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EFFECTS OF INTERPARTICULATE INTERACTIONS ON MIXING HOMOGENEITY

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ABSTRACT

By theoretical approach, the highest degree of mixing of cohesive, interactive powders was derived to conform to the homogeneity of the random mixture of free-flowing, non-interactive constituents. Particulate interactions like adherence of a cohesive drug ingredient to the diluent component, cannot yield ordered mixtures of higher degree of homogeneity under real mixing conditions.

These conclusions were confirmed by mixing experiments, using minor proportions of free-flowing and of cohesive drug constituents, and diluents in excess. With both types of drug powders, the quality of the random mixture was attained. Ordered mixtures of higher degree of homogeneity could not be produced.

INTRODUCTION

In pharmaceutical powder mixing, cohesive powders are frequently processed, which give rise to particulate inter-

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actions during the mixing operation. Especially, on mixing a minor proportion of a finely divided, cohesive drug powder and a major diluent, adherence of the drug to the diluent particles may occur.

The effects of these interactions on the highest degree of mixing are not fully established. Conventional mixing theory considers the best possible mix to be a random mix (1), but does not take into account particulate interactions. More recently, adhesion of one constituent to the other was assumed to be a mechanism of ordering, which may yield ordered systems of higher degree of homogeneity than according to random mixtures (2). Adhesion however, is fundamentally interaction but not order, and so far, convincing experimental evidence of ordered mixutres is not available (3).

In this paper, the highest degree of mixing of cohesive, interactive powders is examined and is compared with that of free-flowing, non-interactive constituents.

THEORY

Non-interactive Powders

With free-flowing constituents, the best possible mix is a fully disordered, randomized arrangement of the individual particles (1). To estimate the quality of binary random mixes, several equations have been proposed, which differ in their applicability:

The common equations of Stange (4) and of Poole et al. (5), as derived from the binomial distribution, are valid in the case of similar particle size of the constituents only (3,6,7). Thus, they are not available for comparison with interactive mixes, where the components may be quite different in particle size. To systems of a minor proportion of active ingredient (up to about 10 % of the total mix) and of a major diluent, the Poisson distribution does apply (8). In this case, the particle size and size distribution of the diluent component is not to be taken

into account (7). From the Poisson distribution, Johnson (8) derived an equation, which may be written as follows:

$$C_R = 100 \sqrt{\frac{\bar{m}}{G}} \qquad \text{(Eq. 1)}$$

where C_R is the coefficient of variation of drug content per dose unit (e.g. tablet) of a random mix; $\bar{m}$ is the representative mean particle weight of drug (monosized drug particles: uniform particle weight m), and G is the mean weight of drug per dose unit.

$\bar{m}$ corresponds to the volume-weighted/volume-number mean diameter $\bar{d}_v$, which is the type of mean particle size representative of mixing homogeneity (9):

$$\bar{m} = \frac{\bar{d}_v^{\,3} \cdot \rho \cdot \pi \cdot F}{6} \qquad \text{(Eq. 2)}$$

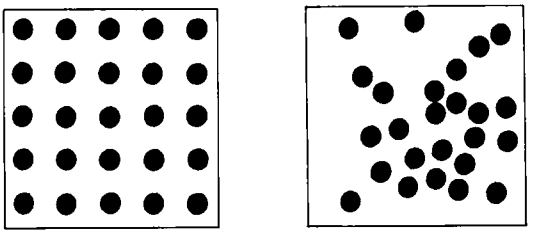
In Eq. 2, ρ is the density and F is the volume shape factor (spheres: F = 1) of the particles.

Interactive Powders

With interactive powders, the highest degree of homogeneity was recently (3,10) shown to be dependent on which type of adhesion process is able to take place during mixing operations (Figure 1):

To produce ordered systems of higher quality than of random mixes, "ordered adhesion" must occur, with regular arrangement of the drug particles onto the surface of the diluent particles. Then the number of the fines adherent to each of the monosized carrier particles is identical.

However, ordered adhesion cannot be attained by mixing but only by means of an ordering mechanism. Mixing, being a process of disordering, at best may effect random arrangement of the fines on the carriers surface ("random adhesion") (3), which results in random variation of the number of the adherent drug particles per diluent grain.



Ordered Arrangement of Adherent Particles ("Ordered Adhesion")

Random Arrangement of Adherent Particles ("Random Adhesion")

FIGURE 1

TYPES OF ADHESION

The coefficient of variation of drug content per dose unit due to random adhesion, C_{RA}, may be derived from the Poisson distribution. With a monosized drug adherent to a monosized diluent, C_{RA} was found (19) as:

$$C_{RA} = 100\sqrt{\frac{1}{n}} \qquad \text{(Eq. 3)}$$

where n is the mean number of drug particles per dose. Since n is equal to:

$$n = \frac{G}{m} \qquad \text{(Eq. 4)}$$

substitution of Eq. 4 into Eq. 3 gives Eq. 5, which conforms to Eq. 1 of the non-interactive random mix with the drug constituent being monosized:

$$C_{RA} = C_R = 100\sqrt{\frac{m}{G}} \qquad \text{(Eq. 5)}$$

Assuming a size distribution of the adherent component that is more adequate to actual situations, again C_{RA} was derived (11) to conform to C_R of the non-interactive random system (cf. Eq. 1):

$$C_{RA} = C_R = 100\sqrt{\frac{\bar{m}}{G}} \qquad \text{(Eq. 6)}$$

The approach of C_{RA} of Eq. 6 implies monosized carrier particles and thus, that the carriers surface per dose is constant. In theory, a size distribution of the diluent may cause somewhat poorer quality of the interactive random mix due to random variation of the carriers surface per tablet loaded with drug, which may effect additional inhomogeneity. In practice however, according zu preliminary investigations, this possible effect of heterosized diluents may be assumed to be of minor importance and not to affect the validity of Eq. 6 seriously.

Further, C_{RA} assumes complete adherence even of the coarsest drug particles. In most real mixes with cohesive drug powders, partial adhesion may occur, with the more cohesive fine fractions adhering to the diluent, and the coarser particles being distributed individually. But according to Eq. 6, the best possible mix is independent of particulate interactions, and thus Eq. 6 also applies to partially interactive mixes.

Conclusions from Theory

In contrast to a common view, adhesion of a minor ingredient to the diluent particles cannot yield ordered mixtures of higher degree of homogeneity than conforming to random mixtures. Eq. 6 provides the highest degree of mixing to be independent of whether complete, partial, or no adherence of the drug to the diluent does occur. Accordingly, the best possible mix of cohesive, interacting powders and that of free-flowing, non-interacting constituents is identical, and equals the quality of the random mix.

To verify this conclusion, mixing experiments have been performed using cohesive, milled drug powders and free-flowing, coarse particle size fractions of the same drugs (Table 1).

TABLE 1

RELEVANT PROPERTIES OF THE DRUG POWDERS

DRUG POWDER	FLOWABILITY	d_{max} (µm)	% WEIGHT SMALLER 50 µm	$\bar{d}_v$ (µm)	ρ (g/ml)
K-dichromate cryst.	free-flowing	500	2,7 %	247	2,68
K-dichromate milled, fraction 125-160 µm	free-flowing	160	-	143	2,68
K-dichromate milled	cohesive	160	63 %	67	2,68
Salicylic acid milled, fraction 200-250 µm	free-flowing	250	-	225	1,44
Salicylic acid milled	cohesive	250	89 %	46	1,44

d_{max} = maximum particle size (coarser fractions removed by sieving)

EXPERIMENTAL

Materials

K-dichromate[1] (two free-flowing and one cohesive quality) was used as a drug model for its particular ease of spectrophotometrical assay. Additional experiments were performed using salicylic acid[2] (one free-flowing fraction and one cohesive quality). Flowability of the drug powders, their relevant particle size properties, and their density (12) are listed in Table 1.

Particle size distributions were assessed by the use of a vibratory sieving machine[3]. Fractionation of the cohesive powders was supported by cautious brushing of the sieve residues.

To the salicylic acid powder, 1 % Aerosil[4] was added as a sieving aid.

$\bar{d}_v$ was derived from the data of particle size analysis as described previously (13). $\bar{m}$ was calculated from Eq. 2 assuming spherical particle shape.

Milling was performed by means of laboratory rotor mill[5]. The main portions of the milled powders were smaller in particle size than 50 µm (Table 1). Cohesive properties are obvious from the high agglomeration tendency shown in Figure 2.

The diluents used were Avicel PH 101[6] (with K-dichromate) and STA-Rx 1500[7] (with salicylic acid), which, in preliminary investigations, showed high stability against segregation with the drug powders studied.

Mixing

Mixtures of a drug concentration of 0,5 % were prepared using a Turbula shaking mixer[8] (30 and 180 minutes mixing time) and a cube revolving mixer[9] (30 minutes). Batch size was varied from 300 g to 500 g, depending on the type of mixer and of diluent, to keep the filling volume of the original mixing vessels approximately at half of their capacity of 2 l and 3,5 l respectively. With the milled salicylic acid fraction 200-250 µm, batch size was 40 g for lack of substance, and a 250 ml vessel was used on the Turbula.

Prior to actual mixing with the labelled amount of the diluent, pre-mixes of 10 % drug concentration (2 % with the salicylic acid fraction) were prepared in a screw capped bottle by shaking for 1-2 minutes by hand. The pre-mixes were passed trough a sieve of 250 µm mesh size (500 µm mesh size with K-dichromate cryst.) to achieve agglomerate break-down of the cohesive milled drug powders. To keep the mixing conditions constant, this procedure was performed also with the free-flowing drug qualities.

Tabletting

The final mixes were directly compressed by the use of a single punch machine[10]. Tablet weight was varied from 20 mg to

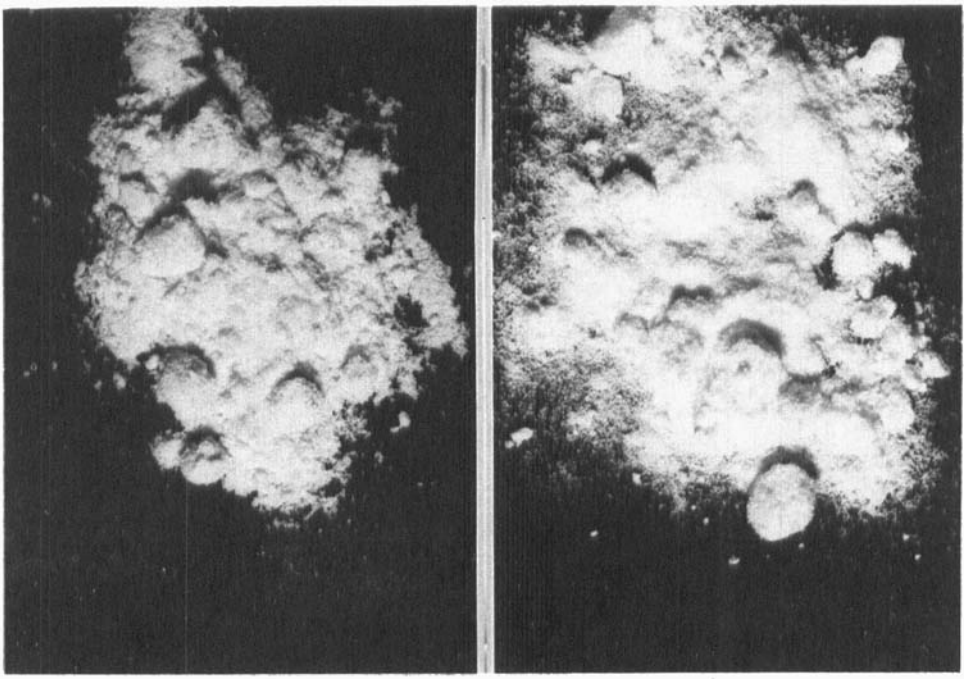


FIGURE 2

COHESIVE DRUG POWDERS

(a) K-dichromate milled $\bar{d}_v$ 67 µm (b) Salicylic acid milled $\bar{d}_v$ 46 µm

1000 mg to produce tablet batches of different labelled drug content in the range from 0,1 mg to 5 mg.

Assay

Individual dose assay of 30 tablets per batch was performed spectrophotometrically[11] at 375 nm (K-dichromate) and at 297 nm (salicylic acid), after extraction by 0,05n KOH and by purified water respectively.

To eliminate the effect of tablet weight variation, the individual drug contents originally found were reduced to the labelled tablet weight before calculation of the coefficient of variation of drug content.

TABLE 2

EFFECT OF PARTICLE SIZE AND OF FLOWABILITY OF DRUG ON VARIATION OF DRUG CONTENT CALCULATED AND FOUND WITH TABLETS

Drug dose level: 1 mg K-dichromate per 200 mg tablet
Mixer: Turbula, 30 min. and 180 min. (pre-mix sieved)

DRUG POWDER	FLOWABILITY	CALCULATED C_R (Interval)	FOUND CV (30 min.)	FOUND CV (180 min.)
K-dichromate cryst. $\bar{d}_v$ 247 µm	free-flowing	14,6 % (11,5-19,8)	12,6 %	15,7 %
K-dichromate fraction $\bar{d}_v$ 143 µm	free-flowing	6,4 % (5,0-8,6)	6,6 %	-
K-dichromate milled $\bar{d}_v$ 67 µm	cohesive	2,1 % (1,6-2,8)	2,1 %	2,2 %

RESULTS

As predicted from Eq. 6, the highest dose uniformity of the tablets was found to be only dependent on drug particle weight $\bar{m}$ (drug particle size $\bar{d}_v$ respectively, cf. Eq. 2), and on drug dose level G, but to be independent of flowability or cohesivity of the drug powders.

Effect of Particle Size and of Cohesivity of Drug

With tablets of 1 mg labelled content of K-dichromate (Table 2), the random drug content variation C_R was calculated as 14,6 %, 6,4 %, 2,1 % respectively, according to the differences in particle size $\bar{d}_v$ of the three drug qualities used. If random homogeneity is achieved, CV, the coefficients of variation of drug content of the assay samples, are expected to be found within the confidence

intervals of C_R given in Table 2, which were calculated on the 95 % probability level assuming normal distribution (15).

After mixing for 30 minutes in the Turbula, the content variations observed (CV 12,6 %, 6,6 %, and 2,1 %) were in excellent agreement with the theoretical values C_R. Prolonged mixing for 180 minutes did not allow higher dose uniformity even with the cohesive drug quality (CV 2,2 %), thus confirming that the best possible mix has been achieved already after 30 minutes.

Effect of Drug Dose Level

The effect of drug dose level was examined using the cohesive K-dichromate milled, and again did agree well to theory (Table 3):

C_R was calculated as 0,9 % (5 mg labelled drug content), 2,1 % (1 mg), and 6,4 % (0,1 mg) respectively. CV found amounted to 1 %, 2,2 % and 6,6 % after 30 minutes mixing in the Turbula. Using the cube revolving mixer of lower shear, almost identical drug content variations were obtained (CV 1,1 %, 2,0 %, and 6,8 %), as a consequence of destroying the drug agglomerates by the sieving operation before actual mixing.

Independence of the results of the type of mixer (Turbula, cube, Table 3), and of mixing time (30 min, 180 min, Table 2), further confirmed that with all experiments, the intensity of the mixing operation was sufficient to produce complete mixes, and that higher than random mixing homogeneity cannot be attained with the cohesive drug powder.

Effect of Type of Drug

With other types of drugs, the highest degree of mixing was also independent of flow properties, as shown by the experiments of Table 4, using the highly cohesive salicylic acid milled ($\bar{d}_v$ 46 µm) and the free-flowing, coarsest size fraction (200-250 µm) of the milled powder. Again, the drug content variations found did conform well to the random content variations C_R, and were

TABLE 3

EFFECT OF DRUG DOSE LEVEL

Drug powder: K-dichromate milled $\bar{d}_v$ 67 µm (cohesive)

Mixing time: 30 minutes (pre-mix sieved)

DOSE LEVEL (TABLET WEIGHT)	CALCULATED C_R (Interval)	FOUND CV Turbula	FOUND CV Cube
5 mg (1000 mg)	0,9 % (0,7-1,2)	1,0 %	1,1 %
1 mg (200 mg)	2,1 % (1,6-2,8)	2,1 %	2,0 %
0,1 mg (20 mg)	6,6 % (5,2-8,8)	6,4 %	6,8 %

TABLE 4

EFFECT OF TYPE OF DRUG

Drug component: Salicylic acid

Mixer: Turbula, 30 minutes (pre-mix sieved)

DRUG	SALICYLIC ACID FRACTION $\bar{d}_v$ 225 µm (free-flowing)		SALICYLIC ACID MILLED $\bar{d}_v$ 46 µm (cohesive)	
DOSE LEVEL (TABLET W.)	CALCULATED C_R (Interval)	FOUND CV	CALCULATED C_R (Interval)	FOUND CV
0,25 mg (50 mg)	18,5 % (14,7-25,2)	18,0 % (19,3 %)*	1,7 % (1,4-2,3)	1,7 %
1 mg (200 mg	-	-	0,86 % (0,68-1,17)	0,96 %
4 mg (800 mg)	-	-	0,43 % (0,34-0,58)	0,58 %

( )* = repeated analysis

only dependent on drug particle size $\bar{d}_v$ ($\bar{m}$ respectively), and on drug dose level G (0,25 - 4 mg per tablet).

DISCUSSION

From theory and experiment, the highest degree of mixing of cohesive powders was found to conform to the quality of the random mixture. This finding suggests that the best possible mix may be estimated by means of the very equations which apply to free-flowing, non-interactive systems. In particular, for dosage forms (e.g. tablets) of small drug content and of major diluent, which primarily give rise to content uniformity problems in practice, the highest dose uniformity may be calculated from Eq. 6, independent of whether free-flowing or cohesive constituents are processed.

The fact that particulate interactions cannot produce ordered mixtures of higher homogeneity, is a consequence of adhesion being a mechanism of interaction rather than order (3). During mixing, adherence of cohesive ingredient particles to the diluent proceeds according to a random process; thus, in the equilibrium situation, at best random arrangement on the carriers surface may be attained. Only the hypothetical "ordered adhesion" with regular arrangement of the adherent particles is both interaction and order (3).

To avoid confusion between order and interaction, the terms "interactive" and "non-interactive" were introduced recently by Egermann and Orr (16) to differentiate between mixes of interactive powders and mixes of free-flowing constituents. "Ordered" should only be applied to systems of higher regularity and of higher degree of homogeneity than according to random mixtures.

SYMBOLS

C_R = coefficient of variation of drug content in the dose units (tablets) of a random mix

C_{RA} = coefficient of variation of drug content in the dose units of an interactive mix produced by random adhesion

CV = coefficient of variation of drug content found in assay samples of 30 tablets

d_{max} = maximum particle size

$\bar{d}_v$ = volume-weighted/volume-number mean particle size (representative to mixing homogeneity)

F = volume shape factor of particles

G = mean weight of drug per dose unit (tablet)

Interval = confidence interval of C_R (n = 30, P = 95 %)

m = uniform particle weight

$\bar{m}$ = representative mean particle weight (corresponds to $\bar{d}_v$)

n = number of tablets per assay sample

P = probability (%)

ρ = density (g/ml)

FOOTNOTES

1. K-dichromate p.a., Merck, West Germany
2. Acidum salicylicum, ÖAB, supplied by Chemosan AG, Austria
3. unknown type, kindly granted by Ciba-Geigy AG, Switzerland
4. Aerosil 200, Degussa, West Germany
5. Condux LS 10 K, Condux-Werk, West Germany
6. FMC Corporation, Philadelphia
7. A.S. Staley Manufacturing Co., Decatur, III
8. Turbula T2A, W.A. Bachofen Maschinenfabrik, Switzerland
9. Cube mixer KB 15 S, Erweka Apparatebau, West Germany
10. EKO, Korsch Maschinenfabrik, West Germany
11. Spectrophotometer PM2 DL, Carl Zeiss, West Germany

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