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The electrokinetic potential of therapeutic proteins and its modulation: Impact on protein stability

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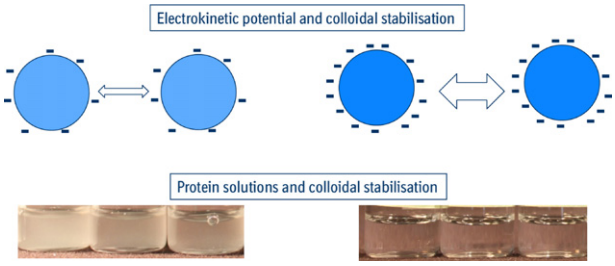
HIGHLIGHTS

- The isoelectric point (IP) of monoclonal antibodies measured by the electrokinetic potential (EP) differs strongly from the theoretical IP.
- EP can be used for the investigation of ion binding/adsorption to proteins.
- EP of biomacromolecules/proteins can be modulated between ±50 mV.
- Using ionic physiological conditions, EP is reduced to ca. ±5 mV.
- For predicting colloidal stability: consider EP and thermodynamic/conformational stability.

GRAPHICAL ABSTRACT



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ABSTRACT

Colloidal protein stability in solution is governed by protein–protein interactions as well as by interactions with surrounding molecules (e.g. excipients, buffer and salt components, solvent molecules) and environmental conditions such as temperature. Also, the thermodynamic stability of a protein has an impact on the overall colloidal stability of protein in an aqueous environment.

Electrostatic interactions between proteins have been described to be of high relevance for colloidal stability, for example the formation of protein particles. One parameter for the evaluation of such interactions in solution is the electrophoretic mobility from which the electrokinetic potential (EP) (also known as the zeta potential, ZP) is obtained. The electrokinetic potential, respective EP, refers to the potential at the shear surface where the protein molecules with their associated sheath of counter-ions and excipients slip through the solution, which is under the influence of an applied external electrical field.

The current study investigated the electrokinetic potential of therapeutic proteins and how and to what extent the electrokinetic potential can be influenced by variations of solution conditions (e.g. pH, salts and buffer components, amino acids, carbohydrates or detergents). The interactions of proteins, such as monoclonal antibodies, with different excipients are discussed in terms of the DLVO theory and colloidal stability, respectively.

Furthermore, the electrokinetic potential is used for the determination of the isoelectric point of several proteins and compared to theoretical values derived from the total net charge based on the primary amino acid sequence.

In addition, we investigated to what extent the electrokinetic potential of proteins can be modulated by solution conditions and whether the electrokinetic potential of various proteins in different solution conditions correlate with experimental derived colloidal and thermal stability.

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