

ZETA POTENTIAL: A KEY FACTOR IN DRUG DELIVERY

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ABSTRACT

This review article deals with measurement and applications of zeta potential, zeta potential in pharmaceutical formulation, Role of zeta potential in stability, material design and preparation. Zeta potential (ζ) is a measure of the magnitude of the repulsion or attraction between particles. Its measurement brings detailed insight into the dispersion mechanism and is the key to electrostatic dispersion control. Stability of colloidal dispersions directly depends upon the zeta potential of system. When a particle is immersed in a fluid, a range of processes causes the interface to become electrically charged. Some of the most commonly found charging mechanisms include adsorption of charged surfactants to the particle surface (for example in an emulsion stabilized by an ionic surfactant), loss of ions from the solid crystal lattice (silver halide particles used in photographic emulsions) and ionization of surface groups (carboxylate in polymer microspheres). The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. For molecules and particles that are small enough zeta potential will exhibit stability, i.e., the solution or dispersion will resist aggregation. The zeta potential is measured by some methods they are electrophoresis, electro osmosis, sediment potential and streaming potential. When the zeta potential is low, the dispersion will break and flocculate. In pharmaceutical field measurement of zeta potential is used to understand dispersion and aggregation processes and also used to determine the presence or absence of charged groups on the surface of materials. In this review, the significance of zeta potential including its method of measurement and zeta potential in pharmaceutical formulation and their stability were discussed.

KEYWORDS: Electric double layer, electro osmosis, streaming potential, sedimentation potential, stability of dispersion.

INTRODUCTION

Zeta potential is a measure of the magnitude of the repulsion or attraction between particles. Its measurement brings detailed insight into the dispersion mechanism and is the key to electrostatic dispersion control.^[1]

Zeta potential is a scientific term for electrokinetic potential in colloidal dispersions. In the colloidal chemistry literature, it is usually denoted using the Greek letter zeta(ζ) hence ζ -potential. The usual units are volts (V) or, more commonly, millivolts (mV).^{[2],[3]}

When a particle is immersed in a fluid, a range of processes causes the interface to become electrically charged. Some of the most commonly found charging mechanisms include adsorption of charged surfactants to the particle surface (for example in an emulsion stabilized by an ionic surfactant), loss of ions from the solid crystal lattice (silver halide particles used in photographic emulsions) and ionization of surface groups (carboxylate in polymer microspheres). These processes lead to the production of a surface charge density, expressed in coulombs per square meter, which is the fundamental measure of charge at the interface. The charge cannot be measured directly, but only via the electrical field it creates around the particle. Thus the surface charge is normally characterized in terms of a voltage at the particle surface, the surface potential, rather than a charge density, although one can usually be calculated from the other. The zeta potential occurs at a distance from the surface and this will be different to the surface potential. In the simplest approximation, the potential decays exponentially with distance from the surface of the particle. The rate of decay is dependent on the electrolyte content of the fluid.^[4]

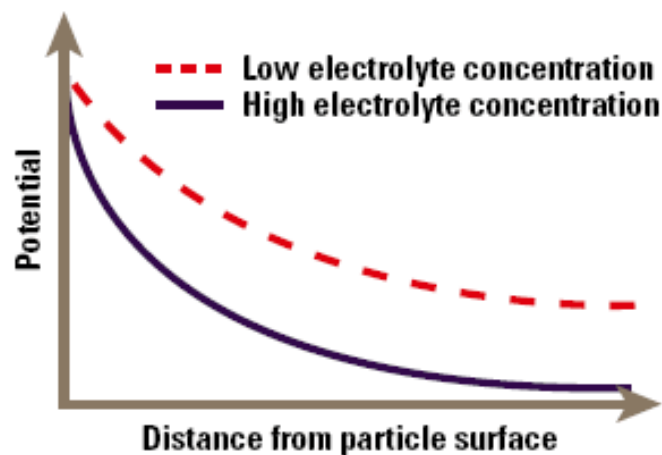


Figure 1: Approximation of zeta potential as a function of distance from the particles' surface.

Electrical Double Layer

In contact with a polar medium such as water, the majority of particles show definite surface charges. The surface charges affect the arrangement of neighbouring ions of polar medium. Ions of the opposite sign also called counter ions will be attracted to the particle surface and the ions of the equal sign also called coions will be repulsed from the surface. The resultant electrical double layer will be developed in such a manner that it neutralizes the particle surface charge. The electrical double layer can be regarded as consisting of two regions or layers: a region closest to the surface (the Stern layer) that is considered immobile (and it may include adsorbed ions) and an outer region (it may include diffused ions that are distributed according to the influence of electrical forces and random thermal motion).^{[5],[6],[7],[8]}

Extent of double layer is influenced by the solution condition such as pH, ionic strength, temperature and pressure.^[9] It

has a very useful parameter in monitoring the electro kinetic behaviour of suspensions.^[10] 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 can be explained by simple mathematics model in equation 1.^[11]

$$\psi = \psi_d \exp [-\kappa x] \dots \dots \dots (1)$$

Where, ψ = Thermodynamic surface potential

ψ_d = Stern potential

x = Distance from the particle surface

κ = Debye-Hückel parameter

The Debye-Hückel parameter can be calculated by the formula:

$$\kappa = [2e^2N_Acz^2/\epsilon\epsilon_0k_bT]^{1/2} \dots \dots \dots (2)$$

Where, e = Proton charge

N_A = Avogadro's constant

C = Concentration of electrolyte

z = Valency of electrolyte

ϵ = Dielectric constant

ϵ_0 = Permittivity of free space

k_b = Boltzmann constant

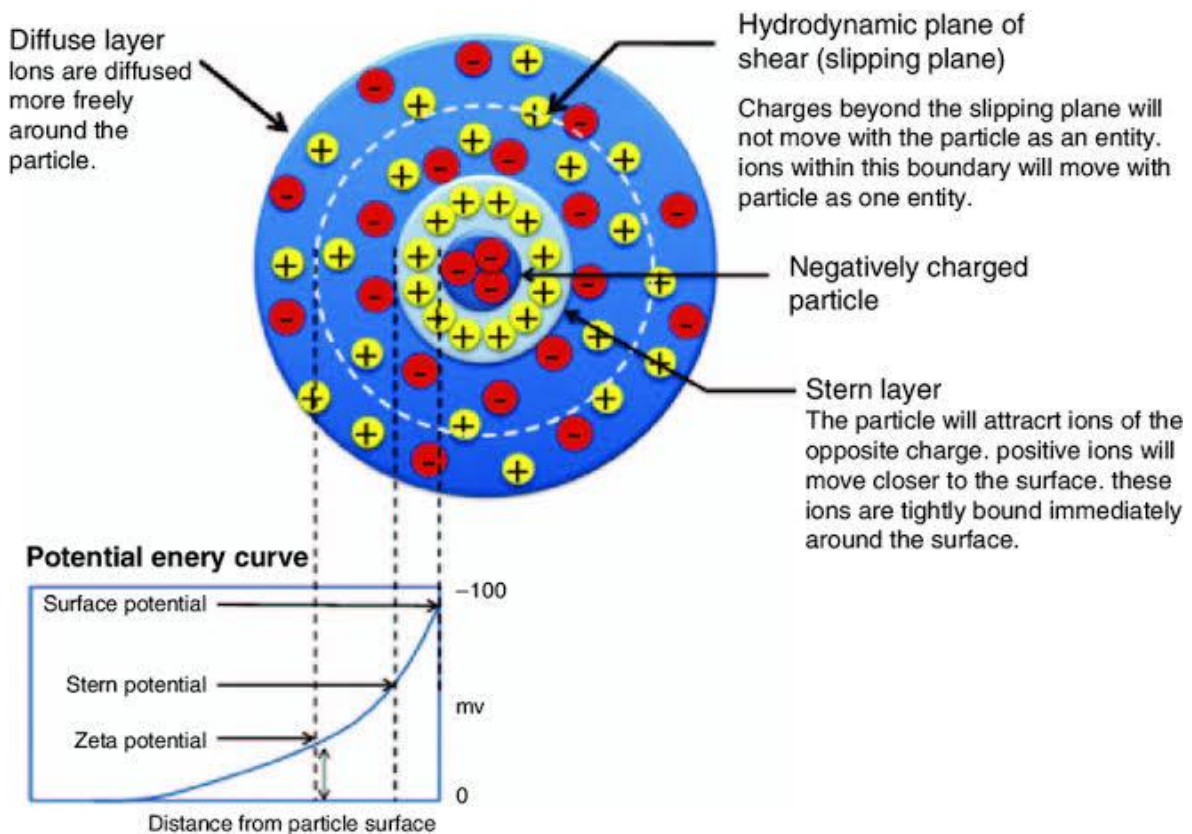


Figure 2: Electrical double layer.^[13]

Methods for Measurement of Zeta Potential

There are many materials available in the market that supplied by the various manufacturer.¹ These are well characterized particles suspended in the systems having electrophoretic mobility. For example: Goethite, it is an official reference material.^[12]

Electrophoresis

It is extensively used due to its simplicity and giving quick results. Electrophoresis has been revealed when a fine dispersion of some dielectric matter in the electrolytic solution is exposed to the effect of an electrical field. Dispersed particle acquires a charge according to dispersion medium; resultant electric double layer is formed. If a liquid phase is prevented to flow in one direction, and the charged particle is allowed to keep in motion in electrical field, they will travel towards cathode or anode according to their charge.

Electro-osmosis

Electro-osmosis is the measurement of the flow of a liquid phase through a porous membrane in the presence of an electrical field with constant temperature. Speed of electro osmotic flow depends on strength of electric field applied on the charged liquid phase.

Streaming Potential

This phenomenon is opposite to electro osmosis. In this method by applying the pressure, the solution is passed through the membrane as a result of which a type of flow potential is incited. It is just proportional to the difference between pressure and the flow speed of the electrolyte solution through the membrane pores.

Sediment Potential

This phenomenon is opposite to electrophoresis. In this the movement of charge particle is measured under the influence of gravitation or sedimentation field in centrifuges. It is rarely used in the study of electro kinetic phenomena because it is very difficult to be measured.

ADVANTAGES

- It can be used to optimize the formulations of suspensions, emulsions and protein solutions, predict interactions with surfaces, and optimise the formation of films and coatings.
- Knowledge of the zeta potential can reduce the time needed to produce trial formulations.
- It can also be used as an aid in predicting long-term stability.^[14]
- The sign and magnitude of zeta potential can be used as a secondary metric to determine surface chemistry changes.^[15]

LIMITATIONS

- Zeta Potential cannot be directly measured.
- When finding the Zeta Potential the size of the double layer must be very thin.
- The zeta potential is not a direct measurement of the stability of a dispersion.^[16]

Factors Affecting Zeta potential

1. pH

In aqueous media, the pH of the sample is one of the most important factors that affects its zeta potential. Imagine a particle in suspension with a negative zeta potential. If more alkali is added to this suspension then the particles tend to acquire more negative charge.

If acid is added to this suspension then a point will be reached where the charge will be neutralized. Further addition of acid may cause a build up of positive charge if the ions are specifically adsorbed. In this case a zeta potential versus pH curve will be positive at low pH and lower or negative at high pH. The point where the plot passes through zero zeta potential is called the isoelectric point and is very important from a practical consideration.

It is normally the point where aggregation is most likely and hence the colloidal system is least stable.^{[14][15]}

A typical plot of zeta potential versus pH is shown in figure 8. In this example, the isoelectric point of the sample is at approximately pH 5.5. In addition, the plot can be used to predict that the sample should be stable at pH values less than 4 (sufficient positive charge is present) and greater than pH 7.5 (sufficient negative charge is present). Problems with dispersion stability would be expected at pH values between 4 and 7.5 as the zeta potential values are between +30 and -30mV.

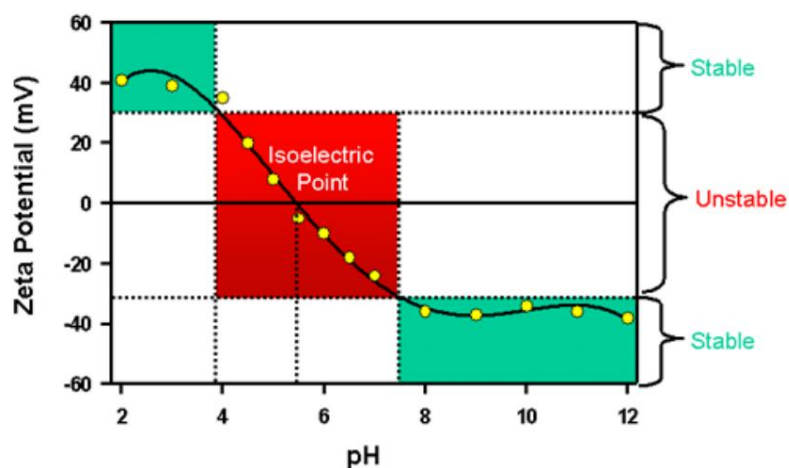


Figure 8: Typical plot of zeta potential versus pH showing the position of the isoelectric point and the pH values in the green sectors where the dispersion would be expected to be stable.^{[14][15]}

2. Conductivity

The thickness of the double layer (κ^{-1}) depends upon the concentration of ions in solution and can be calculated from the ionic strength of the medium. The higher the ionic strength, the more compressed the double layer becomes. The valency of the ions will also influence double layer thickness. A trivalent ion such as Al^{3+} will compress the double layer to a greater extent in comparison with a monovalent ion such as Na^{+} .

Inorganic ions can interact with charged surfaces in one of two distinct ways (i) nonspecific ion adsorption where they have no effect on the isoelectric point. (ii) specific ion adsorption, which will lead to a change in the value of the isoelectric point.

The specific adsorption of ions onto a particle surface, even at low concentrations, can have a dramatic effect on the zeta potential of the particle dispersion. In some cases, specific ion adsorption can lead to charge reversal of the surface.^{[14][15]}

3. Concentration of a formulation component

The effect of the concentration of a formulation component on the zeta potential can give information to assist in formulating a product to give maximum stability. The influence of known contaminants on the zeta potential of a sample can be a powerful tool in formulating the product to resist flocculation for example.^{[14][15]}

Applications of zeta potential

The physical properties of colloids and suspensions are totally dependent on the nature and extent of the particle- liquid interface which means that the behaviour of aqueous dispersions depends upon electrical and ionic structure of the interface. The production and stability of colloids and suspensions are both intimately related to electrical double layer that characterizes the interface. Zeta potential measurements are directly related to the nature and structure of the electric double layer at the particle-liquid interface. Zeta potential measurement is a key factor in the following areas:

Biomedical

Micro electrophoresis is a most useful technique for characterizing the surface of organisms such as bacteria, blood cells, viruses etc. In addition to chemical methods of analysis which can disrupt the organism, zeta potential measurement has given the information about the outermost regions of organisms. The main constituents of biological material (protein, lipid, polysaccharide, nucleic acid) show characteristic charge behaviour.

Detergency

The important factor in detergency is the prevention of dirt re-deposition after its removal. Re-deposition is governed by the influence of detergent adsorption, not only on the zeta potential of the dirt particles, but also on the zeta potential of the fabric surface.

Purification

Zeta potential measurements are useful in maintaining the optimum conditions for purification in a various chemical processes such as removal of impurities from sugar cane juice by precipitating an inorganic material which serves to collect the impurities and it can be achieved by determination of the proper zeta potential.^{[5][6][7][8][9][10][11]}

ZETA POTENTIAL IN PHARMACEUTICAL FORMULATION

When particles carry a strongly positive or strongly negative zeta potential, there is also a strongly repulsive electrostatic interaction between the particles. This prevents the particles from coming close to each other and forming agglomerates.

According to DLVO theory, when the particles are close to each other, van der Waals forces come into effect, which are based on dipole-dipole interactions. These forces have an attractive effect. At a zeta potential close to zero, the repulsive effect of the electrical double layer is small, and coagulation is more likely to occur.

The zeta potential is not a direct measurement of the stability of a dispersion, but it provides a good prediction of stability. Because analysis of the zeta potential is much easier and faster to perform than a stability measurement, the zeta potential is often used to assess the quality of the dispersion.

Changing the electrolyte composition and concentration leads to a shift of the zeta potential.

➤ The following graph visualizes the effect,^[16]

With the increasing addition of a positive polyelectrolyte, the particle size of the sample also changes:

(1) Red, (2) Green, (3) Yellow, (4) Blue, (5) Purple

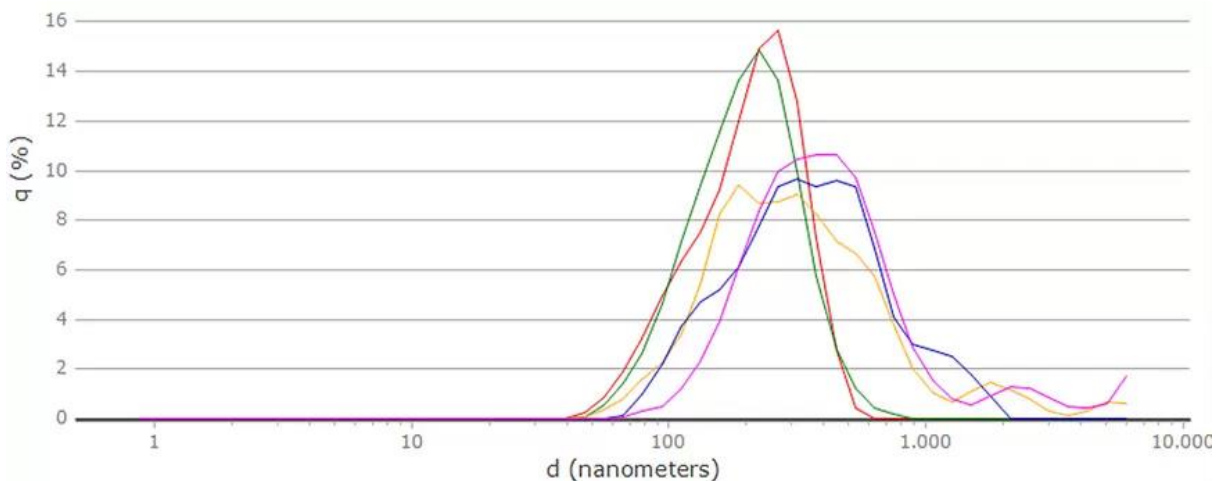


Figure 3: Effects of Zeta Potential.

ROLE OF ZETA POTENTIAL IN STABILITY

COARSE DISPERSION

- In the presence of high Zeta Potential the repulsive electric forces exceed the attractive Vander-Walls Force. The particles dispersed in such a manner are said to be Deflocculated.
- Zeta Potential can be lowered by the addition of opposite charge ion that neutralize the surface potential.
- At a definite concentration of the added ions the electric force are lowered sufficiently and the force of attraction are predominate. This may allow the particle to approach each other more closely and form loose aggregates known as floccules.
- The continuous addition of the flocculating agent may reverse the above process if added in enough concentration to cause the Zeta Potential to increase sufficiently in the opposite direction.
- Role of potential in stability of course dispersion.^[17]

COLLOIDAL DISPERSION

- The zeta potential is an important and readily measurable indicator of the stability of colloidal dispersions. The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion.
- For molecules and particles that are small enough, a high zeta potential will confer stability, i.e., the solution or dispersion will resist aggregation.
- When the potential is small, attractive forces may exceed this repulsion and the dispersion may break and flocculate. So, colloids with high zeta potential (negative or positive) are electrically stabilized while colloids with low zeta potentials tend to coagulate or flocculate as outlined in the below table.^[18]

Table 1: Stability behaviour of a colloidal depending on zeta potential.^[19]

MAGNITUDE OF ZETA POTENTIAL(mV)	STABILITY BEHAVIOUR
0 to 5	Rapid coagulation or flocculation
10 to30	Incipient instability
30 to 40	Moderate stability
40 to 60	Good stability
>61	Excellent stability

PARTICLE SIZE

Electrical potential at the particle surface shows its stability in suspension. Among the factors determining this, particle size is one of the most important: surface area to volume ratio.

1. Lesser the size of particles

With a smaller size of particles, there comes an increased surface area to volume ratio. Thus, it increases the number of surface charges per unit volume such that it can lead to an increase in zeta potential. With smaller sizes of particles, possibly higher zeta potential values might also be manifested because of a large fraction of the sites being on the surface, charged.^[20]

2. Surface Charge Density

Charge density at the particle surface varies directly with zeta potential. Generally, higher charge density is positively correlated with smaller sizes of the particles involved. With a greater electrostatic repulsion between the particles, a more stable colloidal system would result.^[21]

3. Aggregation Behaviour

In a suspension of greater size, there are aggregation than smaller-size particles, which possess low surface energy and weaker electrostatic repulsion. Effective zeta potential can be lowered down in suspension and may lead to instability while the suspensions form aggregates.^[22]

4. Particulate Composition and Functionalization

Properties of material and surface modification also influence the zeta potential. As a matter of fact, in the case of thin particles, coating of the functional groups may increase the surface charge and hence the zeta potential.^[23]

5. Electrolyte Concentration and pH

Zeta potential is sensitive to ionic strength and pH; together they might interact with particle size, and changes within them could act differently on smaller particles from larger ones, making a difference in their zeta potential.^[24]

Materials design and preparation

Particles' behavior during functional materials' manufacture can be tuned by adjusting the pH at different stages of the synthesis process.

As the zeta potential of particles in suspension depends sensitively on the medium acidity, the net surface charge can be selected according to ζ measurements as a function of pH, allowing the control of not only the flocculation, coagulation and peptization processes of colloidal particles in wet synthesis steps, but also of the distribution of the catalyst components by preferential impregnation of active phases onto supports, and of viscosity and preferential interactions during shaping processes.

For instance, correlations between the IEP-pH relative difference and metal cluster size or relative particle_attrition index have been reported.^[25]

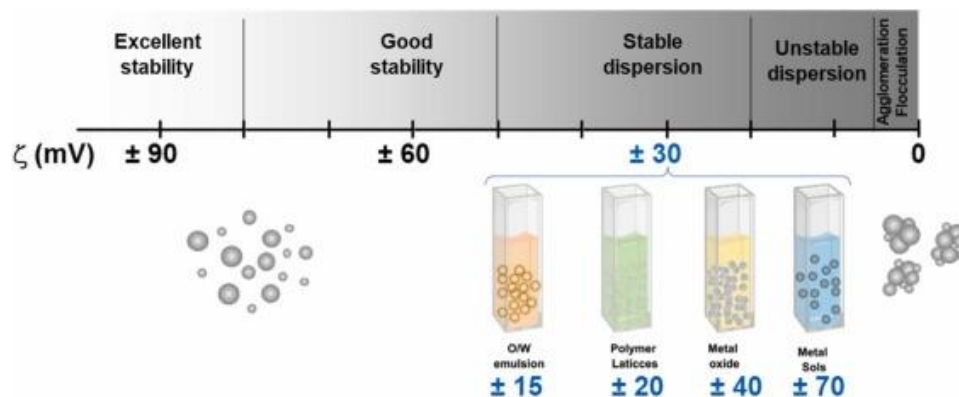


Figure 3: Stability behaviour of a colloidal depending on zeta potential.

Coating of solids

The most important preparation methods for supported catalysts are in liquid phase.

One of the most common methods is the impregnation of porous supports with aqueous solutions or dispersions, as it is cheap and simple.

The surface charge is relevant from the viewpoint of metal loading and metal dispersion, among others.

Although the surface charge is of less relevance from the viewpoint of loading when evaporation impregnation is used, it can be important for metal dispersion.

Some research work carried out on zeta potential on pharmaceutical formulation

S. No	Title	Inventor	Year
1	Zeta potential at extracellular vesicles: Towards understanding the attributes that determine colloidal stability.	G.Midekessa, K. Godakumara Jord	2020
2	Experimental methods in chemical engineering zeta potential	CN Lunardi, AJ Gomes, Fsrocha	2021
3	Zeta potential changing nanoemulsion impact at PEG_-Corona on phosphate cleavage	Szaichik, Cstenbring, M Jelkmann	2020
4	Effect at isotonic solution and peptide adsorption on zeta potential of porous silicon nanoparticle drug delivery formulation	M. Kaasalwnen, E. Makila, J Rikonen	2012
5	Influence of metal oxide nanoparticle concentration on their zeta potential	R Tantra, P schulze, P Guincey	2010
6	Effect of zeta potential on the properties of nano-drug delivery system	S Honry, F Zahir	2013
7	Development and <i>in-vitro</i> evaluation of zeta potential changing self emulsifying drug delivery system for enhanced mucus	W Suchaoain, IP desousa, K Nelsomboon	2016
8	Zeta potential changing self emulsifying drug delivery system containing phosphorylated polysaccharides	J Grienser, S Burticher, S Koliner, I Nardin	2017
9	Self emulsifying drug delivery system containing their zeta potential via a flip-flop mechanism	E Salimi, B Le-Vinh, F Zahir Jouzdani	2018
10	Zeta potential changing self-emulsifying drug delivery system: A promising strategy to sequentially overcome mucus and epithelial barrier	I Nazir, A Furst, N Lupo, A Hupfauf, R Gust.	2019
11	Phosphorylated PEG-emulsifier: Powerful tool for development of zeta potential changing self-emulsifying drug delivery system	JD Wolf, M Kurpiers, RX Golz, S Zaichik	2020

Surface reactivity of nanomaterials

The very high surface-to-volume ratio of nanomaterials makes characterization of the charge at their surface critical for understanding reactivity.

Most nanomaterials cannot act like catalysts-for example, toxic compounds can be inactivated-and need to be inert for application in biomedicine.

The classification of engineered nanomaterials relies on zeta potential (ζ), important also for predicting properties and avoiding experimental testing.

It will influence the way nanomaterials react with biological and environmental surroundings, moving toward chemical manufacturing that is safer, more sustainable.

The stability and toxicity of nanoparticles are assessed by zeta potential measurements. Unstable particles can emit metal ions, whereas the lower surface charges signify higher covalent indices. Values near ± 30 mV give lower reactivity and toxicity, as they tend to favor agglomeration.

Particle dispersion may exhibit significant variations in their stability, which in turn affects its interaction with the biological system; it may even penetrate inside the body.

ζ can be used to identify the surface coats that may improve biocompatibility as well as understand how nanoparticles interact with cells.^{[26][27][28]}

ζ variations, through techniques such as TEM, have been found to differentiate between the binding and the internalization of nanoparticles by cells.

The zeta potential and protein adsorption also depend on the synthesis method of the nanoparticles; positive ζ values favor protein attachment, while negative ζ favors cell-nanoparticle interactions.

Recently, highly promising results considering the use of porous silicon (PSi) nanoparticles as a controlled and targeted drug delivery system have been published. Drugs are typically loaded into PSi nanoparticles by electrostatic interactions, and the drug-loaded nanoparticles are then administered parenterally in isotonic solutions.

Zeta potential has an important role in drug adsorption and overall physical stability of nanosuspensions. In the present study, we used zeta potential measurements to study the impact of the formulation components to the nanosuspension stability.^[29]

The impact of medium was studied by measuring isoelectric points (IEP) and zeta potentials in isotonic media. The role of drug adsorption was demonstrated with gastrointestinal peptides GLP-1(7-37) and PYY (3-36) and the selection of isotonic additive was demonstrated with peptide-loaded PSi nanoparticles.

The results show the notable effect of isotonic solutions and peptide adsorption on zeta potential of PSi nanosuspensions. As a rule of thumb, the sugars (sucrose, dextrose and mannitol) seem to be good media for negatively charged peptide-loaded particles and weak acids (citric- and lactic acid) for positively charged particles.

Nevertheless, perhaps the most important rule can be given for isotonic salt solutions which all are very poor media when the stability of nanosuspension is considered.^{[30][31][32]}

CONCLUSION

Zeta potential is key to understand dispersion and their aggregation process. Zeta potential is used to know about the stability of dispersions zeta potential is a parameter to understand the surface charge characteristics and behaviour of colloidal particle. Zeta potential is essential for optimizing the formulation and ensuring product quality.

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