FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM PULSATILE DOSAGE FORM

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ABSTRACT *The aim of the present study was to design time controlled tablet of Losartan potassium, as chronopharmaceutical drug delivery system by compression coating. Formulation design involves coating polymer ratio (1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 10:0.5, 10:0.75, 10:1.5 w/w) of HPMC K05 and Lactose which were exploited for their pulsatile drug release ability. The basic idea behind the dosage form development is to investigate effect of coating design on lag time and drug release from press-coated pulsatile release tablet. Interaction studies with excipients were conducted by FTIR methods which indicate that there is no interaction between drugs and excipients. Coating materials granules were evaluated for pre compression parameters like bulk density, tapped density, angle of repose, compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability, weight variation, drug content, In vitro drug release. The Formulation was optimized on basis of acceptable tablet properties and in vitro drug release. The results indicate that Formulation F22 for Losartan potassium, press-coated tablets achieve a burst release after 6 h lag time which is applicable as pulsatile drug delivery for hypertension.*

Keywords: *Pulsatile, Chronopharmacokinetics, time delayed, circadian rhythm, Losartan Potassium*

I. Introduction

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new drug delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile[3,4] drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefits to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced externally related system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this area would stretch well into future and ensures the betterment of quality life.

The aim of the present study was to design a time delayed drug delivery system which releases the drug from core tablet[1,2] after a lag time[5,6] of 6hrs by compression coating. Commercial tablets of Losartan were compression coated with granules made up of HPMC polymer (K 05) and lactose. The lag time for drug release depended upon the polymer concentration and thickness of coat. Thickness of coat was altered by altering the amount of granules used for the outer coating[7] in compression.

II. Materials and Equipment

Materials used in the study are Losartan potassium pure drug, Lactose, Starch, Hydroxy propyl methyl cellulose, magnesium stearate, talc, sodium alginate. Equipments used in the study are 1 mg sensitive weighing balance, UV Visible Spectrophotometer, rotary tablet punching machine, tablet hardness tester, friability and disintegration test apparatus.

III. Materials and Equipment Experimental methods

a) Standard Solution in 0.1N HCl for losartan potassium:

100 mg of losartan potassium was dissolved in 5 ml methanol in a 100 ml volumetric flask (A), and the solution was made up to the mark with 0.1N HCl. 10 ml of A was diluted with 0.1N HCl up to 100 ml mark. This standard solution had a concentration of 100 µg/ml (B).

Procedure:

The standard solution of losartan potassium (B) was suitably diluted with 0.1N HCl to obtain a series of standard solution containing 8, 12, 16, 20, 24 µg of losartan potassium per ml. The absorbance of the solutions was measured at 240 nm using UV visible spectrophotometer systronics. 0.1N HCl was used as a blank.

b) Standard Solution in 6.8 pH phosphate buffer for Losartan potassium:

100 mg of losartan potassium was dissolved in 5 ml methanol in a 100 ml volumetric flask (A), and the solution was made up to the mark with 6.8 pH phosphate buffer.10 ml of A was diluted with 6.8 pH phosphate buffer up to 100 ml mark. This standard solution had a concentration of 100 µg/ml (B).

Procedure:

The standard solution of losartan potassium (B) was suitably diluted with 6.8 pH phosphate buffer to obtain a series of standard solution containing 8, 12, 16, 20, 24 µg of losartan potassium per ml. The absorbance of the solutions was measured at 240 nm using UV visible spectrophotometer systronics. Phosphate buffer was used as a blank.

c) Formulation of Tablets:

The tablets were prepared as per formulae given in table 1, 2 and 3 by wet granulation technique. HPMC K05 and lactose were weighed and triturated by geometric mixing technique. Binder like 30% sucrose solution was used in the formulation and the granules are formed. Obtained granules were passed through sieve no 10. The granules were dried at 40^0c for one hour and they are again passed through sieve no 10 for equal size of granules. These granules are lubricated using talc and magnesium stearate and then tablets were punched using Losartan Potassium conventional tablet as core.

Table 1. Formulae of different granules

S.NO	INGREDIENTS	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11
1	Lactose (g)	-	2.5	4	6	5	8	10	10	10	10	10
2	HPMC K05(g)	2	2.5	2	2	1	2	1	0.5	-	0.75	1.5
3	30% Sucrose solution(ml)	-	3	3.6	4.3	2	5	3.8	2.6	2	2.8	4
4	Distilled water(ml	1.8	-	-	-	-	-	-	-	-	-	-
5	Talc (mg)	50	150	150	200	150	250	275	262.5	250	268.75	287.5
6	Magnesium stereate (mg)	50	150	150	200	150	250	275	262.5	250	268.75	287.5
7	Sieve No	10	10	10	10	10	10	10	10.	10	10	10

Table 2. Formulae of different tablets

S. NO	INGREDIENTS	G1 F0	G2 F1	G2 F2	G2 F3	G2 F4	G3 F5	G4 F6	G4 F7	G5 F8	G5 F9	G6 F10	G6 F11	G6 F12
1	HPMC-Lactose granules(mg)	-	200	300	400	500	300	300	350	350	400	400	450	425
2	HPMC granules	200	-	-	-	-	-	-	-	-	-	-	-	-
3	Losartan potassium tablet	1	1	1	1	1	1	1	1	1	1	1	1	1
4	HPMC-Lactose granules(mg)	-	200	300	400	500	300	300	350	350	400	400	450	425
5	HPMC granules	200	-	-	-	-	-	-	-	-	-	-	-	-
6	Rotations	-	11	9	8	7	11.5	10.5	9	9	8	8.5	7.5	8

Table 3. Formulae of different tablets

S. NO	INGREDIENTS	G8 F13	G8 F14	G8 F15	G7 F16	G7 F17	G7 F18	G10 F19	G10 F20	G10 F21	G11 F22	G11 F23
1	HPMC-Lactose granules(mg)	300	350	400	300	350	400	300	350	400	350	350
2	HPMC granules	-	-	-	-	-	-	-	-	-	-	-

3	Losartan potassium tablet	1	1	1	1	1	1	1	1	1	1	1
4	HPMC-Lactose granules(mg)	300	350	400	300	350	400	300	350	400	350	350
5	HPMC granules	-	-	-	-	-	-	-	-	-	-	-
7	Rotations	10	9	8	10	9	8	10	9	8	9	9

Dissolution rate studies for Losartan potassium:

The dissolution rate testing of different Losartan potassium formulations (table2 and 3) was studied using USP XXII dissolution rate testing apparatus, (basket type). The basket was rotated at a speed of 50 rpm and the dissolution fluid (900 ml of 0.1N HCl (for first 2 hours), 6.8 pH phosphate buffer) was maintained at a temperature of 37.50 ± 0.5^0c. At specific time intervals a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for Losartan potassium content by measuring the absorbance at 240 nm using U.V Spectrophotometer. The percent of Losartan potassium dissolved at various time intervals was calculated and plotted against time.

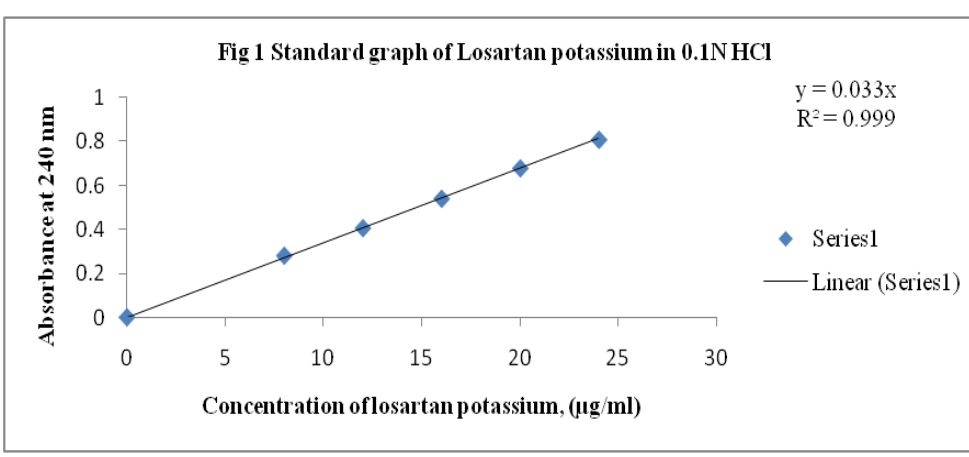
IV. Results and discussion

a) Standard graph of Losartan Potassium in 0.1N HCl:

The absorbance of losartan potassium standard solutions is given in table 4. The corresponding graph was used for knowing the concentration of unknown solutions.

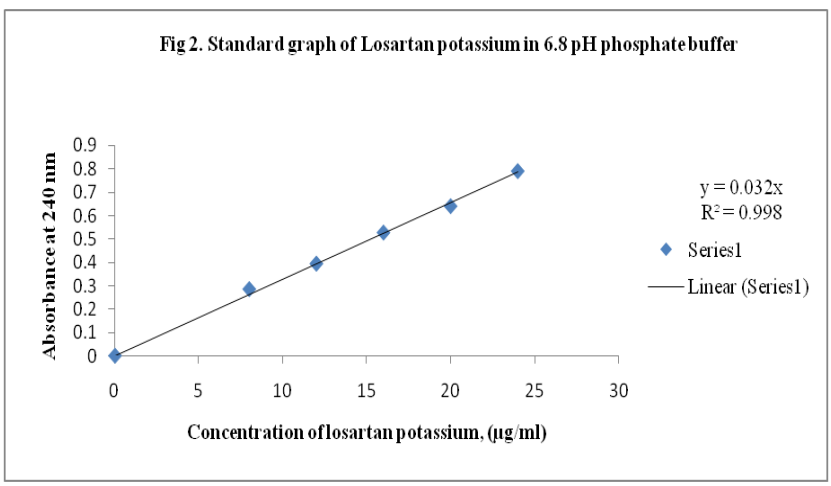
Table 4. Absorbance of losartan potassium standard solutions in 0.1N HCl

S. NO	Concentration, (µg/ml)	Absorbance at 240 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	**8**	0.277	0.273	0.294	0.281	0.011
2	**12**	0.415	0.405	0.401	0.407	0.0072
3	**16**	0.545	0.538	0.542	0.541	0.0035
4	**20**	0.676	0.647	0.719	0.680	0.036
5	**24**	0.806	0.816	0.809	0.810	0.0051



b) Standard graph of Losartan Potassium in 6.8 pH phosphate buffer: The absorbance of losartan potassium standard solutions is given in table 5. The corresponding graph was used for knowing the concentration of unknown solutions.

Table 5 Absorbance of losartan potassium standard solutions in 6.8 pH phosphate buffer						
S. NO	Concentration, (µg/ml)	Absorbance at 240 nm				
		Trail-1	Trail-2	Trail-3	Average	S.D.
1	8	0.290	0.284	0.281	0.285	0.004
2	12	0.415	0.415	0.354	0.394	0.035
3	16	0.554	0.528	0.499	0.527	0.027
4	20	0.661	0.651	0.610	0.640	0.027
5	24	0.812	0.807	0.751	0.790	0.033



c) Pre compression properties of the lubricated granules of the best tablet formulation:

The results of pre compression properties of the granules used in the formulation are given in the below table 6

Table 6. Micrometric properties (Pre compression properties)		
S.NO	Property	Result
1	Angle of repose	29.51^0 (good flow)
2	Tapped density	0.58 g/cc
3	Bulk density	0.49 g/cc
4	Bulkiness	2.04 cc/g
5	Compressibility index	14.3 %
6	Hausner ratio	1.16

d. Post compression properties of best tablet formulations:

The results of post compression properties of the optimized formulation are given in the below table 7.

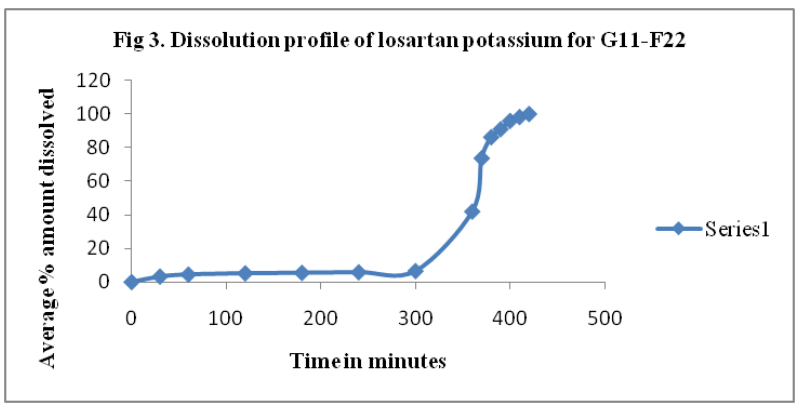
Table 7. Evaluation of post compression parameters		
1	Formulation	G11 -F22
2	Hardness ($Kg/cm^{2)}$	3.75
3	Weight variation (mg) for Losartan potassium (average of 10 tablets)	0.68 ± 5%
5	Friability (%)	0
6	Dissolution time	Breaks after a lag time of 6hrs

e) Dissolution data of Losartan Potassium G11 - F22 formulation:

Dissolution data and corresponding graph of optimized formulation is given in the below table 8 and figure 3.

Table 8. Percent Drug Release of G11 - F22 formulation

S.NO	Time (mins)	Percentage amount dissolved (average of six trails)
1	30	3.28
2	60	4.45
3	120	5.17
4	180	5.45
5	240	5.84
6	300	6.53
7	360	41.95
8	370	73.68
9	380	86.22
10	390	90.98
11	400	95.92
12	410	98.21
13	420	100



V. Conclusion

Granules containing HPMC and lactose in different ratios are used for compression coating. The ratio of lactose and HPMC were changed in a systematic manner so that the final dosage form cracks after a lag time of 6 hrs. 23 different formulae were used for the manufacturing of tablets. The best product that cracks after a lag time of 6 hrs consists of granules containing HPMC and lactose in the ratio1.5:10 (F22). The very same granules can be used for any commercial tablets having a diameter 7 mm and thickness of 3 mm.

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