acid or base and its salt should be the same (because their solubilities are roughly equal at this point). There are, however, numerous examples where this is not the case, for instance doxycycline hydrochloride and doxycycline; sodium salicylate and salicylic acid; and haloperidol mesylate and haloperidol.

These differences suggest that the pH of the solution into which the solid is dissolving (i.e. the boundary layer) is materially different from that of the bulk solvent (and so the solubility of the dissolving species is different from that expected in the bulk solvent). The difference in pH between the boundary layer and bulk solvent arises because the boundary layer is a saturated solution and because dissolution of acids, bases or salts will result in a change in pH; when saturated, the pH change is maximised. Nelson (1957) first noted this correlation during a study of the dissolution of various theophylline salts; salts with higher diffusion layer pH had greater *in vitro* dissolution rates and, importantly, faster *in vivo* absorption.

The pH of the boundary layer at the surface is termed the pH *microenvironment* (pH_{menv}) and is equal to the pH of a saturated solution of the dissolving solid in water. The Noyes-Whitney equation still governs the dissolution rate, but the solubility value is not that of the solute in the dissolution medium but that in a medium of pH_{menv}. As the distance from the surface of the dissolving solid increases, the pH approaches that of the bulk medium (shown earlier in Fig. 23.11).

Effect of salts on partitioning

Ionized species do not partition into organic solvents or non-polar environments. Thus, while solubility may be enhanced by formation of a salt, there is a considerable risk that partitioning will decrease (example data for partitioning of the sodium salt of ibuprofen are given in Table 23.13). There is thus a compromise to be reached between increasing solubility while maintaining bioavailability and it may well be the case that on this basis, the most soluble salt is not taken forward for development.

Table 23.13 Log P and solubility data for ibuprofen sodium salt

pH	Solubility (mg mL^{-1})	log P	% Unionization
4	0.028	n/d	73.81
5	0.156	3.28	21.98
6	1.0	2.42	2.74
7	340.51	0.92	0.28
8	299.04	0.63	0.03

(Sarveiya et al, 2004)

Hygroscopicity

Hygroscopicity refers to the tendency of a substance to attract water from its immediate environment, either by absorption or adsorption. An increase in water content usually results in a change in physicochemical properties. Typically, wet powders will become more cohesive and flowability is reduced. Water also acts to mediate many solid-state reactions, so an increase in water content can often increase the rate of chemical degradation of the active or interaction with any excipients. If the substance is amorphous, then absorption of water causes plasticization of the matrix (effectively the molecular mobility of the molecules is increased) and then major structural change. If the amorphous matrix is a freeze-dried powder, then absorption of water often causes structural collapse. At the extreme, absorption of water will cause amorphous materials to crystallize.

Salts, in particular, usually have a greater propensity to absorb water than the corresponding free acid or base, so the stability of salt forms with respect to environmental humidity must be assured. Some salts (for instance potassium hydroxide or magnesium chloride) are so hygroscopic they will dissolve in the water they absorb, forming solutions. This process is called *deliquescence*. In any event, if water absorption is likely to cause a detrimental change in physicochemical properties, then appropriate steps must be taken to protect the drug candidate or drug product. Typically, this would involve selection of suitable packaging and advising correct storage by the patient.

From an analytical perspective, water uptake is usually determined through a change in mass (although chemical approaches, such as the Karl-Fischer titration, can also be used). Thermogravimetric analysis (TGA) measures mass as a function of temperature, whilst dynamic vapour sorption (DVS) measures mass as a function of humidity at