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A study of supramolecular host–guest interaction of dothiepin and doxepin drugs with cyclodextrin macrocycles

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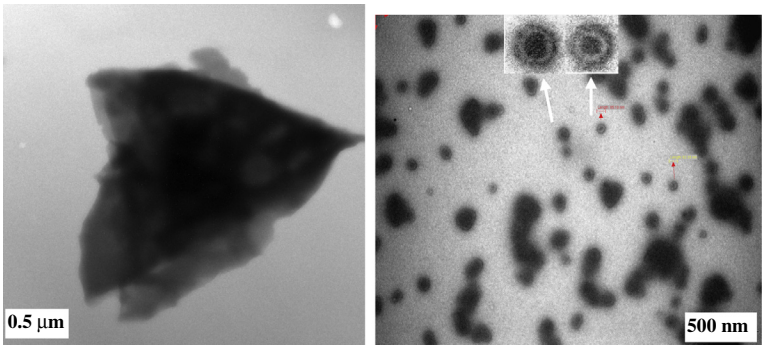
HIGHLIGHTS

- Spectral studies reveal that DOT and DOX drugs form different inclusion complexes with α- and β-CD.
- Both drugs exhibit short life time in aqueous medium and higher in CD medium.
- DOT self assembled to form nano-sized spheres and particles with CD.
- Nanostructures are formed through the intermolecular hydrogen bonding.
- The alkyl chain encapsulation is more favoured in the α-CD cavity than aromatic ring of drugs.

GRAPHICAL ABSTRACT



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ABSTRACT

Inclusion complexation behavior of dothiepin (DOT) and doxepin (DOX) with two cyclodextrins (α-CD and β-CD) were studied by absorption, fluorescence, time resolved fluorescence, scanning electron microscope (SEM), transmission electron microscope (TEM), Fourier transformation infrared spectroscopy (FT-IR), differential scanning colorimetry (DSC), powder X-ray diffraction (PXRD), proton nuclear magnetic resonance (^{1}H NMR) and molecular modeling methods. Absorption and fluorescence spectral studies reveal that both drugs form different types of inclusion complexes with α-CD and β-CD. DOT and DOX exhibit short life time in aqueous medium (DOT ~ 2.29 ns, DOX ~ 1.89 ns) and higher in CD medium (DOT:α-CD ~ 3.45 ns, DOT:β-CD ~ 4.84 ns, DOX:α-CD ~ 3.55 ns and DOT:β-CD ~ 4.33 ns). The supramolecular structure of the nano-sized sphere and agglomerate was established by TEM. Alkyl chain and aromatic ring protons of the drug molecule are entrapped in the CD nanocavities. The significant proton chemical shifts give evidence for expected inclusion complex formation. PM3 calculations suggest that the alkyl chain encapsulation is most energetically favored in α-CD. The positive free energy and entropy changes indicated that both inclusion complexation processes are non-spontaneous and entropy driven.

Introduction

Medicinal chemistry is concerned with the understanding of the chemical and biological mechanisms by which the action of drug molecules can be explained [1–4]. It also tries to establish relations between chemical structure and biological activity and to link the latter to the physical properties of the drug molecules [2]. The discovery of a new and important biologically active compound (drug) usually gives rise to an extended search for closely related compounds of similar, more effective, more specific or even opposite activity [1]. In a number of cases, substitution of one atom or group of atoms in the parent compound results in surprising actions. Further, suitable analytical method is a basic necessity

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for drug development and drug quality control. Hence, it is desirable to concentrate on the spectral characteristics of some drug molecules in different cyclodextrins, so that, useful information can be obtained for correlating the spectral properties with drug action and for selecting suitable conditions for fluorimetric estimation of drugs.

The cyclic oligosaccharides α-, β- and γ-cyclodextrins (cyclohexaamylose, cycloheptaamylose, and cyclooctaamylose) have been the subject of much demanding research [1,2]. Cyclodextrins (CDs) are designed in torus forms which are composed of 6, 7 and 8 glucose units, respectively. The structural characteristic offers a unique ability or inclusion complex formation with various appropriately sized hydrophobic guest compounds [3,4]. Cyclodextrins have been used as models for protein and enzymes because they interact with many drugs in a manner similar to that of proteins and enzymes. Since the inclusion process of drug molecules with CDs leads to important modifications of pharmacokinetic properties of drug molecules like solubility, chemical stability and bioavailability of poorly soluble drugs, they are used to reduce toxicity and control the rate of release so on and so forth [1–4]. Therefore, it is essential to comprehensively understand the effects of inclusion on pharmaceutical drug molecules [2].

In the CD inclusion complexes, guest molecule can become more soluble, improving the chemical and physical properties [5,6]. The CD and drug molecules to form inclusion complexes and such association have been studied widely as models for understanding the mechanism of molecular recognition [7,8]. Recently, supramolecular assemblies with extended aromatic compounds have attracted much attention [9–11]. Further a number of different well-ordered supramolecular materials [11,7] like polyrotaxane [12], rotaxane [13], pseudorotaxane [14], pseudopolyrotaxanes [15], catenane [16], molecular necklaces [17], nanovesicles [18], nanoparticle [19], nanorod [20] and other supramolecular assemblies have been constructed. Further, semiempirical calculations through PM3 method has been applied on the supramolecular inclusion complex systems and many authors predict inclusion process was spontaneous (or) nonspontaneous and driven by enthalpy or entropy or enthalpy–entropy co driven in vacuum phase [21–24]. The host:-guest molecular recognition leads to the extensive application of CD in the fields of medicine, food, organic synthesis, materials environment protection and analytical chemistry, etc. Many researchers are mainly analysed the inclusion complexes by absorption, fluorescence, time resolved fluorescence, FT-IR, and NMR techniques and they reported different types of host:guest inclusion complexes [25,26].

In the present study, we have selected two drugs namely dothiepin hydrochloride (DOT) and doxepin hydrochloride (DOX), the main aim of this study is to investigate the formation of inclusion complex and self assembled nano or microstructures of DOT and DOX with α-CD and β-CD (Fig. 1). DOT and DOX are belonging from tricyclic antidepressant drugs and it is widely used for the treatment for depression and anxiety disorders. CD inclusion complexes self assemble to form various nano and microstructures, that is why DOT/CD and DOX/CD inclusion complexes formation and its self assembled structures were characterized by various analytical techniques. The inclusion complex were analysed by steady state and time-resolved fluorescence spectroscopy, SEM, TEM, FT-IR, DSC, XRD, ^{1}H NMR and semiempirical PM3 methods.

Experiments

Instruments

Absorption spectral measurements were carried out with a Shimadzu (Model UV 1650) UV–vis spectrophotometer and steady-state fluorescence measurements were made by using a Shimadzu spectrofluorimeter (Model RF-5301). The fluorescence lifetime measurements were performed using a picosecond laser and single photon counting setup from Jobin-Vyon IBH. Scanning electron microscopy (SEM) photographs were collected on a JEOL JSM 5610LV instrument. The morphology of DOT and DOX drugs and the inclusion complexes were investigated by TEM using a TECNAI G2 microscope with accelerating voltage 100 kV and 200 kV, using carbon coated copper TEM grid (200 mesh). FT-IR spectra of the DOT, DOX, α-CD, β-CD and the inclusion complexes were measured from 4000 cm^{-1} to 400 cm^{-1} on Nicolet Avatar 360 FT-IR spectrometer using KBr pellets. ^{1}H NMR spectra was recorded on a Bruker AVANCE 400 MHz spectrometer using DMSO-d_6 (99.98%) as a solvent. DSC thermograms were recorded using Mettler Toledo DSC1 fitted with STR^e software, temperature scanning range was from 25 to 250 °C with a heating rate of 10 °C/min. PXRD spectra were recorded with a BRUKER D8 advance diffractometer and the pattern was measured in the 2θ angle range between 5 and 80° with a scan rate 5°/min.

Reagents and materials

DOT, DOX, α-CD and β-CD were purchased from Aldrich Chemical Company and used without further purification. Triply distilled water was used for the preparation of aqueous solutions. All the spectral measurements were performed at the drug concentrations of 4×10^{-5} mol dm^{-3}. The concentration of α-CD and β-CD solutions were varied from 1×10^{-3} to 10×10^{-3} mol dm^{-3}.

Preparation of inclusion complex

α-CD or β-CD (1 mmol) was dissolved in 40 ml distilled water and DOT or DOX (1 mmol) was dissolved in 10 ml methanol and it was slowly added to the CD solution. This mixture was sonicated at 40 °C for 2 h. Then the solution was refrigerated overnight at 0 °C. The DOT:CD and DOX:CD inclusion complex precipitate was recovered by filtration and washed with little amount of ethanol and water to remove uncomplexed drugs and CDs, respectively. This precipitate was dried in vacuum at room temperature for two days and stored in an airtight bottle. These powder samples were used for further analysis.

Molecular modeling studies

The theoretical calculations were performed using Gaussian 03W. The calculations were carried out in the aqueous phase. The initial geometries of the drug and CD molecules were constructed with Spartan 08 and then optimized by PM3 method. α-CD and β-CD were fully optimized by PM3 without any symmetry constraints [22,23]. Because the semiempirical PM3 method has been shown to be a powerful tool in the conformational study of cyclodextrin inclusion complexes and has a high computational efficiency in calculating CD systems, [22,23] it was selected to study the inclusion process of the CD with DOT and DOX in this work.

Results and discussion

Absorption and fluorescence measurements

Table 1 and Fig. S1 depicts the absorption and emission spectra of DOT and DOX in pH ~7 aqueous solutions containing different concentrations of α-CD and β-CD. Both DOT and DOX drugs show the absorption wavelength at ~300, 260, 218 nm and 292, 245s, 210 nm in the non-existence of CD, respectively (Table 1). With