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Quality by Design approach to understand the physicochemical phenomena involved in controlled release of captopril SR matrix tablets

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ABSTRACT

The aim of this study is to obtain swelling controlled release matrix tablets of captopril using the Quality by Design methodology (ICH Q8) and to know the transport mechanisms involved in captopril release. To obtain the area of knowledge, the design of experiments studying the effect of two components (HPMC K15M and ethylcellulose) at different levels has been applied, with the captopril dissolution profile as the product's most important critical quality attribute (CQA). Different dissolution profiles have been obtained with the design of experiments performed, which is a key factor in the development of controlled release matrix tablets. Kinetic analysis according to the equations of Higuchi and Korsmeyer–Peppas demonstrates that the release mechanism is a mechanism of erosion when the whole percentage of the polymer is ethylcellulose, and a diffusion mechanism when the whole percentage of the polymer is HPMC K15M. The physico-chemical characteristics of the gel layer determine the release rate of captopril. The thickness of the gel layer, the porosity which is formed in the matrix upon contact with water, pore size, the swelling rate, the erosion rate of the matrix, and the physico-chemical characteristics of captopril, are factors related to the kinetic equations described and that allow us to predict the release mechanism of captopril. A new relationship of the kinetic equations governing the *in vitro* behavior with the physical characteristics of the gel layer of the different formulations has been established. This study shows that the size of water-filled pores and the degree of crosslinking between the chains of HPMC K15M of the matrix are related to the exponent n of the Korsmeyer–Peppas equation and the type of transport of the captopril from within the matrix to the dissolution medium, that is, if the transport is only through water-filled pores, or if a combination of diffusion occurs through water-filled pores with a transport through continuous polymeric networks.

1. Introduction

The concept of the ICH Q8 guideline is based on defining a design space, which consists in evaluate the impact of material attributes and process parameters on manufacturability and final products critical quality attributes (CQAs) (EMEA, 2004) (Huang et al., 2009). According to QbD, the quality of a product must be "built into" the product and ensured since its design, through an extensive mechanistic understanding of the relations between the product quality and the parameters that can have an impact on it (Tomba et al., 2013).

For the design of new controlled drug delivery systems, it is highly desirable to know exactly the transport mechanisms involved in drug release, and to be able to predict quantitatively the resulting drug release kinetics (Siepmann and Peppas, 2001).

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. This study has conducted extensive characterization using microscopy imaging techniques, kinetic equations and a thorough description of the captopril transport mechanism from inside the tablet to the dissolution medium, since the transport mechanism is related to

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the dissolution rate as well as the *in vivo* behavior of the formulations.

To modulate the release of captopril, two components are combined in the formulation with different physico-chemical properties: HPMC K15M Premium® to form the gel layer delaying the release of captopril, and Ethylcellulose N100® to give porosity to the tablet, increase water uptake and encourage the rapid release of captopril. An ethylcellulose was chosen with a mean particle size of approximately 300 μm and low density, since when increasing the particle size and porosity, the water uptake in the tablet increases (Agrawal et al., 2003; Lin and Lin, 1996).

The two most important consequences of significant polymer swelling in controlled release matrix systems are the length of the diffusion pathways and the mobility of the macromolecules (Siepmann and Siepmann, 2008). Water penetration into the device (via pores and/or through continuous polymeric networks) and creation of water-filled pores are important phenomena in water soluble drugs. In this article, a new relationship between the size of water-filled pores with the phenomena involved in captopril release has been obtained.

The galenic optimization of the formula was developed by applying the SeDeM diagram expert system (Aguilar et al., 2009, 2012; Pérez-Lozano et al., 2006; Suñé-Negre et al., 2005, 2008, 2011a,b), obtaining a viable formula for direct compression (Saurí et al., 2014).

All formulations contain barium sulfate to give density to the tablet (Clarke et al., 1995) for the purpose of retention in the stomach, ascorbic acid as an antioxidant to produce an acid pH in the gastrointestinal system to minimize captopril oxidation (Kadin, 1982; Seta et al., 1988), magnesium stearate, Aerosil® and talc to enhance the flow and lubrication properties of the formula, and Avicel® PH101 to obtain a good cohesion of the tablets.

In this study, dissolution test is the product's most important critical quality attribute (CQA). The aim of this study is to know the transport mechanisms involved in captopril release. This involves extensive scientific knowledge of the system, and so a theoretical description and characterization of each of the variables that has an impact on final product quality has been conducted.

2. Materials and methods

2.1. Materials

The active substance under study is captopril (Farmahispania, Spain).

The excipients used for the formulation of tablets were microcrystalline cellulose (Avicel® PH101, FMC Biopolymer (Norway)), barium sulfate (Panreac, Spain), ascorbic acid (Fagron, Spain), ethylcellulose (Ethylcellulose N100®, Aqualon, (USA)), and hydroxypropylmethylcellulose (HPMC K15M Premium®, Colorcon, Inc. (USA)). Other ingredients used were talc (Fagron, Spain), magnesium stearate (Fagron, Spain), and colloidal silicon dioxide (Aerosil®, Fagron, (Spain)).

2.2. Methods

2.2.1. Experimental design

The design of two-components (formulation 1–7) has been used, in which the variables are the concentration of Ethylcellulose N100® and HPMC K15M Premium® by setting all other components of the formula in a 70% w/w, with a 30% w/w maximum concentration for each of the variables. The different formulations are shown in Table 1. The average hardness values were between 161 and 195 N (see Table 2). The hardness of the tablets was constant in all formulations, since hardness values lower than 80 N, tablets with poor friability would be obtained with values higher than 1.0%.

Table 1
Composition of the different formulations (references 1–7)

Raw materials	Percentage (%)						
	Ref. 1	Ref. 2	Ref. 3	Ref. 4	Ref. 5	Ref. 6	Ref. 7
Ethylcellulose N100®	30	25	20	15	10	5	0
HPMC K15M Premium®	0	5	10	15	20	25	30
Captopril	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4
Aerosil®	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Avicel® PH101	25	25	25	25	25	25	25
Ascorbic acid	20	20	20	20	20	20	20
Barium sulfate	10	10	10	10	10	10	10
Total	100	100	100	100	100	100	100

The critical attribute of quality of major importance is the dissolution rate. Although the absorption of captopril is independent of concentration and dose (Nur and Zhang, 2000), the permeability of captopril is concentration-dependent (Hu and Amidon, 1988). Furthermore, degradation of captopril is inversely proportional to the concentration of dissolved active substance (Hu and Amidon, 1988), which is of great importance to obtain an area of knowledge to allow selecting a formulation at optimum dissolution rate.

2.2.2. Tablet preparation

The blends were compressed in a Bonals® (Cornellà de Ll., Spain) continuous eccentric press, provided with 19 × 10 mm punches. The height varied between 6.15 and 6.45 mm, and the weight was 1 g. In the characterization of the tablets the methods applied were resistance to crushing of tablets and friability.

2.2.3. Drug substance and polymer characterization

In accordance with the general method described in Eur. Pharm. for determining particle size by means of the sieve test, the particle size of a 100 g sample is determined by subjecting a sieve stack to vibration for 10 min at speed 10 (CISA vibrator). Sieve sizes used: 0.355 mm, 0.212 mm, 0.100 mm and 0.05 mm. The percentage of product retained in each sieve is calculated.

2.2.4. Scanning electron microscopy

Dried tablet samples were examined by scanning electron microscopy (SEM JEOL JSM-6510, Japan) using 10 kV accelerating voltage and 5 kV accelerating voltage to view the longitudinal section of the tablets. To observe the amorphous structure of the gel layer, the tablets were placed in a 400 ml glass beaker of with water in a magnetic stirrer for 5 s at 300 rpm. Hydrated tablet samples were examined by the Cryo-SEM method by means of a cryostage (GATAN ALTO-1000, USA) attached to the microscope, which can maintain the structure of the hydrated materials in the most natural state. Hydrated samples were frozen by plunging them into liquid nitrogen and then transferred in vacuum to the cryo-unit system coupled with the SEM. Samples were sublimated at −70 °C for 15 s in the SEM chamber in high vacuum conditions. Then, tablets were relocated in the cryo-unit in order to be sputtered with gold. Covered samples were eventually observed in the SEM at 10 kV and maintaining the temperature at −192 °C. The images were taken using the tablets of formulations 1, 4 and 7.

2.2.5. In vitro dissolution studies

Dissolution was measured with a fully calibrated dissolution apparatus, using the paddle method (Apparatus II, Erweka DT80,