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Parenteral Medications
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Formulation of Small Volume Parenterals

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I. INTRODUCTION

Whereas a *parenteral* can be defined as a sterile drug, solution, or suspension that is packaged in a manner suitable for administration by hypodermic injection, either in the form prepared or following the addition of a suitable solvent or suspending agent [1], the term *small volume parenteral* (SVP) has been officially defined by the United States Pharmacopeia (USP) [2] as ". . . an injection that is packaged in containers labeled as containing 100 ml or less." The USP categorizes sterile preparations for parenteral use according to the physical state of the product as follows:

1. Solutions or emulsions of medicaments suitable for injection
2. Dry solids or liquid concentrates containing no additives which, upon the addition of suitable solvents, yield solutions conforming in all respects to requirements for injections
3. Preparations the same as described in class 2 but containing one or more additional substances
4. Suspensions of solids in a suitable medium which are not to be injected intravenously or into the spinal column
5. Dry solids which, upon the addition of suitable vehicles, become sterile suspensions

Although the term *sterile pharmaceuticals* is applicable to all injections (radiopharmaceuticals included), ophthalmic preparations, and irrigating solutions, this chapter emphasizes the formulation of injectable dosage forms.

The successful formulation of an injectable preparation requires a broad knowledge of physical, chemical, and biological principles as well as expertise in the application of these principles. Such knowledge and expertise are required to effect rational decisions regarding the selection of: (1) a suitable

vehicle (aqueous, nonaqueous, or cosolvent); (2) added substances (antimicrobial agents, antioxidants, buffers, chelating agents, and tonicity contributors); and (3) the appropriate container and container components. Inherent in the above decisions is the obligatory concern for product safety, effectiveness, stability, and reliability. This chapter focuses on the physical-chemical aspects of preparing a stable product in a suitable container recognizing that safety must be established through evaluation of toxicity, tissue tolerance, pyrogenicity, sterility, and tonicity, and efficacy must be demonstrated through controlled clinical investigations.

The majority of parenteral products are aqueous solutions, preferred because of their physiologic compatibility and versatility with regard to route of administration. However, cosolvents or nonaqueous substances are often required to effect solution or stability. Furthermore, the desired properties are sometimes attained through the use of a suspension or an emulsion. Although each of these dosage forms have distinctive characteristics and formulation requirements, certain physical-chemical principles are common. Those common principles will be discussed in a general manner and the differences distinctive of each system will be emphasized. It is important to recognize that the pharmaceutical products derived from biotechnology are on the increase and the formulation of these products requires some unique skills and novel approaches. An attempt will be made to cover some of the formulation approaches for proteins and peptides.

II. FORMULATION PRINCIPLES

A. Influence of the Route of Administration

Since parenteral preparations are introduced directly into the intra- or extracellular fluid compartments, the lymphatic system, or the blood, the nature of the product and the desired pharmacological action are factors determining the particular route of administration to be employed. The desired route of administration, in turn, places certain requirements and limitations on the formulations as well as the devices used for administering the dosage forms. Consequently, a variety of routes of administration (see Chap. 2) are currently used for parenteral products.

One of the most important considerations in formulating a parenteral product is the appropriate volume into which the drug should be incorporated. The intravenous route is the only route by which large volumes (i.e., greater than 10 ml) can be administered, although the rate of administration must be carefully controlled. Volumes up to 10 ml can be administered intraspinally, while the intramuscular route is normally limited to 3 ml, subcutaneous to 2 ml and intradermal to 0.2 ml.

The choice of the solvent system or vehicle is directly related to the intended route of administration of the product. Intravenous and intraspinal injections are generally restricted to dilute aqueous solutions, whereas oily solutions, cosolvent solutions, suspensions, and emulsions can be injected intramuscularly and subcutaneously.

Isotonicity is another factor that must be taken into consideration. Although isotonic solutions are less irritating, cause less toxicity and eliminate the possibility of hemolysis, it is not essential that all injections be isotonic. In fact, for subcutaneous and intramuscular injections hypertonic solutions

Sterile WFI and Bacteriostatic WFI are permitted to contain higher levels of solids than WFI because of the possible leaching of glass container constituents into the water during sterilization and storage. Bacteriostatic WFI should not be sold in containers larger than 30 ml to prevent injection of unacceptably large amounts of bacteriostatic agents (such as phenol and thimerosal).

Water Miscible. These cosolvents have already been discussed. Although water-miscible solvents are used in parenterals, principally to enhance drug solubility, it is important to mention that they also serve as stabilizers for those drugs that degrade by hydrolysis. Mixed-solvent systems may be irritating or increase toxicity, especially when present in large amounts or higher concentrations. A solution containing a high percentage of ethanol will produce pain on injection. It is also important to be aware that when such preparations are administered intravenously, too rapid an injection could result in the precipitation of the drug in the blood stream [25]. Excellent reviews of water-miscible solvents used in parenteral products have been published [16,17].

Nonaqueous. Drugs that are insoluble in aqueous systems are often incorporated in metabolizable oils. Steroids, hormones, and vitamins are incorporated in vegetable oils such as peanut, sesame, corn, olive, and cottonseed. Oil injections are only administered intramuscularly. There are strict specifications for the vegetable oils used in manufacturing intramuscular injections. Storage of these preparations is important if stability is to be maintained. For example, they should not be subjected to conditions above room temperature for extended periods of time. Although the oils used for injections are of vegetable origin, federal regulations require that the specific oil be listed on the label of a product, because some patients have exhibited allergic responses to certain vegetable oils.

Sesame oil is the preferred oil for most of the compendial injections formulated with oil. It is the most stable of the vegetable oils (except to light), because it contains natural antioxidants. Sesame oil has also been used to obtain slow release of fluphenazine esters given intramuscularly [41]. Excessive unsaturation of an oil can produce tissue irritation. The use of injections in oil has diminished somewhat in preference to aqueous suspensions, which generally have less irritating and sensitizing properties. Benzyl benzoate may be used to enhance steroid solubility in oils if desired. Table 4 summarizes the oil injections official in USP XXII.

C. Added Substances

Added substances such as antioxidants, buffers, bulking agents, chelating agents, antimicrobial agents, solubilizing agents, surfactants, and tonicity-adjusting agents must frequently be incorporated into parenteral formulas in order to provide safe, efficacious, and elegant parenteral dosage forms. Any additive to a formulation must be justified by a clear purpose and function. Hospital pharmacists who are involved in intravenous additive programs should be aware of the types of additives present in products that are being combined.

Pharmacopeias often specify the type and amount of additive substances that may be included in injectable products. These requirements often vary