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An Overview on Mixing

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AKHILA J.B*[1], SUBASH CHANDRAN M.P[2], PRASOBH G.R[3], RENJINI A.S[1], SAHISHNA S.S[1], POOJA REJAKUMAR[1]

[1]B Pharm student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502

[2] Professor and Head, Department of Pharmaceutics, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India. 695502

[3]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.695502

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ABSTRACT

This paper describes the various methods of mixing technologies that are used in the pharmaceutical industry. The proper mixing of ingredients is essential to produce good quality products. The proper mixing of ingredients has a major role in the production of pharmaceutical medicinal products. The proper mixing of solids, liquids, semi-solids, and immiscible liquids is essential to produce uniformity in the formulations. In a large-scale production unit, a large number of active ingredients, as well as excipients, are used. In such large-scale industries, proper mixing is essential. For the proper mixing of the pharmaceutical ingredients, various mixing equipment is used, like sigma blade mixer, propellers, Silverson mixer, triple roller mill, etc. The mixing mechanism, various mixing equipment, and their related details are discussed in this review paper.

INTRODUCTION

Over recent decades pharmaceutical processing has undergone a rapid transition from a "processing art" to "processing science". This has been possible due to increasing understanding of processing parameters, better manufacturing equipment, and stricter regulatory requirements. Optimum mixing is a prerequisite for manufacturing all solid dosage forms which involve power mixing and it has an acritical contribution in achieving uniformity of content. An understanding of powder characteristics and behavior is essential to control these operations.

Mixing is defined as a shuffling type unit operation process involving both large and small particle groups and even individual particles.[1] Mixing is an energy-consuming process that produces a random distribution of particles. The mixing of pharmaceutical ingredients in the formulation of pharmaceuticals products is of 4 sections.

Section 1- mixing of solids

Section 2 - mixing of liquids

Section 3- mixing of immiscible liquids

Section 4- mixing of semisolid

The most common classification of mixtures is based on the type of dosage forms they are used to handle.

1. Mixing for solids

Physical properties that affect the ease of solid mixing are,

a. The material density

b. Particle size and distribution

c. Wettability

d. Stickiness

e. Particle shape

Liquid mixing occurs in two stages,

a. Localized mixing which applies sufficient shear to particles of the fluids.

b. A general movement sufficient to take all parts of the material through a shearing zone and to ensure a uniform final product.

The mechanism involved in mixing semi-solids depends on the character of the material which may show considerable variation. Many semisolid form neutral mixtures have no tendency to segregate although sedimentation may occur.

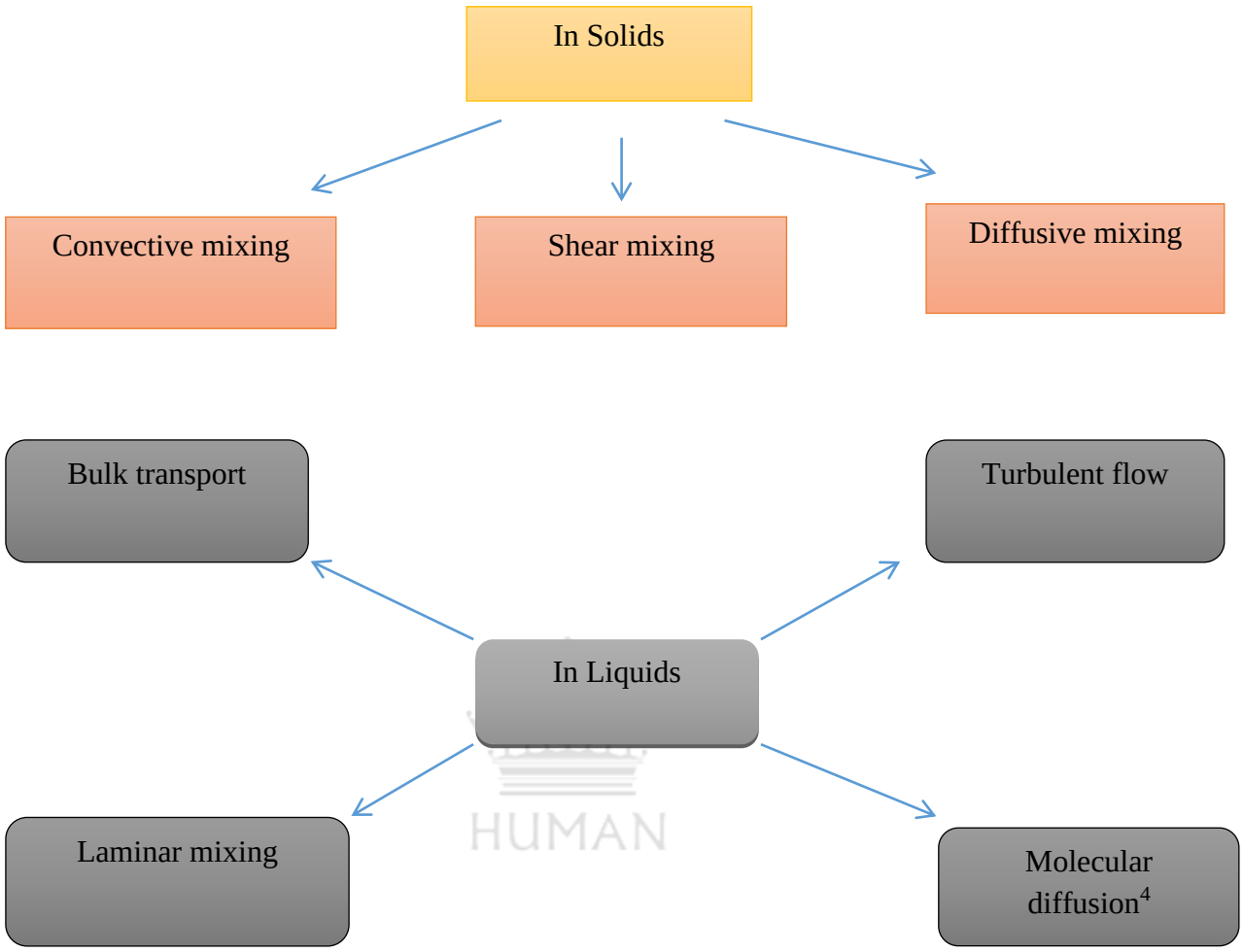
ADVANTAGES OF MIXING

- To obtain uniform composition of mixed components.
- To enhance the physical and chemical reaction of mixed components.
- To improve dissolution and diffusion of the mixture.
- To get a true solution after mixing two miscible liquids.[2]

DISADVANTAGES OF MIXING

- Separate, dual mixers may deliver insufficient and inefficient agitation.
- Re-circulation of high shear mixing system can be difficult to clean and expensive.
- The bottom entry shear mixing system can reduce heat transfer surface area.
- Mechanical heat is buildup within the mix.
- The equipment requires high power.[3]

MECHANISM OF MIXING



APPLICATIONS OF MIXING

Solid mixing

• Wet mixing in the granulation step in the production of tablet and capsule.

• Dry mixing of several ingredients ready for direct compression as in tablets.[5]

• Dry blending of powder in capsules, dry syrups, and compound powder.

• Production of pellets for the capsule.

Liquid mixing

• Liquid mixing promotes heat transfer between liquid and heating source. Uniform heat transfer in the solution yields crystals of the same size.

• Liquid mixing process is essential in the manufacturing of suspensions, emulsion, solutions, aerosols, etc.

Semisolid mixing

• Semisolid mixing is essential for the manufacturing of pharmaceutical products such as paste, ointment, etc.

Immiscible liquid mixing

• Immiscible liquid mixing is needed for the pharmaceutical formulation like emulsion. The liquid makes as miscible by adding emulsifiers like lecithin, soy lecithin, diacetyl tartaric acid, etc.[6]

SOLID MIXING EQUIPMENT

- The powder bed may expand sufficiently; therefore, equipment should never be filled more than about 60% so as to leave sufficient mixing volume.
- The particles should be subjected to movement in three directions.
- The shearing force should be sufficient to prevent aggregation. An appropriate mixing mechanism should be selected and allowed to continue for the optimum time.
- There should be no centrifugal effect so that the powder does not get separated according to its weights.
- The force should not cause breaking of the particles, which may bring about demising due to differences in particle size.
- The mixing process should be stopped abruptly because slow or diminishing forces in one direction might cause demising. Therefore, handling powder blends after mixing is equally important.[7]

Solid mixing equipment includes twin shell blender, ribbon blender, sigma blade mixer, and planetary mixer.

TWIN SHELL BLENDER OR V CONE BLENDER

□□□□ Twin shell blender is made of either stainless steel or transparent plastic. Smaller models take a charge of 20 kg and rotate at 35 rpm, larger one takes a charge of about 1 ton and rotate at 15 rpm. The material is loaded through either of the shell hatches. The material is added approximately 50-60% of its total volume. When V is inverted, the material splits into two portions. This process of dividing and recombining continuously yields ordered mixing.[8] The diagrammatic representation of the construction of a twin shell blender is shown in figure 1.

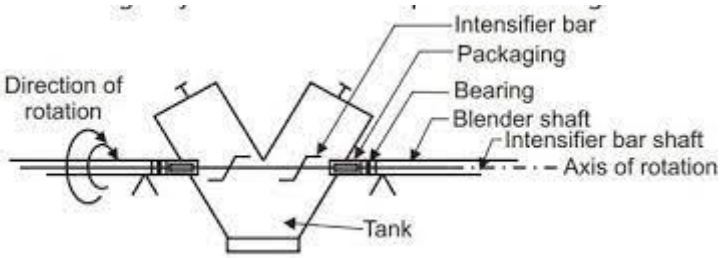


Fig.No. 1: Construction of twin shell blender

If fragile granules are to be blended, a twin shell blender is suitable because of minimum attrition**.** They handle large capacities. Easy to clean, load, and unload. This equipment requires minimum maintenance. It needs high headspace for installation. It is not suitable for the fine particulate system. If powders are free-flowing, serial dilution is required for the addition of low-dose active ingredients.[9] The schematic representation of the twin shell blender is shown in figure 2.

Fig. No.2: Twin shell blender

RIBBON BLENDER

The mechanism of mixing in ribbon blender is shear. Shear is transferred to the powder bed by moving blades in a fixed shell. High shear rates are effective in breaking lumps and aggregates. Convective mixing also occurs as the powder bed is lifted and allowed to cascade to the bottom of the container. An equilibrium state of mixing can be achieved.

It consists of a non-movable horizontal cylindrical shell usually open at the top. It is fitted with two helical blades, which are mounted on the same shaft through the long axis of the trough. The blades have both right- and left-hand twists. The blades are connected to a fixed-speed drive. The ribbon blender is top-loading with a bottom discharge spout. The trough can be closed with a lid. Through the fixed-speed drive, ribbons are allowed to rotate. One blade moves solids slowly in one direction and the other moves them quickly in opposite direction. Different powders are introduced from the top of the trough. The body is covered because considerable dust may be evolved during dry blending and granulating solution may evaporate during wet granulation.[10] The diagrammatic representation of the ribbon blender is shown in figure 3.

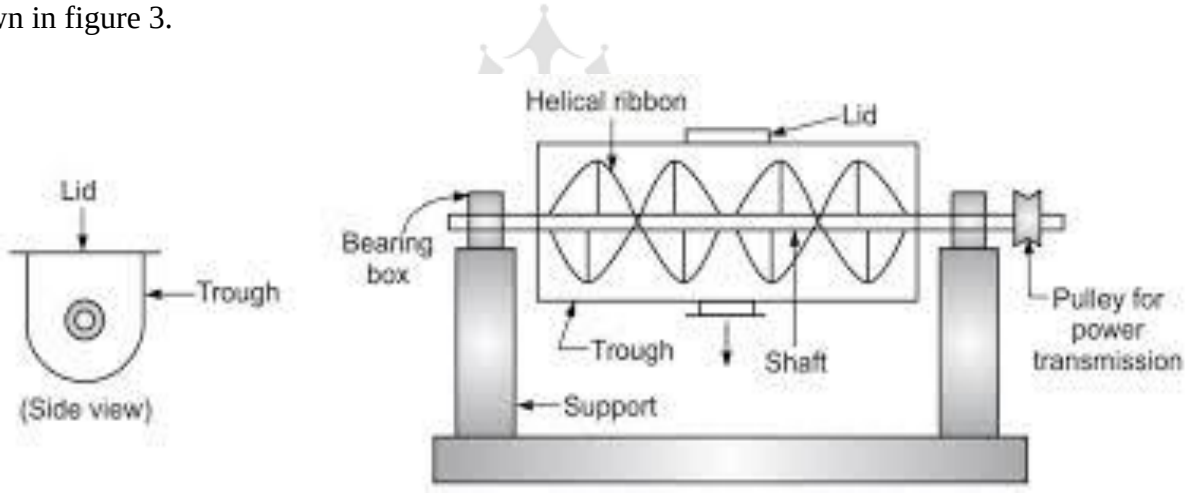


Fig. No. 3: Construction of Ribbon blender

A ribbon blender is used to mix finely divided solids, wet solid mass, sticky and plastic solids. Uniform size and density material can be easily mixed. It is used for liquid-solid and solid-solid mixing. Ribbon blenders have the advantages of, high shear can be applied using perforated baffles, which bring about rubbing and breaking of aggregates, require less space.

It is a poor mixer, because the movement of particles is two-dimensional. Shearing action is less than in planetary mixer. Dead spots are observed in the mixer, though they are minimum.

It has fixed speed drive.[11] The schematic representation of the ribbon blender is shown in figure 4.

Figure 4: Ribbon blender

SIGMA BLADE MIXER

The mechanism of mixing of sigma blade mixer is shearing. The inter- meshing of sigma-shaped blades creates high shear and kneading actions. Convective mixing is achieved by cascading the material. It consists of a double trough-shaped stationary bowl. Two sigma-shaped blades are fitted horizontally in each trough of the bowl. There are connected to a fixed-speed drive that is loaded from the top and unloaded by tilting the entire bowl by means of a rack and pinion drive.[12]

Different powders are introduced from top of the trough. The body is covered because considerable dust may be evolved during dry blending and granulating solution may evaporate during wet granulation.

Through the fixed speed drive, the sigma blades are allowed to rotate. The blades move at different speeds, one usually about twice the speed of the other, resulting in the lateral pulling of the material. They turned toward search other so that the powders moved downwards over the point and then sheared between the blades and the wall of the trough. Thus, cascading action, as well as shear action, can be achieved. The perforated blades help in breaking lumps and aggregates. Thus, a high shear force is set up. The final stage of the mix represents an equilibrium state. The operating conditions of a given mixer can markedly affect the steady-state and thus the quality of the mixing. By means of a rack and pinion drive, the bowl is

tilted to empty the blend[13]. The diagrammatic representation of the construction of the sigma blade mixer is shown in figure 5.

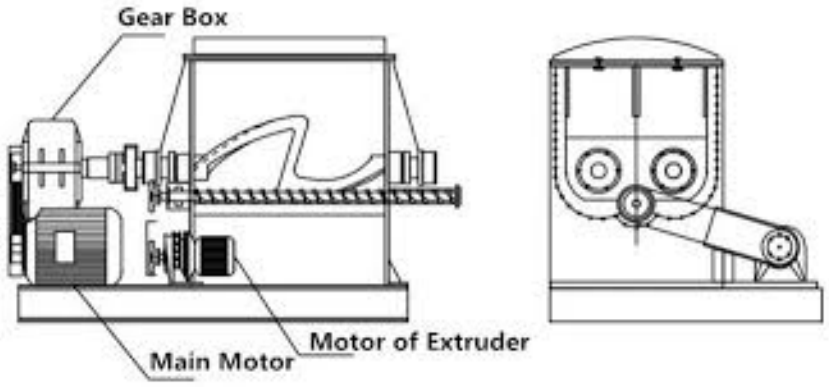


Fig. No.5: Construction of sigma blade mixer

Sigma blade mixer is commonly used for mixing of dough ingredients in the baking industry. It used in wet granulation process in the manufacture of tablet, pill masses, and ointments. It is primarily used for liquid-solid mixing, although it can be used for solid mixing. It creates a minimum dead space during mixing. It has close tolerance between the blades and the side-wall as well as the bottom of the mixer shell. It works at a fixed speed.[14] The schematic representation of the sigma blade mixer is shown in figure 6.

Fig. No. 6: Sigma blade mixer

PLANE TARY MIXER

In the planetary mixer, the blade tears the mass apart, and shear is applied between a moving blade and a stationary wall. The mixing arm moves in two ways, around its axis, and around

the central axis, so that it reaches every spot of the vessel. The plates in the blades are sloped so that the powder makes an upward movement. Therefore, tumbling motion is also obtained.

It consists of a vertical cylindrical shell, which can be removed either by lowering it beneath the blade or raising the blade above the bowl. The mixing blade is mounted from the top of the bowl. It rotates around the ring gear, which further rotates around the mixer blades. It is normally built with variables peeddrive.[15]In the planetary mixer, the agitators have a planetary motion. It rotates on its own and around the central axis so that it reaches all parts of the vessel. The beater is shaped to pass with close clearance over the side and bottom of the mixing bowl. Therefore, literally, there is no dead space in the mixing bowl. The blades tear the mass apart and shear is applied between the moving blade and the stationary wall. Emptying the bowl may be done by hand or by dumping mechanism. The diagrammatic representation of the construction of the planetary mixer is shown in figure 7.

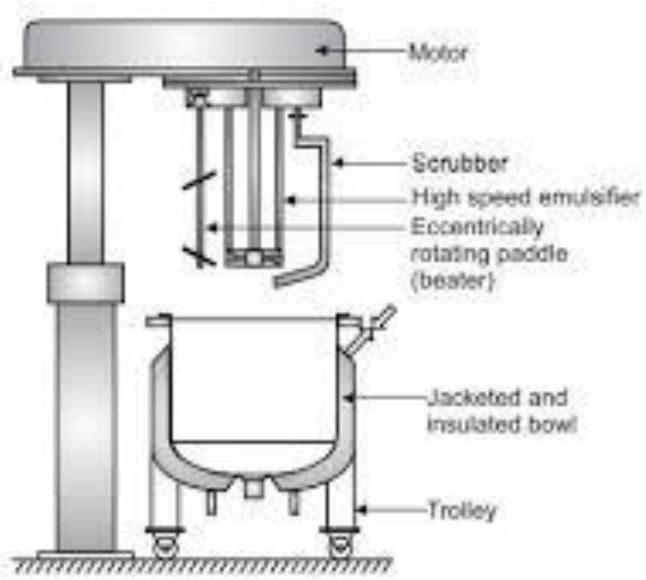


Fig. No. 7: Construction of planetary mixer

It produces precise blends in addition to breaking down of agglomerates rapidly. Low speed is used for dry blending and faster speeds for the kneading action required in wet granulation. This is more useful for the wet granulation process. There are no packing glands in contact with the product. Mechanical heat is built up within the powder mix. It requires high power.[16] The schematic representation of the planetary mixer is shown in figure 8.

Fig. No. 8: Planetary mixer

LIQUID MIXING EQUIPMENT

Mixing devices are used to supply energy to the system so long as to bring about reasonably rapid mixing.[17] Flow currents are responsible for transporting unmixed materials also to the mixing zone. Pitch is defined as the distance the impeller would move through the fluid per revolution.

Mixing devices are technically called impellers. Impellers are classified based on the shape and pitch of the blades that are attached to the central shaft. Three main types of impellers are propellers, turbines, and paddles.

PROPELLERS

A propeller normally contains a number of blades. A three-bladed design is the most common for liquid mixing. The marine-type propeller is similar to a fan or a ceiling fan.

Propellers may be either right or left-handed, depending on the direction of slant of their blades. Four bladed or toothed or similar design propellers are used for a special purpose. The size of the propeller is small, that is the ratio of diameter between propellers and container of 20 liters is sufficient for low viscous liquids. For large tanks, the maximum size of 0.5meter propellers is used. Small propeller turns at full motor speed up to 8000 rpm.[18] The diagrammatic representation of four-bladed propellers is shown in figure 9.

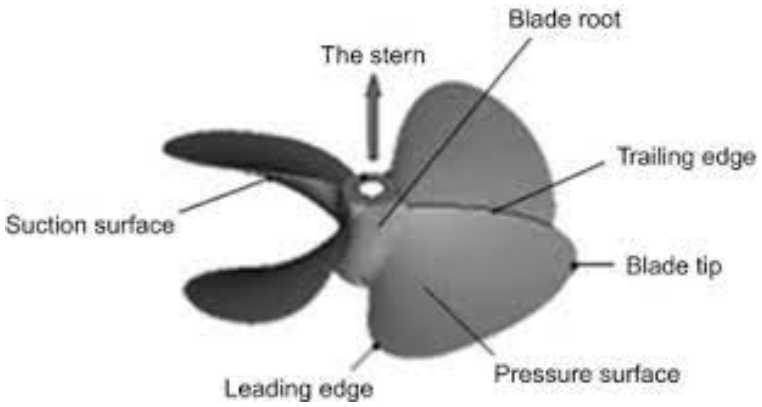


Fig. No. 9: A four-bladed propeller

Propellers are used when high mixing capacity is needed. These are effective in handling liquids having a maximum viscosity of about 2.0 Pascal second. Propellers are not effective with liquids of viscosity greater than 5.0 Pascal second. Example: glycerine, castor oil, etc. The schematic representation of types of propellers is shown in figure 10.

Fig. No. 10: Types of propellers

AIRJET MIXER

When compressed air jets are passed from the bottom of a vessel, air bubbles are formed in the liquid phase. The buoyancy of the bubble lifts the liquid, which is confined to the central portion due to the presence of draft tubes. The liquids flow down from the periphery of the vessel and enter the bottom due to the suction effect. Thus, mixing is achieved.

The liquid is placed in the vessel. Draft tubes replaced surrounding jets. Compressed air or suitable gases are allowed to pass at high pressure from the inlet provided at the bottom of the tank. This causes buoyancy of the bubble, which lifts the liquids from the bottom to the top of the vessel. Draft tubes serve to confine the expanding bubbles and entrained liquids to the

central portion. This results in a more efficient lifting action by the bubbles. The overall circulation brings liquids from all parts of the vessel to the region of the jet self. Thus, mixing is achieved.[19]The diagrammatic representation of the construction of the air jet mixer is shown in figure 11.

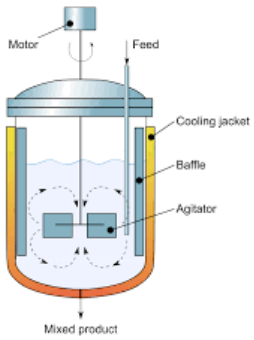


Fig. No. 11: Construction of Airjet mixer

The air-jet mixer is simple and robust. Their maintenance is easy. They are operated at varying levels. The schematic representation of the air-jet mixer is shown in figure 12.

Fig. No. 12: Airjet mixer

IMMISCIBLE LIQUID MIXING EQUIPMENT

Mixing of immiscible liquids is carried in pharmaceutical industries mainly in the manufacturing of emulsions. The equipment used for the preparation of an emulsion is known as an emulsifier.

Factors influencing the selection of emulsifier

- Quantity of emulsion to be prepared
- Flow properties of liquids
- Temperature maintenance

- The desired rate of cooling[20]

SILVERSON MIXER

Silverson mixer produces intense shearing force and turbulence by the use of high-speed rotors. This turbulence causes the liquid to pass through fine interstices formed by closely placed perforated metal sheets. Circulation of materials takes place through the head by the suction produced in the inlet at the bottom of the dispersed liquid into smaller globules.

It consists of long supporting columns connected to a motor that gives support to the head. The central portion contains a shaft, one end of which is connected to the motor and the other end is connected to the head. The head carries turbine blades. The blades are surrounded by a mesh, which is further enclosed by a cover having openings. Circulation of the material ensures the rapid breakdown of the dispersed liquid into smaller globules. Materials circulation takes place through the head by suction produced in the in let at the bottom of the head.[21]

The emulsifier head is placed in the vessel containing immiscible liquids in such a way that it should get completely dipped in the liquids. When the motor is started, the central rotating shaft rotates the head, which in turn rotates turbines blades at a very high speed. This creates a pressure difference. As a result, liquids are sucked into the head from the center of the base and subjected to intense mixing action. Centrifugal force expels the contents of the head with great force through the mesh and onto the cover. As a result, a fine emulsion emerges through the opening of the outer cover. The intake and expulsion of the mixture set up a pattern of circulation to ensure the rapid breakdown of the bigger globules into smaller globules.

It is used for the preparation of emulsions and creams of fine particle size. It is available in different sizes to handle liquids ranging from a few millimeters to several thousand liters. It can be used for batch operations.[22] The schematic diagram of the Silverson mixer is shown in figure 13.

Fig. No. 13: Silverson mixer

SEMISOLIDS MIXING EQUIPMENT

Factors involved in the selection of mixing equipment for semisolids

- Physical properties of materials like density, viscosity, miscibility, etc.
- Economic consideration regarding processing-time required for mixing and power consumption.
- The cost of equipment and maintenance.[23]

Equipment used for the mixing of semisolids is a triple roller mill

TRIPLE ROLLER MILL

The differential speed and narrow space between rollers develop high shear over the material. This causes the crushing of aggregates, particles and also distributes the drug uniformity throughout the semisolid base.

It consists of three parallel rollers of equal diameter. These are made up of hard abrasion-resistant material, normally stainless steel. The rollers are mounted in a rigid framework horizontally. The pressure and gap between the rollers are independently adjustable. A hopper is arranged between the first two rollers. A scraper is attached to the last roller.[24] The gap between the last two rollers is adjusted to be less than the gap between the first two rollers. The rollers are rotated at different speeds. In practice, the first two rollers rotate at a slower speed compared to the second roller. Similarly, the second roller's speed is less than that of the third roller.

The feed is passed through the gap between the first and second rollers. The aggregates and particles are crushed and then abraded by the rubbing action of the rollers, which is developed due to different speeds of rotation. A film of an appreciable thickness of the feed is produced. The material passes from a slow rotating to a fast-rotating roller. Between the second and third roller, the gap is small and produces a thinner reduction of cross sessional area. In the thinning film, more crushing and more abrasion are developed. The diagrammatic representation of the construction of a triple roller mill is shown in figure 14.

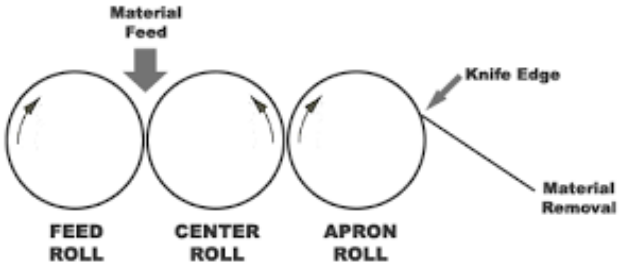


Fig. No. 14: Construction of triple roller mill

The triple roller mill is widely used to mix printing inks, electronic thick films, high-performance ceramics, cosmetics, paints, pharmaceuticals, chemicals, adhesives, foods, etc. It produces more uniform, fewer fines, and oversized particles when it comes to product quality. It is energy-saving equipment for mixing. The schematic diagram of the triple roller mill is shown in figure 15.

Fig. No.15: Triple roller mill

DISCUSSION

Mixing is a shuffling type unit operation process involving both large and small particle groups even individual particles. The proper mixing of the majority of active ingredients and adjuvants is done in the manufacturing of pharmaceutical products with the help of mixing

equipment. The mixing equipment has a wide variety of applications in the pharmaceutical industry. Product uniformity is an important measure of a pharmaceutical product. Product uniformity can be achieved by the use of suitable mixing equipment. There is various equipment used in the mixing of solids, liquids, semisolids, and immiscible liquids. The various solid mixing equipment is a twin shell blender, double cone blender, ribbon blender, sigma blender, and planetary mixer. The twin shell blenders have the advantage of handling large capacities and are easy to clean, load, and unload. The high shear rate of ribbon blenders is effective in breaking lumps and aggregates. Sigma blade mixers are useful for the wet granulation process in the manufacturing of tablets, pills, ointments, etc. The planetary mixer used for the mixing of solids requires high power. Paddles, turbines, propellers, and air-jet mixers are used as a liquid mixers. Propellers are used when high mixing capacity is needed. The maintenance of air-jet mixers should be easy. Silverson mixers are used for the mixing of immiscible liquids to make the liquids miscible by adding an emulsifier. Triple roller mills act as a semisolid mixer. The proper mixing of pharmaceutical ingredients produces uniformity in the product with good quality and efficacy.

CONCLUSION

Mixing is the major process for the manufacturing of various pharmaceutical products. The proper mixing of components increases the uniformity of drug content. If the mixing process is not proper it will affect the quality of pharmaceutical products. For the mixing of solid particles mainly double cone blender, twin shell blender, sigma blender, and ribbon blenders are used. Propellers, paddles, turbines, air-jet mixers, and silverson mixers are used for liquid mixing. The triple roller mill is mainly used for the mixing of semisolids. Solid mixers are most widely used in the pharmaceutical industry to achieve content uniformity. The solid mixer was useful for solid-solid mixing as well as solid-liquid mixing. The solid mixers are used for the wet and dry granulation process in the manufacturing of tablets, pills, powder mass, ointments, etc.

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