CHAPTER VI

DISCUSSION OF RESULTS
DISCUSSION OF RESULTS

The present investigation, Biotechnological studies on cyclodextrin complexation has been undertaken with an objective of studying the complexation between cyclodextrins (β-CD and HPβ-CD) and the three drugs selected namely sparfloxacin (SPF), nifedipine (N) and nimodipine (NM). The feasibility of employing cyclodextrin complexation for enhancing the dissolution rate and bioavailability and for obtaining controlled release of these drugs was also investigated.

Many of the modern drugs belong to the class II under Biopharmaceutical Classification System (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble or poorly soluble in water and aqueous fluids in the pH range of GI tract i.e. pH 1-7.5. Solubility and dissolution rate are the rate controlling steps in their absorption. They exhibit variable bioavailability. These drugs need enhancement in dissolution rate for enhancing their bioavailability. They also pose problems in the design of controlled release products due to their insoluble character. Hence there is a great need to develop technologies for these BCS - Class II drugs for enhancing the bioavailability as well as for controlled release. A survey of the literature revealed that cyclodextrins have immense potential as pharmaceutical excipients in the formulation of drug delivery systems. Cyclodextrins are cyclic, oligosaccharides that form inclusion complexes enclosing insoluble drug molecules in their hydrophobic interior. Cyclodextrin complexation modifies the physico-chemical properties of the drug molecule. Cyclodextrin complexation was found to enhance the solubility, dissolution rate and chemical stability of a drug. Cyclodextrins especially β-cyclodextrin (β-CD) and hydroxy propyl β-cyclodextrin (HPβ-CD), are safer and non-toxic excipients approved in pharmaceutical formulations. In the present investigation these two cyclodextrins (β-CD and HPβ-CD) were evaluated for their application in enhancing the dissolution rate and bioavailability of sparfloxacin, nifedipine and nimodipine and in the design of oral controlled release formulations of nimodipine.

Sparfloxacin is a relatively new diflourinated quinolone having a broad spectrum of antimicrobial activity for oral administration. It is poorly soluble in water and its aqueous solubility
was reported as 6.7 mg/lit\textsuperscript{1}. As such its oral absorption and bioavailability are dissolution rate limited. A few studies were carried out earlier on enhancement of dissolution rate of sparfloxacin. The dissolution rate and absorption rate of sparfloxacin was enhanced by solid dispersion in pregelatinized starch\textsuperscript{1}. In another study\textsuperscript{2} sparfloxacin tablets formulated employing superdisintegrants gave rapid dissolution and exhibited higher dissolution rates. In the present investigation cyclodextrin complexation was tried for enhancing the dissolution rate and bioavailability of sparfloxacin. The feasibility of formulating the cyclodextrin complexes into compressed tablets was also investigated.

Nifedipine and Nimodipine are two widely used calcium channel blockers used in the treatment of angina pectoris and hypertension. These drugs are practically insoluble in water and their absorption is dissolution rate limited. The dissolution rate of nifedipine and nimodipine was enhanced by solid dispersion techniques\textsuperscript{3-8}. In the present work cyclodextrin complexation was tried to enhance the solubility and dissolution rate of these drugs.

Nimodipine has a half life of 1-2 hours, a consequence is the need for frequent (every 4 hours) dosing. As such controlled release products are needed for nimodipine to prolong its duration of action and to improve patient compliance. Controlled release products of nimodipine also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitation associated with conventional tablets and capsules.

As Nimodipine is insoluble in water and aqueous fluids, it poses problems such as low bioavailability and insufficient blood levels in the design of controlled release products. In the present work cyclodextrin complexation was tried first to enhance its solubility and dissolution rate. The feasibility of using the cyclodextrin complexes in the formulation of oral controlled release products of nimodipine was then investigated.
6.1 Phase solubility studies

The complexation of the selected drugs (sparfloxacin, nifedipine and nimodipine) 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.

Phase solubility studies were performed according to the method reported by Higuchi and Connors7. The results of the phase solubility studies are given in Tables 5.1 – 5.6 and shown in Figs. 5.1 – 5.6. With all the three drugs the aqueous solubility was increased linearly as a function of the concentration of β-CD and HPβ-CD in each case.

The phase solubility diagrams for the complex formation between SPF-βCD, SPF-HPβCD, N-βCD, N-HPβCD, NM-βCD and NM-HPβCD are shown in Figs. 5.1 – 5.6.

All the phase solubility diagrams can be classified as Type A, according to Higuchi and Connors7. Because the straight line had a slope less than unity in each case, the increase in solubility was due to the formation of a 1 : 1 M complex in solution with all the three drugs. The apparent stability constant \( K_c \) was calculated from the linear plot of the phase solubility diagram according to the equation,

\[
K_c = \frac{\text{Slope}}{S_0 \text{ (1-slope)}}
\]

where \( S_0 \) = the solubility of the drug in the absence of CD.
The apparent stability constants \( (K_c) \) obtained from the slope of the linear phase solubility diagrams are as follows.

<table>
<thead>
<tr>
<th>Complex</th>
<th>( K_c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPF - ( \beta )CD</td>
<td>210.8 M(^{-1})</td>
</tr>
<tr>
<td>SPF - HP(\beta)CD</td>
<td>275.8 M(^{-1})</td>
</tr>
<tr>
<td>N-(\beta)CD</td>
<td>121.9 M(^{-1})</td>
</tr>
<tr>
<td>N-HP(\beta)CD</td>
<td>253.7 M(^{-1})</td>
</tr>
<tr>
<td>NM-(\beta)CD</td>
<td>470.0 M(^{-1})</td>
</tr>
<tr>
<td>NM-HP(\beta)CD</td>
<td>489.6 M(^{-1})</td>
</tr>
</tbody>
</table>

\( K_c \) values in the range of 200 - 500 m\(^{-1}\) indicated a stronger interaction between the guest molecules (drug) and CD and greater stability of the complex formed. The values of the stability constants indicated that the complexes formed between the drug and CD are quite stable in all cases except N-\(\beta\)CD.

6.2 Preparation of solid CD complexes

For \( A_1 \) type, solid inclusion complexes can be prepared by methods such as kneading\(^9\), freeze drying\(^10\), spray drying\(^11\), and co-evaporation\(^12\). In the present study, kneading and co-evaporation methods were employed to prepare solid inclusion complexes. In each case, solid inclusion complexes were prepared at 1:1, 1:2, and 1:3 ratios of drug and CD. The solid inclusion complexes prepared were found to be fine, free flowing powders. The complexes were evaluated for drug content uniformity, dissolution rate, and dissolution efficiency. Drug contents of various solid inclusion complexes are given in Tables 5.7 - 5.9. In each case, the drug content in the solid inclusion complex was found to be 100 ± 5% of the labelled amount. In each case, low CV values (< 2.0%) in the percent drug content indicated uniformity of drug content in the solid inclusion complexes.
6.3 Dissolution rate study on solid inclusion complexes

The dissolution rate of drug from various cyclodextrin solid inclusion complexes was studied and compared with that of pure drug in each case.

6.3.1 Dissolution rate of SPF - CD complexes

The dissolution rate of sparfloxacin from various cyclodextrin complexes was studied in water containing 1% SLS. SLS was included in the dissolution fluid to maintain sink condition. The dissolution data of SPF-CD complexes are given in Tables 5.10 - 5.13 and the dissolution profiles are shown in Figs. 5.7 - 5.10.

The dissolution data were analysed as per zero order and first order kinetics. The model that best fits the dissolution data was evaluated by calculating the correlation coefficient (r) between the two variables namely time and percent dissolved in the zero order model and time and log per cent remaining in the first order model. The correlation coefficient (r) values in the analysis of the dissolution data as per zero-order and first-order kinetics are given in Table 5.14. The r values were found to be relatively higher in the case of first order model in all the cases. Thus the dissolution of SPF as such and from various cyclodextrin complexes followed first-order kinetics. The corresponding linear plots are shown in Figs. 5.11 - 5.14. From the slope of the first order linear plot the dissolution rate constant $K_1$ (min$^{-1}$) was calculated in each case. The $K_1$ values are given in Tables 5.15, 5.16.

Another parameter suitable for the evaluation of in vitro dissolution has been suggested by Khan$^{13}$ who introduced the parameter Dissolution Efficiency (DE). DE is defined as the area under dissolution curve up to a certain time $t$ expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \left( \frac{\int_0^t y \, dt}{Y_{100 \% \, t}} \right) \times 100$$
The dissolution efficiency can have a range of values depending on the time intervals chosen. In any case, constant time intervals should be chosen for comparison. For example, the index $DE_{30}$ would be related to the dissolution of the drug from the particular formulation after 30 min could only be compared with $DE_{30}$ of other formulations. Summation of the large dissolution data into a single figure $DE$ enables ready comparison to be made between a large number of formulations. $DE_{30}$ values were calculated as per Khan$^{13}$. 

All the dissolution parameters ($T_{90}$, $T_{60}$ %, dissolution in 10 min, $DE_{30}$ and $K_t$) indicated rapid and higher dissolution of SPF from CD complexes when compared to uncomplexed drug. With both $\beta$CD and HP$\beta$CD the dissolution rate and dissolution efficiency of SPF were increased as the concentration of cyclodextrin in the solid complex was increased in each case. Complexes prepared at a ratio of 1 : 3 gave highest dissolution in each case. HP$\beta$CD gave higher enhancement in the dissolution rate and efficiency when compared to $\beta$CD at all ratios tested in both the methods. A 17.7 and 4.9 fold increase in the dissolution rate of SPF was observed respectively with $\beta$CD 1 : 3 complexes prepared by kneading and coevaporation methods. Whereas in the case of HP$\beta$CD 1 : 3 complexes a 87.7 and 17.7 fold increase in the dissolution rate was observed respectively with kneaded and coevaporated complexes.

Solid complexes prepared by kneading method exhibited higher dissolution rates and dissolution efficiency values than those prepared by coevaporation method in each case. The higher dissolution rates observed with kneaded complexes may be due to the better interaction of drug and cyclodextrins during the kneading process. An increase of 17.7 and 87.7 fold in the dissolution rate of sparfloxacin was observed with SPF-$\beta$CD (1 : 3) and SPF-HP$\beta$CD (1 : 3) inclusion complexes prepared by kneading method. The higher dissolution rates and efficiency values observed with SPF-$\beta$CD and SPF-HP$\beta$CD solid complexes is due to the solubilizing effect of cyclodextrins by forming inclusion complexes with SPF in solution. Thus both the solubility and dissolution rate of SPF were markedly enhanced by complexation with $\beta$CD and HP$\beta$CD.
6.3.2 Dissolution rate of N-CD complexes

The dissolution rate of nifedipine from various cyclodextrin complexes was studied in 0.1N HCl containing 10% methanol. Methanol was included in the dissolution fluid to maintain sink condition. The dissolution data of N-CD complexes are given in Tables 5.17 - 5.20 and the dissolution profiles are shown in Figs. 5.15 - 5.18.

The analysis of dissolution data as per zero-order and first order kinetics based on correlation coefficient (r) values (Table 5.21) indicated that the dissolution of nifedipine as such and from the cyclodextrin complexes followed first-order kinetics. The corresponding first-order linear plots are shown in Figs. 5.19 - 5.22. The dissolution efficiency (DE) values were calculated as per Khan. The dissolution parameters of nifedipine and its cyclodextrin complexes are summarized in Tables 5.22 - 5.23.

The solid inclusion complexes of N-βCD and N-HPβCD exhibited higher rates of dissolution and dissolution efficiency values than uncomplexed nifedipine. The dissolution rate and dissolution efficiency of nifedipine were increased as the proportion of cyclodextrin in the solid complex was increased in each case. HP-βCD gave higher enhancement in the dissolution rate and efficiency (DE) when compared to β-CD at all ratios tested in both the methods. A 38.6 and 28.6 fold increase in the dissolution rate of nifedipine was observed respectively with β-CD 1 : 3 complexes prepared by kneading and coevaporation methods. Whereas in the case of HP-βCD 1 : 3 complexes a 44.3 and 38.6 fold increase in the dissolution rate was observed respectively with kneaded and coevaporated complexes.

Solid complexes prepared by kneading method exhibited higher dissolution rates and efficiency values than those prepared by coevaporation method in each case. The higher dissolution rates observed with kneaded complexes may be due to the better interaction of drug and cyclodextrines during the kneading process. An increase of 38.6 and 44.3 fold in the dissolution rate of nifedipine was observed with N-βCD (1 : 3) and N-HPβCD (1 : 3) inclusion complexes prepared by kneading method. The higher dissolution rates and efficiency values observed with N-βCD and N-HPβCD solid complexes is due to the solubilizing effect of
cyclodextrins by forming inclusion complexes with nifedipine in solution. Thus both the solubility and dissolution rate of nifedipine were markedly enhanced by complexation with βCD and HPβCD.

### 6.3.3 Dissolution rate of NM-CD complexes

The dissolution rate of nimodipine from various cyclodextrin complexes was studied in 0.1N HCl containing 10% methanol. Methanol was included in the dissolution fluid to maintain sink condition. The dissolution data of NM-CD complexes are given in Tables 5.24 – 5.27 and the dissolution profiles are shown in Figs. 5.23 – 5.26. The analysis of dissolution data as per zero-order and first-order kinetics based on correlation coefficient (r) values (Table 5.28) indicated that the dissolution of nimodipine as such and from cyclodextrin complexes followed first order kinetics. The corresponding linear first order plots are shown in Figs. 5.27 – 5.30. The dissolution efficiency (DE\(_{50}\)) values were calculated as per Khan\(^{13}\). The dissolution parameters of nimodipine and its cyclodextrin complexes are given in Tables 5.29 and 5.30.

The solid inclusion complexes of NMβCD and NM-HPβCD exhibited higher rates of dissolution and dissolution efficiency values than nimodipine itself. The dissolution rate and dissolution efficiency of nimodipine were increased as the proportion of cyclodextrin in the solid complex was increased in each case. HP-βCD gave higher enhancement in the dissolution rate and efficiency (DE) when compared to β-CD at all ratios tested in both the methods. A 30.68 and 20.9 fold increase in the dissolution rate of nimodipine was observed respectively with β-CD 1:3 complexes prepared by kneading and coevaporation methods. Whereas in the case of HP-βCD 1:3 complexes a 50.68 and 31.80 fold increase in the dissolution rate was observed respectively with kneaded and coevaporated complexes.

Solid complexes prepared by kneading method exhibited higher dissolution rates and efficiency values than those prepared by co-evaporation method in each case. The higher dissolution rates observed with kneaded complexes may be due to the better interaction of drug and cyclodextrins during the kneading process. An increase of 30.68 and 50.68 fold in the dissolution rate of nimodipine was observed with NM-βCD (1:3) and NM-HPβCD (1:3) inclusion complexes prepared by kneading method. The higher dissolution rates and efficiency values
observed with NM-βCD and NM-HPβCD solid complexes is due to the solubilising effect of cyclodextrins by forming inclusion complexes with nimodipine in solution. Thus both the solubility and dissolution rate of nimodipine were markedly enhanced by complexation with β-CD and HP-βCD.

The results of the present study clearly indicated that the solubility and dissolution rate of all the three drugs studied (SPF, N, NM) could be markedly enhanced by complexation with β-CD and HP-βCD.

### 6.4 Formulation studies on SPF – CD complexes

Solid inclusion complexes of SPF-βCD (1 : 3) and SPF – HPβCD (1 : 3) prepared by kneading method were formulated into tablets by both direct compression and conventional wet granulation methods as per the formulae given in Table 5.31. As the solid inclusion complexes are not flowing adequately, micro-crystalline cellulose (MCC), a directly compressible vehicle, was added to CD complexes to improve their flow for direct compression into tablets. Formulations F1, F2 and F3 were made by direct compression method. Formulations F4, F5 and F6 were made by wet granulation method.

All the tablets prepared were found to contain the drug within 100 ± 3% of the labelled claim (Table 5.32). Hardness of the tablets was in the range 6-8 kg/sq.cm. and was satisfactory, the percentage weight loss in the friability test was less than 0.6% in all the tablets prepared.

All tablets prepared by direct compression method (F1, F2, F3) and tablet formulations F4, F5 prepared by wet granulation method disintegrated rapidly within 4.0 minutes (Table 5.32) whereas tablet formulation F6 disintegrated slowly and took more time upto 12-15 min for disintegration. Overall, tablets prepared by direct compression method disintegrated rapidly when compared to those prepared by wet granulation method. All tablets fulfilled the official (I.P.) disintegration time specifications of uncoated tablets.

Thus, all the tablets formulated employing β-CD and HP-βCD complexes were found to be of good quality and fulfilling all the official (I.P) and other requirements of compressed tablets.
The dissolution data and dissolution profiles of sparfloxacin tablets formulated are given in Tables 5.33 – 5.34 and shown in Figs. 5.31 – 5.32. Dissolution parameters were summarized in Tables 5.35 – 5.36.

Analysis of dissolution data as per zero-order and first-order kinetic models based on correlation coefficient (r) values (Table 5.37) indicated that the dissolution of sparfloxacin from all the tablets followed first-order kinetics. First-order linear plots of the dissolution data are shown in Figs. 5.33 – 5.34.

In both direct compression and wet granulation methods tablets formulated employing cyclodextrin complexes (F2, F3, F5, F6) gave higher rates of dissolution and dissolution efficiency values when compared to the corresponding tablets formulated with SPF as such (F1 and F4). Tablets formulated employing β-CD complexes (F2 and F5) gave higher dissolution than those formulated with HP-βCD complexes (F3, F6). The lower dissolution observed with the tablets formulated employing HP-βCD complexes may be due to dry binding nature of HP-βCD.

Among all the tablets formulated, formulation F2 which is based on SPF-βCD (1:3) kneaded complex, gave the highest dissolution. A 17 fold increase in the dissolution rate of SPF was observed with F2 when compared to formulation F1.

Thus SPF – cyclodextrin complexes could be formulated into compressed tablets by both direct compression and wet granulation methods. Sparfloxacin tablets formulated employing β-CD and HP-βCD complexes exhibited rapid and higher dissolution rates and DE values than those formulated with uncomplexed drug. Among the two cyclodextrins, β CD complexes were found to be more suitable for tablet formulation by both direct compression and wet granulation methods.

6.5 Stability studies on selected sparfloxacin tablets formulated

The stability of the dissolution rate characteristics of sparfloxacin tablets formulated employing β-CD (F2 & F5) was evaluated as per ICH guidelines. The tablets were packed in screw capped HDPE bottles and were stored at (i) room temperature (28° ± 1°C) for 6 months and
at (ii) 40° ± 2°C; 75% ± 5% RH for 3 months. At the end of storage period the tablets were tested for their dissolution rate characteristics. The dissolution data of the tablets before and after storage are given in tables 5.38 – 5.39.

No visible changes were observed in these tablets after storage. The dissolution profiles of the tablets (Figs. 5.35 – 5.36) remained unaltered during the storage period at both the temperatures studied. The dissolution characteristics of the tablets were quite stable. The stored tablets also exhibited rapid dissolution of SPF similar to freshly made tablets.

6.6 Pharmacokinetic and bioavailability evaluation of sparfloxacin tablets formulated employing SPF-βCD (1:3) complex

Sparfloxacin tablet formulations based on its cyclodextrin inclusion complexes exhibited markedly higher dissolution rates and dissolution efficiency values when compared to sparfloxacin plain tablets. In vivo evaluation of selected SPF tablet formulations was carried out with a view to assess the pharmacokinetics of absorption and elimination and bioavailability of sparfloxacin from products formulated employing cyclodextrins.

Sparfloxacin tablet formulations F1 (plain tablets) and F2 (tablets formulated employing SPF - βCD (1:3) complex) were subjected to pharmacokinetic evaluation. The results of pharmacokinetic evaluation are given in tables 5.40 – 5.43 and shown in Figs. 5.37 – 5.39.

The pharmacokinetic parameters estimated are summarized in Table 5.44. The biological half-life (t½) was found to be 15.99 ± 1.27 hours following the administration of SPF. The value is in good agreement with the reported t½ 20 ± 4 hours. The good agreement of t½ estimated in the present work by the microbiological assay method with the reported value indicated the suitability of the microbiological method of estimation of serum SPF for pharmacokinetic studies.

The results of pharmacokinetic studies indicated rapid absorption of SPF from formulation F2 when compared to formulation F1. Upon oral administration of F1 a peak concentration (Cₘₚ)
of 0.293 ± 0.008 μg/ml was observed at 4.0 hour after administration. Whereas with formulation F2 a significantly higher (P < 0.05) C_{max} of 0.366 ± 0.04 μg/ml was observed at 3.0 hour.

Percentages absorbed to various times was calculated by Wagner-Nelson\textsuperscript{14} method. The percent absorbed in 1.0 hr and 2.0 hr was found to be 35.9% and 58.05% respectively when F1 was administered. Whereas the corresponding values for formulation F2 were 49.17 ± 4.95 and 78.42 ± 2.28 respectively. The K_{a} was 0.833 hr\textsuperscript{-1} and 1.24 hr\textsuperscript{-1} respectively for F1 and F2. These results indicated the fast absorption of SPF from formulation F2 which is based on SPF - βCD (1:3) complex.

AUC\textsubscript{0-\infty}, was same with the products. The difference in (AUC)\textsubscript{0-\infty}, was not significant (P > 0.05) indicating that the extent of absorption was same with both the formulations F1 and F2.

Thus the sparfloxacin tablets, formulated employing SPF - βCD (1:3) inclusion complex (F2) have exhibited significantly higher rate of absorption of SPF. However, the extent of bioavailability of SPF from F2 formulation remained the same as that from F1. The higher absorption rates observed with formulation F2 is due to the enhanced solubility and dissolution rate of SPF when complexed with β-CD. Thus cyclodextrin complexation has markedly enhanced the solubility, dissolution rate and absorption rate of SPF.

6.7 Preparation and evaluation of nimodipine matrix tablets for oral controlled release

Matrix tablets each containing 120 mg of nimodipine were formulated employing nimodipine alone (formulation F1 and F4) and its CD complexes (formulations F2, F3, F5 and F6) as per the formulae given in Table 5.45. Formulations F1 - F3 contain hydroxy propyl methyl cellulose (HPMC) as matrix material and formulations F4 - F6 contain sodium carboxymethyl cellulose (Sod. CMC) as matrix material. The matrix tablets were prepared by conventional wet granulation method. The matrix tablets prepared were evaluated for hardness, friability, drug content, disintegration time and drug release characteristics.

The matrix tablets prepared were found to be non-disintegrating in water, 0.1N HCl, and phosphate buffer of pH 7.4. The hardness of the tablets was in the range of 7-8 kg/sq.cm (Table 5.46). Percentage weight loss in the friability test was found to be less than 0.2% in all the cases. The tablets in all the batches prepared contained nimodipine within 100 ± 5% of the labelled
content. As such all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

Nimodipine release from the matrix tablets was studied in simulated gastrointestinal fluids for a period of 12 hr as per NF-XII procedure. In this method the tablets were exposed to simulated gastrointestinal fluids of increasing pH from 1.2 – 7.5 to represent a better simulation of in vivo conditions. The release data are given in Tables 5.47 – 5.48 and release profiles are shown in Figs. 5.40 – 5.41.

Release of nimodipine from formulations F1 and F4, which contain nimodipine alone in the matrix material, was found to be very low, 38.46% in 12 hrs in the case of F1 and 25.0% in 12 hr in the case of F4. The poor dissolution and release of nimodipine from these formulations is due to the highly crystalline nature and poor aqueous solubility of nimodipine. Because of very low and slow release of nimodipine, these tablet formulations (F1 and F4) are found to exhibit poor bioavailability. As such matrix tablets formulated employing nimodipine alone are considered not suitable for oral controlled release of nimodipine.

Matrix tablets formulated employing NM-cyclodextrin complexes (F2, F3, F5, F6) gave slow, controlled and complete release of nimodipine over a period of 12 hr.

Nimodipine release from the matrix tablets followed zero-order kinetics (r > 0.99). Plots of percent of drug release versus square root of time (Figs. 5.42 – 5.43) were found to be linear with all the matrix tablets indicating that the drug release mechanism from these tablets was diffusion controlled.

Thus slow, controlled and complete release of nimodipine over a period of 12 hr was obtained from matrix tablets formulated employing its cyclodextrin (β-CD and HP-βCD) complexes and using HPMC, and Sod. CMC as matrix material, which was not possible with similar tablets formulated employing nimodipine as such.

The initial good maintenance doses and the desired sustained release rate for oral controlled release products of nimodipine was calculated based on its pharmacokinetics as per Wagner et al.14 (Table 5.49). An oral controlled release product of nimodipine should contain a total dose of 120 mg (initial dose 30 mg, and maintenance dose 90 mg and should provide the drug from the maintenance dose at a rate of 10.38 mg/hr.
The release rates of various matrix tablets prepared are given in Table 5.50. A comparison of the release rates of the matrix tablets prepared with the theoretical desired release rate ($K_0 = 10.38 \text{ mg/hr}$) indicated that the matrix tablets formulated employing cyclodextrin complexes gave release rates close to the theoretical release rate. Among all the formulations, F5 gave a release rate of 9.60 mg/hr and was found to be more suitable for oral controlled release of nimodipine.

6.8 Pharmacokinetic Evaluation of Matrix Tablets of Nimodipine

Pharmacokinetic evaluation was done on (i) matrix tablets containing nimodipine alone in sodium CMC matrix (formulation F4) and (ii) matrix tablets containing nimodipine - βCD complex in sodium CMC matrix (formulation F5) in healthy human subjects as per a cross-over randomized block design ($n = 4$). From the time versus serum concentration data $C_{\text{max}}$, $T_{\text{max}}$, $(\text{AUC})_{0\text{\text{\text{---}}}\infty}$, percentage absorbed to various times were calculated. The results of pharmacokinetic evaluation are given in Table 5.51 and shown in Fig. 5.44.

The results of pharmacokinetic studies indicated very low absorption of nimodipine from formulation F4, which contained nimodipine as such. A peak concentration ($C_{\text{max}}$) of $12.2 \pm 1.8 \text{ ng/ml}$ was reached in 4.0 hr and the concentrations at all time points were very low. Whereas in the case of formulation F5, the serum concentrations were found to be higher than those observed with formulation F4 (Fig. 5.44). The higher serum concentrations observed with formulation F5 is due to the higher but slow and complete release of nimodipine over 12 hr period from these tablets. Formulation F4, which contained nimodipine alone, gave low release, 25% in 12 hr and as such they also gave very low serum concentrations of nimodipine.

The percentages of nimodipine absorbed to various times following the administration of formulation F5 were calculated by Wagner-Nelson\textsuperscript{14} method. The percent absorbed in 1, 2, 4 and 8 hrs after administration was found to be 20.2, 40.6, 57.5 and 84.7% respectively. These results indicated the slow absorption of nimodipine from formulation F5 over a period of 8-12 hrs. The serum concentrations were stabilized within a narrow range of 27-43 ng/ml during the period from 1.5 to 12 hr. Thus the formulation F5, which is based on NM-βCD complex exhibited good sustained release/absorption characteristics \textit{in vivo}. The $(\text{AUC})_{0\infty}$ was found to be 114.2 and 476.9 ng.hr/ml respectively with formulations F4 and F5. A 4.17 fold increase in the bioavailability
was observed with F5 when compared to F4. Thus the matrix tablets formulated employing NM-βCD (1:1) complex exhibited 4 times higher bioavailability and good in vivo sustained serum concentrations of nimodipine over a period of 12 hrs. Hence formulation F5 was considered a good oral controlled release formulation of nimodipine.
REFERENCES

3. Chowdary, K.P.R., Ramana Murthy, K.V. and Ch.D.S. Prasad, Indian Drugs, 1996, 32(11), 537.