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Research paper

Biopharmaceutical improvement of praziquantel by interaction with montmorillonite and sepiolite

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ABSTRACT

Praziquantel is the drug of first choice for the treatment of the human schistosomiasis. It is administered orally, requiring high doses to overcome adverse biopharmaceutical properties, including high lipophilia and intense hepatic first pass metabolism. According to its biopharmaceutical profile, praziquantel has very low water solubility and high permeability. Therefore, dissolution is the limiting factor for absorption in the gastrointestinal tract. Improvement of the aqueous solubility of the drug would reduce the currently high oral doses. Meanwhile, montmorillonite and sepiolite are clay minerals, with a high adsorption and swelling properties, potentially useful as a low-cost nanocarrier to design praziquantel delivery systems. In this work, the interactions between the drug and clay minerals are studied experimentally, with the aim of improving the biopharmaceutical profile of the drug. The results showed the effective loading of the drug in the clay minerals as well as the significant increase of the dissolution rate and the dissolved amount of praziquantel, potentially improving the bioavailability of the drug.

1. Introduction

Clay minerals, in particular montmorillonite and sepiolite, are widely used pharmaceutical excipients in different pharmaceutical dosage forms, designed for oral and topical administration (López-Galindo and Viseras, 2004; Viseras et al., 2010). Besides their classic pharmaceutical uses, clay minerals may be effectively used in the development of modified drug delivery systems (Aguzzi et al., 2007; Viseras et al., 2010).

Montmorillonite is a dioctahedral 2:1 phyllosilicate with one octahedral sheet and two tetrahedral sheets (T:O:T). An interlayer nanospace exists between each triple-sheet-layer. These layers have isomorphic substitutions of Si^{4+} by Al^{3+} in the tetrahedral sheet and Al^{3+} by Mg^{2+} in the octahedral layer. An important part of the physicochemical properties of montmorillonite depends on the isomorphic substitutions that confer a negative residual charge compensated by cations in the interlayer space. These interlayer spaces represent about 90% of the mineral total surface and are accessible to water molecules and other compounds, yielding a high adsorption capacity for polar molecules (Bergaya and Lagaly, 2006; Aguzzi et al., 2007).

On the other hand, sepiolite is a non-planar phyllosilicate with fibrous morphology. The basal oxygen layer is continuous but the apical oxygens undergo a periodic inversion every 8 octahedral positions. This inversion causes a discontinuous octahedral layer forming long channels, where the water and organic molecules can be adsorbed (Guggenheim et al., 2006).

Because of their high adsorption and cation exchange capacities, both montmorillonite and sepiolite are peculiar nanostructurated material. These solids can retain organic molecules in their structures and after administration release the retained active compounds under controlled conditions, being good candidates for the design of modified delivery systems of several drugs (Viseras et al., 2010). Besides the above mentioned clay minerals, halloysite nanotubes have been also exploited as nanocarriers for several applications (Massaro et al., 2016; Makaremi et al., 2017).

Praziquantel is the drug of choice for an extended parasitic disease, schistosomiasis that it is a parasitic disease caused by *Schistosoma*. The infection is caused by the parasite penetration through the skin of individuals, in contact with contaminated water. It is widely extended, mainly in at least 74 developing countries, in the tropics and subtropics (Chitsulo et al., 2000) and it affects 250 million people approximately, causing over half a million of deaths every year (Steinmann et al., 2006). Behind of malaria, the Schistosomiasis is the second of the most prevalent diseases that affects African children (WHO, 2017).

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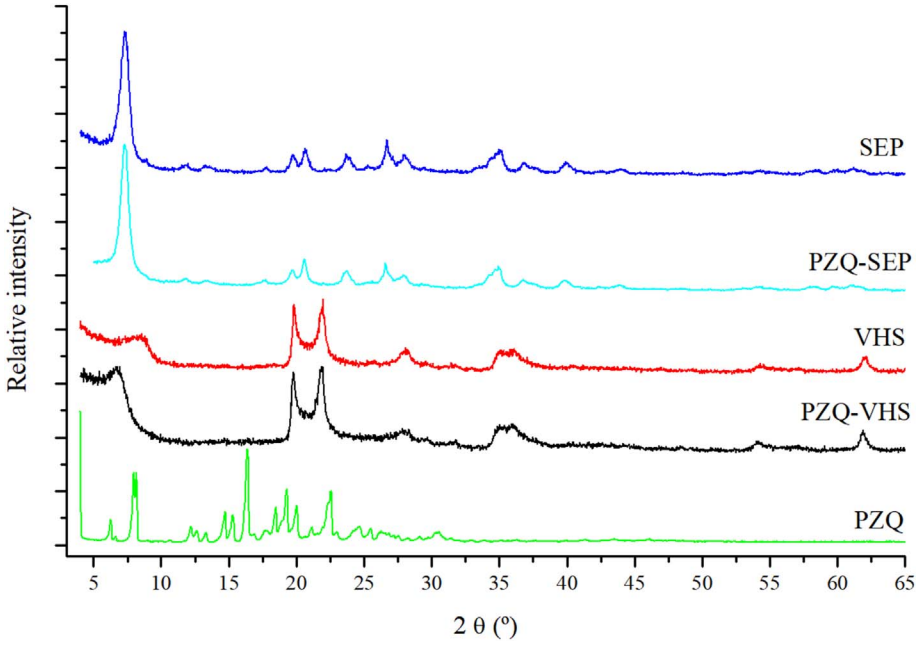

Fig. 1. XRPD patterns of the studied samples.

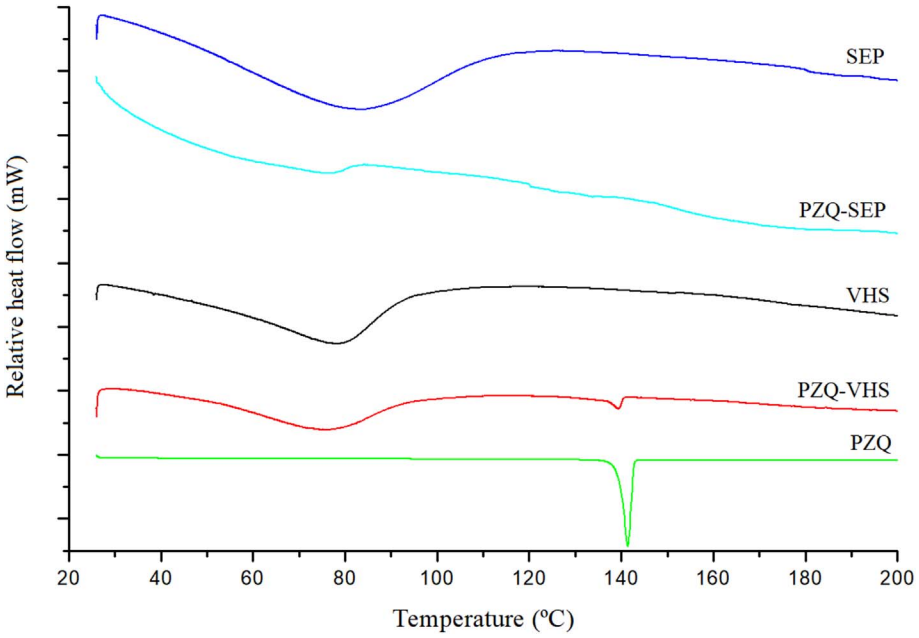

Fig. 2. DSC profiles of the studied samples.

The prevention of the Schistosomiasis is difficult and there is no effective vaccine against the disease. Praziquantel is the most used drug for the treatment of Schistosomiasis (WHO, 2017). However, its extensive use and the lack of compliance during the treatment is causing drug resistance (Wang et al., 2012).

Praziquantel has a chiral center and only the R-(-)-enantiomer possesses anthelmintic activity (Andrews, 1985) even if the actual treatments use a racemic mixture. It is classified in Class II in Biopharmaceutics Classification System (BCS) (FDA, 2017; González-Esquivel et al., 2005), due to its low aqueous solubility and high permeability, and has low absorption in the gastrointestinal tract (GIT) (Amidon et al., 1995). For these reasons, high oral doses are required to treat schistosomiasis. The interaction of praziquantel with montmorillonite in aqueous medium was studied by El-Feky et al. (2015). However, the resultant interaction products did not improve *in vitro* dissolution rates neither *in vivo* absorption rates. Probably, as a result of the presence of water molecules in the interlayer space of the montmorillonite, the entry of praziquantel was hindered and the drug was only absorbed on the external surface, resulting in the absence of relevant biopharmaceutical improvements.

With these premises, aim of this work was to obtain praziquantel/clay mineral interaction products in absence of water as a strategy to improve the effective entrapment of the drug molecules. The potential increase in praziquantel solubility was a rational approach to the improvement of drug bioavailability.

2. Materials and methods

2.1. Materials

Praziquantel (PZQ) was purchased from Sigma Aldrich (S). Ethanol of 99% of purity was used as solvent. Purified pharmaceutical degree