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Protein Characterisation and Quality Control

Chemical instability of protein pharmaceuticals: Mechanisms of oxidation and strategies for stabilization

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Abstract

Oxidation is one of the major chemical degradation pathways for protein pharmaceuticals. Methionine, cysteine, histidine, tryptophan, and tyrosine are the amino acid residues most susceptible to oxidation due to their high reactivity with various reactive oxygen species. Oxidation during protein processing and storage can be induced by contaminating oxidants, catalyzed by the presence of transition metal ions and induced by light. Oxidative modification depends on the structural features of the proteins as well as the particular oxidation mechanisms inherent in various oxidative species, and may also be influenced by pH, temperature, and buffer composition. Protein oxidation may result in loss of biological activity and other undesirable pharmaceutical consequences. Strategies to stabilize proteins against oxidation can be classified into intrinsic methods (site-directed mutagenesis and chemical modification), physical methods (solid vs. liquid formulations) and use of chemical additives. The optimum choice of chemical additives needs to be evaluated on the basis of the specific oxidation mechanism. Oxidation induced by the presence of oxidants in the system is referred to as a non-site-specific mechanism. Under such conditions, oxidation can be effectively inhibited by the appropriate addition of antioxidants or free radical scavengers. metal-catalyzed oxidation is a site-specific process, in which the addition of antioxidants may accelerate the oxidation reaction. Careful screening of chelating agents has been shown to be an alternative method for preventing metal-catalyzed oxidation. © 1995 John Wiley & Sons, Inc.

Citing Literature

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