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DESIGN, DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS USING NATURAL POLYMER FOR HYPERTENSION MANAGEMENT

Lata Kanase*[*1], Shivangni Rathore[2], Revathi A Gupta[3]

[1].Student, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)
[2.] Assist, Professor, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)
[3.] Principal, Institute of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.)

ABSTRACT :

The aim of this study was to design and manufacture two different strengths of the combination product using the same ingredients used in the SR tablet formulation. The release form of these tablets contains an antihypertensive drug belonging to the class of beta-selective adrenergic blockers and does not have partial agonist or membrane stabilizing properties. Extended-release formulations provide sustained release and reduce the potential for side effects. Extended-release forms of this drug are sometimes used to treat high blood pressure and heart failure. The sustained-release formulation of the drug has been shown to be effective in clinical studies. The main objective of this study was to design, manufacture and evaluate a tablet matrix using a hydrophilic natural blocking polymer that delays drug release in the upper gastrointestinal tract and initiates drug release when the alkaline environment of the small intestine is reached. Metholose 90 sh and xanthan gum were investigated as hydrophilic flame retardant polymers. Wet granulation method was used to prepare sustained release matrix tablet. Nine groups of tablets were prepared. The prepared tablets were evaluated for pharmacopoeial and non-pharmacopoeial properties including friability and compressibility index, Hausner ratio, repose angle, friability, hardness, thickness, weight change, % drug content and in vitro drug release studies. It can be concluded that the combination of hydrophilic polymers with suspensions is more suitable for promoting and controlling drug delivery than hydrophilic polymers alone.

Keywords: Carbopol 934P, Chitosan, sodium alginate, sustain release matrix tablet, Losartan

1. Introduction :

Faster and more convenient delivery is also the largest and oldest segment of the entire drug delivery market. The strategy of creating oral release drugs requires the use of hydrophilic polymers to achieve blood levels in the state or tissues so that the treatment is effective and non-toxic in the long term. In order to achieve better therapeutic results, there are different types of drug delivery to choose from; among them, drug delivery systems are more popular due to their advantages such as easy application, convenience and no further intervention. Other drug delivery systems have gained importance. Drug delivery technique was introduced three years ago to overcome the problems faced by traditional medicine such as regular dosage of medical drugs. The aim of the present invention is to design and evaluate a tablet having a release matrix using different release-release natural or synthetic polymers alone or in combination. The aim of this topic is to study the effect of different materials or synthetic polymers and their linkages on drug release information in matrix systems. Comparative analysis and optimization of natural or synthetic polymer blends in SR matrix tablet formulation. The matrix structure of natural biodegradable polymers is designed to slow down the drug release in the upper gastrointestinal tract (stomach and small intestine) and the system partially disintegrates in the intestine to release the drug

1.1 Matrix Tablet

The tablet matrix is one type of controlled drug delivery that constantly distributes the medication using diffusion-controlled and dissolution-controlled techniques. To regulate their release, medications with varying liquid characteristics are divided into a combination of swellable hydrophilic materials, non-swellable hydrophobic materials, or plastic compounds. Direct compression of the drug release, combining the sustained-release material to make a tablet in which the drug is embedded in a sustained-release matrix, is one of the easiest ways to make a sustained-release dosage form. Granulating the solution and putting it in a compound prior to compression is an additional technique.

2. Material and Method :

2.1 Material

Concept Pharma Aurangabad provided a gift sample of losartan potassium, while Merck Chemicals, Mumbai, provided other components such as magnesium stearate, xanthan gum, and Metlose 90 sh100000SR.

2.2 Method

The tablet matrix was prepared using hydrophilic polymers, such as xanthan gum, Metolose and Losartan potassium, in varying amounts. Sift first, then add enough isopropyl alcohol, and then sift the moist materials and bake for 1 hour at 55°C.

3. Experiment :

The tablet matrix was prepared using hydrophilic polymers, such as xanthan gum, Metolose 90sh 10000SR, and Losartan potassium, in varying amounts. Sift first, then add enough isopropyl alcohol, and then sift the moist material from No. 1. Sift 20 and bake for 1 hour at 55°C. The dried granules should be passed through a No. 2. 16 sieve, with part of the granules left on the sieve being disposed of. Lastly, the product is lubricated with a mixture of 1% talc and 0.5% magnesium stearate before being pressed with a 9.5 mm flat punch on a Cadmach single punch machine. Each tablet had 50 mg of losartan potassium, and the weight was adjusted to 250 mg. Each polymer's tablet compression was assessed for tablet characteristics such thickness, weight change, and friability. Matrix Tablet Preparation Using the Wet Granulation Method Wet granulation was used to create sustained-release matrix tablets of losartan potassium. Display the makeup of every matrix model. Metlose 90 sh and xanthan gum are two specific polymers that are present in each formulation of losartan potassium extended-release matrix tablets, either separately or in combination. Magnesium stearate, talc, PVP K-30 as binders, and MCC for its diluting qualities are additional excipients. Each pill had 50 mg of losartan potassium, and the weight was adjusted to 250 mg.

Table. No. 1 Formulations of Losartan potassium matrix tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	50	50	50	50	50	50	50	50	50
Metolose 90sh 10000 sr	50	75	100				25	37.5	50
Xantan gum				50	75	100	25	37.5	50
MCC	135	115	85	135	115	85	135	115	85
PVP K-30	10	10	10	10	10	10	10	10	10
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mag.Stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total Weight	250	250	250	250	250	250	250	250	250

4. Result and Discussion :

4.1 Loss on drying of losartan potassium

The experimental values for the provided sample of losartan potassium were found to be 0.67%, suggesting good agreement between the reported and experimental values, whereas the pharmacopeial limits for LOD of losartan potassium were reported to be no more than 1%.

Table No.2 Evaluation of prepared Losartan potassium powder blend

1. Formulation	2. LooseBulk Density(g/cm)	3. Tapped bulkdensity(g/cm^2)	4. Carr's index(%)	5. Hausner ratio	6. Angleof Repose (degrees)
7. F1	**8. 0.443±0.013**	**9. 0.508±0.008**	**10. 12.69±0.042**	**11. 1.145±0.012**	**12. 31^{0}02'±0.014**
13. F2	**14. 0.466±0.009**	**15. 0.528±0.017**	**16. 11.76±0.031**	**17. 1.133±0.009**	**18. 32^{0}82'±0.019**
19. F3	**20. 0.488±0.007**	**21. 0.522±0.019**	**22. 7.89±0.019**	**23. 1.069±0.014**	**24. 29^{0}75'±0.011**
25. F4	**26. 0.455±0.011**	**27. 0.495±0.013**	**28. 8.68±0.024**	**29. 1.089±0.004**	**30. 30^{0}46'±0.008**
31. F5	**32. 0.469±0.014**	**33. 0.506±0.007**	**34. 8.41±0.015**	**35. 1.077±0.001**	**36. 29^{0}64'±0.002**
37. F6	**38. 0.434±0.008**	**39. 0.498±0.021**	**40. 11.35±0.021**	**41. 1.148±0.009**	**42. 32^{0}26'±0.009**
43. F7	**44. 0.414±0.009**	**45. 0.462±0.012**	**46. 10.33±0.028**	**47. 1.116±0.003**	**48. 32^{0}45'±0.014**
49. F8	**50. 0.472±0.015**	**51. 0.532±0.014**	**52. 11.31±0.035**	**53. 1.127±0.015**	**54. 29^{0}38'±0.026**
55. F9	**56. 0.486±0.007**	**57. 0.539±0.011**	**58. 9.67±0.022**	**59. 1.107±0.007**	**60. 33^{0}18'±0.012**

4.2 Compatibility studies

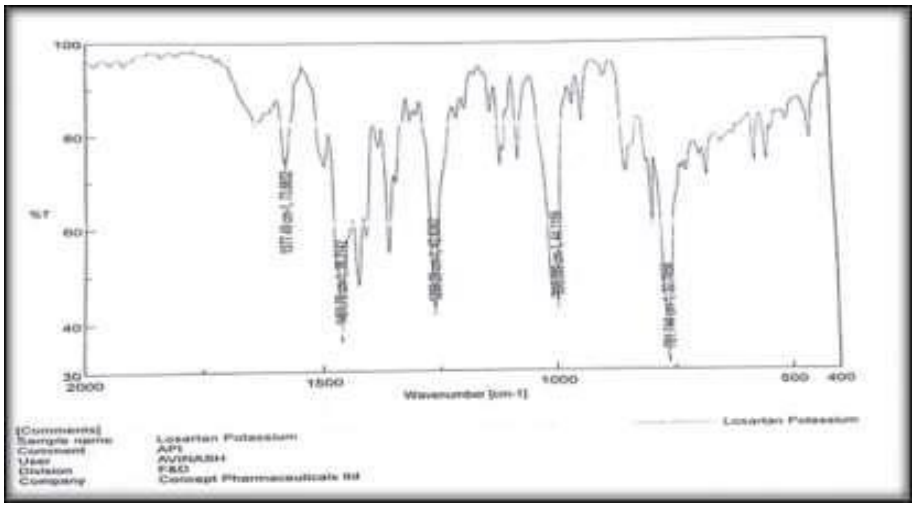

Figure 1. IR Spectrum of Losartan Potassium

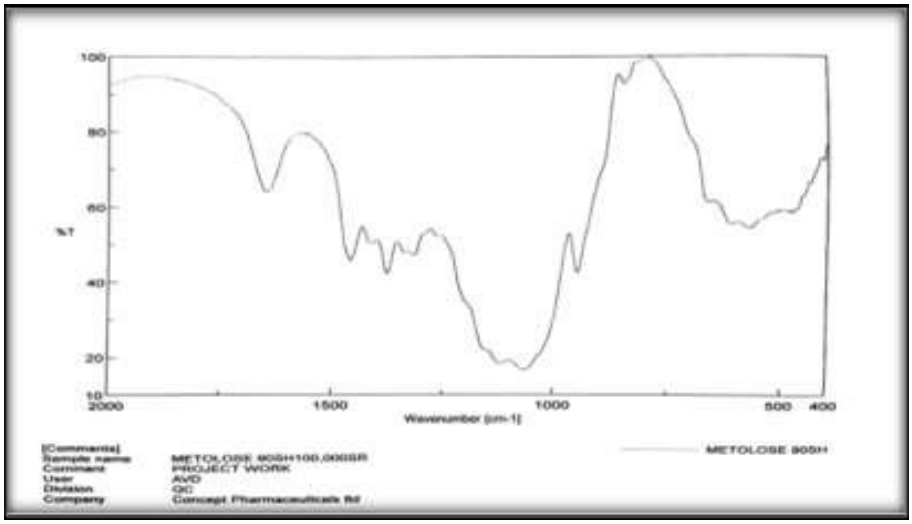

Figure 2. IR Spectra of Metolose 90 Sh 100000SR

4.3 Evaluation of sustained release Losartan Potassium matrix tablets

The sustained release tablet of Losartan was formulated and evaluated by various parameters like Hardness, friability percentage, thickness, content uniformity, weight variation etc.

Table No.2: Standard physical test for matrix tablets

Formulation	Hardness ($kg/cm^{2)}$	Percent friability (%)	Thickness (mm)	Content uniformity (%)	Weight variation
F1	5.1□0.1	0.57±0.03	3.5□0.2	101.20%	252□0.55
F2	5.0□0.1	0.69±0.03	3.7□0.2	99.63%	250□0.47
F3	5.2□0.2	0.49±0.04	3.5□0.1	98.93%	248□0.57
F4	5.2□0.1	0.65±0.02	3.5□0.2	98.28%	251□0.20
F5	5.0□0.2	0.51±0.06	3.8□0.4	96.60%	248□0.43
F6	5.2□0.1	0.62±0.04	3.7□0.3	89.94%	250□0.52
F7	5.1□0.2	0.67±0.06	3.8□0.4	97.23%	251□0.20
F8	5.3□0.1	0.68±0.01	3.5□0.2	98.16%	249□0.81
F9	5.0□0.2	0.55±0.05	3.7□0.3	99.11%	250□0.51

4.4 In-Vitro Release Studies

1. Times in (Hrs)	2. Cumulative Percent drug release		
	3. F4	4. F5	5. F6
6. 0	7. 0	8. 0	9. 0
10. 1	11. 17.93	12. 19.14	13. 14.94
14. 4	15. 36.10	16. 37.77	17. 30.23
18. 8	19. 74.56	20. 78.60	21. 70.48
22. 12	23. 94.28	24. 95.79	25. 86.94

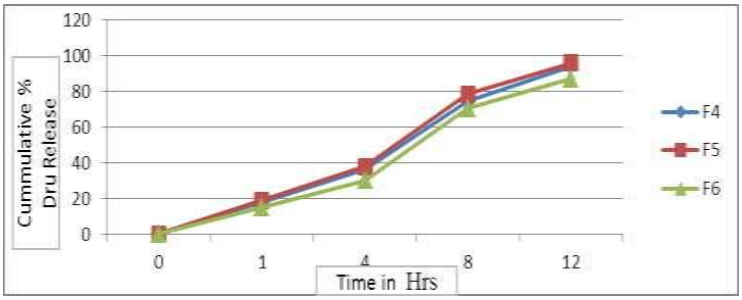

Figure6: In-vitro dissolution profile of F4, F5 and F6 Formulation

Table No. 5: In-Vitro Dissolution data of F7, F8 And F9 Formulation

26. Times in (Hrs)	27. Cumulative Percent drug release		
	28. F7	29. F8	30. F9
31. 0	32. 0	33. 0	34. 0
35. 1	36. 19.24	37. 21.28	38. 23.15
39. 4	40. 31.64	41. 34.52	42. 37.49
43. 8	44. 71.21	45. 73.14	46. 75.32
47. 12	48. 96.23	49. 97.16	50. 99.11

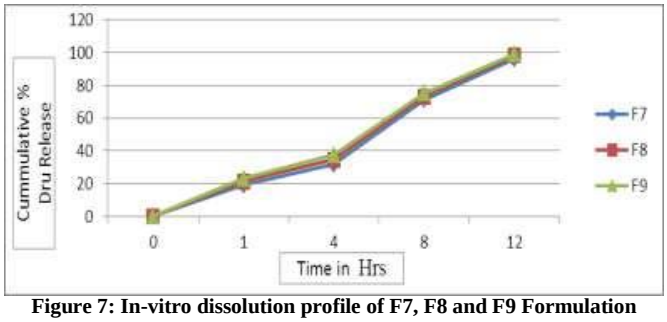

Figure 7: In-vitro dissolution profile of F7, F8 and F9 Formulation

4.5 Kinetic Release

Table No.6: Kinetic data of sustained release matrix tablet of losartan potassium

Formulation Code	Zero Order(R^2)	First order(R^2)	Matrix Model(R^2)	Korsemeyer- peppas model (R^2)
F1	51. 0.9217	52. 0.9835	53. 0.9867	54. 0.9767
F2	55. 0.9524	56. 0.9247	57. 0.9854	58. 0.9925
F3	59. 0.9257	60. 0.9372	61. 0.9688	62. 0.9879
F4	63. 0.9653	64. 0.9428	65. 0.9842	66. 0.9462
F5	67. 0.9565	68. 0.9851	69. 0.9467	70. 0.9904
F6	71. 0.9629	72. 0.9124	73. 0.9871	74. 0.9796
F7	75. 0.9821	76. 0.9457	77. 0.9291	78. 0.9863

F8	**79. 0.9685**	**80. 0.9611**	**81. 0.9894**	**82. 0.9638**
F9	**83. 0.9806**	**84. 0.9629**	**85. 0.9728**	**86. 0.9890**

4.6 Swelling Index

Table No.9: Swelliing index of formulation F1 to F3

Timein (Hrs)	Swelling index		
	Formulation code		
	F1	F2	F3
2	26.16	34.52	38.31
4	32.42	45.75	51.76
6	37.85	53.43	62.71
8	46.61	66.54	73.32
10	39.74	58.21	64.24
12	38.22	54.25	60.22

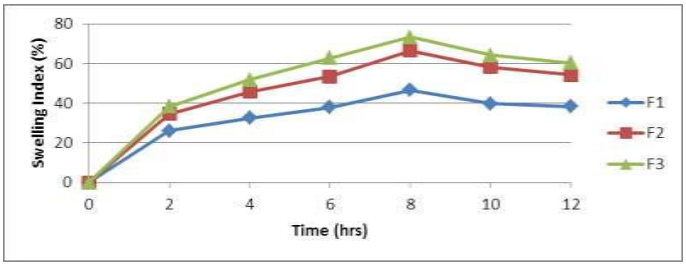

Figure 8. Swelling index of formulation of F1-F3 Formulation

Table No. 12: Parameters studied on F2, F4 and F8 formulations before and after

Parameter	Before stability study		
	F2	F4	F8
Thickness	3.7±0.02	3.5±0.02	3.5±0.02
Hardness	5.0±0.1	5.2±0.1	5.3±0.2
Drug content	99.63%	98.28%	98.16%

Parameter	After stability study		
	F2	F4	F8
Thickness	3.7±0.02	3.5±0.2	3.6±0.1
Hardness	**5.0±0.1**	5.1±0.1	5.3±0.2
Drug content	98.02%	94.13%	97.89%

Table No. 13: Cumulative percent drug release of optimized Formulation F2, before and after stability study

Times in (Hrs)	Cummulative percent drug release	
	Before stability study	After stability study
	F2	F2
0	0	0
1	21.38	21.37
4	38.27	38.12
8	79.24	79.20
12	98.07	98.02

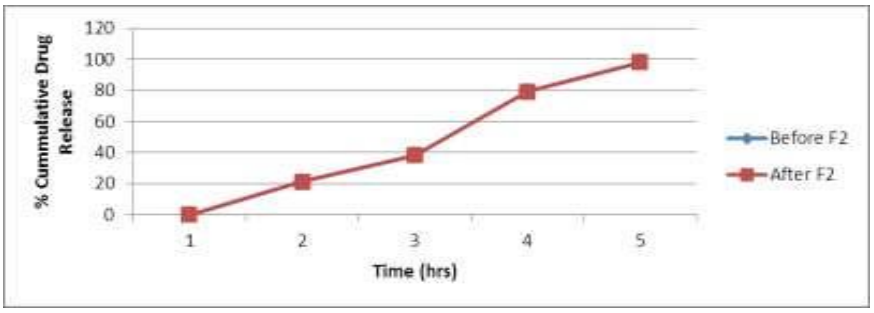

Fig 11: in- vitro Dissolution profile of formulation F2 before and after stability study

Losartan potassium in 0.1 N HCl has a maximum absorption at 250 nm in its UV spectrum. According to I.P. Properties, it was discovered that the medications employed in the recipe are pure. Losartan potassium's UV spectrum in 0.1 N HCl. The interaction between the medicine and the polymer used to create sustained release matrix tablets is shown by the distinctive peaks of pure losartan potassium in the FTIR spectra of the drug containing xanthan gum, the drug including milose 90 sh, and the drug containing pure losartan potassium. They don't engage with one other sufficiently. Losartan potassium has been demonstrated to abide by both Beer's and Lambart's laws. For both 1.2 and 6.8 pH phosphate buffers, the concentration range at 250 nm is 0–10 mg/ml. The low compression index values further confirm the good flow qualities shown by the angle of repose findings for all formulations, which are determined to be within the range. Consequently, it may be said that every powder group has favorable flow characteristics. Good packing is defined as having a density range of 1.2g/cm2, whilst bad packing is defined as having a value over 1.5g/cm2. Each sample has a density that ranges from 0.414 to 0.462 ± 0.46 g/42 ± 0.014 g/cm3, respectively. The outcomes fall within a reasonable range. The Culler compressibility index is used to determine the material's compressibility, and the findings are displayed in the table. All formulations had compressibility percentages between 7.89 ± 0.019% and 12.69 ± 0.042%, indicating appropriate qualities.

Hausner ratios ranged from 1.069 ± 0.014 to 1.148 ± 0.009 which indicates that the product is adequate and has good performance. Tablets of all formulations (F1 to F9) were evaluated for different parameters such as thickness, hardness, weight change, chemical content and friability and the results are shown in the table.

Because pill weight rise was proportionate to hydration rate up to 8 hours, the swelling index rose with time. Later, as the tablet's outermost galled coating dissolves into the dissolving solvent, it gradually drops. Increases in the swelling index were shown to be directly correlated with increases in gum concentration. The swelling index decreases with time, which might be caused by the tablets' galled coating eroding. The improved formulation F2 was used for the stability tests.The formulation was kept for three months (90 days) at 40 °C and 75 °C with 5% relative humidity. Samples were taken out after ninety days and examined for drug content, thickness, hardness, and in vitro drug release tests.

Following an expedited stability analysis, there were no appreciable changes in the tablet's physical parameters, such as its thickness, hardness, and drug content, for formulations F2, F4, and F6.

Conclusion :

Every manufactured formulation has varying amounts of xanthan gum and metolose 90 Sh. All pharmacopoeia standards are satisfied by the developed compositions. The gel's viscosity and the development of a gel layer with a longer diffusion channel both rise with the concentration of metolose 90sh and xanthan gum. The testing procedure for SR Losartan Potassium-50 Tablet is deemed validated based on the good findings of validation parameters for the assay technique, including Precision, Specificity, Linearity & Range, Accuracy (Recovery), and Ruggedness.

Acknowledgements

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