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Spectroscopic studies of solid-state forms of donepezil free base and salt forms with various salicylic acids

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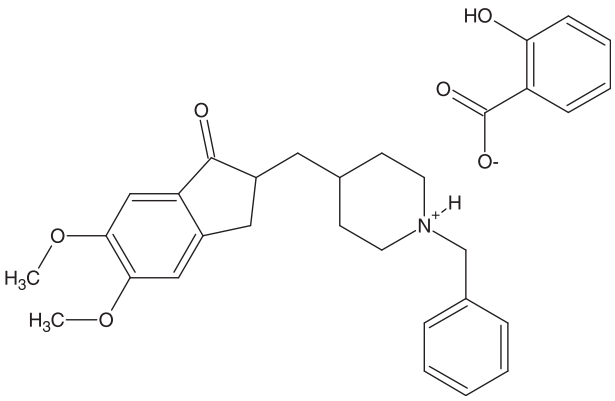
HIGHLIGHTS

- Non-solvated crystalline salts were formed by donepezil with salicylic or 4-methylsalicylic acids.
- Solvated crystalline salts were formed by donepezil salts with 3-methylsalicylic and 5-methylsalicylic acids.
- Solid-state fluorescence from non-solvated donepezil salts came from the salicylate fluorophore.
- Desolvation of solvated donepezil salts yielded glassy solids exhibiting strong green fluorescence.

GRAPHICAL ABSTRACT



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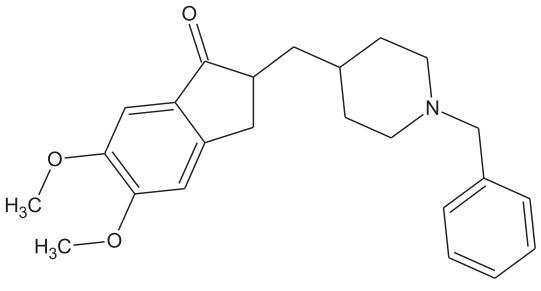
ABSTRACT

The polymorphic forms of donepezil free base have been studied using X-ray powder diffraction, Fourier transform infrared absorption spectroscopy, and differential scanning calorimetry. None of the free base crystal forms was observed to exhibit detectable fluorescence in the solid state under ambient conditions. Crystalline salt products were obtained by the reaction of donepezil with salicylic and methyl-substituted salicylic acids, with the salicylate and 4-methylsalicylate salts being obtained as non-solvated products, and the 3-methylsalicylate and 5-methylsalicylate salts being obtained as methanol solvated products. The intensity of solid-state fluorescence from donepezil salicylate and donepezil 4-methylsalicylate was found to be reduced relative to the fluorescence intensity of the corresponding free acids, while the solid-state fluorescence intensity of donepezil 3-methylsalicylate methanolate and donepezil 5-methylsalicylate methanolate was greatly increased relative to the fluorescence intensity of the corresponding free acids. Desolvation of the solvated salt products led to formation of glassy solids that exhibited strong green fluorescence.

1. Introduction

The hydrochloride salt of donepezil [(*R*,*S*)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one]:



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has been approved for use in the treatment of mild to moderate Alzheimer's disease [1], and has been shown to inhibit acetylcholinesterase activity in human erythrocytes and increase extracellular acetylcholine levels in the cerebral cortex and hippocampus of the rat [2]. Donepezil free base is characterized by unacceptably low aqueous solubility, but the hydrochloride salt has been reported to have a water solubility of 55 mg/mL at 25 °C [3].

When performed in conjunction with crystallographic investigation, solid-state spectroscopic studies are now generally accepted as being able to provide important information regarding the properties of polymorphic systems [4–6], as long as the spectroscopic properties of the molecule are affected by differences in crystal structures. The synergistic use of solid-state infrared absorption, Raman, and nuclear magnetic resonance spectroscopies has been demonstrated in numerous works, and in several studies solid-state fluorescence spectroscopy has been shown able to yield supporting structural information for substances exhibiting luminescence in the solid state [7–10].

In the present work, solid-state fluorescence spectroscopy has been used as part of an overall characterization study of the polymorphic forms of donepezil free base, and several donepezil salts with various salicylic acids. While donepezil free base was not fluorescent in the solid state, its protonation through salt formation yielded a wide range of interesting photophysical behavior. Differences in solid-state fluorescence were observed between solvated and non-solvated salt products, and drastic differences in photophysics were observed between crystalline and amorphous substances.

2. Materials and methods

2.1. Materials

The three polymorphic forms of donepezil free base were generously provided by Dr. Reddy's Laboratories, while 2-hydroxybenzoic acid (salicylic acid), 3-methylsalicylic acid, 4-methylsalicylic acid, and 5-methylsalicylic acid were purchased from Aldrich Chemicals (Milwaukee, WI). Salts containing these acidic coformers were prepared by dissolving equimolar amounts of donepezil and acid in methanol, and allowing the solution to evaporate to dryness. The spontaneously crystallized yields were ground to a fine powder, and characterized without further processing.

2.2. Methods

X-ray powder diffraction (XRPD) patterns were obtained using a Rigaku MiniFlex powder diffraction system, equipped with a horizontal goniometer in the $\theta/2\theta$ mode. The X-ray source was nickel-filtered K-α emission of copper (1.54056 Å). Samples were packed into an aluminum holder using a back-fill procedure, and were scanned over the range of 50–6° 2θ, at a scan rate of 0.5° 2θ/min. Using a data acquisition rate of 1 point per second, the scanning parameters equate to a step size of 0.0084° 2θ. Calibration of the diffractometer system was effected using purified talc as a reference material.

Fourier-transform infrared absorption (FTIR) spectra were obtained at a resolution of 4 cm^{-1} using a Shimadzu model 8400S spectrometer, with each spectrum being obtained as the average of 40 individual spectra. The data were acquired using the attenuated total reflectance (ATR) sampling mode, where the samples were clamped against the ZnSe crystal of a Pike MIRacle™ single reflection horizontal ATR sampling accessory.

Measurements of differential scanning calorimetry (DSC) were obtained on a TA Instruments 2910 thermal analysis system. Samples of approximately 1–2 mg were accurately weighed into an aluminum DSC pan, and then covered with an aluminum lid that was inverted and pressed down so as to tightly contain the powder between the top and bottom aluminum faces of the lid and pan. The samples were then heated over the temperature range of 20–200 °C, at a heating rate of 10 °C/min.

Measurements of total volatile content were made using an Ohaus model MB45 system. The samples were heated isothermally at a temperature of 100 °C for a period of 10 min, whereupon the tested samples were found to have reached constant weight loss.

Fluorescence spectra of the solid samples were obtained on a spectrometer where the appropriate excitation energy of a 250 W xenon arc lamp was isolated by using a combination of glass and solution filters [11]. Approximately 500 mg of sample was packed into a 5-mm glass NMR tube, which was irradiated using front-face excitation. The resulting fluorescence was analyzed by a 0.5 m monochromator (Spex model 1870), having a grating blazed at 500 nm and ruled at 1200 g/mm. The dispersion of this monochromator was 1.2 nm/mm slit width, so with the input and output slits set at 0.5 mm, the resolution of the spectra was 0.8 nm and the reported wavelength values were therefore rounded to the nearest 0.5 nm. The fluorescence was detected by an end-on photomultiplier tube (Thorn EMI type 9558QB having S-20 response).

3. Donepezil free base

The XRPD patterns of the three studied polymorphs of donepezil free base (Forms A, B, and C) are shown in Fig. 1, and these patterns were found to be completely equivalent with those disclosed in a United States patent [12]. The existence of the polymorphism disclosed in this patent is therefore confirmed, as all three diffraction patterns are sufficiently distinctive so as to confirm the existence of different crystals merely by inspection.

DSC thermograms obtained for the three polymorphic forms of donepezil free base are shown in Fig. 2. The melting endothermic transitions of Forms A, B, and C were found to be similar, an observation also disclosed in a US patent [13]. The temperature maximum observed in the DSC thermogram of Form-A was found to be 97.3 °C (enthalpy of fusion equal to 67 J/g), that of Form-B was 96.6 °C (enthalpy of fusion equal to 75 J/g), and that of Form-C was found to be 94.4 °C (enthalpy of fusion equal to 81 J/g). The baselines were all very flat, and did not contain any evidence for a phase transition. The trend in fusion enthalpies indicated that the order of stability of these polymorphic forms

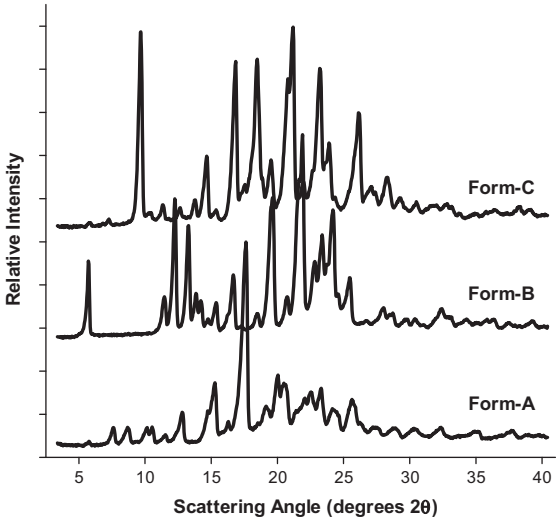

Fig. 1. X-ray powder diffraction patterns of the polymorphic forms of donepezil free base, Form-A, Form-B, and Form-C.