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ORIGINAL ARTICLE

Evaluation of the impact of sodium lauryl sulfate source variability on solid oral dosage form development

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Abstract

Objective: The objective of this study was to investigate the effects of sodium lauryl sulfate (SLS) from different sources on solubilization/wetting, granulation process, and tablet dissolution of BILR 355 and the potential causes. *Methods*: The particle size distribution, morphology, and thermal behaviors of two pharmaceutical grades of SLS from Spectrum and Cognis were characterized. The surface tension and drug solubility in SLS solutions were measured. The BILR 355 tablets were prepared by a wet granulation process and the dissolution was evaluated. *Results*: The critical micelle concentration was lower for Spectrum SLS, which resulted in a higher BILR 355 solubility. During wet granulation, less water was required to reach the same end point using Spectrum than Cognis SLS. In general, BILR 355 tablets prepared with Spectrum SLS showed a higher dissolution than the tablets containing Cognis SLS. Micronization of SLS achieved the same improved tablet dissolution as micronized active pharmaceutical ingredient. *Conclusions*: The observed differences in wetting and solubilization were likely due to the different impurity levels in SLS from two sources. This study demonstrated that SLS from different sources could have significant impact on wet granulation process and dissolution. Therefore, it is critical to evaluate SLS properties from different suppliers, and then identify optimal formulation and process parameters to ensure robustness of drug product manufacture process and performance.

Key words: *Critical micelle concentration; dissolution; micronization; poorly soluble drug; sodium lauryl sulfate; solid dosage form; solubility; supersaturation; surface tension; wet granulation*

Introduction

The solubility behavior of a drug is one of the key factors to affect its oral bioavailability. Drugs with poor aqueous solubility are likely to have a low bioavailability after oral administration because of solubility and dissolution limited absorption[1]. In recent years, the number of poorly soluble drug candidates has risen sharply[2]. When coupled with high therapeutics dose, formulation development of these drugs for oral delivery presents significant challenges to the formulation scientists in the pharmaceutical industry. Improving solubility and/or dissolution rate is necessary for enhancing the oral bioavailability of low solubility drugs[3]. A number of formulation approaches have been used to enhance dissolution and solubility, including pH adjustment with acidifier or basifier[4,5], carrier complexation[6,7], formation of a solid dispersion[8–11], using an amorphous form of the drug[12,13], particles size reduction[14–16], and the use of surfactants[17–20].

Micellar solubilization with surfactants is a common way to enhance the solubility of the poorly soluble drug in the solid dosage forms[21]. The surfactant and micellar system can play one or multiple roles to enhance drug solubility, improve the drug particle wetting and dissolution, and reduce or eliminate drug precipitation. The mechanism of surfactant or micellar solubilization has been extensively studied[22,23]. Micelles possess a number of advantages as a potential drug delivery system for poorly soluble drugs. First, the hydrophobic core of micelles may be used as a reservoir for encapsulation of a variety of poorly soluble drug molecules. Such

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encapsulation substantially increases the bioavailability through solubilization or inhibition of precipitation upon dosage form administration[24]. Second, both ionic and non-ionic surfactants have been frequently used in oral and injectable pharmaceutical systems because of their advantages of compatibility, stability, and minimal binding to proteins[25]. Finally, from the manufacturing point of view, the drug delivery system utilizing surfactants for solubilization is generally more adaptable to large scales and cost-effective than other non-conventional dosage forms such as solid dispersion[26]. Sodium lauryl sulfate (SLS) is an anionic surfactant with a high solubilizing potential and commonly used in solid oral dosage formulation to enhance the solubility of poorly soluble drugs[27,28]. Beside its ability to enhance the solubility and/or dissolution, SLS also affects the manufacturing process of solid oral dosage form such as compaction[29]. There are several commercial sources of SLS. It is known that SLS from different sources contains different amounts of surface-active impurities, most of which are homologous alcohols with surface activities more than two orders of magnitude higher than SLS itself[30]. These surface impurities, known or unknown, may contribute to the functions of a surfactant and change the solubilizing effect of SLS when it is used in the dissolution medium or solid oral dosage form to improve the drug solubility[31]. In addition, SLS from different sources may have different physical properties, such as melting point, particle size, and morphology, which may also influence the dissolution as well as manufacturing process of a drug product.

BILR 355 (11-ethyl-5,11-dihydro-5-methyl-8-[2-[(1-oxido-4-quinolinyl)oxy]ethyl]-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-one) was a non-nucleoside reverse transcription inhibitor (NNRTI) which showed favorable responses against resistant strains of HIV-1. BILR 355 was a free base with a p*K*a of 2.5, which limited options for salt formation. The crystalline form of the drug was a dihydrate and practically insoluble in aqueous media at the physiological pH with a solubility of about 8 μg/mL at pH 2.0 and 2 μg/mL at pH 7.3. Given the high projected dose of >300 mg and poor aqueous solubility, the absorption of BILR 355 would be most likely solubility limited in a solid oral dosage form. Therefore, a solubilizing agent in the formulation was required for boosting the drug solubility and/or dissolution and subsequently enhancing the bioavailability. With a low p*K*a, solubilization by means of pH adjustment with an acidifying agent was very limited. Other approaches had been attempted to improve the solubility/dissolution of BILR 355 such as the use of micronized drug in combination with poloxamer 188 as wetting agent, incorporation of non-ionic surfactant such as Tween 80 or Vitamin E TPGS, and complexation with β-cyclodextrins. The above approaches showed no or minimal improvement in dissolution of BILR 355, when incorporated in a tablet formulation as compared to the formulation containing no solubilizer. SLS was found to be most effective in improving the solubility/dissolution of BILR 355 and selected as the solubilizer for formulation development. However, SLS from various sources behaved differently in BILR 355 tablets. The objectives of this study were to evaluate the effects of SLS from different sources on wet granulation process and in vitro performance of BILR 355 tablets and investigate the potential causes.

Materials

The active pharmaceutical ingredient (API) BILR 355, a crystalline dihydrate, used in this work was an investigation drug from the Boehringer Ingelheim Pharmaceutical Inc. (Ridgefield, CT). SLS of pharmaceutical grade was purchased from two commercial sources, Spectrum Chemicals & Laboratory Products (Gardena, CA) and Cognis (TEXAPON® K12 P PH, NF/Ph.Eur., Düsseldorf, Germany). An ultrapure grade of SLS (>99.0%) was purchased from Sigma-Aldrich (St. Louise, MO) and used for comparison purpose. Table 1 provides information of SLS samples from the vendor Certificate of Analysis (C of A). Other excipients were povidone (Plasdone K-29/32®, ISP Technologies, Wayne, NJ), lactose monohydrate (Fast Flo® 316, Foremost Farms USA, Barboo, WI), microcrystalline cellulose (Avicel® PH 200, FMC Corporation, Philadelphia, PA), sodium starch glycolate (Primojel®, Generichem Corp., Totowa, NJ), colloidal silicon dioxide (AEROSIL®, Degussa, Ridgefield Park, NJ), and magnesium stearate (vegetable grade, Mallinckrodt, St. Louis, MO). These excipients were selected because they are commonly used in tablet formulation. BILR 355 and the SLS from Spectrum and Cognis were used as received and micronized by jet-milling.

Table 1. Analysis results for SLS samples.

Test results	Spectrum Lot A	Spectrum Lot B	Cognis	Sigma ultrapure
Assay (%)[a]	87.7	98.4	96.3	99.5
Assay (%)[b]	93.1	94.0	–	–
Sodium chloride & sodium sulfate (%)[a]	0.69	0.03	2.50	n/a
Unsulfated alcohols (%)[a]	0.47	0.47	0.30	n/a
Melting temperature (°C)[c]	192.4	192.1	198.3	200.4

[a]The data from vendor's Certificate of Analysis. [b]Data from internal analysis using European Pharmacopoeia procedure. [c]The data from DSC analysis, the melting of the dehydrated phase of SLS.

Methods

Particle size distribution and morphology for SLS and BILR 355

The particle size distribution (PSD) of BILR 355 and SLS was measured with a Sympatec HELOS laser diffraction particle sizer (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The morphology and shape of SLS particles were examined using a Hitachi S4700 scanning electron microscope—SEM (Hitachi High Technologies America, Schaumburg, IL).

Thermal analysis of SLS

The thermal behavior of the SLS samples was analyzed by TA Instruments Q1000 differential scanning calorimeter (TA Instruments, New Castle, DE). Approximately 4 mg of SLS sample was weighed into a 40 µL aluminum pan. Pans were hermetically sealed with a pinhole. Samples were heated from 25°C to 220°C at a controlled rate of 10°C per minute. Dry nitrogen was used as purging gas at a rate of 50 mL/min.

Surface tension of SLS solutions

The surface tensions of dilute solutions of SLS from Spectrum, Cognis, and Sigma with concentrations range from 0.01% to 1.0% (w/v) or 0.35 to 34.7 mM were measured at 20 ± 0.2°C. In addition, the surface tensions of Spectrum SLS solutions spiked with NaCl as well as Sigma ultrapure SLS solutions spiked with additional lauryl alcohol were also measured. The method was the Wilhelmy plate technique with a CAHN Dynamic Contact Angle Analyzer (Model # 2120012, Cerritos, CA). The platinum plate was cleaned between each measurement by heating with a butane flame. Calibration was performed prior to the use of the instrument and then verified using purified deionized water (surface tension of 72.8 dynes/cm at 20°C). Three separate measurements were made for each solution. The surface tension values were then plotted as a function of the logarithms of the SLS concentrations (mM), in which the interception of the two straight lines at low and high SLS concentrations was defined as the critical micelle concentration (CMC).

Equilibrium solubility of BILR 355 in SLS solutions

Solubility of BILR 355 at 37 ± 0.2°C was measured in duplicate by adding excess API in 7 mL water with SLS concentrations ranging from 0.01% to 1.0% (w/v) or 0.35 to 34.7 mM. Individual samples were prepared in sealed glass vials and rotated for 48 hours in a 37°C oven. The solution was filtered through 0.45 µm PVDF filter after 48-hour rotation and analyzed by HPLC. Equilibrium was confirmed by sampling at 24 and 48 hours, where the API concentrations at the two time points were similar.

BILR 355 tablet preparation

Seven batches of the tablets were prepared using blends containing BILR 355, lactose monohydrate, microcrystalline cellulose, PVP, sodium starch glycolate, magnesium stearate, and SLS. The tablets contained 150 mg BILR 355. For all batches, the formulation compositions were same except the sources of SLS. The batch size for the granulation was about 106 g and the final batch size for tableting was about 374 g for all seven batches. During the manufacture, BILR 355 was mixed with SLS at 1:1 w/w and PVP, and then granulated with water in a Diosna high shear mixer with 1 L bowl (Diosna, Osnabrück, Germany). The dried granulation was milled and mixed with other excipients and then blended with magnesium stearate for tableting. Tablets were compressed on a Piccola tablet press (Riva, Buenos Aries, Argentina) at 15 rpm using a 19.1 × 9.3 mm oval shape punch/die set to a target hardness of 12.0 kP. For the tablet manufacturing process, the amount of water and granulation time were adjusted to achieve same visual end point, whereas other process parameters were same.

Dissolution testing

Tablet dissolution was performed using the USP Apparatus II (basket method at 100 rpm) on a VanKel VK 7000 dissolution testing system (VanKel, Cary, NC). For better mimicking the tablet dissolution in gastrointestinal tract, a two-step dissolution method was used. The dissolution medium for the first step was 100 mL of simulated gastric fluid (SGF, pH 1.2, HCl/0.15N NaCl) and the medium for the second step was 500 mL of 50 mM sodium phosphate buffer (pH 6.5) containing 0.03% (w/v) SLS [SLS solution, 13% (w/w), Anachemia Chemicals Inc., Rouses Point, New York]. Tablets were tested in 100 mL SGF at 37°C first and then at 30 minutes 400 mL of 62.5 mM sodium phosphate buffer (37°C, pH 7.1) with 0.0375% (w/v) SLS was added to make the final medium. Aliquots were collected at 45, 60, 75, and 90 minutes in the final medium with a final spin to 120 minutes at 250 rpm. All samples were first filtered online using a 10 µm full flow filter (VanKel, Cary, NC) and then immediately filtered offline again through a 0.45 µm filter to remove any fine particles. All dissolution samples were analyzed by HPLC.

Results and discussions

Morphology and particle size distribution

The SEM pictures for the SLS from Spectrum and Cognis (unmicronized and micronized) as well as Sigma are shown in Figures 1–5. For unmicronized SLS from Spectrum, most particles were sphere-like shape with less than 25 μm in length and some aggregates greater than 150 μm. For unmicronized Cognis SLS, most particles were larger, porous, and irregularly shaped aggregates. After micronization, the SLS particle morphology from the two vendors was similar. Significant reduction in particle size was achieved via micronization. For ultrapure SLS from Sigma, the particles were thin plate-like as fused agglomerates, and the surfaces had a lamellar structure with layers of material forming the particles

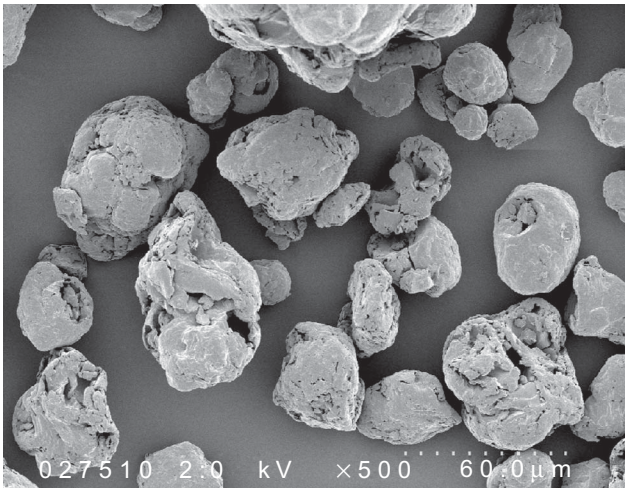

Figure 1. The SEM image of unmicronized SLS from Spectrum.

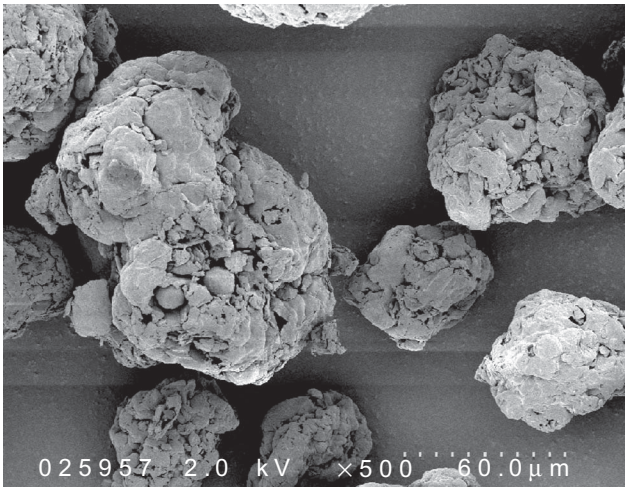

Figure 2. The SEM image of unmicronized SLS from Cognis.

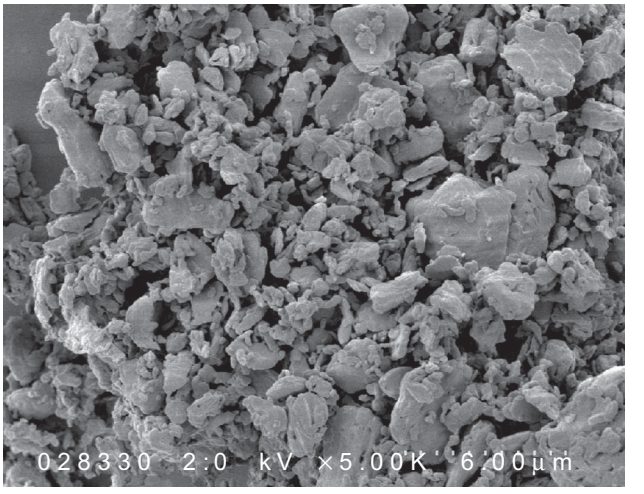

Figure 3. The SEM image of micronized SLS from Spectrum.

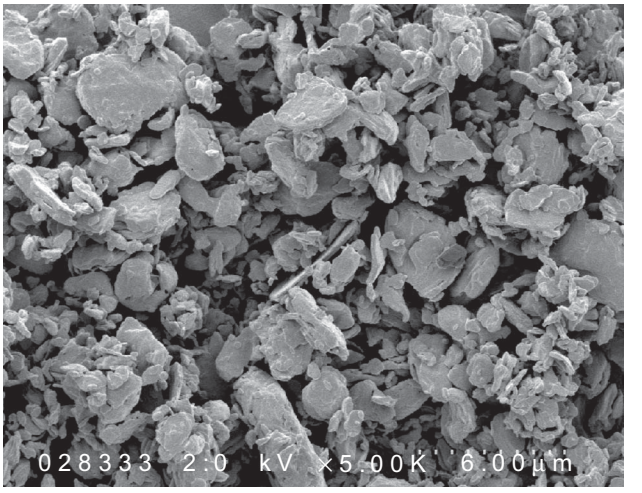

Figure 4. The SEM image of micronized SLS from Cognis.

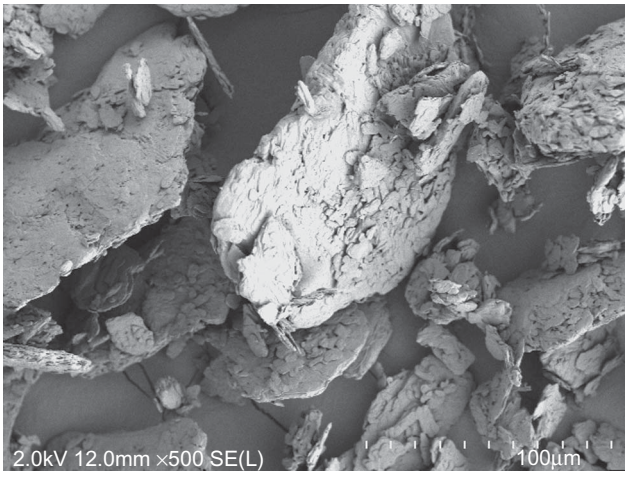

Figure 5. The SEM image of Sigma ultrapure SLS.

ranging from about 2 µm to several hundreds micrometer in diameter.

PSD for SLS samples is shown in Figure 6. Micronization reduced the particle size dramatically and the PSDs for Spectrum (χ90 from 156.5 to 3.39 µm) and Cognis (χ90 from 331.9 to 3.09 µm) were similar after micronization. The PSD of the API was also reduced by micronization, χ90 from 51.3 to 6.14 µm, as shown in Figure 7.

Physical profiling of SLS samples

The differential scanning calorimetry (DSC) thermograms of SLS from different sources are shown in Figure 8. All SLS samples showed two endothermic events, the first one at 75–120°C associated with dehydration and the second one at 192–200°C was the melting of the dehydrated phase. The TGA thermograms of the SLS samples confirmed the weight loss (~1%) at about 80°C

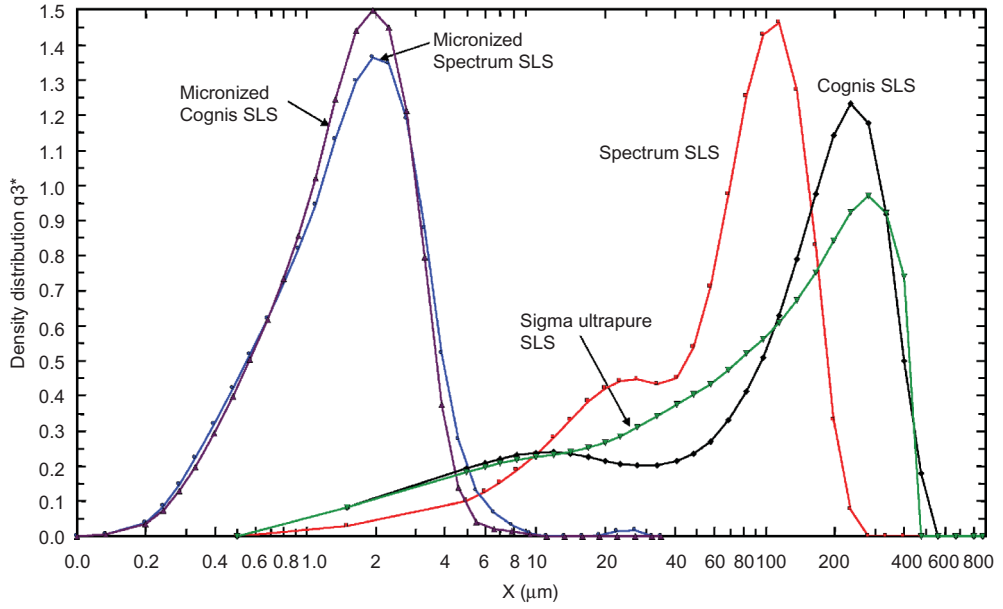

Figure 6. Particle size distribution for SLS samples from Sympatec method.

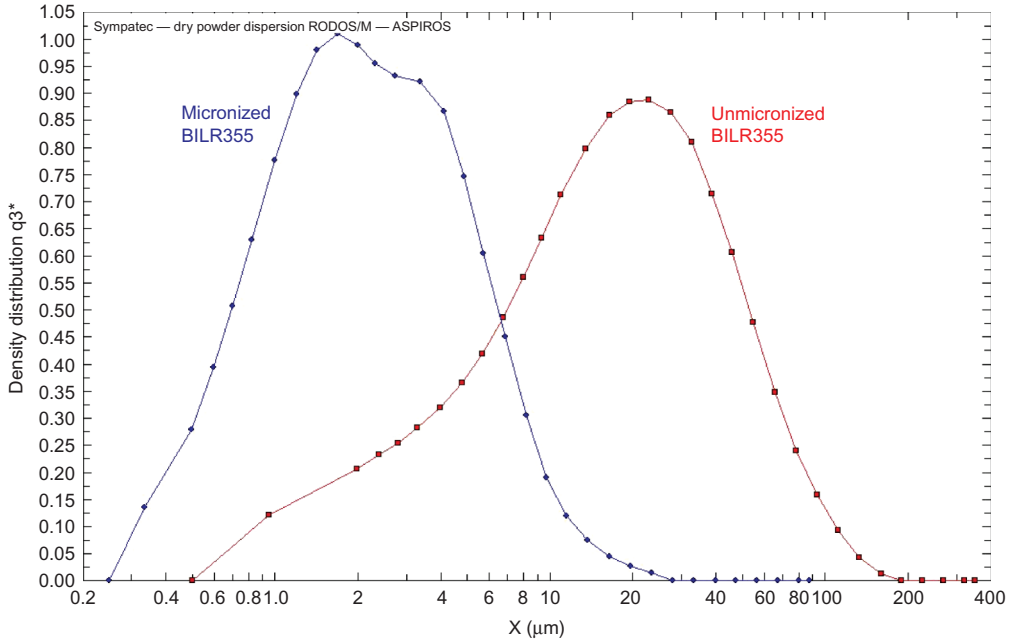

Figure 7. Particle size distribution for BILR 355 samples from Sympatec method.

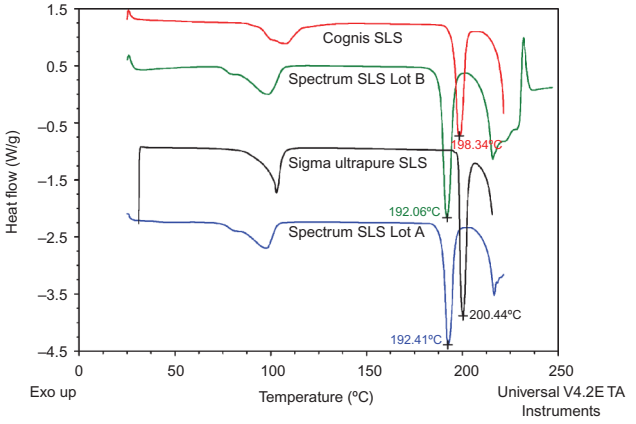

Figure 8. DSC thermograms of SLS from three sources.

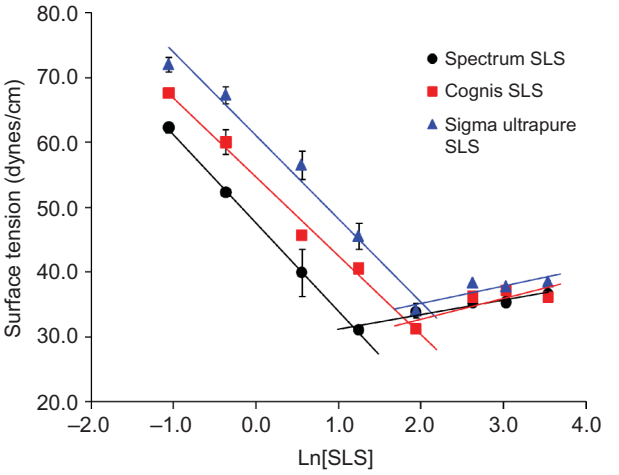

Figure 9. Surface tension of SLS solution. ● Spectrum SLS; ■ Cognis SLS; ▲ Sigma ultrapure SLS.

corresponding to the water content. The melting peak temperature was about 192, 198, and 200°C for Spectrum (both Lot A and B), Cognis, and Sigma ultrapure SLS, respectively. A trend in the melting peak temperatures was observed and ranked as Spectrum < Cognis < Sigma. It is well known that the presence of impurities depresses the melting temperature. The observed melting behavior of the SLS samples suggested the rank order of the purity was Spectrum < Cognis < Sigma ultrapure SLS. The reported assay values of 87.7% and 98.4% for Lot A and B in Table 1 were not supported by their similar melting temperatures. From internal analysis, Spectrum samples, Lot A and Lot B, had similar assay values (purity) of 93.1% and 94.0%, respectively, consistent with melting temperatures. Furthermore, the reported assay value of Spectrum Lot B did not follow the trend of melting temperatures observed for Cognis (96.3%) and Sigma (99.5%). These results suggested that the purities of Spectrum SLS Lot A and B were similar and should be less than that of Cognis SLS.

Surface tension of SLS solutions

Surface tension was used to determine the CMC of SLS. A plot of the surface tensions as a function of the logarithms of the SLS concentrations is shown in Figure 9. The surface tension decreased as the SLS concentration increased and reached a minimum at about 0.1% for Spectrum and about 0.2% for Cognis and Sigma SLS and then leveled off. At low SLS concentrations, the surface tensions followed the order of Spectrum < Cognis < Sigma ultrapure at a given SLS concentration. The CMC calculated from this experiment was 3.40 mM (~0.098%, w/v) for the Spectrum SLS, 6.31 mM (~0.182%, w/v) for the Cognis SLS, and 7.58 mM (~0.219%, w/v) for the Sigma ultrapure SLS. The two Spectrum lots showed similar surface tension profiles which were consistent with the purity by DSC analysis.

The impurities in SLS, such as salt, unsulfated alcohols, and other unknown impurities, can affect surface tension and CMC. First, the salt effect was evaluated by spiking Spectrum SLS with NaCl to match the salt content in Cognis SLS and the surface tensions were measured and plotted in Figure 10. Addition of salt to Spectrum Lot B lowered the surface tension, and the higher salt content could not explain the higher surface tension for Cognis SLS.

A minor difference in the unsulfated alcohol content, 0.47% for Spectrum and 0.30% for Cognis SLS, was given in the vendor's C of As. To evaluate whether a low amount of alcohol would affect the surface tension and CMC, Sigma ultrapure SLS solution was spiked with two levels of lauryl alcohol, 0.50% and 0.75%, respectively,

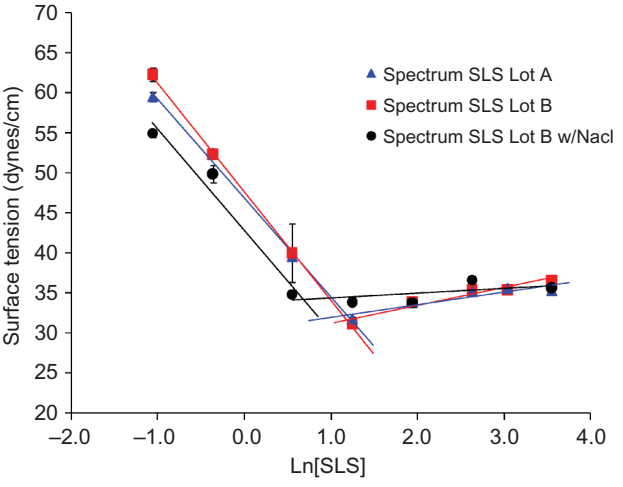

Figure 10. Surface tension of Spectrum SLS solution with and without NaCl. ▲ Spectrum SLS Lot A; ■ Spectrum SLS Lot B; ● Spectrum SLS Lot B with NaCl.

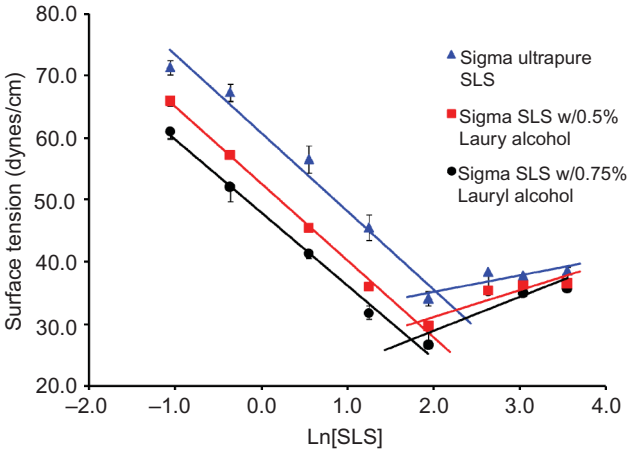

Figure 11. Surface tension of Sigma SLS solution spiked with lauryl alcohol. ▲ Sigma ultrapure SLS; ■ Sigma SLS with 0.5% lauryl alcohol; ● Sigma SLS with 0.75% lauryl alcohol.

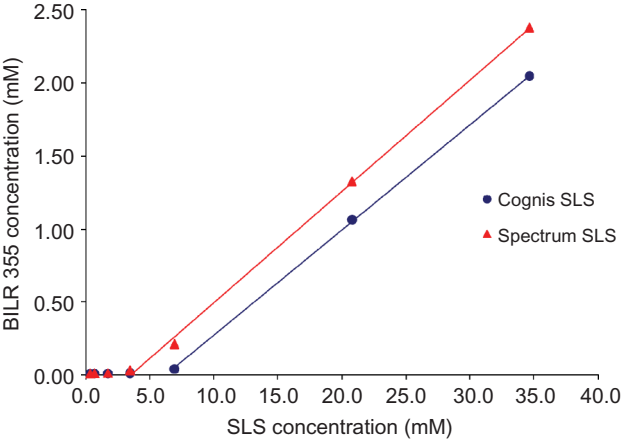

Figure 12. Equilibrium solubility of BILR 355 as function of sodium lauryl sulfate concentration in water at 37°C. ▲ Aqueous solutions with Spectrum SLS; ● aqueous solutions with Cognis SLS.

and the surface tensions were measured and plotted in Figure 11. Although addition of small amount of lauryl alcohol reduced the surface tensions, the CMC of Sigma SLS spiked with lauryl alcohol did not match that of Spectrum SLS.

In addition to the reported salt and unsulfated alcohols, there could be other unknown impurities in Spectrum SLS samples. If the unknown impurities were surface active, they may contribute to the lower CMC of Spectrum SLS[32–36]. Unfortunately, the actual amount and the chemical nature of these impurities were not reported. Based on the surface tension data, it is evident that the higher level of impurity in Spectrum SLS led to lower CMC which would provide greater solubilization of BILR 355 than the purer SLS from other vendors.

Table 2. Solubility of BILR 355 in SLS aqueous solutions at 37°C.

SLS % (w/v)	SLS (mM)	BILR 355 solubility (mM)		Difference (mM)
		Spectrum	Cognis	
0.0	0.0	0.008	0.008	
0.01	0.35	0.010	0.009	0.0001
0.02	0.69	0.011	0.010	0.0001
0.05	1.73	0.013	0.012	0.0001
0.1	3.47	0.033	0.015	0.018
0.2	6.94	0.213	0.043	0.170
0.6	20.81	1.327	1.065	0.271
1.0	34.68	2.379	2.047	0.332
	CMC (mM)	3.398	6.311	−2.913
	Solubilization capacity, κ	0.077	0.072	0.005

Equilibrium solubility of BILR 355 in SLS solutions

The equilibrium solubility of BILR 355 as a function of SLS concentration in water at 37°C is shown in Figure 12. The CMC from solubility measurement agreed well with the results from the surface tension measurement, approximately 0.1% for Spectrum and 0.2% for Cognis SLS. Below the CMC, the drug solubility remained relatively constant. Above the CMC, the drug solubility dramatically increased with increasing the surfactant concentrations and was higher in Spectrum SLS solution than that of Cognis SLS. The total solubility of a drug (S_{tol}) in the presence of a surfactant can be expressed as[37]:

$$S_{tol} = S_w + \kappa \times (C_T - \text{CMC}), \quad (1)$$

where S_w is the aqueous solubility of the solute—BILR 355, κ is the solubilization capacity, and C_T is the total concentration of the surfactant. The solubilization capacity κ is the number of moles of solute solubilized by 1 mole of micellar surfactant and can be used to compare solubilization efficiency for a given solute. Table 2 showed that the solubilization capacity for BILR 355 is higher with Spectrum SLS compared to that of Cognis SLS. Although both CMC and solubilization capacity are indicative of a better solubilization power for Spectrum SLS, the larger difference in CMC between these two sources suggested that CMC played a more dominant role in improving solubility of BILR 355.

Wet granulation process

Wet granulation is a size enlargement process in which small solid particles are converted into large agglomerates to improve the flowability. Wet granulation involves three key processes: wetting and nucleation, consolidation and growth, and breakage and attrition.

The process of wetting and nucleation first brings liquid binder into contact with dry powder and then distributes the liquid evenly throughout the powders to give a distribution of nuclei granules. The nuclei formation is a function of both wetting thermodynamics and kinetics[38]. During the consolidation and growth process, the agglomerates or granules are produced by smaller particles adhering to one another via liquid bridges[39]. It was found that the wettability of a powder mixture had significant effect on the granulation end point where the mean granule particle size decreased as the contact angle of the powder mixtures increased (decreased wettability)[40–42]. Incorporation of the surfactant such as SLS in the formulation improves the wetting of the powder, and therefore facilitates the granule growth. Pepin[43] found that less liquid binder was required to overwet the powder when the low surface tension liquid binder was used.

To compare the effect of particle size and SLS sources, seven batches of BILR 355 tablets were prepared using the same composition and the same batch size with varying particle size and/or sources of SLS. Each batch was granulated to a similar visual end point by adjusting the amount of water and granulation time. The materials and process parameters for each batch are given in Table 3. Comparing Batches A, B, and C, when the granulation time was fixed, the amount of water required for the granulation was about 5%, 7%, and 9% for Spectrum (Batch B), Cognis (Batch C), and Sigma ultrapure (Batch A) SLS, respectively.

As mentioned above, nucleation is the first step of wet granulation where the liquid binder begins to wet the powder and form initial agglomerates. Whether or not wetting is energetically favorable is related to the contact angle between the solid and liquid binder and the spreading coefficient of the liquid phase over the solid phase. In this experiment, API and excipients were the same in all batches except that the SLS was from different sources. Attempts to measure the contact angles between water and SLS were made. However, the contact angles for all samples were very small and approximately zero, indicating that differences in the contact angles between water and powder bed for Batches A, B, and C were negligible. The wetting behaviors may be described by the spreading coefficient of water over the powder bed. The spreading coefficient λ can be expressed as[38]:

$$\lambda = W_A - W_{CL} = \gamma_{SV} - \gamma_{LV} - \gamma_{SL}, \quad (2)$$

where W_A is the work of adhesion for solid–liquid interface; W_{CL} is the work of cohesion for liquid phase; γ_{LV}, γ_{SV}, and γ_{SL} are the surface free energies of liquid–vapor, solid–vapor and solid–liquid interfaces. Because the solid bed had the same composition, the differences in γ_{SV} and γ_{SL} might be assumed negligible among Batches A, B, and C. Using Equation (2), the spreading coefficient would primarily depend on the surface tension of the liquid phase, in which a lower surface tension, γ_{LV}, gave a higher spreading coefficient. During wet granulation, small amount of SLS immediately dissolved in water once water contacted the powder bed, and the diluted SLS solutions then acted as the liquid binder. Thus, the γ_{LV} could be considered as the surface free energy of the dilute SLS solution, where lower surface tension of Spectrum SLS solution produced a larger spreading coefficient. As a result, less amount of water was required for granulating the batch containing Spectrum SLS than the other two. Accordingly, with a fixed granulation time, the amount of water needed for granulation was in the same order of the surface tensions as Spectrum < Cognis < Sigma ultrapure SLS.

When the amount of water was fixed, the granulation time was 1.75 minutes for the batch containing micronized Cognis SLS (Batch D), shorter than 5.75 minutes with unmicronized Cognis SLS (Batch C). This may be explained by an improved wetting efficiency with a reduction of the SLS particle size. Similar trend was seen for Batches B and E with unmicronized and micronized Spectrum SLS, where less water and shorter time were needed for Batch E as compared to Batch B. Reduction of API particle size, however, required more water by comparing Batches F and B, which was likely due to lower wetting efficiency with increasing surface area of the hydrophobic component (API).

Table 3. Materials and process parameters of wet granulation.

	API and SLS combination			
Batch	BILR 355	SLS	Granulation water (%, w/w)	Granulation time (minutes)
A	Unmicronized	Sigma ultrapure	9.02	5.75
B	Unmicronized	Spectrum unmicronized	5.07	5.75
C	Unmicronized	Cognis unmicronized	7.00	5.75
D	Unmicronized	Cognis micronized	7.00	1.75
E	Unmicronized	Spectrum micronized	2.99	2.75
F	Micronized	Spectrum unmicronized	8.02	4.17
G	Micronized	Spectrum micronized	6.44	1.25

Tablet dissolution

The dissolution of the BILR 355 tablet was evaluated using a two-step dissolution method because previous dissolution results by this method were found to correlate well to the in vivo performance of BILR 355 (data not shown). The dissolution profiles of the BILR 355 tablets containing both unmicronized and micronized SLS are shown in Figure 13. For Batch B, about 70% of BILR 355 was dissolved in the solution, giving a drug concentration of 210 µg/mL. The solution was supersaturated at about 20 times of the equilibrium solubility of 10 µg/mL and the supersaturation was maintained up to 120 minutes. For tablets containing Cognis SLS, about 60% of BILR 355 was dissolved with a concentration of 180 µg/mL up to 120 minutes. The difference in dissolution was consistent with the different solubilities of BILR 355 in the corresponding SLS solutions. As discussed previously, the solubility of BILR 355 in Spectrum SLS solution is ~1.2 times of that in Cognis SLS at a SLS concentration of 0.6% (w/v). The percentage of drug dissolved for the tablets containing Spectrum SLS is 1.17 times of that containing Cognis SLS, trending consistently with solubility improvement. Upon micronization, the PSDs of the SLS from two sources were the same and the dissolution profiles of the tablets were similar up to 90 minutes. The tablets containing micronized Spectrum SLS maintained similar supersaturation level to 2 hours; however, precipitation occurred for the tablets containing micronized Cognis SLS approaching the same level as that with unmicronized SLS. Although micronization of SLS improved the dissolution rate, the rate of precipitation could be affected by the degree of supersaturation and other factors.

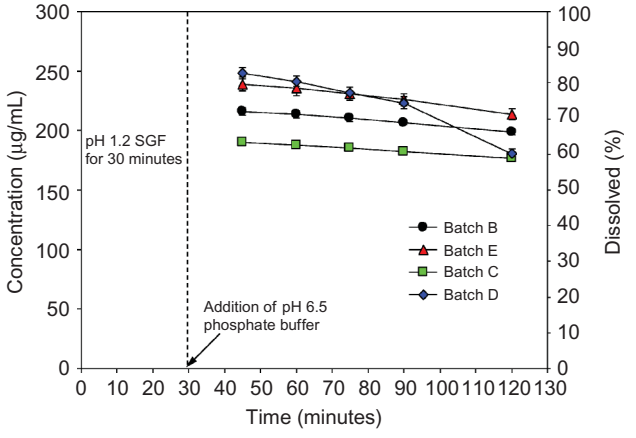

Figure 13. Dissolution profiles of BILR 355 tablets containing unmicronized API—comparison of Spectrum and Cognis SLS. A two-step dissolution method was used. ● Batch B: with unmicronized Spectrum SLS; ▲ Batch E: with micronized Spectrum SLS; ■ Batch C: with unmicronized Cognis SLS; ♦ Batch D: with micronized Cognis SLS.

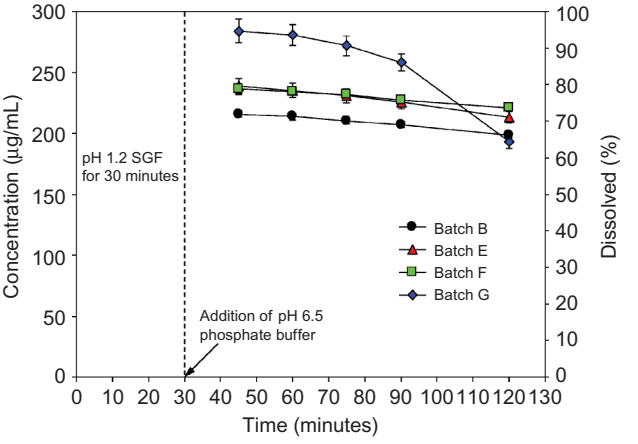

Figure 14. Dissolution profiles of BILR 355 tablets containing Spectrum SLS—comparison of different particle sizes. A two-step dissolution method was used. ● Batch B: unmicronized API with unmicronized Spectrum SLS; ▲ Batch E: unmicronized API with micronized Spectrum SLS; ■ Batch F: micronized API with unmicronized Spectrum SLS; ♦ Batch G: micronized API with micronized Spectrum SLS.

The effect of API particle size on tablet dissolution was also investigated. The dissolution profiles of the tablets containing micronized API with unmicronized and micronized Spectrum SLS are given in Figure 14. Comparing Batches B and F or E and G, the tablets with micronized API dissolved to a greater extent than unmicronized API, indicating that the finer API size facilitated dissolution. The particle size effect was most evident for Batch G with both micronized API and SLS producing the highest initial concentrations. However, the percent dissolved gradually decreased after the initial high concentration and reduced to the same level as that of unmicronized materials at 2 hours. The decrease in the concentration was likely due to high degree of supersaturation exceeding the micellar solubilization capacity.

Most interesting is that Batch E with unmicronized API/micronized SLS performed equally as that of Batch F with micronized API/unmicronized SLS. These results suggested that micronization of SLS alone could achieve the same effect as micronizing API. The dissolution result of Batch G demonstrated that similar dissolution improvement may be attained by combining the micronized API and micronized solubilizing agent while avoiding the co-micronization process.

These findings may have significant implications on the decision regarding API particle size specification and milling operations. Micronization of API is less desirable because of the potential to lose API and polymorph change. Co-micronization may create some other problems such as over-potency or under-potency because of selective loss of solubilizing agent or API during the micronization process. Overall, the formulation strategy

for a poorly soluble drug should be a rationalized approach using the combination of a solubilizing agent and particle size reduction of critical components to achieve an optimal dissolution profile.

Conclusions

SLS was used as a solubilizer for a poorly soluble drug, BILR 355, during solid dosage form development. DSC and surface tension analysis suggested that Spectrum SLS was less pure than Cognis SLS. The solubility measurement confirmed that Spectrum SLS was more effective in solubilizing BILR 355 giving about 20% higher solubility than Cognis SLS. Based on evaluation of SLS from the two sources, it is suggested that the presence of trace surface-active impurities in SLS contributed to the difference in the wetting behavior and solubilization. In wet granulation, less water was required using Spectrum than Cognis SLS. Similarly, in tablet dissolution the percent of drug dissolved was 10% higher with Spectrum than Cognis SLS. These formulation effects were consistent with the solubilization efficiencies from these two sources of SLS. Micronization of either component, SLS or API, yielded the same dissolution profile, which suggested that reduction of particle size of SLS alone was sufficient to improve the dissolution/solubility of the API. The results from this study demonstrate that the SLS from different sources may impact the solubilization, wet granulation, and dissolution in solid dosage form development. During formulation development, it is necessary to understand the effect of SLS when changing sources and particle size to ensure a robust process and a consistent performance of the drug product.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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