

Drug Development[®] & Delivery

July/August 2011 Vol 11 No 6

www.drug-dev.com

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ZETA POTENTIAL

The Zeta Potential & its Use in Pharmaceutical Applications - Part 1: Charged Interfaces in Polar & Non-Polar Media & the Concept of the Zeta Potential

By: David Fairhurst, PhD, Robert W. Lee, PhD

INTRODUCTION

What is the zeta potential (ZP) and why measure it? In order to address these questions, we must first briefly discuss the two fundamental parameters that control the nature and behavior of every system in which one phase is dispersed in another phase; the phases are distinguished by the terms disperse phase (for the phase forming the particles) and the dispersion medium (for the fluid in which the particles are distributed). The two fundamental parameters are the extent of the interface of the disperse phase and the interfacial chemistry of the disperse phase, respectively.

The physical nature of a dispersion depends on the respective roles of the constituent phases; there are numerous examples of dispersed systems, including foams (gas-in-liquid), emulsions (liquid-in-liquid), and aerosols (solid- or liquid-in-gas), that have found application in pharmaceuticals. In this review, we shall focus on the most widely formulated type of dispersion - suspensions (solid-in-liquid). The physico-mechanical and physico-chemical characteristics that constitute the two respective fundamental parameters are summarized in Table 1. The reader may well be acquainted with the measurement of one, or more members, of the former group. However, the interfacial chemistry is often a neglected parameter (particularly in pharmaceutical applications) even though

in formulation of suspensions, it is as important as (and sometimes more so than) the interfacial extent.

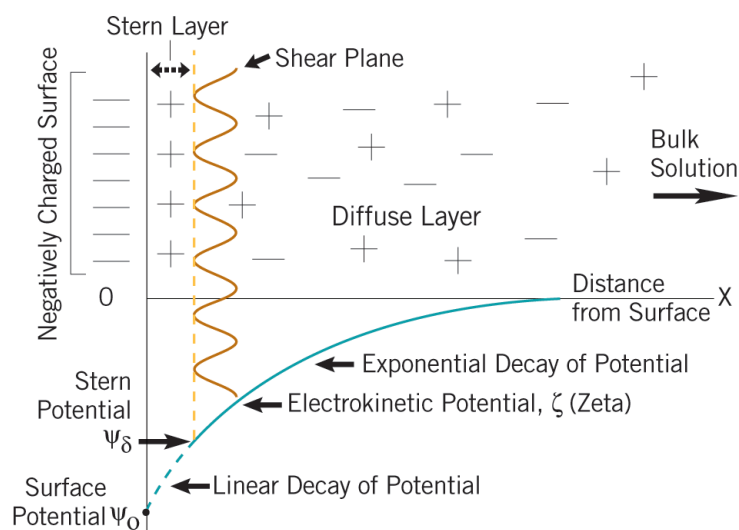
The ZP is a parameter (symbol ζ), which is related to the surface charge, a property that all materials possess, or acquire, when suspended in a fluid. The sign and magnitude of ZP affects process control, quality control, and product specification; at the simplest level, it can help maintain a more consistent product and at a complex level, it can improve product quality and performance. At the

very least, its measurement answers the question: Is the electrical charge on the material particle positive or negative? This information is often sufficient to suggest further steps in formulation or processing. The next higher level of inquiry has to do with quality control: Has the product sufficient electrostatic repulsion to maintain its stability?

The ZP is particularly useful to predict the resistance of an electrocratic (ie, governed by electrostatics) dispersion to coagulation by electrolytes by determining

FIGURE 1

Simplified Model of the Electric Double-layer at a Charged Interface in Aqueous Solution



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the critical ZP (ie, the value of ZP below which the suspension is coagulated). It is often used in determining the critical coagulation concentration (CCC) of an electrolyte (the minimum concentration required for the onset of coagulation); the CCC is proportional to ζ^4/z^2 (where z is the electrolyte counterion valence). However, the ZP has limited value in systems that are completely sterically stabilized, but it is useful in monitoring the adsorption of a nonionic surfactant, or macromolecule, onto a charged particle surface.

THE ORIGIN OF CHARGE IN POLAR MEDIA

All materials will spontaneously acquire a surface electrical charge when brought into contact with a polar medium (ie, water).¹ Generally, an interface in deionized water is negatively charged, but there are materials that can be positively charged. A few examples are shown in Table 2. The various charging mechanisms are:

1. Affinity differences of two phases for electrons
2. Ionization of surface groups
3. Differential ion adsorption from an electrolyte solution
4. Differential ion dissolution from a crystal lattice
5. Surface anisotropy
6. Isomorphous substitution

Mechanism (1) is responsible for the development of the contact potential between dissimilar metals and is important in, for example, corrosion and thermoelectric effects.² For all liquid-liquid interfaces and most solid-liquid interfaces that comprise normal particulate suspensions, this mechanism is of little significance. An exception, though, are metal sols in which it is a dominant process in initially determining the surface charge at the metal-solution interface. Nanoparticulate metal sols are currently being studied in wide variety of applications because they offer greatly

enhanced performance capabilities. In biomedical applications, nanosilver particles have been found to be highly efficient germ killers and are now used in FDA-approved wound dressings; sols of gold nanoshells when irradiated with NIR wavelengths (that pass harmlessly through soft tissue) absorb the radiation and generate sufficient heat to burst the walls of cancerous cells. Because all metallic nanosystems are initially created as sols (ie, colloidal dispersions), their inherent surface charge is critical to any further processing or use.

Mechanism (2) is commonly observed with all metal oxide surfaces (M-OH) as well as materials that contain carboxylic acid - and amine-containing functional groups. In this latter category are proteins, ionic polymers, and polyelectrolytes, many of which are widely utilized in pharmaceutical formulations. They acquire their charge mainly through ionization and/or dissociation. The ionization of these groups (degree of charge development) and the net molecular charge (and thus sign, either positive or negative) depends strongly on the pH of the solution in which they are dispersed.

In mechanism (3), a net surface charge arises through the process of unequal adsorption of oppositely charged ions and may result in either a net positive or net negative surface. Many lyophobic material suspensions (ie, polymer latexes and APIs) fall into this category.

Surfaces that are already charged (ie, by ionization) show a preferential tendency to adsorb counterions (ions of opposite charge to that of the surface - see later section on the Electric Double-Layer), especially those of high valence. It is possible, however, for such adsorption to cause a reversal of charge. If surfactant ions are present, their adsorption will tend to determine the net surface charge. Hydrated surfaces, such as protein and polysaccharide, adsorb ions less

TABLE 1

Fundamental Parameters that Control the Nature and Behavior of all Particulate Suspensions

| Interfacial Extent | Interfacial Chemistry |
|----------------------------------|---------------------------------|
| Particle Size and Distribution | Surface Charge |
| Particle Shape/Morphology | Nature/Type of Group(s) |
| Surface Area (External/Internal) | Number and Distribution |
| Porosity | Dissociation |
| | Preferential Adsorption |
| | Hydrophobic/Hydrophilic Balance |
| | Surface (Interfacial) Tension |
| | Contact Angle |

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readily than hydrophobic (ie, lipid) surfaces.

Ionic solids, such as calcite (CaCO_3), hydroxyapatite [$\text{Ca}_5(\text{PO}_4)_3(\text{OH})$] and barite (BaSO_4) can acquire a surface charge via mechanism (4) by virtue of unequal dissolution of the oppositely charged ions of which they are composed. Addition of small concentrations (ca 10^{-3}M) of Ca^{2+} ions (by using for example, CaCl_2) can be used to adjust the net charge of a suspension of CaCO_3 ; the hardness of water becomes a factor that must be considered.

The Ca^{2+} ion is referred to as a potential-determining ion for the system to distinguish it from ions, such as Cl^- , NO_3^- , and K^+ , that are termed indifferent ions because they are not expected to have any special interaction with the surface. In a similar manner, H^+ and OH^- ions are potential-determining for metal oxide and hydroxide suspensions.

Between these two extremes is what are termed specifically adsorbed ions because they appear to interact in some particular (chemical) way with the surface; surfactants

TABLE 2

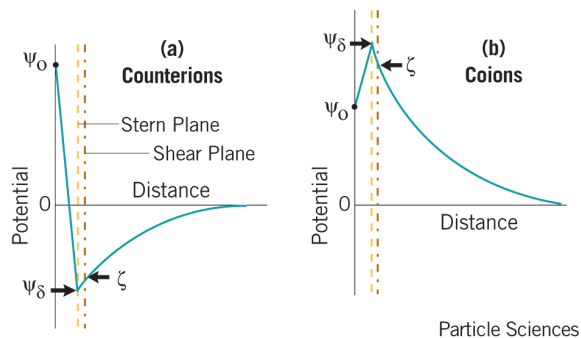
Charge On Materials in Neutral Water

| Positive | Negative |
|--------------------------------------|------------------------------------|
| Ferric Hydroxide | Au, Ag, Pt |
| Aluminum Hydroxide | S, Se |
| Chromium Hydroxide | As_2S_3 , PbS, CuS |
| Thorium Oxide | Stannic Acid |
| Zirconium Oxide | Silicic Acid |
| Basic Dyes (Methylene Blue) | Vanadium Oxide |
| Base Proteins (Protamines, Histones) | Acidic Dyes (Congo Red) |
| | Starch |
| | Viruses, Microbes |
| | Acid Protein (Casein) |

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FIGURE 2A&B

Effect of Specific Adsorption on Zeta Potential



and polyelectrolytes fall into this category.

Mechanism (5) arises from the simple fact that most crystal lattices are anisotropic. Charge development occurs because of n and p defects in the crystal. This results in surface defects and, in the case of mineral oxides, a plethora of amphoteric hydroxyl groups that can undergo reaction with either H⁺ or OH⁻. One pharmaceutically useful material in this group is the silicas.³ This is because, depending on how it was manufactured (synthetic) or processed (natural), the surface properties range from strongly hydrophilic (showing zero contact angle and a thick equilibrium wetted film) because of the surface silanol (-SiOH) groups to strongly hydrophobic (the surface siloxane groups, -Si-O-Si-, have ether-like properties). The silanol groups are weakly acidic, hence, the surface charge of the hydrophilic silicas tend always to be negative.

The oxides of most di- and trivalent metals (ie, MgO and Al₂O₃, respectively) are amphoteric; any dissolution tends to be in the form of the hydroxide, dissociated into its constituent ions (ie, Mg²⁺ + 2OH⁻). In formulation, swings in solution pH must be avoided because it can cause re-precipitation back onto the oxide surface in a different chemical form thus altering the surface chemistry and hence charge.

Mechanism (6), isomorphous substitution, is a more extreme case of mechanism (5). It occurs in aluminosilicate clay materials (ie, montmorillonite and vermiculite), where a large negative charge is initially developed on the clay crystallite because of the difference in valence between the Al³⁺ and the Si⁴⁺ ions.⁴

However, isomorphous substitution with varying proportions of minor elements leads to a dizzying variety and complexity of minerals.⁵ It is this diversity of crystal chemistry that gives rise to the differences in morphology - from the microscopic needles of palygorskite clay to the massive sheets of muscovite mica. Thus, the net surface charge

of any clay is a weighted mean of the various exposed faces, and it critically depends on the clays' prehistory. Hence, care must be taken in formulation when using clays; it may not be possible to substitute or replace one clay from a given manufacture with another from a different manufacturer or supplier. It is critically important that the ZP versus pH profile be determined for suspensions of any clay material.

ELECTRICAL PROPERTIES IN NON-AQUEOUS MEDIA

In solvents with moderate dielectric constants (>10 cf ~80 for water), at least some degree of ionization is possible, and charging mechanisms parallel to those in water can occur. Examples include LMW alcohols, amines, aldehydes, and ketones; they are referred to as leaky dielectrics. Ionic surfactants (ie, Aerosol OT) and some simple ionic salts (ie, LiCl) can dissociate to some extent in such media.

However, the inability of an electrolyte to ionize in fully nonpolar media (solvents of very low dielectric, ~ 2, such as alkanes) has led to a mistaken belief that particles dispersed in such a medium cannot acquire a charge. However, carbon dispersed in benzene develops an appreciable positive surface charge in the presence of calcium alkyl silicate, or a negative surface charge using quaternary ammonium picrate. The sign of charge is opposite what would be expected if the charging mechanism were the adsorption of

the conjugate larger ion. Thus, electrostatic forces are important and can play a key role in stabilizing non-aqueous suspensions, but the charging mechanism is not the same as in aqueous dispersions.^{6,7} In non-aqueous media, it arises through the formation of ions in adsorbed films on the particle surface where acid-base (or electron donor-acceptor) interactions occur between the particle surface and the dispersing agent.^{8,9} A solute that is an electron acceptor (or Lewis acid) will interact with an electron donor (or Lewis base) whether it finds that base on a substrate surface or in the solvent. Thus, acidic (ie, polyvinyl chloride) or basic (ie, poly[methyl methacrylate]) polymers are very effective suspendants of particles in non-aqueous media.

This is an extremely complex subject but very important technologically in electrophotography, electrophoretic displays (*vide* the Amazon Kindle), and electrodeposition of specialty coatings.¹⁰ The industrial importance of electrical charges and surface charging in non-aqueous media has been extensively reviewed; it is of considerable interest in paints and coatings, lubrication technology, agrochemical, and cosmetic formulations and in the development of high-performance ceramics and magnetic recording hardware.¹¹ In pharmaceuticals, it impacts the stabilization of APIs in propellant for drug delivery (to be discussed in Applications of ZP in Part 2).

Traces of polar impurities, especially water, play a key role; not only the magnitude but also the sign of ZP depend on the presence and amount of traces of water.¹²⁻¹⁴ Thus, in any non-aqueous application, it is critically important to determine the water content of all components.

THE ELECTRIC DOUBLE-LAYER

It is first important to recognize that the solvated size of a particle is not the same as the dry size found, for example, in electron micrographic images. The extent of this solvated layer is influenced by the solution conditions, such as composition (ie, pH, ionic strength) as well as temperature and pressure, and it encompasses what is termed the electric double-layer that exists at charged interfaces.¹⁵ The boundary between the edge of this

solvated layer and bulk liquid is termed the shear plane. It needs to be emphasized that it is this total solvated particle size that is measured by dynamic light scattering.¹⁶

Regardless of how charge separation is generated, the distribution of electrical charges at the interface is different from that in the bulk liquid phase. A structure called the electric double-layer will be developed such that the surface charge is neutralized by an adjacent layer in solution containing an excess of ions of opposite charge to that of the surface, ie, counterions. Ions of the same charge as the surface are termed coions. The theory of the electric double-layer, (EDL) is extremely complex and beyond the scope of this review; it deals with this distribution of counterions and coions around a charged particle in solution and hence with the magnitude of the resulting electric potential differences that occur in this region.^{17,18}

The simplest model for the EDL, shown schematically in Figure 1, is that of Stern.¹⁹ The EDL can be regarded as consisting of two regions or layers (hence the term electric double-layer): a region closest to the surface (the Stern layer) that is considered immobile (and it may include adsorbed ions) and an outer region (the diffuse layer) that allows diffusion of ions that are distributed according to the influence of electrical forces and random thermal motion.

The electric potential decreases linearly from Ψ_0 (the actual thermodynamic surface potential) to the Stern potential, Ψ_d , and then it decays exponentially to zero in the diffuse layer. It is described in the most simple mathematical model in the following equation:

Equation 1.

$$\Psi = \Psi_d \exp [-\kappa x]$$

Where x is the distance from the material surface, and κ , called the Debye-Hückel parameter, is defined in the following equation:

Equation 2.

$$\kappa = [2e^2 N_A c z^2 / \epsilon \epsilon_0 k_b T]^{1/2}$$

Where e is the protonic charge, N_A is Avogadro's number, c is the concentration of electrolyte of valence z , ϵ is the dielectric constant, ϵ_0 is the permittivity of free space, and k_b is the Boltzmann constant.

κ^{-1} is called the Debye length and is a measure of the thickness of the electric double-layer. For a single symmetrical electrolyte in water at 25°C, it can readily be computed from the following equation:

Equation 3.

$$\kappa^{-1} = 0.3041 / Z C^{1/2}$$

For aqueous electrolyte solutions, κ^{-1} is in the range of a few tens of nm. Hence, it can be seen that the electric potential depends (through κ) on the ionic composition of the medium. If κ is increased (the electric double layer is compressed), then the potential must decrease.

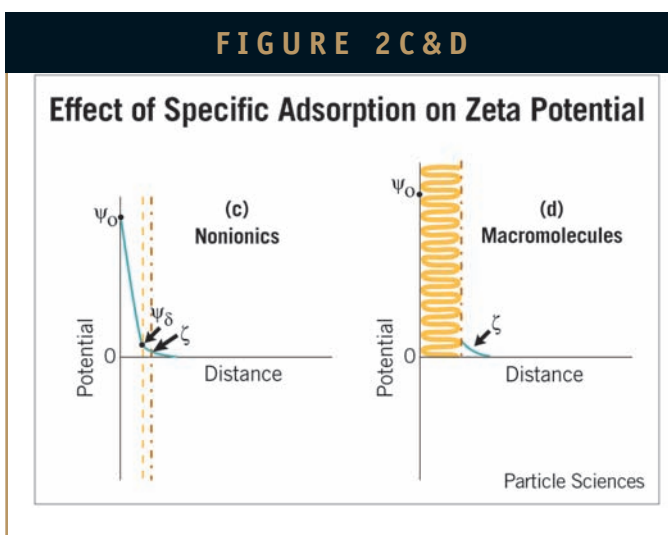
Unfortunately, the fundamental interfacial property ψ_0 (and hence, charge density, σ_0) is fundamentally inaccessible.²⁰ However, what can be derived (and ultimately measured) is an electrokinetic potential termed the ZP. This quantity is defined as the potential at the shear plane - so called because any relative movement of the surface with respect to solution will cause some of the counterions to be sheared off, resulting in only partial compensation of the surface charge. The location of the shear plane is never precisely known (estimates range from ~1 nm to ~10 nm) because in addition to ions, a certain amount of solvent will also be bound to the charged surface. In reality then, rather than a mathematical plane, it

is a region of rapidly changing viscosity (and, possibly dielectric). Thus, ZP is not well defined. Nevertheless, it has become a very useful experimental parameter to monitor electrokinetic behavior of suspensions, especially changes in such behavior.²¹

THE RELATION BETWEEN ZP & SURFACE CHARGE

While it is apparent from the aforementioned that ZP is not the actual thermodynamic (or surface) potential, in theoretical calculations, it is frequently taken to be identical with the Stern potential. Any difference between the Stern potential and ZP will be most pronounced when the real surface charge is very high (ie, completely dissociated COOH groups on polymer latex particle) or at high electrolyte concentrations (ie, physiological saline).

When specific adsorption of charge carriers takes place at a surface, counterion adsorption usually predominates over coion adsorption. Examples would be Ca^{2+} adsorbed on a negatively charged silica surface or PO_4^{3-} on a positively charged alumina surface. With polyvalent and, certainly, surface-active counterions, it is even possible for a reversal of charge to take place within the Stern player, ie, for surface potential and Stern potential (and hence ZP) to have opposite signs (Figure 2 A&B). Further, the adsorption of nonionic (ie, polyoxyethylene-based) surfactants would result in a ZP being close to zero (Figure 2 C&D). Adsorption of surfactants occurs



primarily through hydrophobic bonding. Also, as the MW of any macromolecular species increases, it results in the shear plane being located at a larger distance from the Stern plane and, in consequence, ZP being significantly smaller than ψ_d . All these types of charge-modifying agents are used extensively in formulations of suspensions.

Thus, it is entirely possible that a surface can have an inherent (thermodynamic) charge but have no measurable ZP and vice-versa.²² This does not mean to imply that the ZP measurement is not useful. On the contrary, ZP is in the practical sense the effectiveness of the particle surface charge in solution. While ZP may derive initially from the fundamental number of surface sites (how many, what type, etc), more importantly, from a practical application, are the solution conditions themselves because they control the resulting final sign and magnitude of ZP. The consequence of this to the process of dispersing particles is critical. And importantly, it is useless to quote a ZP value without specifying the suspension conditions under which the measurement was made.

Most suspensions are prepared at some fixed concentration of solids, and because it is necessary to dilute the original material for ZP measurement (Part 2 will cover methods and techniques for measuring ZP), this matter also impacts very much the sample preparation required for ZP measurements. The question then becomes whether one dilutes into pure (distilled/deionized) water under some fixed conditions of pH and specific conductance, and monitors the change with time. This will impact the situation when performing a pH titration. In which direction should the titration be carried out? Does one start at neutral and increase pH to some highly basic condition and then titrate back down to neutral and then continue to decrease the pH to some highly acid condition; or does one go backward and forward? While this may seem to be taking a rather nit-picking approach, it has been demonstrated that ZP measurements of CD4⁺ T-Cells as a function of pH can reflect different rates of the respective ionization and association that occur in the surface functional groups as a consequence of the different changes in the hydration-dehydration reactions involved.²³ Or, does one dilute into the supernatant of the colloidal system itself by checking first the solution

conditions (pH, conductivity, and the interfacial tension)? No matter what, in order to study the effect of adding any charged moiety, it is imperative to start with solution conditions giving an initial constant ZP so that only one variable is changed.

Part 2 will conclude by covering techniques available to measure ZP and as well as provide some applications to illustrate its usefulness.

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BIOGRAPHIES



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