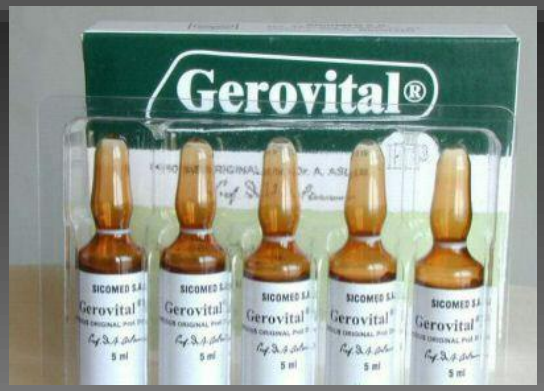
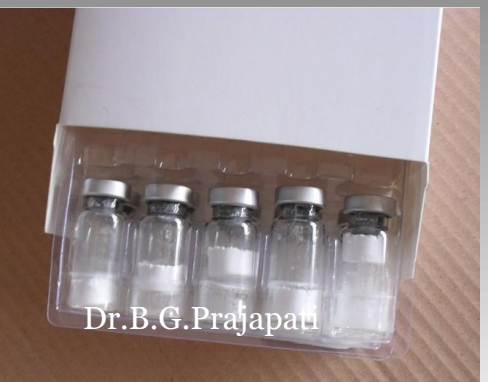
STERILE FORMULATIONS





DR.B.G.PRAJAPATI
SKPCPER

PARENTERAL INTRODUCTION

- para: outside
- enteron: intestine (i.e. beside the intestine)
- Defined as sterile drug,solution or suspension that is packaged in a manner for suitable administration by hypodermic injection either in the form prepared or after addition of a suitable solvent or suspending agent.
- Parenteral products are injected through the skin or mucous membranes into the internal body compartments.
- These are the preparations which are given other than oral routes.

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DEFINITION

Sterile products are dosage forms of therapeutic agents that are free of viable microorganism.

These includes parenteral, ophthalmic and irrigating preparation.

Sterile products are more frequently solutions or suspensions, but may even be solid pellets for tissue implantation.

Sterile Dosage form Categories

Pharmaceutical products. Biological products. Diagnostic agents. Allergenic extracts. Radiopharmaceutical products. Dental products. Genetically engineered or biotechnology products. Liposome and lipid products.

ADVANTAGES

- Quick onset of action.
- Suitable for the drugs which are not administered by oral route.
- Useful for unconscious or vomiting patients.
- Useful for patients who cannot take drugs orally.
- Useful for emergency situations.
- Suitable for nutritive like glucose and electrolyte.
- Suitable for drug with low bioavailability.
- Can be used for Modified/Controlled/Novel Drug Delivery System.

DISADVANTAGES

- Pain on injection.
- Difficult to reverse an administered drug's effects.
- Sensitivity or allergic reaction at the site of injection.
- Requires strict control of sterility & non pyrogenicity than other formulation.
- Only trained person is required Require specialized equipment, devices, and techniques to prepare and administer drugs.
- More expensive and costly to produce.
- In overdose difficult to retrieve.
- Route specific

ROUTES OF ADMINISTRATION

- ROUTES OF ADMINISTRATION

  Three primary routes of parenteral administration are commonly employed
- Subcutaneous
- Intramuscular
- Intravenous
- Other routes: Intra–arterial, Intraarticular, Intraspinal, Intracerebral, Intracardial ,Intrapleural ,Intraocular. Intrapritoneal.

ROUTES OF ADMINISTRATION

- including the joints (intra-ar*ticular),*
- joint fluid area (intrasynovial),
- spinal column (intraspinai),
- spinal fluid (intrathecal),
- arteries (infra-arterial),
- the heart (intracardiac; in an emergency),
- into a vein (intravenous, IV; most common),
- into a muscle (intramuscular, IM),
- into the skin (in-tradermal, ID, intracutaneous),
- under the skin (subcutaneous, SC, sub-Q, SQ, hypodermic, hypo)

Intravenous Route

- Intravenous injection of drugs had its scientific origin in 1656 in the experiments of Sir Christopher Wren, architect of St.
- Paul's a Cathedral and amateur physiologist. Using a " bladder and quill for a syringe and needle, he injected wine, ale, opium, and other substances into the veins of dogs and studied their effects.
- Intravenous medication was first given to humans by Johann Daniel Major of Kiel in 1662 but was abandoned for a period because of thrombosis and embolism in the patients so treated.
- The invention of the hypodermic syringe toward the middle of the 19th century created new interest in intravenous techniques, and toward the turn of the 20th century, intravenous administration of solutions of sodium chloride and glucose became popular.
- Today intravenous administration of drugs is a routine occurrence in the hospital, although recognized dangers are still associated with the practice.

Advantages

- Intravenous drugs provide rapid action compared-with other routes of administration, and because drug absorption is not a factor.In emergencies, intravenous administration of a drug may be lifesaving because of the placement of the drug directly into the circulation and the prompt action that ensues.
- Optimum blood levels may be achieved with accuracy and immediacy not possible by other routes.
- Drugs that are too irritating for intramuscular or subcutaneous administration (e.g., chemotherapy agents) can be given by this route.
- Both **small and large volumes** of drug solutions may be administered intravenously

Disadvantages

- once a drug is administered intravenously, it cannot be retrieved. In the case of an adverse reaction to the drug, for instance, the drug cannot be easily removed from the circulation, as it could, for example, by induction of vomiting after oral administration of the same drug.
- the intravenous dose may differ greatly from the oral dose. Thus, great care must be taken to prevent overdosing or underdosing. Example:The beta-blocker drug class, such as metoprolol, there are vast differences between intravenous (three bolus injections of 5 mg each at about 2-rninute intervals) and oral dosing (100 mg/day).

Possible Complications

- **Thrombosis** formation can results from many factors: extremes in solution pH, particulate material, irritant properties of the drug, needle or catheter trauma, and selection of too small a vein for the volume of solution injected.
- **Phlebitis**, or inflammation of the vein, can be caused by the same factors that cause thrombosis.
- **Air emboli** occur when air is introduced into the vein. The human body is not harmed by small amounts of air, but a good practice is to purge all air bubbles from the formulation and administration sets before use.
- **Particulate material** is generally small pieces of glass that chip from the formulation vial or rubber that comes from the rubber closure on injection vials.

Intramuscular Route

- Provide effects that are less rapid but generally longer lasting than those obtained from IV.
- Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly.
- Depending on the type of preparation, absorption rates vary widely. Solution>Suspension>Emulsion…
- Given deep into the skeletal muscles.
- The point of injection should be as far as possible from major nerves and blood vessels.

Intramuscular Route

- Injuries may include paralysis resulting from **neural damage, abscess, cyst, embolism, hematoma, sloughing of the skin, and scarring.**
- The volume of medication that may be conveniently administered by the intramuscular route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.

Subcutaneous Route/hypodermic

- Used for injection of small amounts of medication.
- Injected at the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen.
- The site of injection is usually rotated when injections are frequently given, as with **daily insulin injections**.
- The **maximum amount of medication** that can be comfortably injected subcutaneously is about **1.3 mL**, and amounts greater than **2 mL will most likely cause painful pressure**.

SC

- Most typically, subcutaneous **insulin needles are 25 to 30 gauge with length of five-sixteenths to five-eighths of an inch**.
- **Irritating drugs** and those in thick suspension may produce **induration**, **sloughing**, or **abscess** and may be painful. Such preparations are **not suitable for subcutaneous injection**.

Intradermal Route

- A number of substances may be effectively injected **into the corium(dremis)**, the more vascular layer of the skin just beneath the epidermis.
- These substances include various agents for **diagnostic determinations, desensitization, or immunization**. The usual site for intradermal injection is the anterior forearm.
- A short (**three-eighths of an inch**) and narrow (**23- to 26-gauge)** needle is usually employed.
- Usually **only 'about 0.1 mL** may be administered in this manner.

IDEAL REQUIREMENTS

- Sterility (must)
- Pyrogen free (must)
- Free from particulate matter (must)
- Clarity (must)
- Stability (must)
- Isotonicity Solvents or vehicles used must meet special purity and other standards.
- Restrictions on buffers, stabilizers, antimicrobial preservative. Do not use coloring agents.
- Must be prepared under aseptic conditions.
- Specific and high quality packaging.

FORMULATION OF STERILE DOSAGE FORM

- Sterile dosage forms can be formulated as solutions, suspension, emulsion, liposomes, microspheres, nano systems and powders to be reconstituted as solution.
- Solvent system suitable for sterile products are limited to those that produce little or no tissue irritation, water is the most common.
- All components must be pure.

STERILE FORMULATIONS

- Sterile dosage forms and delivery systems include injectables (ie, solutions, suspensions, emulsions, and dry powders for reconstitution), intramammary infusions, intravaginal delivery systems, and implants.

SOLUTIONS

- A **solution** for injection is a mixture of 2 or more components that form a single phase that is homogeneous down to the molecular level.
- "Water for injection" is the most widely used solvent for parenteral formulations.
- However, a nonaqueous solvent or a mixed aqueous/nonaqueous solvent system may be necessary to stabilize drugs that are readily hydrolyzed by water or to improve solubility.
- A range of excipients may be included in parenteral solutions, including antioxidants, antimicrobial agents, buffers, chelating agents, inert gases, and substances for adjusting tonicity. Antioxidants maintain product stability by being preferentially oxidized over the shelf life of the product

SOLUTIONS

- Antimicrobial preservatives inhibit the growth of any microbes that are accidentally introduced while doses are being withdrawn from multiple-dose bottles and act as adjuncts in aseptic processing of products.
- Buffers are necessary to maintain both solubility of the active ingredient and stability of the product.
- Chelating agents are added to complex and thereby inactivate metals, including copper, iron, and zinc, which generally catalyze oxidative degradation of drugs.
- Inert gases are used to displace the air in solutions and enhance product integrity of oxygen-sensitive drugs. Isotonicity of the formulation is achieved by including a tonicity-adjusting agent.

SOLUTIONS

- Failing to adjust the tonicity of the solution can result in the hemolysis or crenation of erythrocytes when hypotonic or hypertonic solutions, respectively, are given IV in quantities >100 mL.
- Injectable formulations must be sterile and free of pyrogens. Pyrogenic substances are primarily lipid polysaccharides derived from microorganisms, with those produced by gram-negative bacilli generally being most potent.
- Injectable solutions are very commonly used, and aqueous solutions given IM result in immediate drug absorption, provided precipitation at the injection site does not occur.

SUSPENSION

- A **suspension** for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for 0.5-30% of the suspension. The vehicle may be aqueous, oil, or both.
- Caking of injectable suspensions is minimized through the production of flocculated systems, comprising clusters of particles (flocs) held together in a loose open structure.
- Excipients in injectable suspensions include antimicrobial preservatives, surfactants, dispersing or suspending agents, and buffers.
- Surfactants wet the suspended powders and provide acceptable syringeability while suspending agents modify the viscosity of the formulation.

SUSPENSION

- The ease of injection and the availability of the drug in depot therapy are affected by the viscosity of the suspension and the particle size of the suspended drug.
- These systems afford enhanced stability to active ingredients that are prone to hydrolysis in aqueous solutions.
- Compared with that of injectable solutions, the rate of drug absorption of injectable suspensions is prolonged because additional time is required for disintegration and dissolution of the suspended drug particles.
- The slower release of drug from an oily suspension compared with that of an aqueous suspension is attributed to the additional time taken by drug particles suspended in an oil depot to reach the oil/water boundary and become wetted before dissolving in tissue fluids.

EMULSION

- An **emulsion** for injection is a heterogeneous dispersion of one immiscible liquid in another; it relies on an emulsifying agent for stability.
- Parenteral emulsions are rare because it is seldom necessary to achieve an emulsion for drug administration.
- Untoward physiologic effects following IV administration may occur, including emboli in blood vessels if the droplets are >1 μm in diameter.
- Formulation options for injectable emulsions are also severely restricted because suitable stabilizers and emulsifiers are very limited. Examples of parenteral emulsions include oil-in-water sustained-release depot preparations, which are given IM, and water-in-oil emulsions of allergenic extracts, which are given SC.

EMULSION

- Intravenous fat emulsions (e.g., **In-tralipid,** 10, 20, 30%, Clintec; Liposyn II, 10, 20%, Abbott; Liposyn III, 10,20,30%, Abbott) have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods, usually more than 5 days.
- The product contains up to 30% soybean oil emulsified with egg yolk phospholipids in a vehicle of glycerin in water for injection. The emulsion is administered via a peripheral vein or by central venous infusion.

DRY POWDER

- A **dry powder** for parenteral administration is reconstituted as a solution or as a suspension immediately prior to injection.
- The principal advantage of this dosage form is that it overcomes the problem of instability in solution.

Intravaginal delivery systems

- **Intravaginal delivery systems** include controlled internal drug release (CIDR) devices, progesterone-releasing intravaginal devices (PRID), and vaginal sponges. These systems are used for estrus synchronization in sheep, goats, and cattle.
- Silicone is used in the manufacture of the T-shaped CIDR device and the coil-shaped PRID, whereas intravaginal sponges are made from polyurethane.
- The active ingredients in these systems are synthetic or natural hormones such as progesterone, methylacetoxy progesterone, fluorogestone acetate, or estradiol benzoate.

Intravaginal delivery systems

- An applicator consisting of a speculum and a separate plunger is used to insert sponges into the vaginal cavities of sheep and goats, and PRID into the vaginal cavities of cattle.
- A different type of applicator is used for inserting CIDR devices into the vaginal cavities of sheep, goats, and cattle.
- Retention in the vagina depends on either the entire device (sponges and PRID), or the wings (CIDR device), expanding. With all 3 devices, gentle pressure exerted on the vaginal wall is responsible for retention of the device, which is >95%.

IMPLANTS

- The majority of **implants** used in medicine are compressed tablets or dispersed matrix systems in which the drug is uniformly dispersed within a nondegradable polymer.
- Drug release from dispersed matrix systems involves dissolution of the drug into the polymer, followed by diffusion of the drug through the polymer, and partitioning from the surface of the polymer into the surrounding aqueous environment.
- Implants are available to increase weight gain and feed conversion efficiency in food-producing animals. These implants are typically prepared in a manner similar to tablets.

IMPLANTS

- One controlled-release implant consists of a cylindrical core of silicone, surrounded by an outer layer of estradiol-loaded silicone.
- A range of implants is available to enhance reproductive performance in breeding animals.
- These include ear implants containing norgestomet dispersed in polyethylene methacrylate or silicone, a biocompatible tablet implant containing deslorelin (a GnRH agonist) for use in mares that does not require removal, and a sustained-release pellet of melatonin, which is implanted in the ear of ewes to enhance breeding performance.
- Testosterone pellets are available for implanting in the ears of wethers at doses of 70-100 mg every 3 mo for the prevention of ulcerative posthitis.

Formulation of sterile dosage forms/ Product Development

- **API/Drug**
- **Vehicles:** Water, Water Miscible vehicles, Non aqueous vehicles
- **Excipient/Cosolvent/Cosolubilizers**
  - **Antimicrobial/Preservatives:**
    - Benzyl alcohol, Bezethonium chloride, Butyl Paraben, Chlorobutanol, Metacresol, Methylparaben, Phenol, Phenylmercuric citrate, Propyl paraben, Thimersol

COMPOSITION

- **Solubilizers, Wetting agents or emulsifiers:**
  - Dimethylacetamide, Dioctyl sodium sulfosuccinate, Egg yolk phospholipid, Ethyl alcohol, Ethyl lactate, Glycerin, Lecithin, PEG40, castor oil, PEG 300, Polysorbate 20,40, 80 Povidone , propylene glycol
- **Buffers:**
  - Acetic acid, adipic acid, Benzoic acid and sodium benzoate Citric acid, ;lactic acid, maleic acid, potassium phosphate, sodium actate , sodium citrate and tartrate , tartaric acid
- **Bulking agents or tonicity modifiers:**
  - Glycerin, lactose, mannitol , dextrose, NaCl , sodium sulfate, sorbitol

COMPOSITION

- **Suspending Agents**
  - Helatin , methyl cellulose, pectin, PEG 4000, Na CMC, Sorbitol solution
- **Chelating Agents**
  - EDTA disodium, Edetate calcium disodium, EDTA tetrasodium
- **Local Anaesthetics**
  - Procaine HCl , Benzyl alcohol
- **Stabilizers**
  - Creatinine , glycine , naicinamide , sodium acetyltryptophanate , sodium caprylate , sodium saccharine
- **Antioxidants**
  - Ascorbic acid Sodium bisulfate Sodium metabisulfate , thiourea , BHT, Tocopherol

VEHICLE

- AQUEOUS VEHICLES
- NON AQUEOUS VEHICLES
- WATER-MISCIBLE VEHICLES

AQUEOUS VEHICLES

WATER

- Used for washing, rinsing, and as a vehicle
- The quality aspects of a water system are affected by the quality of the raw or potable water, any processing it receives, and the distribution system.
- If microorganism can exist in water means that the production of sterile water poses special problems of preparation, storage, and distribution.
- The microbial and chemical quality of water is of great importance in parenteral products.

AQUEOUS VEHICLES

- Most raw or potable water used in pharmaceutical processes contains a wide variety of contaminating electrolytes, organic substances, gross particulate matter, dissolved gases, such as carbon dioxide, and microorganisms.
- Bacteria indigenous to fresh raw water include *Pseudomonas* sp., *Alcaligenes* sp., *Flavobacter* sp., *Chromobacter* sp., and *Serratia* sp. Bacteria that are introduced by soil erosion, rain, and decaying plant matter include *Bacillus subtilis, B. megaterium, Klebsiella aerogenes,* and *Enterobacter cloacae.*
- Bacteria that are introduced by sewage contamination include *Proteus* sp., *Escherichia coli* and other Enterobacteria, *Streptococcus faecalis,* and *Clostridium* sp. Stored water bacteria contamination include mainly gram-negative bacteria and other microorganisms, such as *Micrococcus* sp., *Cytophaga* sp., yeast, fungi, and *Actinomycetes.*

Classification of Water

Drinking Water

- Essentially, it should be free from known pathogens and from fecal contamination, such as *E. coli*, but it may contain other microorganisms.
- Frequently contains significant levels of microorganisms and a variety of chemical impurities.
- Chemical and microbiological testing of drinking water usually includes pH, free chlorine, chloride, sulfate, ammonia, calcium and magnesium, carbon dioxide, heavy metals, oxidizable substances, total solids, and bacteriological purity for total microbial count and *E. coli*.

Classification of Water

Purified Water

- Produced by passing the drinking water through anion and cation exchange resin beds or reverse osmosis.
- Ion-exchange treatment will remove dissolved ionic impurities but it does nothing to improve the microbiological quality of the water.
- Ion-exchange beds that are not frequently regenerated with strong acid and alkali will contribute significantly to bacteriological contamination, leading often to pyrogenic problems.

Classification of Water

- Reverse osmosis treatment will remove a large portion of the dissolved minerals, particulates, bacteria, viruses, and pyrogens.
- Chemical and microbiological testing of purified water includes determination of pH, chloride, sulfate, ammonia, calcium, carbon dioxide gas, heavy metals, oxidizable substances, total solids, and bacteriological purity for total microbial count and *E. coli*.

Water for injection

Bacteriostatic Water for Injection

Sterile Water for Injection

AQUEOUS VEHICLES

A. Aqueous vehicle :

1.Water For Injection(WFI) USP :

- Water for injection is intended not only to conform to a high degree of chemical purity but also to be free from pyrogenic substances.
- USP requirement include not more than 10 parts per million of total solids.
- WFI may prepared by either distillation or reverse osmosis.
- Distillation is the most widely used and accepted method of producing sterile pyrogen-free water.
- pH of 5.0 to 7.0

AQUEOUS VEHICLES (WFI)

- The bacterial contaminants of distilled water are usually gram-negative bacteria.
- The heating and storing of water for injection at 80°C will prevent bacterial growth and the production of pyrogenic substances that accompany such growth.
- Chemical and microbiological testing of water for injection include pH, chloride, sulfates, ammonia, calcium, carbon dioxide, heavy metals, oxidizable substances, total solids, and pyrogen.
- Stored in chemically resistant tank.

AQUEOUS VEHICLES

2. Bacteriostatic Water for Injection (BWFI) :

This type of water used for making parenteral solutions prepared under aseptic conditions and not terminally sterilized. Need to meet USP sterility test. It can contain an added bacteriostatic agent when in containers of 30ml or less

AQUEOUS VEHICLES

3. Sterile Water for Injection USP

SWFI containing one or more suitable bacteriostatic agents. Multiple-dose containers not exceeding 30 ml. They are permitted to contain higher levels of than WFI because of the possible leaching of glass container. Sterile Water for Irrigation. Wash wounds, surgical incisions, or body tissue

4. Sodium Chloride Injection, USP

5. Bacteriostatic Sodium Chloride Injection, USP

6. Ringer's Injection, USP,Ringer's Injection, USP

NON AQUEOUS VEHICLES

- Used when **limited water solubility of a medicinal substance or its susceptibility to hydrolysis.**
- **Fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol**, and a number of less often used agents, including **ethyl oleate, isopropyl myristate, and dimethyl acetamide**.

NON AQUEOUS VEHICLES

Properties of a non aqueous vehicles

- The selected vehicle must be **nonirritating, nontoxic in the amounts administered, and not sensitizing**
- It must **not exert a pharmacological activity of its own**
- It should not adversely affect the activity of the medicinal agent
- It should be physicallyl and chemically stable at various pH levels
- Its viscosity must be such as to allow ease of injection (suitable for use in syringes,syringeability)
- Its fluidity must be maintained over a fairly wide temperature range
- Its boiling point should be sufficiently high to permit heat sterilization
- It should be miscible with body fluids
- It should have low vapor pressure to avoid problems during heat sterilization
- It should have constant purity or ease of purification and standardization

NON AQUEOUS VEHICLES

- Nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.
- **USP specifies restrictions on the fixed vegetable oils in parenteral products.**
  - They **must remain clear when cooled to 10°C** (50°F) to ensure the stability and clarity of the injectable product during refrigeration.
  - The oils **must not contain mineral oil or paraffin**, as these materials are not absorbed by body tissues.
  - The fluidity of a vegetable oil generally depends on the proportion of unsaturated fatty acids, such as oleic acid, to saturated acids, such as stearic acid.
  - Oils to be employed in injections must meet officially stated requirements of **iodine number and saponification number.**

NON AQUEOUS VEHICLES

- **Examples of fixed oils used in injections**
- Corn oil, cottonseed oil, peanut oil, and sesame oil. Castor oil and olive oil have been used on occasion .
- Although the toxicity of vegetable oils is generally considered to be relatively low, some patients exhibit **allergic reactions to specific oils**.
- Thus, when vegetable oils are employed in parenteral products, the label must state the specific oil.

WATER-MISCIBLE VEHICLES

Primarily used to effect solubility of drugs and/or reduce hydrolysis.

PRESERVATIVES & BUFFERS

Preservatives

Required to prevent microorganism growth Limited concentration of agents - Phenylmercuric nitrate and Thiomersol 0.01% Benzethonium chloride and benzalkonium chloride, Phenol or cresol 0.5% - Chlorobutanol 0.5%

Buffers

Added to maintain pH Results in stability Effective range, concentration, chemical effect

e.g Citrate and Acetate buffer, and Phosphate buffer

TONICITY ADJUSTERS

- Electrolytes:Nacl
- Non elecrolytes: Glucose,Mannitol,Glycerine
- Ex. Of isotonic:Dextrose injection 5%&Nacl injection 0.9%
- Not important in IM& SC
- Important in ID,intraspinal
- Toncity can be measurement by:

  osmometer,Fragility point

OTHER ADDITIVES

- Surfactant:Polysorbate ethers
- Suspending agent:Methyl cellulose,CMC,PVP
- Emulsifiers:Lecithin
- Chelating agents:Disodium EDTA
- Compexing agent:2-OH propyl b-cyclodextrane
- Protein stabilisers:Amino acids,pvp
- Antioxidants:Ascorbic acid,Cysteine

PACKAGING

- The microbial flora of parenteral packaging components is affected by its composition, transportation exposure, and storage conditions. Packaging components and closure systems used for parenteral filling have to be sterile and pyrogen free.
- Glass containers and rubber stoppers, particularly those transported in cardboard boxes, often contain mold spores of *Penicillium* sp. and *Aspergillus* sp., and bacteria, such as *Bacillus* sp. and *Micrococcus* sp.
- Aluminum, Teflon, metal foils, and other polymeric materials, all of which usually have a smooth impervious surface free from crevices or interstices, are usually free from microbial contamination.

Packaging Design

Commercially available packaging designs for parenteral products are

- glass single-dose ampuls sealed by fusion,
- glass single- or multiple-dose vials with elastomeric closure and
- aluminum overseal; glass or polymeric bottles of more than 50 ml for large volume intravenous administration, and
- cartridges of various designs and components that involve one or more of the above materials, plus the attached needle.

Packaging Material Reqirment

Parenteral containers intended to provide protection from light must meet the requirements for the USP light transmission test (Table). The light-resistant amber color of parenteral containers results from an interaction between iron and sulfur for greenish amber or iron and titanium for brownish amber.

Table Glass and Plastic Light Transmission Limits for Parenteral Containers

	Max. % light transmission at any wavelength between 290 and 450 nm (USP)	
Size	Flame sealed	Closure sealed
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50 and more	15	10

PACKAGING

- Packaging materials:Glass ,Plastic,Rubber
- Sealing Ampoules Ampoules are unique in that the primary and secondary seal are the same.
- Ampoules are sealed by melting a portion of glass in a flame.
- Pull seal – Slow, Reliable, powder or other types with wide opening Roll or Tip seal

CONTAINERS AND CLOSURES

GLASS CONTAINER

Glass is still the container of choice for small volume parenterals because of its chemical resistivity as well as resistant to water, acids, bases, and salts to varying degrees. .

It is composed of silicon dioxide, with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminium, boron and iron.

The basic structural network of glass is formed by silicon oxide tetrahedron.

However, glass can be chemically active under certain conditions, for example, the formation of flakes in neutral saline solutions.

CONTAINERS AND CLOSURES

- Boric oxide will enter into this structure, but most of the other oxides do bot.
- The latter are only loosely bound and relatively free to migrate.
- These migratory oxides may leached into a solution in contact with the glass.
- The oxides thus dissolved may hydrolysed to raise pH of the solution and catalyse or enter into reaction.
- Such occurrences can be minimize by proper selection of glass composition.

TYPES OF GLASS

Type I : A borosilicate glass

Type II: a soda lime treated glass, silicone coated

Type III: a soda lime glass NP: General Purpose soda lime glass, not for parenteral.

Type I glass is composed of silicon dioxide (81%) and boric oxide (13%) with low level of non-network forming oxides.

While Type II and type III glass compounds are composed of relatively high proportion of sodium oxide (14%) and calcium oxide (8%).

Typical Composition of Glass

Table Identification of Glass Types Used in Parenterals

Type	Description	Major chemical composition Component	% Avg.	USP test	Limit size (ml)	0.02 N acid (ml)
I	Borosilicate glass, highly resistant	SiO_2	80	Powdered glass	All	1.0
		Al_2O_3	5			
		Na_2O	7			
		K_2O	0.5			
		B_2O_3	12			
		CaO	1			
II	Sulfur dioxide-treated soda-lime glass, dealkanized inner surface	SiO_2	75	Water attack	100 or	0.7
		Al_2O_3	2			
		Na_2O	10		Over 100	0.2
		K_2O	0.5			
		B_2O_3	3			
		CaO	10			
III	Soda-lime glass, somewhat average chemical resistance	SiO_2	75	Powdered glass	All	8.5
		Al_2O_3	2			
		Na_2O	15			
		K_2O	0.5			
		B_2O_3	3			
		CaO	12			

Type I and II Glass

- As Type I glass is made from a chemically high resistant borosilicate glass. It has low leachability, low thermal coefficient of expansion, and is generally suitable for all parenteral drug products
- Type II glass is made from dealkalized soda-lime glass, containing approximately 10% each of sodium oxide and calcium oxide. The presence of these two oxides makes this type of glass chemically less resistant than Type I.

Type II and III Glass

- However, its chemical resistance can be improved by dealkalization using sulfur dioxide.
- This improved glass inner surface will break down, if it is repeatedly exposed to heat sterilization, thermal depyrogenation, or alkaline detergent treatments.
- Thus, it is suitable for a one time use, for a drug solution that has been buffered to a pH below 7, or a product that is not reactive with this type of glass, like most antibiotic sterile solids.
- Type III glass is also made from a soda-lime glass that contains relatively higher levels of sodium and calcium oxides than Type II. It is generally used for dry drug products.

Treatment to Glass

- Parenteral containers made of glass may be treated in order to reduce alkalinity or improve the inner surface.
- This is usually accomplished by sulfur dioxide hot gas treatment, glass annealing at higher temperature, or hydrofluoric acid washing.

Polymeric Container

PLASTIC COTAINERS

Principle ingredient of plastic containers are thermoplastic polymers like polyethylene, polypropylene, PVC, polycarbonate, polyamide, polystyrene, teflon. Plastic materials used in the medical field have less other additives.

In certain cases, some amount of plasticizer, fillers, antistatic agents, antioxidents and other ingredients may be added.

Most of the plastic containers melt at elevated temperatures except polyethylene and polystyrene. Plastic materials used mainly because they are light weight, no breakable and with low additives have low toxicity and low reactivity with products.

PLASTIC COTAINERS

Reactivity can be occur with sorption of the polymer in some cases. Additive leached and may react with the products.

Most polymers are adversely affected by elevated temperatures required for thermal sterilization and have a relatively high permeability for water vapor.

Significant permeation of gases like oxygen may occur with some plastic containers.

RUBBER CLOSURES

Rubber closures are used to seal the openings of cartridges, vials and bottles and permeate and withdrawal of needle without loss of integrity of the sealed containers.

Rubber closures are compounded of several ingredients like natural rubber or synthetic polymers usually sulfur and 2 mercaptobenzothiazole.

Closure should be completely nonrective with the products.

SEALING

Sealing of Bottles, Cartridges and Vials Primary seal consisting of a tight rubber or plastic closure and secondary seal that holds the primary seal in place. Secondary seals are usually aluminum caps that are crimped on to a thread less container.


Stanabol 50
Stanozolol
10ml
for intramuscular injection
50mg/ml


Stanabol 50
Stanozolol
10ml
for intramuscular injection
50mg/ml

Parenteral containers intended to provide protection from light must meet the requirements for the USP light transmission test (Table). The light-resistant amber color of parenteral containers results from an interaction between iron and sulfur for greenish amber or iron and titanium for brownish amber.

Table Glass and Plastic Light Transmission Limits for Parenteral Containers

	Max. % light transmission at any wavelength between 290 and 450 nm (USP)	
Size	Flame sealed	Closure sealed
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50 and more	15	10


Stanabol 50
Stanozolol
10ml
for intramuscular injection
50mg/ml
British Dragon Pharmaceuticals
www.britishdragon.com

STERILIZATION

STERILIZATION

- Steam sterilization
- Dry heat sterilization
- Sterilization by filtration
- Gas sterilization
- Sterilization by ionizing radiation

SPECIAL TYPES OF PARENTERALS

- Suspension
- Emulsion

SUSPENSION

- Parenteral suspension is a dispersed,multiphased, heterogeneous system of insoluble solid particles intended principally for intramuscular and subcutaneous injection.
- Because a delicate balance of variables is required in order to formulate a suitable product, a suspension is one of the most difficult parenteral forms to prepare.
- Such a product must not cake during shipping and storage and should be easy to suspend and inject through an 18 to 21 gause needle throughout its shelf life.

SUSPENSION

- To achieve these goals it is necessary to control the crystallization, particle size reduction,and sterilization of the drug substance.
- Suspension give prolong drug relese.particle size of drug shoud be small and uniform.
- Suspension require following additives wetting agent,suspending agent,buffering agent, preservative, antioxidant,ionicity agents

Example of ingredients used in aqueous parenteral suspensions

- Suspending agent
- Gelatin, mannitol,povidone
- Surfactants
- Lecithin,polysorbate 80.
- Solubilizing agents
- Propylene glycol
- PH adjustment
- Citric acid, sodium citrate.

Methods for Parenteral Suspension

Two basic method are used to prepare parenteral suspension;

1 .sterile vehicle and powder are combined aseptically.

2.sterile solutions combined and crystal formed in situ.

Problems in Parenteral Suspension

Problems encountered in suspension formulation are:

- Settling and caking.
- Polymorphic transformation.
- Crystal growth.

EMULSIONS

- An emulsion is a heterogenous dispersion of one immiscible liquid in another.
- This inherently unstable system is made possible through the use of an emulsifying agent, which prevent coalescence of the dispersed droplet.
- Parenteral emulsion are rare because it is necessary(and difficult) to achieve stable droplet of less than 1 micron meter to in prevent emboli in blood vessels and it is not usually necessary to achieve an emulsion for drug administration.
- Formulation options are severely restricted through a very limited selection of stabilizers and emulsifiers primarily due to the dual constraints of autoclave sterilization and parenteral injection.

EMULSIONS

Parenteral emulsions are used for several purposes, including :

- Water-in-oil emulsions of allergenic extracts
- Oil-in-water sustained-release depot preparations
- Oil in-water nutrient emulsion.

EMULSIONS

Problems encountered in emulsion formulation:

- 1.creaming and cracking
- 2.Rancidity in oil phase
- 3.Partitioning of preservative between oil and water phase

TESTING

The physicochemical tests includes

- pH,
- Turbidity,
- Residue on drying,
- Iodine number and
- Heavy metal content.
- The biological tests on saline, polyethylene glycol 400 and cottonseed oil extracts includes acute and chronic toxicity on mice and rabbits.