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CHARACTERIZATION OF PROTEIN-EXCIPIENT INTERACTIONS FOR DESIGNING FORMULATION

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Proteins often perform a diverse and complex set of functions within the cell, including catalyzing metabolic reactions, transport of specific substances from one location to another, etc. Therefore, proteins, also called biologics, are regularly used in protein-based therapies to treat diseases. A major potentiality of biologics resides in their intrinsic compatibility with living systems, in comparison with small molecule drugs. Biologics are often characterized by high specificity and potency with low toxicity and thus have interested many pharmaceutical industries. Several challenges confront pharmaceutical scientists involved in the development of protein therapeutics. For instance, the proper stabilization of biologics is one of the major concerns. To overcome this issue, excipients play a major role in stabilizing biologics to prevent protein-protein interactions and hence aggregation. Currently, a detailed molecular understanding of the effect of different physicochemical formulation conditions on the stability of proteins is sparse, as molecular interactions are difficult to investigate experimentally at the molecular level. Thus, computational approaches, as applied in the current study, can provide insight on the single-molecule level. This rational approach is an attempt to understand the combined effect of pH and salinity on the protein stability. We investigated the effect of pH and ionic strength on the wild-type plectasin, and the three variants (PPI41, PPI42, PPI43). Furthermore, independent protein thermodynamic integration MD simulations were performed to understand conformational stability due to the presence of cysteines bonds. These results are further supported by NMR and fluorescence studies. Additionally, studies have been performed to identify potential hotspots for excipient-protein interactions using free energy approaches such as implicit solvent molecular mechanics (MM-PBSA) and explicit solvent linear interaction energy (LIE) methods, relative binding affinities of excipients to the proteins are predicted in order to rank excipients and to determine the effect of excipients on protein dynamics and flexibility. These results will be further supported by NMR studies.

Biography

Sowmya Indrakumar holds a Bachelor of Science (by Research) and Master of Science degree in Biology from Indian Institute of Science, Bangalore, India. Throughout her undergraduate studies, she was a recipient of 'Innovation in Science Pursuit for Inspired Research-Department of Science & Technology (INSPIRE-DST) fellowship. In 2016, she became part of the PIP-PI (http://www.pippi.kemi.dtu.dk/) project as a Ph.D. researcher at Technical University of Denmark, Denmark. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant.

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