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Mixed Micelle System Produced by Interaction Between Transglycosylated Stevia and an Ionic Surfactant Improves Dissolution Profile of Mefenamic Acid

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ABSTRACT

Transglycosylated stevia (stevia-G) can effectively improve the dissolution and bioavailability of poorly water-soluble drugs. Furthermore, addition of an ionic surfactant to stevia-G solution has been shown to enhance the dissolution effect of stevia-G on flurbiprofen. Herein, 4 surfactants, namely sodium dodecyl sulfate, sodium N-dodecanoylsarcosinate, sodium monododecyl phosphate, and lauryltrimethylammonium chloride (LTAC) were screened to investigate their synergistic effect with stevia-G in enhancing the solubility of mefenamic acid (MFA). The ternary formulation containing LTAC produced the highest increase in solubility, whereas the binary MFA/LTAC formulation did not increase the solubility of MFA. Surface tension was evaluated to analyze the interaction between stevia-G and each ionic surfactant, wherein the Rubingh model was applied to predict mixed micelle formation between stevia-G and LTAC. Interaction parameters calculated by the Rubingh model reflected mixed micelle formation between stevia-G and LTAC relative to the self-interactions of the 2 individual surfactants. All interaction parameters in this system showed negative values, indicating a favorable interaction (e.g., hydrogen bond or electrostatic and dipole) between binary components in the mixed micelles. Spray-dried particles of ternary formulations (MFA/stevia-G/LTAC) were prepared to evaluate the dissolution profile and physicochemical properties. Dissolution profiling showed that the concentration of MFA released from spray-dried particles was significantly higher than untreated MFA.

Introduction

Presently, approximately 40% of new candidate drugs are excluded during early developmental stages due to their low bioavailability, which is largely a result of poor water solubility.[1] Furthermore, over 70% of synthetic drug molecules have solubility problems.[2,3] Thus, one of the main objectives of pharmaceutical technology development is improvement in dissolution profiles of poorly water-soluble drugs. A number of techniques have already been investigated and employed, such as solid dispersion systems,[4-6] nanoparticles,[7,8] and surfactants.[9,10]

Recently, the feasibility of transglycosylated food additives as novel pharmaceutical excipients to improve the dissolution and bioavailability of poorly water-soluble drugs has been reported.[11-15] In particular, transglycosylated stevia (stevia-G) (Fig. 1) was found to improve the dissolution and bioavailability of several poorly water-soluble compounds.[16-18] Stevia-G is the transglycosylated form of stevioside, obtained from *Stevia rebaudiana* leaves. Stevia plant contains natural sweetner used in food. An acceptable daily intake of stevia-G has not been known although that of stevia is 12 mg/kg/day.[19] The sweetness of stevia-G may have the potential to mask the bitter taste of many drugs. Stevia-G's self-assembly behavior and micellar drug inclusion capacity could achieve significant enhancement in solubility of poor water-soluble drugs.[20] It is, however, difficult to maintain it in the supersaturated state because the micellar structure of stevia-G is unstable in supersaturated solution. This means that the structure formed by stevia-G was less rigid than that of a commonly used surfactant, because the previous results on the surface tension study of stevia-G and fluorescence study indicated that stevia-G showed a weak surface activity property and formed a hydrophobic core in water.[17] Thus, further addition of an

Abbreviations used: CMC, critical micelle concentration; DLS, dynamic light scattering; FP, flurbiprofen; LTAC, lauryltrimethylammonium chloride; MFA, mefenamic acid; PXRD, powder X-ray diffraction; SDPs, spray-dried particles; SDS, sodium dodecyl sulfate; SLAS, sodium N-dodecanoylsarcosinate; SMP, sodium monododecyl phosphate; Stevia-G, transglycosylated stevia.

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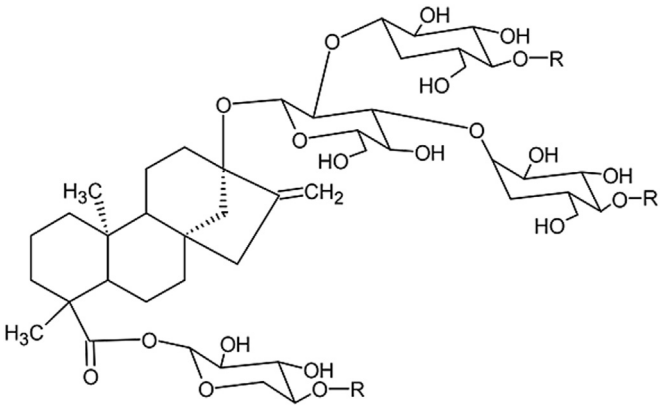

Figure 1. Chemical structure of stevia-G.

excipient to the binary system compound/stevia-G solution could be a promising way to significantly enhance dissolution and stabilize the supersaturated state. Previously, we reported that a polymer of polyvinylpyrrolidone had a long-lasting, solubility-enhancing effect on curcumin in formulations including a transglycosylated compound.[21]

Surfactants have been commonly used as pharmaceutical excipients to increase the solubility of poorly water-soluble drugs.[22] However, the use of surfactants has been limited by their charged characteristics and cytotoxic effects. To decrease the amount of surfactants in formulations, mixed surfactant systems have been used with various pharmaceutical technologies.[23-26] Mixed micelle systems have characteristic properties that are superior to those of single micelle systems, and their synergistic effects can reduce the total amount of surfactant needed.[27] Previously, we reported that addition of sodium dodecyl sulfate (SDS) to stevia-G solution enhanced the dissolution of flurbiprofen (FP).[28] Moreover, the solubility of FP was increased by mixing stevia-G with ionic surfactants, while nonionic surfactants did not exhibit the same increase. These results suggest that stevia-G has a stronger interaction with ionic than nonionic surfactants. The interaction mechanism between stevia-G and ionic surfactants is not yet understood although the concept of mixed surfactant systems has been reported previously.[29-31] We hypothesized that it may be possible to efficiently design pharmaceuticals using stevia-G/surfactant formulations if the concept of the mixed micelle system was applicable to the interaction between stevia-G and ionic surfactants. The mixed micelle system has been explained by the Rubingh model[32] based on the relationship between the mole fraction and critical micelle concentration (CMC) of each component. This model has made a comprehensive theoretical attempt to deal with nonideal mixtures based on the regular solution theory.[33] In addition, we could predict the component ratio of mix micelle from Rubingh model.

In this study, we investigated the effect of stevia-G and ionic surfactants on solubility of mefenamic acid (MFA), poorly water-soluble drug, as well as the mechanism of interaction between stevia-G and the ionic surfactant. Phase solubility and dissolution profiles were evaluated to understand the synergistic effect of stevia-G and ionic surfactants on solubility of MFA. The solubility study was preliminary performed by changing the hydrophobic carbon chain lengths of surfactants (e.g., C8, C12, C16, and C18) because the CMC values were affected by the hydrophobic carbon chain lengths. The solubility of several drugs was improved by using stevia-G and surfactants of C12. Ionic surfactants with various polar head groups but the same hydrophobic chain length were screened via preliminary experiments, and 4 were selected [SDS, sodium N-dodecanoylsarcosinate (SLAS), lauryltrimethylammonium chloride (LTAC), and sodium monododecyl phosphate (SMP)] to further investigate the synergistic effect of the stevia-G/ionic surfactant system on improving the solubility of different target compounds. By evaluating the surface tension of mixed solutions of stevia-G and ionic surfactants, the feasibility of applying the Rubingh model to analyze their interactions was examined. Finally, we evaluated the dissolution profiles of the ternary MFA/stevia-G/LTAC formulation to use the formulation in a practical way for the future.

Materials and Methods

Materials

MFA was kindly supplied by Towa Pharmaceutical Co., Ltd. (Osaka, Japan). Stevia-G (Fig. 1) was a gift from the Toyo Sugar Refining Co. (Tokyo, Japan). SDS was purchased from Nacalai Tesque, Inc. (Kyoto, Japan). SLAS and LTAC were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). SMP was purchased from Tokyo Kasei Co., Ltd. (Tokyo, Japan).

Solubility

The ternary MFA (50 mg)/stevia-G/surfactant formulation was dispersed in distilled water (25 mL) and incubated for 24 h at 37°C with shaking (100 strokes/min; ML-10; Taitec, Co., Ltd., Saitama, Japan). Solubilization effects were determined with reference to those of untreated MFA and bicomponent 1:1 (wt/wt) MFA/surfactant and 1:10 (wt/wt) MFA/stevia-G formulations.

Samples were filtered through a 0.2 μm membrane. HPLC analysis was performed on a Waters Alliance reverse-phase HPLC system with a COSMOSIL 5C18-MS-II column (4.6 × 150 mm; Nacalai Tesque, Inc.) and a mobile phase consisting of acetonitrile and phosphate buffer [adjusted to pH 6.8 with 50:50 (vol/vol) NaOH] in the isocratic flow (flow rate 1.2 mL/min); a wavelength of 254 nm was chosen based on the UV-Vis spectrum. The injection volume was 10 μL, and the analysis was carried out at 40°C.

Particle Size Distribution by Dynamic Light Scattering

The volumetric particle size distribution in the micelle was determined by dynamic light scattering (DLS) analysis using a Microtrac UPA (MicrotracBEL, Corp., Osaka, Japan) without dilution. The mean particle size was taken as the average value of 3 determinations. The detection range of the UPA instrument was 0.3 nm to 6 μm.

Surface Tension

Surface tension was measured by an online tensiometer (SITA, Messtechnik, Germany) which measured the whole dynamic range of each surface tension by measuring bubble pressure. In this study, a long bubble lifetime (1000 ms) was selected. Measurements were carried out after thorough mixing and temperature equilibration at 25 ± 0.5°C.

Verification of Optimum Molar Ratio of Stevia-G and Surfactant

The solubility study of MFA was performed using physical mixture of MFA/stevia-G/LTAC to verify the optimum molecular ratio of mix micelle between stevia-G and LTAC. The ternary MFA (50 mg)/stevia-G/surfactant formulations were dispersed in distilled water (25 mL). Samples were prepared by using different mole ratios of stevia-G:LTAC (0.05:0.95, 0.1:0.9, 0.2:0.8, 0.4:0.6, 0.5:0.5, and 0.8:0.2), where the total amount of stevia-G and LTAC