# Mixing Technologies in the Pharmaceutical Industries

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***Abstract :*** ***This paper presents an overview of mixing technologies implemented across many of today's highly competitive pharmaceutical and medical industries as well as new equipment designs that are increasingly being recognized as potential solutions to prevailing mixing challenges. The desired degree of mixing depends on the purpose of products and the objective of the mixing. Mixing is characterized into three major categories-positive, negative and neutral. Mixing applications falling within the broad spectrum of mass produced pharmaceutical goods and medical devices are too many and complex to discuss in detail hence this paper will touch on a few general classification as well as few examples within that mixing category.***

***Keywords : Liquid-liquid mixing, solid-solid mixing, solid-liquid mixing, propellers, double cone mixers, roller mills, triple roller, agitator, drug spatula.***

**Introduction**

Mixing is one of the most common pharmaceutical operations. It is difficult to find a pharmaceutical product in which mixing is not done at one stage or the other during its manufacturing. Mixing may be defined as the process in which two or more than two components in a separate or roughly mixed condition are treated in such a way so that each particle of any one ingredient lies as nearly as possible to the adjacent particle of other ingredients or components. This process may involve the mixing of gases, liquids or solids in any possible combination and in any possible ratio of two or more components. Some of the examples of large scale mixing practiced in pharmacy are;

- Mixing of powders in varying proportions prior to granulation or tabletting.
- Dry mixing of the materials for direct compression in tablets.
- Dry blending of powders in capsules and compound powder ( insufflations).
- Blending of powders in cosmetics in the preparation of tooth powders, face powders.
- Mixing of two immiscible liquids for preparation of emulsion.

**OBJECTIVES OF MIXING:**

**1. To make simple physical mixture**

In the production of tablets, capsules, sachets and dry powders two or more powders or granules are mixed. In linctuses two or more miscible liquids are mixed completely.

**2. Physical change**

Mixing may aim at producing a change that is physical, for example the solution of a soluble substance. In case of dissolving a solid in a solvent mixing will take place by diffusion but the process will be slow. In this case agitation makes the process rapid.

**3. Dispersion**

In case of emulsions and creams two immiscible liquids are mixed where one liquid is dispersed into other. In suspension and pastes solid particles are dispersed in a liquid by mixing.

**4. Promotion of reaction**

Mixing will usually encourage (and control at the same time) a chemical reaction, so ensuring uniform products.

**TYPES OF MIXTURES**

Mixtures may be divided into three types that differ fundamentally in their behavior:

**Positive mixtures**

Positive mixtures are formed from materials such as gases or miscible liquids, which mix spontaneously and irreversibly by diffusion and tends to approach a perfect mix.There is no input of energy required. If enough time is available the mixing is complete. In general, such materials do not present any problems in mixing.
e.g. Mixing of sodium chloride and sugar in water.

**Negative mixtures**

In negative mixtures, after mixing, the components will tend to separate out. If this occurs quickly, then energy must be continuously input to keep the components in dispersed state. Negative mixtures are more difficult to form and a higher degree of mixing efficiency is required.
e.g. Calamine lotion.

**Neutral mixtures**

Neutral mixtures are static in their behavior, the components having no tendency to mix spontaneously, nor do they segregate when mixed.
e.g. Pastes, ointments and mixed powders.

**MIXING MECHANISMS**

It has been generally accepted that solids mixing proceeds by a combination of one or more of the following mechanisms:

**1. Convective mixing:**

A relatively large mass of material is moved from one part of the powder bed to another - this is called convection. Depending on the type of mixer employed, convective mixing can occur by an inversion of the powder bed, by means of blades or paddles, or by means of a revolving

screw etc.

**2. Shear mixing**

As a result of forces within the particulate mass, slip planes are set up. Depending on the flow characteristics these can occur singly or in such a way that it give rise to laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occur in a direction normal to the interface of such layers is also effective since it too reduces the scale of segregation.

**3. Diffusive mixing**

Mixing by "diffusion" is said to occur when random motion of particles within a particle bed causes them to change position relative to one another. Such as exchange of positions by single particles result in reduction of the intensity of segregation. Diffusive mixing occurs at the interfaces of dissimilar regions that are undergoing shear and therefore results from shear mixing.

**MIXING EQUIPMENTS OF SOILD - SOILD MIXING**

**Tumbling mixers / blenders**

Applications:

Used for mixing / blending of granules or free-flowing powders.

In tumbling mixers, rotation of the vessel imparts movement to the materials by tilting the powder until the angle of the surface exceeds the angle of repose when the surface layers of the particles go into a slide.

A common type of mixer consists of a container of one of several geometrical forms, which is mounted so that it can be rotated about an axis. The resulting tumbling motion is accentuated by means of baffles or simply by virtue of the shape of the container.

**Fig1 Tumbling mixers / blenders**

**Rotating -Shell Mixers**

The drum type, cubical-shaped, double-cone and twin shell blenders are all examples of this class of mixers.

**Drum-type** blenders with their axis of rotation horizontal to the centre of the drum are used quite commonly.

Disadvantages: This suffers from poor cross flow along the axis.

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

**Cubical and polyhedron** shaped blenders with the rotating axis set at various angles also are available.

Disadvantages:- In the polyhedron type blender, because of their flat surface, the powder is subjected more to a sliding than a rolling action which is not conducive to the most efficient mixing.

**Double cone blender** provides a good cross flow with a rolling rather a sliding motion. Normally no baffles are required so that cleaning is simplified.

**Twin shell blender** combines the efficiency of the inclined drum-type with the intermixing that occurs when two such mixers combine their flow. The twin-shell blender takes the form of a cylinder that has been cut in half, at approximately a 450-angle with its long axis, and then rejoined to form a "V"-shape. This is rotated so that the material is alternatively collected in the bottom of the V and then split into two portions when the V is inverted.

**Fig 2 Twin shell blender**

**Agitator mixers**

Agitator mixer for powders can take a similar form to paddle mixers for liquids, but their efficiency is low. Planetary motion mixers are effective, but special design are to be preferred.

This type of mixers employs a stationary container to hold the material and brings about mixing by means of moving screws, paddles or blades.

Use: Since the mixers do not depend entirely on gravity as do the tumblers, it is useful in mixing wet solids, sticky pastes etc.
The high shear forces effectively break up lumps or aggregates

**MIXING EQUIPMENTS OF LIQUID - LIQUID MIXING**
**PROPELLER MIXERS**

The propellers are small impellers that produce a longitudinal movement of liquids. Generally they are small in relation to the container i.e. container diameter to propeller diameter ratio (D/d) » 20.They generally operates at high speeds: up to 8000 rpm. Propeller mixer is not normally effective with liquids of viscosity greater than about 5 Ns/m2 ; which is somewhat greater than glycerin or castor oil.

**TURBINE MIXERS**

A turbine mixer uses a circular disc impeller, to which are attached a number of vertical blades, which may be straight or curved.
Characteristics:
(i) They are usually rotated at a somewhat lower speed than the propeller type.
(ii) D/d ratio is lower than that of propeller type.
(iii) The blades are usually flat, hence, very little axial or tangential flow, the liquid moves rapidly in a radial direction.
(iv) They give rise to greater shear forces than propeller type and these shear forces can be increased further by fitting a diffusing ring. This is a stationary perforated or slotted ring which surrounds the impeller, so that the discharged liquid must pass through the apertures. The diffuser reduces rotational swirling and vortexing, but is most useful in increasing shear forces.
(v) They can deal with more viscous liquids than the propeller mixer, having a range up to 100Ns/m2 approximately the consistency of liquid glucose.

**Use:**
(i) Suitable for viscous liquids.
(ii) Not suitable for suspensions, because no vertical flow is there.
(iii) The higher shear forces and the greater viscosity range give it a special application in the mixing of liquids that may stratify with a propeller and, particularly, in the preparation of emulsions of immiscible liquids.

**Paddle mixers**

Paddle mixers use an agitator consisting usually of flat blades attached to a vertical shaft and rotating at low speed (100 rpm).
Characteristics:
(i) For liquids of low viscosity simple flat paddles are used and the emphasis is on radial and tangential movements.
(ii) Paddles for more viscous liquids generally have a number of blades, often shaped to fit closely to the surface of the vessel, avoiding 'dead spot' and deposited solids.
(iii) An alternative design for the more viscous range of liquids is the planetary motion mixer, which has a smaller paddle that rotates on its own axis, but travels also, in circular path round the mixing vessel. The agitator is fixed at the side of the vessel, to eliminate 'dead spots'.
(iv) The width of the agitator is not more than 1/2 to 2/3rd of the diameter of the vessel, which requires less power than that needed for a full width central agitator, improves the circulation in the vessel, and increases mixing efficiency.

**SOLID-LIQUID MIXING**

During tablet granulation binder solution is added to dry powder mass, and a damp mass is formed which is very difficult to mix with ordinary mixers. So planetary and sigma blenders are used.

**Agitator mixers**

**(i) Planetary motion mixers:**

Construction: It consists of a circular base. Inside the container a blade rotates around its own axis. The axis of the blade again rotates along a shaft. Thus the motion of the blade is similar to the motion of a planet around the sun. The planet is rotating along its own axis and at the same time the planet is rotating around the sun. The design of the blade is as shown in the figure. There is very little clearance between the blade and the wall of the container.

Working: This design allows the revolving blade to handle (mix) a small amount of mass at a time. Again the blade is moving, carrying the mass to other places. The blade is scraping the materials those are sticking to the wall of the container.

Application:

1. This sturdy (strong) mixer is used to mix semisolid ointments.
2. To prepare tablets the powder is mixed with binder solutions. During this wet massing step planetary mixer is used.

**Fig 3 Planetary motion mixers**

**(ii) Sigma Blender:**

**Construction:**

It uses two mixer blades, the shape of which resembles the Greek letter "sigma" (S).The two blades rotates towards each other and operate in a mixing vessel which has a double trough shape, each blade fitting into a trough.

The two blades rotate at different speeds, one usually about twice the speed of the other, resulting in a lateral pulling of the material and divisions into two troughs, while the blade shape and difference in speed causes end-to-end movement.

Use:

• This types of mixers are of sturdy construction and high power, hence, they can handle even the heaviest plastic materials and products like tablet granule, and ointments are mixed readily.

• To reduce the entrainment of air in ointment masses the sigma mixer can be enclosed and operated under reduced pressure, which is an excellent method for avoiding entrainment of air and may assist in minimizing decomposition of oxidizable materials, but it must be used with caution if mixer contains volatile ingredients.

• As with many other mixers, the vessel is jacket for heating or cooling and, in this case, the blades can be hollow for the same purpose. This can be very useful in practice, since some semi-solids may be reduced in viscosity by heating, while with other materials it may be necessary to dissipate the heat resulting from the energy put into the mixing process.

**CONCLUSION**

For small scale we are using mortar and pestle for mixing. For large scale/pharmaceutics we can go for this varieties of mixture. These are easy to perform. B using these instruments we can save time. Work will become faster.

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