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Parenteral Preparations

Parenteral preparations or injectables are the sterile solutions or suspensions of drugs in aqueous or oily vehicles meant for introduction into the body by means of an injection under or through one or more layers of the skin or mucous membrane. Since they are introduced into internal body compartments they must be sterile and free from all types of living microorganisms and microbial products such as toxins, pyrogens, etc., and should be free from particles like dust, fibres, etc. They should be isotonic with body fluids. An utmost care must be taken in the preparation of injectables to avoid all types of physical, chemical or microbial contaminations.

Parenteral preparations must be introduced through the same route for which they are intended, for example, if an oily suspension meant for intramuscular injection is introduced by intravenous injection may prove fatal. Similarly potent drugs meant for administration through intramuscular injection may lead to even death if given by intravenous injection.

ROUTES OF ADMINISTRATION OF PARENTERAL PRODUCTS

Various routes of administration of parenteral products are as follows :

1. Intracutaneous or Intradermal Injections

These injections ar given in between dermis and epidermis. Skin of the left forearm is usually selected for giving the injection. Absorption by this route is slow therefore usually small volume from 0.1 to 0.2 ml is injected. This route is mainly used for testing the sensitivity of the injectables and for diagnostic purposes.

2. Subcutaneous or Hypodermic Injections

These injections are given in the subcutaneous tissue under the skin of the upper arm. The volume of 1 ml or less can be injected by this route. This is the most popular route because it is convenient for the patient and the doctor.

3. Intramuscular Injections

These injections are given into the muscular tissues. The muscles of the

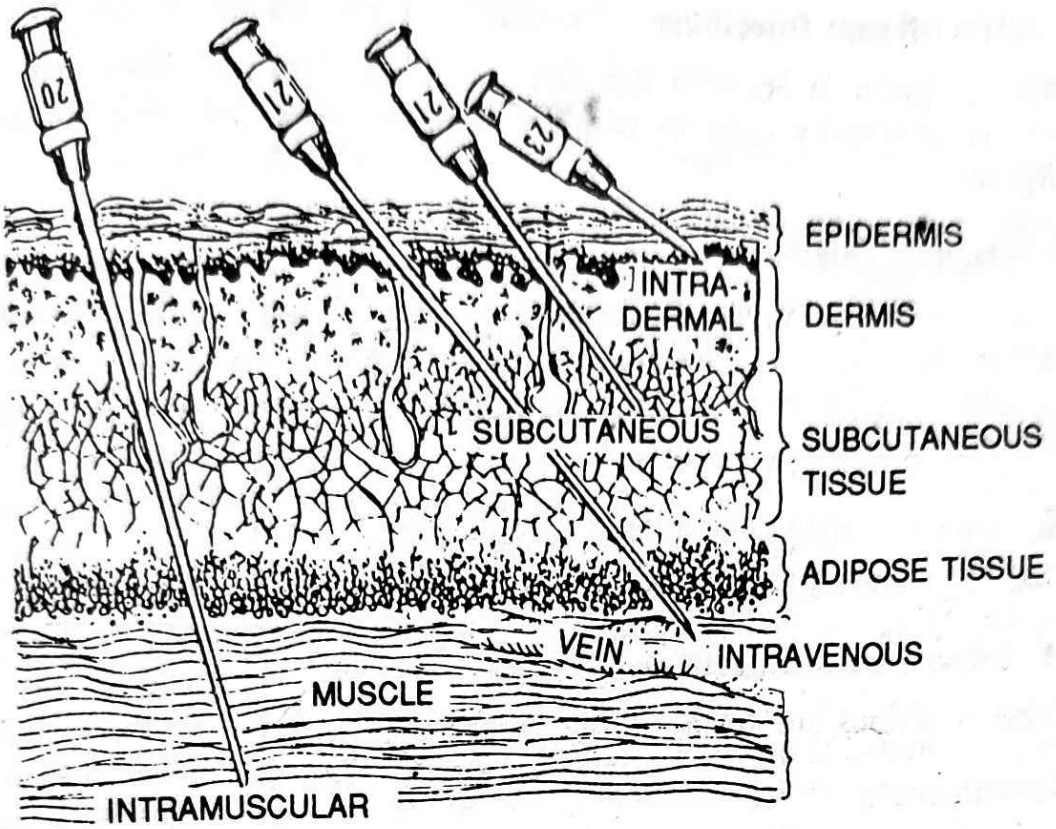


Fig. 12.1 Routes of administration of parenteral products.

shoulder, thigh or buttock are usually selected. Generally volume up to 2 ml is administered by this route and should not exceed 4 ml at one site.

4. Intravenous Injections

These injections are given into the vein therefore directly reach the blood stream. The median basilic vein which is near the elbow is usually selected because it is easily located and connects with the other major veins of the arm. Large volumes of solutions ranging from 1 ml to 500 ml or even more can be injected but volumes of more than 15 ml should be isotonic with blood. Oily injections and suspensions cannot be injected by this route.

5. Intra-arterial Injections

These injections are given directly into the artery when an immediate effect in a peripheral area is required. They are occasionally used.

Less Commonly Used Routes

6. Intracardiac Injections

They are given directly into the heart muscles or ventricle and are used in emergency only.

7. Intrathecal Injections

They are given into the subarachnoid space surrounding the spinal cord. This route is used for giving spinal anaesthesia.

8. Intracisternal Injections

They are given in between the first and second cervical vertebrae. This route is principally used to withdraw cerebrospinal fluid for diagnostic purposes.

9. Peridural Injections

These injections are given between the duramater and the inner aspects of the vertebra, i.e., it is the area of vertebral canal which does not have duramater and its contents. This route is sometimes used for giving spinal anaesthetics in special cases.

10. Intra-articular Injections

These injections are given into the liquid that lubricates the joints.

11. Intracerebral Injections

These injections are given into the cerebrum.

Advantages

1. Parenteral route of administration is used when a rapid onset of action of the drug is required, hence the route is used in emergency cases.
2. This route is preferred when the drugs are inactivated in the G.I.T. or drugs are not well absorbed after oral administration.
3. This is the most suitable route of administration of drugs in treating patients who are non-cooperative, unconscious or are otherwise unable to take the medicine orally.
4. Prolonged action of a drug can be successfully produced by this route.
5. Solutions in volumes from fraction of millilitre to 4 litres can be introduced by parenteral route.

Disadvantages

1. This mode of treatment is more expensive because it requires a technical and trained person for administration.
2. Sterilization is of utmost importance.
3. The administration of drug through wrong route of injection may prove fatal.
4. Daily or frequent administration of injections may pose difficulties to the patient.

Types of Parenteral Preparations:

I) Classification Based on volume:

Small volume parenteral	Large volume parenteral
→ Injection packed in container containing 100ml/less	→ " - 101 - 1000mL
→ Single/multiple use	→ single use
→ Drugs	→ provides Electrolytes & fluids
→ preservatives are used	→ preservatives are not used
→ Administered through various parenteral routes	→ Administered through IV infusion
Eg: Insulin	Eg: saline solution

ii) classification based on mode of Delivery

1) single-Dose - used only once
- should not contain any anti-microbial preservatives

2) Multiple-Dose - used as multiple purpose / many times
- contain Anti-microbial preservatives

3) Intravenous Infusions: They are sterile-pyrogen free solutions prepared with water
- They must be Isotonic.
- They are administered in large volumes → more than 100ml and donot contain any anti-microbial preservatives

4) powders for Injection: They are sterile-pyrogen free solid substances (freeze-dried) distributed in a container
- prescribed volume of liquid is added to form a uniform suspension.

5) Concentrates for Injection:
- concentrates for injections are sterile-pyrogen free intended to use after dilution with a suitable liquid.

6) Implants: These are solid preparations containing one/more active ingredients.
- These are of suitable size and shape suitable to provide release of active ingredient over an extended period of time.
- They are placed in an individual sterile container

iii) Classification based on type of formulation:

1) Solutions:
A solution is a liquid preparation that contains one/more soluble chemical substances dissolved in a suitable solvent.
Eg: Electrolytes

solvent
solute

more time for administration. when

2) Suspension:

These are sterile, pyrogen free, stable, isotonic and non-irritant solution.

- solid content - 0.5% to 5.0% (30% for Antibiotic preparation)
- they contain stabilizing agents. like sodium CMC, Acacia, Gelatin, polysorbate so.

3) Emulsion: Heterogenous solution of immiscible liquid in another

- Emulsifiers like Lecithin, Gelatin and Methyl cellulose are used
- Administered through intravenous & intramuscular route.

4) Dry powders: It is a formulation of lyophilized / freeze-dried powders that must be reconstituted with some suitable solvent to make a liquid formulation before withdrawn from the vial.

suspensions in oily

Essential Qualities of a Parenteral Product

A parenteral product must possess the following characteristics :

1. It should be free from living microorganisms and microbial products.
2. It should be free from pyrogens.
3. It should be free from foreign particles such as dust, fibres, etc.
4. It should be free from chemical contaminants.
5. It should be isotonic with body fluids.
6. It should have matching specific gravity with respect to some body fluids.
7. Multidose injections must contain preservatives.
8. Container/closure must not affect the product.

FORMULATION OF PARENTERAL PRODUCTS

In the development of parenteral products the pharmacist should have thorough knowledge and understanding of the principles involved and utmost care must be taken regarding accuracy, cleanliness and overall quality of the product. The medicinal substances used in the formulation of injections should be free from microbial and pyrogenic contamination. Whenever possible special parenteral grades of drugs which are commercially available should be used.

Only a minimum number of absolutely necessary additives in smallest

possible quantities should be added. Excessive use of additives in parenteral products should be avoided since sometimes the metabolism of these additives becomes a problem. Some of the additives which are commonly used in the formulation of parenteral products are described below :

1. Vehicles

In the development of a parenteral product one will have to use a suitable vehicle for dissolving or suspending the medicaments. The most suitable vehicle for this purpose is water because aqueous preparations are tolerated well by the body and are the safest and easiest to administer. The water should be chemically pure and free from pyrogens. When water free from dissolved gases is required, it should be freshly boiled, cooled and stored in a well closed container to avoid reabsorption of oxygen and carbon dioxide.

Oily vehicles are used when the use of water is contraindicated in one way or the other, e.g., (a) when the medicament in insoluble or slightly soluble in water; (b) to increase the stability of the preparation; or (c) to prolong the duration of action of a drug. The commonly used fixed oils from vegetable origin are cottonseed oil, peanut oil, olive oil, sesame oil, etc. These oils should be free from rancid odour and taste. Mineral oils like liquid paraffin are rarely used since they are not absorbed from the tissues after injection.

Sometimes propylene glycol, polyethylene glycol and glycerin usually diluted with sterile water are used to prepare solutions for injections. They are used as solvents as well as to increase the stability of certain preparations.

Whenever non-aqueous vehicles are used for the preparation of injections, they must be administered by intramuscular injections only, accidental introduction by subcutaneous or intravenous injection may lead to serious results.

2. Added Substances

These substances are added to increase the stability or quality of the product and may include solubilising agents, antibacterial agents, antifungal agents, antioxidants, chelating agents, buffers, isotonicity factors, hydrolysis inhibitors, wetting, suspending and antifoaming agents, etc. These agents should be used only when it is absolutely necessary to use them and they must be used in the minimum possible quantity. These additives must be selected with great care so that they may not affect the entire formulation.

(a) Solubilising Agents

The solubilities of insoluble or poorly soluble drugs in water can be increased by co-solvents, complex formation or by adding surfactants like tweens, polysorbates, etc., which act by miceller solubilization.

(b) Stabilizers

Since oxidation and hydrolysis takes place more rapidly in drugs when they are in solution form therefore they must be suitably protected from oxidation and hydrolysis. To prevent oxidation either a suitable antioxidant is added or the product is sealed in an atmosphere of nitrogen or carbon dioxide so as to replace oxygen in the product thus minimising oxidation. Hydrolysis can be prevented either by replacing a part or whole of water in the preparation by a non-aqueous vehicle or by adjusting the pH of the preparation.

(c) Buffers

When the degradation of the preparation is due to change in pH it can be prevented by adding buffer systems which will maintain the necessary pH at desired level. Acetates, citrates and phosphates are the principal buffer systems used in this way.

(d) Antibacterial Agents

Bacteriostatic or fungistatic agents must be present in multidose containers. They must be added in adequate quantities to prevent the multiplication of microorganisms which may be accidentally introduced into the preparation while withdrawing a dose from the multidose containers. Among the compounds most frequently used as antibacterials agents are benzalkonium chloride 0.01%, phenol or cresol 0.5%, chlorocresol 0.2%, phenylmercuric nitrate 0.002% and chlorobutanol 0.5%. Care must be taken in selecting the antibacterial agent that it should be compatible with all other components of the formulation and should not be removed from solution by rubber closures of the package.

Bacteriostatic agents should not be used in single dose containers because the contents of these remain sterile until opened and the solution is injected but they may be included in those single dose containers which are to be sterilized by 'heating with a bactericide'.

(e) Isotonicity Factors

Parenteral preparations should be isotonic with blood serum or other body fluids to reduce irritation and pain of injection in areas with nerve endings. The isotonicity of a solution may be adjusted by adding sodium chloride, borax, etc., in suitable quantities but these materials should be non-toxic and must be compatible with other components of the formulation.

(f) Wetting, Suspending and Emulsifying Agents

In a parenteral suspension a wetting agent is used to reduce the interfacial energy between the solid particles and the liquid, so as to prevent the formation of lumps. They also act as antifoaming agents to subside the foam produced during shaking of the preparation. The wetting agents

commonly used are tween 80 and sorbitan trioleate. The suspending agents generally used are methyl cellulose, carboxymethyl cellulose, acacia and gelatin.

Emulsifying agents are used in sterile emulsions. For this purpose lecithin is generally used. Gelatin may be added to aqueous vehicles to prolong the effect of the drug.

GENERAL PROCEDURE OF PREPARATION OF INJECTIONS

It is the general requirement that all the parenteral products must be free from foreign particles and micro-organisms. To achieve this aim care must be taken regarding the cleanliness and sterilization of area, atmosphere, persons involved and the materials used in the preparation of injections.

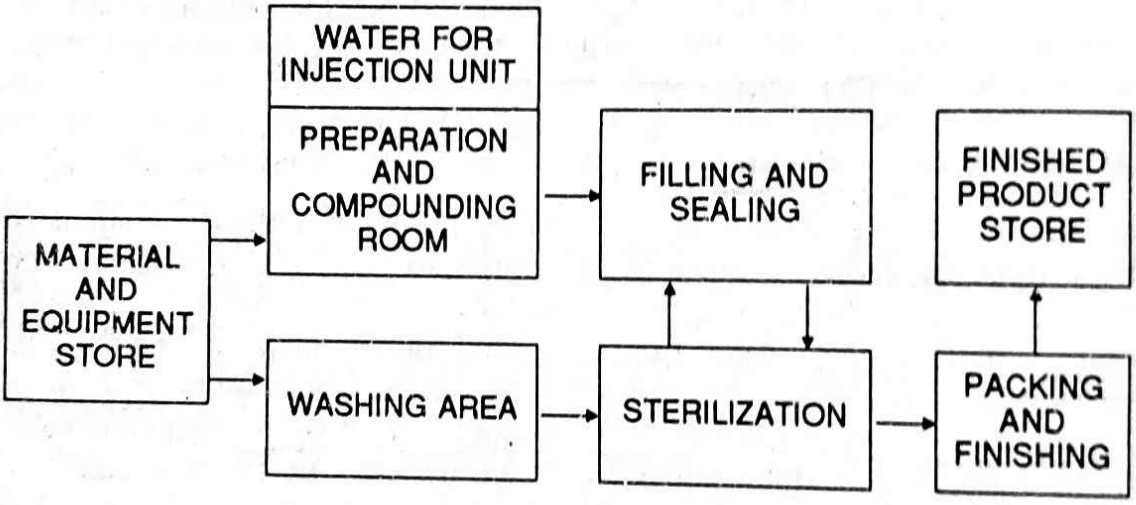


Fig. 12.2 Flow diagram for the manufacture of parenteral products.

The area and atmosphere of the room where the process is to be carried out must be free from dust, fibres and micro-organisms. This can be achieved with laminar flow system and by disinfectants. All the equipments which are likely to come in contact with the preparation must be thoroughly cleaned and sterilized. The workers should be highly trained and skilled. They should wear sterilized special clothings including hoods and gloves. They should take all sorts of precautions to avoid contamination because even the entry of a single microbe can render the product useless and harmful.

Parenteral preparations should be prepared from substances of the highest purity which have been accurately weighed and dissolved in pyrogen free distilled water or any other suitable solvent. Utmost care must be taken regarding the cleanliness in all operations. The solution so formed is passed through different grades of filters to remove foreign particles. The filters may be made from sintered glass, asbestos porcelain, etc. Now a days membrane filters composed of cellulose ester or polycarbonate are commonly used for filtering the parenteral solutions. Bacteria-proof filters are used to remove bacterias from the solutions.

After the preparation and suitable filtration of the solution it is packaged in suitable containers like ampoules, vials or bottles. Before filling the solution into these containers they must be thoroughly cleaned, dried and sterilized. The closures used should be of very high quality and must be sterilized.

On small scale, filling can be carried out with the help of hypodermic syringes attached with long needles, burettes, etc. The sealing of the ampoules can be done by fusion of glass in hot flames of blast burner or blow torch burner specially designed for this purpose. But now a days filling and sealing is done on very sophisticated automatic machines.

After filling and sealing the containers they are sterilized by means of dry heat or moist heat. For dry heat sterilization hot air ovens are used whereas for moist heat sterilization autoclaves are used. Oily and non-aqueous preparations must be sterilized by dry heat at a temperature of 160°C for two hours or at 170°C for one hour. Thermostable aqueous solutions should be sterilized by steam under pressure in autoclave at a temperature of 121°C for 20 minutes. Whereas aqueous solutions of thermolabile drugs cannot be sterilized by autoclaving therefore they must be passed through bacteria-proof filters to remove microbes.

After the filled containers have been sterilized and allowed to cool, they are inspected for clarity. Those containers which pass the clarity test are properly labelled and packaged into final containers.

PRECAUTIONS FOR ASEPTIC WORK TO PREVENT CONTAMINATION

1. As far as possible minimum number of persons should work in the injection department. Lesser the number of persons in the department, less will be the chances of contamination.
2. Persons trained in aseptic techniques should be allowed to work in the injection department.
3. Before entering the sterile area they must wash their hands which should then be treated with antiseptic solution, wear gloves, dress changed, hair covered, wear face mask and a hood over the head. The garments worn must not shed fibres and other particles.
4. The air in the processing area must be free from contaminants which is done by fitting a laminar air flow in the area.
5. Ultraviolet lamps should be fitted above the doors, working tables and room ceilings.
6. Walls should be painted in such a way that they can be easily cleaned, washed and disinfected.
7. There should be minimum hide-outs.
8. Furniture used should be minimum and they should be fitted with stainless steel or sunmica tops and other surfaces.

9. Double door entry should be provided. There should be minimum number of windows which should be of glazed panels. The windows may be kept closed.
10. Equipment is the major source of contamination, therefore, it must be thoroughly cleaned before and after its use. Wherever possible sterilized equipment should be used.
11. Frequent tests should be performed in the aseptic area to check the maintenance of sterility.
12. Whenever contamination is detected, its source should be identified and suitable methods adopted to check contamination.

MANUFACTURING OF PARENTERAL PREPARATIONS

Following steps are involved in the manufacturing of parenteral preparations :

1. Washing and cleaning of containers, closures and equipment.
2. Collection of materials.
3. Compounding the preparation.
4. Filtration.
5. Distributing the preparation in final containers.
6. Sealing the containers.
7. Sterilization.
8. Labelling and packaging.
9. Evaluation of parenteral preparations.

1. Washing and Cleaning of Containers, Closures and Equipment

All the containers, closures, and glass equipments required in parenteral preparations are thoroughly cleaned with detergent then washing with free flowing water followed by rinsing it with water for injection. As far as possible the various components of the apparatus should be separated and then cleaned. For small number of items washing can be done manually but on large scale automatic washing machines are used. High speed bottle brushes and multijet rinsers are used for this purpose. Finally, they are dried and sterilized by suitable methods.

2. Collection of Materials

The various materials required for the formulation of parenteral preparations are weighed and collected in the preparation room. All the ingredients, i.e., the medicaments, vehicles and additives used should be of the highest purity. Whenever water is to be used as vehicle, water free from pyrogens must be used.

3. Compounding the Preparation

For mixing and compounding a set procedure must be followed. Before mixing, the formulator must decide the order of mixing and he should have

clear picture in his mind that what type of preparation will be obtained, i.e., regarding its colour, viscosity, etc.

4. Filtration

The solutions so formed are then passed through a suitable filter media to remove all the foreign particles. If the solutions are required to be sterilized by means of bacteria-proof filters then they are passed through suitable bacteria-proof filter. For this purpose sintered glass, asbestos or porcelain filters are used. Now a days membrane filters composed of cellulose ester or polycarbonate are commonly used for filtering the parenteral solutions.

5. Distributing the Preparation in Final Containers

After filtration and sterilization the solutions are distributed into final containers like ampoules, vials and bottles which are previously cleaned and sterilized. Ampoules are used for filling single doses whereas vials are used for filling multidoses. Bottles are generally used for filling transfusion fluids. On small scale filling can be carried out manually with the help of hypodermic syringes attached with long needles, burettes, etc. On large scale automatic filling machines are used. About 300 or more containers per minute can be filled with these machines.

Powders are little difficult to fill as compared to liquids. On small scale, solids like antibiotics are divided by weighing and then filled into individual containers or approximate quantity of the powdered drug can be filled in the container which is finally weighed on a balance. On large scale filling of powders is done by machines.

At the time of filling the ampoules, care should be taken that the solution should not touch the neck of the ampoule and it should be filled below the constriction of the neck of the ampoule otherwise it may lead to different problems such as cracking and staining at the time of sealing the ampoules.

6. Sealing the Containers

Sealing of the containers should be done as soon as possible to prevent the contamination of the contents. The rubber closures are fitted on the vials and bottles and sealed by crimping the aluminium caps which may be done manually or by mechanical means.

On small scale the ampoules are sealed manually by rotating the neck of the ampoule in the flame of bunsen burner or blast burner to soften the glass which ultimately fuses to close the ampoule. This is known as tip sealing but this is not a sure method of sealing because leakage generally occurs. Another method is that the neck of the ampoule is constantly rotated in the bunsen flame and when the glass softens, the tip is held firmly with a forceps or any other device and pulled quickly away from the body of the ampoule which is still rotated. A small capillary tube is formed which is closed by twisting. This method is known as pull sealing.

Although this is a slow process but the seals are more perfect than tip sealing.

7. Sterilization

Depending on the nature of products they may be sterilized by any suitable method.

Thermostable preparations are sterilized by autoclaving at a temperature of 115°C for 30 minutes or at 121°C for 20 minutes. Oily injections can be sterilized by hot air ovens at 160°C for 2 hours or at 170°C for one hour.

Thermolabile preparations are sterilized by passing through suitable bacteria-proof filters or by means of chemicals.

8. Labelling and Packaging

All the containers, i.e., ampoules, vials and bottles should be properly labelled with name of the preparation, quantity, batch number, lot number, date of manufacture, date of expiry (if any), storage conditions, retail price and manufacturer's address.

The labelled containers should be packaged in cardboard or plastic containers so that there is no breakage during transportation or handling. Ampoules should be packed in partitioned boxes.

Evaluation of Parenteral Preparations

In the preparation of parenteral products strict quality control tests must be carried out throughout the entire process of preparation of a parenteral product to give assurance that the final product meets the required standards. Raw materials must be subjected to quality and pyrogen tests. Various tests, readings and observations must be made during the process to assure that the specifications are being met. Various tests and assays should be performed on the finished preparation to ensure that it meets the required specifications. In addition to the usual chemical and biological tests the following tests should be carried out on the parenteral preparations for their standardization.

(a) Sterility test.
(b) Pyrogen test.
(c) Clarity test.
(d) Leaker test.

(a) Sterility Test

Since all parenteral preparations are required to be sterile, they should be tested for sterility and must comply with the official test for sterility described in U.S.P. These tests are performed on all lots of injections in their final containers. The samples may be taken at random to represent the entire lot of the preparation. Hence the word 'Lot' for sterility testing means that group of product containers which has been subjected to same sterilization procedures.

According to U.S.P. there are two basic methods for sterility testing : (a) Direct inoculation of test samples on culture media; (b) Filtration technique.

In the direct inoculation method an aliquot quantity of the material under test is transferred to culture tubes containing a measured volume of a suitable culture medium like fluid Thioglycolate Medium or Thioglycolate Broth Medium. This whole operation, i.e., opening the containers, taking aliquot quantity of the material under test and transferring it to the culture medium contained in the tubes must be carried out under aseptic conditions and every precaution must be taken to prevent the accidental entry of micro-organisms into the test. These tubes are plugged with sterilized cotton wool and incubated for seven days at a temperature of 30 to 35°C. Positive and negative control tubes containing the culture media must be incubated under same conditions to confirm sterility and growth promoting properties of the medium. The material under test is considered sterile if there is no growth of micro-organisms in the tubes but if there is any turbidity or growth then the test must be repeated 2nd time with fresh sample of material and culture medium because in the first test the bacterial growth may be due to accidental entry of micro-organisms. If the 2nd test also shows the growth it may be repeated 3rd time very carefully and if this time also growth appears then the material fails to pass the sterility test.

If the product has antimicrobial properties they must be neutralized or eliminated by dilution. For solids or oily materials which make the culture medium turbid and make it difficult to conclude whether the turbidity is due to microbial growth or due to material itself, the normal test may have to be modified by subculturing the medium. If turbidity in subculture does not appear the material is sterile but if turbidity appears it is due to microbial growth which shows that the material is not sterile.

(b) Pyrogen Testing

Pyrogens

Pyrogens are the metabolic products of micro-organisms and are produced by all micro-organisms, i.e., gram-negative, gram-positive and fungi, but

gram-negative bacterias generally produce most potent pyrogenic substances. They are soluble, filterable, thermostable and non-volatile substances. Chemically they are lipid in nature, sometimes containing phosphorus and are usually attached to polysaccharide or an amino acid carrier.

When introduced in human beings they cause febrile reactions which include chills and fever with headache and pain in the back and legs. Pyrogens are rarely fatal but they produce significant discomfort to the patient.

The major source of pyrogens in parenteral preparations is the water used for the preparation of injections which can be rendered free from pyrogens by proper distillation of water and storing the water under suitable conditions which does not allow the bacterial contamination to take place. Other solvents and chemicals used in the preparation are another source of pyrogens. Antibiotics produced by fermentation process generally contain pyrogens which must be effectively removed from pharmaceutical preparations containing these antibiotics. Containers and equipments used in the process may be another source of pyrogens which can be washed thoroughly with apyrogenic water to reduce the pyrogenic contents. They can be sterilized by keeping in hot air oven at a temperature of 175°C for 3 to 4 hours. Pyrogens can be destroyed by heating in an autoclave in the presence of an acid, alkali or oxidising agent. They can be removed by adsorbing on some adsorbing agent like activated charcoal, asbestos pads or aluminium hydroxide gel but this method is not suitable for pharmaceutical preparations because some of the drugs may also be adsorbed with the pyrogens. It is better to prevent the introduction of pyrogens than an attempt to remove them.

(c) Pyrogen Test

Pyrogen tests are performed on all aqueous parenteral preparations. In this test rabbits are used as test animals because they show similar physiological response to pyrogenic substances like that of man but the rabbits are very sensitive to external stimuli, therefore they must be handled very carefully. Only the healthy and mature rabbits should be used.

The test is made by introducing a suitable quantity of the sample to be tested into the ear vein of the rabbit. Rectal temperature is noted at 1, 2 and 3 hours after the introduction of the injection. If there is any rise in temperature of 0.6° or more above the normal temperature which has been taken before giving the injection, then the test is considered positive and the preparation contains pyrogens but if the rabbits do not show any rise in temperature then the product is considered free from pyrogens. Generally 5-8 rabbits are used for this test and average is calculated. Now a days number of specialized equipments are available for performing the pyrogen test.

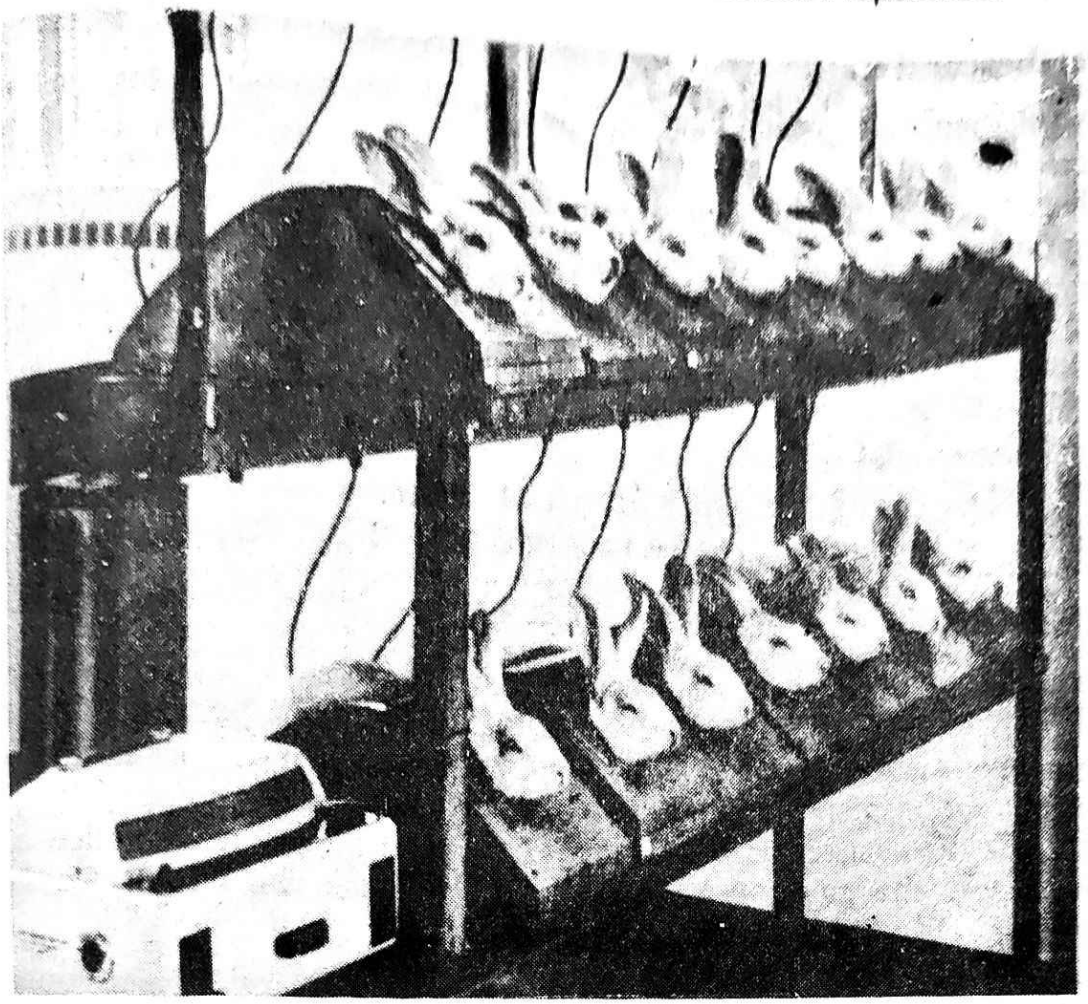


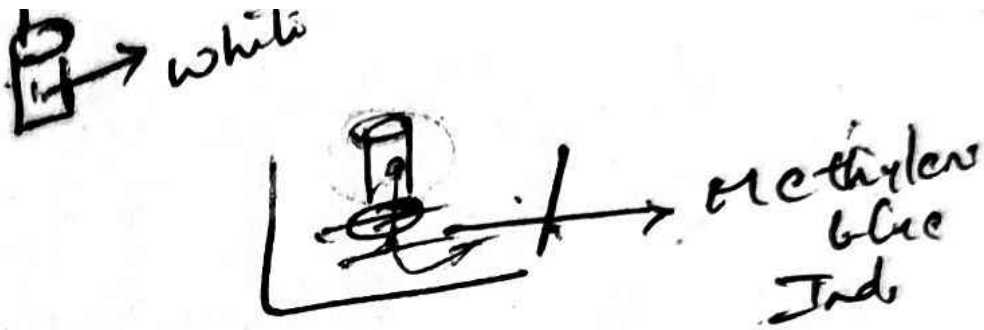
Fig. 12.3 Pyrogen testing.

(d) Clarity Test

The presence of particulate matter in parenteral preparations particularly those which are given intravenously are of serious concern. The particles larger than the size of red blood cells are dangerous, they may block the blood vessels with serious results. Therefore it is very necessary to check the final packages for clarity.

During the preparation of injections the particulate matter may enter from the environment including shedding from the body and clothes of persons, ceilings, walls and furniture of the room, from glass and rubber apparatus, the vehicles and the materials used. The particulate matter may also be introduced during administration if the infusion sets or syringes and needles are not properly cleaned and stored.

For checking the clarity of single dose or multidose packagings the unlabelled containers are held by the neck against strongly illuminated screen of which white surface is used for dark coloured particles and black surface for the detection of light coloured particles. The contents of the containers are slowly inverted and rotated and the solution examined for the presence of turbidity, dust or any other foreign particles. If any particulate matter is visible, the package is rejected. Certain instrumental methods have been developed and are widely used in the industries.



(e) Leaker Test

All the ampoules which have been sealed by fusion must be subjected to leaker test to check that there should not be any passage for leaking of the contents from the containers. This test is performed by dipping the ampoules in a deeply coloured dye solution for which 1% solution of methylene blue is used. The whole process is carried out in a vacuum chamber under negative pressure. When the vacuum is released the coloured solution will enter the ampoules with defective sealing. After careful washing of ampoules from outside, the dye can be seen in the leaker ampoules.

This test is not performed on vials and bottles because of flexibility of rubber, moreover the dye will badly stain the rubber stoppers.

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Ophthalmic Products

Ophthalmic products are the sterile products, meant for instillation into the eye in the space between the eye lids and the eye balls. These products must be sterile and are prepared under the same conditions and by the same methods as other parenteral preparations. Ophthalmic products include:—

Eye-drops
Eye-lotions
Eye-ointments
Eye suspensions
Contact lens solutions.

Essential Characteristics of Different Ophthalmic Preparations

Ophthalmic preparations should possess the following properties:—

1. Foreign particles : All the ophthalmic products should be clear and free from foreign particles, fibres and filaments. Ophthalmic solutions should be clarified very carefully by passing through bacteria proof filters, such as, membrane filters and sintered glass filters. The particle size of the eye suspension should be in an ultra fine state of subdivision to minimise irritation. A separate filter should be used for different ophthalmic products in order to avoid the contamination.

2. Viscosity : In order to perlong the contact time of the drug in the eye, various thickening agents are added in the ophthalmic preparations. Polyvinyl alcohol (1-4%), polyethylene glycol, methylcellulose, carboxy methylcellulose are some of the commonly used thickening agents. These agents improve the viscosity of the preparation. An ideal thickening agent should possess the following properties:—

1. It should be easy to filter.
2. It should be easy to sterilise.
3. It should be compatible with other ingredients.
4. It should possess requisite refractive index and clarity level.

The thickening agents are not included in the formulation of eye drops and eye lotions which are required to be used during or after surgery due to some possible adverse effects on the interior of the eye.

3. Tonicity : Ophthalmic products must be isotonic with lachrymal secretions to avoid discomfort and irritation. It has been observed that eye can tolerate a range of tonicity from 0.5 to 2% sodium chloride. There are certain isotonic vehicles which are used to prepare ophthalmic products like 1.9% boric acid, sodium acid phosphate buffer.

4. pH of the preparation : pH plays an important role in therapeutic activity, solubility, stability and comfort to the patient. Tears have a pH of about 7.4. Eye can tolerate solution having wide range of pH provided they are not strongly buffered, since the tears will rapidly restore the normal pH value of the eye. Alkaloidal salt solutions are stable at pH 2 to 3 but this pH is irritant to the eye. The alkaloids get precipitated at pH above 7 and creates a number of formulation problems.

5. Sterility : Ophthalmic preparation must be sterile when prepared. Pseudomonas aeruginosa is very common gram negative bacteria which is generally found to be present in ophthalmic products. It may cause serious infection of cornea. It can cause complete loss of eye-sight in 24-48 hours.

To maintain sterility in multidose container containing ophthalmic products, a suitable preservative is added. The preservative should be non-toxic, non-irritant and should be compatible with medicament(s). The ophthalmic products are generally sterilised by autoclaving, filtration, through bacteria proof filters and addition of bactericide at low temperature.

6. Surface activity : Vehicles used in ophthalmic preparation must have good wetting ability to penetrate cornea and other tissues. Certain surfactants or wetting agents are added which are found suitable for ophthalmic products. It should not cause any damage to tissues of eye. Benzalkonium chloride, polysorbate 20, polysorbate 80, dioctyl sodium sulpho-succinate, etc., are some of surfactants, which are commonly used.

Types of Ophthalmic Products

Various ophthalmic products include :

1. Eye drops
2. Eye lotions
3. Eye suspensions
4. Contact lens solutions
5. Eye ointments
6. Ophthalmic inserts.

1. Eye Drops

Eye drops are sterile aqueous or oily solutions or suspensions for instillation into the eye. They are usually applied into the space between the eyeball and eyelids or on to the corneal surface. The main requirement of eye drops is that they should be sterile, usually isotonic, buffered and free from foreign particles to avoid irritation to the eye. They usually contain substances having antiseptic, anaesthetic, anti-inflammatory, mydriatic or miotic properties or substances used for diagnostic purposes.

2. Eye Lotions

Eye lotions or eye washes are sterile aqueous solutions used for irrigating the eye. Sodium chloride eye lotion is used to remove foreign substances from the eye. They are usually applied with a clean eye-bath or sterile fabric dressing and a large volume of solution is allowed to flow quickly over the eye.

Eye lotions are usually supplied in concentrated form and are required to be diluted with an equal volume of warm water immediately before use. They should be freshly prepared and should not be stored for more than 2-3 days as they may be contaminated with microorganisms on prolonged storage. Eye lotions should be isotonic and free from foreign particles to avoid irritation to the eye. The drugs used for preparing eye solutions include sodium chloride, sodium bicarbonate, boric acid, borax or zinc sulphate.

3. Eye Suspensions

Eye suspensions are not commonly used as compared to eye drops. They are only prepared when the drug is insoluble in the desired vehicle or unstable in solution form. They are also used to produce the sustained action of the preparation. Eye suspensions should have the following characteristics :

1. They should be sterile.
2. They should be isotonic, buffered and suitably preserved.
3. They should be of the desired viscosity.
4. They should be packaged in dropper type containers.
5. The particle size of the suspension should be non-irritating to the eyes.
6. The suspended particles must not agglomerate into large ones on storage.

4. Contact Lens Solutions

Contact lenses are generally made from hard hydrophobic plastic known as polymethyl methacrylate but now a days some softer hydrophobic lenses are also used.

The wearers of hard contact lenses generally use two types of solutions.

(a) One before inserting the lenses into the eyes which is known as wetting solution.

(b) The other one used for overnight cleaning, soaking and storage which is known as storage solution.

(a) Wetting Solutions

Because of the hydrophobic nature of the polymethyl methacrylate it is poorly wetted by the lacrymal fluid of the eye and requires moistening with a wetting agent to render the surface of the lens hydrophylic, make the insertion easy and comfortable.

Since the contact lens solutions are used daily and years together so they must be prepared very carefully and the ingredients used should be of highest quality. The formulation of contact lens solutions may include a wetting agent, buffering agent, a thickening agent, a substance for adjusting the osmotic pressure, a preservative and a vehicle. The vehicle used is generally purified water. Tap water is not suitable because the dissolved salts present in it may lead to irritation in the eye.

(b) Storage Solutions

The contact lenses must be cleaned after use. After removing from the eye they are cleaned with wetting solution and rinsed with purified water. Then they are stored in a soaking solution with the intention to continue the cleaning process and prevent dehydration.

The formulation of storage solutions generally contain :

(i) A non-ionic surface active agent which will help in cleaning the lenses.

(ii) A blend of preservatives to prevent the bacterial growth. The solution should be changed after every few days because the preservatives may be practically inactivated by the organic materials present in the form of debris.

5. Eye Ointments

These ointments are meant for application to the eye. They should be sterile and free from irritation. The ointment base selected for an eye ointment must be non-irritating to the eye and must permit the diffusion of the drug throughout the secretions of the eye and must melt close to the body temperature.

For the preparation of eye ointments the eye ointment base B.P. is used. This base consists of :

Yellow soft paraffin	80%
Liquid paraffin	10%
Wool fat	10%

EYE DROPS

Eye drops are sterile aqueous or oily solutions or suspensions of drugs that are instilled into the eye with a dropper. They usually contain drugs having antiseptic, anaesthetic, anti-inflammatory mydriatic or meiotic properties.

Essential Characteristics of Eye-drops

1. They should be sterile.
2. They should be iso-osmotic with lachrymal secretions.
3. They should be free from foreign particles, fibres and filaments.
4. They should have almost neutral pH.
5. They should be preserved with a suitable bactericide.
6. They should remain stable during its storage.

Formulation of Eye-drops

The eye drops are prepared in 4 stages. These stages are as under:—

1. Preparation of bactericidal and fungicidal vehicle : The aqueous or oily vehicle is used in the preparation of eye-drops. The aqueous vehicle may support bacterial or fungal growth, so one of the following bactericide may be used to preserve the eye-drops:—

(i)	Phenylmercuric nitrate/acetate	0.002%
(ii)	Benzalkonium chloride	0.01%
(iii)	Chlorohexidine acetate	0.01%

Phenylmercuric nitrate should not be used in eye-drops which are intended for prolonged treatment. Similarly benzalkonium chloride is not suitable as preservative for eye-drops containing local anaesthetics.

2. Preparation of solution of medicament(s) and adjuvants : The medicament(s) are dissolved in the aqueous vehicle containing suitable antimicrobial agent. The adjuvants are also dissolved in the vehicle at this stage to form a stable preparation.

3. Clarification : The eye-drops are clarified by passing the solution through membrane filter having pore size of 0.8 μm. The clarified solution is immediately transferred into final containers and sealed to exclude micro-organism.

4. Sterilisation : The eye-drops are sterilised by autoclaving or heating with bactericide at 98° to 100°C for 30 minutes or filtration through bacteria proof filter.

5. Containers : The eye-drops should be packed in neutral glass containers or in a suitable plastic containers. In olden days, the eye-drops were stored in vertically fluted amber coloured glass bottles fitted with a bakelite cap carrying a dropper. The bottle must conform to limit test for alkalinity of glass. Now-a-days, neutral glass small bottles having capacity of 4 ml to 8 ml are used. It has two polypropylene screw caps, one for attaching a silicon rubber teat to the container and

the other for covering the teat. The plastic squeeze bottles having rigid plastic cap and polythene friction plug containing baffle that produces

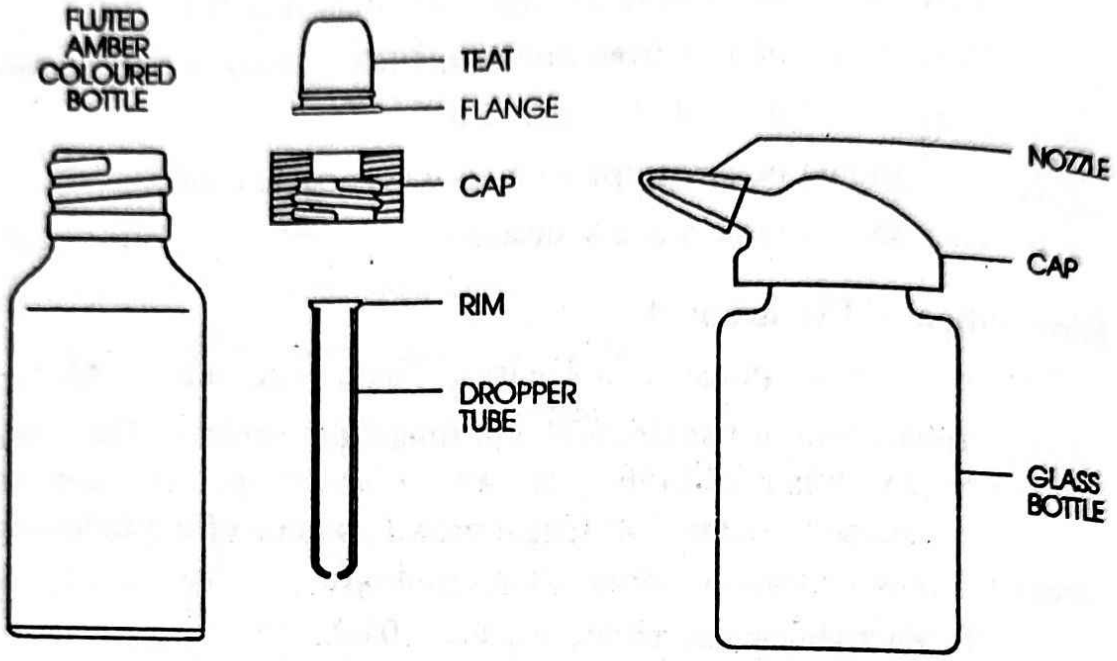

Fig. 12.1 Various containers for eye-drops

uniform drops are also used these days. These are very handy. These bottles are sterilised by gaseous sterilisation method.

Labelling ■

Eye-drops should be labelled 'For External Use Only' along with storage conditions to maintain full activity.

Adjuvants used in the preparation of eye-drops : The following adjuvants are used in the preparation of eye drops:—

1. Thickening agent : The thickening agents, such as, methyl cellulose, carboxy methyl cellulose, polyvinyl alcohol, polyethylene glycol are used to increase the viscosity of eye-drops. It will also help to prolong the contact time of the drug in the eye.

2. Buffers : Buffers are added to adjust and maintain the pH of the eye-drops. The pH of the eye drop is adjusted to maintain chemical stability to reduce discomfort and to improve clinical response. The boric acid, sodium acid phosphate, sodium citrate are commonly used as buffers.

3. Anti-oxidants : They are added in several eye-drops to provide protection from oxidation. Sometimes the eye-drops are protected from oxidation by replacing the air in the container with an inert gas. Sodium metabisulphite (0.05 to 0.5%) and sodium thiosulphate (0.1 to 0.2%) are commonly used as antioxidants.

4. Wetting agents : These are used for proper penetration of eye-drops into the cornea of the eye. Polysorbate 20 and polysorbate 80 are used as wetting agent.

5. Isotonicity adjustment substances : Eye-drops are made isotonic with the lachrymal secretion with the help of various buffers and other solutions.

Precaution Used in Handling Eye-Drops

The following precautions are required to be observed while using eye drops:—

1. If the dropper is separate, always hold it with its tip down.
2. Never touch the dropper surface.
3. Never rinse the dropper.
4. Never use eye-drops that have changed colour.
5. When the dropper is at the top of the bottle, avoid contaminating the cap when removed.
6. After instillation of drops, do not close eyes tightly or blink more often than usual as this may remove the medicine from the place where it is needed.

Example 12.1 Prepare and dispense 100 ml of atropine eye-drops B.P.C.

℞

Atropine sulphate	1 g
Phenylmercuric nitrate Solution 0.002 %	50.0 ml
Purified water, add upto	100 ml

Make an eye-drops.

Direction : To be used as directed.

Method : Dissolve phenylmercuric nitrate in purified water and prepare 0.002% solution. Dissolve atropine sulphate in 50 ml of phenylmercuric nitrate solution. Add purified water to make 100 ml. Filter the solution through membrane filter. Transfer the solution to final container and sterilise it by autoclaving at 115°C for 30 minutes. Clean the bottle, label and dispense.

EYE LOTIONS

These are the sterile aqueous solutions used for washing of the eyes. The eye lotions are supplied in concentrated form and are required to be diluted with warm water immediately before use. They are usually applied with a clean eye-bath or sterilised fabric dressing and a large volume of solution is allowed to flow quickly over the eye.

Eye lotions should be isotonic and free from foreign particles to avoid irritation to the eye. They are required to be prepared fresh and should not be stored for more than two days as the lotion may get contaminated with micro-organisms. The drugs used for preparing eye solutions include sodium chloride, sodium bicarbonate, boric acid, borax or zinc sulphate.

Formulation of Eye-Lotions

Eye lotions are simple solution. They are iso-osmotic with tears because they cause much greater dilution of the lachrymal fluid and, hence, are more likely to cause discomfort if not adjusted. The eye-lotions should be sterile because the large volume is used to remove the irritant from the eye. While removing the irritant from the eye, it become more susceptible to infection. The eye lotions are sterilised by autoclaving or by passing through bacteria proof filters.

Sodium chloride eye lotion and sodium bicarbonate eye lotion are commonly used to remove foreign substances from the eye.

Example 12.3 Prepare and dispense 100 ml of sodium chloride eye lotion B.P.C.

℞

Sodium chloride	9 g
Purified water to produce	1000 ml

Method : Dissolve sodium chloride in purified water and made the final volume by adding more of purified water. Filter through sintered glass filter grade 4. The eye lotion is transferred to the bottle. Close and sealed the bottle sterilise it by autoclaving. Clean the bottle, label and dispense.

Example 12.4 Prepare and dispense 100 ml of sodium bicarbonate eye lotion.

℞

Sodium bicarbonate	35 g
Purified water to produce	1000 ml

Method : Dissolve sodium bicarbonate in purified water. Add more of purified water to make final volume. Filter through sintered glass filter grade 4. The eye lotion is transferred to final container. Close and sealed it. Sterilise it by autoclaving clean the bottle, label and dispense.

Storage

Eye lotions are supplied in amber coloured screw capped fluted bottles. The containers must be labelled clearly "For External Use Only" and avoid contamination during use and discard any unused part after 24 hours.

6. They should be packed in a suitable container, so that it can be easily instilled into the eye.

What are Contact lens solutions? write diff types of contact lenses

CONTACT LENS SOLUTIONS

Contact lenses are usually made from polymethyl methacrylate which is a hard hydrophobic plastic. Nowadays, some softer hydrophilic lenses are also used.

Hard Contact Lenses

Wearers of hard contact lenses generally use two solutions:—

1. Wetting solution : It is used primarily for treating the lenses before insertion. Due to its hydrophobic nature, polymethyl methacrylate is poorly wetted by the lachrymal fluid of the eye. Hence, the contact lenses requires moistening with a wetting agent to make the insertion easy and comfortable. Since the contact lens solutions are required to be used daily for years together, therefore, they should be prepared carefully and all the ingredients used should be of good quality.

The formulation of contact lens solution may contain a wetting agent, thickening agent (cellulose derivative), antimicrobial agent (benzalkonium chloride, chlorohexidine), isotonicity adjusters (sodium chloride) are also added to prepare wetting solution.

2. Storage solution : It is used for overnight cleansing, soaking and storage. The contact lenses after its removal from the eye are cleaned with wetting solution and rinsed with purified water. Then they are stored in a storage solution to prevent dehydration.

The formulation of storage solution contains a non-ionic surface active agent which will help in cleaning the contact lenses. It also contains preservatives to prevent the microbial growth. The solution should be changed after every few days because the preservatives may be practically inactivated by the organic materials present in the form of debris.

Contact lens solutions should be sterile. The label should warn against contamination during use and encourage frequent changes of storage solution.

Soft Contact Lenses

These are soft flexible type lenses. Certain medicaments from eye drops and preservatives from wetting and storage solutions are strongly absorbed by the soft contact lenses. Due to this reason patients wearing soft contact lenses should be advised to remove them before instilling eye drops. For cleaning, soft contact lenses are heated in 0.9% sodium chloride solution. The wetting and storage solution used for hard contact lenses should not be used. Special proprietary storage solution are available. The wetting of soft contact lenses is not a problem because of the hydrophilic nature of the lens. The storage solution should be sterile.

Containers Contact lens solutions are packed in containers designed to minimise the chances of microbial contamination of the product. The solutions are generally stored in plastic container with in-built dropper which prevent the return of used or excess solutions to the container.