Quantitative Structure–Activity Relationship Analysis of the Effect of Metoclopramide and Related Compounds on the Surface Ionization of Fumed Silica

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ABSTRACT: Potentiometric titration curves were generated for fumed silica with various concentrations of dissolved metoclopramide. The effects of various benzamide analogs of metoclopramide, which are positively charged in the titration medium and differ solely by their aromatic substituents, as well as lidocaine, which is also structurally analogous but is mainly in the unionized form, were also studied. At sufficiently high pH, pH 7.0 and above, the silica surface charge was independent of the metoclopramide concentration. A reasonable linear relationship with a positive slope was found between the logarithmic octanol–water partition coefficient (log *P*) values of the compounds and the negative surface charge determined at pH 7.0 and 7.2. These results can be attributed to specific adsorbate–surface interactions rather than concentration effects. The carbonyl oxygens of the benzamide structures most likely form hydrogen bonds with the neutral silanols. The use of positively charged triethylamine and ephedrine resulted in surface charge values that were the least negative in the aforementioned quantitative structure–activity relationship analyses. These results are consistent with ionic interactions between the positively charged aliphatic amine groups and the negatively charged surface silanols occurring simultaneously with the nonionic interactions. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2566–2573, 2015
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INTRODUCTION

Amorphous silica has a variety of applications as a pharmaceutical excipient and has been used extensively in analytical chemistry for chromatographic separations. Silica nanoparticles are commonly used as a glidant or anticaking agent and as a thickening agent in solid and semisolid formulations, respectively. Mesoporous silica can function as a carrier of liquid components, which is then incorporated into the tablet formulation, in order to enhance the dissolution of poorly soluble drugs.[1–4] There is extensive literature regarding the nature and specificity of the physical interactions of a variety of organic materials with amorphous silica. These include small organic molecules adsorbing from organic medium and from the vapor phase as well as macromolecules adsorbing from aqueous medium.[5] The site of interaction is most commonly between the polar functional groups of the adsorbate and the silanol groups on the silica surface. The latter groups form as a result of the hydration of the solid surface and are weakly acidic at normal pH.[6] Details regarding the nature and ionizability of silanols can be found elsewhere in the literature.[7] Aside from enhancing the adsorbability of cations,[7] surface ionization also affects the solubility of solid silica that exists in equilibrium with various silicic acid species that are able to recondense on the surface.[8] This, in turn, may affect the stability of colloidal suspensions as well as the cross-linking or gelation of silica nanoparticles.[8] As a result, the retention within or the release of a drug from a pharmaceutical product containing silica may be altered.

The surface-charge effects of inorganic cations vary depending on the concentration, pH, valency, and whether specific binding or nonspecific binding of solvated ions occurs.[6,8] In complex systems comprising macromolecules, surfactants, and mono- or poly-electrolytes, the zeta potential has been used to elucidate adsorption mechanisms.[9,10] This measurement gives the potential at the interface between the bulk solution and the diffuse layer of counterions surrounding a charged colloidal particle. The usefulness of the zeta potential can be limited because of its dependence on the electrolyte concentration in the dispersion medium among other factors.[11] Potentiometric titration typically gives a constant value for the surface potential and has been used to study the influence of inorganic cations, as described above, and that of cationic surfactants. The latter species have been shown to increase the silica surface charge upon adsorption[12,13] with the surfactant capable of interacting with all ionized groups.[13]

In a previous work,[14] potentiometric titration data was used in conjunction with adsorption isotherms to study the influence of adsorbed metoclopramide, an antiemetic drug, on the ionization of the silica surface. Total drug adsorption was found to be greater than the corresponding number of ionized surface groups. However, the amount adsorbed due to the ionization of the silica surface was directly related to the negative surface charge generated, which proved that ionic interactions were occurring. The surface charge was also independent of the ionic strength of the medium which suggested that specific interactions were occurring. Metoclopramide was also found to adsorb to the unionized silica surface.[14] On the basis of analyses of the adsorption isotherm data[14] and the adsorption

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behavior of metoclopramide to montmorrillonite clay,[15] it was hypothesized[14] that hydrogen bonding between the carbonyl group of metoclopramide and the unionized silanols group occurs in addition to the ionic interactions.

Although the positively charged amine group of metoclopramide was shown to enhance and interact with the negatively charged solid silica surface, the role of the nonionic interactions in the charge formation is yet unknown. In this work, the effect of metoclopramide and closely related compounds on the surface ionization of silica was determined by quantitative structure–activity relationship (QSAR) analysis. The aim of these studies was to determine the effect of various functional groups on the silica surface charge and to assess the applicability of the previously published results[14] to other drug molecules. Probe compounds with various substituents on the phenyl ring as well as those with different p*K*a values were selected and the results were compared with data obtained with compounds lacking the functional groups in question.

EXPERIMENTAL

Materials

VP Aeroperl® 300 Pharma from Evonik-Degussa (Piscataway, New Jersey) was used as the granulated fumed silica. The material was dried in a custom-made tube furnace at 200°C for 6 h under a constant flow of nitrogen gas prior to use. The HCl salts of procainamide, lidocaine, and metoclopramide monohydrate were obtained from Spectrum (Gardena, California). Bromopride base, tiapride HCl, and ephedrine HCl were purchased from Sigma (St. Louis, Missouri) and triethylamine HCl was obtained from Fluka (St. Louis, Missouri). These chemicals were USP grade, except for triethylamine (HPLC grade) and bromopride (analytical grade), and were used as received. The titrant base consisted of various dilutions of 1 N NaOH (standard solution; VWR, Radnor, Pennsylvania). Partition coefficient determinations were made using a freshly opened bottle of 1-octanol (purity 99+%; Sigma–Aldrich, St. Louis, Missouri). This solvent was equilibrated for 24 h at 37°C with an equal volume of distilled water prior to use. Other chemicals used in the syntheses of various compounds were reagent grade and were used without further purification.

Amount of Metoclopramide Remaining in the Silica Suspensions

The adsorption of metoclopramide in the potentiometric titration studies of silica was examined with a separate adsorption study using buffered solutions of sodium phosphate at pH 7.0 (57 mM) and 7.2 (53 mM) at an ionic strength of 0.13 M. Appropriate weights of silica (15–100 ± 0.25 mg) were added to 10 or 15 mL of metoclopramide solutions having concentrations ranging from 1.50 to 12.0 mg/mL. The suspensions were rotated at 30 rpm using a Vanderkamp sustained-release apparatus (model 103906; VanKel, Edison, New Jersey) in a waterbath at 37 ± 1°C. After 1 h, rotation of the samples was stopped with vials in an upright position and the solid silica was allowed to settle for 2 h at the same temperature. The concentration of metoclopramide remaining in the supernatant and the initial drug concentration were assayed by UV analysis at 273 nm with a photodiode-array spectrophotometer (Model 8453; Agilent, Santa Clara, California).

Synthesis of Compounds

HCl salts of 5-chloro-N-[5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide[16] (CMB), 3-diethylamino-4′-nitropropionanilide[17] (DNPA), and 4-nitro-N-[2-(diethylamino) ethyl]-benzamide[18] (NDEB) were synthesized and purified as described in the published literature. The chemical structures were confirmed by ^{1}H-NMR analysis.

Potentiometric Titration

Suspensions of silica were titrated (37°C) in 0.13 M sodium chloride containing various dissolved compounds using the technique described in a previous paper.[14] Titration studies were conducted with various concentrations of metoclopramide ranging from 1.50 to 12.0 mg/mL (1.41 to 33.9 mM). Further titration curves were constructed with approximately 5 mM of other dissolved compounds including the HCl salts of CMB, DNPA, NDEB, tiapride, procainamide, lidocaine, and bromopride base that was acidified using 1 N HCl. Increased concentrations of triethylamine HCl and ephedrine HCl, 7 and 30 mM, respectively, were used because of changing solubilities. The structures of all of the compounds used in the titration studies are given in Figure 1. The silica surface-charge values were reported as surface site densities, with units of ionized groups per nm^2 of surface, at particular pH values, as described in a previous paper.[14] The surface-charge data were plotted versus the initial metoclopramide concentration and the logarithmic octanol–water partition coefficient (log *P*) values of the probe compounds. Simple linear regression analyses by the least-squares method were performed using Kaleidagraph® software (Synergy, Reading, Pennsylvania).

p*K*a and Partition Coefficient Determinations

Aqueous solutions of the aforementioned amine hydrochloride compounds (0.5 mM) were prepared without the addition of neutral salts. These solutions were degassed with helium gas for 30 min immediately prior to the experiment. The p*K*a and log *P* values were determined at 37°C using a microelectrometric titration method that allowed for the simultaneous determination of both values.[19,20] Gran plots were constructed from the titration data to determine the p*K*a value.[21]

RESULTS AND DISCUSSION

The Effect of Metoclopramide Concentration in Solution on the Silica Surface Charge

In a previous paper, the silica surface charge was found to become more negative when metoclopramide is adsorbed; an effect that was independent of ionic strength.[14] In order to determine the variation of the silica surface charge with the surface concentration of the adsorbed drug, potentiometric titration studies with various concentrations of metoclopramide in the titration medium were conducted. In the titration technique employed, titrant uptake by the blank silica filtrate is subtracted from that of the suspension. The assumption is that the metoclopramide concentration in the blank stays constant at all pH values. However, adsorption studies have shown that the amount adsorbed increases with pH.[14] In order to minimize the potential variation of the drug concentration in the blank, appropriate weights of the solid silica were selected. A separate adsorption study showed that at least 92% of the initial