Rates of drug dissolution can be adversely affected, however, by unsuitable choice of formulation additives, even though solids of appropriate particle size are used. Tableting lubricant powders, for example, can impart hydrophobicity to a formulation and inhibit drug dissolution. Fine powders can also increase air adsorption or static charge, leading to wetting or agglomeration problems. Micronizing drug powders can lead to changes in crystallinity and particle surface energy which cause reduced chemical stability. Drug particle size also influences content uniformity in solid dosage forms, particularly for low-dose formulations. It is important in such cases to have as many particles as possible per dose to minimize potency variation between dosage units. Other dosage forms are also affected by particle size, including suspensions (for controlling flow properties and particle interactions), inhalation aerosols (for optimal penetration of drug particles to absorbing mucosa) and topical formulations (for freedom from grittiness).

Solubility

All drugs, regardless of their administration route, must exhibit at least limited aqueous solubility for therapeutic efficacy. Thus relatively insoluble compounds can exhibit erratic or incomplete absorption, and it might be appropriate to use a more soluble salt or other chemical derivatives. Alternatively, micronizing, complexation or solid dispersion techniques might be employed. Solubility, and especially degree of saturation in the vehicle, can also be important in the absorption of drugs already in solution in liquid dosage forms, since precipitation in the gastrointestinal tract can occur, modifying bioavailability.

Solubilities of acidic or basic compounds are pH-dependent and can be altered by forming salts, with different salts exhibiting different equilibrium solubilities. However, the solubility of a salt of a strong acid is less affected by changes in pH than the solubility of a salt of a weak acid. In the latter case, when pH is lower, the salt hydrolyses to an extent dependent on pH and pK_a, resulting in decreased solubility. Reduced solubility can also occur for slightly soluble salts of drugs through the common ion effect. If one of the ions involved is added as a different, more soluble salt, the solubility product can be exceeded and a portion of the drug precipitates.

Dissolution

As mentioned above, for a drug to be absorbed it must first be dissolved in the fluid at the site of absorption. For example, an orally administered drug in tablet form is not absorbed until drug particles are dissolved or solubilized by the fluids at some point along the gastrointestinal tract, depending on the pH-solubility profile of the drug substance. Dissolution describes the process by which the drug particles dissolve.

During dissolution, the drug molecules in the surface layer dissolve, leading to a saturated solution around the particles to form the diffusion layer. Dissolved drug molecules then pass throughout the dissolving fluid to contact absorbing mucosa and are absorbed. Replenishment of diffusing drug molecules in the diffusion layer is achieved by further drug dissolution and the absorption process continues. If dissolution is fast or the drug remains in solution form, the rate of absorption is primarily dependent upon its ability to traverse the absorbing membrane. If, however, drug dissolution is slow due to its physicochemical properties or formulation factors, then dissolution may be the rate-limiting step in absorption and influences drug bioavailability. The dissolution of a drug is described in a simplified manner by the Noyes–Whitney equation:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = kA\,(C_S - C) \tag{1.1}$$

where $\frac{\mathrm{d}m}{\mathrm{d}t}$ is the dissolution rate, k is the dissolution rate constant, A is the surface area of dissolving solid, C_S is the drug's solubility and C is the concentration of drug in the dissolution medium at time t. The equation reveals that dissolution rate can be raised by increasing the surface area (reducing particle size) of the drug, by increasing the solubility of the drug in the diffusion layer and by increasing k which in this equation incorporates the drug diffusion coefficient and the diffusion layer thickness. During the early phases of dissolution, $C_S > C$ and if the surface area, A, and experimental conditions are kept constant then k can be determined for compacts containing drug alone. The constant k is termed the intrinsic dissolution rate constant and is a characteristic of each solid drug compound in a given solvent under fixed hydrodynamic conditions.