J. Pharm. Pharmacol. 1987, 39: 329–334

British Pharmaceutical Conference Science Award Lecture 1986

Order out of chaos

by

John N. Staniforth

Lecturer, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK

Powder mixing forms a central part of many domestic and industrial processes, from relatively uncritical operations involved in cooking, gardening and building to more demanding procedures in nuclear fuel processing, the chemical and agrichemical industries and plastics production. Powder mixing forms an important part of the production of pharmaceutical tablets and capsules where the need for physically stable, homogeneous powders is especially vital in processing low dose drugs whether following granulation or direct compression. Although powder mixing has been carried out for many hundreds or even thousands of years, the science of powder mixing is relatively young, probably originating during the middle of this century. Much of this early scientific work was carried out in order to develop theories which could be applied to mixing processes which were generally very different in type and scale to those carried out pharmaceutically. For this reason it may be worthwhile to reconsider powder mixing theory in light of the sometimes special behaviour of pharmaceutical powders.

Powder mixing—concepts and nomenclature

Probably the first significant scientific work on powder mixing was published in the early 1940s and formed the basis of mixing theory for the next 30 years. Scientists such as Lacey (1943) developed equations which allowed calculation of theoretical variances for completely unmixed (equation 1) and randomly mixed (equation 2) dry binary powder systems (Fig. 1). The aim of this early work was to provide some sort of ruler against which the homogeneity of real powder mixes could be compared (Fig. 2).

$$\sigma_O^2 = x.y \quad (1)$$

$$\sigma_R^2 = \frac{xy}{n} \quad (2)$$

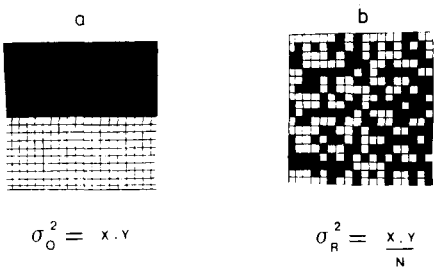


FIG. 1. Schematic representations of (a) a completely unmixed binary system of black and white square particles and (b) a random mix of the same system. The equations represent the theoretical variances of the two extremes of mixing behaviour.

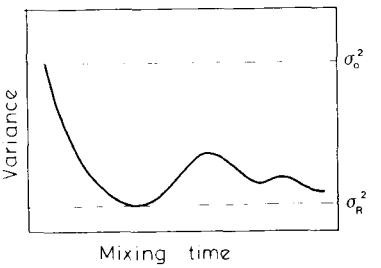


FIG. 2. Example of a mixing profile, showing the use of theoretical variances in setting upper and lower limits for the mixing curve.

where x and y are the proportions of the two component powders and n is the number of particles.

In developing random mixing theory, Lacey assumed that a binary powder system could be treated as a statistical randomization in three dimensions. This approach required that all particles should be identical in every physical respect except colour and, crucially, that all particles should be non-interacting.

This assumption may have been approximately valid for Lacey or Poole et al (1964) when mixing very coarse and very dense powders such as the

oxides of uranium or thorium. Nevertheless, what were acceptably 'non-interacting' powders for chemical engineers became unacceptably 'interacting' when applied to pharmaceutical powders which were generally very fine and relatively low density materials. Travers & White (1971) were the first to decribe the adsorption of fine particles onto 'host' crystals and noted that this prevented the segregation normally associated with differences in particle size predicted by random mixing theory. Hersey (1975) formalized the inaccuracy of applying random mixing theory to pharmaceutical powders and described an alternative approach which he termed 'ordered mixing'. Hersey and co-workers (Yeung & Hersey 1979; Yip & Hersey 1977) observed that mixtures such as those first described by Travers & White (1971) frequently had homogeneities higher than the minimum theoretical variance for an equivalent random mix. Put another way, these adhesive powder mixes were more ordered than the best random mix. This is the origin of the term 'ordered mix' and was widely used to describe the phenomenon in scientific publications until the late 1970s and early 1980s. More recently some workers including Huettenrauch & Keiner (1979), Egermann & Orr (1983) and Thiel & Sberna (1986) have suggested that the term 'ordered' is imprecise and it is now becoming popular to describe the two types of mix as 'non-interactive' (random) and 'interactive' (ordered), presumably in recognition of Lacey's method of discrimination.

There is a compelling reason for resisting the adoption of these terms and it stems from a so far irrefutable scientific fact: all matter interacts. Particles as small as the six or so types of quark mixed in protons and neutrons interact due to the colour force, the strong nuclear force and the weak force. Particles as large as planets mixed in star systems or galaxies interact due to gravitational force. Particles of intermediate dimensions such as powders are acted on by gravitational force and the electric force which includes van der Waals and Coulomb forces.

In other words, as the dimensions of particles increase and the particles change in nature, the forces acting on them change but the interactions remain. Thus, the forces acting to stabilize quarks in a proton are different from those stabilizing protons in atoms, atoms in powder particles or powder particles in a powder mass. Indeed, the force balance may change within a size scale, so that fine powder particles less than say 100 μm diameter will be acted on principally by electric forces whereas above 1000 μm these surface forces are swamped by gravitational forces (Fig. 3). It is powder mixes in which gravity is the predominant stabilizing force that are termed by some workers 'non-interacting'.

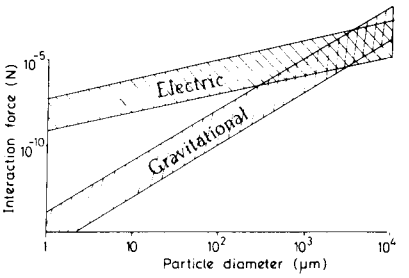


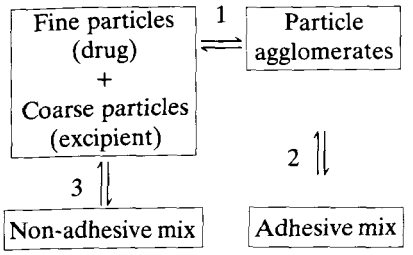
FIG. 3. Relationship between predominant interaction force and particle diameter.

It will now be clear that no powder mix should be regarded as truly non-interacting, although some may be less adhesive than others. In a real powder system, some particles will adhere to others (whether through gravitational or electrical attraction) and some will be unassociated. During the course of mixing, dynamic interactions will cause some adhered particles to become detached whilst other unattached particles may subsequently adhere to others.

In view of these considerations it will be apparent that the main difference between the two extremes of powder behaviour is neither randomness nor ordering, interactiveness nor non-interactiveness. The main difference is that at one extreme the particles are non-adhesive (or non-cohesive) and at the other extreme they are adhesive (or cohesive). These are certainly more scientifically accurate descriptions and they have been recently used by Thiel (1984), Bridgwater and fellow workers (Drahun & Bridgwater 1983) and by Stewart and fellow workers (Soebagyo & Stewart 1985). However, it is probably more useful in practical terms to consider powder mixing as a dynamic process where the exact balance or equilibrium between adhesive and non-adhesive mixing at a given instant is uncertain. This approach has been called 'total mixing' (Staniforth 1981) and can be used as a basis for attempting to control mixture quality by driving the equilibrium in the direction which produces maximum homogeneity and stability.

Such a thermodynamic approach to mixing may prove useful as a means of assessing the complex processes involved in real systems. To elaborate further on the hypothesis of a thermodynamic total mix, consider a binary powder mix consisting of a set of coarse particles (excipient powder) and a set of

fine particles (drug powder). The total mix of those powders is represented as follows.



The agglomeration of fine and coarse particles in process 1 can be regarded as a spontaneous process which is likely to be exothermic. For a particular mass of powder, the surface area and hence surface free energy will be greater for finer particles so that larger particle agglomerates will be formed at the expense of smaller individual particles. This process is analogous to crystal dendritic coarsening whereby potential surface energy is converted to thermal energy. In contrast, the free energy changes in processes 2 and 3 are probably of much less significance.

It is therefore clear that formation of an adhesive mix, which requires process 1 to occur, and containing drug/excipient agglomerates with lower free energies than the individual particles, will be thermodynamically more stable than non-adhesive mixes in which force interactions drive equilibrium 1 to the left and prevent particle agglomeration.

Theory therefore appears to indicate that formation of predominantly adhesive mixes in preference to predominantly non-adhesive mixes may be a successful method of producing physically stable homogeneous powder systems.

Theory into practice

Probably the most obvious method for achieving the objective of maximizing the adhesive component of a total mix is to carry out a size reduction operation on both powders. By increasing the surface area to mass ratio of powders, both surface forces and surface free energies are increased. This approach will probably be successful in improving both homogeneity and physical stability, but it is likely to impair powder flowability (Staniforth 1982a).

An alternative approach would be to increase the surface to mass ratio by producing relatively coarse excipient particles which flow easily, but which are macroporous or have rough surfaces, capable of entrapping large numbers of adherent drug particles. To test this hypothesis, two chemically similar excipients with comparable coarse particles size distributions were used to form homogeneous powder mixes with a fine-particle model drug (Staniforth & Rees 1982b). When the two mixes were subjected to vibration conditions similar to those encountered during routine tablet production (Staniforth 1982b) only one mix remained homogeneous, the other mix was found to segregate. The physically stable mixture contained the excipient Emdex, a coarse macroporous crystal agglomerate of dextrose. The unstable mixture contained Dipac, a coarse relatively smooth surfaced crystal agglomerate of sucrose. Segregation of Dipac/drug mixtures was found to be most intense in conditions of high acceleration and low frequency. The reason for formation of physically stable adhesive mixtures between macroporous coarse particles and fine adherent particles is due to three effects.

(a) Formation of adhesive couples due to multiple interparticle contact (Fig. 4). Particles adhered to smooth surfaces will have only a single adhesive contact.

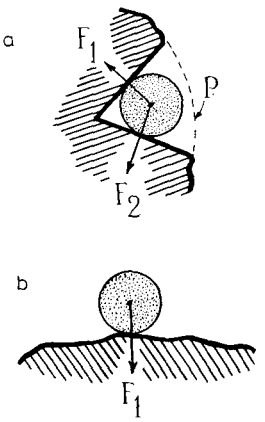


FIG. 4. Diagram showing drug particle adhered (a) in a cleft on an excipient particle surface and (b) on a smooth excipient surface (the arrows represent adhesion forces, F, at point contacts and P is the equivalent spherical projected perimeter).

(b) Prevention of adhered particles being rolled from the carrier surface. Particles can be rolled off surfaces using lower applied forces than those required to pull particles off the same surface. Entrapment of particles in surface clefts ensures that the particle must always be pulled from one surface, no matter which direction the removal force is applied (Fig. 4).

(c) Protection of adhered particles from becoming detached by abrasion during further mixing or

processing. Particles adhered in clefts effectively lie within the carrier particle projected perimeter and are not exposed in the same way as particles adhered to smooth surface carriers (Fig. 4).

These hypothetical assumptions regarding the role of interparticle forces were tested experimentally using an ultracentrifuge technique (Staniforth et al 1981a). The macroporous Emdex and fine drug particles were found to have much higher interparticle forces than smoother surfaced Dipac and drug. This study also revealed that a large proportion of non-adhered drug particles existed in the mix containing Dipac and drug.

Based on this work, excipients have been specifically designed to be highly macroporous (Staniforth et al 1981b; Staniforth & McCluskey 1982; Staniforth 1984) and these were found to have another advantage over smoother excipients. The concentration of drug which such excipients were able to carry without serious loss of stability was much greater than for smoother excipients (Staniforth & Rees 1983). This effect was considered to be due to an increased number of 'active' adhesion sites (Hersey 1975) on each macroporous excipient carrier particle. Smoother excipients with lower numbers of active adhesion sites allowed a larger proportion of drug particles to remain non-adhered and this pushed the mixing equilibrium away from a fully adhesive system leading to increased segregation.

In many cases it may be undesirable or impractical to use specially designed macroporous excipients and other measures will be required to achieve stable homogeneous powder mixes. Once again it will be accepted that driving the equilibrium towards adhesive mixing is desirable if these aims are to be achieved efficiently. Since alteration of particle physical properties such as size or morphology are now ruled out, consideration will be given to modifying surface electric forces directly.

The first way in which this can be achieved is through altering the magnitude and/or the sign of Coulomb forces on particle surfaces.

A type of electrostatic charging known as triboelectrification was possibly first observed by Thales of Miletus in 600 BC when rubbing silk on amber. Charge generation in powders can occur by plastic-elastic collisions as well as by frictional contact and is a common occurrence during routine powder processing. It was found that excipient powders generally charged negatively when contacted with metal or glass surfaces, whereas many charged positively when contacted with plastic surfaces (Staniforth & Rees 1982a). The reason for this behaviour is almost certainly due to the relative differences in energy levels of Fermi electrons in excipients and different substrate surfaces (Staniforth & Rees 1982c). If triboelectric charging is to be used as a method for increasing adhesive mixing then two objectives must be achieved. One is to ensure that excipients and drug particles have different surface charge signs to allow interparticle attraction to occur. The other objective is to increase the magnitude of surface charges to a level where efficient particle collection can occur. This can be achieved by careful selection of equipment, construction materials and process conditions. Triboelectric charging can be achieved efficiently using a cyclone and in many cases, specific charges using this method were found to increase at least 10-fold over simple particle-substrate contacts. Powder mixes formed using the same combinations of drug and excipient powders with and without triboelectrification were found to have very different physical stabilities. Powder mixes formed using triboelectrification were found to be consistently more stable than uncharged mixes (Staniforth & Rees 1982b). In cases where even greater charges are required to improve stability, ionization methods can be used (Staniforth & Rees 1982c).

It was considered that the increased electrostatic attraction between oppositely charged drug and excipient particles facilitated close surface contact.

The resulting increase in surface forces such as Coulomb forces, dipole forces and molecular forces (Cross 1975) will increase the stability of adhesion units. Molecular forces include van der Waals interaction which varies with separation distance according to the inverse 7th power over distances less than 20 nm and the inverse 8th power over larger distances. Thus the strength of the van der Waals forces between two macroscopic bodies depends initially on the true contact area between them. Increased electrostatic attraction could bring two particles into closer apposition which, if less than 20 nm separation, would permanently increase van der Waals adhesion forces by a factor of 10 over uncharged particles. Additionally the true adhesion force would be increased by a factor of at least 20 for materials with low Young's moduli where surface flattening occurred (Dahneke 1972) as a result of increased particle collection velocity through electrostatic charging.

Unfortunately, most pharmaceutical excipients have low resistivity and therefore lose electrostatic charge through earth leakage relatively quickly. After only a few minutes, the Coulomb forces between particles will have decayed by half and

permanent bonding after charging is simply due to improved van der Waals bonding.

However, quasi-permanent electrostatic charges can be developed in some excipient particles by electret formation. Electrets may be considered to be the electrical analogues of a permanent magnet; according to Heaviside (Gutman 1948) an electret is a permanently electrified material having electric charges of opposite signs at its extremities. Electrets can also be produced which are monopolar or multipolar (unlike magnetic materials, Fig. 5). The

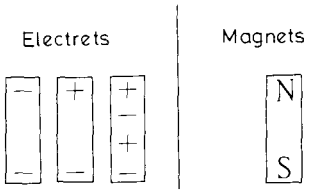


FIG. 5. Comparison of electret types with a permanent magnet.

potential advantage of forming electrets in pharmaceutical excipients lies in the possible increased adhesion due to permanent Coulomb forces between drug and excipient surfaces, which should be additive with increased van der Waals forces. In previously unpublished work, Laycock and Staniforth found that formation of electrets in a cellulose excipient, produced improved interparticle adhesion with fine particle triamterene over that produced using non-electrized material (Fig. 6).

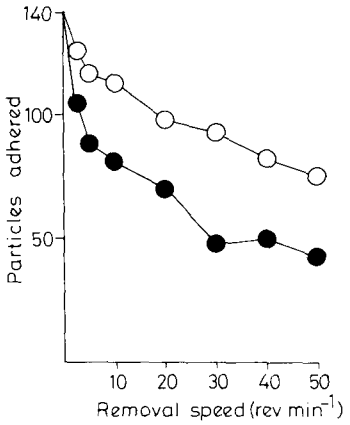


FIG. 6. Adhesion profiles for fine triamterene particles mixed with a non-electrized cellulose excipient and the same excipient made into an electret and having a quasi-permanent charge.

In cases where moisture contents are relatively high, electrostatic charge will diminish in significance as a mechanism by which particle adhesion can be promoted—it will be difficult or impossible to form electrets at even slightly elevated moisture levels. However, increasing moisture content promotes adhesion due to surface tension and suction pressure (F_{STSP}) in liquid films (Staniforth 1985)

$$F_{STSP} = \gamma D f(\theta, \delta)$$

where γ is the surface tension of the liquid layer, D is the fine particle diameter and $f(\theta, \delta)$ is a function of θ the contact angle and δ the bridge angle. F_{STSP} values for 45 μm diameter particles bound in 500 μm adhesion units vary from $2{\cdot}33 \times 10^{-6}$ to $1{\cdot}45 \times 10^{-5}$ N according to the method of calculation. It has been found in practice that an increase in moisture content of only 0·5% can transform a physically unstable, segregated mix containing a direct compression fructose excipient into a physically stable, homogeneous mix (Staniforth 1985).

Although the foregoing examples show that judicious control of various surface forces can be used to produce adhesive binary powder mixes which are extremely stable and homogeneous, it must be remembered that very few solid dose formulations are concocted from just two components. For tablets to be produced repeatedly successfully, a third component must be added, a lubricant powder.

Probably the most commonly used lubricant is magnesium stearate, and when this component is added to binary adhesive mixes, some unusual things can occur. For example, a stable adhesive binary mix containing sucrose and salicylic acid was found to have very poor drug content uniformity following addition of magnesium stearate. The loss of homogeneity was considered by Lai & Hersey (1979) to be due to the action of magnesium stearate stripping larger quantities of salicylic acid particles from binary adhesive units. Further work showed that magnesium stearate caused a change in the adhesion force profile of drug/excipient adhesive units (Staniforth et al 1982).

Lubricants act to reduce particle-substrate and particle–particle friction. Because friction occurs at surfaces, lubricants as a group are most efficient with maximum specific surface area, which is most easily achieved by producing very finely divided powders. Inevitably, these fine particles will be adhesive and will interact easily with other powders, such as drug particles which become coated with a lubricant film, stripping them away from carrier surfaces or preventing initial adhesion of drug particles to

carriers. In either case, it has been found without exception that magnesium stearate reduces the stability of pharmaceutical powders. Although this may be due simply to particle size differences it is almost certainly exacerbated by the electrostatic characteristics of magnesium stearate. Other lubricants such as hydrogenated vegetable oil and sodium stearyl fumarate do not appear to have such deleterious effects on powder mix homogeneity or stability.

Conclusions

The theory of powder mixing takes account of particle interactions which can produce adhesive mixtures. Both force and thermodynamic considerations suggest that adhesive mixtures should be more resistant to segregation than non-adhesive mixtures, i.e. they should have improved physical stability. As a result of testing this hypothesis, the following principles emerge for successful formation of homogeneous, stable adhesive mixtures.

(a) Coarse carrier substrates (excipients) should be macroporous or have rough surfaces.

(b) Electrostatic charge interactions can be controlled with beneficial results in terms of improved physical stability of normally unstable, segregating systems. Improved stability can be obtained either with or without permanent electrification.

(c) In cases where moisture contents of powders are relatively high, the importance of electrostatic charging as a method of stabilization will probably be less than the improved stability due to surface tensional forces.

(d) Production of stable binary mixes is no guarantee that a ternary or other multi-component mix will also be stable. Addition of each new component powder requires the same consideration as formation of a simple binary mix.

REFERENCES

Cross, J. (1975) Inst. Phys. Conf. Series No. 27, Chapter 3, pp 202–213

Dahneke, B. J. (1972) J. Colloid Interface Sci. 40: 1–13

Drahun, J. A., Bridgwater, J. (1983) Powder Technol. 36: 39–53

Egermann, H., Orr N. A. (1983) Ibid. 36: 117–118

Gutman, F. (1948) Rev. Mod. Phys. 20: 457–468

Hersey, J. A. (1975) Powder Technol. 11: 41–44

Huettenrauch, R., Keiner, I. (1979) Int. J. Pharm. 2: 59–60

Lacey, P. M. C. (1943) Trans. Inst. Chem. Engineers 21: 53–59

Lai, F. K., Hersey, J. A. (1979) J. Pharm. Pharmacol. 31: 800

Poole, K. R., Taylor, R. F., Wall, G. P. (1964) Trans. Inst. Chem. Engineers 42: T305–T315

Soebagyo, S. S., Stewart, P. J. (1985) Int. J. Pharm. 25: 225–236

Staniforth, J. N. (1981) Int. J. Pharm. Tech. Prod. Mfr. 2: 7–12

Staniforth, J. N. (1982a) Int. J. Pharm. 11: 109–117

Staniforth, J. N. (1982b) Ibid. 12: 199–207

Staniforth, J. N. (1984) Int. J. Pharm. Tech. Prod. Mfr. 5: 1–12

Staniforth, J. N. (1985) Powder Technol. 45: 73–77

Staniforth, J. N., McCluskey, J. A. (1982) Int. J. Pharm. Tech. Prod. Mfr. 3: 76–80

Staniforth, J. N., Rees, J. E. (1982a) J. Pharm. Pharmacol. 34: 69–76

Staniforth, J. N., Rees, J. E. (1982b) Ibid. 34: 700–706

Staniforth, J. N., Rees, J. E. (1982c) Int. J. Pharm. Tech. Prod. Mfr. 3: 69–72

Staniforth, J. N., Rees, J. E. (1983) J. Pharm. Pharmacol. 35: 549–554

Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1981a) Ibid. 33: 485–490

Staniforth, J. N., Rees, J. E., Kayes, J. B., Priest, R. C., Cotterill, N. H. (1981b) Drug Develop. Ind. Pharm. 7: 179–190

Staniforth, J. N., Rees, J. E., Lai, F. K., Hersey, J. A. (1982) J. Pharm. Pharmacol. 34: 141–145

Thiel, W. J. (1984) Powder Technol. 39: 147–149

Thiel, W. J. Sberna, F. J. (1986) J. Pharm. Pharmacol. 38: 166–171

Travers, D. N., White R. C. (1971) Ibid. 23: 260S–261S

Yeung, C. C., Hersey, J. A. (1979) Powder Technol. 24: 106–107

Yip, C. W., Hersey, J. A. (1977) Ibid. 16: 189–192