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A fluorescence study on the interaction of telmisartan in triblock polymers pluronic P123 and F127

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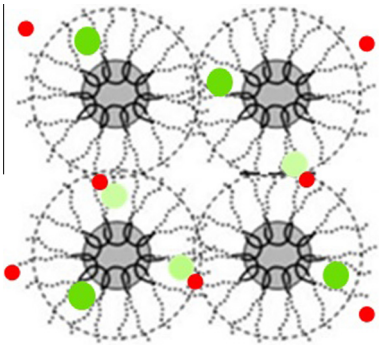
HIGHLIGHTS

- Telmisartan resides in the corona of pluronic and experiences restricted diffusion.
- Quenching of telmisartan fluorescence is due to static and collisional interactions.
- Higher hydrophilic content in pluronic promotes complex formation.

GRAPHICAL ABSTRACT



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ABSTRACT

Telmisartan is a poorly soluble drug used in treatment of hypertension. There is a recent interest to use pluronic for improving the solubility and bioavailability of these drugs. In this study the interaction of telmisartan with P123 and F127 has been carried out using steady state and time dependent fluorescence study. Quenching of telmisartan fluorescence by potassium iodide is controlled by interactions arising from collisions and complex formation. A comparison of the fluorescence of telmisartan in pluronics with the well understood fluorescence of 8-anilino-1-naphthalene-sulfonic acid, a known fluorescent molecular probe, indicates that telmisartan is generally present in a relatively polar microenvironment with restricted diffusive motion.

Introduction

Telmisartan (TS), an angiotensin II receptor antagonist, is used as an antihypertensive drug for the treatment of arterial hypertension. It is one among the several drugs sparingly soluble in water and other biofluids. Poor solubility reduces the oral bioavailability of the drug. Several efforts such as conversion of crystalline drug to amorphous form [1], addition of pH modifiers in the dose [2], synthesis of spherical mesoporous silica nanoparticles for drug loading [3] and preparation of solid dispersions using hydrophilic polymer [4–7] like pluronic F127 also known as poloxamer 407 [8] are being made to improve the solubility and enhance the bioavailability of telmisartan. Zhang et al. [3] prepared spherical mesocellular foam using pluronic P123 triblock polymer with cetyltrimethyl ammonium bromide (CTAB) and used it to load telmisartan. There is a growing trend to use polymers like P123 and F127 to improve the solubility of drugs like telmisartan and it is important to understand the interaction of telmisartan to the polymers. Understanding the mechanism of their interaction/location of the drug in the polymers are important for controlling the loading and release mechanism of the drug. Pluronics are also being used for the solubilization of poorly soluble drug molecules such as carbamazepine

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[9]. These polymers have been used as effective anticancer drug delivery system for cancer chemotherapy [10]. Das et al. [11] used pluronic F127 to enhance the solubility of the drug curcumin in the alignate–chitosan nanoparticles for delivery to cancer cells. The solubility of drugs such as paclitaxel [12] and docetaxel [13] has been enhanced using pluronic P123. Pluronics are non-ionic amphiphilic molecules composed of hydrophilic poly(ethyleneoxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) triblock polymers (PEO–PPO–PEO). They self-assemble in aqueous solutions into spherical micelles and at higher concentrations, organize into higher order cubic structures [14,15]. The critical micellar concentration (CMC) of pluronics is highly sensitive to changes in temperature [15]. Pluronics form spherical micelles in which the hydrophobic PPO blocks form the core surrounded by corona of hydrophilic PEO-blocks [16]. The CMC values reported in literature vary substantially due to polydispersity between different batches and different systems [17]. The micelles organize into cubic structures to form thick non-transparent gels typically above ~20 wt% polymers [18]. In this work pluronic has been used in a concentration range above CMC and below cubic structure formation which results in transparent hydrogels. On increasing the concentration above CMC there is increase in micelle aggregation number and micellar molecular weight along with clustering of micelles into larger aggregates [19].

Molecular structure of telmisartan is rich in functional groups such as biphenyl and benzimidazole (Supplementary material) that give this drug an inherent luminescent nature. Fluorescence detection of telmisartan in HPLC analysis with a lower limit of quantitation has been studied by several authors [20–22]. Bano et al. [23] carried out a fluorescence quenching study on telmisartan with Y(III) and Nd(III). They observed static quenching of telmisartan by Y(III) and Nd(III) due to the formation of a non-fluorescent complex in the ground state. The p*K*a values of sartan molecules influence their absorption by the body, distribution in the tissues and elimination. Cagigal et al. [24] reported the p*K*a value of a number of sartan molecules including telmisartan, which has a p*K*a value of 4.45 corresponding to the acid–base equilibrium owing to the carboxylic group. The fluorescent behavior of telmisartan is different from the other sartans molecules due to absence of a biphenyltetrazole group and low fluorescence at lower pH than at basic pH [24]. Tway and Love [25] demonstrated that even though benzimidazole and their analogues can undergo π to π^* or charge transfer transition, in water charge transfer transitions would be predominant [25].

A non-covalently bound probe molecule remains in a micelle or reports from a particular micelle due to strong electrostatic attraction between the two [26]. For neutral micelles like pluronic, neutral probe molecules are solubilized in the corona region and ionic probes at the surface region of the micelle [27]. Pluronic micellisation and gelation has been studied earlier using fluorescence of coumarin 153 which senses the microenvironment of the corona region and does not exhibit any difference in fluorescence parameters studied [27]. Whereas a modified coumarin molecule with a long hydrocarbon chain was able to satisfactorily report the micelle to gel transition [27]. Solvation dynamics in the interior of P123 is greatly influenced by the location of the probe: a fast solvent response arises from bulk like peripheral region and slow solvent response from the core region [28].

8-Anilino-1-naphthalene-sulfonic acid (ANS) is a widely used negatively charged hydrophobic fluorescent molecule. It is minimally fluorescent in polar environments, such as aqueous solutions (quantum yield about 0.004), but its fluorescence emission dramatically increases in non-polar environments [29,30]. In organized media multiple fluorescence lifetime arise for ANS due to photorelaxation or multiple ground states [31]. ANS fluorescence is affected by changes in its microenvironment such as hydrophobicity, electrostatic interactions, polarity and viscosity [32].

In the present investigation ANS was used as a fluorescent probe to study the microenvironment of the polymer. This was further used to understand the interaction of telmisartan with pluronic, using steady state and time resolved fluorescence spectroscopy. Quenching of telmisartan fluorescence using KI as quencher was carried out to infer the location of telmisartan in the microheterogeneous environments of two polymers, pluronic P123 and F127, in their aqueous solutions.

Materials and methods

Pluronic P123, pluronic F127 and 8-anilino-1-naphthalene-sulfonic acid were obtained from Sigma Aldrich and were used as supplied. The same batch of pluronic P123 and F127 were used for all the experiments. Telmisartan was provided as a kind gift from Hetero drugs, Hyderabad, India and was used without further purification. HPLC grade methanol (Merck, India) and triple distilled water was used for preparing the samples.

Sample preparation

Stock solutions containing 10^{-3} M ANS or telmisartan were prepared in methanol and were further diluted with triple distilled water. Pluronic solutions were prepared by dissolving accurately weighed amount of the polymer in 10^{-5} M probe/drug solution. The final probe/drug concentration in the samples was 10^{-5} M containing 1% (v/v) methanol in water. The samples were left in refrigerator for 3 days for complete dissolution. The polymer concentrations were fixed such that at highest concentrations the gels remained visibly transparent at all temperatures. All experiments were carried out thrice on separate days and the data shown is the mean of 3 different experiment sets.

Fluorescence measurements

Fluorescence measurements were carried out with a Horiba Jobin Yvon Fluorolog 3 Spectrofluorometer. Temperature for the experiments was controlled by circulating water through a jacketed cuvette holder from a water bath (Lab Companion Circulator, India). Temperature was also checked inside the cuvettes before and after the experiments; the variation was negligible. All experiments were repeated at least thrice on different days.

Fluorescence lifetime measurements

Fluorescence lifetime measurements were carried out using Horiba Jobin Yvon TCSPC lifetime instrument in a time-correlated single-photon counting arrangement. A 370 nm nano-LED was used as the light source. The pulse repetition rate was set to 1 MHz and the instrumental 'full width at half maximum' of the 370 nm LED, including the detector response was ~1.1 ns and for 295 nm LED it was ~0.8 ns. The instrument response function was collected using a colloidal silica solution (Ludox). The decay data were analyzed using IBH reconvolution software. The quality of curve fits was judged on the basis of the χ^2 value ($0.99 \leqslant \chi^2 \leqslant 1.3$) and the randomness of residuals. The average fluorescence lifetime (τ_{avg}) values are obtained by the following equation [33]:

$$\tau_{avg} = \sum_{i=0}^{n} \alpha_i \tau_i^2 \Big/ \sum_{i=0}^{n} \alpha_i \tau_i$$

where τ_i is the individual lifetime with corresponding amplitudes (α_i).