1

Mixing Theory

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1.1 Introduction

Mixing of ingredients, or dispersion of one phase in another, is an essential step in many pharmaceuticals processes. For example, the vast majority of manufacturing routes to form an active pharmaceutical ingredient (API) make use of crystallization, which involves a number of mixing steps in a liquid phase, such as: dispersion and dissolution of solid reagents into a solvent, blending of liquid reagents with the solvent phase, creation of super-saturation through mixing, for example with an anti-solvent addition, chemical reaction, or heat removal and suspension of the API crystals during subsequent growth (Kirwan & Orella, 2002; Paul *et al.,* 2004). Each of these operations involves a mixing step, which is aimed at removing gradients of concentration, temperature or solids mass fraction within the crystallizer vessel, to give a more uniform environment for chemical reaction and/or crystal growth.

A second example may be taken from later in a pharmaceutical manufacturing process: during the formulation of solid dosage forms, dry-powder mixing of an API with excipients (themselves mixtures of binders, diluents, flow modifiers and granulating agents) is required to produce suitable physical, flow and mechanical properties for tableting (for example Lee, 2002). Here, the objective is to remove concentration differences within the dry powder mix, so that each tablet contains a mixture with exactly the same properties and with a tightly-controlled amount of the API. Other forms of oral dosage may involve the

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blending of suspensions, emulsions and syrups to give a formulated liquid product; again the objective of mixing is to ensure that each dosage contains almost exactly the same amount of the active ingredient.

These examples demonstrate that in a mixing process the objective is to reduce inhomogeneities in composition to an acceptable level, to provide a more uniform processing environment and/or a more uniform product. The examples also illustrate that there are differences between fluid mixtures of miscible phases and particle mixtures, which can, in principle, unmix; for example, by segregation effects (Sommier *et al.*, 2001). Segregation often occurs in free-flowing powders and is driven by differences in particle size and density. The phenomenon occurs when particulate mixtures are shaken (Rosato *et al.,* 1987), or during flow within or between vessels (e.g. discharge from a vessel). During shaking or shear flow, there is relative motion between particles and small particles can fall into gaps beneath larger particles. Thus, the larger particles tend to rise to the surface, whereas small particles percolate downwards. Therefore, segregation can cause a previously well-mixed material to undergo unmixing into a non-uniform solid form; a way to counteract the tendency to segregate is to introduce a binder or adjust the moisture content to produce cohesion within the particulate mixture. In many processes a granulation operation follows the blending stage to prevent segregation in subsequent processing steps (Fung & Ng, 2003).

A distinction may also be drawn between batch and continuous flow mixing processes, although similar measures of mixing quality may be defined for both. Almost all current pharmaceutical processes operate by transferring batches of material between stages of the manufacturing process, rather than by continuous inflow and outflow to process equipment. Therefore this chapter will focus mainly on batch mixing processes, where the purpose is to use fluid mechanics, molecular diffusion and dispersion effects to produce spatially homogeneous mixtures; up to a point, an increase in the batch time will lead to an improvement in the mixture quality, that is a reduction in the level of spatial inhomogeneities, but thereafter, the degree of mixedness will not improve. The chapter will address the question of what is an 'acceptable' measure of mixedness; the idea of a *scale of scrutiny* of the mixture will be introduced in Section 1.3 and various measures of the quality of a mixture will be discussed. The examples given here consider two rather different situations of mixing (1) between components in a liquid and (2) between different types of solid particles. In this context it is useful to differentiate between fine and coarse-grained mixtures and this is discussed in Section 1.4. Selection of different definitions of the endpoint for a mixing process will be considered in Section 1.5, to consider their sensitivity at various stages of mixing and their sensitivity to sampling methods.

Recently the pharmaceuticals industries have paid increasing attention to continuous manufacturing operations, as potentially they could significantly reduce production costs and provide more reliable manufacturing routes; see, for example, Schaber *et al.* (2011). Therefore, the final section (Section 1.6) of this chapter will consider continuous mixing of ingredients. In such operations the mixing objective is to obtain a product with a homogeneous distribution of ingredients in the correct proportions, which requires careful metering of the feed flow rates, as well as achieving a high degree of homogeneity. In continuous flow devices, the output product composition should not vary in time and the processing history of each element of the mixture should be the same. Variations in the feed composition to a continuous flow mixer can be compensated to an extent by allowing 'mixing in time', that is not all elements of fluid spend the same amount in the mixer, allowing materials that have arrived early, to mix with

materials that have arrived late. Thus the concept of a residence time distribution will be introduced in Section 1.6 to describe the process of back-mixing, or mixing in time. Furthermore it will be shown that back-mixing can effectively filter out higher frequency variations in feed composition and still give a uniform product. Thus, there are processing advantages and disadvantages in having some width to the residence time distribution.

Throughout this chapter, the term *concentration* will be used quite generally to described the composition of a material within a mixture; for a single liquid phase the term can be interpreted as mass (or mole) fraction, or mass (or moles) per unit volume of a specific component; for particulate mixtures it could represent mass fraction, number fraction or volume fraction of one type of solid; for a multi-phase mixture it could be the volume or mass fraction of a specific phase. In general, the mixedness will be judged from a statistical measure of the distribution of concentrations of key components within samples drawn from a mixture.

1.2 Describing Mixtures

In practice, the whole of the composition of a mixture cannot be determined at a single time, so sampling is often used to assess the state of mixedness; sampling at an appropriate scale of scrutiny will be discussed in Section 1.3, but first the degree of uniformity between samples will be considered. The average concentration of a species in the whole mixture is determined by the amounts of all components added and can be calculated straightforwardly from a mass balance. The average species concentrations obtained from samples drawn from this mixture ought to have values distributed about the average for the whole mixture; it is the width of this distribution that provides information about the quality of the mixture, not the average value from the various samples.

Figure 1.1 shows an example of an idealized mixture comprising 50% white particles and 50% black particles. The whole mixture is divided into 36 samples, each containing 16 particles. Figure 1.1(a) is a homogeneous, but non-random mixture; each sample contains exactly eight white particles (or 50% white particles), which is exactly the same as the mean concentration of the mixture. Figure 1.1(b) shows the number of particles in each sample and indicates that there are no spatial differences in concentration; hence the mixture can be regarded as perfectly mixed. This mixture is 'perfect' in the sense that each sample contains *exactly* the same concentration as the whole mixture average; in other words there is no variance between the samples. The probability of forming such a mixture by a stochastic process is rather small, so this situation is very unlikely to occur in a conventional mixing process.

In contrast, Figure 1.1(c) shows a mixture that has been generated entirely randomly by giving each particle an equal probability of being black or white; the overall composition of the whole mixture is still 50% white particles, but each sample now shows deviations from the whole mixture mean, as shown in Figure 1.1(d). Some samples contain as few as four particles, whereas others have 12 or 13, compared to the expected eight, which might lead to the conclusion that the material is not well mixed. However, further mixing, or randomization, of the particles will not lead to any significant improvement in the distribution of white particles between the samples. Figure 1.1(c) represents a more realistic picture of a perfectly mixed material, yet it is highly likely that a given sample concentration will show a large difference from the mean value, particularly when the number of particles in the sample is small.

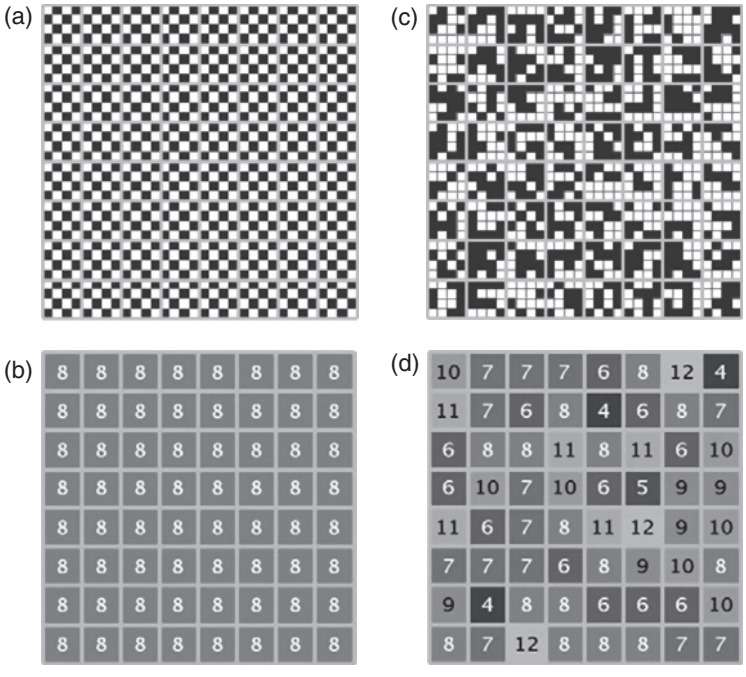


Figure 1.1 *Idealized mixtures of 50% white and 50% black particles (a) non-random perfect mixture, (b) number of white particles in each 4 × 4 sample of the non-random mixture (c) random mixture and (d) number of white particles in each 4 × 4 sample of the random mixture*

A simple definition of 'complete mixing' could be defined as the state where there are equal concentrations of components in each sample, which is the same as in the mixture overall. However, this example shows that statistical variations between samples in a fully random mixture leads to the conclusion that such a simple definition is of no practical use. Therefore, the principle applied later in this chapter to define the 'well-mixed' state will make use of a comparison back to the best state that can be achieved by random distribution processes, for example a mixture of the sort shown in Figure 1.1(c). Essentially, this will be what is regarded as 'well-mixed' since any further mixing would yield no statistical improvement in the mixture quality. Thus any description of the quality of a mixture must be able to distinguish between the sample-to-sample variations that can occur for a fully randomized mixture and those that result from incomplete mixing.

1.3 Scale of Scrutiny

The previous section described how sampling is required to assess the variability of the concentrations in a mixture, which begs the question, 'What is an appropriate size for each sample?' The end use for a mixed product determines the quality of mixing that

will be required and this can only be established by viewing samples of the mixture at an appropriate *scale of scrutiny.* Danckwerts (1953a) defined this scale of scrutiny to be the 'minimum size of regions of segregation which would cause the mixture to be regarded as unmixed', Scrutinizing a mixture on the scale of a whole batch of formulated product is essentially useless: if the correct proportions of ingredients have been charged in the first place, then the whole mixture must have the required average composition. At the other extreme, scrutiny at the scale of a single particle will show a completely segregated mixture. What is required is to scrutinize a sample of the mixture at an appropriate scale, determined by the end use of the product. For example, a pharmaceutical product is designed to deliver a fixed amount of a key component, usually the API, in each unit dose taken by the patient. Thus, the scale of scrutiny could be the mass contained in one tablet of the product, which could lie between 10 mg and 5 g in typical human patient dosages (Berthiaux *et al.*, 2008). *In-situ s*ampling of particulate mixtures from within a blender at this scale of scrutiny is not straightforward to achieve and involves removal of a representative mass from within a flowing bed, for example using a thief probe. Muzzio *et al.* (2003) provide a detailed discussion of the requirements of various designs of thief probe and highlighted the difficulties in obtaining accurate composition data for their use in determining mixture quality. Thief probes cause a disruption to the powder mixture and there can be uneven flow of the different powder species into the probe; segregation of different components can occur as the mixture is sampled. These problems are compounded in continuous systems and with cohesive materials that do not flow easily in the sample cavity. Thus the issues with sampling are to obtain (1) an appropriate mass of the mixture, corresponding to the scale of scrutiny and (2) a representative sample, with the same composition as within the mixer.

Figure 1.2 illustrates the effect of changing the scale of scrutiny on the mixture quality in an idealized mixture. The left-hand sample appears to be homogeneous and on this scale of scrutiny the mixture is completely mixed; there are no visual signs of concentration differences. Increasing the magnification at which the first sample is viewed shows up differences in concentration, until at the highest magnification, the mixture appears to be completely segregated, since individual particles can be clearly identified. In all cases the sample contains the same proportions of the key component, since it is the same mixture. It appears that this mixture quality would be acceptable at the left-hand scale of scrutiny, but completely unacceptable at the right-hand scale of scrutiny.

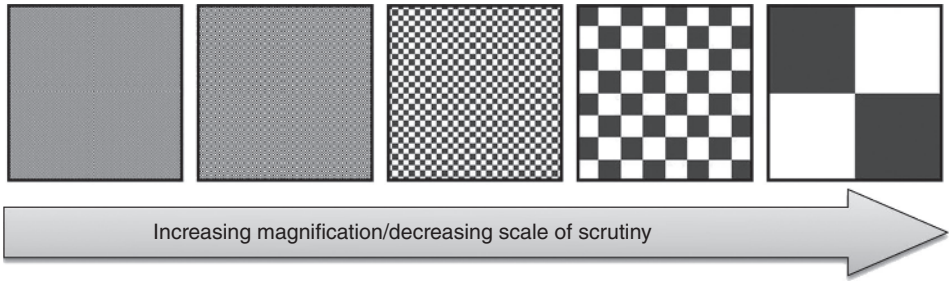


Figure 1.2 *The effect of decreasing the scale of scrutiny on the perceived quality of the mixture*

As described previously, once the scale of scrutiny has been determined, then samples at this scale can be obtained from the mixture and assessed for their homogeneity using the statistical measures described later in Section 1.5. Thus, the scale of scrutiny determines the sample mass required for any off-line analysis of product quality. For example, the FDA (2003) make recommendations about the analysis of samples drawn from blenders or from intermediate bulk containers; the guidelines state that sample sizes between 1 and 10 times the dosage unit should be investigated. Thus, the scale of scrutiny (that is the sample mass) is often taken as three times the dose mass.

In-line assessment of the homogeneity of a blend using a Process Analytical Technology (PAT) instrument would require an assessment of the effective sampling mass to justify that the FDA requirements are satisfied. Pernenkil and Cooney (2006) provided an example of such as assessment for a NIR PAT assessment of two-component powder blending, by estimating the sample size from the probe diameter and the measurement penetration depth. The mass of powder scanned per sample was estimated and compared to the mass in a single dose; hence the number of samples to be scanned and averaged to equate to a scale of scrutiny of 3 times the dose size could be calculated.

1.4 Quantifying Mixedness for Coarse and Fine-Grained Mixtures

1.4.1 Coarse and Fine-Grained Mixtures

The mixtures discussed in the previous section and shown schematically in the right-hand images of Figure 1.2 are examples of *coarse-grained* mixtures. When examined at these scales of scrutiny, a sample contains a relatively small (countable) number of discrete particles, which can be individually identified. Figure 1.3(a) shows a coarse-grained mixture comprising light and dark particles; the material appears highly segregated and the composition changes abruptly from point to point, when moving from a light particle to a dark particle. In contrast Figure 1.3(b) shows a *fine-grained* mixture. At the same scale of scrutiny, a sample contains such a large number of particles that the material can be treated as a continuum. In this case the concentration varies smoothly from point to point and finite concentration gradients exist within the mixture. Fluids behave as fine-grained mixtures, since each sample will contain a very large number of molecules and for practically useful scales of scrutiny the material can be regarded as a continuum. Mixtures of very finely-divided powders may also be considered to be fine-grained, since each sample will contain a very large number of individual particles.

Fluid and coarse-grained particulate mixtures differ in other respects. With the former, random motion of the molecules leads to diffusion, which causes a flux of material down concentration gradients to produce a more uniform mixture. However, molecular diffusion is a slow process and so this mixing mechanism is only effective at removing very small scale concentration gradients. In contrast, there is no such random motion for coarse particles and moreover, in practice small differences in diameter can lead to unmixing or segregation effects (see Section 1.1); small particles tend to percolate through the interstices created between larger particles, creating an unmixing effect based on size.

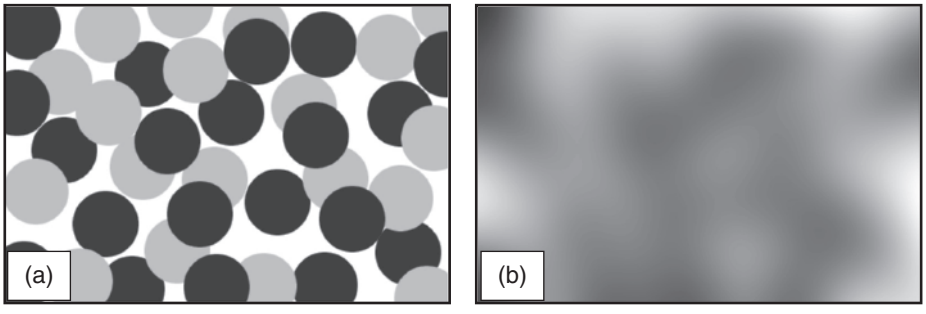


Figure 1.3 *(a) a coarse-grained mixture and (b) a fine-grained mixture*

1.4.2 Scale and Intensity of Segregation

Danckwerts (1953a) proposed that two measures are required to quantify the mixedness, namely a *length scale of segregation* and an *intensity of segregation.* The former indicates the physical size of the unmixed regions in an imperfect mixture, whereas the latter represents the degree to which there are variations in concentration between samples. Both measures are affected by the selection of the sample size or scale of scrutiny (see Section 1.3), as will be illustrated with some examples. The top left image in Figure 1.4 shows a highly segregated mixture (coarse-grained), in which individual regions of distinctly different concentration are visible: in qualitative terms, the length scale of segregation is large, because the regions of unmixed material have a significant size compared to the scale of scrutiny. Moving to the right in Figure 1.4, the size of the unmixed regions becomes smaller (the length scale of segregation decreases), although the mixture remains highly segregated between black and white areas. Moving downwards in Figure 1.4, the regions of unmixed material remain of the same size, but the concentration gradients are increasingly smeared out, that is the intensity of segregation decreases. The effect is created here by blurring the interface regions between black and white regions, in a process analogous to diffusion. The combination of decreases in intensity and length scale of segregation results in the mixture becoming increasingly more fine-grained as it approaches the perfectly mixed (uniform concentration) state, as shown in the bottom right image of Figure 1.4. Here, individual particles are not visible and neither are concentration gradients. In other words, the mixture is well-mixed.

Danckwerts (1952) provided quantitative definitions for the intensity and length scale of segregation based on measurements of the concentration fields. Consider an imperfect binary mixture of components A (white) and B (black), containing mass fractions a and b, respectively, at any point in the mixture. A mass fraction $a = 1$ would represent pure component A at that point in the mixture, whereas $a = 0$ would represent pure component B and for a binary components $a + b = 1$. The average mass fraction of A in the mixture would be given by

$$\bar{a} = \frac{1}{n}\sum_{i=1}^{n} a_i \tag{1.1}$$

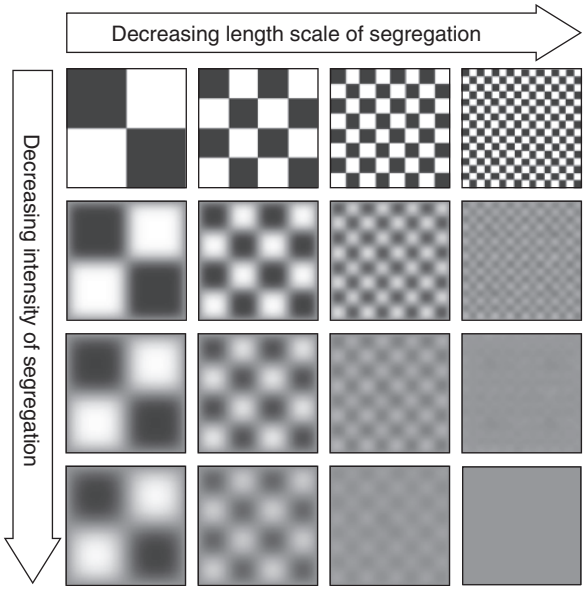


Figure 1.4 *The effects of changing scale and intensity of segregation on the quality of the mixture*

where a_i is the concentration of *A* in sample *i* drawn from the mixture and *n* is the number of samples. The sample size should be less than or equal to the required scale of scrutiny, as discussed in Section 1.3. The mean composition $\bar{a}$ provides almost no useful information about the quality of the mixture, only that it contains the correct proportions of *A* and *B*. In contrast, the variance of the sample concentrations, a_i, provides a useful statistic to characterize differences from the mean, $\bar{a}$, and is defined by

$$\sigma^2 = \frac{1}{n-1}\sum_{i=1}^{n}\left(a_i - \bar{a}\right)^2 \tag{1.2}$$

A perfect mixture might be thought to have a variance of zero, but as Figure 1.1 illustrates, this is unlikely to happen in practice. Lacey (1943) showed that for a fully randomized binary mixture of the same-sized particles, the variance is given by

$$\sigma_r^2 = \frac{\bar{a}\left(1-\bar{a}\right)}{n_p} \tag{1.3}$$

where n_p is the number of particles in each sample (determined by the required scale of scrutiny). Returning to the random mixture shown in Figure 1.1(c), the samples shown each contain 16 particles and the variance calculated from equation (1.2) is $\sigma^2 = 0.018$, which compares well with the value of $\sigma_r^2 = 0.017$ from equation (1.3). Thus further randomization of the mixture in Figure 1.1(c) would not result in an improvement in its uniformity and hence σ_r^2 represents the lowest variance that can practically be achieved.

The maximum variance for a binary mixture occurs for a completely segregated mixture in which each sample contains only one particle and so this represents the worst case.

$$\sigma_0^2 = \bar{a}\left(1-\bar{a}\right) \tag{1.4}$$

Hence, Danckwerts (1952) defined his intensity of segregation as one measure of mixedness, according to

$$I = \frac{\sigma^2}{\sigma_0^2} = \frac{\sigma^2}{\bar{a}\left(1-\bar{a}\right)} \tag{1.5}$$

so that for a completely segregated mixture $I = 1$ and for a perfectly uniform mixture $I = 0$. Note that Danckwert's definition does not include the variance, σ_r^2 of a fully random mixture containing n_p particles, given by equation (1.3) and hence the minimum value of the intensity of segregation is in practice given by σ_r^2 / σ_0^2. Therefore one way to characterize the quality of a mixture would be to take repeated samples of a given size and then calculate the variance from equation (1.2) and the intensity of segregation from equation (1.5). Specifications may then be prescribed for the satisfactory uniformity of the mixture in terms of a suitable range of the intensity of segregation.

The length scale of segregation provides information about the size of unmixed regions and is calculated from an autocorrelation coefficient, defined as

$$R\left(r\right) = \frac{\overline{\left(a\left(\mathbf{x}\right)-\bar{a}\right)\left(a\left(\mathbf{x}+\mathbf{r}\right)-\bar{a}\right)}}{\overline{\left(a\left(\mathbf{x}\right)-\bar{a}\right)^2}} \tag{1.6}$$

where $a(\mathbf{x})$ is the concentration at position $\mathbf{x}$ (taken over at a suitable scale of scrutiny), whereas $a(\mathbf{x}+\mathbf{r})$ is the concentration at distance r away (at the same scale of scrutiny), as shown in Figure 1.5. The overbars in equation (1.6) represent an average over the whole mixture, for various positions $\mathbf{x}$ and distances *r.* In Figure 1.5, the average concentration is $\bar{a} = 0.5$.

Consider a position $\mathbf{x}$ centred in circle C_1, which is a region of approximately uniform, below-average concentration, $\left(a(\mathbf{x})-\bar{a}\right) < 0$. Here it is assumed that the scale of scrutiny is small, such the position $\mathbf{x}$ represents a point. Moving small distances away from $\mathbf{x}$ within the circle gives $\left(a(\mathbf{x}+\mathbf{r})-\bar{a}\right) < 0$, so that the product in the numerator of equation (1.6) on average remains positive in this region. If the radius r extends outside the circle C_1, then $\left(a(\mathbf{x}+\mathbf{r})-\bar{a}\right)$ could be either negative or positive so that, when averaged over many positions, the numerator becomes close to zero. This is also true for other regions of approximately constant concentration, for example areas C_2 and C_3. Within these regions the concentrations are fairly well correlated with each other, but when the pairs of points lie too far apart there is almost no correlation. The denominator in equation (1.6) simply normalizes the autocorrelation so that it falls in the range $-1 < R(r) < 1$. So, the correlation function decreases from 1 to around zero at large distances *r,* as shown in Figure 1.6.

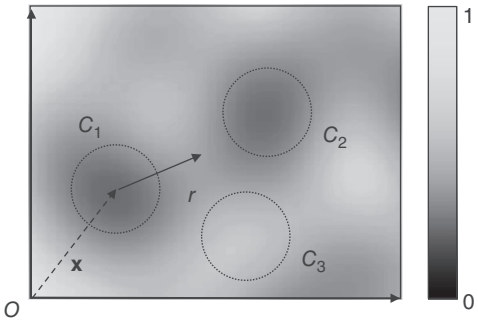


Figure 1.5 *An illustration of the calculation of the autocorrelation function for a mixture*

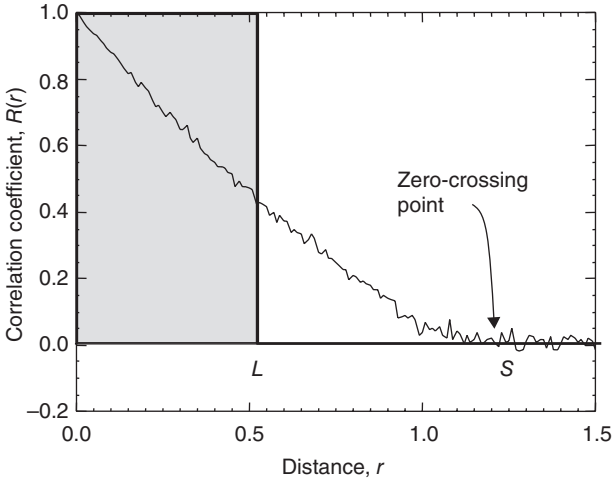


Figure 1.6 *The autocorrelation function for a mixture showing the definition of the length scale of segregation*

Using these ideas of spatial correlation of concentration fields, the length scale of segregation was defined by Danckwerts (1957) as

$$S = \int_0^{\infty} R(r)\ dr \approx \int_0^{\xi} R(r)\ dr \tag{1.7}$$

In practice, the correlation function does not remain exactly at zero for large distances r and hence the upper limit is usually replaced by the first zero-crossing point $r = \xi$, as shown in Figure 1.6. The figure also provides an interpretation of the length scale *L:* the real correlation function is replaced by a region of perfect correlation over a distance *S,* signifying the size of the unmixed regions of almost uniform concentration.

A volume of segregation may also be defined as

$$V = 2\pi \int_0^{\infty} r^2 R(r)\ dr \approx 2\pi \int_0^{\xi} r^2 R(r)\ dr \tag{1.8}$$

and for a linear correlation function

$$V = \frac{4\pi}{3} S^3 \tag{1.9}$$

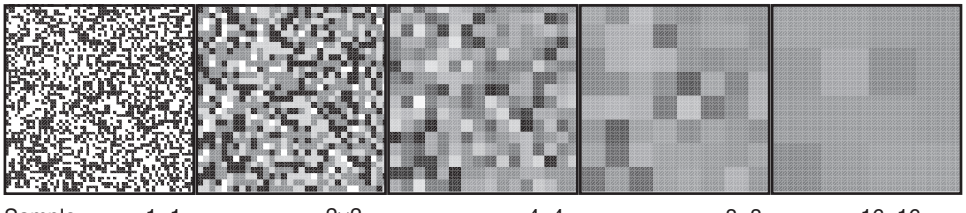
which indicates that S will represent the radius of the unmixed regions.

The length scale of segregation is a useful concept for coarse-grained mixtures in which individual particles may be distinguished; however, it conveys little information about variations in concentration between different samples from the mixture, which is why the intensity of segregation is also required.

Figure 1.7 shows an analysis of a 50:50 binary mixture that is fully randomized; in the left hand picture, the mixture is viewed at the scale of scrutiny of a single particle; moving towards the right, the sample sizes increase, showing the effects of choosing different scales of scrutiny. Here the correlation coefficient has been obtained using a Monte-Carlo technique; the mixture is sample at 5000 pairs of points a distance r apart ($r = 1$ corresponds to the length of the side of one of the black or white particles that form the mixture). For a sample containing a single particle, $n_p = 1$, the mixture is completely segregated, and hence the intensity of segregation is $I = 1$. For larger scales of scrutiny, the intensity of segregation is always close to the theoretical value given by equation (1.3) and hence it decreases as the number of particles in the sample increases. For a well-mixed system,

$$I \approx \frac{\sigma_r^2}{\sigma_0^2} = \frac{1}{n_p} \tag{1.10}$$

The values show in Figure 1.7 correspond almost exactly to equation (1.10), with any minor differences caused by the numerical calculation method. Visually, the mixture



Sample	1×1	2×2	4×4	8×8	16×16
Intensity	1.00	0.25	0.06	0.01	0.00
Scale	0.5	0.9	1.8	3.1	6.1

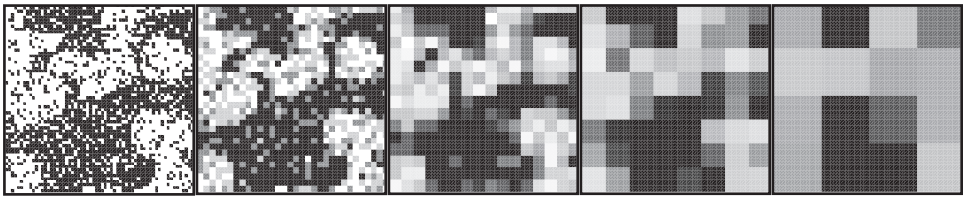
Figure 1.7 *The effect of the scale of scrutiny on the intensity and length scale of segregation for a fully random mixture (lengths scales are multiples of the particle size)*

becomes less segregated as the sample size (scale of scrutiny) increases. The length scale of segregation for the left-hand image ($n_p = 1$) is about half the particle size and remains at approximately half the length scale of each sample. From this point of view the mixture is well-mixed; the size of the unmixed regions is comparable with the radius of the sample size.

Figure 1.8 shows a incompletely mixed situation, with intensities of segregation that are considerably higher than for the equivalent sample size in Figure 1.7; even as the scale of scrutiny increases, there are noticeable differences in concentration between samples drawn from the same mixture. Furthermore, the length scale of scrutiny for $n_p = 1$ (left hand image) is considerably larger than half the particle size, indicating that there are regions of unmixed concentrations. Increasing the scale of scrutiny (moving to the right) decreases the intensity of segregation, but the values are considerably larger than for the equivalent sample size in Figure 1.7. In Figure 1.8 the length scale also increases with the sample size; it is only for the $n_p = 16 \times 16$ sample, that the length scale of segregation approaches half the sample size; that is, the sample size is now close to the size of the unmixed regions, which are clearly visible in the left hand image.

So the last two examples, illustrate how when viewed at an appropriate scale of scrutiny (that is the required sample size which will depend on the end use for the mixture), then the concepts of length scale and intensity of segregation can be used to obtain quantitative information about the quality of the mixture, in terms of both the size of the unmixed regions and their uniformity. The mixture of Figure 1.7 is coarse grained and so when the sample size is small, it appears as being segregated, even though it is in fact fully randomized. The intensity of segregation is high for $n_p = 1$ and $n_p = 4$, because Danckwerts's definition of the intensity does not account for the variance of a random mixture with sample size n_p. Other workers have included this effect in their definition of mixedness quantities, as described in the next section.

In practice, in batch mixing operations, the length scale of segregation is difficult to obtain, as the spatial autocorrelation function is required by equations (1.6) and (1.7), that is it requires pairs of concentrations to be measured, at known distances apart (Rielly *et al.*, 1994). Consequently the majority of workers have tended to focus on the intensity of segregation, or similar measures of mixedness (see Section 1.5); the intensity of segregation is more easily obtained from an assessment of the variance between samples withdrawn from



Sample	1×1	2×2	4×4	8×8	16×16
Intensity	1.00	0.48	0.31	0.21	0.11
Scale	1.9	3.7	5.1	6.4	8.3

Figure 1.8 *The effect of the scale of scrutiny on the intensity and length scale of segregation for a poorly mixed mixture (lengths scales are multiples of the particle size)*

the batch, without knowledge of their spatial positions. In contrast, for continuous blenders, the definition of the correlation function can be applied in the time domain to samples that are continuously monitored at the exit from the mixer. Weinekötte and Reh (1995) redefined the scale of segregation in terms of a temporal autocorrelation function when written in the form

$$R(\tau) = \frac{\overline{\left(a(t)-\overline{a}\right)\left(a(t+\tau)-\overline{a}\right)}}{\overline{\left(a(t)-\overline{a}\right)^2}} \tag{1.11}$$

where τ is the time delay and $a(t)$ is the concentration at time t. The scale of segregation can then be calculated by adapting equation (1.7)

$$S = \dot{m} \int_0^\infty R(\tau)\ d\tau \tag{1.12}$$

where $\dot{m}$ is the mass flow rate leaving the mixer. In this case, the scale of segregation represents the mass of the unmixed regions. The definition of the intensity of segregation for a continuous blender remains the same as in equation (1.5), but with the variance calculated from the temporal variation of the outlet concentration, $a(t)$. Weinekötte and Reh (1995) also showed how both the scale and intensity of segregation can be conveniently obtained from the power spectral density of the outlet concentration from a continuous mixer.

1.5 *Determining the End-Point of Mixing:* Comparison of Mixing Indices

The previous section describes two methods to characterize the end-point of a mixture, which could be applied to samples withdrawn from a batch blender or from measurements at the exit from a continuous mixer. In this section, a number of these statistical measures of mixedness will be compared and critically reviewed to determine their effectiveness in establishing an end point of mixing.

The definition of mixing indices dates back to Lacey (1943) who proposed various statistical measures to represent the closeness of approach to the randomly mixed state. In general, mixing indices are defined as

$$M = \frac{\text{amount of mixing that has occurred}}{\text{amount of mixing that could occur}} \tag{1.13}$$

The most extreme conditions are given by an initially fully segregated mixture with variance σ_0^2 given by equation (1.4) and a fully randomized sample with a variance of σ_r^2 given by equation (1.3). Hence, Lacey (1943) proposed

$$M = \frac{\sigma_0^2 - \sigma^2}{\sigma_0^2 - \sigma_r^2} \tag{1.14}$$

which varies between 0 (completely segregated) and 1 (fully randomized). This definition has been criticized in the past (Harnby, 1985), because even in a poor quality mixture the variance is closer to σ_r^2 than σ_0^2 and hence the useful range is restricted to $0.75 < M < 1$. A feature of this definition of a mixing index is that it shows some sensitivity to the number of particles in a sample, through the variance of a fully randomized sample, with σ_r^2 given by equation (1.3). Therefore a small improvement in the degree of homogeneity could be obtained by grinding or crushing the particles, whilst still containing the same scale of scrutiny in terms of the mass of the sample. In practice, however, grinding to particle sizes below about 1 μm becomes ineffective, because cohesive interactions cause multi-particle agglomerates to form. As a consequence zero variance mixtures are still difficult to achieve (Staniforth, 1982).

Many other mixing indices have been proposed in the literature, but they all take a similar form to that originally defined by Lacey (1943). Rielly *et al.* (1994) and Fan *et al.* (1990) have reviewed the range of mixing indices available, as summarized in Table 1.1. In the majority of cases a mixing index of 0 represents a fully segregated mixture, whereas a mixing index of unity corresponds to a fully mixed situation.

Table 1.1 *Definitions of mixing indices from the literature for use with particulate systems*

Source	Mixing index	Fully segregated	Full mixed
Rose and Robinson (1965)	$M_1 = 1 - \frac{\sigma}{\sigma_0}$	0	$1 - \frac{\sigma_r}{\sigma_0}$
Miles (1962)	$M_2 = 1 - \frac{\sigma^2}{\sigma_0^2}$	0	$1 - \frac{\sigma_r^2}{\sigma_0^2}$
Lacey (1954)	$M_3 = \frac{\sigma_0^2 - \sigma^2}{\sigma_0^2 - \sigma_r^2}$	0	1
Weidenbaum and Bonilla (1955)	$M_4 = \frac{\sigma_r}{\sigma}$	σ_r / σ_0	1
Beaudry (1948)	$M_5 = \frac{(\sigma_0 / \sigma) - 1}{(\sigma_0 / \sigma_r) - 1}$	0	1
Yano *et al.* (1956)	$M_6 = \frac{\sigma}{\sigma_0}$	1	σ_r / σ_0
Ashton and Valentin (1966)	$M_7 = \sqrt{\frac{\ln\sigma_0^2 - \ln\sigma^2}{\ln\sigma_0^2 - \ln\sigma_r^2}}$	0	1
Lacey (1943)	$M_8 = \frac{\sigma_0 - \sigma}{\sigma_0 - \sigma_r}$	0	1
Westmacott and Lineham (1960)	$M_9 = \frac{\sigma^2}{\sigma_0^2}$	1	σ_r^2 / σ_0^2

Although these definitions relate to coarse particulate mixtures, they could also be applied to fine-grained or fluid systems, in which case the variance σ_r^2 would be taken to equal zero. These analyses of the end point of a particulate blending operation are often conducted for a binary mixture of particles with equal sizes and hence there is no difference between a mass- or number-based definition of the concentration. In practice, however, mixtures will often contain a range of particle sizes and will be characterized by mass concentrations of particular species. In this case Poole *et al.* (1964) has shown that the random variance, σ_r^2, is given by

$$\sigma_r^2 = \frac{\bar{a}(1-\bar{a})}{W}\left[(1-\bar{a})\sum_i (f_i W_i)_A + \bar{a}\sum_i (f_i W_i)_B\right] \tag{1.15}$$

where $\bar{a}$ is the mass fraction of *A* in a mixture with total sample mass of *W*, f_i is the mass fraction of particles of *A* in size range *i* with mean particle mass of W_i (and similarly for species *B*. Mixtures containing particles with different sizes are often subject to segregation and hence mixing indices do not always increase monotonically with increasing time. For example, Harnby (1985) present mixing index data for a Rotocube, in which Lacey's definition of M_3 (see Table 1.1) initially increases with time, passes through a maximum and then decreases to an asymptotic value of around 0.85 as a result of particle segregation. The tumbling action of batch mixers such as the Rotocube will initially provide some blending of dry powders, but at later stages will result in a degree of segregation, such that the fully random state is never achieved with non-uniformly sized particles.

Rielly *et al.* (1994) compared the mixing indices of Table 1.1 by examining a simplified model that described the evolution of the concentration variance of a binary mixture of uniformly sized particles. In general blending between binary components occurs by a combination of mechanisms:

1. Convection and shear mixing, in which groups of particles are displaced or slip relative to each other over large distances. Convection without shear or relative displacement of particles is not effective for mixing.
2. Diffusion, in which particles move relative to each other over small scales, as a result of random collisions; in general, there will be a flux of particles down the concentration gradient, because of random collisions.

In a batch mixer, a diffusion type model may be used to describe the rate at which binary particles mix. For example, in a rotating cylinder mixer, of length *L*, the following axial diffusion equation may be written:

$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial z^2} \tag{1.16}$$

where *a* is the concentration of particles of *A* at axial distance *z* from the end of the mixer and at time *t*; *D* is an axial diffusion coefficient. In equation (1.16) is assumed that radial diffusion is very fast (due to cylinder rotation), whereas axial diffusion is much slower. Initially the mixer is fully segregated containing equal concentrations of *A* and *B* particles

in the left and right hand ends of the mixer. Therefore, the initial and boundary conditions for equation (1.16) are

$$\text{at } t = 0, \qquad \begin{aligned} a &= a_0 \text{ for } 0 < z < L/2 \\ a &= 0 \quad \text{for } L/2 < z < L \end{aligned} \tag{1.17}$$

$$\text{at } t > 0, \qquad \frac{\partial a}{\partial z} = 0 \text{ at } z = 0 \text{ and } z = L \tag{1.18}$$

There is an analytical solution to equation (1.16) for $a(z,t)$, subject to these boundary conditions, from which the variance of the concentration distribution of A particles may be calculated from

$$\sigma^2 = \frac{2}{\pi^2} \sum_{j=1}^{\infty} \left(\frac{\sin\left(j\bar{a}\pi\right)}{j} \right)^2 \exp\left(-\frac{2j^2\pi^2 Dt}{L^2} \right) \tag{1.19}$$

where $\bar{a}$ is the mean concentration of species A in the mixer. The variance from equation (1.19) is plotted in Figure 1.9(a) for the case of binary mixture with mean concentration, $\bar{a} = 0.5$, giving an initial fully segregated variance of $\sigma_0^2 = 0.25$. The calculated variance fall rapidly at first (note the logarithmic axis) and then becomes asymptotic to zero at long times, which is realistic only for fine-grained mixtures in which the scale of scrutiny contains a very large number of particles. In other words, the mixture can attain $\sigma_r^2 \approx 0$. Figure 1.9(b) shows the various mixing indices plotted against dimensionless time for a sample containing a large number of particles. Mixing indices M_6 and M_9 decrease with increasing time, starting from an initial value of unity and falling towards a final value of zero; they show poor sensitivity at long times. Mixing indices M_2 and M_3 become equal for the special case of $\sigma_r^2 \approx 0$ and follow the more usual convention of starting at 0 (fully segregated) and finishing at 1 (fully mixed). However, neither of these indices show much sensitivity during the final stages of mixing. Similarly indices M_1 and M_8 become equal for

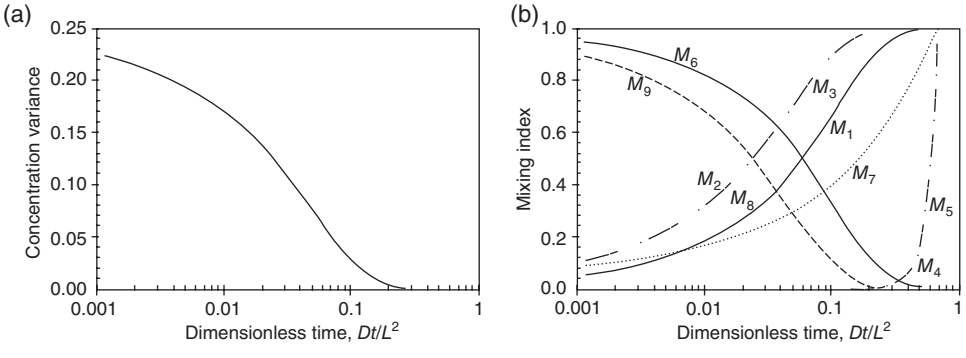


Figure 1.9 *Comparison of the variance from equation (1.19) for the diffusion model and some commonly used mixing indices for a sample size of 10^6 particles*

samples containing large numbers of particles, but also show poor sensitivity in the final stages of mixing. M_4 and M_5 show no sensitivity at early times, and extreme sensitivity in the final stages of mixing. They also highlight one of the problems with the diffusion model, which is that it predicts variances that are below σ_r^2 and hence can yield values of M_4 and M_5 greater than 1; as will be shown later, both M_4 and M_5 show significant dependence on the number of particles in the sample, that is they depend on the scale of scrutiny. Ashton and Valentin (1966) proposed the use of logarithms in their definition of M_7 to overcome such problems; Figure 1.9(b) shows that indeed M_7 shows good sensitivity to changes in the degree of mixedness in both the early and late stages of mixing and therefore is one of the better mixing indices that can be selected.

An alternative model for the kinetics of the mixing process may be formulated. Oyama and Ayaki (1955) proposed a first-order dependence for the decrease of the concentration variance towards the randomized variance, σ_r^2, as indicated in

$$\frac{d\sigma^2}{dt} = -k\left(\sigma^2 - \sigma_r^2\right) \tag{1.20}$$

where k^{-1} may be regarded as a time-constant. Integrating equation (1.20) gives

$$\frac{\sigma^2 - \sigma_r^2}{\sigma_0^2 - \sigma_r^2} = \exp(-kt) \tag{1.20}$$

which is illustrated in Figure 1.10 for the case of a sample containing 10 particles. In contrast to the diffusion model (Figure 1.9), the first-order model shows that the variance becomes asymptotic to a non-zero value at long times. The variance also depends on the number of particles within the sample, since this affects the fully randomized variance, σ_r^2, through equation (1.3). Figure 1.10(b)–(d) show that both M_4 and M_5 show sensitivity at large times, but also exhibit significant dependence on the number of particles in the sample, that is they depend on the scale of scrutiny.

This is a disadvantage, as these mixing indices are affected by the chosen scale of scrutinty; the only become independent of sample size, when the number of particles becomes very large. The indices M_2 and M_3 are almost indistinguishable for samples containing 100 or mode particles, as are the mixing indices represented by M_1 and M_8. All of these indices are relatively insensitive in the final stages of mixing. However, as noted in connection with the diffusion model (Figure 1.9), the use of logarithms in the definition of M_7 gives good discrimination over the full range of mixing times and hence is recommended.

1.6 Continuous Flow Mixers

1.6.1 Idealized Mixing Patterns

The majority of this chapter has focussed on mixing in batch process systems, where the spatial distribution of components approaches a well-mixed condition with increasing batch time. Batch processes are inherently unsteady and are often best suited to small scale production, or for multi-product manufacturing processes; hence the vast majority of

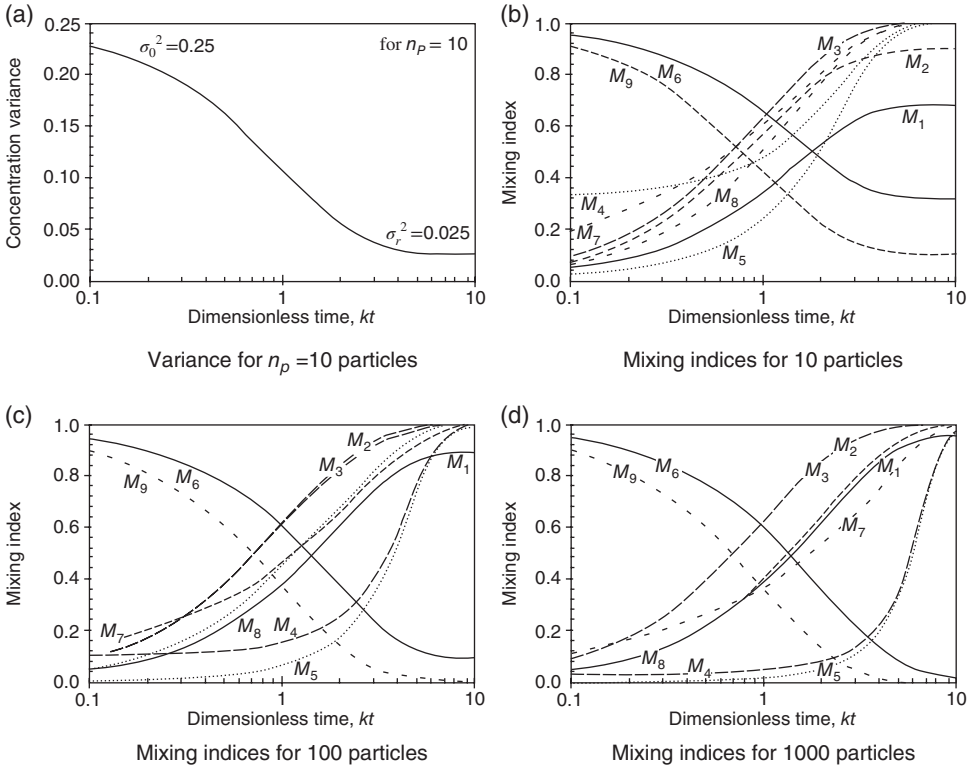


Figure 1.10 *Comparison of the variance and some commonly used mixing indices for diferent sample sizes. The concentration variance is assumed to decrease by a first-order process with time constant* k^{-1}

pharmaceutical operations are conducted as batch processes. Recently, however, pharmaceutical companies have become more interested in continuous flow processes that can be intensified and applied even for small scale production runs.

Continuous processes are designed to operate under steady conditions and the well-mixed state is usually approached with increasing *residence time* within a mixer. The residence time may be defined as the time that a fluid (or solid) element remains within the mixer, or the age of an element in the device. The plug flow reactor (PFR) has an idealized mixing pattern, in which all ingredients in the mixture experience exactly the same residence time and hence receive equal amounts of processing within the mixer. Figure 1.11 shows that a PFR exhibits perfect mixing in the radial direction, but no mixing in the axial direction. Consider an experiment in which an input pulse of tracer material is injected into the plug flow; it mixes immediately in the radial direction and will be advected axially at a velocity, u. With no mixing in the axial direction, the concentration distribution is independent of position z in the mixer, (or the age of the fluid element, $\tau = z/u$) and the pulse of tracer propagates along the mixer without change of shape.

For many operations, for example reaction, crystallization, heat treatment and sterilization, this is the ideal flow pattern to ensure a consistent product, so long as there are

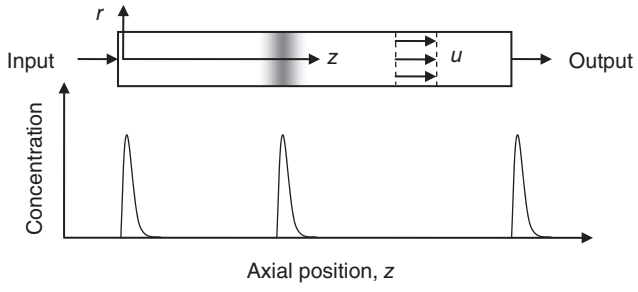


Figure 1.11 *An idealized plug flow device*

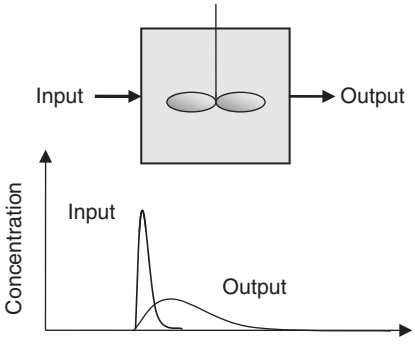


Figure 1.12 *An idealized continuous stirred tank reactor*

negligible variations in the feed composition, since each fluid element receives experiences exactly the same history within the device.

In contrast, the continuous flow stirred tank reactor (CSTR) is the other extreme of idealized mixer. As soon as feed enters the device it becomes instantly mixed with fluid already inside the CSTR. At any instant in time, the contents of the CSTR are spatially homogeneous and the outlet stream contains the same composition as is in the vessel. Figure 1.12 shows that as soon as a pulse of tracer enters the CSTR, the output concentration starts to rise; mixing with lower concentrations already present within the tank, causes dilution and a reduction in concentration, in comparison with the input. The CSTR is characterized by a broad range of residence times; all ages of fluid inside the vessel have an equal probability of leaving through the outlet. Therefore, some fluid elements leave very shortly after they have arrived inside the CSTR and others remain for a very long time. In this way variations in the feed composition are smoothed out by the process of mixing in time, which will be described in the next section. Such a process is also described as back-mixed, because fluid elements of different age mix with each other.

1.6.2 Residence Time Distributions

The idealized mixing patterns of the PFR and CSTR have different distributions of the residence time. Danckwerts (1953b) defined the residence time distribution (RTD) in the same way as a probability density function: $E(t)\ dt$ is the probability that a fluid element

will have an residence time between t and $t + dt$. The cumulative probability that the fluid has a residence time less than T is

$$\Pr(t < T) = \int_0^T E(t)\ dt \tag{1.21}$$

and hence

$$\Pr(t < \infty) = \int_0^\infty E(t)\ dt = 1 \tag{1.22}$$

The RTD can be easily measured for process equipment by introducing a pulse of tracer (mathematically this is a Dirac delta function, $\delta(t)$) at the inlet to the device and measuring the outlet concentration as a function of time. The RTD may then be obtained from

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)\ dt} \tag{1.23}$$

Normalization using the integral in the denominator of equation (1.23) simply ensures that equation (1.22) is satisfied.

Figure 1.13 shows a typical residence time distribution, of a device that exhibits a considerable degree of back-mixing, or mixing in time, as well as a time delay or plug flow component – the latter is evident because there is an initial delay in the $E(t)$. The cumulative probability (see equation (1.23)) for $T = 10\,\text{s}$ is given by the area under the curve and in this case is 85%. The mean residence for the device may be obtained from the first moment of the RTD

$$\tau = \int_0^\infty tE(t)\ dt = \frac{V}{q} \tag{1.24}$$

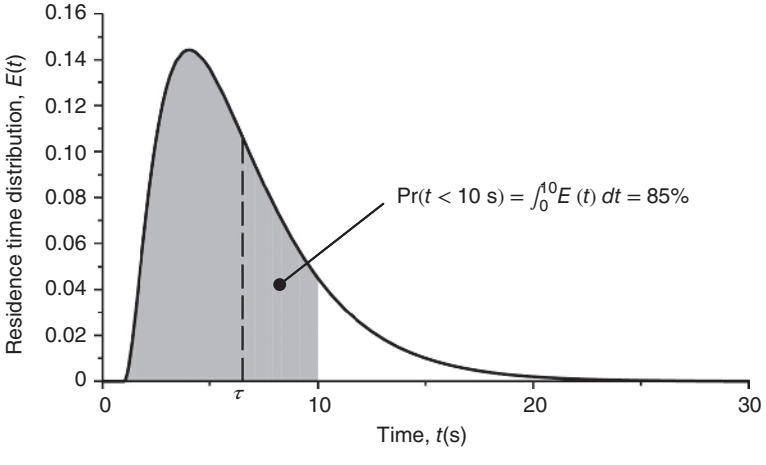


Figure 1.13 *The residence time distribution function*

where V is the volume of the vessel and q is the volumetric flow rate passing through the vessel.

1.6.3 Back-Mixing and Filtering of Disturbances Using a CSTR

Knowledge of the RTD, $E(t)$, allows calculation of the output response, $C_1(t)$ of the system to any variation in the input or feed concentration, $C_1(t)$, using the principle of convolution given by

$$C_1(t) = \int_0^t E(t')\ C_0(t-t')dt' \tag{1.25}$$

Back-mixing allows continuous flow mixers to produce more consistent product compositions, even when the feed composition is varying; effectively these mixers filter disturbances that have a much shorter time scale than the mean residence time. As an example, consider a pulse disturbance in the feed concentration to a PFR and a CSTR, each with a mean residence time of $\tau = 5$ s. The RTDs for these idealized mixers are

$$\text{PFR} \qquad E(t) = \delta(t-\tau) \tag{1.26}$$

$$\text{CSTR} \qquad E(t) = \frac{e^{-t/\tau}}{\tau} \tag{1.27}$$

Applying the convolution integral of equation (1.25) and (1.26) for a square pulse of 1 s width, using the RTDs given by equations (1.26) and (1.27), gives the results shown in Figure 1.14. The pulse is unchanged by passing through the PFR, whereas it effect is attenuated and filtered by passing through the CSTR. This will be the case for pulse widths that are small compared to the mean residence time of the CSTR. This simple example illustrates why CSTRs are used as buffer tanks to smooth out disturbances in continuous flow processes.

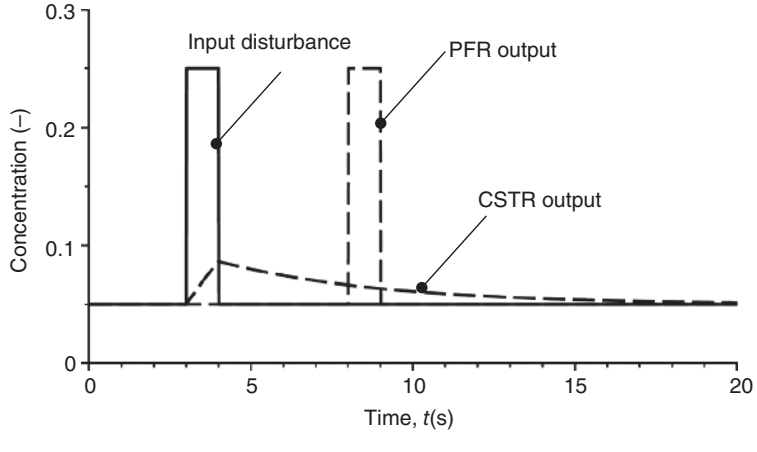


Figure 1.14 *The response of a PFR and CSTR to a disturbance*

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