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Enhancement of albendazole dissolution properties using solid dispersions with Gelucire 50/13 and PEG 15000

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ABSTRACT

The role of two carriers —Gelucire 50/13 and PEG 15000— was evaluated to improve the characteristics of the dissolution of albendazole, an anthelmintic drug with very low solubility and dissolution rate. Solid dispersions were elaborated by using the fusion method. The results from solid-state characterisation techniques (DSC, HSM, FTIR and PXRD) reported immiscibility and absence of interactions in the solid phase.

In vitro release studies of binary systems showed a substantial enhancement of dissolution performance when compared with the control, which constitutes an actual alternative to increase the bioavalilability and/or reduce the dosage of the currently marketed formulations.

1. Introduction

Solubility and dissolution rate in the GI fluids constitute the limiting steps of the bioavailability of orally-administered drugs considered as type II, according to the Biopharmaceutical Classification System (BCS) [1], e.g. all those APIs with an adequate permeability but a low solubility and/or dissolution rate. Over the years, many strategies were proposed and applied to overcome these limitations, including salt formation, cosolvents, complexation, use of metastable polymorphs, amorphous phases, cocrystals, nanosizing and combination with carriers as solid dispersions [2–8]. Among them, solid dispersions offer some significant advantages, such as pH independent release [9], inexpensive and easy manufacture, process reliability, low excipient cost and easy access to a wide variety of them.

In recent years, the strategy of solid dispersion is generating a renewed interest because it is taking advantage of the adaptation of the industrial manufacturing process used for plastic materials for many years. This process —known as hot-melt extrusion (HME)— simplifies the dispersion of hydrophobic drugs into low melting point hydrophilic carriers as well as their processing into a solid dosage form, for instance, into tablets, capsules, pellets and more [10–14].

ABZ (methyl [5-(propylthio)-1H-benzimidazol-2-yl] carbamate) is a benzimidazole drug widely used in antiparasitic therapy for diseases such as neurocysticercosis and hydatidosis. This API —including its active metabolites— constitutes one of the most effective and broad-spectrum anthelmintic agents [15,16]. In addition, recent studies have revealed the ABZ as a potential antitumor agent [17]. Unfortunately, ABZ shows a poor and erratic absorption at the GI tract, being considered as a type II BCS class drug, fact that is related to its very low water solubility [18,19].

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The reported investigations are focused on exploring the capability of Gelucire 50/13 —a PEG-glyceride derivative that constitutes a surface active carrier— and PEG 15000 in order to incorporate ABZ through the fusion method [20–22] and to evaluate the release profiles of binary systems, since dissolution rate is the limiting step to reach adequate bioavailability for this drug.

2. Materials and methods

2.1. Materials

ABZ was purchased from Sigma-Aldrich Co. (St. Louis MI, USA). Gelucire 50/13 (GEL) was a gift by Gattefossè (Saint-Priest, Lyon, France). PEG 15000 (PEG) was supplied from Merck (Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation of solid dispersions

Solid dispersions were prepared by using the fusion method: appropriate amounts of ABZ (10, 20 and 40% w/w) were added to the previous molten carrier and then stirred with the aid of a stirring rod until the total dispersion of the drug. During the process, temperature was maintained at 75 °C for GEL and 90 °C for PEG. After slow cooling to ambient T, solidified samples were milled to obtain powder and sieved (500 μm). Simultaneously, physical mixtures were prepared at the same drug:carrier ratios for reference purposes. A summary of composition and elaboration methods for all the samples is reported in Table 1.

2.2.2. Differential scanning calorimetry (DSC)

DSC thermograms were recorded by using a Mettler FP 80 series equipment (Greifensee, Switzerland) under static air atmosphere in the range from 30 to 300 °C, at a heating rate of 10 °C min^{-1}. Samples of pure components and their binary systems (about 10 mg each) were filled in 40 μl aluminium crucibles and closed with perforated lids to allow the release of gas during thermal analysis.

2.2.3. Hot-stage microscopy (HSM)

HSM studies were performed by a Mettler FP 82HT hot plate and a Mettler FP85 HT unit control coupled to a microscope with a photographic recording device (Olympus BH-2, C5060-ADU adapter, Olympus Camedia C-5060, Tokyo, Japan). The starting temperature was set to 30 °C and this value increased at variable heating rate to a maximum of 240 °C.

Table 1
Composition and preparation methods of binary systems.

Formulation code	Polymer	Drug:polymer composition ratio w:w	Elaboration method
ABZ-GEL PM 10%	GEL	1:9	Physical mixing
ABZ-GEL PM 20%	GEL	2:8	Physical mixing
ABZ-GEL PM 40%	GEL	4:6	Physical mixing
ABZ-GEL SD 10%	GEL	1:9	Fusion method
ABZ-GEL SD 20%	GEL	2:8	Fusion method
ABZ-GEL SD 40%	GEL	4:6	Fusion method
ABZ-PEG PM 10%	PEG	1:9	Physical mixing
ABZ-PEG PM 20%	PEG	2:8	Physical mixing
ABZ-PEG PM 40%	PEG	4:6	Physical mixing
ABZ-PEG SD 10%	PEG	1:9	Fusion method
ABZ-PEG SD 20%	PEG	2:8	Fusion method
ABZ-PEG SD 40%	PEG	4:6	Fusion method

Table 2
Thermal evaluation of samples.

Formulation	1st thermal event			2nd thermal event		
	T_{peak} (°C)	T_{onset} (°C)	ΔH (J/g)	T_{peak} (°C)	T_{onset}(°C)	ΔH (J/g)
ABZ	–	–	–	232.8	208.9	−148.0
GEL	62.5	44.4	−102.0	–	–	–
PEG	82.6	64.8	−156.0	–	–	–
ABZ-GEL PM 10%	65.3	46.2	−108.0	168.2	137.9	−4.9
ABZ-GEL PM 20%	63.5	44.9	−88.7	171.9	145.3	−12.1
ABZ-GEL PM 40%	62.4	46.8	−78.5	199.2	145.2	−9.9
ABZ-GEL SD 10%	58.8	39.8	−91.5	161.4	142.9	
ABZ-GEL SD 20%	56.2	39.0	−76.8	172.5	150.5	
ABZ-GEL SD 40%	57.2	39.4	−51.8	198.9	176.0	
ABZ-PEG PM 10%	82.8	64.6	−127.0	–	–	–
ABZ-PEG PM 20%	80.3	64.0	−102.0	184.7	154.2	−9.0
ABZ-PEG PM 40%	78.8	63.7	−83.1	201.3	176.8	−13.3
ABZ-PEG SD 10%	77.9	63.3	−107.0	153.0	151.4	−2.3
ABZ-PEG SD 20%	73.3	59.4	−93.1	176.6	154.3	−8.6
ABZ-PEG SD 40%	76.2	60.8	−80.4	204.2	201.3	−12.4

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