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Mixed micelles of sodium cholate and Brij30: Their rheological behaviour and capability towards solubilization and stabilization of rifampicin

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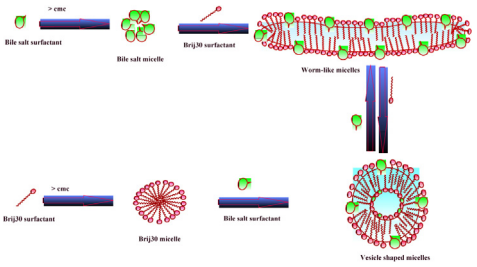
HIGHLIGHTS

- NaC aggregates showed micellar growth upon addition of Brij30.
- The solubility of rifampicin was higher in NaC micellar systems.
- The solubilization capacity of NaC decreased with increase in Brij30.
- The mixed micelles are more protective for oxidation of drug.
- The formulation enhances solubility, stability and bioavailability of the drug.

GRAPHICAL ABSTRACT



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ABSTRACT

Rifampicin is wide-spectrum antibiotic but being poorly water soluble and unstable towards oxidation, it requires high dose in order to reach therapeutic plasma concentrations thereby making its adverse effects like hepatotoxicity more prominent. Sodium cholate (NaC), Brij30 and their mixed micellar systems were evaluated for their solubilization and stabilization capability towards rifampicin. NaC aggregates showed micellar growth upon addition of Brij30 surfactant inferred by characterization using rheology and were found to form both wormlike micelles and vesicles. The solubility of rifampicin was found to be higher in NaC micellar systems due to an appreciable interfacial solubilization favoured by electrostatic interactions. The solubilization capacity of mixed micellar systems decreased with increase in Brij30 surfactant concentration. A comparative study of stability of rifampicin against oxidation with H_2O_2 showed that the micelles were able to stabilize the drug. The mixed micellar systems possessed much more solubilization efficiency than Brij30 micellar systems and at the same time proved markedly more protective against oxidation of rifampicin when compared to NaC besides being stable to large stress and having the desirable characteristics of their viscoelasticity, thus proving to be the ideal systems for solubilization and stabilization of rifampicin. These experimental results are expected to be important for enhancing the solubility, stability and hence bioavailability of rifampicin.

1. Introduction

Surfactant molecules self-assemble to form various micellar structures above their cmc, whose geometry depends on surfactant concentration. The increase in concentration of the surfactant induces a transition from dilute individual spherical micelles to semi dilute and entangled wormlike micelles imparting viscoelasticity to the system followed by formation of more ordered vesicular micelles at higher surfactant concentrations [1]. Wormlike micelles are of considerable interest both from theoretical and industrial/technological applications point of view. From fundamental perspective they act as model of 'equilibrium polymers' also called 'living polymers' [2–4] as these are extended linear macromolecular structures constantly breaking and reforming without any mechanical degradation. The spontaneous restoring property

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together with the drag reduction capability makes them very useful as heat-transfer fluids, hard-surface cleaners [5–8], fracturing fluids in oil fields [9] and in personal care products [10] for which both their high viscosity and elastic properties are exploited. Wormlike micelles of biocompatible or biodegradable surfactants have potential applications as drug delivery systems [11]. These have been employed as carriers of fatty acids and amino acid derived oils in medicines, cosmetics and foods [12], for the transdermal transport of caffeine or theophylline [13], for transferring cytotoxic drugs to cells [9] and as sieving matrixes for the separation of DNA fragments by capillary electrophoresis [14].

Polyoxyethylene ether (POE) surfactants like Brij30 have been studied extensively in pharmaceutical systems [15,16] due to their minimum toxicity. Bile salts are physiologically relevant, biocompatible and biodegradable molecules which undergo aggregation in aqueous solution. They have been employed for the solubilization of many poorly water soluble drugs like Griseofulvin [17], glutethimide [17], digoxin [18], leucotriene-D4 antagonists [19], gemfibrozol [20], etc. owing to their good acceptability for pharmaceutical products. Since dilute bile salt solutions present small micelles with low aggregation number due to the steric hindrance of the large steroidal skeleton, their solubilization capacity is limited. However, with the increase in concentration of bile salt like deoxycholates [21–23] they adopt a helical structure or polymer-like aggregation aided by the intermolecular hydrogen bonding between the hydroxyl and the carboxyl groups together with partial back-to-back hydrophobic interaction resulting in increase in hydrophobic domain of the micelles. This consequently enhances its solubilization capacity towards hydrophobic compounds [22]. Further, the same could be achieved by employing mixed micelles of bile salts and surface active agents which are reported to form wormlike cylindrical micelles having, therefore, better solubilization capability [24–26]. While going through the literature, we found most of the investigations having objective of studying formation of mixed micelles and their consequent pharmaceutical applications involve phospholipids and bile salts which need the use of organic solvents like chloroform and methanol for fabrication. Therefore, in this endeavour we present rheological characterization, i.e. flow behaviour and viscoelastic properties of mixed micelles of sodium chloate (NaC) and conventional non-ionic surfactant Brij30. Such mixed micelles are easy to prepare without aid of organic solvents together with its good acceptability in pharmaceutical research. To the best of our knowledge, such a study has not been reported in the literature.

In continuation, these mixed micelles were evaluated for their potential to act as solubilization medium towards hydrophobic drug like rifampicin. Rifampicin is a strategic medication recommended by the World Health Organization for the treatment of endemic diseases [27] and is one of the principal chemical therapies in combating tuberculosis and hanseniasis [28]. It is also used to treat osteomyelitis and prosthetic joint infections [29] and has some effectiveness against vaccinia virus [30,31]. Rifampicin is a hydrophobic drug with low aqueous solubility [32] and hence problems with its bioavailability in both fixed and single dose formulations are reported [33]. The therapeutic activity of rifampicin gets hampered due to its poor bioavailability attributed to its degradation in gastro-intestinal tract, variability in absorption and metabolism, pH dependent solubility, changes in crystalline nature, etc. [34,35]. For the effective treatment the dose requirement increases which makes the adverse effects of rifampicin like liver damage (hepatotoxicity) more prominent. Also the overexposure of bacterial species to rifampicin makes them resistant due to the mutations that alter residues of the rifampicin binding site on RNA polymerase resulting in decreased affinity for rifampicin [36]. An increase in the solubility, effectiveness, stability and thus bioavailability of rifampicin without altering the dose requirement is demanded and a number of previous studies are reported in this regard. Oliveira et al. [37] increased aqueous solubility of rifampicin through formation of cyclodextrin molecular complexes. Bhasin et al. [33], however, used microemulsion composed of oleic acid and Tween 80 as drug delivery system for rifampicin. On the other hand, Arguelho et al. [38] employed chitosan as carrier material for the protection and release of rifampicin. They observed that rifampicin is absorbed by chitosan in an acid medium, and released in an alkaline medium which is vital information for optimization of the absorption of rifampicin. In view of this, mixed micelles of sodium cholate and Brij30 were evaluated for their potential to act as suitable solubilization media for rifampicin with the focus on the extent of solubility enhancement and determining location of solubilization site within these nanostructures using spectrophotometric and fluorimetric techniques. Further stability of rifampicin against oxidation by H_2O_2 within these aqueous micellar systems was studied to evaluate the prospective potential of such systems as valid medium for solubilization. The experimental results of this study is important from both fundamental as well as technological point of view for enhancing the solubility, stability and hence bioavailability of rifampicin which may pave way to develop its suitable pharmaceutical formulation required for various medical complicacies.

2. Experimental

2.1. Materials

Rifampicin was obtained from Himedia laboratories (India, 98%). Brij30 and cholic acid sodium salt hydrate (NaC) amphiphiles were Aldrich products (>98%). H_2O_2 used was of analytical grade. All the chemicals were used as received. The chemical structures of rifampicin and surfactants are presented in Scheme 1.

2.2. Methods

2.2.1. CMC determination

The *cmc* values were determined from the surface tension (γ) vs logarithm of surfactant concentration (log [surfactant]) plots (Fig. 1). Surface tension measurements were made with a Kruss 9 tensiometer by the platinum ring detachment method. Surfactant concentration was varied by adding concentrated surfactant solution in small instalments and reading were taken after thorough mixing and temperature equilibration. The temperature was maintained at $25 \pm 0.1\,^{\circ}C$ by circulating water from a HAAKE GH thermostat. The accuracy of measurements was within ± 0.1 dyne cm^{-1}.

2.2.2. Rheological measurements

Steady and dynamic rheological experiments were performed on Anton Paar MCR-102 rheometer equipped with a peltier temperature control system with an accuracy of $\pm 0.01\,^{\circ}C$. Cone-plate geometries (diameter of 49.985 with cone angle of 1.006°) were used for the measurements. In steady shear experiments the shear rate was typically increased from 0.0001 to 10,000 s^{-1}. In oscillatory measurements a frequency sweep at constant stress was performed to obtain the dynamic viscoelastic functions such as the shear storage modulus G' and loss modulus G'' as a function of angular frequency 'ω'. The experiments were carried out at $25\,^{\circ}C$ and for each experiment a new sample was used and the measurements were carried out in duplicate with good reproducibility.

2.2.3. Solubility and stability experiments

The solubility of rifampicin and its stability against oxidation with H_2O_2 was determined spectrophotometricaly with a Schimazdu Spectrophotometer (model UV-1650). The drug was added