

REVIEW ARTICLE

Concepts and Techniques of Pharmaceutical Powder Mixing Process: A Current Update

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ABSTRACT

Majority of the active ingredients and adjuvants used for the manufacture of pharmaceutical dosage forms constitutes in the powder form. The market for solid dosage forms involving powder processing is large and is growing day by day. Handling and processing of powders is central to pharmaceutical operations. But it poses numerous problems due to their unpredictable and irregular behavior. With recent technological developments, the pharma industry is overcoming the hurdles in making a quality product, which is substantiated by its compliance with regulatory requirements. This article deals with sequential approaches to be enforced by the pharmaceutical industries to draw out new technical responses to change with respect to mixing, granulation and direct compression techniques to ensure a stable and quality product.

KEYWORDS: Demixing, mixtures, impaction mixer, blend uniformity.

INTRODUCTION:

Over recent decades the pharmaceutical processing has undergone a rapid transition from being 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 of all solid dosage forms which involves powder mixing and it has a critical contribution in achieving uniformity of content. An understanding of powder characteristics and behaviour is essential to control these operations.

Mixing is defined as shuffling type unit operation process involving both large and small particle groups and even individual particles¹. Mixing is energy consuming process which produces a random distribution of particles. It is dependent on the probability that an event happens in a given time and once the desired mixing has been attained, it is essential that the particles in the mix cease movement so that the system may exist in a state of static equilibrium without segregation. Some of the parameters affecting efficient mixing are:

a) Particle parameters like particle size, particle shape, size distribution, particle density, cohesivity, hygroscopicity and hardness.

b) Type of mixer: Speed, time, batch volume and movement

c) Segregation tendency of individual components based on density difference².

This review explores the nature of the mixture formulations and tries to draw conclusions for the selection of a suitable mixer for the manufacture of quality and stable products.

DRY MIXING:

Mixing of solid powders has gradually evolved from being an empirical process to being a meticulously controlled process. Much of the scientific understanding of mixing process has emerged from the behaviour of non-cohesive binary particulate systems. For mixing to occur the individual particles must be redistributed repeatedly within the bulk, either by tumbling, shearing, scooping, kneading or impaction. When the powder particles are freely distributed within the bulk, there will be formation of either free flowing or non-free flowing (cohesive) mixtures depending on the particle size. Particles of larger diameter tend to be free flowing and particles of small diameter tend to be cohesive due to inter particulate forces associated with the individual particles.

Significant strides have been made in understanding the dry mixing process. This includes use of powder flow analysers³ and computers. Recent studies have also established the use of Near Infra Red Spectroscopy (NIRS) and UV- Spectroscopy which can be utilized to ensure the homogeneity of powder mixture (Fig-1).

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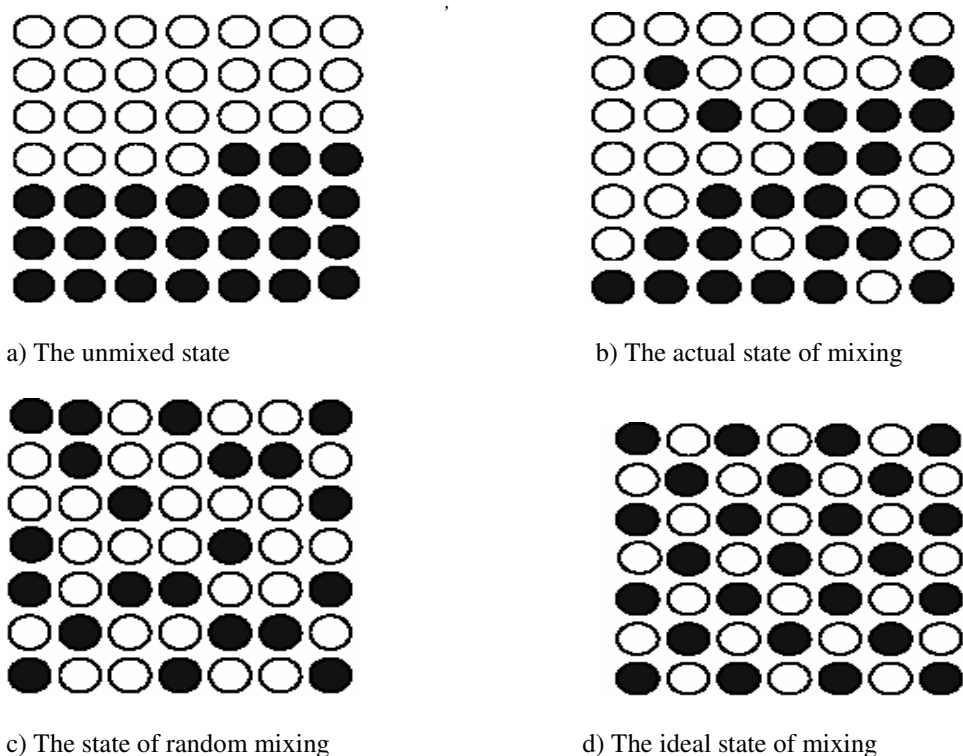


Figure 1: Visualization of the different qualities of mixing

TYPES OF MIXTURES:

a) Free flowing mixtures

Free flowing powders have desirable features like minimal need of lubricant and effective contact with die cavity. They suffer from a serious drawback of segregation of individual components in post mixing processing. The particles can move smoothly and independently in a particular direction due to the interparticulate forces. The free flowing powders need to be handled and stored in a proper manner by packing the products in polythene bags and applying vacuum, before sealing.

b) Cohesive mixtures

The cohesive mixture exhibits “stick-slip” characteristics and the components are not free flowing, the individual particles are repeatedly broken down and allowed to redistribute within the system to ensure a satisfactorily mixed product. The scale of segregation is less, but the intensity of segregation will be more due to the retaining of structure by the small agglomerates throughout the mixing process⁴. Some of the parameters contributing to the formation of cohesive mixtures are moisture, electrostatic charges, Van der waals forces and solid bridges between the particles.

c) Ordered mixtures

If one of the constituents of the powder mix is added to a fine, micronized form then on mixing the larger particles may adsorb some of these smaller particles to active sites on their surface where they are held tenaciously⁵. Ordered mixtures are formed by mechanical, adhesion or

coating forces such that the ordered unit will be the smallest possible sample of the mix and will be of near identical compositions to all other ordered units in the mix.

MECHANISM OF MIXING:

Mixing involves the following steps -

- Convective movement of relatively large portions of the bed (Macromixing)
- Shear failure, which reduces the scale of segregation
- Diffusive movement of individual particles (Micromixing)

A quantitative theory was developed to describe mechanism of mixing in particulate systems in which one component is present only in a trace quantity. Theoretical expressions were derived to predict the role of mixing of the drug moiety.

SEGREGATION OR DEMIXING:

All powder mixture have variable tendency to separate during the processing, which can result in poor quality product. Reasons responsible for demixing are, (i) difference in particle size of various constituents (ii) density differences of various constituents (iii) drug-excipient interaction (iv) degree of agglomeration⁶

The three main mechanisms for segregation of powders are:

Percolation: In a packed bed of powder, gravity causes small particles to move into the voids between larger particles, due to relatively larger differences in particle size.

Vibration: Upon vibrating of a bed of powder, smaller particles will gradually move under the bigger ones and thus lead to a separation of the differently sized particles. It is this phenomenon that causes heavy objects (e.g. stones or aircraft bombs) to rise slowly in beds of sand or soil upon repeated cultivation of the land.

Transportation: During the transport of powders, the particles will be constantly accelerated and decelerated, due to differences in trajectories of particles with different masses and/or sizes these particles will be separated during transportation. Similar effects happen when such powders are poured on a heap. The heavier particles will roll to the outside of the heap while the smaller concentrate in the centre of the powder heap. The shape of the particles also plays an important role during this type of segregation process. Special precautions must be taken during handling of these powders by reducing the transportation velocity or the falling height segregation is minimized.

EVALUATION OF POWDER MIXTURE:

Mixing process is critically affected by a multitude of parameters like mixing time, mechanism of mixing, type of mixer and batch size⁷. Various methods have been developed to quantify the quality of mixture.

MIXING INDEX

There is always some variation in the composition of the samples drawn from a random mixture and the standard deviation in the composition of large number of such samples can be determined, provided an accurate assay method is available⁸. A random mix gives samples with low standard deviation as compared to mixture of the same components that have not reached the random state. This phenomenon is used to define mixing index, which is expressed as,

$$M = S_r / S_{act}$$

Where, S_r is the Standard deviation of samples drawn from a fully random mix

S_{act} is actual Standard deviation determined on the partially mixed system.

SCALE OF SCRUTINY

Danckwert established the concept of scale of scrutiny which describes the minimum size of the regions of segregation in a particular mixture which would cause it to be regarded as insufficiently mixed. A poor mixture will have large scale of segregation and high intensity of segregation and vice versa. As the scale and intensity of the mixture is reduced the mixture passes from a stage of being unsatisfactory to satisfactory mixture.

A study revealed that the surface energy of the powder particles can be utilized to ensure the powder mix uniformity⁹. There is also change in surface energy with respect to size reduction or milling which in turn affects the uniformity of the powder mix^{10,11}. The quality

assessment of the mixture is only valid at that scale of scrutiny.

MIXER SELECTION:

An ideal mixer should be capable of producing complete blend in reasonable time without damaging the product. Additionally it should be dust-tight, require low maintenance and energy, can be discharged and cleaned easily. All these properties cannot be found in a single mixer. However, a logical selection of a mixer can be done based on -

- Powder characteristics of the constituents of the mixture
- Quality requirements of the product
- Process requirements and limitations.

Additionally the following points need to be considered, to ensure overall success of a mixing process -

- i. Does the mixer have flexibility to cope with a variable batch size?
- ii. Can the mixing vessel can be transported between the operations like loading, mixing, packaging?
- iii. Does it have easy access for sampling?
- iv. How well can the mixer separate the process materials?
- v. Does the mixer require frequent cleaning? If so what are the standards?
- vi. What should be the nature of the mixing surface?

The effectiveness of a mixer depends on the powders to be mixed, the time of mixing, number of rotations of the mixer and other factors, which may be characterized by complex mathematical relationship¹². The performance of the mixers can be predicted by using different powders with the general theory of powder mixing¹³ using Powder mixing monitor¹⁴ (POMM). (Fig-2).

BLEND UNIFORMITY- REGULATORY VIEWPOINT:

In response to the concerns by ANDA applicants regarding inconsistency review in chemist's recommendations, the US FDA published draft guidance in August 1999 for blend uniformity analysis¹⁵. The FDA indicated that there is a strong need for routine blend uniformity testing following process validation to ensure content uniformity within the blend. It is insufficient to show that adequate distribution of the drug is obtained in the final product; it must be demonstrated within the blend also. This guidance gives the basics of the powder mix and the representative sample¹⁶. The sample was based on thief blend and if the % RSD is less than 1, then the sample passes the test. The FDA guidelines state that the USP criteria for content uniformity are 85-115%. But the industry standard for the Blend uniformity is 90-110%. Following the FDA guidelines makes the validation process difficult^{17, 18}. So to make the task easy for validation, a range of 90-110% is necessary.

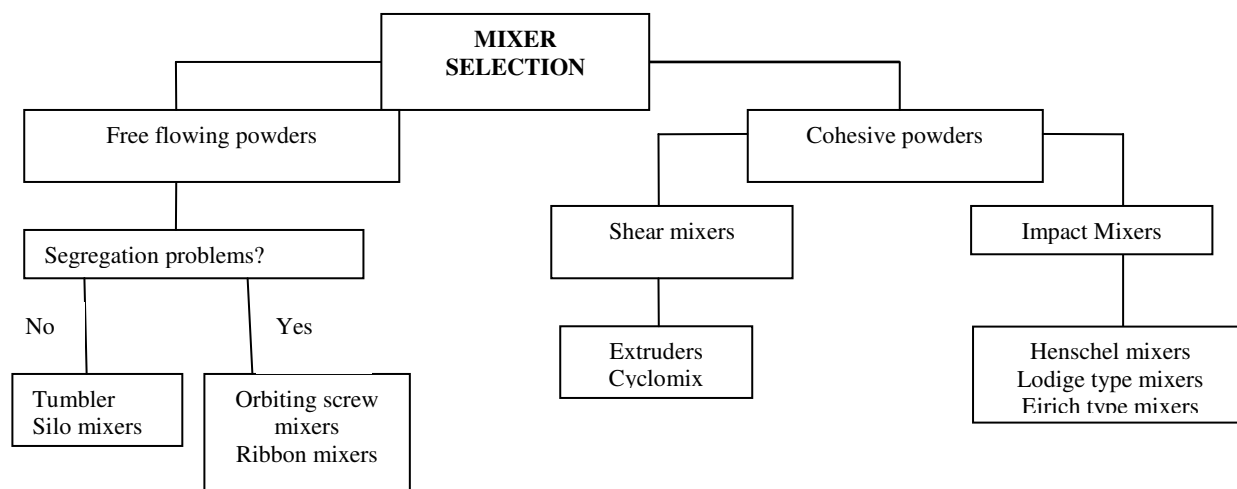


Figure 2: Simplified mixer selection chart

But the important questions to be answered are,

- i) How can one obtain a truly representative sample if the particles are of different size and with different materials?
- ii) How can one get a true sample based on the existing sampling methods?

To overcome above problems, sampling methods are given keen consideration¹⁹.

There are two types of sampling, namely Stratified sampling and Nested sampling.

Stratified sampling is the process of selecting samples deliberately from various locations within a lot or batch or from various phases of a process. This type is especially targeted to mixing in blender or in compression, which have a higher risk of failure in content uniformity. Nested sampling is the process of selecting samples from one particular location within the system.

To obtain a truly representative sample the following golden rules must be emphasized.

1. A powder should be sampled when it is in motion
2. The whole stream of powder should be sampled for short increments of time, instead of part of the stream being sampled for the whole time²⁰.

The powder mixture cannot be sampled from moving stream because of

- The configuration of the mixer
- Size of the batch
- Possibility of mixture segregation biasing the sample.

So one is left with two options. They are

- Scoop sampling of the bulk mixture or
- Thief probing of the bulk mixture.

Thief probing is preferred because the samples can be taken from deep within the powder bed and a reasonable degree of random sampling is achieved. Even a small diameter Thief probe is available which eliminates the process of segregation. A four-thief probe design was found out for effective sampling. Thief sampling is not always predictive of the uniformity of the drug content of the finished dosage forms. Blending validation has become mandatory partly through GMP and through court action (The Barr decision). With the existing technology, one such situation, where the methodology for sampling causes bias is content uniformity, especially if the blended materials are not cohesive^{21, 22}. Also core sampler can be used for effective sampling from the vessel without disturbing the column of the powder. In commercial blenders multiple cores are used to characterize blend homogeneity which in turn used to determine the content uniformity accurately²³. Modified "Pneumatic Lance" is also utilized for sampling but this causes segregation of samples partly²⁴.

The root causes of blend or product content uniformity problems³⁷ are,

- 1) Non-optimum blending²⁵
- 2) Thief sampling error²⁶.
- 3) Segregation²⁷
- 4) Weight control²⁸
- 5) Loss of component²⁹
- 6) Analytical error³⁰
- 7) Insufficient particle distribution³¹.

Sequential steps have to be followed to troubleshoot such problems^{32, 33}. A new statistical approach was proposed to evaluate blend-sampling errors and a systematic method is established for in process blend test. Blend sampling errors plays an important role in formulation of dosage form where blend homogeneity is must^{34, 35}.

The sample thief is the state -of-the- art powder sampling technology used by the pharmaceutical industry today for the purpose of Blend Uniformity Analysis. Unfortunately, sample thieves are intrusive devices that are prone to sampling error³⁶.

From the blenders, the samples should be selected from at least two depths along the axis of the blender. For convective mixers the corners and the discharge port are preferred.

The standards³⁷ for blend uniformity is as follows:
 Readily passing -RSD is less than 4%
 Marginally passing-RSD is more than 4% but less than or equal to 6%.
 The limit in both the cases is 90-110%.
 The USP Standard is 85-115% and RSD is not more than 7.8%

CONCLUSION AND PERSPECTIVE:

To achieve a stable quality product the carrier particles must be large enough and the electrostatic charge interactions must be controlled in a segregating system. The final selection of the mixer is based on the mixture meeting the quality requirements and the mixing equipments meeting the specific requirements of the product. But the quality regulation and the process approval are the limiting barrier to this step. Proper selection of the mixing mechanism based on the particle size, shape and density of the substance to be mixed, speed, bulk volume and time of operation of the mixer should be optimized to get a uniform mixture. Joint research and development between the pharmaceutical manufacturers and mixing equipment suppliers are needed to ensure that they will also be capable of meeting the requirements of the future.

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