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Ordered Mixing or Spontaneous Granulation?

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SUMMARY

Ordered mixes were produced using a fructose-based excipient as a coarse carrier component and fine-particle pyridoxine hydrochloride (vitamin B_6) as the adherent component. Prior to mixing, the fructose agglomerates were conditioned for 48 h at either 0% RH or 55% RH at 20 °C. Under these conditions, one lot of fructose had a moisture content of 0.24 wt.% and the other lot had a moisture content of 0.74 wt.%. Following mixing, the powders were subjected to vibration at various frequencies in the range 25 to 200 Hz and accelerations in the range 9.81 to 39.24 m/s^2. It was found that whilst ordered mixes produced using fructose at 0.24 wt.% moisture content were unstable, those produced using 0.74 wt.% moisture content fructose were extremely stable and segregation resistant.

The formation of ordered units with increased adhesion in carriers with higher moisture content suggested that these ordered mixes could be considered as spontaneous granulations.

INTRODUCTION

Hersey [1] first introduced the concept of ordered mixing to explain the behaviour of interacting particles in a powder. Fine particles adhere to other particles to form so-called ordered units. Some potential adhesive or cohesive forces responsible for the formation of ordered units or interparticle bonds were described by Hersey [1] and by others [2, 3, 4]: London–van der Waals and other dipole forces; electrostatic or Coulomb forces; forces due to the presence of water such as surface tension forces and capillary suction potential forces; mechanical forces due to static frictional contact or interlocking of rough or re-entrant particle surfaces; chemical forces such as occur in chemisorption or hydrogen bonding. The Table shows some examples of ordered mixing systems studied in which one of these interactions was considered to be the predominant force responsible for binding particles in ordered units.

Comparison of this group of forces with a similar list produced for interparticle attractive forces in granules is, perhaps not surprisingly, very similar. The only significant difference between the list above and one compiled by Rumpf [9] for granules, is the absence of solid bridges as a class of forces responsible for formation of ordered units.

TABLE

Some examples of forces responsible for binding particles in ordered units

Adhesion force	Ordered unit	Reference
London–van der Waals forces	Considered to contribute to most ordered units	Staniforth *et al.* [5]
Electrostatic force	Coarse saccharide-based carrier particles and fine potassium chloride particles following tribo-electrification	Staniforth and Rees
Surface tensional or capillary forces	Coarse sucrose crystals and fine salicylic acid particles mixed at three different humidities	Stephenson and Thiel [7]
Mechanical forces	Highly re-entrant, macro-porous lactose or glucose carrier particles and fine potassium chloride particles	Staniforth *et al.* [8]
Chemical forces	No practical examples	

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On the basis of this apparent similarity between granules and ordered units, there may be some justification for describing ordered mixing as a type of direct granulation. However, it is known that ordered units are prone to become destroyed during processing and, in general, particles in ordered units are far less strongly adhered than equivalent particles in granules.

THEORY

The force balance which exists at a given interparticle contact will be influenced by both particle properties and the particle environment. For example, it is likely that as particle diameter reduces below 100 μm, the van der Waals component of particle adhesion will become significant. In a low-humidity environment, contact or frictional electrification may lead to significant interparticle electrostatic forces, but at elevated humidities, the electrostatic component of particle adhesion will be less significant than forces due to the presence of adsorbed or condensed liquid layers.

The theoretical contribution of London–van der Waals forces to the adhesion of a fine and a coarse particle in an ordered unit can be calculated. For a fine drug particle with a 45 μm diameter resting on the surface of a coarse excipient particle having a diameter of 500 μm, the interparticle contact can be assumed to approximate to that for a sphere resting on a flat plate [4]:

$$F_A = \frac{AR}{6H^2}$$

where F_A is the London–van der Waals force, A is the Hamaker constant, R is the radius of the sphere and H is the separation distance between particle surfaces, taken to be 4×10^{-10} m, *i.e.*, $F_A = 1 \times 10^{-6}$ N. However, the surface of the coarse excipient particle is porous and the drug particle can therefore be considered to be in extended contact with the carrier particle, so that

$$F_{AE} = \frac{AR}{6H^2} + \frac{A}{6\pi H^3}\pi\rho^2$$

or

$$F_{AE} = \frac{2AR}{12H^2}\left(1 + \frac{\rho^2}{RH}\right)$$

where F_{AE} is the London–van der Waals force for extended contact and ρ is the radius of interparticle contact.

For a particle located on a slightly textured surface, $\rho = 1 \times 10^{-6}$ m, *i.e.*, $F_{AE} = 2.6 \times 10^{-4}$ N.

This adhesion force is comparable with a value obtained experimentally for relatively smooth carrier particles, with slightly textured surfaces: 3.8×10^{-4} N. Adhesion forces of this order were found to be characteristic of unstable ordered units [5].

In cases where the pores or clefts in a carrier surface are too small to produce an increased van der Waals attraction, other means of enhancing the overall interparticle adhesion have been used. One method used to reduce disruption of ordered units by vibration of powder mixes was electrostatic charging which significantly reduced segregation [6].

Another method of improving interparticle adhesion is used in moist granulation and is due to adsorbed or condensed liquid layers on particle surfaces.

Several equations have been derived to allow calculation of adhesion forces between particles due to surface tension and suction pressure in liquid films [10, 11]. These may be summarised using the following equation:

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

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.

Values for F_{STSP} for particles in the ordered unit described above vary between 2.33×10^{-6} and 1.45×10^{-5} N, according to the method of calculation. Although these values are below those for van der Waals forces for fine particles adhered in clefts or pores, it is assumed that surface tension or suction potential forces will be responsible for (a) drawing particle surfaces closer together and (b) causing extended interparticle contact, and this will produce an increase in dispersion forces between the two particles.

The aim of the present study was to investigate the effect of the presence of surface moisture on the stability of ordered units formed between a hygroscopic coarse excipient particle and a fine particle model drug.

MATERIALS AND METHODS

Tabfine, type F94M (manufactured by Finnish Sugar Company, Espoo, Finland, supplied by Forum Chemicals, Reigate, Surrey, U.K.) is an agglomerated fructose-based direct compression tableting excipient and was used as the coarse carrier system. Fine-particle pyridoxine hydrochloride (vitamin B_6) was used as the adherent drug fraction at a concentration of 1 wt.%.

Tabfine F94M was conditioned at two different humidities prior to mixing with pyridoxine hydrochloride powder. One lot of Tabfine F94M powder was dried to constant weight and stored at 0% RH in a desiccator containing fresh silica gel, for 48 h. A second lot of fructose-based Tabfine was allowed to equilibrate at a relative humidity of 55% at 20 °C. The dried fructose agglomerates were found to have a moisture content of 0.24 wt.%, whereas the fructose agglomerates stored at 55% RH had a moisture content of 0.74 wt.%.

Ordered mixes containing Tabfine F94M and pyridoxine hydrochloride were produced by a two-stage process: initially, geometric mixing, or trituration, of the drug and excipient powders was carried out so as to ensure that the fine drug particles and agglomerates of particles were broken up and uniformly dispersed throughout the excipient system. Secondly, the premixed powders were loaded into a cube blender (Erweka GmbH, Frankfurt, F.R.G.) and mixed for approximately 30 min. The homogeneity of the mixed powders was analysed by filling an interlocking stack of small Perspex cylinders with powder and removing samples at ten different levels. The samples were analysed for drug concentration by dissolving in volumetric flasks made up to 100 ml with distilled water and measuring the absorbance of the solutions at 290 nm using a U.V. spectrophotometer (Shimadzu Instruments, Kyoto, Japan). The standard deviation and coefficient of variation of the ten sample concentrations were determined.

The interlocking cylinder stack was then re-assembled and filled with the powder mix of known homogeneity. The stack was clamped in place on a vibration table (Fig. 1) and vibrations of known frequency and acceleration were applied using a vibration conditioning amplifier (Derritron Electronics, Folkestone, U.K.). Frequencies were monitored using a frequency counter (Ferranti Electronics, Manchester, U.K.) attached to the output of the conditioning amplifier. Accelerations were monitored using an accelerometer mounted on the horizontal base plate of the cylinder holder on the vibration table, as shown in Fig. 1. The output from the accelerometer was fed into a signal conditioning amplifier and then to a vibration level monitor set to read R.M.S. accelerations.

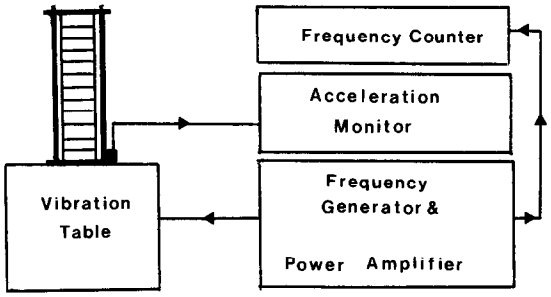

Fig. 1. Schematic diagram of vibration model.

Following vibration under set conditions for 15 min, the homogeneity of the powder mix was re-determined using the sampling technique and spectrophotometric method described above.

RESULTS AND DISCUSSION

The difference in moisture content between the two lots of fructose-based Tabfine was only 0.5 wt.%, but the physical stability of the two powder mixes formed was very different. Ordered mixes containing the low moisture content Tabfine F94M were found to be extremely unstable when subjected to vibration under different conditions (Fig. 2). The segregation tendency of low moisture content mixes as characterised by the response surface shown in Fig. 2 was typical of that for other ordered mixes where segregation occurs [12], *i.e.*, maximal segregation occurred in conditions of low frequency and high acceleration. For these powder mixes, the segregation tendency was of a magnitude characteristic of that for unstable systems considered to behave like partially ordered random mixes.

In contrast, mixtures containing the higher moisture content Tabfine F94M (0.74 wt.%) were found to be the most stable of any of the drug–excipient systems studied, there

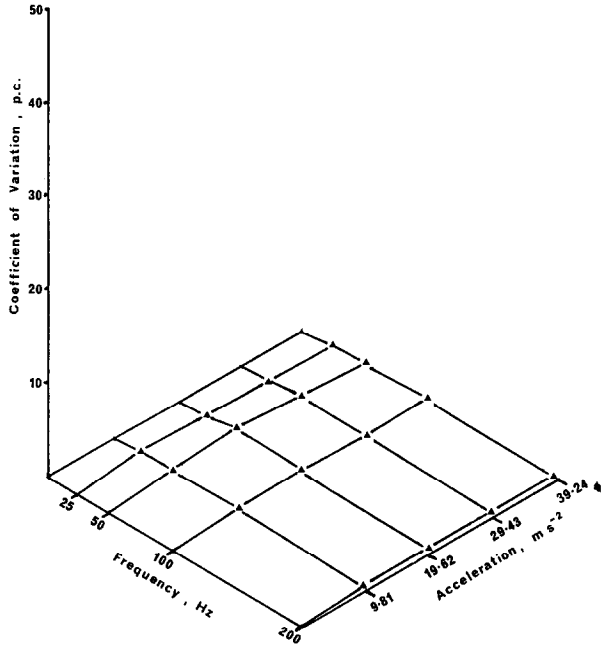

Fig. 2. Relationship between coefficient of variation of spot samples drug content and vibration frequency and acceleration for ordered mixes containing 1 wt.% pyridoxine hydrochloride and Tabfine F94M with a moisture content of 0.24 wt.%.

being no evidence of segregation under any of the test conditions (Fig. 3). This apparent difference in behaviour may be partly due to occlusion of the powder bed by the more cohesive Tabfine F94M with 0.74 wt.% moisture content, although even the lower moisture content sample immobilized large proportions of the powder under several different vibration conditions (Fig. 4).

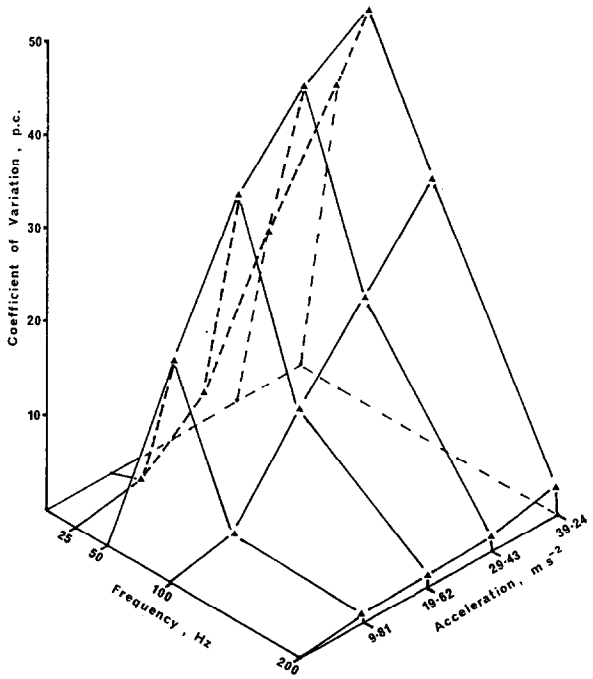

Fig. 3. Relationship between coefficient of variation of spot sample drug content and vibration frequency and acceleration for ordered mixes containing 1 wt.% pyridoxine hydrochloride and Tabfine F94M with a moisture content of 0.47 wt.%.

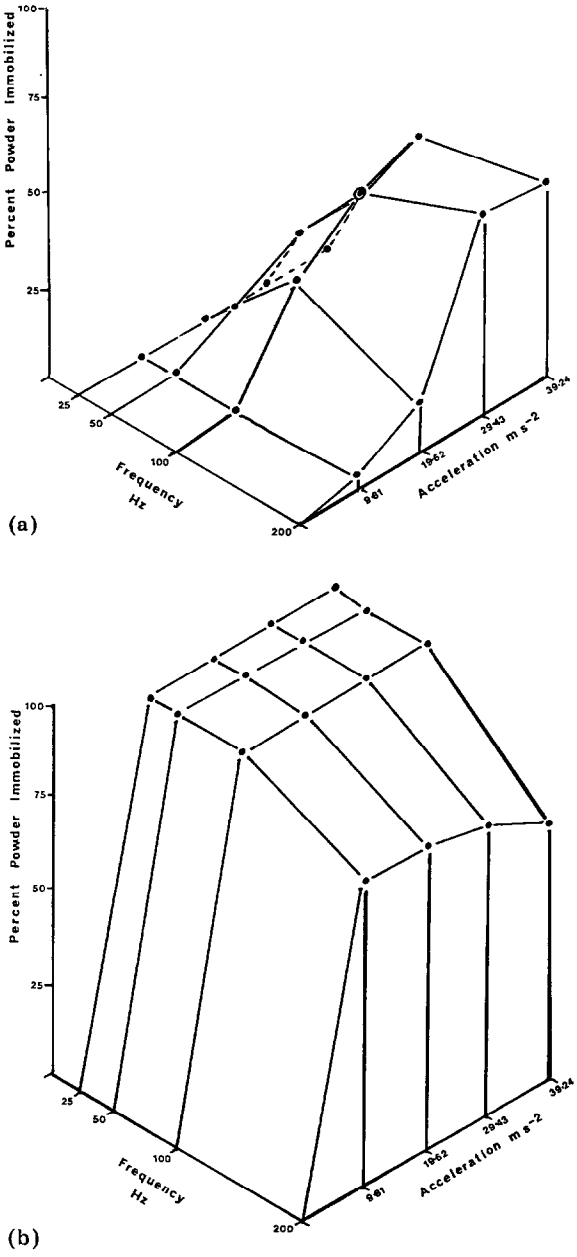

Fig. 4. Relationship between vibration frequency and acceleration and the percentage of the powder bed immobilized through changes in packing geometry for Tabfine F94M with moisture content of (a) 0.24 wt.% and (b) 0.74 wt.%.

It is considered to be more likely that the higher moisture content sample of Tabfine F94M held the increased mass of water as a surface film which was condensed at inter-particle contacts to form pendular bonds of the type commonly found in moist granules.

The critical humidity above which water could be expected to condense to form a capillary system between particle contacts can be calculated [13]. It is suggested [14] that below an RH of 65% capillary forces play no part in particle adhesion. However, according to the value taken for the B.E.T. coefficient for air–water or air–water saturated with fructose, the prediction of the point of condensation changes markedly. In addition, water exhibits special behaviour at surfaces, where polarity has a marked influence on adsorption because of the ability of the water molecule to form H^+ bonds and water may undergo chemisorption as well as physisorption [15]. Water may also be associated non-stoichiometrically within the fructose lattice and it might be expected that although most of the water would be present as a thin adsorbed film at 55% RH, there may be at least some parts of the particle surface where capillary condensation could occur and contribute to particle bonding.

In either case, the striking result of the presence of elevated surface moisture levels appears to be a spontaneous granulation of drug and excipient particles through formation of extremely stable ordered units.

CONCLUSION

The stability of ordered mixes formed between fine pyridoxine hydrochloride particles and coarse fructose agglomerates was found to be extremely sensitive to the moisture content of carrier particles.

Low moisture content carrier particles formed unstable ordered mixes, whereas at a slightly higher moisture content, the fructose agglomerates formed ordered mixes which were extremely stable.

The segregation resistance of these fructose systems and the apparent role of moisture in formation of strong ordered units suggested that ordered mixing could be considered to be a spontaneous or direct granulation.

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