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Synthesis and characterization of new copolymers of ethyl methacrylate grafted on tapioca starch as novel excipients for direct compression matrix tablets

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ABSTRACT

In last years, the introduction of new materials for drug delivery matrix tablets has become more important. This paper evaluates the physicochemical and mechanical properties of new graft copolymers of ethyl methacrylate (EMA) on tapioca starch (TS) and hydroxypropylstarch (THS), synthesized by free radical polymerization and dried in a vacuum oven (OD) or freeze–dried (FD). Infrared and ^{13}C NMR spectroscopies confirm the change of chemical structure of the copolymers and X-ray diffraction shows up the higher amorphization of copolymers respect to the carbohydrates. Particle size analysis and SEM indicate that graft copolymerization leads to an increase of particle size and a more irregular shape. Graft copolymerization implies decrease of density and moisture content values. Heckel equation shows that copolymers have less densification by particle rearrangement and fragmentation than carbohydrates. Concerning the drying methods, FD products have larger plasticity and lower elasticity than OD copolymers. Graft copolymerization produces a decrease of the applied pressure necessary to obtain tablets, ejection force and friction work. Furthermore, graft copolymers show longer disintegration time than tablets from raw starches. These qualities suggest 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

Monolithic devices or matrices represent a substantial part of the drug delivery systems. In pharmaceutical industry, the matrices for oral administration are commonly manufactured as tablets by direct compression [1]. However, it is well known that direct compression is possible only for a limited number of substances. Many of the materials widely used for tablet formulation are difficult to compress because of their elastic compression behaviour and poor flow properties [2].

In the last years, the introduction of new materials for drug delivery devices has become more important. Among these, synthetic and some natural polymers have been used and their production has grown in great extent. Starch is an abundant, inexpensive, natural biopolymer that can be metabolised by the human body. Moreover, it is relatively inert and does not react with many active drug substances. These favourable properties promote its applications for the production of pharmaceuticals [3–6]. However, starches possess poor flow properties and undergo elastic deformation during the tableting process [7]. In contrast, starch can be easily modified with a variety of useful monomeric and polymeric products by physical and chemical means. Graft copolymerization of synthetic polymers onto a polysaccharide backbone offers one of the best ways to get new copolysaccharides with enhanced properties for important applications [8,9]. Thus, polyacrylics occupy a significant position as grafted polymers [10].

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Recently, a new generation of graft copolymers combining semi-synthetic (cellulose and potato starch derivatives) and synthetic (methyl methacrylate) polymers has been introduced [11–14]. However, it was probed that depending on the type of carbohydrate and monomer used, the properties of the copolymer will be different [9], and consequently, may not have identical properties as excipients in tablet preparations. There is still a wide range of acrylic monomers and natural polymers that can be tested. While in Europe potato starch is widely used, in most tropical countries there are many other sources for starch, which can be used in tableting. Commonly grown starch-containing plants are maize, rice, and tapioca or cassava [15].

Native tapioca starch possesses many desiderable filler properties but it has poor flowability and compressibility [16]. The latter two parameters have a particular importance for direct compression tablets [15,17]. Furthermore, the filler should yield tablets of adequate crushing strength without having to apply an excessive compression force [18,19]. Atichokudomchai et al. [17] have modified native tapioca starch showing that these new products were useful as filler in direct compression tablet preparation. Due to the good results obtained with the described materials, we estimate of interest to synthesize and characterize new graft copolymers derived from tapioca starch and hydroxypropyl tapioca starch in order to evaluate its usefulness in direct compression matrix tablets. The chosen monomer for grafting is ethyl methacrylate (EMA), a synthetic monomer that gives rise to biocompatible and non toxic acrylic polymers and possesses hydrophobic character and can be easily polymerized [20,21]. A comparison among these new graft copolymers and the native starches, used as received, will be made. This paper also evaluates the effect of the carbohydrate nature and drying process (vacuum oven and freeze–dried) on the physico-chemical and mechanical properties of the powdered materials as well as the porous structure of the tablets obtained from the new copolymers.

2. Experimental

2.1. Materials

Tapioca starch (TS) (Tapioca Starch, batch MCB 3053) (±17% of amylose) and hydroxypropyl tapioca starch (THS) (Tapioca Textra, Batch KCB 8010) were kindly supplied by National Starch & Chemical (Manchester, UK) as natural and semi-synthetic polymers. Ethyl methacrylate (EMA) (Merck, Hohenbrunn, Germany) was chosen as acrylic monomer for graft copolymerization.

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 synthesized by free radical copolymerization of EMA and different starches (tapioca starch – TS and hydroxypropyl tapioca starch – THS) following the procedure described by Echeverría et al. [12]. The carbohydrate (40 g), either tapioca starch or hydroxypropyl tapioca starch, was dispersed in 550 ml of bidistilled water. The medium was purged with purified nitrogen and the bath temperature was maintained at 30 °C. Next, 118 mL of EMA was added, followed by the initiator solution (50 ml of 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 (two lamps of 100 W in the vis wavelength range). Thus, the synthesized TSEMA and THSEMA were filtered off and 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 reaction solvent guarantees, not only an effective dispersion of all the reactants and reagents, but also the absence of toxic substances in the final product [12].

The solids obtained were dried using two different methods: drying in a vacuum oven (Vacucell 22, Gräfelting, Germany) at 50 °C (0.5 Pa) until constant weight (OD copolymers) or freeze–drying (at −80 °C for 48 h and 0.1 Pa) in a Cryodos-80 apparatus (Terrasa, Spain) until powdered product was got (FD copolymers). Finally, the starch-based copolymers (TSEMA) 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 were demonstrated by comparison of three batches of each product (data not shown). Once the reproducibility of the synthesis was established, the preparation in high extension of the copolymers was carried out.

In order to study the efficiency of the graft copolymerization reaction, the poly-ethylmethacrylate (PEMA) homopolymer was removed from the total reaction product, with tetrahydrofuran (THF), by soxhlet extraction for 72 h. So, the pure graft copolymer was obtained. Afterwards, the grafted PEMA was isolated from carbohydrate chains by acid hydrolysis with perchloric acid (60%) in a glacial acetic acid medium [22]. The results are shown as the mean values of two replicates. The quantification of the PEMA homopolymer and the grafted PEMA was recorded by the following parameters [22]:

- Percent grafting efficiency (% GE) (Eq. (1)) was used to quantify the amount of homopolymer formed during the grafting reaction:

$$\%\mathrm{GE} = \frac{\text{Graft copolymer weight}}{\text{Total product weight}} \times 100 \qquad (1)$$

- Percentage grafting (% G) (Eq. (2)) was used to assess the metacrylic–carbohydrate ratio in the copolymer:

$$\%\mathrm{G} = \frac{\text{Grafted metacrylic polymer weight}}{\text{Grafted carbohydrate weight}} \times 100 \qquad (2)$$

2.2.2. Spectroscopy characterization

2.2.2.1. IR spectroscopy. IR-spectra were recorded on a FT-IR spectrometer Nicolet 510 (CA, USA), using potassium bromide tablets. One hundred scans were collected for each sample at a resolution of 4 cm^{-1} over the wavenumber region 4000–400 cm^{-1}.