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Cocrystal formation, crystal structure, solubility and permeability studies for novel 1,2,4-thiadiazole derivative as a potent neuroprotector

Artem O. Surov[a], Tatyana V. Volkova[a], Andrei V. Churakov[b], Alexey N. Proshin[c], Irina V. Terekhova[a], German L. Perlovich[a,*]

[a] Institution of Russian Academy of Sciences, G.A. Krestov Institute of Solution Chemistry RAS, 153045 Ivanovo, Russia
[b] Institute of General and Inorganic Chemistry RAS, Leninsky Prosp. 31, 119991 Moscow, Russia
[c] Institute of Physiologically Active Compounds of Russian Academy of Sciences, 142432 Chernogolovka, Russia

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ABSTRACT

The cocrystallization approach has been applied to modify the poor solubility profile of the biologically active 1,2,4-thiadiazole derivative (**TDZ**). Extensive cocrystal screening with a library of coformers resulted in formation of a new solid form of **TDZ** with vanillic acid in a 1:1 molar ratio. The cocrystalline phase was identified and characterized by thermal and diffraction analyses including single-crystal X-ray diffraction. The energies of intermolecular interactions in the crystal were calculated by solid-state DFT and PIXEL methods. Both calculation schemes show good consistency in terms of total energy of the intermolecular interactions and suggest that the cocrystal is mainly stabilized via hydrogen bonds, which provide ca. 44% of the lattice energy. Since the cocrystal contained the hydroxybenzoic acid derivative as a coformer, the solubility profile of the cocrystal was investigated at different pHs using eutectic concentrations of the components. Furthermore, the influence of the cocrystallization on the permeability performance of the 1,2,4-thiadiazole through an artificial regenerated cellulose membrane was also evaluated. In addition, the thermodynamic functions of the cocrystal formation were estimated from the solubility of the cocrystal and the corresponding solubility of the pure compounds at various temperatures. The cocrystal formation process was found to have a relatively small value of the driving force (-5.3 kJ·mol^{-1}). The most significant contribution to the Gibbs energy was provided by the exothermic enthalpy of formation.

1. Introduction

It has been estimated that approximately 40% of the market drugs and 70% of active pharmaceutical ingredients (API) in company pipelines are poorly water-soluble (Thayer, 2010). Many of these compounds belong to class II and class IV of the biopharmaceutical classification system (BCS), making aqueous solubility and/or insufficient permeability the main limiting factors of their bioavailability (Takagi et al., 2006). A number of formulation approaches have been offered to enhance the solubility of poorly soluble drugs, including particle size reduction, development of amorphous solid dispersions, various nanoparticulate delivery systems and lipid-based formulations, etc. (Williams et al., 2016). An alternative approach to overcoming the solubility challenge without modifying the pharmacophore structure of an API is to develop new crystalline forms such as polymorphs, solvates, salts or cocrystals. Indeed, salt formation is one of the common procedures for improving the aqueous solubility of a drug and nowadays more than 50% of APIs are marketed as salts (Pudipeddi et al., 2002). This solid form, however, is limited to APIs that possess a suitable (basic or acidic) ionisable site for proton transfer and salt formation. In this case, the cocrystallization approach has great advantages as molecular cocrystals can be formed regardless of the APIs ionisable status and their formation depends on complementary functional groups in the API and coformer molecules, with hydrogen bonding or other forms of interactions between the groups (Good and Rodríguez-Hornedo, 2009; Schultheiss and Newman, 2009).

Membrane permeability along with solubility in biological fluids is one of the most important characteristics determining bioavailability during oral absorption, renal re-absorption, excretion, skin permeation, distribution and moving to the target organ (Amidon et al., 1995). It is

Abbreviations: API, active pharmaceutical ingredient; BCP, bond critical point; BCS, biopharmaceutical classification system; CCDC, Cambridge Crystallographic Data Centre; DFT, density functional theory; DSC, differential scanning calorimetry; HPLC, high-performance liquid chromatography; MWCO, molecular weight cut off; QTAIMC, quantum theory of atoms in molecules and crystals; TDZ, 1,2,4-thiadiazole; XRPD, X-ray powder diffraction

* Corresponding author.
E-mail address: glp@isc-ras.ru (G.L. Perlovich).

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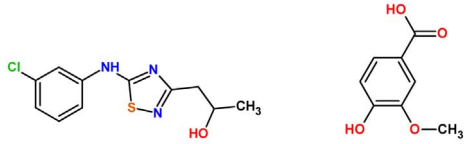
well-known that using successful, solubility-enabling formulations such as cyclodextrins (Loftsson et al., 2005), biopolymers (Baghel et al., 2016), lipids (Mu et al., 2013), surface active agents (Eros, 2005), polyols, organic acids, hydrotropes (Ahuja et al., 2007) can modify the membrane permeability of API (Dahan et al., 2010; Miller et al., 2012). We may suppose that a similar effect on drug solubility may be produced by cocrystal-based formulations. Meanwhile, this aspect is rarely considered when cocrystals with appropriate solubility and stability properties are designed. As it was reported by Miller et al. (2012) for polymeric solubility-enabling formulations and by Saikia et al. (2015) for cocrystals, the enhanced solubility of the lipophilic drug could result in modulated permeability. It means that when considering the cocrystals, the solubility–permeability interplay should be taken into account. Moreover, the cocrystal does not often produce the expected increase in drug concentration due to rapid precipitation of the native drug crystal in the dissolution medium (Alhalaweh et al., 2016).

Compounds containing a 1,2,4-thiadiazole core constitute an important class of heterocyclic compounds that exhibit different types of biological activity including anti-inflammatory, antihypertensive, antibacterial and anticonvulsant properties (Castro et al., 2006; Li et al., 2013). Furthermore, it has been confirmed that many thiadiazole-related compounds are potential drugs in the treatment of disorders of the central nervous system such as the Alzheimer's disease due to the antioxidant properties, the influence on muscarinic acetylcholine receptors (Macleod et al., 1990) and inhibition of acetylcholinesterase activity (Martinez et al., 2000). Compounds containing a 1,2,4-thiadiazole fragment also display high inhibitory activity against glycogen synthase kinase-3β and, therefore, can be used for treatment of neuropathology, disordered motor function, chronic inflammatory process, cancer and diabetes of type II (Martinez, 2004).

In our previous work, the ability of a wide range of structurally related phenyl derivatives of 1,2,4-thiadiazole to inhibit glutamate-stimulated calcium ion uptake was tested (Perlovich et al., 2012). As a result, such compounds were found to be active against the *N*-methyl-D-aspartate receptor which is responsible for the neuronal signaling processes, memory consolidation, and synaptic plasticity. One of the most potent inhibitory activities among the investigated substances was observed for the 1,2,4-thiadiazole molecule containing the chloride atom in the meta-position of the phenyl ring (1-[5-(3-Chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol) (Fig. 1). On the other hand, this compound was found to show one of lowest water solubility compared to the other 1,2,4-thiadiazole derivatives in the series, which may cause serious drawbacks in further development. The poor solubility of the selected 1,2,4-thiadiazole was modified by cocrystallization. A new solid form of the API with vanillic acid was found (Fig. 1). In this research, the cocrystal was characterized by differential scanning calorimetry, powder and single crystal X-ray diffraction. Based on crystallographic data, the energies of intermolecular interactions and crystal lattice energy of the cocrystal were evaluated by solid-state DFT and PIXEL calculation methods. Since the cocrystal contains a hydroxybenzoic acid derivative as the coformer, the cocrystal solubility profile was investigated at different pHs using eutectic concentration. Furthermore, the thermodynamic parameters of cocrystal formation process were obtained and discussed. In addition, the influence of cocrystallization on the permeability performance of the 1,2,4-thiadiazole was also investigated.



TDZ Vanillic acid

Fig. 1. Molecular structure of the studied 1,2,4-thiadiazole derivative (**TDZ**) and vanillic acid.

2. Material and methods

2.1. Compounds and solvents

The synthesis of 1-[5-(3-chloro-phenylamino)-1,2,4-thiadiazol-3-yl]-propan-2-ol (**TDZ**) was based on the method of Vivona et al. (1977) and described by us earlier (Surov et al., 2015a). The solvents and coformers were purchased from various suppliers and were used as received without further purification.

2.2. Grinding experiments

The grinding experiments were performed using a Fritsch planetary micro mill, model Pulverisette 7, in 12 ml agate grinding jars with ten 5 mm agate balls at a rate of 500 rpm for 30 min. In a typical experiment, 80 mg of the 1,2,4-thiadiazol and a coformer mixture in a 1:1 or 2:1 molar ratio were placed in a grinding jar, and 40 µl of solvent (methanol, ethanol, acetonitrile, acetone) was added with a micropipette.

2.3. Solution crystallization

In the solution crystallization experiments, 1,2,4-thiadiazole (60 mg, 0.22 mM) was dissolved with vanillic acid in the 1:1 molar ratio in acetone, methanol or acetonitrile and stirred at room temperature until a clear solution was obtained. The resulting solution was filtered into a 10 ml vial, covered by parafilm perforated with a few small holes, and allowed to evaporate slowly until a crystalline material was formed.

2.4. X-ray diffraction experiments

Single-crystal X-ray diffraction data were collected on a Bruker SMART APEX II diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å). Absorption corrections based on measurements of equivalent reflections were applied (Sheldrick, 1997). The structures were solved by direct methods and refined by full matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms (Sheldrick, 2007). All the hydrogen atoms were found from the difference Fourier map and refined isotropically. The crystallographic data for the cocrystal of **TDZ** with vanillic acid (1:1) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications under the CCDC number 1530732. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

X-ray powder diffraction (XRPD) data of the bulk materials were recorded under ambient conditions in Bragg-Brentano geometry with Bruker D8 Advance diffractometer with $CuK\alpha_1$ radiation (λ = 1.5406 Å).

2.5. DSC experiments

Thermal analysis was carried out using a PerkinElmer DSC 4000 differential scanning calorimeter with a refrigerated cooling system (USA). Approximately 1 mg of the sample was hermetically sealed in standard aluminum pan (40 µl) and scanned in a 20 ml min^{-1} nitrogen purge flow at the rate of 10 K·min^{-1}. The unit was calibrated with indium and zinc standards. The accuracy of the weighing procedure was ± 0.01 mg.

2.6. Solubility experiments

2.6.1. Solubility of pure compounds

The solubility of 1,2,4-thiadiazol and vanillic acid was measured by the shake-flask method in the hydrochloric buffer (0.1 M aqueous hydrochloric acid solution and potassium chloride) with pH 2.0 at 20.0,