

Review

Protein aggregation and its inhibition in biopharmaceutics

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Abstract

Protein aggregation is arguably the most common and troubling manifestation of protein instability, encountered in almost all stages of protein drug development. Protein aggregation, along with other physical and/or chemical instabilities of proteins, remains to be one of the major road barriers hindering rapid commercialization of potential protein drug candidates. Although a variety of methods have been used/developed to prevent/inhibit protein aggregation, the end results are often unsatisfactory for many proteins. The limited success is partly due to our lack of a clear understanding of the protein aggregation process. This article intends to discuss protein aggregation and its related mechanisms, methods characterizing protein aggregation, factors affecting protein aggregation, and possible venues in aggregation prevention/inhibition in various stages of protein drug development.

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Keywords: Protein aggregation; Aggregation mechanism; Protein refolding; Protein formulation; Protein stabilization

Abbreviations: A β , amyloid β peptide; BSA, bovine serum albumin; CAB, carbonic anhydrase B; CD, circular dichroism; rConIFN, recombinant consensus α -interferon; CspA, cold shock protein A; rhdNase, recombinant human deoxyribonuclease; DSC, differential scanning calorimetry; DTT, dithiothreitol; EDTA, ethylenediaminetetraacetic acid; aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; rFVIII, recombinant factor VIII; rFIX, recombinant factor IX; rFXIII, recombinant factor XIII; rhGCSF, recombinant human granulocyte colony stimulating factor; GDH, glutamate dehydrogenase; pGH, porcine growth hormone; rhGH, recombinant human growth hormone; GdnHCl, guanidine hydrochloride; GSH, reduced glutathione; GSSG, oxidized glutathione; rHA, recombinant human albumin; HP- β -CD, hydroxypropyl- β -cyclodextrin; HSA, human serum albumin; IFN- β , interferon- β ; IFN- γ , interferon- γ ; IgG, immunoglobulin G; IL-1 β , interleukin-1 β ; IL-2, interleukin-2; rhIL-1ra, recombinant human interleukin-1 receptor antagonist; IR, infrared spectroscopy; rhKGF, recombinant human keratinocyte growth factor; LDH, lactate dehydrogenase; LMW-UK, low molecular weight urokinase; Mab, monoclonal antibody; rhMGDF, recombinant human megakaryocyte growth and development factor; NMR, nuclear magnetic resonance spectroscopy; PAGE, polyacrylamide gel electrophoresis; PBS, phosphate buffered saline; PEG, polyethylene glycol; PVA, polyvinyl alcohol; RH, relative humidity; RP-HPLC, reversed phase HPLC; RNase A, ribonuclease A; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; SDS, sodium dodecyl sulfate; SEC-HPLC, size exclusion HPLC

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1. Introduction

The past two decades saw an explosive growth in biopharmaceutics, fueled by the advancement of

sensitive and high-throughput analytical methodologies. Yet, a rapid commercialization of protein drug candidates has not been fully realized due to the presence of many road barriers. One undisputable

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