Kinetics of Monoclonal Antibody Aggregation - Going From Elevated Towards Lower Temperatures

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Monoclonal antibodies and other therapeutic proteins are gaining increasing importance as pharmaceutical compounds due to recent advances in biotechnology and their very specific mode of action, resulting in higher drug efficacy and reduction of adverse side effects [1]. Modern production processes yield the protein of interest at very high purity. However, under a broad range of conditions proteins could be only marginally stable in solution, and preserving their stability under long-term storage represents a challenge in product development [2]. Aggregation of the protein molecules into soluble oligomers as well as micron-sized precipitates is viewed as the largest threat to product safety due to the potential immunogenicity of the protein aggregates and the resulting danger to the patient. In this respect, a large effort is dedicated in liquid formulation development to the optimization of the composition of the final product in terms of solution pH, buffer species and potential additives. This optimization is both time and effort consuming, since the resulting parameter space to be investigated is very large [3].

In this context, accelerated studies at elevated temperatures represent a common strategy to test the aggregation and other potential degradation reactions of biopharmaceuticals. The possible drawback of this approach is, however, the question about the validity of the information gathered at higher temperatures for the actual temperatures encountered in storage and shipment, as well as the extrapolation of the degradation rates observed at elevated temperatures to lower temperatures [4].

Gaining a fundamental understanding of the aggregation process at the microscopic level would be highly beneficial to overcome limitations of accelerated studies as well as to design rationally optimized formulations [5,6]. The scope of this work is to apply a combination of model simulations and experimental data to investigate the mechanistic details of the aggregation process of a model monoclonal antibody over a broad range of temperatures.

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