SUMMARY
There is a considerable variation in extent and clinical relevance of food-drug interactions. The presence of food within gastrointestinal (GI) tract can markedly alter the oral bioavailability of drugs. These changes can lead to variations in efficacy and toxicity profiles because medications are often taken under conditions of varying food and fluid intake. Food drug interactions are being reviewed periodically and are found to be an interesting area of research with a profound potential for the scientific community.

For certain drugs like furosemide, studies have exhibited that food is a factor which may influence the potency or pattern of response within and between patients. Though as reported in literature, the pharmacokinetic evidence of a food-drug interaction is not accompanied by any major changes in clinical effect. The clinical relevance of these findings needs further investigation since these diuretics are often taken at breakfast time by patients in and out of hospital.

Hence, this study was planned to investigate the effect of 5 dietary treatments viz., high fat vegetarian, low fat vegetarian, high fat non-vegetarian, low fat non-vegetarian & low fat vegetarian rice diets on the bioavailability and diuretic effect of furosemide. The bioavailability & diuresis were also determined under fasting condition and it was used as reference for comparison.

The study was designed as open label, balanced, randomized, six period, six sequence, single dose, cross over bioavailability study on furosemide (Lasix®) in 18 healthy, adult, male, human volunteers. A wash out period of 7 days was maintained between the six periods. One subject dropped out in the third period and one more subject dropped out from the study in the fourth period. The remaining 16 volunteers completed all the six periods of the study.

The analysis was carried out by an HPLC method which was validated for selectivity, linearity, accuracy, precision and stability (including bench top and in injector stability). The chromatograms were processed using class VP software and the pharmacokinetic analysis was done using Win Nonlin Software Version 1.5 (SCI, USA). Statistical analysis was performed on the pharmacokinetic parameters using SAS software version 8.1 (SAS Institute Inc., Cary NC, and USA).
All diets produced a significant decrease in both the rate ($C_{\text{max}}$) & extent of (AUC) absorption. The maximum decrease was observed with low fat non-vegetarian diet and minimum decrease was observed with high fat vegetarian diet, indicating the role of both the source and dietary fat. No significant difference was observed between low fat vegetarian & low fat vegetarian rice diet ruling out the role of rice content of diet.

The $t_{\text{max}}$ values were delayed in the presence of food, due to delay in the gastric emptying rate and these differences were significant, with maximum delay observed in low fat vegetarian rice diet (as carbohydrates delay and extend absorption over longer periods of time rather than completely inhibiting absorption) and equivalent minimum delay in low fat non vegetarian & high fat vegetarian diet.

All diets decreased the diuresis, though statistically significant reduction was observed only with low fat vegetarian, low fat non-vegetarian & low fat vegetarian rice diet and not with high fat vegetarian & high fat non-vegetarian diet as compared to the fasting state. The pharmacodynamic results indicated the role of fat and not the source and rice content of diet, which is in contrast to the pharmacokinetic results that indicated the role of both fat and source of diet and not rice content of diet.

The results obtained in the present study indicate that furosemide may conveniently and advantageously (maintained therapeutic efficacy) be administered after high fat vegetarian food. The therapeutic implications of this finding for the vast majority of Indian population, which is vegetarian, are considerable.

The recommendation of US: FDA to use high fat non vegetarian food for bioavailability studies in fed state needs a re-look, as far as furosemide is concerned. Further studies related with measuring the natriuretic and diuretic response of loop diuretics in relation with food are warranted so as to determine the clinical relevance of food-drug interaction. Optimally, such studies should be carried out on subjects admitted to a metabolic unit.