TABLE 17.2
Pharmacokinetic Parameters Following Oral and Intravenous Administration of Danazol Formulations to Fasted Male Beagle Dogs ($n = 5$)

Formulation	C_{max} (μg/mL)	T_{max} (hr)	AUC[a] (μg/mL·hr)	Absolute Bioavailability
Cyclodextrin oral	3.94 ± 0.14	1.2 ± 0.2	20.4 ± 1.9	106.7 ± 12.3
Nanoparticle dispersion	3.01 ± 0.80	1.5 ± 0.3	16.5 ± 3.2	82.3 ± 10.1
Conventional dispersion	0.20 ± 0.06	1.7 ± 0.4	1.0 ± 0.4	5.1 ± 1.0
Cyclodextrin IV			19.8 ± 0.6	100

Source: Data generated by NanoSystems, Elan Drug Technologies, a member of the Elan Corporation, plc.
[a] Based on NONLIN 84 AUC values normalized to a dose of 20 mg/kg.

Therefore, the fraction of unabsorbed drug decreases as overall bioavailability increases. Nanoparticles in particular provide for a large surface area available for dissolution since sizes are generally <1000 nm in diameter and *in vivo* agglomeration is minimized by particle stabilization. Table 17.2 illustrates the absolute oral bioavailability of several Danazol formulations: nanoparticle dispersion, solubilized cyclodextrin oral formulation, and conventional suspension. Danazol represents a poorly water-soluble compound (10 μg/mL) whose oral bioavailability is dissolution limited. The results indicated that size reduction of Danazol crystals from 10 μm as conventional suspension to sizes less than 200 nm nanoparticle dispersion resulted in approximately a 16-fold increase in absolute bioavailability (Liversidge and Cundy, 1995). Studies with an oral phenytoin nanoparticle dispersion indicated increases in absorption of nearly threefold when administered to healthy volunteers as compared to an aqueous suspension of micronized drug substance (Wood et al., 1995). For the anti-inflammatory agent naproxen, it has been demonstrated in the rat that size reduction of naproxen from 20–30 μm to 270 nm led to results indicating decreased gastric irritation following oral administration as well as a fourfold increase in the rate of absorption (Liversidge and Conzentino, 1995). Furthermore, in human clinical trials, the time to onset of action of a nanoparticle oral suspension of naproxen reached significant plasma levels (t90) in less than 20 min, which was 12-fold faster than commercial formulations of larger particle size (Figure 17.11).

Nanoparticle technology provides for stable solid-in-liquid dispersions of drug with particle sizes generally <1000 nm, thus making an ideal medium for aerosol delivery of poorly water-soluble drugs to the nasal cavity or pulmonary region (Ostrander et al., 1999; Jacobs and Muller, 2002; Rasenack et al., 2003; Irngartinger et al., 2004; Hernandez-Trejo et al., 2005; Gonda, 2006). Surface area coverage by nanoparticle aerosols can be markedly increased relative to micron-sized particles. For example, the theoretical surface area covered by 50 μL of spray volume at a drug concentration of 0.5 mg/mL with particles ~5 μm apart can be calculated to be 0.095 cm2 for 5 μm particles, but increases to 1493 cm2 for 0.2 μm particles. Nebulization studies using a cascade impactor have been performed with nanoparticle dispersions of beclomethasone diproprionate (BDP) of mean particle size 260 nm as compared to an aqueous suspension of BDP having a particle size of 10.5 μm (Ruddy and Eickhoff, 1996; Wiedmann et al., 1996). The cumulative mass fraction of BDP obtained from the cascade impactor was recorded as a function of the cutoff diameter of the impactor stage (i.e., aerosol size in μm). The data suggested that ~80% of nanodispersion formulations reaching the impactor could be found in the <2.5 μm aerosol droplets and represented *respirable* particles. In contrast, the larger micronized BDP formulation, that is, mean diameter ~10.5 μm, showed <40% of the particles to be present in the <2.5 μm aerosol droplets with rapid falloff to only ~10% particles in the 1.25 μm aerosol droplets. In conclusion, size reduction to nanoparticles improved the delivery efficiency of BDP by nebulization as compared to micronized suspensions.