

In vivo evaluation of newly developed losartan potassium sustained release dosage form using healthy male Indian volunteers.

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Abstract

Sustained release (SR) matrix tablets of losartan potassium were prepared by wet granulation using xanthene as the polymer. The studies indicated that the drug release can be modulated by varying the concentration of the polymer and the fillers. The estimation of losartan potassium from human plasma method involves simple protein precipitation techniques using nifedipine as internal standard. Chromatographic separation was carried out on a reversed phase C₁₈ column using mixture of 0.5% triethyl amine (pH 3.5) and acetonitrile (60:40, v/v) at a flow rate of 1.0 mL/min with UV detection at 225 nm. The method was validated and found to be linear in the range of 20-300 ng/ml. An open, randomized, two-treatment, two period, single dose crossover, bioavailability study in 24 fasting, healthy, male, volunteers was conducted. Various pharmacokinetic parameters including AUC_{0-t}, AUC_{0-∞}, C_{max}, T_{max}, T_{1/2}, and elimination rate constant (K_{el}) were determined from plasma concentration of both formulations. These results indicated that the analytical method was linear, precise and accurate. The sustained and efficient drug delivery system developed in the present study will maintain plasma losartan potassium levels better, which will overcome the drawbacks associated with the conventional therapy.

Keywords: *In vivo* evaluation; Sustained release; Dissolution; pharmacokinetic studies.

Introduction

Losartan potassium (LP) is chemically 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. LRT is the first of a unique class of oral antihypertensive agents referred to as angiotensin II receptor antagonists¹. It is an antihypertensive agent. Besides a couple of Analytical and bioanalytical methods²⁻¹² not much literature is reported for the determination of losartan potassium in biological samples. Therefore, the aim of the present investigation was to develop a new, sensitive (20 ng/ml) HPLC method for the estimation of losartan potassium in human plasma. The method was applied to a bioequivalence study of losartan potassium 5.0 mg tablets. The outcome of a study depends upon the reliability, reproducibility and sensitivity of the analytical methodology employed. Therefore, the bioanalytical method was validated in accordance with USFDA guidelines prior to the initiation of the study.

Experimental

Chemicals and reagents

Working standard of losartan potassium with 99.96% purity was obtained from German Remedies Ltd., Mumbai, India. nifedipine (purity 99.56%) working standard was obtained from Cadila Health Care Ltd., Ahmedabad, India). Acetonitrile (HPLC grade), obtained from Qualigens Fine Chemicals, Mumbai ortho phosphoric acid, methanol, and perchloric acid (all analytical grade reagent) were purchased from S.D. Fine Chem. Ltd., Mumbai. Losartan Potassium was a gift sample from Vasudha Pharma Chem Ltd (Hyderabad, India). HPMC (Methocel – K100–CR, apparent viscosity, 2% in water at 20 C is 80,000-12000 cP), xanthan and starch 1500 were gift samples from Colorcon Asia Pvt Ltd (Goa, India). Polyvinyl pyrrolidone (PVP-K-30) was a gift sample from Anshul Agencies (Mumbai, India). Aerosil was purchased from Degussa India Pvt Ltd (Mumbai, India). In house mill Q water was used throughout the study. Fresh frozen human plasma used in the method development was obtained from the Vijay Hospital, Ooty, and was stored at 20 °C until required.

Development of Losartan potassium Sustained Release (SR) tablets



Losartan potassium SR tablets were prepared by the wet granulation method. All the composition, with the exception of magnesium stearate and aerosil were thoroughly mixed in a tumbling mixer for 5 min and wetted in a mortar with isopropyl alcohol. The wet mass was sieved (16 mesh) and granules were dried at 60 °C for 2 h. The dried granules were sieved (22 mesh) and these granules were lubricated with a mixture of magnesium stearate and aerosil (2:1). The losartan potassium tablets were prepared using an electrically operated punching machine. Compression was performed after granulation process with a single punch press applying a compression force of a 9 KN (preliminary work) or 12 KN (experimental design), equipped with a 6 mm flat-faced punch. For the preliminary work, batches of 100 tablets were prepared. Each batch of experimental design consisted of 100 tablets (drug content in the tablet was 25 mg). Three batches were prepared for each formulation and the compositions of different batches of losartan potassium SR tablets are given in Table 1. The compressed tablets were evaluated for average weight & weight variation, thickness, diameter, drug content and content uniformity, hardness, friability, disintegration and *In vitro* drug release.

Instrumentation and chromatography

The HPLC system consisted of a HPLC 2010 A HT (Shimadzu Ltd., Japan), Auto injector port with 100µL loop (Rheodyne, USA) and UV detector (Shimadzu Ltd., Japan). The wavelength of the detector was set at 225 nm. Detector output was quantified on CLASS VP (Version 6.01) chromatography software. Separation was carried out on a Princeton SHER C₁₈, 4.6µm 250 mm, Japan, using mixture of 0.5% triethyl amine (pH 3.5) and acetonitrile (60:40, v/v) as a mobile phase, at a flow rate of 1 mL/min. Total analysis time was 10 min. All analysis was performed at room temperature¹³⁻¹⁸.

Preparation of calibration standard

Stock solutions of losartan potassium and nifedipine (I.S) (1 mg/mL) were in water and stored at 4°C. The stock solution of losartan potassium was further diluted with water to give series of standard solutions. Calibration standard of losartan potassium (20,60,80,101,120,150,182 and 300, ng/ml) were prepared by spiking appropriate amount of the standard solution in blank plasma.

Quality control standards

Lowest quality control standards (LQC), median quality control standards (MQC) & highest quality control standards (HQC) were prepared by spiking drug free plasma with losartan potassium to give solutions containing 101, 150 and 182 ng/ml, respectively. They were stored at 20 °C till analysed.

Sample preparation

Calibration standards, validation QC samples and healthy volunteer plasma samples were prepared by adding 0.5 ml plasma to 2.0ml centrifuge tube and added 0.5 ml (10 µg/ml) of internal standard and 0.5 ml of precipitating agent (10% v/v perchloric acid) vortexed for 2 min. The resulting solution was centrifuged at 4000 rpm for 7 min. The supernatant layer was separated and estimated by HPLC.

Validation

Validation is a process which involves confirmation or establishment by laboratory studies that a method / procedure / system / analyst can give the required accuracy, precision, sensitivity, ruggedness, etc. In the most basic form, validation of an analytical procedure demonstrates that the procedure developed is suitable for its intended purpose. Validation of the method was carried out after the development of the HPLC methods. Validation parameters tested were, Selectivity/ Specificity, Sensitivity, Linearity, Precision and Accuracy, Within-batch precision and accuracy, Intra-day precision and accuracy, between batch / Inter-day precision and accuracy. Stabilities, Short Term Stock Dilution Stability, Long Term Stock Solution Stability, Freeze Thaw Stability, Bench Top (BT) Stability, Long-Term (LT) Stability, Autosampler Stability, Recovery, Ruggedness, Robustness.

Selectivity/ Specificity

A method is said to be specific when it produces a response only for a single analyte. Method selectivity is the ability of the method to produce a response for the analyte in the presence of other interferences. In order to prove that the method chosen was specific and selective the following two sets of samples were processed and injected into the HPLC using the extraction procedure. Blank samples from six different lots of biological matrix (plasma containing K₂ EDTA as anticoagulant). Samples from the same six lots of biological matrix mentioned in step spiked with the analyte at the lower limit of quantification (LLOQ) of the calibration curve and with the internal standard at the concentration level in the study.

Sensitivity

It is expressed as limit of quantitation. It is the lowest amount of analyte in a sample matrix that can be determined. The lower limit of quantification for losartan potassium was 20.0 ng/ml.

Linearity

Linearity and range of the methods were analyzed by preparing calibration curves using different concentrations of the standard solution containing the internal standard. The calibration curve was plotted using response factor and concentration of the standard solutions. Linearity was established using four calibration curves over the range of 20.0 to 300.0 ng/ml for



losartan potassium using the weighted least square regression analysis.

A calibration curve consisted of Aqueous standard at middle concentration level to check retention time of analyte and internal standard. Blank sample (matrix sample processed without internal standard and analyte). Zero sample (matrix sample processed with internal standard but without analyte) Eight non-zero standards covering the expected range. The lowest and highest standards were prepared in duplicates.

Precision and Accuracy

The precision and accuracy of the method was determined by analyzing two batches each consisting of one set of calibration curve with six replicates of quality control samples at four concentration levels [Quality Control samples at the lower limit of quantification (QCLLQ), Low (QCL), Middle (QCM) and High(QCH)].

Precision

Precision is expressed as the percentage coefficient of variation (%CV) which is calculated.

Intra-run Precision

Intra-run precision was determined by calculating the percentage coefficient of variation (% CV) of the results obtained in the same run.

Intra-day Precision

Intra-day precision was determined by calculating the percentage coefficient of variation (% CV) of the results obtained in the same day.

Inter-day Precision

Inter-day precision was determined by calculating the percentage coefficient of variation (% CV) of the results obtained over at least two days.

Accuracy

Accuracy is reported as % nominal of the analyzed concentration.

Intra-run Accuracy

Intra-run accuracy was determined by calculating the percentage nominal of the calculated concentration from the actual values for quality control samples at each concentration level analyzed in a single run and the mean of percentage nominal at each level was reported.

Intra-day Accuracy

Intra-day accuracy was determined by calculating the percentage nominal of the calculated concentration from the actual values for quality control samples at each concentration level analyzed in a single day and the mean of percentage nominal at each level was reported.

Inter-day Accuracy

Inter-day accuracy was determined by calculating the percentage nominal of the calculated concentration from the actual value for quality control samples at each concentration level analyzed over at least two days and the mean of percentage nominal at each level was reported.

Stock Solution Stability

Short Term Stock Dilution Stability

The stability of stock dilutions of analyte and the internal standard was evaluated at room temperature. Aqueous stock dilution of the analyte and the internal standard were prepared. One portion of the stock dilution was placed in the refrigerator between 2-8 C, while the other portion was placed at room temperature for 24 h. Stock dilution stored at room temperature (stability samples) was compared with refrigerated stock dilutions considered as 'comparison samples'. Six replicate injections of the above solutions were made.

Long Term Stock Solution Stability

The stability of the stock solution when stored in the refrigerator for a given period of time was determined. Stock solutions of the analyte and internal standard were prepared and stored in the refrigerator between 2-8 C for 7 days (stability stock). The stock solution stabilities of the analyte and the internal standard were determined with a comparison stock solution, which was prepared freshly. Five replicate injections of the above solutions were made. The response of comparison samples were corrected by multiplying with correction factor to nullify the difference between the measured weights or the dilutions made.

Freeze Thaw Stability

This test was done to ensure that the analyte was stable in the biological matrix even after multiple freeze-thaw cycles. Six quality control samples each at low and high concentrations stored below -50 C for at least 24 h were removed from the deep freezer and were allowed to thaw unassisted at room temperature (fT4 samples). These samples were frozen again below -50 C for at least 12 h. Another set of six quality control samples at low and high concentration levels (fT3 samples) were removed from the deep freezer along with the fT4 samples and thawed unassisted. Both sets of samples were replaced back into the deep freezer.

At least after 12 h of freezing, fT4, fT3 and another set of six samples each at low and high concentration levels (fT2 samples) were removed from the deep freezer and thawed unassisted. All



the samples were replaced back into the deep freezer. At least after 12 h of freezing, FT4 samples were taken out from deep freezer, thawed unassisted to room temperature and analyzed with freshly prepared calibration curve (CC) solutions.

Bench Top (BT) Stability

Six quality control samples each at Quality Control sample at Low concentration (QCL) and Quality Control sample at High concentration (QCH) levels were stored at room temperature for 3 and 6 h. The above samples were analyzed along with freshly prepared calibration curve standards by using the method being validated.

Long-Term (LT) Stability

To assess the stability of the analyte in the biological matrix under the same conditions of storage as that of the study samples for the time period between the date of first sample collection and the date of last sample analysis, the following test was performed.

Six samples of each quality control samples at low and high concentrations were stored below -50 C in the deep freezer. The stability of the analyte was evaluated by comparing each of the back calculated concentrations of stability Quality Control sample (QCs) with the mean concentrations of the respective QCs analyzed in the first accepted precision and accuracy batch.

Auto sampler Stability

To evaluate the stability of the samples in the autosampler after processing for the anticipated run time, six sets of quality control samples each at low and high concentrations were placed in the auto sampler for 24 h and 48 h. The quality control samples were retained in the autosampler to prove auto sampler stability. After the lapse of the test time, the samples placed in the auto sampler were injected into the system along with freshly prepared calibration curve standards. The stability of the analyte was evaluated by comparing the back calculated concentration of stability samples from the freshly prepared calibration curve with their respective nominal concentrations.

To determine the auto sampler stability of the internal standard, the mean peak area obtained for the internal standard of the stability samples was compared with that of the mean of internal standard area of accepted non-zero calibration curve solution (CC's) and the percent change was calculated.

Recovery

Absolute recovery of a bio analytical method is the measured response obtained from a certain amount of analyte added to and extracted from the biological matrix, expressed as a percentage of the response obtained for the true concentration of the pure authentic standard which has not been subjected to the extraction procedure. To determine recovery of this method, six replicates of aqueous quality control samples (un extracted) with concentrations close to spiked Quality Control sample at Low

concentration (QCL), Quality Control sample at Middle concentration (QCM) and Quality Control sample at High concentration (QCH) concentration (extracted) were prepared. These un extracted samples were injected along with precision and accuracy batch. The mean and standard deviation for the percent recovery obtained and there by the percent variation (%CV) was calculated at each concentration level. The overall percent recovery was calculated as the mean of recoveries obtained at the three quality control levels (QCL, QCM and QCH). The overall percent variation (% CV) was also calculated. The percentage recovery for the internal standard was also calculated. The peak area response of the internal standard obtained for the extracted QCM sample (analyzed in the precision and accuracy batch) was compared with the mean area response of the internal standard obtained for the un extracted QCM samples.

Ruggedness

Ruggedness of the method was studied by changing the experimental conditions such as operators, instruments, source of reagents, solvents and column of similar type. Chromatographic parameters such as retention time, asymmetric factor, capacity factor and selectivity factor were evaluated.

Robustness

Robustness of the method was studied by injecting the standard solutions with slight variations in the optimized conditions namely, $\pm 1\%$ in the ratio of acetonitrile in the mobile phase, ± 0.5 units in the pH of the buffer, ± 0.5 mL volume of the triethylamine in aqueous phase and ± 0.1 mL of the flow rate

Clinical design

The study protocol was approved by The Institution Ethics Committee. Twenty four healthy male Indian subjects with mean age group 20–30 years and average weight 65.8 ± 6.1 kg were included in the study. Subjects were excluded from the study if one of more of following criteria were present at time of medical screening: allergic to losartan potassium, history or clinical data of renal or liver disease, positive test for hepatitis B, HIV, history of alcohol, drug addiction or donated blood within 72 days prior to study. Test and reference formulation of losartan potassium 25.0 mg tablet were administered with 240 ml of water. The study was conducted according to the principles outlined in the declaration of Helsinki. The study was conducted as 12 2 single dose, randomized, open, and complete crossover design. Volunteers were fasted overnight before and 4 h after drug administration. Blood sample (5 ml) were collected at 0.00 h and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 of post drug administration through an indwelling cannula into heparinised glass vials. After drug administration standard breakfast and lunch were provided at 4 and 6 h post dose. The blood samples were immediately centrifuged, plasma was separated and stored at 20 °C until analysed. After a washout



period of 7 days, the study was repeated in the same manner to complete the crossover design. The plasma samples obtained at various time intervals were analysed by the HPLC method developed.

Pharmacokinetic analysis

The plasma concentration profile obtained was fed into PK solution, computer software on Microsoft excel®, to determine the pharmacokinetic parameters. The maximum losartan potassium concentration C_{max} and the corresponding peak time T_{max} were determined by the inspection of the individual drug plasma concentration–time profiles. The elimination rate constant K_{el} was obtained from the least-square fitted terminal log-linear portion of the plasma concentration–time profile. The elimination half-life $T_{1/2}$ was calculated as $0.693/K_{el}$. The area under the curve to the last measurable concentration (AUC_{0-t}) was calculated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + C_t/K_{el}$ where C_t is the last measurable concentration.

Result and Discussion

Development of Losartan potassium SR tablets

The physical properties of different batches of developed tablets are given in Table 2 of losartan potassium respectively. All the batches showed uniform thickness. The average percentage deviation of 20 tablets of each formula was less than $\pm 5\%$ and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India 1996). Good uniformity content was found among three different batches of tablets. Another measure of tablets strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablets formulations showed acceptable pharmaco technical properties and complied with the specifications for weight variation, drug content, hardness and friability.

In vitro release

A suitable *in vitro* dissolution method serves as a valuable quality control tool to assess batch to batch release performance and to assure the physiological availability of the drug. The *in vitro* dissolution test is also used to guide formulation development and to monitor manufacturing process. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale-up of the bio-batch to the production batch.

All the batches have shown that as the polymer concentration increases, the drug release rate decreases for losartan potassium. (Figure 1).

The *in vitro* drug release characteristics of the developed sustained release (SR) and the marketed immediate release (IR) tablets were studied. Dissolution data for all the experiments were

highly reproducible and hence only the average values were plotted. The dissolution of the marketed IR tablets indicated that more than 80% of the drug is released within 1h, which complies with the pharmacopoeial specifications. In all the batches, we observed that as the polymer concentration increases, the drug release rate decreases.

To know the mechanism of drug release from these formulations, the data were treated according to zero-order (cumulative amount of drug released versus time), first-order (log cumulative percentage of drug released versus time), Higuchi (Cumulative percentage of drug released versus square root of time) and Peppas (log cumulative percentage of drug released versus log time) equations¹⁹⁻²¹ which are clearly revealed in Figure 2-5 for losartan potassium. *In vivo* studies were carried out for the optimized formulation (F3) in twelve healthy human volunteers and the pharmacokinetic studies were carried out for the optimized formulation and compared with the marketed formulation.

Bioavailability study design and data handling

A single dose, randomized, complete, two treatments cross over study was conducted in healthy human subjects for the selected drug formulations. Twelve volunteers aged between 20-30 years were selected. Seven days prior to the commencement of the study, volunteers were subjected to preliminary screening, standard clinical and biochemical investigations.

After overnight fasting, the volunteers were given code numbers and allocated to the treatment in accordance with the randomized code. The order of treatment administration was randomized in two sequences (AB and BA) in blocks of two. In each dosing session, volunteers received Reference Product A (Immediate release formulations) and Test B (Sustained release formulations). A wash out period of seven days was allowed between dose administrations. Blood samples (4 ml) were collected at 0 (before drug administration), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 h post dosing. The samples were centrifuged and plasma was separated. There were no serious adverse effects observed during the entire study.

Validation of HPLC methods

Estimation of the drugs selected²² in plasma samples from the volunteers was carried out using optimized chromatographic conditions. The validation parameters such as accuracy, precision (repeatability and reproducibility), linearity and range, sensitivity (limit of detection and limit of quantitation), robustness/ruggedness, stability, selectivity/specificity and system suitability were evaluated.

Specificity

HPLC-UV analysis of the blank human plasma samples showed the separation of losartan potassium and nifedipine no interference with either of these was observed. Hence the specificity of the method was established by comparison with human plasma



(control). Representative chromatograms of extracted blank plasma, are shown in Fig. 6. Indicating no interference in the blank plasma and in drug-free human plasma at the retention time of 5.2 for the drug losartan potassium and at the retention time of 10.6 for the IS.

Sensitivity

The limit of reliable quantitation was set at the concentration of the LOQ QC, 20.0 ng/mL for losartan potassium and lowest non-zero standard (Fig. 7).

Linearity

A regression equation with a weighing factor of $1/\text{concentration}^2$ was judged to produce the best fit for the concentration/detector response relationship for losartan potassium in human plasma. The linearity range for losartan potassium was found to be 20.0, 60.0, 80.0, 101.0, 120.0, 150.0, 182.0 and 300.0 ng/ml. The curve is given in Figure 8 with correlation coefficient (r^2) was greater than 0.99.

Precision and Accuracy

The precision of the assay was measured by the percent coefficient of variation over the concentration range of LOQ, low, middle and high quality control sample of losartan potassium during the course of validation. The accuracy of the assay was defined as the absolute value of the ratio of the calculated mean values of the LOQ, low 100.097 ± 1.297 , 99.10%, middle 149.514 ± 0.378 , 99.67 and high 181.716 ± 0.518 , 99.84 quality control samples to their respective nominal values, expressed as percent.

Stabilities

The stability studies of plasma samples spiked with selected drugs were subjected to three freeze-thaw cycles, short term stability at room temperature for 3 h and long term stability at -70°C over four weeks. In addition, stability of standard solutions was performed at room temperature for 6 h and freeze condition for four weeks. The mean concentrations of the stability samples were compared to the theoretical concentrations. The results indicate that selected drugs in plasma samples can be stored for a month without degradation in frozen state. The results of short term storage at room temperature stability 100.78 ± 0.625 , 0.620 , 99.78 and 180.316 ± 1.341 , 0.744 , 99.07 and freeze-thaw cycles indicate no degradation of selected drugs in plasma as well as in sample solution and hence plasma samples could be handled without special precautions.

Recovery

Analyte recovery from a sample matrix (extraction efficiency) is a comparison of the analytical response from an amount of analyte

added to that determined from the sample matrix. 86.29, 87.95 and 84.28 results indicate that the recovery of losartan potassium was consistent at all levels.

Ruggedness and robustness

The ruggedness and robustness of the methods were studied by changing the experimental conditions. No significant changes in the chromatographic parameters were observed when changing the experimental conditions (operators, instruments, source of reagents and column of similar type) and optimized conditions (pH, mobile phase ratio and flow rate).

In vivo data analysis

Pharmacokinetic parameters such as peak plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the plasma concentration-time curve (AUC_{0-t} & $\text{AUC}_{0-\infty}$), elimination rate constant (k_{el}) and elimination half-life ($t_{1/2}$) were calculated separately and the blood level data of selected formulations were compared and are presented in the Table 3. Mean plasma concentration-time profile of losartan potassium was given in Figure 3.

Statistical analysis

The pharmacokinetic parameters of two different drug formulations of losartan potassium were compared statistically by one way ANOVA (analysis of variance) using SPSS version 16.0. P-value of <0.05 was considered as statistically significant. The results were expressed as the mean \pm S.D. The pharmacokinetic parameters C_{max} , AUC_{0-t} and $\text{AUC}_{0-\infty}$ of the immediate release and sustained release formulations of losartan potassium were found to be significantly different by one way ANOVA.

Conclusion

The sustained release tablets of losartan potassium were well absorbed and the extent of absorption was higher than that of the marketed tablet. An HPLC-UV based method has been developed for quantification of losartan potassium in human plasma. The sensitivity and simplicity of the method makes it suitable for pharmacokinetic studies. The statistical comparison of AUC and C_{max} clearly indicated no significant difference in the two formulations of 25.0 mg of losartan potassium tablets.

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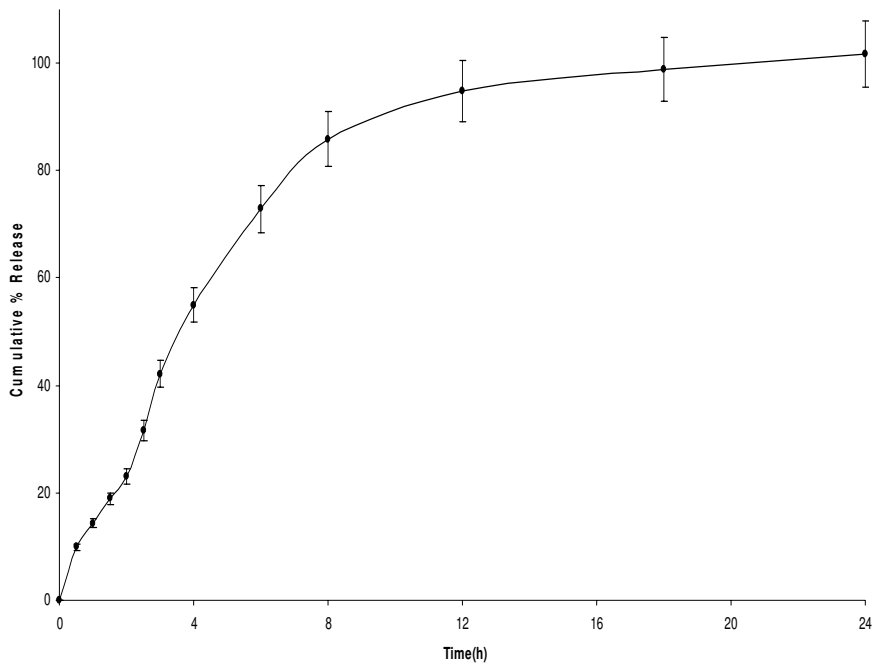


Figure 1: Release profiles of Losartan potassium from HPMC (polymer) containing Formulation

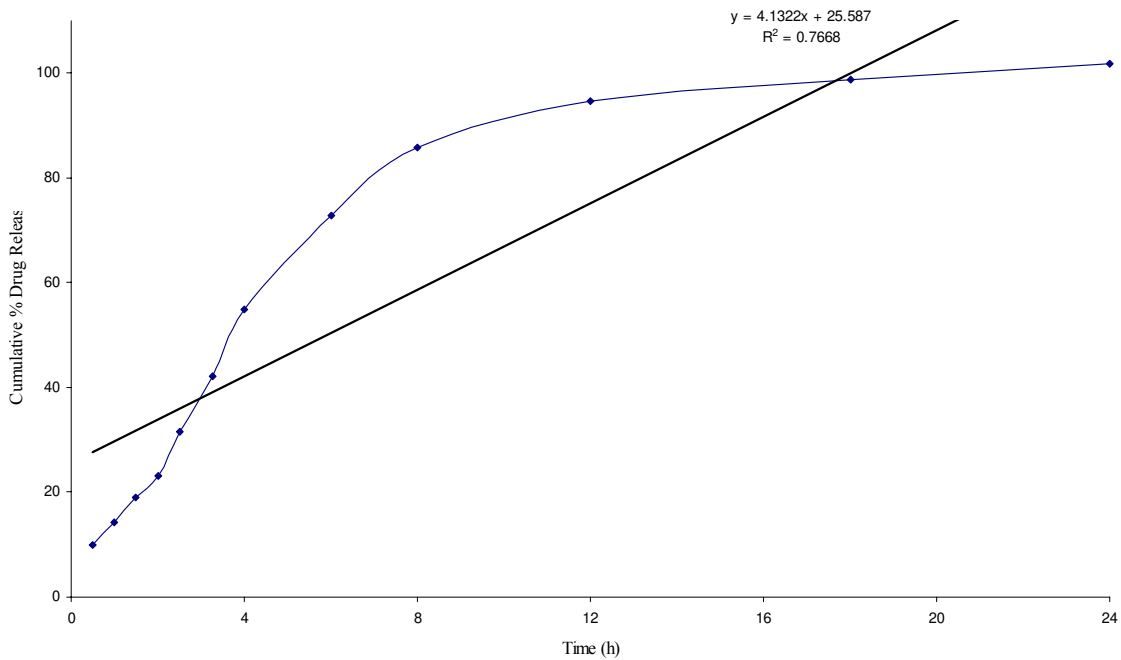


Figure 2: Zero order chart of optimized Losartan potassium formulation



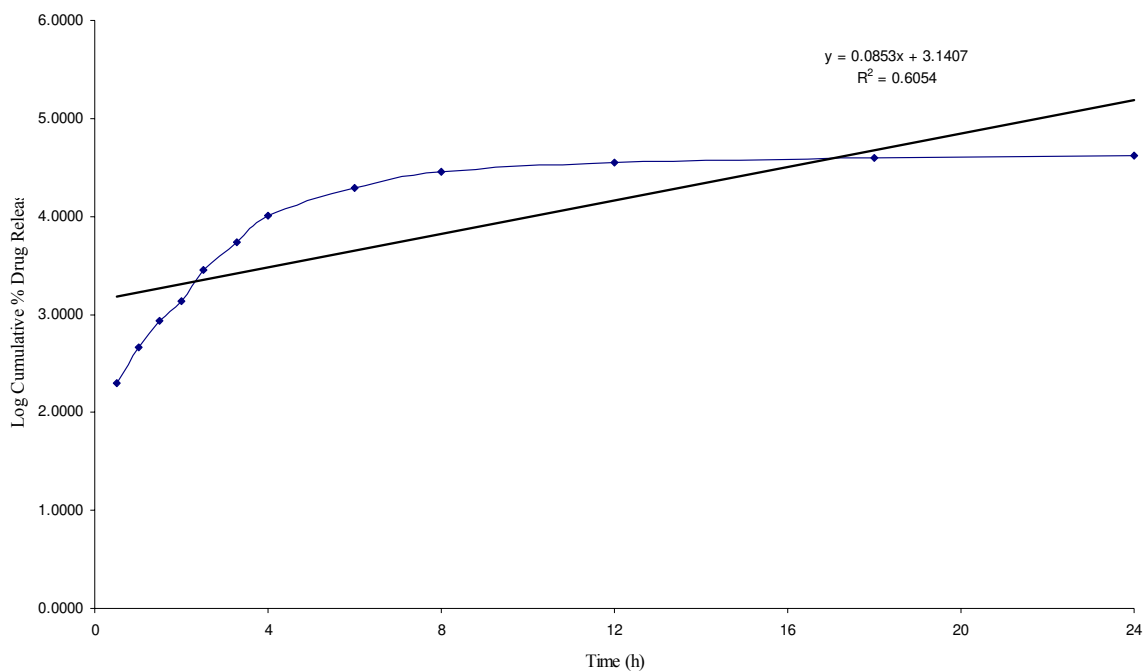


Figure 3: First order chart of optimized Losartan potassium formulation

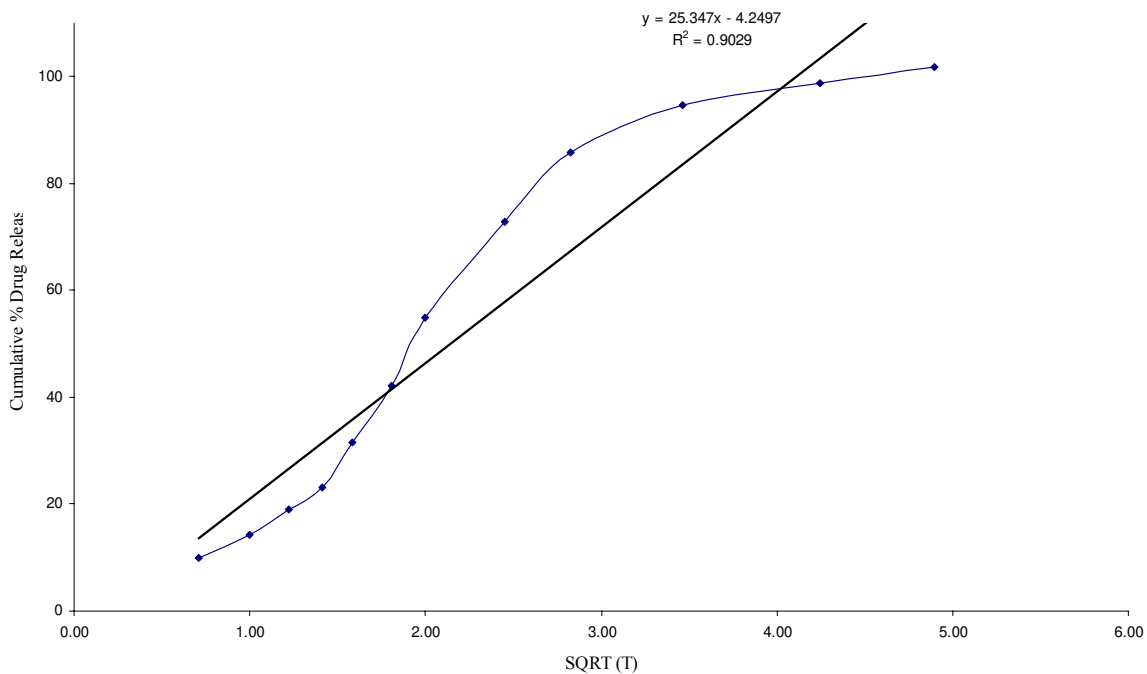


Figure 4: Higuchi chart of optimized Losartan potassium formulation



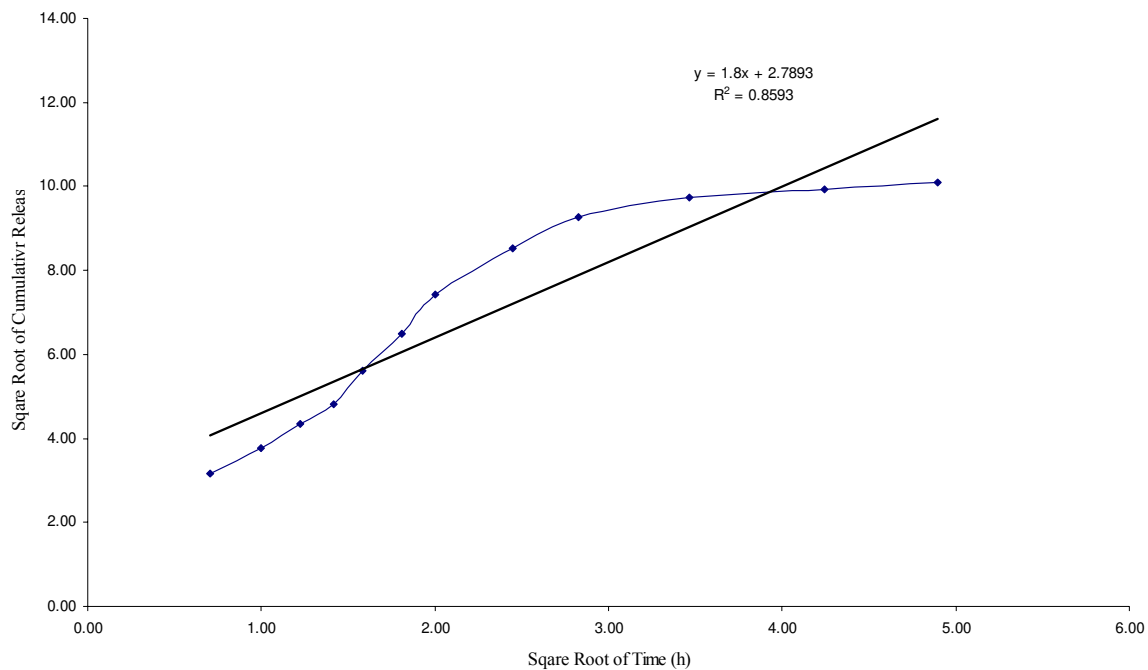


Figure 5: Peppas chart of optimized Losartan potassium formulation

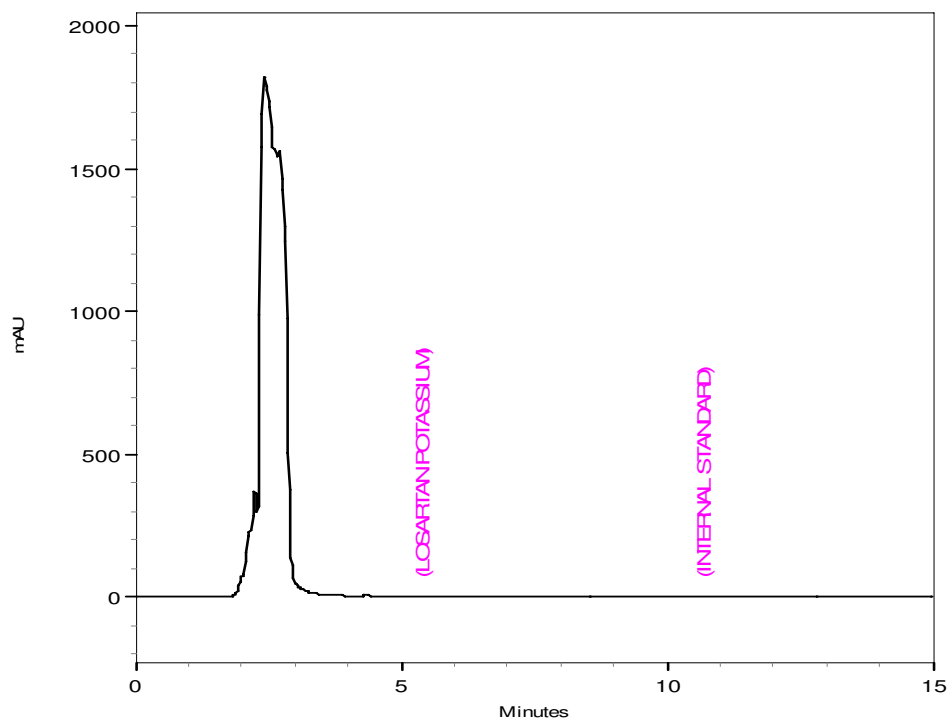


Figure 6: Typical chromatogram of Blank Plasma



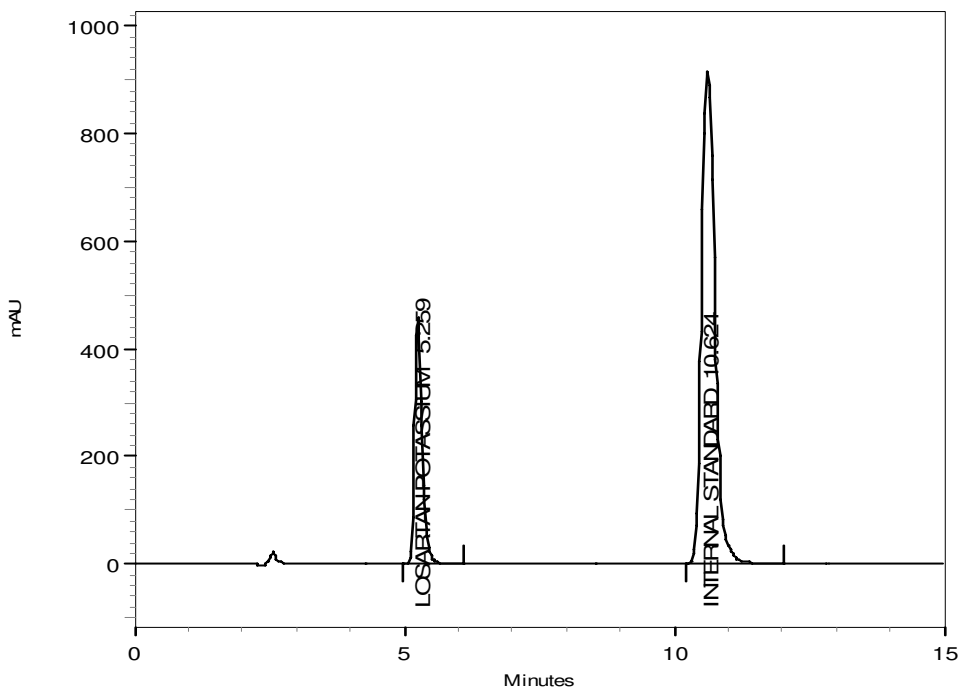


Figure 7: Typical chromatogram of Standard

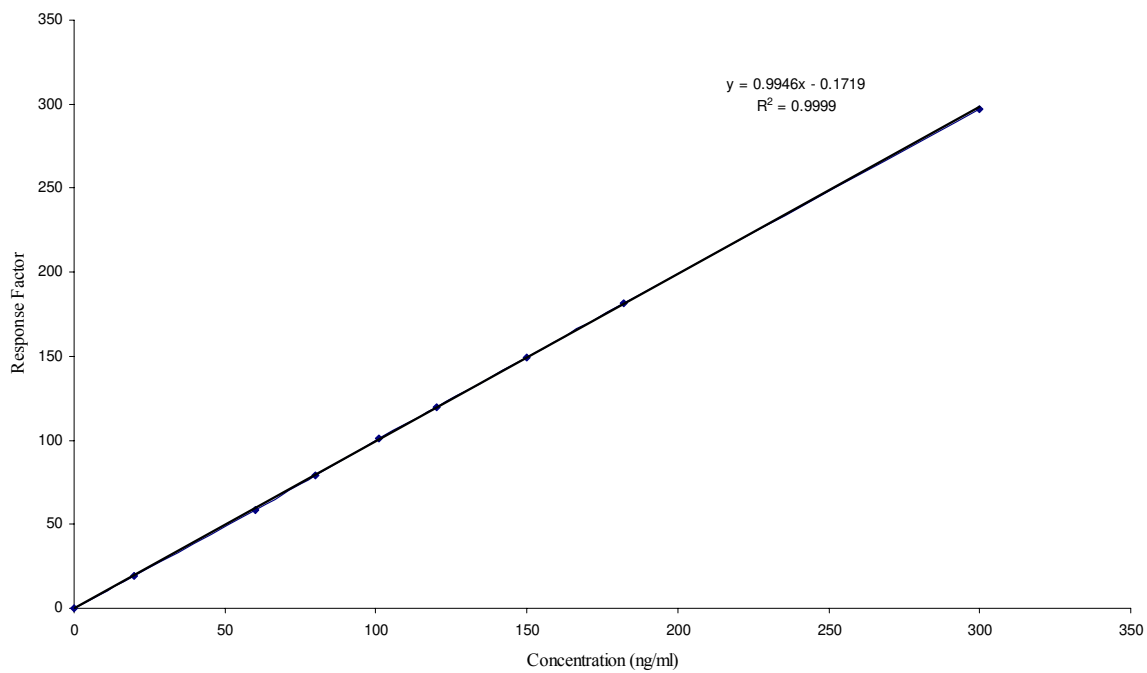


Figure 8: Calibration curve of Losartan potassium



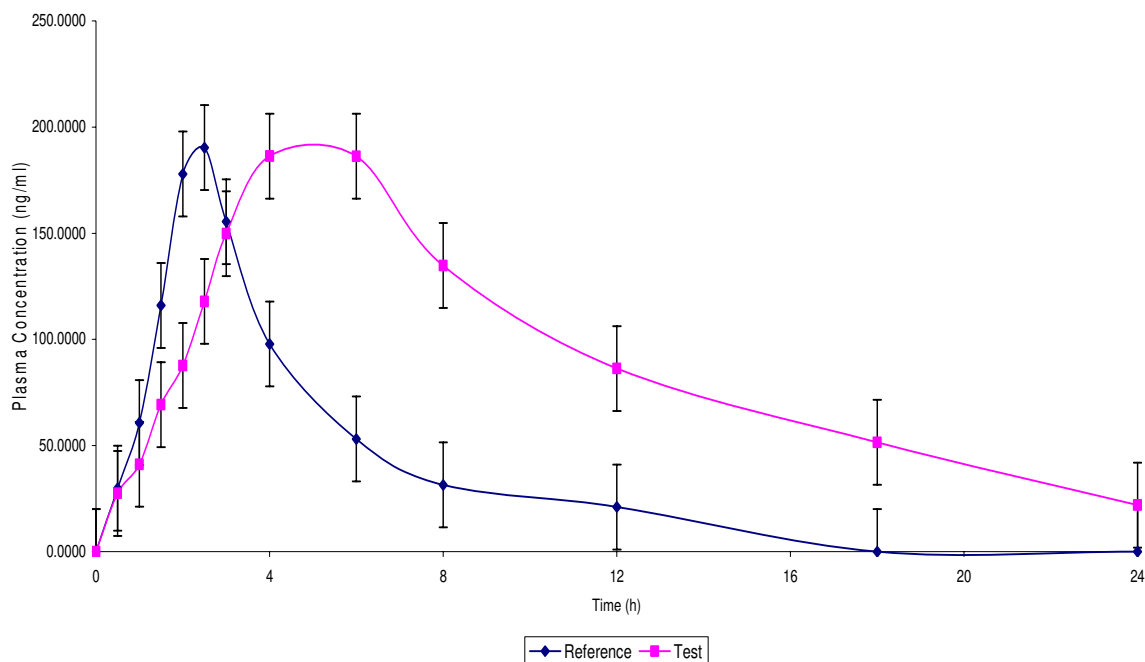
MEAN CONCENTRATION - TIME CURVE FOR VOLUNTEERS
(REFERENCE AND TEST)

Figure 9: Mean plasma concentration-time profile of Losartan potassium from developed Sustained release tablets (test) and marketed immediate release tablet (Reference)

Table 1 : Formulation prepared by wet granulation method (F₁-F₁₆) for Losartan potassium

F _a	LP	HPMC	Xanthen	Avicel Ph 101	Magnesium Stearate	Aerosil	PVP-K-20/30	Total (mg/tab)
F1	25	5	----	62	2	1	5	100
F2	25	10	----	57	2	1	5	100
F3	25	15	----	52	2	1	5	100
F4	25	20	----	47	2	1	5	100
F5	25	25	----	42	2	1	5	100
F6	25	30	----	37	2	1	5	100
F7	25	35	----	32	2	1	5	100
F8	25	40	----	27	2	1	5	100
F9	25	----	5	62	2	1	5	100
F10	25	----	10	57	2	1	5	100
F11	25	----	15	52	2	1	5	100
F12	25	----	20	47	2	1	5	100
F13	25	----	25	42	2	1	5	100
F14	25	----	30	37	2	1	5	100
F15	25	----	35	32	2	1	5	100
F16	25	----	40	27	2	1	5	100



^a Code of formulations**Table 2** : Comparison of the physical properties of the matrix tablets containing losartan potassium

Formulation	Hardness (Kg/cm ²) ^b	Thickness (mm) ^b	Weight (g) ^b	Friability (%) ^b
F _a				
F1	5.1±0.65	3.6320±0.04	0.1056±0.0011	0.357±0.07
F2	5.0±0.79	3.6080±0.05	0.1058±0.0016	0.357±0.07
F3	5.0±0.61	3.6020±0.05	0.1058±0.0013	0.387±0.08
F4	4.9±0.82	3.6240±0.03	0.1062±0.0015	0.352±0.06
F5	5.0±0.79	3.5920±0.03	0.1064±0.0011	0.351±0.08
F6	5.1±0.65	3.6060±0.05	0.1048±0.0008	0.328±0.06
F7	5.0±0.79	3.6100±0.02	0.1060±0.0010	0.349±0.05
F8	4.6±0.65	3.6080±0.04	0.1056±0.0009	0.328±0.11
F9	5.0±0.79	3.6080±0.04	0.1058±0.0008	0.298±0.05
F10	5.3±0.83	3.6160±0.02	0.1066±0.0011	0.347±0.05
F11	5.0±0.79	3.5880±0.05	0.1058±0.0008	0.348±0.05
F12	5.1±0.74	3.5960±0.03	0.1066±0.0011	0.349±0.12
F13	4.7±0.57	3.5028±0.03	0.1062±0.0008	0.361±0.07
F14	5.2±0.57	3.5720±0.03	0.1058±0.0008	0.342±0.06
F15	5.0±0.79	3.600±0.01	0.1060±0.0012	0.384±0.05
F16	5.1±0.82	3.6100±0.02	0.1062±0.0015	0.363±0.07

^a Code of formulations, ^b Results represents the mean of replicate determination with the standard deviation given in parenthesis**Table 3** : Mean pharmacokinetic profile (n=6)

	C _{max}	T _{max}	AUC _{0-t}	T _{1/2}	K _{eli}	AUC _{0-∞}
IR	201.177 ±1.503	2.333 ±0.258 856	362 ±91.640	2.882 ±0.096	0.237 ±0.014	945.306 ±87.774
SR	200.302±2.523†	5.333±1.032‡	2146.630±248.330†	6.080±0.125†	0.114±0.002†	2337.663±252.467†

† Significantly higher than Immediate Release tablets.

‡ Significantly lower than Immediate Release tablets.

SR Sustained release

