PHARMACEUTICS – II

(Industrial & Quality Control)

READING MATERIAL FOR PHARMACY TECHNICIAN STUDENTS

SECOND YEAR
PART-II

Reading Material

PHARMACEUTICS-II
(Industrial and Quality Control)

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PREFACE

Previously course contents of 02 years Pharmacy Technician Diploma Course approved by Pharmacy Council of Pakistan (PCP) were taught to the Pharmacy Technician students in PCP recognized Pharmacy Technician institutes/colleges in Punjab, AJK & Islamabad. Different reading materials of said course were prepared out of Pharmacy Council of Pakistan approved course contents by the owners / faculty of Pharmacy Technician Colleges and were available in the form of notes/hand books at respective Colleges / Institutions.

Under the dynamic vision and Leader ship of Worthy Chief Minister Punjab, Khawaja Salman Rafique, Minister, Ali Jan Khan, Secretary, SHC&ME Department P&S Healthcare Department, took an innovative initiative to formulate a uniform reading material from the available PCP approved course contents of Pharmacy Technician Diploma course and PPC has officially developed a uniform reading material of Pharmacy technician course subject wise.

Punjab Pharmacy Council has reviewed, consolidated and presented a uniform Reading Material to be taught to Pharmacy Technician students in Punjab, AJK & Islamabad, as per College/Institute annual academic calendar to improve and ensure the provision of best quality of pharmacy education.

This official uniform reading material of each subject of PCP approved 02 years Pharmacy Technician Diploma Course is available in the form of official hand book subject wise at Punjab Pharmacy Council and shall be taught to students in PCP recognized Pharmacy Technician Colleges/Institutes in Punjab, AJK & Islamabad with immediate effect. PPC technician examinations will also be taken out of this official uniform reading material and contents of Pharmacy Technician Diploma Course.

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CHAPTER 1

GENERAL INTRODUCTION OF PROCESSES AND USED EQUIPMENTS

1.1 MIXING:

Mixing may be defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particles of other ingredients or components.

This process may involve the mixing of gases, liquids or solids in any possible combination and in any possible ratio of two or more components.

Mixing is one of the most common pharmaceutical operations. It is difficult to find a pharmaceutical product in which mixing is not done at one stage or the other during its manufacturing.

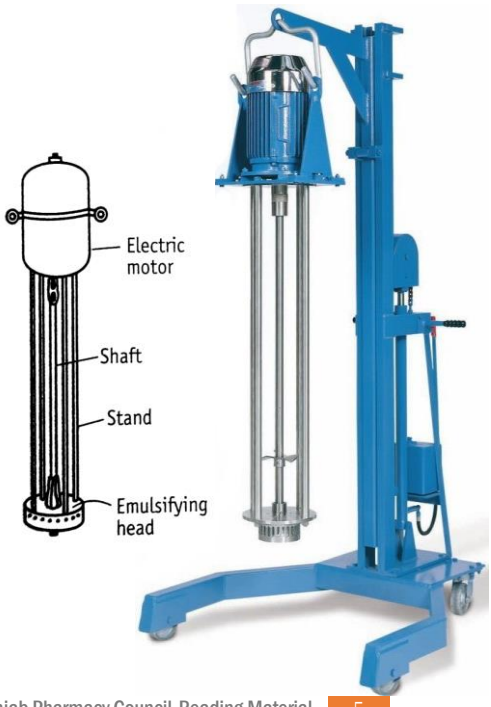
Equipment used in Mixing process

1. **Silverson Homogenizer**
2. **V-Type Mixer**

1.1.1 Silverson Homogenizer:

Silverson Homogenizer is a mixer. With the help of this liquid mixture, suspensions, fluid emulsions, syrups can be prepared.

Columns support the working head of homogenizer, turbines head or blades of head are driven by shaft fitted to a motor above the supporting column.



The speed of motor is variable depending on the product as well as on the quantity of the sample to be prepared or mixture to sieve or mesh.

1.1.2 V-Type Mixer

V-Type mixer is used for large scale mixing of powder. It consists of a container, which is mounted so that it can be rotated about an axis resulting in tumbling motion.

Efficiency of this type of mixer largely depends on the speed of rotation. V-Type mixer works on the principle of connective movement and shear mixing.

1.2 SIZE REDUCTION:

Size reduction is the process of reducing the particle size of a substance to a finer state to powder. Size reduction process is also referred to as comminution and grinding. When the particle size of solids is reduced by mechanical means it is known as milling.

Size reduction increases the surface area of drugs that help in rapid solution formation in the case of chemical substance.

Equipments used in Size Reduction process:

A wide variety of size reduction equipment is available.

1. **Hammer Mill**
2. **Ball Mill**

1.2.1 Hammer Mill:

In a hammer mill, swinging hammerheads are attached to a rotor that rotates at high speed inside a hardened casing.

The hammer mill consists of a steel casing in which a central shaft is enclosed to which a number of swinging hammers are attached. When the shaft is rotated the hammers swing out to a radial position. On the lower part of the casing a screen of desired size is fitted which can be easily replaced according to the particle size required.

The material is crushed and pulverized (to make or crush into dust or powder) between the hammers and the casing and remains in the mill until it is fine enough to pass through a screen, which forms the bottom of the casing.

It is rapid in action, and is capable of grinding many different types of materials. The particle size of the material to be reduced can be easily controlled by changing the speed of the rotor, hammer type, shape and size of the screen

1.2.2 Ball Mill:

The ball mill, which is also known as a jar mill, consists of horizontally rotating hollow vessel of cylindrical shape with the length slightly greater than its diameter. It is responsible for size reduction.

The mill is partially filled with the balls of steel or paddles which act as grinding medium. If pebbles are

used, it is known as paddle mill or if rods/bar are used it is called as bar mill in which length is about four times that of diameter and in which the balls are somewhat smaller than the ball mill.

If balls of different sizes are used in a conical ball mill they segregate according to size and provide progressive grinding, most ball mills utilized in pharmacy are switch operated.

1.3 Drying:

Drying is a mass transfer process consisting of the removal of water or another solvent by evaporation from a solid, semi-solid or liquid.
This process is often used as a final production step before selling or packaging products. A source of heat and an agent to remove the vapor produced by the process are often involved. In bio-products like food, grains, and pharmaceuticals like vaccines, the solvent to be removed is almost invariably water.

Equipment used in Drying process

1. **Belt dryer**
2. **Vacuum Tray dryer**

1.3.1 Belt Dryer:

Belt dryer is continuous drying equipment. Belt Dryer is widely used for chemical, food, and pharmaceutical industries. It is especially suitable for drying raw materials that are good in breath-ability and in the shapes of piece, strip or granule. It is also possible to dry the pasted raw material such as filter cake after shaping through granulator or extruder

1.3.2 Vacuum Tray Dryer:

Vacuum Tray Dryer is used mainly for drying of high grade, temperature and oxygen sensitive products. Vacuum Tray Dryer is highly suitable for drying hygroscopic substances, which are dried to very low residual moisture, content level.

Vacuum Tray dryer is the most commonly used batch dryer. They are box-shaped and loaded and unloaded via a door. Inside are several heating plates mounted one above the other on which the product is placed in trays.

1.4 FILTRATION:

The separation of solids from a liquid by means of porous medium or screen which retains the solids and allows the liquid to pass is called filtration.

In the laboratory, filtration is often carried out using simple filtration apparatus (gravity filtration) or Buchner set (vacuum or suction filtration).

Equipments used in Filtration Process

1.4.1 Vertical Pressure Leaf Filter

For filtration of liquids with suspended solid contents up to 7%. No filter clothe requirement. Automatic dislodging of filtered cake by pneumatic vibrator or oscillating sluice header. Dry or wet cake discharge is possible.

1.4.2 Tubular Centrifuge Filter:

The Tubular Centrifuge comprises of bowl, specially designed slow acceleration motor & starter. The bowl rotates at 15000 r.p.m. generating a centrifugal force of 16000 times the gravitational force. The liquid mixture to be separated enters the nozzle of the Centrifuge placed at the bottom base. The Centrifugal force acts on the liquid entering to their specific gravities. The lighter liquid forms the inside layer and heavier liquid forms the outside (Toward wall to bowl) layer. Since the Mixture is entering continuously in the bowl, two phases are discharged continuously from two separate holes provided on the top portion of the bowl. During clarification job, one discharge hole of the bowl is closed and continuous discharged on clarified liquid is possible. Solids accumulated inside the bowl can be removed manually after stopping machine.

1.5 EVAPORATION:

The concentration of solutions (most often, solutions of solids in water) by the partial vaporization of the solvent during boiling. During this process the concentration, density, viscosity, and boiling point of the solution are raised. In a supersaturated solution, the dissolved material precipitates out.

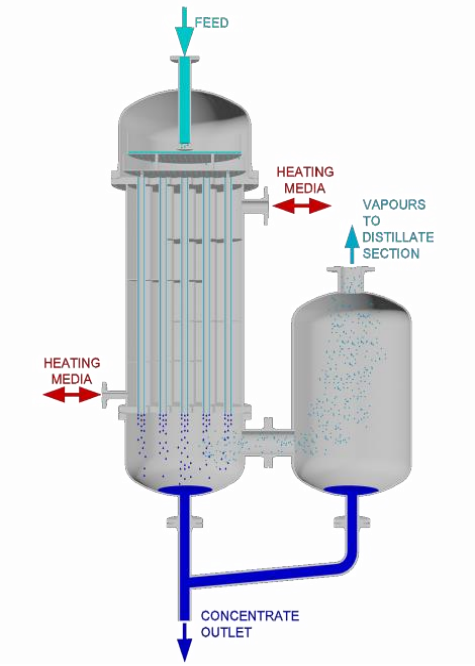
The boiling point of the solutions is always higher than the boiling point of the pure solvents; the difference between them, called the temperature depression. It grows with an increase in the concentration of the dissolved substance and in external pressure. Evaporation is used in the chemical and food industries, as well as in other branches of industry.

Equipments used in Evaporation Process

1. **Falling Film Evaporator**
2. **Natural/Forced Circulation Evaporator**

1.5.1 Falling Film Evaporator:

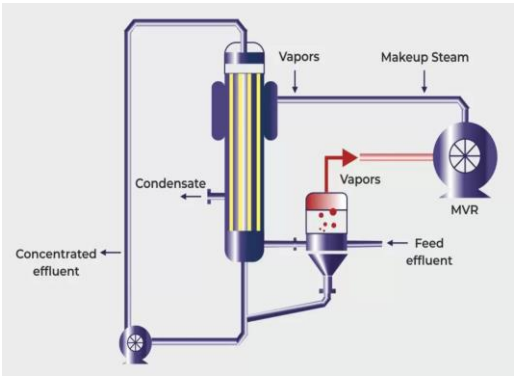
This type of evaporator is generally made of long tubes (4–8 m or 13–26 ft in length), which are surrounded by steam jackets. The uniform distribution of the solution is important when using this type of evaporator. The solution enters and gains velocity as it flows downward.



This gain in velocity is attributed to the vapor being evolved against the heating medium, which flows downward as well. This evaporator is usually applied to highly viscous solutions, so it is frequently used in the chemical, food, and fermentation industries.

1.5.2 Natural/ Forced Circulation Evaporator

Natural circulation evaporators are based on the natural circulation of the product caused by the density differences that arise from heating. In an evaporator using tubing, after the water begins to boil, bubbles will rise and cause circulation, facilitating the separation of the liquid and the vapor at the top of the heating tubes.



The amount of evaporation that takes place depends on the temperature difference between the steam and the solution. Problems can arise if the tubes are not well

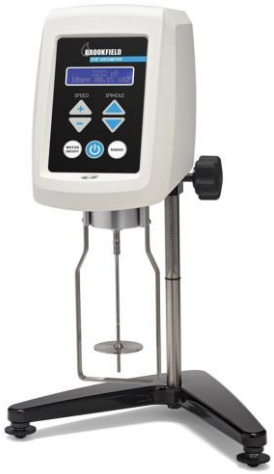
immersed in the solution. If this occurs, the system will be dried out and circulation compromised. In order to avoid this, forced circulation can be used by inserting a pump to increase pressure and circulation.

1.6 RHEOLOGY:

Rheology is the science concerned with the determination of material flow under the influence of stress.

Equipment used in Rheology process

1.6.1 Brookfield Viscometer



It is a rotational viscometer. It utilizes a spindle immersed (to put completely under the surface of liquid) in the sample and measure the resistance to movement of rotating part. Various spindles and several rotational speeds are available for given viscosity range. In some viscometers, lob/spindle remain stationary and rotates up.

Spindle is rotated at various speeds. Then knob is also rotated in reverse order and the same numbers of readings are observed. Temperature should be very well controlled for this purpose.

CHAPTER 2

A BRIEF INTRODUCTION TO THE FORMULATION AND MANUFACTURING OF SOLID, SEMISOLID, LIQUID AND PARENTERAL DOSAGE FORMS.

Pharmaceutical Formulation:

Pharmaceutical formulation, in pharmaceutics, is the process in which different chemical substances, including the active drug, are combined to produce a final medicinal product.

Formulation studies involve developing a preparation of the drug, which is both stable and acceptable to the patient. For example orally taken drugs, this usually involves incorporating the drug into a tablet or a capsule.

The objective of the formulation project is to design and manufacture medicines that deliver the drug to the patient in the required amount, at the optimum rate necessary to achieve the desired therapeutic benefit and better shelf life/ stability of the product.

Formulation and Manufacturing Solid Dosage Forms:

Most common solid dosage forms are tablets and capsules. We will discuss the manufacturing of these most commonly used solid dosages forms.

Formulation and Manufacturing of Tablets:

Tablets are the most common solid oral dosage form for many reasons including ease of manufacturing, convenience for the patient, accurate dose administration, and better stability than liquids and parenteral dosage forms.

Formulation of Tablet:

Tablet formulation generally consist of drug (or drugs) together with a varying number of other substances called excipients

- Drug(s)
- Diluents (microcrystalline cellulose, lactose)
- Binders (PVP)
- Lubricants (magnesium stearate, talc)
- Buffers
- Stabilizers
- Distintegrant (MCC, Alginates)
- Colorants (Titanium dioxide, Riboflavin)
- Flavors and Sweeteners (sucrose, Mannitol, dextrose)

Manufacturing of Tablet:

The three current methods for formation of compressed tablets are

1. Wet granulation method
2. Dry granulation method
3. Direct compression

Wet Granulation Method

Wet granulation method is a widely employed method for the production of compressed tablets…

Following Steps are involved in Wet Granulation Method

1. Weighing and blending the ingredients
2. Preparing the wet granulation
3. Screening the damp mass into pellets or granules
4. Drying
5. Dry screening

6. Lubrication and blending
7. Making tablets by compressing in machines

Dry Granulation Method:

This method is used when wet granulation is not applicable. There is no use of solvent in this method. In this method granulation is formed not by moistening or adding a binding agent to the powdered mixture but by compacting large masses of the mixture and subsequently crushing and sizing into granules.

Following steps are involved in Dry Granulation

1. Weighing and blending the ingredients
2. Slug formation by compression
3. Crushing of slug
4. Screening into granules
5. Mixing of lubricants
6. Making tablets by compressing in machines

Direct Compression:

Chemical substances occurring in granules form and having good adhesive properties can be compressed directly into tablets without formation of granules e.g. Aspirin.

Formulation and Manufacturing of Capsules:

Capsules are dosage form containing unit doses of drugs enclosed in a hard or soft soluble shell of gelatin, starch or similar material and intended to be swallowed whole orally.

Hard gelatin capsule shells are manufactured in two sections, the capsule body and a shorter cap.

The large-scale or small-scale preparation of filled hard gelatin capsules is divided into the following general steps.

1. Developing and preparing the formulation
2. Selecting the capsule size

3. Filling the capsule shells
4. Capsule sealing (optional)
5. Cleaning and polishing the filled capsules

Formulation and Manufacturing Semisolid Dosage Forms:

Ointments, creams, and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed on the surface of the eye, or used nasally, vaginally, or rectally. Most of these preparations are used for the effects of the therapeutic agents they contain. The non-medicated ones are used for their physical effects as protectants or lubricants.

Formulation of Semisolid Dosage Form:

A wide range of raw materials is available for the preparation of a semisolid dosage form. Apart from the usual drug/medicament, listed below APIs are also used such as.

- Preservatives
- Antioxidants
- Solubilizers
- Thickening agents
- Emulsifying agent
- Antimicrobial agents
- Coloring agent

The basic constituents of a semisolid dosage form are unique to its composition. The choice of suitable raw materials for a formulation development is made on the basis of the drug delivery requirements. Semisolid dosage forms can exist as single-phase systems (the drug substance in solution in the semisolid material) or as more complex two-phase or multiphase systems. An example of a complex multiphase system is oil in water emulsion with suspended solid particles.

Most common semisolid dosage forms are ointments and creams. We will discuss the manufacturing of these most commonly used semisolid dosages forms.

Ointments:

Ointments are greasy-semisolid preparations for application to the skin. An ointment is a fatty preparation of such consistency as to be easily applied to the skin. They may be medicated or non-medicated.

Manufacturing of Ointment:

There are two most commonly used methods for the preparation of ointment

1. **Trituration or mechanical method**
2. **Fusion method**

Trituration or Mechanical Method:

In this method finely subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base followed by dilution with gradually increasing amounts of the base.

Fusion Method:

In this method the ingredients are melted together in descending order of their melting points and stirred to ensure homogeneity.

Manufacturing of Cream (Emulsion):

Creams are semi-solid emulsions usually for application to the skin. They may be medicated or non-medicated. Creams are divided into two types:

1. Oil-in-water (O/W) creams which are composed of small droplets of oil dispersed in a continuous phase
2. Water-in-oil (W/O) creams which are composed of small droplets of water dispersed in a continuous oily phase

Most common methods for the preparation of Emulsion are:

1. Wet gum method
2. Dry gum method
3. Bottle method

Wet Gum Method:

A primary emulsion can be prepared by various methods. However it depends on type of ingredients involved in mainly stable preparation of fixed oil water and acacia (ratio in parts 4:2:1) is prepared by the following methods.

- Two parts of water and one part of acacia mixture is to be triturated with a mortar and pestle until a smooth mucilage is formed.
- Oil is to be added slowly with continuous triturating until a smooth cream of primary emulsion is formed.
- The mixture should be again triturated for another 5 minutes and then water is added to make up the volume with continuous triturating.

Dry Gum Method:

A primary emulsions of fixed oil, water and acacia (ratio in parts 4:2:1) is prepared by the following methods.

- The oil is mixed in acacia using mortar and pestle until acacia powder is distributed uniformly.
- Purified water is to be added and rapidly triturated until it forms the primary emulsion.
- Add other additives and remaining quantity of water is added with continuous trituration to finish the product.

Bottle Method:

It is a modified method of dry gum method. The ratio of oil, water and acacia should be 3:2:1 or 2:1:1 to prepare the emulsion. As the low viscosity of the volatile oil requires a higher proportion of acid.

- The oil is mixed in acacia by shaking the bottle uniformly
- Add measured quantity of water and shake until uniform emulsion is formed.

Formulation and Manufacturing liquid Dosage Forms:

A liquid dosage form is the liquid form of a dose of a chemical compound used as a drug or medication intended for administration or consumption.

Formulation of Liquid Dosage Forms:

Liquid dosage form generally consists of drug (or drugs) together with a varying number of inactive substances called excipients e.g.

- Sweetening agents
- Flavoring agents
- Coloring agents
- Viscosity control
- Preservatives
- Antioxidants

Most common liquid dosage form is syrup/ oral solution. We will discuss the manufacturing of syrup/ oral solution.

Manufacturing of Syrup/ Oral Solution:

"Syrups are concentrated aqueous preparations of sugar or sugar substitute with or without flavoring agents and medicinal agents."

Mostly syrup contains the following components in addition to the medicinal agents and water.

- Sugar (usually Sucrose) or Sugar Substitute used to provide sweetness and viscosity
- Preservative
- Flavoring agents
- Coloring agents

Some may also contain special solvents, solubilizing agents and thickeners. Depending on the physical and chemical characteristics of the ingredients, there are four different methods used for the manufacturing of syrups:

1. Solution with heat or hot method
2. Agitation without heating
3. Addition of sucrose to a medicated liquid or to a flavored liquid
4. Percolation

Solution with Heat or Hot Method:

For Thermo-Stable or Non-Volatile Ingredients:

1. Sugar is generally added to the purified water.
2. Heat is applied until the sugar is dissolved.
3. Then other heat-stable components are added to the hot syrup.
4. The mixture is allowed to cool and the volume is adjusted by addition of water.

For thermo-labile or volatile ingredients, the method is as follows:

- Sugar is added and dissolved by heating the mixture.
- The mixture is allowed to cool rapidly at room temperature.
- The volatile or thermo-labile ingredients are then added to the cooled syrup.

Agitation (to shake) without Heating:

On small scale, sucrose and other ingredients are added to the purified water in a container larger than the final volume of the syrup. The mixture is agitated. The process is time consuming but yields a more stable product.

On large scale, huge glass-lined or stainless steel tanks with mechanical stirrers or agitators are employed in preparation.

Sometimes, solvents other than water are used. In these preparations the water-soluble ingredients are first mixed in small amount of water before being added to that substance.

Addition of sucrose to a medicated liquid or to a flavored liquid:

In some preparations where tinctures or fluid extracts are to be employed as ingredients, the unnecessary alcohol-soluble contents of that tincture or fluid extract is separated out by mixing with water and are allowed to settle the unnecessary and insoluble ingredients and filtered. Sugar is then dissolved in the filtrate obtained by heating or simply agitating the mixture thoroughly.

If the tincture is miscible, then it is simply added to the simple syrup to make a flavored syrup.

Percolation:

In this method, an extract is percolated out from the medicinal component of the drug source, and added to the syrup. Or, sucrose may be percolated to prepare the syrup.

Formulation and Manufacturing of Parenteral Dosage Forms:

Parenteral Dosage Forms:

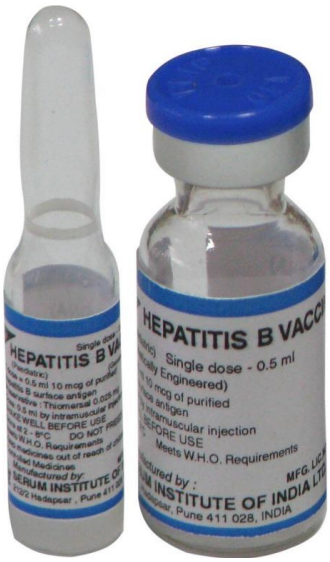
A pharmaceutical dosage form that is injected via different routes such as intramuscularly, subcutaneous, intravenous or others. These are important pharmaceutical dosage forms with the common characteristic of sterility; means they must be free from microorganisms.

Most Common Injectables are…

- Injections
- Intravenous infusions
- Powders for injections

Manufacturing of Sterile Injectables:

The manufacturing process should meet the requirements of Good Manufacturing Practice. The quality of starting materials, the design and maintenance of the equipment, and the method of manufacture must be such as to ensure the stability of the active substance and the final product, which is sterile and free of pyrogens and particulate matter. From the clinical point of view, all parenteral preparations must be pyrogen-free.



Methods of Sterilization:

Sterilization is necessary for the complete destruction or removal of all microorganisms (including spore-forming and non-spore-forming bacteria, viruses, fungi, and protozoa) that could contaminate pharmaceuticals or other materials and thereby constitute a health hazard.

The efficacy of any sterilization process will depend on the nature of the product, the extent and type of any contamination, and the conditions under which the final product has been prepared.

Following methods are used for sterilization:

- Heating in an autoclave (steam sterilization)
- Dry-heat sterilization
- Filtration
- Gas sterilization
- Exposure to radiation

Whatever method of sterilization is chosen, the procedure must be validated for each type of product or material, both with respect to the assurance of sterility and to ensure that no adverse change has taken place within the product.

CHAPTER 3

ADDED SUBSTANCES LIKE PRESERVATIVES, ANTIOXIDANTS SOLUBILIZER, SUSPENDING AGENTS, BUFFERS, STABILIZERS

To produce a drug substance in a final dosage form requires pharmaceutical ingredients. For example, in the preparation of solutions, one or more solvents are used to dissolve the drug substance, flavors and sweeteners are used to make the product more attractive and acceptable, preservatives may be added to prevent microbial growth, and stabilizers, such as antioxidants and chelating agents, may be used to prevent decomposition, lubricants to assist smooth tablet formation, disintegrating agents to promote tablet breakup after administration, and coatings to improve stability, control disintegration, or enhance appearance.

Ointments, creams, and suppositories acquire their characteristic features from their pharmaceutical bases. Thus, for each dosage form, the pharmaceutical ingredients establish the primary features of the product and contribute to the physical form, texture, stability, taste, and overall appearance.

Preservatives:

A preservative is a naturally occurring or synthetically produced substance that is added to products such as pharmaceuticals, foods, paints, biological samples, wood, etc. to prevent or inhibit the growth of microorganisms to avoid the degradation of the product/ medicinal product, risk of infection or undesirable chemical changes.

Common Preservatives used in Pharmaceutical Products:

Benzoic acid, sodium benzoate, quaternary ammonium salts, Butyl paraben, Methyl paraben, Chlorobutanol

Antioxidants:

Oxidation is a chemical process that transfers electrons from one substance to another and can produce free radicals. Free radicals can enter the body from a number of environmental sources, including cigarette smoke; toxins, sunlight and pesticides, and can damage the body's cells or cause cell death. According to the National Cancer Institute, free radical cell damage may lead to cancer.

Antioxidants are used to reduce the oxidation of active substances and excipients in the finished product. Commonly antioxidants are included in pharmaceutical products to enhance the stability of therapeutic agents.

Common Antioxidants used in Pharmaceutical Products:

- Ascorbic acid
- Sodium ascorbate
- Sodium bisulfite

Solubilizer:

The excipients used to solubilize drugs in oral and injectable dosage forms are called solubilizers. Solubilizer is used to improve the solubilization of hydrophobic substances and to increase bioavailability. They are also used to stabilize suspensions and prepare colloids and gels.

There are many solubilized oral formulations such as oral solutions, syrups, elixirs, or solutions.

Common Solubilizers used in Pharmaceutical Products:

- Alcohol
- Corn oil
- Glycerin
- Mineral oil
- Purified water
- Water for injection
- Sterile water for injection

Suspending Agents:

Agents used in pharmaceutical suspensions to increase viscosity. An agent used in suspension to increase the viscosity of the continuous phase so that the particles remain suspended for a sufficiently long time.
Most suspending agents perform two functions.

Besides acting as a suspending agent they also impart viscosity to the solution. Suspending agents form film around particle and decrease inter-particle attraction. Suspending agents also act as thickening agents. They increase in viscosity of the solution, which is necessary to prevent sedimentation of the suspended particles.

The stability of the suspension depends on the types of suspending agents rather than the physical properties of the drugs.

List of Suspending Agents:

- Acacia
- Tragacanth
- Bentonite
- CMC
- Xanthan gum
- Powdered cellulose
- Gelatin
- Methylcellulose
- Sodium Carboxymethylcellulose
- Microcrystalline cellulose

Buffers:

A buffer solution is an aqueous solution consisting of a mixture of a weak acid and its conjugate base (salt of weak acid) or a weak base and its conjugate acid (salt of weak base). Buffers are used to resist change in pH upon dilution or addition of acid or alkali.

Buffering agents have variable properties, some are more soluble than others, and some are acidic while others are basic.

Examples Buffers:

- Potassium phosphate,
- Sodium acetate
- Sodium citrate, anhydrous and dihydrate
- Acetic acid-sodium acetate
- Boric acid-sodium borate
- Citric acid-sodium citrate
- Phosphoric acid-potassium phosphate

Applications of Buffers:

Buffer solutions are used frequently in pharmaceutical practice, particularly in the formulation of ophthalmic solutions. Buffer solutions are used in fermentation processes. They are also used in chemical analysis and calibration of pH meters. Majority of biological samples that are used in research are made in buffers.

Stabilizers:

Stabilizer is a chemical, which tends to inhibit the reaction between two or more other chemicals. Many products contain excipients that can be categorized as stabilizers in a general sense. Using suspending agents to prevent sedimentation, adding a preservative to prevent microbial spoilage or a buffer to adjust pH for optimum stability are all examples of stabilizers being added to enhance product stability.

CHAPTER 4

FILLING PACKAGING AND VARIOUS MATERIALS USED FOR PACKAGING

Packaging:

Packaging is an art as well as science in preparing a product for transport, storage, display and use. Suitable packaging is important for suitable purity, potency, and stability of a product. In some cases major part of the formulation process is concerned with selecting the right package for the product by using it's physical and chemical characters.

4.1 Components of Package:

A package consist of:

- **Container**
- **Closure**
- **Carton or outer cover / pack**
- **Box**

4.1.1 Container:

In which product is placed is called container

4.1.2 Closure:

Closure, which seals the container to exclude oxygen, carbon dioxide, moisture, bacterial contamination etc and to prevent the loss of water and volatile substances from product.

4.1.3 Carton or Outer:

Carton or outer pack are used for secondary protection against mechanical and environmental hazards and also serves for display of written information.

4.1.4 Box:

Multiples of the products are packed in box. It also defend against external hazards.

4.2 Requirements for a Packaging Material

The suitability of the container and closure depends upon the followings;

- Non-toxic
- Non-reactive to product
- Impart no taste or color to the product
- Fulfill stability needs of the product
- Protection against external hazards
- Reasonable cost in relation to the cost of product
- Good for speed packing
- Good for speed transportation
- Must be FDA approved

4.3 Factor influencing the choice of Packaging Material

Following are major factors that influence the choice of packaging material:

4.3.1 The Product:

The physical and chemical characteristics of the drug, the excipients, the formulation, and, type of patient (baby, child, teenager, adult, elderly, infants etc) must be considered while dealing with the pharmaceutical product. Apart from the properties of drug, package style to attract patient and other legal requirements should also be considered during selection.

4.3.2 The Market:

The channel of sale should be considered, i.e. where, when, how and by whom it is to be used or administered (e.g. doctor, dentist, nurse, patients etc), whether for home trade and/ or export.

4.3.3 The Distribution and Transport System:

The distribution system should be carefully monitored, e.g. conventional wholesale/ retail outlet or direct or selective outlets. Transport system require additional protection if intermediate storage facilities are non-existent.

4.3.4 Manufacturing Facilities:

The stability of the manufacturing facilities should be considered due to new package, increased sale, improvements in Good Manufacturing Practice, revised product, new product etc.

4.4 Function of Packaging:

The various functions of packaging are followings;

- Protective function
- Storage function
- Loading & Transport functions
- Identification

4.4.1 Protective Function:

Protective function of packaging essentially involves protecting the contents from the environment and vice versa. The packaging must prevent any contamination, damage or other negative impact upon the environment and other goods also.

4.4.2 Storage Function:

The materials used for packaging should be stored properly so as to preserve the quality of the material both before packaging and once the package contents have been used.

4.4.3 Loading and Transport Functions:

Packaging has a crucial (involving a big decision) impact on the efficiency of transport, handling and storage of goods. Packaging should therefore be designed to be easily handled and to permit space-saving storage.

4.4.4 Identification:

The packaging should give clear identification of the product at all stages. The life of the patient may depend upon rapid and correct identification in emergencies. Packaging also serves as a mean to identify the manufacturer of the product. The manufacturer must consider the packaging requirement for the usage of product in different localities.

4.5 Properties of Packaging Materials:

To afford the necessary protection, the materials from which the container is to be made must show certain basic properties, which can be divided into four groups.

4.5.1 Mechanical Properties:

The materials used should possess sufficient mechanical strength to withstand while handling, filling, closing and processing.

4.5.2 Physical Properties:

- The material should be impervious (Not allowing something to pass through) to any possible contaminants, for example, solids, liquids, gases, vapors or microorganisms.
- The container must be able to withstand heat if the processing includes sterilization.
- The surface must be capable of clear labeling, often difficult, for example, with plastics.
- The packaging must have a suitable size.

- The material must protect from light if necessary, that is, it must be ultraviolet absorbent.
- The container must not absorb substances from the products; e.g. absorption of water from creams in to cardboard box.

4.5.3 Chemical properties:

- The container and the closure should not react together, either alone or in the presence of the product.
- The product should not react with the container or closure, as might happen if alkaline substances are placed in aluminum containers.
- Substances must not be extracted from the product, such as the loss of bactericides from injection solution to rubber.
- The container or closure must not yield (Produce or provide) substances to the product; for example, alkali from glass, plasticizers from plastics etc.

4.5.4 Biological Properties

The material of the container must be able to withstand attack by insects if this hazard is likely to be encountered. The packing should not support mold growth. The risk is greatest with cellulose substance and if the use of such materials is unavoidable, the attack may be minimized by impregnation.

4.6 Materials Used In Packaging:

- Paper (Cellulose fiber)
- Rubber
- Glass
- Plastic
- Metal

4.6.1 Paper (Cellulose Fiber):

The use of paperboard materials (cellulose fiber) is very important part of pharmaceutical packaging. Cartons are used for a high percentage of pharmaceutical products for a number of reasons, increasing display area, providing better display of stock items and the collating of leaflets, which would otherwise be difficult to attach to many containers. Cartons also provide physical protection especially to items such as metal collapsible tubes. Carton therefore tends to be a traditional of pharmaceutical packaging.

4.6.2 Rubber:

Rubber components may be made from either natural or synthetic sources. Natural rubber has got good resealing power (multi-dose injection), fragmentation and coring (means by which particles are created when a needle is passed through a rubber) when compared to synthetic rubber.

Synthetic rubbers have many properties. The main types of rubber used for pharmaceutical products include natural rubber. Rubber components are likely to contain more additives (A substance added to something in small quantities, typically to improve or preserve it.) than plastics. Hence product-package interactions should be properly tested before they are used for injectabels or intravenous type products. Rubber gaskets are also sound in aerosols and metered-dose pump systems.

4.6.3 Glass:

Glass is commonly used in pharmaceutical packaging because it possesses superior protective qualities.

Advantages of Glass Containers:

- Economical
- Readily available container of variety of sizes and shapes
- Impermeability
- Strength and rigidity
- Has FDA clearance
- Does not deteriorate
- Easy to clean
- Effective closure and resolves are applicable.
- Colored glass, especially amber, can give protection against light when it is required

Disadvantages of Glass Containers:

Fragility (quality of being easily damaged or destroyed.)

4.6.4 Plastic:

Plastics in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality, and the freedom of design to which they lend themselves. Plastic containers are extremely resistant to breakage and thus offer safety to consumers along with reduction of breakage loss at all levels of distribution and use.

Advantages of Plastic Containers:

Plastic containers have a number of advantages over other

containers or dispenses.

- Low in cost
- Light in weight
- Durable
- Pleasant to touch
- Flexible facilitating product dispensing
- Odorless and inert to most chemicals
- Unbreakable
- Leak proof
- Able to retain their shape throughout their use

Disadvantages of Plastic Containers:

Plastics appear to have certain disadvantages like interaction, adsorption, absorption, poor labeling, stress cracking, lightness and hence poor physical stability.

4.6.5 Metal:

The collapsible metal tube is an attractive container that permits controlled amounts to be dispensed easily, with good re-closure and adequate environmental protection to the product. The risk of contamination of the portion remaining in the tube is minimal, because the tube does not "suck back." It is light in weight and unbreakable, and it allows high-speed automatic filling operations.

4.6.6 Tin:

Tin containers are preferred for food, pharmaceuticals, or any product for which purity is an important consideration. It offers a good appearance and compatibility with a wide range of products.

4.6.7 Aluminum:

Aluminum tubes offer significant savings in product shipping costs because of their lightweight. They provide good appearance.

4.6.8 Lead:

Lead has the lowest cost of all tube metals and is widely used for nonfood products such as adhesives, inks, paints, and lubricants. Lead should never be used alone for anything taken internally because of the risk of lead poisoning. The inner surface of the lead tubes is coated and is used for products like fluoride toothpaste.

CHAPTER 5

AN UNDERSTANDING OF QUALITY CONTROL OF PHARMACEUTICALS

The word quality relates to characteristics of a product from both a qualitative and quantitative point of view. In quality control process, laboratory techniques and activities are used to fulfill the requirement of Quality. Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations. In this competitive industrial age, quality has become an important part for any kind of product.

Quality control has different perspectives in different industries. In some industries quality control would mean that the end product should come up to certain standards of quality. However quality control in pharmaceuticals is meant to ensure the output of batches of pharmaceutical products conforming to established specifications of identity, purity, strength and other characteristics.

Thus besides raw materials, the containers in which the medicines are filled and packed, the machinery and even the personnel have to go through certain quality control checks and measures.

The main goal of quality control in pharmaceuticals is the assurance of safety for its use by the patients.

It is essential that well qualified trained personnel be employed to supervise the formulation, processing, testing, packaging and labeling of the drugs, maintenance of machinery, equipments and sanitation.

CHAPTER 6

QUALITY ASSURANCE SYSTEM ADOPTED IN PHARMACEUTICAL INDUSTRY

Quality assurance is any systematic process is to see whether a product or service being developed is meeting specified requirements.

Quality assurance is achieved through the collaborative efforts of the following…

1. Drug manufacturer (QA system adopted in pharmaceutical industry)
2. National Drug Regulatory Authorities
3. World Health Organization (WHO)

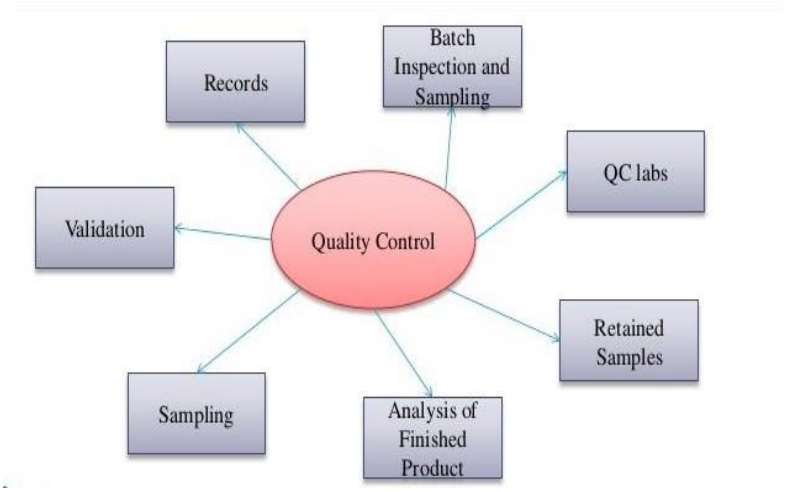
Drug Manufacturer (QA System Adopted In Pharmaceutical Industry)

Drug manufacturers are primarily responsible to ensure quality, safety and efficacy of their products. They are legally, morally and ethically bound to guarantee the standard of their products to safeguard public health.

Quality control of pharmaceuticals done at four stages…

At first stage, all the raw materials, active as well as non-active, the containers and packing material are tested for their quality.

At second stage, certain checks and tests are instituted during the course of manufacturing which aim at assuring the perfect manufacturing processes.



At third stage, when the products are ready for marketing, it is the responsibility of the quality control unit to approve and authorize for marketing only those products which meet the standards of quality.

At final stage, medical representatives

of the firm pick up the samples from the market at frequent intervals to ensure that they keep up their quality during the shelf life assigned to these products.

National Drug Regulatory Authorities:

The national drug regulatory authorities are responsible to ensure and supervise that manufacturers and importers fulfill their responsibility in making standard medicine.

World Health Organization:

World health organization is major share in quality assurance of pharmaceutical supply systems with the main objective of providing highest possible level of health for the entire population of the world. WHO is providing guidelines on various approaches to quality-assurance.

CHAPTER 7

STORAGE OF PHARMACEUTICALS

The storing of pharmaceutical products and materials up to their point of use is called storage of pharmaceutical products.

Requirements for storage of Pharmaceutical Products:

The storage condition of pharmaceutical products must be in compliance with the following requirements or other special requirements that are mentioned in good storage practice.

- Storage facilities must comply with the Law.
- Precautions must be taken to prevent unauthorized persons from entering storeroom.
- Storeroom should be of sufficient capacity to allow the orderly storage of the various categories of pharmaceutical products.
- Storeroom should be designed or adapted to ensure good storage conditions. They should be clean and dry and maintained within acceptable temperature and humidity limits.
- Storeroom should be clean, and free from accumulated waste and vermin.
- Receiving area should be designed and equipped to allow incoming containers of pharmaceutical products to be cleaned, if necessary, before storage.
- Radioactive materials, dangerous drugs, psychotropic substances etc should be stored in dedicated areas that are subject to appropriate additional safety and security measures.

- Pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.
- A system should be in place to ensure that pharmaceutical products due to expiry first are sold and/or distributed first.
- Broken or damaged items should be stored separately from usable stock and disposed properly.
- Storeroom should be provided with adequate lighting to enable all operations to be carried out accurately and safely.
- Recorded temperature and humidity monitoring data should be available for review. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained.
- Equipment used for monitoring of storage conditions should be calibrated and maintained at defined intervals. Relevant records should be kept and available for inspection by Department of Health.
- All facilities for the storage of poisons should be licensed or approved and should have proper security control.

CHAPTER 8

DOCUMENTATION IN PHARMACEUTICAL INDUSTRY

Document is any written statement or proof of any activity in pharmaceuticals. Documentation is to define the manufacturers system of information & control, to minimize the risk of misinterpretation & errors inherent in any oral or casually written communication, to provide unambiguous procedures to be followed, to provide confirmation of performance, to allow calculations to be checked & to allow tracing of batch history.

Documents are a mirror to show actual image of any pharmaceutical company. Documents and products are produced in pharmaceutical industry but regulatory bodies are interested to see documents first. Different documents can describe the different activity in pharmaceutical industry and its actual image.

Good documentation is a systematic procedure of preparation, checking, verifying, issuing, storing and reviewing of any documents. Batch record is an important document kept along with reserve sample until one year of expiry of the product, and final products are released only after proper review of BMR, even after testing of Product from QC, product would not be released without review and completing of BMR and other documents.

Every activity should be available in written form as SOPs is a requirement of GMP. Control of document is also an important part of GDP to reduce error and misuse of any document. Master copy for all activities should be prepared such as SOPs started from

Draft copy and finalizing it after checking and reviewing and approved by QA Department. Final copy should be printed as Master copy and stamped as "master copy" by red ink.

A photocopy of master copy should be issued to concerned department with stamped "control copy". A record should be maintained for issuing any documents with sign & date. Every document must have effective date, review date and revision no.

Objectives of Documents:

- To define the specifications and procedures for all materials and method of manufacturing and control.
- To ensure that all personnel concerned with manufacturing know what to do and when to do it.
- To ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale.
- To ensure the existence of documented evidence, trace ability, and to provide records and an audit trail that will permit investigation.
- It ensures the availability of the data needed for validation, review and statistical analysis.

Different types of documents and records:

Documentation and records used throughout the manufacturing process, as well as supporting processes (e.g. Quality Control or Quality Assurance), must meet the basic requirements of GDP. These include (but are not limited to):

- Batch Record Forms
- Bills of Materials (BOMs)
- Specifications
- Policies
- Protocols

- Standard Operating Procedures (SOPs)
- Work Instructions (WIs)
- Test Methods
- Checklists
- Forms/Log sheets
- Training Assessments
- Electronic and hardcopy Quality records (e.g. non-conformance, corrective and preventative actions, internal inspection, change control, training records etc.)
- Certificate of Analyses (CoA) or Certificate of Compliance (CoC)
- Technical transfer reports
- Validation documentation

Standard Operating Procedure (SOP):

An SOP is a written document or instruction detailing all steps and activities of a process or procedure. These should be carried out without any deviation or modification to guarantee the expected outcome. Any modification or deviation from a given SOP should be thoroughly investigated and outcomes of the investigation documented according to the internal deviation procedure.