Stability of amorphous tadalafil in Soluplus matrix studied using 1H-NMR techniques and BPP model

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Introduction

We present the results of microheterogeneous samples, which are solid dispersions of hydrophobic drug - tadalafil (TD) in a matrix of an amphiphilic polymer. This polymer is a derivative of vinylpyrrolidone of the trade name Soluplus (SOL, BASF, Germany). Solid dispersions (1:1) were prepared by milling (M). Based on published experimental results [1-3], T1 relaxation time was determined using ^{1}H-NMR spectroscopy. The measurements were performed in a function of temperature with the aim to study the molecular dynamics of the system.

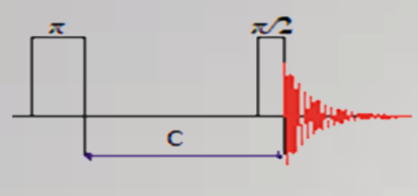
Methods

Hydration of Samples

After dehydration over silica gel (72 h), the samples were hydrated in a desiccator over a surface of distilled water (RH=100%) at room temperature. Then, to determine dry mass of the samples, they were dried at 70 °C for 72 h. Samples of dry, mildly-hydrated (15%), and hydrated (30%) complex where measured.

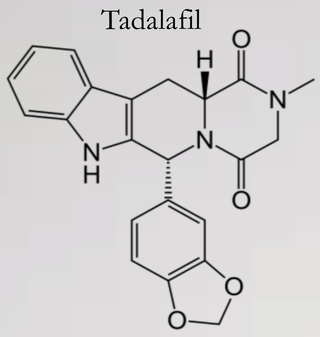
NMR spectra

^{1}H-NMR Relaxation Spectroscopy was used to obtain T_1 relaxation times in function of temperature in range from 295K to 210K with 5K interval. ^{1}H-NMR spectra were acquired using a Bruker Avance III 300 spectrometer (Bruker Biospin), operating at the resonance frequency 300 MHz for protons (at B_0 = 7 T) with a transmitter power of 400 W ($\pi/2$ = 1.94 µs, dead time 7.5 µs, repetition time 5 s).



Pulse sequence

Tadalafil



^{1}H-NMR Spectra

A superposition of two Gaussian functions for the solid matrix, and a Lorentz function for the liquid fraction, were fitted to the results of the frequency domain measurements.

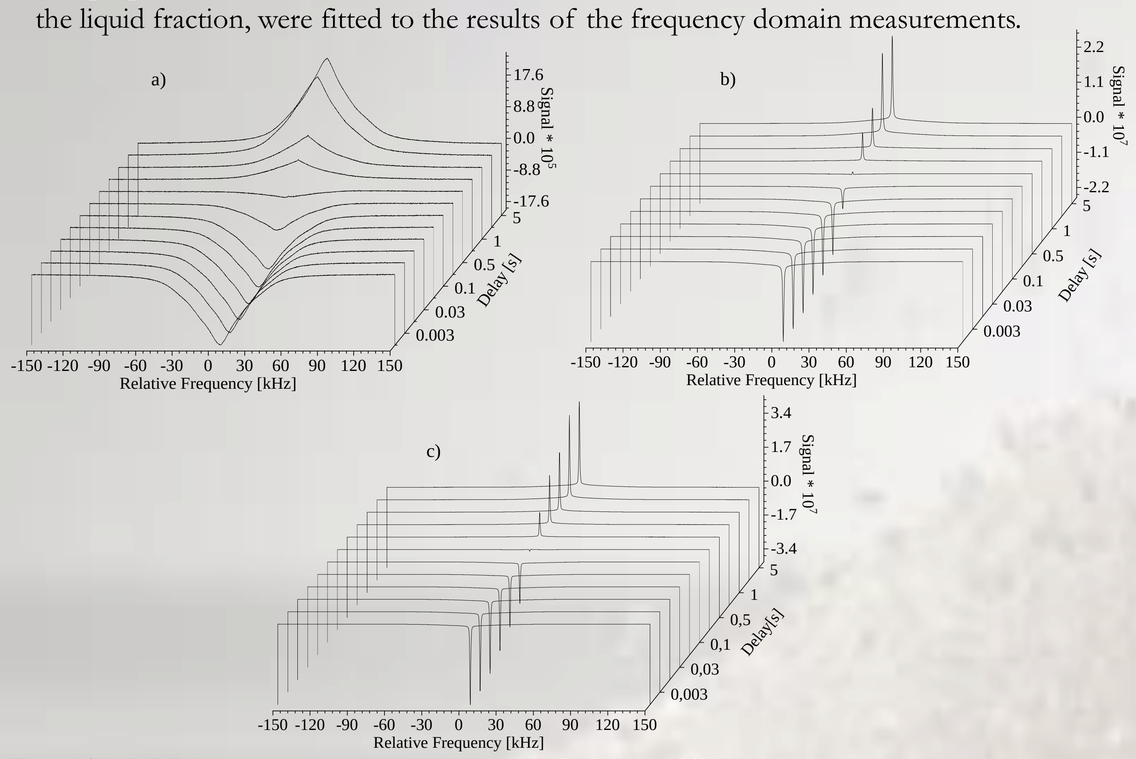


Figure 1. ^{1}H-NMR Relaxation spectroscopy spectra of dispersion constants in 0.5TD_M and with hydration levels (a) $\Delta m/m_0$ = 0, (b) $\Delta m/m_0$ = 0.15, (c) $\Delta m/m_0$ = 0.3; recorded at 275 K.

$$G(\nu) = \frac{A_{S1}}{\sqrt{\pi ln2}\Delta\nu_{S1}} exp\left[-2 * \left(\frac{\nu-\nu_{S1}}{\sqrt{2ln2}\Delta\nu_{S1}}\right)^2\right] + \frac{A_{S2}}{\sqrt{\pi ln2}\Delta\nu_{S2}} exp\left[-2 * \left(\frac{\nu-\nu_{S2}}{\sqrt{2ln2}\Delta\nu_{S2}}\right)^2\right] + \frac{2A_{L1}}{\pi}\left[\frac{\Delta\nu_{L1}}{4*(\nu-\nu_{L1})^2+\Delta\nu_{L1}^2}\right]$$

For the solid dispersion of tadalafil in Soluplus, the half-width of both solid fractions is stable at about 55 kHz and at 15 kHz. For the liquid fraction, the sum of the fractions was fitted, in contrast to the results obtained using the single-pulse method [1,2].

After ploting the areas together in function of time delay between impulses. The magnetization recovery of every fraction and T_1 relaxation time were identified in the sample.

A modified Bloembergen, Purcell and Pound model (BPP model) was fitted to the obtained T_1 spin-lattice relaxation time dependence for protons as a function of temperature to determine the activation energy, the average distance between spins, and the temperature of the relaxation time minimum.

$$\frac{1}{T_1} = \frac{3}{10}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma^4\hbar^2}{r^6}\left(\frac{\tau_C}{1+\omega^2\tau_C^2} + \frac{2\tau_C}{1+4\omega^2\tau_C^2}\right)$$

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For the dry sample of 0.5TD_M temperature dependency of T_1 relaxation time where observed for both solid fractions showed below.

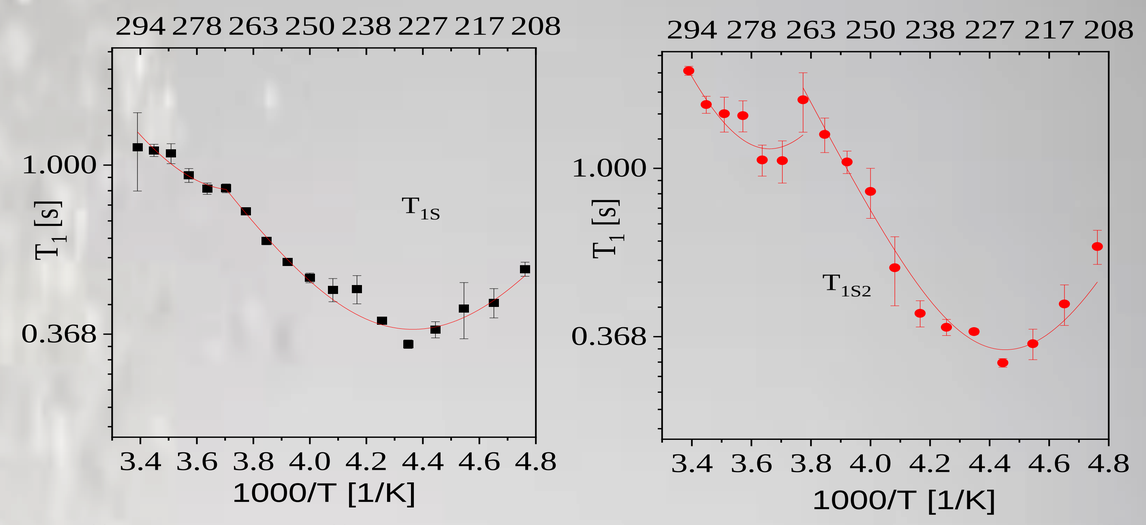


Figure 2. Temperature dependence of T_1 spin-lattice relaxation times for 1st (a) and 2nd (b) protons of the solid fractions of dry 0.5TD_M.

T_{1s}				T_{1s2}			
E_{a1} (275K)	r_1 (275K)	E_{a2} (230K)	r_2 (230K)	E_{a1} (275K)	r_1 (275K)	E_{a2} (225K)	r_2 (225K)
22.4 ± 6.3 kJ/mol	2.12 ± 0.01 Å	19.4 ± 0.7 kJ/mol	1.91 ± 0.01 Å	33.7 ± 7.5 kJ/mol	2.03 ± 0.02 Å	28.3 ± 2.1 kJ/mol	1.87 ± 0.01 Å

For sample hydrated up to 15% of dry mass averaging of relaxation times for all identified fractions were observed.

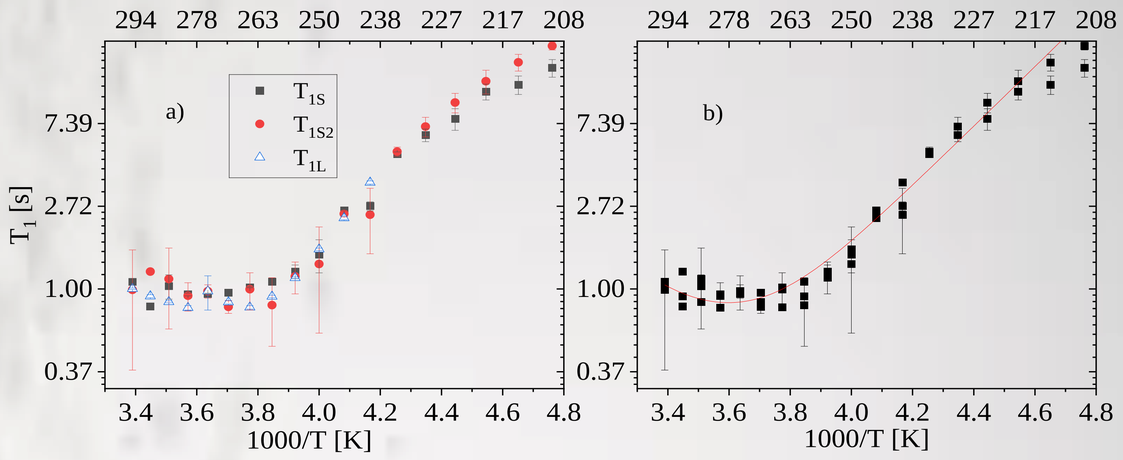
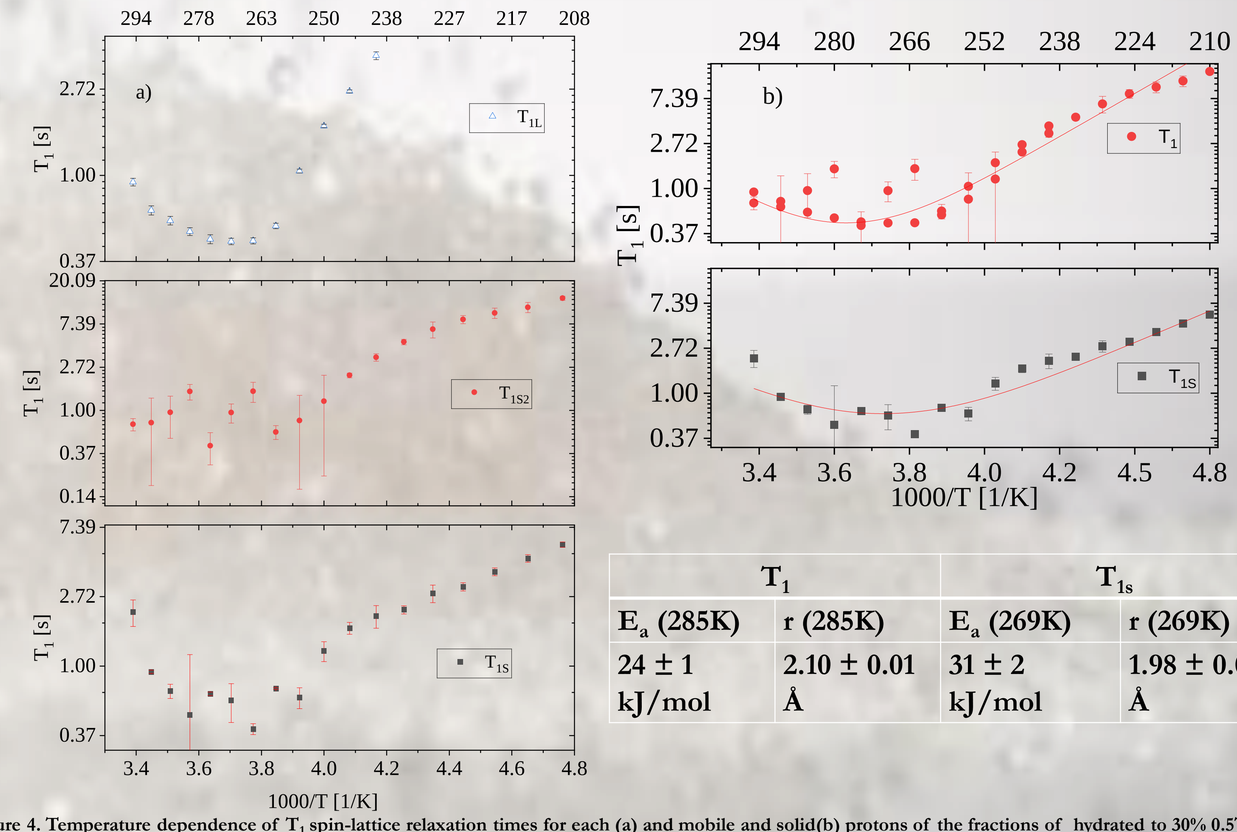


Figure 3. Temperature dependence of T_1 spin-lattice relaxation times for each (a) and sum (b) protons of the fractions of hydrated to 15% 0.5TD_M.

T_1	E_a (278K)	30 ± 1 kJ/mol	r (278K)	2.18 ± 0.03 Å



T_1		T_{1s}	
E_a (285K)	r (285K)	E_a (269K)	r (269K)
24 ± 1 kJ/mol	2.10 ± 0.01 Å	31 ± 2 kJ/mol	1.98 ± 0.01 Å

Figure 4. Temperature dependence of T_1 spin-lattice relaxation times for each (a) and mobile and solid(b) protons of the fractions of hydrated to 30% 0.5TD_M.

Conclusions

- ^{1}H-NMR spectroscopy is an effective method for determining the nature of the hydration level of a microheterogeneous system. It can resolve whether a water-soluble solid fraction adsorbed from the gas phase is present in the system. The absence of a water vapour soluble solid fraction was demonstrated using Soluplus tadalafil dispersion constants as an example.
- The temperature dependence of the spin-crosslink relaxation times for the dehydrated solid dispersion of tadalafil in Soluplus indicates an indirect spin exchange regime (two different solid components) and in both cases is effectively described by the Bloembergen-Purcell-Pound (BPP) model with a minimum T_1 value at 230 K. Hydration of the solid dispersion of tadalafil in Soluplus changes the nature of the spin exchange to a fast exchange regime. This proves that water is largely responsible for the efficiency of the spin-network relaxation process.
- The activation energy of molecular motions, determined from the BPP model (Bloembergen, Purcell and Pound model), corresponds to the energy of hydrogen bonding (E_a = 19 - 35 kJ·mol^{-1}).
- Determined on the basis of the BPP model, the distance between a pair of relaxing protons (r), corresponds to the hydrogen bonds of medium strength and is about 2 Å.

1. P. Nowak, A. Krupa, **K. Kubat**, et all., *Water vapour sorption in tadalafil-Soluplus co-milled amorphous solid dispersions*, Powder Technology 346, 2019, 383-384
2. K. Kubat, A. Krupa, W. Brniak, A. Węgrzyn, D. Majda, A. Bogdał, H. Harańczyk, *Data regarding particle size distribution, thermal properties and gaseous phase hydration of co-milled solid dispersions composed of tadalafil and Soluplus*, Data in Brief, August 2022, Volume 43
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