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Infrared, Raman and ultraviolet with circular dichroism analysis and theoretical calculations of tedizolid

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ABSTRACT

Tedizolid is the newest antibacterial agent from the oxazolidinone class. For its identification, FT-IR (2000 −400 cm^{-1}) and Raman (2000–400 cm^{-1}) analyses were proposed. Studies of the enantiomeric purity of tedizolid were conducted based on ultraviolet–circular dichroism (UV-CD) analysis. Density functional theory (DFT) with the B3LYP hybrid functional and 6-311G(2df,2pd) basis set was used for support of the analysis of the FT-IR and Raman spectra. Theoretical methods made it possible to conduct HOMO and LUMO analysis, which was used to determine the charge transfer for two tedizolid enantiomers. Molecular electrostatic potential maps were calculated with the DFT method for both tedizolid enantiomers. The relationship between the results of *ab initio* calculations and knowledge about the chemical –biological properties of *R*- and *S*-tedizolid enantiomers is also discussed.

1. Introduction

Optically active medicinal products are often synthesized as racemates or mixtures of two enantiomers due to the high cost and technical difficulty associated with their asymmetric synthesis. However, since the report of the case of thalidomide, researchers have gradually realized that often only one of the enantiomers has the desired therapeutic activity and favourable pharmacological profile (eutomer), while the second (distomer) is inactive or even may contribute to greater toxicity [1]. Today, it is widely accepted that a pair of enantiomers should be considered as two different compounds, and therefore the authorities responsible for the registration of drugs encourage the pharmaceutical industry to register single isomers. Moreover, taking into consideration the complexity of the stereoselective synthesis, the possibility of the formation of various impurities during this process should be noted.

In terms of the biological effect of optically active pharmaceuticals, the body may interact with each enantiomer differently, metabolize them by separate pathways, and produce different pharmacological responses. The stereoselectivity of the drug can be observed at the first moment when the drug is introduced into the body and then when it is distributed into the appropriate compartment. Chirality is especially pronounced in the processes of absorption, distribution, stereoselective metabolism, and elimination of the chiral drug [2–5], which can additionally affect the pharmacokinetics, pharmacodynamics, and toxicity. Moreover, distomers may possess different carcinogenicities and teratogenicities. Therefore, with regard to optically active compounds, the US Food and Drug Administration Agency (FDA) tightened requirements for full documentation of biological and toxicological tests of new drug entities with racemate and individual enantiomers as well. In addition, the documentation should include data on the possible conversion of one isomer into the other, because optically pure pharmaceuticals may undergo racemization *in vivo*. Hence, the development of chiral separation methods is crucial for ensuring the quality, safety, and efficacy of drugs.

The analytical methods of choice, which allow separation of

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optical isomers and determination of the entire profile of impurities, are chromatographic (gas chromatography and high performance-liquid chromatography) and electrophoretic techniques [6–9]. Undoubtedly the most promising analytical technique is capillary electrophoresis (CE), which is an attractive enantioseparation technique mainly due to its high efficiency, which allows observation of small stereochemical effects of chiral selector–select and interactions that are invisible to other techniques.

However each of these techniques requires the transfer of substances into a solution. For this reason, low solubility of the drug may cause further problems with the preparation of samples for the next stage of the procedure. On the other hand, when the quality control of the drug is performed in the solid state, this procedure appears to be unnecessary. An interesting alternative of great importance in relation to analysis of enantiomers compared to separation techniques is spectroscopic methods with the participation of circular dichroism (CD), which is particularly suitable for analysis of optical isomers [10,11]. Unfortunately, there is still a need to use solvents in some spectral methods involving circular dichroism. Therefore, in the case of very slightly soluble substances, techniques that enable the realization of spectral analysis in the solid state should be recommended. Currently, there are a few literature reports dealing with the use of spectroscopic techniques in the solid state to define the optical isomers in medicinal products [12–14].

Quantum chemical calculations provide substantial support for the analysis of optically active bioactivity compounds, as evidenced by numerous reports describing the employment of such analyses for various medicinal substances [15–19]. The application of quantum chemical calculations for the selected molecules should always be considered along with the impact of environmental conditions during geometry optimization and calculations of molecular properties [20,21].

Taking into account the limitations that have been mentioned above concerning the analysis of very slightly soluble substances in the assessment of their chiral purity, as the first choice in the evaluation of the optical purity of enantiomers UV-CD analysis seem to be an appropriate approach. Further evaluation of the purity of enantiomers for substances that are very slightly soluble should be carried out in the solid state by applying appropriate and sensitive spectral techniques. Tedizolid (single *R*-isomer) is the newest antibacterial agent from the oxazolidinone class, which was approved by the FDA in 2014 and positively endorsed by the CHMP (Committee for Medicinal Products for Human Use) in 2015. Due to the oxazolidinones' spectrum of activity and therapeutic recommendations, they are considered as very important antibacterial agents with a high potential for further drug design development [22]. Tedizolid shows activity against all major pathogenic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci as well as *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Enterococcus faecalis*. Most importantly, tedizolid is active against strains possessing the Cfr methyltransferase gene responsible for staphylococcal resistance to linezolid [23]. Structure–activity relationships (SAR) for tedizolid have revealed that: (i) 2-methyl-2H-tetrazol-5-yl and pyridine-3-yl rings are responsible for interaction with peptidyltransferase centre (PTC), (ii) the 3-fluoro-phenyl ring improves antibacterial activity, (iii) 1,3-oxazolidin-2-one with 5-*R* configuration is necessary for antibacterial activity, and (iv) the hydroxymethyl group is esterified by phosphate in order to improve both the water solubility and bioavailability of the molecule (Fig. 1) [24].

The aim of this study was to obtain the spectral characteristic of tedizolid by application of FT-IR and Raman spectra and to study the enantiomeric purity of tedizolid by using UV-CD spectra. During the identification of the appropriate bands and evaluation of their intensity, analyses of FR-IR and Raman spectra were supported by quantum chemical calculations using the Becke three-parameter Lyn-Yan-Parr (B3LYP) hybrid functional with the 6-311G(2df,2pd) standard basis set. In additional to the characteristics previously determined from the spectra of tedizolid isomers, electronic properties such as the HOMO-LUMO orbitals and molecular electrostatic potentials (MEP) maps for both *R*- and *S*-tedizolid enantiomers were determined by performing tests.

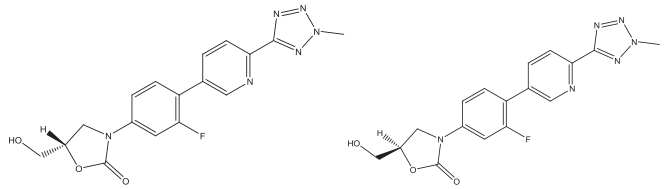

Fig. 1. Chemical structures of enantiomers of tedizolid.

2. Experimental methods

2.1. Substance for studies

Tedizolid (purity by HPLC: 98.92%; e.e.: 99.56%) and its *S*-enantiomer (purity by HPLC: 98.09%; e.e. data not available) were purchased from Shanghai Haoyuan Chemexpress Co., Ltd. (Shanghai, P.R. China). All other chemicals and solvents were obtained from Merck KGaA (Germany) and were of analytical grade. High quality pure water was prepared using an Exil SA 67120 purification system (Millipore).

2.2. Spectroscopic methods

The vibrational infrared spectra of *R*- and *S*-tedizolid enantiomers were recorded between 4000 and 100 cm^{-1} in powder, at room temperature, with an FT-IR Bruker Equinox 55 spectrometer equipped with a Bruker Hyperion 1000 microscope. Raman scattering spectra were obtained with a LabRAM HR800 spectrometer (HORIBA Jobin Yvon) with laser excitation at $\lambda_{exc} = 633$ nm (He–Ne laser). In each case, the power of the laser beam focused on the sample was less than 1 mW to avoid damaging the sample. Tedizolid enantiomers were established using a Jasco J-715 Circular Dichroism spectrometer.

2.3. Computation details

The harmonic vibrational frequencies for spectroscopic analysis (for FT-IR and Raman spectra) were carried out with density functional theory (DFT) using the B3LYP hybrid functional with the 6-311G(2df,2pd) standard basis set and its variations with diffuse basis functions [25]. The obtained frequencies for FT-IR and Raman spectra were scaled by a factor of 0.97 according to Computational Chemistry Comparison and Benchmark DataBase maintained by The National Institute of Standards and Technology of USA. Theoretical computational calculations of the optimal geometry, frontier molecular orbitals (FMOs), and molecular electrostatic potential (MEP) maps were carried out at the same level of theory for optimized structures. For the purpose of visualization, GaussView was used. In a process of geometry optimization, two different conformations of each enantiomer were taken under consideration. The conformers were presented in Fig. 2 along with their relative