CASE STUDY 5 (*Continued*)

the saturated concentration of dasatinib at pH 4.0 was 3.6×10^{-2} mg/mL. At pH 6.3, the value dropped 5-fold. The dissolution profile of a 20-mg dasatinib tablet was determined with USP apparatus II (paddles). In 30 min, 80% of dasatinib was dissolved at pH 1.2; while less than 1% was dissolved at pH 6.5. A more prudent approach using mini-gastrointestinal simulator to assess dissolution change from pH 1.2 to pH 6.0 was also reported. Consistent with the findings from USP apparatus II, the amount of dissolved dasatinib significantly reduced (41.9% vs. 5.6%) from pH 1.2 to pH 4.0.

Gastric fluid secretion may be reduced in cancer patients while aging and/or concomitantly receiving gastric acid modulating agents. As expected, a large variability on dasatinib exposure was observed in patients. Wang et al. (2013) reported a population pharmacokinetic model of dasatinib established on the basis of more than 6000 dasatinib concentration observations obtained from approximately 1000 patients in 7 clinical trials. It has been shown that a linear two-compartment pharmacokinetic model adequately described the observed concentration data. The model assumed a random interindividual variability (IIV) on major pharmacokinetic parameters. Furthermore, an interoccasion variability (IOV) was included to account for the random changes on relative bioavailability for the same patient receiving dasatinib at various dosing occasions. It has been shown that a large proportion of overall variability for dasatinib exposure can be explained by the variability in relative bioavailability (IIV of 34.6% and IOV of 37.4%), contributing more than the variability in the apparent plasma clearance (IIV of 28.8%).

Dedicated clinical pharmacology studies were conducted in the development program to further assess the effect of gastric acid modulating agents on dasatinib exposure and to inform dosing instruction. Eley et al. (2009) reported a 3-period, 3-way crossover, drug–drug interaction study conducted in 24 healthy subjects receiving dasatinib, dasatinib in combination with famotidine (a H_2 blocker), and dasatinib in combination with aluminum/magnesium hydroxide (antacids). The study has shown that dasatinib exposure was reduced by 60% when famotidine was given 10 h prior to dasatinib dosing. In addition, a reduction of 55%–58% dasatinib exposure was observed when dasatinib was given together with aluminum/magnesium hydroxide; whereas no dasatinib exposure change was observed when alumimum/magnesium hydroxide was given 2 h before dasatinib dosing. One additional clinical pharmacology study was conducted to assess the effect of omeprazole (a proton pump inhibitor) on dasatinib exposure in 14 healthy subjects (FDA, 2006). About 40% reduction in dasatinib exposure was observed in patients receiving omeprazole at steady state. Based on the findings, the U.S. package insert of SPRYCEL indicates that concomitant use of dasatinib with an H_2 blocker or a proton pump inhibitor is not recommended. Simultaneous administration of dastinib with an acid-neutralizing antacid should be avoided. Rather, the use of antacids at least 2 h before or 2 h after the dosing of SPRYCEL should be considered.

Additional exploratory effort has been put to restore the reduction of dasatinib absorption due to hypochlorhydria. Yago et al. (2014) reported a three-treatment, three-way, crossover study. Healthy subjects received dasatinib, dasatinib after pretreatment with rabeprazole (a PPI), and simultaneous administration of dasatinib with betaine hydrochloride after pretreatment with rabeprazole. The study showed that rabeprazole reduced dasatinib exposure by 80%–90%. However, coadministration of betaine hydrochloride increased dasatinib C_{max} and AUC by 15- to 7.5-fold, restoring them to 105%–121% of the levels when dasatinib was given alone. The results suggested that simultaneous administration of betaine acid with dasatinib can be a potential strategy to ensure adequate absorption of dasatinib in patients with elevated gastric pH.