PHARMACEUTICS, PREFORMULATION AND DRUG DELIVERY

Cyclodextrin Multicomponent Complexation and Controlled Release Delivery Strategies to Optimize the Oral Bioavailability of Vinpocetine

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ABSTRACT: In the present work, to maintain a suitable blood level of vinpocetine (VP) for a long period of time, VP-cyclodextrin-tartaric acid multicomponent complexes were prepared and formulated in hydroxypropylmethylcellulose matrix tablets. *In vitro* and *in vivo* performances of these formulations were investigated over a VP immediate release dosage form. Solubility studies were performed to evaluate the drug pH solubilization profile and to assess the effect of multicomponent complexation on VP solubility. The drug release process was investigated using United States Pharmacopeia apparatus 3 and a comparative oral pharmacokinetic study was subsequently undertaken in rabbits. Solubility studies denoted the pH-solubility dependence of VP and solubility improvement attained by complexation. Dissolution results showed controlled and almost complete release behavior of VP over a 12-h period from complex hydroxypropylmethylcellulose-based formulations. A clear difference between the pharmacokinetic patterns of VP immediate release and VP complex-based formulations was revealed. The area under the plasma concentration-time curve after oral administration of complex-based formulations was 2.1–2.9 times higher than that for VP immediate release formulation. Furthermore, significant differences found for mean residence time, elimination half-life, and elimination rate constant values corroborated prolonged release of VP from complex-based formulations. These results suggest that the oral bioavailability of VP was significantly improved by both multicomponent complexation and controlled release delivery strategies. J Pharm Sci 96:2018–2028, 2007

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INTRODUCTION

Vinpocetine (VP) is a vincamine derivative that has been used in clinical practice in Europe for nearly three decades for the treatment of disorders arising from cerebrovascular and cerebral degenerative diseases.[1,2] VP is thought to increase the cerebral flow in the ischemic areas of patients with cerebrovascular disease, decrease platelet aggregability in patients with transient ischemic attack or stroke, increase red blow cell deformability in stroke patients, and have neuroprotective abilities and a protective effect against brain ischemia.[3,4]

VP is mainly used as immediate oral dosage forms containing 5 mg of the active ingredient, with a daily dosage regimen that can vary between 5 mg × 3/day to 20 mg × 3/day.[5] Unfortunately, the very limited aqueous solubility and wettability of VP can give rise to problems of both formulation and low bioavailability (~6.7%).[6] Indeed, VP is a poorly water-soluble base-type drug that presents pH-dependent solubility. As the solubility and dissolution relationships in the gastrointestinal tract can be critical for the oral bioavailability of poorly soluble weak bases as VP, because of the possibility of drug precipitation upon entry into the small intestine that may also affect the amount of drug available for uptake through the intestinal mucosa,[7] the use of cyclodextrin (CD) multicomponent complexation with βCD, sulfobutyl ether (SBE)βCD, tartaric acid (TA), and polyvinylpyrrolidone (PVP) has been attempted to overcome such VP solubility and dissolution drawbacks.

One potential method of optimizing the efficacy of drug activity is through the use of rationally designed carrier materials such as CDs. In the past decades, CD complexation has been extensively applied to enhance the solubility, dissolution, and bioavailability of poorly water-soluble drugs. Therefore, the use of CDs as excipients in different dosage forms has received much attention because upon complex formation advantages such as improved bioavailability, reduction of unwanted side effects, or improved stability have often been claimed. The improvement in absorption rate of drugs administered in solid dosage forms has been related to the increase in both solubility and dissolution rates of the complexes as compared with pure drug.[8] More recently, a concern with the amount of CDs in dosage forms due to toxicological considerations, formulation bulk, and production costs encouraged the development of methods that could enhance the complexation efficiency of CDs, by using a third additive such as water-soluble polymers[9,10] and hydroxy acids.[11]

In previous works, we have reported the combined use of both βCD and SBEβCD, water-soluble polymers [PVP and hydroxypropylmethylcellulose (HPMC)], and hydroxy acids (TA) to improve VP solubility.[12,13] Considering that VP has an elimination half-life of 2–6 h[14] and requires chronic administration, a controlled release dosage form could provide increased clinical value over conventional formulations, as a result of improved therapeutic effect and patient compliance by reducing dosing frequency, a more constant or prolonged therapeutic effect, and possible enhanced bioavailability. Then, in an effort to reach better dissolution properties as well as controlled release rate of VP, we have prepared VP-CD-TA multicomponent complexes and an optimal formulation was subsequently designed by the combination of these complexes into HPMC-based hydrophilic tablet dosage forms (Ribeiro et al., submitted for publication).

Because dissolution rate of poorly soluble drugs is a function of their water-solubility, enhancement of drug solubility is expected to improve its bioavailability. Recently, SBEβCD, a chemically modified CD, became a more interesting option than βCD to achieve complexation because of better physicochemical properties and improved inclusion behavior. Studies had proven that this CD derivative is able to increase drug oral bioavailability.[15,16] Thereby, the present study was undertaken to evaluate, by means of *in vivo* absorption studies in the rabbit model, the feasibility of using VP-βCD-TA and VP-SBEβCD-TA multicomponent complexes in association with HPMC matrix tablets as strategies to improve VP oral bioavailability and also to obtain a prolonged therapeutic effect of the drug as compared with an immediate release formulation.

EXPERIMENTAL

Materials

VP was purchased from Covex (Madrid, Spain). βCD [Kleptose®; molecular weight (MW) 1135]