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Pluronic-SAILs (surface active ionic liquids) mixed micelles as efficient hydrophobic quercetin drug carriers

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ABSTRACT

The present manuscript reports a systematic investigation on the solubilization of hydrophobic drug Quercetin (QCT) in pluronic F108 and its mixed micelles with surface active ionic liquids (SAILs) having same alkyl chain length but different hydrophobic head groups viz. 1-dodecyl-3-methylimidazolium bromide [Mim]; N-dodecyl-Nmethylpiperidinium bromide, [Pip]; N-dodecyl-Nmethylpyrrolidinium bromide, [Pyr]. Employing UV–visible spectroscopy, we have determined the solubility, loading efficiency and partition coefficient of QCT in the pluronic F108 and F108-SAILs mixed micelles. The F108-SAIL mixed micellar system possessed higher solubilization capacity for QCT. Further, the effect of varying composition of mixed micelles on the solubilization of QCT has also been evaluated and discussed in detail. A significant difference between the hydrodynamic diameter (D_h) of loaded and unloaded F108 as well as F108-SAILs mixed micelles confirmed that QCT has been solubilized in these micelles. Differential pulse voltammetry (DPV) measurements have been successfully employed to determine the possible location of the QCT in the both pluronic F108 and pluronic F108-SAILs mixed micelles. These measurements indicated that most of QCT is solubilized in the core of the F108 and F108-SAILs mixed micelles. In vitro drug release study of three different F108-SAILs mixed micellar formulations show sustained release behavior according to their interaction with the QCT. Higher anticancer effects were observed in the case of micellar QCT than the free QCT confirm the efficiency of the prepared formulations. The results demonstrated that the composition of mixed micelles had a profound effect on solubilization capacity and the drug release behavior from the F108-SAILs mixed micelles can be easily tuned by changing the head group of SAILs.

1. Introduction

Flavonoids are a broad class of low molecular weight, secondary plant phenolics identified by the flavan nucleus. They are widely distributed in the leaves, seeds, bark and flowers of plants, over 4000 flavonoids have been identified till date [1]. Among these, Quercetin (QCT) is one of the most abundant natural flavanoid that is widely distributed in various fruits and vegetables and is important because of its pharmacological and therapeutic effects [2]. QCT exhibits anti-inflammatory, anti-neoplastic and cardioprotective activities. QCT is anticipated to be one of the next antineoplastic drug with extremely high efficiency [4–5]. QCT is a hydrophobic drug and encounter bioavailability problems. An extensive amount of work has been done to solubilize and deliver the QCT by different means such as beta-cyclodextrin inclusion complexes, liposomes, ethyl acetate in water emulsions, solidified self-nanoemulsifying system, controlled-release packaging films and different individual micelles [3].

Pluronics, the tri-block copolymers are composed of polypropylene oxide (PPO)-polyethylene oxide (PEO)-polypropylene oxide (PPO) units. They are amphiphilic in nature and aggregate to form micelles having core region made of PPO and corona region consisting of PEO units [4]. Pluronic micelles have raised growing interest for the innovative design of drug delivery systems due to their excellent biocompatibility and non toxicity [5]. Recent reports suggest that, these polymers are able to sensitize multidrug resistant (MDR) cancer cells leading to enhanced drug transport across cellular barriers [6].

There are numerous reports published in literature dealing with the solubilization of hydrophobic drugs in the pluronic micelles [7–8]. These reports mainly focus on use of single pluronics. However, the high critical micelle concentration (*cmc*) values of these polymers may be disadvantageous as the loaded micelles undergo significant dilution on administration resulting in low stability of micelles [9]. It has been well established in literature that as compared to single surfactant solutions, mixing of different type of surfactant solutions exhibit synergism in terms of better surface activities and lower *cmc* values. Also the mixed micelles offer significant advantages in terms of higher thermodynamic and kinetic stability as well as higher drug loading capacities [10]. Fortunately, in recent years, ionic liquids (ILs) have evolved as a new class of

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environmentally benign and tunable designer solvents. They are used as solvents and/or materials in the fields of pharmaceutical drug delivery and active pharmaceutical ingredient formulation because of their unique and tunable physicochemical and biological properties [11]. The ILs having long chain cations are amphiphilic and are known as surface active ionic liquids (SAILs). There are few reports in which ILs are used for delivering hydrophobic drugs. Recently Moniruzzaman *et. al.* studied the solubility of poorly water soluble drug acyclovir in the IL/oil microemulsion for trans dermal drug delivery. They tested the solubility of acyclovir in imidazolium based IL/Tween-80/Span-20/isopropyl Myristate containing IL/oil microemulsions and observed that drug molecules are loaded in the IL core. They concluded that the successful solubility of poorly water soluble drug acyclovir may be attributed to the formation of hydrogen bonds between the IL anions and the polar groups of the acyclovir [12].

Mahajan et al. previously reported the binding ability of SAIL (C_{14}mimBr) for the drugs dopamine hydrochloride (DH) and acetylcholine chloride (AC). The results have been compared with that of conventional cationic surfactant, tetradecyltrimethylammonium bromide (TTAB). DH binds more strongly with the investigated SAILs than AC due to cation–π interactions between the aromatic region of DH and the positive charge of the surfactant molecules. The greater binding constant values were found for DH-C_{14}mimBr than DH -TTAB has been due to π–π interactions of the π system of DH and imidazolium ring of C_{14}mimBr. These results are encouraging for exploiting the SAILs as drug carrier than conventional surfactant [13].

Vashishat *et. al.* studied solubilization of poorly water soluble drug phenothiazine in the mixed micellar media comprising of SAIL (1-dodecyl-3-methylimidazolium) and bile salts (sodium cholate and sodium deoxycholate). They found that solubility of phenothiazine in mixed micellar media of SAIL and bile salts have been found to be dependent on the hydrophobicity and the size of the micelles [14].

Since SAILs are known to exhibit low toxicity there is no report about the solubilization of hydrophobic drug in the pluronic-SAILs mixed system. So this work engenders the keen interest for how SAILs micelles modify the properties of pluronic micelles in the mixed micellar media for solubilizing the poorly water soluble drug QCT. In the present work from the UV–visible measurements, the solubilization behavior of QCT in pluronic F108 ($PEO_{129}PPO_{50}PEO_{129}$) and binary mixtures of F108 with SAILs viz. 1-dodecyl-3-methylimidazolium bromide [Mim]; N-dodecyl-*N*-methylpiperidinium bromide, [Pip]; N-dodecyl-*N*-methylpyrrolidinium bromide, [Pyr] have been studied. The hydrodynamic diameter (D_h) of the loaded and unloaded micelles has been studied using dynamic light scattering (DLS) measurements. Further, the solubilization locus of QCT in F108 micelles and F108-SAIL mixed micelles has been adjudged with the help of differential pulse voltammetry (DPV) and proton nuclear magnetic resonance (^{1}H NMR) measurements. In vitro drug release studies were performed to have an idea about the release behavior of the drugs from the mixed systems.

2. Materials and methods

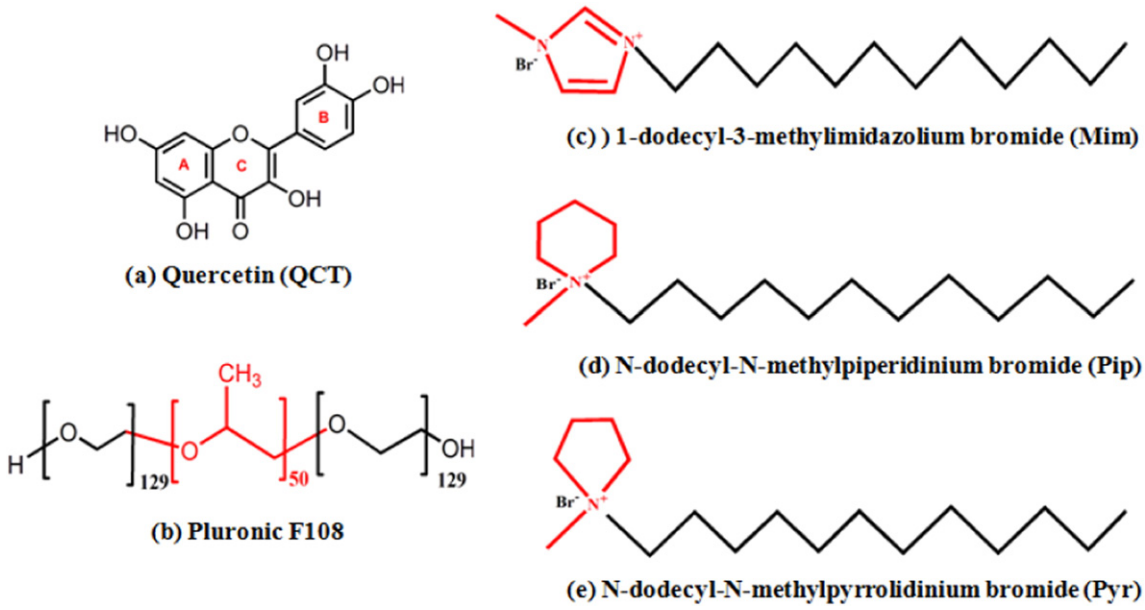
2.1. Materials

Pluronic F108, Quercetin (QCT), 1-methylimidazole, *N*-methylpiperidine, *N*-methylpyrrolidine, 1-bromododecane with purities ≥ 98% were purchased from Sigma Aldrich. All other chemicals used were of analytical grade and used without any further purification. The SAILs; Mim, Pip and Pyr were synthesized according to the procedure mentioned in literature [15–16] and characterized using ^{1}H NMR. The molecular structures of QCT, F108 and SAILs are shown in Scheme 1.

2.2. Methods

2.2.1. Solubilization study of QCT drug

The solubility of QCT was screened in the pluronic F108, SAILs and F108-SAILs mixed micelles. Pre weighed amounts of QCT were added to the vials containing 5 mL of micellar solutions. The sample vials were sealed with screw caps and stirred for a period of 12 h with a magnetic stirrer at a temperature of 37 ± 2 °C. The solutions were filtered using millipore filter (0.20 μm) to remove undissolved QCT. The concentration of solubilized QCT in these micelles was determined using Shimadzu (UV-1800) UV–Vis double beam spectrophotometer. To eliminate the effect of the surfactant on the UV absorbance, the surfactant concentration was kept the same in both reference and the measurement cells. Molar absorption coefficient of QCT was found to 14.80×10^3 L mol^{-1} cm^{-1} calculated from the calibration curve of the QCT in methanolic solutions. All experiments were performed in triplicate. Using this molar absorption coefficient, the solubility of QCT has been determined in F108, different SAILs and F108-SAILs mixed micelles.



Scheme 1. (a) Quercetin [QCT] (b) Plurronic F108 (c) 1-dodecyl-3-methylimidazolium bromide [Mim] (d) N-dodecyl-*N*-methylpiperidinium bromide [Pip] (e) N-dodecyl-*N*-methylpyrrolidinium bromide [Pyr]