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DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS, EQUILIBRIUM SOLUTION AND LIPID-WATER PARTITION COEFFICIENT OF O-19, A PROMISING PRODRUG CANDIDATE OF O-DESMETHYLVENLAFAXINE

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ABSTRACT

Compound **O-19** is a promising prodrug candidate of O-desmethylvenlafaxine (ODV) with excellent oral bioavailability and improved brain uptake. In present investigation, with the aim to gain the information on druggability of **O-19**, the DSC analysis and physicochemical properties including solubility (S), lipid/water partition coefficient (Log P) coupled with solid state stability evaluation were performed and compared with ODV. Results indicated that **O-19** showed unique double peaks associated with the crystal transition during differential scanning calorimeter (DSC) processing as well as excellent stable properties during storage in room temperature. Its solubility and Log P exhibited similar trends towards ODV and mainly influenced by the countered pH environment. Herein, this work would be helpful for the further development of **O-19** as a novel antidepressant drug.

KEYWORDS

Compound **O-19**, DSC analysis, solubility, Log P

1. INTRODUCTION

With the development of social economics, the pace of life and work is accelerating, more and more people have suffered from various kinds of central nervous system (CNS) diseases, among which depression is one of the most common neuropsychiatric disorders affecting approximately 20% of the population at any time during their lifetime [1]. The World Health Organization (WHO) estimated that depression will become the second leading cause of long-term disability in the world by the year 2020, second only to ischemic heart disease [2, 3]. Despite a wide range of the therapeutic drug options, however, like most CNS drugs, antidepressant medication is also subject to the problems of delayed onset and high variability [4-7]. Thus, the search of enhancing drug delivery for optimizing the ideal antidepressant therapy remains an ongoing concern [8].

Venlafaxine (VEN) is a selective serotonin and norepinephrine uptake inhibitor (SNRI) without blocking muscarinic acetylcholine, histaminergic and α 1-adrenergic receptors, which was firstly marketed in US in 1994 for the treatment of major depressive disorder (MDD) [9, 10]. After oral administration, VEN is well absorbed in gastrointestinal tract and metabolized by cytochrome P450 2D6 (CYP2D6) isoenzyme in liver to produce O-desmethylvenlafaxine (ODV), the major metabolite accounting for 56% of the total metabolites of VEN. ODV exerts similar antidepressant activity compared with VEN, and possesses a much longer half-life ranging from 9 to 13 h [11]. In addition, ODV is mainly metabolized by uridine diphosphate (UDP)-glucuronosyltransferases, not CYP2D6 isoenzyme, making it less prone to be affected by genetic polymorphism than that of VEN [12, 13]. These favorable properties made ODV being marketed in US as a novel antidepressant in 2008, but unexpectedly, it failed to be approved in EU due to an unsatisfactory risk-benefit balance in both hot flushes and depression [14]. Moreover, the recommended minimum effective dose of ODV is up to 50 mg/day, it may explain the

efficacy deficiency found in some situations [15, 16]. The bioavailability of ODV in humans is approximately 80%, raising the question of whether its high-dose is caused by the low drug exposure in brain after oral administration. Therefore, in previous study, we designed and synthesized several lipophilic phenolic esters of ODV to enhance its blood-brain barrier (BBB) permeability. In pharmacokinetic evaluation, compound 1n(O-19), the piperonylic acid ester of ODV exhibited high capacity to improve the relative bioavailability of ODV both in rats and in dogs, as well as potentiating the brain uptake of ODV in rats, making it a promising prodrug candidate of ODV with elevated brain uptake [17].

In present investigation, the DSC analysis and physicochemical properties including solubility (S), lipid/water partition coefficient (Log P) coupled with solid state stability evaluation were performed to provide additional information for identification and formulation development of compound O-19.

2. MATERIALS

4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl)phenol (ODV) was from Bide Pharmatech. Co. Ltd (HPLC Purity > 98%, Shanghai, China). Other chemicals including, sodium hydroxide, potassium dihydrogen phosphate, disodium hydrogen phosphate were obtained from Civi Chemical Technology Co. Ltd. (Shanghai, China). Other solvents with analytical grade were purchased from Sino-pharm Chemical Reagent Co., Ltd. (Shanghai, China).

Differential scanning calorimeter (DSC) analysis was conducted by using a Mettler Toledo STAR® thermal analysis system, version 9.30 DSC 821® (Mettler-Toledo AG, Greifensee, Switzerland). Ultraviolet-Visible (UV-Vis) full wavelength scanning and absorbance determination were recorded by an UV-2550/UV-Vis Spectrophotometer (Shimadzu Corporation, Kyoto, Japan).

3. METHODS

3.1 DSC analysis

The DSC analysis was conducted by using a Mettler Toledo STAR® thermal analysis system with nitrogen as protective gas (100 ml/min-1) at a linear heating rate of 10°C min⁻¹. The examinations were performed in the temperature interval 30-250°C, the heating speed is 5k/min, and the sample mass range is 5-10 mg [18].

The DSC parameters: temperature interval: 30-250°C; heating rate: 10°C/min; amplitude: 0.5 or 1°C; period: 0.5 or 1 min.

3.2 Equilibrium solubility

3.2.1 Full-field wavelength scanning

The proper concentration of ODV and O-19 solution was analyzed at the wavelength of 190-600 nm, respectively. It was found that ODV has the maximum absorption at 320 nm, and the O-19 had the maximum absorption at 310 nm.

3.2.2 Preparation of standard solutions

The concentrations of ODV and O-19 stock solutions were 10 g/mL, 20 g/mL, 30 g/mL, 40 g/mL, 50 g/mL, 60 g/mL, 70 g/mL, 80 g/mL, respectively, using methanol as solvents. The absorbance of ODV was measured at 320nm and the absorbance of O-19 was measured at 310nm. With the mass concentration (Y) as the longitudinal coordinate and the absorbance (X) as the transverse coordinates, the standard curves were made respectively. The ODV regression equation was calculated to be $Y = 1.1621X - 0.025$, $R^2 = 0.9978$, and O-19 regression equation was $Y = 0.0106X + 0.0689$, $R^2 = 0.9989$.

3.2.3 Equilibrium solubility

Two sets of five different gradients of phosphate buffer solution (PBS) with pH values of 2.0, 5.0, 6.8, 7.4, and 8.0 were prepared according to the method listed in Chinese Pharmacopoeia (2015 edition), and different pH-gradient phosphate buffers were configured and adjusted with NaOH. The PBS buffer solution was transferred to test tubes with volume of 10 mL, and ODV and O-19 were sonicated at 37°C for 5 min to promoted is solution. The tubes were placed in a water bath thermostat and the temperature was maintained at 37±1°C for 12 h (130 r/min). After centrifugation (20°C, 4500 r/min, 20 min), the supernatant of the saturated solution was absorbed and filtered, after proper dilution, the absorbance was measured and the solubility was calculated [19].

3.3 Lipid-water partition coefficient

Lipid-water partition coefficient was determined according to the previously reported method with minor modifications. Prepare 50 mL of 0.5 mg/mL ODV-octanol solution and 0.5 mg/mL O-19-octanol solution with 100 mL of octanol solution saturated with water as the solvent. In both groups, accurately measure 5 mL of ODV-octanol and O-19-octanol solution into test tubes, and accurately measure 5 mL of phosphate buffer with different pH gradients. Add into two groups of test tubes and place the test tubes in a water bath. In a constant-temperature shaker, the temperature was maintained at 37±1°C for 12 hours (130r/min), centrifuged after standing (20°C, 4500 r/min, 20min) to make ODV and O-19 fully dissolved in oil and water phases. The distribution was balanced. After standing, the upper oil phase solution and the lower aqueous phase solution were taken and filtered. After being properly diluted, the absorbance was measured and the lipid-water partition coefficient (P) was calculated as follows:

$$P = C_0 / C_w$$

Where C_0 and C_w are the mass concentrations of ODV/O-19 in the oil and water phases, respectively.

4. RESULTS AND DISCUSSION

4.1 DSC analysis

DSC is an emerging technique for thermal analysis that has been widely used to measure the thermodynamic properties relating to transitions in

materials as a function of temperature and time. Modulated Differential Scanning Calorimetry (MDSC) is modification of conventional DSC that would provide more additional information for the compound of interest. Recently, MDSC has been used for the evaluation of drug stabilities [20]. As shown in Figure 5, The DSC curves of piperonylic acid (PA), ODV and O-19 were obviously different, with an endothermic peak at 234.44°C for PA and an endothermic peak at 255.86°C for ODV. However, O-19 exhibited an endothermic peak at 141.37 °C followed by an endothermic peak at 163.31°C, which might be due to the fact that the crystal transition of O-19 could be carried out during the heating process.

Figure 1: DSC thermograms for piperonylic acid (PA), ODV and O-19.

To further prove the hypothesis, DSC analysis was performed on O-19 stored for one month, two months and three months, respectively (Figure 6). There were still two endothermic peaks with similar peak value observed. It is speculated that the steady state crystal is formed by the metastable compound of O-19.

Figure 2: DSC thermograms for O-19 stored for one month, two months and three months.

Therefore, in the production and processing processes, attention should be paid to controlling the temperature at about 141°C to avoid affecting the drug efficacy and safety due to crystal transformation. If the production and processing temperature is higher than 141°C, it is necessary to separate the two crystal forms so as to avoid crystal transformation.

4.2 Equilibrium solubility

As shown in Figure 6 and 7, the solubility of ODV and O-19 varies greatly under different pH conditions ranging from 2 to 9, but the solubility of O-19 is far greater than that of ODV at different pH values. The solubilities of the two compound of interest were larger in the acidic condition, and ODV showed the maximum solubility 11.01mg/mL, while O-19 exhibited the maximum solubility 0.22 mg/mL, when the pH value was 2. As the pH increases, protons decrease and the hydroxyl groups in the solution increase, which would destroy the hydrogen bonds in the N-H, resulting in hydrophobicity.

Figure 3: Solubility of ODV in different pH buffer solution.

Figure 4: Solubility of O-19 in different pH buffer solution.

According to the selected different pH conditions as much as possible to reflect the human gastrointestinal tract at different parts of the pH, more accurately reflect the drug in the human gastrointestinal tract in different parts of the dissolution and penetration. Therefore, the increase in the pH value could reduce the solubilities of both ODV and O-19, indicating that these two drugs might be more soluble in stomach than in intestinal tract.

4.3 Lipid-water partition coefficient

The lipid-water partition coefficient (P) is an important parameter in drug delivery systems. When the P value was low ($\text{Log } P < -2$), excessive thermodynamic barrier would prevent the drug from penetrating through the lipid membrane; when the P value was high ($\text{Log } P > 3$), stronger lipophilicity will cause the drug to be difficult to pass from both sides of the membrane. Immobile water layer spreads. Therefore, in drug design, it should be considered whether it is within the optimal P value ($-1 < \text{Log } P < 2$). From Figure 9 and 10, we can see that the Log P value of ODV ranges from 0.12 to 0.95, and the Log P value of O-19 ranges from -0.02 to 1.37, which all accorded with the ideal range from absorption, indicating that these two drugs might be well absorbed in human gastrointestinal tract. Although the lipid-water partition coefficient does not fully reflect the permeability of the drug in the body, it has some guidance for predicting the distribution of the drug in the body.

Figure 5: The Log P values of ODV in different pH buffers at 37°C.

Figure 6: The Log P values of O-19 in different pH buffers at 37°C.

5. CONCLUSION

In summary, O-19, the newly synthesized prodrug of ODV has prominent properties for development. It has distinguished IR spectroscopic peaks compared with parent drug ODV and unique double peaks associated with the crystal transition during heating processing using DSC as well as excellent stable properties during storage. Its solubility and Log P showed similar trends towards ODV and mainly influenced by the countered pH environment, indicating that esterification does not alter its physical and chemical properties significantly. Its improved BBB permeability might be due to other mechanisms, such as transporter-mediated cross into the brain, which deserved to be explored further.

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