Chapter 8 | Shaifali Bhalla

Parenteral Drug Delivery

CHAPTER OUTLINE

OBJECTIVES

1. Describe the different routes of parenteral delivery and the factors influencing the absorption of drugs from different injection sites.
2. Define parenteral drug delivery and describe its advantages over other routes of drug administration.
3. Describe the characteristics of parenteral dosage formulations.
4. Explain the purpose of components of parenteral formulations: vehicle, co-solvent, buffer, tonicity agent, preservative, protectant, surfactant, and antioxidant.
5. Differentiate among dosage formulations available for parenteral administration and explain how drug is released from various injectable preparations.
6. Examine the application of drug-targeting systems in parenteral drug delivery.
7. Describe the use of specialized parenteral delivery devices.

Overview of Parenteral Delivery

Parenteral delivery has been defined by the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration (FDA) as the administration of a drug by injection, infusion, or implantation.[1] *Parenteral delivery* means introducing drugs into the body outside of the enteral route; that is, outside of the gastrointestinal tract.[2] This delivery route can also be used to administer drugs directly to specific body organs and tissues to produce a desired therapeutic effect at a target site while minimizing systemic side effects.

Common routes of parenteral administration are described in the following sections. Table 1 lists the routes of parenteral administration.

Common Routes of Parenteral Delivery

Intravenous Injection

Drugs administered by the intravenous (IV) route provide the fastest onset of action because they are injected directly into the systemic circulation, and there is no lag time or absorption phase for the drug. Drugs administered by the IV route exhibit 100% **bioavailability**.

The three most common methods by which drugs are delivered IV are IV bolus, continuous IV infusion, and patient-controlled analgesia.

- IV bolus is IV administration of a dose of a drug all at once, typically in a few minutes, within or into a vein or veins.
- IV drip or IV infusion is IV administration of a drug within or into a vein over a sustained period. For a drug with a narrow therapeutic range, IV infusion can control the amount of drug administered over a fixed time period by controlling the infusion rate. Loading doses are administered at the start of IV infusions for drugs that have long biological half-lives. This quickly achieves effective serum concentrations of the drug. Steady-state serum concentrations can be maintained by giving the drug as a continuous IV infusion at a constant rate over longer periods.[3]

Table 1.
Routes of Parenteral Administration*

Name	Definition/characteristics of administration
Epidural	Administration on or over the dura mater
Intra-articular	Administration within a joint
Intra-arterial	Administration within an artery or arteries
Intracardiac	Administration within the heart
Intracavitary	Administration within a pathologic cavity, such as occurs in the lung in tuberculosis
Intradermal	Administration within the dermis
	Injection is given into the dermal layer of the skin.
Intralymphatic	Administration within a lymph channel or node
Intramuscular	Administration within a muscle
	Injection is given into the muscle fibers of the upper arm or gluteal area.
Intraosseous	Administration directly within the marrow of a bone
	The needle is injected right through the bone and into the soft marrow interior.
Intraperitoneal	Administration within the peritoneal cavity
Intraspinal	Administration within the vertebral column. Refers to both epidural and intrathecal routes.
Intrathecal	Administration within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles. Injection is into subarachnoid spaces.
Intravenous	Administration within or into a vein or veins
	Injection is given directly into the vein.
Intracerebroventricular	Administration within a ventricle of the brain
Intravitreal	Administration within the vitreous body of the eye
Subcutaneous	Administration beneath the skin; also known as hypodermic injection
	Injection is given below the epidermis and dermis layer of the skin.

*From Center for Drug Evaluation and Research.[1]

The preferred route for analgesics is a continuous IV infusion, because it produces less fluctuation in serum concentrations of the drug than do intermittent intramuscular (IM) injections.

- Patient-controlled analgesia is designed to deliver IV bolus doses in addition to a slow, continuous IV infusion.[4] This method allows patients to self-administer analgesics as needed for breakthrough pain. The drugs most commonly delivered by this route are narcotic analgesics such as fentanyl,[5] methadone,[6] and morphine.[3]

Drugs that are commonly administered by the IV route are analgesics, general anesthetics, antiviral agents, antibiotics, immunosuppressive agents, antifungal agents, antibacterial agents, antihypertensive agents, vasodilators, antiarrhythmic drugs, and chemotherapeutic agents.

The IV route is not without adverse effects. IV injections are administered directly into the venous circulation, and hence highly vascular and perfused organs, such as the heart, lungs, liver, and kidney, rapidly acquire the drug. In some cases, however, a sudden increase in serum drug concentration may lead to toxicity. This can be prevented by giving a slow IV bolus injection. Other drugs with poor aqueous solubility may precipitate from solution and produce an embolism. Proper selection of the diluent and slow IV administration allows for proper mixing of the drug in the circulation. Finally, some vehicles may cause adverse effects in pediatric patients. For example, phenobarbital sodium is dissolved in propylene glycol, which may cause hyperosmolality in infants.[7] In addition, because the alcohol and aldehyde dehydrogenase pathway that metabolizes propylene glycol is not well developed in infants and children younger than 4 years, repeated use of IV injections containing propylene glycol can lead to toxicity.

Lipid-soluble drugs like diazepam can easily cross the blood-brain barrier and are effective when given by the IV route. However, lipid-insoluble drugs are ineffective when given by the IV route if the desired target site of action is in the brain. Thus, lipid-insoluble drugs often need to be administered by specialized routes of delivery that bypass the blood-brain barrier. These specialized routes include intraspinal and intracerebroventricular injection, which will be discussed later in this chapter.

Intramuscular Injection

Drugs that may be irritating to the subcutaneous (SC) tissues are administered via IM injection. The IM injection site is usually the deltoid muscle of the upper arm or the vastus lateralis muscle in the anterolateral aspect of the middle or upper thigh. A needle long enough to reach deep into the muscle must be used and should be inserted at an angle of 80 to 90 degrees. Because of the time required for the drug to become available from the muscle to the systemic circulation, IM injections have a longer time to onset of effect and

a longer duration of action than IV injections. The rate of absorption and extent of availability of drugs depend on biopharmaceutical factors such as formulation characteristics and the physiology of the injection site.[8] IM injections are safer than IV injections; however, incorrect IM administration techniques can result in blood clots, scarring of the skin, abscesses, and nerve damage leading to paralytic conditions.

Different formulation and delivery strategies are used for the administration of water-insoluble drugs. Water-insoluble drugs are solubilized in solvents such as propylene glycol and mineral oil for injection. These nonaqueous vehicles stay at the site of injection and release the drug slowly, which results in prolonged serum drug concentrations and a longer duration of action. Sparingly soluble ionizable drugs prepared as solutions for injection must be buffered to physiologic pH.[8] Precipitation of the drug may occur as a result of this change in pH. Absorption may be prolonged as the drug redissolves in tissue fluids.[9,10]

Another factor affecting drug absorption is the blood flow to the injection site. IM injections given into the deltoid muscle in the arm are absorbed faster than gluteal injections. This difference is likely due to the increased blood flow in the deltoid muscle and lower blood flow in the gluteus maximus muscle, which has a high content of adipose tissue. Slower rates of absorption after gluteal injections were seen in a higher percentage of women than men.[8,9,11] Moreover, the injection volume is limited depending on the site of administration. Large muscles like the gluteal muscle can effectively absorb 4 to 5 mL of injected solution, whereas smaller muscles like the deltoid muscle in the arm can absorb up to 2 to 3 mL.[11]

IM injections are available in immediate-release formulations as well as depot formulations for sustained release. Examples of these formulations are described in the following sections.

Immediate-Release Intramuscular Injection

Water-soluble drugs are dissolved in aqueous vehicles and prepared as solutions for injection. On IM injection, they distribute into the circulation and release the drug rapidly. The usual onset of action is 30 minutes, and the duration of action depends on the drug's half-life. One example is thyrotropin alfa for injection (Thyrogen®), a sterile, lyophilized product that forms a solution after reconstitution and is injected IM for immediate release.[12,13]

Depot Formulations for Intramuscular Injection

Depot injections release the drug slowly and maintain serum drug concentrations for a longer duration. Depot injections are long-acting dosage formulations indicated for maintenance treatment rather than initiation of therapy. Depot formulations are available as oil-based injections (eg, fluphenazine enanthate and estradiol cypionate), aqueous suspensions (eg, penicillin G procaine and penicillin G benzathine, methylprednisolone acetate [Depo-Medrol®], and medroxyprogesterone acetate/estradiol cypionate [Lunelle®]), and microspheres (eg, leuprolide acetate [Lupron Depot®]).

An example of a long-acting depot formulation containing the drug in the form of salt is fluphenazine enanthate (Prolixin Enanthate® injection).[14] It is indicated for the maintenance treatment of nonagitated patients with chronic schizophrenia. Fluphenazine enanthate is water insoluble and is therefore dissolved in oil. On IM administration, it forms a depot of the drug dissolved in oil.[15,16] The drug is released slowly from the depot and enters the blood circulation. Dosing intervals vary from 2 to 6 weeks and are determined by the response of the patient to therapy.

An example of an aqueous suspension acting as a depot is penicillin G benzathine/penicillin G procaine suspension (Bicillin® C-R). The injection contains water-insoluble drugs suspended in an aqueous vehicle. It is a stabilized, long-acting aqueous suspension containing sodium citrate buffer and the suspending agents lecithin and carboxymethylcellulose (CMC). The active ingredients are hydrolyzed in the blood to penicillin. The slow absorption from the IM injection site and subsequent hydrolysis leads to prolonged serum levels of penicillin, which allows dosing every 2 to 3 days when repeated doses are needed.[17]

Encapsulating drugs in polymer matrices and biodegradable microspheres provides a way to maintain therapeutic levels of the drugs for a longer time. An example of a polymer-based microsphere system used in depot formulations is leuprolide acetate for depot suspension (Lupron Depot®). Lupron Depot® microspheres are indicated for IM injection and are available in a prefilled dual-chamber syringe. The drug chamber contains leuprolide acetate, incorporated in a biodegradable polymer of polylactic acid and D-mannitol.[18] The dilu-

ent chamber contains sodium CMC, water for injection, D-mannitol, polysorbate, and glacial acetic acid to maintain pH. The microspheres form a depot at the site of injection, and the drug is released slowly at a constant rate as a result of the hydrolysis of the polymer. Depending on the prescribed dose, Lupron Depot® can be injected once every 1 to 4 months.[19] Other examples of microsphere formulations are discussed in detail in the section Polymeric Biodegradable Systems for Parenteral Administration.

Subcutaneous Injection

SC injections are given into the SC or fatty layer of tissue below the epidermis and dermis. These injections are also referred to as *hypodermic injections* because the drug is administered beneath the skin.[1,8] SC injections are usually small-volume injections and are administered at an angle of 45 degrees to the skin. They can generally be self-administered and are easy to administer with minimum discomfort. Patient education regarding proper SC injection techniques is important to minimize infection and other local adverse effects.

Drugs are absorbed at a slower rate after SC injections than after IM injections because there is less blood flow to the fatty tissue below the skin than to the muscle. The rate of absorption also depends on the penetration coefficient and the amount of drug at the site.[2] Absorption takes place through the capillary wall in the connective tissue. Penetration of drugs into the connective tissue depends on the concentration gradient of drugs across the capillary wall and connective tissue, the area of the membrane exposed to the solution, and the distance of diffusion. Medications that are injected by this route include vaccines, heparins, insulins, growth hormone, and epinephrine.

Intradermal Injection

Intradermal (ID) injections are administered within the dermis layer of the skin,[1] the upper layer of the skin just below the epidermis. ID injections are very-small-volume injections (0.1 mL) and are used to deliver drugs to produce local effects. Examples of uses of ID delivery are injections for skin testing, antigen delivery to evaluate for allergic reactions, and administration of vaccines (eg, influenza vaccine).[8] ID administration of vaccines has been shown to enhance immune response more effectively than SC administration.[20] Thus, the ID route may target lymph nodes more efficiently than the SC route.

Specialized Routes

Intrasynovial

Intrasynovial injection is administration of a drug directly into the synovial cavity of a joint.[1] This form of parenteral delivery is used for the treatment of inflammation in patients with rheumatoid arthritis and collagen vascular diseases. Drugs administered by this route include methylprednisolone acetate and triamcinolone acetonide, which are available as injectable suspensions. The duration of action is significantly increased when a drug is injected intrasynovially. Repeated injections, if given, are generally administered no more frequently than every 3 months.

Intra-Articular

Intra-articular injection is administration of a drug within a joint. Intra-articular administration of local anesthetics and adjuvants is an alternate method for postoperative analgesia. Patients who have undergone ligament reconstruction and experience moderate to severe postoperative pain can benefit from intra-articular injection of ropivacaine and morphine via a catheter in the knee joint. This approach decreases the need for supplemental IV morphine.[21] For the first few hours after intrasynovial or intra-articular injection, local discomfort in the joint may occur, but this is rapidly followed by effective relief of pain and improvement of local function.

Intraspinal

Intraspinal delivery is administration of drugs directly into the vertebral column.[1] It includes epidural and intrathecal injection. With epidural injection, drug is delivered to the outside of the dura and not into the cerebrospinal fluid. Thus the clinical effects are more localized to the spinal cord. Drugs can be delivered by a single bolus injection or as a continuous infusion (Figure 1).[22] Advanced primary or metastatic cancer pain, thoracic and lumbar pain, nerve root injuries, and neuropathic pain are treated with intrathecal injections and infusions of opioids, local anesthetics, clonidine, baclofen, and other drugs used for the treatment of chronic pain, cancer pain, and intractable spasticity.[23]

Morphine sulfate extended-release liposome injection (DepoDur®) is a special liposomal dosage formulation injected into the epidural space.[24,25] DepoDur® injection is a sterile, preservative-free suspension of multivesicular liposomes containing morphine sulfate present as a suspension in 0.9% sodium chloride solution. On epidural injection, the multivesicular liposomes release morphine

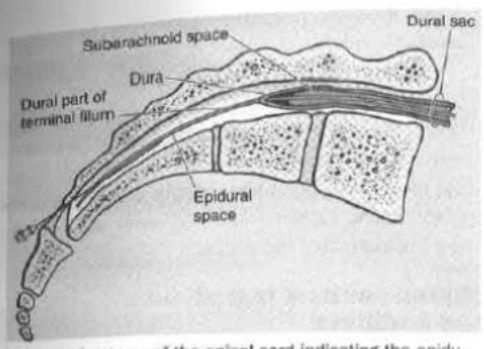

Figure 1. Anatomy of the spinal cord indicating the epidural space and the **subarachnoid space**. (Reprinted with permission from Moore and Dalley.[97])

systemically and into the intrathecal space through the meninges at a slow rate over a prolonged period.[26] When given as a single dose 30 minutes preoperatively, DepoDur® has produced persistent analgesia for 48 hours postoperatively. The distribution, metabolism, and elimination pattern of liposomal morphine sulfate is similar to that after delivery of other parenteral morphine formulations. DepoDur® is designed for single-dose administration and does not accumulate significantly in patients with impaired renal or hepatic function. Other examples of liposomal formulations are described in detail in the section on special IV delivery systems.

Intrathecal and Intracerebroventricular

Intrathecal injection is the administration of drugs within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.[1] When lipid insoluble drugs are needed to treat some neurologic disorders, it is necessary to bypass the blood-brain barrier and deliver drugs directly into the brain. This can be achieved by intrathecal administration, in which drugs are injected into the cerebrospinal fluid surrounding the spinal cord, or by direct injection of drugs into the brain by intracerebroventricular injection, which is an invasive approach.[27] Intrathecal injections can be given as a single dose or as continuous infusion via an indwelling catheter. Drugs that require long-term intrathecal infusion can be delivered by intrathecal catheters connected to an SC implanted infusion device. The intrathecal route is commonly used to deliver small lipophilic molecules for pain management. Opioid analgesics such as morphine, hydromorphone, and fentanyl are effective when delivered by the intrathecal route.[28,29]

Intracerebroventricular administration is commonly used for chemotherapy treatment of gliomas or for delivering neurotrophic factors to many areas of the central nervous system.[30]

Intra-Arterial

The intra-arterial route is used to reduce drug exposure to the systemic circulation and to increase drug concentrations in the areas supplied by the artery into which the drug is injected. The intra-arterial route is used to deliver chemotherapeutic drugs such as cisplatin to treat head and neck cancer and to inject vasopressin to control gastrointestinal bleeding. New and safe angiographic techniques enable the placement of microcatheters into small arteries under direct vision using fluoroscopy.[31] However, intra-arterial injections have been associated with embolism, occlusion of arteries, and drug toxicity.

Advantages and Disadvantages of Parenteral Delivery

The main advantages of parenteral delivery are the following:

1. It can be used in patients who are unable or refuse to take medications by mouth.
2. Rapid and complete absorption of drugs from the systemic circulation takes place if the drug is administered IV as a solution.
3. **First-pass hepatic metabolism** is avoided, which leads to improved bioavailability for drugs that undergo significant first-pass metabolism after oral administration.
4. Smaller doses can be used with IV administration than with oral administration.
5. The parenteral route avoids drug degradation in the gastrointestinal tract. A large number of proteins are administered parenterally.
6. IV administration of drugs has been shown to provide a more predictable pharmacokinetic and pharmacodynamic profile for drugs than oral administration.
7. The route of parenteral delivery can be tailored to the needs and condition of the patient. Direct injection of the drug by the IV route is beneficial in emergency situations when the need for therapeutic action is immediate. For a slower onset and a longer duration of action, drugs can be administered IM.

Although parenteral delivery is preferred for many drugs, administering drugs by this route has some disadvantages:

1. Aseptic precautions must be followed to avoid contamination and minimize the risk of infection when the drug is being administered.
2. Most often, parenterally delivered drugs are administered by trained health care professionals in clinics and hospitals. This is more inconvenient and costly than self-administration of drugs.
3. For self-administration of all parenteral dosage formulations, patients must be adequately trained, which can be time consuming and resource intensive.
4. Manufacturing is also more costly than the manufacture of conventional tablets and capsules.
5. Once drugs are injected IV, they cannot be removed easily from the bloodstream. This can be a problem if an incorrect dose or drug is administered, because adverse effects can result. Dialysis or hemofiltration can be used to remove excess drug, but these are complicated procedures and can cause discomfort to the patient.
6. Injections may be accompanied by pain and infection at the site of injection.

General Characteristics of Parenteral Delivery Systems

Certain requirements must be satisfied for dosage formulations and delivery systems to be approved for injection.

1. They must be free of pyrogens. Because of microbial contamination, pryogens or fever-producing substances may be found in parenteral formulations. These substances can lead to complications after the formulation is injected; therefore, all parenteral formulations must be pyrogen free.
2. They must be sterile. All parenteral formulations must be free of all microbial organisms. Sterilization is the process by which all living and pathogenic organisms are destroyed and removed from the formulation. The most common techniques used to sterilize injection formulations and parenteral implants are steam and dry heat. If the drug is heat labile, gas sterilization by ethylene oxide, filtration using filters with various pore sizes for different formulations, and ionizing radiation techniques may be used. The individual components of dispersions or suspensions such as drugs, suspending agents, stabilizers, and tonicity agents must be sterilized separately and then combined in the formulation.
3. They must be isotonic. Tonicity-adjusting agents decrease the hemolysis of blood cells and reduce pain and irritation at the injection site. Large-volume injectable preparations must be isotonic with blood (ie, must have the same **osmolality** as blood or other body fluids). Large-volume parenterals are given to prevent electrolyte imbalance.[32]

Pharmaceutical Ingredients and Additives

Parenteral dosage formulations are composed of the following pharmaceutical ingredients and additives:

1. Vehicles
2. Co-solvents
3. Other additives: buffers, tonicity-adjusting agents, antimicrobial preservatives, protectants, surfactants, antioxidants

Vehicles

Vehicles for injections must be sterile as well as particle and pyrogen free. Examples of vehicles and essential vehicle characteristics for water- and oil-based injections are shown in Table 2.

Co-Solvents

Co-solvents are used to solubilize drugs that must be injected as solutions. Drugs with poor water solubility may be formulated with co-solvents such as ethanol, propylene glycol, and polyethylene glycol (PEG) 300. Co-solvent solutions are confined to IV and IM use. For IV administration, the injection must be administered slowly to prevent precipitation of the drug and to avoid cardiovascular toxicity from the co-solvent. If drug precipitation occurs during IM injection, the dosage formulation tends to act like a depot injection, which results in delayed absorption of the drug. Precipitation may also result in incomplete absorption of the drug from the precipitate, which leads to lower therapeutic levels of the drug and pain at the injection site.

A good example of co-solvent use is phenytoin injection. Phenytoin (sodium injection) is a clear, colorless solution containing propylene glycol, ethanol, and water for injection. Phenytoin is insoluble in water; therefore, propylene glycol and ethanol are used as co-solvents to dissolve phenytoin and produce a clear solution for IV

Table 2.
Vehicles for Injections

Vehicle	Examples	Characteristics
Aqueous injections	Sterile water for injection	Distilled and sterilized
	Sterile saline for injection	Used as a final-step solvent for sterile solids or for dilution of sterile solutions
	Bacteriostatic water for injection	Distilled and sterilized Contains preservative Used for multiple-dose containers Limited use in large-volume parenteral infusions Contraindicated for use in neonates Contraindicated for epidural and intrathecal injections
	Sterile water for irrigation	Purified, pyrogen free, and sterile Does not have to meet particulate standards for large-volume parenteral infusions Typically available in a volume of 1 L or more in a screw-cap container
Oil-based injections	Oils for injection Sesame, corn, peanut, mineral, soybean, and cottonseed oils	Pure, sterile, low free fatty acid content Used for intramuscular depot injections Allergic reactions can occur Vehicle composition must be listed on label

injection. Sodium hydroxide or hydrochloric acid is used as buffering agents to adjust the pH of the injection to 12. Precipitation or crystallization of phenytoin may occur if the pH is altered or if the co-solvents or vehicles are modified. The drug is administered slowly as an IV bolus injection, at a rate no faster than 50 mg/min in adults to prevent cardiovascular adverse effects. The alkalinity of the injection can result in irritation, pain, and inflammation at the injection site. Hence, each injection of phenytoin should be followed by a 0.9% sodium chloride IV infusion through the same catheter or needle to avoid irritation at the site of injection.[33] Alternatively, phenytoin can be administered as an IV infusion over 15 to 30 minutes. To avoid precipitation, phenytoin should be diluted with 0.9% sodium chloride or lactated Ringer injection. Use of an inline filter is recommended with such infusions. Phenytoin injection should not be administered IM because of its erratic absorption and tissue reactions at the IM injection site. Fosphenytoin is a prodrug of phenytoin that is freely soluble in water and hence does not produce the discomfort and erratic absorption associated with phenytoin.

Other Additives

Buffers

Major concerns during parenteral administration of drugs are maximization of the solubility and stability of drugs and improvement of patient comfort during the injection process. Weak acids and weak bases are used as buffers to maintain an optimal pH of the injection, which can enhance the solubility and stability of some drugs. Drug solubility and absorption also depend on the formulation pH. Therefore, buffers play an important role in the absorption of drugs from injection sites. Examples of commonly used buffers are citric acid/monosodium citrate, acetic acid/sodium acetate, phosphoric acid/monosodium phosphate, benzoic acid/sodium benzoate, and tris(hydroxymethyl)aminomethane (TRIS buffer). Buffers such as citrate and TRIS undergo minimal changes in pH during freezing cycles in **lyophilization**. Therefore, the addition of low concentrations of these buffers is most suitable for lyophilized formulations.[34]

One example of the use of buffers is in ondansetron hydrochloride (Zofran®) injection. Zofran® is available as a clear, colorless, sterile solution for injection. The active ingredient, ondansetron, is buffered using citric acid monohydrate and sodium citrate dehydrate to minimize patient discomfort at the injection site while maintaining drug solubility. Zofran® is indicated for IM or IV injection and should not be mixed with any other injections, because precipitation may occur as a result of changes in pH.[35]

Tonicity-Adjusting Agents

Isotonicity is needed to reduce pain and irritation and to prevent hemolysis of blood cells at the site of injec-

tion. Injection routes that require isotonicity are intra-articular, ID, and central nervous system routes such as intrathecal, epidural, and intracerebroventricular. As noted earlier, large-volume parenteral injections must be isotonic with blood; that is, their osmolality must be the same as that of blood or other body fluids. Large-volume parenteral injections are single-unit doses of more than 100 mL that generally contain water, dextrose, and sodium. Amino acids are often added. Due to the large volume being administered to the patient, preservatives should not be used, because large amounts may cause toxicity.[2,32] Examples of solutions that are isotonic are 5% dextrose in water (D5W), glycerin, mannitol, and 0.9% sodium chloride.

Antimicrobial Preservatives

Antimicrobial preservatives are used in multiple-dose vials to prevent microorganism growth. Most preservatives are bactericidal or fungistatic. Preservatives are used to prolong the shelf life of formulations. Appropriate amounts of preservatives must be selected for parenteral formulations, because large amounts can cause toxicity and irritation after injection. Commonly used preservatives include benzyl alcohol, benzethonium chloride, methylparaben, chlorobutanol, chlorocresol, propylparaben, and thimerosal. Epidural and intrathecal injections should be preservative free to prevent nerve damage.

Protectants

Protein-based therapeutic agents are more susceptible to degradation, which results in loss of biological activity, shorter shelf life, and possibly increased side effects. Hence, proteins are formulated as freeze-dried powders to preserve the stability of the drug. Protectants are used to safeguard proteins during the four stages of lyophilization (freeze drying): freezing, drying, storage, and rehydration.[36] These agents stabilize the structure of protein and peptide drugs through the freezing and drying stages. During the freezing stage of lyophilization, the protein solution is filled into a glass vial and cooled in a lyophilizer. As the vial cools to a temperature below the freezing point, pure ice crystallizes out of the solution and the liquid becomes more concentrated. During this freeze-concentration process, a glass transition temperature is reached, and the protectants form a glassy matrix in the interstitial spaces between the crystals.[36] The stabilizing effect is attributed to hydrogen bonding between the protectants and protein molecules. This mimics the hydrogen bonding between protein molecules and water that is being replaced during the freeze-drying process. The drug and water molecules are immobilized in the viscous glassy matrix. This also results in stabilization of the formulation, because very high activation energies are required for any reaction to occur. Examples of commonly used protectants are sugars like glucose, lactose, and trehalose.[34]

Surfactants

Surfactants are used for solubilization of lipid-soluble drugs, for preparation of oil-in-water emulsions, and as wetting agents. Examples of surfactants are lecithin, various phospholipids, polysorbate (Tweens®), and polyoxyethylene castor oils such as Cremophor® EL. Lecithin is a mixture of triglycerides and phospholipids and is used as a surfactant in fat emulsions. Egg and soybean phospholipids are common sources of lecithin. Tween® series (Tween® 20 and 80) and sorbitan mono-oleate are also used as surfactants for parenteral use. Cremophor® EL, or polyoxyethylated 35 castor oil, is a nonionic surfactant used to solubilize cyclosporine, paclitaxel, and fat-soluble vitamins for injections. A major disadvantage of Cremophor® EL, however, is its potential to cause serious hypersensitivity reactions.

Cyclosporine injection, (Sandimmune® Injection) is available as a 5-mL sterile ampule for administration as a slow IV infusion. Absorption of cyclosporine from the gastrointestinal tract after oral administration is variable and incomplete; hence it is formulated as an injection. Sandimmune® contains Cremophor® EL and alcohol and requires further dilution with 0.9% sodium chloride injection or D5W injection before use. Alcohol is used as a co-solvent with Cremophor® EL.[37] Nitrogen replaces the air in the ampule to improve the stability of cyclosporine by preventing oxidation. Cremophor® EL can cause an anaphylactic reaction; therefore, the patient must be observed for the first 30 minutes after the start of the IV infusion. If anaphylaxis occurs, the infusion should be stopped, and the patient should be treated with oral cyclosporine. Cremophor® EL or polysorbate 80 can also cause phthalate stripping from devices made of polyvinyl chloride. Polyvinyl chloride is a plastic polymer used to provide flexibility in various medical devices, and one of its components, di(2-ethylhexyl)phthalate, can leach out of medical devices into solutions that are in

contact with the plastic.[37,38] This is a major concern, because phthalate can have adverse effects on the testes, liver, and lungs. Hence, the drug solution should be inspected visually for particulate matter and discoloration if the infusion system contains polyvinyl chloride or di(2-ethylhexyl)phthalate tubing.

Antioxidants

Antioxidants are added to formulations to prevent oxidation reactions between the drug and free radicals and thus to increase the stability of the drug present in the injection. By being preferentially oxidized, antioxidants prevent oxidative degradation of the drug. Common antioxidants used are ascorbic acid, cysteine, sodium bisulfite, sodium metabisulfite, tocopherols, and monothioglycerol. An alternative way to prevent oxidation of a drug is to remove the air from the drug ampule or vial and to replace it with an inert gas like nitrogen.

General Categories of Injectables

According to the *United States Pharmacopoeia*, injectables can be divided into five major categories:[39]

1. Injection
2. For injection
3. Injectable emulsion
4. Injectable suspension
5. For injectable suspension

The categories of injectables are described in the following sections.

Injection

Injections are liquid preparations that are drug substances or solutions thereof. Injections can be aqueous solutions or solutions in oil.

Aqueous solutions are the most common and versatile parenteral formulation and can be administered by all the parenteral routes. An immediate therapeutic effect of the drug is seen after IV administration of an aqueous solution. In contrast, a slower onset of action is observed when a drug is administered by the SC route. An example of an aqueous solution injection is human insulin of recombinant DNA origin (Velosulin® BR). Velosulin® BR is a clear solution of insulin in phosphate buffer meant for SC injection. The onset of action is rapid (30 minutes), and the peak effect is observed between 1 and 3 hours after administration. The duration of effect is 8 hours after injection.[40]

Drugs that are water insoluble but lipid soluble may be formulated as solutions by dissolution in vegetable oils. Oil-based injections may cause fat emboli, and therefore should be injected IM but not IV. When such formulations are administered into the muscle, the onset of action is generally slower because of the time required for drug dissolution and absorption from the muscle site. As a result, the duration of action is longer than with water-soluble drugs. An example of an oil-based injection is estradiol cypionate, (DEPO®-Estradiol) for IM injection. Cottonseed oil is used as the vehicle to dissolve the drug. Chlorobutanol anhydrous (a chloral derivative) is used as a preservative for DEPO®-Estradiol injection. Before use, the vial should be warmed by rolling the vial between the two hands and should be shaken gently to redissolve any particles or crystals that may have formed if the formulation was accidentally stored at low temperatures.[41] DEPO-Estradiol® can be administered every 4 weeks.

For Injection

"For injection" formulations are dry solids that, on the addition of suitable vehicles, yield solutions that conform in all respects to injection requirements. Drugs that are not stable in solution are first prepared as a solution, sterilized by filtration, and then freeze-dried as powders. Formulating drugs as freeze-dried powders increases their stability and shelf storage. These powders can then be reconstituted into solution immediately before use with a suitable vehicle. An example of a drug available as a "for injection" product is cefuroxime (Zinacef®) for injection. Cefuroxime is not stable in solution and is provided as a sterile crystalline powder for injection. The solution is prepared by dissolving the powder in 8 mL of sterile water for injection, and it is injected IV. If the contents of the vial are dissolved in 3 mL of sterile water for injection, the drug forms a suspension and it is injected IM.[42]

Injectable Emulsion

Injectable emulsions are liquid preparations of a drug substance dissolved or dispersed in a suitable emulsion medium. An emulsion is a dispersion of two immiscible liquids, the dispersed phase and the continuous phase.

The dispersed phase is finely subdivided and uniformly distributed as droplets throughout the medium or the continuous phase.[43] An emulsion is an effective delivery system for solubilization of water-insoluble drugs. It produces a dosage formulation with increased stability and sustained-release characteristics.[43,44]

IV emulsions usually contain lipid-soluble drugs dissolved in an oil-based vehicle for injection. On IV injection, emulsions must mix with aqueous body fluids to access the target site. Emulsions release drug at a slower rate than solutions but more promptly than IM depot injections.[43] When they are in direct contact with the bloodstream, the dispersed phase droplets of emulsions should be smaller than 1 μm. Maintaining a small droplet size is essential to provide a large surface area of interaction with the aqueous environment,[44] and to minimize the risk of capillary embolism.

Propofol is a sedative-hypnotic agent used as an IV general anesthetic. Because of its high lipid solubility, propofol is formulated as a fat emulsion, Diprivan® (propofol injectable emulsion, USP). Propofol was previously solubilized in Cremophor® EL; however, Cremophor® EL has the main disadvantage of causing anaphylactic reactions. The currently available dosage formulation contains 1% propofol solubilized with glycerol, soybean oil, and lecithin. Diprivan® contains ethylenediaminetetraacetic acid as an antimicrobial preservative agent, whereas newer generic formulations of propofol contain benzyl alcohol or sodium metabisulfite. The main advantage of the fat emulsion is rapid distribution into peripheral tissues, which results in an immediate onset and a shorter duration of action.[45]

Fat emulsions are administered for total parenteral nutrition. Formulations for total parenteral nutrition contain water, sources of nutrient fat (cottonseed, safflower, and soybean oil), surfactants, tonicity agents, and antioxidants as required. The main route for parenteral nutrition is IV, through either central (subclavian, internal jugular, external iliac, or cephalic) or peripheral veins. Peripheral parenteral nutrition is associated with phlebitis and infection; therefore, it is recommended for short-term therapy only in patients with robust peripheral veins.[2,43]

Injectable Suspension

Injectable suspensions are liquid preparations of solids suspended in a suitable liquid medium. A suspension is a dispersion system in which the undissolved solid drug is present in a sterile aqueous vehicle. The undissolved drug should be capable of aspiration into a syringe and should resuspend easily. Suspensions are generally prepared for drugs that are unstable in solution. Drugs in a suspension are generally more stable than drugs in a solution or emulsion and can be administered by IM, SC, and intra-articular injection. Drugs in aqueous suspensions are more rapidly acting than are those in oil-based suspensions. Aqueous suspensions can be used for immediate release and sustained release. Examples of aqueous suspensions are described in the following sections.

Aqueous Suspensions for Immediate Release

Novolin® N Innolet® is a human insulin isophane (neutral protamine Hagedorn [NPH] insulin) suspension containing 100 units of insulin per milliliter and is indicated for SC administration.[46] The suspension is cloudy and milky. The cloudy material is the drug, insulin, which generally settles at the bottom of the vial or reservoir of a prefilled pen injector. When the latter is used, the contents must be uniformly mixed by rotating the pen gently. Each injector contains a small glass ball to ensure proper mixing of the suspension particles. The Innolet® may contain some air in the syringe; therefore, the air must be forced out by an air shot before the injection is administered to the patient. The Innolet® is designed as a dial-a-dose delivery system. The onset of action is delayed, and duration of action is longer than that of regular insulin solution.

Aqueous Suspensions for Sustained Release

If a drug is poorly soluble, on administration as a depot injection, it can form an insoluble depot of drug particles and release the drug slowly over a long time. Depo-Medrol® is an example of a sterile, aqueous suspension of methylprednisolone acetate for sustained release.[47] In addition to the drug, Depo-Medrol® contains sterile water, benzyl alcohol, PEG 3350, polysorbate 80, and sodium chloride. PEG 3350 increases the viscosity of the injection, and sodium chloride is a tonicity-adjusting agent. This formulation is given as an intra-articular injection to treat osteoarthritis or as an IM, intralesional, or intrasynovial injection to treat inflammation. Consistent and prolonged release of the drug from the particles in suspension as a result of its slow dissolution provides sustained therapeutic effect.

Another suspension available commercially as an IM or SC injection is Depo-Provera®, which provides a sustained release of the contraceptive medroxyprogesterone acetate (MPA). The active ingredient, MPA, is insoluble in water and is formulated as an aqueous suspension in PEG and polysorbate 80. Methylparaben and propylparaben are added as preservatives, and sodium chloride is used to adjust the tonicity of the injection.

Depo-Provera® is available as Depo-subQ Provera 104™ for SC injection[48] and Depo-Provera® Contraceptive Injection (Depo-Provera® CI)[49] for IM injection. Depo-subQ Provera 104™ for SC injection is available in prefilled syringes, which should be shaken well before injection to disperse the drug. MPA is absorbed systemically after SC injection, and steady-state serum concentrations are reached after multiple SC injections into the abdomen or the anterior thigh. Slow dissolution of MPA from the suspension is beneficial, because Depo-subQ Provera 104™ is administered once every 12 to 14 weeks.[48] Depo-subQ Provera 104™ delivers 104 mg of medroxyprogesterone per dose. Depo-Provera® CI IM is administered every 12 weeks into the deltoid or gluteal muscle. It is available in vials and prefilled syringes, which must be shaken well to ensure uniform suspension of the drug. The half-life of MPA is approximately 50 days, and steady-state serum concentrations are reached in 3 weeks.[49] Depo-Provera® CI delivers 150 mg medroxyprogesterone per dose.

For Injectable Suspension

"For injectable suspension" formulations are dry solids that, on the addition of a suitable vehicle, yield a dispersion conforming in all respects to the requirements of an injectable suspension. Drugs that are poorly soluble in water and are unstable are provided as "for injectable suspension" formulations. The drug is supplied as a dry powder with suspending agents and is reconstituted in the appropriate vehicle immediately before injection. Formulation as "for injectable suspension" ensures the stability of the drug.

Azacitidine for injectable suspension (Vidaza™), which is available as a sterile lyophilized powder for SC injection, is used to treat myelodysplastic syndromes such as refractory anemia and chronic myelomonocytic leukemia. Azacitidine is insoluble in organic solvents such as ethanol and propylene glycol and is slightly soluble in ethanol/water (50/50) and 5% Tween® 80 in water. Hence, it is formulated as a sterile, lyophilized powder and forms a suspension on reconstitution in 4 mL sterile water for injection. The lyophilized powder is available in a single-use, preservative-free vial and contains mannitol as a tonicity-adjusting agent. Doses of more than 4 mL should be divided and administered at two different SC sites to prevent bruising and redness. The drug is rapidly absorbed after SC injection, and its absolute bioavailability is 90%. The recommended dosage is 75 mg/m^2 for 7 days every 4 weeks.[50]

Abarelix for injectable suspension (Plenaxis™) was indicated for use in patients with advanced symptomatic prostate cancer when luteinizing hormone–releasing hormone agonist therapy was contraindicated. Plenaxis™ contained abarelix as a sterile dry powder for reconstitution with 0.9% sodium chloride. Plenaxis™ was available as a single-use vial containing a complex of anhydrous free-base abarelix peptide (113 mg) with CMC (19.1–31 mg) as a suspending agent. The abarelix-CMC complex had a pH of 5 ± 1, and the dose of abarelix after reconstitution was 100 mg. A depot suspension was formed after reconstitution. It was injected IM, and the drug was released slowly from the depot.[51] After an initial induction period with doses given on days 1, 15, and 29, abarelix injections were repeated every 4 weeks while treatment was continued. The sale of Plenaxis™ on the market has been discontinued for economic reasons.

Special Intravenous Delivery Systems

In addition to the five major types of injectables, special IV delivery systems have been developed based on patients' needs and drug characteristics.

Liposomes for Injection

Liposomes are closed spherical microscopic vesicles composed of a phospholipid bilayer that has the ability to encapsulate therapeutically active drugs. Liposomes act as drug carriers to enable loading of various therapeutic moieties such as small drug molecules, nucleotides, proteins, and plasmids.[52] Incorporation of a drug into a lipid complex (liposomal encapsulation) substantially affects the functional properties of the drug.[53] Different lipid-complex or liposomal products may contain the same active drug but may vary in the lipid component. Liposomes are formulated by mixing specific proportions of amphiphilic substances such as cholesterol and

phospholipids. These substances then arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. The lipophilic moieties of the bilayers face each other, creating an inner hydrophobic environment in the membrane. Lipophilic or amphiphilic drugs can be associated with the nonpolar parts of lipid bilayers. The hydrophilic molecular head groups face the outer water phase and the inner aqueous core of the vesicles.[54] Liposomes undergo degradation when given orally due to the acidic pH of the stomach and are also broken down by intestinal enzymes and bile salts. Hence, the preferred route of delivery of liposomes is IM or IV injection or IV infusion.[52,55]

Examples of liposomal delivery systems include drugs such as doxorubicin and amphotericin B.

Doxorubicin Hydrochloride Liposome Injection

Doxorubicin hydrochloride liposome injection (Doxil®) contains doxorubicin hydrochloride encapsulated in STEALTH® liposomes. STEALTH® liposomes of Doxil® are formulated with surface-bound methoxypolyethylene glycol by a process referred to as *pegylation*. This process protects the liposomes from detection by the mononuclear phagocytic system and increases blood circulation time.[56] Preclinical studies and clinical trials have shown that the use of Doxil® produces higher concentrations in tumor sites than administration of free doxorubicin hydrochloride.[57] Liposomal doxorubicin possessing the same properties as Doxil® is available in the United Kingdom as Caelyx®.[58,59] The average diameter of STEALTH® liposomes is 100 nm. Precipitation of the drug occurs inside the liposome without causing degradation of the liposome. Therefore, leakage of the drug is minimized, and at least 90% of the drug remains encapsulated during circulation.[60] These liposomes are stable in blood, and the half-life of doxorubicin is 55 hours in humans. The small size and long circulation half-life of liposomes ensure that the liposomes can be delivered through the tumor vasculature. The volume of distribution is significantly decreased after encapsulation of doxorubicin in the liposome, which reduces the risk for nephrotoxicity.[56,57] Because of the long half-life, Doxil® liposomes are administered once every 4 weeks. The shelf life of these liposomes is similar to that of other injectable formulations.

Lipid-Associated Amphotericin

Amphotericin B is used to treat systemic antifungal infections. Common problems associated with conventional amphotericin B treatment are breakthrough infections, nephrotoxic effects because of high dosages, and infusion-related toxicity. A number of lipid-associated and liposomal amphotericin formulations have been developed with the aim of enhancing efficacy and reducing the severe toxicity associated with the drug. Lipid-associated formulations yield lower concentrations of amphotericin in the kidneys and remain concentrated in the reticuloendothelial tissues such as the liver and spleen; therefore, they demonstrate improved efficacy and lower toxicity.[61]

Amphotericin B Liposome for Injection

Amphotericin B liposome for injection (AmBisome®) is a sterile, nonpyrogenic lyophilized product for slow IV infusion using a controlled-infusion device.[62] AmBisome® consists of **unilamellar bilayer liposomes** with amphotericin B intercalated within the membrane. Because of its lipophilic nature, the amphotericin B molecule becomes an integral part of the AmBisome® liposome structure. AmBisome® penetrates the cell wall of extracellular and intracellular forms of susceptible fungi. The liposomal formulation forms a translucent suspension after reconstitution with sterile water for injection and further dilution with D5W.[62] Mixing with other drugs or with saline may cause precipitation of the drug from the liposomes. The reconstituted formulation is administered over 2 hours by IV infusion. Steady-state concentrations are achieved within 4 days of the start of dosing. Slow redistribution of the formulation from the tissues leads to a long terminal half-life of the drug, which increases the time the drug spends in the body. The concentration of amphotericin in the kidney tissue is lower with AmBisome® than with conventional amphotericin B treatment. Hence, the incidence of infusion-related renal adverse events is lower with AmBisome.[63] Excretion of amphotericin after AmBisome® administration has not been investigated.

Lipid-Based Complex

Amphotericin B lipid complex injection (Abelcet®) is a sterile, pyrogen-free suspension for IV infusion. Abelcet® consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid molar ratio. To prepare the admixture for infusion, the vial is shaken gently to ensure that there is no sedimentation of the suspended drug particles. A 5-μm filter needle is used to deliver the contents of the vial into an infusion bag

containing D5W injection. The contents of the infusion bag must be thoroughly mixed before infusion. If the infusion time exceeds 2 hours, the contents of the bag must be shaken again to prevent any sedimentation of drug particles. Unused drug should be discarded because the single-use formulation does not contain bacteriostatic agents or preservatives. Assays used to determine levels of free amphotericin can also be used to measure blood levels of amphotericin after administration of the lipid complex formulation[64,65]; however, blood level monitoring of amphotericin is not used commonly in clinical practice.

Polymeric Systems for Parenteral Delivery

Prolonged-release parenteral formulations control the release of drugs over a period of days to weeks. Various drugs are being formulated as microspheres for IM or SC depot injection. Both biodegradable and nonbiodegradable polymers are available to provide sustained release. Most nonbiodegradable polymer delivery systems release the drug by diffusion. Diffusion-controlled delivery systems have the advantage of providing a predetermined rate of drug release and delivery but are dependent on drug characteristics and the permeability of the polymer.[66] These delivery systems are feasible for drugs that have low molecular weights and high solubility, and that dissolve and remain in the polymer matrix. Nonbiodegradable polymer systems must be surgically removed. Biodegradable polymers are natural or synthetic polymers that undergo degradation in vivo, thereby releasing the dissolved or dispersed drug and producing biocompatible or nontoxic products.[66] Most biodegradable polymers are nontoxic and are easily eliminated from the systemic circulation; therefore, they are preferred over nonbiodegradable polymers. The release of drug from biodegradable polymers depends on two processes. In the initial phase, the release is controlled by diffusion of the drug. In the second phase, the drug bound to the polymer matrix is released by erosion of the matrix.[67] The rate of hydration of the polymer matrix depends on uptake of water by the polymer.

Polymeric Biodegradable Systems for Parenteral Administration

Synthetic biodegradable polymers include polyesters, polyanhydrides, polyamides, and polyorthoesters. Polyesters include polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer, poly-lactic-co-glycolic (PLGA). PGA is more hydrophilic, and its water uptake is relatively higher than that of PLA, which is more hydrophobic. Therefore, PLA releases the drug more slowly than the PGA matrix.[66,68] The approach of encapsulating drugs in different polymer matrices and biodegradable microspheres provides a way to maintain therapeutic levels of drugs for a longer time. This increases the duration of action and reduces the need for multiple injections, which are painful and inconvenient.

Drugs available in biodegradable polymer–based sustained-release parenteral formulations include octreotide acetate (Sandostatin® LAR Depot for IM injection), recombinant somatropin (Nutropin Depot® for SC administration), triptorelin (Decapeptyl® SR for IM injection), leuprolide acetate (Lupron Depot® for IM injection), goserelin acetate (Zoladex® for SC implantation), and carmustine (Gliadel® Wafer for intracranial implantation). Dosage formulations containing PLGA and polyanhydride microspheres are described in the following sections.

Poly-Lactide-co-Glycolide Microspheres

Octreotide acetate for injectable suspension (Sandostatin® LAR Depot) is an example of a formulation containing PLGA microspheres. It is a long-acting depot preparation formulated for IM injection.[69] The drug is encapsulated in the biodegradable polymer PLGA. Cleavage of the polymer ester linkage occurs through tissue hydrolysis and results in slow release of the drug.[70,71] This allows the maintenance of drug levels over an extended period and injection of the depot preparation every 28 days.[70] Mannitol is added to the microspheres to improve suspending properties in the injection. Sandostatin® LAR Depot should be administered IM into the gluteal muscle; sites may need to be alternated to avoid irritation due to repeated injection. Injection into the deltoid muscle should be avoided because it causes discomfort and pain at the injection site. This depot preparation should not be injected IV or SC.

Another example of an injectable suspension using biodegradable PLGA microspheres is somatropin (of recombinant DNA origin) for sustained release (Nutropin Depot®). Nutropin Depot® is a "for injectable" suspension prepared for SC injection. It consists of sterile, free-flowing micronized particles of recombinant human growth hormone embedded in biodegradable

PLGA microspheres. On injection, recombinant human growth hormone is released from the microspheres into the SC tissues by diffusion. Further release of the drug occurs via polymer degradation and diffusion. Distribution, metabolism, and elimination of recombinant human growth hormone after release from the depot formulation is similar to that after administration of the somatropin daily-use formulation. Nutropin Depot® is administered once or twice a month, and the dose should be adjusted based on the chosen dosing frequency. The lyophilized powder should be suspended only in the diluent provided with the formulation and administered using the needles supplied in the kit.[72]

Other drugs available in formulations containing microspheres for sustained-release injection are triptorelin (Decapeptyl® SR) and leuprolide acetate (Lupron Depot®). Decapeptyl® SR is a microsphere dosage formulation of triptorelin encapsulated in PLGA microspheres for sustained release. Chemically, triptorelin is a decapeptide and an analog of luteinizing hormone–releasing hormone. The suspension medium for the injection contains polysorbate and sodium CMC. The recommended therapy regimen for Decapeptyl® SR is one IM injection every 4 weeks.[73] Lupron Depot® is a depot suspension meant for IM injection.[74] Depending on the dose used, Lupron Depot® can be injected every 1 or 3 months for treatment of endometriosis and once every 1, 3, 4, or 6 months for treatment of prostate cancer.[18,19]

Polyanhydride Microsphere Polymer Implants

Implants are parenteral dosage formulations used as a reservoir for prolonged release of various drugs. As in the case of microspheres, implants can be biodegradable or nonbiodegradable. Implants generally can be administered SC or implanted intracranially via a surgical procedure, whereas microspheres are generally administered by SC or IM injection.

Goserelin acetate implant (Zoladex®) contains a potent synthetic decapeptide analog of luteinizing hormone–releasing hormone and is prescribed for the treatment of prostate and breast cancer. Zoladex® is available as a sterile biodegradable pellet.[75,76] It is administered SC every 12 weeks into the anterior abdominal wall below the navel line. At the injection site, the polymer becomes hydrolyzed and releases the drug for up to 3 months. Slow and continuous release of the drug ensures that effective steady-state serum concentrations are maintained.

Another implant used for slow release of a drug over time is an implant of polifeprosan 20 with carmustine (Gliadel® Wafer). Gliadel® Wafer is administered as an intracranial implant and requires surgical intervention for placement. It is used to treat brain tumors such as high-grade malignant gliomas and recurrent glioblastoma multiforme as an adjunct to surgery and radiation therapy. Gliadel® is the only FDA-approved brain cancer treatment capable of providing localized delivery of chemotherapy directly to the site of the tumor.[77] Gliadel® wafers are composed of a biodegradable polyanhydride copolymer matrix system (prolifeprosan 20) and are 1.45 cm in diameter and 1 mm thick. The copolymer, polifeprosan 20, consists of poly[bis(p-carboxyphenoxy)propane:sebacic acid] in a 20:80 molar ratio. The drug is distributed homogenously in the polymer matrix. The wafer shape allows slow release of the drug over time, and several wafers can be implanted into the brain cavity after excision of the tumor. More than 70% of the copolymer degrades in 3 weeks. The monomer carboxyphenoxypropane is eliminated through the kidney in animals. The second monomer, sebacic acid, is an endogenous fatty acid and is metabolized by the liver and exhaled in the form of carbon dioxide. The pharmacokinetics of the copolymer in humans is not known. In some cases, wafer remnants consisting of water and monomers formed after polymer degradation may remain in the brain cavity. These can be removed if surgery is repeated to implant new Gliadel® wafers.[78]

Polymeric Nonbiodegradable Systems for Parenteral Administration

Various nonbiodegradable delivery systems have been developed for sustained release of drugs by parenteral administration. Nonbiodegradable systems allow for longer release of drugs than do biodegradable systems. The control of the drug release rate is generally accomplished by the membrane in nonbiodegradable systems and is more effective than in biodegradable systems.[79] The main disadvantage of nonbiodegradable systems is the need for surgical insertion and removal.

Leuprolide acetate is available as a sterile, nonbiodegradable, osmotically driven implant (Viadur®) designed for controlled-rate delivery of the drug. Unlike Zoladex®, which is injected SC, Viadur® is surgically inserted SC for the treatment of advanced prostate cancer in men. Surgical insertion must be

performed by health care professionals who have been trained in proper insertion techniques and have suturing skills. Local anesthetic must be administered at the injection site before insertion to prevent pain. The titanium alloy reservoir in the implant contains a polyurethane rate-controlling membrane, a polyethylene diffusion moderator, and an elastomeric piston.[80] The osmotic tablets present in the implant system are composed of sodium chloride, sodium CMC, povidone, magnesium stearate, and sterile water for injection. These tablets are not released with the drug formulation. In the initial stages of release, water and other biological fluids diffuse into the implant, and the drug is released by diffusion. Viadur® provides continuous release of the drug for up to 1 year. The implant is removed after 12 months and a new one is inserted depending on the treatment regimen for the patient. After removal and reinsertion, steady-state serum concentrations are maintained.[81]

Another example of a nonbiodegradable implant is the etonogestrel implant (Implanon®). Implanon® is a single flexible subdermal implant system with a contraceptive life of 3 years. The 40-mm-long and 2-mm-wide flexible rod in Implanon® contains ethylene vinyl acetate impregnated with 68 mg of etonogestrel.[82] The implant releases approximately 40 µg of etonogestrel every day and prevents ovulation in women. With surgical intervention, the rod is implanted SC in the inner side of the upper arm under local anesthesia. The implant remains intact in the body and must be removed by a surgical procedure under local anesthesia. The drug is released from the implant via diffusion and absorbed into the bloodstream. The main advantage of Implanon® is the release of low daily doses of the drug, which contributes to prolonged contraceptive action.[83] The implant does not interfere with breast-feeding and can be inserted during the lactation period to provide safe and effective contraception. Implanon® has been approved by the FDA; however, it is not yet available on the market.

Polymer Nanoparticles

Nanoparticles have been developed to act as carriers for poorly water-soluble drugs and thereby increase bioavailability. They are solid colloidal particles, generally 200 nm in diameter.[84] Nanoparticles serve as carriers for a variety of agents, including antigens, drugs, enzymes, and vaccines. They are also used as vaccine adjuvants and delivery systems. Polymers like polyalkylcyanoacrylate, and polyesters (PLGA) are used in nanoparticles for parenteral delivery.[85] Because vehicle toxicity is one of the major side effects of taxane formulations, novel dosage formulations such as those containing nanoparticles and liposomes free of Cremophor® EL have been developed. Incorporation of paclitaxel into liposomes eliminates hypersensitivity reactions associated with the vehicle Cremophor® EL and also decreases toxicity from the intrinsic pharmacologic action of the drug. An example of paclitaxel incorporated into nanoparticles is Abraxane® injection.

Abraxane® injection is a Cremophor®-free, albumin-bound nanoparticle formulation of paclitaxel for treatment of metastatic breast cancer. It is available as a "for injectable suspension" formulation and was developed to eliminate the toxicity associated with Cremophor® EL. Abraxane® is administered by IV infusion.[86] The albumin-bound nanoparticles interact with gp60, a protein on the endothelial cell lining of blood vessels, which facilitates transport of the drug from the bloodstream into tumor sites. This transport mechanism results in higher concentrations of paclitaxel in the tumor sites. The infusion is given over a shorter period of time than the Taxol® injection formulation of paclitaxel, and no special IV equipment is needed. Because the formulation contains no solvents, premedication to prevent severe hypersensitivity reactions is not needed. Therefore, Abraxane® has a much more favorable side effect profile than paclitaxel formulations containing Cremophor® EL.[87]

Specialized Devices

Various delivery systems have been developed to provide specific drug targeting, rate-controlled drug delivery, and increased patient compliance and convenience. Some examples of specialized devices for improved parenteral delivery of drugs are implantable pumps and preloaded syringes.

Implantable Pumps

Implantable drug delivery pumps were first developed with the aim of providing external control of delivery rate or administering volumes of drug that may be

beyond the capabilities of conventional sustained-release dosage formulations. Implantable systems provide continuous therapeutic serum drug levels. Major applications of such devices include delivery of insulin to patients with diabetes and of chemotherapeutic agents to cancer patients. Implantable pumps are also used for the treatment of Alzheimer disease and spasticity, and for long-term pain control. When patients do not respond to oral or parenteral analgesics, implantable pumps are used to deliver a continuous flow of analgesic drugs and provide enhanced relief from pain. Implantable delivery systems consist of a medication chamber, a pump that is used to infuse the medication, and a catheter attached to the pump. The pump is implanted surgically into the lower abdomen, and the medication is released through a tunneled catheter. The medication chamber is refilled by inserting a needle into the septum of the chamber. Pumps can be refilled with medication by physicians or registered nurses. The two main categories of implantable pumps are bellows-activated mechanical pumps and programmable electronic pumps.[88] Electronic pumps are more commonly used, because the rate of drug delivery can be controlled externally by the physician. These devices are described in detail in the following section.

Electronic Pumps

Electronic pumps are battery operated, and their main advantage is that they allow external control of the delivery rate and amount of drug being infused. The physician can also maintain a computer-generated report of the pump status, bolus doses of medication used, and the amount of drug remaining in the pump. The pumps can be programmed using telemetric computer-generated radio waves. Electronic pumps are less sensitive to changes in body temperature than are mechanical pumps.

Battery life depends on the type of pump, programmable parameters, and drug flow rate. When the battery wears out after a few years of use, a programmable electronic pump must be surgically removed and replaced. If problems arise with the mechanical components, a soft alarm can be heard from the pump; the physician should be consulted, and the pump may need to be replaced.[89] The major disadvantage of electronic pumps is the cost of the programming units required to send the telemetry signal to the pump.[88]

Preloaded Syringes

Preloaded syringes have been developed for the self-administration of drugs by patients in the convenience of their homes or workplaces. These devices are easy to use and eliminate the need to prepare injections for self-administration, which leads to improved patient compliance.

Sumatriptan succinate is available as a prefilled autoinjector pen with disposable cartridges (Imitrex STATdose System®). The drug is delivered SC by pressing a button on the pen and does not require the use of needles or syringes. The 6-mg injection can be administered up to a maximum of twice per 24-hour period. A major advantage of the 4-mg injection STATdose System® is that three injections may be used within the same period.[90] This is beneficial for patients who suffer from cluster headaches and need frequent doses of Imitrex®. Oral sumatriptan is effective for most patients, but the Imitrex STATdose System® provides effective pain relief for patients who wake up with a migraine already in progress and for patients with nausea and vomiting.[90]

Exenatide injection (Byetta®) is a prefilled pen-injector device with a glass cartridge containing exenatide solution. The injection contains mannitol as a tonicity-adjusting agent and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution. Each prefilled pen is used to deliver premeasured doses and contains solution for multiple injections. Byetta® is prescribed for twice-daily SC administration for 30 days, and each prefilled pen provides a total of 60 doses of exenatide for treatment in type II diabetes mellitus. Patient education regarding injection technique, proper storage, and timing of injections if other drugs are being administered is critical. Byetta® should be injected 60 minutes before morning and evening meals. If a dose is missed, the next dose should be administered at the scheduled time. Byetta® is not intended for IM or IV injection.[91,92]

Other examples of drugs provided in preloaded devices are insulin detemir (recombinant DNA origin) injection (Levemir® FlexPen®),[93] human insulin isophane suspension (Novolin® N Innolet®),[46] pramlintide acetate (Symlin®),[94] and fondaparinux sodium (Arixtra®).[95,96]

Learning Points

Learning Point 1

A patient has schizophrenia and requires maintenance therapy. He has been prescribed oral drug X every 12 hours. Because of his recurrent schizophrenic episodes, the patient forgets to take doses at the scheduled times. Therefore, patient compliance and effective treatment are major issues. Drug X is water insoluble. What is the most appropriate alternative dosage formulation in this situation?

An oil-based depot formulation of drug X by IM injection with a duration of action of 4 to 6 weeks may be the most effective way to maintain therapeutic drug levels for a prolonged period. On IM administration, the drug will form a depot at the site of injection. The drug will be released slowly from the depot formed at the injection site, which will result in prolonged effective serum concentrations and reduce the need for frequent injections. The decreased frequency of dosing and maintenance of therapeutic serum concentrations should lead to effective therapy and improved patient compliance.

Learning Point 2

A lipid-insoluble drug, drug I, is prescribed to a patient for the treatment of Parkinson disease. Its major site of action is in the central nervous system, and sustained levels of this drug in the brain correlate with improved control of Parkinson disease symptoms. When drug I is given via IV injection, however, the patient does not respond to the drug. Why does the patient continue to experience symptoms in spite of drug therapy?

When drug I is given IV, it distributes into the systemic circulation, which leads to an immediate increase in serum drug levels. Because of its lipid insolubility, however, it does not cross the blood–brain barrier. Therefore, a likely explanation is that the drug is not delivered to the brain, which is the major site of drug action in the treatment of Parkinson disease. Therefore, drug I needs to be administered by a specialized route of delivery that bypasses the blood-brain barrier. Drug I could be administered by intrathecal or intracerebroventricular injections to ensure delivery of the drug directly into the brain and surrounding fluid.

Learning Point 3

Microspheres are designed for sustained release ranging from hours to several days or months. Microspheres are composed of synthetic biodegradable polymers like PLA, PGA, and PLGA. Encapsulating a drug in different polymer matrices provides an effective way to maintain therapeutic levels of the drug for a longer time. What is the mechanism of release of the drug from specialized drug delivery systems such as microspheres? How can the release of a drug over time be modified by using microspheres as delivery systems?

The rate of release of drugs from microspheres depends on the molecular weight and composition of the polymers. PGA is more hydrophilic, and water uptake is relatively higher with PGA than with PLA, which is more hydrophobic. Hence, a PLA polymer matrix releases drug more slowly than a PGA matrix. By varying the amount of PLA and PGA, the rate of release of the drug over time can be controlled. For slower release (up to 3–4 months), PLA can be used to form the polymer matrix of the microspheres. In comparison, a slightly faster rate of release (1 month) can be achieved by using PGA in the polymer matrix. In the latter case, the microspheres contain the monomers PLA and PGA in a ratio of 75:25.

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