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Mini Review

Predictive Screening Tools Used in High-Concentration Protein Formulation Development

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ABSTRACT

This review examines the use of predictive screening approaches in high-concentration protein formulation development. In addition to the normal challenges associated with protein formulation development, for high-concentration formulations, solubility, viscosity, and physical protein degradation play major roles. To overcome these challenges, multiple formulation conditions need to be evaluated such that it is desirable to have predictive but also low-volume and high-throughput methods in order to identify optimal formulation conditions very early in development without time- and material-consuming setups. Many screening techniques have been reported for use in high-concentration formulation development, but not all fulfill the requirements mentioned previously. This review summarizes the advantages and disadvantages of different screening approaches currently used in formulation development and the correlation of predictive data to protein solubility, viscosity, and stability at high protein concentrations.

Introduction

During the last years, versatile applications and the intense interest of both research groups and the pharmaceutical industry has led to a rapid progression in biopharmaceutical development. In this context, 2 general trends can be recognized. On the one hand, a shift from the use of classical monoclonal antibodies (mAbs) to more complex mAb-based structures, such as fragment antigen binding fragments, Fc-fusions, and multispecific mAbs, has taken place.[1] On the other hand, patient-centered medicine gets more important, and new drugs have to be not only safe and efficient but also easy and ready to use. Thereby, despite their limited injection volumes, subcutaneous and intramuscular routes of administration are preferred especially for chronic treatments because they enable home administration and short treatment times. Consequently, the use of high-concentration protein formulations (HCFs) is a common strategy to achieve sufficient doses even when special challenges have to be overcome.[2]

The increasing complexity of new biological drugs and the requirement for HCF to satisfy patient needs require the screening of a high number of formulation conditions to address viscosity, stability, and solubility issues associated with HCF development.[2] Since material is typically limited in the early phase of development, high-throughput (HTP) and low-volume methods are necessary to predict protein stability, solubility, and viscosity without the use of time- and material-consuming studies.[3,4] A large number of predictive methods have been published to date. This review summarizes the wide variety of predictive methods and discusses their advantages and disadvantages in the context of HCF development.

Important Aspects of HCF Development and Indicative Parameters

As mentioned previously, the main issues in HCF development are formulation viscosity, protein stability, and solubility.[2] Protein stability in general can be divided into chemical and physical degradation processes. Since chemical degradation occurs at low and high protein concentrations equally, this review focuses only

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on physical degradation pathways. Physical stability, solubility, and viscosity are somehow related to the same root cause—the agglomeration of protein molecules in solution.[2,5]

In general, the topic of physical protein stability and underlying mechanisms has been extensively discussed in the past, and nomenclature differs between references.[6-8] Thus, some definitions have to be made in the context of this review. Agglomeration is defined as an umbrella term and can be divided into protein aggregation and self-association. Furthermore, aggregation is defined as agglomeration of non-native or partially unfolded molecules that is effectively irreversible, whereas self-association is defined as agglomeration of native or non-native molecules that is effectively reversible and increases with increasing protein concentration.[9,10] In practice, agglomeration processes can be very complicated and need to be carefully investigated for each protein. One has to distinguish between conformational stability, as characterized by protein unfolding and determined by free energy (ΔG) level, and colloidal stability, as characterized by protein-protein interactions (PPIs) between native or (partially) unfolded proteins that can trigger agglomeration.[11] Several mechanisms can occur in parallel and also additional mechanisms exist such as aggregation as a result of chemical degradations, but these are out of scope of this review.

Figure 1 illustrates simplified protein self-association and aggregation pathways and the inter-relationship of physical stability and solubility or viscosity. Assuming solubility as the maximum amount of protein in solution whereby the solution remains visibly clear, proceeding agglomeration can readily be understood to cause protein precipitation, which is defined as the formation of visible agglomerates as a result of exceeded solubility.[2] In addition, it has been reported that any kind of agglomeration leads to altered particle sizes and decreased molecule mobility in solution, resulting in increased viscosity.[12,13]

To optimize viscosity, stability, and solubility, it is essential to know the exact degradation mechanism(s) of a single protein and to define rate-limiting step(s). For protein unfolding followed by aggregation and precipitation of denaturized protein, protein unfolding is the rate-determining step and should be minimized. To improve stability, ΔG should be measured and optimized. For protein self-association followed by precipitation, protein association is the rate-determining step and must be controlled. In this case, PPI should be measured and optimized.[4,11,14]

Predictive Screening Tools Available for HCF Development

Table 1 summarizes predictive screening approaches that are currently used in protein formulation development with special regard being given to the suitability for use in HCF development. Therefore, important screening requirement such as screening concentrations, HTP, and low-volume abilities are also listed. Since many screening setups are described in literature, this review has a narrow focus on methods applied in protein formulation development, using therapeutic proteins, and references including correlating data to assess the predictive power of each method.

Excluded from Table 1 are publications that describe predictive methods not applied in protein formulation development or methods applied in protein formulation development that do not provide correlating data. Closely related to the topic but also out of scope of this review are screening techniques that focus solely on HTP and automation or the evaluation of protein molecules with best biophysical properties from a set of multiple development candidates. Recent literature on those topics is already available.[38-41] Nevertheless, in the context of this so-called developability assessment that is intended to minimize the risk of stability, solubility, or viscosity issues during preclinical and clinical development, several methods can also be useful in protein formulation

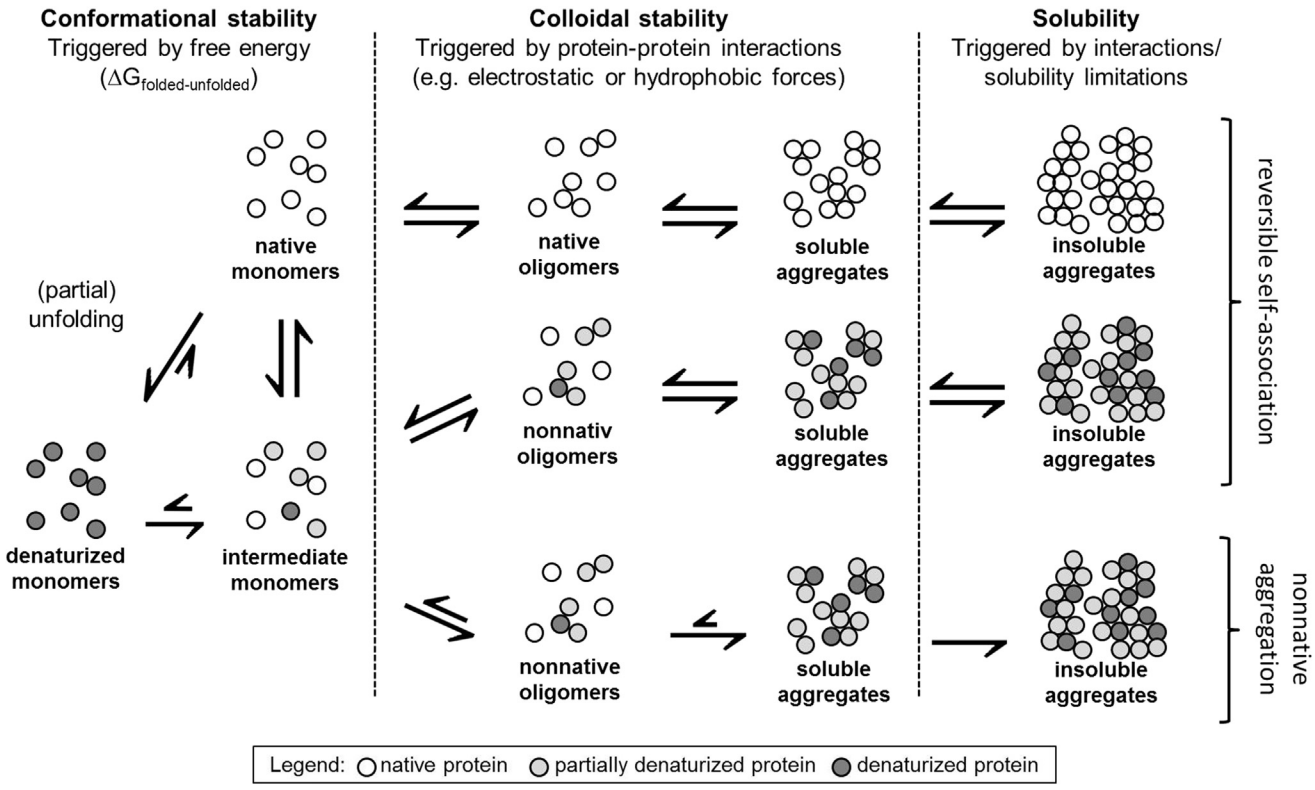

Figure 1. Simplified mechanisms and inter-relationship of protein unfolding, self-association, and aggregation.