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Interaction of biocompatible natural rosin-based surfactants with human serum albumin: A biophysical study

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ABSTRACT

Biophysical insight into interaction of biocompatible rosin-based surfactants with human serum albumin (HSA) was studied at physiological conditions using various spectroscopic, calorimetric and molecular docking approaches. The binding constant (K_b), enthalpy (ΔH^0), entropy (ΔS^0) and Gibbs free energy change (ΔG^0) were calculated by spectroscopic and calorimetric method. We have also calculated the probability of energy transfer by FRET analysis. The circular dichroism study showed that the cationic surfactant QRMAE significantly altered the secondary structure of HSA as compared to the nonionic rosin surfactants. The thermodynamic study was performed by ITC to determine binding constant as well as change in enthalpy of HSA in presence of rosin surfactants. It clearly showed that hydrogen binding and hydrophobic interaction play an important role in the binding of HSA to rosin surfactants. We have also performed molecular docking studies to locate the binding site on HSA and to visualize the mode of interaction. The present study provides a significant insight into HSA–rosin surfactants interaction, which also improves our understanding of the possible effect of rosin surfactants on human health.

1. Introduction

Rosin, a plant derivative, is obtained from oleoresins of pine trees and the *Pinus soxburghui, Pinus longifolium* and *Pinus toeda* are its major sources [1]. It is a non-volatile solid form of resin and produced by heating fresh liquid resin to vaporize the volatile liquid turbine components. It mainly consists of abietic- and pimeric-type rosin acids with hydrophenthrine rings having cycloaliphatic and aromatic structures [2], thus, having prominent hydrophobicity for its use as marine antifouling materials [3]. Rosin can be modified into a large number of derivatives such as salts, esters, maleic anhydride adducts, and hydrogenated disproportionate rosins, which have several applications in the manufacture of adhesives, paper sizing agents, printing inks, solders, fluxes, surface coatings, insulating materials, and chewing gums [4–8]. Rosin possesses excellent film-forming properties and its derivatives are progressively used for their pharmaceutical applications. In pharmaceuticals companies, rosin is used in microencapsulation, film-forming and coating, matrix materials in tablets for sustained and controlled release [9–11]. Owing to the pharmaceutical applications of rosin derivatives these materials are concerns of several studies and proved themselves as good biodegradable and biocompatible substances [2,9,12–14].

Design of some rosin surfactants for various applications has also been endeavoring [15]. Surfactants, which themselves are a broad range of substances, are amphiphilic substances and their uses are ubiquitous. Amphiphilic character of rosin surfactants which imparts them some outstanding properties that include reduction of surface and interfacial tensions, formation of micelles and microemulsions, enhanced oil recovery, solubilization of drugs, stabilizer and excipients in drug formulations, etc. [16,17]. A lot of surfactants, for instance, petroleum derived ones are available for the use in various industries, but they are unable to achieve the requirements for non-toxicity, environmental protection and sustainable development. The interest in synthesizing bio-based surfactants that includes at least one moiety from natural substances has increased unusually due to their cost

Abbreviations: FRET, Förster resonance energy transfer; HAS, Human serum albumin; CD, Circular Dichroism; QRMAE, quaternary amine of rosin diethylaminoethyl ester; RMPEG-750, ester of rosin acid with polyethylene glycol monomethyl ether; RMA (MPEG-750), ester of rosin maleic anhydride with polyethylene glycol monomethyl ether; ITC, Isothermal titration calorimetry.

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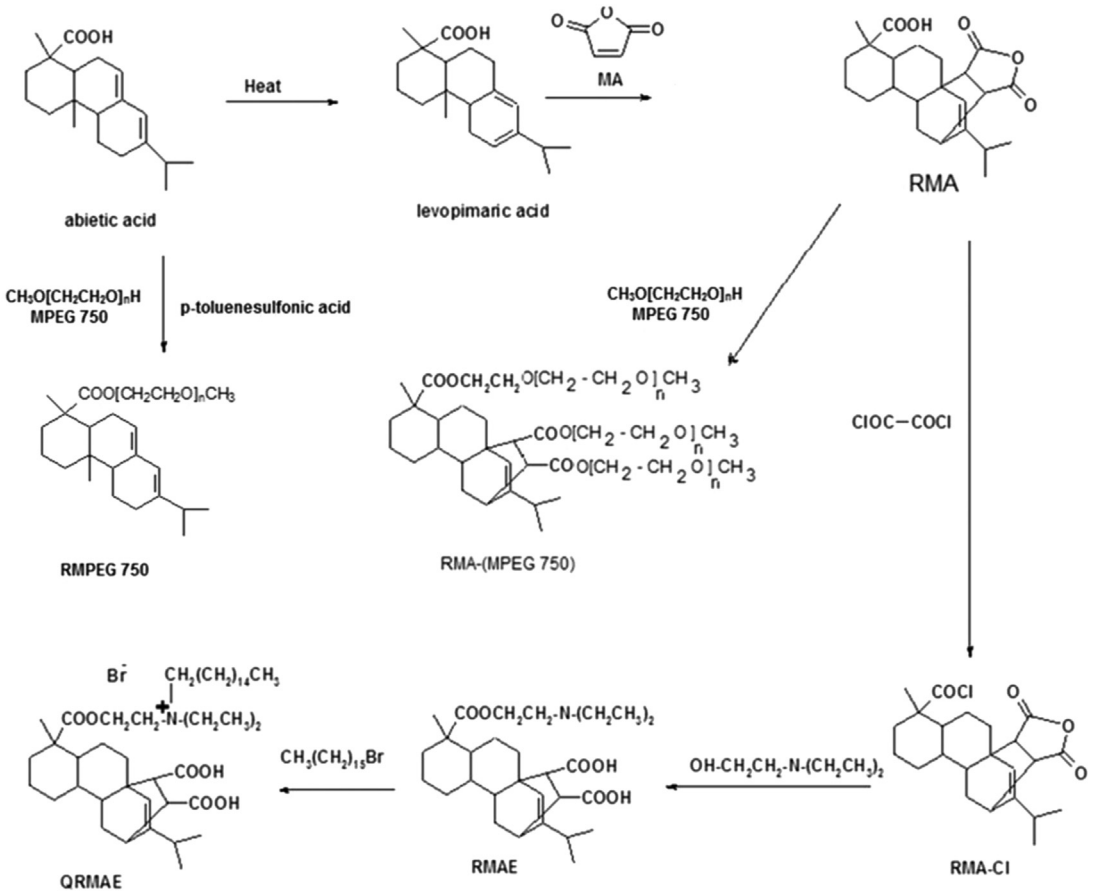

Fig. 1. Scheme for synthesis of rosin surfactants QRMAE, RMPEG 750 and RMA-(MPEG 750).

effectiveness [18]. Some sugar-based surfactants were found to be more effective as compared to existing non-ionic surfactants for use in parenteral drug formulations [19]. The other renewable sources from which these bio-based surfactants can be obtained includes amino acids, lactic acids, steroids, monoterpenes, rosin acids, fatty acids and some aromatic compounds [20]. Among these, rosin acids are relatively a novel source of hydrophobic groups and can be used as starting material for the production of surfactants with natural origin [21]. We have synthesized three different rosin-based surfactants viz., quaternary amine of rosin diethylaminoethyl ester (QRMAE), ester of rosin acid with polyethylene glycol monomethyl ether having a molecular weight of 750 (RMPEG 750) and ester of rosin maleic anhydride with MPEG 750 (RMA-(MPEG 750) [22,23].

Interaction of surfactants with albumins and other proteins is widespread and well studied aspect of the protein chemistry [24]. Surfactants play important roles in protein chemistry. It is generally accepted that surfactants unfold or denature the proteins but they may also induce the secondary structures in proteins depending on their concentration [25]. However, rosin's surfacatants may either motivate or inhibit the aggregation process of protein that depends on the providing conditions for the surrounding systems of proteins [26–28]. Recently, SDS was found to induce protein aggregation in several proteins depending on their isoelectric points [29]. On the basis of the well observed role of surfactant in protein chemistry and use of former in pharmaceuticals we have studied the effect of bio-based rosin surfactants on the conformation of well-known and much imperative plasma protein, i.e., human serum albumin (HSA). HSA is a highly aboundend serum protein (40 mg/ml) that comprises 50–60% of the total plasma protein in humans [30,31]. About 40% of the total albumin is present in circulatory plasma whereas the remaining 60% is distributed about in viscera and half in muscle and skin [32]. Albumin is produced by liver at a rate of 0.7 mg per hour. The turnover is first order with an average half life of 19 days. HSA contain 585 amino acid residues [33] with a molecular weight of 66.43 kDa [34], heart-shaped molecule, containing three structurally homologous domains each of which displays specific and functional characteristics [35]. Each of these three domains is composed of sub-domains A and B, providing flexibility to the protein molecule [36]. This flexibility allows the protein to variety of ligands [25]. As conformational adaptability of HSA extends well beyond the immediate vicinity of the binding site(s), cooperativity and allosteric modulation arise among binding sites which makes HSA similar to a multimeric protein [37]. Therefore, studies on this aspect can provide information of the structural features that determine the therapeutic efficacy of drugs [38].

The aim of this study is twofold first, rosin-based surfactants are used as important ingredients in pharmaceuticals and it is very likely that they will interact with proteins present in plasma and, in particular, serum albumin. Therefore, understanding the binding mechanism of these substances with serum albumin is of upmost importance. Secondly, it is desirable to see the effect of novel surfactants on protein conformation which provides important roles of conventional surfactants in protein chemistry.

2. Materials and methods

2.1. Materials

Fatty acid free human serum albumin (A1887) was procured from Sigma, USA, whereas Sodium di-hydrogen orthophosphate,