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Novel hybrid formulations based on chitosan and a siloxane compound intended for biomedical applications

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ABSTRACT

The present study reports on the obtaining of chitosan/siloxane–based microspheres by coacervation/precipitation method and their use as efficient drug delivery vehicles for ciprofloxacin, one antibacterial synthetic drug belonging to fluoroquinolones group. These new hybrid formulations were analyzed in terms of structural characterization (FTIR, SEM, TG, DSC techniques), swelling capacity and in vitro drug release. The release mechanism of the model drug was investigated by means of several kinetic models, i.e., zero order, first order, Higuchi model, Korsmeyer–Peppas model, Hixson–Crowell model, Baker–Lonsdal model, Weibull model and Schott model.

1. Introduction

Despite its intensive use in different fields of research and application, chitosan (CH) continues to awaken the researcher's interest due to its outstanding physicochemical and biological characteristics. Being one of the most abundant natural polysaccharides, CH is a positively charged natural polymer, is biocompatible, biodegradable, non–toxic and presents antibacterial properties [1]. Due to its coagulation ability and immuno–stimulating activity [1], CH is widely used with success in various domains, such as tissue engineering, wound healing, food additives, drug delivery, cancer diagnosis, water treatment or cosmetics [2]. The presence of functional groups (like hydroxyl, amino or *N*–acetyl) allows CH to self-assemble into a variety of supramolecular structures either through a chemical reaction [3] or via the so–called ISISA process (Ice Segregation Induced Self Assembly process), which is based on the unidirectional freezing of a hydrogel material [4]. The self–assemble ability offers to CH carriers a tremendous potential with application in fields, such as peptide/protein delivery, vaccine delivery, controlled drug release [2], gene delivery [5,6]. Beside its special properties, CH presents also some drawbacks connected with the poor solubility in organic solvents, low mechanical strength and poor chemical resistance in acidic media [7]. In order to avoid these types of issues CH structure is widely modified with different compounds, such as natural polymers (e.g. alginate, starch, cellulose), synthetic polymers (e.g. poly(ethylene glycol), poly(ethylene oxide), poly(ε-caprolactone), poly(ethylene glycol)–*co*–poly(lactone)diacrylate) [2] or silica–based compounds [8–10]. In some situations the dissolution or degradation of CH is avoided also by the addition of cross–linking agents such as glutaraldehyde, formaldehyde, [10] epichlorhydrine [11], dialdehyde starch, sulphuric acid [9], etc. Taking into consideration the CH properties and the advantages that a silica–based compound could offer (large surface area, enhanced mechanical resistance, improved physical properties), a special attention was given to the obtaining of CH/siloxane hybrid materials due to improved properties and enhanced application fields [10,12–14].

The aim of the present paper was to obtain new formulations based on CH/siloxane hybrid materials intended for the delivery of a model drug, i.e., ciprofloxacin (CPF) which is a second generation quionolone efficient against gram positive and negative bacteria. This drug is widely used to treat conjunctivitis, keratitis, gonorrhoea, osteomyelitis, infections of the urinary and respiratory tracts, low respiratory tract infections, a.s.o [15]. The hybrid materials described in this work were obtained in the form of hydrogel microspheres using the coacervation/preparation method and were further dried by freeze–drying technique. The mechanism release of the model drug was investigated by means of several mathematical models, i.e., zero order, first order, Higuchi model, Korsmeyer–Peppas model, Hixson–Crowell model, Baker–Lonsdal model, Weibull model and Schott model. Although several papers presented the preparation of drug delivery formulations based on CH microspheres [11,16–20] to our knowledge this paper is the first one reporting the obtaining of chitosan microspheres through coacervation/precipitation method incubated with a model drug (an antibiotic) and coated with a siloxane compound. Most often, the drug delivery

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formulations based on CH modified with siloxane compounds involved the use of CH in the form of films or membranes [21–23].

2. Experimental section

2.1. Materials

Chitosan (CH) of medium molecular weight, ciprofloxacin (CPF), 98% (HPLC), 3–(chloropropyl)–trimethoxysilane (CPTMS) with a purity of 97%, 1–ethyl–3–(3–dimethylaminopropyl) carbodiimide hydrochloride (EDC), *N*–hydroxysuccinimide (NHS) and sodium hydroxide pellets were purchased from Sigma Aldrich.

2.2. Preparation method

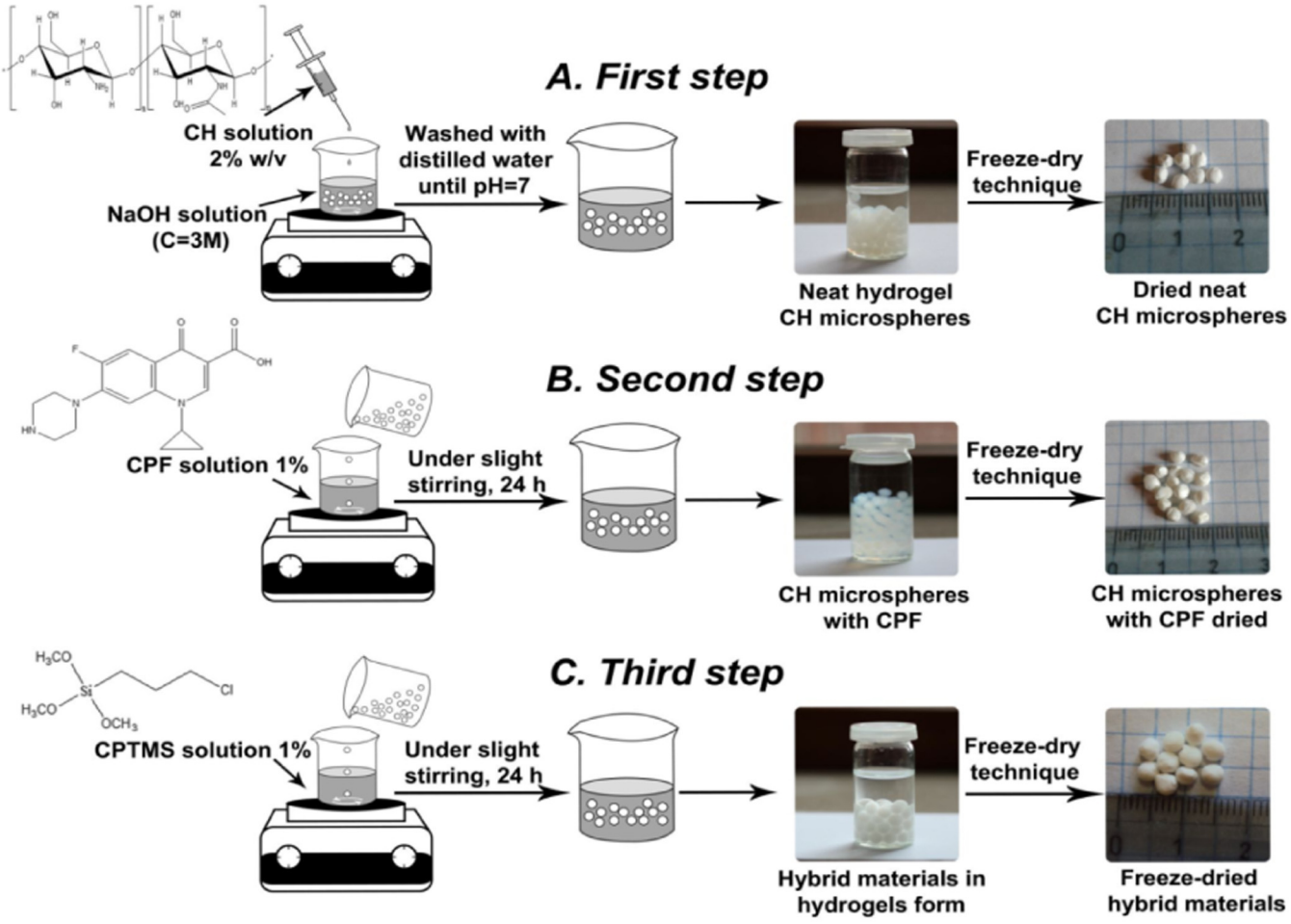
The preparation procedure of the hybrid samples is schematically represented in Scheme 1. The CH microspheres were obtained using the coacervation/precipitation method [24]. Briefly, a solution of 2% CH was obtained by dissolving the CH powder in an aqueous solution of 1% acetic acid and the solution was stirred for 24 h at room temperature. The CH microspheres were obtained by dropping the CH solution in sodium hydroxide (NaOH, 3 M) using a needle and after precipitation the microspheres were left under very slow agitation for another 1 h. In order to remove any alkali traces the CH microspheres were washed with distilled water until the pH = 7. In the second step, a CPF aqueous solution (1%) was prepared and left under vigorous stirring for several hours until solubilisation was achieved. It is well known that CPF is one of the weakly basic drugs and is insoluble in water at neutral pH. For this reason sulfuric acid was used (at pH = 5.5–6) in order to facilitate the solubility of the drug. The coupling between CH and CPF was favoured by coupling agents, 1–ethyl–3–(3–dimethylaminopropyl) carbodiimide hydrochloride/*N*–hydroxysuccinimide (EDC/NHS). The molar ratio CPF:EDC:NHS was 1:1:1 and the CH microspheres, in hydrogel form, were transferred in this system and left under stirring at 40 °C for 24 h.

In the third step an amount of CPTMS (1%) was placed in an acidic aqueous solution and left under stirring at 40 °C for 6 h. The CH microspheres containing CPF were washed with distilled water, transferred in this solution and left under stirring for other 24 h. In the final step, the hybrid materials containing CPF were washed with distilled water and dried by freeze–drying technique. Both unmodified and CH microspheres containing CPF were freeze–dried and subjected to structural characterization, too.

2.3. Drug entrapment efficiency

The drug entrapment was calculated using 50 mg of microspheres crushed in a glass mortar and the powder obtained was introduced in 100 ml of HCl solution 0.1 N and kept under stirring for 4 h. In the next step, the solution was filtered and the drug content was analyzed following the evolution of the band located at 277 nm using a UV–VIS spectrophotometer. The entrapment efficiency was determined using formula (1) [25]. The quantity of drug entrapped in the microspheres resulted to be 40% of the initial quantity.

$$\text{Drug Entrapment } \% = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$



Scheme 1. Schematic representation of the hybrid microspheres preparation.