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Homogeneity of pharmaceutical dispersed systems

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Pharmaceutical dispersions include an extremely important group of formulations for the administration of drugs. A consideration of the homogeneity or dose uniformity requirements of some pharmaceutical dispersions, including tablets, capsules, ointments, suspensions, lotions, emulsions and suppositories is given. Assessment of homogeneity, assuming possible required limits of dose conformity, enables a calculation of the particle size requirements. These may be limited by parameters other than homogeneity, for example, sedimentation in suspensions and physical stability of emulsions. The concept of homogeneity applied to these systems is useful for following the progress of powder mixing or other dispersion operations. It is also useful in examining the feasibility of achieving the desired degree of dispersion. Dose conformity could be an extremely important problem in some cases, where standards do not exist.

Buslik (1973) recently introduced a new concept of homogeneity based upon that weight of sample required to give, as a standard, a definite degree of variation between samples. For simplicity, a standard deviation of 1 % in sample composition or weight was taken as the standard degree of variation. Then the weight of sample (W_1) necessary to be taken in order to give this degree of variation is taken as being inversely proportioned to the homogeneity (H)

$$H = \frac{1}{W_1} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (1)$$

In view of the enormous range of values for homogeneity (H) that could be obtained, an analogy with pH measurement of hydrogen ion concentration was used to express the homogeneity as H_i the negative logarithm of the sample weight (W_1)

$$H_i = \log H = \log \frac{1}{W_1} = -\log W_1 \quad .. \quad .. \quad .. \quad (2)$$

The standard deviation, σ, of one ingredient (G %) in random samples of weight, W, in a binary mixture is given by

$$\sigma = [G\,(100 - G)\,w/W]^{0.5} \quad .. \quad .. \quad .. \quad (3)$$

where w is the particle weight.

When $\sigma = 1$, as required by Buslik's definition, then

$W = W_1$ and

$$W_1 = G\,(100 - G)\,w \quad .. \quad .. \quad .. \quad .. \quad (4)$$

Substituting from equation (1)

$$H = 1/W_1 = 1/G\,(100 - G)\,w \quad .. \quad .. \quad .. \quad (5)$$

Substituting from equation (2)

$$H_i = -\log W_1 = -\log [G (100 - G) w] \quad .. \quad .. \quad (6)$$

Buslik demonstrated the universal application of this measure of homogeneity by obtaining values for the wide range of systems given in Table 1. It is interesting to note that two of the applications cited by Buslik are of pharmaceutical importance. It is the purpose of this paper to extend the work of Buslik to the study of pharmaceutical disperse systems from the viewpoints of both the preparation of the dosage form and the standards of homogeneity or content uniformity (dose uniformity) that may be used for their quality control.

THEORY

Where a standard of dose uniformity is required, either by a pharmacopoeia or as a manufacturing control, a value can be attributed to σ, the maximum allowable per cent standard deviation between doses. Thus, if 99·7% of the doses is required to be within 10% limits about the mean assuming a normal distribution, then

$$\pm 3\sigma = \pm 10\% \text{ of mean (expressed as \%)} \quad .. \quad .. \quad (7)$$

This calculated maximum per cent standard deviation, σ_A, is given by

$$\sigma_A = [G (100 - G) w/W]^{0.5} \quad .. \quad .. \quad .. \quad (8)$$

Knowing the dose size, W, enables calculation of the dispersed particle weight, w, and assuming spherical particles, its size. The use of such calculations for powder mixing and, hence, for tablet and capsule homogeneity, has been demonstrated by Hersey (1972) and Johnson (1972). Substitution of equation (8) in equation (6) leads to a generalized equation for calculating homogeneity from the dose and required dose conformity, thus

$$H_i = -\log W_1 = -\log \sigma_A^2 W \quad .. \quad .. \quad .. \quad .. \quad (9)$$

APPLICATION TO PHARMACEUTICAL DISPERSE SYSTEMS

1. *Binary powder mixtures*

Powder mixtures are prepared before granulation for tableting or encapsulation and for a variety of other dosage forms that contain at least two solid ingredients. Traditionally, such mixtures have been followed by considering their heterogeneity (Wiedenbaum, 1958; Valentin, 1967). In such cases the standard deviation, s, of a sample ingredient calculated from a number of samples taken from the mixture is expressed as some ratio of the theoretical standard deviation for a completely randomized mixture, σ_R. An index of homogeneity (s/σ_A) was proposed by Hersey (1967, 1970) based on the required degree of homogeneity to comply with official standards, σ_A. It has been recently demonstrated (Hersey, 1973) that there is a simple logarithmic relation between s/σ_A and H_i for a given powder system during the mixing operation. Further, whereas the value of s/σ_A directly indicates the stages of mixing, i.e.

when $s/\sigma_A > 1{\cdot}0$ mixing is incomplete

$s/\sigma_A = 1{\cdot}0$ mixed to specification

$s/\sigma_A < 1{\cdot}0$ mixed within specification,

the universal value of H_i has little practical value unless directly compared with that value of H_i required to meet the specification.

In real powder systems, the powders will be distributed with respect to particle size and the weight, w, is an effective mean particle weight, $\Sigma(fw)$. For such real systems, this weight may be calculated using the formula of Stange (1954), as modified by Poole, Taylor & Wall (1964), where (fw) is the fractional weight contribution for each particle size fraction to the mean particle weight for that component in the mixture. A similar equation was proposed by Buslik (1950).

2. *Multicomponent powder mixtures*

Multicomponent powder systems have been examined theoretically by Stange (1963) and Harnby (1967), to give an equation of the form

$$\sigma_p^2 = \frac{p^2}{W}\left[\left(\frac{1-p}{p}\right)^2 p\Sigma(fw)_p + q\,\Sigma(fw)_q + r\,\Sigma(fw)_r \ldots\right] \quad .. \quad (10)$$

where σ_p is the standard deviation of the proportion of component, p, in the randomized mixture, q and r are the relative proportions of the other components, and $\Sigma(fw)$ is the effective mean particle weight of the component given by the subscript.

Assuming that the particles are all reduced to an equivalent size before mixing, a normal requirement in practice, then

$$\Sigma(fw)_p = \Sigma(fw)_q = \Sigma(fw)_r = w \quad .. \quad .. \quad .. \quad (11)$$

Since, for the three component system of P, Q and R

$$q + r = 1 - p$$

then equation (10) reduces to

$$\sigma_p^2 = \frac{w}{W}p(1-p) \quad .. \quad .. \quad .. \quad .. \quad (12)$$

which is identical to equation (3), when using per cent standard deviation. Thus, the homogeneity of a single component in a multicomponent powder mixture may be established using equation (9). A practical example of multicomponent mixing to the desired degree of homogeneity has been considered by Cook & Hersey (1973).

3. *Tablets and capsules*

In the example of the pharmaceutical tablet quoted by Buslik (1973), 1 g tablets contained 15% of one ingredient and 85% of the other. The tablets were required to contain these proportions to within $\pm 1\%$ for 99·99% of the tablets. Assuming a normal distribution, Buslik calculated $\sigma_A = 1/3{\cdot}9$ and using equation (3)

$$w = 5{\cdot}16 \times 10^{-5}\ g,$$

which is equivalent to particles of 434 μm diameter, assuming spherical particles of density 1·2 g cm^{-3}. Since the sample size is 1 g, equation (9) gives $H_i = 1{\cdot}2$.

In actual pharmaceutical practice, the tablet would probably be composed of 15% drug and 85% diluent and, by analogy with U.S.P. XVIII, content uniformity requirements would allow a variation of $\pm 15\%$. If we can assume that the results

are normally distributed and that the manufacturer required 99·7% of the tablets to fall within the above limits, substitution in equation (7) gives

$$\pm 3\,\sigma_A = \pm 15 \times 0{\cdot}15 \therefore \sigma_A = 0{\cdot}75$$

Substitution in equation (3) gives

$$w = 4{\cdot}414 \times 10^{-4}\ g,$$

which is $\equiv$ to particles of 888 μm diameter, assuming spherical particles and a density of 1·2 g cm^{-3} as previously. By substitution in equation (9) $H_i = 0{\cdot}25$.

Buslik's criteria for homogeneity of tablets are relatively severe; as a result there is a doubling of the particle size necessary to achieve the required degree of dispersion using the U.S.P. criteria for homogeneity.

The homogeneity of capsules follows exactly the same type of calculation as for tablets.

4. *Ointments and pastes*

In topical preparations, powdered drugs are dispersed in a suitable vehicle for application to the skin. It is undoubtedly desirable that there is standardization of dose uniformity over the area of application in such preparations, especially where potent drugs, e.g. the corticosteroids, are incorporated. Official standards, however, do not exist. It is simply necessary that a given weight or volume consisting of many doses, contains the standard weight of drug. The problem is analogous to that which existed in tablets and which was questioned by Train (1960).

Since the powder might normally be expected to be reduced to dimensions of the order of 10 to 100 μm, whereas the continuous phase will be of molecular dimensions, then, since

$$w = d\,\Sigma(fw)_c + c\,\Sigma(fw)_d$$

(Poole & others, 1964) in which c and d are the proportions of continuous and dispersed phases respectively, and $c \gg d$

and $\Sigma(fw)_d \gg \Sigma(fw)_c$

thus $w = c\,\Sigma(fw)_d.$

Let us consider a 0·1% dispersion of a steroid powder in an ointment base. Reasonable limits that might be required for content uniformity are ± 15% (by analogy with the tablet problem). Assuming that 99·7% of the values are required to fall within these limits and a normal distribution, then

$$\sigma_A = 5{\cdot}0 \times 10^{-3}$$

A suitable dose is difficult to define in such a situation. An effective area of homogeneity might be a more useful concept. Let us consider that homogeneity is required for each 1 mm^2 of area of application and that the film applied is 50 μm in thickness (equivalent to the size of an impalpable powder).

Assuming an ointment density of 1 g cm^{-3}, then

$$W = 5 \times 10^{-5}\ g$$

and substituting these values in equation (9) gives $H_i = 8{\cdot}9$.

The particle weight necessary to achieve this degree of homogeneity can be calculated from equation (3)

$$w = 6{\cdot}25 \times 10^{-10}\ g$$

assuming spherical particles and a density of 1·0 g cm^{-3}.

D (particle diameter) = 10·6 μm if all particles are of equal size, however,

$$w = c\,\Sigma(fw)_d$$

$$\therefore \quad \Sigma(fw)_d = 6{\cdot}25 \times 10^{-10}$$

and $$D = 10{\cdot}6\ \mu m\ .$$

This is the particle size (maximum) for dispersion of the corticosteroid to the required degree of homogeneity.

5. *Suspensions*

As in the previous example, dose content uniformity is required for oral suspensions. In this example, the amount of drug might be expected to be present at the 1% level and the dose would be 1 teaspoonful (5 cm^3). Thus

$$\sigma_A = 5 \times 10^{-2}$$

assuming an allowable variation for 99·7% of the doses of $\pm$15% and a normal distribution. W = 5 g assuming the density is 1·0 g cm^{-3}.

Substituting in equation (9) gives $H_i = 1{\cdot}2$, and substitution in equation (3) gives

$$w = 6{\cdot}25 \times 10^{-4}\ g$$

thus $$\Sigma(fw)_d = 6{\cdot}25 \times 10^{-6}\ g$$

and D = 1·06 mm assuming spherical particles and a density of 1·0 g cm^{-3}.

This particle size level in a mobile vehicle would give considerable problems with regard to sedimentation and caking. It may be argued that, for such suspensions at this concentration and dose level, the limiting effect on particle size is not homogeneity requirements, but sedimentation properties.

6. *Emulsions*

In Buslik's paper a 10% oil in water emulsion is considered from the viewpoint of homogeneity. It was assumed that the droplets ranged in size from 0·1 to 1·0 μm diameters and were of 0·8 g cm^{-3} density. This gave H_i values between 9·4 and 12·4 (Table 1).

The particle sizes quoted were limited by the physical stability of the particular emulsion system and may have no particular significance to the desired degree of homogeneity for pharmaceutical applications.

Consider an emulsion system for oral administration. The concentration of 10% oil is given above, assuming the same homogeneity requirements as for the previous examples, then, for a 5 cm^3 dose,

$$\sigma_A = 5 \times 10^{-1}$$

and W = 5 g (assuming an overall density of 1·0 g cm^{-3}).

Substitution in equation (9) $H_i = -0{\cdot}8$.

Table 1. *Values of homogeneity of various systems* (after Buslik, 1973).

System	Value of homogeneity H_i
Pure hydrogen gas	>23·5
Pure sodium chloride crystal	22·0–22·2
Air	19·1
10% oil-in-water emulsion	9·4–12·4
15% drug in tablet	1·2
Partially mixed industrial materials with—	
(*a*) random segregation of 1 lb;	—6·1
(*b*) random segregation of 1 ton	—9·4
The Universe	—46·3

Clearly a 10% oil-in-water emulsion to be taken orally at the 5 cm^3 dose level is likely to be more homogeneous than that necessary for dose content uniformity. The degree of dispersion is necessitated by the stability requirements of the emulsion system.

7. *Lotions*

Consider the above emulsion to be used as a lotion and requiring the same area-to-area homogeneity as required for ointments (paragraph 4). Thus, although σ_A is the same as for the emulsion above,

$$\sigma_A = 5 \times 10^{-1}$$

the dose level is identical to that for ointments

$$W = 5 \times 10^{-5}$$

substitution in equation (9), gives $H_i = 4{\cdot}2$.

The particle size necessary for this degree of homogeneity $w = 6{\cdot}94 \times 10^{-8}$ g

$$\Sigma(fw)_d = 7{\cdot}71 \times 10^{-10}\ \mathbf{g}$$

and D = 56·9 μm assuming equal spherical particles of density, 0·8 g cm^{-3}.

Even at this dose level the particle size necessary for emulsion stability appears to be a more important consideration than that necessary for the desired degree of homogeneity.

8. *Aerosols*

An interesting case might exist with powder aerosols consisting of mixtures. Calculation might show that the necessary particle size level for adequate homogeneity for dose uniformity requirements might be too small to be retained in the respiratory system and be exhaled after the dose is administered. In such cases, it might be necessary to use drug alone in the aerosol formulation. Nevertheless, there is still a problem with the metered dose of drug dispersed in propellent.

9. *Tablet lubricant*

With tablets a further problem arises which is not associated with dose uniformity. It is necessary to lubricate each tablet, thus there will be a necessary degree of homogeneity of the tablet lubricant in each tablet. The lubricant is present in each

tablet as a small proportion (0·25 to 1·0%) of the tablet weight and the sample size is a small concentric cylinder around the tablet representing perhaps an order of 1/100 of the total tablet weight. This is an explanation of the necessity to reduce the particle size of tablet lubricants, although the problem may be alleviated by the spreading or flow of the lubricant under the pressures used in preparing the tablet.

10. *Suppositories*

Suppositories of sample weight 1 g often contain a significant proportion of drug. Consider a suppository containing 20% of active ingredient, then, for the usual limits used in this paper $\sigma_A = 1{\cdot}0$

since $W = 1{\cdot}0$

substituting in equation (9) $H_i = 0$.

This value has no special significance on the Buslik scale of homogeneity. Again, calculation of the particle size suggests that sedimentation of the particles in the molten base may be the limiting factor on particle size and not the homogeneity requirements.

STUDIES ON MIXING FEASIBILITY OF DISPERSED SYSTEMS

In the foregoing sections, a method has been described for

(*a*) calculating the desired degree of homogeneity (H_i) to comply with a necessary or desirable standard for dose uniformity of dispersed systems;

(*b*) calculating the particle size of the dispersed phase necessary to achieve this degree of homogeneity.

Care must be exercised in the practical application of the particle size value obtained since this is an effective mean particle size and should be taken, in practice, as the maximum particle size. It is also assumed that this size material is efficiently dispersed throughout the continuous phase so that the equations of random samples apply.

An alternative approach is to measure the particle size distribution of the dispersed phase (or the phase to be dispersed) and to calculate the effective mean particle weight. This enables a calculation of the maximum homogeneity attainable with the system H_i^*. The value of $(H_i^*-H_i)$ then gives an indication of the feasibility of preparing the dispersion to the necessary standard of homogeneity. Where this value is high positive, as in the emulsion example, where H_i^* is 12·4 and H_i is −0·8 then $(H_i^*-H_i) = 13{\cdot}2$, there is every possibility that a dispersion meeting the dose uniformity requirements can be prepared. As this value is reduced, the feasibility of meeting such a specification is also reduced. As it becomes zero or negative, the specification cannot be met and further particle size reduction is necessary.

This value for indicating the feasibility of dispersing to a given specification is similar to the mixing margin previously suggested ($\sigma_A-\sigma_R$) (Hersey, 1967), although it might be suggested that the ratio σ_A/σ_R might provide a more useful measure, since this will be analogous to the term $(H_i^*-H_i)$ given above.

Table 2. *Summary of values of homogeneity for various pharmaceutical dispersed systems.*

System	Drug concentration %	Dose size g	Value of H_i (a)
Tablet	15·0	1·0	0·25
Ointment	0·1	5×10^{-5}	8·9
Suspension	1·0	5·0	1·2
Emulsions	10·0	5·0	—0·8
Lotions..	10·0	5×10^{-5}	+4·2
Suppositories	20·0	1·0	0·0

(a) Assuming limits of ±15% in 99·7% of the doses in a normal distribution.

CONCLUSIONS

Powder mixing is a well documented and recognized problem. For this reason, standards exist for content (dose) uniformity of certain low dosage tablet preparations. Values of homogeneity (Table 2) for the systems examined in this paper suggest that serious thought should be given to the establishment of dose uniformity of certain topical preparations of highly potent drugs. It is perhaps fortunate, that dose-response effects may not be so critical for topical formulations and that diffusion both in the preparation and intradermally will enlarge the effective area dose level, decreasing to some unknown extent, the requirements for homogeneity.

The concept of homogeneity of dispersed systems is a useful tool for the examination of mixing and dispersion processes and for the elucidation of problems which may be of practical significance.

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