan is its capability to produce nanostructure using simple procedures conducted under mild conditions [21–25]. Chitosan based nanomaterials mimicking natural structures (crustaceous shells or extracellular matrices) have also been reported [23–26]. When used in tablets, chitosan role can change depending on its proportion. Evaluation of chitosan-microcrystalline cellulose blends as direct compression excipients has shown that chitosan promotes flowability of powder mix and rapid disintegration of the tablet. However, incorporation of equal proportion of microcrystalline cellulose and chitosan affords an extended-release tablet. It was concluded that in combination with microcrystalline cellulose chitosan promotes tablet disintegration at low concentration and enables extended-release at higher concentration [27]. Crosslinked chitosan was investigated as sustained release agent in tablets. In granular form, particles of CHI crosslinked with tripolyphosphate exbibited some limitations like inefficient drug loading and incomplete release [28]. Associated with anionic polymers (i.e. xanthan gum), CHI was used for wet granulation of a model drug with high solubility in gastric fluid (paracetamol) [29]. From the data generated it was concluded that this approach has sufficient potential to sustain the release of paracetamol. Another type of CHI application consists of its incorporation in vaginal tablets. Two-layer vaginal tablets, containing different polymeric ratios (i.e. 20 mg Na-CMC; 50 mg Carbopol® 934; 20 mg chitosan) were selected as optimal due to swelling index and dissolution/erosion capability [30].

Despite largely investigated at laboratory scale, the inexpensive and easily accessible chitosan is still not used as excipient in oral formulations on an industrial scale partially due to concerns related to its solubility: these materials are soluble in acidic media and insoluble in neutral and alkaline fluids. Many formulations found in the literature required addition of different ingredients to enhance compressibility and improve the drug dissolution profiles [31,32]. Chemical procedures targeting advanced deacetylation and reacylation with more hydrophobic groups have been studied together with the interaction of covalently-modified chitosan matrices with both charged and uncharged chemical species. These approaches were recommended for drugs targeting the small intestine or the colon [17].

The novelty of this work is that, to the best of our knowledge, it is the first report showing a rearrangement at the surface of chitosan tablets following exposure to acidic medium, mimicking the physiological gastric residence. This effect of self-stabilization of chitosan was also investigated in monolithic tablets based on CHI: carboxymethylstarch (CMS) mixtures. Used as excipient in tablets, CMS can protect bioactive agents during gastric residence. At pH 1.2, being protonated, it affords a more compact matrix and better control of drug release in the intestinal medium where the carboxyl groups are deprotonated fostering hydration and swelling of the tablet [13]. In the present study the contribution of electrostatic interactions was evaluated in two series of tablets containing: *i*) a variable ratio of the two polymers CHI:CMS and b) a constant amount of cationic polymer (CHI) combined with various amounts of anionic (CMS) and - neutral high amylose starch (HAS) as filler in order to keep the mass of tablets constant. The structural changes were monitored by spectroscopic analysis. The effects of exposure of tablets based on various polymers to simulated gastric and intestinal fluids were investigated by *in vitro* dissolution assays and compared.

2. Materials and methods

2.1. Materials

Two different chitosans were used in this study: one (CHIa) obtained in-house by an advanced deacetylation procedure [33] of chitosan from Protan Co. (Drammen, Norway), the other one (CHIb), degree of deacetylation (DDA) 85%, was purchased from Marinard Biotech Inc. (Canada). CMS was prepared starting with high amylose starch from National Starch, USA, and using a procedure previously published [34]. Gelatinized high amylose starch (HAS) used as filler, was prepared following a procedure found in the literature [35]. The other chemicals were from Sigma (USA) and were reagent grades and used without further purification.

2.2. Evaluation of the degree of deacetylation

The estimation of DDA of the two grades of CHI was done using ^{1}H NMR and FT-IR analysis.

2.3. Proton nuclear magnetic resonance (^{1}H NMR)

High resolution ^{1}H NMR spectra were recorded on a 500 MHz Varian Innova NMR spectrometer. CHI samples were dissolved in 1% trifluoroacetic acid (TFA) in D_2O.

2.4. Fourier-transform infrared spectroscopy (FTIR)

CHI tablets (6% in KBr pellets of 100 mg) were made in a Carver hydraulic press Model C-3912 (Wabash, IN, USA), at 8 T. For each CHI grade three tablets were made and evaluated by FTIR. Absorbance spectra were recorded in a Bomem MB-100 FT-IR spectrophotometer (Hartmann &Braun) with a deuterated triglycine sulfate (DTGS) detector. The spectra were obtained at a 2 cm^{-1} resolution as an average of 64 scans, with air as background.

2.5. Tablet preparation, their stability in SGF and dissolution tests in vitro

Monolithic tablets (200 mg, 12 mm diameter) were made by direct compression (in a Carver hydraulic press, at 2.5 T) of CHIa or CHIb with 20% acetaminophen (as model drug) mixed powders.

Two series of tablets (200 mg each), all containing 20% acetaminophen, were made in the same conditions, and contained as follows: Series I) CHI and CMS in different ratios (w/w, 0:3, 1:2, 1:1, 2:1, 3:0), Series II) a constant load of CHI, variable CMS and HAS as filler (as shown in Table 1). To investigate the behavior of preparations in gastric acidity, tablets based on CHI:CMS (1:1) and loaded with 5% bromocresol green (10 mg pH indicator per tablet), were also prepared by direct compression of mixed powders, as described above. Each tablet was incubated for 120 min in 50 mL of SGF at 37 °C and 50 rpm (incubator shaker, series 25D, New Brunswick Scientific Co., NJ, USA). The tablet integrity and color modifications were observed on the whole and on cross-sectioned tablets.

Tablet shapes and swelling were monitored in a rotary shaker (50 rpm), first for 2 h in 50 mL SGF, and then, after being transferred to 50 mL SIF, they were monitored for up to 20 h (50 rpm) as per recommendations of US Pharmacopeia for dissolution tests. Tablets containing bromocresol green as pH indicator were first exposed to SGF in order to visualize the water front penetration into the tablets. Kinetic studies of the drug release were conducted in a

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