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A critical evaluation of fasted state simulating gastric fluid (FaSSGF) that contains sodium lauryl sulfate and proposal of a modified recipe

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Abstract

The aim of this work is to evaluate one of the most commonly used fasted state simulating gastric fluids (FaSSGFs), which contains sodium lauryl sulfate (SLS) ($FaSSGF_{SLS}$), and propose a more appropriate surfactant concentration. Surface tension studies clearly show that the critical micelle concentration (CMC) of SLS in the relevant media (a media whose pH and sodium chloride concentration are representative of physiological conditions) is significantly lower ($p < 0.05$) than 8.67 mM, which is the SLS concentration in $FaSSGF_{SLS}$. The CMC of SLS in the relevant media was determined to be 1.75 mM. Based on this a modified recipe is proposed in which the concentration of SLS is sufficient to achieve a surface tension similar to that *in vivo* without causing artificial micellar solubilization. Solubility, intrinsic dissolution, and GastroPlus™ modeling studies are presented to support and give rationale for the modified recipe. In addition, a comparison between the modified recipe and other FaSSGFs reported in the literature is made.

Keywords: Dissolution; Gastrointestinal; Solubility; Surfactants; Wetting; Micelle

1. Introduction

Among the main properties of fasted state gastric fluid, which have direct impact on drug solubility/dissolution, are pH and surface tension. Typical pH values in the stomach in the fasted state are with in the range 1.4–2.1 (Dressman et al., 1998; Dressman and Lennernas, 2000). 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 on the order 35–45 mN/m (Dressman and Lennernas, 2000; Efentakis and Dressman, 1998; Finholt and Petersen, 1978). This low surface tension is, in part, due to the presence of pepsin which is surface active. However, the minimum surface tension that can be achieved due to pepsin is ~57 mN/m (Vertzoni et al., 2005). This indicates that surfactants other than pepsin are also present in the stomach. To date, these surfactants have not been absolutely identified. Synthetic surfactants (e.g. sodium lauryl sulfate; SLS) have been typically used to lower the surface tension of aqueous media to levels similar to those *in vivo*.

The impact of surface tension on dissolution is apparent for hydrophobic drugs. Due to their high interfacial tension, upon exposure to aqueous media the drug particles tend to aggregate to minimize surface area and consequently minimize surface free energy. As a result, the effective surface area decreases and dissolution rate decreases. The presence of a surfactant in the aqueous media can enhance the wetting of drug particles by lowering the advancing contact angle. This aids in displacing an air phase at the surface and replacing it with a liquid phase. In other words, the effective surface area increases and consequently, dissolution increases.

SLS containing Fasted State Simulating Gastric Fluid ($FaSSGF_{SLS}$) (Dressman et al., 1998) is probably the most commonly used FaSSGF. The composition of $FaSSGF_{SLS}$ is shown below:

HCl	0.01–0.05 N
SLS	8.67 mM
NaCl	0.2%
Distilled water	qs

The reported critical micelle concentration (CMC) of SLS in water at 25 °C is 8.32 mM (Jain et al., 2004). It is clear the concentration of SLS in $FaSSGF_{SLS}$ is close to its CMC in water. However, the CMC of ionic surfactants is strongly dependent on

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ionic strength. Therefore, it is expected that the CMC of SLS in $FaSSGF_{SLS}$ would be lower than 8.32 mM.

In the literature, significant attention has been placed on achieving a FaSSGF surface tension similar to that *in vivo* through the use of different types of surfactants. However, not much work has been done to optimize the concentration of surfactants in FaSSGF. The main objective of this work is to evaluate the level of SLS in $FaSSGF_{SLS}$ with respect to surface tension needed versus artificial micellar solubilization. The second objective is to propose a new SLS concentration in FaSSGF, which is sufficient to achieve a surface tension similar to that *in vivo* without potentially causing artificial micellar solubilization.

2. Materials and methods

2.1. Materials

Ibuprofen, progesterone, and sodium chloride were obtained from Sigma–Aldrich Chemical company (St. Louis, MO), SLS from Mallinckrodt (Phillipsburg, NJ), and compound B (weak base, $pK_a \sim 2.5$) 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. Surface tension

Wilhelmy plate method (KRUSS tensiometer, Kruss GmbH, Germany) was used to determine the critical micelle concentration of SLS in water, 0.01N HCl, 0.01N HCl/0.2% NaCl, and 0.05N HCl/0.2% NaCl at 37 °C. The reason behind using 0.01N and 0.05N HCl with 0.2% NaCl is that these are the concentrations used in $FaSSGF_{SLS}$ which result in physiologically relevant pH values and NaCl concentration (Dressman et al., 1998; Dressman and Lennernas, 2000).

2.2.2. Solubility

Solubility of three APIs (weak acid, weak base, and non-ionizable; ibuprofen, compound B, and progesterone; respectively) in media containing different concentrations of SLS was determined using shake-flask method at 37 °C. In addition, solubility of compound B in fasted state simulating intestinal fluid (FaSSIF) (Dressman et al., 1998) was also determined. Excess API was placed in test tubes to which the appropriate media was added. Suspensions were then shaken overnight after which they were filtered using 0.22 μm PVDF filters (the first 1 mL of each filtrate was discarded). Filtrates were then analyzed using HPLC. Solubility experiments were conducted in duplicates.

2.2.3. Intrinsic dissolution

The intrinsic dissolution rates (IDR) of ibuprofen in $FaSSGF_{SLS}$, and 1.75 mM SLS/0.01N HCl/0.2% NaCl (modified-FaSSGF; m-FaSSGF) were determined using rotating disk method (Woods apparatus). Ibuprofen powder (100 mg) was compressed to form a circular compact, with a radius of 0.4 cm, in a rotating disk die at 1000 lbs for 1 min using a hydraulic laboratory press (Fred Carver, Inc., Wabash, IN). The die was then mounted onto a dissolution tester shaft with a single face exposed to 500 mL dissolution media (37 °C). Samples were analyzed using HPLC at different time points.

2.2.4. HPLC assay

The HPLC system consisted of an Agilent 1100 series with a PDA detector (Agilent Technologies, Santa Clara, CA). An Alltima Phenyl column (250 mm × 4.6 mm, 5 μm, Alltech Associates, Deerfield, IL) and 10 μL injections were used for the three test analytes. For progesterone and compound B, the mobile phase comprised 60:40 (acetonitrile/0.1% trifluoroacetic acid in water) with a flow rate of 1.5 mL/min. For ibuprofen, the mobile phase comprised 50:50 (acetonitrile/0.2% 1N HCl in water) with a flow rate of 1.5 mL/min. The PDA detector wavelength was set at 245 nm, 215 nm and 210 nm for progesterone, compound B and ibuprofen, respectively. The retention times for progesterone, compound B and ibuprofen were 3.9 min, 4.1 min and 5.0 min, respectively.

2.2.5. Spectral test

The spectral test was performed to investigate the location of progesterone and ibuprofen in SLS micelles. The ultraviolet spectrum (HP 8453 spectrophotometer, Shimadzu Corp., Tokyo, Japan) was used to determine the wavelength at maximum absorption λ_{max} in $FaSSGF_{SLS}$, hexane, *n*-butanol and 0.01N HCl/0.2% NaCl.

2.2.6. GastroPlus™ modeling

GastroPlus™ (Simulations Plus Inc., Lancaster, CA) was used to simulate the absorption of compound B after oral administration of 30 mg capsules in the fasted state. Simulation results were then compared to actual *in vivo* data. *In vivo* data had been collected after administration of a capsule (30 mg/capsule) of compound B to healthy fasted-humans ($N = 6$, mean *in vivo* data was used for comparison) in a previous single dose safety study. Input variables and accepted default values for GastroPlus™ simulation are shown in Table 1. Input parameters for physiological conditions (e.g. transit times, volumes) used in modeling are consistent with human fasted state conditions (GastroPlus™ default values for human fasted state conditions). Other parameters are used as determined *in vitro* (e.g. particle size, solubility in FaSSIF) or *in silico* (e.g. diffusion coefficient, permeability). Solubility in FaSSIF was used in the simulation to represent intestinal solubility. Solubility in the stomach, on the other hand, was allowed to float (different values were used) until an agreement between simulation results and *in vivo* data was achieved.

3. Results and discussion

3.1. Effect of media on the CMC of SLS

Surface tension measurement is a common method for determining CMC. As surfactant concentration increases, surface tension decreases according to the Gibbs adsorption equation (Eq. (1)). Eventually a point is reached at which the interface

Table 1
Input variables (compound B) and accepted default values for GastroPlus™ simulation

General simulation and compound B parameters	Physiological parameters	Pharmacokinetics
Log P: 4.8	Human fasted conditions	Body weight: 70 kg
pK_a: 2.5	Absorption model: log D model	First pass extraction: 60%
Dosage form: immediate release capsule with 30 mg dose	Stomach transit time: 0.25 h	Blood to plasma concentration ratio: 1
Lower limit solubility (stomach): permitted to float	Dose volume: 250 mL	Clearance: 0.14 L h^{-1} kg^{-1}
Intestinal solubility: 0.001 mg/mL	Small intestine transit time: 3.3 h	V_c: 3.4 L kg^{-1}
Mean precipitation time: 1250 s	Small intestine radius: 1.2 cm	–
Particle density: 1.2 g/cc	Small intestine length: 300 cm	–
Effective permeability: 3×10^{-4} cm s^{-1}	Colon volume: 1200 mL	–
Effective particle radius: 5 μm	–	–

becomes saturated. Consequently, surface excess levels off. If the structure permits, the surfactant forms micelles at that point (region). The concentration at that point (region) is referred to as the CMC:

$$\Gamma_2 = -\frac{c}{RT}\left(\frac{\partial\gamma}{\partial c}\right) \quad (1)$$

where Γ is the surface excess, c the surfactant concentration in bulk, R the gas constant, T the temperature, and γ is surface tension.

Surface tension versus SLS concentration in different media is shown in Fig. 1(a). Determination of CMC values in the different media can be seen in Fig. 1(b). Fig. 1(c) clearly shows that the CMC of SLS is strongly dependent on ionic strength.

The CMC of SLS in 0.01N HCl/0.2% NaCl, and 0.05N HCl/0.2% NaCl is 1.75 mM and 0.91 mM, respectively. Since the composition of $FaSSGF_{SLS}$ is 8.67 mM SLS/0.01–0.05N HCl/0.2% NaCl, this means that most of SLS in $FaSSGF_{SLS}$ is present as micelles. In addition, the concentration of SLS micelles is different depending on pH. In 0.01N HCl/0.2% NaCl a SLS concentration of 1.75 mM gives the same surface tension (~34 mN/m) as 8.67 mM SLS without micelles.

It is important to note that surface excess (Γ), as apparent from the slopes in Fig. 1(b), in all media is significantly lower than that in water ($p < 0.05$). Since CMC in the other media is lower than that in water (Fig. 1(b)), more surfactant goes to the bulk to form micelles rather than go to the surface. Consequently, Γ is lower (Al-Maaieh and Aburub, 2007).

3.2. Micellar solubilization

The total solubility of a weak acid (pH is $\ll$pK_a) or a non-ionizable molecule in the presence of micelles can be described using the following equation:

$$S_{tot}^{surf} = S + kC_{mic} \quad (2)$$

where S_{tot}^{surf} is the total solubility of solute in surfactant solution, S the solubility in the absence of surfactant, k the molar solubilization capacity, and C_{mic} is the concentration of micelles in solution.

The total solubility of a weak base in the presence of micelles can be described using the following equation:

$$S_{tot}^{surf} = S_u + S_u 10^{(pK_a - pH)} + k_u C_{mic} + k_i C_{mic} \quad (3)$$

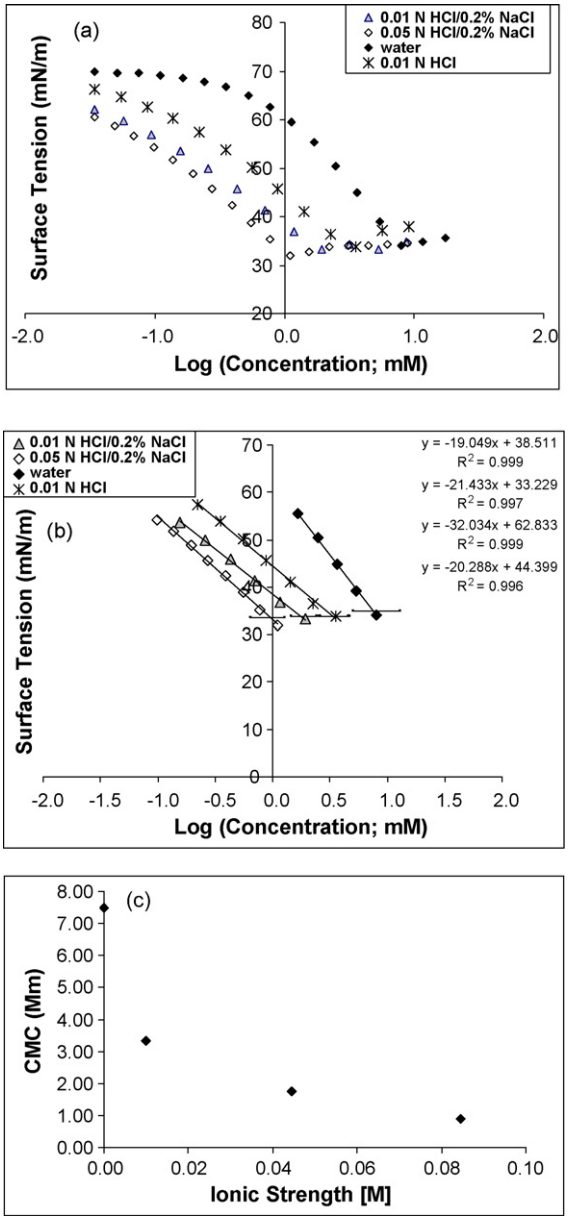

Fig. 1. Plots of (a) surface tension vs. log SLS-concentration at 37 °C, (b) CMC determination, and (c) effect of ionic strength on CMC.

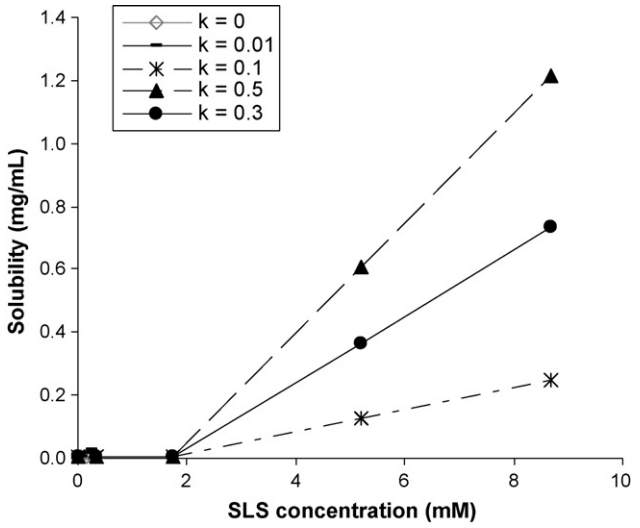

Fig. 2. Simulation of the effect of solubilization capacity on micellar solubilization of a non-ionizable molecule (assumptions: molecular weight = 350, CMC = 1.75 mM, S = 0.005 mg/mL).

where S_u is the solubility of the free unionized solute, k_u and k_i are the molar solubilization capacities of unionized and ionized drug, respectively.

According to the aforementioned, if the concentration of SLS in the media is greater than its CMC; the potential for solubility overestimation exists. How significant is solubility overestimation (if any) due to having 6.92 mM SLS micelles [SLS concentration in $FaSSGF_{SLS}$ (8.67 mM) − CMC_{SLS} in $FaSSGF_{SLS}$ (1.75 mM) = 6.92 mM] in $FaSSGF_{SLS}$? This depends on the micellar solubilization capacity, k, which is compound dependent.

To study the effect of solubilization capacity on micellar solubilization of a non-ionizable molecule, simulation studies were conducted using Eq. (2) (Fig. 2). Clearly, the presence of 6.92 mM SLS micelles in $FaSSGF_{SLS}$ can cause dramatic overestimation of solubility.

The low surface tension in the stomach is in part due to pepsin. However, while pepsin is surface active it is not known to form micelles. Therefore, micellar solubilization due to pepsin is not expected. Lower gastric surface tension has also been attributed to bile salts due to reflux. Rhodes et al. (1969) reported an average concentration of 80 μM total bile salts in the stomach in 10 healthy volunteers in the fasted state. Lindahl et al. (1997) reported a median of 100 μM bile salts in aspirates from healthy volunteers, while Efentakis and Dressman (1998) reported an average value of 275 μM in four of eight healthy volunteers, noting that no bile salts were detected in the gastric aspirates of the other four of the subjects. In all cases, the concentration of bile salts is orders of magnitude lower than reported CMC values of bile salts (e.g. 20 mM, 18 mM, 13 mM, and 17 mM for sodium cholate, sodium taurocholate, sodium deoxycholate and sodium taurodeoxycholate; respectively) (Coello et al., 1996). Hence, one would not expect any significant bile salt micellar solubilization in the stomach.

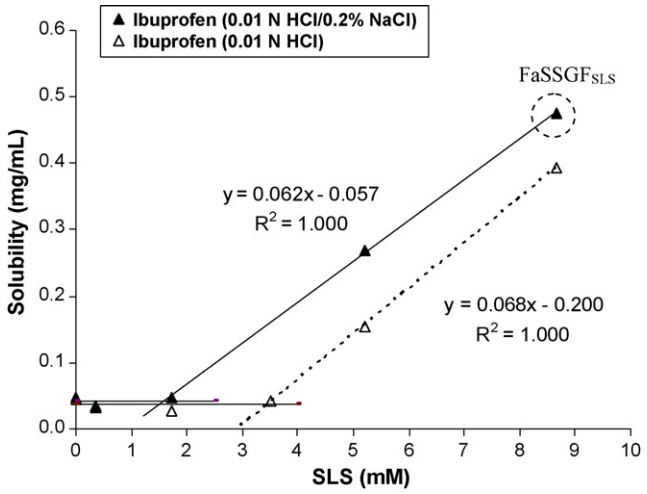

Fig. 3. Solubility of ibuprofen in 0.01N HCl and 0.01N HCl/0.2% NaCl having different concentrations of SLS at 37 °C.

3.3. Solubility of ibuprofen and progesterone

These compounds were chosen as examples of a weak acid and a non-ionizable molecule. Figs. 3 and 4 clearly show that the solubilities of ibuprofen and progesterone are strongly dependent on SLS concentration. Both compounds have high solubilities in $FaSSGF_{SLS}$ due to the presence of SLS micelles.

The CMC of SLS in 0.01N HCl/0.2% NaCl was determined from the solubility data of ibuprofen and progesterone (inflection points in solubility versus SLS concentration curves) to be 1.59 mM and 1.71 mM, respectively. These values are consistent with that determined by surface tension method (1.75 mM, Fig. 1(b)). The aforementioned, further supports that most of SLS in $FaSSGF_{SLS}$ is present as micelles.

The decrease in solubilization capacity (slopes in Figs. 3 and 4) of ibuprofen and progesterone upon increasing ionic strength (i.e. addition of NaCl) indicates that both compounds are not solubilized in the core of SLS micelles but rather

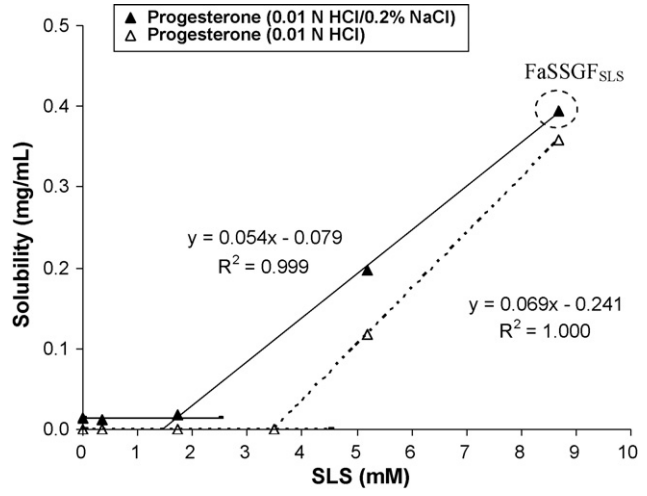

Fig. 4. Solubility of progesterone in 0.01N HCl and 0.01N HCl/0.2% NaCl having different concentrations of SLS at 37 °C.

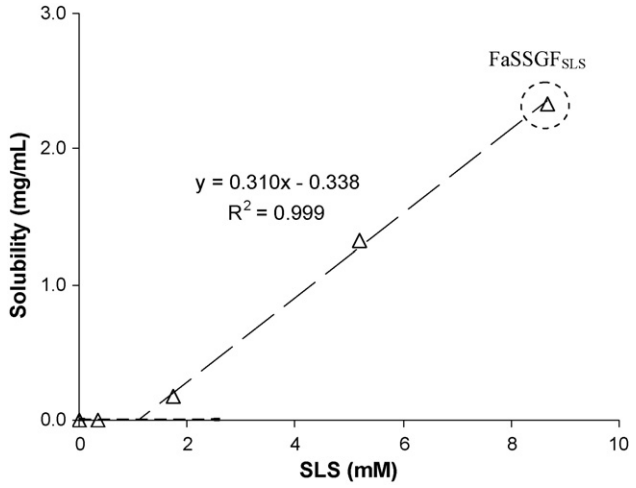

Fig. 5. Solubility of compound B in 0.01N HCl/0.2% NaCl having different concentrations of SLS at 37 °C.

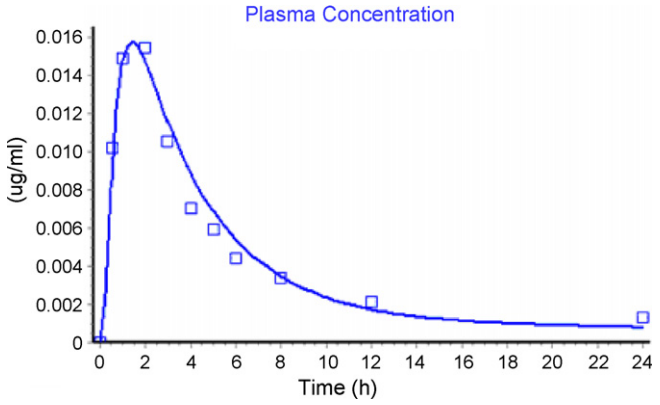

Fig. 6. *In vivo* plasma concentration vs. time profile (squares) following oral administration of a 30 mg capsule of compound B. GastroPlus™ simulation (solid line) (gastric solubility adjusted to get agreement with *in vivo* data).

in a more polar region like the palisade layer. Increasing ionic strength results in a decrease in repulsion between similarly charged ionic surfactant head groups, thereby, decreasing the CMC and increasing the aggregation number of SLS micelles (Alkhamis et al., 2002). The decrease in mutual repulsion of ionic head groups results in closer packing of surfactant molecules in the palisade layer causing a decrease in the volume in the palisade layer and a resulting decrease in the volume available there for solubilization (Alkhamis et al., 2002).

3.4. Solubility of compound B and GastroPlus™ modeling

As with ibuprofen and progesterone, the solubility of compound B is strongly dependent on SLS concentration and is high in FaSSGF$_{SLS}$ due to the presence of SLS micelles (Fig. 5). The equilibrium pH through out compound B solubility studies was maintained essentially constant (pH ∼ 2.4). Therefore, the (pK_a − pH) term in Eq. (3) is a constant and the slope of total solubility versus SLS concentration curve is the sum of the solubilization capacities for the ionized and un-ionized species ($k_u + k_i$). The solubility of compound B in FaSSGF$_{SLS}$ was determined to be 2.33 mg/mL. Compound B solubility in a media similar to FaSSGF$_{SLS}$ but with a lower SLS concentration (1.75 mM instead of 8.67 mM) was determined to be 0.17 mg/mL.

Most drugs are absorbed from the small intestine. Hence, their intestinal solubility is critical for simulation whereas their gastric solubility is not. However, for compounds that have high gastric solubilities compared to intestinal, gastric solubility can also be critical for simulation. In the case of compound B, using FaSSGF$_{SLS}$ solubility to represent stomach solubility in GastroPlus™ simulation did not result in good agreement between simulation results and in vivo data. Keeping all simulation parameters the same including intestinal solubility (FaSSIF) the gastric solubility that resulted in a simulation which agrees with *in vivo* data was determined to be 0.14 mg/mL (Fig. 6). This value is in very good agreement with compound B solubility in the modified-FaSSGF$_{SLS}$ (0.17 mg/mL). This clearly supports that the concentration of SLS in FaSSGF$_{SLS}$ is high and causes over estimation of *in vivo* gastric solubility for the model compound B. A lower SLS concentration, 1.75 mM, which achieves a surface tension similar to that in vivo without causing artificial micellar solubilization appears to be more appropriate. Similar overestimation of solubility due to the use of FaSSGF$_{SLS}$ was also shown by Pedersen et al. (2000). The authors reported that the solubility of danzol in FaSSGF$_{SLS}$ was 66 times higher than the mean solubility in human gastric fluids.

3.5. Intrinsic dissolution

Intrinsic dissolution rate (IDR) of ibuprofen in FaSSGF$_{SLS}$ and m-FaSSGF$_{SLS}$ (8.67 mM SLS/0.01N HCl/0.2% NaCl, and 1.75 mM SLS/0.01N HCl/0.2% NaCl; respectively) was determined as shown in Fig. 7. IDR of ibuprofen in FaSSGF$_{SLS}$ (26.1 μg min^{-1} cm^{-2}) is significantly higher than in m-FaSSGF (6.8 μg min^{-1} cm^{-2}) ($p < 0.05$). The higher IDR is likely due to micellar solubilization. However, the ratio of intrinsic dissolu-

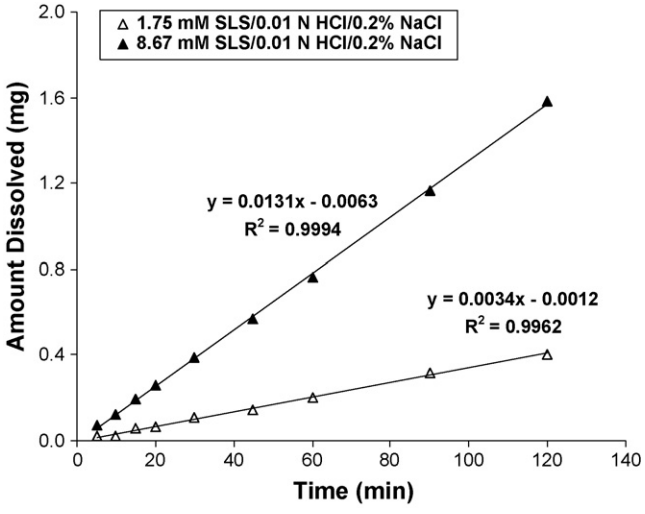

Fig. 7. Intrinsic dissolution of ibuprofen in different media at 37 °C.

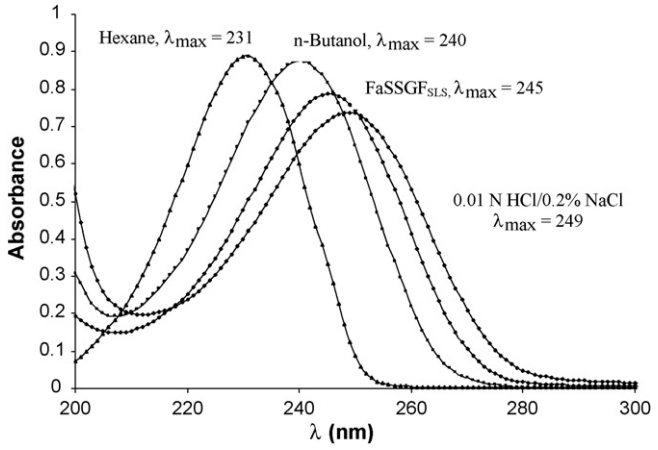

Fig. 8. Absorption spectra of progesterone in hexane, *n*-butanol, $FaSSGF_{SLS}$, and 0.01N HCl/0.2% NaCl.

tion rates (Eq. (4)) was determined to be 3.8. This is less than what would be expected due to the increase in solubility (13.7 fold). Such behavior is not uncommon and is likely due to the smaller diffusivity of micellar species (Sheng et al., 2005; Jinno et al., 2000)

$$\frac{\mathrm{IDR(FaSSGF_{SLS})}}{\mathrm{IDR(mFaSSGF_{SLS})}} \quad (4)$$

3.6. Spectral test

Ultraviolet (UV) spectroscopy can be utilized to determine the location of solubilization in the micelle, where the environment of solubilization is used to locate the solubilizate sites (Alkhamis et al., 2002). If the compound is solubilized in the inner core (non-polar) of the micelle, its UV spectra will be similar to its UV spectra in a non-polar solvent. However, if the compound is solubilized in the outer region (polar) of the micelle, its UV spectra will be closer to that in an aqueous media. Spectral test (Fig. 8) shows that the absorption spectrum of progesterone in $FaSSGF_{SLS}$ lies between that in 0.01N HCl/0.2% NaCl and *n*-butanol and is shifted far from that in hexane. This indicates that the micellar solubilization environment of progesterone in SLS micelles is semi-polar rather than non-polar. Hence, progesterone is not solubilized in the core of SLS micelles but rather in a more polar region like the palisade layer. The aforementioned conclusion can also be reached by examining the λ_{max} values in the different media (Fig. 8). Similar behavior was seen with ibuprofen in that λ_{max} in $FaSSGF_{SLS}$ (197 nm) is between the λ_{max} values in 0.01N HCl/0.2% NaCl (195 nm) and *n*-butanol (199 nm) and is shifted far from that in hexane (204 nm).

3.7. Literature fasting state simulating gastric fluids

Examples of fasted state simulating gastric fluids, composition and physicochemical properties, are shown in Table 2. The first two FaSSGFs (a and b) have surfactant concentrations much higher than CMC. USP FaSSGF has a higher surface tension than what is expected *in vivo*. The fourth FaSSGF (d) is clearly

Table 2
Examples of fasted state simulating gastric fluids and proposal of a modified-$FaSSGF_{SLS}$ (m-$FaSSGF_{SLS}$)

Property	a: $FaSSGF_{SLS}$ (Dressman et al., 1998)	b: $FaSSGF_{Triton}$ (Galia et al., 1999)	c: $FaSSGF_{USP}$	d: Vertzoni et al. (2005)	e: m-$FaSSGF_{SLS}$	*In vivo* data (Dressman et al., 1998, 1990; Efentakis and Dressman, 1998; Finholt and Petersen, 1978; Lindahl et al., 1997; Rhodes et al., 1969; Vertzoni et al., 2005)
pH	1.3–2.0	1.2	~1.2	1.6	2.0	1.4–2.1
Surface tension (mN/m)	34	32	~57	43	~34	41.0 (6.0)
NaCl (%)	0.2	0.2	0.2	0.2	0.2	0.4 (0.2)
SLS (mM)	8.67	–	–	–	1.75	–
Triton X-100 (%)	–	0.1	–	–	–	–
Pepsin (mg/mL)	–	–	3.2	0.1	–	~0.8
NaTc (μM)	–	–	–	80	–	Variable (~80)
Lecithin (μM)	–	–	–	20	–	–

superior to the first three. However, while all its components are physiological; both NaTc and Lecithin are not naturally present in the stomach and their levels due to reflux are highly variable. In addition, due to the presence of pepsin, the media has to be freshly prepared to avoid degradation, and using it for equilibrium solubility studies (long equilibration times) is questionable (pepsin degradation).

As an alternative we are proposing a modified-FaSSGF$_{SLS}$ (e) that does not contain too many components and is simple to prepare. While this recipe does not contain pepsin, which is physiologically present in the stomach, it achieves similar physicochemical properties to those *in vivo* (e.g. surface tension and pH). Equally important, the concentration of surfactant in m-FaSSGF$_{SLS}$ is sufficient to achieve a surface tension similar to that *in vivo* without causing artificial micellar solubilization. Finally, it is important to note that the presence of SLS might cause an artificial under estimation of solubility in cases where a less soluble salt/complex forms between lauryl sulfate and the drug.

4. Conclusion

Most of the SLS in FaSSGF$_{SLS}$ is present as micelles. The presence of these micelles can potentially cause overestimation of gastric solubility due to artificial SLS-micellar solubilization. This was shown to be true for three model compounds (weak acid, weak base and non-ionizable).

A simple recipe for FaSSGF is proposed (1.75 mM SLS, ~0.01N HCl, 0.2% NaCl). In this recipe the concentration of surfactant is sufficient to achieve a surface tension similar to that in vivo without causing artificial micellar solubilization.

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