



Sterile Products

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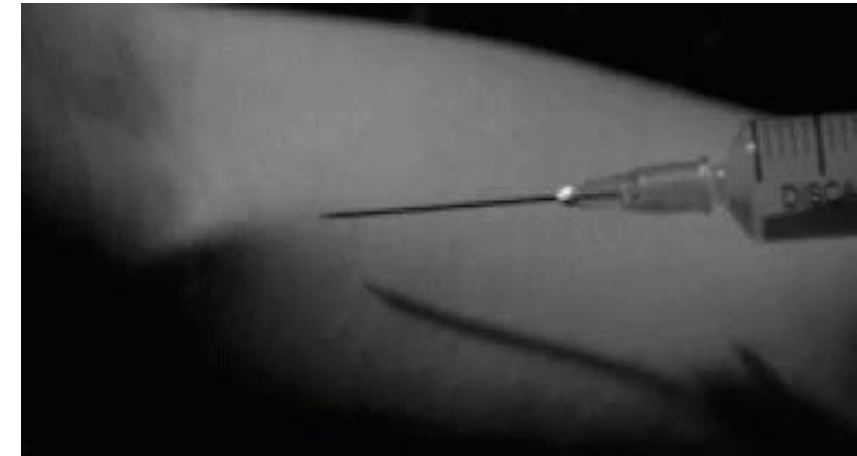
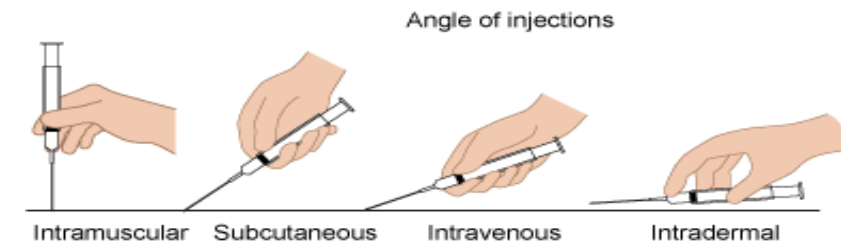
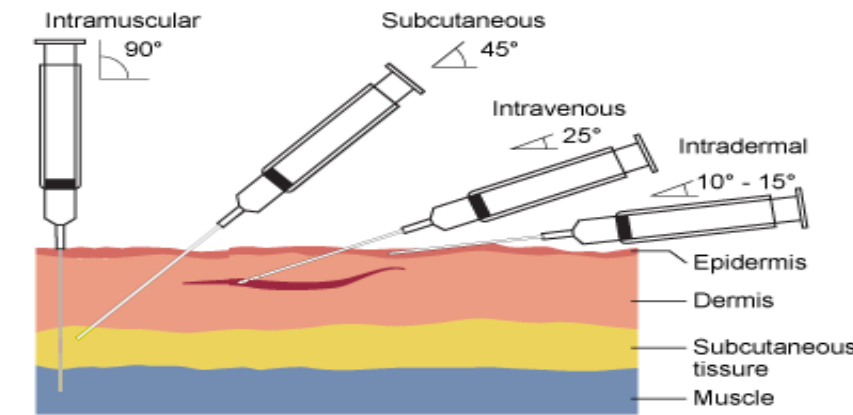
Sterile Products

- These are dosage forms of therapeutic agents that are **free** of viable microorganisms (MO).
- These include **Parenteral, ophthalmic, and irrigating** preparations.
- Of these products, **Parenteral products** are **unique because** they are injected through the skin or mucous membranes into the 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**:
 1. **Be free** from microbial contamination and toxic components,
 2. As well as possess an exceptionally **high level of purity**.



Parenteral Administration

- 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 preparation may be given by various routes:
- Intravenous (IV).
- Intramuscular (IM).
- Subcutaneous (SC.).
- Intradermal (ID).
- Intraperitoneal (IP).
- After IV injection, the drug will be immediately available, and there is no need for absorption.



Parenteral Administration

- **All other routes**, at least 1) a blood vessel wall, and usually, 2) one or more tissue cell walls, must **be permeated before** the drug can enter circulation.
- Most often, this occurs by **passive diffusion** and is most favorable when the drug has **both** lipophilic and hydrophilic properties, with the lipophilic being predominant.
- For **non**vascular injection, absorption is **affected by** factors such as the:
 1. Size and number of **blood vessels** supplying the tissue.
 2. The **movement** (exercise) of the tissue following injection.
 3. Physical and chemical **properties of the drug**.
 4. **Characteristics of the dosage form** as whether it is a solution, suspension, or emulsion; the nature of the vehicle, and pH.

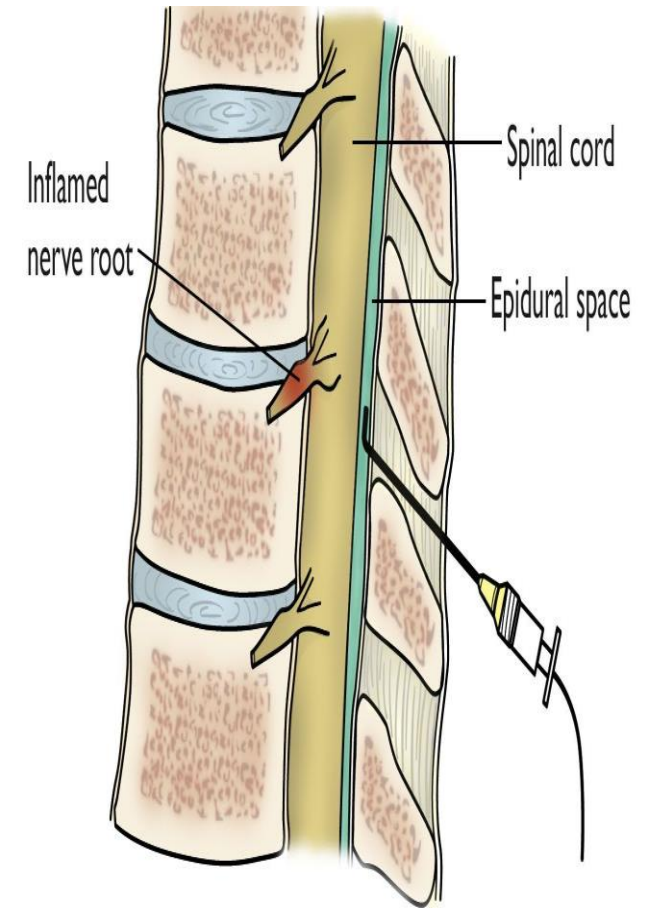
Parenteral Administration

- Once in the circulating blood, the **physiologic effect** of a therapeutic agent is affected by:
 1. The **extent** to which it distributes throughout the body,
 2. The **degree of binding** to plasma proteins,
 3. Its **rate of elimination** by hepatic metabolism and/or renal excretion.



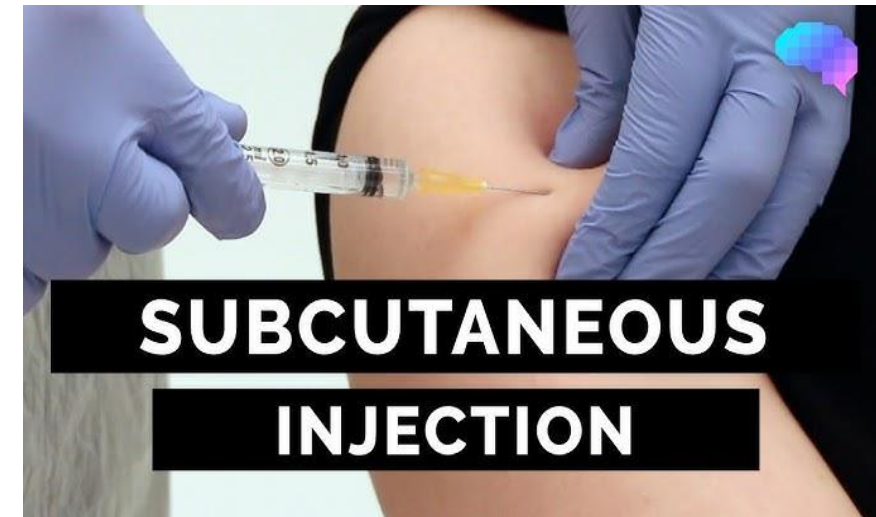
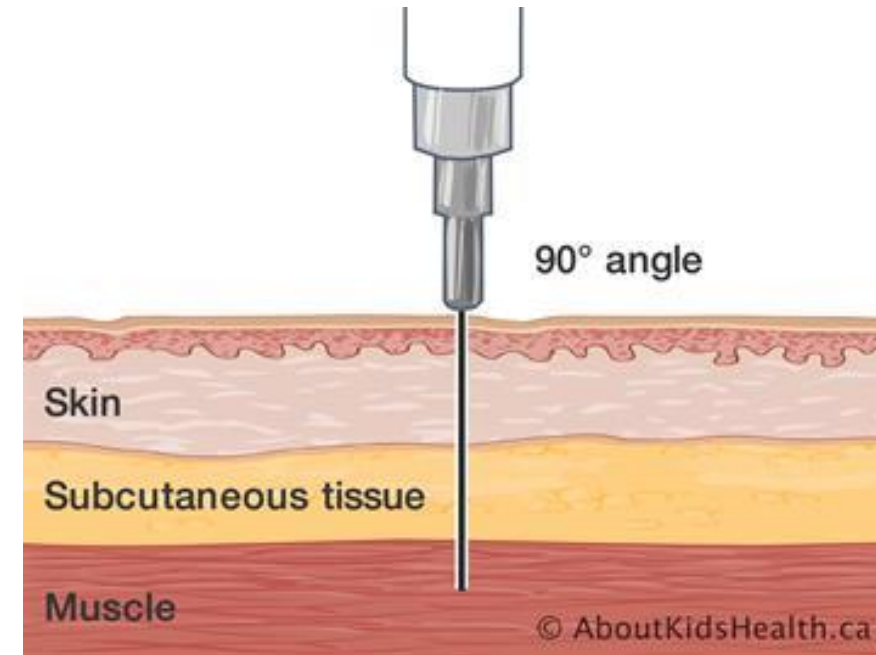
Parenteral Administration

- Intravenous (IV) and intraspinal (IS) 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.



Parenteral Administration

- **IM, SC, or ID** preparation can be in the form of **solutions, susp. 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.



Parenteral Administration

- The **nature of preparation** can significantly influence:
 1. The **rapidity of onset** or the therapeutic effect of a drug,
 2. The **duration** of the effect, and
 3. 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. →
 1. The **chemical and physical properties** of a drug must be determined,
 2. Drug **interaction** with any desired excipients must be studied,
 3. The effect of each step of the process on the drug's **stability** must be studied and understood.

Parenteral Administration

- We should notice that:
- Preparations for the eye, though **not** introduced into internal body cavities, 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.



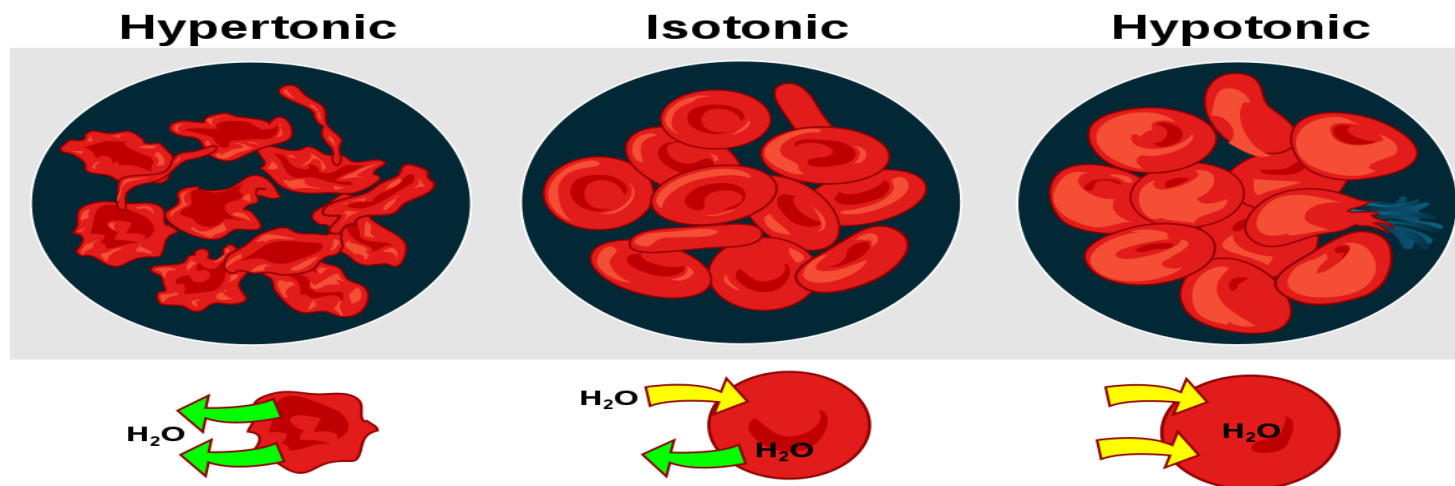
Effect of Route of Administration

- 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:
 1. The **intradermal (intracutaneous)** injection volume should be not more than **0.2 ml** because 1- tissue volume is **small and compact**. Also, 2- the absorption is quite **slow** owing to a lack of blood vessels.
 2. **S.C.** injections may be **1 ml** or less.
 3. **IM** injections, it will be difficult to inject volumes larger than **2 ml**. (it is ok to be larger but it will be difficult for example painful)
 4. **Intraspinal injections** could be **10 ml** or less.
 5. **Only** by the **IV route** may large volumes be given safely (with careful control of the rate of administration).
 - Usually not more than **one liter** at a time
 - 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 Overview

X

- Another term that affects the route of administration is isotonicity:
- **Isotonicity** is related to the state of being isotonic or having equal tension or tonicity.
- Isotonicity occurs in a cell when its solute concentration is the same as the solute concentration of the environment surrounding the cell.
- The result is there is **no net movement** of the water and permeable solutes.
- Example inside and outside red blood cells



Effect of Route of Administration

- **Isotonicity** is of great importance (why parenteral should be isotonic):
 1. Isotonicity is a characteristic that is probably of **the greatest importance** for **intraspinal** injections **because** **1-** the circulation of the cerebrospinal fluid is slow, and **2-** disturbances of osmotic pressure **quickly cause** headache and vomiting.
 2. Since **intracutaneous** injections are given mostly for diagnostic purposes, **non-isotonic** solutions **may cause** false signs of irritation.
 3. **Isotonicity** is **preferable** for the comfort of the patient but is **not essential** for **SC and IM** injections.
 - **Note:** For the **rapid absorption** of drugs given **intramuscularly**, a slightly **hypertonic** solution **may** increase the rate by causing local effusion of tissue fluids.
 4. **Usually**, IV fluids should be isotonic, although slow administration of a paratonic solution may be performed safely if rapid dilution with the blood occurs.

Effect of Route of Administration

- **Type of the Dosage Form Allowed:**
- In general, **only solutions** of drugs in **water** may be given intravenously.
- **Suspensions** may not be given **IV** 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.

Effect of Route of Administration

- **Ophthalmic Preparations**
- Ophthalmic preparations are formulated in much the same way as parenteral solutions.
- The eye is particularly sensitive to irritation; therefore, the formulation should be directed toward 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.
- A foreign body sensation has been found to increase as the concentration of suspended particles, regardless of size, approaches 5%.



Effect of Route of Administration

- **Sterility Requirements:**
- 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.

- **Ophthalmic Preparations:**
- These are products to be instilled into the eye, they are non-parenteral by definition but they have the same 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. →

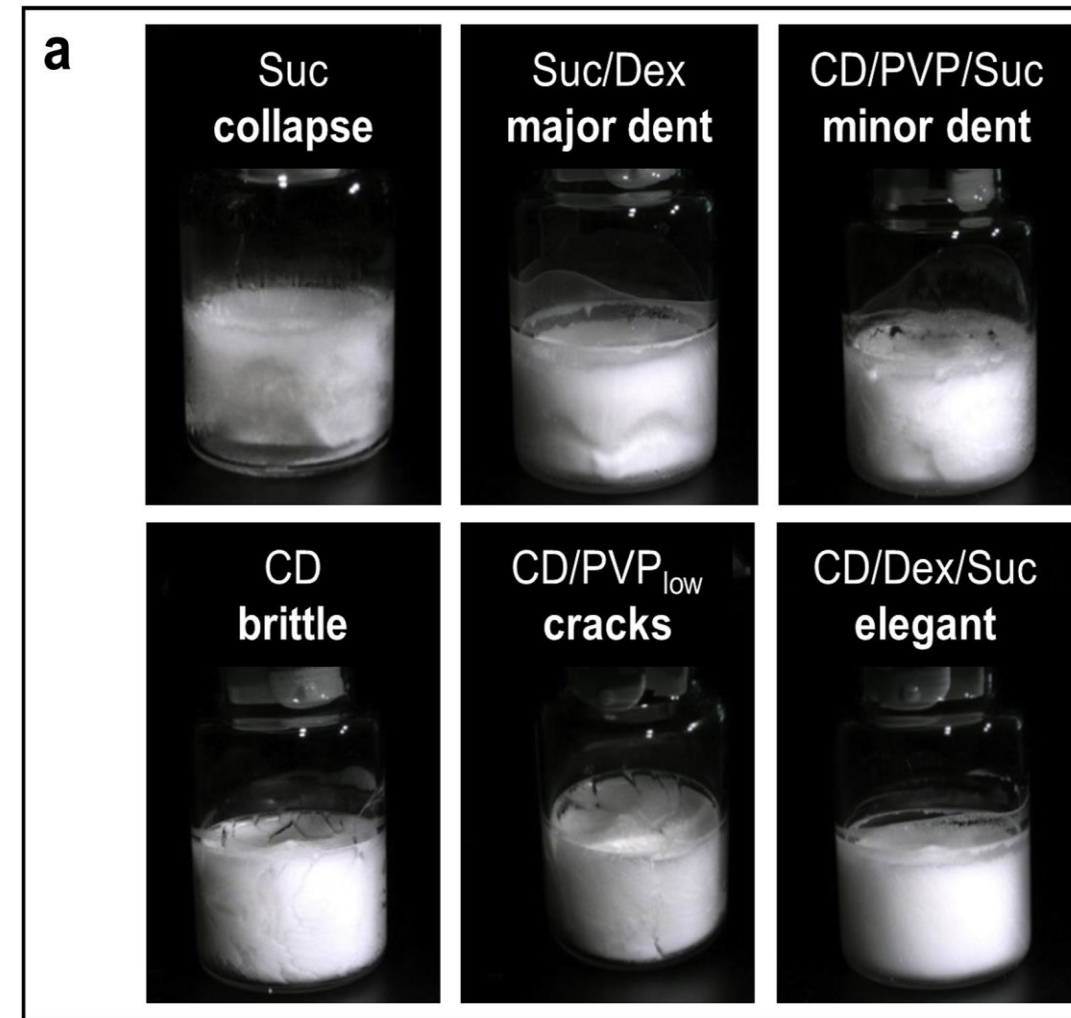


- These preparations require:
 1. **Buffers** to stabilize the pH of the product
 2. Additives to render it **isotonic** or nearly so.
 3. **Stabilizers** such as antioxidants, when appropriate for the particular ingredients.
 4. Ophthalmics used in larger quantities, such as eye irrigation, or the case of devices such as contact lenses, are usually relatively uncomplicated solutions similar to large-volume parenteral.
 5. One characteristic **not** as critical for ophthalmic 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.



- The percentage of solids in the frozen plug should be between approximately 2 and 25%.
- Among the **best salts** for providing 1) uniform crystal size, 2) uniform color and texture, 3) physical strength, and 4) 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 appear crusty and crumbly.



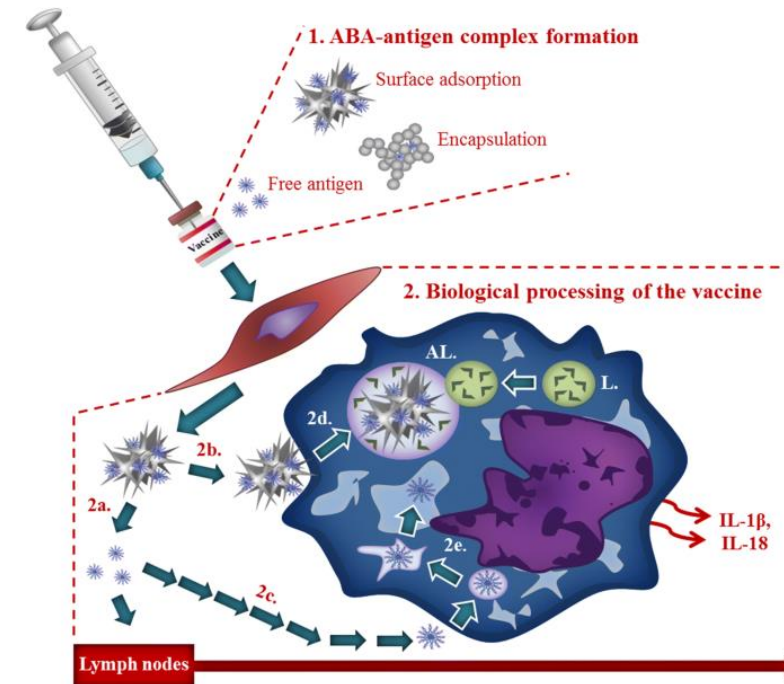
- These formulations are designed ideally to provide slow, constant, and sustained release of a drug over a prolonged period of time, essentially to simulate and **replace** the more hazardous, continuous I.V. infusion of a drug.
- **Classification of long-acting preparations: → 4 types:**
 - A. In one 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.



- **Techniques** (types) for formulating **dissolution control products**:
 1. The formation of drug **salts with very low aqueous solubility** is one of the **most common** approaches to this type of formulation.
 2. 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.
 3. Further, the **suspension** of the drug particles in vegetable oils, especially if gelled with substances such as **aluminum monostearate**, produces prolonged absorption rates.

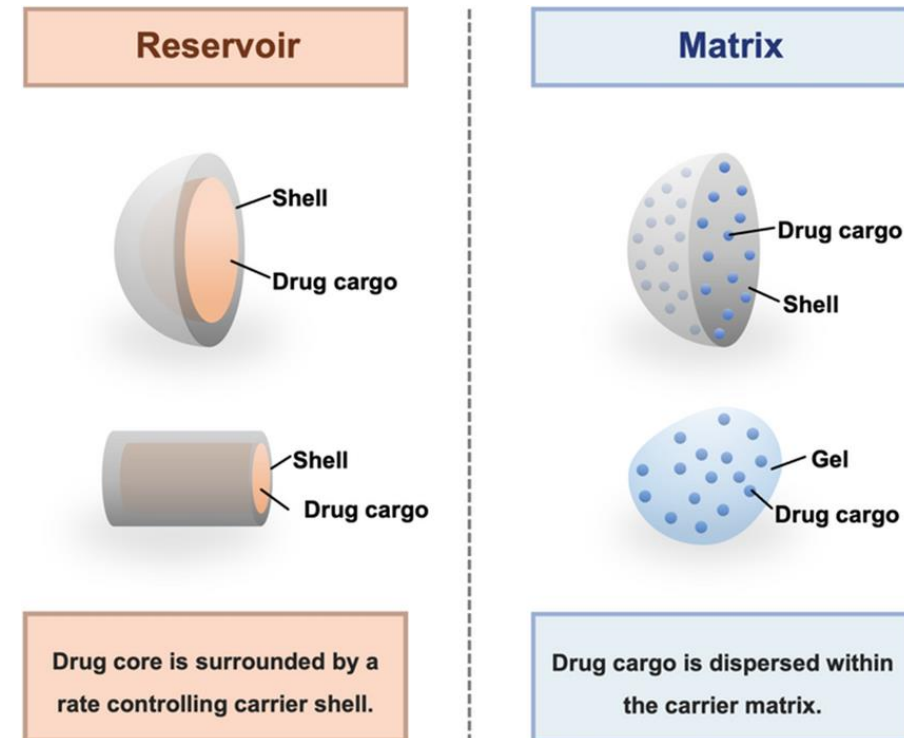
B. Adsorption-type depot preparations: Another type of depot formulation is produced by the binding of drug molecules to adsorbents. →

- Only the free portion, in equilibrium with that which is bound, can be absorbed.
- → As the 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.



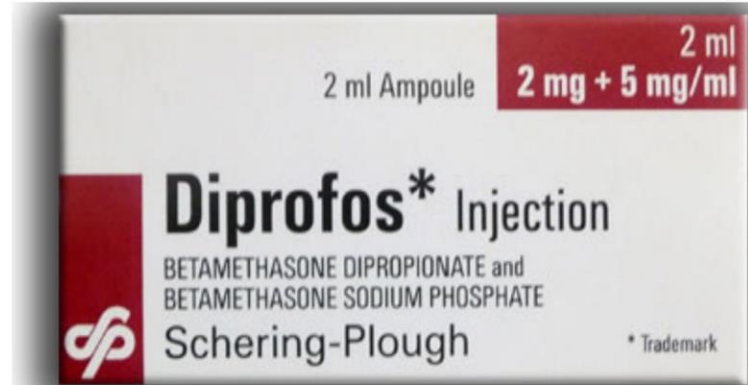
C. A third type of depot preparation is the **encapsulation type depot preparation**, in which biodegradable or bioabsorbable macromolecules such as **gelatin, phospholipids, and long-chain fatty acids** become a diffusion **matrix** for the drug.

- The drug is **encapsulated within the matrix**, and the release of drug molecules is controlled by **1) the rate of permeation out of the diffusion barrier** and **2) the rate of biodegradation** of the barrier macromolecules.



D. A fourth type is the **esterification type depot preparation**, in which esters of a drug that are bio-erodible are synthesized.

- The esterified drug is deposited in tissue at the site of injection to form a **reservoir of the drug**.
- The rate of drug absorption is **controlled by 1) the partitioning** of the drug esters **from** the reservoir **to** tissue fluid and **2) the rate at which the drug ester regenerates** the active drug molecule.
- Often, these esters are dissolved or suspended in **oleaginous vehicles**, which further **slows** the release.



Formulations:

Parenteral Suspensions

1. The solids content of parenteral suspensions usually ranges between 0.5 and 5% but may go as high as 30% in some antibiotic preparations.
2. The 1) amount of solids and the 2) 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.
3. Probably the most important requirement for parenteral suspensions is small and uniform particle size.



Formulations:

Parenteral 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:
 1. **The rigid requirement** for particle size control to prevent emboli in blood vessels,
 2. **The limited choice of emulsifiers** and stabilizers of low toxicity, and
 3. **The preservation** of the oil phase against the development of rancidity.



Formulation Development

- The formulation of a sterile product involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product.
- Rarely is it preferable to dispense a drug singly as a sterile dry powder unless the formulation of a stable liquid preparation is not possible.
- Parenteral formulation generally contains the following:
 1. The therapeutic agent.
 2. **Vehicle or solvent** selection: Aqueous systems, or non-aqueous systems.
 3. **Solutes:** (Added substances) can be antibacterial, antioxidants, buffers, tonicity contributors, chelating agents, and inert gases.
 4. **Containers.**

Therapeutic Agent

- A therapeutic agent is a chemical compound subject to the physical and chemical reactions characteristic of the class of compounds to which it belongs.
- Therefore, a **careful evaluation** must be made of every **combination** of two or more ingredients to ascertain whether or not adverse interactions occur, and if they do, of ways to **modify the formulation** so that the reactions are **eliminated or minimized**.
- The formulation of sterile products is **challenging**, with respect to the knowledge and ingenuity (experience) of the persons responsible.

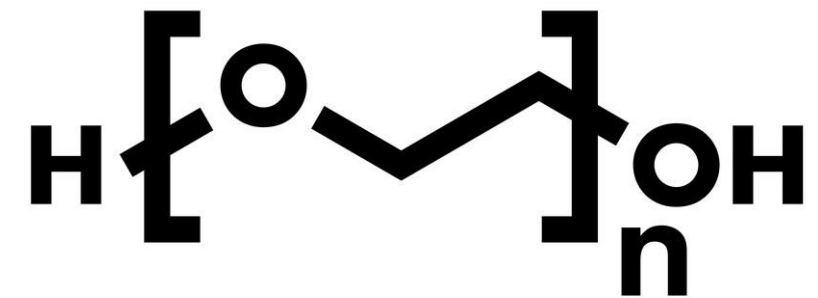


Vehicle or Solvent System

- **Aqueous Systems**: the most frequently employed vehicle for sterile products is water since it is the vehicle for all-natural body fluids.
- **Tests for quality and purity of water:**
- One of the most inclusive tests for the quality of water is the total solids content, a **gravimetric evaluation** of the dissociated and undissociated organic and inorganic substances present in water.
- The 10 ppm total **solids** officially **permitted** for Water for Injection (WFI) **may be** much too high when used as the **vehicle** for many products.
- Water shall contain a minimal amount of organic compounds. Such compounds are undesirable for two main reasons: **1)** they may be toxic, and/or **2)** they may serve as sources of nutrition for microorganisms.
- In practice, WFI normally should **not** have a conductivity of more than **1 micromho** (1 megohm, approximately 0.1 ppm NaCl) and total organic carbon (TOC) not more than **500 ppm**.

Vehicle or Solvent System

- **Non-aqueous and Mixed solvents**
- In the formulation of sterile pharmaceutical products, it is **sometimes necessary** to **eliminate** water entirely or in part from the vehicle, **primarily because** of **1)** solubility factors or **2)** hydrolytic reactions.
 - Water-**immiscible** solvents include fixed oils, ediyol oleate (**ethyl** oleate), isopropyl myristate, and benzyl benzoate.
- The **most frequently used non-aqueous** solvents are polyediylene glycol (polyethylene glycol), propylene glycol, and fixed oils.



PEG

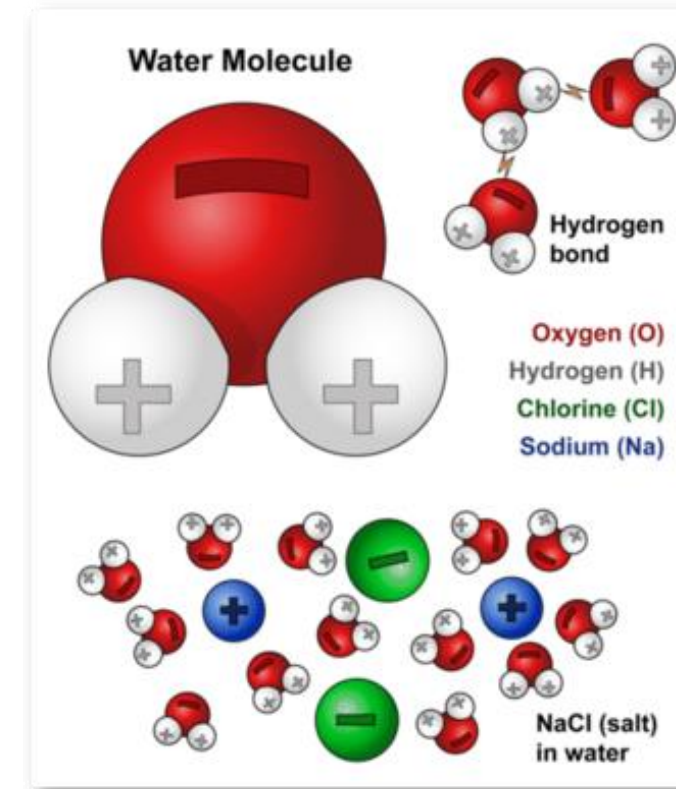
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Vehicle or Solvent System

Solvent selection:

- A parenteral therapeutic agent is given by preference as a solution.
- If aqueous, → the solution is **physiologically compatible** with body tissues, and the **biological response** elicited should be reasonably **predictable**.
 - The **high dielectric constant** of water makes it possible to **dissolve** ionizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances as alcohols, aldehydes, ketones, and amines.
 - Conversely, water is a **poor solvent** for nonpolar compounds, such as alkaloidal bases, which require non-polar solvents.



Vehicle or Solvent System

- Since **therapeutically active** compounds given by injection range in property from **highly polar** to **non-polar**, → solvents having complementary properties must be employed if a solution is to be **achieved**.
- Adding to the complexity of solvent selection is the requirement that the solvents to be injected **must be** of low toxicity to body tissues.
 - Ether is a solvent for testosterone, but is **highly irritating** to body tissues and **cannot be used alone** as a solvent for an injectable preparation.
 - Frequently, the desired solubility can be achieved with mixed solvents, e.g. the use of **approximately 40% ethanol in water to solubilize** the digitalis glycosides.

Vehicle or Solvent System

- Compounds that are dissolved in water are often **subject to degradative reactions**, such as hydrolysis, oxidation, decarboxylation, and racemization.
- The formulation must be designed, in such cases, to minimize the degradative effects.

A. Often, these reactions are markedly affected by the pH of the solution:

1. Epinephrine in solution undergoes **racemization and oxidation**, → this can be reduced by:
 - But if the pH is maintained at **3.0 or less**, a little reaction occurs.
 - The oxidation reaction can be further reduced by **displacing atmospheric oxygen** with an inert headspace gas and adding 0.1% (w/v) sodium metabisulfite as an antioxidant.
2. Atropine sulfate rapidly **hydrolyzes** in solution, but if the pH is maintained with a buffer system at about **3.5 to 4.0**, hydrolysis does not occur at a significant rate.

Vehicle or Solvent System

B.The use of a mixed solvent system often reduces degradative reactions.

- Barbituric acid derivatives **hydrolyze readily in water**, particularly at a low pH.
 - It has been shown, however, that pentobarbital sodium is soluble and stable in a vehicle containing **60%** polyethylene glycol 400 and **10%** ethanol in **water at a pH of 8**.
- The hydrolysis reactions **do not occur in an anhydrous**, non-polar vehicle, such as fixed oil, although the presence of a small amount of water may permit slight reactions.
- Oleaginous injections are subjected, however, to the **disadvantages of being** viscous (thus difficult to administer, particularly in **cold weather**) and of involving the frequent incidence of **pain upon injection**.

Solutes (Added Substances)

1. The physical and chemical **purity of solutes** used for sterile preparations must also be exceptional.
 - Obviously, the contaminants entering a product with a solute have the same effect as if they entered via the vehicle.
 - Even small traces of contaminants may be **detrimental to products**, necessitating purification of the solute.
 - For a few substances (for example, ascorbic acid and calcium gluconate), special **parenteral grades** are commercially available.
2. In addition, solutes should be **free from microbial and pyrogenic** contamination.
 - This entails not only the **proper quality** of the chemical as **procured** but also **storage conditions** designed to prevent contamination, particularly after a container has been opened.
 - **Preferably**, production lots should be designed to **use the entire contents** of packages of chemicals **whenever possible**.

Solutes (Added Substances)

- Substances added to a product to **enhance its stability** are essential for almost every product.
- Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes.
- At the same time, these agents **must be prevented from adversely affecting** the product.
- In general, added substances **must be**:
 1. **Nontoxic** in the quantity administered to the patient.
 2. They should **not interfere** with the **therapeutic efficacy** or with the assay of the active therapeutic compound.
 3. They must also **be present and active** when needed throughout the useful life of the product.
- Therefore, these agents must be selected with great care and must be evaluated as to their effect on the entire formulation.

Solutes (Added Substances)

- **1- Antibacterial agents**
- Antibacterial agents in **bacteriostatic concentration** must be included in the formulation of products packaged in **multiple-dose vials**, and are **often included** in formulations **to be** sterilized by marginal processes or made by aseptic manipulation.
- An example is **benzalkonium chloride** in a maximum concentration of 0.01% and **benzyl alcohol** in conc. 0.5-10 %.



Solutes (Added Substances)

Antioxidants

- Included in many formulations **to protect** a therapeutic agent susceptible to oxidation, **particularly** under the accelerated conditions of **thermal sterilization**, may function in at least two ways., i.e.
 1. By being preferentially oxidized (reducing agents), and thereby gradually **used up**, → **competing** with the active ingredients for oxidation). In this case, they are **consumed by time**,
 2. Or by blocking an oxidative chain reaction in which they are **not usually consumed**.
 3. In addition, certain compounds have been found to act as **synergists**, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions.
 4. Chelating agents: A fourth group of compounds is useful in this connection in that they are **complex with catalysts** that otherwise would accelerate the oxidative reaction.

Solutes (Added Substances)

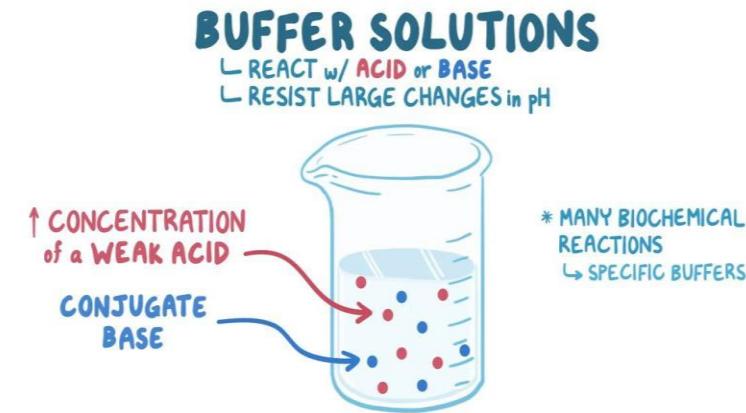
Antioxidants (continue)

- Because of the differences in action, **combinations of these agents** are sometimes used.
- **Antioxidants (reducing agents):** Ascorbic acid, Sodium bisulfite
- **Antioxidants (blocking agents):** Ascorbic acid esters, Butylated hydroxytoluene (BHT)
- **Synergists** Ascorbic acid, Citric acid
- **Chelating agents** Ethylene diamine tetraacetic acid salts (EDTA)
- **Note:** It should also be mentioned that for those products in which oxygen enters into a degradative reaction, an antioxidant effect can be achieved **by displacing** oxygen (air) from contact with the product.
- Usually, this is **accomplished by** saturating the liquid with either **nitrogen or carbon dioxide** and sealing the final container after displacing the air above the product with the gas.

Solutes (Added Substances)

Buffers

- Buffers are added to **maintain the required pH** for many products, as changes in pH may cause significant alterations in the rate of degradative reactions.
- Changes in pH may occur during storage as a result of:
 1. The **dissolution of glass** constituents in the product,
 2. The **release of constituents** from rubber closures or plastic components in contact with the product,
 3. The **dissolution of gases and** vapors from the airspace in the container, and diffusion through the rubber or plastic component,
 4. Or **reactions** within the product.



- Buffers **must have** the capacity to maintain the pH of the product against these influences, **but not** enough to prevent the body fluids from overwhelming the buffer following administration. **Because:→**
 - In most cases, the **biological effectiveness of the drug is maximum** at or near the biological fluid pH rather than at the stabilizing pH of the injected product.
- **Acetates, citrates, and phosphates** are the principal buffer systems used,
 - But buffer systems **making use of other ingredients** in the formulation are **often used** to reduce the total number of ingredients in the product.

Solutes (Added Substances)

Tonicity contributors:

- Compounds contributing to the isotonicity of a product **reduce the pain** of injection in areas with nerve endings.
- Various agents are used in sterile products to adjust tonicity.:
 - **Simple electrolytes** such as **sodium chloride** or other sodium salts and **non-electrolytes** such as **glycerin and lactose** are **most commonly** used for this purpose.
- These materials are the **last ingredient** added to the formulation after other ingredients and after the osmolality of the formulation has been measured.

TONICITY and OSMOSIS

Hypertonic



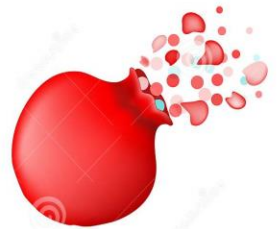
Isotonic



Hypotonic



Cytolysis



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Solutes (Added Substances)

Chelating agents

- Chelating agents may be added to **bind**, in **nonionizable form**, trace amounts of heavy metals, which **if** free, would catalyze degradative changes.
- The chelating agent most commonly used is the **trisodium** or **calcium disodium salt** of ethylenediamine tetra-acetic acid in a concentration of about **0.05% (w/v)**.

Inert gases:

1. These have been used **to displace oxygen** from a solution and **reduce** the possibility of **oxidative** changes in the formulation.
2. Inert gases may be used to **stabilize solutions** in other ways. For example, **sodium bicarbonate** injection decomposes, particularly **during autoclaving**, to produce sodium carbonate, carbon dioxide, and water. → Saturation of the solution with **carbon dioxide** **inhibits** this reaction and stabilizes the solution.

Solutes (Added Substances)

Protein stabilizers:

- A number of ingredients have been shown to stabilize proteins, both in the dry and solution state.
- 1. Serum albumin competes with therapeutic proteins for **binding sites in glass** and other surfaces and **minimizes the loss** of the protein caused by surface binding.
- 2. A number of different types of substances are used as **cryoprotectants** and **lyoprotectants** to minimize protein denaturation during freeze-drying.
- **Note:** Antioxidants, buffers, and chelating agents are also used to stabilize proteins in solution when necessary.

Containers

- **Glass containers** traditionally have been used for sterile products, many of which are **closed with rubber stoppers**.
- Interest in **plastic containers** for parenteral is **increasing**, and such containers are being **used for commercial ophthalmic preparations and IV solutions**.
- Containers are important **because** they are in direct contact with the products.
- **No** container presently available is **totally nonreactive**, particularly with **aqueous solutions**.



1- Plastic containers

- The principal ingredient of the various plastic materials used for containers is a thermoplastic polymer.
- Although most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes.
 - These ingredients are **not** usually chemically bound in the formulation (of the container) and, **therefore**, **may migrate** out of the plastic and **into** the product under the conditions of production and storage.
 - Considerable variability also has been encountered in the **purity** of the commercially available polymers.

Plastic containers (continue)

- Plastic containers are **used mainly because** they are:
 - Light in weight, non-breakable, and when low in additives, → have low toxicity and low reactivity with products.
- **Tissue toxicity** can occur from certain polymers, but additives are a **more common cause**.
- Reactivity due to sorption(absorption and/or adsorption) has been found to occur **most frequently with polyamide polymers**, but additives leached from any of the plastic materials may interact with the ingredients of the product.

2- Glass containers

- Glass is **still the preferred material** for containers for injectable products.
- The two general types of glass are: **1) Soda-lime** and **2) borosilicate**.
 - **Note:** The glass that is **most resistant chemically** is composed almost entirely of **silicon dioxide**, but it is **1) relatively brittle** and **2) can only be melted and molded at high temperatures**. → glass usually is modified to improve glass properties.
- **Chemical Resistance testing:**
- The USP provides **1) Powdered Glass** and **2) Water Attack tests** for evaluating the chemical resistance of glass.
- The test results are measures of **the amount of alkaline** constituents leached from the glass by purified water under controlled **elevated temperature** conditions;
 - The Powdered Glass test is performed on the **ground, sized glass particles**, and
 - The Water Attack test is **performed on whole containers**.

Glass Containers

- **Physical Characteristics**
- The protection of **light-sensitive products** from the degradative effect of ultraviolet rays may be one of the important physical characteristics of a glass container.
- Ultraviolet rays can be completely filtered out by the use of **amber glass**.



Glass containers

- On the basis of the results from the official tests, glass compounds are classified into **four** types.
 1. The **greatest chemical resistance** is provided by **Type I**,
 2. and the least chemical resistance is provided by **NP (non-parenteral)** glass.
 3. Also within the above two types, there are **Types II and III**.
- **Type I** glass is **preferred** for most sterile products,
- **but** Types II and III may be used when:
 1. The product **has a non-aqueous vehicle** or
 2. The **period of contact** with the aqueous vehicle is **brief (short)**, as with dry powders reconstituted just prior to use, or
 3. If the **non-reactivity** between the glass and the product **has been established**.

Container use Considerations

- **Single-dose containers** are intended to provide sufficient drug for just **one** dose,
 - The integrity of the container is **destroyed** when opened so that it **cannot** be reclosed and used again.
- Single-dose containers may range from **liter bottles of IV** solutions to **1 ml**, or smaller, cartridges.
- The desire for **1) further reduction** in the risk of contamination, both bacterial and viral, and **2) increased control** over the administration of drugs, particularly in a hospital, has led to the recent development of **single-dose, disposable** administration units.
- For **most** of these units, the product container is a **glass cartridge** with plastic and metal **fitments separated** from immediate contact with the product.



Rubber Closure

- Rubber closures are **used to seal the openings** of cartridges, vials, and bottles, providing a material soft and elastic enough to permit **entry and withdrawal** of a hypodermic needle without loss of the integrity of the sealed container.
- **Ideally**, closures should be completely nonreactive with the product with which they are in contact.
- No such ideal compound exists; therefore, each rubber compound **should be tested** for compatibility with each preparation with which it is to be used.



Rubber Closure

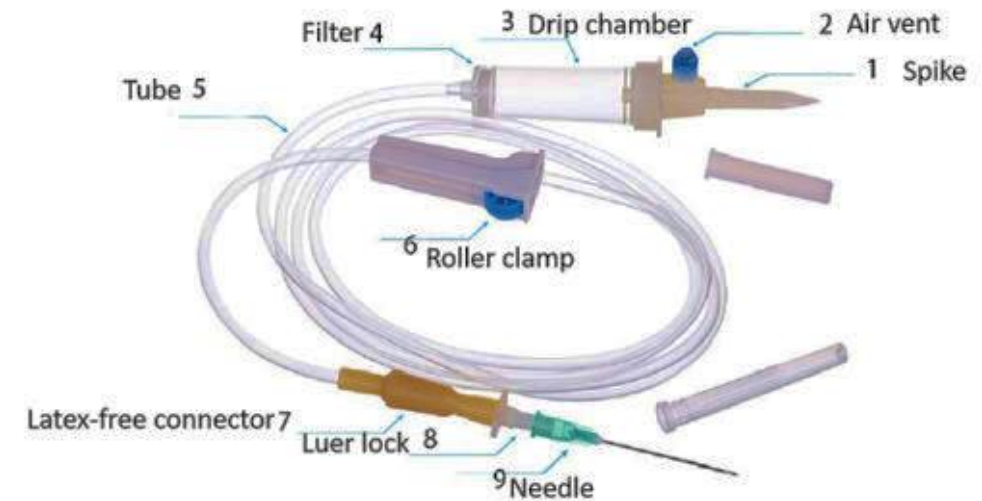
- Two general compatibility problems exist:
 1. **The leaching** of ingredients from the rubber compound with subsequent reaction with ingredients of the product, and
 2. **The removal of ingredients** from the product by sorption by the rubber compound or by vapor transfer through the closure.
- Several properties of rubber closures are significant, particularly **elasticity, hardness, and porosity.**
- Rubber closures must be sufficiently elastic to provide a **snug fit** between the closure and the neck and lip of the glass container.



Devices

- Devices associated with sterile products include the following:

1. Administration sets for large volume parenteral (LVPs)
2. Filter needles
3. Hypodermic needles
4. Hypodermic syringes
5. In-line filters
6. Plastic irrigating solution bottles
7. Plastic LVPs containers
8. Plastic ophthalmic dropping bottles
9. Transfer needles
10. Transfer sets



- Although the contact time of the product with the device is usually brief, it is **intimate**; therefore, compatibility between the device and the product must be evaluated.
- For example, it has been shown that insulin can be adsorbed by PVC tubing during the time of contact for administration of an IV solution, approximately 6 h.

Production of Parenteral Products

- The production process includes all of the steps from the accumulation and combining of the ingredients of the formula to the enclosing of the product in the individual container for distribution.
- Intimately associated with these processes are the **1) personnel** who carry them out and **2) the facilities** in which they are performed.
- The **most ideally planned** processes can be **rendered ineffective** by personnel who do not have the right attitude or training, **or** by facilities that do not provide an efficiently-controlled environment.
- To enhance the assurance of successful manufacturing operations, all process steps must be carefully reduced to writing after being shown to be effective.

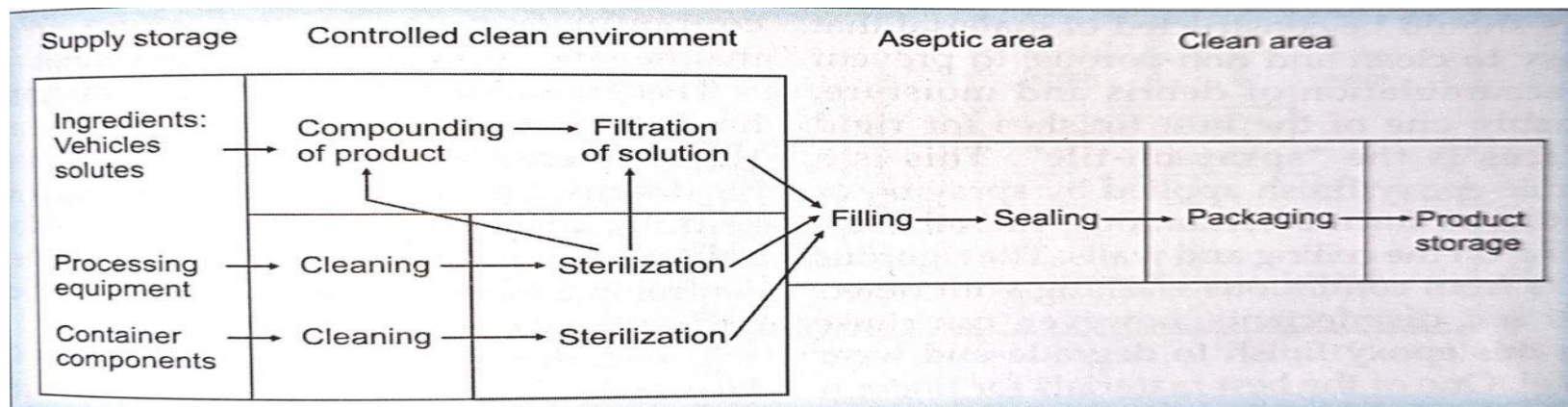


Fig. 23.3: Diagram of flow of materials through the production department

Quality Control

- Three common areas for quality controls include:
 - A. **Incoming Stock:** encompasses routine tests on all ingredients as well as special evaluations such as
 1. Pyrogen test on WFI.
 2. Glass tests on containers.
 3. Identity test on rubber closure.
 4. Microbial load (bioburden) test to determine the number and type of M.O. present.
 - B. **Manufacturing (processing):** involves all of the innumerable tests, readings, and observations made throughout the manufacturing process of a product, including
 1. **Conductivity** measurement during distillation of WFI.
 2. **Conformation of the volume** of fill-in product containers.
 3. Recording of cycle time and temperature for thermal sterilization of the product.
 4. And confirming the count and identity of labels for the product.

C. Finished product: The production control includes all of the final assays and tests to which the product is subjected. In addition to the usual chemical and biological tests, a sterile product is subjected to:

1. Leaker test (when applicable).
2. Clarity test.
3. Pyrogen test (when applicable).
4. Sterility test.



Leaker test

- **Ampoules** are intended to provide a hermetically sealed container for a single dose of a product, thereby completely barring any interchange between the contents of the sealed ampoule and its environment.
- The leak test is intended **to detect incompletely-sealed** ampoules so that they may be discarded.
- **Tip-sealed** ampoules are **more likely** to be incompletely sealed than those that have been **pull-sealed**.
- In addition, small cracks may occur around the seal or at the base of the ampoule as a result of improper handling.
- **Vials and bottles** are **not subjected** to such a leak test because the rubber **closure is not rigid**; however, bottles are often sealed while a vacuum is being pulled so that the bottle remains evacuated during its shelf-life.



Clarity Test

- Clarity is a relative term, the meaning of which is markedly affected by the **subjective evaluation** of the **observer**.
- Unquestionably, a clean solution having a high polish **conveys to the observer** that the product is of exceptional quality and purity.
- It is practically impossible, however, to prepare a lot of a sterile product so that every unit of that lot is perfectly free from visible particulate matter, i.e., from particles that are **30 to 40 μm** and larger in size.
- Although the particulate matter is of primary concern in products given intravenously, **all parenteral** products should be free from insoluble particles.



Clarity Test

- **Suspensions, emulsions, or dry solids**, in addition to solutions, should be compounded and processed under clean conditions to minimize the presence of foreign particles.
- The visual inspection of a product container is usually done by **individual human** inspection of each externally clean container under good light, baffled against reflection into the eyes, and viewed **against a black and white** background, with the contents set in motion with a **swirling action**, since a moving particle is much **easier** to see than one that is stationary.



Pyrogens and Pyrogen Test

- Water used in parenteral and irrigating solutions **should be free of pyrogens**.
- To achieve this, proper controls must be maintained in the preparation and storage of water.
- Pyrogens are products of the metabolism of microorganisms. Most bacteria and many molds and viruses have been reported as producing pyrogens.
- The **Gram-negative** bacteria produce the **most potent** pyrogenic substances as endotoxins.
- Chemically, pyrogens are **lipid substances** associated with a carrier molecule, which is usually a polysaccharide but may be a peptide.
- About **1 h** after injection into man, pyrogens produce a **marked rise** in body temperature, chills, body aches, cutaneous vasoconstriction, and a rise in arterial blood pressure.
- Antipyretics eliminate the fever, **but not** the other systemic effects of pyrogens.
- The **fever response to pyrogens in rabbits** is the basis for the official pyrogen test.

Sterility Test

- All products labeled “**sterile**” must pass the sterility test, having been subjected to an effective process of sterilization.
- The test for sterility is intended for detecting the presence of a viable form of microbes in pharmacopeial preparations.

Method A: Membrane Filtration

- A suitable unit consists of a closed reservoir and a receptacle (container) between which a properly supported membrane of appropriate porosity is placed.
- A membrane suitable for sterility test has a nominal pore size not greater than **0.45 μm** , a diameter of approximately **47 mm**, and effectiveness in retaining microorganisms has been established.
- **Cellulose nitrate filters**, for example, are used for **aqueous, oily, and weakly alcoholic solutions**;
- **Cellulose acetate filters** are used for **strongly alcoholic solutions**.
- Specially adapted filters may be needed for certain products such as antibiotics.

Sterility Test

- **Method B: Direct Inoculation**
- Apart from testing oily solutions, creams, ointments, and solid products, the direct inoculation method is utilized **particularly for surgical devices, sterile devices, surgical dressings, and sutures**, in cases where the membrane filtration method (method A) **appears difficult**.
- In this test, the quantity of the preparation to be examined is transferred directly into the culture medium so that the volume of the product is not more than 10% of the volume of the medium unless otherwise prescribed.