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CHAPTER 41

Parenteral Preparations

Michael J Akers, PhD

Parenteral (Gk, *para enteron*, beside the intestine) dosage forms differ from all other drug dosage forms because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and upon pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally administered drugs are relatively unstable and generally high potent drugs that require strict control of their administration to the patient. Because of the advent of biotechnology, parenteral products have grown in number and usage around the world.

This chapter will focus on the unique characteristics of parenteral dosage forms and the basic principles for formulating, packaging, manufacturing, and controlling the quality of these unique products. The references and bibliography at the end of this chapter contain the most up-to-date texts, book chapters, and review papers on parenteral product formulation, manufacture, and quality control.

OVERVIEW OF UNIQUE CHARACTERISTICS OF PARENTERAL DOSAGE FORMS

Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

- All products must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.
- Products should be isotonic although strictness of isotonicity depends on the route of administration. Products to be administered into the cerebrospinal fluid must be isotonic. Ophthalmic products, while not parenteral, also must be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) essentially should be isotonic or at least very close to isotonicity. IV infusions must be isotonic.
- All products must be stable (not only chemically and physically like all other dosage forms, but also "stable" microbiologically, ie, sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelflife of the product).
- Products must be compatible (if applicable) with IV diluents, delivery systems, and other drug products co-administered.

The author recognizes the long time contributions of Dr. Kenneth Avis. Dr. Avis died in January 1999. Dr. Avis authored this chapter in Remington since 1965. To honor his memory, the author has maintained most of his organization of this chapter with new material and revised information added where appropriate.

FORMULATION PRINCIPLES

Parenteral drugs are formulated as solutions, suspensions, emulsions, liposomes, microspheres, nanosystems, and powders to be reconstituted as solutions. This section will describe the components that are commonly used in parenteral formulations focusing on solutions and freeze-dried products. General guidance also will be provided on appropriate selection of the finished sterile dosage form and initial approaches used to develop the optimal parenteral formulation.

VEHICLES

WATER—Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet United States Pharmacopeia (USP) specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas, and solid contaminating substances from water. These two methods for preparation of WFI and specifications for WFI are discussed later in this chapter. With the possible exception of freeze-drying, there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

WATER-MISCIBLE VEHICLES—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to solubilize certain drugs in an aqueous vehicle and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations usually are given intramuscularly. There are limitations with the amount of these co-solvents that can be administered because of toxicity concerns, greater potential for hemolysis, and potential for drug precipitation at the site of injection.[1] Formulation scientists needing to use one or more of these solvents must consult the literature (eg, reference [2]) and toxicologists to ascertain the maximum amount of co-solvents

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