

divided into metabolism and absorption. The P-glycoprotein is believed to play an important role in the efflux of drugs, which results in poor absorption of these drugs. Therefore, pomegranate juice might be an inducer of P-glycoprotein in the intestine and reduce the absorption of candesartan. Also it has recently been reported that pomegranate juice affects intestinal uptake transporters as well as P-glycoprotein (Dresser and Bailey, 2003; Lilja et al., 2003). Thus, we conclude that the decrease in the AUC of candesartan by pomegranate juice could be due to the induction of enteric p-glycoprotein activity and/or due alteration in the intestinal uptake transporters system. However, this hypothesis needs to be explored in future studies.

In addition the difference in T max between rats and humans, candesartan maximum concentration where reached after 30min ($\frac{1}{2}$ hr) in rats compared to 3-4 hr's in human. The overall rate of biotransformation of candesartan in rats is markedly different from that in humans; However, the major metabolic pathways of the drug are almost similar in both rats and humans (Lertratanangkoon and Horning, 1982)., However, it is difficult to extrapolate our results, which were obtained in rats, to humans. Quantitative evaluation of pomegranate-drug interaction in humans needs to be verified by studies in humans. Therefore, further investigations in humans are necessary to develop our findings.

Validation

A full method validation according to ICH and EMA guidelines were performed for our analytical method to demonstrate the reliability of a our method for the determination of candesartan concentration in a specific rat plasma.