CHAPTER VII

SUMMARY, CONCLUSION AND RECOMMENDATIONS
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The areas of current interest in pharmaceutical biotechnology which have a significant impact on clinical therapy are enhancement of dissolution rate and bioavailability of insoluble and poorly soluble drugs and development of controlled release drug delivery systems. Many of the modern drugs belong to the class II under Biopharmaceutical Classification System (BCS), which are characterized by low solubility and high permeability and exhibit low and variable dissolution and bioavailability and pose problems in the design of controlled release products due to their insoluble character. Sparfloxacin (antibacterial), nifedipine (antianginal and antihypertensive) and nimodipine (antianginal and antihypertensive) belong to BCS-Class II and require enhancement in solubility and dissolution rate for increasing their oral bioavailability and development of controlled release drug delivery systems. The present investigation, biotechnological studies on cyclodextrin complexation, has been undertaken with an objective of studying the complexation between two cyclodextrins, β-cyclodextrin (β-CD) and hydroxy propyl β-cyclodextrin (HPβ-CD) and the selected drugs sparfloxacin (SPF), nifedipine (N) and nimodipine (NM). The feasibility of employing cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability and for obtaining controlled release of these insoluble drugs was investigated.

Complexation of the selected drugs (SPF, N, NM) with β-CD and HPβ-CD, the effect of CD complexation on the solubility, the type of phase solubility diagram and the stability constant of the CD complexes formed were investigated by phase solubility studies. Solid inclusion complexes of SPF, N and NM with β-CD and HPβ-CD in each case were prepared at 1:1, 1:2 and 1:3 ratios of drug and CD by two methods namely kneading and coevaporation methods. The complexes were evaluated for drug content uniformity, dissolution rate and dissolution efficiency.

Solid inclusion complexes of SPF-βCD (1:3) and SPF-HPβ-CD (1:3) prepared by kneading method were formulated into tablets by both direct compression and conventional wet granulation method and the resulting tablets were evaluated for drug content, hardness, friability, disintegration time, and dissolution rate characteristics. The stability of the dissolution rate
characteristics of sparflloxacin tablets formulated employing \( \beta \)-CD were evaluated as per ICH guidelines.

*In vivo* evaluation of sparflloxacin tablet formulations F1 (plain tablets) and F2 (tablets formulated employing SPF-\( \beta \)CD, 1:3 complex) was carried out in human subjects. Serum concentrations of sparflloxacin were determined by the microbiological assay method developed in the present investigation. From the time versus serum concentration data, \( C_{\text{max}} \), \( t_{\text{max}} \), \( K_{\text{el}} \), \( \text{AUC}_{\infty} \) and \( K_a \) were calculated.

Controlled release matrix tablets each containing 120 mg of nimodipine were formulated employing nimodipine alone and its CD complexes and using sodium carboxy methyl cellulose (sodium CMC) and hydroxypropyl methyl cellulose (HPMC) as matrix materials. The matrix tablets were prepared by conventional wet granulation method and were evaluated for hardness, friability, drug content, disintegration time and drug release characteristics. Nimodipine release from the matrix tablets was studied in simulated gastro-intestinal fluids for a period of 12 hr. Pharmacokinetic evaluation was done on (i) matrix tablets containing nimodipine alone in sodium CMC matrix (Formulation F4) and (ii) matrix tablets containing nimodipine - \( \beta \)CD complex in sodium CMC matrix (Formulation F5) in healthy human subjects as per a cross-over randomized block design (\( n = 4 \)).

From the results obtained the following conclusions are drawn:

1. The aqueous solubility of all the three drugs was increased linearly as a function of the concentration of \( \beta \)-CD and HP\( \beta \)-CD in each case.

2. All the phase solubility diagrams can be classified as type \( A_L \). The increase in solubility was due to the formation of a 1:1M complex in solution with all the three drugs.

3. The apparent stability constants (\( K_c \)) were in the range 210 – 489.8\( M^{-1} \) indicating that the complexes formed between the drug and CD are quite stable in all cases except N-\( \beta \)CD.

4. The dissolution of drug (SPF, N, NM) from solid cycloexther inclusion complexes followed first order kinetics.

5. All the dissolution parameters (\( T_{50}, T_{90}, \% \text{ dissolved in } 10 \text{ min}, \text{DE}_{50} \text{ and } K_{1} \)) indicated rapid and higher dissolution of the drug from CD complexes when compared to the
corresponding uncomplexed drug. The dissolution rate and dissolution efficiency were increased as the concentration of CD in the solid inclusion complex was increased in each case.

6. HPβ-CD gave higher enhancement in the dissolution rate and in the dissolution efficiency when compared to βCD at all ratios tested with all the three drugs.

7. Solid complexes prepared by kneading method exhibited higher dissolution rates and dissolution efficiency values than those prepared by coevaporation method in each case.

8. An increase of 17.7 and 87.7 fold in the dissolution rate of SPF, 38.6 and 44.3 fold in the dissolution rate of N and 30.68 and 50.68 fold in the dissolution rate of NM was observed respectively with βCD (1 : 3) and HPβCD (1 : 3) inclusion complexes prepared by kneading method.

9. All the tablets prepared fulfilled the official (I.P.) requirements of drug content, hardness friability and disintegration time.

10. Tablets prepared by direct compression method disintegrated rapidly when compared to those prepared by wet granulation method.

11. Dissolution ofsparfloxacin from all the tablets formulated followed first-order kinetics in both direct compression and wet granulation methods.

12. Tablets formulated employing cyclodextrin complexes gave higher rates of dissolution and dissolution efficiency values when compared to the corresponding tablets formulated with SPF as such.

13. The tablets formulated employing HPβCD complexes gave lower dissolution than those formulated with βCD due to dry binding nature of HPβCD.

14. Among all, the tablets formulated with SPF-βCD (1 : 3) kneaded complex gave highest dissolution and a 17 fold increase in the dissolution rate of SPF was observed with this formulation when compared to plain tablets.

15. No visible changes were observed in the tablets after storage. The dissolution profiles of the tablets remained unaltered during the storage period. The stored tablets also exhibited rapid dissolution of SPF similar to freshly made tablets.
16. The results of the pharmacokinetic studies indicated rapid absorption of SPF from formulation F2 when compared to formulation F1. The Ka was 0.833 h^{-1} and 1.24 hr^{-1} respectively for F1 and F2. AUC_{t} was same with both the products.

17. The sparflaxacin tablets formulated employing SPF-βCD (1 : 3) inclusion complex have exhibited significantly higher rate of absorption of SPF. But the extent of bioavailability of SPF from formulation F2 remained the same as that from F1.

18. All the matrix tablets prepared were found to be nondisintegrating in water, 0.1N HCl and phosphate buffer of pH 7.4.

19. Drug release from the matrix tablets was diffusion controlled and followed zero order kinetics.

20. Tablets containing nimodipine as such gave very low release, 25-38% in 12 hr.

21. Slow, controlled and complete release of nimodipine over a period of 12 hr was obtained from matrix tablets formulated employing its cyclodextrin complexes, which was not possible with similar tablets formulated employing nimodipine as such.

22. Among all the formulations, F5, which is based on NM-βCD (1 : 1) complex in a matrix of sodium CMC, gave a release rate of 9.6 mg/hr and was found to be more suitable for oral controlled release of nimodipine.

23. The results of pharmacokinetic study indicated the slow absorption of nimodipine from Formulation F5 over a period of 8 – 12 hr. The serum concentrations were stabilized within a narrow range of 27 – 43 ng/ml during the period from 1.5 to 12 hr.

24. A 4.17 fold increase in the bioavailability was observed with F5 when compared to F4.

25. The matrix tablets formulated employing NM-βCD (1 : 1) complexes exhibited four times higher bioavailability and good in vivo sustained serum concentrations of nimodipine over a period of 12 hr.

26. Formulation F5 was considered as a good oral controlled release formulation of nimodipine.
Recommendations

The results of the present investigation clearly indicated that the solubility and the dissolution rate of sparfloxacin, nifedipine and nimodipine (three drugs belonging to BCS class II category with low solubility) could be greatly enhanced by complexation with β-CD and HPC-CD. The increase in solubility is due to the formation of stable 1 : 1M complexes between the drug and CD molecules in solution. The solid inclusion complexes of drug and CD exhibited several times higher dissolution rates and dissolution efficiency values than the corresponding uncomplexed drugs.

Sparfloxacin - CD complexes could be formulated into compressed tablets by both direct compression and wet granulation methods and the resulting tablets exhibited rapid and higher dissolution rates and dissolution efficiency values than those formulated employing sparfloxacin as such. The higher dissolution rates of these tablets remained unaltered during stability studies carried out as per ICH guidelines. Sparfloxacin tablets formulated employing SPF-βCD (1 : 3) inclusion complexes exhibited significantly higher rates of absorption when compared to those formulated with sparfloxacin alone. But the extent of bioavailability remained the same in both the cases.

Matrix tablets formulated employing nimodipine - βCD (1 : 1) inclusion complexes gave slow, controlled and complete release of nimodipine over a period of 12 hr, which was not possible with similar tablets formulated employing nimodipine as such. Matrix tablets formulated employing cyclodextrin complexes exhibited good controlled release characteristics, both in vitro and in vivo.

Basing on the results of the investigation cyclodextrin complexation with β-CD and HPC-CD is recommended for enhancing the solubility and dissolution rate of sparfloxacin, nifedipine and nimodipine. Cyclodextrin complexes can be formulated into compressed tablets with higher rates of dissolution and absorption by both direct compression and wet granulation techniques. Cyclodextrin complexes can also be used in the design of controlled release matrix tablets of insoluble drugs for obtaining slow, controlled and complete drug release over higher periods of time.

The work carried out on matrix tablets of nimodipine resulted in the development of new technology of enhancing the solubility and dissolution rate of insoluble drugs (such as nimodipine).
by cyclodextrin complexation before formulation into controlled release tablets. The cyclodextrin complexes with higher solubility and dissolution rate could be employed in the formulation of matrix tablets for obtaining controlled release of such insoluble drugs.