

BIOCOMPATIBLE CHOLINIUM FATTY ACID-BASED IONIC LIQUIDS AS GREEN ALTERNATIVES TO CONVENTIONAL SURFACTANTS FOR BIOMEDICAL APPLICATION

モハマド, コルバン, アリ

<https://hdl.handle.net/2324/4110486>

出版情報 : Kyushu University, 2020, 博士 (工学), 課程博士
バージョン :
権利関係 :

(様式2)

氏 名 : モハマド コルバン アリ

論 文 名 : BIOCOMPATIBLE CHOLINIUM FATTY ACID-BASED IONIC LIQUIDS AS GREEN ALTERNATIVES TO CONVENTIONAL SURFACTANTS FOR BIOMEDICAL APPLICATION

(医療応用のための従来の界面活性剤に代わる環境調和型代替としての生体適合性コリン脂肪酸を基体としたイオン液体)

区 分 : 甲

論 文 内 容 の 要 旨

During the last several years, ILs have been at the top of the most promising research materials and technology in the scientific fields. ILs are not only applicable to be covered the classical areas of knowledge but also expended as an important candidate to solve critical problems such as clean and efficient energy. In the pharmaceutical industries, the researchers are facing unparalleled challenges to develop the effective drug delivery systems for achieving targeted pharmacological response of many drugs because of their polymorphism, limited solubility, permeability, and bioavailability. To address these limitations, an IL based formulation is a promising approach to design the smart delivery of drugs. Particularly ILs were found to play a unique role in the pharmaceutical industry as clean and multifunctional properties for a variety of applications. This neoteric class of solvents, ILs, generally present interesting properties, such as negligible vapor pressure at relatively ambient conditions, high thermal, chemical, high surface activity and electrochemical stability, and broadly tunable properties with regard to polarity, hydrophobicity, and solvent miscibility. One of the major challenges in the pharmaceutical research is the increasing number of active pharmaceutical ingredients (APIs) possessing limited aqueous solubility in the biopharmaceuticals classification system class II drugs. In last few years, ILs have been considered as solvents and/or materials in the field of pharmaceuticals with the possibility of improved performance

such as improved solubility, stability, and drug delivery. In the last decade, ionic liquid (ILs)-based microemulsions (MEs) have been tested as potential nanocarriers for TDD. ILs are tunable designer solvents and play a versatile role at all phases of ME systems by altering water, oil and surfactant components. Recently, researchers have introduced ILs as a surface-active IL (SAIL) to serve as a surfactant by combining cations and anions with long alkyl chains for formulating different organized assemblies and improving the physico-thermal stabilities of MEs over aqueous conventional systems. In this thesis, we mainly focused on the synthesis and characterization of surface-active ionic liquids (SAILs) and evaluated their feasibility for biomedical applications.

In chapter-2, we preliminary reported a series of potentially low toxic and halogen free choline–fatty-acid-based surface-active ionic liquids (SAILs) were synthesized and their aggregation behavior in aqueous medium was evaluated. A series of fatty acids such as oleic acid, linoleic acid and erucic acid were selected as anions and cholinium as the cation because of their low toxicity and biocompatibility. All synthesized SAILs were highly viscous with high yield and purities (> 97.0%). Then all the SAILs were characterized using ^1H and ^{13}C nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry, and elemental analyses. The surface-active properties of the SAILs were investigated by tensiometry, conductometry, and dynamic light scattering measurements. The critical micelle concentration (CMC) values for the newly synthesized SAILs in water were found to be 2 to 4 times lower than those of the conventional ionic surfactants, SDS and SDBS because of the presence of a longer hydrophobic alkyl chain or/and the size difference of the cations (Cho^+ and Na^+), which are less hydrated by water and provide the strong electrostatic repulsion between the charged head groups in the surface layer. In addition, the thermodynamic properties of micellization (ΔG_m^0 , ΔH_m^0 , and ΔS_m^0) indicated that the micellization process of the SAILs is spontaneous, exothermic, and entropy-driven at room temperature. Then the formation of spherical micelles with a range of 3.9-5.6 nm in diameter was determined by the dynamic light scattering measurement. The cytotoxicity of the SAILs was evaluated using mammalian cell line NIH 3T3. Moreover, the toxicity profile of [Cho][Ole] falls in the range of

almost harmless compared to that of Tween 80. In addition, [Cho][Eru] is more toxic than [Cho][Ole], which is less toxic than some traditional surfactants. Finally, we believe that this environmentally friendly SAILs can be used as potential alternative to conventional surfactants for various fields, including biological and biomedical applications.

In chapter-3, as a follow-up to previous study, we reported novel cholinium fatty acid IL surfactant-based microemulsions (MEs) with pharmaceutically acceptable components, which have superior solubility with a series of insoluble or sparingly soluble drug molecules when compared with that of conventional Tween-80-based MEs. In this study, a series of SAILs was formulated a novel IL/O MEs by a mixture of SAIL, sorbitan laurate (Span-20) and isopropyl myristate. Based on the constructed pseudo-ternary diagrams, SAILs played the vital role as a surfactant while Span-20 acted as the co-surfactant, showing excellent solubility of the drug into the MEs system prepared with a ratio of 2:1 (SAIL[Cho][Ole]: Span-20). The droplet shape, size and size distribution of MEs were investigated through dynamic light scattering and found well-distributed particle size in the range of 6.5 to 21.2 nm, demonstrating the spherical micelles formation and the presence of IL is in the core of MEs. In order to explore the MEs as a potential drug carrier, we have investigated the solubility of some sparingly soluble drug molecules (e.g., celecoxib, acyclovir, methotrexate and dantrolene sodium) into the MEs system and found excellent solubility of such drugs in the ME system as compared with conventional tween-80 surfactant-based ME because of the formation of hydrogen bonds and electrostatic interactions among the head groups of SAIL surfactants, the anions of ILs and the polar groups of drug molecules. Then the inherent stability of the micro-carrier containing drug molecules was investigated via visual observation and droplet size determination over 2 months at 25 °C. During the storage (up to 120 d), the MEs exhibited no precipitation of drugs, color change, turbidity, phase separation and flocculation. Finally, in vitro cytotoxicity of the new carrier was evaluated using 3-dimensional reconstructed human epidermis model and found the cell viability of SAIL based MEs (94%) was almost similar as compared with tween-80 based MEs (96%) at the same IL concentration (4%). The results will undoubtedly change the perception of conventional Tween-80-based ME formulations and the introduced SAIL-based MEs represent

promising target drug delivery systems.

In conclusion, the obtained results (chapter 2 & 3) suggest that SAILs could be a potent biocompatible surfactants to eliminate the use of traditional toxic surfactants for oral/ topical/ transdermal delivery of poorly water-soluble drugs, since they allow an improved solubility of poorly water-soluble drugs.