الكلية	الصيدلة
القسم	الصيدلانيات
المادة باللغة الانجليزية	Industrial Pharmacy I
المادة باللغة العربية	صيدلة صناعية I
المرحلة الدراسية	الرابعة
اسم التدريسي	م.م. وسام خلف رافع
عنوان المحاضرة باللغة الانجليزية	Sterile Products Part1
عنوان المحاضرة باللغة العربية	المنتجات المعقمة (الجزء الاول)
رقم المحاضرة	9
المصادر والمراجع	The Theory and Practice of Industrial Pharmacy By Leon Lachman et al.

محتوى المحاضرة

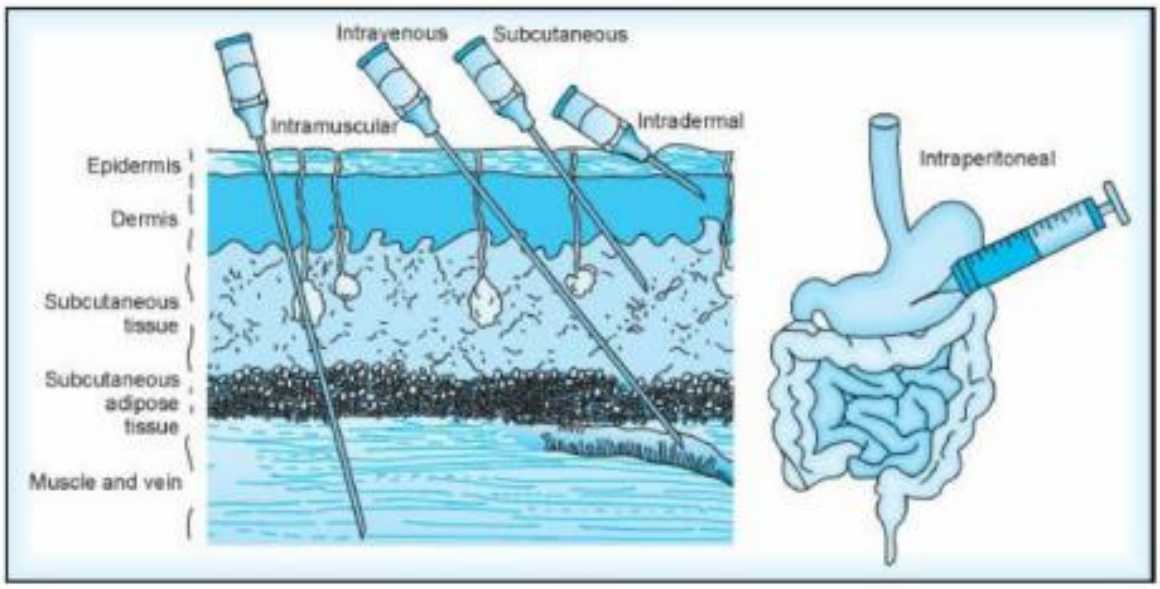
Sterile Products

Sterile products are dosage forms of therapeutic agents that are free of viable microorganisms. Principally, these include parenteral, ophthalmic, and irrigating preparations. Of these, parenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. Thus, because they have circumvented the highly efficient first line of body defense, i.e. the skin and mucous membranes, they must be free from microbial contamination and toxic components,

as well as possess an exceptionally high level of purity.

All components and processes involved in the preparation of these products must be selected and designed to eliminate, as much as possible, contamination of all types, whether of physical, chemical, or microbiologic origin.

Parenteral preparations may be given by various routes: intravenous, intramuscular, subcutaneous, intradermal and intraperitoneal.



When injection occurs via an intravascular route, complete drug availability occurs immediately; no absorption is necessary. For all other routes, at least a blood vessel wall, and usually one or more tissue cell walls,

must be permeated before the drug can enter the circulation. Most often, this

occurs by passive diffusion and is most favourable when the drug has

both

lipophilic and hydrophilic properties, with the former being predominant.

With non-vascular injections, absorption is also affected by such factors as the size and number of blood vessels supplying the tissue, the movement (exercise) of the tissue following injection, the physical and chemical properties of the drug and such characteristics of the dosage form as whether it is a solution, suspension, or emulsion, the nature of the vehicle, and its pH. Once in the circulating blood, the physiologic effect of a therapeutic agent is affected by the extent to which it distributes throughout the body, by the degree of binding to plasma proteins and by its rate of elimination by hepatic metabolism and/or renal excretion.

Intravenous and intraspinal preparations are rarely given in a form other than aqueous solutions. The danger of blockage of fine capillaries, particularly in the brain, precludes the use of

forms other than solutions for IV administration, although emulsions have been given in which the particle size of the dispersed phase is carefully controlled. The sensitivity of the nerve tissues generally precludes the use of anything but the purest of solutions for intraspinal medication. Preparations given intramuscularly, subcutaneously, or

intradermally can be administered as solutions, suspensions, or emulsions.

Even solid pellets may be implanted subcutaneously or intramuscularly. The vehicles can range from Water for Injection, to glycols, to fixed oils. Although care must be exercised to avoid undue tissue irritation, mild local irritation is permissible at these injection sites.

The nature of a preparation can influence significantly the rapidity of onset of a therapeutic effect from a drug, the duration of the effect, and the form of the absorption pattern achieved. Therefore, the development of the formulation for a parenteral product must be integrated carefully with its intended administration in a patient.

The chemical and physical properties of a drug must be determined, its interaction with any desired excipients must be studied, and the effect of each step of the process on its stability must be studied and understood.

Preparations for the eye, though not introduced into internal bodycavities, are placed in contact with tissues that are very sensitive to contamination. Therefore, similar standards are required for ophthalmic preparations.

Irrigating solutions are now also required to meet the same standards as parenteral solutions because during an irrigation

procedure, substantial amounts of these solutions can enter the bloodstream directly through open blood vessels of wounds or abraded mucous membranes.

EFFECT OF ROUTE OF ADMINISTRATION

The intended route of administration has a marked effect on the formulation of a parenteral product. The volume in which a dose of the drug must be encompassed is one factor to consider. For intracutaneous injections a volume of more than 0.2 ml rarely is used because tissue volume is small and compact; also, absorption is quite slow owing to the lack of blood vessels. Volumes of 1 ml or less may be injected subcutaneously and only occasionally are volumes of more than 2 ml given intramuscularly. Volumes of 10 ml or less may be given intraspinally, but only by the IV route may large volumes be given safely, provided careful control of the rate of administration is undertaken. It is not convenient to administer a volume of more than 20 ml by a syringe, and usually it is not practical to set up an infusion unit for less than 250 ml. Isotonicity is a characteristic that is probably of greatest importance for intraspinal injections because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic

pressure quickly cause headache and vomiting. Since intracutaneous injections are given mostly for diagnostic purposes, nonisotonic solutions may cause false signs of irritation. Isotonicity is preferable for the comfort of the patient, but is not essential for SC and IM

injections. For the rapid absorption of drugs given intramuscularly, a slightly hypertonic solution may increase the rate by causing local effusion of tissue fluids. Usually, IV fluids should be isotonic, although slow administration of a paratonic solution may be performed safely if rapid dilution with the blood occurs.

In general, only solutions of drugs in water may be given intravenously. Suspensions may not be given because of the danger of blockage of the small blood vessels. Aqueous or oleaginous suspensions and oleaginous solutions cannot normally be given subcutaneously because of the pain and irritation caused. Muscle tissue tolerates oils and suspended particles fairly well and is therefore the only route normally suitable for their administration.

The administration of a drug deep into the muscle tissue results in a pool of the product at the site of injection. From this depot,

the drug is released at a rate determined to a large extent by the characteristics of the formulation.

Whether the solvent is aqueous or oleaginous affects the rate of absorption; oleaginous solutions are usually more slowly absorbed. Increasing the viscosity of solutions slows the absorption, just as gelatin or polyvinylpyrrolidone in water and aluminum monostearate in oils. Utilizing modifications of the drug molecule to render it less soluble (for instance, the formation of various esters or salts) permits

the production of stable suspensions, causing a marked reduction in the rate of absorption of the drug from the depot. Thus, utilizing various modifications in formulation of the product makes it possible to retard the rate at which a drug is released from a depot. Ophthalmic preparations are formulated in much the same way as parenteral solutions. The eye is particularly sensitive to irritation; therefore, formulation should be directed towards minimizing irritation. Normally, clean aqueous solutions are preferable for ophthalmic use. Suspensions of solids have been used in the eye when the therapeutic need superseded the need to avoid irritating effects, as for the suspensions of corticosteroids used occasionally. It has been found that a foreign body sensation increases as the concentration of suspended particles, regardless of size, approaches 5%. Sterile products are most frequently solutions or suspensions, but may even be solid pellets for tissue implantation. The control of a process to minimize contamination for a small quantity of such a product can be achieved with relative ease. As the quantity of product increases, the problems of controlling the process to prevent contamination multiply. Therefore, the preparation of sterile products has become a highly specialized area in pharmaceutical processing. The standards established, the attitude of personnel and the process control must be of a superior level.

FORMULATIONS

Ophthalmic Preparations

Products to be instilled into the eye, while not parenterals by definition, have many similar, and often identical, characteristics. The formulation of stable, therapeutically-active ophthalmic preparations requires high purity of ingredients as well as freedom from chemical, physical (particles), and microbial contaminants. These preparations usually require buffers to stabilize the pH of the product, additives to render it

isotonic or nearly so, and stabilizers such as antioxidants when appropriate for the particular ingredients. Those ophthalmics used in larger quantities, such as eye irrigants, or in the case of devices such as contact lenses, are usually relatively uncomplicated solutions similar to large-volume parenterals. One characteristic not as critical for ophthalmics is freedom from pyrogens since pyrogens are not absorbed systemically from the eye; however, insofar as pyrogens are indicative of a microbiologically clean process, they should not be present.

Freeze-dried Products

Solutions intended to be freeze-dried must be aqueous, for the drying process involves the removal of water by sublimation. Since the solution is in existence for only a brief period during processing, stability problems related to the aqueous system are practically nonexistent. However, the formulation must reflect the characteristics to be imparted to the solid residue (cake) after drying, and those required of the solution after reconstitution at the time of use. Often, the drug alone does not give sufficient solid residue or the

characteristics appropriate for the product; therefore, substances often must be added to provide the characteristics desired.

Among the characteristics required of a good cake are (1) a uniform colour and texture, (2) a supporting matrix of solids sufficient to maintain essentially the original volume after drying and (3) sufficient strength to prevent crumbling during storage. In addition, the nature and amount of solids in the solution largely determine (1)the eutectic temperature of the frozen solution, the subzero temperature at which the frozen material will melt, which determines the temperature below which the product must be held during freeze-drying, (2) the rate of thermal and vapour transfer through the product during the process of drying and (3)the rate of solution of the product during reconstitution. The percentage of solids in the frozen plug should be between approximately 2 and 25%.Among the best salts for providing uniform crystal size, uniform colour and texture, physical strength, and rapid reconstitution are the monobasic and dibasic sodium phosphates. Sodium chloride is often used, but when used alone, the cake tends to shrink markedly in volume and to appear crusty and crumbly. When organic substances, such as mannitol, sorbitol, sucrose, and gelatin are used to provide solids for the cake, care must be taken during the heating, particularly

during the terminal stages of drying, to avoid discolouration of the cake

by charring. Added substances required in the formulation must not be volatile under the conditions of drying; therefore, antibacterial agents such as phenol, chlorobutanol, and benzyl alcohol should not be used.

Long-acting Formulations

Long-acting parenteral drug formulations are designed, ideally, to provide slow, constant, and sustained release of a drug over a prolonged period of time, essentially to simulate and replace the more hazardous, continuous i.v. infusion of a drug. In one type of depot formulation, which is referred to as "dissolution controlled," the rate of drug absorption is controlled by the slow dissolution of drug particles, with subsequent release to tissue fluid surrounding the bolus of product in the tissue. The formation of drug salts with very low aqueous solubility is one of the most common approaches to this type of formulation. Control of the particle size also can contribute to slow dissolution in that larger particles or crystals dissolve more slowly than small crystals with proportionately more surface area. Further, the suspension of the drug particles in vegetable oils, and especially if gelled with substances such as aluminum monostearate, produces prolonged absorption rates. Another type of depot formulation is produced by the binding of drug molecules to adsorbents. Only the free portion, in equilibrium with that which is bound, can be absorbed. As drug is absorbed, a shift in equilibrium is

established, and the drug is slowly released from the bound state to the free state. This is particularly exemplified by the binding of vaccines to aluminum hydroxide gel to provide a sustained release. A third type of depot preparation is the encapsulation type, in which biodegradable or bioabsorbable macromolecules such as gelatin, phospholipids, and long-chain fatty acids become a diffusion matrix for the drug. The drug is encapsulated within the matrix, and release of drug molecules is controlled by the rate of permeation out of the diffusion barrier and by the rate of biodegradation of the barrier macromolecules. A fourth type is the esterification type depot preparation, in which esters of a drug that are bioerodible are synthesized.

The esterified drug is deposited in tissue at the site of injection to form a reservoir of drug. The rate of drug absorption is controlled by the partitioning of the drug esters from the

reservoir to tissue fluid and by the rate at which the drug ester regenerates the active drug molecule. Often, these esters are dissolved or suspended in oleaginous vehicles, which further slow the release.

Suspensions: The solids content of parenteral suspensions usually ranges between 0.5 and 5%, but may go as high as 30% in some antibiotic preparations. The amount of solids and the nature of the vehicle determine the viscosity of the product, an important factor because of syringeability, the facility with which the product is passed in and out of a syringe. The property of thixotropy is sometimes utilized,

particularly with oleaginous suspensions, to provide the sedimentation stability of a gelled preparation during storage and the syringeability of a fluid at the time of administration.

Probably the most important requirement for parenteral suspensions is a small and uniform particle size.

The stabilization of a suspension for the period between manufacture and use presents a number of problems. As indicated, solids gradually settle and may cake, causing

difficulty in redispersion prior to use. Surface active agents may aid in the preparation and stabilization of a suspension by

reducing the interfacial tension between the particles and the vehicle.Polysorbate 80, lecithin, Emulphor EL-620 and Pluronic F-68 are among thesurface active agents that have been used in parenteral suspensions. The concurrent addition of a hydrocolloid, such as sodium carboxymethylcellulose, may enhance the effect of the surfactant and cause loss of surface charge of the dispersed particles, water repellency, and the tendency to agglomerate. The following is an example of such a formulation:

Cortisone acetate, microfine 25 mg
Polysorbate 80 (surface active agent) 4 mg
Sodium CMC (protective colloid) 5 mg
Sodium chloride (for tonicity effect) 9 mg
Benzyl alcohol (antibacterial) 9 mg
Water for Injection, to make 1 ml

Emulsions:

The principal problem in the formulation of parenteral emulsions is the attainment and maintenance of uniform oil droplets of 1 to 5 μm in size as the internal phase. With emulsions, separation of the phase does not occur as readily as with suspensions because the difference in density between the oil and water is relatively small. One such product, an emulsion

of a natural vitamin K1, has been stabilized with lecithin. The preparation of a parenteral emulsion is troublesome. It is made more difficult by the rigid requirement for particle size control to prevent emboli in blood vessels, by the limited choice of emulsifiers and stabilizers of low toxicity, and by the preservation of the oil phase against the development of rancidity.