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FORMULATION AND RELEASE DISTINCTIVENESS OF A NOVEL MODIFIED DRUG DELIVERY DEVICE IN TREATMENT OF HYPERTENSION: LOSARTAN POTASSIUM MATRIX TABLETS

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ABSTRACT

Angiotensin-II receptor blocker losartan, approved by the FDA in 1995, is used to treat hypertension, diabetic nephropathy, and to lower the risk of stroke. A considerable increase in the risks of heart, brain, kidney diseases is caused by hypertension, sometimes known as the "silent killer," which is the first world's largest cause of premature death. Adults in low- and middle-income countries who are between the ages of 30-79 are affected by hypertension, with the number of cases rising from 650 million to 1.28 billion during the past 30 years. Because it could not have any symptoms or warning indications, 46% of adults are unaware of it. Matrix tablets of Losartan potassium as Systems for delivering drugs with a sustained release are intended to prolong the therapeutic effect of a drug after it has been administered in a single dose. Hydrophobic and hydrophilic matrices have been utilized for polymeric matrices in matrix tablets, which regulate the drug's release and have different solubility qualities. Designing and characterizing tablets with a sustained release of losartan potassium are the goals of the current work. Matrix tablets containing 50 mg losartan were developed using 3 different polymers; HPMC-K4, HPMC-K15 &synthetic Ethyl Cellulose (EC) with sodium alginate in different drug polymer ratios (30, 40, 50 mg) respectively. According to the study, the formulation S3 using (HPMC-K4: Sodium alginate as in 50:50 ratio) demonstrated sustained drug release at a rate of 95.1% and displayed the greatest swelling index when compared to other formulations.

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INTRODUCTION

Hypertension or elevated blood pressure also known as "Silent killer", is a medically serious condition that globally adults between the aged group of 30-79 years are unaware of it affected an estimated of 1.28 billion. [1]Hypertension is a key risk factor for cardiovascular diseases. Currently 46 % of people with hypertension are undiagnosed, and of those diagnosed, around half are not taking antihypertensive medications.[2]

Losartan potassium is an orally active angiotensin-II receptor antagonist used in the treatment of hypertension as it lowers a person's blood pressure by relaxing the blood vessels to allow for more effective blood flow.The main limitation of the drug is its low therapeutic effectiveness which is due to narrow therapeutic index, poor bioavailability (25-35%) and short biological half- life (1.5 to 2.5 hour).Conventional tablets should be administered 2-3 times to maintain plasma drug concentration. [3] So, to increase therapeutic efficacy, reduce frequency of administration and for better patient compliance once daily sustained release Losartan potassium matrix tablets were prepared.

Matrix systems offer several advantages relative to other extended release dosage form like easy to manufacture, versatile, effective and can be made to release high molecular weight compounds. Since the drug is dispersed in the matrix system, accidental leakage of the total drug components is less likely to occur.Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective. [4]

The current study aims at developing oral sustained release tablets of losartan potassium using HPMC-K4, HPMC-K15 &synthetic Ethyl Cellulose (EC) with sodium alginate in different drug polymer ratios (30, 40, 50 mg) respectively as release controlling polymer. HPMC has always been a first choice for formulation of hydrophilic matrix systems because of providing robust mechanism, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment's and methods.

Sodium alginate has been used to study the effects of various formulation and process variables, including the increase in polymer concentration, viscosity grades, particle size, press speed, the presence of lubricants, the hardness of the tablet, and the solubility of the drug, on the drug release profile. In order to create films and matrixes for sustained-release dosage forms, ethylcellulose has been used. Drug diffusion, polymer relaxation, and tablet erosion were all taken into account while elucidating the drug release mechanism of tablets made of directly compressed ethylcellulose. [5] Absent the polymer's ability to swell, the hydrophobic mass's porosity is essentially what controls its release.Although EC is regarded as being insoluble, it can nevertheless absorb water. It can form hydrogen bonds with water simply because of the polarity difference between the ethyl group and the oxygen atom in the polymer. When EC absorbs water, it swells and the release of the medication is slowed. Surface erosion causes an initial rapid release, followed by a slowdown in release because the tablet's outer layers are worn out and must be penetrated to get to the un-dissolved medication. [6]

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant support to disintegration. [7, 8]

MATERIALS AND METHODS

Losartan was obtained as gift sample from Shiram Pharmaceuticals (Mumbai). Sodium alginate was obtained from Loba chemicals (Mumbai), Ethyl cellulose from Ases chemical works (Jodhpur), HPMC-K4, HPMC-K15 were purchased from Pharmaceutical Excipients (Gujarat), Carbopol, Magnesium stereate were purchased from S. D. fine chem Ltd (Mumbai) and all other chemicals and solvents used were of analytical grade.

Experimental/Methodology

Preparation of Losartan matrix tablets

Matrix tablets were prepared using HPMC-K4, HPMC-K15 & ethyl cellulose as same concentration as drug by taking sodium alginate in the formulation in various proportions (30, 40 and 50 mg) by Wet granulation method.The various excipients used were listed table no. 1 were thoroughly mixed and passed through sieve no. 60. The drug was geometrically blended with weighed quantities of excipients and various polymers mixed along with drug using pestle mortar. Granulation was done with a solution of calculated quantity of PVP K30(binding agent) in sufficient isopropyl alcohol (granulating agent) The wet mass was passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc and compressed into tablets using 8 station rotary compression machine fitted with flat-faced punches. [9, 10, 11]

Table 1: Preparation of Losartan potassium matrix tablets (350 mg)

Ingredients (mg/tablet)	Formulation & Code (S1-S9)								
	S1	S2	S3	S4	S5	S6	S7	S8	S9
Losartan potassium	50	50	50	50	50	50	50	50	50
HPMC-K4	50	50	50	-	-	-	-	-	-
HPMC-K15	-	-	-	50	50	50	-	-	-
Ethyl Cellulose	-	-	-	-	-	-	50	50	50
Sodium Alginate	30	40	50	30	40	50	30	40	50
Carbopol	10	10	10	10	10	10	10	10	10
Lactose	130	120	110	130	120	110	130	120	110
Mannitol	70	70	70	70	70	70	70	70	70
Mg Stereate	4	4	4	4	4	4	4	4	4
Talc	6	6	6	6	6	6	6	6	6
Total	350	350	350	350	350	350	350	350	350

Standard curve of Losartan Potassium in 0.1 N HCl (pH-1.2) at 206 nm.

Table 2: Calibration curve data of Losartan potassium.

CONCENTRATION (ug/ml)	ABSORBANCE
0	0.000
5	0.102
10	0.203
15	0.298
20	0.387
25	0.469
30	0.566
35	0.656
40	0.745
45	0.832
50	0.918

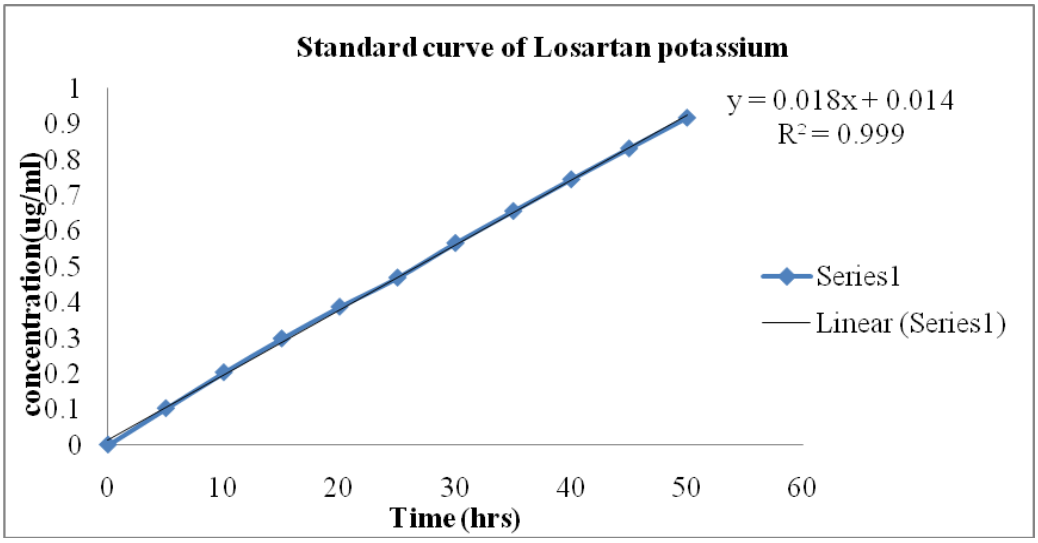

Fig.1: Standard curve of Losartan potassium.

PRE-COMPRESSION PARAMETERS: [12, 13, 14]

Angle of Repose

Fifty grams (50 g) of powder was placed in a glass funnel above 10 cm from the flat surface. The granules were then run down from the funnel opening by removing the cotton plug from the funnel opening. The formed heap height (h) and heap radius (r) were recorded. The angle of repose (θ) is calculated as:

Angle of repose = $\tan^{-1}$ h/r

Bulk and Tapped Densities

Both bulk density (BD) and tapped density (TD) were measured. A 5 g quantity of powder of each formulation (previously shaken to break up any agglomerates that had formed) was placed in a dry 25 ml graduated cylinder. The powder was carefully leveled without compaction and the unexplained apparent volume was read to the nearest scale unit. After observing the initial volume, the cylinder is mechanically tapped and further volume readings are taken until a slight change in volume is observed. BD and TD were calculated using the following formulas:

Density = weight of the powder/ volume of the substance

Percentage Compressibility (Carr's index) and Hausner's ratio

The Carr's index was calculated from the difference between the tapped and the bulk densities divided by the tapped density and the ratio expressed as a percentage. The Hausner's ratio is the ration between the tapped and bulk density.

Carr's index = [(TD-BD)/TD] ×100
Hausner's ratio = TD/BD

POST-COMPRESSION PARAMETERS: [15, 16]

Weight variation test and Uniformity of weight

For weight variation test, individually weighing 20 tablets, calculating the average weight and comparing the individual tablet weight to the average weight. For the same, uniformity of weight was calculated to ensure the tablet's weight variation was in the I.P limit.

Tablet Thickness and Diameter

Randomly selected 10 tablets from each formulation batch were subjected to measure thickness and diameter using digital vernier caliper and mean of these readings was taken as the mean tablet thickness.

Hardness

The diametric compression forcerequired to break a tablet called tablet's hardness. The Pfizer type of hardness tester was used in this study.

Friability

Tablet friability was measured using a Roche Friabilator. Ten tablets were weighed, placed in a Roche Friabilator and spun at 25 rpm for 4 minutes. The tablets were then dedusted, reweighed and the percentage weight loss calculated. A friability of less than 1% was considered adequate, according to I.P.

Percentage Friability = Weight loss/ Initial weight × 100

Swelling behavior/ Swelling index (S.I.)

The degree of swelling was measured as percentage weight gain of the tablets. The swelling behavior of all formulations was investigated. One tablet of each formulation was stored in a Petri dish containing pH 7.4 phosphate buffer. After 0.083 hours, the tablets were removed, dried with tissue paper and weighed. Thereafter, tablet weights were recorded at 0, 1, 2, 4, and 6 hours and the procedure continued until the end of 20hours. Weight gain from tablets was calculated using the following formula: [17]

Swelling index = {(Wt-Wo)/Wo} × 100

Where, Wt = weight of tablet at time t (hr) &Wo = weight of tablet at zero time.

Drug Content

The tablets were powdered and an amount equivalent to 50 mg of the average weight of Losartan in the tablet powder was accurately weighed and transferred to a 100 ml volumetric flask. First, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 minutes. The volume was then made up to 100 ml with buffer. The solution in the volumetric flask was then filtered and 1 ml of the filtrate was diluted and analyzed at 206 nm using a UV-Vis spectrophotometer (Shimadzu UV-2450, Japan). The drug content of each sample was estimated from its standard curve. [18]

Disintegration test

Six tablets from each batch were placed in each compartment of the Lab India disintegration apparatus (DT 1000) with water thermo stated at 37 ± 0.5^{o}C as the medium. [19]

In-vitro drug release studies

The ability of Losartan potassium matrix tablets is to remain intact in the physiological environment of the stomach and small intestine was assessed by mimicking passage from the mouth to the colon. Drug release studies were performed by him in 900 mL of 0.1 N HCl for 2 hours using a USP XXIII dissolution apparatus (Type I, 100 rpm, 37.5±0.5°C). The dissolution medium was replaced with 900 ml pH 7.4 phosphate buffered saline (PBS) and dissolution continued for 24 hours. At specified times (2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours and 20 hours), 5 ml samples were removed and analyzed using a UV-visible spectrophotometer (Shimadzu UV- 2450, Japan). A volume of 5 mL of filtered fresh dissolution medium was added to make up the volume after each sampling to maintain sink conditions during the dissolution test. [20, 21-30]

RESULT AND DISCUSSION

The granules of formulation from **S1-S9** were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The angle of repose for batch S1-S9 observed with result of range from 24.575 ± 1.432 to 29.122 ±1.208, Bulk density ranges from 0.294± 0.026 to 0.514± 0.013, tapped density ranges from 0.344±0.004 to 0.588±0.024 with compressibility index &hausner's ratio ranges from 10.139±2.018 to 16.580±1.243 and 1.112±0.029 to 1.198±0.031 respectively.

Table 3: Pre-compression parameters-properties of granules.

Pre-compression Parameters	Angle of Repose(θ)	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Compressibility Index (%)	Hausner's Ratio
S1	26.924±1.191	0.470± 0.013	0.539±0.026	12.801±1.672	1.146±0.023
S2	27.728 ± 1.102	0.504± 0.019	0.588±0.024	14.285±1.623	1.166±0.027
S3	26.708 ± 1.611	0.336± 0.044	0.384±0.018	12.500±1.278	1.142±0.008
S4	25.564± 1.467	0.422± 0.025	0.493±0.025	14.401±2.328	1.168±0.032
S5	29.122 ±1.208	0.514± 0.013	0.572±0.038	10.139±2.018	1.112±0.029
S6	25.348± 0.911	0.322 ±0.009	0.383±0.012	16.580±1.243	1.198±0.031
S7	27.282± 0.876	0.492± 0.021	0.552±0.019	10.869±1.259	1.121±0.033
S8	28.144 ± 1.586	0.294± 0.026	0.344±0.004	14.534±1.837	1.170±0.028
S9	24.575± 1.432	0.446± 0.011	0.515±0.023	13.398±1.105	1.154±0.039

Losartan matrix tablets different formulation's S1-S9 were subjected to evaluation tests such as uniformity of weight, tablet thickness, tablet diameter, hardness, friability, drug content, swelling index and in-vitro drug release studies. The findings from all formulations passed the test for uniformity of weight as per official as in weight variation test, the percentage average deviation of all tablet formulations were found within the limit as per Indian pharmacopoeia.

Table 4: Characterization of Sustained release matrix tablets of Losartan Potassium.

Parameters Formulation	Thickness (mm)	Weight variation (mg)	Friability (%)	Hardness (kg/cm2)
S1	5.114±0.007	344.1±0.129	0.85±0.036	3.9±0.176
S2	4.124±0.005	345.1±1.852	0.59±0.093	3.5±0.085
S3	5.102±0.016	349.5±0.058	0.72±0.033	4.1±0.109
S4	4.198±0.078	346.8±1.334	0.77±0.058	3.8±0.185
S5	4.167±0.011	346.4±1.671	0.69±0.065	4.6±0.125
S6	5.116±0.018	350.2±2.222	0.78±0.034	4.9±0.136
S7	4.237±0.022	355.2±1.785	0.69±0.085	4.2±0.138
S8	5.109±0.051	352.6±2.452	0.74±0.085	4.4±0.124
S9	4.368±0.096	352.2±1.282	0.73±0.056	4.0±0.342

The range of thickness of Tablets from formulation S1-S9 found between 4.124±0.005 (S2) to 5.116±0.018 (S6); weight variation test studies showed range from 344.1±0.129 (S1) to 355.2±1.785(S7); friability percentages were in range from 0.59±0.093 (S2) to 0.85±0.036 (S1); the formulation S6 showed a comparatively high hardness value of 4.9±0.136 kg/cm^2 whereas formulation S2 showed low harness value of 3.5±0.085 kg/cm^2 . Strength of the tablets was confirmed by friability estimation. The swelling index was calculated with respect to time. The swelling index increases with time as because tablet gain weight proportionally with rate of hydration up to certain limit. As passed time, the swelling index decreases gradually due to dissolution of outermost gelled layer of tablets into dissolution medium. The swelling effects of formulations were still continuing even after 20 hours which indicates the drug released from the above formulations were sustained to other formulations. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index (Fig. 2). Tablets with higher amount of gums showed slow erosion of the gelled layer.

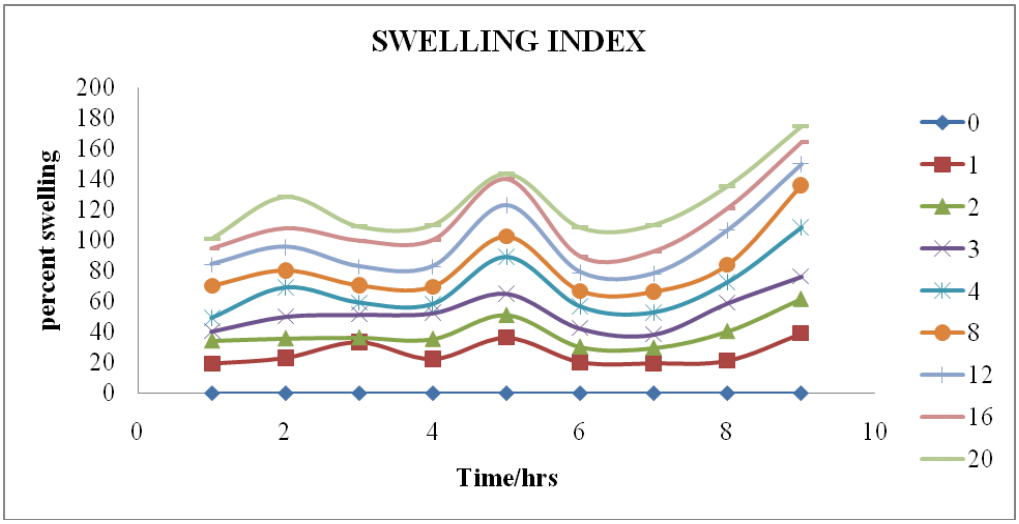

Fig.2: Percentage swelling of formulation with Time from S1-S9.

To study the release kinetics, data obtained from in- vitro drug release studies of formulation S1-S9 were plotted in various kinetic models such as: zero order as cumulative percentage of drug released vs. time; first order as cumulative percentage of drug remaining vs. time; Higuchi's model as cumulative percentage of drug released vs. square root of time; KorsmeyerPeppa et al's as log cumulative percentage of drug released vs. log time. Good uniformity in drug content was found among different batches of the tablets, and Sustained Release tablets were prepared by the wet granules Method using different combination of HPMC K4, HPMC K15,Ethyl Cellulose,and Sodium Alginate with a view to obtain sustain release matrix tablet for oral drug delivery.

The release Percentage Yield of formulations S1, S2, S3, S4, S5, S6, S7, S8, S9 were obtained as 88.4, 91.5, 95.1, 77.6, 82.4, 83.3, 73.8, 83.3, and78.2 respectively. All formulations showed satisfactory percentage yield. It indicates that S3 showed best Sustained Release property Compare than S1, S2, S4, S5, S6, S7, S8 and S9.

The Same amount of HPMC K4 and different amount of Sodium Alginate affect the release of drugs. High Amount of Sodium Alginate the release of the drug was also high.

Three formulations Prepared containing HPMC K4 and Sodium alginate (50:30, 50:40,50:50) were prepared. Three formulations containing HPMC K15 and Sodium alginate (50:30, 50:40, 50:50) were prepared, similarly three formulations containing Ethyl cellulose and Sodium alginate (50:30,50:40,50:50) were prepared.Formulation S3 best formulation because the maximum drug release was observed in S3 (95.1%).

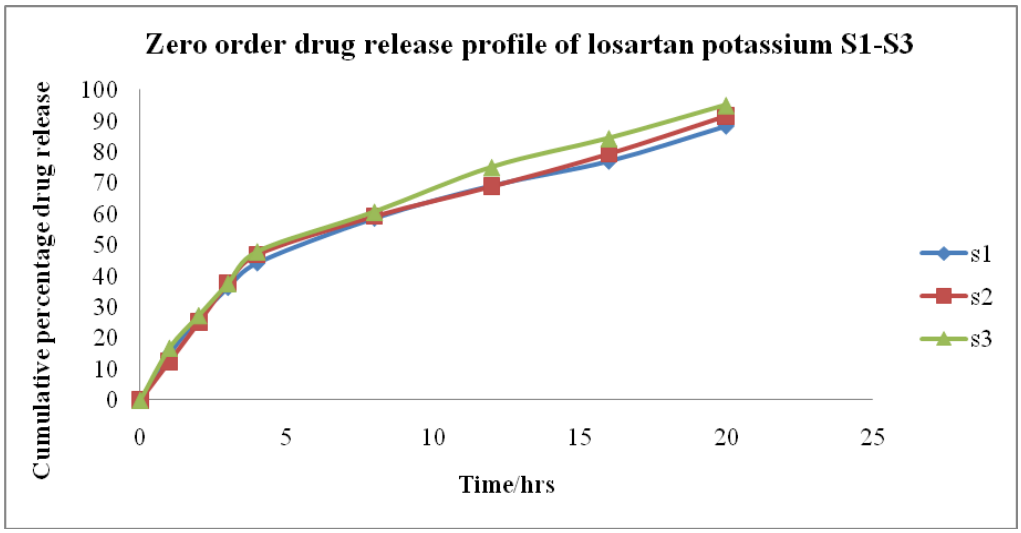

Fig.3: Zero order drug release profile of losartan potassium S1-S3.

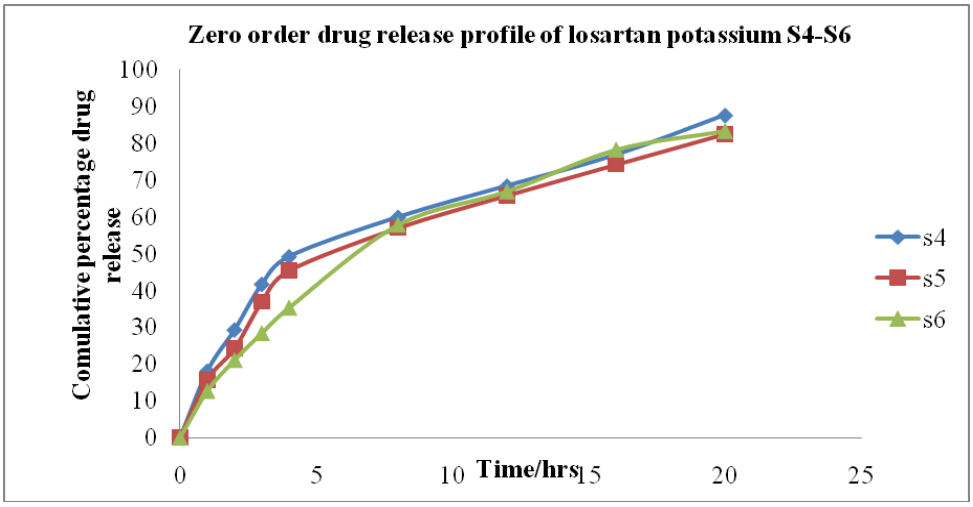

Fig.4: Zero order drug release profile of losartan potassium S4-S6.

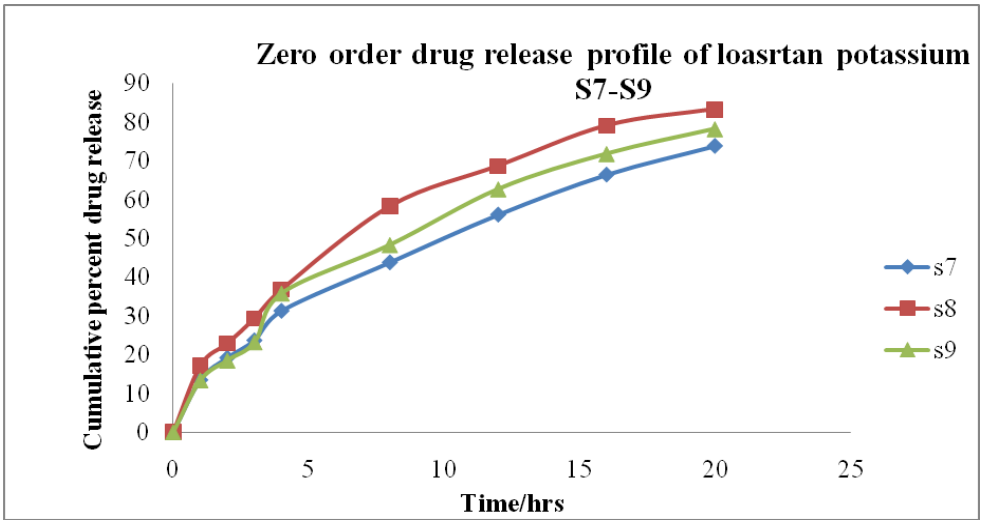

Fig.5: Zero order drug release profile of Losartan potassium S7-S9.

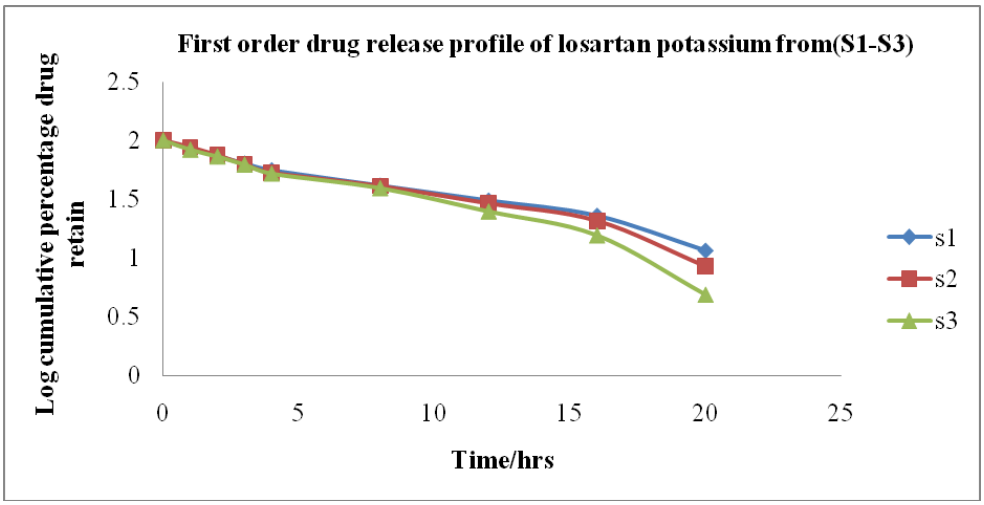

Fig.6: First order drug release profile of losartan potassium S1-S3.

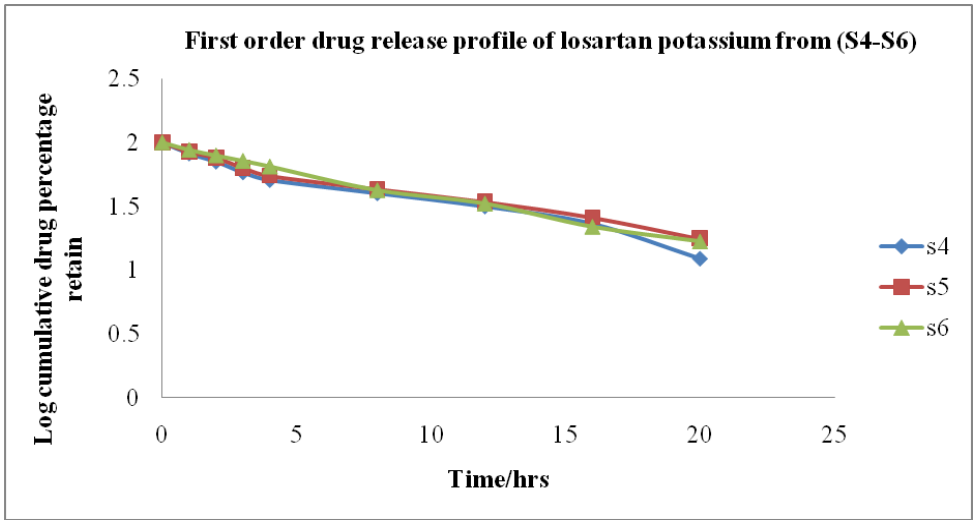

Fig.7: First order drug release profile of Losartan potassium S4-S6.

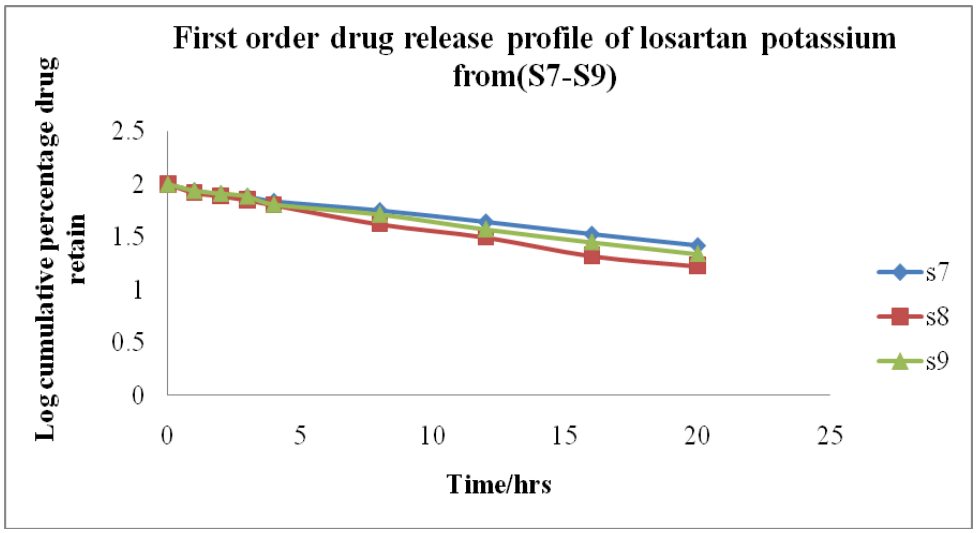

Fig.8: First order drug release profile of Losartan potassium S7-S9.

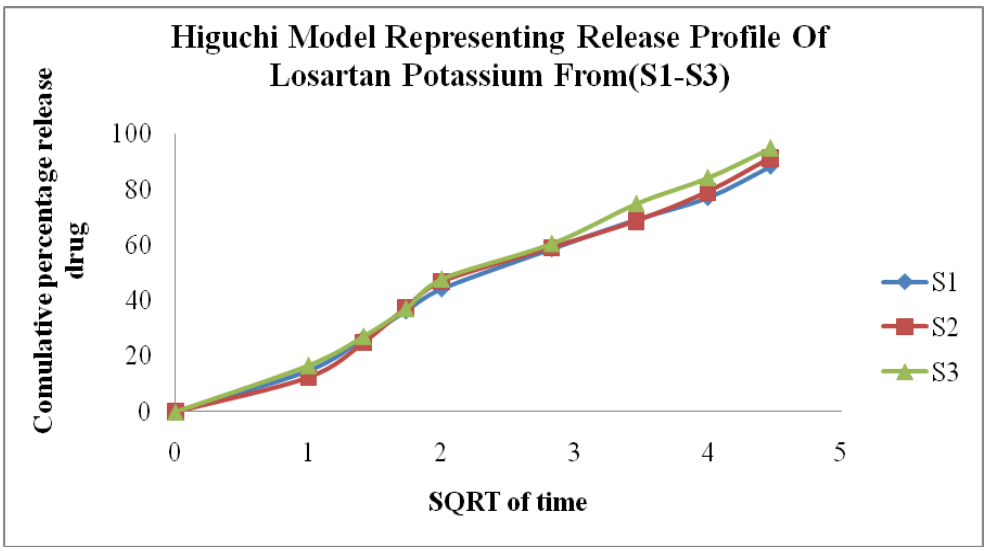

Fig.9: Higuchi Model drug release profile of Losartan potassium S1-S3.

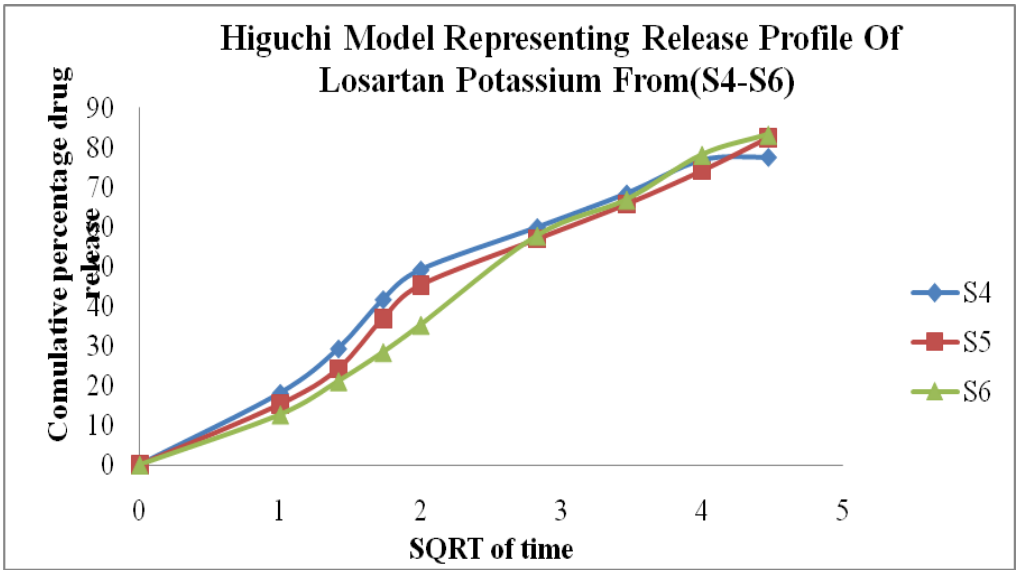

Fig.10: Higuchi Model drug release profile of Losartan potassium S4-S6.

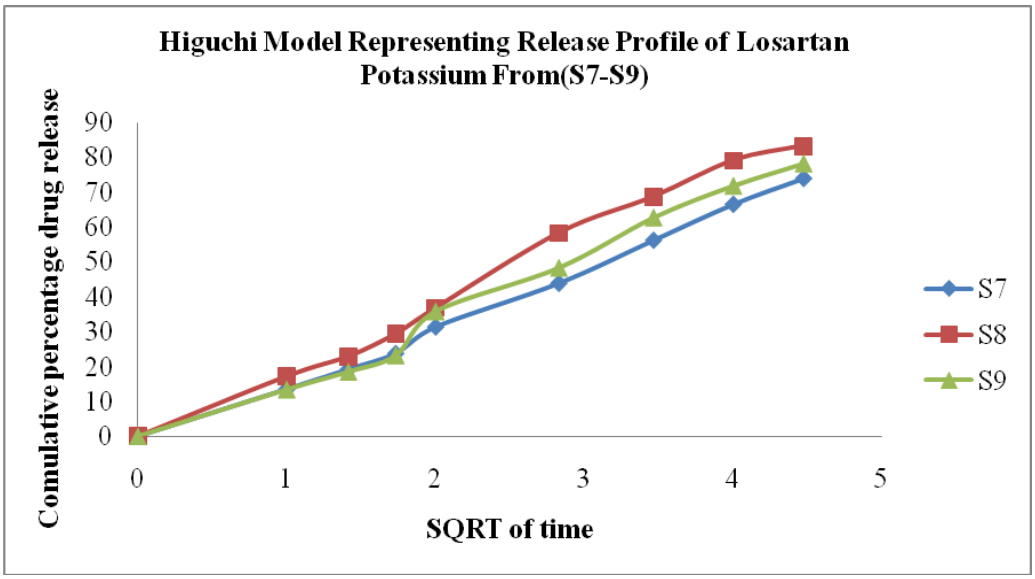

Fig.11: Higuchi Model drug release profile of Losartan potassium S7-S9.

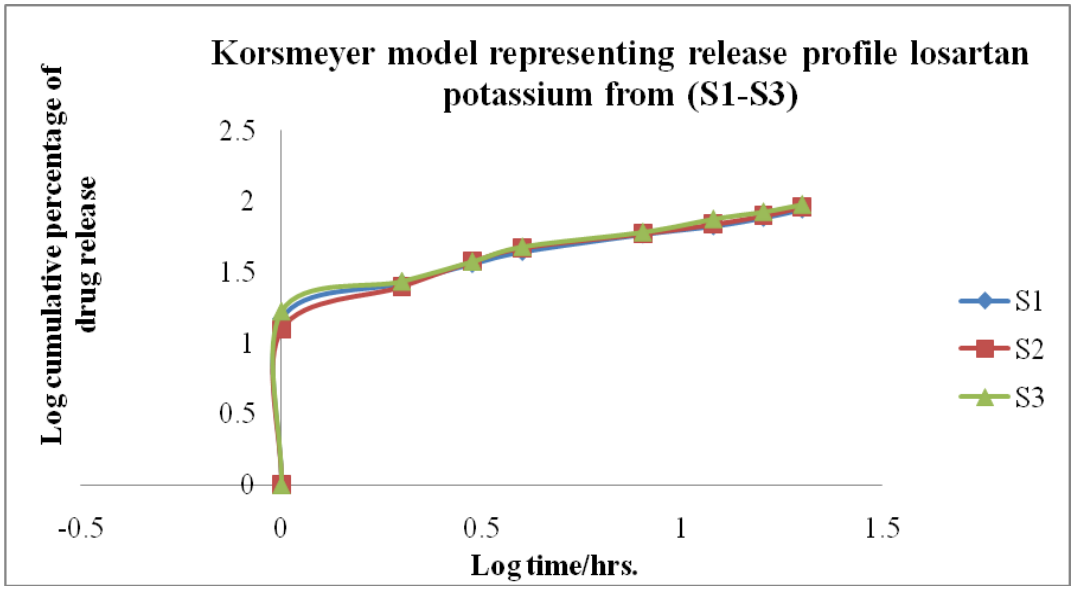

Fig.12: Korsmeyer model representing release profile losartan potassium from (S1-S3).

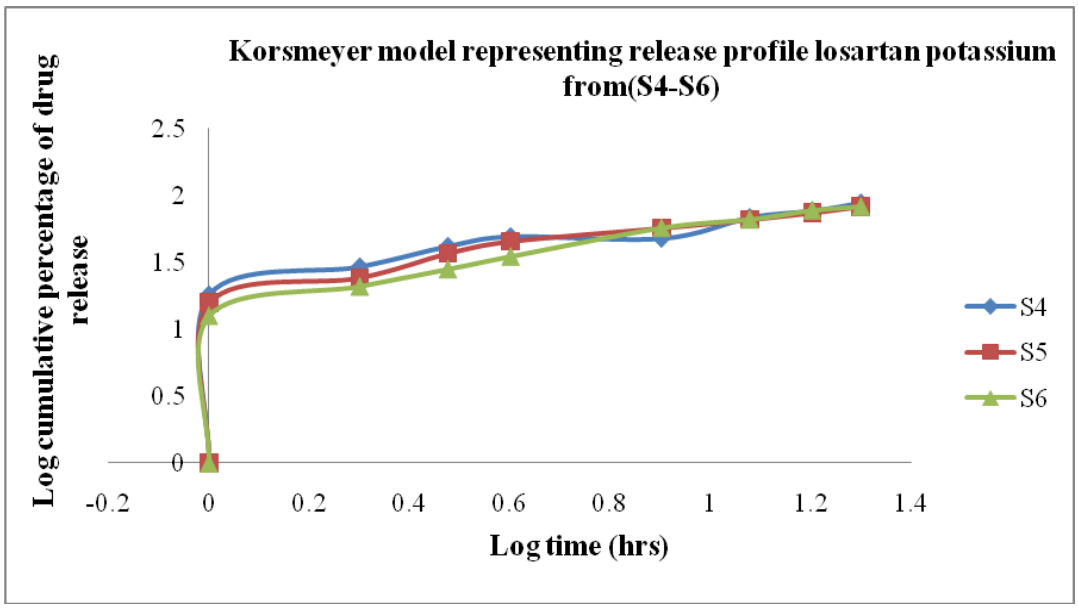

Fig.13: Korsmeyer Model Representing Release Profile of Losartan Potassium from S4- S6.

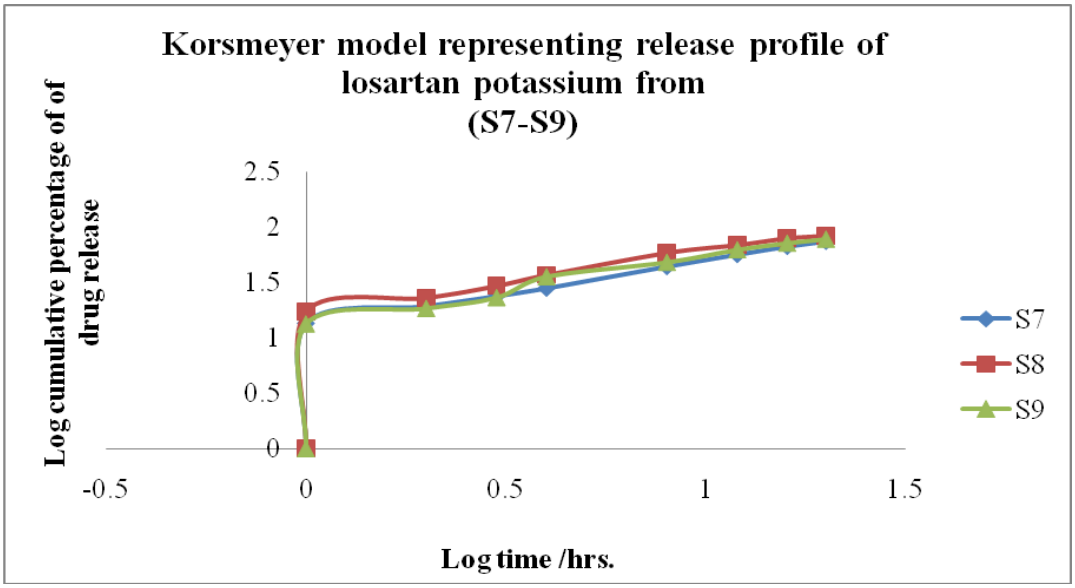

Fig.14: Korsmeyer Model Representing Release Profile of Losartan Potassium from S7- S9.

CONCLUSION

Matrix tablets containing HPMC-K4, HPMC-K15and ethyl cellulose with varying concentration of sodium alginate were analyzed. Here formulation **S3** containing HPMC-K4: Sodium alginate in ratio of 1:1 was found to be as it prolongs the release of Losartan potassium up to 20 hours. Among all batches S3 was found to be most effective in sustaining the release of Losartan potassium. In future research is required to investigate the applicability of HPMC-K4& sodium alginate in molding modified release drug delivery systems and other extended release delivery systems. Based on the satisfactory results of validation parameters for assay method such as Precision, specificity, linearity, range, accuracy & ruggedness it is concluded that the method of testing assay for Losartan Potassium sustained release matrix tablets stands validated.Formulation S3 was found to be the best formulation because we used high value of sodium alginatethat has provided good result of all evaluation parameter. In future consideration for treatment of hypertension, the designing concept of matrix tablets in sustains release is better and has better bioavailability using Sodium alginate as polymer.

Author's Statements

Competing Interests

The author declares that there is no conflict of interest regarding the publication of this paper.

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2. Loba chemicals (Mumbai), India

REFERENCES

1. Organisation WH. World Health Organization. A global brief on hypertension. Report. 2015 April 2015. Contract No.: WHO/DCO/WHD/2015.2.
2. Virani S.S., Heart Disease and Stroke Statistics—2021 Update A Report from the American Heart Association. Aha journals. 2021, 143(8), e254-e743.https://doi.org/10.1161/CIR.0000000000000950
3. https://www.drugs.com/losartan.html
4. Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, in Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Edition, Revised and Expanded, Drugs and the Pharmaceutical Sciences, Marcell Dekker, Inc. New York, 72: 575-609, 1995.
5. Loyd V. Allen, Jr et al: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams & Wilkins, Philadelphia, 9: 257-271, 2009.
6. Prathyusha KN, Hemalatha B, Padmalatha K. A New Controlled Release Polymer for floating tablets of Losartan Potassium. Asian Journal of Pharmaceutical Research. 2021 Dec 1; 11(4).
7. https://www.sciencedirect.com/topics/nursing-and-health-professions/matrix-tablet#:
8. Aseri A., Garg S., Nayak A., Trivedi S., Katewa J., Formulation and release distinctiveness of a novel modified drug delivery device: Gum ghati matrix tablets containing Metronidazole. Indo American Journal of Pharmaceutical Research, 2015, 5(01), 450-457.
9. Wani TU, Khan NA. Formulation of carbopol capsules for sustained release of losartan potassium. Journal of Drug Delivery and Therapeutics. 2019 Apr 15; 9(2-s):92-7.
10. Amer MA, Essa EA, Donia AA, El Maghraby GM. Development and evaluation of liquid oral controlled release systems for Losartan potassium. Journal of Applied Pharmaceutical Science. 2019 Aug 3; 9(8):086-93.
11. Gunda RK, Manchineni PR. Development and evaluation of losartan potassium sustained release tablet formulations. World Journal of Current Medical and Pharmaceutical Research. 2019:25-31.
12. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, Foudah AI, Alrobaian MM, Shukla R, Singh S, Kesharwani P. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. Heliyon. 2020, 6(11):e05459.
13. Nayakulu BR, Kumar NR, Kumar CK, Abhilash PR. Formulation and evaluation of floating matrix tablet of Losartan for gastroretentive drug delivery. Asian Journal of Pharmacy and Technology. 2016 Jun 28; 6(2):85-90.
14. Kumar KK, Swathi M, Srinivas L, Basha SN. Formulation and evaluation of floating in situ gelling system of losartan potassium. Pharm Lett. 2015; 7: 98-112.
15. Reddy T. Kiran JV, Duraival S, Pragath K B. Formulation and In-Vitro Evaluation of CefiximeTrihydrate Sustained Release Matrix Tablets, IJCPRR, 2014, 3(4): 110-129.
16. Krishnarajan D, Reddy C.M, Kanikanti S, Senthil NK., Formulation and evaluation of sustained release matrix tablets of levofloxacin using natural polymer, Pharmacophore. 2013, 4 (5):146-157.
17. Khan KA, Khan GM, Muzammal M, Al Mohaini M, Alsalman AJ, Al Hawaj MA, Ahmad A, Niazi ZR, Shah KU, Farid A. Preparation of Losartan Potassium Controlled Release Matrices and In-Vitro Investigation Using Rate Controlling Agents. Molecules. 2022 Jan 27; 27(3):864.
18. Purnima P, Arun P, Shailendra P, Bhavesh P, Neelesh D. Formulation and Evaluation of Sustained Release Matrix Tablets of Losartan Potassium. WJPS. 2019, 8(12), 1041-1047. ISSN 2277-7105.
19. Suryadevara V, Lankapalli SR, Vejella UM, Mupparaju S, Chava S. Formulation and evaluation of losartan potassium osmotic controlled matrix tablets. Indian J Pharm Educ. 2014 Oct 1; 48:18-26.
20. Sayed I, Abdel-Rahman, Gamal MM, El-Badry M, Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets, Saudi Pharmaceutical Journal, 2009, 17: 283-288.
21. Viswanath V, Chandrasekhar U, Rao BN, Prakash KG. Development and evaluation of sustained release matrix tablets of losartan potassium. International Journal of Applied Pharmaceutical Sciences and Research. 2016 Dec 6; 1(04):127-32.
22. Reddy Y, Chetty C, Kumar K, Dachinamoorthi D. Formulation and Optimization of Extended Release Matrix Tablets of Losartan Potassium Using Response Surface Methodology (RSM). J Pharm Res Int. 2017 Jan 10; 19(5):1-2.
23. Wani TU, Mir KB, Fazli AA, Raza SN, Khan NA. HPMC/Carbopol based extended release gastroretentive dosage form of losartan potassium: Formulation and in vivo pharmacokinetic evaluation in rabbits. Journal of Drug Delivery Science and Technology. 2020 Dec 1; 60:102006.
24. Rahamathulla M, Saisivam S, Alshetaili A, Hani U, Gangadharappa HV, Alshehri S, Ghoneim MM, Shakeel F. Design and Evaluation of Losartan Potassium Effervescent Floating Matrix Tablets: In Vivo X-ray Imaging and Pharmacokinetic Studies in Albino Rabbits. Polymers. 2021 Oct 10; 13(20):3476.
25. AbouObaid NI, Al-Jenoobi FI, Ibrahim MA, Alam MA. Losartan potassium sustained release pellets with improved in vitro and in vivo performance. Pharmaceutical Development and Technology. 2020 Oct 20; 25(9):1031-42.
26. Zhou B., Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Open Access Published. Aug. 24, 2021, 398(10304), 957-980. DOI:https://doi.org/10.1016/S0140-6736(21)01330-1.
27. Khan KA, Khan GM, Shah KU, Niazi ZR, Khan H, Ahmad A, Shah PA, Ullah A, Tahir M, Jan SU. Design, Preparation and evaluation of various parameters of controlled release matrices of losartan potassium using polymers combination. Pakistan Journal of Pharmaceutical Sciences. 2020 Sep 3; 33.

28. Dhobale AV, Mahale AM, Shirsart MK, Joshi DA, Dhembre GN, Thakare MM. Design, Development and Characterization of Losartan Potassium Sustained Release Matrix Tablet. WJPPS. 2018, 7(01); 1349-1362. ISSN: 2278-4357.
29. Kalbhare SB, Redasani VK, Bhandwalkar MJ, Pawar RK, Bhagwat AM. Role of aminated derivatives of natural gum in release modulating matrix systems of losartan potassium: Optimization of formulation using Box-Behnken design. Asian Journal of Pharmaceutical Research. 2021 Apr; 11(2):73-4.
30. Khan KA, Khan GM, Danish MZ, Khan H, Rehman F, Mehsud S. Formulation and in-vitro evaluation of directly compressed controlled release matrices of Losartan Potassium using Ethocel Grade 100 as rate retarding agent. International Journal of Pharmaceutics. 2015 Dec 30; 496(2):759-65.

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