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Similarity of solid state structures of *R*- and *S*-isomers of clopidogrel hydrogensulphate salt

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The present study showed, that the crystal structures of *R*-isomer and the polymorphic form 1 of clopidrogrel hydrogensulphate *S*-isomer are very similar.

Clopidogrel hydrogensulphate, which exists in two enantiomeric forms, i.e., *R*(−) and *S*(+) enantiomer, is a potent platelet anti-aggregation drug. The corresponding *R*-isomer at carbon 8 is less active and less well tolerated in pharmaceutical use (Kotar-Jordan et al. 2005).

(+)Clopidogrel hydrogensulphate salt of is known to crystallize in different polymorphic and pseudopolymorphic forms among which polymorphic forms 1 and 2 are commercially used in solid dosage forms on the market (Koradia et al. 2004).

It was proposed on the basis of crystallographic data that arrangement and conformation of organic clopidogrel moiety and inorganic hydrogensulphate moiety differ among crystalline forms of the *S*(+) isomer. The crystalline structure of form 2, which has already been resolved, is orthorhombic and less dense than the crystalline structure of form 1 which is monoclinic (Bosquet et al. 2002).

On the other hand the crystal structure of form 1 has not been resolved yet. There are also no available data in the literature for crystallization and crystal structure of the *R*-isomer.

The aim of our work was to prepare a crystalline form of the *R*- isomer of clopidogrel hydrogensulphate salt, and to evaluate and compare solid state analytical parameters of the *R*-isomer with the analytical data for polymorphic forms 1 and 2 of the *S*-isomer.

Optical rotation, melting points and melting enthalpies of two crystalline polymorphic forms of clopidogrel hydrogensulphate and *R*-isomer of clopidrogrel hydrogensulphate are shown in the Table. Optical purity of the tested samples was confirmed by measuring their specific optical rotation. Similar values for onset temperature and melting enthalpy were obtained for the *R*-isomer and the polymorphic form 1 of the *S*-isomer.

Beside the similarity of the thermal behavior of the *R*-isomer and form 1 of the *S*-isomer, FT-IR spectra and XRPD diffractograms for both samples are comparable.

The ^{13}C solid state NMR spectrum of *R*-isomer is practically identical to the spectrum of clopidogrel hydrogensulphate form 1 (Fig. 1). We can therefore conclude that the *R*-isomer and the polymorphic form 1 exhibit very similar conformation and packaging of the molecules in the crystals. ^{1}H solid state NMR spectra show only a small difference in chemical shift for hydrogen bonded acidic proton of hydrogensulphate anion, which might indicate small difference in strength of hydrogen bonding when comparing form 1 of the *S*-isomer and the *R*-isomer of clopidogrel hydrogensulphate (data not shown).

Experimental

1. Materials

Clopidogrel hydrogen sulfate form 1 and 2 were prepared by Krka, d.d., Novo mesto according to the process described Bosquet et al. 2002 using acetone as crystallization solvent.

2. Methods

2.1. Process for preparation of the crystalline form of the R-isomer of clopidogrel hydrogen sulphate

(-)-(*R*)-methyl 2-(2-chlorophenyl)2-(6,7-dihydrothieno(3,2-*c*)pyridin-5 (4*H*)-yl)acetate camphor-10-sulphonate (16.6 g) was dissolved in 66 ml of methylene chloride at room temperature with addition of 66 ml of a saturated solution of sodium hydrogen carbonate and stirred for 1 h. The layers were separated and the organic phase was additionally dried with sodium sulphate. The solvent was evaporated and 9.8 g of oily product was dissolved in 41 ml of acetone. 3.16 ml of 93.6% sulphuric acid was gradually added to the solution at 20°C and stirred for 20 h. at 20–25°C. The crystallized product was filtered off and washed with 100 ml of chilled acetone. The crystals were dried in a vacuum drier at 50°C.

2.2. X-ray powder diffraction (XRPD)

X-ray diffractograms of powder samples were obtained by a Phillips PW 1710 diffractometer (CuKα radiation, $3 \leq 2 \leq 31°$).

2.3. Solid state ^{13}C and ^{1}H nuclear magnetic resonance (NMR)

Spectra were obtained by a Varian Unity Inova 300 MHz spectrometer using 5 mm "Magic Angle" and by a Varian Inova 600 MHz NMR spectrometer using 3.2 mm "NB Double Resonance HX MAS". Larmor frequencies of proton and carbon atoms were 302.98 MHz and 76.19 MHz in NMR spectra and 599.77 MHz and 150.83 MHz on the 600 MHz NMR spectrometer. Carbon and proton chemical shifts were presented relatively to HMB (hexamethylbenzene) external standard used as a secondary reference. Rotation frequencies were 5 kHz on the 300 MHz spectrometer, and 20 kHz during ^{1}H measurements and 10 kHz during ^{13}C measurements on the 600 MHz NMR spectrometer.

2.4. FT-IR spectroscopy

Infrared spectra in KBr pellets were recorded within the wave number range of 4000–400 cm^{-1} with a Perkin-Elmer FTIR spectrometer 1720X at resolution 4 cm^{-1}.

2.5. Thermal analysis

DSC was performed by Mettler DSC 822e (dynamic N_2 atmosphere, heating rate 10 °C/min). Thermal effects were evaluated using Pyris software.

Table: Optical rotation ($[\alpha_D^{20}]$), melting points(T_{onst}) and enthalpies (H) for tested samples of clopidogrel hydrogensulphate

Sample	$[\alpha_D^{20}]$	DSC; T_{onst}/ H	DSC(literature data)[3]; T_{onst}/ H	XRPD/IR
(+)-Enantiomer (*S*-isomer) form 1	+56.17°	183.0 °C/83 J/g	181.2 °C/77 J/g	Clopidogrel hydrogensulphate form 1
(+)-Enantiomer (*S*-isomer) form 2	+56.26°	179.7 °C/88.1 J/g	176.0 °C/87 J/g	Clopidogrel hydrogensulphate form 2
(−)-Enantiomer (*R*-isomer)	−55.40°	182.0 °C/78.6 J/g	–	Clopidogrel hydrogensulphate form 1

[3] literature data (Bosquet et al. 2002)

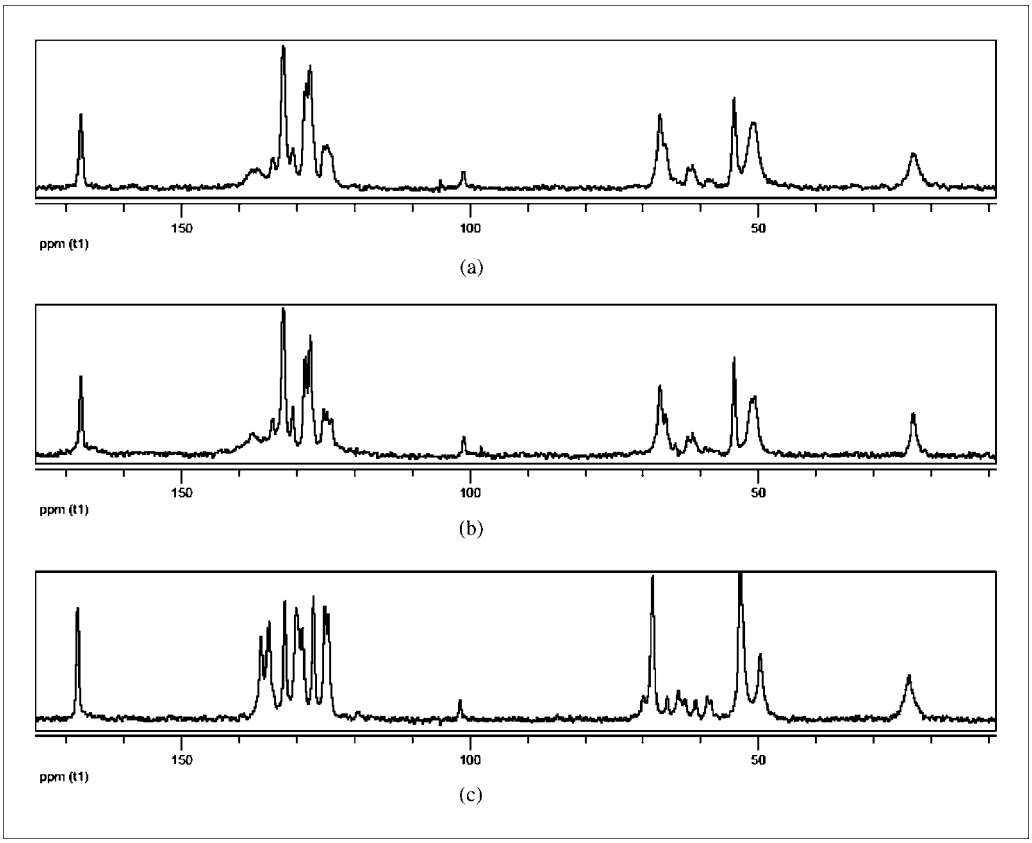

Fig. 1: Comparison of ^{13}C solid state NMR spectra of (a) clopidogrel hydrogensulphate Form 1, (b) R isomer of clopidogrel hydrogensulphate and (c) clopidogrel hydrogensulphate Form 2

2.6. Optical rotation

$\left[\alpha_D^{20}\right]$ measurements were performed on polarimeter Rudolph Research Analytical, model Autopol V automatic polarimeter (C = 10 mg/ml; cuivete = 100 mm; T = 20°C).

From the results we can conclude that the *R*-isomer of clopidogrel hydrogensulphate exhibits very similar conformation and packaging in the crystals as the polymorphic form 1 of clopidogrel hydrogensulphate *S*-isomer.

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