

produce a tablet dosage form containing a drug which is active at a dose of 1 mg, other components (e.g. a diluent, binder, disintegrant and lubricant) will be needed both to enable the product to be manufactured and for it to be handled by the patient.

Whenever a product contains more than one component, a mixing or blending stage will be required in the manufacturing process. This may be to ensure an even distribution of the active component(s), an even appearance or that the dosage form releases the drug at the correct site and at the desired rate. The unit operation of mixing is therefore involved at some stage in the production of practically every pharmaceutical preparation and control of mixing processes is of critical importance in assuring the quality of pharmaceutical products. The importance of mixing is illustrated below by the list of products which invariably utilize mixing processes of some kind:

- tablets, capsules, sachets and dry powder inhalers – mixtures of solid particles
- linctuses – mixtures of miscible liquids
- emulsions and creams – mixtures of immiscible liquids
- pastes and suspensions – dispersions of solid particles.

Mixing and its control are also important in unit operations such as granulation, drying and coating.

This chapter considers the objectives of the mixing operation, how mixing occurs, and the ways in which a satisfactory mix can be produced and maintained.

## Definition and objectives of mixing

Mixing may be defined as a unit operation that aims to treat two or more components, initially in an unmixed or partially mixed state, so that each unit (particle, molecule, etc.) of the components lies as nearly as possible in contact with a unit of each of the other components.

If this is achieved, it produces a theoretical ‘ideal’ situation, i.e. a *perfect mix*. As will be shown, however, this situation is not normally practicable, is actually unnecessary and, indeed, is sometimes undesirable.

How closely it is attempted to approach the ‘ideal’ situation depends on the product being manufactured and the objective of the mixing operation. For example, when mixing a small amount of a

potent drug in a powder mix, the degree of mixing must be of a high order to ensure a consistent dose. Similarly, when dispersing two immiscible liquids or dispersing a solid in a liquid, a well-mixed product is required to ensure product quality/stability. In the case of mixing lubricants with granules during tablet production, however, there is a danger of ‘overmixing’ and the subsequent production of a weak tablet with an increased disintegration time (discussed in Chapter 30).

## Types of mixtures

Mixtures may be categorized into three types that differ fundamentally in their behaviour.

### Positive mixtures

Positive mixtures are formed from materials such as gases or miscible liquids which mix *spontaneously* and *irreversibly* by diffusion and tend to approach a perfect mix. There is no input of energy required with positive mixtures if the time available for mixing is unlimited, although input of energy will shorten the time required to obtain the desired degree of mixing. In general, materials which mix by positive mixing do not present any problems during product manufacture.

### Negative mixtures

With negative mixtures, the components will tend to separate out. If this occurs quickly, then energy must be continuously input to keep the components adequately dispersed, e.g. with a suspension formulation where there is a dispersion of solids in a liquid of low viscosity. With other negative mixtures, the components tend to separate very slowly, e.g. emulsions, creams and viscous suspensions. Negative mixtures are generally more difficult to form and to maintain and require a higher degree of mixing efficiency than do positive mixtures.

### Neutral mixtures

Neutral mixtures are said to be static in behaviour, i.e. the components have no tendency to mix spontaneously or segregate spontaneously once work has been input to mix them. Examples of this type of mixture include mixed powders, pastes and ointments. Neutral mixes are capable of demixing, but this requires energy input (as discussed in relation to powder segregation later in this chapter).