through the stomach unchanged, as the coating is unaffected by the acidic environment. On the other hand, the enteric coating dissolves in the basic environment of the intestines. The drug is released and then free to pass into the systemic circulation.

Excipients can also have a positive impact on the permeability of a compound. As discussed in previous chapters, passive diffusion plays a major role in permeability. There are a number of excipients referred to as bioenhancers that can be incorporated into a solid dosage form for the purposes of increasing compound permeability. Typical examples include Tween®-80 (Polysorbate-80), sodium lauryl sulfate (sodium dodecyl sulfate), Labrafil® (PEGylated oils), and Labrasol® (PEGylated caprylic/capric glycerides). In some cases, these agents form mixed micelles with membrane lipids or increase the fluidity of the cell membrane, making compound permeation easier and faster. In other cases, excipients interact with lipids at the membrane surface increasing the hydrophobicity on the membrane surface, which allows a compound to enter the membrane more easily.[29]

The choice of excipients is only one aspect of formulation that must be considered prior to beginning a clinical program. Particle size of the API can have a significant impact on whether or not a drug can be effectively delivered, especially when the rate of dissolution is a limiting factor. As the particle size of a therapeutic agent decreases, the overall surface area available for dissolution increases. Decreasing the particle size of a drug product from 10 μm to 200 nM, for example, increase the overall surface area by a factor of 50.[30] The significant increase in surface area can increase the rate of dissolution, which can, in turn, increase the bioavailability and systemic exposure of a candidate compound. The bioavailability of the synthetic steroid Danocrine® (Danazol, Figure 9.10), for example, jumps from 5.1% in a

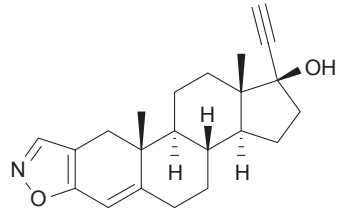

FIGURE 9.10 Danocrine® (Danazol).

conventional formulation to 82.3% when nanoparticles are employed in an oral formulation (average particle size of 169 nM). The C_{max} also increases, jumping from 0.2 μg/mL to 3.01 μg/mL.[31] A number of different milling processes have been developed to facilitate micro- and nanoparticle production (e.g., ball mill, fluid energy mill, cutter mill, and hammer mill).[32] It is important to keep in mind, however, that particle size reduction does not affect the absolute solubility of a given compound. Solubility is a