ibuprofen reduced ibuprofen effective dose by 58% (Raffa *et al.* 2010). However, increasing GlcN dose did not increase the antinociceptive effect when combined with ibuprofen (Tallarida *et al.* 2003). A recent study by Qinna et al. has shown that GlcN increases paracetamol BA by reducing its metabolism in addition to a reduction in hepatocyte injury after administration of high doses of paracetamol (Qinna *et al.* 2015). Therefore, this study was conducted to investigate the effect of GlcN on PRN PK and metabolism since GlcN has been reported to alter the BA of many drugs. To study such interaction, a validated, sensitive, precise and simple reversed phase HPLC method was developed for the estimation of small concentrations of PRN HCl in serum and Krebs buffer. This chromatographic method was validated using EMEA guidelines with acceptable ranges of accuracy, precision, linearity, recovery, limits of quantitation, and detection.

Cimetidine is a CYP450 enzyme inhibitor which affects PRN PK by decreasing its hepatic first-pass metabolism, therefore increasing PRN plasma concentration and its pharmacological effect in humans (Heagerty *et al.* 1981; Reimann *et al.* 1981). On the other hand, Herman et al has reported that chronic administration of rifampin (a CYP450 inducer) led to a marked reduction in PRN steady-state concentration (Herman *et al.* 1983). Based on these studies, both cimetidine and rifampin were used as controls in the experiments performed here. Our results on Sprague-Dawley rats have shown that cimetidine increased PRN concentration levels in *in vivo* **(Table 3.49, Figure 3.20)**; *in situ* SPIP **(Figure 3.22)** and in hepatocyte isolation and cell culture **(Figure 3.25)**. On the contrary, rifampin