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Preparation and characterization of acetylated starch nanoparticles as drug carrier: Ciprofloxacin as a model

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ABSTRACT

The objective of this study was to characterize in-vitro the potential of acetylated corn starch (ACS) particles as a matrix for the delivery of ciprofloxacin (CFx). ACS was successfully synthesized and optimized by the reaction of native corn starch using acetic anhydride and acetic acid with low and high degrees of substitution (DS). The nanoprecipitation method was applied for the formation of the ACS-based nanoparticles, by the dropwise addition of water to acetone solution of ACS under stirring. The effects of acetylation and nanoprecipitation on the morphology and granular structure of ACS samples were examined by the FT-IR, XRD, DSL and SEM techniques. The efficiency of CFx loading was also evaluated via encapsulation efficiency (EE) in ACS nanoparticles. The average degree of acetyl substitution per glucose residue of corn starch was 0.33, 2.00, and 2.66. The nanoparticles size of the ACS and ACS-loaded with CFx were measured and analyzed relative to the solvent:non-solvent ratio. Based on the results, ACS nanoparticles with DS of 2.00 and water:acetone of 3:1 had 312 nm diameter. Increasing DS in starch acetate led to increase in the EE from 67.7 to 89.1% and with increasing ratio of water/acetone from 1:1 to 3:1, the EE raised from 48.5 to 89.1%. X-ray diffraction indicated that A-type pattern of native starch was completely transformed into the V-type pattern of acetylated starch. The scanning electron microscopy showed that the different sizes of pores formed on the acetylated starch granules were utterly converted into the uniform-sized spherical nanoparticles after the nanoprecipitation.

1. Introduction

Starch is a natural, renewable, biodegradable, biocompatible, and cost-effective polysaccharide, which has been widely used in various applications [1,2]. It is the second most abundant biomass material in nature after cellulose [3]. Starch is a carbohydrate storage product found in all plants containing chlorophyll, such as corn, potato, rice, tapioca, wheat, sorghum and barley [4]. The amount and type of associated material vary depending on which part of plant the starch comes from. One major difference is due to the source, such as from cereal seeds (corn, wheat, etc.), from tubers (potato) or from roots (tapioca). Starch is white, insoluble in cold water because of the polymerized structure, and has hydrogen bonding between adjacent chains. Starch is composed of linear molecules called amylose and branched molecules called amylopectin [5]. Their structures, physical and chemical properties are compared in Table 1 [6]. The starch industry extracts and refines starches by wet grinding, sieving, and drying processes. It is either used as extracted from the plant and is called “native starch”, or it undergoes one or more chemical modifications to reach specific properties and is called “modified starch” [7].

Recently, polymer nanoparticles have attracted significant interest in chemistry, pharmaceutics and biomaterial science for biomedical application and controlled release [8,9]. Among the known carbohydrate polymers, starch has been used in the fields of drug delivery and biocatalysts, because of its advantages, such as improving drug solubility and stability, decreasing drug toxicity and side effects, and excellent biocompatibility and storage stability [10,11]. However, native starch is not suitable for controlled drug release due to its physical and chemical properties [12]. To further meet and improve its properties and extend the application of starch in the food and biomedical areas, all kinds of modifications including blending and chemical modification, such as oxidation, crosslinking and hydroxypropylation, have been considered by many researchers [13–15]. Chemical modification is the most useful tool to customize the overall performance of native starch. Acetylated starch as a starch derivative can be produced by esterification of native starch with acetic anhydride (AA). Through

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this modification, these starch derivatives are broadly used in the food, textile, paper and biomedical applications owing to their film forming, stabilizing, and thickening properties, which are apparently superior to the native starch. In view of these facts, the acetylated starch is considered as a promising alternative for the development of a product with a higher additional value, achieving more reasonable and efficient use of starch in many industries [5]. In acetylated starch, part of hydroxyl groups in anhydroglucose units of starch have been converted to acetyl groups. A low degree of substitution (DS) with 0.01–0.2 acetylated starch has been applied in many areas, such as film forming, binding, adhesion, thickening, stabilizing and texturing [16]. Acetylated starch with low DS is commonly obtained by esterification of native starch with AA in an aqueous medium in the presence of an alkaline catalyst [17]. However, high DS acetylated starches have received much attention in recent years for their solubility in acetone and chloroform and for their thermoplasticity. Also, high DS acetylated starches can have very different properties such as hydrophobicity, melt processibility, and a number of non-food applications, which have been suggested such as tablet binders, hot melt adhesives, coating, cigarette filters, biodegradable packaging materials and pharmaceutical [13]. Moreover, substantial investigations are being carried out on the use of nanoparticles as the sustained and controllable drug release carriers because nanoparticles have been always considered as a significant way to enhance the stability of drugs, therefore resulting in the boosted therapeutic efficacy and lowering of the drug toxicity and degradation [18]. Generally, the drug-loaded nanoparticles have combined several key-properties: non-toxicity, biocompatibility, biodegradability, high target site selectivity and specific interactions with biological systems. They also raise the residence time and drug concentration at the target site [19,20].

The aim of the present work reported herein was to synthesize and optimize the acetylated corn starch (ACS) nanoparticles. The effect of acetylation and nanoprecipitation on the morphology and granule structure of starch samples were examined by the FT-IR, XRD and SEM. The antibiotic drug chosen for the present investigation is ciprofloxacin (CFx), which could be encapsulated into the ACS nanoparticles. CFx belongs to the class of systemic second generation antibacterial fluoroquinolones widely used to treat a variety of infectious processes such as gonococcal infections, osteomyelitis, enteric, respiratory, and urinary tract infections [21]. In this study, the parameters such as the size of nanoparticles and DS affecting the efficiency of starch-based CFx-loaded nanoparticles were investigated systematically.

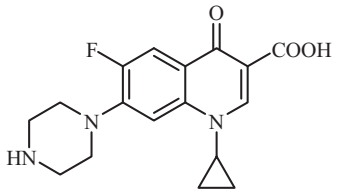


Fig 1. Chemical structure of CFx (free base).

2. Materials and methods

2.1. Materials

An edible corn starch (CS) product from Glugosan Co. (Iran) was used for all the experiments. The starch contained 11% moisture by weight. A portion of the starch was kept under vacuum at 50 °C overnight to obtain dry starch with 1 wt% moisture content. CFx was supplied by Temad Co. (Iran) as the monohydrate hydrochloride salt ($C_{17}H_{18}FN_3O_3{\cdot}HCl{\cdot}H_2O$). Fig. 1 shows the chemical structure of CFx free base. All other chemicals used in this study were analytical grade and purchased from Merck Co. (Germany). All solutions were prepared using deionized water.

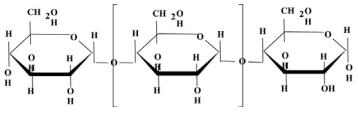
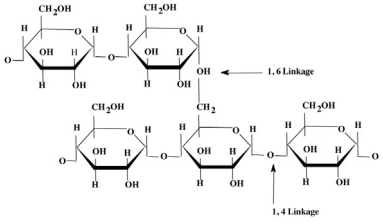
2.2. Preparation of acetylated corn starch (ACS)

According to the literature, a series of ACS samples with high and low DS were prepared using two modified methods as following:

2.2.1. ACS with high DS

The CS was dried at 50 °C for 24 h before reaction to avoid the interference of moisture. Based on Table 2, a certain amount of dried CS and glacial acetic acid were placed into a 250 mL two-neck flask equipped with a condenser on a magnetic stirrer. After 10 min, a uniform suspension was obtained and then cooled AA was added to the mixture. After stirring for 15 min, sulfuric acid was added dropwise to the flask contents. The reaction mixture was stirred for 1 h at 90 °C. By changing the chemicals ratio, it was possible to prepare esters with three different DSs. The reaction was terminated by adding an alkaline solution of sodium hydroxide or calcium oxide to neutralize the acid. At the end of the reaction, the precipitate was filtered and washed with excess distilled water three times, and then oven-dried at 80 °C overnight. Finally, the resultant solid was milled, sieved and stored in an airtight container for future

Table 1
Comparison of the amylose and amylopectin components of starch [6].

Specifications	Amylose	Amylopectin
Molecular structure		
Geometric shape in solution	Flexible helical coils, 6 glucose residues per turn	Low ionic strength—ellipsoid, (pancake shape) High ionic strength—spheroid
Glucosidic linkages	α-(1 → 4)	α-(1 → 4) branching through α-(1 → 6) every 18–27 glucose units
Ratio	20–25% potato/corn/wheat 17% tapioca	75–80% potato/corn/wheat 83% tapioca
Color with iodine	Dark blue	Reddish
Molecular weight	≈10^5	≈10^8