CHAPTER X

SUMMARY AND CONCLUSIONS

The thesis describes factorial studies on enhancement of solubility, dissolution rate, bioavailability and formulation development of selected BCS class II drugs namely etoricoxib and aceclofenac. The thesis consists of 10 Chapters.

Introduction and objectives of the investigation are described in Chapter I. Etoricoxib and aceclofenac, widely prescribed anti-inflammatory and analgesic drugs belong to class II under BCS and exhibit low and variable oral bioavailability due to their poor aqueous solubility. They are practically insoluble in water and aqueous fluids. As such their oral absorption is dissolution rate limited and they require enhancement in solubility and dissolution rate for increasing their oral bioavailability. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar solubilization. Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and
dissolution rate. In the present investigation cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) were tried to enhance the solubility, dissolution rate and bioavailability of etoricoxib and aceclofenac. The major objective is to evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) on the solubility, dissolution rate and bioavailability of etoricoxib and aceclofenac in a series of $2^2$ factorial experiments and to evaluate the feasibility of formulating etoricoxib and aceclofenac tablets with enhanced dissolution rate and dissolution efficiency employing drug-CD-surfactant complex systems. The other objectives include: to evaluate the dissolution kinetics and characteristics of Drug-CD and Drug-CD-Surfactant inclusion complexes and tablets formulated employing them; to evaluate the compatibility of the selected drugs with cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) by IR and DSC spectral studies; to evaluate the physical state of drug in the drug-CD-surfactant inclusion complexes by XRD study; Pharmacokinetic evaluation of aceclofenac-βCD and aceclofenac-βCD-Kolliphor HS15 complexes in comparison to aceclofenac pure drug with a view to evaluate their in vivo performance and to evaluate the stability of selected tablets formulated employing drug-CD-Kolliphor HS15 inclusion complexes.
Literature on cyclodextrins including recent research on cyclodextrin complexation is given in Chapter II. Chapter III contains literature on drugs investigated and past research work on the selected drugs. Literature on surfactants investigated is reviewed in Chapter IV. Analytical methods used are described in Chapter V. U.V. Spectrophotometric methods were used for estimation of etoricoxib and aceclofenac in in vitro studies. A known HPLC method was used for the estimation of aceclofenac in plasma samples after revalidation.

Factorial studies carried out on the effects of cyclodextrins and surfactants on the solubility and dissolution rate of etoricoxib and aceclofenac are described in Chapter VI. In the present study cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) were tried to enhance the solubility and dissolution rate of etoricoxib and aceclofenac, two widely prescribed anti-inflammatory and analgesic drugs. The individual main effects and combined (interaction) effects of cyclodextrins and surfactants on the solubility and dissolution rate of etoricoxib and aceclofenac were evaluated in a series of $2^2$ factorial experiments. From the results obtained the following conclusions are drawn.
1. The solubility of etoricoxib was markedly enhanced by cyclodextrins (βCD and HPβCD) and by surfactants (Kolliphor HS15 and Pluronic F127). A 4.35 and 30.37 fold increase in the solubility of etoricoxib was observed respectively with βCD (5mM) and Kolliphor HS15 (2%) when used alone. A combination of βCD (5mM) and Kolliphor HS15 (2%) gave a 54.43 fold increase in the solubility of etoricoxib.

2. A 1.28 and 30.37 fold increase in the solubility of etoricoxib was observed respectively with HPβCD (5mM) and Kolliphor HS15 (2%). A combination of HPβCD (5mM) and Kolliphor HS15 (2%) gave a 14.76 fold increase in the solubility of etoricoxib.

3. A 4.35 and 7.3 fold increase in the solubility of etoricoxib was observed respectively with βCD (5mM) and Pluronic F127 (2%). A combination of βCD (5mM) and Pluronic F127 (2%) gave a 8.72 fold increase in the solubility of etoricoxib.

4. A 1.53 and 7.3 fold increase in the solubility of etoricoxib was observed respectively with HPβCD (5mM) and Pluronic F127 (2%). A combination of HPβCD (5mM) and Pluronic F127 (2%) gave a 13.20 fold increase in the solubility of etoricoxib.

5. The individual main effects as well as combined effects of CDs (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) in enhancing the solubility of etoricoxib are highly significant (P < 0.01).
6. The order of increasing enhancement in the solubility of etoricoxib observed with various CDs and Surfactants was Kolliphor HS15 > Pluronic F127 > βCD > HPβCD.

7. Among all combinations, βCD-Kolliphor HS15 gave greater enhancement in the solubility of etoricoxib (54.43 fold). The order of increasing enhancement in the solubility of etoricoxib observed with various combinations was βCD- Kolliphor HS15 > HPβCD-Kolliphor HS15 > HPβCD- Pluronic F127 > βCD- Pluronic F127.

8. The solubility of aceclofenac was also markedly enhanced by cyclodextrins (βCD and HPβCD) and by surfactants (Kolliphor HS15 and Pluronic F127). A 1.57 and 21.72 fold increase in the solubility of aceclofenac was observed respectively with βCD (5mM) and Kolliphor HS15 (2%) when used alone. A combination of βCD (5mM) and Kolliphor HS15 (2%) gave a 28.97 fold increase in the solubility of aceclofenac.

9. A 1.47 and 21.72 fold increase in the solubility of aceclofenac was observed respectively with HPβCD (5mM) and Kolliphor HS15 (2%). A combination of HPβCD (5mM) and Kolliphor HS15 (2%) gave a 22.31 fold increase in the solubility of aceclofenac.

10. A 1.57 and 7.91 fold increase in the solubility of aceclofenac was observed respectively with βCD (5mM) and Pluronic F127 (2%). A combination of βCD (5mM) and Pluronic F127 (2%) gave a 10.54 fold increase in the solubility of aceclofenac.
11. A 1.47 and 7.91 fold increase in the solubility of aceclofenac was observed respectively with HPβCD (5mM) and Pluronic F127 (2%). A combination of HPβCD (5mM) and Pluronic F127 (2%) gave a 9.47 fold increase in the solubility of aceclofenac.

12. The order of increasing enhancement in solubility of aceclofenac observed with various CDs and Surfactants was Kolliphor HS15 > Pluronic F127 > βCD > HPβCD.

13. Among all the combinations, βCD-Kolliphor HS15 exhibited greater enhancement in the aqueous solubility (28.97fold) of aceclofenac. The order of increasing enhancement observed with various combinations was βCD- Kolliphor HS15 > HPβCD- Kolliphor HS15 > βCD- Pluronic F127 >HPβCD- Pluronic F127.

14. The individual main effects as well as combined effects of CDs (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) in enhancing the solubility of aceclofenac are highly significant (P < 0.01).

To evaluate the individual main and combined effects of cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) on the dissolution rate of etoricoxib and aceclofenac, solid inclusion complexes of Drug-CD-Surfactant were prepared in each case as per $2^2$ factorial design and were evaluated. From the results obtained the following conclusions are drawn.
15. Drug-CD and Drug-CD-Surfactant complexes gave rapid and higher dissolution of etoricoxib and aceclofenac when compared to the corresponding pure drug.


17. The dissolution rates ($K_1$) and Dissolution efficiency ($DE_{15}$) values were several times higher in the case of CD-Surfactant complexes when compared to those of pure drug with both etoricoxib and aceclofenac.

18. Among individual effects, CDs (βCD and HPβCD) gave higher enhancement in the $K_1$ and $DE_{15}$ of etoricoxib than the surfactants (Kolliphor HS15 and Pluronic F127). The order of increasing enhancement in $K_1$ and $DE_{15}$ observed with various CDs and surfactants was $\beta$CD > HPβCD > Kolliphor HS15 > Pluronic F127. $\beta$CD gave highest increase in $DE_{15}$ (6.44 fold) and $K_1$ (5.50 fold) of etoricoxib.

19. The results of ANOVA indicated that all individual and combined effects in enhancing the dissolution rate ($K_1$) of etoricoxib were highly significant ($P < 0.01$) except the combined effect of HPβCD-Pluronic F127.

20. Among the combined effects, $\beta$CD-Kolliphor HS15 and $\beta$CD-Pluronic F127 gave highest enhancement in dissolution rate ($K_1$) of etoricoxib (5.95-6.35 fold).
21. Among the individual effects, CDs (βCD and HPβCD) gave higher enhancement in the $K_1$ and $DE_{15}$ of aceclofenac than the surfactants (Kolliphor HS15 and Pluronic F127). The order of increasing enhancement in dissolution rate ($K_1$) observed with various CDs and surfactants was $\beta$CD > HPβCD > Kolliphor HS15 > Pluronic F127.

22. The results of ANOVA indicated that all individual and combined effects in enhancing the dissolution rate ($K_1$) of aceclofenac were highly significant ($P < 0.01$).

23. Among the combined effects, $\beta$CD-Kolliphor HS15 gave highest enhancement in dissolution rate ($K_1$) of aceclofenac (9.04 fold).

The compatibility of the selected drugs (etoricoxib and aceclofenac) with CDs (βCD and HPβCD) and surfactants (Kolliphor HS15 and Pluronic F127) used in the study was evaluated by FTIR and DSC study.

24. FTIR spectra and DSC thermograms indicated no chemical interaction between etoricoxib, aceclofenac, CDs and surfactants.

25. The physical state of drug in the CDs-surfactant inclusion complexes was evaluated by XRD. The XRD indicated a reduction in the crystallinity or partial amorphization of drug (etoricoxib and aceclofenac) during entrapment in CDs by the presence of surfactant.
Factorial studies carried out on the formulation and evaluation of etoricoxib and aceclofenac tablets employing cyclodextrins and Kolliphor HS15 are described in chapter VII. The feasibility of formulating the Drug-CD-Kolliphor HS15 complex systems in to compressed tablets with enhanced dissolution rate was investigated. The individual main and combined (interaction) effects of CDs and Kolliphor HS15 on the dissolution rate of (i) etoricoxib and (ii) aceclofenac from tablet formulations was investigated in a series of $2^2$ – factorial experiments. Tablets of (i) etoricoxib (100 mg) and (ii) aceclofenac (100 mg) were formulated employing selected combinations of CD ($\beta$CD and HP$\beta$CD) and Kolliphor HS15 in each case as per a $2^2$ factorial design. The tablets were prepared by wet granulation method and were evaluated. From the results obtained the following conclusions are drawn.

1. Drug-CD and Drug-CD-Kolliphor HS15 complex systems could be formulated in to compressed tablets by wet granulation method.

2. All the tablets prepared employing drug-CD and drug-CD-Kolliphor HS15 complex systems were of good quality fulfilling the official (I.P) standards with regard to hardness, friability, disintegration time and drug content.

3. Drug dissolution from the tablets formulated employing drug-CD and drug-CD-Kolliphor HS15 complexes followed first order kinetics with both etoricoxib and aceclofenac.
4. Tablets formulated employing CDs and Kolliphor HS15 gave relatively higher rates of dissolution ($K_1$) and dissolution efficiency ($DE_{30}$) values when compared to those of plain tablets with both etoricoxib and aceclofenac.

5. The order of increasing dissolution rate ($K_1$) observed with various tablets was $E_1$ (plain) < $E_2$ (βCD) = $E_6$ (HPβCD) < $E_3$ (Kolliphor HS15) < $E_8$ (HP βCD-Kolliphor HS15) < $E_4$ (βCD-Kolliphor HS15) in the case of etoricoxib and $A_1$ (plain) < $A_2$ (βCD) = $A_6$ (HPβCD) < $A_3$ (Kolliphor HS15) < $A_8$ (HP βCD-Kolliphor HS15) < $A_4$ (βCD-Kolliphor HS15) in the case of aceclofenac.

6. Etoricoxib tablet formulations $E_4$ and $E_8$, which are formulated employing βCD-Kolliphor HS15 and HPβCD-Kolliphor HS15 respectively, gave much higher dissolution rates when compared to plain tablets, $E_1$. A 42.5 and 34.2 fold increase in $K_1$ was observed respectively with formulations $E_4$ and $E_8$ when compared to formulation $E_1$ (plain tablets).

7. The dissolution efficiency ($DE_{30}$) was also increased from 4.56% for formulation $E_1$ to 41.54 % and 36.59 % respectively for formulations $E_4$ and $E_8$.

8. Aceclofenac tablet formulations $A_4$ and $A_8$, which are formulated employing βCD-Kolliphor HS15 and HPβCD-Kolliphor HS15 respectively, gave much higher dissolution rates when compared to plain tablets, $A_1$. A 21.35 and 16.85 fold increase in $K_1$ was observed respectively with formulations $A_4$ and $A_8$ when compared to formulation $A_1$ (plain tablets).
9. The dissolution efficiency (DE$_{30}$) was also increased from 7.29% for Formulation A1 (plain tablets) to 43.32 % and 39.36 % respectively for formulations A4 and A8.

10. ANOVA indicated that the individual main effects of βCD, HPβCD and Kolliphor HS15 and their combined effects in enhancing the dissolution rate ($K_1$) of etoricoxib and aceclofenac tablets were highly significant ($P < 0.01$).

11. βCD and Kolliphor HS15 alone gave an enhancement of 9.7 and 12.5 fold in the dissolution rate ($K_1$) of etoricoxib tablets respectively. Whereas in combination βCD-Kolliphor HS15 gave 42.5 fold increase in the dissolution rate.

12. HPβCD and Kolliphor HS15 alone gave an enhancement of 9.7 fold and 12.5 fold in the dissolution rate ($K_1$) of etoricoxib tablets respectively. Whereas HPβCD and Kolliphor HS15 in combination gave a 34.2 fold increase in the dissolution rate.

13. βCD and Kolliphor HS15 alone gave an enhancement of 4.75 and 6.10 fold in the dissolution rate ($K_1$) of aceclofenac tablets respectively. Whereas in combination βCD-Kolliphor HS15 gave 21.35 fold increase in the dissolution rate.

14. HPβCD and Kolliphor HS15 alone gave an enhancement of 4.85 fold and 6.10 fold in the dissolution rate ($K_1$) of aceclofenac tablets respectively. Whereas in combination HPβCD and Kolliphor HS15 gave a 16.85 fold increase in the dissolution rate.
Studies carried out on Pharmacokinetic evaluation of aceclofenac-βCD-Kolliphor HS15 complexes are discussed in Chapter VIII. Drug-CD and Drug-CD-Kolliphor HS15 inclusion complexes gave markedly higher dissolution rates of etoricoxib and aceclofenac. Pharmacokinetic evaluation was done on aceclofenac - βCD and aceclofenac-βCD-Kolliphor HS15 complexes in comparison to aceclofenac pure drug with a view to evaluate their in vivo performance. From the results obtained the following are the conclusions drawn.

1. Aceclofenac was found to be absorbed slowly when given orally and a peak plasma concentration ($C_{\text{max}}$) of 11.35±0.7 µg/ml was observed at 4.0 h after administration. The absorption rate constant ($K_a$) was found to be 0.4859 h$^{-1}$.

2. All the pharmacokinetic parameters (Table 8.2) namely $C_{\text{max}}$, $T_{\text{max}}$, $K_a$ and (AUC)$_0^\infty$ indicated rapid and higher absorption and bioavailability of aceclofenac when administered as CD complexes.

3. The absorption rate constant ($K_a$) was found to be 1.7583 h$^{-1}$, 2.3918 h$^{-1}$ respectively with aceclofenac - βCD (1:2) and aceclofenac – βCD- Kolliphor HS15 (1:2:0.05) complexes, whereas in the case of aceclofenac $K_a$ was only 0.4859 h$^{-1}$.

4. A 3.62, and 4.92 fold increase in the $K_a$ was observed respectively with aceclofenac - βCD (1:2) and aceclofenac – βCD- Kolliphor HS15 (1:2:0.05) complexes when compared to aceclofenac pure drug.
5. \((\text{AUC})_{0}^{\infty}\) (extent of absorption) was also much higher in the case of CD complexes when compared to aceclofenac pure drug. \((\text{AUC})_{0}^{\infty}\) was increased from 111.50 µg.h/ml for aceclofenac pure drug to 174.35 and 207.27 µg.h/ml for aceclofenac - βCD (1:2) and aceclofenac – βCD- Kolliphor HS15 (1:2:0.05) complexes respectively.

6. A 1.56 and 1.85 fold increase in \((\text{AUC})_{0}^{\infty}\) was observed respectively with aceclofenac - βCD (1:2) and aceclofenac – βCD-Kolliphor HS15 (1:2:0.05) complexes when compared to aceclofenac pure drug.

7. The biological half-life \((t_{1/2})\) was found to be 4.77, 3.91 and 4.58 h respectively following the oral administration of aceclofenac, and its CD complexes, aceclofenac - βCD (1:2) and aceclofenac – βCD- Kolliphor HS15 (1:2:0.05) indicating that the elimination characteristics of aceclofenac have not changed when it was administered as CD complexes.

8. βCD has markedly enhanced both the rate \((K_{a})\) and extent \((\text{AUC})\) of absorption (i.e. bioavailability) of aceclofenac. Addition of Kolliphor HS15 has further enhanced both the rate of absorption and extent of absorption of aceclofenac from aceclofenac – βCD- Kolliphor HS15 (1:2:0.05) complex.
Stability studies carried out are described in Chapter IX. The stability of tablets formulated employing Drug-CD-Kolliphor HS15 complex was evaluated as per ICH guidelines. Drug content and dissolution profiles of the tablets remained unaltered after storage for 3 months at $40^0 \pm 2^0$ C and $75 \pm 5$ % RH. The fast dissolution characteristics of the tablets remained unaltered during the storage period with both etoricoxib and aceclofenac.

**Significant Contributions:**

The results of the present investigation clearly indicated that the individual main effects as well as combined effects of CDs ($\beta$CD and HP$\beta$CD) and surfactants (Kolliphor HS15 and Pluronic F127) in enhancing the solubility and dissolution rate ($K_1$) of etoricoxib and aceclofenac are highly significant ($P < 0.01$). Combination of Kolliphor HS15 with CDs ($\beta$CD and HP$\beta$CD) resulted in a much higher enhancement in the solubility and dissolution rate ($K_1$) of etoricoxib and aceclofenac than is possible with CDs and Kolliphor HS15 alone. $\beta$CD- Kolliphor HS15 gave 54.43 and 28.97 fold increase in the solubility of etoricoxib and aceclofenac respectively. $\beta$CD- Kolliphor HS15 also gave a 5.95 and 3.81 fold increase in the dissolution rate ($K_1$) of solid inclusion complex of etoricoxib and aceclofenac respectively. FTIR and DSC studies indicated no physical and chemical interaction between the selected drugs and CDs and Kolliphor HS15.
Drug-CD-Kolliphor HS15 inclusion complexes could be formulated into tablets by wet granulation method and the resulting tablets also exhibited rapid and higher dissolution rate ($K_1$) and dissolution efficiency ($DE_{30}$) values when compared to plain tablets and tablets containing CDs alone. Etoricoxib tablets formulated employing drug- βCD- Kolliphor HS15 gave a 42.5 fold increase in the dissolution rate of etoricoxib when compared to plain tablets. Aceclofenac tablets formulated employing drug-βCD- Kolliphor HS15 gave 21.35 fold increase in the dissolution rate of aceclofenac when compared to plain tablets. In the in vivo pharmacokinetic evaluation, aceclofenac-βCD-Kolliphor HS15 inclusion complex exhibited a 4.92 fold increase in the absorption rate ($K_a$) and 1.85 fold increase in the (AUC) 0-∞ when compared to aceclofenac pure drug. Tablets formulated employing drug-CD-Kolliphor HS15 inclusion complexes were also quite stable with regard to fast dissolution rate characteristics during stability studies. Hence a combination of cyclodextrins ( βCD and HPβCD ) and Kolliphor HS15 is recommended for enhancing the solubility, dissolution rate and bioavailability of etoricoxib and aceclofenac and for formulation of their tablets with fast dissolution rate characteristics.
Future Directions (Scope for further work):

1. Scale up studies are to be conducted to prepare Drug - CD – Surfactant complexes and their tablet formulations in Pilot Scale and then in Industrial Scale.

2. Stability studies on promising formulations developed are to be conducted over longer period of time.

3. Pharmacodynamic studies are to be conducted to evaluate the therapeutic efficacy of the formulations developed.