International Journal of Pharmaceutics 428 (2012) 183–186

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Note

Nanocomposite formation between alpha-glucosyl stevia and surfactant improves the dissolution profile of poorly water-soluble drug

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ARTICLE INFO

Article history:
Received 2 December 2011
Received in revised form
19 December 2011
Accepted 7 January 2012
Available online 14 January 2012

Keywords:
α-glucosyl stevia
Flurbiprofen
Surfactant
Dissolution enhancement
Nanocomposite

ABSTRACT

The formation of a hybrid-nanocomposite using α-glucosyl stevia (Stevia-G) and surfactant was explored to improve the dissolution of flurbiprofen (FP). As reported previously, the dissolution amount of FP was enhanced in the presence of Stevia-G, induced by the formation of an FP and Stevia-G-associated nanostructure. When a small amount of sodium dodecyl sulfate (SDS) was present with Stevia-G, the amount of dissolved FP was extremely enhanced. This dissolution-enhancement effect was also observed with the cationic surfactant of dodecyl trimethyl ammonium bromide, but not with the non-ionic surfactant of *n*-octyl-β-D-maltopyranoside. To investigate the dissolution-enhancement effect of Stevia-G/SDS mixture, the pyrene I_1/I_3 ratio was plotted versus the Stevia-G concentration. The pyrene I_1/I_3 ratio of Stevia-G/SDS mixture had a sigmoidal curve at lower Stevia-G concentrations compared to the Stevia-G solution alone. These results indicate that the Stevia-G/SDS mixture provides a hydrophobic core around pyrene molecules at lower Stevia-G concentrations, leading to nanocomposite formation between Stevia-G and SDS. The nanocomposite of Stevia-G/SDS showed no cytotoxicity to Caco-2 cells at a mixture of 0.1% SDS and 1% Stevia-G solution, whereas 0.1% SDS solution showed high toxicity. These results suggest that the nanocomposite formation of Stevia-G/SDS may be useful way to enhance the dissolution of poorly water-soluble drugs without special treatment.

Many new drug entities are poorly water-soluble. Therefore, one of the main themes of pharmaceutical research is strategy for improving the dissolution profiles of drugs. Various techniques have been used to improve the dissolution profile of poorly water-soluble drugs, including the use of surfactants (Wong et al., 2006), inclusion complexation (Wang et al., 2009) and solid dispersions (Boghra et al., 2011; Tho et al., 2010). We have already reported the formation in aqueous media of micelle-like nanostructures by α-glucosyl stevia (Stevia-G), a trans-glycosylated food additive, which improve the dissolution and bioavailability of poorly water-soluble drugs (Uchiyama et al., 2011). However, a high concentration of Stevia-G is required to achieve significant dissolution enhancement.

Surfactants are commonly used as pharmaceutical excipients to increase the solubility of insoluble drugs (Sakeer et al., 2010). However, the use of surfactants is limited by their charged nature and irritative effect. Mixed surfactant systems comprised of common surfactants, such as alkyl sulfates and alcohol ethoxylates, have been extensively investigated (Croce et al., 2004; Griffiths et al., 1999; Penfold et al., 1999). Mixtures of surfactant solution form mixed micelles through specific interactions between the heterostructured surfactants. Mixtures have characteristic properties that are superior to those of the single component. (Mehta et al., 2009; Yan et al., 2009; Zhang et al., 2010). The synergistic effect of mixed surfactant systems may reduce the total amount of surfactants used in pharmaceutical applications (Garcia et al., 1992). This might be significant advantage in the case of pharmaceuticals, which require the limited use of surfactants owing to toxicity-related complications.

The aim of the present study was to investigate the possibility of the formation of nanocomposites of Stevia-G and surfactants that would improve the dissolution profile of poorly water-soluble drugs. Flurbiprofen was used as poorly water-soluble model drug and sodium dodecyl sulfate (SDS), dodecyl trimethyl ammonium bromide (DTAB) and *n*-octyl-β-D-maltopyranoside (OMP) were used as surfactants with Stevia-G. The dissolution profiles of flurbiprofen from the tricomponent of FP/Stevia-G/surfactant were compared to those of the untreated drug. To demonstrate the specific interaction between Stevia-G and the surfactant, the microenvironmental change around pyrene and changes of surface tension value were also assessed.

We investigated three type surfactants: anionic, cationic and non-ionic. The dissolution profiles of FP from the simple mixing of a FP/Stevia-G/SDS tricomponent containing 50 mg FP in distilled water (50 mL, shaking speed; 60 spm) were determined with reference to those of untreated FP and bicomponents of FP/SDS (1/1

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doi:10.1016/j.ijpharm.2012.01.016

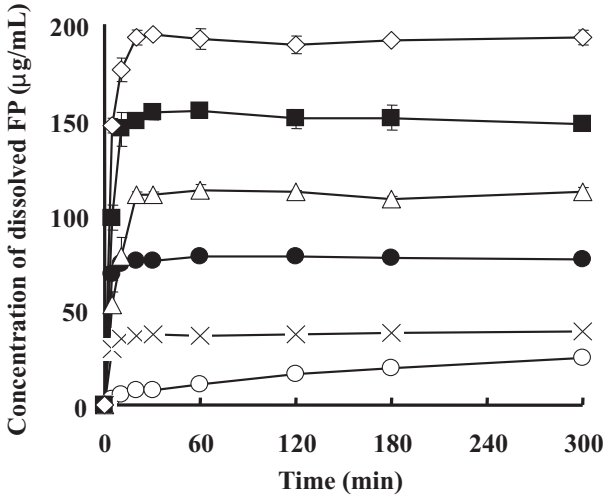

Fig. 1. Dissolution profiles of FP from Stevia-G/SDS systems in distilled water (○), Untreated FP, (×) bicomponent of FP/SDS (1/1 w/w); (●), bicomponent of FP/Stevia-G (1/10 w/w); (△), tricomponent of FP/Stevia-G/SDS (1/10/0.2 w/w/w); (■), tricomponent of FP/Stevia-G/SDS (1/10/0.5 w/w/w); (◊), tricomponent of FP/Stevia-G/SDS (1/10/1 w/w/w).

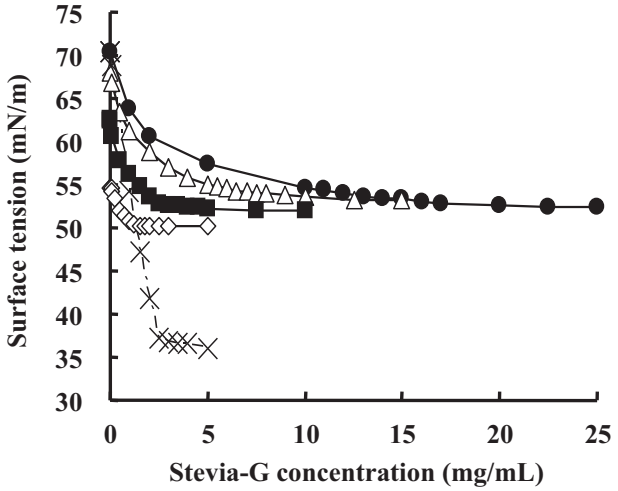

Fig. 2. Changes in surface tension as a function of Stevia-G concentration in distilled water (●), Stevia-G solution; (×) SDS solution; (△), Stevia-G solution with 0.2 mg/mL SDS; (■), Stevia-G solution with 0.5 mg/mL SDS; (◊), Stevia-G solution with 1 mg/mL SDS.

w/w) and FP/Stevia-G (1/10 w/w) (Fig. 1). The solubility of FP was estimated as ca. 35 μg/mL in distilled water after incubation at 37 °C for 1 week. The dissolved amount of FP from the FP/SDS (1/1 w/w) bicomponent was almost the same as the solubility of FP itself while the concentrations of FP following dissolution from the FP/Stevia-G (1/10 w/w) bicomponent were 2-fold higher than that of the untreated FP. We have already reported the nanostructure formation by Stevia-G in aqueous media, and demonstrated that this nanostructure can encapsulate a poorly water-soluble drug (Uchiyama et al., 2011). On the other hand, the amount of dissolved FP from the FP/Stevia-G/SDS tricomponent was dramatically increased compared to that of untreated FP, or either bicomponent, FP/SDS (1/1 w/w) or FP/Stevia-G (1/10 w/w). In addition, the concentration of dissolved FP in the tricomponent system increased with the SDS amount. Specifically, the amount of FP dissolved from the FP/Stevia-G/SDS (1/10/1 w/w/w) tricomponent was about 7-fold that of untreated FP. Changes in surface tension were assessed to investigate the dissolution-enhancement effect and interaction between Stevia-G and SDS. Fig. 2 shows the plots of the surface tension in binary mixtures of SDS and Stevia-G of different compositions. The surface tension of SDS and Stevia-G solution reached a break point at 2.5 mg/mL SDS and 15 mg/mL Stevia-G concentration, respectively, whereas the surface tension values of the binary mixture of Stevia-G/SDS were slightly lower than that of the Stevia-G solution. The break point of surface tension of the binary mixture of Stevia-G/SDS solution was achieved by a lower Stevia-G concentration compared of that of the Stevia-G solution alone.

The I_1/I_3 ratio of the fluorescence spectra of pyrene was plotted to assess the aggregation process of the Stevia-G/SDS system in greater detail. Pyrene has been often used for the investigation of microenvironmental changes in micellar solutions (Tsubonea and Ghoshb, 2004). Fig. 3 shows plots of the pyrene I_1/I_3 ratio index in binary mixtures of SDS and Stevia-G of different compositions. The critical micelle concentration (cmc) of Stevia-G and SDS solution calculated from the pyrene I_1/I_3 plot was about 16 and 2.5 mg/mL respectively. As the SDS concentration contained in Stevia-G solution increased, the pyrene I_1/I_3 ratio reached a constant value at lower Stevia-G concentrations. This result indicates that a binary mixture of Stevia-G/SDS provides a hydrophobic environment around pyrene molecules under low Stevia-G concentrations, causing a hybrid nanocomposite to form between Stevia-G and SDS. The cmc values of the Stevia-G solution with 0.2 mg/mL SDS, 0.5 mg/mL SDS and with 1.0 mg/mL SDS were 7.2, 2.5 and 0.8 mg/mL, respectively. The decrease in cmc results in an increase in the solubilization potential in the micellar systems.

The size of nanocomposite formed by interaction between Stevia-G and SDS was several nanometers as determined by dynamic light scattering (data not shown). Although that range of size might not be measured accurately by dynamic light scattering, the existence of nanocomposite was at least confirmed. The mixed-surfactant system shows favorable characteristics in comparison to micelles formed by single surfactants (Liang et al., 2011; Zhang et al., 2011). In mixed-surfactant systems, it is well-known that physical properties, such as the cmc, can be significantly lower than would be expected from the properties of the pure components (Penfold et al., 1999). Such solubilizing-enhancement effects—highly valuable in the pharmaceutical field—are due to the occurrence of interactions between different surfactants. Patel and Joshi (2008) reported the possibility of using a mixed surfactant system as a carrier in a solid dispersion (Patel and Joshi, 2008). They showed that mixed surfactant blends showed higher solubility than the individual surfactants. The synergistic behavior of mixed surfactant systems may be exploited to reduce the total amount of surfactants used in particular applications.

Fig. 4(a) shows the effect of the addition of DTAB, a cationic surfactant, on dissolution profiles of the FP in distilled water. The amount of dissolved FP from a FP/DTAB (1/4 w/w) bicomponent was almost the same as the estimated FP solubility. On the other hand, the concentration of dissolved FP from the FP/Stevia-G/DTAB (1/10/4 w/w/w) tricomponent was markedly improved, with 4.5-times higher solubility than untreated FP.

Fig. 4(b) shows the dissolution profiles of FP from tricomponents of FP/Stevia-G/OMP in distilled water. OMP is a nonionic surfactant consisting of a hydrocarbon chain linked to a sugar residue. The addition of OMP to an FP/Stevia-G bicomponent did not improve the amount of dissolved FP nearly to the same degree as the FP/Stevia-G/SDS and FP/Stevia-G/DTAB tricomponents. The pyrene I_1/I_3 ratio of the Stevia-G/DTAB mixture indicated a sigmoidal curve at the lower Stevia-G concentration compared to the Stevia-G solution alone. However, the pyrene I_1/I_3 ratio plot from binary mixtures of OMP/Stevia-G was almost same as that of Stevia-G solution alone (data not shown). These results may suggest that Stevia-G interacts more strongly with ionic surfactants than nonionic surfactants. Fig. 5 shows the schematic representation of a nanocomposite formed by SDS and Stevia-G-aggregated nanostructure. Data from

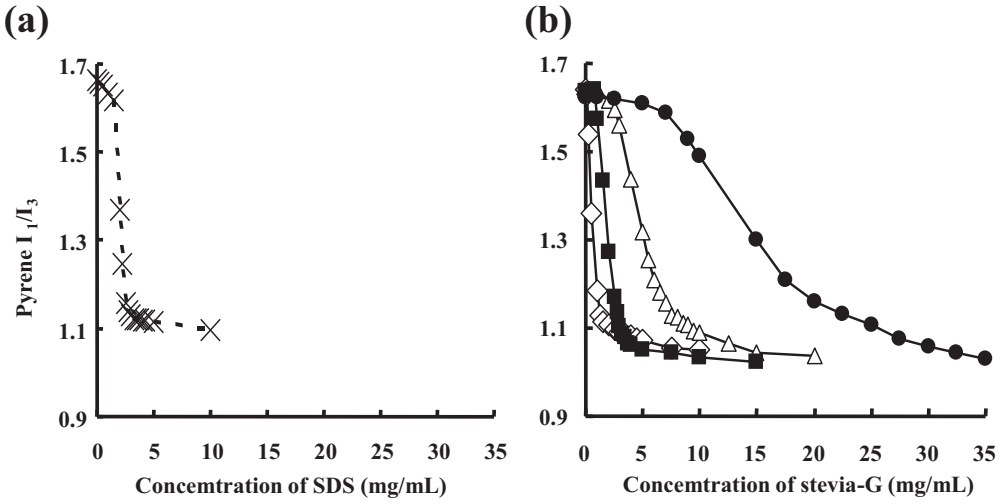

Fig. 3. Plot of Pyrene I_1/I_3 ratios versus (a) SDS and (b) Stevia-G concentration (●), Stevia-G solution; (×) SDS solution; (△), Stevia-G solution with 0.2 mg/mL SDS; (■), Stevia-G solution with 0.5 mg/mL SDS; (◊), Stevia-G solution with 1 mg/mL SDS).

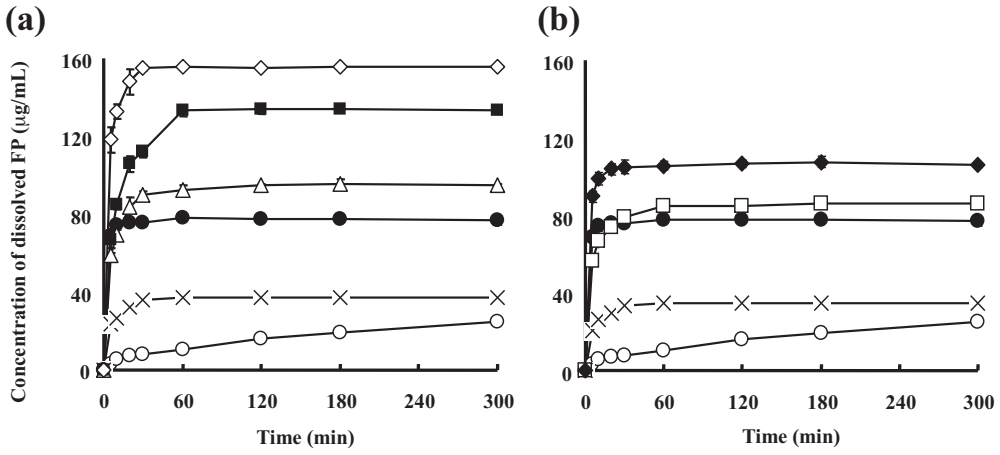

Fig. 4. Dissolution profiles of FP from (a) Stevia-G/DTAB system and (b) Stevia-G/OMP systems in distilled water. (○), Untreated FP; (×) bicomponent of FP/DTAB (1/4 w/w) or bicomponent of FP/OMP (1/4 w/w); (●), bicomponent of FP/Stevia-G (1/10 w/w); (△), tricomponent of FP/Stevia-G/DTAB (1/10/1 w/w/w); (■), tricomponent of FP/Stevia-G/DTAB (1/10/2 w/w/w); (◊), tricomponent of FP/Stevia-G/DTAB (1/10/4 w/w/w); (□), tricomponent of FP/Stevia-G/OMP (1/10/1 w/w/w); (♦), tricomponent of FP/Stevia-G/OMP (1/10/4 w/w/w)).

the dissolution studies and pyrene I_1/I_3 ratio plot may indicate that SDS or DTAB was able to intercalate into nanostructures of Stevia-G-aggregates such as Fig. 5. Meanwhile, OMP may not form an intercalated structure, since no effect of dissolution enhancement was observed. The intercalation of the nonionic surfactant was reported to shield the repulsive interactions between the charged headgroups of the ionic surfactant, enhancing the electrostatic stabilization of the mixed micelles. In addition, the contribution of an

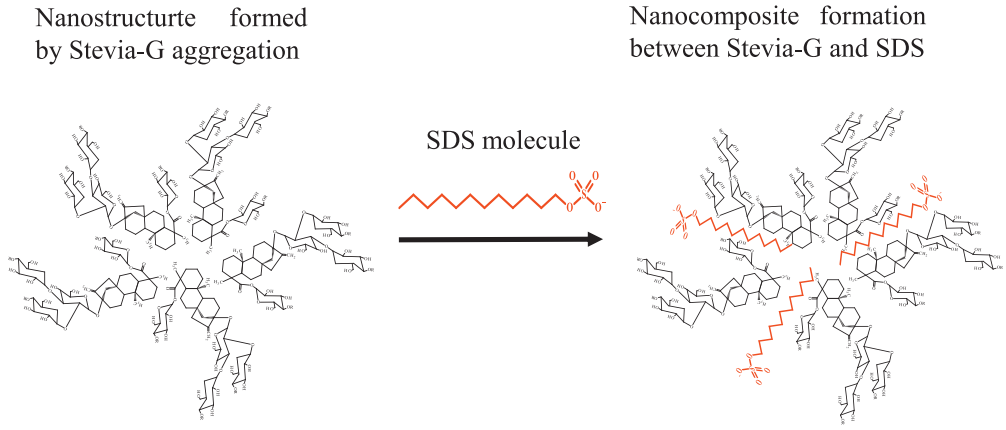

Fig. 5. Schematic representation of nanocomposite formation among SDS and Stevia-G-aggregated nanostructures.

attractive ion–dipole interaction between the headgroups of ionic and nonionic components enhances the thermodynamic stability (Hierrezuelo et al., 2005). The interaction between Stevia-G and SDS reduced the repulsion of charged headgroups of SDS and may stabilize the micelle structure. The thermodynamic stability of the mixed micelle would enhance the incorporability of solutes into the micellar phase.

There was no cytotoxicity to Caco-2 cells at levels of 1% Stevia-G solution (see Supporting information Fig. S1). In the case of the SDS solution, a significant decrease of viability was observed even for a 0.1% solution. Meanwhile, the viability of Caco-2 cells remained unchanged when the cells came into contact with a binary mixture of 1% Stevia-G/0.1% SDS solution, indicating the very low cytotoxicity of the binary mixture. Clearly, low toxicity is a key advantage for pharmaceutical oral formulations.

In conclusion, the nanocomposite formation of Stevia-G/surfactant with simple blending in distilled water will be a useful way to enhance the dissolution profile of flurbiprofen without special treatment.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan(22790041). We thank Toyo Sugar Refining Co., Ltd., for the kind gift of α-glycosyl transferase-treated stevia.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2012.01.016.

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