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CHAPTER 84

Parenteral Preparations

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Dosage forms of drugs are designed to make it possible to introduce a drug into the body of a human or animal patient. Since the well-being, or even the life, of the patient may be affected, the dosage form must be designed and prepared in a manner intended to promote the safety of the patient. Concurrently, it is essential that the dosage form compliment or enhance the therapeutic effectiveness of the drug.

Parenteral (Gk, *para enteron* = beside the intestine) is the route of administration of drugs by injection under or through one or more layers of the skin or mucous membranes. Since this route circumvents these highly efficient protective barriers of the human body, exceptional purity of the dosage form must be achieved. The processes used in preparing it must embody good manufacturing practices that will produce and maintain the required quality of the product. New developments in process technology and quality control should be adopted as soon as their value and reliability have been established as a means for further improving the quality of the product.

History[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications thereof developed slowly during the next century and a half. In 1855 Dr Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Louis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), Stanislaus Limousin was developing a suitable container, the all-glass ampul. In the middle 1920s Dr Florence Seibert provided proof that the disturbing chills and fever which often followed the intravenous injection of drugs was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures.

Of the recent developments that have contributed to the high quality standards currently achievable in the preparation of parenteral dosage forms, the two that have probably contributed most are the development of HEPA-filtered laminar airflow and the development of membrane microfiltration for solutions. The former made it possible to achieve ultraclean environmental conditions for processing sterile products, and the latter made it possible to remove from solutions by filtration both viable and nonviable particles of microbial size and smaller. However, many other developments in recent years have produced an impressive advance in the technology associated with the safe and reliable preparation of parenteral dosage forms. The following list identifies a few of the events which have contributed to that development.

1926—Parenterals were accepted for inclusion in the fifth edition of the *National Formulary*.
1933—The practical application of freeze-drying to clinical materials was accomplished by a team of scientists at the University of Pennsylvania.
1938—The Food, Drug and Cosmetic Act was passed by Congress, establishing the Food and Drug Administration (FDA).
1944—The sterilant ethylene oxide was discovered.
1946—The Parenteral Drug Association was organized.
1961—The concept of laminar airflow was developed by WJ Whitfield.
1962—The FDA was authorized by Congress to establish current good manufacturing practices (CGMP) regulations.
1965—Total parenteral nutrition (TPN) was developed by SJ Dudrick.
1972—The Limulus Amebocyte Lysate test for pyrogens in parenteral products was developed by JF Cooper.

Administration

Injections may be classified in five general categories:

1. Solutions ready for injection.
2. Dry, soluble products ready to be combined with a solvent just prior to use.
3. Suspensions ready for injection.
4. Dry, insoluble products ready to be combined with a vehicle just prior to use.
5. Emulsions.

These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intraarticular and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the blood stream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal and intrathecal administration require the highest purity standards because of the sensitivity of nerve tissue to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is

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