CHAPTER 7

MIXING

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Abstract

Mixing is a fundamental unit operation in pharmaceutical manufacturing, essential for achieving homogeneity in various formulations. This process involves the combination of two or more components to produce a uniform mixture, crucial for ensuring consistent drug content and performance. Different types of mixing are employed based on the physical state of materials, including solid-solid, solid-liquid, and liquid-liquid mixing. The selection of appropriate mixing equipment, such as ribbon blenders, planetary mixers, or high-shear mixers, depends on the nature of the materials and desired outcome. Factors affecting mixing efficiency include particle size distribution, density differences, and rheological properties of the components. The concept of mixing mechanisms, including convection, diffusion, and shear, is explored to understand the principles underlying effective mixing. Challenges in pharmaceutical mixing, such as segregation and over-mixing, are addressed, along with strategies to overcome them. Quality control measures, including blend uniformity testing and in-process controls, are discussed to ensure the consistency of the final product

Keywords: *Homogenization, Blending, Uniformity, Segregation, Mixing equipment, Process optimization*

Learning Objectives

After completion of the chapter, the student should be able to:

- Define mixing and its importance in pharmaceutical formulations.
- Explain the principles and mechanisms of mixing processes.
- Describe different types of mixing equipment used in pharmaceutical manufacturing.
- Discuss the factors affecting mixing efficiency and homogeneity.
- Explain the concept of mixing time and its optimization.
- Analyze the challenges in mixing different types of pharmaceutical materials.
- Evaluate methods for assessing the quality and uniformity of mixing.

Mixing may be defined as a unit operation in which two or more components, in an unmixed or partially mixed state, are treated so that each unit (particle, molecule etc.) of the components lies as nearly as possible in contact with a unit of each of the other components.

If this is achieved it produces a theoretical 'ideal' situation, i.e. a ***perfect mix***.

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.

SOLID-SOLID MIXING

Mechanism of solid-solid mixing

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 equipment

- The ideal mixer should produce a complete blend rapidly with as gentle as possible a mixing action to avoid product damage.
- It should be cleaned and discharged easily,
- be dust-tight and
- require low maintenance and
- low power consumption
- mixers should be earthed to dissipate the static charge on particles.

Tumbling mixers / blenders

Applications:

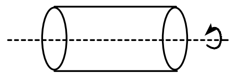
Used for mixing / blending of granules or free-flowing powders.

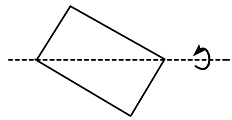
In tumbling mixers, rotation of the vessel imparts movement to the materials by tilting the powder until the angle of the surface exceeds the angle of repose when the surface layers of the particles go into a slide.

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*.

Rotating -Shell Mixers

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

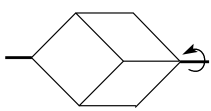




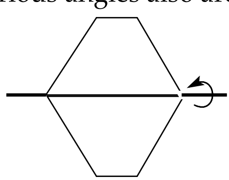
Drum-type blenders with their axis of rotation horizontal to the centre of the drum are used quite commonly.

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.

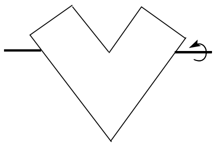


Cubical and polyhedron shaped blenders with the rotating axis set at various angles also are available.



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 45^0-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.

Mechanism

This is quite effective because the bulk transport and shear, which occur in tumbling mixers generally, are accentuated by this design.

A bar containing blades that rotate in a direction opposite to that of the twin shell often is used to improve agitation of the powder bed, and may be replaced by a hollow tube for the injection of liquids.

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

- If the rotation speed is too slow ⇒ does not produce desired tumbling or cascading motion nor does it generate rapid shear rates.
- If the rotation speed is too high ⇒ produce centrifugal force sufficient to hold the powder to the sides of the mixer and thereby reduce efficiency.
- If the rotation speed is optimum⇒ depends on the

size, shape, r.p.m. Commonly in the range of 30 to 100 rpm.

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 force effectively break up lumps or aggregates.

RIBBON BLENDER

The *ribbon blender* consists of a relatively long trough-like shell with a hemispherical bottom. The shell is fitted with a shaft on which are mounted spiral ribbons, paddles or helical screws, alone or in combination. These mixing blades produce a continuous cutting and shuffling of the powder by circulating the powder from end to end of the trough as well as rotationally. The shearing action that develops between the moving blade and the trough serves to break down powder agglomerates.

Disadvantages: They are not precision blenders and they are difficult to clean.