Carbohydrate Polymers 80 (2010) 71–77

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Graft tapioca starch copolymers as novel excipients for controlled-release matrix tablets

Marta Casas, Carmen Ferrero, Mª Rosa Jiménez-Castellanos *

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González, 41012 Sevilla, Spain

ARTICLE INFO

Article history:
Received 1 October 2009
Received in revised form 27 October 2009
Accepted 28 October 2009
Available online 30 October 2009

Keywords:
Tapioca starch
Graft copolymers
Breaking force
Drying methods
Matrix tablets
Release kinetic
Fronts movement

ABSTRACT

This paper studies new graft tapioca copolymers as an alternative for the formulation of controlled-release matrix tablets, using anhydrous theophylline as model drug. Copolymers were synthesised by free radical copolymerisation of ethyl methacrylate with tapioca starch (TS) or hydroxypropyl starch (THS), being alternatively dried by two methods: oven or freeze-drying. The influence of carbohydrate nature, drying process and breaking force on drug release was evaluated. Radial drug release and fronts movement were also studied using special devices consisting of two Plexiglass® discs. The paper demonstrates the use of these new copolymers as excipients for controlled drug release. All tablets behave as inert matrices controlling drug release mainly by diffusion. However, TSEMA matrices demonstrated to have better binding properties with lower release than THSEMA tablets. Drying process and breaking force had a significant influence on dissolution behaviour only in THSEMA matrices. Porosity and tortuosity values explained the higher drug release observed for THSEMA matrices with low crushing force and for freeze-dried copolymer tablets.

1. Introduction

Among the different approaches for oral prolonged-release dosage forms, matrix tablets have been the most widely used because of the simple and low-cost manufacturing process (Ferrero & Jiménez-Castellanos, 2002). A variety of polymers is employed as matrix-forming excipients whose characteristics may play a key role and significantly influence the behaviour of these devices.

Starches are natural biopolymers widely used as fillers, binders and disintegrants in the pharmaceutical fields as they are cost-effective, non-toxic and can be metabolised by the human body (Demirgöz et al., 2000; Dumoulin, Cartilier, & Mateescu, 1999; Pifferi, Santoro, & Pedrani, 1999). However, native starches are not suitable for controlled drug delivery systems due to poor flow and compressibility and, most notably, fast release properties in physiological fluids (Dumoulin et al., 1999; Kost & Shefer, 1990). In spite of this, it has been demonstrated that compression force can be used to obtain slower release of drug in starch matrices (Weyenberg, Vermeire, Remon, & Ludwig, 2003). Depends on the variety of starch its chemical composition changes and this also change its physical properties, which means that the different starches may not be interchangeable as regards a specific pharmaceutical use (Pifferi et al., 1999). Tapioca starch is differentiated from other starches by its low level of residual materials, lower amylose content (17%) and high molecular weights of amylose and amylopectin. These properties make tapioca a good native starch for direct use in industrial applications and a starting material for physical and chemical modifications (BeMiller & Whistler, 2009).

Recently, it has been introduced a new generation of graft copolymers combining natural or semi-synthetic (tapioca starch derivatives) and synthetic (ethyl methacrylate – EMA) polymers. The products tapioca starch–ethylmethacrylate (TSEMA) and hydroxypropyl tapioca starch–ethylmethacrylate (THSEMA) were synthesised and dried by two different methods: drying in a vacuum oven (OD copolymers) or freeze-drying (FD copolymers) (Casas, Ferrero, & Jiménez-Castellanos, 2009).

These polymers were thoroughly characterised physicochemical and technologically by NMR, IR spectrophotometry, X-ray diffraction and compression properties studies. One of the technological improvements of the new copolymers was the possibility to obtain an adequate crushing strength of TSEMA and THSEMA tablets using lower compression force and lower ejection force than for raw commercial starches (Casas et al., 2009). It was also remarkable the longer disintegration time values observed, similar to Preflo®, a commercial direct compression diluent for sustained released tablets (Sanghvi, Collins, & Shukla, 1993). Concerning the drying methods, FD products showed different compaction properties, with higher plasticity and lower elasticity than OD copolymers, but similar disintegration times.

* Corresponding author. Tel.: +34 954556836; fax: +34 954556085.
E-mail address: mrosa@us.es (M.R. Jiménez-Castellanos).

0144-8617/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2009.10.065

Due to the good results obtained with the tapioca starch graft copolymers described, the aim of this work was to study the drug release of systems prepared with EMA copolymers as matrix-forming materials and anhydrous theophylline as model drug. Raw materials (tapioca or hydroxypropyl tapioca starch) were used as reference. Also, this paper evaluated the influence of carbohydrate nature, drying process (freeze-dried and oven-dried) and compression force (70–80 N and 140–150 N) on the mechanistic aspects of drug release from these matrices. Drug release phenomena were studied using Higuchi (1963), Korsmeyer, Gurny, Doelker, Buri, and Peppas (1983) and Peppas and Sahlin (1989) kinetic equations because of its major appliance. Fronts movement were evaluated according to Ferrero, Muñoz-Ruiz, and Jiménez-Castellanos, (2000) in order to understand in greater detail the internal processes controlling drug release. Finally, in order to relate drug release and fronts movement data, radial drug release (Bettini, Colombo, Massimo, Catellani, & Vitali, 1994) was also evaluated.

2. Materials and methods

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 copolymerisation.

Anhydrous theophylline (Theophylline BP 80, Roig Farma, Barcelona, Spain, batch 0212030) was chosen as model drug.

Stearic acid (Estearina, Roig Farma, Barcelona, Spain, batch 90003410) was selected as lubricant.

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

Copolymers were synthesised by free radical copolymerisation of EMA and different starches (tapioca starch – TS and hydroxypropyl tapioca starch – THS) following the procedure described by Echeverría, Silva, Goñi, and Gurruchaga (2005). The carbohydrate (40 g), either tapioca starch or hydroxypropyl tapioca starch, was dispersed in 550 ml of bidistilled water into a four-necked round bottom flask (1 L). 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 synthesised 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 (Echeverría et al., 2005).

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.

2.2.2. Mixtures preparation

Anhydrous theophylline (24%, w/w) and polymer (TS, THS or graft copolymers) (75%, w/w) were mixed for 15 min using a double cone mixer (Retsch, Haan, Germany) at 50 rpm. After addition of stearic acid (1%, w/w), the mixing procedure was continued for a further 5 min.

2.2.3. Powder and particle characterisation of mixtures

2.2.3.1. Apparent particle density. The apparent particle density of the products were determined, in triplicated, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2007). Due to the high diffusivity of helium, this method was considered to give the closest approximation to the true density (Viana, Jouannin, Pontier, & Chulia, 2002).

2.2.3.2. Flow properties. An automated flowmeter system developed by Muñoz-Ruiz and Jiménez-Castellanos (1993) was used to estimate the flow rate of the different samples. A glass funnel with an internal diameter of 10 mm and an angle of 30° with respect to the vertical was selected as vessel (European Pharmacopoeia, 2007). Weight data were acquired by means of a balance (Mettler AE50, Zürich, Switzerland) connected to a personal computer, using adequate software. The results are shown as the mean value (g/s) of three replicates.

2.2.4. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz, Gallego, del Pozo, Jiménez-Castellanos, & Domínguez-Abascal, 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compression characteristics of mixtures, a quantity of powder (500 mg) was preweighed and manually fed into the die (12 mm) and flat-faced compacts were prepared at two different breaking forces: 70–80 N and 140–150 N. In the case of the mixtures based on raw materials, TS or THS, the tablets were manufactured only at 70–80 N, due to the impossibility to make them at higher pressures. Typical compaction parameters (maximum upper pressure – P, expansion work – W_e, apparent net work – W_{an}, plasticity – Pl) described by Doelker (1978) and Järvinen and Juslin (1981) were collected from four tableting cycles.

In order to produce a sufficient number of tablets for physical testing, the machine was equipped with a forced feeding system and the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70–80 N or 140–150 N breaking force).

Apparent particle density and compression data from the different mixtures were statistically analysed by one way analysis of variance (ANOVA) using the SPSS® program version 14.0. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted as significant when $p < 0.05$.

2.2.5. Standard physical test of tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius CP224S, Göttingen, Germany) tablets according to European Pharmacopoeia (2007).

The thickness of 10 tablets was measured individually using an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The breaking force (European Pharmacopoeia, 2007) of 10 tablets was determined by diametrical loading with a Schleuninger-2E tester (Greifensee, Switzerland).