Summary and Conclusion

Presently, new drug candidates are rising due to advances in combinatorial chemistry and high throughput screening. However, most of them exhibit solubility problems and thereby exhibit poor bioavailability. If the drug has reasonable membrane permeability (BCS Class II drugs) then the rate limiting process of absorption is the dissolution step. Thus, the present study was aimed to enhance the dissolution of selected BCS Class-II drugs. Various formulation strategies are available for dissolution enhancement. Solid dispersion is most commonly used technology for dissolution enhancement. But it has some disadvantages which limits its use for commercial purpose. In the present work the problems of solid dispersions are addressed and a hybrid technique is developed combining melt and adsorption processes to form SDA.

Solid dispersion adsorbates were prepared using surfactant based carriers and adsorbent Neusilin. The purpose of using Neusilin was to arrest conversion of amorphous to crystalline form and also improvement of flow of solid dispersion.

Three drugs were selected from BCS Class-II, namely Ritonavir, Lamotrigine and Febuxostat. The developed technique was validated using fourth drug Candesartan cilexetil. The formulation development was done by employing the concept of Quality by Design. The dissolution enhancement and stability of formulation are important QTPP. The process parameters were kept constant so that the CMA’s were systematically identified. Ishikawa diagram is presented in the work. The effect of carriers (Lutrol F127, Labrasol and Transcutol) individually and in combination was studied by Simplex Lattice Design in case of Ritonavir. Full and reduced mathematical models were evolved. The use of PLSR showed better predictive ability (i.e. lower value of residuals). The amount of carrier (Lutrol F127) and amount of adsorbent (Neusilin) were optimized using factorial design in LTG. The effect of amount of carrier and adsorbent was studied using Box-Behnken design in case of FEB. The optimized formulations were then subjected to physical characterization like flow properties, FTIR, DSC and XRD analysis. Convolution modeling has been done of the three drugs to predict in vivo plasma concentration profile. This is extremely important for the selection of bio-batch so that failure is not seen in pilot or full scale in-vivo testing at industry level. For this back calculation in Wagner-Nelson method was adopted. Stability studies were also carried out for three months under accelerated conditions. Both the fresh and stressed
formulations exhibited insignificant differences in dissolution profiles for all the three drugs as confirmed by t-test and $f_2$ value.

The mechanism of dissolution enhancement was studied by formulating solid dispersion of drug with carrier and adsorbent individually. FTIR study was also performed for identification of molecular interaction of drug with the excipients. The physicochemical properties of the drug (dose and molecular weight) were then correlated with the amount of carrier needed for dissolution enhancement. The mathematical relationship can be used for knowing the range of carrier needed for any unknown BCS Class-II drugs provided the dose and molecular weight are known. In the present study candesartan cilexetil was chosen as fourth drug for prediction purposes. Thus, it can save time and money involved in preliminary trials before optimization.

Also, the developed technique was validated using another surfactant based carrier Vitamin E-TPGS. Optimized formula was used for preparing SDAs of all the four drugs replacing Lutrol F127 with TPGS. It also showed significant enhancement in dissolution for all the drugs in comparison to pure drug. The outcome of the study can be used to resolve the issue of chemical incompatibility on a drug-to-drug basis and also for cost adjustments. Both the excipients are permitted by regulators.

Thus, the hybrid technique of melt adsorption indeed resulted in dissolution enhancement of BCS Class-II drugs. The developed formulation overcomes the problems of conventional solid dispersions like poor flow and poor physical stability (conversion of amorphous to crystalline form). The developed formulation comprises use of surfactant based carrier which is mainly responsible for dissolution enhancement and an adsorbent for improving the flowability and stability. Increase in dissolution rate is due to increased wetting, micellar solubilization of drug in carrier and amorphization of drug by hydrogen bonding. Neusilin is mainly responsible for good flowability and stability.

Quality by design approach helped us in systematic formulation development and optimum point was achieved in shortest time with minimum efforts. Carrier quantity was found to be an important (critical) material attribute. It is proposed that weightage shall be given on the quantity of carrier for having consistent improvement in drug dissolution. Attention shall also be placed on quality of carrier. The outcome of the present study also revealed that dose of the
drug and the molecular weight of the drug are important considerations for deciding the requirements of excipients. Thus, using this methodology dissolution could be enhanced for any BCS Class-II drugs.

It is known that solubility enhancement can also be achieved from the microparticles generated using organic solvents. One of the salient features of the present work is freedom from the use of organic solvent. Hence, analysis as per ICH guidance document is avoided. The present study addresses the current problem of poor flow of solid dispersion and poor dissolution performance on standing (due to conversion of amorphous form of drug to crystalline form of drug). The findings may be adopted at industry since the concept of QbD was adopted. The proposed hybrid technique appears to have great future.