particulate interactions. These interactions can, to some extent, be thought of as the interactions of the diffuse layers around individual particles and hence the electrical double layer provides the basis for understanding inter-particulate interactions. The DLVO theory describes these interactions.

The DLVO theory (Chapter 5 provides more detail) is concerned with predicting the stability of lyophobic ('solvent-hating') colloids and is relevant here because of the particle size of pharmaceutical suspensions. Essentially, it calculates the energies of attraction and repulsion between similar particles and predicts the overall energy of interaction. From this, deductions can be made as to the likely behaviour of the suspension, e.g. whether particles coalesce and settle, or remain evenly dispersed throughout the medium. This is arguably the most important question in pharmaceutical suspension formulation development, as a fundamental specification for such a formulation is dose reproducibility, which is most easily achieved from a system which remains well dispersed under all conditions.

To calculate the total energy of interaction, V_T, between two particles, the values of V_A and V_R are summed, as shown in Equation 26.2. V_R is the energy of electrical repulsion and by convention this carries a positive sign. V_A is the energy of Van der Waals attractions and by convention is given a negative sign.

$$V_T = V_A + V_R \tag{26.2}$$

Figure 26.3 shows the values of V_A, V_R and V_T for two similar particles suspended in a medium and interacting. Further detailed relationships involving

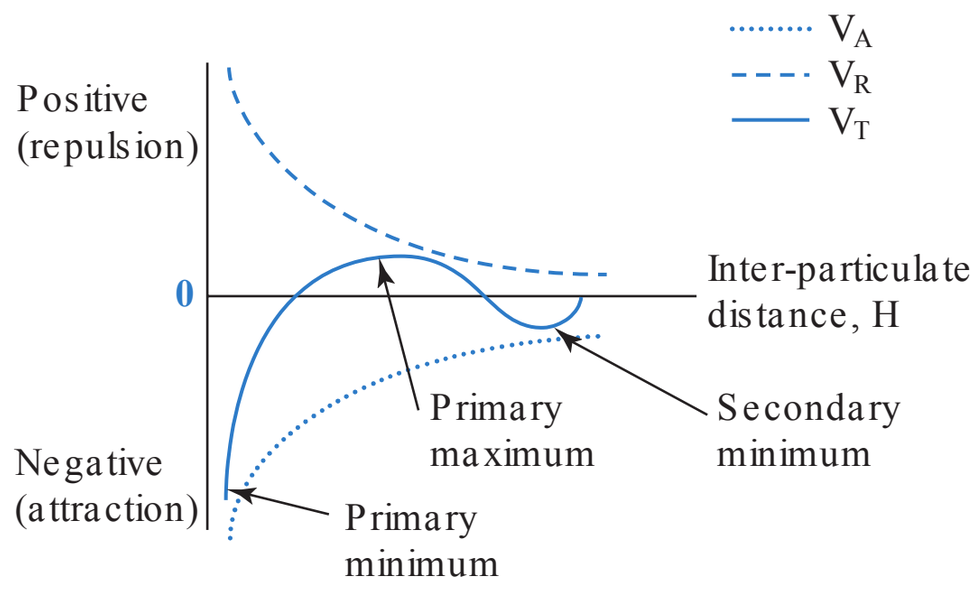

Fig. 26.3 • The energy of interaction between two similar particles, as described by the DLVO theory.

V_A and V_R can be found in Chapter 5. It is important to note that the V_A and V_R curves shown in Figure 26.3 are not mirror images of each other.

The easiest way to consider what happens when two particles interact is to remember that the V_T line gives the overall energy of interaction and that this will change depending on the distance between the two particles. There are three important zones, or values of V_T, in the DLVO diagram: the primary minimum, the secondary minimum and the primary maximum, and the behaviour of the suspension will be dependent on which zone the particles are in. It must also be remembered that all particles will have some thermal energy and will show some movement, whether caused by Brownian motion, the effects of gravity or by external agitation.

The primary minimum

The 'primary minimum' zone is described as a 'minimum' because the total energy is calculated to be below zero (remember that repulsive energy is described as positive and attractive energy as negative). It is described as 'primary' because it is the largest negative deviation from zero. Particles in the primary minimum zone show a higher energy of attraction than repulsion and are therefore likely to move closer together. Imagine two particles are just far enough apart that the energy of attraction balances out the energy of repulsion, so that the overall energy of interaction is zero. Any movement of the particles which brings them closer together will result in an overall mathematical decrease in V_T, i.e. V_T is now attractive and the particles will continue to move closer together. As they do so, the strength of the overall attractive forces increases, moving the particles still closer together, resulting in a further increase in the attractive forces, and so on. The kinetic energy that the particles have (= kT, where k is the Boltzmann constant and T the temperature in Kelvin) is not high enough to overcome the attractive energy, V_T and therefore the particles will eventually aggregate irreversibly. Particles will initially show 'flocculation', whereby the individual particles are loosely attracted to each other, but still act independently; subsequently they will demonstrate 'coagulation' where particles will collide and form larger particles. Such behaviour is undesirable for pharmaceutical suspensions as it will have serious negative effects on the reproducibility of dosing from the system. These changes are illustrated in panel A of Figure 26.4.