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Improving Biopharmaceutical Properties of Vinpocetine Through Cocrystallization

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ABSTRACT

Vinpocetine is a poorly water soluble weakly basic drug ($pK_a = 7.1$) used for the treatment of several cerebrovascular and cognitive disorders. Because existing formulations exhibit poor bioavailability and scarce absorption, a dosage form with improved pharmacokinetic properties is highly desirable. Cocrystallization represents a promising approach to generate diverse novel crystal forms and to improve the aqueous solubility and in turn the oral bioavailability. In this article, a novel ionic cocrystal of vinpocetine is described, using boric acid as a coformer, and fully characterized (by means of differential scanning calorimetry, solid-state nuclear magnetic resonance, powder and single-crystal X-ray diffraction, and powder dissolution test). Pharmacokinetic performance was also tested in a human pilot study. This pharmaceutical ionic cocrystal exhibits superior solubilization kinetics and modulates important pharmacokinetic values such as maximum concentration in plasma (C_{max}), time to maximum concentration (t_{max}), and area under the plasma concentration-time curve (AUC) of the poorly soluble vinpocetine and it therefore offers an innovative approach to improve its bioavailability.

Introduction

Crystalline forms are the preferred dosage forms for active pharmaceutical ingredients (APIs) for use in drug products. Generally, single and multicomponent crystals show superior stability to their amorphous counterparts, and their synthesis (crystallization) tends to afford highly pure products that are reproducible and scalable.[1] Moreover, different crystal forms can exhibit different physicochemical properties that will affect the pharmacokinetics of the drug. For these reasons, during the early stages of drug development, novel crystal forms of the API are searched for through screening processes and their physicochemical properties are identified.[2-9] These novel crystal forms might include polymorphs or multicomponent crystals such as salts, solvates, hydrates and, more recently, cocrystals. Cocrystals are solids that are crystalline single-phase materials composed of 2 or more different molecular and ionic compounds, generally in a stoichiometric ratio, which are neither solvates nor simple salts.[10] The current attraction to cocrystals as novel crystal forms is attributed to their ability to change key properties of APIs *via* inclusion of additional molecules through reliable, therefore designable, interactions (i.e., supramolecular synthons).[11] A large library of potential coformers can be built using databases containing pharmaceutically approved substances such as the GRAS (generally recognized as safe) list for example, which contains ingredients recognized by the United States Food and Drug Administration to be safe under specified conditions. These substances can serve as coformers in order to obtain new crystal forms with improved solubility,[12,13] compressibility,[14] or stability[15] that ultimately impact on bioavailability.[16]

The main challenge during pharmaceutical cocrystal development is the rational selection of coformers for a particular drug molecule, because it is not realistic to screen the whole chemical catalogue. Following a proven crystal engineering[17] approach,

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possible coformers can be chosen to form robust supramolecular interactions (synthons) with the desired drug molecule, taking into consideration supramolecular synthon hierarchy.[18] This supramolecular synthesis strategy[11,19] primarily relies on crystallographic data found in the Cambridge Structural Database.[20]

This approach, however, has yet to offer clear predictions about whether there will be desirable property improvement in the resulting cocrystals, although efforts have been made to correlate the physicochemical properties of coformers to those of the resulting cocrystals.[21]

In particular, among pharmaceutical cocrystals, ionic co-crystals have proven to be a viable route to enhance solubility/bioavailability of poorly soluble drugs.[22] Recently, a pharmaceutical ionic cocrystal containing 2 active ingredients, Entresto™ used to treat chronic heart failure, gained approval from the Food and Drug Administration.[23]

The target of this study, vinpocetine (Fig. 1), is a semisynthetic derivative of the natural alkaloid vincamine, showing a series of pharmacological properties in relation to cerebral circulation and on vascular resistance, particularly in the area of blood vessels.[24] Vinpocetine has been shown to impact the cerebral circulation and metabolism and improve various types of cerebrovascular circulatory disorders such as the cerebral infarction, cerebral hemorrhage, cerebral arteries cirrhosis,[25] and for the long-term treatment of cognitive disorders and related symptoms.[26] Due to its low aqueous solubility, and extensive first-pass metabolism, vinpocetine presents low oral bioavailability (~6.7%)[27,28] and, as a consequence, its clinical use is limited. In this context, the aim of this investigation is to improve the solubility and bioavailability of vinpocetine with an ionic cocrystal.

Materials and Methods

Materials

Vinpocetine E.P. grade was a kind gift from Linnea SA (Riazzino-Locarno, Switzerland) with a purity of 99.8% and was used without further purification. Boric acid was supplied by Sigma-Aldrich (St. Louis, MO) and used without further purification. Acetonitrile with a purity of 99.9% was supplied by Sigma-Aldrich.

Synthesis of Vinpocetine-Boric Acid Cocrystal (1)

Using the following procedure, 1 was prepared by slow evaporation: a mixture of vinpocetine (50.1 mg, 0.14 mmol) and boric acid (26.1 mg, 0.42 mmol) was transferred into a glass vial. Subsequently, 14 mL of acetonitrile was added to the solid mixture and stirred for 30 min at 45°C. The clear solution was then left for slow evaporation under ambient conditions.

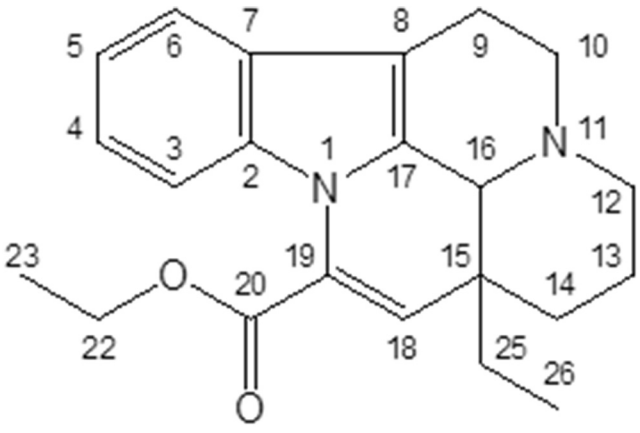

Figure 1. Structure of vinpocetine with atom-numbering scheme.

Crystal Form Characterization

Single-crystal X-Ray Diffraction. Single-crystal analysis for 1 was performed on a Bruker-AXS D8 QUEST diffractometer (Bruker, Madison, WI) using a microfocus generator of Mo Kα radiation (λ = 0.71073 Å) and CMOS PHOTON detector. Data for 1 were collected at 100 K[‡]. Lattice parameters were determined from least-squares analysis, and reflections were integrated using SAINT (Bruker).[29] The structure was solved by direct methods and refined by full matrix least squares based on F^2 using X-Seed software.[30] All nonhydrogen atoms were anisotropically refined. All hydrogen atoms bonded to carbon, nitrogen, and oxygen atoms were placed geometrically and refined with an isotropic displacement parameter fixed at 1.2 times *Uq* of the atoms to which they were attached. Hydrogen atoms bonded to methyl groups were placed geometrically and refined with an isotropic displacement parameter fixed at 1.5 times *Uq* of the carbon atoms.

Powder X-Ray Diffraction. The cocrystal structure of 1 was characterized using a D8 Bruker X-ray powder diffractometer (Bruker) using Cu Kα radiation (λ = 1.54178 Å), 40 kV, 40 mA. Data were collected at room temperature on a sample manually ground in an agate mortar. The data were collected over an angular range of 5° to 40° 2θ value in continuous scan mode using a step size of 0.05° 2θ value and a scan rate of 5°/min.

Moreover, a calculated powder X-ray diffraction (PXRD) diffractogram was generated from the single-crystal structure of 1 using Mercury 2.2 (Cambridge Crystallographic Data Centre, Cambridge, UK) and compared with the pattern obtained from the bulk sample.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed on a PerkinElmer Diamond differential scanning calorimeter (PerkinElmer, Waltham, MA) with a scan range of 25°C-250°C and scan rate of 10°C/min under nitrogen atmosphere.

Solid-state NMR Spectroscopy

Solid-state nuclear magnetic resonance spectra (SSNMR) were recorded with a Bruker Advance II 400 instrument operating at 400.23, 100.64, and 40.55 MHz for ^{1}H, ^{13}C, and ^{15}N nuclei, respectively. Cylindrical 4 mm o.d. zirconia rotors with a sample volume of 80 μL were employed and spun at 12 (^{13}C) or 9 (^{15}N) kHz. All ^{13}C and ^{15}N cross-polarization magic angle spinning (CPMAS) experiments employed the RAMP-CP pulse sequence (^{1}H 90° pulse of 3.05 μs) with TPPM ^{1}H decoupling with a radio frequency field of 75 kHz during the acquisition period. ^{13}C spectral editing experiments were performed with the cross-polarization polarization inversion pulse sequence with polarization inversion times of 65 and 70 μs for pure vinpocetine and 1, respectively in order to obtain CH_3 and C_q positives, CH nulls, and CH_2 negatives. ^{13}C and ^{15}N chemical shifts were referenced with the resonance of

[‡] Crystallographic Information File for 1 is available from CCDC: ref. number 1498771. Crystal data 1: colorless plate, 0.200 × 0.100 × 0.100 mm^3. Sum formula $C_{44}H_{60}B_6N_4O_{17}$, M = 981.82, crystal system monoclinic, $P2_1$ space group (No. 4), V = 2428.2(3) Å^3, Z = 2, D_c = 1.343 g/cm^3, F_{000} = 1036, Bruker Quest, Mo Kα radiation, λ = 0.71073 Å, T = 100(2) K, $2\theta_{max}$ = 55.3°, 29882 reflections collected, 11136 unique (R_{int} = 0.0494). Final *GooF* = 1.021, R_1 = 0.0502, wR_2 = 0.0821, R indices based on 8152 reflections with I > 2(I) (refinement on F^2), 652 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.100 mm^{-1}. Absolute structure parameter = 0.2(4).