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Prediction of mixing efficiency of pharmaceutical granules

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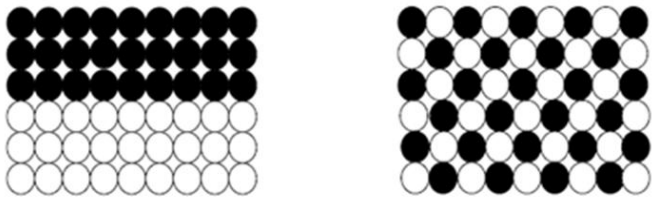
Abstract
Mixing of ingredients, or dispersion of one phase into another, is an operation widely and most commonly used in pharmaceutical Industry. It is difficult to find a pharmaceutical product in which mixing is not done at one stage or the other during its manufacturing. Whenever a product contains more than one component a mixing or blending stage is must required in the manufacturing process to ensure even distribution of active ingredients, to ensure an even appearance, to ensure that he dosage form releases the drug at the correct dose at the desired rate etcA pharmaceutical formulation with low amount of active ingredient will be in effective or with too high amount of active ingredient may be lethal. So, mixing is very important process and the final mixture required should be completely mixed and homogenous for such type of formulations

Keywords: Prediction, pharmaceutical granules, homogenous

Introduction
Mixing is defined as the intermingling of two or more dissimilar portions of materials resulting in attainment of a desired level of uniformity either physically or chemically or 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 particles of other ingredients or components. The most important use of mixing is the production of a homogeneous blend of several ingredients which neutralizes variations in concentration using the minimum amount of energy and time.

Mechanisms of solid-solid mixing
Mixing is defined as the intermingling of two or more dissimilar portions of materials resulting in attainment of a desired level of uniformity either physically or chemically or 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 particles of other ingredients or components. The most important use of mixing is the production of a homogeneous blend of several ingredients which neutralizes variations in concentration using the minimum amount of energy and time.

Mechanisms of solid-solid mixing
The homogeneity of the solid-solid mixing and mixing quality is determined pharmaceutically by mixing time. The mechanism of mixing process of solids can be of *dispersive* or *convective.* Dispersive mixing is mainly intended for the completely random change of place of the individual particles. If the ingredients are spatially separated at the beginning of the process, long times will be required to mix them through dispersive mixing alone, since there is a very low number of assorted neighbors.
Convective mixing causes a movement of large groups of particles relative to each other and is also a sort of macro mixing. Convection increases the number of assorted neighbors and thereby promotes the exchange processes of mixing. A material mass is divided up or convectively mixed through the rearrangement of a solid‟s layers or by the fall of a stream of material on another layer. The whole volume of material is continuously divided up into groups and then mixed again. The forced convection can be achieved by rotating element paddles. The dimension of the groups, which are composed of just one unmixed ingredient, is continuously reduced due to splitting action of the rotating paddles.



(a) Randomly unmixed (b) Perfectly mixed

Fig. 1.2 Potential mixing states of a two component mixture

Prediction of mixing efficiency

The standard method used for predicting mixing efficiency involves physical sampling from depth of the mixture. [2] It is a three dimensional, completely manually operated, irreversibly invasive method. In physical sampling, dealing with the solid particles, samples are withdrawn manually from time to time from the mixture and the statistical variation in composition among samples is commonly used as a measure of degree of mixing. Depending on the statistical requirements, the sample size is about 4-50 g in case of μm particles. Using particles of millimeters sized, the sample mass needed to make an exact statistical statement on the basis of the measurements will amount to several hundred grams or even kilograms. Consequently, the methods presently applied to determine the mixing efficiency of millimeter sized particles are characterized by the mixer having to be emptied completely. As emptying completely can leads to demixing or change in mixture state, no conclusions can be drawn with respect to the mixing efficiency in the mixer. [7]

Whatever if mixing quality is measured on basis of variance values"σ^2", which reflects the homogeneity of a mixture and the extent to which mixing of solid particles have take place. The proportion of particles of each color is calculated from samples taken from various spots.

Depending upon the values of σ^2 from no. of various particles, Lacey index 'b' is calculated for analyzing the mixing index. [8] This method relies on sampling, and calculating how well each compound is present in the sample. This is a measure of mixing effectiveness of a solid-solid binary mixture on the basis of both continuous and binomial variances σ^2.[9] to calculate the variances 'σ_z^2' of a complete random mix of uniform particles, distinguishable by color, following equation is applied:

$$\sigma_r^2 = \frac{p(1-p)}{n} \qquad \text{Equation (1)}$$

Where "p" is the overall proportion of particles of one color, and "n" is the number of particles in each sample.

At t =0, a completely unmixed randomized material, variance "σ_δ^2" will be indicated as per following equation:

$$\sigma_\delta^2 = p(1-p) \qquad \text{Equation (2)}$$

The variance 'σ_z^2' at any time (t), can be calculated by same equation (1) for samples taken at different time. When a material is partially mixed, then the degree of mixing or mixing index "b" may be defined as:

$$b = \frac{\sigma_\delta^2 - \sigma_z^2}{\sigma_\delta^2 - \sigma_r^2} \qquad \text{Equation(3)}$$

According to above equations, mixing index (b) should be equal to "0" for an unmixed material and "1" for a completely randomized mixture.

For a multi-component mixture, the variance of constant sample mass by physical sampling is time-dependent and can be calculated by some other types of variances like stochastic variance ('σ_z^2'), measurement variance ('σ_m^2') and systematic variance ('$\sigma_{Syst.}^2$').

Stochastic variance ('σ_z^2') calculate the ratio between the mass fraction of the any one component and the residual fraction of the total mixture. The measurement variance ('σ_m^2') is calculated from the preliminary tests and denotes the reproducibility of the mixture. The systematic variance ('$\sigma_{Syst.}^2$') has the value 0 in the stationary state and it denoted the completion of the mixing process or completely randomized mixture. [10] A good review about these various variances can be found from the work of Daumann et al.

The variance calculated by using Lacey index (b) is much easier and simplified to calculate or processed as compared to other types of variation discussed above. So, that we used the lacey index equation to determinethe mixing efficiency in our experimentation work.

In manual procedures, physical sampling of mixture is done while keeping in mind the 3D aspects of mixture. No doubt, the maximum accuracy in predicting mixing efficiency can be obtained by these physical methods, but still these are very laborious and time consuming procedures. The speed of prediction of mixing efficiency can be much more increased by switching from 3D sampling to 2D sampling and that too in a non-invasive manner. The digital images are among such 2D samples, which can allow mixing efficiency calculations from surface analysis. The mixing efficiency is predicted in physical sampling by number fractions or weight fractions. Similar type of fractions and then variances can be calculated from 2D surface images also. It is aim of current study to find out whether the same purpose can be fulfilled by the 2D surface images or not. Further, in physical sampling, samples withdrawal manually requires stopping of mixer and causes disturbance to mixture, sometimes it may also require complete discharge of mixture from the mixer. These all difficulties with the 3D sampling can be avoided by using the 2D images. The analysis from images is known as image analysis and it can be completely automated for mixing processes and does not causes any disturbance to the mixture. In addition, image analysis methods offer several advantages *viz* storage of data for future access, equal applicability in small and large processing lots, options for real time studies, and generating feedback loop system for automatic control of mixing process. Due to the advantages we have planned to study image analysis method to predict the mixing efficiency of solid particles against standard physical sampling method.

Advantage of Image Analysis

Image analysis methods offer several advantages *viz.* storage of data for future access, equal applicability in small and large processing lots, options for real time studies, and generating feedback loop system for automatic control of mixing process. Due to the advantages we have planned to study image analysis method to predict the mixing efficiency of solid particles against Standard physical sampling method.

The images will be taken from the surface of the binary mixer by a digital camera at various intervals Instead of manual sampling and will be processed and analysed. It is being expected that the 2D images can serve the same purpose as that of manual sampling without any disturbances to the mixture. For image analysis the particles used for mixing should be of different colors but should be differentiable, e.g. color particles. The objective of present study is to calculate the mixing efficiency by both image analysis and physical sampling and then comparing them for equivalence studies on the basis of correlation/similarity.

Work Envisaged

Rational of study

The main objective of this proposed work was **t**o study mixing efficiency of the mixture of two different colored pharmaceutical granules by image analysis and physical counting methods and then to correlate the results of both methods to examine the usefulness of image analysis method of predicting mixing efficiency.

Objectives of work

To find out the mixing efficiency of solid/solid mixture by physical sampling and image analysis method Correlation and comparison of manual and image analysis technique.

Plan of work

The following plan of work was proposed to achieve desired goals/objectives.

1. Literature survey

2. Selection of particle material
a) Selection of spherical particles
b) Selection of non-spherical particles

3. Mixing experiment
(a) Mixing experiment by physical sampling
(b) Mixing experiment by image analysis
(c) Mixing experiment by mixed procedure

4. Comparison of methods
(a) Correlation analysis
(b) Optimum mixing time

(c) Error analysis
(d) Similarity test (f_2)

Materials
Black/yellow color mustard seeds were purchased from local market, Rohtak. Precipitated calcium carbonate was purchased from Avantor Performance Material Ltd., India. Shellac flakes, ethyl alcohol were purchased from CDH, New Delhi, India. Ethyl alcohol used was of analytical grade. All chemicals used were at least lab grade

Equipments

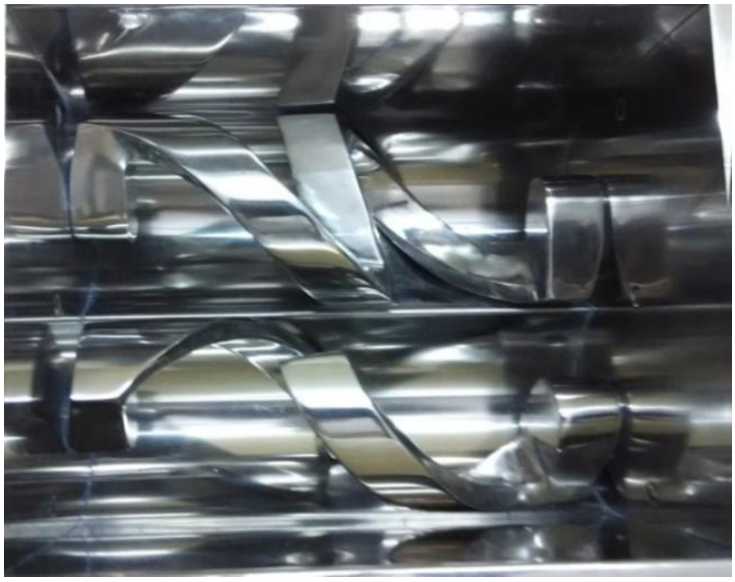
Sigma mixer	Make by Shakti Pharma Tech., Ahmadabad, India
Blender	Rolex Double Cone Blender
Sieves	Set of sieves from sieve no. 22-30 of BSP
Weighing balance	Analytical weighing balance
Digital camera	SLR camera fitted with 18-55 mm zoom lens (make by Sony Nex-5, Thailand)

Selection of mixing particles
As the image analysis method was studied for determining the mixing efficiency of millimeter sized particles; both spherical as well as non-spherical particles were considered for mixing experiments in 1:1 wt% proportion.

Selection of spherical particles
Mustard seeds of two different colors (yellow and brown) were used as spherical particles because mustard seeds are of equal and uniform size and can be differentiated from each other easily by color.

Selection of non- spherical particles
For non-spherical particles, pharmaceutical granules of calcium carbonate (white and blue) were prepared by wet granulation method using 30%w/v ethanolic solution of shellac as granulating agent. The wet mass was passed through a set of 22-30 BSS sieves and dried in air for 8h. The dried pharmaceutical granules were further passed through same sieve set in order to get double refines 22-30 sieve size granules for mixing experiment.

Mixing Experiments
Mixing experiment by physical sampling
The mixing experiment was carried out in a R&D scale sigma-mixer (Make: Shakti Pharma Tech, model no. SHMD-AC, CE) fitted with camera at a fixed length for capturing images. At time$t$ = 0s, equal wt. of both yellow and brown color seeds were placed in two layers depicting total unmixed state. The mixer was started and operated at a speed of 45 rpm and sampling was done physically at fixed time intervals of 20s up to 300s and then at every 300s up to 3000s. These spots were uniformly distributed throughout the mixing surface, such that adjacent sampling points were not affected by sampling and were at maximum distance from each other. After sampling black and yellow particles were counted in each sample and there fractions were calculated for calculating further variance values "$\sigma r2$". The "$\sigma 0$ 2" was calculated from t = 0s readings. After calculating variances, mixing index "b" was calculated. The experiment was performed five times in order to report error values. The experiment was repeated under same conditions for non-spherical (pharmaceutical granules) particles except for different sampling time intervals, i.e. 2s up to 20s, then 4s up to 60s, followed by 8s up to 100s and 12s up to 160s and at last 16s up to 208s.



Sampling points in the Sigma-arm mixer

Mixing experiment by image analysis
As the mixer was fitted with SLR camera, so images were also captured at all sampling time points just before physical sampling. Thus for the mixing analysis, sampling was done by images at same time points used for physical sampling. The camera was pre setted at; focal length of 4.5mm, shutter speed of 1/8s and at a fixed distance of 1.5 feet from mixture surface. The resolution of each digital image was 4592×3056 pixels. After taking images, images were processed through various steps to finally calculate the value of mixing index "bIA". Steps adopted for calculating mixing index were:

Image processing and "Mixing index" calculations
Image J 1.34S software of the National Institute of Health, USA was used for processing of images of mixture [5]. On each image, sampling spots as shown in Fig.3 were selected and then converted into binary spot images. The black and white area fractions were calculated using "*set measurement"* command of software under "*Analyze tab"*. The "$\sigma r2$" and "$\sigma 02$" were calculated using area fractions followed by calculation of "bIA". The results were reported as average "bIA" values *vs*. time. The flow chart of procedure for digital image processing for area fraction measurements is given below

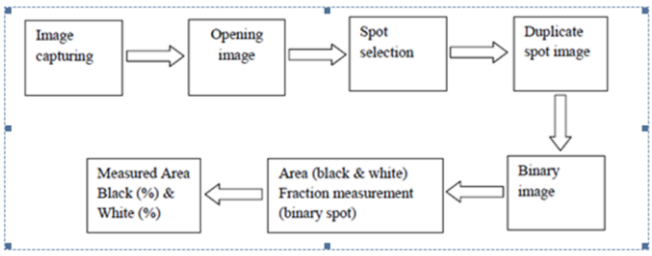


Fig.4.2 Flow chart scheme for area fraction measurement in Image J software

Mixing experiment by mixed method
In addition to physical sampling and image analysis, intermediate method involving manual counting of different

particles from digital images was also carried out. Mixing index "bMM" was calculated on the basis of numbers of particles counted from image manually. This also resulted into a number based Mixing index "bMM" and the results were reported as "bMM" value *vs.* time.

Comparison of methods

Correlation analysis

Various "b" values calculated above by physical sampling, mixed method and image analysis were correlated with each other for explaining the usefulness of techniques. Among these methods physical sampling was the reference method and image analysis was the test method. The correlation coefficients (r) were calculated for the "bi" values obtained for all the three methods. A value of correlation coefficient greater than 0.9 was considered as a highest level of correlation between the methods.

Similarity test (f2)

A similarity test f2 was applied for comparison of data sets obtained for various methods. The f2 value is a point-to-point comparison of values at common time points. The method is based on calculation of residual values and gives quantitative comparison instead of qualitative or graphical comparison. The general equation for f2 value is represented as follows:

$$f_2 = 50 \times log \times \left(\left(1 + \frac{1}{n} \times \sum (r - t)^2\right)^{-0.5}\right) \times 100$$

Where n is no. of samples, r is reference "bPS" value and t are test "bi" values. The f2 value>50 describes the similarity of two data sets while the value<50 indicates dissimilarity between data sets.

Optimum mixing time

The optimum mixing times were predicted by tangents intersection point in "bi" *vs.* time graphs for both spherical and non-spherical particles. The intersection point described the time, where mixing is maximum or variation is minimum. So, comparison of optimum mixing times from various methods acted as a parameter for setting usefulness or non-usefulness of test methods.

Error analysis

The %CV was calculated from repeated experiments using formula given as:

$$\%CV = \frac{SD}{Avg.\text{"}b\text{"}} \times 100$$

Where SD = Standard Deviation.

Result & Discussion

Mixing by physical sampling

The data set of mixing index (bPS) for five independent mixing experiments involving spherical and non spherical particles have been given in Table 5.1 and 5.2. The value of mixing index "*b*" are >1 for spherical particles and < 1 for granules or non-spherical (granules) particles. This variation in standard deviation (SD) (Fig. 5.1 & 5.2) for spherical particles is almost half as that for non-spherical particles. The difference may be spotted due to the lackness of sphericity in granules as compared to spherical particles, which might have created difficulty in mixing in case of non-spherical particles.

Mixing by mixed method

The data set of mixing index "bMM" for five independent mixing experiments involving spherical and nonspherical particles have been given in Table 5.4 and 5.5. The value of mixing index "bMM" are >1 for spherical particles and < 1 for non-spherical (pharmaceutical granules) particles.. The difference in SD is not so large, hence, both spherical and non-spherical mixings are appearing similarly predicted by mixedmethod.

Mixing by image analysis

The data sets of mixing index "bIA" for five independent mixing experiments involving spherical and nonspherical particles have been given in Table 5.5 and 5.6. The values of mixing index "bIA" are >1 for both spherical and non-spherical particles. The SD values (Fig. 5.7 & 5.8) are somewhat larger for non-spherical particles than spherical particles, however the difference can be considered small as compared to original values at this high significant figures level.

Comparison of methods

Correlation analysis

The correlation coefficients "r" between various methods for spherical particles have been given in Table 5.7. The "r" was found to be 0.5 between image analysis and mixed method while the "r" value was >0.9 for both physical sampling *vs* image analysis and physical sampling *vs* mixed method. This shows that standard physical sampling method and image analysis method are equivalent with each other For non-spherical, correlation coefficient "r" was found to be >0.9 between all methods indicating good correlation between all methods. On an overall, the value of "r" was greater for the image analysis method as compared to mixed method, so image analysis is more similar/equivalent to standard method and can be used for predicting mixing efficiencies.

Table 5.7 Correlation coefficient "r" between various methods for spherical particles

	Physical sampling	Mixed method	Image analysis
Physical sampling	-	0.99997	0.999987
Mixed method	-	-	0.504234
Image analysis	-	-	-

Table 5.8 Correlation coefficient "r" between various methods for non-spherical particles

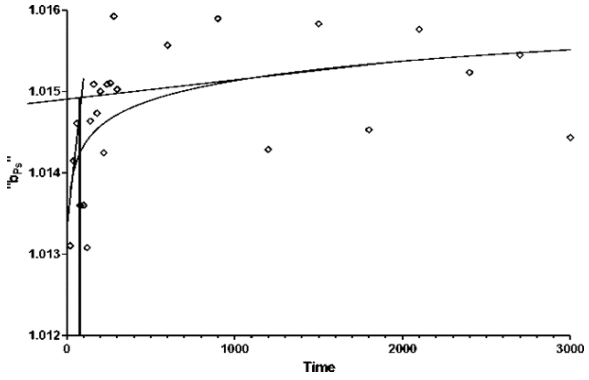
	Physical sampling	Mixed method	Image analysis
Physical sampling	-	0.999927	0.999941
Mixed method	-	-	0.999909
Image analysis	-	-	-

Optimum mixing time

Mixing time for spherical particles

The values of optimum mixing time for spherical particles was found to be about 70s, 60s & 70s by physical sampling,

mixed method and image analysis method. The mixing time is quite similar for standard physical method and image analysis method.



Optimum mixing time by mixed method for spherical particles

Mixing time for non-spherical particles

The values of optimum mixing time for spherical particles was found to be about 24s, 12s & 15s by physical sampling, mixed method and image analysis method (Fig. 5.12, 5.13 & 5.14) respectively. The mixing time predicted by image analysis and mixed method is appearing half as that predicted by physical method but still optimum mixing time by image analysis is more near to that predicted by standard physical sampling. Therefore, image analysis is again better method, which can gives result near to standard method.

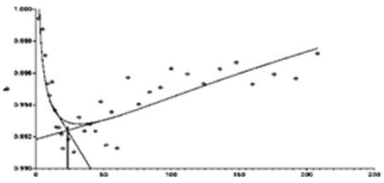


Fig. 5.2 Optimum mixing time by physical sampling for non-spherical particles

Error analysis

The graphical plot of %CV for all the three methods have been shown in Fig. 5.15 and 5.16 for spherical and non-spherical particles respectively. The variation in %CV of image analysis method is least among all for both spherical and non-spherical particles. This indicated stability of image analysis towards predicting mixing efficiency. Further the profile of %CV of image analysis is matching with physical sampling indicating similarity of image analysis method with standard method. The variations in mixed method were deviating by large, so method was not considered useful.

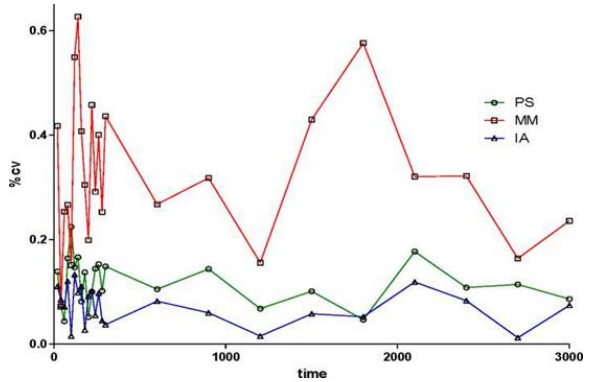


Fig. 5.3 % Coefficient of variation (%CV) of mixing indices for spherical particles by various methods

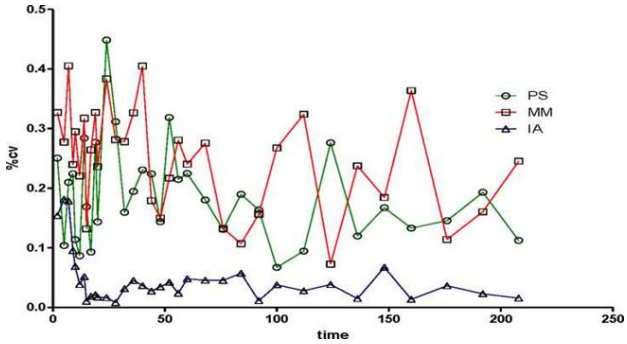


Fig 5.4 % Coefficient of variation (%CV) of mixing indices for non-spherical particles by various methods

Similarity test (f2) analysis

The similarity factors (f2) between various methods for spherical and non-spherical particles have been given in Table 5.9 & 5.10. The f_2 value were found to be >50 for all methods. This shows similarity between all methods. On an overall, the "f2" value was greater for the image analysis method as compared to mixed method for both spherical and non-spherical particles, so image analysis is maximum useful for predicting mixing efficiencies.

Table 5.9 Similarity factor "f_2" between various methods for spherical particles

	Physical sampling	Mixed method	Image analysis
Physical sampling	-	96.27	123.86
Mixed method	-		93.59
Image analysis	-	-	-

Table 5.10 Similarity factor "f_2" between various methods for non-spherical particles

	Physical sampling	Mixed method	Image analysis
Physical sampling	-	112.32	114.72
Mixed method	-	-	107.99
Image analysis	-	-	-

Summary & Conclusion

In this work, the mixing efficiency of solid-solid mixing of two different color particles by means of the mixing index at different time intervals was calculated. For this particular purpose, Mixing index was calculated by using different methods i.e. physical sampling, mixed method and image analysis method. All the methods used for predicting mixing efficiency was compared and correlated with each other.

The two types of particles; spherical and non-spherical particles were taken for mixing experiment. Mustard seeds (yellow and brown color) were selected as spherical particles and pharmaceutical granules (white and blue color) were used as non-spherical particles. Methylene blue dye was blended with calcium carbonate blue color pharmaceutical granules. The mixing experiment was firstly done by spherical particles in a sigma-arm mixer. The speed of mixer was fixed at 45 rpm and sampling was done at prefixed time points. The samples were taken from five different locations within the mixer. The experiment was repeated five times for average value. The above experiment was also performed separately for non-spherical particles in a similar manner as that for spherical particles.

The no. based fraction of particles were calculated for physical samples and mixed methods. The area fraction of particles was measured with the help of Image J software for image analysis method. From the above fractions, the mixing

index “bi” were calculated and used for relating different methods.

All the methods used for mixing efficiency prediction were compared with each other by means of Correlation analysis, optimum mixing time calculation, error analysis and similarity test applied on “bi” values. For spherical particles, the value of correlation coefficient “r” was >0.9 for physical sampling vs image analysis and physical sampling vs mixed method and 0.5 for image analysis and mixed method. For non-spherical particles, the value of correlation coefficient “r” was found to be >9 between all the methods.

The highest values of “r”were found for physical sampling vs image analysis. Hence, image analysis can be used instead of mixed method.

The mixing time calculated from tangent intersection points showed that in case of spherical particles, as well as non-spherical particles, image analysis was the For spherical and non-spherical particles, the %CV was found to be least for image analysis method. The variations in mixed method were deviating by large, so this method was not recommended.

The values of similarity factor “f2” between all the methods were found to be > 50 for both spherical and non-spherical particles which showed the similarity between methods. The image analysis method showed highest similarity with standard method (physical sampling), hence finished for considering as replacement for standard physical mixing method.

It is concluded that the image analysis method is similar to standard physical sampling method in predicting mixing efficiency. So, we can use the image analysis in place of physical sampling method. The use of image analysis in place of physical sampling makes the experiment very simple and easy and non-invasive.

In addition to this, image analysis having so many other advantages over physical sampling makes itself a best method.

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