Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 289 (2005) 1–30
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Review

Protein aggregation and its inhibition in biopharmaceutics

Wei Wang*

Biotechnology Division, Bayer HealthCare, 800 Dwight Way, Berkeley, CA 94701, USA

Received 13 May 2004; received in revised form 20 August 2004; accepted 12 November 2004

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/designed 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.

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

Abbreviations: Aβ, 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, quanidine 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-1β, interleukin-1β; 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

* Present address: Pfizer Inc., 700 Chesterfield Parkway West, Chesterfield, MO 63017, USA. Tel.: +1 636 247 2111; fax: +1 636 247 5030.
E-mail address: wei.2.wang@pfizer.com.

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.11.014

Contents

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