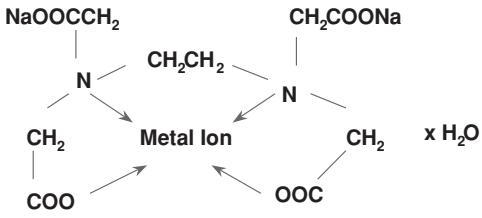

Range of concentrations: 0.004–0.05%

Figure 6-9 Structure of ethylenediaminetetraacetic acid (EDTA) disodium salt and how it binds metal ions.

do not absolutely remove all oxygen. The only approach for completely removing oxygen is to employ isolator technology where the entire atmosphere can be recirculating nitrogen or another nonoxygen gas.

Elaboration of the use of antioxidants and other approaches employed to stabilize oxygen-sensitive protein drugs in solution may be found in chapter 8.

Tonicity Agents

While it is the goal for every injectable product to be isotonic with physiologic fluids, this is not an essential requirement for small-volume injectables that are administered intravenously. However, products administered by all other routes, especially into the eye or spinal fluid must be isotonic. Injections into the subcutaneous tissue and muscles also should be isotonic to minimize pain and tissue irritation. Tonicity-adjusting agents most commonly used are electrolytes (sodium chloride most common), glycerin, and mono- or disaccharides.

Cryoprotectants and Lyoprotectants

These substances serve to protect biopharmaceuticals from adverse effects due to freezing and/or drying of the product during freeze-dry processing. Sugars (nonreducing) such as sucrose or trehalose, amino acids such as glycine or lysine, polymers such as liquid polyethylene glycol or dextran, and polyols such as mannitol or sorbitol all are possible cryo- or lyoprotectants. Several theories exist to explain why these additives work to protect proteins against freezing and/or drying effects. Excipients that are preferentially excluded from the surface of the protein are the best cryoprotectants, and excipients that remain amorphous during and after freeze-drying serve best as lyoprotectants. These concepts of additive stabilization of biopharmaceuticals during freezing, drying, and/or in the dry state are covered in chapter 10.

Competitive Binders

These additives are used if the active ingredient is known to bind excessively to container and manufacturing equipment surfaces. Such additives compete with the active ingredient for the surface-binding sites and keep the active ingredient from losing potency or activity in the dosage form. Historically, the best or most commonly used competitive binder has been human serum albumin (HSA) at concentrations ranging from 0.1% to 1.0%.

Concerns used to exist over potential viral contamination of natural substances such as HSA. Attempts to identify other potential competitive binding agents as effective as HSA have generally been unsuccessful, although it has been reported that Polysorbate 80, albeit at fairly high concentrations, inhibited recombinant Factor VIII adsorption at solid–water surfaces (17). Recombinant HSA removed the viral contamination fears and is now used in commercial products.

Other Additives

Other purposes for solute additives in sterile product formulations include bulking agents for freeze-dried products, suspending agents and wetting agents for suspensions, emulsifying agents for emulsions, viscosity-inducing agents for topical ophthalmic products, and the specialized polymers used to formulate advanced sustained-, prolonged-, extended-, delayed-, or