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Time Delayed Drug Delivery Systems For Diseases Following A Circadian Pattern

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Abstract : *The responsiveness of the body to drugs — their pharmacokinetics has been shown to vary considerably with the circadian cycle. Careful control of the release of drugs in the circadian cycle can be used to increase the therapeutic efficacy and/or decrease the toxicity of a drug. Hypertension has been shown to follow a circadian pattern: both heart rate and blood pressure peak early in the morning. Time-delayed formulations (Pulsatile) are the only way to ensure that the drugs are released into the body at the correct time. These formulations can be used for almost all drug types and for any therapeutic indication. The aim of the present study was to design a time delayed drug delivery system which releases the drug after a lag time of 4/6/8hrs by compression coating. Commercial tablets of Valsartan were compression coated with granules made up of HPMC polymer (K 05 / E 5 LV) 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 in compression.*

Keywords : *Time Delayed, Pulsatile, Chronopharmacokinetics, Compression Coating, HPMC, Circadian Cycle*

I. Introduction

Time delay release systems are required in three main therapeutic areas: cardiovascular, sleep maintenance, and pain / morning stiffness associated with arthritis. These were chosen because they are therapeutic areas with a clear clinical need. It is well known that individuals with rheumatoid arthritis suffer significantly with pain and stiffness upon wakening, severely impacting on their normal daily functions. The pulsatile[3,4] drug delivery system provides an immediate night time release of drug, followed by a seven-hour time delay before pulsatile release of a second dose of the drug. This formulation offers immediate pain relief at nighttime, allowing pain free sleep, and subsequently provides delivery of pain relief prior to waking.

The cardiovascular formulation is designed to target drug delivery before wake-up. Hypertension has been shown to follow a circadian pattern whereby both heart rate and blood pressure peak early in the morning, as well as the commonly occurring a.m. surge. Hence a timed delay release formulation is required for the delivery of anti-hypertensive drugs in the middle of the night, prior to wake-up, when the risk of an adverse cardiovascular event such as a fatal heart attack is greatest. There are various approaches to design timed delay formulations: reservoir devices with dissolving barrier layers / erodible coatings, rupturable pulsatile[8, 9, 10] drug delivery systems, and pulsincap systems.

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 4/6/8hrs by compression coating. Commercial tablets of Valsartan were compression coated with granules made up of HPMC polymer (K 05 / E 5 LV) 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. Methodology

Required quantity of HPMC, lactose which are mentioned in table 1, was weighed and mixed thoroughly to form a homogenous mixture by geometric dilution method. 30 % sucrose solution was prepared and used as binder. The binder was added drop by drop to the above mixture and damp mass was prepared. The damp mass was wet screened using sieve.no-10 and the granules were dried. The dried granules were passed through sieve no-10/20 and lubricated. Talc and Magnesium stearate were added at concentration of 2.5 % based on weight of the granules. The powder was passed through sieve no-100 and lubricated. Required ratios (for e.g.: 325:325, 350:350) of granules were weighed and (Riboflavin model drug) tablet was placed in the middle and the tablets were compressed. A model drug like Riboflavin is used as a model drug which will change the colour of the dissolution fluid upon release of the drug and helps in easy identification of drug release from the dosage form. Optimised formulae were tested with inclusion of Valsartan tablet in the place of

Riboflavin model drug as the core tablet[11, 12] and tested. Formulae for the granules and formulations are given in the following tables

Table 1: Formulae of different granules G1-G10

Ingredients	**G1**	**G2 (1:1)**	**G3 (1:2)**	**G4 (1:3)**	**G5 (1:5)**	**G6 (1:5)**	**G7 (1:4)**	**G8 (1:4)**	**G9 (1:10)**	**G10 0.5:10**
Lactose	-	2.5g	4g	6g	5g	10g	8g	4g	10gm	10gm
HPMC K05	2g	2.5g	2g	2g	1g	2g	2g	1g	1gm	0.5gm
30% sucrose solution	-	3ml	3.6ml	4.3ml	2ml	5.2ml	5ml	2ml	4ml	2.6ml
Talc	50mg	150mg	150mg	200mg	150mg	300mg	250mg	75mg	275mg	262mg
Magnesium stearate	50mg	150mg	150mg	200mg	150mg	300mg	250mg	75mg	275mg	262mg
HPMC E5LV	-	-	-	-	-	-	-	-	-	-
Water	1.8ml	-	-	-	-	-	-	-	-	-

Table 2: Formulae of different granules G11-G19

Ingredients	**G11 0:10**	**G12 0.75:10**	**G13 1.5:10**	**G14 1.75:10**	**G15 1.25:10**	**G16**	**G17**	**G18**	**G19**
Lactose	10gm	10gm	10gm	10gm	10gm	5gm	10g	-	5gm
HPMC K05	-	0.75gm	1.5gm	1.75gm	1.25gm	1gm	1.5gm	5gm	5gm
30% sucrose solution	2ml	2.8ml	4ml	4.5ml	2.6ml	4.4ml	-	-	-
Talc	250mg	268.75mg	287.5mg	294.5mg	280mg	250mg	2.5%	2.5%	2.5%
Magnesium stearate	250mg	268.75mg	287.5mg	294.5mg	280mg	250mg	2.5%	-	-
HPMC E5LV	-	-	-	-	-	4gm	-	-	-
Water	-	-	-	-	-	-	-	-	-
15% HPMC E5LV solution	-	-	-	-	-	-	3ml	-	-

Table 3: Formulae of different granules G20-G25

Ingredients	**G20**	**G21**	**G22**	**G23**	**G24**	**G25**
Lactose	1gm	500mg	150mg	200mg	200mg	-
HPMC K05	5gm	500mg	50mg	50mg	30mg	-
30% sucrose solution	-	-	-	-	-	-
Talc	2.5%	-	-	-	-	2.5%
Magnesium stearate	-	-	-	-	-	-
HPMC E5LV	-	5gm	400mg	350mg	370mg	10gm

Table 4: Formulae of different tablets F1-F9

Tablet	**F1 (G1)**	**F2 (G2)**	**F3 (G2)**	**F4 (G2)**	**F5 (G2)**	**F6 (G3)**	**F7 (G4)**	**F8 (G4)**	**F9 (G5)**
HPMC granules	200mg	-	-	-	-	-	-	-	-
HPMC-lactose granules	-	200mg	300mg	400mg	500mg	300mg	300mg	350mg	350mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1	1
HPMC granules	200mg	-	-	-	-	-	-	-	-
HPMC-lactose granules	-	200mg	300mg	400mg	500mg	300mg	300mg	350mg	350mg
Rotations	-	11	9	8	7	11.5	10.5	9	9

Table 5: Formulae of different tablets F10 – F18

Tablet	**F10**(G5)	**F11**(G6)	**F12**(G6)	**F13**(G7)	**F14**(G7)	**F15**(G7)	**F16**(G7)	**F17**(G8)	**F18**(G8)
HPMC granules	-	-	-	-	-	-	-	-	-
HPMC-lactose granules	400mg	400mg	425mg	450mg	300mg	350mg	400mg	300mg	350mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1	1
HPMC granules	-	-	-	-	-	-	-	-	-
HPMC-lactose granules	400mg	400mg	425mg	450mg	300mg	350mg	400mg	300mg	350mg
Rotations	8	8 & half	8	7& half	10	9	8	10	9

Table 6: Formulae of different tablets F19 – F25

Tablet	**F19** (G8)	**F20** (G10)	**F21** (G11)	**F22** (G11)	**F23** (G13)	**F24** (G13)	**F25** (G14)
HPMC granules	-	300mg	350mg	400mg	-	-	-
HPMC-lactose granules	400mg	-	-	-	325mg	350mg	310mg
Riboflavin (model drug)	1	1	1	1	1	1	1
HPMC granules	-	300mg	350mg	400mg	-	-	-
HPMC-lactose granules	400mg	-	-	-	325mg	350mg	310mg
Rotations	8	10	9	8	9	9	9.5

Table 7: Formulae of different tablets F26 – F33

Tablet	**F26 (G18)**	**F27 (G17)**	**F28 (G20)**	**F29 (G21)**	**F30 (G22)**	**F31 (G23)**	**F32 (G24)**	**F33 (G25)**
HPMC powder (K05)	300mg	300mg	-	-	-	-	-	300mg
HPMC-lactose powder	-	-	300mg	300mg	300mg	300mg	300mg	-
Riboflavin (model drug)	1	1	1	1	1	1	1	1
HPMC powder (K05)	300mg	300mg	-	-	-	-	-	300mg
HPMC-lactose powder	-	-	300mg	300mg	300mg	300mg	300mg	-
Rotations	9	-	8.25	9	9.5	9.5	9.75	8

II.I Dissolution rate studies for Valsartan

The dissolution rate testing of different Valsartan tablets were 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, 6.8 pH phosphate buffer) was maintained at a temperature of $37.5^0c \pm 0.5^0c$. 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 Valsartan content by measuring the absorbance at 250 nm using U.V Spectrophotometer. The percent of Valsartan dissolved at various time intervals was calculated and plotted against time.

Table 8: Dissolution Testing Conditions for Valsartan

S.NO	**Type**	**Basket type dissolution rate testing apparatus.**
1	Medium	0.1N HCl for 2 hrs followed by 6.8 pH phosphate buffer (900 ml)
2	Buffer	6.8 pH Phosphate buffer (900 ml).
3	Temperature	37.5 ± 0.5^0 C.
4	Speed	50 rpm.
5	Volume	900 ml.
6	Samples were withdrawn for time intervals	30min and every 1hr until the tablet breaks. After breaking (4/6/8 hrs) of the coat, samples are withdrawn for every 10 minutes.

III. Results And Discussion

III.I Standard graph of Valsartan in 0.1N HCl

The absorbance of Valsartan standard solutions is given in table9. The corresponding graph was used to know the concentration of unknown solutions.

Table 9: Absorbance of Valsartan standard solutions in 0.1N HCl

S. NO	**Concentration, (µg/ml)**	**Absorbance at 250 nm**			
		Trail-1	**Trail-2**	**Trail-3**	**Average**
1	**5**	0.155	0.133	0.160	0.149
2	**10**	0.279	0.277	0.287	0.279
3	**15**	0.409	0.422	0.414	0.415
4	**20**	0.570	0.581	0.559	0.570
5	**25**	0.721	0.735	0.705	0.720
6	**30**	0.881	0.850	0.858	0.863

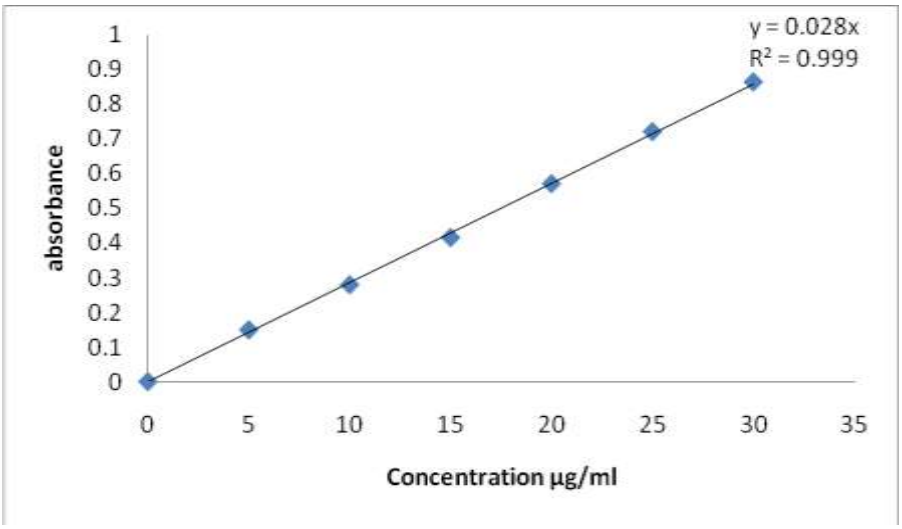

Fig1: Standard graph of valsartan in 0.1N HCl

III.II Standard graph of Valsartan in 6.8 pH phosphate buffer

The absorbance of valsartan standard solutions is given in table 10. The corresponding graph was used to know the concentration of unknown solutions.

Table 10: Absorbance of Valsartan standard solutions in 6.8 pH phosphate buffer

S. NO	Concentration, (µg/ml)	Absorbance at 250 nm			
		Trail-1	Trail-2	Trail-3	Average
	5	0.181	0.137	0.188	0.168
2	10	0.303	0.284	0.321	0.302
3	15	0.488	0.466	0.519	0.491
4	20	0.610	0.591	0.655	0.618
5	25	0.801	0.809	0.805	0.805
6	30	0.948	0.909	0.920	0.925

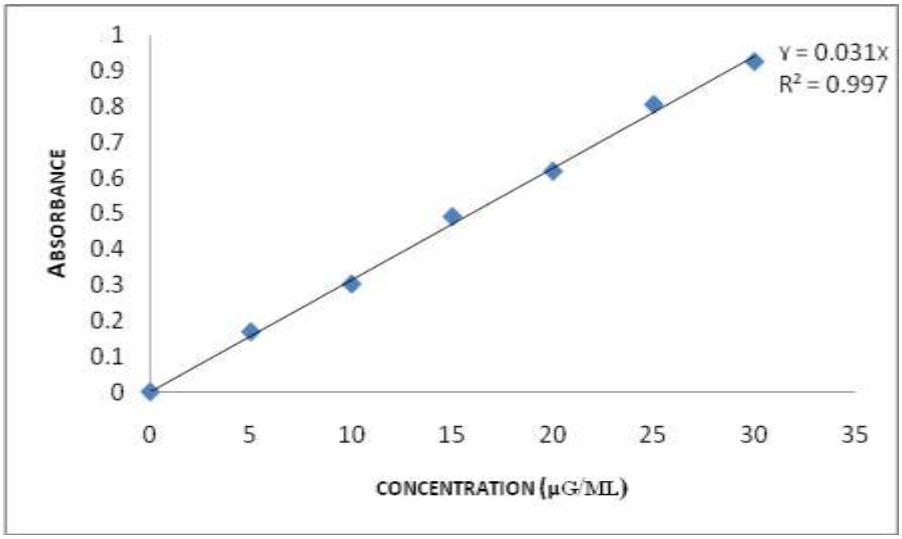

Fig 2: Standard graph of Valsartan in 6.8 pH phosphate buffer

Using the above standard graphs Valsartan from the various formulations prepared using the above mentioned formulae was evaluated and the optimized formulae were selected for the required target time of 4, 6 and 8 hours. Formulae of the optimized formulations were given in the table 11 and 13.

Table 11: Optimized formula for 4 hrs

Tablet	HPMC powder	Valsartan tablet	HPMC powder	Rotations	Break time
F33	300 mg	Valzar-40	300 mg	8	4 hrs

Table 12: Dissolution data of Valsartan F33

S.No	Time in minutes	Avg % Dissolved of 3 trails
1	30 min	1.92
2	60 min	2.22
3	120 min	2.59
4	180 min	2.98
5	240 min (4hr)	33.15
6	245 min	43.06
7	250 min	60.84
8	255 min	68.21
9	260 min	77.64
10	265 min	85.16
11	270min	100

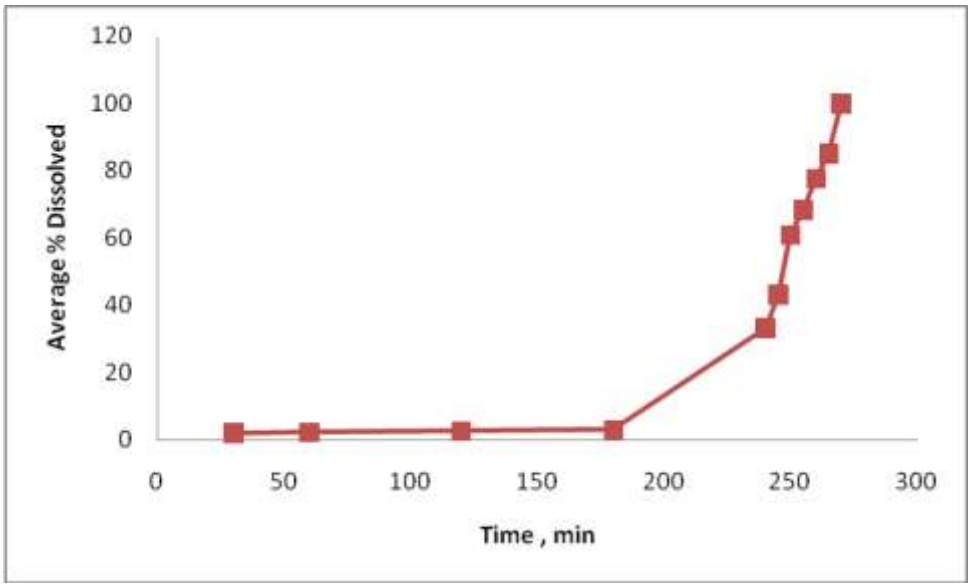

Fig 3: Dissolution profile of F33

Table 13: Optimized Formula for 6 & 8 hours

Tablet	HPMC-lactose granules	Valsartan tablet	HPMC-lactose granules	Rotations	Break time
F24	350mg	Valzar-40	350mg	9	6 hrs
F25	310mg	Valzar-40	310mg	9.5	8hrs

Table 14: Dissolution data of Valsartan F24

S.No	Time in minutes	Avg % Dissolved of 3 trails
1	30 min	1.15
2	60 min	1.98
3	120 min	4.78
4	180 min	3.54
5	240 min	3.06
6	300 min	3.07
7	360 min (6 hr)	4.49
8	390 min	9.58
9	400 min	15.68
10	410 min	20.40
11	420 min	24.75
12	430 min	30.2
13	440 min	74.03
14	450 min	100

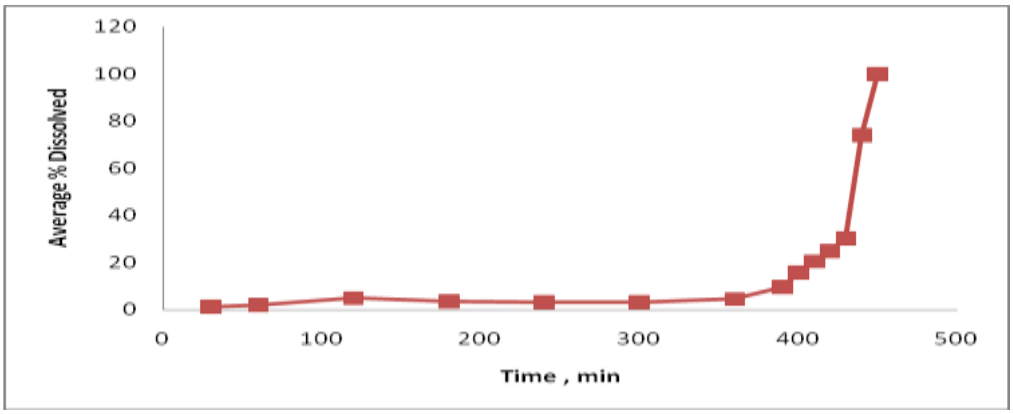

Fig 4: Dissolution profile of F24

Table 15: Dissolution data of F25

S.No	Time in min	Avg % Dissolved of 3 trails
1	60	4.88
2	120	3.96
3	180	5.92
4	240	2.52
5	300	2.65
6	360	4.11
7	420	5.1
8	480(8hr)	11.86
9	490	19.85
10	500	25.59
11	510	29.66
12	520	35.54
13	530	67.47
14	540	100

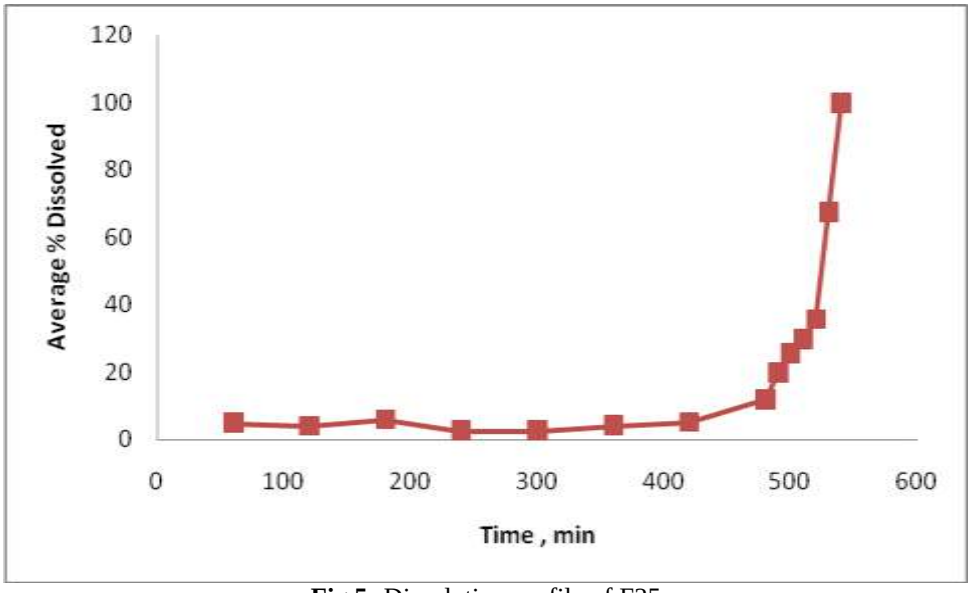

Fig 5: Dissolution profile of F25

III.III Pre-compression and Post- Compression properties of optimized formulae

Table 16 Micrometric properties (1-4) and post Compression properties (5-8) for F33

S.NO	Property	Result
1	Angle of repose	26.28^0 (good flow)
2	Bulk density	0.4 g/cc
3	Compressibility Index	20 %
4	Hausner ratio	1.25
5	Hardness ($Kg/cm^{2)}$	3.6 kg/cm^2

6	Weight variation (mg) for (average of 10 tablets)	0.60 ± 5%
7	Friability (%)	0.23 %
8	Dissolution time	Breaks after a lag time of 4hrs

Table 17 Micrometric properties (1-4) and post Compression properties (5-8) for F24

S.NO	Property	Result
1	Angle of repose	29.51^0 (good flow)
2	Bulk density	0.49 g/cc
3	Compressibility Index	14.3 %
4	Hausner ratio	1.16
5	Hardness ($Kg/cm^{2)}$	3.75 kg/cm^2
6	Weight variation (mg) for (average of 10 tablets)	0.68 ± 5%
7	Friability (%)	0
8	Dissolution time	Breaks after a lag time of 6hrs

Table 18 Micrometric properties (1-4) and post Compression properties (5-8) for F25

S.NO	Property	Result
1	Angle of repose	35.31^0 (good flow)
2	Bulk density	0.505 g/cc
3	Compressibility Index	15.78 %
4	Hausner ratio	1.18
5	Hardness ($Kg/cm^{2)}$	4.1 kg/cm^2
6	Weight variation (mg) for (average of 10 tablets)	0.62 ± 5%
7	Friability (%)	0.42%
8	Dissolution time	Breaks after a lag time of 8hrs

IV. Conclusion

Granules containing HPMC and lactose in different ratios were used for compression coating of Valsartan tablets. The ratio of lactose and HPMC were changed in a systematic manner so that the final dosage forms deliver the drug after a lag time of 4/6/8 hrs. 33 different formulations were made using different granules. These granules were used for preparing time delayed delivery systems of Riboflavin. All the tablets were tested for delivery time by dissolution testing procedure in 0.1N HCl and 6.8 pH phosphate buffers. The best formulae granules were used for compression coating of Valsartan marketed tablets, Valzar-40. The very same granules can be used for any commercial tablets having a diameter 7 mm and thickness of 3 mm. Further In-vivo study in human volunteers can be carried out to confirm the drug release rate.

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