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Design and Evaluation of Time controlled Pulsatile Drug Delivery Systems for Diseases Following a Circadian Pattern

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ABSTRACT

The role of chronotherapeutics in hypertension is based on the recognition that blood pressure does not remain constant throughout the day. Instead, it tends to be higher in the early morning hours and lower in the evening hours. The aim of the present study was to design time controlled outer coat of the tablet which releases the inner core at a lag time of 3/5/7 hrs, as chronopharmaceutical drug delivery system by compression coating. Formulation design involves the coating polymer ratio (1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1 w/w etc) of HPMC E5LV and HPMC E10M or HPMC K100M which were exploited for their cracking 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. Coating materials-powders were evaluated for pre compression parameters like bulk density, angle of repose, compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability, weight variation, drug content and In vitro drug release. The Formulation was optimized on basis of acceptable tablet properties and in vitro drug release. The results indicate that Formulation F21, F22 & F32 for press-coated tablets achieve a burst release after 3/5/7 hrs lag time which is applicable as timed drug delivery system.

Keywords: Chronotherapeutics, Pulsatile drug delivery system, Telmisartan, compression coating

I. INTRODUCTION

Compression coating, or press-coating, has been introduced during the period 1950-1960 to formulate incompatible drugs. This coating became interesting in the last two decades owing to the advantages over liquid coating since the process does not need the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet (Nidhi 2012, Prasanthi 2011). Nowadays, pharmaceutical aspects of compression-coated tablets in dosage form development are: to protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs; to separate incompatible drugs from each other and achieve sustained release; and to modify drug release pattern for the diseases following circadian pattern (Bi Botti 2004, Nitin 2004). However, some drawbacks of compression coating technique include the requirement of reliable and reproducible central positioning of the core tablet within the compression-coated tablet, the need for a multiple-step process or a special tableting machine. A compression-coated tablet consists of a core tablet which is coated by compression with a solid barrier. The barrier could contain polymeric material, diluents. Compression coated tablets could be modulated to provide different release patterns depending on the drug distribution and plus with different type of controlling polymer used in core and coat.

II. METHODS AND MATERIAL

Materials used in the study are Telmisartan tablet, lactose, HPMC K 100M, HPMC E10M, HPMC E5LV, sucrose, Starch, Talc, Magnesium stearate, Potassium dihydrogen phosphate, Di sodium hydrogen phosphate.

Equipment used in the study is Elite tablet punching machine, Lab India disso 2000 dissolution apparatus, Pfizer hardness tester, RemiFriabilator, Schimadzu 1 mg sensitive balance, Systronics pH meter.

A. Estimation of Telmisartan using UV Spectroscopy

1) Standard solution in 0.1N Hcl for Telmisartan: 50 mg of Telmisartan was dissolved in 50 ml methanol in a 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 100µg/ml (B). The standard solution of Telmisartan (B) was suitably diluted with 0.1N HCl to obtain a series of standard solution containing 2, 4, 6, 8, 10 & 12 µg of Telmisartan per ml. The absorbance of the solutions was measured at 296 nm using UV visible spectrophotometer systronics. 0.1N HCl was used as a blank.

2) Standard solution in 6.8 pH phosphate buffer for Telmisartan: 50 mg of Telmisartan was dissolved in 50 ml methanol in a 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 100µg/ml (B). The standard solution of Telmisartan (B) was suitably diluted with 6.8 pH phosphate buffer to obtain a series of standard solution containing 2, 4, 6, 8, 10 & 12 µg of Telmisartan per ml. The absorbance of the solutions was measured at 296 nm using UV visible spectrophotometer systronics.6.8 pH Phosphate buffer was used as a blank.

B. Formulation of tablets

1) Method of Preparation of Granules by Wet Granulation Technique: Required quantity of HPMC, lactose were weighed and mixed thoroughly by geometric dilution method. 30 % sucrose solution was prepared, which acts as binder (weigh 3 gm of sucrose and dissolve in 10 ml of water). The binder was added drop by drop and damp mass was prepared. The damp mass was wet screened using sieve.no-10 and granules were dried. The dried granules were passed through sieve no-10 and lubricated by adding Talc and Magnesium stearate by passing through sieve no-100 (2.5 % based on weight of the granules). Then required ratios (for eg: 300:310, 310:320) of granules were weighed and tablet (model drug) is placed in the middle and the pulsatile or time controlled tablet (Amidon 1993, Bodmeier 1996) is compressed.

Table 1. formulae of granules g1 to g7

Ingredients	G1	G2	G3	G4	G5	G6	G7
Lactose	10 g	10 g	10 g	10 g	10 g	10 g	10 g
HPMC E10M	1.5 g	-	-	0.5 g	0.3 g	0.3 g	0.27 g
HPMC K100M	-	0.75 g	0.4 g	-	-	-	-
30% Sucrose solution	3.5 ml	4 ml	3.5 ml	3.8 ml	3 ml	-	-
4% starch solution	-	-	-	-	-	2 ml	-

5% Starch solution	-	-	-	-	-	-	2.5 ml
Talc	0.21 g	0.19 g	0.18 g	0.16 g	0.18 g	0.25 g	0.24 g
Magnesium stearate	0.21 g	0.19 g	0.18 g	0.16 g	0.18 g	0.25 g	0.24 g

TABLE 2. FORMULAE OF GRANULES G8 TO G14

Ingredients	G8	G9	G10	G11	G12	G13	G14
Lactose	10 g	10 g	10 g	8 g	10 g	10 g	10 g
HPMC E10M	0.27 g	0.8 g	1.2 g	1 g	0.8 g	1.3 g	-
HPMC K100M	-	-	-	-	-	-	0.1 g
30% sucrose solution	3 ml	2.5 ml	3 ml	-	-	-	1.2 ml
35% sucrose solution	-	-	-	3.4 ml	-	-	-
0.25% HPMC E10M solution	-	-	-	-	3.5 ml	4 ml	-
Talc	0.26 g	0.22 g	0.20 g	0.21 g	0.22 g	0.26 g	0.25 g
Magnesium stearate	0.26 g	0.22g	0.20 g	0.21 g	0.22 g	0.26 g	0.25 g

TABLE 3. FORMULAE OF DIFFERENT TABLETS F1 TO F8

Ingredients	F1 (G1)	F2 (G2)	F3 (G3)	F4 (G4)	F5 (G5)	F6 (G6)	F7 (G7)	F8 (G8)
HPMC-lactose granules	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1
HPMC-lactose granules	310 mg	310 mg	310 mg	310 mg	310 mg	310 mg	310 mg	310 mg
Rotations	-	11	9	8	7	11.5	10.5	9
Break time	>8 hrs	>8 hrs	6.5 hrs	7.5 hrs	8 hrs	< 1 hr	4 hrs	2 hrs

TABLE 4. FORMULAE OF DIFFERENT TABLETS F9 TO F16

Ingredients	F9 (G9)	F10 (G10)	F11 (G11)	F12 (G12)	F13 (G13)	F14 (G7)	F15 (G2)	F16 (G5)
HPMC-lactose granules	300 mg	300 mg	300 mg	300 mg	300 mg	290 mg	290 mg	300 mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1
HPMC-lactose granules	310 mg	310 mg	310 mg	310 mg	310 mg	300 mg	300 mg	310 mg
Rotations	-	11	9	8	7	11.5	10.5	11
Break time	4 hrs	1 hr 30 min	Tablet was not formed	3 hrs	2 hrs	1.5 hr	2 hrs	6 hrs 20 min

Table 5. Formulae Of Different Tablets F17 To F24

Ingredients	F17 (E10M)	F18 (1:4)	F19(1:3)	F20 (E5LV)	F21 (1:5)	F22 (1:6)	F23 (1:7)	F24 (2:6)
HPMC mixture (E10M:E5LV)	210 mg	220 mg	220 mg	230 mg	220 mg	220 mg	220 mg	220 mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1
HPMC mixture (E10M:E5LV)	220 mg	230 mg	230 mg	240 mg	230 mg	230 mg	230 mg	230 mg
Rotations	11	11	12	12	12	12	11	12
Break time	6 hrs	4 hrs	6 hrs	1.5 hrs	3 hrs	5 hrs	4 hrs	6 hrs

TABLE 6. FORMULAE OF DIFFERENT TABLETS F25 TO F31

Ingredients	F25(2:6)	F26(3:8)	F27(2:9)	F28 (2:7)	F29 (1:1)	F30 (1:2)	F31 (1:3)	F32 (2:1)
HPMC mixture (E10M:E5LV)	220 mg	220 mg	230 mg	230 mg	230 mg	230 mg	230 mg	230 mg
Riboflavin (model drug)	1	1	1	1	1	1	1	1
HPMC mixture (E10M:E5LV)	230 mg	230 mg	240 mg	240 mg	240 mg	240 mg	240 mg	240 mg
Rotations	11	12	12	12	12	12	12	12
Break time	5hr 30 min	6 hrs	4 hrs	5 hrs	>8 hrs	>8 hrs	4 hrs 50 min	7 hrs

TABLE 7. FORMULAE OF DIFFERENT TABLETS F32 TO F39

Ingredients	F33 (1:6)'	F34 (1:4)'	F35 (1:3)'	F36 (1:3)'	F37 (2:3)'	F38 (1:2.5)'	F39 (1:5)'
Mixture of HPMC (K100M:E5LV)	220 mg	220 mg	220 mg	250 mg	220 mg	230 mg	220 mg
Riboflavin (model drug)	1	1	1	1	1	1	1
Mixture of HPMC (K100M:E5LV)	230 mg	230 mg	230 mg	260 mg	230 mg	240 mg	230 mg
Rotations	12	12	12	12	12	12	11
Break time	4 hrs	4 hrs	4 hrs	4 hrs 20 min	>8 hrs	4 hrs 30 min	5 hrs 30 min

TABLE 8.OPTIMIZED FORMULAE

Tablet	HPMC powder(E10M:E5LV)	Telmisartan tablet	HPMC powder(E10M:E5LV)	Rotations	Break time
F21 (1:5)	220 mg	1	230 mg	12	3 hrs
F22 (1:6)	220 mg	1	230 mg	12	5 hrs
F32 2:1)	230 mg	1	240 mg	12	7 hrs

C. **Evaluation of Pre Compression properties:**

The powders were evaluated for Angle of repose, Bulk density, Compressibility index, Carr's index, Hausner ratio.

1) Determination of Angle of Repose:A two side open ended cylinder was selected and placed it on a graph paper and the powder was poured in to the cylinder. The cylinder was gradually moved up and the powder formed a heap on the graph sheet. The height and radius of the heap was measured. From the radius and height of the heap, the angle of repose was calculated using the below formula.

$$\text{Angle of Repose } (\Theta) = \text{Tan}^{-1} (H/R)$$

h = height of a pile, r = radius of pile base

2) Determination of Bulk Density: 40 g of the powder was accurately weighed and filled in a 100ml graduated cylinder and the powder was tapped three times. Bulk density (BD) was calculated in g/ml by the formula.

$$(BD) = M/Vo$$

M = mass of powder taken, Vo = unsettled apparent volume

3) Determination of %Compressibility Index: 40 g of the powder was taken in a 100 ml measuring cylinder and was subjected for hundred tapings and the volume was noted. Compressibility Index was calculated using following equation:

$$CI\ (\%) = [(Dt - Db)/Dt] \times 100$$

Dt = tapped density, Db = bulk density

4) Determination of Hausner's Ratio: The Hausner ratio indicates the flow ability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula:

Hausner Ratio = Dt/Db

Dt = tapped density, Db = bulk density.

D. Evaluation of Post Compression Properties:

1) Hardness: The hardness of the three prepared tablets was measured by using the Pfizer tablet hardness tester and the hardness of the each tablet was recorded.

2) Weight variation: Weight variation was calculated as per method descried in I.P. Twenty tablets were selected at random and their average weight was determined using an electronic balance. The tablets were weighed individually and compared with average weight.

3) Drug content: The tablet was taken in a mortar and pestle; it was made into powder and transferred in to a 100 ml volumetric flask. 10ml methanol was added and made up to the mark with Distilled water solution. This solution was suitably diluted for 100 dilutions with Distilled water solution and was assayed at 296nm for Telmisartan.

4) Disintegration test: 6 tablets were placed into a testing basket assembly, which is introduced into a special holder and placed into a water bath. The water inside the water bath is heated to 30-45°c. The disintegration baskets are moved smoothly up and down for 28-32 stokes per minute and for a distance of 55mm. The samples are disintegrated if no solid rest is left within the basket.

5) Dissolution rate studies for Telmisartan: The dissolution rate testing of different Telmisartan 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, 6.8 pH phosphate buffers) was maintained at a temperature of 37.50 ± 0.5^{0}c. At specific time intervals a 5 ml aliquot of dissolved medium was withdrawn and was replaced with fresh medium of equal quantity of dissolution medium. The samples were suitably diluted with dissolution medium and assayed for Telmisartan content by measuring the absorbance at 296 nm using UV Spectrophotometer. The percent of Temisartan dissolved at various time intervals was calculated and plotted against time. 0.1 N Hcl was used as dissolution fluid for first two hours followed by 6.8ph phosphate buffer. Samples were withdrawn for every one hour until the tablet beaks. After breaking of the coat, samples were withdrawn at an interval of every 5minutes.

III. RESULTS AND DISCUSSION

A. **Standard graph of Telmisartan in 0.1N HCl:** The absorbance of Telmisartan standard solutions is given in table 9. The corresponding graph was used for knowing the concentration of unknown solutions.

TABLE 9.ESTIMATION OF TELMISARTAN IN 0.1N HCL

S. No	Concentration (µg/ml)	Absorbance at 296nm
1	0	0
2	2	0.141
3	4	0.223
4	6	0.317
5	8	0.413
6	10	0.509
7	12	0.617

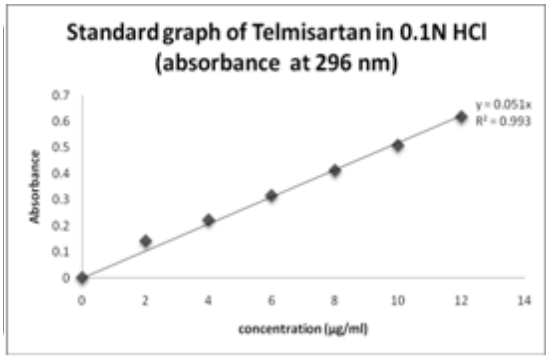

Figure 1. Standard graph of Telmisartan in 0.1N HCl

B. Standard graph of Telmisartan in 6.8pH phosphate buffer:

The absorbance of Telmisartan standard solutions is given in table 10. The corresponding graph was used for knowing the concentration of unknown solutions.

TABLE 10.ESTIMATION OF TELMISARTAN IN 6.8PH PHOSPHATE BUFFER

S.No	Concentration (µg/Ml)	Absorbance At 296nm
1	0	0
2	2	0.119
3	4	0.219
4	6	0.316
5	8	0.407
6	10	0.498
7	12	0.586

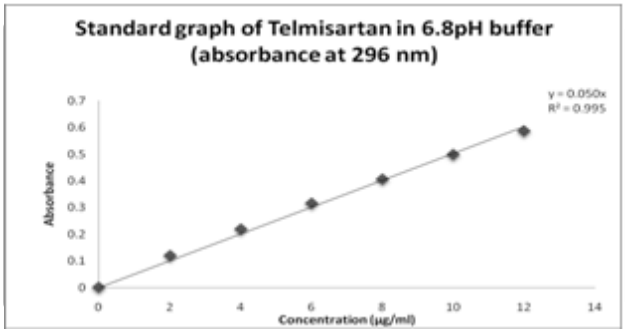

Figure 2. Standard graph of Telmisartan in 6.8 pH phosphate buffer

C. Pre compression properties of the powders of the best tablet formulations

TABLE 11.MICROMERITIC PROPERTIES FOR F21

S.No	Property	Result
1	Angle of repose	17.5º(good flow)
2	Bulk density	0.4 g/cc
3	Compressibility Index	20 %
4	Hausner ratio	1.25

TABLE 12.MICROMERITIC PROPERTIES FOR F22

S.No	Property	Result
1	Angle of repose	17º(good flow)
2	Bulk density	0.49 g/cc
3	Compressibility Index	14.3 %
4	Hausner ratio	1.16

TABLE 13.MICROMERITIC PROPERTIES FOR F32

S.No	Parameter	Result
1	Hardness ($Kg/cm^{2)}$	4.1 kg/cm^2
2	Weight variation (mg) for (average of 10 tablets)	0.62 ± 5%
3	Friability (%)	0.42 %
4	Dissolution time	Breaks after a lag time of 7 hrs

D. Post compression properties of best tablet formulations

TABLE 14.POST COMPRESSION PARAMETERS OF F21

S.No	Parameter	Result
1	Hardness (Kg/cm2)	3.6 kg/cm2
2	Weight variation (mg) for (average of 10 tablets)	0.60 ± 5%
3	Friability (%)	0.23 %
4	Dissolution time	Breaks after a lag time of 3 hrs

TABLE 15.POST COMPRESSION PARAMETERS OF F22

S.No	Parameter	Result
1	Hardness (Kg/cm2)	3.75 kg/cm2
2	Weight variation (mg) for (average of 10 tablets)	0.68 ± 5%
3	Friability (%)	0
4	Dissolution time	Breaks after a lag time of 5 hrs

TABLE 16.POST COMPRESSION PARAMETERS OF F32

S.No	Property	Result
1	Angle of repose	17.89 °(good flow)
2	Bulk density	0.505 g/cc
3	Compressibility Index	15.78 %
4	Hausner ratio	1.18

E. Dissolution data of optimized formulations

1) Dissolution data of F21: Release of Telmisartan drug started after a lag time of 3 hours.

TABLE 17.DISSOLUTION DATA OF F21

S.no	Time	% of drug dissolved
1	0 hr	0
2	1 hr	0
3	2 hrs	0
4	3 hrs	17
5	3 hrs 15 min	21
6	3 hrs 20 min	31
7	3 hrs 25 min	49
8	3 hrs 30 min	64
9	3 hrs 35 min	70
10	3 hrs 40 min	73
11	3 hrs 45 min	75
12	3 hrs 50 min	78
13	3 hrs 55 min	84
14	4 hrs	91
15	4 hrs 5 min	95
16	4 hrs 10 min	100

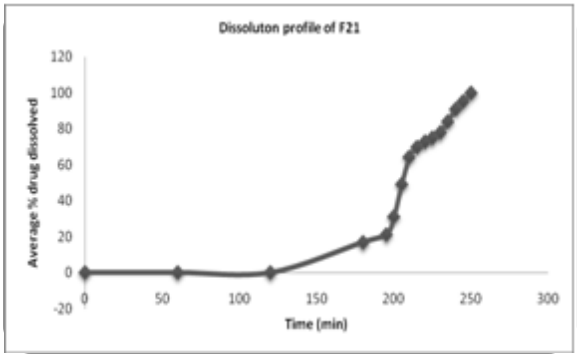

Figure 3. Dissolution profile of F21

2) Dissolution data of F22: Release of Telmisartan drug started after a lag time of 5 hours.

TABLE 18.DISSOLUTION DATA OF F22

S.no	Time	% of drug dissolved
1	0 hrs	0
2	1 hr	0
3	2 hrs	0
4	3 hrs	0
5	4 hrs	0
6	4 hrs 45 min	14
7	4 hrs 50 min	16
8	4 hrs 55 min	17
9	5 hrs	22
10	5 hrs 5 min	24
11	5 hrs 10 min	26
12	5 hrs 15 min	28
13	5 hrs 20 min	35
14	5 hrs 25 min	59
15	5 hrs 30 min	68
16	5 hrs 35 min	75
17	5 hrs 40 min	90
18	5 hrs 45 min	100

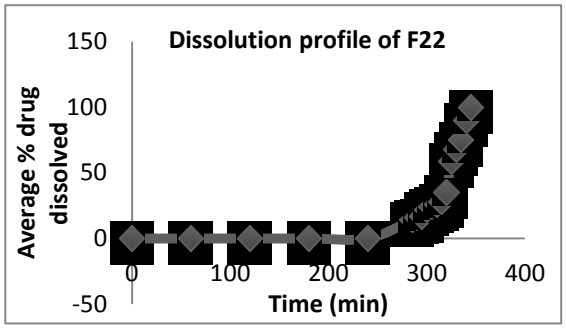

Figure 4. Dissolution profile of F22

3) Dissolution data of F32: Release of Telmisartan drug started after a lag time of 7 hours.

TABLE 19.DISSOLUTION DATA OF F32

S.no	Time	% of drug dissolved
1	0 hrs	0
2	1 hr	0
3	2 hrs	0
4	3 hrs	0
5	4 hrs	0
6	5 hrs	0
7	6 hrs	0
8	6 hr 55 min	19.35
9	7 hrs	22.8
10	7 hrs 5 min	28.6
11	7 hrs 10 min	32.7
12	7 hrs 15 min	36.5
13	7 hrs 20 min	38.6
14	7 hrs 25 min	41
15	7 hrs 30 min	43
16	7 hrs 35 min	46.5
17	7 hrs 40 min	53
18	7 hrs 45 min	53.2
19	7 hrs 50 min	54
20	7 hrs 55 min	96.8
21	8 hrs	100

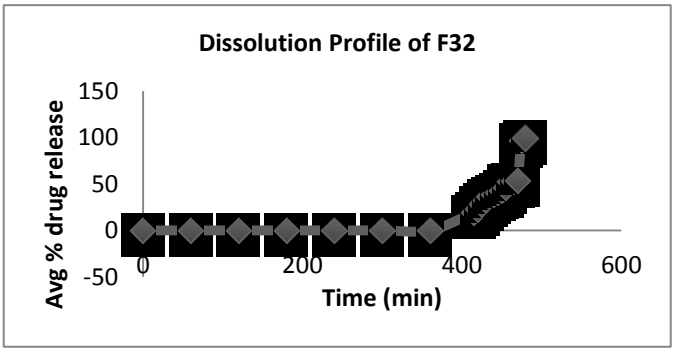

Figure 5. Dissolution profile of F32

IV. CONCLUSION

Mixture of polymers containing different grades of HPMC in different ratios are used for compression coating. The ratio of different grades of HPMC were changed in a systematic manner so that the final dosage forms cracks after a lag time of 3/5/7 hrs. All together 39 formulations were prepared and these mixtures were used for preparing timed delivery systems of Riboflavin. All the tablets were tested for delay in release by dissolution testing procedure in 0.1N HCl and 6.8 pH phosphate buffers. The best composition was used for compression coating of Telmisartan tablets. Compression coated tablets that release the drug after 3/5/7 hrs and release the drug completely from the inner core of the tablet within 1hr were successfully developed.F21-The best product that releases the drug after a lag time of 3 hrs consists

of HPMC E5LV and HPMC E10M in the ratio of 5:1.F22-The best product that releases the drug after a lag time of 5 hrs consists of HPMC E5LV and HPMC E10M in the ratio of 6:1.F32-The best product that releases the drug after a lag time of 7 hrs consists of HPMC E5LV and HPMC E10M in the ratio of 1:2. These mixtures were used for Telmisartan (Telsartan 20) marketed tablets.

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