

- using filling machine hoppers designed so that powder residence time is minimized
- using equipment where several operations can be carried out without transferring the mix, e.g. a fluidized-bed drier or high-speed mixer/granulator for mixing and granulating
- production of an ‘ordered’ mix. This technique is also referred to as *adhesive* or *interactive* mixing and is described in more detail below.

Ordered mixing

It would be expected that a mix composed of very small and much larger particles would segregate because of the size differences. Sometimes, however, if one powder is sufficiently small (micronized) it may become adsorbed onto ‘active sites’ on the surface of a larger ‘carrier’ particle and exhibit a great resistance to being dislodged. This has the effect of minimizing segregation while maintaining good flow properties. It was first noticed by Travers & White (1971) during the mixing of micronized sodium bicarbonate with sucrose crystals when the mixture was found to exhibit minimal segregation. The phenomenon is referred to as ordered mixing, as the particles are not independent of each other and there is a degree of order to the mix. If a carrier particle is removed then some of the adsorbed smaller particles will automatically be removed with it. Ordered mixing has also been used in the production of dry antibiotic formulations to which water is added before use to form a liquid or syrup product. In these cases the antibiotic in fine powder form is blended with, and adsorbed onto the surface of, larger sucrose or sorbitol particles (Nikolakakis & Newton 1989).

Ordered mixing probably occurs to a certain extent in every pharmaceutical powder mix due to interactions and cohesive/adhesive forces between constituents. It is most likely to occur when smaller particles exist, as these have a high specific surface area and thus the attractive forces holding the particles to the adsorption site are more likely to be greater than the gravitational forces trying to separate the components.

Pharmaceutical powder mixes are therefore likely to be partly ordered and partly random, the extent of each depending on the component properties. With an ordered mix, it may be possible to achieve a degree of mixing which is superior to that of a random mix which may be beneficial for potent drugs.

Ordered mixing has been shown to be important in direct-compression tablet formulations (Chapter 30) in preventing segregation of drug from direct compression bases.

Dry powder inhaler formulations also utilize ordered mixing to deliver drugs to the lungs (Chapter 37). In this case, the drug needs to be in a micronized form in order to reach its site of action. By adsorbing the drug onto larger carrier particles (usually lactose), it is possible to manufacture a product which will provide an even dosage on each inhalation.

Segregation in ordered mixes

Although ordered mixes can reduce or prevent segregation, it may still occur if:

- *the carrier particles vary in size* – different-sized particles will have different surface area to weight ratios and will contain different amounts of adsorbed material per unit mass. If the different-sized carrier particles separate (e.g. by percolation segregation), drug-rich areas where the smaller carrier particles congregate may result. This is referred to as *ordered unit segregation*
- *there is competition for the active sites on the carrier particle* – if another component competes for sites on the carrier it may displace the original adsorbed material which may then segregate due to its small size. This is known as *displacement segregation* and has been shown to occur under certain circumstances with the addition of the lubricant magnesium stearate to tablet formulations
- *there are insufficient carrier particles* – each carrier particle can only accommodate a certain amount of adsorbed material on its surface. If there is any excess small-sized material that is not adsorbed on to the carrier particles, this may quickly separate. This is referred to as *saturation segregation* and may limit the proportion of the active component that can be used in the formulation.

With an ordered mix, particles may be dislodged if the mix is subjected to excessive vibration. The extent to which this occurs depends on the forces of attraction between the components and therefore on how tightly the adsorbed particles are attached to the surface. The orientation of the particles is also important, particles protruding out from the surface