



The influence of the adsorption of metoclopramide on the surface ionization of fumed silica



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ABSTRACT

The effect of adsorbed metoclopramide on the surface ionization of fumed silica was studied using potentiometric titration. Adsorption isotherms of metoclopramide to unionized and negatively-charged silica surfaces were generated and compared to the titration data. The adsorption of metoclopramide caused the silica surface charge to become more negative with increasing pH that was independent of ionic strength which suggested that specific adsorbate-surface interactions were occurring. Adsorption studies showed that metoclopramide adsorbs to the unionized silica surface. Ionization caused drug adsorption to increase which was consistent with at least two distinct surface adsorption sites. The ratio of the additional amount of metoclopramide adsorbed to the surface ionized group density determined from the titration curves was approximately unity which showed conclusively that the negatively-charged silanols constitute one of the surface adsorption sites. Potentiometric titration has been shown to be a useful technique for determining the number and types of adsorption sites on the silica surface.

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1. Introduction

Silica is a versatile pharmaceutical excipient which has applications in various dosage forms. In solid dosage forms, it is mainly used as a glidant and anti-caking agent. It reduces interparticulate adhesion of tableting powders thereby improving their flow during manufacture (Cab-O-Sil®, 2000; Aerosil® 200 Pharma., 2001). In semi-solid and liquid formulations, its ability to form gels allows it to be used as a thickening agent (Cab-O-Sil®, 2000; Aerosil® 200 Pharma, 2001; Syloid®, 2002). Silicas are often used as a moisture adsorbent to protect the final product. Mesoporous silica can also be used as a carrier in the preparation of liquisolid compacts of poorly soluble drugs for improving their bioavailability (Aeroperl® 300 Pharma, 2014; Charnay et al., 2004; Heikkilä et al., 2007; Vranikova and Gajdziok, 2013). In this technique, the drug is dissolved in a liquid vehicle and then incorporated into a porous solid carrier material to obtain a dry, free-flowing powder (Balaji et al., 2014; Spireas, 2002; Syed and Pavani, 2012).

The silica surface consists of silanol groups which are weakly acidic and deprotonate at normal pH to form negatively charged surface species giving rise to an electrical double layer. Detailed

discussion of the nature of the silanol surface groups can be found elsewhere in the literature (Foissey and Persello, 1998). The silica-water surface chemistry affects the behavior of colloidal suspensions, the dissolution of silica, as well as the formation of silica gels and may therefore, influence the performance of pharmaceutical products *in vivo* (Iler, 1979a). The variation of the silica surface charge in the presence of inorganic cations as a function of pH and ionic strength has been extensively studied (Foissey and Persello, 1998). For inorganic cations, most researchers have found that the monovalent cations exhibit mostly non-specific binding and follow the Hofmeister series while divalent cations mostly form specific surfaces complexes. The behavior of heavy metal ions is more complex and depends on the adsorption medium (Foissey and Persello, 1998). To measure the surface charge, potentiometric titration can be employed to determine the potential at the Stern layer, the innermost layer of a charge particle. Absolute and reproducible values can be obtained if all titrateable species are accounted for (Foissey and Persello, 1998). Electrophoretic mobility measurements can be used to calculate the zeta potential, which is the potential at the surface of hydrodynamic shear of a colloidal particle (Hiemenz, 1977). The zeta potential is a relative value and depends on the concentration of electrolytes in the medium. A review of the techniques of these surface potential measurements and the results for silica is given in the literature (Foissey and Persello, 1998).

The adsorption of large organic molecules, including polymers and surfactants, to the surface of silica particles in aqueous

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medium has been reviewed in the literature (Somasundaran and Zhang, 2000; Killman, 2000). Adsorption occurs through various mechanisms depending on the nature and the size of the adsorbents, impurities and the presence of any competing or bridging species. The zeta potential of these complex systems has been measured in order to assess adsorption mechanisms (Somasundaran and Zhang, 2000). The adsorption of cationic surfactants depends on the pH, electrolyte concentration, surface charge density and structure of the surfactant (Atkin et al., 2003). These factors also influence the nature of surfactant aggregates formed on the silica surface (Atkin et al., 2003). Small organic molecules may interact through hydrogen bonding, ionic interactions and via the delocalized π -electron cloud on the phenyl ring of the adsorbate (El Shafei, 2000). Even though the adsorption mechanisms of a variety of organic adsorbates have been extensively studied, their effect on the charge formation of silica surface groups is not well characterized. For cationic surfactants, researchers have found that the amount adsorbed generally increases with pH upon which the ionization of surface groups also increases (Wängnerud and Olofsson, 1992; Goloub et al., 1996). The effect of small organic cations has been examined in a study published by Tadros and Lyklema (1968) who found that the silica surface-charge density was less negative but independent of concentration with tetraethylammonium chloride. This result was unlike that of small inorganic cations with concentration-dependent surface ionization effects. The compound was most likely in the Stern layer on the silica surface but unable to penetrate the surface gel layer which exists due to the short polysilicic acid chains on the surface of precipitated silica used in the study. The authors hypothesized that specific interaction of the amine functional group with the negatively-charged surface groups may also be occurring.

In this work, the variation of the silica surface charge in the presence of a simple drug molecule, metoclopramide, was systematically studied in order to elucidate the effect of metoclopramide–silica interactions on the surface ionization. Metoclopramide, an anti-emetic drug, possesses a tertiary amine which is positively charged at normal pH (Hanocq et al., 1973). The drug also possesses polar moieties including a carbonyl group and a primary amine attached to the phenyl ring. The drug was found to physically adsorb to the surface of Veegum®, a montmorillonite clay, which possesses permanently negatively-charged and neutral silanol groups. Metoclopramide was found to interact with both surface groups (Bandopadhyay, 2006). Similar adsorption mechanisms may reasonably be expected with silica. Fumed silica was used as the adsorbent due to the absence of surface polysilicic acid chains. A granulated grade of fumed silica for pharmaceutical use was chosen which was mesoporous with a sufficiently large surface area, of high purity, and did not form gels due to its large particle size (Meyer et al., 2008; Aeroperl® 300 Pharma, 2014). This allowed ready separation of the solid from the supernatant. As a result, potentiometric titration studies on both the suspension and the blank as well as adsorption studies by mass balance could easily be performed. The absolute values obtained from these experiments were then used to make mechanistic inferences regarding the metoclopramide–silica interactions.

2. Materials and methods

2.1. Materials

The granulated fumed silica Aeroperl® 300 Pharma was obtained from Evonik-Degussa (Piscataway, NJ). Procainamide HCl, lidocaine HCl, and metoclopramide HCl monohydrate were purchased from Spectrum (Gardena, CA). Ephedrine HCl and triethylamine HCl were obtained from Sigma–Aldrich (St. Louis,

MO) and Fluka (St. Louis, MO), respectively. These materials were USP grade, except for triethylamine (HPLC grade), and were used as received. A 1 N NaOH standard solution (± 0.005 N) from Fisher (Fair Lawn, NJ) was used to prepare various concentrations of the titrant base. All other chemicals were of analytical grade.

2.2. Solubility determination of silica

The solubility of silica at 37 °C was determined by measuring the concentration of dissolved silicon. The dissolution medium consisted of buffered solutions of sodium phosphate at pH 6.0, 7.2, and 8.0 ($I = 0.13$ M and 0.28 M) whose molar concentrations ranged from 44 mM to 96 mM and 89 mM to 200 mM, respectively. Formic acid was substituted for phosphate to prepare pH 5.0 buffer due to large deviations (>0.03) in the sample pH. A constant weight of silica was dried in a custom-made tube furnace at 200 °C for 6 h under a constant flow of nitrogen gas prior to use. Silica weights of 25 ± 0.5 mg or higher were used to which 20 mL of the buffer solution was added. These concentrations were the same as those used in the potentiometric titration studies. The suspensions were then rotated at 30 rpm using a Vanderkamp sustained-release apparatus (Model 103906, VanKel Edison, NJ) in a water bath at 37 ± 1 °C over 24 or 48 h. Samples were taken at specific time points. Separate suspensions were prepared for each time point with three different solids concentrations at each pH. At the specific sampling times, rotation was stopped and the solid silica was allowed to settle for 30 min at the same temperature. The supernatant of the samples was filtered through a 0.22 μ m polyvinylidene fluoride (PVDF) syringe filter. The concentration of dissolved silicon was determined using an inductively-coupled plasma-optical emission spectrometer (ICP-OES) (Model 720-ES, Varian, Palo Alto, CA) at 251.611 nm with an internal standard of 1 ppm Yttrium. The concentration of dissolved silicon was plotted against time at each initial silica concentration. The solubilities were calculated by multiplying the data by the ratio of the molecular weight of silicon dioxide to that of silicon.

2.3. Determination of the specific surface areas

The specific surface areas of silica as received and after equilibration in aqueous medium were determined by Brunauer–Emmett–Teller (BET) analysis of nitrogen-vapor adsorption isotherms using a Quantasorb sorption instrument (Model QS-16, Quantachrome, Boynton Beach, FL). Aliquots (100 mL) of 0.13 M sodium chloride degassed with helium were added to approximately 140 mg and 300 mg of dried silica to each of two bottles. The filled bottles were then rotated at 30 rpm in a sustained-release apparatus at 37 ± 1 °C for 48 h. The solid silica in each suspension was collected by vacuum filtration using a Buchner funnel with a 0.45 μ m hydrophilic PVDF (HVLP) filter paper and washed with 1 L of distilled water. The wet silicas were then dried in a custom-made tube furnace, as described previously, and their surface areas were determined.

2.4. Mass titration

Solutions of procainamide HCl, ephedrine HCl, triethylamine HCl, lidocaine HCl and metoclopramide HCl (Fig. 1) were prepared by dissolving approximately 75 mg of each compound in 50 mL of 0.13 M sodium chloride solution. These solutions and a 50 mL aliquot of neat 0.13 M sodium chloride were degassed with helium gas for 1 h prior to use. Eight silica samples ranging from 15 to 250 (± 0.5) mg were weighed in polyethylene vials and mixed with 5 mL aliquots of the previously prepared solutions. The vials were rotated at 30 rpm using a sustained-release apparatus in a water bath at 37 ± 1 °C. After 36 h, each vial was placed in an enclosed

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