International Journal of Pharmaceutics 412 (2011) 95–98

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Weak bases and formation of a less soluble lauryl sulfate salt/complex in sodium lauryl sulfate (SLS) containing media

Shobha N. Bhattachar[a], Donald S. Risley[a], Pornpen Werawatganone[b], Aktham Aburub[a,*]

[a] Eli Lilly and Company, Pharmaceutical Sciences R&D, Lilly Research Laboratories, Indianapolis, IN 46285, USA
[b] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Pathumwan, Bangkok 10330, Thailand

ARTICLE INFO

Article history:
Received 4 January 2011
Received in revised form 17 March 2011
Accepted 10 April 2011
Available online 16 April 2011

Keywords:
Sodium lauryl sulfate
Solubility
Salt
Complex

ABSTRACT

This work reports on the solubility of two weakly basic model compounds in media containing sodium lauryl sulfate (SLS). Results clearly show that the presence of SLS in the media (e.g. simulated gastric fluid or dissolution media) can result in an underestimation of solubility of some weak bases. We systematically study this phenomenon and provide evidence (chromatography and pXRD) for the first time that the decrease in solubility is likely due to formation of a less soluble salt/complex between the protonated form of the weak base and lauryl sulfate anion.

1. Introduction

While the stomach is not the main absorption site for most drugs, solubility/dissolution in its contents can potentially have significant impact on the rate and/or extent of absorption (Dressman et al., 2007). Poorly soluble weak acids like NSAIDs have limited solubility in the stomach. Therefore, their dissolution in the stomach is expected to have limited impact on absorption (Potthast et al., 2005). Weak bases, on the other hand, likely have significantly higher solubility in the stomach compared to the small intestine. Hence, their gastric solubility/dissolution can have significant impact on absorption (Kostewiczl et al., 2004).

Surface tension and pH are among the main properties of fasted state gastric fluid, which have direct impact on drug solubility/dissolution. Typical pH values in the stomach in the fasted state are 1.4–2.1 (Dressman et al., 1998). The importance of pH on solubility/dissolution is obvious for weakly acidic and basic active pharmaceutical ingredients (API). Typical surface tension values in the fasted state stomach are in the range 35–45 mN/m (Efentakis and Dressman, 1998). The presence of pepsin, which is surface active, contributes to the low surface tension. However, the lowest surface tension that can be achieved due to pepsin is approximately 57 mN/m (Vertzoni et al., 2005). The aforementioned suggests that surfactants other than pepsin are also present in the stomach (e.g. bile salts due to reflux from small intestine (Vertzoni et al., 2005)).

For *in vitro* evaluations, synthetic surfactants (e.g. sodium lauryl sulfate; SLS) have been commonly used to lower the surface tension of aqueous media to levels similar to those found *in vivo* and/or to enhance solubility (Pabla et al., 2009). In addition to all the other parameters such as pH, buffer capacity and ionic strength, it is important that the simulated fluids used to test bio-relevant solubility and dissolution have similar surface tension as the biological fluids. This is because, when the commonly hydrophobic drug particles come in contact with aqueous media, the resulting high interfacial tension between the medium and the solid causes the particles to aggregate. Consequently, the effective surface area decreases and dissolution rate decreases. Lowering the surface tension of an aqueous media improves the wetting of hydrophobic drug particles by lowering the advancing contact angle (Aburub et al., 2008). This aids in displacing an air phase at the surface and replacing it with a liquid phase, which results in an increase in the effective surface area and consequently, dissolution rate.

In a previous work (Aburub et al., 2008) we discussed the use of SLS in simulated gastric fluid along with recommendations for an appropriate concentration. However, we pointed out that it is important to note that the presence of SLS might cause an artificial underestimation of solubility in cases where a less soluble salt/complex forms between lauryl sulfate anion and the protonated form of the drug. While some reference to this phenomenon has been mentioned in the literature (Jain et al., 2004), it has not been systematically studied. In this work, we study the solubility of two model compounds in SLS-containing media. We clearly show that the presence of SLS can negatively impact solubility. We propose that the decrease in solubility is due to formation of a less

* Corresponding author. Tel.: +1 317 655 0869; fax: +1 317 655 2770.
E-mail addresses: aburub_aktham@lilly.com, zaktham@yahoo.com (A. Aburub).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.04.018

Table 1
Solubility samples for TMP and LY.

Sample	Composition of media
1	0.01 N HCl
2	0.2% NaCl in 0.01 N HCl
3	0.2% NaCl + 0.05% SLS in 0.01 N HCl
4	0.2% NaCl + 1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl
5	1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl

soluble salt/complex between the protonated form of the weak base and lauryl sulfate anion and provide data (chromatography and pXRD) to support that.

2. Materials and methods

2.1. Materials

Trimethoprim (TMP, weak base $pK_a \sim 6.6$, molecular weight ~ 290) and sodium chloride were obtained from Sigma–Aldrich Chemical company (St. Louis, MO), SLS (molecular weight ~ 288) from Mallinckrodt (Phillipsburg, NJ), and compound LY (weak base $pK_a \sim 6.1$, molecular weight ~ 494) from Eli Lilly and Company (Indianapolis, IN). All other chemicals were of analytical or high-performance liquid chromatography (HPLC) grade.

2.2. Methods

2.2.1. Solubility

TMP and Lilly Compound (LY) were stirred over 48 h on a rotisserie mixer at room temperature in a set of five media (5 mL/media) each in screw capped vials as shown in Table 1. In addition, solubility in water was also determined for reference. In the TMP slurries, the amount of compound added into each vial was 25 mg. In the LY slurries, it was 10 mg (as the overall solubility profile of LY is lower than that of TMP). In addition, for slurries 4 and 5 in Table 1, the molar equivalent amount of SLS was 0.50% w/v for TMP and 0.12% w/v for LY slurries.

At the end of the mixing time, pH was measured after which solutions were filtered and solutions and solid phases were collected for further analysis. In order to collect the solution phase, a portion of the slurry was syringe filtered using 0.45 μm PTFE membrane filters. The filtrate was collected after discarding the first several drops. In order to collect the solid phase (solubility residue), the slurry was passed through a 0.45 μm PTFE membrane filter disc placed on a sintered glass base attached to a vacuum filter assembly. The collected solids were then placed in vacuum desiccators overnight to allow the samples to dry. The concentrations of TMP or LY and SLS in the solutions were measured by HPLC. The composition of the solid phase samples was determined by re-dissolving the solid residues in mobile phase and then assaying for TMP or LY, LS and chloride by HPLC.

2.2.2. Powder X-ray diffraction (pXRD)

pXRD patterns of dried solubility residues (as described in the solubility section) were obtained on a Siemens D5000 X-ray powder diffractometer, equipped with a Cu Kα source (λ = 1.54056 Å) and a Kevex solid-state detector, operating at 50 kV and 40 mA. Zero-signal quartz sample holder and a rotating stage were used. Each sample was scanned between 4 and 40 in 2θ, with a scan rate of 1 s/step, with 1 mm divergence and receiving slits and a 0.2 mm detector slit.

2.2.3. HPLC assay for TMP and LY

The HPLC system consisted of an Agilent 1100 series with an ultraviolet (UV) detector set at 220 nm and a Zorbax Bonus-RP column (75 mm × 4.6 mm, 3.5 μm) (ambient temperature), all from Agilent Technologies, Santa Clara, CA. For TMP, the mobile phase comprised 10:90 (acetonitrile with 0.1% trifluoroacetic/water with 0.1% trifluoroacetic acid) with a flow rate of 1.0 mL/min and 2 μL injections. For LY, the mobile phase comprised 30:70 (acetonitrile with 0.1% trifluoroacetic/water with 0.1% trifluoroacetic acid) with a flow rate of 1.5 mL/min and 5 μL injections. The retention times for TMP and LY were 5.9 min and 6.2 min, respectively. The samples and individual standards were weighed accurately and diluted with 25% acetonitrile/75% water for TMP or 50% acetonitrile/50% water with 0.1% trifluoroacetic acid for LY. The three-point standard curve was calculated by least-squares regression analysis of peak area versus concentration and the line was forced through the origin. The linearity for all of the HPLC-UV assays resulted in an $R^2 > 0.999$. The samples ($n = 2$) were prepared to be within the standard range which was between 0.05 and 0.25 mg/mL. The concentration of each analyte was determined by comparing the peak area of the sample to the standard curve.

2.2.4. HPLC assay for lauryl sulfate and chloride

For lauryl sulfate the HPLC system consisted of an Agilent 1100 series (Agilent Technologies, Santa Clara, CA) integrated with an Alltech 800 Evaporative Light Scattering Detector (ELSD) (Alltech Associates, Deerfield, IL). The detector settings were 50 °C, 3.75 bar nitrogen and gain setting of 2. A Phenomenex Synergi 4 RP-80 column (150 mm × 4.6 mm, 4 μm) (ambient temperature) was used for the separation (Phenomenex, Torrance, CA). Mobile phase A comprised 75 mM ammonium acetate adjusted to pH 4.7 (with acetic acid) and mobile phase B was acetonitrile. The gradient started at 50:50 (A:B) until 0.5 min, then a 6.5 min linear gradient to 85% B, followed by a 0.5 linear gradient back to 50:50 (A:B) and then allowed to equilibrate for 5 min before the next injection. A flow rate of 1.0 mL/min and 20 μL injections was used. The retention times for lauryl sulfate, TMP and LY were 4.0 min, 2.4 min and 5.9 min, respectively. The sample and standards were weighed accurately and diluted in 50% acetonitrile/50% water. The three-point standard curve was calculated by least-squares regression analysis of peak area versus concentration (the line was not forced through the origin). The linearity for all of the HPLC-ELSD assays resulted in an $R^2 > 0.999$. The samples ($n = 2$) were prepared to be within the standard range which was between 0.1 and 0.4 mg/mL. The concentration of each analyte was determined by comparing the peak area of the sample to the standard curve. Chloride was determined by using an anion exchange column with a HPLC-ELSD system (Alltech Associates, Deerfield, IL) (Risley et al., 1996).

3. Results and discussion

The solubility values of TMP and LY in the different media (1 through 5 and water) are summarized in Table 2. Equilibrium pH values are also summarized in Table 2.

TMP has a solubility of 3.01 mg/mL in 0.01 N HCl, which is similar to the 3.13 mg/mL solubility in the presence of NaCl (Table 2, sample 1 vs 2). The lack of dependence of TMP solubility on the presence of NaCl in the media suggests that TMP does not form a HCl salt under the experimental conditions used in this work. The aforementioned is supported by analysis of the residual solubility solid samples, which does not show any chloride (Table 3).

The presence of SLS in the media clearly results in solubility depression; samples 3, 4, and 5 (Table 2). This is attributed to the formation of a less soluble TMP–lauryl sulfate salt/complex (Fig. 1). To support that, the residual solids at the end of the solubility exper-

Table 2
Summary of solubility data (RSD, typically <2%; $n = 2$).

Sample	TMP (mg/mL)	TMP Eq. pH	LY (mg/mL)	LY Eq. pH
1 [0.01 N HCl]	3.01	6.13	1.53	2.45
2 [0.2% NaCl in 0.01 N HCl]	3.13	6.14	0.92	2.46
3 [0.2% NaCl + 0.05% SLS in 0.01 N HCl]	2.59	6.17	0.06	2.28
4 [0.2% NaCl + 1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.87	4.18	0.20	2.39
5 [1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.43	4.16	0.02	2.34
Water	0.29	7.56	<0.01	7.93

Table 3
Summary of solid phase composition of TMP in samples 1 through 5.

	Weight fraction				
Sample	TMP	Lauryl sulfate (LS)	Cl	Total	Approx mole ratio
1 [0.01 N HCl]	1.00	0	0	1.00	100% TMP
2 [0.2% NaCl in 0.01 N HCl]	1.00	0	0	1.00	100% TMP
3 [0.2% NaCl + 0.05% SLS in 0.01 N HCl]	0.98	0.07	0	1.05	14:1 (TMP:LS)
4 [0.2% NaCl + 1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.66	0.35	0	1.01	2:1 (TMP:LS)
5 [1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.64	0.34	0	0.98	2:1 (TMP:LS)

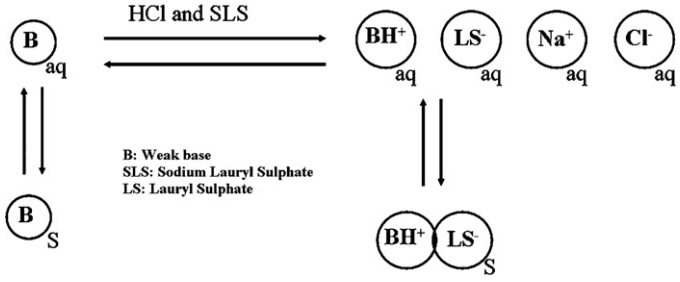

Fig. 1. Formation of a less soluble protonated base/lauryl sulfate salt/complex.

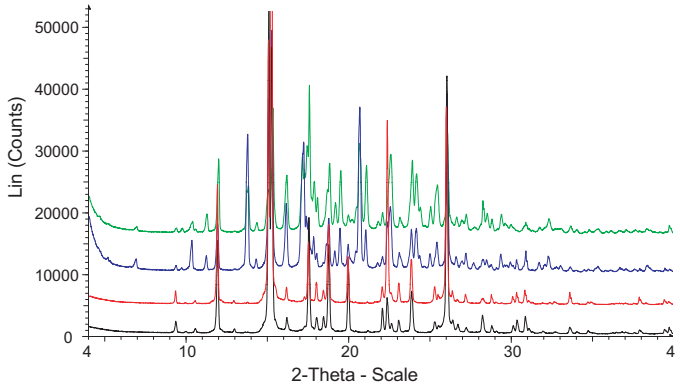

Fig. 2. Powder X-ray diffractograms of dried solubility residues collected from TMP solubility experiments (top to bottom: sample 5, sample 4, sample 3, and TMP reference).

iments were analyzed for lauryl sulfate (LS) (Table 3). All samples 3, 4, and 5 contain LS in the solid state. The greater than one TMP to LS molar ratio seen in samples 3, 4, and 5 suggests that the residual solids contain TMP free base as well. The pXRDs of residual solids from samples 4 and 5 (Fig. 2) suggest that they are crystalline and are similar. However, those pXRD patterns are different from the reference TMP pXRD but have many common peaks. This confirms solid state change. The pXRD of residual solid from sample 3 (Fig. 2) appears to be similar to that of the TMP reference. The failure of pXRD to show solid state change in the residue is likely due to the small percent of TMP–LS salt/complex in residue 3 (Table 3).

The decrease in TMP, which is a weak base, solubility in the presence of SLS cannot be explained by pH since the equilibrium pH values in the presence of SLS are either similar or lower than those in the absence of SLS (Table 2).

It is noteworthy that in the presence of equimolar concentration of SLS, the presence of NaCl results in a ~2-fold increase in TMP solubility (sample 4 vs 5; Table 2). The presence of NaCl (higher ionic strength) causes a decrease in the critical micelle concentration of SLS, which likely results in greater SLS micellar solubilization of the compound.

LY has a solubility of 1.53 mg/mL in 0.01 N HCl (Table 2), which decreases to 0.92 mg/mL in the presence of NaCl. This decrease can be explained by common ion effect. LY has a weakly basic pK_a of 6.1, which makes a HCl salt formation in 0.01 N HCl plausible. The HCl salt precipitates out and if the media has higher concentration of chloride (e.g. contains NaCl), solubility decreases as a result of common ion effect. The aforementioned is supported by analysis of the solid phase collected from solubility slurry # 3 (Table 4) in which the LY to chloride molar ratio is 1:0.8. Solid state data from samples 1 and 2 are not included because the gel-like consistency of the solid phase in these samples made it difficult to collect the solids.

The presence of SLS in the media clearly results in solubility depression; samples 3, 4, and 5 (Table 2). This is attributed to the formation of a less soluble LY–lauryl sulfate salt/complex (Fig. 1). To support that, the residual solids at the end of the solubility experiments were analyzed for lauryl sulfate (LS) (Table 4). All samples 3, 4, and 5 contain LS in the solid state. In fact, samples 4, and 5; which contained equimolar concentration of LS and LY at the beginning of the experiment have a 1:1 LY to lauryl sulfate molar ratio in the solid state. Unlike LY, which is crystalline, the pXRDs of residual solids from samples 3, 4, and 5 (Fig. 3) suggest that they are predominantly amorphous. This implies that the LY–lauryl sulfate complex is amorphous. The single sharp diffraction peak at 32 2θ could be due to the presence of LY–HCl in the solid as detected by Cl^- analysis per Table 4 or more likely due to sample holder.

The decrease in LY, which is a weak base, solubility in the presence of SLS cannot be explained by pH since the equilibrium pH values in the presence of SLS are lower than those in the absence of SLS (Table 2).

Similar to what was seen with TMP, in the presence of equimolar concentration of SLS; the presence of NaCl results in an increase in the solubility of LY (sample 4 vs 5; Table 2). Again, likely that's due to lowering of the CMC of SLS due to the higher ionic strength.

Table 4
Summary of solid phase composition of LY in samples 3, 4 and 5.

Sample	Weight fraction				
	LY	Lauryl sulfate (LS)	Cl	Total	Approx mole ratio
3 [0.2% NaCl + 0.05% SLS in 0.01 N HCl]	0.81	0.14	0.05	1.00	1:0.2:0.8 (LY:LS:Cl)
4 [0.2% NaCl + 1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.63	0.35	0	0.98	1:1 (LY:LS)
5 [1 molar equivalent SLS (0.50% for TMP and 0.12% for LY) in 0.01 N HCl]	0.64	0.31	0	0.95	1:1 (LY:LS)

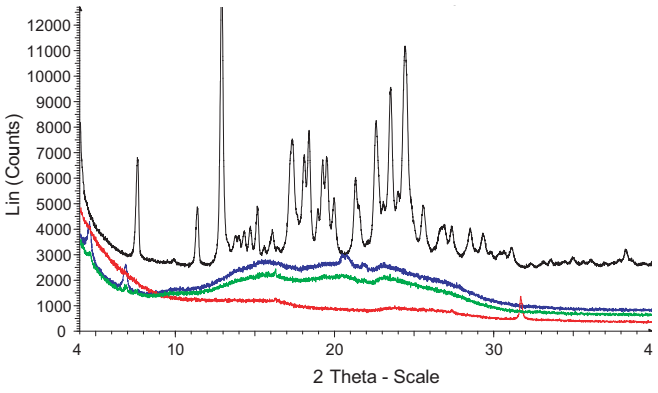

Fig. 3. Powder X-ray diffractograms of dried solubility residues collected from LY solubility experiments (top to bottom: LY, sample 4, sample 5, and sample 3).

This work clearly shows that the presence of SLS in media simulating gastrointestinal fluids or dissolution media can result in underestimation of a weak base's solubility due to in advertent formation of lauryl sulfate/weak base salt/complex. In such cases, SLS containing media may need to be avoided if the intent is biorelevance. In addition, the incorporation of small amounts of SLS in solid oral formulations of weak bases needs to be carefully studied.

4. Conclusions

In this work we clearly show that the solubility of two model weak bases in SLS-containing media decreases due to the presence of SLS. We also present, for the first time to our knowledge, chromatography as well as powder X-ray diffraction data supporting solid state change and precipitation of a less soluble lauryl sulfate salt/complex.

Acknowledgements

The authors would like to thank Mary Cooper and Robert Price for analytical support.

References

Aburub, A., Risley, D.S., Mishra, D., 2008. A critical evaluation of fasted state simulating gastric fluid (FaSSGF) that contains sodium lauryl sulfate and proposal of a modified recipe. Int. J. Pharm. 347, 16–22.
Pabla, D., Akhlaghi, F., Zia, H., 2009. A comparative pH-dissolution profile study of selected commercial levothyroxine products using inductively coupled plasma mass spectrometry. Eur. J. Pharm. Biopharm. 72, 105–110.
Dressman, J., Amidon, G., Reppas, C., Shah, V., 1998. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharm. Res. 15, 11–22.
Dressman, J., Vertzoni, M., Goumas, K., Reppas, C., 2007. Estimating drug solubility in the gastrointestinal tract. Adv. Drug Deliv. Rev. 59, 591–602.
Efentakis, M., Dressman, J., 1998. Gastric juice as a dissolution medium: surface tension and pH. Eur. J. Drug Metab. Pharmacokin. 23, 97–102.
Jain, A., Ran, Y., Yalkowsky, S.H., 2004. Effect of pH–sodium lauryl sulfate combination on solubilization of PG-300995 (an anti-HIV agent). AAPS PharmSciTech 5 (article 45).
Kostewiczl, E., Wunderlichl, M., Brauns, U., Becker, R., Bock, T., Dressman, J., 2004. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. J. Pharm. Pharmacol. 56, 43–51.
Potthast, H., Dressman, J., Junginger, H., Midha, K., Oeser, H., Shah, V., Vogelpoel, H., Barends, D., 2005. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. J. Pharm. Sci. 94, 2121–2131.
Risley, D., Peterson, J., Griffiths, K., McCarthy, S., 1996. An alternative method for the determination of chloride in pharmaceutical drug substances using HPLC and evaporative light-scattering detection. LC–GC 14, 1040–1047.
Vertzoni, M., Dressman, J., Butler, J., Hampenstall, J., Reppas, C., 2005. Simulation of fasting gastric conditions and its importance for in vivo dissolution of lipophilic compounds. Eur. J. Pharm. Biol. 60, 413–417.