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Influence of surfactants upon protein/peptide adsorption to glass and polypropylene

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Abstract

This paper explores the use of surfactants as a pharmaceutical excipient to reduce adsorptive losses of protein/peptide drugs. The predominant adsorption mechanism for protein/peptide drugs is shown to change with the surface and conditions of study. In the presence of surfactants, where the surfactant-surface interaction is greater than the surface-protein/peptide interaction, drug adsorption is reduced and/or eliminated. Anionic (sodium dodecyl sulfate), cationic (dodecyltrimethylammonium chloride and benzalkonium chloride) and nonionic surfactants (Polysorbate 20 and Poloxamer 188) are evaluated as possible protein/peptide adsorption controlling excipients. For protein/peptide adsorption onto glass, where an electrostatic interaction predominates, only the most hydrophobic surfactants (Polysorbate 20 and benzalkonium chloride) were significantly effective. Protein/peptide adsorption to polypropylene, where a hydrophobic/dehydration mechanism predominates, allows additional surface-active agents to be effective in reducing drug adsorption.

Keywords: Adsorption; Surfactant; Protein; Peptide; Glass; Polypropylene

1. Introduction

During the manufacture (formulation and packaging) and use of pharmaceutical products, the drug comes into contact with a variety of surfaces. Protein/peptide drugs often interact adversely with these surfaces resulting in loss from solution, denaturation and/or aggregation. An understanding of these adsorptive interactions could greatly improve the development, processing and stability for protein/peptide drug products.

When adsorption of a protein/peptide drug occurs, the drug molecule exchanges solution interactions for surface interactions where the free energy of exchange is negative (Andrade and Hlady, 1986; Norde, 1986). The energetics of this peptide adsorptive process arise from predominantly two mechanisms. One dominant mechanism is the result of charge-charge, or electrostatic interactions. A second dominant mechanism arises from hydrophobic interactions accompanied by dehydration of the protein/peptide

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molecules and of the surface. Here, the entropic losses brought about by the loss of molecular motion of the protein/peptide molecules are more than offset by the entropic gains resulting from the 'dehydrated' water molecules being freed from the protein/peptide drug molecule and from the surface. Lesser mechanisms include those resulting from charge-dipole, dipole-dipole and van der Waals interactions. Additionally, hydrogen bonding often plays a role in the adsorptive process. However, its energetics are usually quite small.

Salmon calcitonin (sCT) and bovine serum albumin (BSA) are two protein/peptides known to adsorb to glass and plastics resulting in loss from solution. Experimental assays were developed and compared for the quantification of protein/peptide adsorption to surfaces using sCT as a model compound (Duncan et al., 1994). sCT in a pH 4 water was found to adsorb to type I borosilicate glass in the amount of 250 ng/cm^2 over the concentration range of 2.5–20 μg/ml. Numerous authors have evaluated BSA adsorption to a variety of surfaces (Kondo and Higashitani, 1992).

sCT was chosen as a model positively charged protein/peptide drug while BSA was employed as a neutral protein/peptide drug under the conditions of this study. Their adsorption to glass, which carries a negative potential at pH values above 2.5, and polypropylene, a neutral hydrophobic polymer, provide adsorption systems with favorable interaction conditions. The positively charged sCT and the negative potential of the glass represent optimal conditions for electrostatic interactions, while the neutral BSA and the neutral polypropylene present a system for hydrophobic/dehydration interactions. Kondo and Higashitani (1992) found that large proteins, such as ovalbumin and BSA, showed highest affinity to polystyrene around their isoelectric points indicating the importance of the hydrophobic interaction between the proteins and the surface.

To the simple system of drug (sCT or BSA) and surface (glass or polypropylene), surfactants were added to evaluate their effect upon drug adsorption. Preliminary studies have indicated that surfactants lower drug adsorption to solid surfaces (Ruzgas et al., 1992; Duncan et al., 1993; Welin-Klintstrom et al., 1993). The ability of surfactants in solution to reduce the surface interaction of a protein/peptide drug is thought to occur by either a surface effect, where the surfactant is able to interact with the solid surface and thereby decrease the drug-surface interactions, or by a solution effect, where the surfactant sufficiently alters the solution properties and thus enhances drug-solution interactions.

In this study surfactants are considered as possible adsorption controlling excipients. Anionic, cationic and non-ionic surfactants are added to protein/peptide drug solutions in an effort to reduce the drug adsorption to pharmaceutical surfaces. The mechanisms of protein/peptide surface interactions and surfactant influence are elucidated by pursuing the following areas of investigation: (1) characterization of the surfactants; (2) quantification of sCT and BSA adsorption to glass and polypropylene; and (3) evaluation of surfactant-surface interactions.

2. Materials and methods

2.1. Surfactants

The anionic surfactant, sodium dodecyl sulfate (SDS), was purchased from Sigma Chemical. The cationic surfactant, dodecyltrimethylammonium chloride (DTACl) was obtained from Eastman Kodak Co. and benzalkonium chloride (50%, NF; BzCl) from Spectrum Chemical Mfg Corp. Benzalkonium chloride, a mixture of alkyldimethylbenzylammonium chlorides, is a common and effective preservative for ophthalmic, topical and intranasal products. The nonionic surfactant, polysorbate 20 USP/NF (Tween 20) was purchased from Spectrum Chemical Mfg Corp. and Poloxamer 188 NF was obtained from BASF Corp.

The anionic surfactant, SDS, the cationic surfactant, DTACl, and the nonionic surfactant, Tween 20, all have an backbone length averaging 12 carbons and will be considered the three 'core' surfactants of this investigation. The surfactants were used at concentrations 10–20% of their

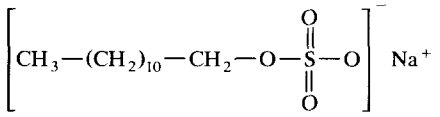
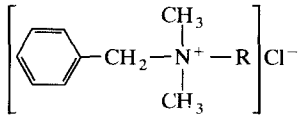
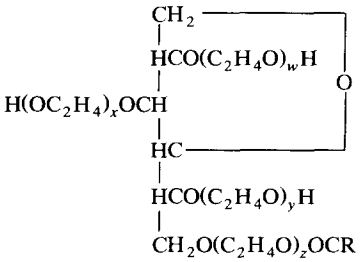
CMC values. The concentrations for SDS (0.02%), DTACl (0.02%) and BzCl (0.025%) are all approx. 0.7×10^{-3} M. The concentration of Tween 20 at 0.002% is 17.7×10^{-6} M.

Table 1 (surfactant characteristics) displays the structure, critical micelle concentration (CMC) and molecular weight of the major surfactants investigated. The CMC determinations were made using a Fisher Tensiomat 21 and a platinum-iridium ring with a circumference of 5.930 cm to measure surface tension. The surface tension at concentrations above the CMC was found to plateau between 40 and 47 dyn/cm^2 for all the surfactants. These similar surface tensions were a result of selecting surfactants with similar length hydrocarbon chains. The measured surface tension was plotted against surfactant concentration. Linear regression was performed on the portion before the minimum surface tension was reached and upon the region of steady surface tension. The resulting equations were solved for the point of intersection which was interpreted as the CMC. The CMC values obtained conformed to available published values (Handbook of Pharmaceutical Excipients, 1986; Hiemenz, 1986; Rosen, 1989).

2.2. Model protein / peptide drugs

The two model protein/peptide drugs investigated were salmon calcitonin (sCT) and bovine serum albumin (BSA). Synthetic salmon calci-

Table 1
Surfactant characteristics

Surfactant	Molecular weight (g/mol)	CMC (m/l)	Structure
Anionic			
Sodium dodecyl sulfate (SDS)	233.38	8.1×10^{-3}	
Cationic			
Dodecyltrimethylammonium chloride (DTA Cl)	263.90	1.5×10^{-2}	$CH_3(CH_2)_{11}N(CH_3)_3Cl$
Benzalkonium chloride (BZCl)	360.0	3.0×10^{-3}	 $R = C_8H_{17}$ to $C_{18}H_{37}$
Nonionic			
Polysorbate 20 (Tween 20)	1126	2.5×10^{-4}	 polyoxyethylene sorbitan monoester $w + x + y + z = 20$
Poloxamer 188	8350		$HO(CH_2CH_2O)_a \cdot (CH(CH_3)CH_2O)_b \cdot (CH_2CH_2O)_aH$ $a = 75$ and $b = 30$

tonin, purified by HPLC, was obtained from Armour Pharmaceutical Company, a division of Rhone-Poulenc Rorer. The material used possessed a peptide purity of 97–99% and an average potency of 5000 IU/mg. sCT is a polypeptide hormone comprised of 32 amino acid residues with a cysteine-cysteine disulfide bridge between residues 1 and 7 forming a ring at the N-terminal (Azria, 1989). It has an isoelectric point around 9, thus sCT carries a net positive charge under neutral and acidic pH conditions.

Bovine serum albumin, as a lyophilized powder, with a purity of 99% and 'essentially fatty acid free' was purchased from Sigma Chemical Co. BSA is a globular protein composed of 610 amino acids and has a molecular mass of 66300 Da. It possesses a helical content of 55% and 17 disulfide bridges (Martin et al., 1983). It is soluble in water and salt solutions. The isoelectric point is between 4.7 and 4.9, making it neutral under the conditions of study (pH 4.8).

2.3. Surfaces

10 ml, borosilicate, type I glass vials and borosilicate glass beads (3 mm in diameter) were purchased from Kimble Glass Co. The vials and beads were cleaned by rinsing with deionized water and heating at 200°C for 3 h. During experiments these vials were sealed with 20 mm teflon faced gray butyl (1883) closures obtained from West Co. Care was taken to avoid any contact between the solutions and the closures. Surface area was determined by geometric calculation to average 55.2 cm^2 and a surface area to volume ratio of 18.4 cm^{-1} was used.

Polypropylene tubing with an internal diameter of 0.20 cm and an outer diameter of 0.27 cm was purchased from Cole-Parmer Instrument Company. The tubing was rinsed with distilled-deionized water and air dried prior to use. A teflon faced seal was used to cap the ends. The average surface area was determined to be 68.3 cm^2 giving a surface area to volume ratio of 17.1 cm^{-1}.

2.4. Buffers

The 0.05 M acetate buffer was chosen as a simple pharmaceutical buffer which is effective under low pH conditions (sCT has greatest stability between pH 3.8 and 4.2). The 0.05 M acetate buffer at an ionic strength of 0.15 μ with a pH of 4 was made by mixing 0.016 M sodium acetate, 0.034 M acetic acid and 0.134 M sodium chloride. For the BSA adsorption studies a 0.05 M acetate buffer at an ionic strength of 0.15 μ and pH 4.8, made by mixing 0.037 M sodium acetate, 0.013 M acetic acid and 0.113 sodium chloride, was employed.

2.5. Adsorption experiment

The method for quantification of drug adsorption is used as described by Duncan et al. (1994). Briefly, a volume of drug solution of a known concentration was added to each system. 3 ml were placed in the glass system which is comprised of a glass vial with glass beads and 4 ml was injected into the polypropylene tubing. The solution was allowed to equilibrate at room temperature in a quiescent state with the container overnight. Triplicate samples were withdrawn. The concentration of drug in solution for the initial and equilibrium samples was determined via a colorimetric protein assay or a HPLC assay with a UV detector.

The colorimetric assay was a commercial protein assay purchased from Pierce to determine spectrophotometrically sCT or BSA concentration in solution. The HPLC assay for sCT was an isocratic RP-HPLC method with a C4 column, mobile phase of acetronitrile and saline, and a UV detector adapted from that described by Lee et al. (1991). The isocratic RP-HPLC assay for BzCl consisted of a C18 column, mobile phase of acetonitrile and sodium perchlorate buffer at pH 3 and a UV detector at 210 nm.

3. Results

3.1. Effect of ionic strength

The ionic strength was found to influence the level of sCT adsorbed to glass and polypropylene. Fig. 1 shows that as the ionic strength is increased, adsorption to glass decreased and ad-

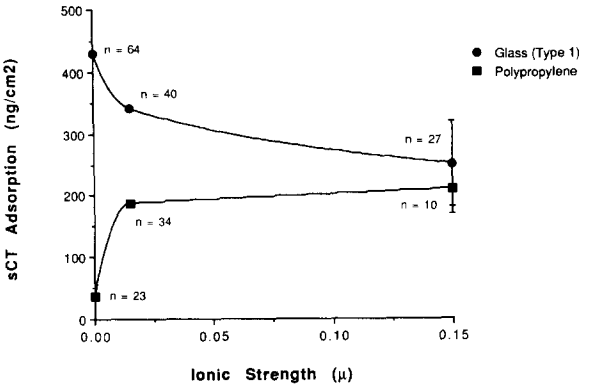


Fig. 1. Effect of ionic strength on sCT adsorption to glass and to polypropylene.

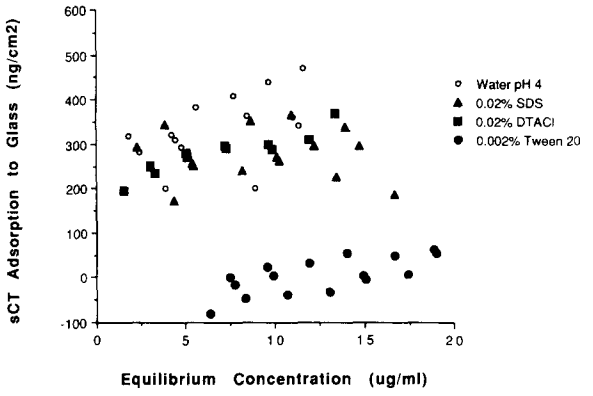


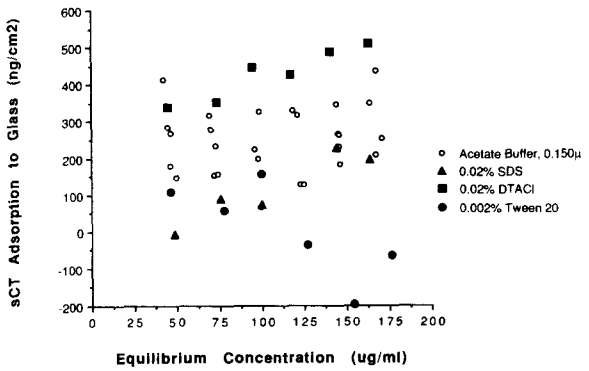
Fig. 2. Influence of surfactants on sCT adsorption to glass in water.

sorption to polypropylene increased. The adsorption of sCT onto type I borosilicate glass was about 430 ng/cm^2 at an ionic strength of zero. As the ionic strength is increased, this adsorption decreased to 330 ng/cm^2 ($\mu = 0.015$) and to 260 ng/cm^2 ($\mu = 0.15$). The adsorption of sCT onto polypropylene was about 50 ng/cm^2 at an ionic strength of zero and increased with ionic strength to 180 ng/cm^2 ($\mu = 0.015$) and to 209 ng/cm^2 ($\mu = 0.15$). Under isotonic conditions ($\mu = 0.15$), the amount of sCT adsorbed to glass and polypropylene was approximately equal.

3.2. *Influence of surfactants upon sCT adsorption to glass*

The influence of the three core surfactants, SDS, DTACl and Tween 20, on sCT adsorption to glass in a water system was evaluated and the results are given in Fig. 2. Tween 20 was effective in reducing adsorption while SDS and DTACl had no influence upon the level of sCT adsorbed. The addition of Tween 20 reduced sCT adsorption to glass from an average of 400 ng/cm^2 to an average of only 5 ng/cm^2, essentially zero.

Similar results were obtained with these core surfactants in the isotonic ($\mu = 0.15$) acetate



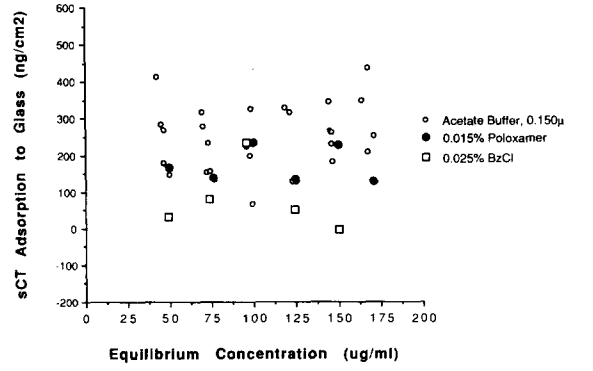


Fig. 3. (A) Influence of surfactants on sCT adsorption to glass in 0.05 M, 0.15 μ acetate buffer, pH 4.0. (B) Influence of surfactants on sCT adsorption to glass in 0.05 M, 0.15 μ acetate buffer, pH 4.0.

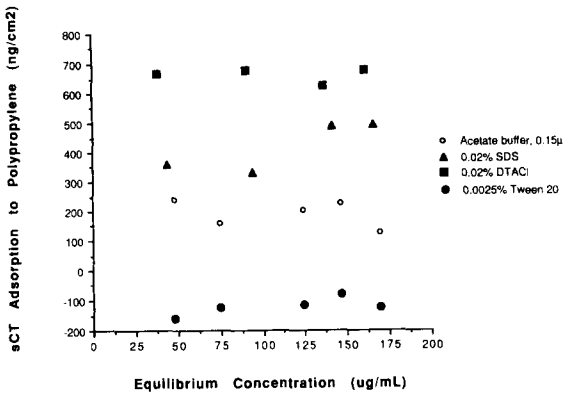


Fig. 4. Influence of surfactants on sCT adsorption to polypropylene in 0.05 M, 0.15 μ acetate buffer at pH 4.0.

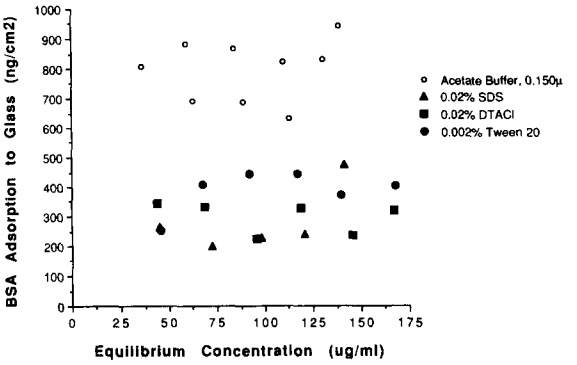


Fig. 5. Influence of surfactants on BSA adsorption to glass in 0.05 M, 0.15 μ acetate buffer, pH 4.8.

buffer shown in Fig. 3a. The addition of SDS and DTACl did not reduce sCT adsorption to glass, while the addition of Tween 20 lowered sCT adsorption from an average of 250 ng/cm^2 to 0 ng/cm^2. Increasing the length of the hydrophobic chain by employing the cationic surfactant BzCl reduced sCT adsorption by 70% (statistically significant at $p < 0.05$) to an average of 80 ng/cm^2, as displayed in Fig. 3b. Conversely reducing the hydrophobic content of the nonionic surfactant by employing Poloxamer 188 gave adsorption levels averaging 171 ng/cm^2, which are significantly ($p < 0.05$) higher than those obtained with the addition of Tween 20.

3.3. Influence of surfactants upon sCT adsorption to polypropylene

Fig. 4 shows the influence of the core surfactants upon sCT adsorption to polypropylene. At an ionic strength of 0.15 μ the addition of SDS and DTACl gave higher levels of sCT adsorption. Only Tween 20 lowered sCT adsorption from an average of 200 ng/cm^2 to a negligible level (≤ 0).

3.4. Influence of surfactants upon BSA adsorption to glass and polypropylene

BSA adsorption to glass was lowered from an average of 835 ng/cm^2 with buffer alone to 325 ng/cm^2 with the addition of any one of the core surfactants; SDS, DTACl or Tween 20. These results are displayed in Fig. 5. This reduction in BSA adsorption, although statistically significant, was only down to a level of 325 ng/cm^2, an amount greater than sCT adsorption levels.

The adsorption of BSA to polypropylene in the absence and presence of the core surfactants is given in Fig. 6. Here, the addition of Tween 20 was able to reduce the amount of BSA adsorbed to polypropylene by a statistically significant level from an average of 350 ng/cm^2 to 53 ng/cm^2. Neither SDS nor DTACl lowered BSA adsorption a statistically significant amount. The presence of SDS exerted no effect upon the amount of BSA adsorbed. The presence of DTACl lowered adsorption of BSA to an average of 200 ng/cm^2, although this reduction was not statistically significant.

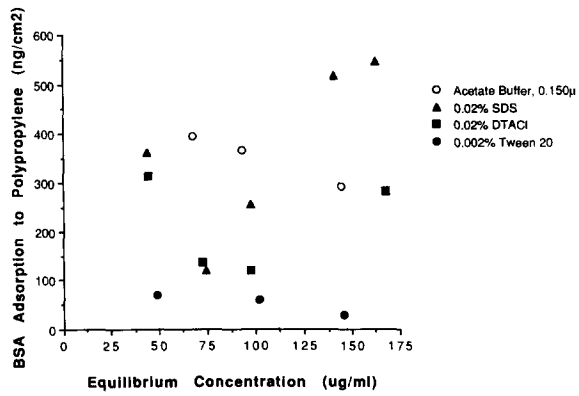


Fig. 6. Influence of surfactants on BSA adsorption to polypropylene in 0.05 M, 0.15 μ acetate buffer, pH 4.8.

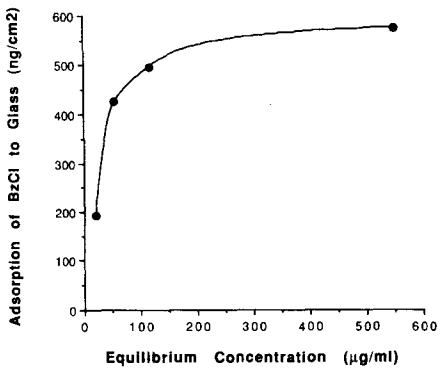


Fig. 7. Adsorption of BzCl to glass in 0.05 M, 0.15 μ acetate buffer, pH 4.0.

The drug adsorption findings with the core surfactants are summarized in Table 2.

3.5. Adsorption of BzCl

Fig. 7 demonstrates the Langmuir type adsorption isotherm obtained from an experiment conducted to evaluate the adsorption of BzCl to glass. BzCl adsorption to glass reached a plateau at 575 ng/cm^2 as evaluated over the equilibrium concentration between 25 and 550 μg/ml. Solving the Langmuir equation for the maximum adsorption capacity of the surface yields a value of 613.5 ng/cm^2. This amount would present a monolayer with each molecule covering 10 Å^2 of the surface.

4. Discussion

The data presented in Fig. 1 clearly demonstrate the adsorption of sCT onto glass to be predominantly controlled by an electrostatic interaction between the positively charged sCT molecule and the negatively charged glass surface (Norde, 1986). The adsorption of BSA to glass was also found to decrease with increasing ionic strength indicating an electrostatic interaction mechanism is operative here as well. Under low ionic strength conditions (μ = 0.01) at a pH near 5, Kondo and Higashitani, 1992 found BSA adsorption to silica (about 325 ng/cm^2) was greater than to polystyrene (about 280 ng/cm^2). Fig. 1 also shows the mechanism of sCT adsorption to polypropylene to be one of the hydrophobic/dehydration type (Andrade and Hlady, 1986). The ability of the surfactants to reduce drug adsorption was slightly influenced by the ionic strength conditions of study.

4.1. Anionic surfactant – SDS

The anionic surfactant, SDS, proved more effective at reducing sCT and BSA adsorption to glass than would be predicted for an electrostatic adsorption mechanism. Under the conditions of study (pH 4) the sCT molecule carried a net positive charge and the glass surface carried a negative potential. Thus, SDS would be electrostatically attracted to the sCT molecule and repelled from the glass surface. It was observed that higher concentrations of SDS with sCT and BSA caused the drugs to precipitate. The reduction in drug adsorption to glass was due either to a solution interaction between the surfactant and the drugs or to hydrophobic/dehydration interactions with the surfactant and the surface. The inability of SDS to eliminate sCT or BSA adsorption to glass is considered due to its inability to

Table 2
Influence of surfactants upon adsorption of drug to surfaces (0.05 M acetate/NaCl buffer at 0.150 μ)

Surface	Protein	Adsorption in ng/cm^2 with surfactant:			
		None	SDS	DTACl	Tween 20
Glass	sCT	250 ± 90	96 ± 137 [a]	427 ± 70 [a]	≤ 0 ± 45 [a]
	BSA	835 ± 155	282 ± 111 [a]	298 ± 53.5 [a]	388 ± 73 [a]
Polypropylene	sCT	192 ± 47.5	420 ± 87 [a]	665 ± 24 [a]	≤ 0 ± 82 [a]
	BSA	352 ± 53.6	360 ± 178	214 ± 100	53 ± 21 [a]

[a] Surfactant addition caused a significant change in average level of adsorption at $p \leq 0.05$.

approach the surface and block adsorption. SDS was not effective in reducing adsorption to polypropylene for either sCT or BSA.

4.2. Cationic surfactant – DTACl and BzCl

The corresponding cationic surfactant, DTACl, was unable to reduce sCT adsorption to glass or to polypropylene. In fact, these results were contrary to our predictions which suggested the positively charged DTACl would adsorb to the glass (negative potential) and thereby block drug adsorption and reduce losses from solution. Rather, the addition of DTACl produced statistically significant increased levels of adsorption rather than the expected decreased levels. The opposite results were observed with BSA, where DTACl reduced adsorption levels to glass and had no effect with polypropylene. It appears that the DTACl works by a solution effect which enhances adsorption of the positively charged sCT molecule more than the neutral BSA.

Increasing the hydrophobic content of the cationic surfactant by moving from DTACl to BzCl resulted in effective elimination of sCT adsorption. Therefore, for adsorption onto glass where an electrostatic interaction dominates, it is the surfactant hydropobicity and not its charge content which is important in reducing/elimination glass-drug interactions. Precluding possible surfactant-drug interactions the protein/peptide can effectively compete with surfactants for glass adsorption sites, provided these competing surfactants are not especially hydrophobic. This not only explains the cationic surfactant results but it also explains the findings with nonionic surfactant.

4.3. Nonionic surfactant – Tween 20 and poloxamer

The low CMC value demonstrated by Tween 20 indicates a desire of the hydrophobic chains of these molecules to leave the aqueous phase. At concentrations below the CMC, this may be accomplished by adsorbing to the glass surface or associating with the drug molecule. The nonionic surfactant, Tween 20, showed itself to reduce/eliminate sCT and BSA adsorption onto glass and onto polypropylene.

Reducing the hydrophobic content of the surfactant greatly eliminated its ability to reduce protein/peptide drug adsorption to glass and polypropylene. By increasing the hydrophilic polyoxyethylene segment from 20 units (Tween 20) to an average of 75 units (Poloxamer) and replacing the hydrophobic monolaurate portion (Tween 20) with polyoxypropylene (Poloxamer) the nonionic surfactant loses hydrophobicity. The less hydrophobic Poloxamer 188 is thus more readily solvated and less inclined to exchange these solution interactions for surface interactions, leaving the sCT to adsorb to the glass.

4.4. Mechanisms

The hydrophobic content of the surfactant appears to be the factor of greatest importance regarding its ability to reduce protein/peptide adsorption to surfaces as demonstrated for sCT and BSA. The CMC, which is used as a relative indicator of hydrophobic content of a surfactant, is the minimal concentration where micelles will form. Micelle formation is a physical attempt to dehydrate the hydrophobic chains by removing them from aqueous content and is a direct indicator of the relative desire for these chains to leave the polar aqueous solution. The low CMCs measured for Tween 20 and BzCl indicate the desire of these surfactants to exchange solution interactions for surface interactions. The adsorption of Tween 20 from aqueous solution, pH 6.5 water, to calcium carbonate surfaces has been reported by Ivanova and Shchukin (1993).

The demonstrated ability of BzCl to adsorb to glass and polypropylene suggests that this surfactant-surface interaction is greater than the protein/peptide-surface interaction, enabling the BzCl to block sCT adsorption to the surface. The surface adsorption of BzCl probably has some orientation. The calculated surface area per molecule of 10 $Å^2$ suggests an orientation perpendicular to the surface, based upon findings with fatty acid adsorption (Adamson, 1976). Thus,

the whole molecule is not able to lay out on the surface. The positively charged benzene ring head is not thought to be attracted to the surface based upon the ineffectiveness of DTACl at decreasing drug adsorption. In contrast, the importance of hydrophobic content for surfactant success in reducing adsorption leads us to conclude that a portion of the hydrophobic tail is adsorbed to the surface. The remainder of the BzCl molecule would reside in solution near the surface where the positively charged head group works to further discourage adsorption by electrostatic repulsion.

Welin-Klintstrom et al. (1993) evaluated the adsorption of several surfactants to a gradient surface ranging from a hydrophobic silica ($SiCH_3$) to a hydrophilic silica (SiOH). The nonionic (pentaethylene glycol mono-*n*-dodecyl ether) and cationic (cetyltrimethylammonium bromide) surfactants adsorbed to a greater extent than the anionic (SDS) which only adsorbed to the hydrophobic region. All the surfactants were significantly effective in removal of preadsorbed fibrinogen from the hydrophobic region while none were found to be effective in the hydrophilic region of the surface.

With the addition of surfactants to protein/peptide solutions, where the surfactant-surface interaction is greater than the surface-protein/peptide interaction, drug adsorption is reduced/eliminated. The adsorption of protein/peptide drugs was shown to contain both electrostatic and hydrophobic mechanisms. The predominant adsorption mechanism changes with the surface (glass or polypropylene) and the conditions of study (drug and ionic strength). For sCT adsorption onto glass, where an electrostatic interaction predominates, greater surfactant hydrophobicity is required to eliminate the glass-sCT interactions. BSA adsorption to glass appears composed of a larger hydrophobic content which allows additional surface-active agents able to effectively compete against the BSA-surface interactions. The strong hydrophobic interaction of the uncharged BSA molecule with the uncharged polypropylene surface require a very hydrophobic surfactant (Tween 20) to reduce adsorption.

5. Conclusions

This investigation shows that some surfactants are able to reduce/eliminate protein/peptide drug adsorption to glass and polypropylene. The hydrophobic content of the surfactant appears to be the factor of greatest importance regarding its ability to reduce protein/peptide adsorption to surfaces as demonstrated with sCT and BSA. The nonionic surfactant, Tween 20, proved to be the most effective in eliminating adsorption of both sCT and BSA to either surface. The effectiveness of a nonionic surfactant (Tween 20) could be reduced/eliminated by increasing the hydrophilic content (Poloxamer 188). Conversely, it was shown that the effectiveness of a cationic surfactant (DTACl) in reducing adsorption could be increased by increasing the hydrophobic chain length (BzCl).

The proposed mechanism of surfactant action in reducing/eliminating protein/peptide drug adsorption to pharmaceutical surfaces is the ability to out compete the drug for surface adsorption sites. While some surfactant-solution interactions may work to favor drug-solution interactions, evidence shows the surfactants to adsorb to hydrophobic (polypropylene) and hydrophilic (glass) surfaces.

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References

Adamson, A.W., *Physical Chemistry of Surfaces*, Wiley, New York, 1976, p. 400.

Andrade, J.D. and Hlady, V., Protein adsorption and materials biocompatability: A tutorial review and suggested hypothesis. *Adv. Polym. Sci.*, 79 (1986) 1–63.

Azria, M., *The Calcitonins: Physiology and Pharmacology*, Karger, Basel, 1989, pp. 1–19.

Duncan, M., Gilbert, M., Lee, J. and Warchol, M., Development and comparison of experimental assays to study protein/peptide adsorption to surfaces. *J. Colloid Interface Sci.*, 165 (1994) 341–345.

Duncan, M., Lee J. and Warchol, M., Influence of surfactants on protein/peptide adsorption to pharmaceutical surfaces. *Pharm. Res.*, 10 (Suppl.) (1993) S-137, PT 6041.

Handbook of Pharmaceutical Excipients, Sodium lauryl sulfate, American Pharmaceutical Association, Washington, DC/The Pharmaceutical Society of Great Britain, London, 1986, pp. 271–272.

Hiemenz, P.C., *Principles of Colloid and Surface Chemistry*, 2nd Edn, Dekker, New York, 1986, p. 432.

Ivanova, N.I. and Shchukin, E.D., Mixed adsorption of ionic and non-ionic surfactants on calcium carbonate. *Colloids Surfaces A: Physicochem. Eng. Aspects*, 76 (1993) 109–113.

Kondo, A. and Higashitani, K., Adsorption of model proteins with wide variation in molecular properties on colloidal particles. *J. Colloid Interface Sci.*, 150 (1992) 344–351.

Lee, I.H., S. Pollack, Hsu, S.H. and Miksic, J.R., Influence of the mobile phase on salmon calcitonin analysis by reversed-phase liquid chromatography. *J. Chromatogr. Sci.*, 29 (1991) 136–140.

Martin, D.W., Jr, Mayes, P.A. and Rodwell, V.W., *Harper's Review of Biochemistry*, LANGE Medical, Los Altos, CA, 1983, pp. 31, 561.

Norde, W., Adsorption of proteins from solution at the solid-liquid interface. *Adv. Colloid Interface Sci.*, 25 (1986) 267–340.

Rosen, M.J., Micelle formation by surfactants. *Surfactants and Interfacial Phenomena*, Wiley, New York, 1989, pp. 125–129.

Ruzgas, T.A., Razumas, V.J. and Kulys, J.J., Sequential adsorption of γ-interferon and bovine serum albumin on hydrophobic silicon surfaces. *J. Colloid Interface Sci.*, 151 (1992) 136–143.

Welin-Klintstrom, S., Askendal, A. and Elwing, H., Surfactant and protein interactions on wettability gradient surfaces. *J. Colloid Interface Sci.*, 158 (1993) 188–194.