Lec. 1 Mixing

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Reference: The Theory and Practice of Industrial Pharmacy by Leon Lachman

MIXING

Almost every pharmaceutical product contains more than one component, and this necessitates mixing or blending stages in their manufacturing process mixing as a process "in which two or more ingredients in separate or roughly mixed condition are treated so that each particle of any one ingredient is as nearly as possible adjacent to a particle of each of the other ingredients.

The term blending is synonymous with mixing, and segregation is the opposite.

Mixing tends to result in a randomization of dissimilar particles within a system. This is to be distinguished from an ordered system in which the particles are arranged according to some iterative rule and thus follow a repetitive pattern.

Mixing is a fundamental step in most process sequences, and is normally carried out:

1-To control heat and mass transfer

2-To secure uniformity of composition so that small samples withdrawn from a bulk material represent the overall composition of the mixture 3-To improve single phase and multi-phase systems 4-To promote physical and chemical reactions, such as dissolution, in which natural diffusion is supplemented by agitation. Mixing can be classified as positive, negative, or neutral **Positive mixing:** applies to the systems where spontaneous, irreversible and complete mixing would take place, by diffusion. positive mixtures, such as a mixture of two gases or two miscible liquids do not present any problems during mixing.

Negative mixing: are generally more difficult to form and maintain, and require a higher degree of mixing ,any two-phase systems such as suspensions of solids in liquids, emulsions and creams tend to separate out quickly, unless energy is continually expended on them.

Neutral mixing: occurs when neither mixing nor de-mixing takes place unless the system is acted upon by an external energy input. Neutral mixtures are static in behavior, have no tendency to mix spontaneously or segregate spontaneously and include mixture of powders, pastes and ointments.

Flow Characteristics

Fluids may be generally classifies as Newtonian and non Newtonian, depending on the relationship between their shear rates and the applied stress.

Forces of shear are generated by interactions between moving fluids and the surfaces over which they flow during mixing.

The rate of shear may be defined as the derivative of velocity with respect to distance measured normal to the direction of flow. The viscosity is the ratio of shear stress to the shear rate.

For **Newtonian fluids**, the rate of shear is proportional to the applied stress, and such fluids have a dynamic viscosity that is independent of flow rate.

While for **non-Newtonian fluids** apparent dynamic viscosity is a function of the shear stress.

Fluid MIXING

Mixing Mechanisms

Mixing mechanisms for fluids fall essentially into four categories: bulk transport, turbulent flow, laminar flow, and molecular diffusion. Usually, more than one of these mechanisms is operative in practical mixing situations.

1-Bulk transport

The movement of a relatively large portion of the material being mixed from one location in the system to another constitutes bulk transport. A simple circulation of material does not necessarily result in efficient mixing.

2-Turbulent mixing

The phenomenon of turbulent mixing is a direct result of turbulent fluid flow which is characterized by a random fluctuation of the fluid velocity at any given point within the system. Turbulent flow can be conveniently visualized as a composite of eddies of various sizes. **Eddy:** is defined as a portion of fluid moving as a unit in a direction

often contrary to that of the general flow.

Large eddies tend to break up forming eddies of smaller and smaller size until they are no longer distinguishable.

3-laminar mixing

Streamline or laminar flow is frequently encountered when

- 1- highly viscous fluid are being processed. It can also occur if 2-stirring is relatively gentle &
- 3- may exist adjacent to stationary surface in vessels in which the flow predominantly turbulent.
- When 2 dissimilar liquids are mixed through laminar flow, the shear that is generated stretches the interface between them.
- If the mixer employed folds the layers back upon themselves, the no. of layers & hence the interfacial area between them, increase exponentially with time.
- This relationship is observed because the rate of increase in interfacial area with time is proportional to the instantaneous interfacial area.

Example

Consider the case where the mixer produces a folding effect $\&$ generates a complete fold every 10 seconds. Given an initial fluid layer thickness of 10 cm a thickness reduction by a factor of 10^{-8} is necessary to attain layers 1 nm thick, which approximate molecular dimensions. Since a single fold results in a layer thickness reduction of one half, n folds are required where

 $(1\backslash 2)^n = 10^{-8}$

or in logarithmic form, $\log[(1/2)^n] = n \log 1/2 = \log 10^{-8} = -8$

 $n = -8/\log 1/2 = 26.6$

Thus the time required for mixing is equal to n times 10 seconds (226 sec) or 4.43 min.

Good mixing at the molecular level requires a significant contribution by molecular diffusion after the layers have been reduced to reasonable thickness by laminar flow.

4- molecular diffusion

The primary mechanism responsible for mixing at the molecular level is diffusion resulting from the thermal motion of the molecules when it occurs in conjunction with laminar flow,

molecular diffusion tends to reduce the sharp discontinuities at the interface between the fluid layers and if allowed to proceed for sufficient time result in complete mixing.

The process described by Fick" s 1st law of diffusion:

 $\frac{dm}{m}$ = -DA $\frac{dc}{m}$ dt dx

D depends on the viscosity and the size of the diffusing molecules. The concentration gradients at the original boundaries is a decreasing function of time, approaching zero as mixing approaches completion.

Scale & intensity of segregation

Danckwerts has suggested 2 criteria to describe degree of mixing (quality of randomness or goodness of mixing) 1-Scale of segregation Scale of segregation is expressed in 2 ways either linear or volume scale. Linear scale represent an average value of diameter of the lumps where the volume scale represent the average lump volume.

2-Intensity of segregation is a measure of the variation in composition among the various portions of the mixtures.

TIME OF MIXING

FIG. 1-1. The intensity of segregation, I, and the scale of segregation, S, as a function of time. Bulk transport, turbulent mixing, and molecular diffusion are predominant over the time periods A, B, and C, respectively. The linear scale of segregation may be seen to increase at the end of the mixing operation. The final mixture will be uniform in composition and may be considered a single lump with a linear scale equal to the linear dimensions of the mixer.

Equipment

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A system for liquid mixing commonly consists of two primary components: (1) a tank or other container suitable for holding the material being mixed, and (2) a means of supplying energy to the system so as to bring about reasonably rapid mixing.

Power may be supplied to the fluid mass by means of an impeller, air stream, or liquid jet

Besides supplying power, these also serve to direct the flow of material within the vessel.

Baffles, vanes, and ducts are also used to direct the bulk movement of material in such mixers, thereby increasing their efficiency. When the material to be mixed is limited in volume so that it may be conveniently contained in a suitable mixer, batch mixing is usually more feasible, however, for larger volumes continuous mixing is preferred.

Batch mixing

1-Impellers

Liquids are most commonly mixed by impellers rotating in tanks. These impellers are classified as (i) propellers, (ii) turbines and (iii) paddles.

The distinction between impeller types is often made on the basis of the type of flow pattern they produce, or on the basis of the shape and pitch of the blades.

The flow pattern may be analyzed in terms of three components: 1) radial (perpendicular to the impeller shaft), 2) Axial or longitudinal (parallel to the impeller shaft), 3) tangential (tangential to the circle of rotation around the impeller shaft) . These may occur singly or in various combinations.

Diagrammatic representation of flow patterns induced by impellers: (A) Radial flow, (B) Axial flow, (C) Tangential flow

a-Propellers

Propellers of various types and forms are used, the three-blade design is most commonly used with fluids.

The blades may be set at any angle or pitch, but for most applications, the pitch is approximately equal to the propeller diameter.

Propellers are most efficient when they run at high speeds in liquids of relatively low viscosity. Although some tangential flow does occur, the primary effect of a propeller is due to axial flow. Also, intense turbulence usually occurs in the immediate vicinity of the propeller.

b-Turbines

They are usually distinguished from propellers in that the blades of the latter do not have a constant pitch throughout their length.

When radial-tangential flow is desired, turbines with blades set at a 90-degree angle to their shaft are employed. With these type of impellers, a radial flow is induced by the centrifugal action of the revolving blades .

Turbines having tilted blades produce an axial discharge quite similar to that of propellers.

Because they lend themselves to a simple and rugged design, these turbines can be operated satisfactorily in fluids 1000 times more viscous than fluids in which a propeller of comparable size can be used.

c-Paddles

Paddles are also employed as impellers and are normally operated at low speeds of 50 rpm or less.

Their blades have a large surface area as compared to the tank in which they are employed, a feature that permits them to pass close to the tank walls and effectively mix viscous liquids and semisolids which tend to cling to these surfaces. Circulation is primarily tangential, and consequently, concentration gradients in the axial and radial directions may persist in this type of mixer even after prolonged operation.

Operating procedures should take these characteristics into account. With such mixers, for example, ingredients should not be layered when they are added to the mixing tank.

2-Air Jets

Air jet devices involve sub-surface jets of air, or less commonly of some other gas, for effective mixing of certain liquids.

Of necessity and for obvious reasons, the liquids must be of low viscosity, nonfoaming, nonreactive with the gas employed, and reasonably nonvolatile. The jets are usually arranged so that the buoyancy of the bubbles lifts liquids from the bottom to the top of the mixing vessel.

This is often accomplished with the aid of draft tubes ,these serve to confine the expanding bubbles and entrained liquids, resulting in a more efficient lifting action by the bubbles, and inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, bringing it into the turbulent region in the vicinity of the jet. The overall circulation in the mixing vessel brings fluid from all parts of the tank to the region of the jet itself. Here, the intense turbulence generated by the jet produces intimate mixing.

3-Fluid Jets

They utilize liquids pumped at high pressure into a tank for mixing. The power required for pumping can often be used to accomplish the mixing operation, either partially or completely.

In such a case, the fluids are pumped through nozzles arranged to permit a good circulation of material throughout the tank In operation, fluid jets behave somewhat like propellers and they generate turbulent flow axially. However, they do not themselves generate tangential flow, like propellers. Jets also may be operated simply by pumping liquid from the tank through the jet back into the tank.

Continuous or In-line Mixers

The process of continuous mixing produces an uninterrupted supply of freshly mixed material, and is often desirable when very large volumes of materials are to be handled. It can be accomplished essentially in two ways:

1-in a tube or pipe through which the material flows and in which there is very little back flow or recirculation,

2-or in a mixing chamber in which a considerable amount of holdup and recirculation occur.

To ensure good mixing efficiency, devices such as vanes, baffles, screws, grids, or combinations of these are placed in the mixing tube.

Practical Considerations

Vortexing

A vortex develops at the center of the vessel when liquids are mixed by a centrallymounted vertical-shaft impeller.

This particularly is characteristic of turbine with blades arranged perpendicular to the impeller shaft.

These impellers tend to induce tangential flow, which does not itself produce any mixing, except possibly near the tank walls where shear forces exist, instead, swirl and the vortex formation. This is true except at very low impeller speeds or at very high liquid viscosities (>20,000 cps), neither of which is normally encountered in practice in the pharmaceutical industry.

When a vortex is formed, air is drawn into the impeller and is dispersed into the liquid, which is undesirable, as it may lead to foaming, especially if surfactants are present, and also because the full power of the impeller is not imparted to the liquid. The entrapped air also causes oxidation of the substances in certain cases and reduces the mixing intensity by reducing the velocity of the impeller relative to the surrounding fluid.

Vortixes may be avoided by (i) changing arrangement of the impeller, (ii) changing the tank geometry, (iii) using a push-pull propeller, (iv) using baffles and (v) using diffuser ring.

Figs 1.10A to D: Different arrangements of impellers in a vessel with flow pattern to prevent vortex: (A) Off-centre; (B) Inclined; (C) Side-entering; (D) Push-pull propeller

Table 1.1: Comparative mixing characteristics of various types of impellers

Mixer selection

Equipment selection

Factors that must be taken into consideration include:

1-the physical properties of the materials to be mixed such as the density, viscosity and miscibility.

2-Economic considerations regarding processing ex. time required for mixing and the power expenditure necessary.

3- Cost of the equipment and its maintenance.

1- Monophase system

Fluids of relatively low viscosity are best mixed by method that generate a high degree of turbulence & at the same time circulate the entire mass of material. These requirements are satisfied by air jets , fluid jets & the various high speed impellers. A viscosity of approximately 10 poise may be considered as a practical upper limit for the application of these devices.

Thick creams & ointments &pastes are of such high viscosity that is difficult if not impossible to generate turbulence within their bulk & laminar.

Mixing may be done with a turbine of flat blade design. These devices is insensitive to the power consumption to density and or viscosity. They are good choice when emulsification or added solids may change these quantities during the mixing.

2- Polyphase system

The mixing of 2 immiscible liquids requires the subdivision of one of these phases into globules, then distributed throughout the bulk of the fluid. These globules are successively broken down into smaller one.

Two primary forces play here: 1-the interfacial tension of the globules in the surrounding liquid and 2- forces of shear within the fluid mass.

The first force tends to resist the distortion of globule shape fragmentation to small globule where the opposite with the 2nd force.

The selection of equipment depends upon the viscosity of the liquids and this is made according to the mechanism by which intense shearing forces can best be generated.

In case of low-viscosity system, high shear rates are required and produced by passing the fluid under high pressure through small orifices or by bringing it into contact with rapidly moving surfaces.

Highly viscous fluids such as are encountered in the production of ointments, are efficiently dispersed by the shearing action of 2 surfaces in close proximity and moving at different velocities with respect to each other.

This is achieved in paddle mixers in which the blades clear out the walls. These mixers generate shear to reduce globule size and induce sufficient circulation of materials to ensure efficient mixing.

• The mixing of finely divided solids with a liquid of low viscosity in the production of a suspension depends on the separation of aggregates & distribution of these particles in the fluid. This process occurs in a single mixing operation provided that shear forces of sufficient to disrupt aggregates.

As the % of solids is increased or if highly viscous fluids are employed, the solid – liquid system takes on the consistency of a paste or dough. The choice of mixer is either knead or mull the materials.

Kneaders operate by pushing of the material by squeezing $\&$ deforming them at the same time. Such mixers take several forms.

• Usually have counter – rotating blades or heavy arms that work the plastic mass. Shear forces are generated by the high viscosity of the mass & are effective in deaggregation & distribution of the solids in the fluid vehicle.

Kneaders Sigma-Blade Mixer

Sigma-blade mixer has counter-rotating blades or heavy arms that work the plastic mass. The blades rotate tangentially with a speed ratio of about 2:1. The shape and difference in rotational speed of the blades facilitate lateral pulling of the material and impart kneading and rolling action on the material .Shear forces are also generated by the high viscosity of the mass and are thus effective in deaggregation as well as distribution of solids in the fluid vehicle.

: Schematic representation of a top-loading sigma-blade mixer with overlapping blades

Planetary Mixer

It imparts planetary mixing action, whereby the mixing element rotates round the circumference of the mixer"s container, awhile simultaneously rotating about its own axis.

The double rotation of the mixing element and its offset position reduces the dead zones and avoids vortex formation.

Mulling Mixers

Mulling mixers provide forces that incorporate kneading, shearing, smearing, and blending of materials for a total uniform consistency.

This process produces just enough pressure to move, intermingle and push particles into place without crushing, grinding, or distorting the ingredients. The result is a final mixture of truly uniform consistency in both physical and

chemical structure.

Mulling mixers are efficient in deaggregation of solids, but are typically inefficient in distributing the particles uniformly throughout the entire mass. These devices are suitable for mixing previously mixed material of uniform composition, but containing aggregates of solid particles. In the event of segregation during mulling, a final remixing may be necessary.

Schematic representation of the mulling mixer

Roller Mills

Roller mills consist of one or more rollers and are commonly used. Of these, the three-roller types are preferred.

In operation, rollers composed of a hard, abrasion-resistant material, and arranged to come into close proximity to each other are rotated at different rates. Depending on the gap, the material that comes between the rollers is crushed, and also sheared by the difference in rates of movement of the two surfaces.

In which a small volume of liquid is to be mixed with a large quantity of solids. This process is one of coating the solid particles with liquid $\&$ of the transfer of liquid from one particle to another.

The liquid is added slowly to reduce the tendency of the particles to lump. But when the particles tend to stick together because of surface tension of the coating liquids, the equipment used is the same as that for pastes.

If the solids remain essentially free flowing , the equipment is the same as that used for solids mixing.

Mixing of solids

- In the manufacture of tablets or granules normally a number of additives are added. Therefore, mixing of powder becomes essential part of the process.
- Mixing is considered as a critical factor, especially in case of potent drugs and low dose drugs where high amounts of adjuvants are added.
- The diverse characteristics of particles such as size, shape, volume, surface area, density, porosity, and flow charge contribute to the solid mixing. From the definition of mixing, the ideal situation or "perfect mix" in this case would be produced when each particle lies as closely as possible in contact with a particle of the other component.

Although a perfect mixture would offer a point uniformity, such arrangement is virtually impossible to get in practice by any mixing equipment. Powder mixing, however, is a "chance" process and in practice the best type of mix likely to be obtained is a "random mix" where the probability of finding one type of particle at any point in the mixture is equal to its proportion in the mixture.

Segregation is the central problem associated with the mixing and handling of the solid particles, such segregation of particulate solids can occur during mixing as well following the mixing operation. Solids tend to segregate by virtue of differences in the size, density, shape, and other properties of the particles of which they are composed. The second requirement for segregation can be met by the Earth is gravitational field, or by a centrifugal, electrical, magnetic field generated in the course of processing

Factors Affecting Demixing

1)Particle Size and Size Distribution a difference in the particle sizes of components of a formulations the main cause of segregation in powder mixes. Smaller particles tend to fall through the voids between larger particles, and thus move to the bottom of the mass

Segregation problem due to particle size difference can be reduced by: a) Selection of a particular sized fractions (e.g. by sieving to remove fines or lumps) to achieve drug and excipients of the same narrow particle size range.

b) Milling of components to either reduce the particle size range or to ensure all that particles are below approximately 30 μm, at which size segregation does not tend to cause serious problems .

c) Granulation of the powder mix (size enlargement) so that large numbers of different particles are evenly distributed in each segregating unit/granule.

2) Particle shape

Particle shape is important because as the shape of a particle deviates more significantly from a spherical form, the free movement it experiences along its major axis also decreases. Spherical particles exhibit the greatest flowability, and are therefore more easily mixed, but they also segregate more easily than non-spherical particles.

Irregular or needle-shaped particles may become interlocked, decreasing the tendency to segregate once mixing has occurred.

Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range reduces the tendency to segregate.

3) Particle Charge

The mixing of particles whose surfaces are non-conducting (electrically) often results in the generation of surface charges, as evidenced by a tendency of the powder to clump following a period of agitation.

Surface charging of particles during mixing is undesirable, for it tends to decrease the process of interparticulate "diffusion."

Solid -solid mixing mechanisms

1. **convective mixing** is an analogous to bulk transport.

This mixing can occur by an inversion of the powder bed by means of

1-blades or paddles,

2- revolving screw or by any method of moving a relatively large mass of material from one part of the powder bed to another.

2-shear mixing

As a result of forces within the particulate mass , slip planes are set up and this give rise to laminar flow. When shear occurs between regions of different composition & parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers.

3-Diffusive mixing by diffusion

When random motion of particles within a powder bed causes them to change position relative to one another. Such an exchange of positions by single particles result in a reduction of the intensity of segregation.

Diffusive mixing occurs at the interfaces of dissimilar regions that are undergoing shear $\&$ therefore results from shear mixing.

Equipments/Batch Tumblers/Blenders

A tumbling mixer consists of a container of the one of several geometric forms, which is mounted so that it can be rotated about an axis to cause movement of the material in all planes, which is necessary for rapid overall mixing. The resulting tumbling motion is accentuated by means of baffles, lifter blades or simply by virtue of the shape of the container Various types of tumblers with different geometric shapes such as twin-shell, double-cone, drum, cube and tetrahedral blenders are commercially available ,which may be rotated about almost any axis depending on the manufacturer.

The popular twin-shell blender is of this type and takes the form of a cylinder that has been cut in half at approximately a 45-degree angle with its long axis, and then rejoined to form a "V" shape.

This is rotated so that the material is alternately collected at the bottom of the "V" and then split into two portions when the "V" is inverted. This is quite effective because the bulk transport and shear, which occur in tumbling mixers, generally, are accentuated by this design.

The efficiency of tumbling mixers is highly dependent on the speed of rotation.

Rotation that is too slow neither produces the desired intense tumbling or cascading motion, nor does it generate rapid shear rates.

On the other hand, rotation that is too rapid tends to produce centrifugal force sufficient to hold the powder to the sides of the mixer, and thereby, reduces efficiency.

Agitator Mixers

Agitator mixers employ a stationary container to hold the material and bring about mixing by means of moving screws, paddles, or blades.

Since these mixers do not depend entirely on gravity as do the tumblers, they are useful in mixing solids that have been wetted, and are therefore in a sticky or plastic state.

The high shear forces that are set up are effective in breaking up lumps or aggregates. Well-known mixers of this type include the following:

-Ribbon Mixer/Blender

It consists of a horizontal cylindrical tank usually opening at the top and fitted with helical blades or ribbons The blades are mounted on the horizontal axle by struts, and are rotated to circulate the material to be mixed. The helical blades are wound (in most cases) in the opposite directions to provide for the movement of material in both directions along the axis of the tank. Although little axial mixing in the vicinity of the shaft occurs, mixtures with high homogeneity can be produced by prolonged mixing even when the components differ in particle size, shape, or density, or there is some tendency to aggregate.

FIG. 1-12. Side view of a top-loading ribbon blender. The blades are mounted on the horizontal axle by struts (not shown) and are rotated to circulate the material to be mixed. The spiral blades are wound (in most cases) in opposite directions to provide for movement of material in both directions along the axis of the tank. These mixers may be emptied either through ports in the bottom or by inverting them.

1-Ribbon blender

2-The helical flight mixer powders are lifted by a centrally located vertical screw & allowed to cascade to the bottom of the tank.

Continuous Mixers

A characteristic of solids mixing equipment is that all else being equal, mixtures produced by large mixers have greater variations in composition than those produced by small mixers.

This is an important consideration when relatively small portions of the mixture are required to fall consistently within a narrow composition range.

Continuous mixing processes are somewhat analogous to those discussed under fluid mixing. Metered quantities of the powders or granules are passed through a device that reduces both the scale and intensity of segregation, usually by impact or shearing action.

Barrel Type Continuous Mixer

In this mixer, the material is mixed under tumbling motion .The presence of baffles further enhances the mixing. When the material approaches the midpoint of the shell, a set of baffles causes a part of the material to move backwards. Such a mechanism provides intense mixing of ingredients.

Zig-zag Continuous Blender

It consists of several "V"-shaped blenders connected in series ,when the blender is inverted, the material splits into two portions, one-half of the material moves backwards, while the other moves forward. In each rotation, a part of the material moves towards the discharge end.

Mixer Selection

Mixer Property

An ideal mixer should produce a complete blend rapidly with as gentle mixing action as possible to avoid product damage. It should be dust tight, cleaned and discharged easily, and require low maintenance and low power consumption.

Rotating shell mixers suffer from poor cross-flow along the axis.

The addition of baffles or inclining the drum on the axis increases cross-flow and improves the mixing action.

In cubical and polyhedron-shaped blenders, due to their flat surfaces, the powder is subjected more to a sliding than a rolling action, a motion that is not conductive to efficient mixing.

In double cone blenders the mixing pattern provides a good cross-flow with a rolling rather than sliding motion. The uneven length of each shell in twin-shell blender provides additional mixing action when the powder bed recombines during each revolution of the blender. Twin-shell and double-cone blenders are recommended for precision blending.

The shearing action that develops between moving blades and trough in agitator mixers serves to breakdown powder agglomerates.

Ribbon mixers are not precision blenders and also suffer from the disadvantage of being more difficult to clean than the tumblers and having a higher power requirement.

The mechanical heat build-up and the relatively higher power requirement are the drawbacks also associated with sigma blade and planetary mixers. However, the shorter time interval necessary to achieve a satisfactory blend may offset these factors.

Blendex provides efficient batch and continuous mixing for a wide variety of solids without particle size reduction and heat generation.

Material Property

Powders that are not free-flowing or that exhibit high forces of cohesion or adhesion between particles of similar or dissimilar composition are often difficult to mix owing to agglomeration.

The clumps of particles can be broken down in such cases by the use of mixers that generate high shear forces or that subject the powder to impact.

The use of agitators preferably planetary and sigma blade are recommended for such powders.

For strongly cohesive materials, it is typically necessary to fragment agglomerates through the introduction of high shear, "intensification," devices such as agitators or mills that energetically deform grains on the finest scale.