OTHER STABILIZERS TO MINIMIZE DRUG DEGRADATION

The literature contains many examples of excipient stabilization phenomena with injectable drugs. The following are only a few examples. Sugars and polyols, such as ethylene glycol, glycerol, glucose, and dextran, at high concentrations, can inhibit the metal-catalyzed oxidation of human relaxin (23). All but dextran act as chelating agents in complexing transition metal ions, whereas dextran, which has a higher binding affinity to metal ions and undergoes depolymerization in a metal-catalyzed oxidation, protects relaxin by a radical scavenging mechanism.

Mannitol has been shown to inhibit the iron-catalyzed oxidation of Met-containing peptides (22,24). Mannitol is the most commonly used excipient in freeze-dried formulations often serving a dual role as a bulking agent and a stabilizer.

Fibroblast growth factors, both acidic and basic, possess nearly identical three-dimensional structures of 12 antiparallel β-strands arranged with approximate threefold-internal symmetry (25). Acidic fibroblast growth factor was found that its tendency to aggregate in solution was inhibited by a variety of polyanionic additives such as inositol hexasulfate or sulfate β-cyclodextrin and by a number of commonly used excipients such as sucrose, dextrose, trehalose, glycerol, and glycine. In all cases, these interactions between acidic fibroblast growth factor and various excipients resulted in an increase in the protein's Tm, the midpoint of the temperature of the transition from the folded to unfolded protein. Basic fibroblast growth factor has a major degradation pathway that involves not only aggregation and precipitation, but also a succinimide replacement of aspartate at position 15 of the protein sequence (26). Adjusting solution pH from 5 to 6.5 and storage at low temperatures will help to avoid this reaction.

A variety of co-solvents can stabilize proteins in solution because the co-solvent is preferentially excluded from surface interaction with the protein (27). Co-solvents behaving this way include glycerol and sorbitol. Polyethylene glycol (PEG) also is preferentially excluded from the protein, yet will still denature or destabilize proteins in solution.

OPTIMIZING PHYSICAL STABILITY

Physical stability problems are rare with small molecules except with sparingly soluble molecules that are borderline soluble in the formulation vehicle. However, proteins, because of their unique ability to adopt higher order secondary and tertiary three-dimension structures, tend to undergo a number of physical changes, independent of chemical modifications. Physical instability of proteins is sometimes a greater cause for concern and is more difficult to control compared to chemical instability. Many proteins, particularly when exposed to stressful conditions, for example, extremes in temperature, will unfold such that the hydrophobic portions become exposed to the aqueous environment. Such exposure will promote aggregation or self-association, possibly leading to physical instability and loss of biological activity since the interaction with the receptor site requires folded structures with correct conformation. The relationship of the different pathways of physical destabilization of proteins is shown in Figure 8-5.

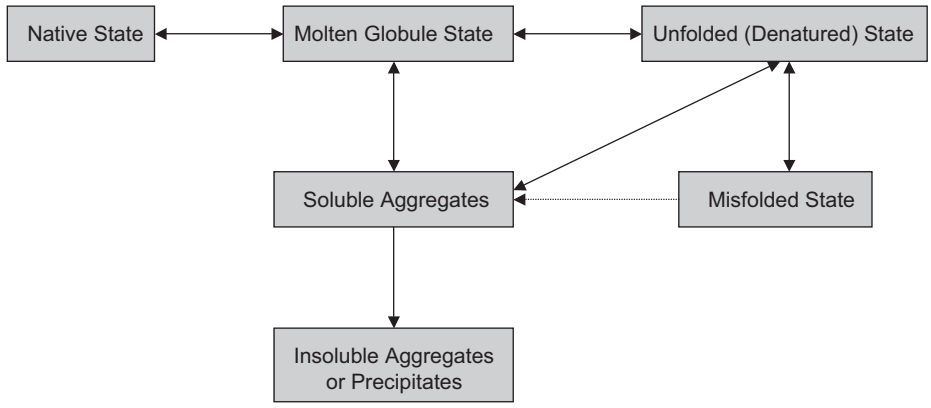

Figure 8-5 Schematic pathway of physical degradation of a protein. *Source*: From Ref. 28.