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Research paper

Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: Physicochemical and technological characterisation

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A B S T R A C T

Nowadays, graft copolymers are being used as an interesting option when developing a direct compression excipient for controlled release matrix tablets. New graft copolymers of ethyl methacrylate (EMA) on waxy maize starch (MS) and hydroxypropylstarch (MHS) were synthesised by free radical polymerization and alternatively dried in a vacuum oven (OD) or freeze-dried (FD). This paper evaluates the performance of these new macromolecules and discusses the effect of the carbohydrate nature and drying process on their physicochemical and technological properties. Grafting of EMA on the carbohydrate backbone was confirmed by IR and NMR spectroscopy, and the grafting yields revealed that graft copolymers present mainly a hydrophobic character. The graft copolymerization also leads to more amorphous materials with larger particle size and lower apparent density and water content than carbohydrates (MS, MHS). All the products show a lack of flow, except MHSEMA derivatives. MSEMA copolymers underwent much plastic flow and less elastic recovery than MHSEMA copolymers. Concerning the effect of drying method, FD derivatives were characterised by higher plastic deformation and less elasticity than OD derivatives. Tablets obtained from graft copolymers showed higher crushing strength and disintegration time than tablets obtained from raw starches. This behaviour suggests that these copolymers could be used as excipients in matrix tablets obtained by direct compression and with a potential use in controlled release.

1. Introduction

New classes of excipients are currently available, derived from old and new materials, alone or in combination, adapted to the manufacture of high-performance pharmaceutical dosage forms [1]. In this sense, polymers are playing an important role in the development of new materials with different properties and several uses, and are being synthesised by different methods [2–4]. Like other excipients, polymers cannot be considered as mere inert supports for the active principles, but as essential functional components of modern pharmaceutical formulations [1].

Among the current approaches in the development of new polymeric systems, the synthesis of graft copolymers is an easy method for modifying the properties of native polymers such as starch. The low cost, non-toxicity, biodegradability and biocompatibility of this carbohydrate [5] make starch-based graft copolymers a focus of increasing attention [6]. Moreover, the use of tetravalent cerium species to initiate such synthesis attracts great interest because of ease of polymerization [7–9]. In this sense, copolymers obtained from potato starch derivatives and methacrylates have shown a potential value as direct compression excipients for controlled release matrices [10–12]. However, both the chemical composition of the starch and the modification techniques have a considerable influence on the physical properties of the modified starches [13,14].

Starch is a natural biopolymer composed principally of two polysaccharides: the linear amylose and the heavily branched amylopectin. Whereas amylopectin has stabilizing effects, amylose forms gels and has a strong tendency to form complexes with lipids and other components [13]. Waxy maize starch, with amylose content less than 1% [15], could be a candidate for tablet adjuvants, with one of its main advantages being increased storage stability [13]. Moreover, waxy maize starch has been shown to be more effective with regard to swelling and drug release retardation than are normal starches [16,17]. Nevertheless, like other starches, it is generally chemically modified to fulfil the demands of pharmaceutical industry. One common modification is the hydroxypropylation of starch that increases the hydrophilic character of the starch granules leading to higher swelling power [17].

Chemical modification of starch via vinyl graft copolymerization is an important technique to combine the good performances of starch and synthetic polymers. Grafting is preferred to physical blending as the grafted polymer chains are linked covalently with the backbone polymer, having beneficial effects on the properties of the composite [8]. Among vinyl monomers, ethyl methacrylate

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was chosen for the present study because of its known biocompatibility and non-toxic behaviour, together with its hydrophobic character and ease of polymerization [18,19].

Then, the purpose of the present work was to synthesise new graft copolymers of ethyl methacrylate (EMA) on waxy maize starch (MS) and hydroxypropylstarch (MHS) and to reach a better understanding of this group of copolymers, in order to evaluate its utility in direct compression in comparison with the raw starches. This paper discusses the effect of the carbohydrate nature and drying process on the physicochemical and mechanical properties of the powdered materials as well as the porous structure of the tablets obtained from these new macromolecules.

NMR, IR and X-ray diffraction techniques were used to obtain information on copolymers structure. Particle size, shape and surface morphology were also taken into consideration when evaluating the flow properties and consolidation characteristics of the new materials, due to the implications of these parameters in the manufacturing of solid dosage forms. Finally, compressed porous tablet structures were evaluated using mercury porosimetry.

2. Materials and methods

2.1. Materials

Waxy maize starch (Amioca powder TF, batch MCH 308) and waxy maize hydroxypropylstarch (N-Lite L, batch KCK 3649) were kindly supplied by National Starch & Chemical (Manchester, UK).

Ethyl methacrylate (Merck, Hohenbrunn, Germany) was used as monomer.

All the reagents used for the synthetic process were of analytical grade.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20 °C).

2.2. Methods

2.2.1. Synthesis of graft copolymers and grafting yields

Copolymers were synthesised by free radical copolymerization of EMA and different starches (waxy maize starch (MS) and waxy maize hydroxypropylstarch (MHS)) following the procedure described by Echeverria et al. [12]. The carbohydrate (40 g) was dispersed in 550 mL of bidistilled water at 30 °C under a nitrogen atmosphere. Next, 118 mL of EMA was added, followed by the addition of 50 mL of the initiator solution (0.1 M ceric ammonium nitrate in 1 N nitric acid) 15 min later. Grafting was allowed to proceed for 4 h under a constant light source. The products obtained were filtered, and the solid was exhaustively washed with diluted nitric acid and bidistilled water until neutral pH was reached. A noteworthy aspect to mention is that the use of water as a reaction solvent guarantees not only the solubility of all the reactants and reagents, but also the absence of toxic substances in the final product [12].

The products obtained (waxy maize starch-ethyl methacrylate, MSEMA and waxy maize hydroxypropylstarch-ethyl methacrylate, MHSEMA) were alternatively dried by two different methods: drying in a vacuum oven (0.5 Pa) at 50 °C until constant weight (OD copolymers) or freeze-drying (freezing process at −80 °C for 48 h and sublimation process at 0.1 Pa) (FD copolymers). The starch-based copolymers (MSEMA) were crushed at 10,000 rpm in a knives mill (Retsch ZM 200, Haan, Germany) to obtain powdery samples.

The reproducibility of the synthetic and drying processes was demonstrated for three batches of each copolymer (data not shown).

In order to evaluate the composition of the solids obtained, the PEMA (poly-ethyl methacrylate) homopolymer was removed from the total reaction product, with tetrahydrofuran (THF), by soxhlet extraction for 72 h. Afterwards the grafted PEMA was isolated from the carbohydrate chains by acid hydrolysis with perchloric acid (60%) in a glacial acetic acid medium [20]. The following parameters were calculated:

- Percent grafting efficiency (%GE) Eq. (1) to quantify the amount of homopolymer formed during the grafting reaction [21]

$$\%GE = \frac{\text{Graft copolymer weight}}{\text{Total product weight}} \times 100 \tag{1}$$

- Percentage grafting (%G) Eq. (2) to assess the methacrylic-carbohydrate ratio in the copolymer [21]

$$\%G = \frac{\text{Grafted methacrylic polymer weight}}{\text{Grafted carbohydrate weight}} \times 100 \tag{2}$$

The results are shown as the mean value of two replicates.

2.2.2. Spectroscopy characterisation

2.2.2.1. IR spectroscopy. Fourier-transform infrared (FT-IR) spectra were recorded with a FT-IR spectrometer Nicolet 510 (California, USA). One hundred scans were collected for each sample at a resolution of 4 cm^{-1} over the wavenumber region 4000–400 cm^{-1}. Samples were prepared in KBr discs.

2.2.2.2. NMR spectroscopy. Materials were dissolved in a mixture of d_6-DMSO and d_5-pyridine solvents (1/1) to give a concentration of 3% w/v. ^{13}C NMR spectra measurements were recorded at 30 °C on a FT-NMR Bruker Avance 500 (Wissembourg, France) for each product. Chemical shifts are quoted in ppm relative to tetramethylsilane as internal reference.

2.2.2.3. X-ray powder diffraction measurements. X-ray diffraction patterns were recorded using a Siemens Kristalloflex D-5000 (Haan, Germany) diffractometer. The sample was exposed to Ni-filtered CuKα radiation with the X-ray generator running at 36 kV and 26 mA. The scan rate employed was 1° (2θ)/min.

2.2.3. Powder and particle characterisation

2.2.3.1. Particle size analysis. Particle size analysis was carried out on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) using 500, 355, 250, 180, 125, 90, 63, 45, 38 μm calibrated sieves (Cisa, Barcelona, Spain). From plots of powder weight (%) versus size (mm), typical parameters from a particle size distribution were determined: mean particle diameter, standard deviation (SD) and kurtosis and skewness coefficients [22].

2.2.3.2. Scanning electron microscopy (SEM). The particulate samples were sputter coated with a thin layer of gold (Edwards Pirani 501 Scan-Coat Six, Crawley, West Sussex, UK) under high vacuum and were examined using a scanning electron microscope (Philips XL-30, Eindhoven, Holland). Microphotographs were obtained at 4000× magnification.

2.2.3.3. Apparent particle density. The apparent particle densities of the powders were determined [23], in triplicate, by means of an air comparison Ultrapycnometer 1000 (Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas. Due to the high diffusivity of helium, this method was considered to give the closest approximation to the true density [24].