twice that of polymorph A. Even with a large particle size, polymorph B still gave better blood levels than polymorph A, showing the relative importance of the solid state. Similar effects have been seen with solvated pharmaceuticals. Abdou (1989) has summarized the work of Poole et al., which shows that ampicillin anhydrate gave higher blood levels in humans compared to ampicillin trihydrate.

There are numerous accounts in the literature of increased bioavailability in animals when changing the solid state. Kato and Kohetsu (1981) showed that form II amobarbital is more rapidly absorbed *in vivo* than form I. Dissolution rate experiments in water at 37°C showed a 1.6 times faster dissolution rate *in vitro* for form II compared to form I. Yokoyama et al. (1981) found that form III of 6-mercaptopurine was 1.5 times as bioavailable in rabbits as form I. It was six to seven times as soluble as the form I polymorph in studies by Kuroda et al. (1982). Kokubu et al. (1987) examined the therapeutic effect of different polymorphs of cimetidine in inhibition of ulcers in the rat. Pharmacokinetic studies found that form C was 1.4–1.5 times as bioavailable as forms A and B. This translated into a greater protection against stress ulceration, as shown in Table 19.4. The effect of form C was significant compared to forms A, B, and D, which were all equivalent.

Other studies have demonstrated that polymorph differences do not always translate into bioavailability differences. Gunning et al. (1976) have published results for disopyramide, an example of a drug that showed similar dissolution rates for both forms (I and II). Bioavailability studies in healthy human volunteers also showed no differences in bioavailability from identical capsule formulations of the two polymorphs. Umeda et al. (1984) reported on the case of benoxaprofen, in which the two forms had no significant differences in bioavailability in rabbits, despite a 1.5 times solubility advantage for form I over form II. Bioavailability differences for solid states need to be verified by *in vivo* studies, and in those cases where there is no advantage, the more stable form should be developed for stability reasons.

Amorphous solids represent an attractive approach for improving the oral bioavailability of poorly soluble drugs. As a result of their higher free-energy state, amorphous solids exhibit higher solubility and faster dissolution than their crystalline forms. These enhanced properties may result in an improved bioavailability if solubility or dissolution of the drug is the limiting step for absorption in the gastrointestinal tract. Kim et al. (2008) found that an amorphous form of atorvastatin calcium, prepared by an antisolvent process, resulted in an increase of 3.4 times for both the intrinsic dissolution rate and apparent solubility in water at 37°C compared to the crystalline form. Similar results were seen with an amorphous atorvastatin solid prepared by a spray-drying method. These increases in dissolution and apparent solubility were enough to increase the bioavailability 2–4 times in rats.

Due to the inherent physical instability of amorphous solids, the majority of *in vivo* studies utilize an amorphous solid dispersion containing a polymer excipient to stabilize the amorphous state.

TABLE 19.4
Comparison of the Four Crystalline Forms of Cimetidine in Their Ulcer Inhibitory Effect in Rats at 12.5 mg/kg

Treatment	Mean Ulcer Area (mm)	Inhibition (%)
Control	22.3 ± 4.3	0
Form A	6.9 ± 2.1	69.1 ± 25.3
Form B	8.7 ± 4.8	60.8 ± 31.1
Form C	2.8 ± 1.7	87.4 ± 26.7
Form D	8.0 ± 2.6	64.1 ± 25.7

Source: Kokubu, H. et al., *Int. J. Pharm.*, 35, 181–183, 1987. With permission.