Drugs with k values below 0.1 mg^{-1} cm^{-2} usually exhibit dissolution rate-limiting absorption. Particulate dissolution can also be examined where an effort is made to control A, and formulation effects can be studied.

Dissolution rate data, when combined with solubility, partition coefficient and pK_a results, provide an insight into the potential in vivo absorption characteristics of a drug. However, in vitro tests only have significance when they are related to in vivo results. Once such a relationship has been established, in vitro dissolution tests can be used as a predictor of in vivo behaviour. The importance of dissolution testing has been widely recognized by official compendia, as well as drug regulatory authorities, with the inclusion of dissolution specifications using standardized testing procedures for a range of preparations.

A guide for predicting the intestinal absorption of drugs for orally administered medicines based on the solubility, dissolution and permeability of drugs, the Biopharmaceutics Classification System (BCS) was established in 1995. This system has proved extremely useful in aiding the design of oral medicines and has recently been extended to incorporate drug absorption and transport and the effects of metabolism.

Partition coefficient and pK_a

As pointed out earlier, for relatively insoluble compounds the dissolution rate is often the rate-determining step in the overall absorption process. Alternatively, for soluble compounds the rate of permeation across biological membranes is the rate-determining step. Whilst dissolution rate can be changed by modifying the physicochemical properties of the drug and/or altering the formulation composition, the permeation rate is dependent upon the size, relative aqueous and lipid solubility and ionic charge of drug molecules, factors which can be altered through molecular modifications. The absorbing membrane acts as a lipophilic barrier to the passage of drugs which is related to the lipophilic nature of the drug molecule. The partition coefficient, for example between oil and water, is a measure of lipophilic character.

The majority of small molecular weight drugs are weak acids or bases and, depending on the pH, exist in an ionized or unionized form. Membranes of absorbing mucosa are more permeable to unionized forms of drugs than to ionized species because of the greater lipid solubility of the unionized forms and the highly charged nature of the cell membrane which results in the binding or repelling of the ionized drug, thereby decreasing penetration.

The dominating factors that therefore influence the absorption of weak acids and bases are the pH at the site of absorption and the lipid solubility of the unionized species. These factors, together with the Henderson–Hasselbalch equations for calculating the proportions of ionized and unionized species at a particular pH, constitute the pH-partition theory for drug absorption. However, these factors do not describe completely the process of absorption since certain compounds with low partition coefficients and/or which are highly ionized over the entire physiological pH range show good bioavailability and therefore other factors are clearly involved.

Crystal properties: polymorphism

Practically all drug substances are handled in powder form at some stage during manufacture into dosage forms. However, for those substances composed of, or containing, powders or compacted powders in the finished product, the crystal properties and solid-state form of the drug must be carefully considered. It is well recognized that drug substances can be amorphous (i.e. without regular molecular lattice arrangements), crystalline, anhydrous, at various degrees of hydration or solvated with other entrapped solvent molecules, as well as varying in crystal hardness, shape and size. In addition, many drug substances can exist in more than one form with different molecular packing arrangements in the crystal lattice. This property is termed polymorphism and different polymorphs may be prepared by manipulation of conditions of particle formation during crystallization such as solvent, temperature and rate of cooling. It is known that only one form of a pure drug substance is stable at a given temperature and pressure, with the other forms, termed metastable, converting at different rates to the stable crystalline form. The different polymorphs vary in physical properties such as dissolution and solid-state stability, as well as processing behaviour in terms of powder flow and compaction during tableting in some cases.

These different crystalline forms can be of considerable importance in relation to ease or difficulty