Table 20.2 Examples of drugs where a reduction in particle size has led to improvements in bioavailability

Drug	Therapeutic class
Digoxin	Cardiac glycoside
Nitrofurantoin	Antifungal
Medroxyprogesterone	Hormone acetate
Danazol	Steroid
Tolbutamide	Antidiabetic
Aspirin	Analgesic
Sulfadiazine	Antibacterial
Naproxen	Non-steroidal anti-inflammatory
Ibuprofen	Non-steroidal anti-inflammatory
Phenacetin	Analgesic
Griseofulvin	Antifungal
Fenofibrate	Lipid regulating agent
Megestrol acetate	Apetite loss
Aprepitant	Anti-emetic
Rapamycin	Immunosuppressant
Lapinovir/ritonavir	HIV protease inhibitors

products are the immunosuppressant Rapamune®, the anti-emetic Emend® and the lipid regulating agent TriCor® containing fenofibrate. Megace® ES is an oral nano-suspension of megestrol acetate for the treatment of appetite loss, severe malnutrition, or unexplained significant weight loss in AIDS patients. It is a reformulation of the oral suspension using Nanocrystal® technology to improve the dissolution rate, absorption rate and bioavailability of the original formulation. The formulation is less viscous and allows a quarter of the volume to be dosed, thus aiding patient swallowing and compliance.

As well as milling with wetting agents, the effective surface area of hydrophobic drugs can be increased by the addition of a wetting agent to the formulation. The presence of polysorbate 80 in a fine suspension of phenacetin (particle size less than 75 μm) greatly improved the rate and extent of absorption of the phenacetin in human volunteers compared to the same-size suspension without a wetting agent. Polysorbate 80 helps by increasing the wetting and solvent penetration of the particles and by minimizing aggregation of suspended particles, thereby maintaining a large effective surface area. Wettability effects are highly drug specific; however wetting agents are routinely added to many formulations.

If an increase in the effective surface area of a drug does not increase its absorption rate, it is likely that the dissolution process is not rate limiting. For drugs such as penicillin G and erythromycin, which are unstable in gastric fluids, their chemical degradation will be minimized if they remain in the solid state. Thus, particle size reduction would not only serve to increase their dissolution rate but would simultaneously increase chemical degradation and therefore reduce the amount of intact drug available for absorption.

Solubility in the diffusion layer, C_s. The dissolution rate of a drug under sink conditions, according to the Noyes–Whitney equation (Eqn 20.2), is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle, C_s. The aqueous solubility of a drug is dependent on the interactions between molecules within the crystal lattice, intermolecular interactions with the solution in which it is dissolving, and the entropy changes associated with fusion and dissolution. In the case of drugs that are weak electrolytes, their aqueous solubility is dependent on pH (as discussed in Chapter 2). Hence in the case of an orally administered solid dosage form containing a weak electrolyte drug, the dissolution rate of the drug will be influenced by its solubility and the pH in the diffusion layer surrounding each dissolving drug particle. The pH in the diffusion layer – the microclimate pH – for a weak electrolyte will be affected by the pK_a and solubility of the dissolving drug and the pK_a and solubility of the buffers in the bulk gastrointestinal fluids. Thus differences in dissolution rate will be expected in different regions of the gastrointestinal tract.

The solubility of weakly acidic drugs increases with pH and so as a drug moves down the gastrointestinal tract from the stomach to the intestine, its solubility will increase. Conversely, the solubility of weak bases decreases with increasing pH, i.e. as the drug moves down the gastrointestinal tract. It is important therefore for poorly soluble weak bases to dissolve rapidly in the stomach, as the rate of dissolution in the small intestine will be much slower. The antifungal drug ketoconazole, a weak base, is particularly sensitive to gastric pH. Dosing