International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 972-990 www.ijprajournal.com ISSN: 2249-7781

Complete Review on "An Overview of Production in Capsule Department"

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Date of Submission: 01-08-2021 Date of Acceptance: 11-08-2021

ABSTRACT: Capsules are among the most popular of all dosage forms. They are Chemically stable, easy to administer, attractive, and can be easily compounded. Manufacturing of capsules is a special pharmaceutical unit operation in pharmaceutical industries. A number of modified techniques are used for production of capsules. Capsules have been used for administering medications to patients more than a century and have an important role in drug delivery. When a primary care provider prescribes a tablet, the choice is usually, but not always, limited to commercially available products. A capsule, however, can be prepared extemporaneously, which provides dosing flexibility for the primary care provider and the pharmacist.

This article concerns with the production of capsule dosage form which has numerous advantages over other dosage forms.The object is to be present a review and to discuss aspects of production in terms of pharmaceutical unit operation i.e, the technical operations of capsules preparation that comprise the various steps involve in production of capsules. Mainly a systemic approach should be followed during the production of capsules in various parameters should be maintained in the production area also.

INTRODUCTION:

Manufacturing section of pharmaceutical industry decide the economic health of the organization. It has to follow several regulations as per GMP. Regular monitoring in every stage of production which starts from receiving of the material from the store and ends until the final pack reach the NDP, is to be perform by the production, QA & QC departments. Requirements of Quantum of production is as per production scheduled submitted or decided by the logistics department. Responsibility of the production department is not only to fulfill the target but also to maintain the quality requirements as per GMP and to follow the norms let down by Quality Assurance Department.

Capsules are gelatin shells filled with the ingredients that make up an individual dose. Dry powders, semi-solids, and liquids that do not dissolve gelatin may be encapsulated. Capsules account for about 20% of all prescriptions dispensed.In the manufacture of pharmaceuticals, **encapsulation** refers to a range of dosage forms—techniques used to enclose medicines—in a relatively stable shell known as a **capsule**, allowing them to, for example, be taken orally or be used as suppositories. The two main types of capsules are:

- Hard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g. processes of extrusion or spheronization. These are made in two halves: a smaller-diameter "body" that is filled and then sealed using a larger-diameter "cap".
- Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animalprotein (mainly gelatin) or plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose). Other ingredients can be added to the gelling agent solution including plasticizers such as glycerin or sorbitol to decrease the capsule's hardness, coloring agents, preservatives, disintegrants, lubricants and surface treatment.

Since their inception, capsules have been viewed by consumers as the most efficient method of taking medication. For this reason, producers of drugs such as OTC analgesics wanting to emphasize the strength of their product developed the "caplet", a portmanteau of "capsule-shaped tablet", in order to tie this positive association to more efficiently-produced tablet pills, as well as

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being an easier-to-swallow shape than the usual disk-shaped tablet Medication.

Gelatin capsules, informally called **gel caps** or **gelcaps**, are composed of gelatin manufactured from the collagen of animal skin or bone.

Vegetable capsules, introduced in 1989,are made up of cellulose, an important structural component in plants. To be more specific, the main ingredient of vegetarian capsule is hydroxypropyl methyl cellulose (HPMC). In the current market, gelatin capsule is more broadly used than vegetarian capsule because its cost of production is lower.

ADVANTAGES OF CAPSULES :

»The advantages of the capsule include the ability of being effective oxygen barrier and excellent chemical stability, which could improve product stability. For example, components are unstable, sensitive to temperature, light and heat can be made into capsule forms. Moreover, capsules are good in uniformity of dosage units, and capsules can be made into different types to meet the needs.

»Ease of use due to the fact that it is smooth, slippery and easy to swallow.

»Suitable for substances having bitter taste and unpleasant odor.

»As produced in large quantities it is economic, attractive and available in wide range of colors.

»Minimum excipients required.

»Little pressure required to compact the material.

»Unit dosage form.

»Easy to store and transport.

» Unique mixes of ingredients are possible.

» Sealed hard gelatin capsules can be good oxygen barriers.

» Protection for sensitive ingredients.

» Capsules can be opened to obtain powdered ingredients.

» Reduced gastrointestinal irritation.

DISADVANTAGES OF CAPSULES

» Capsules are not suitable containers for liquids that dissolve gelatin, such as aqueous or hydroalcoholic solutions.

» Very soluble salts, such as bromides or iodides should not be dispensed in capsules, as the rapid release of such materials

» may cause gastric irritation

» Not suitable for highly soluble substances like potassium chloride, potassium bromide, ammonium chloride, etc.

» Not suitable for highly efflorescent or deliquescent materials.

» Special conditions are required for storage

» The hygroscopic drugs cannot be filled in capsules. They absorb water present in the capsule shell and hence make it very brittle, which ultimately breaks into pieces.

» The concentrated preparations which need previous dilution are unsustainable for capsules because it may lead to irritation in stomach if administered as such.

» They are easily tampered.

» They are subjected to the effects of the relative humidity and to microbial contamination.

» Deliquescent materials cannot be incorporated, they may cause hardening or brittle capsules.

Types of capsules

1. Hard gelatin capsules.
2. Soft gelatin capsules.
3. Enteric-coated capsules.
4. Sustained-release capsules.
5. Rectal capsules.

1)Hard gelatin capsules:

Fig : Hard gelatin capsule

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These capsules are hard by external touch. They incorporate a solid powder form of drug ingredients. They are filled in the space held by gelatin shells.These shells are cylindrical in shape. One of the shells is of a larger diameter than the other. But the other with a shorter diameter is usually longer.
The former is known as the cap, and the latter is called a body. These two shells can be separated to expose the contents inside.

2)Soft gelatin capsules:

Fig: Softgel capsules in the form of cod liver oil capsules

These as soft to touch, elastic, and a bit flexible.They incorporate a liquid form of drug ingredients. Hence they are soft to touch.They are mostly used to administer essential oils, vitamins, etc.Unlike hardgelatintype, their shells can't be opened.These capsules are completely sealed by the heat process.They can only be ruptured and dissolved.Soft Gelatin capsules are one piece, hermetically Saled, soft gelatin shells containing a liquid, a suspension, or a semisolid. The Nomenclature for this dosage form has now been changed to soft gel .

3)Enteric-coated capsules:

These are capsules that are designed to release the drug in the intestine. They resist degradation in the stomach and stay intact until they reach the intestine. Once they reach the intestine, they release their contents.This is due to their insolubility in acidic pH in the stomach. But again, they are soluble in basic pH, which is present in the intestine.Enteric-coated capsules

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Enteric coating is a useful strategy for the oral delivery of drugs like insulin which rapidly degrade in the stomach, as it prevents the drug being released in the acidic conditions of the stomach before reaching the intestine.

4)Sustained-release capsule :

A sustained release capsule excellent in adhesion characteristics in the gastrointestinal tract, stability and so on is provided. The capsule is characterized in that a polymer excellent in initial adhesion and a polymer excellent in shape-retaining ability are dispersed in a liquid substance in the capsule, that a physiologically active substance is dispersed or dissolved in the liquid substance and that the moisture content in the whole preparation is not more than 2%.

5)Rectal capsules:

These are capsules that are meant to be inserted into the rectum for local effect. The drug is released in the rectum region for immediate effect.Also, the drug can escape the first-pass metabolism by the liver.On the other hand, a **rectalcapsule** is a modification of the suppository in a sense and can be prepared in a manner similar to the preparation of soft **capsules.**

PROCESS FLOW CHART OF CAPSULE DEPARTMENT :

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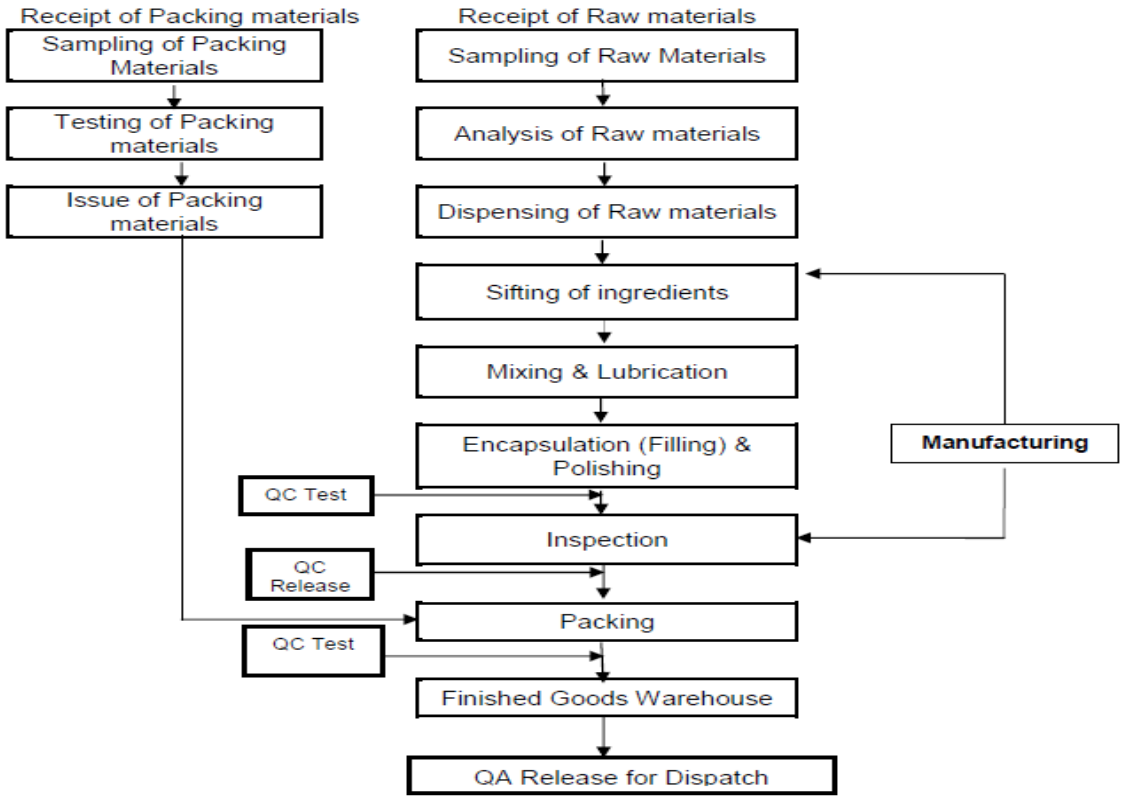

Fig: Process flow chart Capsule manufacturing.

General requirements:

Raw materials for hard gelatin capsule shell manufacturing

Hard gelatin capsule shell is composed largely of gelatin. Other than gelatin, it may contain materials such as plasticizer, colourants, opacifying agents, and preservatives which either enable capsule formation or improve their performance. Hard gelatin capsules also contain 12–16% water, but the water content can vary, depending on the storage conditions.

a. Gelatin

Gelatin is by far the most common and most well-known material used to produce hard capsule shells. It is a generic term for a mixture of purified protein fractions obtained from irreversible hydrolytic extraction of collagen obtained from the skin, white connective tissue, and bones of animals.

Depending on the source of the collagen and the method of extraction, two types of gelatin can be produced – type A gelatin and type B gelatin. Type A gelatin is made from pork skin via acid hydrolysis and has an isoelectric point between 7.0 and 9.0. Type B gelatin is prepared by alkaline hydrolysis of bovine bones and has an isoelectric point between 4.8 and 5.0. Because of this difference in isoelectric points, both gelatins show solubility differences at different pH values.

Traditionally capsules may be manufactured by using both types of gelatin, but combinations of pork skin and bone gelatin are often used to optimize shell characteristics because bone gelatin contributes firmness, whereas pork skin gelatin contributes plasticity and clarity.

Gelatin derived from Gelatin grade is further specified by bloom strength. This is measured in a Bloom gelometer which determines the weight in grams that is required to depress a standard plunger in a 6.67% w/w gel under standard conditions.

Gelatin is stable in air when dry but is subject to microbial decomposition when it becomes moist.

b. Plasticizer

Plasticizers are added to gelatin to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatin.

c. Colourants

Most frequently, hard gelatin capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product.

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Colorants used must meet the regulatory requirements of those countries where the product will be sold. Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used.

d. Opacifying agents

Opacifiers (e.g., titanium dioxide) may be included to make clear gelatin opaque. Opaque capsules may be employed to provide protection against light or to conceal the contents.

e. Preservatives

Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture. Manufacturers operating their plants to Good Manufacturing Practice (GMP) guidelines no longer use them. In the finished capsules, the moisture levels, 12–16% w/ v, are such that the water activity will not support bacterial growthbecause the moisture is too strongly bound to the gelatin molecule.

Raw Materials for Capsules

The raw materials used in the manufacture of both hard and soft gelatin capsules are similar. Both contain gelatin, water, colorants and optional materials such as process aids and preservatives.

1. Gelatin –gelatin is the major component of the capsules and has been the material from which they have traditionally been made. Gelatin has been the raw material of choice because of the ability of a solution to gel to form a solid at a temperature just above ambient temperate conditions, which enables a homogeneous film to be formed rapidly on a mould pin.

The reason for this is that gelatin possesses the following basic properties:

• It is non-toxic, widely used in foodstuffs and acceptable for use worldwide.
• It is readily soluble in biological fluids at body temperature.
• It is good film-forming material, producing a strong flexible film
• The gelatin films are homogeneous in structure, which gives them strength.

Some of the disadvantages with using gelatin for hard capsules include: it has a high moisture content, which is essential because this is the plasticizer for the film and, under International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conditions for accelerated storage testing, gelatin undergoes a cross linking reaction that reduces its solubility.

Gelatin is a translucent brittle solid substance, colorless or slightly yellow, nearly tasteless and odorless, which is created by prolonged boiling of animal skin connective tissue or bones.

Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly a mixture of both types is used considering availability and cost. Difference in the physical properties of finished capsules as a function of the type of gelatin used is slight. Blends of bone and pork skin gelatins of relatively high strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, therby reducing haze or cloudiness in the finished capsule.

Physical properties of gelatin: Gelatin is a protein product produced by partial hydrolysis of collagen extracted from skin, bones, cartilage, ligaments, etc. The natural molecular bonds between individual collagen strands are broken down into a form that rearranges more easily. Gelatin melts when heated and solidifies when cooled again. Together with water it forms a semi-solid colloidal gel.

Production of gelatin: On a commercial scale, gelatin is made from by-products of the meat and leather industry, mainly pork skins, pork and cattle bones, or split cattle hides. Contrary to popular belief, horns and hooves are not commonly used. The raw materials are prepared by different curing, acid, and alkali processes which are employed to extract the dried collagen hydrolysate. The entire process takes several weeks.

2.Colorants– The color of pharmaceutic product plays an important role in their use. Color is used principally to identify a product in all stages of its manufacture and use. In the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products. The colorants that can be used in capsules are of two types:

water soluble dyes or insoluble pigments: To make a range of colors dyes and pigments are mixed together as solutions or suspensions. Three

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Volume 6, Issue 4 July-Aug 2021, pp: 972-990 www.ijprajournal.com ISSN: 2249-7781

most commonly used dyes are erythrosine, indigo carmine and quinolone yellow. The two types of pigments used are iron oxides- black, red and yellow and titanium dioxide which are white and used to make the capsule opaque. Capsules are colored by the addition of colorants to the gelatin solution during the manufacturing stage.

3. Process aids –Preservatives and surfactants are added to the gelatin solution during capsule manufacture to aid in processing. Gelatin solutions are an ideal medium for bacterial growth at temperatures below 55○ C. preservatives are added to the gelatin and colorant solutions to reduce the growth of microorganisms until the moisture content of the gelatin film is below 16% w/v. at moisture content below that value, the bacterial population will decline in numbers with time.

The materials used as preservatives include: sulfur dioxide which is added as the sodium salts bisulfite or metabisulfite, sorbic acid or the methyl propyl esters of para hydroxy-benzoic acid, and the organic acids, benzoic and propanoic acids.

Some hard gelatin capsules may contain 0.15 % w/w of sodium lauryl sulphate which functions as wetting agent, to ensure that the lubricated metal moulds are uniformly covered when dipped into the gelatin solution. Capsules are available in many different sizes and shapes and can be used for the administration of powders, semisolids and liquids. Unpleasant tastes and odors of drugs are effectively masked by the practically tasteless capsule shell which dissolves or is digested in the stomach after about ten to twenty minutes. Capsules also can be used as a means of providing accurately measured doses for administration rectally or vaginally.

MANUFACTURING OF CAPSULES :

Method of production of empty hard gelatin shells: Some of the major suppliers of empty gelatin capsules are: Eli Lilly and Company, Warner Lambert's Capsugel (formerly Park Davis) and R. P. Scherer Corporation.

The metal moulds at room temperature are dipped into a hot gelatin solution, which gels to form a film. This is dried, cut to length, removed from the moulds and the two parts are joined together, these processes are carried out as a continuous process in large machines.

The completely automatic machine most commonly used for capsule production consists of mechanisms for automatically dipping, spinning, drying, stripping, trimming, and joining the capsules.

• Stainless steel pins are used on which the capsule is formed and controls some of the final critical dimensions of the capsule.

• One hundred and fifty pairs of these pins are dipped in to gelatin sol of carefully controlled viscosity to form caps and bodies simultaneously. The pins are usually rotated to distribute the gelatin uniformly, during which time the gelatin may be set or gelled by a blast of cool air.

• The pins are moved through a series of controlled air drying kilns for the gradual and precisely controlled removal of water. The capsules are striped from the pins by bronze jaws and trimmed to length by stationary knives while the capsule halves are being spun in chunks or collects. After being trimmed to exact length, the cap and body sections are joined and ejected from the machine. The entire cycle of the machine lasts approximately 45 min.

• Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and the speed and time of dipping. Mold pin dimensions, precise drying, and machine control relating to cut lengths are matters that are critical to the final dimensions. Precise control of drying conditions is essential to the ultimate quality of the cast film.

The in-process quality controls include periodic monitoring, and adjustment when required, of film thickness, cut lengths of both cap and body, color, and moisture content.

Inspection processes to remove imperfect capsules which were previously done visually, have recently been automated following the development and patenting of a practical electronic sorting mechanism by Eli Lilly and Company. This equipment mechanically orients the capsules and transports them past a series of optical scanners, at which time those having detectable visual imperfections are automatically rejected.

Properties of empty capsule –empty capsules contain a significant amount of water that acts as a plasticizer for the gelatin film and is essential for their function. The standard moisture content specification for hard gelatin capsules is between 13 % w/w and 16 % w/w. This value can vary depending upon the conditions to which they are exposed that is at low humidity's they will lose moisture and become brittle, and at high humidity's they will gain moisture and soften. The moisture

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content can be maintained within the correct specification by storing them in sealed containers at an even temperature. Capsules are readily soluble in water at 37○ C. When the temperature falls below this, their rate of solubility decreases. At below about 30○ C they are insoluble and simply absorb water, swell and distort. This is an important factor to take into account during disintegration and dissolution testing. Because of this most Pharmacopoeia have set a limit of 37○ C ± 1○ C for the media for carrying out these tests. Capsules made from have different solubility profile, being soluble at temperatures as low as 10○ C.

Types of materials for filling into hard gelatin capsules:

Dry solids – powders, pellets, granules or tablets

Semisolids– suspensions or pastes

Liquids– non-aqueous liquids

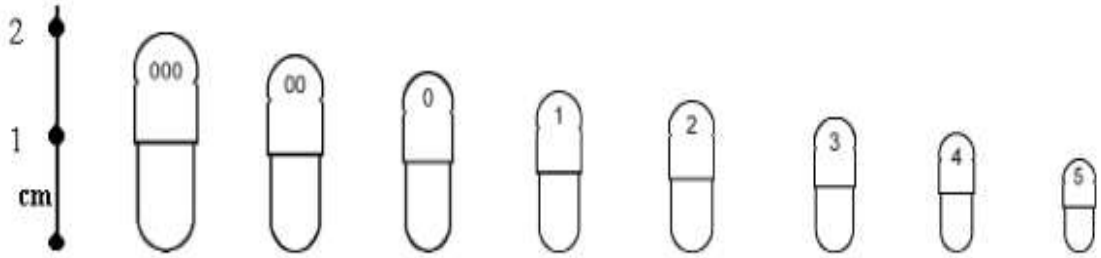
Capsule shell filling :

Hand operated hard gelatin capsule filling machines– hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical.

A hand operated gelatin capsule filling machine consists of the following parts

1. A bed with 200-300 holes.
2. A capsule loading tray
3. A powder tray
4. A pin plate having 200 or 300 pins corresponding to the number of holes in the bed and capsule loading tray.
5. A lever
6. A handle
7. A plate fitted with rubber top.

fig: Size of hard gelatin capsules -Capsule size chart



Empty Hard Gelatin Capsule Physical Specifications

Size	Outer Diameter (mm)	Height or Locked Length (mm)	Actual Volume (mL)	Typical Fill Weights (mg) 0.70 Powder Density
000	9.91	26.14	1.37	960
00	8.53	23.30	0.95	665
0	7.65	21.70	0.68	475
1	6.91	19.40	0.50	350
2	6.35	18.00	0.37	260
3	5.82	15.90	0.30	210
4	5.31	14.30	0.21	145
5	4.91	11.10	0.13	90

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All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds, and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled .

Figure : Hand operated hard gelatin capsule filling machine

Working: The empty capsules are filled into the loading tray which is then placed over the bed. By opening the handle, the bodies of the capsules are locked and caps separated in the loading tray itself which is then removed by operating the liver. The weighed amount of the drug to be filled in the capsules is placed in powder tray already kept in position over the bed. Spread the powder with the help of a powder spreader so as to fill the bodies of the capsules uniformly. Collect excess of the powder on the platform of the powder tray. Lower the pin plate and move it downward so as to press the powder in the bodies. Remove the powder tray and place the caps holding tray in position. Press the caps with the help of plate with rubber top and operate the lever to unlock the cap and body of the capsules. Remove the loading tray and collect the filled capsules in a tray. With 200 hole machine about 5000 capsules can be filled per hour and with 300 hole machine 7500 capsules can be filled per hour. On large-scale manufacturing various types of semiautomatic and automatic machines are used. They operate on the same principle as manual filling, namely the caps are removed, powder filled in the bodies, caps replaced and filled capsules are ejected out. With automatic capsule filling machines powders or granulated products can be filled into hard gelatin capsules. With accessory equipment, pellets or tablets along with powders can be filled into the capsules.

Capsule filling devices :

A number of different manually operated capsule filling devices are commercially available for filling up to 50 or 100 capsules at a time. The method of using these machines requires a careful determination of the capsule formulation. The powder is blended as previously discussed. Empty gelatin capsules are placed into the device and, oriented so that the cap is on top. The machine is worked to separate the base from the cap and the portion of the machine holding the caps is removed and set aside. The capsule bases are allowed to "drop" into place so that the tops are flush with the working surface. The powder mix is spread over the working surface. A plastic spatula can be used carefully to spread the powder uniformly and evenly into the capsule bases or the machine can be "tapped" to spread the powder and drop it down into the capsule bases. A small device consisting of several "pegs" on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is spread evenly over and into the capsule bases and tamped. These procedures are repeated until all of the powder is in the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged.

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Fig: Automated capsule filling machine.

Filling capsules with a semisolid mass: If the material to be placed into hard gelatin capsules is a semisolid, it can be encapsulated by either forming a pipe or pouring a melt.

1. Pipe: If the material is sufficiently plastic, it can be rolled into a pipe with a diameter slightly less than that of the inner diameter of the capsule in which it will be enclosed. The desired quantity of material is cut using a spatula or knife, the length determining the weight of the material enclosed. The pieces may be dusted with corn starch (check patient allergies) prior to individual insertion into the capsules.

If a material is too fluid to be worked as described, it may be necessary to add cornstarch or some similar material to yield a more firm consistency. The quantity to be added can be determined empirically.

2. Semisolid pour: If the material is too firm to roll into a pipe but its melting point is satisfactory, it can be melted and poured into the capsule bases, cooled, and the caps replaced. A stand to hold the capsule bodies may be fashioned from a block of wood into which a series of holes the diameter of the capsule caps is drilled. When capsule caps are glued into these holes, capsule bases may be inserted for filling without scratching or marking by the wood.

This method also can be used to enhance the bioavailability of drugs, which are poorly soluble and exhibit bioavailability problems. For this purpose, the drug is added to a melt of a material such as polyethylene glycol (PEG). The mixture is heated and stirred until the powder is either melted or thoroughly mixed in the PEG. The melt is cooled to just above the melting point of the PEG and poured into the capsule shells as described. When this method is used, the desired quantities can be measured using a pipet, syringe, or calibrated dropper to deliver the volume to the individual capsules.

Liquids in Hard Gelatin Capsules

Liquids can be prepared in hard gelatin capsules if the gelatin is not soluble in the liquid to be encapsulated; alcoholic solutions and fixed and volatile oils work well. It may be necessary to determine the solubility of gelatin in the liquid by experimentation. The liquid can be measured accurately using a pipette (micropipet) or a calibrated dropper and dropped into the gelatin base, taking care not to touch the opening. The gelatin caps can be touched, open end down, on a moist towel to soften the gelatin at the opening of the caps or a cotton swab dipped in warm water can be rubbed around the edge of the capsule cap to soften. The cap is placed over the base containing

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the liquid with a slight twist and the softened edge of the cap should form a seal with the base to prevent leakage. Prior to packaging, these capsules should be placed on a clean, dry sheet of paper and observed for leakage. Another method of sealing makes use of a warm gelatin solution that is painted around the capsules and the inside of the caps prior to placing on the base.

Industrial scale filling – the machines for industrial -scale filling of hard gelatin capsules come in great variety of shapes and sizes, varying from semi- to fully automatic and ranging in output from 5000 to 15000 per hour. Automatic machines can be either continuous in motion, like a rotary tablet press, or intermittent, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsule.

The dosing systems can be divided into two groups:
Dependent– dosing systems that use the capsule body directly to measure the powder. Uniformity of fill weight can only be achieved if the capsule is filled completely eg. Auger filling.

Independent- dosing systems where the powder is measured independently of the body in a special measuring device. Weight uniformity is not dependent on filling the body completely.
With this system the capsules can be part filled.

Types of excipients used in powder-filled capsules

• **Diluents**– diluents are the excipients that are usually present in the greatest concentration in a formulation and they make up the necessary bulk when the quantity of the active ingredient is insufficient to make up the required bulk eg. Lactose, maize
starch, calcium sulfate etc.
•**Lubricants and Glidants** – which reduce powder to metal adhesion and promote flow properties eg. Magnesium stearate, talc.

• **Wetting agents**– which improve water penetration for poorly soluble drugs eg. Sodium lauryl sulfate.

• **Disintegrants**– which produce disruption of the powder mass crospovidone, sodium starch glycolate.

Cleaning and Packaging

It is imperative that every precaution to minimize traces of moisture or body oils on capsules be taken to reduce powders sticking to the surface, which would create disagreeable appearance and taste. Cleaning capsules is difficult if they have become moist or sticky. The capsules should be handled so that they retain their dryness and shiny appearance. Use of gloves provides a more hygienic environment and helps preserve the dry, shiny capsule appearance. An old method, where gloves are unavailable, is:
(1) Wash and dry hands thoroughly,
(2) Keep the fingers dry by the friction of a towel that is stripped through the tightly clenched fingers until a clearly perceptible heat is generated,
(3) Four or five capsules may be prepared before there will be a need to repeat the process. If the capsules have been kept dry, clinging surface powder can be removed by rolling between folds of a cloth or by shaking in a cloth formed into a bag or hammock. Another method of cleaning capsules is to place them in a container that is filled with sodium bicarbonate, sugar or salt then gently to roll the container. The contents then can be poured into a 10 mesh sieve and the "cleaning salt" allowed to pass through the screen, which collects the capsules. It must be emphasized that these cleaning methods are only effective if the capsules have been kept clean and dry. Once capsules become soiled and dull, they cannot be cleaned effectively.
ROTOSORT is a new filled capsule-sorting machine sold by Eli Lilly and Company. It is a mechanical sorting device that removes loose powder, unfilled joined capsules, filled or unfilled bodies, and loose caps. It can handle up to 150,000 capsules per hour, and it can run directly off a filling machine or be used separately.

Difficulties in filling capsules

1. **Deliquescent or Hygroscopic powders**– a gelatin capsule contain water which is extracted or taken up by a hygroscopic drug and renders the capsule very brittle which leads to cracking of the capsule. The addition of an adsorbent like magnesium carbonate, heavy magnesium oxide or light magnesium oxide overcomes this difficulty provided the capsules are packed in tightly closed glass capsule vials.
2. **Eutectic mixtures**– certain substances when mixed together tend to liquefy and form a pasty mass due to the formation of a mixture which has a lower melting point than room temperature. For filling these types of substances each troublesome

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ingredient is mixed with an absorbent separately then mixed together and filled in capsules. The absorbents used are magnesium oxide and kaolin. Another method in dealing with such type of difficulty is that the substances are mixed together so as to form a eutectic mixture, then an absorbent like magnesium carbonate or kaolin is added.

3. **Addition of inert powders –** when the quantity of the drug to be filled in capsules is very small and it is not possible to fill this much small amount in capsules then inert substance or a diluent is added so as to increase the bulk of the powder, which can be filled easily in capsules.

4. **Use of two capsules –** some of the manufacturers separate the incompatible ingredients of the formulation by placing one of the ingredients in smaller capsule, and then placing this smaller capsule in a larger capsule containing the other ingredients of the formulation.

5. Filling of granular powder– some powders which lack adhesiveness and most granular powders are difficult to fill in the capsules by punch method because they are not compressible and flow out of the capsule as soon as they are lifted from the pile of powder into which they are punched. To overcome this difficulty the non-adhesive powders should be moistened with alcohol and the granular powders should be reduced to powder before filling into capsules.

MICROENCAPSULATION

Microencapsulation is a process by which individual particles of an active agent can be stored within a shell, surrounded or coated with a continous film of polymeric material to produce particles in the micrometre to millimetre range, for protection and /or later release.

Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules, with useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale. Microencapsulation can also be used to enclose solids, liquids, or gases inside a micrometric wall made of hard or soft soluble film, in order to reduce dosing frequency and prevent the degradation of pharmaceuticals.

In its simplest form, a microcapsule is a small sphere comprising a near-uniform wall enclosing some material. The enclosed material in the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Some materials like lipids and polymers, such as alginate, may be used as a mixture to trap the material of interest inside. Most microcapsules have pores with diameters between a few nanometers and a few micrometers. The coating materials generally used for coating are:

- Ethyl cellulose
- Polyvinyl alcohol
- Gelatin
- Sodium alginate

The definition has been expanded, and includes most foods, where the encapsulation of flavors is the most common. The technique of microencapsulation depends on the physical and chemical properties of the material to be encapsulated.Many microcapsules however bear little resemblance to these simple spheres. The core may be a crystal, a jagged adsorbent particle, an emulsion, a Pickering emulsion, a suspension of solids, or a suspension of smaller microcapsules. The microcapsule even may have multiple walls.

Reasons for encapsulation:

The reasons for microencapsulation are numerous. It is mainly used to increase the stability and life of the product being encapsulated, facilitate the manipulation of the product and provide for the controlled release of the contents. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it releases the contents, as in the controlled release of drugs or pesticides. The problem may be as simple as masking the taste or odor of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

In environmental science, a pesticide may be microencapsulated to minimize leaching or volatilization risks.

Techniques of Microcapsule manufacture

Physical methods:

Pan coating:

This process widely used in the pharma industry, is the oldest industrial procedure for forming small, coated particles or tablets. The particles are tumbled in a pan or other device.

Centrifugal extrusion:

Liquids are encapsulated by a rotating head containing concentric nozzles. In this process, a jet

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of core liquid is surrounded by a sheath of wall solution or melt.

Vibrational nozzle:

Core-shell encapsulation or microgranulation (matrix-encapsulation) can be done using a laminar flow through a nozzle and an additional vibration of the nozzle or the liquid. The vibration has to be done in resonance with the Rayleigh instability and leads to very uniform droplets. The liquid can consist of any liquids with limited viscosities (0-10,000 mPa·s have been shown to work), e.g. solutions, emulsions, suspensions, melts etc. The solidification can be done according to the used gelation system with an internal gelation (e.g. sol-gel processing, melt) or an external (additional binder system, e.g. in a slurry). The process works very well for generating droplets between 20–10,000 µm (0.79–393.70 mils); applications for smaller and larger droplets are known. The units are deployed in industries and research mostly with capacities of 1–20,000 kg per hour (2–44,000 lb/h) at working temperatures of 20–1,500 °C (68–2,732 °F), or room temperature up to that of molten silicon. Heads are available with from one up to several hundred thousand nozzles.

Spray–drying:

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages are the ability to handle labile materials because of the short contact time in the dryer and the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300 mPa·s. Applying this technique, along with the use of supercritical carbon dioxide, sensitive materials like proteins can be encapsulated.

Physicochemical methods

Ionotropic gelation:

Ionotropic gelation occurs when units of uric acid in the chains of the polymer alginate, crosslink with multivalent cations. These may include, calcium, zinc, iron and aluminium.

Coacervation-phase separation:

Coacervation-phase separation consists of three steps carried out under continuous agitation.

1. Formation of three immiscible chemical phases: liquid manufacturing vehicle phase, core material phase and coating material phase.
2. Deposition of coating: core material is dispersed in the coating polymer solution. Coating polymer material coated around core. Deposition of liquid polymer coating around core by polymer adsorbed at the interface formed between core material and vehicle phase.
3. Rigidization of coating: coating material is immiscible in vehicle phase and is made rigid. This is done by thermal, cross-linking, or dissolution techniques.

Chemical methods

Interfacial polycondensation:

In interfacial polycondensation, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten-Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, polyuret hane. Under the right conditions, thin flexible walls form rapidly at the interface. A solution of the pesticide and a diacid chloride are emulsified in water and an aqueous solution containing an amine and a polyfunctional isocyanate is added. Base is present to neutralize the acid formed during the reaction. Condensed polymer walls form instantaneously at the interface of the emulsion droplets.

Interfacial cross-linking:

Interfacial cross-linking is derived from interfacial polycondensation, and was developed to avoid the use of toxic diamines, for pharmaceutical or cosmetic applications. In this method, the small bifunctional monomer containing active hydrogen atoms is replaced by a biosourced polymer, like a protein. When the reaction is performed at the interface of an emulsion, the acid chloride reacts with the various functional groups of the protein, leading to the formation of a membrane. The method is very versatile, and the properties of the microcapsules (size, porosity, degradability, mechanical resistance) can be customized. Flow of artificial microcapsules in microfluidic channels:

In situ polymerization:

In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface. In one process, e.g. cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5µm/min. Coating thickness ranges 0.2–75 µm (0.0079–2.9528 mils). The coating is uniform, even over sharp projections. Protein microcapsules are biocompatible and biodegradable, and the presence of the protein backbone renders the

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membrane more resistant and elastic than those obtained by interfacial polycondensation.

Matrix polymerization:

In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple method of this type is spray-drying, in which the particle is formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change.

Release methods and patterns:

Even when the aim of a microencapsulation application is the isolation of the core from its surrounding, the wall must be ruptured at the time of use. Many walls are ruptured easily by pressure or shear stress, as in the case of breaking dye particles during writing to form a copy. Capsule contents may be released by melting the wall, or dissolving it under particular conditions, as in the case of an enteric drug coating. In other systems, the wall is broken by solvent action, enzyme attack, chemical reaction, hydrolysis, or slow disintegration.

Microencapsulation can be used to slow the release of a drug into the body. This may permit one controlled release dose to substitute for several doses of non-encapsulated drug and also may decrease toxic side effects for some drugs by preventing high initial concentrations in the blood. There is usually a certain desired release pattern. In some cases, it is zero-order, i.e. the release rate is constant. In this case, the microcapsules deliver a fixed amount of drug per minute or hour during the period of their effectiveness. This can occur as long as a solid reservoir or dissolving drug is maintained in the microcapsule.

A more typical release pattern is first-order in which the rate decreases exponentially with time until the drug source is exhausted. In this situation, a fixed amount of drug is in solution inside the microcapsule. The concentration difference between the inside and the outside of the capsule decreases continually as the drug diffuses.

Nevertheless, there are some other mechanisms that may take place in the liberation of the encapsulated material. These include, biodegradation, osmotic pressure, diffusion, etc. Each one will depend on the composition of the capsule made and the environment it is in. Therefore, the liberation of the material may be affected by various mechanisms that act simultaneously.

QUALITY CONTROL TESTS OF CAPSULES

» Weight Variation
» Content Uniformity
» Disintegration
» Dissolution
» Chemical or biological assay.

Weight variation: For capsules, since our average weight is 295.9 mg, the deviation of individual net weight should not exceed the limits given below: From the results, all our capsules are having a deviation of ± 10%, which means that all capsules have uniform weights. This may indicate the uniformity of the capsules production.

Content uniformity: Uniformity of Content is a pharmaceutical analysis parameter for the quality control of capsules or tablets. Multiple capsules or tablets are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each capsule or tablet.The preparation complies if not more than one (all within limits) individual content is outside the limits of 85 to 115% of the average content and none is outside the limits of 75 to 125% of the average content. The preparation fails to comply with the test if more than 3 individual contents are outside the limits of 85 to 115% of the average content or if one or more individual contents are outside the limits of 75% to 125% of the average content.

Disintegration: It is the time required for the Capsule to break into particles, the disintegration test is a measure of the time required under a given set of conditions (environmental) for a group of capsules to disintegrate into particles.

Disintegration is to be Performed to determine whether capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions.

Since its inception in the 1930s, disintegration testing has become an important quality control (QC) test in pharmaceutical industry, and disintegration test procedures for various dosage forms have been described by the different pharmacopoeias.

In 1948, the British Pharmacopoeia (BP) adopted a disintegration test for tablets based on observing the disintegration behavior in test tubes.

The basket-rack assembly apparatus, first adopted by the United States Pharmacopoeia (USP) in 1950.

Basket-Rack Assembly Parameters & Specification :

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Parameters	Specification
Beakers	1000 mL each
Height of beaker	138 – 160 mm
Inside diameter	97- 115 mm
Frequency of shaft raising and lowering basket	29 – 32 CPM
Distance of shaft for raising & lowering the basket	53 – 57 mm
Diameter of tube holding plates	88 – 92 mm
Thickness of tube holding plates	5 – 8.5 mm
Six open-ended transparent tubes of length	75 – 80 mm

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Inner tube diameter	20.7 – 23 mm
Stainless steel wire cloth (square weave aperture)	1.8 – 2.2 mm
Wire diameter	0.57 – 0.66 mm

Dissolution:

Fig: Capsule dissolution tester one vessel.

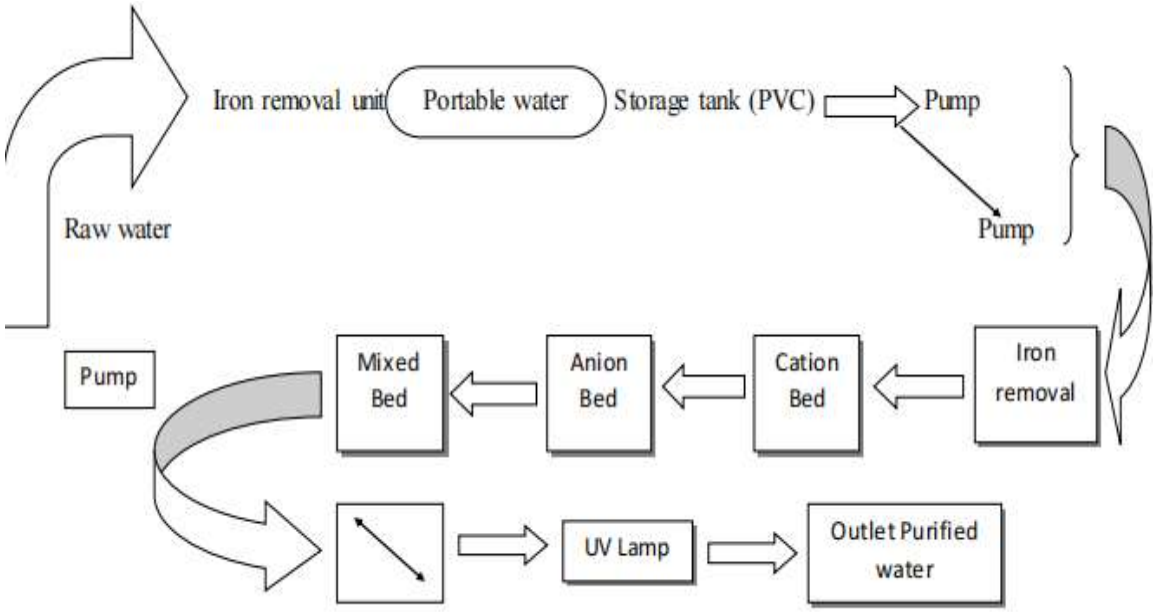
The two-stage dissolution method developed for the enteric-coated beads in capsule formulation consists of a two-hour acid stage dissolution in 0.1 N HCl with one sampling time point at the end, and a one-hour buffer-stage dissolution in pH 6.8 phosphate buffer with five sampling time points. The medium is changed by the analyst from the acid to the buffer after the first stage has been completed.

Temperature	Humidity	Effect on Capsule shell
21-24°C	60%	Capsules become softer,tackier and bloated
Greater than 24°C	Greater than 45%	More rapid and pronounced effects – unprotected capsules melt and fuse together

Fig :Effect of Temperature and Humidity on Capsule shell

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 972-990 www.ijprajournal.com ISSN: 2249-7781

Several conditions maintained in capsule department



AIR HANDLING UNIT:

An air handler, or air handling unit (often abbreviated to AHU), is a device used to regulate and circulate air as part of a heating, ventilating and air-conditioning system. Air handling unit (AHU) comprise of air supply, coarse filtration, heating or cooling and HEPA filtration. Flow of air into the room may be horizontal or vertical. Normally in AHU producing class A (class 100L), class B (class 100T) and class C (class 1000) HEPA filters may be located in the air handling units. In less clean room these may be located terminally. There may be alternative locations for return air and ceiling return air. A clean room should be designed with low level return air. Where ceiling return air grills are used, a higher air change rate may be required to achieve a specified clean room classifications. There are various AHU configurations which can be used. These have been following –

1) Re-circulation system:

In this system bulk of air is re-circulated and a small percentage of fresh air is introduced. Depending upon the air bone contaminants in the return air, it may be acceptable to use re-circulated air. If re-circulated air is used in AHU, HEPA filters are installed in the supply air stream to remove air; else it may result in cross contamination. if there are no HEPA filters in the system, re-circulated air should not be used.

2) Full fresh air system:

An AHU can be designed with 100% supply of fresh air. But such systems are designed only where toxic substances are handled. The relative pressures between supply and air exhaust system should be such that air exhaust system operates at a lower pressure than the supply system.

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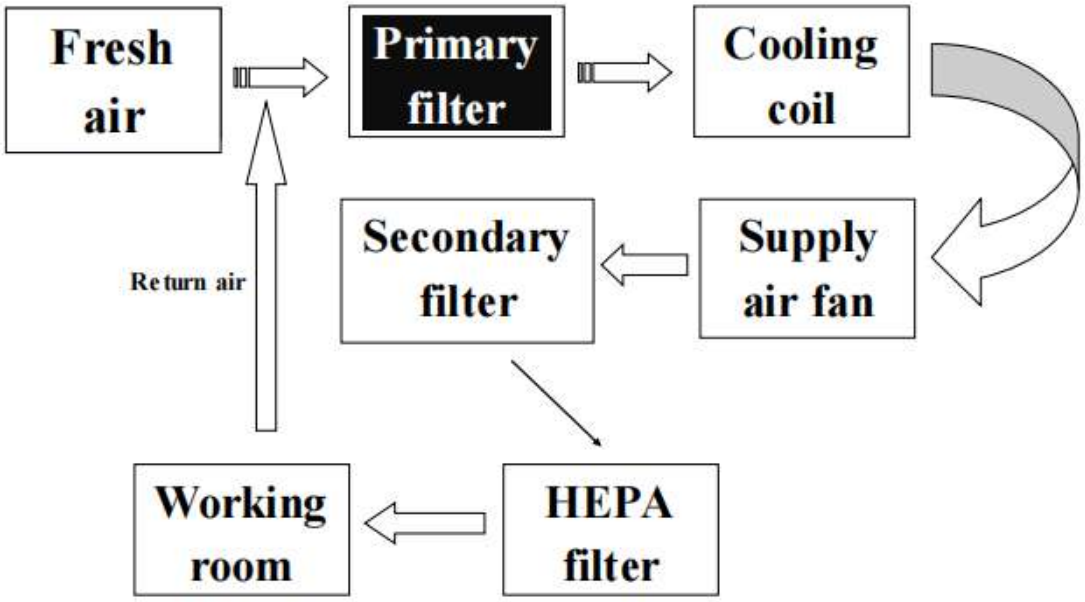

Fig:Schematic diagram of AHU

Fig : Air Handling System

Recent updates in Capsule technology:

A) **New products by Capsugel:**

1. Capsugel has introduced Oceancaps capsules, these capsules made from all natural fish gelatin derived from farm-raised fish, they have the same characteristics as traditional gelatin capsules, including appearance, machinability, mechanical properties, hygroscopic and oxygen properties, chemical stability, and versatility. Plus, they are odorless and tasteless

2. Licaps new 000 size capsules are ideal for maximizing liquid dosage with a fill capacity of 1000mg to 1400mg depending on the density of the liquid fill material. This two-piece capsules has been specially designed to be sealed for secure containment of liquids and semi-solids without banding. Available in both gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules they are available in a variety of colors to meet your specific needs.

B) **New product by Natco Pharma :** Hyderabad based NATCO Pharma Limited has launched LUKATRET - a medicine used in the treatment of a rare form of leukemia. LUKATRET (Tretinoin - all Trans retinoic acid) available in the form of 10

mg. capsules (in a pack of 100 capsules) is used in the treatment of Acute Promyelocytic Leukemia (APL). LUKATRET is a treatment option for remission induction in newly diagnosed, relapsed and / or refractory, chemotherapy non-responsive patients and for patients where anthracycline based chemotherapy is contraindicated. Use of Lukatret results in differentiation and clinical remission.

C) **New products by Banner Pharmacaps Inc.**: Banner Pharmcaps has developed an Enteric Softgel called Entericare, with enteric properties built into the shell matrix of the capsules for delivering very potent (small quantities) as well as drugs that require larger quantities and provide sustained delivery for more than an 8- to 12-hour period.

D) **New product by Shionogi Qualicaps :**QUALI-V, developed by Shionogi Qualicaps, is the first HPMC capsule developed for eventual use in pharmaceutical products.

Conclusion: In view of the above facts, we have learned about the activities, responsibilities in production of capsule department. Microencapsulation and co-ordination with other related department specially quality control, quality assurance & maintenance in an important & essential role to maintain in a smooth production.

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