protein/peptide concentration must be understood. From preformulation studies, protein/peptide chemical and physical degradation pathways will be better understood so that the final formulation, manufacturing process, and packaging system will be rationally developed.

The second principle is that the route of administration must be known in order to select the final dosage form, vehicle, volume, and tonicity requirements for the product. For example, if the primary route of administration is intravenous, the vehicle has to be water although some water-miscible cosolvents can be used. The volume can be limitless (unless an antimicrobial preservative is part of the formulation in which case the volume is limited to 15 mL), and the tonicity does not necessarily have to be isotonic because the injected solution will be rapidly diluted. However, if the route of administration will be subcutaneous or intramuscular, then the vehicle can be aqueous or nonaqueous, the volumes are limited (usually no more than 2 mL for subcutaneous, 3 mL for intramuscular), and the tonicity of the product needs to be more tightly controlled since the product is not quickly nor readily diluted. The rate of injection also is a factor to be considered in the selection of final formulation ingredients in that some ingredients, including the protein/peptide itself, can be irritating and even cause local inflammatory reactions if injected too quickly and/or at too high a concentration.

The third principle involves careful screening for selection of solutes for solubilization, stabililization, and preservation, and tonicity adjustment must take place. This will be covered in detail in chapter 8.

The fourth principle asks what are the potential effects of the manufacturing process on the stability of the protein/peptide in the final formulation? Proteins/peptides cannot withstand terminal sterilization techniques (heat, gas, radiation) and, thus, must be sterilized by aseptic filtration. The filter used must be qualified so that it does not bind the protein/peptide. The effect of flow rate during filtration and filling on solution stability must be studied. Also, the effect of shear (mechanical stress) that is encountered during manufacturing must be known. Time limitations must be established from the time the protein solution is compounded until it is sterile filtered in order to avoid any increase in endotoxin levels from whatever the bioburden, however small, may be in the nonsterile solution.

The fifth principle concerns the importance of the selection of the most compatible container/closure system. Formulation scientists must appreciate that the container and closure system is just as important as the final solution formulation in assuring long-term stability and maintenance of sterility and other quality parameters of the product. Proteins and peptides are well known to adsorb to glass, so experiments must be designed to study this possibility and, if adsorption occurs significantly, additives such as albumin must be considered to reduce the adsorption. Glass leachates and particulates are possible and the formulator must be aware of this. Experiments must be conducted to ensure elimination of this potential problem. The choice of rubber closure is particularly important because of known potential for the closure to leach some of its own ingredients into a solution, to adsorb components of the protein/peptide formulation, to core (rubber particulates) when penetrated by a needle, to generate particulates, and to leak because of problems with the fitment on the glass vial, or resealability of the elastomer after needle penetration. Studies on adsorption of the protein to plastic surfaces will be necessary if the final product will be a plastic container. Even if plastic is not part of the primary container, protein–plastic compatibility studies should be done since plastic tubing, such as silicone or polyvinyl chloride, will be used in pharmaceutical process equipment (e.g., filling machines) and the final dosage form might be added to large volume parenteral solutions contained in plastic bags.

The final principle requires studies to be conducted to understand the effects of distribution and storage on the stability of the final product. Temperature excursions during shipping, mechanical stress, exposure to light, and other simulated shipping and storage conditions must be studied. From these studies, appropriate procedures for distribution and long-term storage of these relatively unstable dosage forms can be developed.

SPECIAL PROBLEM

Assume that you are a new formulation scientist, recently hired. You obviously want to make a favorable impression on your management and peers. You are given an assignment to develop a parenteral formulation of a brand new molecule. Let us assume that there is very little known