Journal of Molecular Structure 1105 (2016) 1–10

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Novel perchlorate and phosphate salts of vinpocetine: Characterization, relative solid-state stability evaluation and Hirshfeld surface analysis

Yu-heng Ma [a, b], Shu-wang Ge [a], Wei Wang [a], Qiang Zheng [c], Yun-wei Zuo [c], Chang-jiang Zhong [c], Bai-wang Sun [a, *]

[a] School of Chemistry and Chemical Engineering, Southeast University, Nanjing 210096, PR China
[b] Jiangsu Chia Tai Qingjiang Pharmaceutical Co., Ltd, PR China
[c] Department of Chemical and Pharmaceutical Engineering of Southeast University Chengxian College, Nanjing 210088, PR China

ARTICLE INFO

Article history:
Received 16 June 2015
Received in revised form
12 September 2015
Accepted 19 October 2015
Available online 21 October 2015

Keywords:
Dosage form
Salt
Vinpocetine
Hirshfeld surface
Stability

ABSTRACT

Salt formation is a very common and effective method of improving a drug's physicochemical properties such as hygroscopicity and physical stability at different humidity conditions. Aqueous solubility is another important parameter that can be improved by salt formation; however this strategy has not yet been evaluated for the important alkaloid drug, Vinpocetine. A poorly water-soluble basic drug (water solubility value≈ 5 μg/ml and pKa value of 7.31), vinpocetine was converted into two novel salts in this work, with perchloric acid and phosphoric acid in a 1: 1 M ratio. However, an unexpected phase transformation occurred in one of the salts after the stability test, which is a major concern in studies on dosage form. The conversion of the salt to free base could be related to the temperature-humidity profile of the type II salt (formed by vinpocetine and phosphoric acid). When the temperature was more than 70 °C under high humidity conditions of more than 80%, the phase transformation occurred immediately. To gain further understanding of this phenomenon, single crystals of the two novel salts were prepared and characterized by single crystal X-ray diffraction, Powder-XRD, infrared spectroscopy, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Constituents of the crystalline phase were also investigated in terms of Hirshfeld surface. The structures were found to be stabilized by H···H, C—H···O, O—H···N and C—H···π intermolecular interactions. Our stability studies showed that both these two novel salts could improve the stability of vinpocetine, however the type I salt (formed by vinpocetine and perchloric acid) offers more advantages. This finding will provide valuable information for vinpocetine dosage form development.

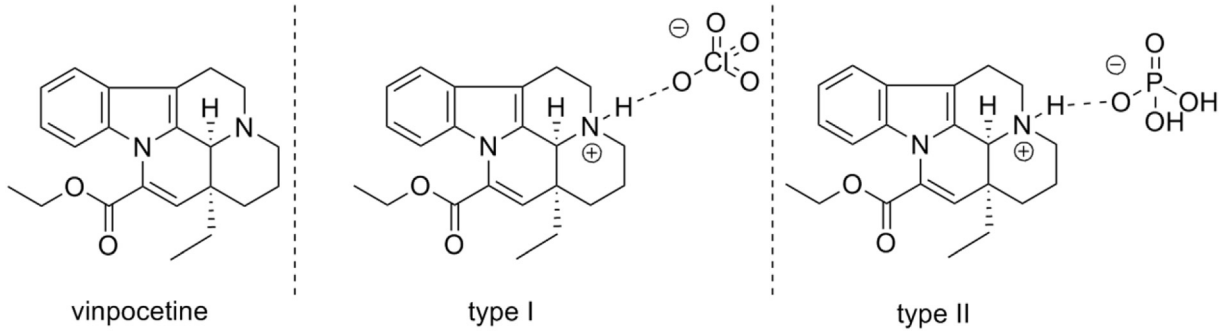
1. Introduction

Active pharmaceutical ingredients (APIs) often exist in different polymorphic forms [1–3], which have been studied widely and play an important role in the pharmaceutical industry [4]. Researchers have shown much interest in polymorphism since the different polymorphic forms exhibit different physical or chemical properties [5–7]. However, sometimes this phenomenon is highly undesirable during processing of drugs due to lack of predictability and controllability [8–10]. One potential method to overcome the drawbacks of polymorphism is to modify the crystal structure of the APIs by formation of co-crystals, salts, hydrates or solvates [11]. These modified versions show less tendency towards polymorphic behavior. Among these different methods, formation of co-crystals and salts is especially interesting. While salt formation has been the traditional approach, the creation of co-crystals (neutral complexes) has recently developed as a potential alternative.

In the crystalline solid state, there is only a slight difference between a salt and a co-crystal [12]. Although the definitions of salt and co-crystals have been a topic of considerable debate, there are now generally accepted literature definitions within the broader context for these terms. The most recent definition was

* Corresponding author.
E-mail address: chmsunbw@seu.edu.cn (B.-w. Sun).

http://dx.doi.org/10.1016/j.molstruc.2015.10.029
0022-2860/



Scheme 1. Hydrogen bonding synthons identified in Vinpocetine and two salts (type I and type II).

proposed during an Indo-U.S. bilateral meeting, and states that: co-crystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds, generally in a stoichiometric ratio, which are neither solvates nor simple salts [13,14]. Moreover, the U.S. Food and Drug Administration (FDA) has elected to classify co-crystals as API-excipient molecular complexes, where the co-crystal may be treated as a drug product intermediate rather than the drug substance. On the other hand, a new salt of the same API is considered as a new drug entity [15]. When an acid is reacted with a base, the resulting product will be a salt or a co-crystal. The general rule is that if the ΔpKa ($pKa_{base} - pKa_{acid}$) is greater than 2–3, the product will be a salt. Cruz-Cabeza [16] found a linear relationship between ΔpKa and the probability of proton transfer: when the ΔpKa> 1.3, there is a greater than 50% probability of the complex being a salt. Gilli [17] used the strength of donor-acceptor hydrogen bonds based on the ΔpKa, and determined that salts will be formed if ΔpKa> 3, and co-crystals will be formed when ΔpKa < −3.

Among the widely used alkaloids are vincamine, vinpocetine (ethyl-apovincamine-22-oate) and its derivatives. Vinpocetine was brought to the market in 1978, and is a well-known drug used for the treatment of ischemic stroke and other cerebrovascular diseases [18,19]. To date, no significant side effects, toxicities, or contraindications have been reported at therapeutic doses of this drug. However, vinpocetine is a sparingly water soluble drug. Although vinpocetine has good pharmacological properties and shows considerable therapeutic effects, its clinical usefulness is limited by its very poor bioavailability (~6.7%) due to its poor aqueous solubility and hepatic first-pass metabolism [20,21]. Thus, there is a need to improve its poor aqueous solubility in order to increase its oral absorption.

The purpose of our work was to apply the salt formation strategy to vinpocetine in order to develop a novel drug entity with improved aqueous solubility and good stability. A search of the literature and Cambridge Crystallographic Data Centre (CCDC) showed that no co-crystal or salt structure of vinpocetine has been reported so far. In an earlier work, we prepared salts of vinpocetine with a series of inorganic acids (hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid and perchloric acid). We applied the solution crystallization technique and found that only the perchloric acid and phosphoric acid react with vinpocetine to yield crystals with two different shapes (Scheme 1). These two crystals are believed to be salts as the ΔpKa is more than 3. The two crystals were characterized by single-crystal X-ray diffraction, Powder-XRD, IR spectroscopy, thermal analysis (DSC and TGA) and Hirshfeld surfaces analysis, and the results are described in the below sections.

Table 1
Crystal data and structure refinement for Vinpocetine and two salts (type I and type II).

	Type I	Type II
CCDC	1037658	1037659
Empirical formula	$C_{22}H_{27}N_2O_6Cl$	$C_{22}H_{29}N_2O_6P$
Formula weight	450.91	448.44
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P 21	C 2
a, Å	6.9140(14)	18.248(4)
b, Å	11.711(2)	6.4100(13)
c, Å	13.989(3)	21.004(4)
α (°)	90.00	90.00
β (°)	99.90(3)	108.93(3)
γ (°)	90.00	90.00
V, Å^3	1115.8(4)	2324.0(8)
Z	2	4
T/*K*	293(2)	293(2)
Density (calculated), g/cm^3	1.342	1.282
Absorption coefficient, mm^{-1}	0.212	0.158
h, *k*, *l* (min, max)	(0,8), (−14,14), (−16,16)	(−22,20), (0,7), (0,25)
Parameters	287	288
F(000)	476	952
Goodness-of-fit on F2	1.036	1.085
Final R indices [I > 2σ(I)]	R1 = 0.0872	R1 = 0.0450
	ωR2 = 0.2688	ωR2 = 0.1177