International Journal of Pharmaceutics 368 (2009) 154–159

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Anion effects on electrostatic charging of sterically stabilized, water insoluble drug particles

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ARTICLE INFO

Article history:
Received 2 September 2008
Received in revised form 1 October 2008
Accepted 8 October 2008
Available online 18 October 2008

Keywords:
Stability
Surfactant
Hydrophobicity
Surface charge
Zeta potential

ABSTRACT

Water-insoluble suspensions of itraconazole and budesonide were sterically stabilized using nonionic polymers (poloxamer 188 or polysorbate 80) and probed for polymer–anion interactions by measuring changes in particle zeta potential. Anions comprising a range of functionalities and aqueous solubilities were examined. Results showed that the more hydrophobic anions partitioned to the particle interface, and a simple model for predicting anion adsorption was developed from their calculated properties. Anions with a calculated Klopman water solubility less than 10 μM or a calculated log $P > 3.5$ were adsorbed to the particle–polymer interface effectively increasing the overall particle charge. Anions of similar hydrophobicities with sulfonate or sulfate functionalities showed a much higher degree of particle charging compared with their carboxylate and phosphonate analogs at pH 9.5. In addition, the electrostatic charging of particles occurred at lower solution concentrations of sulfonate derivatives. These results suggest that the relative basicity of the oxoanion functionality may influence protonation or ion-pairing phenomena of the anions when adsorbed at the particle–polymer interface. Cetyltetramethylammonium bromide (CTAB) produced a positively charged particle consistent with the model developed for anion adsorption. Particle charging of sterically stabilized drug suspensions appeared largely independent of drug and polymer type. Anion hydrophobicity (solubility) and headgroup functionality dictated the observed charging behavior.

1. Introduction

Nanoparticulate formulations are gaining popularity for the injectable delivery of poorly water-soluble drugs. Compared to other methods for formulating poorly soluble drugs for injection, nanosuspensions are advantageous in that they allow the combination of high drug loading, reduction of toxic co-solvents and excipients, and opportunities for sustained and/or targeted release. Many types of pharmaceutical nanoparticle formulations exist, including crystalline drug nanoparticles (Merisko-Liversidge et al., 2003; Rabinow, 2004), solid lipid nanoparticles (Wissing et al., 2004), hydrogels (Huang et al., 2004; Sahiner et al., 2007), and protein-bound nanoparticles (Ng et al., 2006) to name a few. However, suspensions intended for parenteral administration are often challenging dosage forms to develop. In addition to the stringent requirements for injectables (e.g. sterility, syringeability, biocompatibility, chemical stability), suspensions must also exhibit physicochemical stability against processes such as aggregation, Ostwald ripening, and irreversible sedimentation (Akers et al., 1987). Since suspensions are inherently thermodynamically unstable, achieving sufficient kinetic stability is a challenging yet critical step in formulation of these dosage forms. Although suspension formulations may be frozen, lyophilized, or spray-dried to mitigate suspension instability risks, consideration must still be given to ensuring that the desired product characteristics are achieved after reconstitution.

In general, colloidal stability of a particle dispersion can be achieved utilizing one of the following mechanisms: steric stabilization, electrostatic stabilization, or electrosteric stabilization. Effective steric stabilization reagents are often selected from nonionic surfactants, such as polyethyleneoxide–polypropyleneoxide copolymers (poloxamers), poloxamines, and polysorbates (Chaubal et al., 2006). In particular, poloxamer 188 (Pluronic® F-68) and polysorbate 80 (Tween® 80) are widely used due to their status as approved excipients for intraveneous injection. The stabilization conferred by these surfactants, particularly the block copolymers, has been studied in detail. In aqueous systems, improved stabilization is most commonly enthalpically driven, where the repulsive barrier between particles arises from the energy required to disrupt hydrogen bonding between the polymer chains and the surrounding water molecules (Napper, 1970; Evans et al., 1972). Interparticle repulsion is also attributed to the decrease in entropy

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doi:10.1016/j.ijpharm.2008.10.004

that would result from chain compression and entangled polymer segments.

Ionic surfactants or complexing ions are commonly used to impart electrostatic stability to particles in a suspension (Myers, 2006). Increasing the net charge of the electrical double layers surrounding the particles creates a repulsive potential that is greater than the attractive interparticle van der Waals potential, as described by DLVO theory (Deryaguin and Landau, 1941; Verwey and Overbeek, 1948). The extent of particle charging and by extension electrostatic stabilization is typically assessed by measuring particle electrophoretic mobility. The particle zeta potential quantifies the electrical charge at the hydrodynamic shear plane where absolute values greater than 30 mV are generally considered electrostatically stable suspensions. In pharmaceutical injectable applications, anionic surfactants such as bile salts, alkyl sulfonates, zwitterionic phosphatides (Rieger, 1996), and free fatty acids (Washington and Davis, 1987; Werling et al., 2008) are commonly used to impart particle charge. In many cases, a combination of both ionic and nonionic stabilizers are used to create electrosterically stabilized colloids (Muller and Bohm, 1998; Merisko-Liversidge et al., 2003; Romero-Cano et al., 1998; Stenkamp et al., 2001).

The ability of a surfactant to associate with a solid surface is dependent on several factors, including pH, ionic strength, temperature, structure, charge density, and other properties of both the surface and the surfactant (Rieger, 1996). This complexity can make formulation optimization a daunting task where particle stability is only one suspension property under consideration. Often times, the selection of the excipients in a pharmaceutical nanosuspension formulation may be determined by an empirical approach given the limited number of FDA approved surfactants to consider. One may simply generate suspensions within a limited range of formulations that vary dispersant types and relative concentrations while monitoring particle size over time (Kesisoglou et al., 2007). In general, it is desirable to minimize the amount of additives in order to avoid Ostwald ripening (Merisko-Liversidge et al., 2003) and/or micelle depletion effects (Jodar-Reyes et al., 2006) without compromising stability. Formulation optimization can be complicated by the fact that excipients may also affect the fate of the particles *in vivo*. For example, poloxamers and poloxamines in injectable dosage forms can influence particle opsonization, rate of uptake by the mononuclear phagocyte system, and particle distribution in tissues (Moghimi, 1995).

The work presented here explores structure–activity relationships between nonionic polymer and anionic molecule combinations in order to more clearly elucidate electrosteric stabilization requirements of nanoparticulate drug suspensions. Crystalline nanosuspensions of two water-insoluble model drugs, itraconazole and budesonide, were dispersed with representative nonionic polymers poloxamer 188 and polysorbate 80. Ionic additives were added to the sterically stabilized suspensions, and zeta potential measurements determined whether ion adsorption at the polymer–nanoparticle surface had occurred. By exploring a broad range of monoanion types, the anion properties and functionality resulting in the highest particle surface charge were determined. While surface functionality effects on particle charge and stability has been demonstrated for other systems (Bergman et al., 2008), understanding such charging behavior at the nonionic polymer–hydrophobic drug interface is particularly useful for drug formulation and delivery applications.

2. Materials and methods

2.1. Materials

All chemicals were used as received without further purification. Sodium acetate and sodium chloride were purchased from Mallinckrodt (Hazelwood, MO, USA). Dimyristylphosphatidylglycerol (DMPG) and mPEG-DSPE were purchased from Genzyme (Cambridge, MA, USA). Cetyltrimethylammonium bromide (CTAB) was purchased from TCI America (Portland, OR, USA). Budesonide was purchased from Vinchem (Chatham, NJ, USA). Itraconazole was purchased from DSM Pharma (Parsippany, NJ, USA). Poloxamer 188 was purchased from Spectrum (New Brunswick, NJ, USA) and Polysorbate 80 was purchased from J.T. Baker (Phillipsburg, NJ, USA). All other chemicals were purchased from Sigma–Aldrich (Saint-Louis, MO, USA).

2.2. Hydrophobic drug suspension preparation

Suspension samples were prepared at a scale of 30–40 mL. The drug powder (itraconazole or budesonide) and nonionic polymer surfactant were mixed using an IKA Ultraturrax T8 (Staufen, Germany). This presuspension was transferred into an Avestin EmulsiFlex-C5 homogenizer (Ottawa, Canada) reservoir and homogenized at 20,000 + 2000 psi until a particle size of approximately 0.8–0.9 μm was reached. Homogenization times varied for the different formulations and were approximately 3.5 h for formulation A, 1 h for formulation B and 2 h for formulation C. Two batches of formulation A were prepared and used interchangeably while just single batches of B and C were produced. The sample formulations are shown in Table 1 and were diluted in salt/surfactant solutions for surface charge analyses as described below. The particle sizes were essentially unchanged by the dilution step, and therefore, the zeta potential measurements described below were made on particles with mean sizes in the range 700–1000 nm.

2.3. Sample preparation and zeta potential measurements

Ionic surfactants were generally prepared as 0.1 M stock solutions in water with some surfactants prepared at more dilute concentrations due to limited solubility. Each surfactant was pH adjusted using sodium hydroxide to a pH around 9.5 or greater. Surfactant solutions were added to the sample and diluent to achieve the desired concentration. The typical mixture used for zeta analysis was prepared with 5 mL of 5 mM cyclohexylaminoethanesulfonic acid (CHES) buffer (pH 9.5), 50 μL of 1 wt.% sample suspension, and 50 μL of 0.1 M surfactant with volume ratios adjusted for the more dilute surfactant concentrations.

Zeta potentials were measured using a Zetasizer Nano ZS with MPT-2 autotitrator (Malvern Instruments, Malvern, UK). Titration curves were generated using a titration sequence from pH 9.0 to 2.0 of a 15 mL aliquot produced from 100 μL of 1 wt.% suspension added to 40 mL 1 mM NaCl diluent at pH 9.5. The mixture was titrated using 0.1N HCl in increments of 1.0 pH units. The Smoluchowski model was used to generate zeta potential data from electrophoretic mobilities (Hunter, 2001). Minimally, duplicate zeta potential measurements were made per each sample condition up to $n = 6$. The mean relative standard deviation was calculated to be 6%.

2.4. Particle sizing

The Horiba LA-920 Laser Scattering Particle Size Distribution Analyzer (Irvine, CA, USA) was used to examine the particle size distribution after the suspension preparation step. Base suspensions were diluted approximately 100-fold with filtered distilled water to achieve the appropriate scattering intensities required for the measurement. The relative refractive indices used for particle size distribution (PSD) determination were 1.22 with an imaginary term of 0.1 for itraconazole and 1.18 with an imaginary term of 0.0 for budesonide. The measurement cell recirculation speed was set to 2, and no sonication was used for these measurements.

Table 1
Nanosuspension base formulations prior to anion addition.

Formulation ID	Drug (1 wt.%)	Polymer (0.1 wt.%)	Osmotic agent (2.2 wt.%)	pH (unbuffered)	Mean particle size (nm)
A	Itraconazole	Poloxamer 188	Glycerin	8.0	760[a]
B	Budesonide	Poloxamer 188	Glycerin	8.0	950
C	Itraconazole	Tween 80	Glycerin	8.0	820

[a] Average of two preparations.

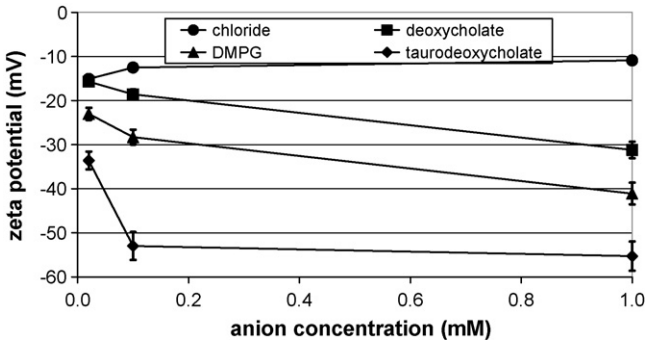

Fig. 1. Zeta potential of Poloxamer-coated itraconazole particles at pH 9.5 as a function of representative anion concentrations. The error bars represent the mean relative standard deviation of 6% for the measurement.

2.5. pH measurements

An Orion Model 330 pH meter with a combination electrode (Thermo, Model PerPHect Electrode Glass Combination pH probe) was calibrated with either 1.68, 4.01, 6.86 or 9.18 standard buffer solutions (Radiometer Analytical S.A., France) bracketing the expected pH range of the samples and pH measurements were performed after inverting the sample 20 times. All pH measurements were found to be within 0.15 pH units of their targeted value.

2.6. Physical property calculations

Physical properties for the anions were determined using Molecular Modeling Pro Plus version 6.2.4 (ChemSW, Fairfield, CA, USA). The water solubility computational result is referred to here as the Klopman solubility (Klopman et al., 1992), and the log *P* (octanol/water partition coefficient) method is based on summing contributions from atom types (Viswanadhan et al., 1989). The hydrophilic–lipophilic balance (HLB) of a molecule is approximately equal to dividing the molecular weight of the water-soluble portion by the total molecular weight and multiplying by 20. The software uses a slight modification of the method of Griffin for calculating HLB (Griffin, 1954). The percent hydrophobicity is calculated as the percent of the surface area of the molecule that is hydrophobic.

3. Results

The zeta potential measurements for itraconazole suspension A in representative anion-containing diluents are shown in Fig. 1 as a function of anion concentration. A diluent pH of 9.5 was chosen to promote fully ionized functional groups producing monoanionic species. The data showed a less negative zeta potential for elevated chloride concentrations, but a more negative zeta potential for increased hydrophobic anion concentrations. The result for chloride reflects a simple electrostatic screening effect where the chloride salt reduces the double layer thickness, effectively decreasing the measured particle charge at the hydrodynamic slip plane. The more hydrophobic anions deviate from simple double layer effects due to anion adsorption at the polymer–particle aqueous interface. Based on this initial zeta potential data, 1 mM salt concentrations were chosen as a reasonable anion concentration for discriminating between adsorbing and nonadsorbing anion behavior. Additionally, anionic surfactant concentrations exceeding 1 mM are typically limited by solubility considerations. While specific anion concentration dependencies and phase behavior are expected to vary widely, elucidating such detailed concentration behavior for each anion is beyond the scope of this work.

The molecular structures of the various anion types probed in this study are shown in Fig. 2 with their corresponding IDs, chemical names, and zeta potential measurements summarized in Table 2. The structures were chosen to span a range of functionalities and hydrophobicities. The zeta potential results in Table 2 reflect a broad range of particle charging behavior with values

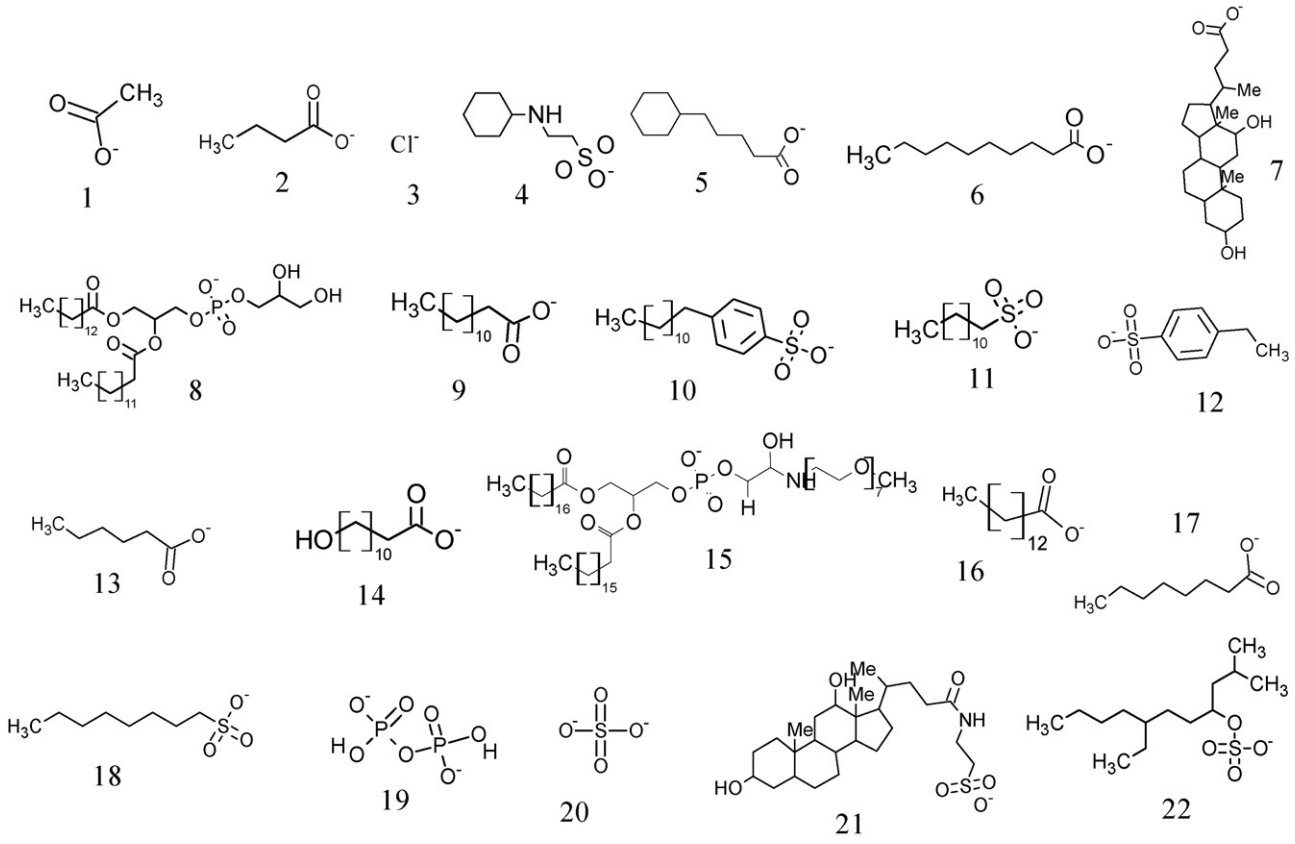

Fig. 2. Molecular structures of anions with numerical identification corresponding to data presented in Table 2.

Table 2
Zeta potential of poloxamer-coated itraconazole in the presence of 1 mM anion and 5 mM CHES buffer at pH 9.5.

Anion ID	Anion type[a]	Zeta (mV)[b]
1	Acetate	−11.4
2	Butyrate	−15.4
3	Chloride	−10.9
4	Cyclohexylaminoethanesulfonate (CHES)	−13.2
5	Cyclohexylpentanoate	−17.1
6	Decanoate	−15.3
7	Deoxycholate	−29.6
8	Dimyristylphosphatidylglycerol (DMPG)	−36.3
9	Dodecanoate	−19.2
10	Dodecylbenzenesulfonate	−54.2
11	Dodecylsulfonate	−27.2
12	Ethylbenzenesulfonate	−17.7
13	Hexanoate	−10.0
14	Hydroxydodecanoate	−16.9
15	mPEG-DSPE	−19.5
16	Myristate	−23.7
17	Octanoate	−11.9
18	Octylsulfonate	−16.7
19	Pyrophosphate (dianion)	−9.1
20	Sulfate	−15.6
21	Taurodeoxycholate	−48.9
22	Tetradecylsulfate	−57.3

[a] Sodium salts.
[b] Mean relative standard deviation ~6% with $n = 2–6$.

from −10 to −57 mV. The tetradecylsulfate, taurodeoxycholate, and dodecylbenzenesulfonate had the most negative zeta potentials at −57, −49, and −54 mV, respectively, and thus were the most favorable diluents for imparting negative charge to the particles in suspension at pH 9.5. Simple, hydrophilic anions such as acetate, chloride, and CHES had the least negative zeta potential. CHES was specifically chosen as an appropriate pH buffer for all the samples owing to its nonadsorbing behavior. The results showed a strong anion dependence on particle charge, and not surprisingly the more hydrophobic, surfactant-like anions tended to create particles with more negative charge.

The zeta potential for a subset of anions in the two additional drug–polymer formulations, B (budesonide/Poloxamer 188) and C (itraconazole/Tween 80), are shown in Table 3. Each formulation in CHES had slightly differing absolute values of particle zeta potential owing to the unique overall surface compositions and aqueous particle morphologies. To facilitate direct comparison between formulations, each zeta potential within a formulation family (A, B, or C) was normalized to the chloride-containing composition. The chloride anion was chosen as the control as it represents the simplest, nonadsorbing salt. Comparing the zeta ratios in Table 3, the trends with anion type were found to be similar across the three formulations. Specifically, the particle charge increased with anion type as follows: chloride < octylsulfonate < dodecanoate < myristate ~ deoxycholate < DMPG < taurodeoxycholate. The similar trends in relative particle charge as a function of anion suggests that anion properties are more important in driving adsorption and particle charging behavior than the specific drug/polymer interface. A more detailed analysis is presented below.

Table 3
Zeta potential of polymer-coated model drugs in the presence of 1 mM anion and 5 mM CHES buffer at pH 9.5.

Anion diluent	Suspension formulation					
	A		B		C	
	Zeta	Ratio[a]	Zeta	Ratio[a]	Zeta	Ratio[a]
CHES only	−12.0	NA	−17.3	NA	−19.4	NA
Chloride	−10.9	1.0	−16.2	1.0	−18.7	1.0
Deoxycholate	−28.4	2.6	−42.4	2.6	−41.5	2.2
DMPG	−36.3	3.3	−57.1	3.5	−59.6	3.2
Dodecanoate	−19.2	1.8	−29.5	1.8	−37.5	2.0
Myristate	−23.7	2.2	−36.2	2.2	−50.3	2.7
Octylsulfonate	−16.7	1.5	−26.4	1.6	−33.6	1.8
Taurodeoxycholate	−48.9	4.5	−83.2	5.1	−66.6	3.6

[a] Ratio of anion diluent zeta potential to chloride diluent zeta potential.

4. Discussion

Overall, the variety of anion-containing diluents generated a range of particle surface charges. Simple water-soluble salts like sodium chloride produced particle zeta potentials between −5 mV and −20 mV. These relatively low zeta values are not typically associated with electrostatic stabilization. Thus, suspensions in simple salts would rely on steric stabilization attributes of the nonionic polymers. The most hydrophilic monoanions do not adsorb at the particle interface and are not potential determining ions for the drug suspension particles.

Possible driving forces for anion adsorption include chelation, ion pairing, hydrogen bonding, or hydrophobic effects. In this work, anion hydrophobicity and charged functional group were systematically varied. The anion calculated properties of HLB, log(solubility), log *P*, and percent hydrophobicity were plotted as a function of zeta ratio in Fig. 3. The property–zeta ratio individual correlation coefficients were all below 0.6 in magnitude indicating relatively poor linear fits. When one probes the relationships for threshold effects, it appears that a minimal water solubility and threshold value of log *P* (~3.5) are required for effective particle charging.

A more detailed plot of calculated anion solubilities (Klopman et al., 1992) versus zeta ratios is shown in Fig. 4. Anions with a calculated solubility less than 10 μM had zeta ratios greater than 1.5 translating to more than a 50% increase in particle charge compared with the chloride control. This is not surprising given that the least soluble anions have the most hydrophobic character and therefore exhibit prototypical surfactant behavior. Molecules with log *P* values greater than 3.5 have more lipophilic character and therefore, are also predictive of increased electrostatic charging of the polymer-coated particles. HLB and percent hydrophobicity did not appear to have the same threshold relationship with particle charging behavior. The more hydrophilic anions (calculated Klopman solubilities > 10 μM or log *P* < 3.5) maintained zeta ratios between 0.8 and 1.5 and did not impart significant charge to the particle surface.

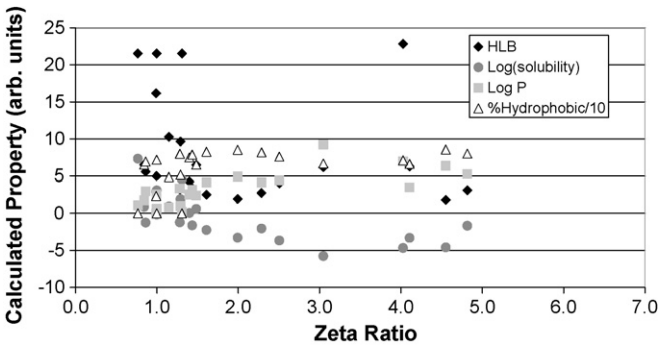

Fig. 3. The calculated HLB, log(solubility), log *P*, and percent hydrophobicity for the anions from Table 2 are plotted as a function of zeta ratio for suspension A particles (pH 9.5 in 1 mM anion solutions). The properties are not linearly correlated to particle charging evidenced by the observed correlation coefficients between the calculated property and zeta ratio of −0.21 (HLB), −0.51 (log[solubility]), 0.55 (log *P*), and 0.42 (percent hydrophobicity). The percent hydrophobicity has been divided by 10 to fit the data to a single *y*-axis scale.

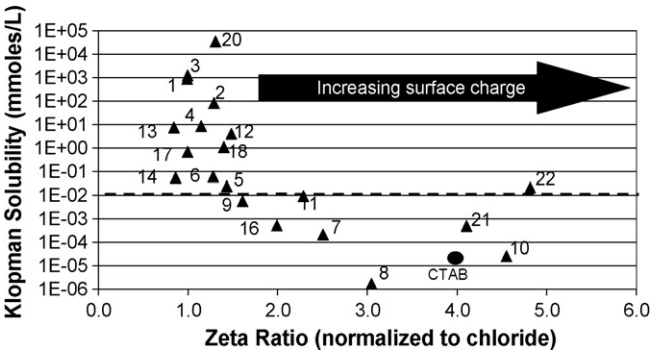

Fig. 4. The calculated solubility for the anions from Table 2 (ID numbers included) are plotted as a function of zeta ratio for suspension A particles (pH 9.5 in 1 mM anion solutions). The plot shows that anions with a Klopman solubility less than 10 μM (below dashed line) were effective at increasing the zeta ratio which represents an increase in the particle surface charge. The cation CTAB was added for comparison as a filled circle.

While the Klopman solubility calculation is useful for predicting particle charging behavior, some inherent limitations need to be mentioned. One limitation is that the calculated solubilities may be a factor of 10–100 away from actual solubilities (not too unreasonable for such a diverse set of molecules). Examples include tetradecylsulfonate (22) which had a calculated solubility that seemed to be overestimated for a branched, hydrophobic anion, and mPEG-DSPE (15) which had an underestimated calculated solubility of 10^{-12} mM. It is also important to point out that the calculated solubility limit for the most effective ions at particle charging were all less than the actual 1 mM concentrations used experimentally. Despite these limitations, the Klopman solubility method still provides a simple, rational framework for predicting the degree of hydrophobicity required for an anion to partition to the hydrophobic segments of the drug–polymer interface and impart a particle charge increase.

More interestingly, Fig. 4 clearly demonstrates that the charged head group functionality of the surfactant molecule significantly influences the particle charge when comparing compounds of similar hydrophobicity. Comparing dodecylsulfonate (11) with dodecanoate (9) revealed simple sulfonate substitution of the carboxylate group created a more negative particle zeta potential despite identical alkane chains of the monoanions. A similar trend was observed comparing structurally similar deoxycholate (7) with taurodeoxycholate (21). At pH 9.5 both pairs of compounds should be fully deprotonated in solution and thus of equal charge, but the sulfonate surfactant derivatives impart a higher net negative charge to the drug particles. In fact, the highest zeta ratios were obtained for anions 10, 21, and 22 which are all sulfonate or sulfate derivatives. In addition, a lower dosage requirement for particle charging behavior was observed for taurodeoxycholate (Fig. 1). Clearly, the sulfonate derivatives had some unexpected advantages compared to the carboxylate-containing molecules at pH 9.5.

There are a few possibilities to consider for the increased charge associated with sulfonate surfactants. First, the pK_a of the sulfonic acid group is signifcantly lower than that for the carboxylic and phosphonic acid groups. As anionic molecules are driven to the surface, the electrostatic repulsion between neighboring anions can be mitigated by protonation or ion-pairing. The sulfate and sulfonic acid oxoanion groups are least susceptible to these charge neutralization mechanisms due to the weak basicity of the headgroup. Another important consideration is the solution phase behavior of the anionic surfactants. Double-layer structures, micelle formation, and complex phase behavior may also contribute to unique interfacial interactions that influence overall particle charge. The data in this study is insufficient to unambiguously define the mechanism for enhanced particle charging in sulfonate-containing solutions.

The Klopman solubility requirements for particle charging were also satisfied for a cationic surfactant example. Cetyltrimethylammonium bromide (CTAB) solutions produced a particle zeta potential of +49 mV for poloxamer-coated itraconazole (formulation A). The calculated Klopman water solubility places it in a favorable range for adsorption as indicated in Fig. 4 where the absolute value of the zeta ratio is 4.1. CTAB showed a magnitude of particle charging comparable to the sulfonate derivatives. As a quaternary amine, CTAB does not have any acid-base equilibria available to potentially reduce its charge via protonation on the particle surface. Although cationic surfactants appear to fit the particle charging model well, one recognizes that the model is currently limited to monovalent species in the alkaline pH regime.

Interestingly, the type of nonionic polymer or hydrophobic drug did not have a significant influence on the relative zeta potential. For the drug–polymer formulations that included itraconazole–poloaxmer 188, itraconazole–Tween 80, and budesonide–poloxamer 188, the anion influence on particle charging was similar. This substrate independent behavior is consistent with ionic surfactant adsorption being driven by the hydrophobic effect. Overall, results are readily interpreted by a simple surfactant rationale, and the calculated solubility provides an accessible tool for helping direct electrosterically stabilized formulations. The colloidal stability of these test nanosuspensions should be impacted by the particle charging behavior but is beyond the scope of work presented here. Extracting the value of more highly charged particles from sulfonate- and sulfate-containing formulations will be realized through future efforts that (1) demonstrate improved physicochemical stability and (2) establish suitability as an approved excipient.

5. Conclusions

In the development of an injectable pharmaceutical suspension formulation, several requirements must be satisfied, not the least of which is colloidal stability. Empirical approaches are often time-consuming and may not yield an optimal combination of excipients. In this work, structure–activity relationships for anion adsorption on sterically stabilized hydrophobic model drug particles were investigated. Itraconazole and budesonide particles were dispersed using either EO-PO block co-polymers (poloxamer 188) or polyoxyethylene sorbitanmonooleate (polysorbate 80). The sterically stabilized suspensions showed strong interactions with hydrophobic anions evidenced by an increased surface charge due to anion adsorption. The anion solubility computed by the method of Klopman showed a reasonable correlation with surface adsorption. Anions with a calculated Klopman solubility less than 10 μM readily partitioned to the particle–polymer interface when their actual solution concentration was 1 mM. Calculated log P values greater than 3.5 were also associated with an increase in particle charging behavior.

Anions of similar hydrophobicities with sulfonate or sulfate headgroups showed a higher degree of particle charging compared with carboxylate and phosphonate headgroup analogs. The relatively weak basicity of the sulfonate/sulfate oxoanion compared to the carboxylate and phosphonate groups may reduce the degree of protonation or ion-pairing when packed on the surface. The cationic surfactant, CTAB, yielded similar charging effects compared to the sulfonate groups. The results of anion partitioning were largely independent of drug and polymer types indicating that anion hydrophobicity is the principal driving force.

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