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MONITORING HOMOGENEITY

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ABSTRACT

Homogeneity or dose uniformity is an increasing problem in pharmaceutical technology. Sampling is considered from the practical viewpoint, since this is the most neglected area in the literature. The methods of expressing dose uniformity results are considered and homogeneity, rather than heterogeneity, is suggested as the most suitable solution. Problems of multicomponent systems and dispersed systems in continuous media are also outlined. The use of tracers in mixing problems is deprecated.

INTRODUCTION

Homogeneity is a complex problem having implications in the areas of process control and quality control of many pharmaceutical products. Few products of our industry require the direct marketing of a single physiologically active substance. Medicines, or pharmaceuticals, are mixtures or dispersions of one or more active

substances in, frequently, a large number of inert, or excipient, materials. The pharmaceutical industry markets pharmaceuticals. The subject of Pharmaceutics is the understanding of the problem created by the addition of other materials or excipients, to the active drug in order to produce a product in a suitable dose form. The problems encountered include stability, bio-availability and homogeneity.

Homogeneity is not only a problem in powder technology affecting powder mixtures and tablets, but extends to other areas including ointments, creams, aerosols, suppositories, suspensions, emulsions, etc., and may even extend to miscible liquid preparations.

SAMPLING

In order to assess homogeneity, it is necessary to sample the product. Total (100%) inspection is frequently impossible, since most tests performed are of a destructive nature.

Size of Sample

In pharmacy, perhaps the most simple definition in sampling is that of sample size - unlike some other industries. The size of sample must be fixed at the dose size, whether this is a single tablet, a suppository or a dose of an emulsion. This definition was established relatively early (1) in the growth of pharmaceutical technology. Dose size, however, may not always be

simple to define. The problem of halved, or even quartered, tablets involve both the error in the patient breaking across the score and reduction in dose size from that normally accepted and tested. One should be highly critical of such practices.

The dose of a topical preparation should be a relatively small area of thin film weighing down to, perhaps, 10^{-5}g (2). The number of analysts examining content uniformity of topical preparations at this level of scrutiny must, indeed, be small.

Type of Sampling

Should samples be taken according to an ordered or random sampling scheme? The answer depends largely on the purpose of the sampling. To check whether a process is in control and does not show cyclic or periodic variation requires an ordered sampling plan. Such a scheme should always be used whenever a new process is being adopted, or if any variation in the process is being tried, or when new ingredients are being used. To test if a product is attaining the required conformity, a random sampling scheme is better, giving a more valid estimate of the mean and standard deviation of the universe.

Attribute inspection, or inspection of defectives, whilst normally being non-destructive, is not such a useful scheme as variable inspection, where a smaller number of samples can be used to evaluate the number of outlying samples.

No. of Samples

The number of samples to be taken from a batch depends on the supplier's risk and consumer's risk levels and will be affected by the cost of sample analysis. These factors must be balanced. The more samples that are taken will give a greater accuracy in the estimation of the parameters of the universe. A sample size of 30 is usually accepted as a minimum number. The universe population has little influence on the sample size and it is, therefore, better to take a large number of samples from a very large batch size, rather than smaller lots of samples from a number of smaller batches.

Mechanism of Sampling

The actual taking of the sample can pose problems. Random sampling of finished products such as tablets should be relatively easy, providing a truly random pattern is used. Sampling of powder mixtures can be achieved using a variety of available designs of "thieves", but great care must be taken to avoid bias - which must always be checked. For example, fine particles may adhere to the "thief" and thus be omitted from the subsequent analysis. Solid and semi-solid dosage forms may be randomly sampled using a spatula after designing a random sampling plan. The technology of sampling is complex and considerably more attention must be paid to this aspect of quality control.

HETEROGENEITY

The Randomized System

Subsequent to the assays being performed, the results must be usefully expressed. For binary systems, the measured standard deviation, s, will be between the standard deviation of the completely unmixed system, σ_o and that of the completely randomized mixture, σ_R (assuming random mixing) (3,4)

$$\sigma_o^2 = xy$$

$$\sigma_R^2 = xy/N$$

where x and y are the proportions of the two ingredients X and Y

and N is the number of particles present in the mixture. The measured heterogeneity may thus be compared with the unmixed and/or completely randomized mixture in order to measure the degree of mixing. This is the basis of a number of mixing indices used in practice, (4-6)

$$M = \sigma_R/S$$

$$M = S/\sigma_R$$

$$M = \frac{\log \sigma_o^2 - \log S^2}{\log \sigma_o^2 - \log \sigma_R^2}$$

As the sample size is decreased, the number of particles, N, in the sample weight increases, giving a lower possible value for σ_R.

The use of such mixing indices are given by many workers (4-8). When $S/\sigma_R = 1$, the mixture has attained the theoretical completely randomized state. It might be expected that a mixing curve of S/σ_R versus time would approach this value asymptotically. When segregation, or demixing, occurs there is a deviation from lower to higher values of S/σ_R with increase in time of mixing. If particle size raduction occurs, as in many mixing machines, the curve may show a "better-than-random" situation, although this is probably due to the fact that the size reduction, increasing the number of particles present in the sample weight, has not been taken into account in the evaluation of σ_R.

In practice, the equations of Lacey for calculating the theoretical standard deviations of unmixed and random systems are only ideal solutions for binary systems of homosized particles. However, they may be extended to cover particle size distributions (9,10) and to multi-component mixtures. The particle size equation has also been simplified (5), viz.

$$\sigma_R^2 = xy \Big/ \frac{M}{x\Sigma(fd)_y + y\,\Sigma(fd)_x}$$

where M is the sample weight

and $\Sigma(fd)$ is the effective mean particle weight of that component denoted by the suffix.

Thus, multicomponent systems, in which each ingredient

occurs in a particle size distribution can be evaluated.

$$\sigma_R^2 = \frac{x^2}{M}\left[\left(\frac{1-x}{x}\right)^2 x\,(\Sigma fd)_x + y\,(\Sigma fd)_y + z\,(\Sigma fd)_z + \ldots\right]$$

where z is a third component and all other symbols are as before.

Allowances for each weight fraction of each ingredient are made in order to calculate Σfd for each material. This requires a preliminary particle size classification and density determination.

The required uniformity

An alternative to comparing the measured standard deviation, S, with that of the randomized mixture, σ_R, is to compare S with the standard deviation required by the product specification - either as required by a pharmacopoeial or an in-company standard, σ_A, (13).

For example, where tablets must lie between ±15% of the mean value then, at the $3\sigma_A$ level for tablets containing 1% of active ingredient

$$3\sigma_A = .15 \times .01$$

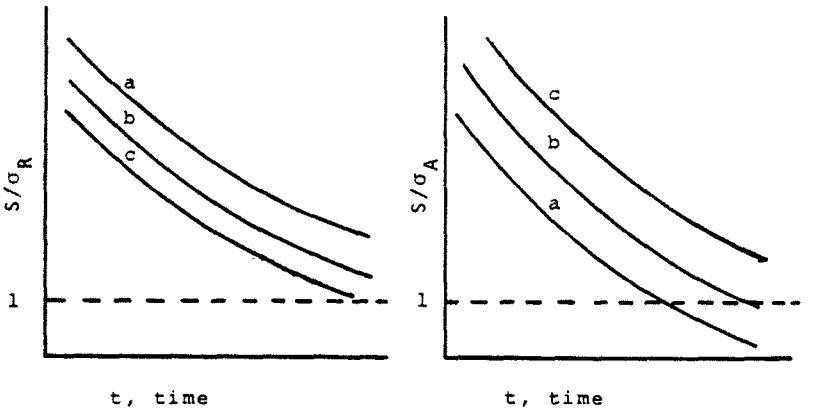
$$\sigma_A = .0005$$

For a comparison of values of S/σ_R with S/σ_A during mixing experiments for

a) different particle size of ingredients (Fig.1)

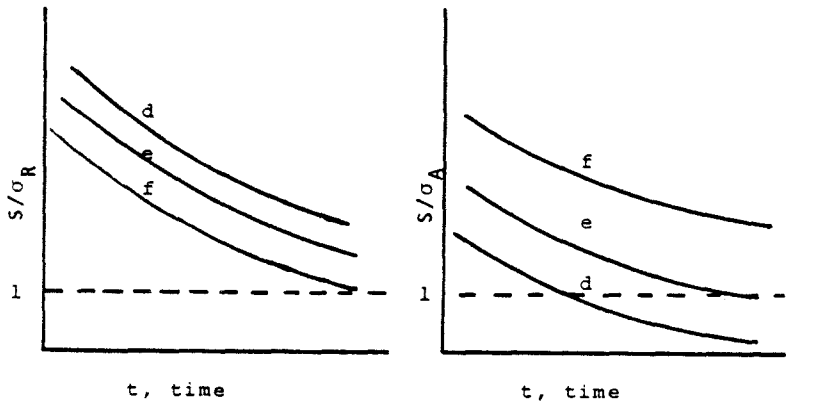
b) different proportions of ingredients (Fig.2)

see the appropriate figures. They show that coarse particles in high dilutions are easier to randomize, but



a fine particles, b medium and c course particles

FIG.1. Typical results of mixing of different particle size of ingredients.



d 1:1 mixture e 1:10 mixture f 1:100 mixture

FIG.2. Typical results of mixing of different proportions of ingredients

hard to mix to within specification. Thus, since the converse is also true, fine particles in equal proportions are chosen in practice, with serial dilution to ultimate proportions when necessary, in order to achieve the maximum degree of homogeneity.

Comparison of σ_R and σ_A enables a prediction of the mixing to be made. Where $\sigma_A - \sigma_R$ is high positive, there is a good chance of mixing to within specification in practice. Where $\sigma_A = \sigma_R$ or $\sigma_A - \sigma_R$ is negative, the product cannot be mixed to within specification. Such calculations are easily performed prior to a mixing operation and should be part of any exercise in establishing particle size standards for any product ingredient to be subjected to a mixing operation.

Use of tracers

At this point it might be interesting to look at a practice used for following powder mixing in the pharmaceutical industry. Frequently, one ingredient in a multicomponent mixture is assayed and used to evaluate the whole condition of the mixture. The ingredient chosen is often a dye, which is relatively easy to assay using ultraviolet spectroscopy. Materials may also be added to pilot scale mixing operations for this purpose alone.

Analysis of each component in a multicomponent mixture has shown up to a 400 fold difference between

the actual coefficient of variation of one ingredient and that predicted by a chemically and physically similar ingredient acting as a tracer (14).

Individual components in a multicomponent mixture do not mix at equal rates and, whilst some are mixing, others may be segregating. The use of tracers must on this evidence, be condemned as being completely useless.

HOMOGENEITY

More recently, the introduction of a new concept (15) allows the results of mixing and content uniformity determinations to be compared with the absolute homogeneity of the system. The concept considers a definite degree of heterogeneity (say, a standard deviation of 1%) and that homogeneity may be expressed as the reciprocal of heterogeneity. By taking a fixed standard deviation, the sample size (W_1) necessary to give this deviation becomes the variable measured. Homogeneity (H) is then defined by the following equation,

$$H = \frac{1}{W_1}$$

or, an index of homogeneity (H_i) as

$$H_i = \log H = \log \frac{1}{W_1} = -\log W_1$$

Since a definite degree of variation is chosen, there is correlation between H_i and S/σ_A, where σ_A is the degree of variation necessary to meet the product specification. Conversely, there is no correlation between H_i and S/σ_R,

since σ_R is dependent upon the properties of the system being mixed, especially the particle size (16).

Homogeneity may be used as a basis for particle size calculations in pharmaceutical systems in the following manner. Consider a binary system, in which the ingredients (x and y) have been mixed to the theoretically completely randomized state, then

$$\sigma_R = \left[xy.\frac{w}{W}\right]^{\frac{1}{2}} \qquad N = \frac{W}{w}$$

where w = mean particle weight and W is the sample weight. If σ_R = 1%, then W = W_1 and

$$\frac{W_1}{10^4} = xy.w$$

(Note : the 10^4 term is introduced since σ_R is given as a percentage whilst both x and y are given as proportions)

then $H_i = -\log[10^4\ xy.w]$

However if $\sigma_R = \sigma_A$ (the desired degree of homogeneity)

then $\sigma_A = \left[xy.\frac{w}{W}\right]^{\frac{1}{2}}$

which on substitution gives

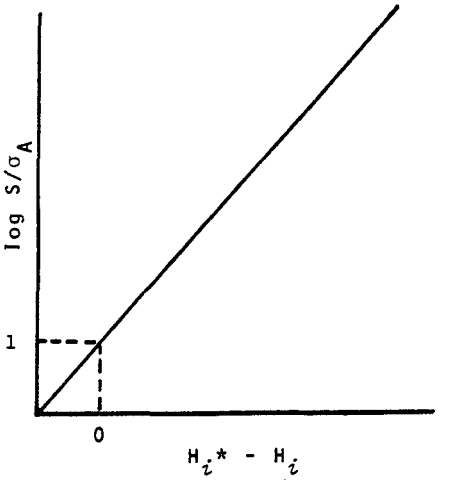
$$H_i = -\log[\sigma_A{}^2.W.10^4]$$

(Note : σ_A is not given in percentage terms here. If calculated as a percentage the equation reduces to $H_i = -\log[\sigma_A{}^2 W]$. Thus, knowledge of the standard specification will allow calculation of the index of homogeneity (H_i) and also the mean particle weight (w) and, hence, the mean particle size. This mean size is

recommended to be taken, in practice where real particle systems are being used, as an upper limit, since complete randomisation is unlikely to be achieved and a safety-factor is thereby introduced. Examples of this type of calculation can be found for dispersed systems of all types, whether there is a continuous phase present or not (17).

Homogeneity (H_i) may also be used to follow powder mixing operations. Since homogeneity gives an absolute figure (although relative to the standard of deviation taken), the units of homogeneity do not give a simple indication of the state of the mixture. This may be overcome by calculating the required homogeneity and plotting the difference between this (H_i*) and the homogeneity (H_i) at the various stages of the mixing operation (see Fig.3). Homogeneity may also be calculated for multicomponent systems and used for both particle size calculations, for following the mixing operation, or for assessing the content uniformity of the components in a final sample form, such as tablets and capsules (18).

Homogeneity indices offer the only method of indicating uniformity of ordered systems (19). Ordered mixtures probably occur more widely than at first thought and, because of the advantages such systems offer, mixing to an ordered state, as opposed to a



Relation between homogeneity indices (S/σ_A) and ($H_i^*-H_i$)

FIG.3.

randomised state, will be induced to a greater extent in the future. Proportionalisation operations leading to ordered systems in dosage forms also lead to homogeneity indices as the preferred method of expressing content uniformity.

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