Table 8.4 Important Components of Protein Formulations

Formulation Variables	Desired Attributes	Examples
pH	Provides good physical properties of protein, minimizes degradations	
Stabilizer	Inhibits degradations, effective at low concentrations	Surfactants, sugars, salts, antioxidants
Solubilizer	Improves the solubility, effective at low concentrations	Salts, amino acids, surfactants
Buffer	Good buffering capacity, stable to temperature change, stable to freezing, good safety record	Phosphate, acetate, histidine, glutamate
Tonicity modifier; bulking agent	Inert, good safety record	Sodium chloride, sorbitol, mannitol, glycine

manage by other formulation means. The optimization of pH is a simple but very useful solution for such problems. Most chemical reactions are also affected by pH, e.g., deamidation, cyclic imide formation, disulfide scrambling, peptide bond cleavage, and oxidation. Other functional excipients should also be carefully evaluated for the benefit of the product (e.g., use of sucrose to stabilize protein during lyophilization and storage in the dried solid).

A protein solution can typically be stabilized against aggregation and precipitation by optimizing solution pH and ionic strength; adding sugars, amino acids, and/or polyols; and using surfactants. Comprehensive evaluation of optimal pH and osmotic conditions is a key element of formulation development to prevent protein aggregation or precipitation. Irreversible aggregation due to denaturation can be prevented with surfactants, polyols, or sugars.

In many cases, nonionic detergents (surfactants) are added to increase stability and to prevent aggregation. The protein–surfactant interaction is hydrophobic, so these compounds stabilize proteins by lowering the surface tension of their solution and binding to hydrophobic sites on their surfaces, thus reducing the possibility of protein–protein interactions that could lead to aggregate formation. The nonionic detergents Tween 20 and Tween 80 can prevent the formation of soluble protein aggregates with surfactant concentrations below the critical micelle concentrations. Polysorbate (Tween) 80 added to IgG solutions stabilizes small aggregates and prevents them from growing into larger particles. Chelating agents can also be used to prevent metal-induced protein aggregation.

An analysis of common components of biological drugs formulations shows that most ingredients are used as the following:

1. Buffering agents to assure that the pH is maintained at the most stable level, and these include phosphates, citrates, and acetates