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Micelle enhanced and native spectrofluorimetric methods for determination of sertindole using sodium dodecyl sulfate as sensitizing agent

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ABSTRACT

Two stability indicating spectrofluorimetric methods were developed and validated for the determination of sertindole (SER) in the presence of its acid and oxidative degradates at λ_{ex} 257 nm and λ_{em} 335 nm. Method A was based on measuring the native fluorescence of SER using isopropanol as solvent. Method B was based on the enhancement of native fluorescence of SER quenched in aqueous media by using micellar microenvironment created by sodium dodecyl sulfate (SDS) anionic micelles using Britton Robinson Buffer (BRB) pH 3.29 as solvent. Different factors affecting fluorescence intensity; both native and enhanced, were carefully studied to reach the optimum conditions of measurements. The proposed spectrofluorimetric methods were validated in accordance with ICH guidelines and were successfully applied for the determination of SER in bulk powder and pharmaceutical preparation with high sensitivity and stability indicating power. They were also statistically compared to the manufacturer methods with no significant difference in performance.

1. Introduction

Sertindole (SER), 1-[2-[4-[5-chloro-1-(4-fluorphenyl)indol-3-yl]piperidin-1-yl]ethyl] imidazolidin-2-one [1] an atypical antipsychotic is used for the treatment of schizophrenia by acting as an antagonist at central dopamine (D_2), serotonin (5-HT_2), and α_1-adrenergic receptors, whereas it has a low affinity for cholinergic muscarinic and histamine H_1 receptors [2]. The effect on (D_2) receptors is more pronounced in the limbic dopamine system compared with the nigrostriatal system. This selectivity had made SER highly effective against the positive and negative symptoms of schizophrenia, with a low rate of extrapyramidal side effects [3]. SER is chemically classified as a phenyl indole, where fluorescence was expected in its molecules that are aromatic and contain multiple conjugated double bonds with high degree of resonance stability and delocalized π-electrons that can be placed in low lying excited singlet states [4].

Literature review revealed that SER is non-official in any pharmacopeia, and that several methods were reported for its determination in biological fluids and pharmaceuticals using HPLC [5–11], OPLC [12], UPLC [13,14], voltammetry [15], and electrophoresis [16], however no methods had been reported for the determination of SER in pharmaceuticals using fluorimetry.

The objective of this study was to use SER fluorescence to develop two stability indicating spectrofluorimetric methods. Method A was based on native fluorescence of SER in a non-polar solvent. Method B was based on the use of sensitizing agent to create micellar microenvironment to sequester SER due to its non-polarity inside the hydrophobic core of the micelles and protect its molecules from the quenching effect of polar solvents (Fig. 1). Accordingly less toxic, cheaper and environment friendly solvents can be used with nearly reserved sensitivity achieved using non polar solvents. Conditions affecting both native and enhanced fluorescence were carefully studied to optimize measuring conditions. The proposed spectrofluorimetric methods were validated according to ICH guidelines [17] and successfully applied for the determination of SER in its bulk powder and pharmaceutical formulation with high sensitivity and stability indicating power.

2. Experimental

2.1. Instrumentation

Fluorescence spectra and measurements were taken on a Shimadzu spectrofluorimeter Model RF-1501 equipped with xenon lamp and 1-cm quartz cell connected to Epson LX-300 + II printer (Japan). Excitation and emission wavelengths were set at $\lambda_{em}/\lambda_{ex}$ = 335 nm/257 nm.

Additional instruments were used including: Metler Toledo analytical balance (AB265-S, Switzerland), thermostatic water bath (Memmert, Germany), rotavapor (Buchi, Switzerland), sonicator (Crest, New York), and a digital pH meter (HANNA, pH 211, Romania).

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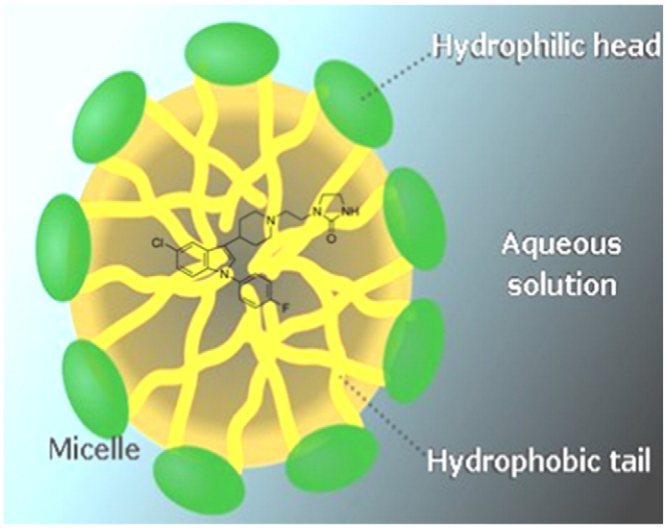

Fig. 1. Sequestered non polar sertindole molecules in SDS micelles hydrophobic core.

2.2. Materials and reagents

2.2.1. Pure sample

Sertindole was kindly supplied by the Lundbeck scientific office in Cairo, its potency was found to be 100.05% ± 1.44 using the manufacturer HPLC method.

2.2.2. Commercial tablets

Serdolect® 16 mg tablets, B.N. 2156270, were kindly supplied by the Lundbeck, Egypt scientific office. Each tablet is labeled to contain 16 mg of SER.

2.2.3. Solvents and reagents

All solvents used were of HPLC grade and reagents were of analytical grade. Methanol, ethanol, isopropanol (Scharlau, Spain), cetyl trimethyl ammonium bromide (CTAB) (GPR, England), Tween 80, sodium hydroxide, sodium dodecyl sulfate (SDS) (Qualiken, India) each of 0.4% (w/v), acetic acid, boric acid, phosphoric acid (Adwic Co., Egypt), 30% hydrogen peroxide (Panerac, Spain), and hydrochloric acid 36% (Fischer scientific, UK) were used. Bidistilled water was prepared by double glass distillation and filtration through a 0.45 μm membrane filter and referred to as "water".

2.2.4. Degraded sample

The acid degradate was prepared by heating 33 μg mL^{-1} SER in alcoholic 5 M HCl at 90 °C for 3 h in thermostatic water bath. The solution was then neutralized with 5 M NaOH and evaporated in rotavapour at 70 °C till dryness. The residue was then dissolved in ethanol, filtered and re-evaporated to dryness in rotavapour at 40 °C. SER oxidative degradates were prepared by leaving 200 μg mL^{-1} of SER prepared in 3% (v/v) ethanolic hydrogen peroxide for 48 h at room temperature. The solution was then evaporated to dryness in rotavapour at 40 °C. The residues of the acid and oxidative degradates were diluted with isopropanol to obtain concentration of, 200 μg mL^{-1} for each degradate.

2.2.5. Solutions

2.2.5.1. Standard solutions. For methods A & B 200 μg mL^{-1} was prepared by dissolving appropriate amount of SER in isopropanol. This stock solution was subsequently used for preparation of working standard solutions in a concentration range of 2–20 μg mL^{-1} by further dilution with isopropanol.

2.2.5.2. Britton-Robinson Buffer (BRB) solutions. Britton-Robinson Buffer (BRB) solutions (pH 1.81 to 11.98) were prepared by adding different volumes of 0.2 M sodium hydroxide solution into a 100 mL of mixed acid, each containing 0.04 M solution of boric acid, ortho-phosphoric acid and acetic acid [18].

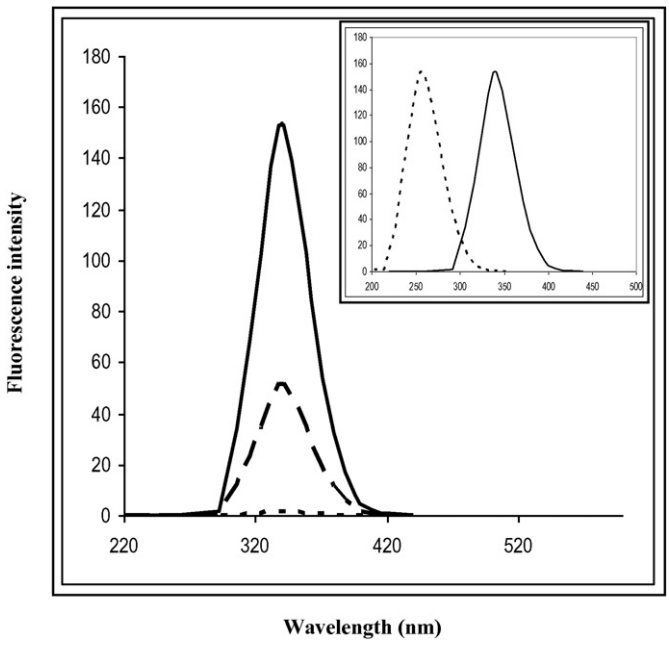

Fig. 2. Emission spectra of native fluorescence of 1 μg mL^{-1} of sertindole (——), its acid degradate (– – – –) and its oxidative degradate(- — -) in isopropanol at λ_{em} = 335 and λ_{ex} 257 nm. Inset: excitation (– – –) and emission (——) spectra of native fluorescence of 1 μg mL^{-1} of sertindole in isopropanol at λ_{em} 335 nm and λ_{ex} 257 nm.

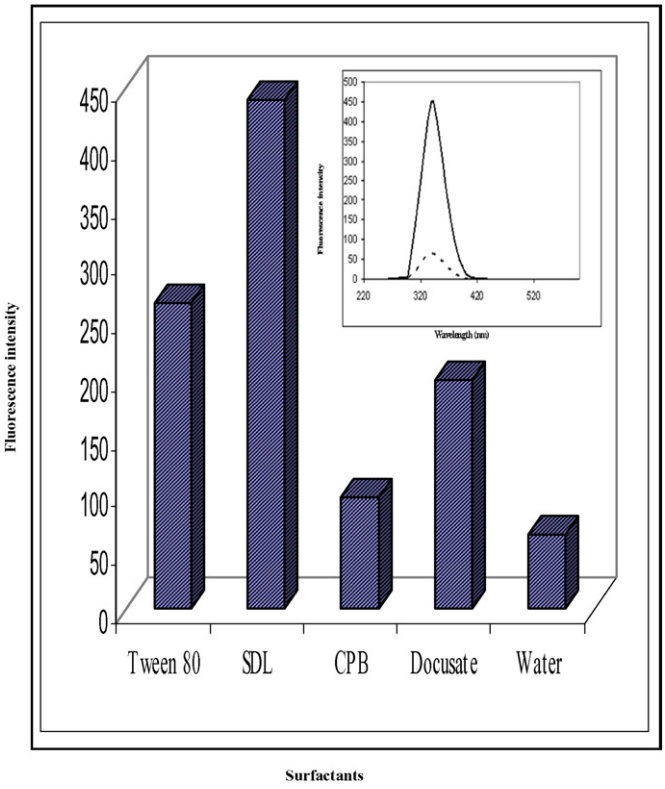

Fig. 3. Effect of different surfactants on the fluorescence intensity of 4 μg mL^{-1} of sertindole in aqueous micellar microenvironment at λ_{em} 355 and λ_{ex} 257 nm. Inset: emission spectra of 4 μg mL^{-1} of sertindole in water (– – – –) and sertindole in SDS micelles enhanced media pH 3.29; BRB (——) at λ_{em} 335 nm and λ_{ex} 257 nm.