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A Review on Binding interactions between Anti-bacterial Drugs and Human serum albumin using fluorescence spectroscopy

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ABSTRACT

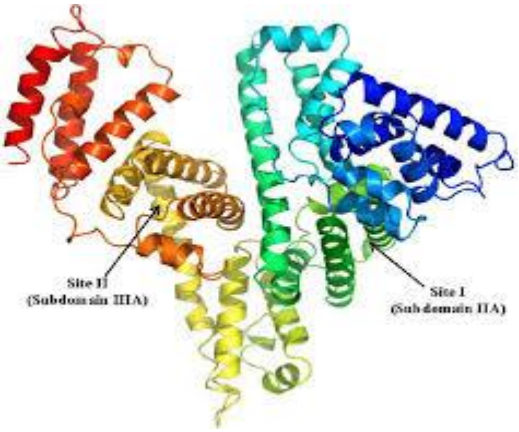
Human serum albumin is a highly water soluble globular monomeric plasma protein with a relative molecular weight of67 KDa. It hasthe centre of attention in the pharmaceutical industry due to their ability to bind tovarious drug molecules. This review will address the properties of binding site of drugs in IIA subdomain within the structure of HSA and also the mechanism of interaction of drugs with human serum albumin has been studied using fluorescence spectroscopic technique. It Is allowed us to characterize the strength and modes of binding, mechanism of fluorescence quenching, and intermolecular interactions for the DRUG-HSA complexes. We determined that DRUG and HSA form two stable low-energy complexes, leading to conformational changes and quenching of protein fluorescence. Stern–Volmer analysis of the fluorescence also revealed a collision-independent static mechanism for fluorescence quenching upon formation of the DRUG–HSA complex. The Stern –volmer analysis shown that the tryptophan residues of albumin are not fully accessible to the dug and predominantly static mechanism is operative.

Keywords: **Human serum albumin, fluorescence quenching, binding site, Drugs.**

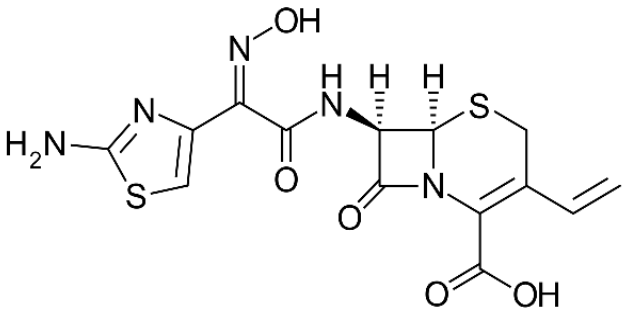
INTRODUCTION

HSA is the most abundant protein in human blood plasma which constitutes about half of a serum protein and it is produced in the liver. In addition, HSA also transports hormones, fatty acids, unconjugated bilirubin and their compounds. It maintains oncotic pressure. Drug interaction with human serum albumin generally enhances the distribution and bioavailability of the drug depending on the specific pharmacokinetic properties of the drug molecules. Additionally, because of its abundance, human serum albumin plays a significant role in the pharmacokinetic behaviour of a variety of drugs, including: drug half-life in the bloodstream, decreasing drug toxicity, and improving drug targeting specificity. Fluorescence quenching of a substance by interaction with another, which is added in increasing amounts, can be used as a technique to measure the binding affinities between some macromolecules and ligands acting as suppressors (quenchers). A gradual decrease in the fluorescence emission intensity of HSA is observed in the presence of increasing concentrations of drug suggesting the presence of tryptophan residue of the HSA at or near the drug binding site. HSA has one Trp (Trp 214) and its fluorescence is solely due to the excitation of this residue of HSA located in the binding domain-IIA (site I) at the bottom. The quenching data was analysed using the Stern-Volmer equation:

Binding constants and the number of binding sites for static quenching, the binding constant (Ka) and the number of binding sites (n) can be determined by plotting the double logarithm regression curve of the uorescence data with the
Modified Stern–Volmer equation.
logF0 – F/F
¼ log Ka + n log [Q]



Fluorescence Spectra Measurement in antibacterial drugs:



Chemical structure of Cefdinir

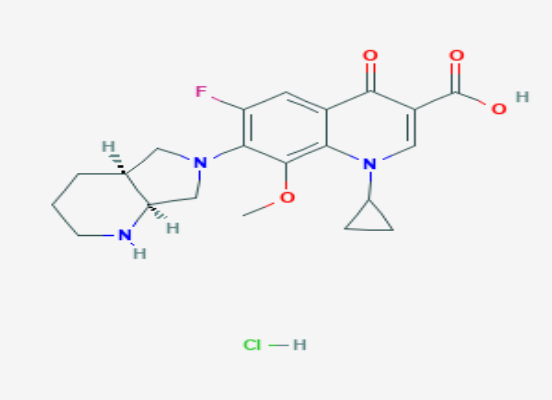
Cefdinir also known as Omnicef, is a semi-synthetic, broad-spectrum antibiotic belonging to the third generation of the cephalosporin class. It has been proven to be effective for the treatment of common bacterial infections in the ear, sinus, throat, lungs, and skin. **Cefdinir** was approved by the FDA in 1997 to treat a variety of mild to moderate infections and was initially marketed by Abbvie. Because of its chemical structure, it is effective against organisms that are resistant to first-line cephalosporin therapy due to the production of beta-lactamase enzymes.

The drug was found to quench the intrinsic fluorescence of human serum albumin. However, there was no significant shift in the wavelength for maximum emission (332 nm) in all cases except at pH 8.0, indicating thereby that under these conditions the binding does not cause any major conformational change in the protein molecule. At pH 8.0, a 10 nm blue shift in the fluorescence emission spectrum was observed.

Moxifloxacin hydrochloride (MOXH):
Moxifloxacin is used to treat certain infections caused by bacteria such as pneumonia, and skin, and abdominal (stomach area) infections. Moxifloxacin is also used to prevent and treat plague (a serious infection that may be spread on purpose as part of a bioterror attack.

Moxifloxacin is taken by mouth in the form of tablet. It is usually taken with or without food once a day for 5 to 21 days. The length of treatment depends on the type of infection being treated.

Moxifloxacin is a fluoroquinolone antibacterial drug. Moxifloxacin binds to and inhibits the bacterial enzymes DNA gyrase (topoisomerase II) and topoisomerase IV, resulting in inhibition of DNA replication and repair and cell death in sensitive bacterial species. The effect of MOXH on the fluorescence intensity of HSA at 298 K was observed. HSA generated an obvious fluorescence emission band at 337 nm, which was gradually quenched increasing MOXH concentrations In addition, MOXH alone did not emit fluorescence at the highest concentration. Therefore, such a decrease in intensity can be ascribed to the quenching of HSA by MOXH. The quenching mechanism is frequently categorized intodynamic quenching, static quenching, or a combination of both two, which can be distinguished by their differential dependence on temperature.

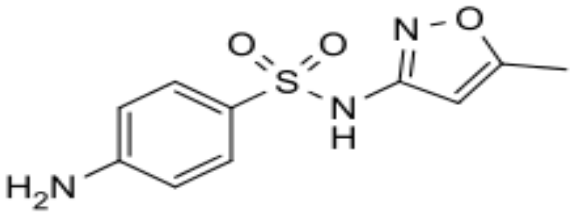


Chemical structure ofMoxifloxacin hydrochloride

Sulfamethoxazole:

Sulfamethoxazole is a sulphonamide bacteriostatic antibiotic that is most commonly used in combination with trimethoprim as the drug Bactrim. In this combination, sulfamethoxazole is useful for the treatment of a variety of bacterial infections, including those of the urinary, respiratory, and gastrointestinal tracts.

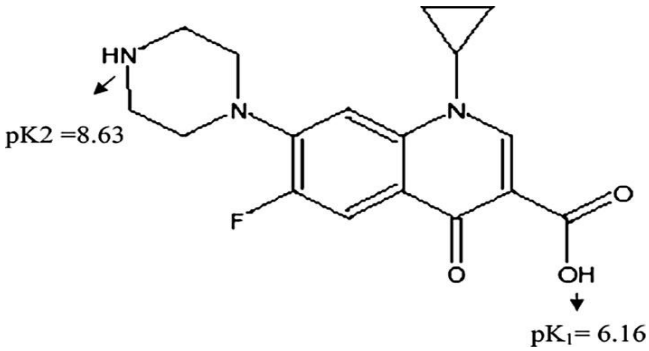
Sulfamethoxazole competitively inhibits dihydropteroate synthase preventing the formation of dihydropteroic acid, a precursor of folic acid which is required for bacterial growth. Sulfamethoxazole is a bacteriostatic sulfonamide antibiotic that interferes with folic acid synthesis in susceptible bacteria.



Chemical structure of sulfamethoxazole

Fluorescence spectroscopic analysis of the emission quenching at different temperatures revealed that the quenching mechanism of human serum albumin by SMZ was static mechanism. The binding constant values for the SMZ–HSA system were obtained to be 22500L/mol at 288K, 15600L/mol at 298K, 8500L/mol at 308K.The fluorescence intensity of HSA gradually decreased as increasing the concentration of SMZ, indicating that there was the interaction between SMZ and HSA. It was clear that HSA had a strong fluorescence emission band at 333nm by fixing the excitation wavelength at 280nm, while the drug SMZ had no intrinsic fluorescence.

Ciprofloxacin:



Chemical structure of Ciprofloxacin

Ciprofloxacin belongs to a class of drugs called quinolone antibiotics. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It will not work for virus infections (such as common cold, flu). Using any antibiotic when it is not needed can cause it to not work for future infections. Fluorescence measurements were performed on a spectrofluorimeter, model RF-5301 PC. The fluorescence Spectra were measured at 25 ± 0.1 _C with a 1 cm path length cell. Both excitation and emission slits were set at 3 nm. Intrinsic fluorescence was measured by exciting the protein solution at 295 nm and emission spectra were recorded in the range of 300–400 nm. Fluorescence quenching data of HSA complexed with markers in the absence and presence of CFX were analysed to obtain various binding parameters. The binding constant (Kb) and binding affinity were calculated.

CONCLUSION

In this paper we investigated the interaction between fourdrugs (cefdinir, Moxifloxacin,Hydrochloride, Ciprofloxacin, Sulfamethoxazole) with HSA Fluorescence spectroscopy. The interaction studies indicate that the probable quenching mechanism of fluorescence of HSA by these drugs is static quenching mechanism. The drugs can interact with HSA.Fluorescence spectroscopic methods were applied to explore the binding characteristics, and conformational changes of drugs with HSA. The Fluorescence spectroscopy demonstrated that anti-bacterial drugs interacted with HSA through the complex formation via static mechanism, which was proved by time-resolved fluorescence. According to the fluorescence data, binding of drugs to HSA was relatively strong with binding constants (Ka) shown with specific examples. The present reviews s suggested that binding with drug changed the conformation of HSA, and increased the hydrophobicity around the Trp residues. This review might contribute to a better understanding of binding mechanism of anti-bacterial drugs with HSA.

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