8 Formulation and stability of solutions

Ready-to-use solution dosage forms comprise the largest percentage of sterile dosage forms in the marketplace. The solution formulation must be resistant both to physical and chemical degradation. Drugs in solution are subject to several major mechanisms of degradation–hydrolytic, oxidative, photolytic, and, for proteins, covalent and noncovalent aggregations, deamidation, cleavages, oxidation, and surface denaturation reactions.

Optimal formulations can minimize or prevent these degradation reactions. Typical additives that help to stabilize injectable drugs in solution include surface-active agents, buffers, sugars, salts, antioxidants, chelating agents, competitive binders, and amino acids. Also, storing solutions at colder temperatures (i.e., refrigerated or even frozen) can help to minimize drug degradation. Drugs in solution also may have a tendency to form insoluble forms, therefore, physical stabilization is vitally important. This chapter focuses on formulation and stabilization of sterile drugs in solution, particularly biopharmaceutical drugs with more complex structures that present greater or a wider variety of challenges (1,2). There are many other primary literature resources for sterile solution drug formulation including an exhaustive updated review article on protein stability by Manning et al. (3). Proteins and other biopharmaceutical molecules not only readily degrade chemically, but also, and perhaps more readily, are prone to physical instabilities such as aggregation and precipitation.

OPTIMIZING HYDROLYTIC STABILITY

Hydrolysis is the reaction between water and the drug molecule resulting in the loss of potency and stability. One of the first major studies to be conducted in early drug dosage form development is to determine the solubility and stability of the drug in solution as a function of pH. Therapeutic proteins, being structurally more complex with secondary and tertiary structures and amino acids of differing properties being potentially exposed to an aqueous environment, experience a variety of potential degradation pathways over a broad pH range. While small molecules do not have this range of potential degradation pathways, many follow pH-stability profiles like the one depicted for penicillin in Figure 8-1. It is common for weak electrolytes to have "V-shaped" degradation versus pH profile where the objective with such molecules is to identify the pH range where drug stability is greatest. However, typically, the pH range where stability is greatest also is where drug solubility is lowest, again clearly shown in Figure 8-1. Solution pH and type of solvent used also significantly matters for minimizing protein aggregation, an example of which is shown in Figure 8-2 for recombinant human granulocyte colony-stimulating factor (rhGCSF).

Proteins and some small molecules may degrade in solution by more than one mechanism and each degradation mechanism has a different pH-stability profile. Tissue plasminogen activator undergoes dimer formation, loss of clot lysis or peptidolytic activity, each of which have slightly different pH-stability profiles. Glucagon in solution will degrade by hydrolysis, oxidation, and aggregation; the same is true for growth hormone. Insulin degrades by hydrolysis (deamidation) and formation of higher molecular weight forms as do many other protein molecules.

Hydrolysis or deamidation occurs with peptides and proteins containing susceptible asparagines (Asn) and glutamine (Gln) amino acids, the only two amino acids that are primary amines. The side chain amide linkage in a Gln and Asn residue may undergo deamidation to form free carboxylic acid. Deamidation can be promoted by a variety of factors including high pH, temperature and ionic strength (1).

Minimizing hydrolytic stability of drugs, particularly peptides and proteins, can be accomplished through one or more of the following approaches:

1. Optimization of amino acid sequence; that is, engineering protein structures to remove unstable amino acids or insert amino acid that sterically hinder Asn or Gln