Nuclear Magnetic Resonance Investigation of the Interaction of Water Vapor with Sildenafil Citrate in the Solid State

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Received 3 August 2004; revised 7 October 2004; accepted 8 October 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20271

ABSTRACT: Solid-state carbon-13 (^{13}C) and nitrogen-15 (^{15}N) nuclear magnetic resonance (NMR) have been used to investigate how water interacts with sildenafil citrate. When the humidity is altered, the water concentration in the solid compound changes in a reversible manner. The proportion of occupied sites depends on the humidity, but the water concentration never reaches a rational (e.g., 1:1) stoichiometric ratio to form a true hydrate. The NMR spectra were obtained under several humidity-controlled conditions to determine what changes occur as the water content is varied and where the water is located in the crystal structure. Only one set of ^{15}N and ^{13}C signals is observed for each humidity level. This shows that water incorporated into the crystal lattice of sildenafil citrate is very mobile and exchanges rapidly on the NMR time scale between various sites. The ^{13}C data are consistent with formation of a hydrogen bond between a water molecule and one carbonyl of the citrate anion. The spectra also show that the water content affects the environment (perhaps influencing the average conformation) of the propyl group. Additionally, ^{15}N dipolar dephasing experiments show that the sildenafil molecule is only protonated in the piperazine ring. The work is supported by solution-state NMR. J Pharm Sci 94:516–523, 2005

Keywords: solid state NMR; moisture sorption; dehydration; crystal structure; ^{13}C NMR; ^{15}N NMR; sildenafil citrate; Viagra™

INTRODUCTION

Understanding the solid-state characteristics of drug substances is vital for the pharmaceutical industry. In particular, ingress of water into a drug or a formulated product can have important consequences for handling and storage, so methods for studying such phenomena are needed. Cross-polarization magic-angle spinning (CPMAS) nuclear magnetic resonance (NMR) is a highly useful technique for obtaining qualitative and quantitative information about interactions in the solid state. In this article, we describe the concerted use of carbon-13 (^{13}C) and nitrogen-15 (^{15}N) CPMAS NMR backed up by solution-state NMR, to provide insights into the interaction (at the molecular level) of water with solid sildenafil citrate (shown in Scheme 1), which is the active component of Viagra™.

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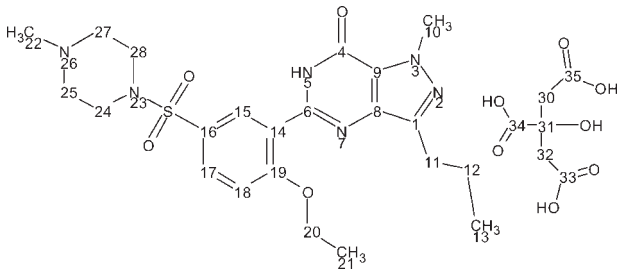
Journal of Pharmaceutical Sciences, Vol. 94, 516–523 (2005)



Scheme 1.

Sildenafil citrate is a monobasic salt, with the citrate anion deprotonated at C34, according to its pK_a.[1] Its structure without the acid-base proton transfer is shown, together with the numbering scheme of the atoms, in Scheme 1. Similarly to many organic solids, sildenafil citrate takes up water reversibly on exposure to high humidity. Dynamic Vapour Sorption measurements show that 0.78 moles of water are associated with solid sildenafil citrate at 30°C/90% relative humidity (RH). Powder X-ray diffraction data show no significant differences between samples equilibrated under ambient conditions (ca. 45% RH) and samples equilibrated at 0 or 90% RH. The material does not form a stoichiometric hydrate on exposure to 90% RH.

A second point of interest relates to the acid/base interaction. It is desirable to know whether the sildenafil moiety is protonated at both N2 on the pyrazole ring and N26 in the piperazine ring, or solely at N26. This question is addressed herein by ^{15}N CPMAS NMR, using the dipolar dephasing technique. Interest also attaches to the second-order splitting of some ^{13}C CPMAS signals arising from residual dipolar coupling to the quadrupolar ^{14}N nucleus. This interaction is not fully averaged by MAS (see the review by Harris and Olivieri[2]).

EXPERIMENTAL

A ^{13}C-{^{1}H} NMR spectrum of sildenafil citrate was acquired in DMSO-d_6 (Fluorochem 100%) using a Varian Inova 500 spectrometer, operating at 125.69 MHz with a ^{1}H decoupling frequency of 499.83 MHz, and equipped with a 3-mm PFG direct-detection X-{^{1}H} tuneable broad-band probe. The sample concentration was 80 mg mL^{-1} and the data were acquired at 303 K. A spectral width of 30019 Hz (239 ppm) was used and the spectrum was referenced to the signal for tetramethylsilane (TMS) via that of dimethyl sulfoxide (DMSO) at 39.5 ppm.

A two-dimensional (2D) ^{1}H-^{15}N GHMBC (Gradient selected Heteronuclear Multiple Bond Correlation)[3] spectrum was also acquired in DMSO-d_6 (Fluorochem 100%) on a different Varian Inova 500 spectrometer, operating at 499.96 MHz for ^{1}H and equipped with a 5-mm PFG inverse-detection ^{1}H-{X} tuneable broad-band probe, tuned for ^{15}N at 50.73 MHz. The sample concentration was 91 mg mL^{-1} and data were acquired at 303 K. The spectra were obtained using 1D spectral widths of 7017.5 Hz (14 ppm) for ^{1}H and 25,000 Hz (493 ppm) for ^{15}N, with 4096 points in t2, 128 increments in t1, and 196 transients per increment. A final data matrix of 4 K × 1 K points was obtained after processing. The free induction decays were acquired in absolute value mode and transformed using p-type selection, with shifted Gaussian weighting in f2 (gf = 0.086, gfs = 0.075) and shifted sine-bell weighting in f1 (sb1 = 0.004, sbs1 = 0.001). The 3 z-gradient pulses had durations of 2 ms each and approximate strengths of 10, 10, and 2 G cm^{-1}.

Four 300-mg samples of microcrystalline (powdered) sildenafil citrate were prepared for solid-state NMR analysis as follows. One sample was used without further preparation; two samples were hydrated over a saturated solution of lithium sulfate (88% RH[4]) in a desiccator at ca. 21°C for 3.5 days and 7 days, respectively. The fourth sample was dehydrated in a desiccator over phosphorus pentoxide for 7 days (0% RH).

Solid-state ^{13}C CPMAS and ^{15}N CPMAS data were acquired on a Varian UNITY*plus* NMR spectrometer operating at 299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C, and 30.41 MHz for ^{15}N, using a Doty Scientific MAS probe with a 7-mm o.d. rotor. Solid-state ^{15}N CPMAS data were also obtained on a Chemagnetics CMX200 MHz NMR spectrometer operating at 200 MHz for ^{1}H and 20.28 MHz for ^{15}N, using an MAS probe with a 7.5-mm o.d. rotor. For the dipolar-dephasing pulse sequence,[5] a dephasing time of 100 μs was used.

The ^{13}C CPMAS spectra for the four samples were acquired at 75.43 MHz using the flip-back technique[6] with a spectral width of 30,008 Hz (398 ppm), 3584 data points, recycle delay 5 s, contact time 1 ms, 300–600 transients, acquisition time 0.06 s, and spin rate 4800–4900 Hz. The spectra were transformed with 32 K data points, without apodization. The spectra were referenced by replacement to TMS via the spectrum of adamantane (high-frequency signal at $\delta_C = 38.4$ ppm).