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Nanostructured products of the drug theophylline caused by charge transfer interactions and a binary solvent system: Morphology and nanometry

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ABSTRACT

The chemistry of the charge transfer (CT) or proton transfer (PT) interactions of drugs has received considerable attention in the chemistry, biology, pharmacology and medicine. The current study focused on the drug theophylline (TP) at the nanoscale. CT or PT nanoparticles of the drug TP with various organic acceptors were obtained by the slow evaporation of methanol–dichloromethane (1:1) as the binary solvent system. The structure and morphology of the nanoparticles were characterized by physicochemical and spectroscopic techniques, such as UV–visible, IR, ^{1}H NMR and ^{13}C NMR spectroscopies; XRD; SEM; TEM; and elemental and thermal analyses. Notably, it has been found that the complexation of TP with an organic acceptor leads to highly organized nanoparticles with a main diameter in the range of 6–13 nm.

1. Introduction

The study of nanostructured materials has become a popular area of research because of their unique physical and chemical properties. Furthermore, charge-transfer (CT), proton-transfer (PT) and H-bonding interactions between either drugs or biological compounds and small organic or inorganic molecular acceptors have attracted considerable interest because of their unique physical and chemical properties and wide range of applications [1–9]. The chemistry of these interactions is an important topic in the pharmacology, chemistry, biology and medicine. During the last decade, considerable efforts have focused on the interactions between drugs and acceptors both in the solid state and in solution. Such interactions play crucial roles in many processes; therefore, understanding these interactions is important for understanding the drug–receptor binding and the drug's mechanism of action as well as obtaining quantitative estimates of the drugs [10–18]. To investigate these roles more fully, the physical and chemical properties of the drug–acceptor complexes can be enhanced if the complexes are prepared on the nanoscale, and the use of a binary solvent system can help to achieve this goal. Binary solvent systems have been found to be more effective than single solvent systems in the preparation of particles with specific structures and particle size distributions [19]. For several years, we have investigated the synthesis, characterization and application of various CT and PT interactions [20–50]. As part of our continuing interest in this field, in this work, we sought to obtain nanoscale CT or PT complexes containing the drug theophylline (TP) using a binary organic solvent system. 1,3-Dimethyl-7*H*-purine-2,6-dione (TP, or 1,3-dimethylxanthine) is a naturally occurring alkaloid [51] that has a stimulating effect on respiration. Its structure is shown in Fig. 1S. This drug is used widely as a bronchodilator and respiratory drug in the treatment of infant apnea, the asthmatic acute phase in children, symptoms associated with acute and chronic asthmatic conditions, bronchospasm, chronic obstructive pulmonary disease and emphysema in adults [52–54].

The current study focused on the following objectives:

(i) Synthesizing CT or PT nanoparticles of TP with different organic acceptors (i.e., PA, DNBA, CLA and CHL).
(ii) Verifying the complexation stoichiometry using CHN elemental analysis and spectrophotometric titrations.
(iii) Calculating the formation constant (K), molar extinction coefficient (ε) and other spectroscopic data using the Benesi–Hildebrand equations.
(iv) Characterizing the nanoparticles based on spectral (UV–vis, IR, ^{1}H and ^{13}C NMR) and elemental data.
(v) Obtaining the thermal properties using TG technique.
(vi) Determining the kinetic–thermodynamic parameters (i.e., E^{*}, A, ΔS^{*}, ΔH^{*} and ΔG^{*}) using the Coats–Redfern and Horowitz–Metzger equations.

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(vii) Observing and differentiating the microstructures of these nanoparticles using X-ray diffraction (XRD) and scanning electron microscope (SEM) techniques.
(viii) Proving the nanometry using transmission electron microscopy (TEM).

2. Experiment and calculations

2.1. Chemicals and solutions

All of the chemicals used were of analytical grade and were used as purchased. Theophylline (TP; $C_7H_8N_4O_2$; 180.164) was supplied by Sigma-Aldrich Chemical Co. (USA) with a stated purity of greater than 99% and was used without further purification. The organic acceptors picric acid (PA; $C_6H_3N_3O_7$; 229.10), 3,5-dinitrobenzoic acid (DNBA; $C_7H_4O_6N_2$; 212.12), chloranilic acid (CLA; $C_6H_2Cl_2O_4$; 208.98) and chloranil (CHL; $C_6Cl_4O_2$; 245.88) (Fig. 1S) (in each case, purity > 99.9%) were purchased from Merck (Darmstadt, Germany) and were used without modification. HPLC-grade methanol and dichloromethane were also purchased from Merck (Darmstadt, Germany). Standard stock solutions of the drug and acceptors at a concentration of 5.0×10^{-3} M were freshly prepared prior to each series of measurements by dissolving precisely weighed quantities in a 100 mL volumetric flask. The stock solutions were protected from light. Solutions for spectroscopic measurements were prepared by mixing appropriate volumes of the drug and acceptor stock solutions with the solvent immediately prior to recording the spectra.

2.2. Physicochemical measurements

2.2.1. CHN analysis

To ascertain the constituents, purity and compositions of the synthesized complexes, the carbon, hydrogen and nitrogen contents were analyzed with a Perkin-Elmer 2400 series CHN microanalyzer (USA).

2.2.2. UV–vis spectra

The UV–vis spectra were recorded in methanol–dichloromethane over a wavelength range of 200–800 nm using a Perkin-Elmer Lambda 25 UV/vis double-beam spectrophotometer with quartz cells. The path length of the cells was 1.0 cm.

2.2.3. IR spectra

The infrared (IR) spectra of the solid products (as KBr discs) were acquired at room temperature using a Shimadzu FT-IR spectrophotometer (Japan) over the range of 4000–400 cm^{-1} with 30 scans at a 2 cm^{-1} resolution.

2.2.4. ^1H and ^{13}C spectra

^1H and ^{13}C NMR spectra were collected on a Bruker DRX-250 spectrometer operating at 600 MHz. The measurements were performed at ambient temperature using DMSO-d_6 (dimethylsulfoxide, d_6) as the solvent and TMS (tetramethylsilane) as the internal reference.

2.2.5. Thermal analyses

Thermogravimetric (TG) analyses were performed using a Shimadzu TGA-50H thermal analyzer (Japan) with standard platinum TG pans. The measurements were conducted at a constant heating rate of 10 °C/min over the temperature range of 25–600 °C in a nitrogen atmosphere using alumina powder as the reference material.

2.2.6. XRD analysis

The X-ray diffraction (XRD) profiles were obtained using a PANalytical X'Pert PRO X-ray powder diffractometer. The instrument was equipped with a Ge(III) secondary monochromator, and Cu $K\alpha_1$ was employed as the radiation source, with a wavelength of 0.154056 nm. The samples were ground to a fine powder, spread over 1 cm^2, and then placed in a beam of monochromatic X-rays. The samples were scanned with 2θ between 5° and 90°.

2.2.7. SEM analysis

The microstructure and morphology were analyzed by a scanning electron microscope (SEM, Quanta FEG 250 instrument). The instrument was operated at an accelerating voltage of 20 kV.

2.2.8. TEM analysis

The particle size was analyzed by a transmission electron microscope (TEM, JEOL JEM-1200 EX II, Japan). The instrument was operated at an accelerating voltage of 60–70 kV.

2.3. Nanoparticle syntheses

A simple synthetic protocol has been used for the preparation of nanostructured CT or PT complexes of TP. A typical procedure for the preparation is briefly described as follows. First, 2 mmol of TP in a methanol–dichloromethane binary solvent system (20 mL) was added to 20 mL of a solution containing 2 mmol of the acceptor (either PA, DNBA, CLA or CHL) in the same solvent system. The resulting mixture was stirred at room temperature for approximately half an hour. A change in color occurred, and the solution was allowed to evaporate slowly at room temperature, resulting in the precipitation of the solid complexes. The formed products were isolated, filtered and further purified using the solvent system and a recrystallization process to obtain the pure products. The products were then collected and dried in vacuo for 48 h. The nanoparticles were characterized by spectroscopy (UV–vis, IR, ^1H and ^{13}C NMR) as well as elemental and thermal analyses. The excellent agreement between the experimental and calculated values of C, H and N indicates that the obtained nanoparticles are free of impurities. The stoichiometry of the TP interaction with the acceptors was found to have a 1:1 ratio.

TP free drug: white powder; IR (KBr, cm^{-1}): υ_{max} 3121 ν(N–H), 1718 ν_{as}(C═O), 1667 ν_s(C═O), 1567 ν(C═N), 1446 ν(C═C), 1187 ν_{as}(C–N). Anal. Calcd for $C_7H_8N_4O_2$ (180.16): C, 46.67; H, 4.48; N, 31.10; Found: C, 46.56; H, 4.45; N, 31.14. ^1H and ^{13}C NMR spectral data for the TP and its complexes were provided in the Supplementary data.

TP–PA complex: yellow crystals; IR (KBr, cm^{-1}): υ_{max} 3425 $\upsilon(^+N–H\cdots O^-)$ 3122 ν(N–H), 2787, 2712, 2609 υ(N–H···O), 1715 ν_{as}(C═O), 1671 ν_s(C═O), 1546 (C═N), 1487 ν(C═C), 1189 ν_{as}(C–N). Anal. Calcd for $C_{13}H_{11}N_7O_9$ (409.27): C, 38.15; H, 2.71; N, 23.96; Found: C, 38.10; H, 2.68; N, 23.99.

TP–DNBA complex: pale yellow crystals; IR (KBr, cm^{-1}): υ_{max} 3432 $\upsilon(^+N–H\cdots O^-)$ 3123 ν(N–H), 2786, 2711, 2605 υ(N–H···O), 1715 ν_{as}(C═O), 1671 ν_s(C═O), 1545 ν(C═N), 1487 ν(C═C), 1188 ν_{as}(C–N). Anal. Calcd for $C_{14}H_{12}N_6O_8$ (392.28): C, 42.86; H, 3.08; N, 21.42; Found: C, 42.80; H, 3.04; N, 21.47.

TP–CLA complex: reddish-brown powder; IR (KBr, cm^{-1}): υ_{max} 3121 ν(N–H), 1714 ν_{as}(C═O), 1672 ν_s(C═O), 1569 ν(C═N), 1445 ν(C═C), 1184 ν_{as}(C–N). Anal. Calcd for $C_{13}H_{10}Cl_2N_4O_6$ (389.15): C, 40.12; H, 2.59; N, 14.40; Found: C, 40.19; H, 2.65; N, 14.36.

TP–CHL complex: yellowish-brown powder; mp 274–278 °C, IR (KBr, cm^{-1}): υ_{max} 3122 ν(N–H), 1715 ν_{as}(C═O), 1668 ν_s(C═O), 1565 ν(C═N), 1486 ν(C═C), 1187 ν_{as}(C–N). Anal. Calcd for $C_{13}H_8Cl_4N_4O_4$ (426.04): C, 36.65; H, 1.89; N, 13.15; Found: C, 36.61; H, 1.96; N, 13.20.

2.4. Calculations

The spectroscopic data were used to calculate the formation constant (K), the molar extinction coefficient (ε) [55], the energy of the interaction (E_{CT}) [56], the oscillator strength (f) [57], the transition dipole moment (μ) [58] and the standard free energy ($\Delta G°$) [59] for