DISCUSSION OF RESULTS
DISCUSSION OF RESULTS

The present study was performed to evaluate the influence of certain inorganic electrolytes on the controlled release of freely soluble salt form of the drugs from Controlled release matrix tablets of polyethylene oxides. The drug candidates used in the study were Verapamil Hydrochloride and Losartan Potassium. These two drugs are widely used as antianginal and antihypertensive drugs. The electrolytes used were dried aluminum hydroxide, aluminum sulphate, calcium carbonate, magnesium carbonate, sodium bicarbonate and sodium carbonate. Two grades of controlled release Polyethylene oxides such as PEO WSR 301 and PEO WSR 303 were used as polymers for matrix tablet formulations.

Verapamil Hydrochloride is freely soluble in distilled water, methanol and chloroform. More than 90% of Verapamil Hydrochloride is rapidly absorbed after oral administration. It undergoes rapid first-pass hepatic metabolism after conventional dose administration which gives bioavailability from 20-35%. It has elimination half life of 2.8-5.4 hrs.

Losartan Potassium is freely soluble in distilled water and methanol but insoluble in chloroform. It is well absorbed after oral administration and undergoes hepatic first pass metabolism. The systemic bioavailability of conventional tablets is approximately 33%. It has elimination half-life of about 2 hrs.

Based on the physico-chemical and bio-pharmaceutical properties Verapamil Hydrochloride and Losartan Potassium were selected as drug candidates for formulating controlled release matrix tablet formulations.

Literature survey revealed that these two drugs were formulated as controlled release dosage forms as matrix tablets, coated beads, microcapsules, reservoir devices by employing various methods. In the present study, formulations were developed with these drugs by employing pharmaceutically acceptable electrolytes in the polyethylene oxide matrix tablets with an objective to achieve linear controlled release over an extended period of time.
A simple sensitive UV-Spectrophotometric methods were used for the estimation of Verapamil Hydrochloride and Losartan Potassium. Verapamil Hydrochloride was measured UV-Spectrophotometrically at a \( \lambda \max \) of 278 nm and Losartan Potassium was measured at a \( \lambda \max \) of 205 nm, these methods were utilized for the estimation of both the drugs in the matrix tablets and in the \textit{in-vitro} dissolution studies. \textit{In-vivo} pharmacokinetic studies of Verapamil Hydrochloride and Losartan Potassium were determined by HPLC methods in rabbit plasma fluids. These methods were found to be suitable for estimation of Verapamil Hydrochloride and Losartan Potassium in controlled release matrix tablets. IR spectral studies were performed for selected matrix tablet formulations during dissolution studies to check \textit{in-situ} reaction between the drugs and electrolytes. Accelerated stability studies on some selected matrix tablet formulations were conducted as per ICH guidelines.

6.2 Preparation of Controlled Release Matrix Tablets of Verapamil Hydrochloride and Losartan Potassium:

Controlled release matrix tablets of Verapamil Hydrochloride and Losartan Potassium were prepared by direct composition process using 10 station minipress (clit). The composition of drug and polymer ratio in all the tablet formulations was kept constant, while the electrolyte concentration was varied. The composition of various tablet formulations were given in tables 4.3 to 4.14.

The direct compression process used for making matrix tablets was found to be ideal and easy to produce. Polymers such as Polyethylene oxide WSR 301 and Polyethylene oxide WSR 303 were exhibiting good flow properties, which enables the process very easy. Talc and magnesium stearate at 1% concentration was blended with the mixture of contents, to enhance the flow properties. All the powder blends were evaluated for flow properties such as carr’s index and angle of repose prior to the compression as matrix tablets. The direct compression process was found to be ideal for inclusion of electrolytes into matrix system. Electrolytes may undergo dissociation if they are subjected to wet granulation process. Some electrolytes undergo precipitation, if solvents are used for granulation. Hence direct compression process was employed in the present work for the preparation of controlled release matrix, tablets of Verapamil Hydrochloride and Losartan Potassium. All batches of matrix tablets were compressed under identical conditions to
minimize processing variables. Then these tablets were evaluated for physical parameters such as weight uniformity, hardness, friability and drug content uniformity.

6.3 Flow properties:

Flow properties of various powder blends before direct compression were evaluated. The flow properties such as carr’s index and angle of repose were measured for all the powder blends.

Carr’s index:

A simple test was used to evaluate the flowability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down. The carr’s index values for all the powder blends were in the range of 5-15% indicated the good or excellent flow characteristics.

Angle of repose:

It is the maximum angle possible between the horizontal surface to the heap of the powder. The powder flow properties are determined to know the good or bad material flow by conducting this process. The angle of repose for all the powder blends were in the range of 20° indicated the excellent flow characteristics.

Physical Parameters of Matrix Tablets

The Controlled release matrix tablets formulations produced by direct composition process were having good quality and have a smooth texture without cracks on the tablet surface.
Weight Uniformity:

The matrix tablets were then evaluated for the uniformity in weight. This test is highly desirable that all the tablets of a particular batch should be uniform in weight. The weight ranges of different batches of tablets were depicted in tables 4.19 to 4.22. The weight range of all batches of matrix tablets was uniform and was within the IP limits. The IP limits of percentage deviation in tablet weights were given in table.

Hardness:

Hardness of the tablets was determined by using Monsanto hardness tester (Tab-machines, Mumbai). The hardness of tablets depends on the weight of the material used, space between the upper and lower punches at the time of compression and pressure applied during compression. The hardness values of different batches of matrix tablets were given in tables 4.19 to 4.22

Friability:

Friability test for matrix tablets were performed by using Roche friabilator (Remi Equipment, Mumbai). This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The loss in weight and damages to the surface of tablets were found to be negligible and were within the limits of friability loss. The % loss in the weight of the matrix tablets were given in tables 4.19 to 4.22.

Content Uniformity:

Controlled release matrix tablet formulations of Verapamil Hydrochloride and Losartan Potassium were analyzed for drug content by known UV- Spectrophotometric methods. This test is highly essential for determining the actual amount of drug content present in the matrix tablets. All batches of matrix tablet formulation were confirmed to have the claimed amount of drug as per USP specifications of Verapamil Hydrochloride and Losartan Potassium extended release formulations respectively. The actual amount of drug present in the matrix tablet formulations were depicted in tables 4.19 to 4.22
**DRUG RELEASE STUDIES**

Verapamil Hydrochloride release from the matrix tablets were studied in 1.2pH acetic buffer for the first two hours followed by 6.8 pH phosphate buffer as medium over a period of 12 hrs. Losartan Potassium release from the matrix tablets was studied in acidic medium of pH 1.2 for 2 hrs followed by phosphate buffer medium of pH 6.8 for remaining period up to 12 hrs.

**Verapamil Hydrochloride and Losartan Potassium release characteristics from matrix tablets of Polyethylene oxide WSR 301:**

Verapamil Hydrochloride and Losartan Potassium at a constant dose were individually compressed with different proportions of polyethylene oxide WSR 301 (1:0.5, 1:1, 1:15, and 1:2.0). Then these matrix tablet formulations were subjected to drug release studies. Matrix tablet formulation with drug and polymer ratio of 1:1.5 with polyethylene oxide WSR 301 as a polymer (VP3, and LP3) were found to be ideal for controlled release of the drugs. The results were given in tables 4.24 to 4.37 and shown in graphs 4.3 to 4.16.

**Verapamil Hydrochloride and Losartan Potassium release characteristics from matrix tablets of Polyethylene Oxide WSR 303:**

Verapamil Hydrochloride and Losartan Potassium at a constant dose were individually compressed with different proportions of polyethylene oxide WSR 303(1:0.5, 1:1, 1:15, and 1:2.0). Then these tablet formulations were subjected to drug release studies. Matrix tablet formulations with drug and polymer ratio of 1:1 with polyethylene oxide WSR 303 as a polymer (LP3 and LP32) were found to be ideal for Controlled release of the drug. The results were given in tables 4.38 to 4.51 and shown in graphs 4.17 to 4.30.

Hence these two polymers at a drug to polymer ratio of 1:1.5 with PEO WSR 301 and 1:1 with PEO WSR 303 were kept constant for further matrix tablet formulations compressed along with electrolytes.
The matrix tablet formulations of polyethylene oxide 301 and polyethylene oxide 303 were found to release the drug at a faster rate, where as drug release from the matrix tablets containing electrolytes were found to be slow and spread over long period of time. The corresponding release rate constants were calculated and given in table 4.5 to 4.55. Drug release from the matrix tablets depend on drug and polymer ratio and electrolytes employed in preparation. As the proportion of the polymer was increased, the release of drug was decreased to certain extent. Good linear relationship was observed between polymer concentration and drug release to certain extent. The linearity in drug release was found up to drug and polymer ratio of 1:1.5 and 1:1 with PEO WSR 301 and PEO WSR 303 respectively. Further increase in the polymer concentration, showed no significant linear relationship. Electrolyte concentration (for some electrolytes) in matrix tablets was found to have good linear relationship with the drug release from the matrix tablets.

**Influence of electrolyte employed on drug release from Polyethylene WSR 301 and Polyethylene WSR 303 matrix tablets:**

The electrolyte employed has significant influence on drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablet of PEO WSR 301 and PEO WSR 303 polymers. The electrolytes employed in the study are aluminum hydroxide gel, aluminum sulphate, calcium carbonate, dibasic calcium phosphate, magnesium carbonate, magnesium trisilicate, sodium bicarbonate and sodium carbonate. The rate of release from these matrix tablets prepared with different electrolytes in each case was found to be first order and controlled by both diffusion and dissolution mechanisms.

The influence of each and individual electrolyte on drug release were given below

A) **Aluminium Hydroxide**: It has high influence on drug release from the matrix tablets of poly ethylene oxide wsr-301 and poly ethylene oxide wsr-303. Good linear relationship was observed between dried Aluminium hydroxide concentration and drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablets. As the concentration of aluminium hydroxide increases, the drug release from the matrix tablets
was slow and extended for a prolonged period. Aluminium hydroxide at 40 mg per tablet concentration was found to produce linear drug release, from the matrix tablets over an extended period of time with Verapamil Hydrochloride and Losartan Potassium. The corresponding results were shown in graphs 4.4, 4.31, 4.39 and 4.45.

B) Aluminium Sulphate: It has mild influence on drug release from the matrix tablets of poly ethylene oxide wsr-301 and poly ethylene oxide wsr-303. The drug release from the matrix tablet was found to be constant even with varying proportions of Aluminium sulphate. The same effect was observed in case of Verapamil Hydrochloride and Losartan Potassium matrix tablets. The results were shown in graphs 4.4, 4.31, 4.39 and 4.45.

C) Calcium Carbonate: It has high influence on drug release from the matrix tablets of poly ethylene oxide wsr-301 and poly ethylene oxide wsr-303. Good linear relationship was observed between Calcium Carbonate concentration and drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablets. The drug release was slow and extended for prolonged period as the concentration of Calcium Carbonate was increased. Calcium Carbonate at 20mg per tablet concentration was found to produce ideal drug release from the matrix tablets. The corresponding results were shown in graphs 4.6, 4.13, 4.20 and 4.27.

D) Magnesium Carbonate: It has high influence on drug release from the matrix tablets of poly ethylene oxide wsr-301 and poly ethylene oxide wsr-303. Good linear relationship was observed between Magnesium Carbonate concentration and drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablets. The drug release was slow and extended for prolonged period as the concentration of Magnesium Carbonate was increased. Magnesium Carbonate at 20mg per tablet concentration was found to produce ideal drug release from the matrix tablets. The corresponding results were shown in graphs 4.7, 4.14, 4.21 and 4.28.

E) Sodium Bicarbonate: It has high influence on drug release from the matrix tablets of poly ethylene oxide wsr-301 and poly ethylene oxide wsr-303. Good linear relationship was observed between Sodium Bicarbonate concentration and drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablets. The drug release was slow and extended for prolonged period as the concentration of Sodium
bicarbonate was increased. Sodium bicarbonate at 20mg per tablet concentration was found to produce ideal drug release from the matrix tablets. The corresponding results were shown in graphs 4.8, 4.15, 4.22 and 4.29.

F) Sodium carbonate: It has high influence on drug release from the matrix tablets of poly ethylene oxide WSR-301 and poly ethylene oxide WSR-303. Good linear relationship was observed between Sodium Carbonate concentration and drug release (both Verapamil Hydrochloride and Losartan Potassium) from the matrix tablets. The drug release was slow and extended for prolonged period as the concentration of Sodium Carbonate was increased. Sodium Carbonate at 20mg per tablet concentration was found to produce ideal drug release from the matrix tablets. Similarly at 40mg per tablet concentration, it was found to produce ideal drug release from the matrix tablets. The corresponding results were shown in graphs 4.9, 4.16, 4.23 and 4.30.

It was found that the optimal concentration of each and every electrolyte for ideal drug release was varied. It was also observed that the optimal concentration of each and every electrolyte for ideal drug release of Verapamil Hydrochloride and Losartan Potassium was varied. The optimal concentration of electrolyte required for Losartan Potassium was high when compared to the optimal concentration of electrolyte for Verapamil Hydrochloride release. This was due to the variation in the solubility of Verapamil Hydrochloride and Losartan Potassium. Verapamil Hydrochloride has very high solubility (1 in 1) than Losartan Potassium (1in20) in aqueous solutions.

The inclusion of electrolytes within the swollen matrix for controlling the release of drug was due to fundamental structural changes in gel boundary and intragel pH, thus induces the textural variations in the swollen matrix. It was observed that electrolyte solubility and formation of buffer threshold within the matrix plays an essential role in effective interaction with drug and textural changes. The solubility if electrolyte was also playing an important role in maintaining a ph value inside the matrix. Electrolytes such as Aluminium Sulphate and Sodium carbonate have high solubility in aqueous phase, diffuse rapidly with the drug and hence no much control on drug release. But the effect of high solubility on controlling drug release was ruled out in case of sodium compounds. Further it was due to low pKa value of electrolyte which may dissociate completely and display low buffer capacity is the reason for not processing the desired release characteristics.
Thus electrolytes having high pKa values are more suitable for maintaining suitable pH inside the matrix. For example electrolytes such as calcium carbonate, magnesium carbonate, sodium carbonate etc., are having high pKa values and having the pH is greater than 10 in aqueous solutions possess desired control on drug release from the matrix tablet. The solubility pKa and pH values of electrolytes used in this study were given in the following table 5.1.

**Table 5.1**

**SOLUBILITY, pKa AND pH VALUES OF ELECTROLYTES**

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Water Solubility</th>
<th>pKa</th>
<th>pH of 1% in distilled water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al. hydroxide</td>
<td>Insoluble</td>
<td>4.81, 10.93</td>
<td>8.09</td>
</tr>
<tr>
<td>Al. sulphate</td>
<td>Highly soluble</td>
<td>4.81, 7.14</td>
<td>4.85</td>
</tr>
<tr>
<td>Cal. Carbonate</td>
<td>Insoluble</td>
<td>6.37, 10.33</td>
<td>9.56</td>
</tr>
<tr>
<td>Mag. Carbonate</td>
<td>Insoluble</td>
<td>6.37, 10.33</td>
<td>10.08</td>
</tr>
<tr>
<td>Sod. Bicarbonate</td>
<td>Soluble</td>
<td>6.37, 10.33</td>
<td>8.07</td>
</tr>
<tr>
<td>Sod. Carbonate</td>
<td>Soluble</td>
<td>6.37, 10.33</td>
<td>10.89</td>
</tr>
</tbody>
</table>
Mechanism of Drug Release from the Matrix Tablet Formulations:

Therapeutic systems will never be dependent on dissolution only or diffusion only. However, the predominant mechanism allows easy mathematical description. In practice, the dominant mechanism for release will overshadow other process enough to allow classification as either dissolution rate limited or diffusion controlled. Bio erodible devices, however, constitute a group of systems for which mathematical descriptions of release characteristics can be quite complex.

The mechanism of release from simple erodible slabs, cylinders and sphere has been described. A simple expression describing release from all three of these erodible devices is

$$\frac{M_t}{M_\infty} = 1 - (1-K_d t/C_0 a)^n$$

Where $n=3$ for a sphere, $n=2$ for a cylinder, and $n=1$ for a slab. The radius of a sphere or cylinder or the half height of a slab is represented by $a$. $M_t$ is the mass of a drug release at time $t$, and $M_\infty$ is the mass released at infinite time. As a further complication, these systems can combine diffusion and dissolution of both the matrix material and the drug. The complexity of the system arises from the fact that, as the polymer dissolves, the diffusional path length for the drug may change. Zero order release can occur only if surface erosion occurs and surface areas does not change with time. The disadvantages of these matrix systems are that the release kinetics are often hard to control, since many factors affecting both drug and the polymer must be considered.

To analyze the mechanism of drug release studies from the obtained data, various calculation were analyzed based on the equation, first order constant, Higuchi’s constant, and the koresmeyer peppas constant respectively. The following are the equations used:

$$\ln Q = k_t t$$

$$Q = k_t t$$

$$\frac{M_t}{M_\infty} = k t^n$$
Where Q in the equation is cumulative percent drug remained, while ‘Q’ in the equation is cumulative amount of drug released, \( M_t / M_{\infty} \) is the fraction of drug released, ‘t’ is the release time and ‘k’ is the constant incorporating the structural and geometrical characteristics of the release device. If the value of \( n=0.45 \) indicates Case I (Fickian) diffusion or square root of time kinetics, \( 0.45 < n < 0.89 \) indicates anomalous (non Fickian, drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, \( n=0.89 \) indicates case II transport and \( n > 0.89 \) indicates super case II transport. Linear regression analysis was performed for all these equations and regression coefficients (r) are determined. These were shown in graphs from 4.59 to 4.88.

FTIR SPECTRAL STUDIES

FTIR spectral studies were performed on some selected matrix tablets of Verapamil Hydrochloride and Losartan Potassium during the dissolution studies. FTIR spectral studies were performed on BRUKER FTIR spectrophotometer using potassium bromide pellets. FTIR spectra of pure drugs of Verapamil Hydrochloride and Losartan Potassium were taken initially to check the basic functional groups present in them.

The spectra of various matrix tablet formulations were taken during dissolution studies. The matrix tablet formulations were withdrawn from the dissolution flask at 6hrs of duration and were dried at ambient conditions. The dried tablets were crushed as to fine powder and were used for spectral studies. The spectra of Verapamil Hydrochloride and Losartan Potassium pure drugs and various matrix tablet formulations were shown in Fig: 2 and Fig: 3 respectively.

The spectra of Verapamil Hydrochloride exhibited principle peaks at wave numbers of 2961 cm\(^{-1}\) (C-H Stretching), 2236 cm\(^{-1}\) (C≡N Stretching), 1593 cm\(^{-1}\) (C≡N Stretching), 1518 cm\(^{-1}\) (C=C Aromatic Stretching) and 1260 cm\(^{-1}\) (C-O Stretching). The spectra of matrix tablet formulations VP3 (VPM & PEO WSR 301), VPA6 (VPM, PEO WSR 301 & Dried Aluminium hydroxide) and VPC44 (VPM, PEO WSR 301 & Calcium carbonate) exhibited all the principle peaks present in the Verapamil Hydrochloride pure drug.
The spectra of Losartan Potassium exhibited principle peaks at wave numbers of 3352 cm\(^{-1}\) (O-H Stretching), 2908 cm\(^{-1}\) (C-H Stretching), 1606 cm\(^{-1}\) (C=N Stretching), 1593 cm\(^{-1}\) (C=C Stretching) and 767 cm\(^{-1}\) (C-Cl Stretching). The spectra of matrix tablet formulations LP3 (LP & PEO WSR 301), LPA6 (LP, PEO WSR 301 & Dried Aluminum hydroxide) and LPS55 (LP, PEO WSR 303 & Sodium carbonate) exhibited all the principle peaks present in the Losartan Potassium pure drug.

The spectral studies of both Verapamil Hydrochloride and Losartan Potassium matrix tablet formulations exhibited no more changes in the principle peaks and all the peaks were observed at specific wave numbers as that of their respective pure drugs. Thus these studies indicated that there were no major interactions between the functional moieties of drug molecules with the polymer or with the electrolytes incorporated in them. The \textit{in-situ} reaction between the drug and the electrolytes may be due to competition towards uptake of dissolution fluids rather than drug and electrolytes chemical interactions. The \textit{in-situ} reactions were further analyzed by checking the swelling characteristics of the matrix tablets during the course of the dissolution.

**SWELLING BEHAVIOR OF THE MATRIX TABLETS**

The swelling behavior of some selected matrix tablets were measured by percentage swelling index at various time intervals and were shown in tables 4.23. The percentage of swelling in the formulations VP3 and LP3 were very high during the dissolution. These matrix tablets were compressed without any electrolytes. The matrix tablet formulations VPA6, VPC44, LPA6 and LPS55 having electrolytes were exhibited low swelling rate during the first 2-6 hrs followed by gradual increase in the swelling.
PHARMACOKINETIC STUDIES

Pharmacokinetic studies of Verapamil Hydrochloride and its controlled release matrix tablet formulations:

In the present work Verapamil Hydrochloride as a solution, matrix tablet formulations VP3, VPA6 and VPC44 were subjected to pharmacokinetic studies in rabbits. These formulations were administered to rabbits through the oral route at a dose of 10mg/rabbit and serum Verapamil Hydrochloride concentration was determined by HPLC method.

Pharmacokinetic parameters such as maximum serum concentration ($C_{\text{max}}$) and the time of its occurrence ($t_{\text{max}}$) were read directly from the individual serum concentration-time profiles. The other pharmacokinetic parameters like biological half life($t_{1/2}$), mean residence time(MRT) and area under the curve ($AUC_{0-a}$) were calculated by model independent computer programme “PK SOLUTIONS” (Summit Research Services, USA) which measures the $t_{1/2}$ from the regression of the terminal phase of concentration time plot. MRT was calculated by dividing the AUMC$_{0-a}$ and $AUC_{0-a}$ was calculated by linear trapezoidal rule. The results were given in the table 4.56 and shown in graph 4.115.

The results from the oral administration of Verapamil Hydrochloride solution (oral solution) indicated that Verapamil Hydrochloride is rapidly absorbed from the rabbit gastro intestinal tract with a $C_{\text{max}}$ of $390.0 \pm 19.5$ ng/ml and $t_{\text{max}}$ of $0.75 \pm 0.1$ hrs. Controlled release matrix tablet formulations after oral administration achieved, $C_{\text{max}}$ of serum concentrations of Verapamil Hydrochloride $175.0 \pm 8.8$, $173.8 \pm 8.7$ and $169.8 \pm 8.5$ ng/ml with $t_{\text{max}}$ of $4.0$ hrs.

The oral administration of Verapamil Hydrochloride solution resulted in a low and quite variable AUC of $839.9 \pm 41.5$ ng/ml/hr. Where as the oral controlled release matrix tablet formulations resulted in AUC of $2099.4 \pm 106.1$, $2190.6 \pm 111.0$, $2177.1 \pm 109.4$ng/mg/hr respectively. The $t_{1/2}$ value obtained for oral solution was found to be $2.20 \pm 0.04$ hrs and for controlled release matrix tablet formulations ,the $t_{1/2}$ values were $4.30 \pm 0.1$, $8.76 \pm 0.24$, $10.06 \pm 0.14$ hrs respectively. Similarly the MRT was found to be

186
increased from $3.37 \pm 0.5$ hrs for oral solution to $9.52 \pm 0.1$, $14.2 \pm 0.1$ and $15.8 \pm 0.87$ hrs respectively with controlled release matrix tablet formulations.

These results thus indicated that Verapamil Hydrochloride from controlled release matrix tablet formulations was released and absorbed slowly over longer periods of time which in turn maintained the serum concentrations within a narrow range over longer periods of time. It was also observed that Verapamil Hydrochloride from matrix tablets containing electrolytes (VP3, VPA6 and VPC44) was released slowly over longer periods of time than when compared to the matrix tablet without electrolyte (VP3). As the serum concentrations of Verapamil Hydrochloride were maintained within a narrow range over 2 to 12 hrs with the matrix tablet formulations (especially VPA6 and VPC44), these tablets were considered suitable for once a day administration.

**Pharmacokinetic studies of Losartan Potassium and its controlled release matrix tablet formulations:**

In the present work, Losartan Potassium as a solution, matrix tablet formulations LP3, LPA6 and LPS55 were subjected to pharmacokinetic studies in rabbits. These formulations were administered to rabbits through oral route at a dose of 10 mg/ rabbit and plasma concentrations were determined by spectrofluorometric method.

Pharmacokinetic parameters such as maximum serum concentration ($C_{\text{max}}$) and the time of its occurrence ($t_{\text{max}}$) were read directly from the individual serum concentration-time profiles. The other pharmacokinetic parameters like biological half life($t_{1/2}$), mean residence time (MRT) and area under the curve (AUC$_{0-a}$) were calculated by model independent computer programme “PK SOLUTIONS”(Summit Research Services, USA) which measures the $t_{1/2}$ from the regression of the terminal phase of concentration time plot. MRT was calculated by dividing the AUMC$_{0-a}$ and AUC$_{0-a}$ was calculated by linear trapezoidal rule. The results were given in the table 4.57 and shown in graph 4.116.

The results from the oral administration of Losartan Potassium solution (oral solution) indicated that Losartan Potassium is rapidly absorbed from the rabbit gastrointestinal tract with a $C_{\text{max}}$ of $366.2 \pm 18.1$ ng/ml and $t_{\text{max}}$ of $0.75 \pm 0.1$ hrs. Controlled release matrix tablet formulations after oral administration achieved a $C_{\text{max}}$ of plasma
concentrations of Losartan Potassium 202.5 ± 10.2, 201.2 ± 10.1 and 201.7 ± 10.1 ng/ml with a $t_{\text{max}}$ of 4.0 hrs.

The oral administration of Losartan Potassium solution resulted in a low and quite variable AUC of 1052.2 ± 52.5 ng/ml/hr. Whereas the oral controlled release matrix tablet formulations resulted in AUC of 2517.5 ± 126.5, 2626.6 ± 130.5, 2601.95 ± 130.9 ng/mg/hr respectively. The $t_{1/2}$ value obtained for oral solution was found to be 3.15 ± 0.1 hrs and for controlled release matrix tablet formulations, the $t_{1/2}$ values were 4.76 ± 0.2, 11.23 ± 0.1, 11.57 ± 0.5 hrs respectively. Similarly the MRT was found to be increased from 4.76 ± 0.05 hrs for oral solution to 10.15 ± 0.01, 17.86 ± 0.03 and 18.63 ± 0.14 hrs respectively with controlled release matrix tablet formulations.

These results thus indicated that Losartan Potassium from controlled release matrix tablet formulations was released and absorbed slowly over longer periods of time which in turn maintained the serum concentrations within a narrow range over longer periods of time. It was also observed that Losartan Potassium from matrix tablets containing electrolytes (LPA6 and LPS55) was released slowly over longer periods of time than when compared to the matrix tablet without electrolyte (LP3). As the plasma concentrations of Losartan Potassium were maintained within a narrow range over 2 to 12 hrs with the matrix tablet formulations (especially LPA6 and LPS55), these tablets were considered suitable for once a day administration.
ACCELERATED STABILITY STUDIES

The formulations which showed good *in vivo* performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the tablets and on drug release from the matrix tablets. The matrix tablets VP3, VPA6 and VPC44 containing Verapamil Hydrochloride and LP3, LPA6 and LPS55 containing Losartan Potassium were subjected to accelerated stability studies. The results of these studies were given in tables 4.60 to 4.65 and shown in graphs 4.117 to 4.121.

The results thus indicated that there was no visible and physical changes observed in the matrix tablets after storage. It was also observed that there was no significant change in drug release from the matrix tablets. The slow and controlled drug release characteristics of the matrix tablets remained unaltered. Thus the drug release characteristics of controlled release matrix tablets designed were found to be quite stable.