10

Centrifugation

Theory of Centrifugation
Classification of Centrifuges
Equipment

Centrifugation is a unit operation employed for separating the constituents present in a dispersion with the aid of centrifugal force.

Centrifugal force is used to provide the driving force for the separation. It replaces gravitation forces in the sedimentation. Centrifugation is particularly useful when separation by ordinary filtration is difficult, for example, separating highly viscous mixtures and colloidal dispersions (particle size less than 5 mm), in which difference in the densities is less. In short, centrifugation provides a convenient method of separating either two immiscible liquids or a solid from a liquid. The equipment used for the separation are known as *centrifuges*.

Process of Centrifugation

The centrifuge consists of essentially a container in which a mixture of solid and liquid or two liquids is placed and rotated at high speeds. The mixture is separated into its constituent parts by the action of centrifugal force on their densities. A solid or liquid of higher specific gravity is thrown outward with greater force. Therefore, it is retained at the bottom of the container leaving a clear supernatant layer of pure liquid.

The speed of a centrifuge is commonly expressed in terms of the number of revolutions per minute of the rotor.

Applications

Production of bulk drugs : Centrifugation technique is used to separate crystalline drugs such as aspirin from the mother liquor. Free flowing product results due to the removal of traces of mother liquor and avoidance of effervescence.

Production of biological products : Most of the proteinaceous drugs and macromolecules are present as colloidal dispersion in water. By normal methods, it is difficult to produce them in large scale. Centrifugal methods are used for the separation of these constituents from water. Insulin can be obtained in pure form by selectively precipitating other fractions of proteins and subsequently separating them by ultracentrifugation. Centrifugation is employed for separating the blood cells from blood.

Biopharmaceutical analysis of drugs : Drugs present in the blood, tissue fluids and urine are normally present in the form of colloidal dispersions. Centrifugation is used for separating the drugs. This method is essential for the evaluation of pharmacokinetic parameters and bioequivalence studies.

Evaluation of suspensions and emulsions : Centrifugation method is used as a rapid empirical test parameter for the evaluation of suspensions and emulsions. Normally, creaming is slow process in emulsions. This process can be hastened by inducing stress condition (using a centrifuge). A stable emulsion should not show any signs of separation even after centrifuging at 2000-3000 revolutions per minute at room temperature.

Determination of molecular weight of colloids : Determination of molecular weight of a polymer is not possible by usual method. Ultracentrifugation methods are used for determination of molecular weight of serum albumin, insulin, methylcellulose. Centrifugation (ultra-centrifugation) is also used for ascertaining the degree of homogeneity of the sample. For example, insulin is a monodisperse protein composed of two polypeptide chains, whereas gelatin is found to be polydisperse protein with fractions of molecular weight 10,000 to 1,00,000.

This chapter deals with the principles of centrifugation, equipment used and examples of the use of the methods in pharmacy practice on commercial scale.

THEORY OF CENTRIFUGATION

In a colloidal dispersion, the dispersed phase may be either a solid or a liquid. Particles having a size above 5 μm sediment at the bottom due to gravitation force. In such cases, separation of solids is possible by simple filtration. If particles are of the order of 5 μm or less, they undergo Brownian motion. Hence, they do not sediment under gravity. Therefore, a stronger force, centrifugal force is applied in order to separate them. The sedimentation also depends on the densities of the dispersed phase and dispersion medium. If the difference in the densities of these phases is less, again separation is difficult. By applying centrifugal force, it is possible to facilitate (increase the rate of sedimentation) the separation process.

Centrifugal Effect or Relative Centrifugal Force (RCF)

The centrifugal operation is described by equations including the gravitational constant. The derivation is as follows.

Consider a body of mass m kg rotating in a circular path of radius r metres at a velocity of v metres per minute (Figure 10-1). The force acting on the body in a radial direction is given by:

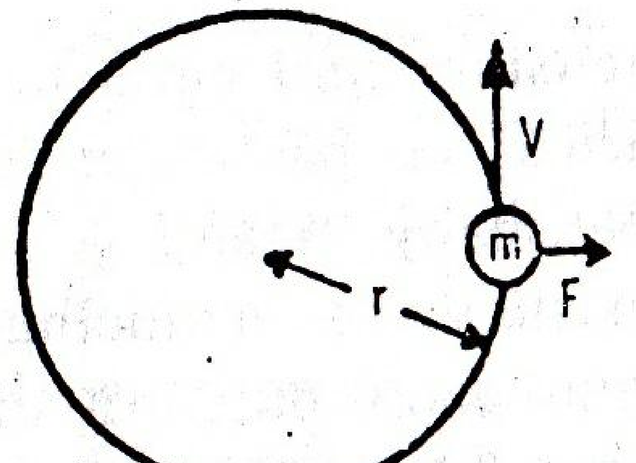

Figure 10-1. Principle of centrifugation.

$$\text{Force acting in radial direction, } F = \frac{mv^2}{r} \tag{1}$$

where F = centrifugal force, N

The same body is experiencing gravitational force (newton). It can be expressed as:

$$\text{Gravitation force, } G = mg \tag{2}$$

where g = acceleration due to gravity, m/s^2

The *centrifugal effect* is expressed as a ratio of centrifugal force to gravitational force. In other words, centrifugal effect is a force, which is a number of times greater than the gravitation force.

Separating power of a centrifuge is expressed as a ratio of the centrifugal force to the gravitation acceleration. This ratio may have a value as high as 10^4.

The centrifugal effect can be expressed as:

$$\text{Centrifugal effect, } C = \frac{\text{force acting in radial direction}}{\text{gravitational force}} = \frac{F}{G}$$

$$= \frac{mv^2}{mgr} = \frac{v^2}{gr} \tag{3}$$

But $v = 2\pi rn$, where n = speed of rotation (revolutions per second of centrifuge). Substituting this in equation (3) yields

$$C = \frac{(2\pi rn)^2}{gr} = \frac{4\pi^2 r^2 n^2}{gr} = \frac{4\pi^2 r\, n^2}{g} \tag{4}$$

Since $2r = d$, where d = diameter of the rotation. Substituting the value in equation (4) gives:

$$C = \frac{2\pi^2 d\, n^2}{g} \tag{5}$$

The gravitational constant has a value of 9.807 m/s^2, so that equation (5) can be simplified as:

$$\text{Centrifugal effect} = 2.013\, n^2 d \tag{6}$$

In equation (6), n is expressed in s^{-1} and d is in metres.

Whether the measurement of d is made from the free surface of liquid or from the tip of the tube to the centre of a centrifuge should be mentioned while reporting the centrifugal effect.

From equations (5) and (6), it can be inferred that

- Centrifugal effect $\propto$ diameter.
- Centrifugal effect $\propto$ (speed of rotation)^2.

Equation (5) helps in the selection of the type of centrifuge and other experimental conditions.

- If it is required to increase the centrifugal effect, it is of greater advantage to use a centrifuge of the same size at a higher speed rather than using a larger centrifuge at the same speed of rotation.
- It is always better to use the smallest size of centrifuge that has the appropriate capacity, since the centrifuge (equipment) is subjected to considerable stress in operation, largely due to the pressure of the fluid on the walls. It can be shown that the pressure is directly proportional to the square of the speed and the diameter. This principle is useful for the separation of two liquids as in emulsions.
- The centrifuge is designed to suit the required purpose. If a large amount of material is to be processed and a low centrifugal effect is sufficient to separate, then it is economical to use a large centrifuge operating at a low speed.

The centrifugal sedimentation of very small particles requires high centrifugal effect. For this purpose, equipment of a small diameter is used, but operated at very high speed. For example, tubular bowl centrifuge functions on this principle.

The centrifuge is comparable to a pressure vessel. Therefore, it must be handled with the same care as that of a high-pressure autoclave.

CLASSIFICATION OF CENTRIFUGES

Centrifuges are classified based on their mechanisms of separation.

Sedimentation Centrifuge

Sedimentation centrifuge is a centrifuge that produces sedimentation of solids based on the difference in the densities of two or more phases of the mixture.

The efficiency depends on the velocity of rotation to which the mixture is subjected. Examples are horizontal continuous centrifuge, supercentrifuge and conical disc centrifuge.

Ultracentrifugation : When extremely fine solid matter is to be separated from a liquid for example in colloidal research, ultracentrifuge is used. In this instrument, a relatively small rotor is operated at speeds exceeding 1,00,000 revolutions per minute and with forces up to one million times gravity.

Centrifuges have replaced the gravity separators to a considerable extent in production operations because of their effectiveness in separation.

Uses : (1) Suspensions containing low concentration of solids can be separated quickly.

(2) Lanolin is recovered from the wool by scouring process.

(3) Olive and fish liver oils are purified by removing dirt and water.

(4) The liquid/liquid phases are separated in the extraction of drugs, for example, manufacture of antibiotics.

(5) Bacterial enzymes are prepared by removing bacteria.

(6) Blood plasma is separated from whole blood.

(7) Starch is collected after washing and purification stages.

(8) In the manufacture of insulin, liquor is clarified so as to remove the precipitated proteins.

Advantages : (1) Centrifuges are compact and occupy a very small space.

(2) The separating efficiency is very high, so that the particles are deposited very rapidly. It is suitable, if the sediment is a fluid deposit or sludge.

(3) Two immiscible liquids are easily separated on a continuous process.

(4) By controlling the speed of rotation and rate of flow, coarse particles are separated, while finer particles remain in the suspension.

Disadvantages : (1) The construction of sedimentation centrifuges is complicated.

(2) Its capacity is limited.

Filtration Centrifuge

Filtration centrifuge is a centrifuge in which solids pass through the porous medium based on the difference in the densities of the solid and liquid phases.

In this type the container contains a porous wall through which the liquid phase may pass and on which the solid phase is retained. Examples are perforated basket centrifuge and semi-continuous centrifuge. The solids that form a porous cake can be separated in the filtration centrifuge. Normally perforated wall is covered with a filter medium such as canvas or metal cloth.

Uses : (1) When solid recovery is the primary goal, centrifugation must be considered as an alternative to simple filtration.

(2) It is also used for removing unwanted solids from a liquid. For example, precipitated proteins are removed from insulin.

Advantages : (1) It can handle slurries with a high proportion of solids and even those having paste like consistency.

(2) The final product has very low moisture content.

(3) In this method, the dissolved solids are separated from the cake.

Disadvantages : (1) The entire cycle is complicated resulting in considerable labour costs.

(2) It is a batch process or semi-continuous type.

(3) The solids may form a hard cake, due to the centrifugal force, which is difficult to remove.

Classification Based on Scale of Usage

Laboratory scale : Horizontal spinning arm type
Angle centrifuge (45 to 50 angle)
High speed centrifuge (10,000 revolutions per minute)
Ultracentrifuge (85,000 revolutions per minute)

Commercial scale
Batch type : Perforated basket centrifuge
Semi-continuous scale : Short-cycle batch centrifuge
Continuous centrifuge : Supercentrifuge

EQUIPMENT

Centrifuges of different types are available to meet the specific requirements of the slurry and the end product. In addition, experimental conditions are established by considering the factors affecting the process. Some of them are:

- Nature of slurry
- Flow of feed or slurry
- Centrifuge dimensions
- Densities of the materials to be separated
- Bottle (centrifuge) size
- Centrifugation time

Some pharmaceutically important centrifuges are discussed below.

PERFORATED BASKET CENTRIFUGE

In this centrifuge, a basket is mounted above a driving shaft. Such an arrangement is described as *under-driven*. Conversely, if the basket is suspended from a shaft, it is described as *over-driven*. These are used for batch processes. An under-driven bowl centrifuge is described below.

Principle : Perforated basket (bowl) centrifuge is a filtration centrifuge. The separation is through a perforated wall based on the difference in the densities of solid and liquid phases. The bowl contains a perforated side-wall. During centrifugation, the liquid phase passes through the perforated wall, while solid phase is retained in the bowl. The solid is removed after cutting the sediment by a blade after stopping the centrifuge.

Construction : The construction of a under-driven perforated basket centrifuge is shown in Figure 10-2. It consists of a basket, made of steel (sometimes covered with vulcanite or lead) or copper or monel or any other suitable metal. The basket material of construction should be such that it offers the greatest resistance to corrosion. The basket may have a diameter of 0.90 metres and a capacity of 0.085 metre cube. The

diameter of the perforations should be selected based on the size of crystals to be separated. In case, the size of perforations is bigger than that of the particles, a filter cloth is employed.

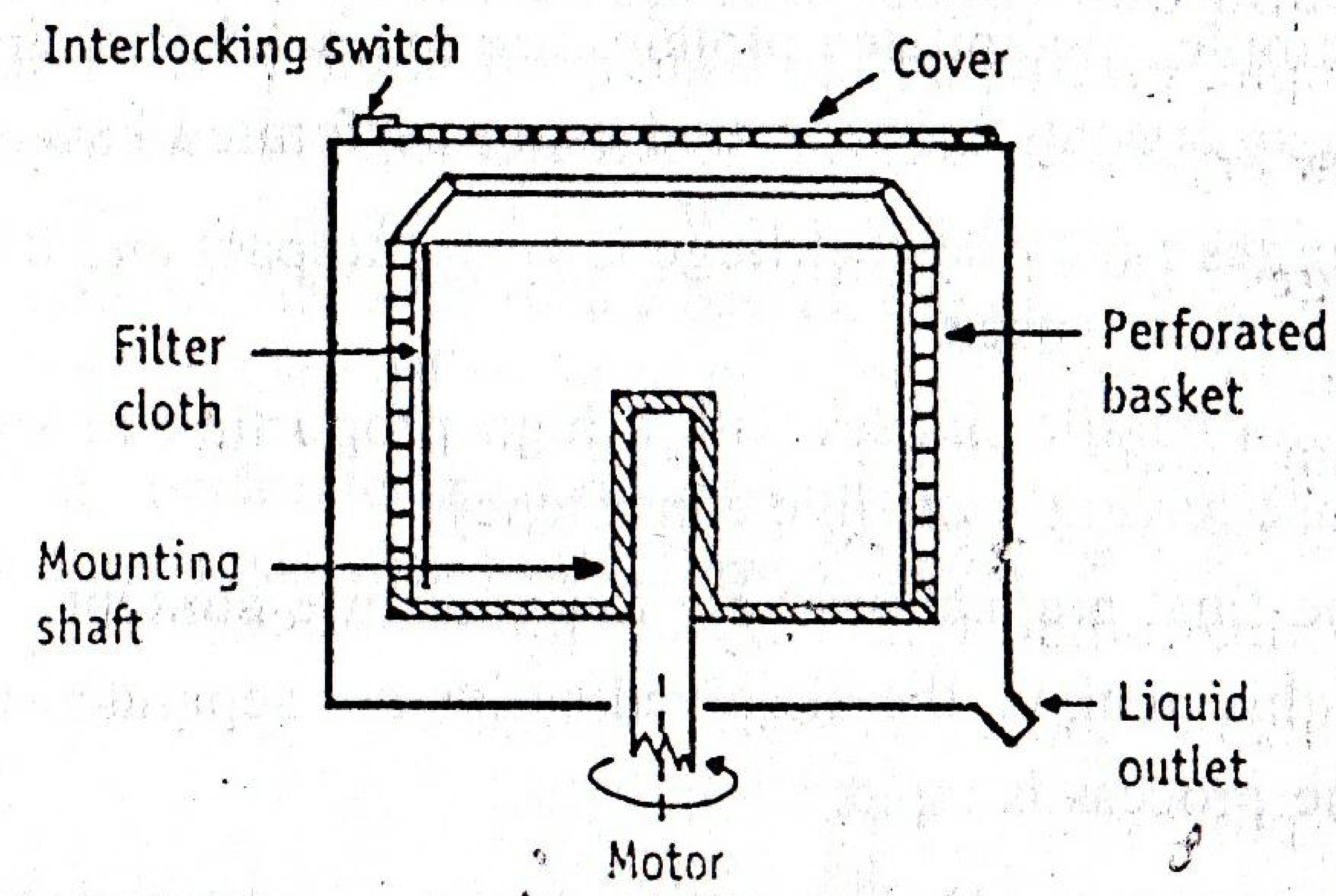

Figure 10-2. Construction of perforated basket centrifuge.

The basket is suspended on vertical shaft and is driven by a motor using suitable power systems such as belt pulleys, water turbines and electric motors. The basket may require about 5 kilowatt power for starting and 2 kilowatt power for running. Sometimes, steel hoops are used externally to strengthen the basket. Surrounding the basket, a casing (stationary) is provided which collects the filtrate and discharges it at the outlet.

Working : The material is kept in the basket when the basket is stationary. The amount of material should be optimum, otherwise, during centrifugation it puts a great strain on the basket. The loading of material must be done to give even distribution. Power is applied to rotate the basket and maximum speed must be attained quickly. The basket runs at 1000 revolutions per minute. The power required for running is small compared to the power required for starting and bringing it to the full speed.

During centrifugation, the liquid passes through the perforated wall, while the solid phase retains in the basket. The liquid leaves the basket and is collected at the outlet. The cake is then spun to dry as much as possible. Sometimes higher speeds are used so that the cake will be completely dried. After a definite period of time, the power is turned off. By applying a brake the centrifuge is stopped. The basket is brought to rest. The solid cake is cut using a blade and then unloaded manually.

Uses : (1) Perforated basket centrifuge is extensively used for separating crystalline drugs (such as aspirin) from the mother liquor. Free flowing product can be obtained because mother liquor is removed completely.

(2) It is also used for removing unwanted solids from a liquid. For example, precipitated proteins are removed from insulin.

(3) Sugar crystals are separated using perforated basket centrifuge.

Advantages : (1) The centrifuge is very compact and it occupies very little floor space.

(2) It can handle slurries with a high proportion of solids and even those having paste like consistency.

(3) The final product has very low moisture content.

(4) In this method, the dissolved solids are separated from the cake.

(5) The process is rapid.

Disadvantages : (1) The entire cycle is complicated resulting in considerable labour costs.

(2) It is a batch process.

(3) If the machine is adapted for prolonged operation, there is considerable wear and tear of the equipment. On prolonged operation, the solids may form hard cake, due to the centrifugal force, which is difficult to remove simultaneously.

Variants : For the separation of fine crystals, the perforations of 3 millimetres in diameter are sufficient. But for finely ground materials, the basket is lined with fine meshed gauze or with a cloth supported on a coarser gauge. When a mixture of liquids is to be separated, the denser liquid is collected near the walls and the lighter liquid forms an inner layer. Overflow weirs are arranged so that the two constituents are continuously removed.

NON-PERFORATED BASKET CENTRIFUGE

Principle : This is a sedimentation centrifuge. The separation is based on the difference in the densities of solid and liquid phases without a porous barrier. The bowl contains a non-perforated side-wall. During centrifugation, solid phase is retained on the sides of the basket, while the liquid remains at the top, which is removed by a skimming tube.

Construction : The construction of a under-driven non-perforated basket centrifuge is shown in Figure 10-3. It consists of a basket, which

may be made of steel or any other suitable metal. The basket is suspended on vertical shaft and is driven by a motor using a suitable power system.

Working : The suspension is fed continuously into the basket. During centrifugation, solid phase is retained on the sides of the basket, while liquid remains on the top. The liquid is removed over a weir or through a skimming tube (Figure 10-3). When a suitable depth of solids has been deposited on the walls of the basket, the operation is stopped. The solids are then scraped off by hand or using a scraper blade.

Uses : Non-perforated basket centrifuge is useful when the deposited solids offer high resistance to the flow of liquid.

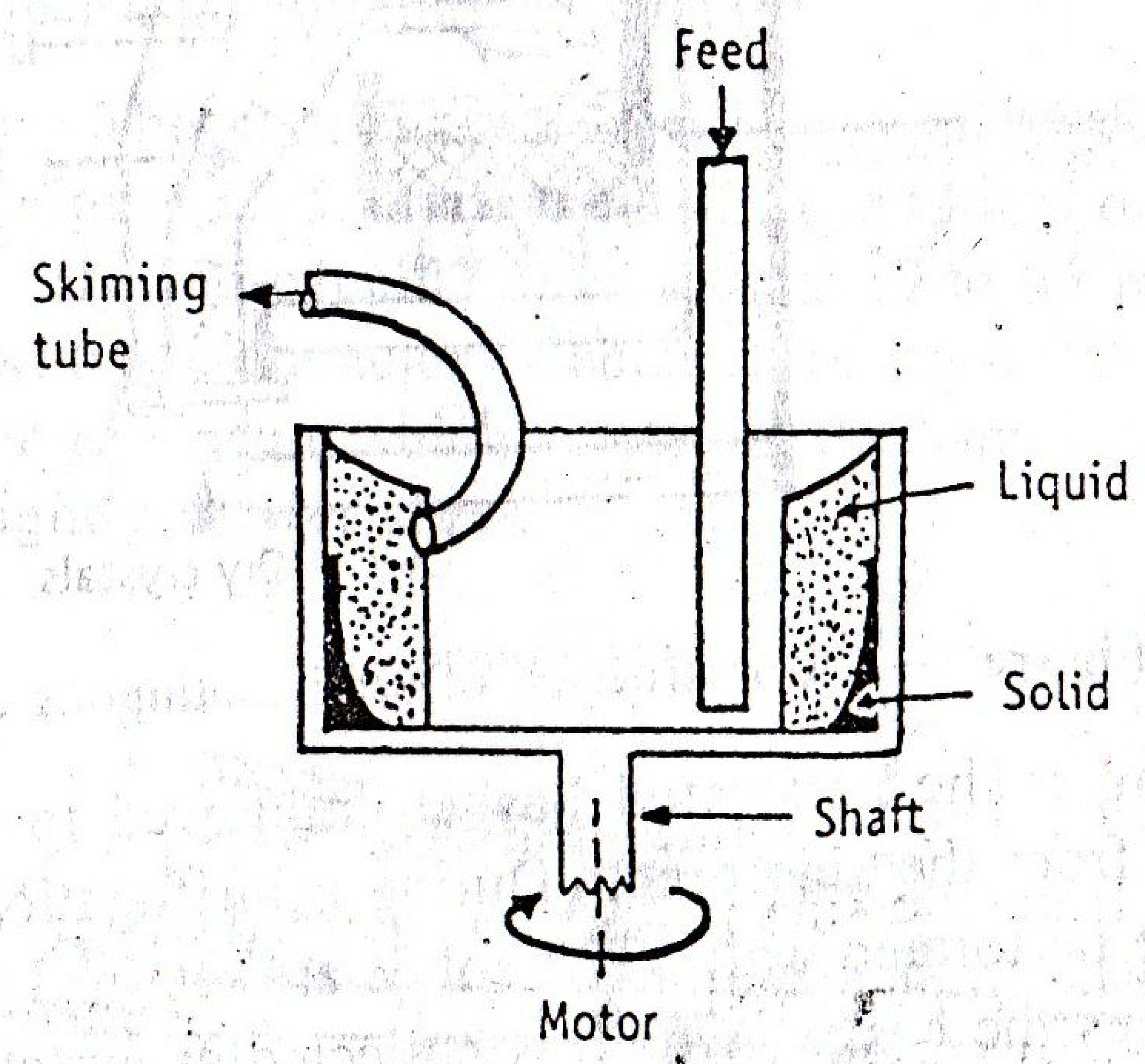

Figure 10-3. Construction of non-perforated basket centrifuge.

SEMI-CONTINUOUS CENTRIFUGE OR SHORT CYCLE AUTOMATIC BATCH CENTRIFUGE

Principle : Semi-continuous centrifuge is a filtration centrifuge. The separation is through a perforated wall based on the difference in the densities of solid and liquid phases. The bowl contains a perforated side-wall. During centrifugation, the liquid phase passes through the perforated wall, while solid phase retains in the bowl. The solid is washed and removed by cutting the sediment using a blade. It is a short cycle automatic batch centrifuge.

Construction : The construction of a semi-continuous centrifuge is shown in Figure 10-4. It consists of a vertical perforated basket, which is supported from a horizontal shaft driven by a motor. From the open side of the basket, provisions are made at the centre to introduce feed and wash pipe through horizontal tubes. A feeler (not shown) rides over the feed, which is connected to diaphragm valve through air supply. The feeler controls the thickness of the feed. Hydraulic cylinder attachment is made in such a manner that the discharge chute enters from the sides of basket, when discharge of crystals is desirable.

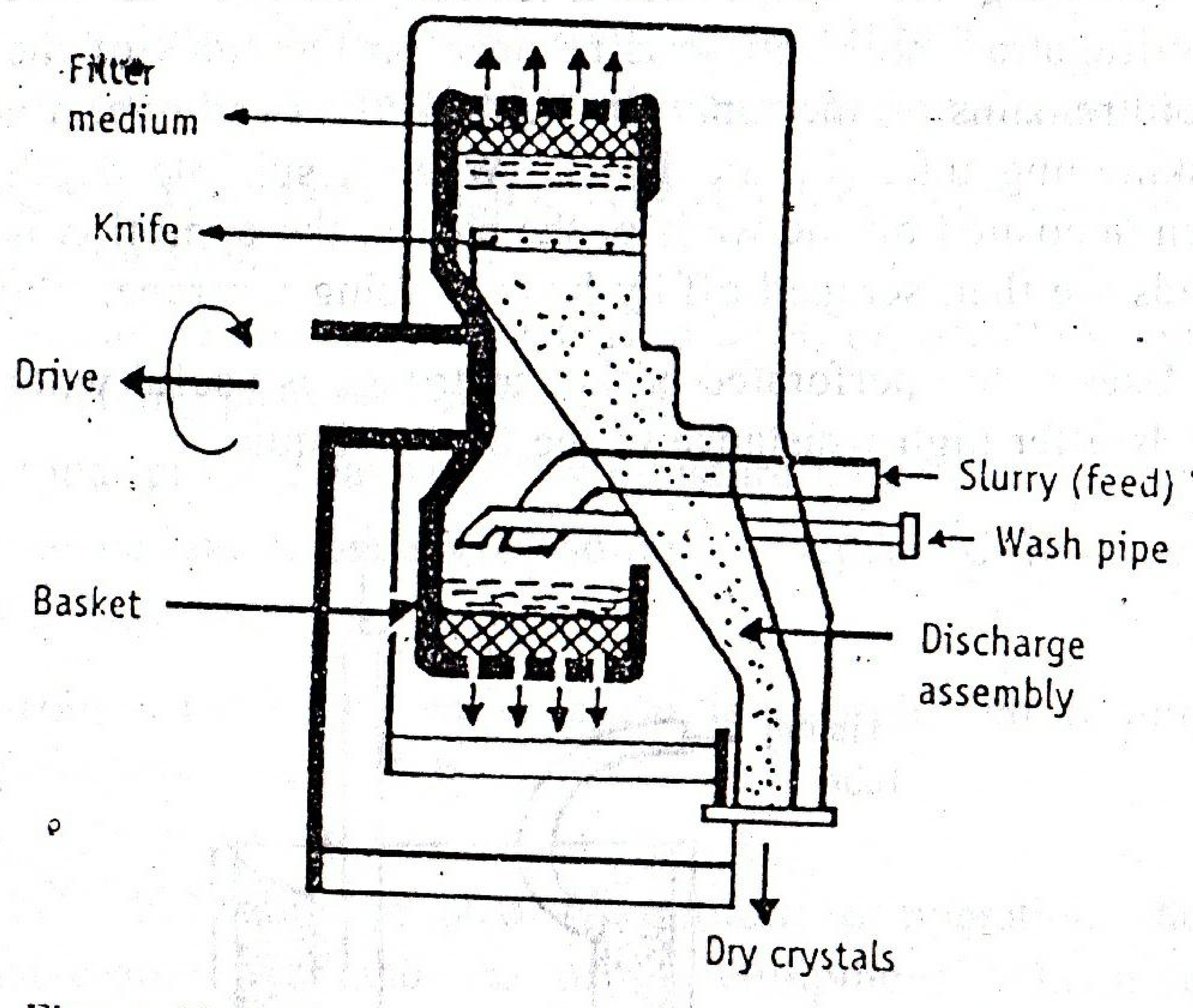

Figure 10-4. Construction of semi-continuous centrifuge.

Working : The perforated basket is allowed to rotate and slurry is introduced from the side pipe. During centrifugation, the slurry passes through the perforated wall. The solids are retained in the basket, while filtrate leaves the basket, which is collected at outlet. Further, the cake is washed with water. The wash escapes from the basket through the filtrate outlet.

After achieving the desired thickness (50 to 70 millimetres), the feeler cuts off the air supply to a diaphragm valve that automatically shuts off the entry of slurry. The hydraulic cylinder is actuated, which lifts the knife along with the discharge chute. The knife does not cut the cake completely down to the screen, but leaves a layer of crystals that acts as a filter medium for further separation in the next cycle. The residual crystals may be given a brief wash before starting the next cycle.

Through a timer and air supply mechanisms, diaphragm valve controls all steps. Therefore, the entire cycle is semiautomatic. The discharged crystals may contain 2 to 4% of moisture.

Advantages : Short-cycle automatic batch centrifuge is used when solids can be drained fast from the bowl.

Disadvantage : During discharge, considerable breakage of crystals is possible. Many moving parts are involved making the construction and functioning complicated.

CONTINUOUS HORIZONTAL CENTRIFUGE

Principle : This is a sedimentation centrifuge. The separation is based on the difference in the densities of solid and liquid phases without a porous barrier. When slurry is introduced through the shaft of the screw element into conical bowl, sedimentation of solids takes place due to centrifugal action. The solids are lifted up by the screw element, while the liquid phase is continuously drained.

Construction : The construction of a horizontal continuous centrifuge is shown in Figure 10-5. It consists of a cylindrical or conical bowl mounted horizontally and capable of rotating at 50 to 65 revolutions per second. The bowl has a diameter of about 0.5 metres. Within the bowl, a screw conveyor is placed which rotates in the same direction as the bowl, but at a slightly slower speed.

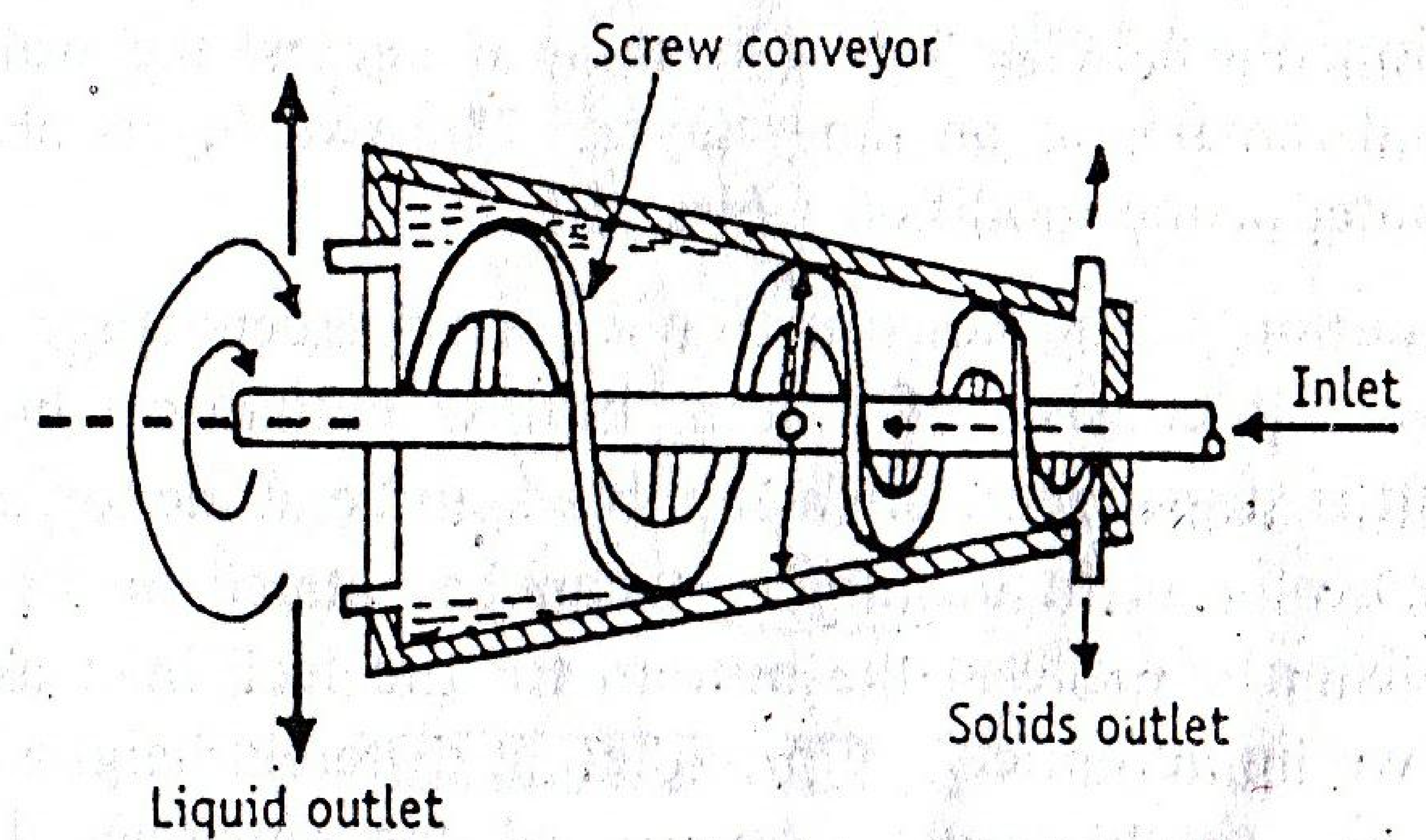

Figure 10-5. Construction of the horizontal continuous centrifuge.

Working : The bowl and the screw conveyor are allowed to rotate using suitable power supply. The slurry is introduced through the shaft as shown in Figure 10-5. The liquid moves into the wider portion of the bowl. Sedimentation of solids takes place due to centrifugal action. The solids are lifted by the screw element, while the liquid phase is continuously drained. The solid material is carried towards outlet by the conveyor and is discharged continuously. The solids are conveyed to a dry 'beach' where they get dried.

Uses : Horizontal continuous centrifuge is used when a high proportion of solids is present in the slurry.

Advantages : (1) Continuous centrifuge is very flexible in operation.

(2) It is capable of handling solids as large as 10 to 15 millimetres or as small as a few microns.

(3) It can be used for slurries with concentrations ranging from 0.5 to 50%.

Variants : The conical form as shown in Figure 10-5 is in common use, but some materials are difficult to convey when dry. for example, if the material is soft and compressible. In such cases, a cylindrical bowl is used with a short conical section near the outlet. As a result, the solid is submerged in the liquid for most of the time and is separated only when it is near the discharge point.

SUPERCENTRIFUGE

Supercentrifuge is a continuous centrifuge used for separating two immiscible liquid phases.

Principle : Supercentrifuge is a sedimentation centrifuge. The separation is based on the difference in the densities between two immiscible liquids. Centrifugation is done in the bowl of small centrifuge. During centrifugation, the heavier liquid is thrown against the wall, while the lighter liquid remains as an inner layer. The two layers are simultaneously separated using modified weirs.

Construction : The construction of a supercentrifuge is shown in Figure 10-6. It consists of a long hollow cylindrical bowl of small diameter. It is suspended from a flexible spindle at the top and guided at the bottom by loose-fit bushing. It can be rotated on its longitudinal axis. Provision is made at the bottom for the feed inlet using pressure system. Two liquid outlets are provided at different heights at the top of the bowl, for simultaneous recovery of the separated liquids using modified weirs.

Working : The centrifuge is allowed to rotate on its longitudinal axis at a high frequency usually about 2000 revolutions per minute with the help of drive-assembly. The feed is introduced from the bottom of the centrifuge using a pressure system. During centrifugation, two liquid phases separate based on the difference in their densities. The heavier liquid is thrown against the wall, while the lighter liquid forms an inner layer. Both liquids rise to the top of the vertical bowl.

The liquid-liquid interface (the so-called neutral zone) is maintained by an hydraulic balance. These two layers are simultaneously separately removed from different heights through modified weirs (as shown in Figure 10-6). Thus the supercentrifuge can work for continuous separation of immiscible liquid phases.

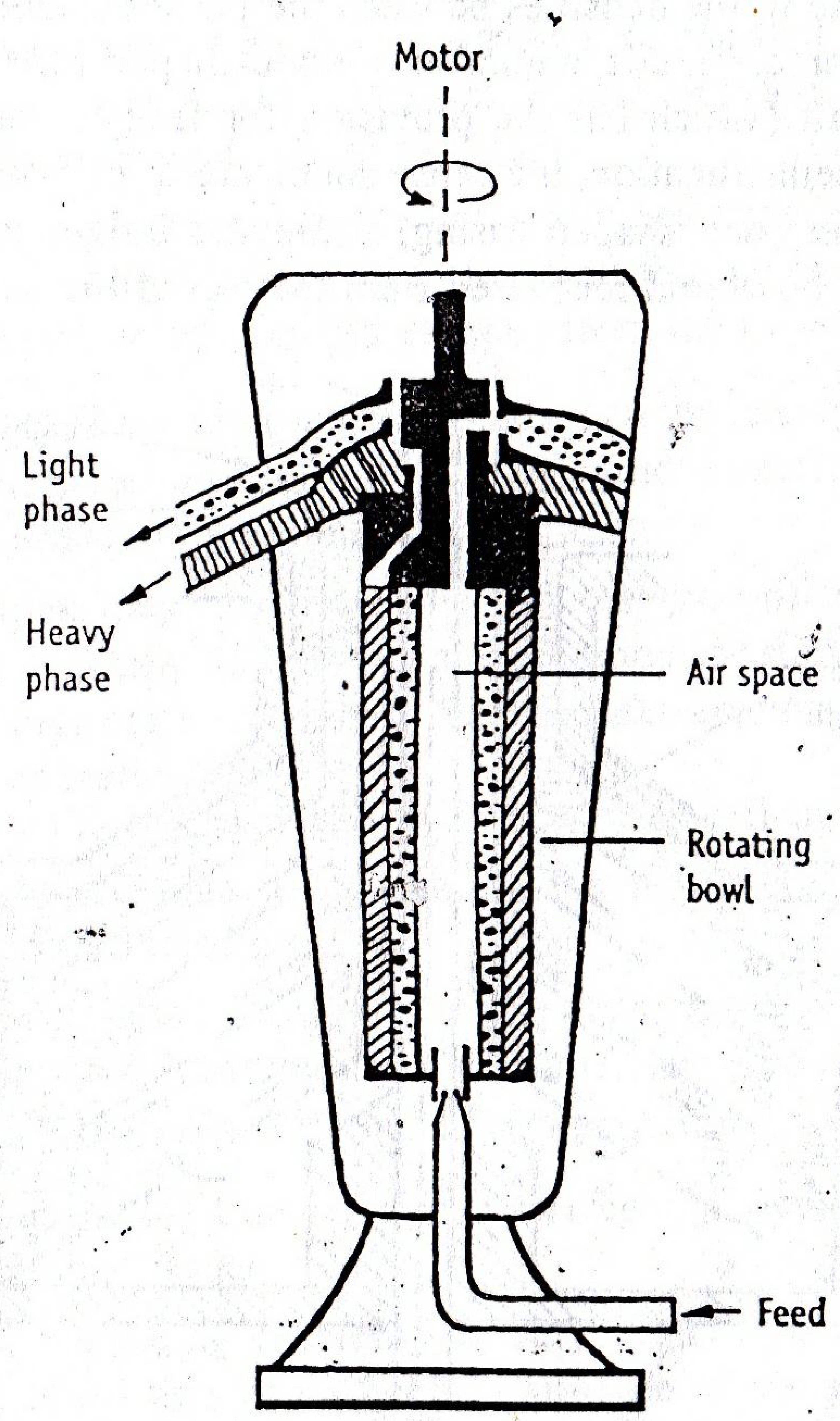

Figure 10-6. Construction of supercentrifuge.

Use : Supercentrifuge is used for separating liquid phases of emulsions in foods and pharmaceuticals.

Variants : *Tubular bowl centrifuge* : It is used to separate solids and liquids, when the solid content is low. It is a cylindrical bowl and other facilities remain the same. During centrifugation, clear liquid overflows from the weir at the top, solids are deposited on the wall and are removed at intervals, if necessary. Capacity of this centrifuge is limited.

CONICAL DISC CENTRIFUGE OR DE LAVAL CLARIFIER

As it is a clarifier, solids or immiscible liquids are present in low concentration in the feed. Complete clarification of the feed is possible by centrifugal means.

Principle : It is a sedimentation centrifuge. The separation is based on the difference in the densities between the phases under the influence of centrifugal force. In this, a number of cone-shaped plates are attached to a central shaft (which has the provision for feed) at different elevations. During centrifugation, the dense solids are thrown outwards to the underside of the cone shaped casing, while the lighter clarified liquid passes over the bowl and recovered from the top of the cone.

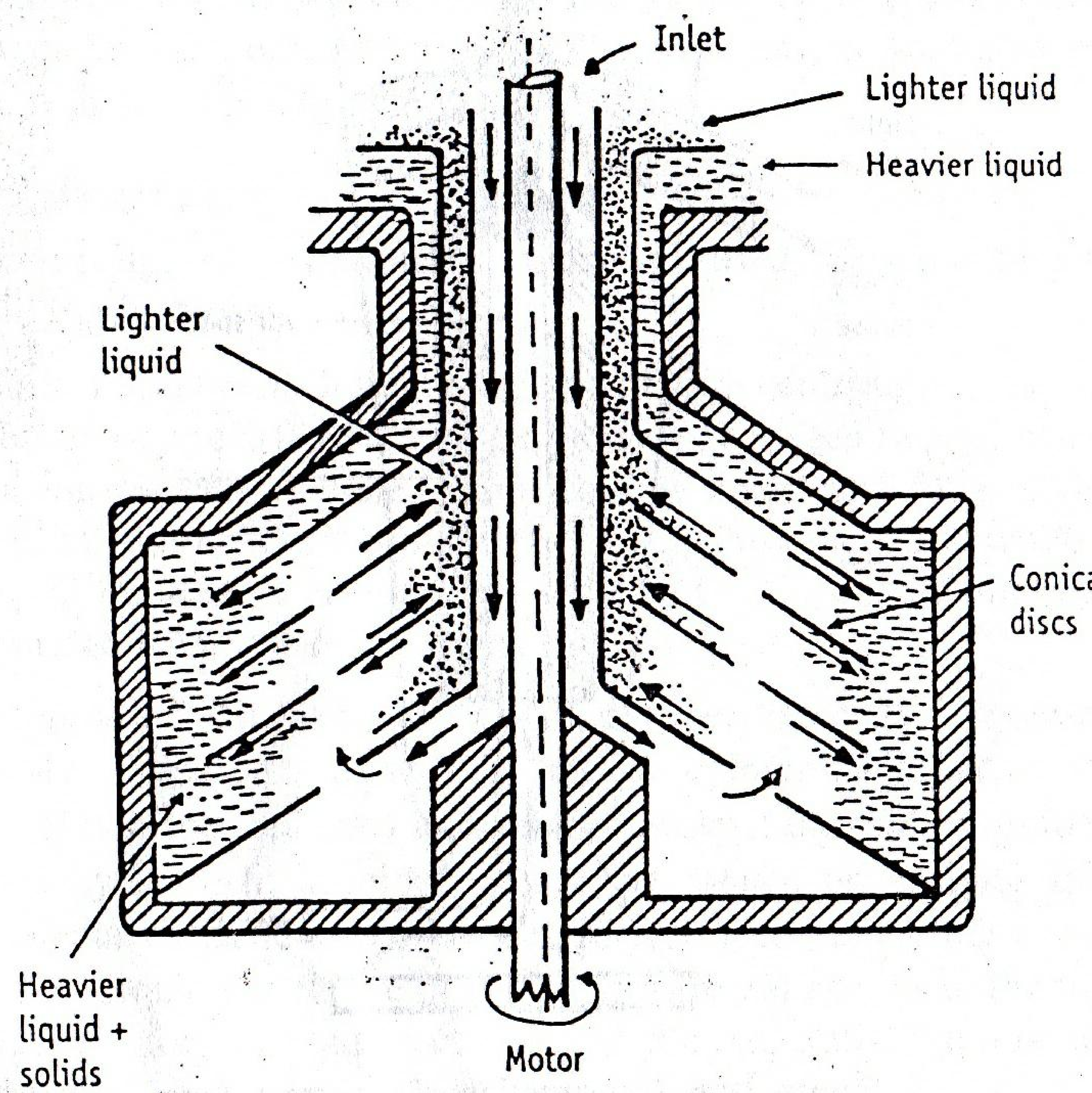

Figure 10-7. Construction of the conical disc centrifuge.

Construction : The construction of a conical disc centrifuge is shown in Figure 10-7. It consists of a shallow form of bowl containing a series of conical discs attached to the centre shaft at different elevations. The discs are made up of a thin sheet of metal or plastic separated by narrow spaces. Matching holes in the discs about half way between the axis and the wall of the bowl form channel through which the liquid passes. A concentric tube is placed surrounding the central drive shaft.

Working : Centrifuge is allowed to rotate. Low speed and short time of centrifugation is sufficient to give high degree of clarification. The feed is introduced through the concentric tube surrounding the shaft. The feed flows down and enters into the spaces between the discs (shown by the arrows). During centrifugation, the liquid flows into the channels (holes at the centre of the disc) and upward past the discs. These substances move along the surfaces of the discs to the limits of the inner and outer layers. The solids and heavy liquids are thrown outward and move underside of the discs.

Then the solids deposit at the bottom of the cone, which is removed intermittently. The lighter liquid moves to the upper side of the discs. The liquid raises to the top and escapes from the outlet.

Uses : (1) Two immiscible liquids can be easily separated by a continuous process after liquid/liquid extraction as in case of manufacture of antibiotics.

(2) Suspensions containing low concentration of solids can be separated quickly. Solids that are gelatinous or slimy can be separated by disc cone centrifuge. Such substances may plug the filter in other methods.

(3) Starch is collected after washing and purification stages.

(4) In the manufacture of insulin, the liquor is clarified to remove the precipitated proteins.

(5) Concentration of one fluid phase as in the separation of cream from milk, concentration of rubber latex, removing solids from lubricating oils, inks and beverages are possible.

Advantages : (1) Conical disc centrifuges are compact occupying a very small space.

(2) The separating efficiency is very high, so that the particles are deposited very rapidly. It is suitable, if the sediment is a fluid deposit or sludge.

(3) By controlling the speed of rotation and rate of flow, particles are separated into two size fractions.

Disadvantages : (1) The construction of a conical disc centrifuge is complicated.

(2) Its capacity is limited.

(3) It is not suitable if the sediment of solids forms a hard cake.

Glossary of Symbols

C = Centrifugal effect, m/s^2.
d = Diameter of the rotation, m.
F = Centrifugal force, N.
G = Gravitation force, N.
g = Acceleration due to gravity, m/s^2.
m = Mass of the body, kg.
r = Speed of the rotation, revolutions per second.
r = Radius from the centre to the moving body in a circular path, m.
v = Velocity of the moving body, m/s

QUESTION BANK

Each question carries 2 marks

1. Write two pharmaceutical applications of centrifugal sedimentation.
2. What are basket centrifuges? Describe their applications.
3. Write the applications of perforated basket centrifuges.
4. Explain the principle behind centrifugal separation.

Each question carries 5 marks

1. Classify industrial centrifuges. Write construction and working of a perforated basket centrifuge.
2. Give five pharmaceutical applications of industrial centrifuges.
3. Describe continuous centrifuges, giving their advantages.
4. Describe the construction and working of a Sharples supercentrifuge.
5. Describe the theory of centrifugation.

Each question carries 10 marks

1. Discuss construction and working of a discontinuous centrifuge for solid separation.
2. Describe the construction and working of a centrifuge used for the separation of slurry containing high percentage of solids.
3. Describe the construction and working of a centrifuge used for the separation of two liquid phases as in case of emulsions.