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Microwave-assisted graft copolymerization of amino acid based monomers onto starch and their use as drug carriers

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ABSTRACT

This paper describes the synthesis of two amino acid-based monomer and their graft copolymerization onto starch and utilization of the prepared graft copolymers as drug carriers. The two monomers were synthesized and reacted with acryloyl chloride to get the corresponding acryloylamino acid, which were further grafted onto starch using the microwave-assisted grafting technique. All factors affecting the efficiency of the grafting reaction were studied and the prepared graft copolymers were fully characterized. Atenolol, as a model drug in the form of salt was immobilized onto the graft copolymers by ionic bonds and the loading was confirmed by use of FT-IR, TGA and NMR. The drug release was studied in both acidic and alkaline media and it was found that the release takes place in alkaline medium rather than in acidic medium and this indicates that these polymers can be used as carriers for drugs whose target is the colon.

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1. Introduction

The use of microwave irradiation instead of conventional heating offers the advantages of pollution reduction, low cost and high productivity, this is in addition to simple handling and processing (Lidstrom, Tierney, Wathey, & Westman, 2001; Osman, El-Newehy, Al-Deyab, & El-Faham, 2012). Recently, the utilization of microwave irradiation in organic synthesis and polymerization reaction has become a popular technique (Al-Hazimi, El-Faham, Gazzali, & Al-Farhan, 2012; Ghazzal, El-Faham, Abd-Megeed, & Al-Farhan, 2012; Osman et al., 2012). Many researchers reported the use of microwave-assisted synthesis in the preparation of different types of flocculants based on natural polymers, like polyacrylamide grafted inulin (Rahul, Jha, Sen, & Mishra, 2014), polymethylmethacrylate grafted psyllium (Mishra, Sinha, Dey, & Sen, 2014), polyacrylamide grafted agar (Rani, Mishra, Sen, & Jha, 2012) and polyacrylamide grafted Casein (Sinha, Mishra, & Sen, 2013).

The utilization of drug delivery systems based on polymeric materials improves the drug's efficiency, reduces the drug's toxicity, reduces the drug's side effects and improves the recovery percentages. In general, the controlled-release drug delivery systems were found to increase the therapeutic activity of the drug, and on the other hand decrease its side effects and reduces the number of drug required to be admitted to the body during treatment period as well. Also, the use of controlled-release drug delivery system enables the drug to be targeted only to desired organs or tissues (Friend, 2005; George & Abraham, 2006; Kenawy, El-Newehy, Abdel-Hay, & Raphael, 2001; Kenawy, El-Newehy, Abdel-Hay, & Ottenbrite, 2008; Van den Mooter, Weuts, De Ridder, & Blaton, 2006; Yan, Zhuo, & Zheng, 2001).

Moreover, amino acids, as constituents of the peptides, when incorporated into synthetic or natural polymers, by means of for example grafting, they can give totally new biomaterials having a wide variety of properties, which can be modulated by changing the components of the macromolecular backbone during synthesis. Over the past decades, natural polymers such as cellulose, starch and chitosan can be used in designing biomaterials, which can find a wide range of application areas such as in controlled-release drug delivery systems and biocompatible scaffolds in the field of tissue engineering. Moreover, modification of polysaccharide using grafting as a powerful method improves its properties as well as enlargement its use.

In the past decades, polymer–drug conjugates were used to develop highly advanced controlled-release drug delivery systems, which could to great extent improve the drug's therapeutic efficiency (Babazadeh, 2007, 2008; El-Newehy, Elsherbiny, & Mori, 2013; Hoste, Winne, & Schacht, 2004; Kenawy, El-Newehy, et al., 2008; Kenawy, Abdel-Hay, El-Newehy, & Ottenbrite, 2008; Khandare & Minko, 2006; Nichifor, Schacht, & Seymour, 1997). Optimization of the therapeutic properties of drugs, safety and

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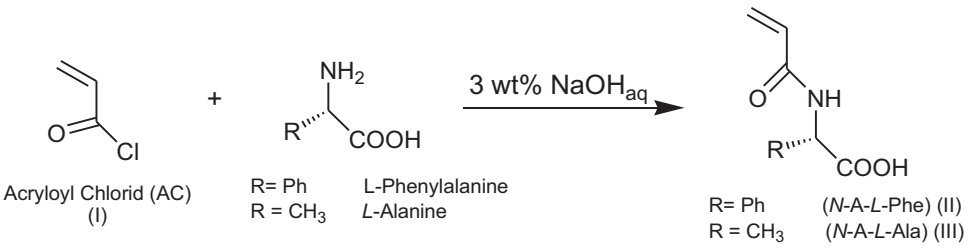

Scheme 1. Monomer synthesis; *N*-acryloyl-*L*-phenylalanine (*N*-A-*L*-Phe) (II) and *N*-acryloyl-*L*-alanine (*N*-A-*L*-Ala) (III).

affectivity can be controlled by the design of polymeric drug delivery systems [10,11]. The drug can be fixed directly onto the polymer backbone or via a spacer in which the carrier is a polymeric material and could be either inert synthetic polymer or natural biodegradable one (Babazadeh, 2008; El-Newehy et al., 2013).

Amino acids, the constitutional components of both peptides and accordingly the higher proteins are capable of constructing highly ordered hierarchical structures, which may scale from few nanometers to several micrometers. Synthetic polymers containing amino acids can be used in different applications such as stationary phases with chiral recognition properties (Babazadeh, Edjlali, & Rashidian, 2007), absorbents for different metal ions (Oishi, Lee, Nakagawa, Onimura, & Tsutsumi, 2002), controlled-release drug delivery systems and biocompatible materials (Barbucci, Casolaro, & Magnani, 1991; Lekchiri, Morcellet, & Morcellet, 1987).

Starch as a natural polymer that can be obtained from agro-sources, is abundant in nature, renewable, and biodegradable polymer (Bentolila et al., 2000; Casolaro & Barbucci, 1991).

In addition, starch is a promising material in drug delivery specifically to the colon, non-food applications as well as the production of biodegradable plastics drug delivery (Çalgeris, Çakmakçı, Ogan, Kahraman, & Kayaman-Apohan, 2012; Casolaro & Barbucci, 1991; Curvelo, de Carvalho, & Agnelli, 2001)

The work in the present study aims at optimizing the grafting conditions for amino acid-based polymers onto starch to prepare amino acid-based polymers-grafted-starch as a carrier for drugs. Grafting process was carried out by use of low concentration of potassium persulfate as an initiator, using microwave (MW) irradiation technique. The effect of grafting time, temperature and the monomer/starch ratio were studied. The structure of the prepared amino acid-based monomers-grafted-starch was confirmed by Fourier transform infrared (FTIR) spectra, elemental microanalysis (as nitrogen percent (N%)) as well as NMR spectra. In addition, the native and grafted starch samples were characterized by TGA. The grafting process was found to be temperature and duration dependent, in addition to its great dependence on the monomer/starch ratio. Atenolol was used as a model drug in this study and its loading and controlled release from the amino acid-grafted-starch were extensively studied.

2. Experimental

2.1. Materials

Starch (Corn starch) (73% amylopectin and 27% amylose), acryloyl chloride and atenolol were purchased from Aldrich. *L*-alanine (98%) and *L*-phenylalanine (98%) were purchased from ACROS. All other chemicals, materials and solvents were of laboratory grade and were used as received without any further purifications.

2.2. Instruments and characterization techniques

Microwave (Monowave 300, Anton paar) maximum filling volumes of 6 mL and 20 mL, for 10 mL vial and 30 mL vial, respectively. Maximum operation pressure 30 bar, Maximum IR temperature 300 °C, Max fiber-optic temperature 300 °C, Maximum power 850 W, Vial material is borosilicate glass and silicon carbide, Cap material is PEEK and Seal material is Teflon-coated silicone.

^{1}H NMR spectra were recorded by use of JEOL JNM-PM X90 Si-NMR Spectroscopy instrument. Thermogravimetric analysis (TGA) was carried out by use of TA-Q500 System. 5–10 mg sample was heated in the temperature range of 30–800 °C at a heating rate of 10 °C min^{-1} under inert nitrogen atmosphere.

Fourier-transformer infrared (FT-IR) spectra were recorded using TENSOR 27, Bruker. UV spectra was recorded by use of PerkinElmer Lambda 35 UV–vis spectrophotometer.

2.3. Monomers synthesis

N-acryloyl-*L*-phenylalanine (*N*-A-*L*-Phe) (II) and *N*-acryloyl-*L*-alanine (*N*-A-*L*-Ala) (III) were synthesized according to a reported method [11], in which *L*-phenylalanine (150 mmol) was dissolved in 100 mL of 3 wt% aqueous NaOH and then was kept at 0 °C in an ice-bath. Acryloyl chloride (160 mmol) was added dropewise and at the end of the addition, the reaction mixture was kept under continuous stirring for 2 h. The mixture was then acidified to pH 1–3 using 6 N HCl, and stirring was continued for an additional 1 h at 25 °C. The resulting mixture was extracted with ethyl acetate (100 mL) for three times and dried over anhydrous manganese sulphate. The solution was filtered and concentrated on rotavapor to one fourth. The residual solution was purified by the column chromatography technique, by use of ethyl acetate as an eluent (Scheme 1).

2.4. Microwave assisted grafting of monomers onto starch

2.4.1. Microwave assisted synthesis of starch/Poly(N-acryloyl-L-phenylalanine) graft copolymer (S/PAPhe) (VI)

Calculated amount of (*N*-A-*L*-Phe) (II), dissolved in water, was added to starch in water slurry. These components were mixed well and then transferred, quantatively to the microwave reaction vessel (30 mL), together with catalytic amount of potassium persulfate (KPS) initiator (0.090 g) and the reaction vessel was claimed on the turntable of the microwave oven. The microwave irradiation time is adjusted to the desired duration. After the irradiation time is vanished, the reaction vessel was removed from the microwave oven and its contents were allowed to cool to the room temperature and the kept as such at room temperature for extra 24 h in order for the grafting reaction to be completed. The graft copolymer in the form of gel-like mass was poured from the microwave reaction vessel into a beacker containing excess amount of acetone in order to precipitate the graft copolymer and separate it

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