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In vitro and *In vivo* Evaluation of Losartan Potassium Matrix Tablets Containing Poly(ethylene oxides)

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In the present investigation controlled release formulations of losartan potassium were formulated using poly(ethylene oxides) as release rate controlling polymer. Different excipients like ethyl cellulose, di calcium phosphate and starch 1500 were used in the preparation of matrix tablets and evaluated for their influence on controlled drug release. The matrix tablets were prepared by direct compression process and evaluated for hardness, weight variation, friability, swelling index and for *in vitro* release of the drug. Biopharmaceutical evaluation of satisfactory formulations were also carried out and parameters like C_{max}, t_{max}, AUC_{0-t} and $AUMC_{0-t}$ were determined. The studies were conducted on Newzealand rabbits. All the physical characteristics evaluated for the tablets were found to be within the acceptable limits. Higher polymeric content of poly(ethylene oxide) in the matrix tablets decreased the release rate of drug. At lower polymeric level the rate and extent of drug release was elevated. On the other hand the excipients like dibasic calcium phosphate, starch 1500 and ethyl cellulose have significantly retarded the release rate of losartan potassium. *In vivo* pharmacokinetic study proves that the losartan potassium from test tablets show prolonged release and may be able to sustain the therapeutic effect which can be further proved by pharmacodynamic study.

Key Words: Losartan potassium, Matrix tablets, Poly(ethylene oxides), Excipients.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, cost effective manufacturing process. Oral controlled drug delivery systems have received much attention of the researchers. The rationale for developing a controlled release formulation is to enhance its therapeutic benefits, reducing its side effects and improving the management of diseased condition. A number of strategies have been developed to obtain controlled release of the drug in the body. These include a simple matrix tablet to more technologically sophisticated products which are introduced to the market place. Among the various polymers used in the fabrication of matrix tablets hydrophilic polymeric matrices have attracted many researchers due to their wide applications in controlled drug delivery. Among the various hydrophilic polymers used, poly(ethylene oxides) (PEO) are most important materials used in the preparation of the matrix tablets because of its non-toxicity, high water-solubility and swellability[1-4]. It is also proved that polyethylene oxides can be used as alternative to HPMC for the preparation of matrix tablets[5,6]. In the formulation of matrix tablets various formulation factors such as the polymer type and concentration, the drug particle size, presence of additives and excipients in the final formulation can modify the drug release from the matrices[7,8]. A little information is available about the effect of excipients and additives on the drug release rate from the poly(ethylene oxides) matrix tablets. The influence of various hydrophilic and hydrophobic diluents is important as these excipients can effect the matrix swelling, erosion and solubility of the drug candidates and this regulate the release kinetics. The inclusion of excipients affects the dissolution performance of a matrix by dilution effect on the polymer matrix, hence in this present investigation the effect of various types of excipients on the matrix erosion and drug diffusion were studied. In the present study, various matrix tablets formulations of losartan potassium were prepared with different types of natural and synthetic polymers..

EXPERIMENTAL

Losartan potassium was kindly supplied from Dr. Reddy's Laboratories Ltd., (Hyderabad), PEO's (polyox WSR 303), dibasic calcium phosphate (DCP) and pregelatinized starch (starch 1500) were of analytical grade and procured commercially from S.D. Fine Chemicals, Mumbai. All other chemicals were of analytical grade and were used as received.

Preparation of matrix tablets: The matrix tablets containing losartan potassium was prepared by a direct compression process. POLYOX WSR 303 was used as a swellable polymer which controls drug release. The controlled release tablet formulations consisted of a drug and polymer were prepared in different ratios. Microcrystalline cellulose was added as diluent at different proportions to the matrix tablets to achieve uniform weight. The drug, polymers and diluent were screened through #45 sieve and preblended in a laboratory scale double cone blender. The lubricant 0.5 % magnesium stearate was added and the blend was mixed again prior to compression. The drug blends were directly compressed by using cadmach rotary compression machine using 9 mm flat punches. The different forms of tablets compressed together with their compositions are given in the Table-1.

TABLE-1
COMPOSITIONS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Ingredients [mg/tablet]	FL1	FL2	FL3	FL4	FL5	FL6	FL7	FL8
Losartan potassium	100	100	100	100	100	100	100	100
Polyox-WSR 303	75	100	75	100	75	100	75	75
Dicalcium phosphate	123.5	98.5	---	---	---	---	---	---
Starch 1500	---	---	123.5	98.5	---	--	---	--
MCC	---	---	---	---	123.5	98.5	73.5	48.5
Ethyl Cellulose	---	---	---	---	---	---	50	75
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt of tablet (mg)	300	300	300	300	300	300	300	300

Evaluation of tablets: The prepared tablets were evaluated as per standard procedure for weight variation (n = 20), hardness (n = 6), drug content, thickness (n = 20), friability and for water uptake characteristics. The hardness of the matrix tablets was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test (n = 20) was conducted using roche friabilator. Thickness of the tablets was measured by digital vernier caliper. Drug content of losartan potassium was analyzed by measuring the absorbance of standard and samples at a wavelength of 205 nm using digital UV double beam spectrophotometer (Elico model SL-218).

***In vitro* drug release characteristics:** Drug release from the matrix tablets was assessed by dissolution test (n = 3) using USP type II dissolution apparatus equipped with paddles at 37 ± 0.5 ºC with an rpm of 75. The test was performed using 900 mL of 0.1 N HCl (for 2 h) and phosphate buffered solution, pH 6.8 (up to 24 h) as dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 mL aliquot of samples were withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 205 nm. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies were analyzed according to the following equations of the first-order model, Higuchi model and the Korsmeyer-Peppas model respectively.

$$\ln Q = k.t \quad (1)$$

$$Q = k.t^{1/2} \quad (2)$$

$$M_t/M_a = Kt^n \quad (3)$$

where Q in the equation (1) is cumulative per cent drug remained, while Q in the equation (2) is cumulative per cent drug released, where $M_t/M\alpha$ 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. The values of n were obtained by linear regression analysis. A 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[9]. Linear regression analysis was performed for all these equations and regression coefficients (r) were determined.

***In vivo* studies:** The selected test formulation of prolonged release tablets containing losartan potassium were evaluated by *in vivo* test for determining pharmacokinetic parameters. The test was executed after getting proper approval from IAEC. Rabbits of either sexes weighing between 1 to 3 kgs were selected. Only nine rabbits were sanctioned. Three were used for reference standard and six were used for test formulations. Rabbits were selected after checking whether they were used for other any other experiments. All rabbits were housed in animal house as per CPCSEA norms. Selected rabbits were fasted overnight on the penultimate day before actual experimentation. They were allowed access to drinking water alone. Dose to be administered was taken based on previous literature reports[10]. The experiment was started by administering 15 mg of losartan potassium (plain drug) dissolved in distilled water through a plastic tube placed in the mouth of the rabbit. This tube was approximately 35 cms with a diameter of 1 cm (approximately). The tube was inserted gently to reach the stomach and administration was done. Distilled water was pushed through a syringe (with out needle). This was to ascertain that all the losartan reaches the stomach. After administration, at periodic time intervals blood sample was withdrawn using fine gauge needle from the marginal ear vein. Collected blood samples were stored in freezer before analysis. Sampling times were 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h. For test formulation, tablets were assayed and one tablet was administered as a whole through the tube. All other steps were the same as that of the reference standard.

Drug extraction procedure from plasma: Blood samples were thawed and centrifuged at 14,000 X g for 15 min. Plasma was separated using micropipette. Plasma was used for further quantitative evaluation. Plasma was deproteinated using acetone. Then the precipitate was separated by centrifugation 12,000 X g for 5 min. The supernatant liquid was collected and used for quantitative evaluation. The supernatant liquid was diluted with the mobile phase and RP HPLC method was followed for evaluation[11].

Analytical method: Agilent made RP-HPLC instrument was used for the determination of plasma concentrations of Losartan potassium. C_{18} column is used in the instrument. The mobile phase composition used for analysis is phosphate buffer

solution of dibasic potassium phosphate and disodium hydrogen phosphate (0.02 M pH 7.0) and this buffer is mixed with acetonitrile in the ratio of 85 :15 (v/v). The flow rate for the mobile phase is 1 mL/min and the detection is carried out at 250 nm.

RESULTS AND DISCUSSION

All batches of losartan potassium matrix tablets were manufactured under similar conditions to avoid the processing variables. The prepared tablets were evaluated for various physical parameters such as weight uniformity, hardness, drug content, friability and thickness (Table-2). The formulated matrix tablets met the pharmacopoeial requirement in uniformity of weight, hardness, percentage friability and thickness. Tablet weights varied between 300 and 302 mg (average 301 mg), hardness between 4.0 to 5.0 kg/cm^2 (average 4.5 kg/cm^2), thickness between 3.00 and 3.10 mm and friability loss was in the range of 0.32 to 0.47 % (average 0.40 %). The drug content for the formulations was assayed spectrophotometrically at 205 nm. The assayed content of drug in various formulations varied between 98 and 100 % (average 99 %).

TABLE-2
PHYSICAL PARAMETERS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Formulation	Weight Uniformity (mg) ± S.D (n = 20)	Hardness (Kg/cm²) (n = 6) ± S.D	Friability (%) (n = 20)	Drug Content (%) (n=6) ± S.D
FL1	300 ± 2	4.0 ± 0.4	0.31	98.9 ± 0.5
FL2	301 ± 2	4.7 ± 0.3	0.32	99.3 ± 0.42
FL3	300 ± 1	4.6 ± 0.3	0.29	99.4 ± 0.54
FL4	300 ± 1	4.5 ± 0.4	0.29	98.8 ± 0.50
FL5	301 ± 1	4.4 ± 0.5	0.33	100 ± 0.10
FL6	300 ± 2	4.6 ± 0.5	0.32	100 ± 0.20
FL7	301 ± 1	4.7 ± 0.5	0.28	99.3 ± 0.30
FL8	300 ± 1	4.5 ± 0.5	0.34	99.3 ± 0.40

The *in vitro* drug release studies were conducted for all the matrix tablet formulations. The tablets extended the drug release from 10 to 22 h. The formulations containing microcrystalline cellulose and starch 1500 extended the release of Losartan potassium up to 20 h. Insoluble but weakly swellable fillers such as microcrystalline cellulose remain with in the gel structure and results in decreased release rate[12]. Hence microcrystalline cellulose and dibasic calcium phosphate as insoluble diluents provided the slower rate of drug release. These excipients have minimum swelling property which contributions to the swollen matrix for poly(ethylene oxide) and retards water penetration. It is also reported that microcrystalline cellulose most likely acts as a strong tablet binder which decreases the tablet porosity and retards the release of losartan potassium from tablet formulations[13]. The formulations containing starch 1500 a slightly soluble filler, the drug release from the matrix tablets was extended up to 20 h. This may be due to the diluent prevented the easier penetration of dissolution medium into matrix and thus prevented the polymer matrix erosion. This may be due to swelling of starch 1500 upon exposure to dissolution medium forming a gel layer which controlled the release rate of losartan potassium from poly(ethylene oxide) matrix. The formulation containing ethyl cellulose along with poly(ethylene oxide) prolonged the drug release upto 22 h. Since, ethyl cellulose is a hydrophobic polymer and cannot swell in a manner similar to poly(ethylene oxide). It may be due to increased gel barrier strength which retards drug release. Presence of both hydrophilic and hydrophobic polymer which allows little swelling but did not allow rapid diffusion of the drug from the matrix. The formulation containing both hydrophilic and hydrophobic polymer combination no burst release was observed. The drug release from the tablet formulations with 98-100 % and are best explained by first order plots and Peppas model. The formulations are best fitted to Peppas model, with in values ranging from 0.54 to 0.80 suggesting non-Fickian diffusion *i.e.* the drug release is governed by the Polymer Swelling, Drug dissolution and matrix erosion (Table-3). Higher proportion of poly(ethylene oxide) in the matrix resulted in delayed and the drug release over an extended period of time. No visible and physical changes were observed in the matrix tablets after accelerated storage conditions. *In vivo* pharmacokinetic studies were conducted on selected formulations in rabbits as animal model. The drug extraction procedure from the rabbit plasma and the HPLC method for determining the plasma drug concentration followed were ideal and accurate for the *in vivo* studies. The results showed that losartan potassium administered as plain drug alone reaches highest concentration of 6.1 mcg/mL after 1 h of administration. The test tablets reaches after 6 and 8 h of administration and also the maximum concentration reached is 4.7 and 4.6 mcg/mL (Table-4). But the AUC and AUMC show statistically significant difference (t-test and F- test) ($p < 0.05$). This clearly proves that the total amount of losartan exposed to blood is higher and is also more sustained than the raw material alone. The results proved the prolonged release for 22 h and drug

TABLE-3
In vitro PHARMACOKINETIC PARAMETERS OF VARIOUS MATRIX TABLET FORMULATIONS OF LOSARTAN POTASSIUM

Formulations	First order constants (h^{-1})	Correlation coefficient (r)	Dissolution rate constants ($mg/h^{1/2}$)	Correlation coefficient (r)	Peppas constant (n)	Correlation coefficient (r)
FL 1	0.268	0.986	27.48	0.997	0.74	0.997
FL 2	0.152	0.989	25.62	0.998	0.69	0.998
FL 3	0.116	0.995	30.12	0.977	0.71	0.992
FL 4	0.199	0.997	26.62	0.999	0.64	0.993
FL 5	0.110	0.996	30.99	0.998	0.63	0.989
FL 6	0.087	0.990	24.32	0.988	0.54	0.994
FL 7	0.238	0.980	28.07	0.996	0.70	0.995
FL 8	0.151	0.997	22.69	0.991	0.75	0.988

TABLE-4
In vivo PHARMACOKINETIC PARAMETERS OF SELECTED FORMULATIONS OF LOSARTAN POTASSIUM

Parameters	Formulation FL6	Formulation FL8	Reference
C max	4.66 mcg/mL	4.76 mcg/mL	6.1 mcg/mL
T max	6 h	8 h	1 h
AUC (0 to t)	65.8 mcg/h	62.9 mcg/h	23.8 mcg/h
AUMC (0 to t)	438.1mcg h* h/mL	428.1mcg h* h/mL	68 mcg h* h/mL

was released slowly within a narrow range for prolonged period of time (Fig. 1).

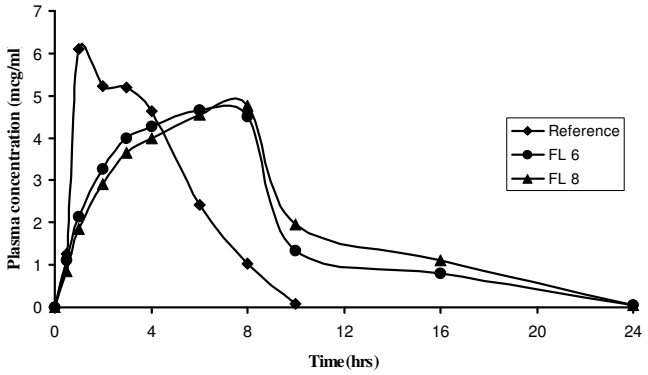

Fig. 1. Plasma concentration-time profiles of losartan potassium

Conclusion

This work has provided a novel simple approach to formulate an oral and swellable controlled release matrix tablets of losartan potassium. The controlled release matrix tablets were successfully formulated using poly(ethylene oxide) and different excipients for delivery of drug over an extended period of time. *In vivo* pharmacokinetic study proves that the losartan potassium from test tablets show prolonged release and may be able to sustain the therapeutic effect which can be proved by pharmacodynamic study.

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REFERENCES

1. A. Apicella, B. Cappello, M.A.D. Nobile, M.I.L. Rotonda, G. Mensitieri and L. Nicolais, *Biomaterials*, **14**, 83 (1993).
2. C.J. Kim, *J. Pharm. Sci.*, **84**, 303 (1995).
3. C.J. Kim, *Pharm. Res.*, **12**, 1045 (1995).
4. L. Maggi, L. Segale, M.L. Torre, E.O. Machiste and U. Conte, *Biomaterials*, **23**, 1113 (2002).
5. C.J. Kim, *J. Pharm. Sci.*, **84**, 303 (1995).
6. C.J. Kim, *Drug Dev. Ind. Pharm.*, **24**, 645 (1998).
7. L.C. Feely and S.S. Davis, *Int. J. Pharm.,* **41**, 83 (1988).
8. J.E. Hogan, *Drug Dev. Ind. Pharm.*, **15**, 975 (1998).
9. R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri and N.A. Peppas, *Int. J. Pharm.*, **15**, 25 (1983).
10. A. Madgulkar, M. Bhalekar and M. Swami, *AAPS Pharm. Sci. Tech.*, **10**, 743 (2009)
11. D.L. Hertzog, J.F. McCafferty, X. Fang, R.J. Tyrrell and R.A. Reed, *J. Pharm. Biomed. Anal.*, **30**, 747 (2002).
12. B.J. Lee, S.G. Ryu and J.H. Cui, *Drug Dev. Ind. Pharm.,* **25**, 493 (1999).
13. G.E. Peck, G.J. Baley, V.E. McCurdy and G.S. Banker, in eds.: H.A. Lieberman, L. Lachman and J.B. Schwartz, Tablet Formulation and Design, Pharmaceutical Dosage Forms, Tablets, Marcel Dekker, New York, edn. 2, pp. 109-112 (1989).