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Parentral Dosage Form

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Abstract:
A parenteral dosage is a sterile drug product, which is presented in the form of solution, suspension, emulsion, or reconstituted lyophilized powder, suitable for administration by injection. Typical routes of administration of a parenteral dosage form include subcutaneous, intramuscular, and intravenous delivery. Parenteral dosage forms can also be administered via intrathecal, intracisternal, intraarterial, intraspinal, intraepidural, and intradermal routes to achieve local or systemic effects. This chapter outlines the aspects of pharmaceutical analysis that are required to monitor the quality of parenteral products from development stage through to the marketing phase. Emphasis is placed on analytical methods or techniques that are either unique to or require some modification to be applicable to this class of pharmaceutical product. The chapter also examines the sterility test, microbial limit tests, bacterial endotoxin test, and particulate matter test. A detailed presentation of cleaning validation—an increasingly critical aspect of pharmaceutical analysis—is presented with practical examples including all necessary calculations.

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I. INTRODUCTION

Parenteral dosage forms are those administered directly into body tissue rather than via the alimentary canal. "Parenteral" is derived from the Greek words para (beside) and enteron (the intestine) and also refer to subcutaneous, intramuscular or intravenous administration of drugs. Parenteral drug delivery can pose significant risk to the patient since the natural barriers of the body (gut, skin and mucous membranes) are bypassed. The highest standard for quality and purity must be maintained throughout dosage form manufacture to protect the patient from physical, chemical and microbial contaminants(1). A single contaminated vial out of a batch of thousands can seriously injure a patient (or worse). The minimum quality standard for pharmaceutical manufacturers are expressed in the current good manufacturing practices (cGMPs), which are constantly evolving as technology advances. Nonsconimal infections associated with parenteral drug therapy remain a significant issue(2).

There is an immediate onset of pharmacological action, unlike tablets which take approximately 45 minutes to have an effect once taken. This is extremely important in pain management or in case of psychotic patient who needs immediate treatment with an anti-psycotic agent. Also, unlike tablets, where a certain amount of drug is lost due to the body breaking it down or removing it from the bloodstream, drug administered by IV are 100 percent bioavailable to the body(3). Drugs are also administered by parenteral route if a targeted part of the body needs treatment. For example, if a patient is having issue with a knee, drugs can be injected directly into the knee for maximum effect. This technique also allows for some of the more toxic drugs to be targeted to specific sites without contaminated bloodstream. Finally, drugs are administered parenterally because they would be destroyed if administered orally. Many of the new drugs coming out of discovery are biologically based (proteins, monoclonal antibodies, etc.,), and the body simply sees these drugs as another source of protein if taken orally and releases enzymes to break them down for food(4). For these types of products, parenteral option is the only option for administration, although some can be applied topically. The drawbacks to parenteral products are as follows:

- Pain on injection
- Site must be sterilized before administration
- Bypasses the body's natural defenses against action
- Cannot be taken back once administered (e.g., wrong drug administered)

There are several different parenteral formulations that are available for parenteral administration; they are as follows:

- Solutions ready for injection
- Dry, soluble products (freeze-dried or powder fill) ready to be combined with a solvent prior to administration
- Suspensions ready for injection
- Dry, insoluble products ready to be combined with a solvent prior to administration
- Emulsions
- Liquid concentrates ready for dilution prior to administration.

PARENTERAL DRUG DELIVERY ROUTES

Subcutaneous(SC), Intamuscular(IM) and Intravenous(IV) are most common modes of administration. The fastest onset of action is achieved via the IV route since the injection is directly into the vein. Relatively large amounts of fluid can be delivered quickly and efficiently using the IV route. Slower and more variable onset of action typically occurs IM and SC administration since the drug must be absorbed into the bloodstream from the site of injection. Formulation can be designed to provide sustained-release profiles therefore reducing the number of injection required and the associated risk. Examples of "depot" formulations include DEPO-PROVERA Contraceptive Injection, which is administered deep IM every 13 weeks and depo-subQ provera 104 which is administered SC in the anterior thigh or abdomen every 12 to 14 weeks.

Intravitreal dosing has increased significantly in recent years because of new treatments for nevovascular wet age-related macular degeneration(AMD) such Lucentis (ranibizumb injection) and Macugen (pegaptanid sodium injection). The intradermal(ID) route is commonly used for very small volume injections(0.1 mL) such as the tuberculosis skin test [or tuberculin purified derivative(PPD) test](5). Intra-articular injection directly into joint synovial fluid are routinely used to administer corticosteroids or hyaluronic acid derivatives are used to relieve the symptoms of osteoarthritis. Intrathecal (intraspinal) and intaepidural injections are used to deliver anaesthesia, analgesic, antiinfective and some cancer therapies. Intracisternal administration is used to deliver critical therapeutics directly to the caudal region of the brain. Less common parenteral routes include intraarterial, intracardiac (e.g., epinephrine for cardiac resustication), intapleural, intraperitoneal and intraosseous (bone)(6).

Table 1 :- Parenteral Drug Delivery Routes

Route	Administrationvolume
Subcutaneous(SC)	Low, generally <2mL
Intramuscular(IM)	Medium, 2mL-5mL
Intravenous(IV)	High
Intravitreal	Low, generally <0.1mL
Intradermal(ID)	Low, 0.1mL
Intra-articular	Medium
Intrathecal	Low
Intraepidural	Low
Intracisternal	Medium
Intra-arterial	High
Intracardiac	Medium
Intrapleural	Medium
Intraperitoneal	High
Introsseous	Medium

Injectable Solutions

Injectable solutions are those products in which the drug, any added excipients and any added cosolvents are truly dissolve in the vehicle (usually water). These types of products have the potential to be injected by any route of administration into the body.

Injections should be sterile, isotonic and free from foreign particles, such as dust, fibres etc(7).

The formulation of parenteral products involves careful consideration of the following requirements:-

- Stability
- Sterility
- Free from pyrogen
- Free from foreign particle
- Isotonicity
- Specific gravity
- Chemical purity

Injectable Suspensions

Suspensions are the products where the active ingredient is extremely insoluble in the solution used to deliver it. Suspension are the formulated as such so when they are injected to a precise location, the drug crystals slowly dissolve, slow release of the drug to the surrounding capillaries where it is absorbed into the bloodstream.

The route of administration is typically intramuscular(IM), but they have also been administered by the subcutaneous, intradermal, intralesional or intra-articular routes. Suspensions can never be administered by the IV route, as the drug crystals would block capillaries and cause necrosis of tissues(8).

Injectable Emulsions

If an injectable drug is desired with a rapid onset of action but the drug is extremely insoluble in water, an emulsion might be a suitable alternative. Emulsions can be considered oil in water(o/w) or water in oil(w/o) emulsions, either small oil droplets in a water base or small water droplets in an oil base respectively, depending on the identity of the dispersed and continuous phase(9). Many emulsion are used cosmetically or as pharmaceutical creams to be administered topically on the skin. For injectable emulsions , the o/w form is traditionally used. In these types of products, the poorly water soluble drug is easily dissolved in oil (soyabean, cottonseed, peanut, etc.) and then suspended using high shear stress to turn the oil into fine droplets suspended in the water base.

This inherently unstable system is made possible through the use of an emulsifying agent, which prevents coalescence of the dispersed droplets. Parenteral emulsion are rare because it is necessary to achieve (and difficult) stable average droplets of less than 1µm to prevent emboli in the blood vessels(10).

Parenteral emulsion are used for several purposes:

1. Water-in-oil emulsion of allergic extracts(given subcutaneously)
2. Oil-in-water sustained-release depot preparation(given Intramuscularly)
3. Oil-in-water nutrient emulsions(given intravenously)

Formulation Development

The formulation development is a key area of product development that can determine patentability, lifecycle and the success of a pharmaceutical product. The goal of formulation development is to have a product that addresses all four requisites of an ideal product from a patient point of view. It should be:-

- Safe
- Efficacious
- Stable
- Acceptable/tolerable

From the point of marketing and commercial economics, the product should be easy to manufacture, relatively easy to use or present, and should have optimum shelf life at convenient storage condition, such as room temperature.

- Pre-formulation assessment
- Pre-formulation development
- Formulation development
- Process development
- Process compatibility
- Scale-up

Types of vehicle

Aqueous vehicles- The vast majority of injectable products are administered as aqueous solutions because of the physiological compatibility of water with body tissues. The high DC of water makes it possible to dissolve ionizable electrolytes and its hydrogen-bonding potential facilitates the solution of alcohols, aldehydes, ketones and amines. WFI is the solvent of choice for making parenterals. It must be prepared fresh and be pyrogen-free. It must meet all the chemical requirements for sterile purified water in addition the requirements for bacterial endotoxins.

Non-aqueous vehicles- Drugs that are insoluble in aqueous systems are often incorporated in vegetable oils such as peanut, sesame, corn, olive and cottonseed. Oil injections are only administered intramuscularly. There are strict specification for the vegetable oils used in manufacturing intramuscular injections(17). Sesame oil is the preferred oil for most of the compendia injections formulated with oil. It is the most stable of the vegetable oils(except to light), because it contains natural antioxidants.

Process Effect

To provide for the assurance that all quality attributes will be achieved on a repetitive basis, the following are essential:

1) The dosage form is designed with the knowledge of the desired functional and quality control characteristics of the finished product.
2) The qualification procedures are adequate to ensure reliability of equipment, effectiveness of the process and the integrity of the processing environment.
3) Personnel are trained in contamination control techniques.
4) There is adequate documentation of all procedures and tests.

Such a development sequence combined with validation requirements suggests a formalized program culminating in a product that can be reliably processed(21).

The processing responsible for developing formulations should have:

1. Scale-up procedures
2. Preliminary technical documentation
3. Design of processing and validation protocols
4. Use of process analytical technologies (PAT) for monitoring and control purposes
5. Qualification/validation runs
6. Final technical documentation and authorizations

II. CONCLUSION

The pareneteral route of administration is the most effective route for delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients.

Biopharmaceutical considerations are aimed at achieving the required drug concentration for pharmacological response and include the intended mode of administration, desired onset of action and the dose required. In formulation of parenteral products many formulation principles are follows such as influence of the route of administration, selection of vehicle, Added substances (buffers, antioxidants, antimicrobial preservatives, tonicity adjusting agents, bulking agents, chelating agents, solubilizing agents and surfactant), special types of parenterals (Suspensions, emulsions, liposomes, nanosuspensions, dried forms), formulation development process.

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