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Pectin/anhydrous dibasic calcium phosphate matrix tablets for *in vitro* controlled release of water-soluble drug

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ABSTRACT

Different pectin/anhydrous dibasic calcium phosphate (ADCP) matrix tablets have been developed in order to obtain controlled release of a water-soluble drug (theophylline). Swelling, buoyancy and dissolution studies have been carried out in different aqueous media (demineralized water, progressive pH medium, simulated gastric fluid, simulated intestinal fluid and simulated colonic fluid), to characterize the matrix tablets. When the pectin/ADCP ratio was ≥0.26 (P1, P2, P3 and P4 tablets) a continuous swelling and low theophylline dissolution rate from the matrices were observed. So, pectin gel forming feature predominated over the ADCP properties, yielding pH-independent drug release behavior from these matrices. On the contrary, pectin/ADCP ratios ≤0.11 (P5 and P6 tablets) allowed to achieve drug dissolution pH dependent. Consequently, the suitable selection of the pectin/ADCP ratio will allow to tailor matrix tablets for controlled release of water-soluble drugs in a specific manner in the gastrointestinal tract.

1. Introduction

Hydrophilic matrix tablets are the most promising controlled release systems among researchers in oral solid formulations due to the simplicity of their formulation, ease of manufacturing, their low cost, FDA acceptance and applicability to drugs with a wide range of solubility (Dürig and Fassihi, 2002; Sako et al., 2002; Williams et al., 2002). A hydrophilic and/or swellable matrix consists of a mixture of one or more active ingredients with one or more gel-forming agents, which are usually compressed to form tablets (Rao and Devi, 1988; Hogan, 1989). The polymer of choice must exhibit good compression characteristics and suitable swelling properties in contact with the aqueous medium in order to ensure the rapid formation of an external layer (Badillo and Ghaly, 2008) which acts as a "protective" coat for the matrix, and is considered to be the element controlling the drug release kinetics (Colombo et al., 2000).

Many different polymers have been used in swellable controlled release systems, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide and Carbopol® among others, as they swell after coming in contact with water (Maderuelo et al., 2011). As synthesizing a new polymeric substance and satisfying the safety controls entails enormous costs, the focus has shifted more recently to natural polymers, and more specifically to polysaccharides such as pectin. This polymer is a relatively inexpensive and heterogeneous acidic water-soluble polysaccharide widely applied and investigated due to its biocompatibility, biodegradability and non-toxicity (Liu et al., 2003; Hiorth et al., 2003; Maestrelli et al., 2008). It is also used as a carrier and coating material in matrix tablets in the pharmaceutical sector (Rubinstein et al., 1993), either alone or co-formulated with water insoluble polymers such as Eudragit® NE30D and RL30D (Semdé et al., 2000a,b), with other natural polymers like chitosan (Macleod et al., 1999a,b; Ofori-Kwake et al., 2004), and with cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) (Kim and Fassihi, 1997a,b). Pectin has bioadhesive properties on gastrointestinal tissues (Schmidgall and Hensel, 2002; Liu et al., 2005; Thirawong et al., 2007; Sriamornsak and Wattanakorn, 2008; Thirawong et al., 2008), and these interactions and the duration of contact make it effective as a device for

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controlled release drug delivery (Wattanakorn et al., 2010). Pectin is fermented in the colon by microflora (Dongowski and Anger, 1996). All these characteristics point to pectin as being a promising biopolymer for numerous pharmaceutical and biomedical applications (Thirawong et al., 2008).

The study also investigated the influence of several factors on the properties and dissolution performance of the matrix system, including the polymer content, substitution type and viscosity of the polymer; the solubility and particle size of the drug; the presence of other polymers and excipients; and the surface area and shape of the matrix tablets. Process parameters such as the method of incorporating raw materials, blending time, compression force, and conditions for dissolution studies also play a key role (Sia Heng et al., 2001). Several authors have studied the effect of different additives on drug release. Some studies have suggested that the presence of insoluble fillers such as dicalcium phosphate led to slower controlled drug release with more linear dissolution profiles (Jamzad et al., 2005), even when diluents like Emcompress® or Avicel® PH-101 were used with low amounts of polymer (Vargas and Ghaly, 1999). Additives can therefore be applied to adjust the drug release rate due to their influence on parameters such as gel thickness (Conte et al., 1988), polymer swelling rate (Colombo et al., 1999), and drug diffusion (Gao and Fagerness, 1995).

Parameters other than the formulation should be considered in studies on drug delivery from hydrophilic matrices. It should be noted that each of these formulations is subject to continuous peristalsis and shear forces and to a range of pH environments for different periods of time during their passage through the gastrointestinal tract (Fallingborg, 1999), where chemical and mechanical changes can potentially affect these systems and modify the drug release rate (Abrahamsson et al., 1998). In view of the varying conditions prevailing along the gastrointestinal tract, dissolution test parameters must be defined to ensure a discriminatory method that enables changes to be identified in processes and/or formulations, and serves to establish a possible *in vitro/in vivo* correlation (Mudie et al., 2010).

The present study therefore proposes to combine different proportions of pectin to produce physical gels with anhydrous dibasic calcium phosphate (ADCP) – a tablet diluent with good flow properties – with the aim of obtaining different matrix tablets capable of controlling water-soluble drug release in the gastrointestinal tract. The water-soluble model drug theophylline anhydrous (THE) has been included in the designed formulations.

2. Materials and methods

2.1. Materials

Theophylline anhydrous (THE) (batch: 048K0709) was purchased from Sigma–Aldrich (Saint Louis, USA). Pectin (batch: 9373200010) with 60–70% galacturonic acid, and pepsin (batch: 8947200011) were provided by Guinama (Valencia, Spain). Anhydrous dibasic calcium phosphate (ADCP) (batch: 1006) was provided by Mendell (Bodenheim, Germany). Magnesium stearate PRS-CODEX (MgSt) (batch: 85269ALP) was purchased from Panreac (Barcelona, Spain). Kollidon® 30 (PVP K30) (batch: 98-0820) was supplied by BASF (Ludwingshafen, Germany). Pancreatin USP (batch: A0257028) was purchased from Acros Organic (NJ, USA), and Pectinex® Ultra SP-L (26,000 FDU/mL) (batch: KRN05620) was a generous gift from Novozymes (Bagsvaerd, Denmark). All other reagents were of analytical grade. The water used was demineralised in all cases.

2.2. Preparation of matrix tablets

Matrix tablets were prepared containing 50 mg of THE, pectin and ADCP in varying ratios (Table 1). In order to optimize the compacting process, an intermediate wet granulation step was introduced before compression. The granules were made by adding PVP K30 – previously dissolved in ethanol – to a physical mixture of THE, pectin and ADCP. The wet mass was then passed through a 0.5 mm mesh and dried at 40 °C for 12 h. 2% MgSt (w/w) was added to the granules before compression. 600 mg of the blend was weighed, and tablets were obtained using a Bonals® B 40 eccentric machine (Barcelona, Spain) with concave punches with a diameter of 13 mm, applying the maximum compression force accepted by the formulation. The compacting pressure was kept constant during the preparation of each batch. A control batch (C), without pectin, was prepared in the same conditions. The tablets fulfilled the tests for hardness (Pharma Test – PTB 311; Hainburg, Germany), average weight, drug content, diameter and thickness.

2.3. Swelling characterization

Swelling studies were conducted in different media to study the influence of composition and pH media on the matrix behavior. The media used were: demineralised water, progressive pH medium, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

The progressive pH medium was composed of an aqueous mixture of 37% 0.05 M hydrochloric acid, 85% 0.05 M ortho-phosphoric acid, and 0.05 M glacial acetic acid with a pH value of 1.5, which was maintained during the first 2 h of the assays. 10 M NaOH was then added to the medium until the pH increased to a value of 4.0, and then maintained for the following 2 h. Finally, another aliquot of 10 M NaOH was added to obtain a pH value of 6.8 and maintained until 24 h (Ruiz-Caro and Veiga-Ochoa, 2009). The SGF and SIF were prepared according to the 34th United States Pharmacopeia (USP, 2011).

Swelling tests were conducted with a thermostated water shaking bath (Selecta® UNITRONIC 320 OR, Barcelona, Spain) with an experimental temperature of 37 ± 0.1 °C and a shaking rate of 42 U/min. Before the matrix tablets were introduced in the test medium, each tablet was fixed to a metallic disc of 20 mm using a cyanoacrylate adhesive (Loctite®, Henkel, Austria) in order to ensure constant contact between the tablet surface and the aqueous medium, and to improve the handling of the tablets during the test.

Table 1
Composition of the different batches manufactured.

Formula	Components (mg)					Pectin/ADCP ratio
Code	Pectin	ADPC	THE	PVP	MgSt	
P1	440	48	50	50	12	9.17
P2	300	188	50	50	12	1.6
P3	200	288	50	50	12	0.69
P4	100	388	50	50	12	0.26
P5	50	438	50	50	12	0.11
P6	30	458	50	50	12	0.07
C	0	488	50	50	12	0