5. SUMMARY

Oral bioavailability of the BCS class II drugs, rofecoxib and nimesulide, was significantly improved by augmentation in their solubility and dissolution characteristics through diverse formulation approaches.

Phase solubility studies of rofecoxib with water-soluble carriers and cyclodextrins (CDs) revealed improvement in drug solubility as a linear function of carrier amount. The $A_t$ type of solubility curves suggested first-order 1:1 interactions between the carriers and the drug. Negative magnitudes of Gibbs free energy of transfer indicated spontaneity of solubilization process. The negative enthalpy and entropy values for drug-CD complexes in solution state depicted exothermic nature of the complexation process associated with more ordered system.

The dissolution performance of pure rofecoxib was enhanced manifold by formulating binary systems of the drug with myriad type of carriers. Among the wide range of carriers, blockcopolymers (poloxamer 407 & 188), CDs ($\beta$-CD, HP-$\beta$-CD, SBE-$\beta$-CD), citric acid (CA) and water-soluble polymers (Polyvinyl pyrrolidone, PVP) were found to be highly promising in that order. Mathematical modeling of the drug release data indicated that drug dissolution was primarily governed by Fickian diffusion mechanism and the Korsemeyer-Peppas model was found to be the most befitting kinetic model to the in vitro data. High synergism was obtained between poloxamer 407 and PVP for dissolution enhancement of rofecoxib.

Implementation of response surface methodology (RSM), through second-order central composite design, using the synergistic blend of poloxamer 407 and PVP revealed significant interaction between the two polymers at their respective high levels. Quadratic second-order relationship was obtained between the two factors (poloxamer and PVP) and various dissolution parameters taken as the response variables. Optimization through brute-force method, overlay plots and the desirability functions located formulation ROPT6 (Poloxamer : PVP:: 75 mg : 67 mg) as the “optimum” formulation over the entire experimental domain. Linear correlations obtained between the predicted and observed values of response variables, and the randomized residuals validated the high prognostic ability of the quadratic model developed for optimizing rofecoxib solid dispersions.
Summary

Solid state characterization studies provided distinct insight into the mechanistics of drug-carrier interactions which could be responsible for high dissolution enhancement. The FTIR studies revealed no chemical interaction between the drug and the carrier(s). The PXRD studies, however, depicted partial loss in drug crystallinity in both drug-poloxamer binary system and the drug-poloxamer-PVP optimized ternary system. The SEM studies portrayed lack of regular shape of the drug and the carriers in solid dispersion in comparison to the physical mixture, which further ratified reduction in drug crystal quality. Therefore, it could be inferred that partial loss of drug crystallinity, particle size reduction and improved wetting were the prime factors responsible for high drug dissolution performance. Real time stability studies at room temperature showed no significant loss in drug dissolution characteristics until one year.

In vivo pharmacodynamic evaluation in rats showed significantly faster onset of action for the optimized formulation with respect to the marketed formulation, its corresponding physical mixture and the pure drug. The optimized formulation was significantly more effective at varied time periods than other drug treatments. The in vivo evaluation corroborated that the dissolution augmentation achieved through various formulation approaches was able to improve the oral bioavailability of the poorly soluble drug. Albeit the drug has lately been withdrawn from the market but its solubility and dissolution enhancement results can be extrapolated rationally to other poorly soluble drugs too.

By and large, the phase-solubility studies with nimesulide yielded A_l type of curves with sugars, polyols, water-soluble polymers and CDs. However, with hydrotropes and blockcopolymers, both the types of curves viz. A_l and B_s were obtained. A_l types of solubility curves were associated with negative values of Gibbs free energy, indicating spontaneous nature of solubilization process. The B_s type of solubility curves indicated limited solubility of the drug-carrier complex. Analogous to rofecoxib, nimesulide-CD complexes in solution state exhibited negative values of enthalpy and entropy values indicating the process to be exothermic in nature with better orderly arrangement of the complexed molecules.

Besides CDs, solid dispersions with poloxamers and PVP were observed to be highly effective in enhancing drug dissolution among all other drug-carrier binary systems.
Mathematical modeling of drug release data corroborated the high degree of fitness with Weibull model and Korsemeyer-Peppas model. Drug release was governed primarily through Fickian diffusion. Poloxamer-CD systems showed high degree of synergism for nimesulide dissolution enhancement. RSM studies employing D-Optimal design unraveled cubic relationship between the two factors (HP-β-CD and poloxamer) and the various dissolution parameters. Marked influence of higher order interactions on dissolution performance was discerned. The cubic model, quite uncommon in routine pharmaceutical field, was found to be significant in this case. The optimum formulation selected through numeric and graphical optimization was found to be NOPT1 (HP-β-CD: Poloxamer : : 86.22 mg : 22.24 mg). The low percentage prediction errors along with higher linear correlations between predicted and observed values ratified the prognostic abilities of RSM.

Solid state characterization studies revealed distinct loss of crystallinity in case of binary systems of nimesulide and poloxamer, which may responsible for high dissolution rates. However, in case of optimized ternary system of nimesulide, HP-β-CD and poloxamer, the drug was only partly complexed with the CD molecules and was present in crystalline form. The very high dissolution observed with the optimized formulation thus could be the sum of dissolution enhancement through inclusion complexation and the formation of highly soluble noninclusion self-assembling microaggregates of HP-β-CD with the poloxamer. The tablet dosage form of optimized formulation showed superior dissolution performance to various fast release commercial brands of nimesulide. No significant alteration in the dissolution performance of the tablets could be inferred during the stability studies.

The optimized formulation, pure drug, marketed formulation and i.v. solution were subjected to pharmacokinetic studies in rabbits. The plasma profiles of nimesulide following oral and i.v. administration were fitted to 1-CBM model using PC-NONLIN pharmacokinetic software and an in-house software, PKICBM. The magnitude of pharmacokinetic parameters revealed markedly slow, inconsistent and incomplete drug absorption in rabbits, ascribable to its poor solubility in gastrointestinal fluids. Significant differences were observed between the groups for various drug absorption parameters like $K_a$, AUC, $T_{lag}$, etc., indicating marked improvement in rate and extent of nimesulide absorption with both of the formulations vis-à-vis pure drug. This can be explained due to significant augmentation in the dissolution and/or solubility
characteristics of nimesulide using supersaturated systems or inclusion complexes. Treatments did not bear significant influence on any other pharmacokinetic parameters like clearance, $t_{1/2}$, and MRT, indicating no significant influence of various treatments on drug disposition. Besides significant augmentation in drug absorption rate, both the formulations revealed nearly 3-fold enhancement in the extent of bioavailability too vis-à-vis pure drug. The optimized formulation, however, exhibited marginally better faster drug absorption, as indicated by slightly higher values of $K_a$ and lower values of lag time and $T_{max}$ vis-à-vis the marketed formulation. Nevertheless, the extent of absorption was found to be equivalent for both the formulations.

Level A IVIVR was successfully established between the values of drug fractions dissolved and absorbed. Further, Level C correlations also successfully demonstrated between the in-vivo absorption rate parameters ($K_a$, $T_{max}$, and $T_{lag}$) and the in-vitro dissolution parameters (DE$_{30min}$, MDT). Statistically high significance of such IVIVC relationships corroborate the apt choice of the dissolution medium, i.e., SIF with surfactant.

In nutshell, the current studies accomplished marked improvement in the rate and extent of bioavailability of rofecoxib and nimesulide, as divulged from their highly superior pharmacokinetic and pharmacodynamic potential. This would culminate, in all plausibility, to early onset, and increased intensity and duration of therapeutic effect. High significance of IVIVC/IVIVR designate that the bioavailability enhancement obtained with both the drugs is due to remarkable aggrandization in their solubility and dissolution performance using various formulation strategies adopted in the present work. Use of experimental designs was found to be highly advantageous in optimizing these oral drug delivery systems with high degree of fruition and prognostic ability. Results obtained in these investigations can certainly facilitate the design and development of oral formulations of other BCS class II drugs too with their enhanced bioavailability potential.