Summary
SUMMARY

Background:

• 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 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 a sparingly soluble BCS class II drug Rofecoxib. It was selected as model drug in present study as it exhibits very less solubility i.e. 0.01 mg/ml in water.

• Various formulation strategies are available to enhance the dissolution of sparingly soluble drugs. In order to enhance the dissolution of selected sparingly soluble drug, different approaches were tried. Solid dispersion by coprecipitation melt, surface solid dispersion and inclusion complex techniques were used to enhance the dissolution as these techniques are simple, convenient, economic and advantageous in improving the dissolution of poorly soluble drugs.

• The present study was performed using various hydrophilic carriers. These carriers increase solubility and/or wettability of drug and/or decrease the crystallinity of drug, thereby improves the bioavailability. Solubility/Phase solubility study was conducted to evaluate the ability of carrier in improving solubility of RXB. Preliminary investigations were made to identify process and formulation factors influencing dissolution.

• It is desirable to develop an acceptable formulation in shortest possible time using minimum number of human hours and raw materials. In addition to the art of formulation, the technique of experimental design is an efficient method of indicating the relative significance of a number of variables and their interactions. Thus, it was employed to systematically optimize the formulation in present study.

• Instrumental analysis like FTIR, DSC, TGA and XRD can help in identifying the physicochemical interaction as well as state of the drug (crystalline/amorphous) in the formulation. These methods were utilized in present investigations to evaluate mechanism of enhancement of drug dissolution.
Summary

- Solid dispersion/inclusion complex based tablet formulations shows quicker effect compared to conventional tablet formulations. In the present study, attempts were made to develop tablet formulation from optimized powder formulations of solid dispersions/inclusion complex.

Rofecoxib Coprecipitates:
- Hydrophilic carriers like PEG and PVP were used to prepare binary and ternary coprecipitates.
- Central composite design was used to evaluate effect of independent variables; carrier's ratio volume of solvent ($X_1$) and (PEG: PVP ratio, $(X_2)$) on $Y_{60}$, $t_{50}$ and Yield.
- Higher PEG: PVP ratio and higher volume of solvent was found advantageous in improving dissolution as well as yield of the product. The study indicated that ternary dispersions are faster in improving the dissolution than binary dispersions.
- The best batch exhibited entire drug released in 1 hr.
- Characterization study revealed that dissolution enhancement of RXB from coprecipitates is attributed due to combined effect of amorphous nature of PVP and higher solubilizing capacity of PEG.
- Tablet formulations showed hardness, compression and disintegration problems which were resolved by adding binder, directly compressible adjuvant and superdisintegrants.
- Tablet formulation containing crosscarmellose sodium as superdisintegrant showed promising result.

Rofecoxib Melts:
- Poloxamer, a low melting carrier was used to prepare solid dispersion (in form of melt) of RXB.
- Process parameters were optimized and effect of variables like Temperature to which drug-melt mixture cooled($X_1$) and Drug to carrier ratio($X_2$) on $Y_{30}$ and $t_{90}$ were systematically optimized using $3^2$ factorial design.
Summary

- Dissolution of melt showed that lower Temperature at which drug-carrier mixture cooled and higher drug to carrier ratio is favorable for improving dissolution of drug.
- Characterization study demonstrated decrease in the crystallinity and/or dissolution of drug in melted carrier for dissolution enhancement.
- Best batch exhibited entire drug released in 1 hr.
- Tablet formulations were developed and problems like hardness, compression and disintegration were solved by adding directly compressible adjuvant, binder and superdisintegrant.
- Tablet formulation containing crosscarmellose sodium as superdisintegrant showed promising result.

Rofecoxib Surface Solid Dispersion:

- Gelucire 44/14, amphiphilic carrier and adsorbent granulated colloidal silicon dioxide (VP Aeroperl 300/30) were used to develop surface solid dispersion.
- Preliminary investigations were made to identify process variables and effect of amount of drug($X_1$), amount of gelucire($X_2$) and amount of adsorbent ($X_3$) on $Y_{120}$, $t_30$ and Carr’s Index were systematically optimized using Box-behnken design.
- Improved dissolution as well as flowability was observed in surface solid dispersion with lower amount of drug and higher amount of carrier and adsorbent.
- The characterization study indicated decrease in crystallinity of drug and polymer in surface solid dispersion.
- The best batch exhibited entire drug release in 2 hr. This may be due to less solubility of RXB in melted gelucire compared to solubility of RXB in melted PXM or in PEG-PVP-DCM solution.
- The formulation has good flowability. However, due to waxy nature of Gelucire, tablet formulation was found difficult. This problem was resolved by adding directly compressible diluent and superdisintegrants.
- The tablet containing superdisintegrant L-HPC showed least D.T.
**Summary**

**Rofecoxib Inclusion Complex:**
- β-cyclodextrin was used to prepare inclusion complex. Inclusion complex was prepared by kneading followed by drying method.
- Preliminary investigations were done and effect of Drug to cyclodextrin ratio, Kneading time and Temperature of Drying on \( Y_{0.0} \) and \( Y_{0.5} \) were optimized using 2\(^2\) factorial design.
- Lower drug to cyclodextrin (molar ratio), higher kneading time and drying temperature demonstrated higher dissolution.
- The best batch formulation exhibited entire drug release in 40 min.
- Characterization study revealed that entrapment of most of the drug in cyclodextrin cavity is responsible for improvement of dissolution.
- Tablet formulations have good hardness as well as D.T. To improve further its properties, superdisintegrants were added.
- The tablet containing crosspovidone shown D.T. in 1.12 min(72 sec)

**Comparison of Developed Formulations:**
- All the optimized powder formulations were compared and rate of enhancement of dissolution was found in following order:
  - Inclusion complex>Melts>Coprecipitates> Surface solid dispersion
- All the optimized tablet formulations were compared with marketed products (Conventional and MDT). Higher dissolution from all optimized tablets was observed compared to marketed products. It was observed that inclusion complex based tablets exhibited highest dissolution i.e. 1 hr

**Stability Studies:**
- The promising powder and tablet formulation of each approach was subjected to stability study at 25°C and 60% RH for 5 weeks. Increase in dissolution of RXB was observed from stressed surface solid dispersion. This may be due to H-bonding between drug and adsorbent upon storage. However, the comparison of dissolution profile of fresh and stressed sample of all optimized formulation exhibited insignificant difference as confirmed by Student’s t-test and \( f_2 \) statistics. The stressed
powder formulations were also characterized by FTIR, DSC, TGA and XRD studies. Results of these were found similar before and after storage indicating stability of the product.

Carvedilol Formulations:
• To validate the results obtained with RXB, another BCS class-II drug CAR was selected.
• The CAR coprecipitates, melts, surface solid dispersion and inclusion complex were prepared as per the optimized formulations of RXB. Other formulations were also developed to study effect of various process and formulation factors on dissolution of CAR. All the CAR formulations exhibited enhanced dissolution than pure CAR. Promising formulation of CAR was compared with promising formulation of RXB. Dissolution of CAR was found similar or higher than RXB.