Measurement of Surface pH of Pharmaceutical Solids: A Critical Evaluation of Indicator Dye-Sorption Method and its Comparison With Slurry pH Method

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ABSTRACT: Two methods for the measurement of surface pH of pharmaceutical solids, namely, the dye-sorption method and the slurry pH method, were compared. High purity drug substances, instead of excipients, were used as model solids, because acidic or basic impurities present in excipients could influence slurry pH. Solid test samples were prepared by sorption of methanol–water solutions of several indicator dyes, and their diffuse reflectance UV-visible spectra were measured. The solid surface pH values were estimated by comparing base-to-acid peak ratios of the diffuse reflectance UV-visible spectra of solid samples to the calibration plots of dye solutions in aqueous standard buffers of known pH. In the slurry pH method, pH values of concentrated slurries of the compounds in water were considered to represent solid surface pH. The agreement between the two methods was mixed and depended on the compound or the indicator used. It was concluded that in many cases calibration plots of indicator dye spectra in aqueous buffers were not applicable to the solid state, and, as a result, the reliability of the method was low. The slurry method provided a simple and reliable measurement of surface pH indicating that concentrated slurry may closely represent solid surface pH. J Pharm Sci 97:1831–1842, 2008

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INTRODUCTION

The concept of micro-environmental or surface pH of pharmaceutical solids is important in pharmaceutical development.[1,2] Drug stability[3–5] and dissolution[6,7] of pharmaceutical preparations have been modulated by influencing the solid surface pH. Dissolution of salts of weak acids or bases has been successfully explained by the micro-environmental pH in the diffusion layer.[8–11] Modified or controlled release pharmaceutical dosage forms have also been developed by changing micro-environmental pH.[12–14] Despite increased recognition of the importance of micro-environmental pH in the development of pharmaceutical dosage forms, there is no generally accepted agreement on what the micro-environmental

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pH for pharmaceutical solids is and how to measure it.

Atoms or molecules at the surface of a solid are at a higher state of energy due to the lower coordination number than those in the bulk. Interfacial sorption of liquids or gases is a means to lower surface free energy. When molecular interactions across interfaces involve acid–base (A–B) reactions (i.e., proton or electron donating or sharing leading to complex or adduct formation), solid surface acidity or basicity arises. Examples of solid acids include natural clay minerals (e.g., kaolinite, bentonite), cation exchange resins, mixtures of oxides (SiO_2, Al_2O_3), and inorganic chemicals (ZnO, TiO_2). Examples of solid bases include anion exchange resins, mixtures of oxides (SiO_2, Al_2O_3), and inorganic chemicals (MgO, ZnO). Experimental techniques to measure acidity or basicity of solids have been well described in the chemistry literature.[15–17]

Although A–B reactions are common in clay minerals, ion exchange resins or inorganic oxides, such reactions of solid acidity (or basicity) are limited among pharmaceutical solids. Takahashi and Yamamoto[1] investigated Lewis acidity of lactose, sucrose and wheat starch and found it to be nearly zero. On the other hand, they found measurable Lewis acidity for inorganic excipients, namely, natural aluminum silicate, dibasic calcium phosphate, and talc. The basicity of magnesium stearate is due to its MgO content.[18]

Surfaces of organic pharmaceutical solids lack the highly reactive groups of inorganic clays that impart surface acidity, and strong Lewis acidity is not common. However, surface acidity or basicity is still important for pharmaceutical systems, but the concept is described in a rather empirical manner as the microenvironment of a solid, a term used to represent the microscopic layer present around a solid particle in which the solid forms a saturated solution in the sorbed water. The pH of the solution or suspension in the sorbed layer of water is referred to as the microenvironmental pH or solid surface pH (a term that will be used in the rest of this work). Serajuddin and Jarowski[11] defined the solid surface pH as the pH in the aqueous diffusion layer on the surface of a drug substance as the thickness of the layer, h, approaches zero ($pH_{h=0}$). They established that the surface pH of a pharmaceutical solid corresponds to the pH of its saturated solution (or slurry) in water. Although the concept of solid surface pH is yet rather empirical, its implications are just as important as the better described A–B reactions.

Sun and Berg[16] reviewed different techniques for solid surface acid–base characterization. Methods to characterize inorganic solid acids or bases include colloidal titration, indicator dye sorption, Infra-red (IR), X-ray photoelectric spectroscopy (XPS), calorimetry, and inverse gas chromatography.[15,16] Methods such as direct potentiometry (measurement of the pH of a slurry), indicator dye sorption, confocal microscopy,[19] solid-state NMR, and electron spin resonance[12,20] have been described for the determination of solid surface pH of pharmaceutical solids.

In the slurry pH method a concentrated suspension of the solid in water is prepared and the pH is measured by potentiometry. The pH of the concentrated slurry is considered to reflect the pH of the solid surface.[11,21] The indicator dye-sorption method of determining solid surface pH was originally reported by Walling.[22] A few reports[23–25] described the determination of solid surface pH of pharmaceutical materials by diffuse reflectance spectrum of adsorbed dyes on the solid. The surface pH of the solid was calculated by comparing the UV-visible diffuse reflectance spectrum (DRS) of the adsorbed dye to its DRS in solution as a function of pH. Zinchuk et al.[26] reported measurement of Hammett acidity function of pharmaceutical solids using a similar measurement principle.

The indicator dye-sorption method attracted considerable attention in the pharmaceutical field because of its simplicity and visual nature. The spectral measurement can be made on a dry or nearly dry solid, whereas most other methods such as slurry pH, electron spin resonance, or confocal fluorescent microscopy techniques require considerable level of water to measure the mobility of the probe. In the indicator dye-sorption method, the color of an adsorbed dye is compared to that of its color in a solution of known pH.[23–25] The implicit assumption of the technique is that the ionization constant (pK_a) of the indicator dye remains unaltered in the adsorbed state. It also becomes necessary to assume in this method that the spectral properties of the ionized and unionized forms of the indicator dye remain unchanged (or change by the same factor) in the adsorbed state relative to the solution state. The questions that naturally arise are: Can the color change of a dye in solution be extrapolated to that on the solid surface? How does the pH determined by this

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