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FORMULATION AND DEVELOPMENT OF TELMISARTAN TABLETS EMPLOYING FACTORIAL DESIGNS AND STABILITY

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Abstract:

The individual main effect and combined effect of commonly used β Cyclodextrin, Binders, disintegrants on the dissolution rate of telmisartan tablets were studied in 2^3 factorial designs employing selected combinations of 3 factors (β Cyclodextrin, Binders, disintegrants) of eight formulations of telmisartan tablets were prepared and evaluated All the telmisartan tablets were prepared good quality with regard to drug content, hardness, friability and disintegration time to fulfill official (IP) specifications of uncoated tablets. Many variations were observed in all the dissolution parameters of tablets prepared due to formulation variables. The ANOVA of dissolution rate (K_1) indicates the individual main effect and combined effect of β Cyclodextrin, Binders, disintegrants on the dissolution rate constant (K_1) are significant ($P < 0.05$). The ANOVA of dissolution efficiency (DE_{30}) indicates that individual main effect and combined effect of β Cyclodextrin, Binders, disintegrants on the dissolution efficiency (DE_{30}) are significant ($P < 0.05$). Telmisartan tablets formulations F_{abc} formulated employing 1:2 ratio of β Cyclodextrin (Factor A) and Gelatin (2%) as a Binder (Factor B) and Primogel(5%) as Disintegrant (Factor C) gave highest dissolution rate of Telmisartan 97.5% in 60 min. The increasing order of dissolution rate observed with various formulations was $F_{abc} > F_{bc} > F_c > F_{ac} > F_{ab} > F_b > F_a > F_1$. The optimize telmisartan tablets (Fabc) formulated employing1:2 ratio of β Cyclodextrin, Gelatin (2%) and Primogel(5%) are compare to the marketed product (mytel 80). The Differential factor (f_1) and similarity factor (f_2) indicate identical/similar dissolution profile comparable to marketed product (mytel80).The stability studies were conducted as per ICH guidelines.

Keywords: *Factorial Design, ANOVA, Binder, Disintegrant, Stability, βCD.*

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INTRODUCTION:

Telmisartan, a potent widely prescribed antihypertensive drug belongs to class-II under BCS and exhibit low and variable oral bioavailability due to absorption of Telmisartan is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing oral bioavailability. Very poor aqueous solubility of the drug also gives rise to difficulties in the formulation of solid dosage forms and leads to poor and variable dissolution rate and oral bioavailability. In the case of poorly soluble drugs, the formulation variables greatly influence the dissolution rate and bioavailability of drug from tablet. Tablet dosage form contains a number of excipients to serve various purposes. Binder is a critical ingredient in tablet that influences tablet characters.

Complexation[1] with Cyclodextrin has gained acceptance for increases the solubility and dissolution rate of low soluble drugs.

MATERIALS AND METHODS:

Materials

Telmisartan (A gift sample from Dr.Reddy's laboratories, Hyderabad)
LactoseIP (SDFCL Lewis d fine-chem. limited, Mumbai)
β Cyclo dextrin (Balaji drugs private limited)
Gelatin (MERCK Specialties private limited)
Potato starch (MERCK Specialties private limited)
Primogel(Dr.Reddy's laboratories, Hyderabad)
Poly vinyl Pyrrollidone (LOBA chemie PVT.LTD, Mumbai)
Talc (LOBA chemie PVT.LTD, Mumbai)
Magnesium Stearate (Oxford laboratory, Mumbai) I.P were procure from commercial source
All the materials use were of pharmacopeia grades.

Methods

Preparation of Telmisartan tablets

Each tablet containing 80 mg of Telmisartan were prepared by conventional wet granulation method as per formula given in the table.1.The required quantity of telmisartan, Lactose and half the amount of potato starch were mix thoroughly in a motor it in the case of formulation containing Primogel after was added dried granules before compression. The binder solution was added and mix thoroughly to form dough mass the wet mass was passed through sieve number #10, to obtain wet granules were dried at 60^0 C for 1 hour, the dried granules were pass through the sieve number #16 to break the aggregates. The lubricants Talc (2%), Magnesium stearate (2%) the remaining disintegrant (potato starch, Primogel(CCS) pass through sieve number 100 on to dried granules and blended in a closed polythene bags a tablet granules were compressed into tablets on a single punch tablet compression machine using 9mm round and flat punch.

Table1: Formulae of Telmisartan Tablets Prepared Employing as per 2^3 Factorial Designs.

S.no	Name of the ingredients (mg)	Formulations							
		F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
1.	Telmisartan	80	80	80	80	80	80	80	80
2.	Lactose	185	25	180	20	197.5	37.5	192.5	32.5
3.	β Cyclodextrin	_	160	_	160	_	160	_	160
4.	PVP	8	8	-	-	8	8	-	5
5.	Gelatin	_	_	5	5	_	_	5	5
6.	Potato starch	25	25	25	25	_	_	_	_
7.	Primogel	_	_	_	_	12.5	12.5	12.5	12.5
8.	Talc	8	8	8	8	8	8	8	8
9.	Magnesium Stearate	8	8	8	8	8	8	8	8
10	Total (mg)	315	315	315	315	315	315	315	315

Content active Ingrident:
Accurately weighed five tablets and powdered the tablets. The tablet powder is equivalent to 60 mg of Telmisartan was taken into boiling test tubes and extract with 4 into 10ml quantity of methanol. The methanol extracted were collected into 50ml volumetric flask and the volume was made up to 50ml in methanol the solution was subsequently diluted with phosphate buffer pH 6.8 and essay for drug content by UV-spectrophotometric method.

Hardness:
Hardness of the tablet was tested using MONSANTO hardness tester.

Friability:
Friability of the tablet was tested using ROCHY friabilator.

Disintegration time:
Disintegration time was determined in LABINDIA tablet disintegration test apparatus using distilled water as fluid.

Dissolution rate studies:
The dissolution rate of telmisartan from the tablets were studied in 900 ml of phosphate buffer of pH 6.8 using DS 8000 (LABINDIA) eight station dissolution test apparatus with the paddle stirrer at 50 rpm, a temperature of 37 $\pm 0.5^0$C was maintained throughout the study the tablets contain 80mg of telmisartan were used in the tests. The sample of the dissolution media 5ml was withdrawn through a filter (0.45 microns) at different intervals of time suitable in diluted and assay for Telmisartan at 227 nm the sample of dissolution fluid withdrawn at each time was replaced with fresh fluid each dissolution study were replicated four times (n=4).

Analysis of data:
The dissolution data were analyzed as per zero order and first order kinetic model. The dissolution efficiency (DE_{30}) [13] and dissolution rate constant (K_1) values analyze as per ANOVA of 2^3 factorial designs [2]-[7].

Stability:
The stability of the optimized tablets of were evaluated as per ICH guidelines for accelerated stability testing. The storage conditions for accelerated testing (as per ICH and WHO) are $40^0 \pm 2^0$ C and 75 ± 5 % RH for solid dosage forms for 6 months. WHO prescribed testing at 0, 1, 2, 3, and 6 months during storage .
In the present study, a storage condition of $40^0 \pm 2^0$ C and 75 ± 5 % RH for 6 months was used for short term accelerated testing. In each case, the tablets were packed in screw capped HDPE bottles and were stored at $40^0 \pm 2^0$ C and 75 % RH for 6 months. After storage for 6 months, the products were tested for drug content and dissolution rate as per the methods described earlier.

RESULTS AND DISCUSSION:

The objective of the research is telmisartan tablet formulation was employed by 2^3 Factorial Design [8]-[12] employing β Cyclodextrin, Binders, Disintegrants are the 3 factors are using this study. The 2 levels of the 3 factors used such as Factor A (β Cyclodextrin are 0%,1:2 ratio drug: β Cyclodextrin), the 2 levels of the Factor B (Binders) are Poly Vinyl Pyrrollidone 3.2%, Gelatin 2% of drug content, the 2 levels of Factor C (Disintegrant) are Potato Starch 10%, Primogel 5% of drug content. Eight Telmisartan tablet formulations employing selected combinations of three factors as per 2^3 Factorial Design were formulated shown in table 1. To evaluate their individual main and combined effect on the dissolution rate of telmisartan tablets. All the prepared granules were shows their precompressional properties shown in table 2. Exhibits excellent to good flow properties.

Table 2: Precompression Properties

S.no	Formulations	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)
1.	F_1	13.47	0.31	0.47	11.59
2.	F_a	14.8	0.42	0.38	8.82
3.	F_b	16.2	0.40	0.39	8.69
4.	F_{ab}	16.8	0.38	0.31	8.82
5.	F_c	17.3	0.39	0.37	11.56
6.	F_{ac}	18.7	0.42	0.40	10.14
7.	F_{bc}	17.9	0.45	0.47	11.54
8.	F_{abc}	18.1	0.41	0.40	11.42

Table 3: Physical characteristics of Telmisartan Tablets Prepared

S.no	Formulations	Drug content (%)	Hardness(kg/cm^2)	Friability (%)	Disintegration time(min)
1.	F_1	98.7	5.0	0.80	4.8
2.	F_a	99.2	5.1	0.71	4.4
3.	F_b	99.1	4.4	0.70	4.5
4.	F_{ab}	98.9	5.1	0.80	3.8
5.	F_c	98.3	5.2	0.75	1.0
6.	F_{ac}	99.3	5.3	0.84	2.3
7.	F_{bc}	98.2	5.2	0.71	2.4
8.	F_{abc}	99.4	5.3	0.81	2.28

All the tablets prepared evaluated for drug content, hardness, friability, disintegration time. Physical characterizations of Telmisartan tablets preparation are given in table 3. The hardness of the tablets was in the range 4.5-5.7kg/cm^2, the weight loss in the friability was less than 0.90% in all the cases. The telmisartan drug content of tablets prepared was within 100±2.5% many variations was observed in the Disintegration the dissolution characteristics of Telmisartan tablet preparation the Disintegration time was in the range 1.0 min-4.8 min the telmisartan tablet formulation F_c disintegrate rapidly with in 1min, all other tablets are the slowly 2.3-4.8min respectively**.** However all Telmisartan tablets prepared were good quality and fulfill the official specifications of uncoated tablets (IP).

The dissolution of telmisartan from the tablets prepared was studied in phosphate buffer 6.8 each dissolution test replicated four times (n=4). The dissolution data of the tablet prepared are given in the table 4. The dissolution data were analyzed as per zero order and first order kinetic model in each model the correlation coefficient value (r) was calculated in all the cases 'r' value in the first order model higher than those in zero order model indicating that the drug release on the tablets followed first order kinetics model. The first order dissolution profile shown in Fig.2. The dissolution parameters of various tablets are summarized in table 5. As many variations were observed in all the dissolution parameters due to formulation variables. To evaluate individual main and combined effect of three factors namely β Cyclodextrin (A), Binder (B), Disintegrant (C) this study was conducted as per 2^3 Factorial Design. The three factors were studied two levels each the total of eight formulations corresponding to eight treatments (Selective factors) as per 2^3 Factorial Study were made and evaluated.

The dissolution parameters such as dissolution rate constant (K_1) and dissolution efficiency [13] (DE_{30}) were subjected to Analysis of Variance (ANOVA) to find out the significance of individual main and combined effect of the three factors involved. The results of ANOVA of dissolution rate constant (K_1) indicated that the individual main effect of the three factors such as Factor A (β Cyclodextrin), Factor B (Binder) and Factor C (Disintegrant) and combined effect of the three factors are significant ($P < 0.05$) due to the Binders, Disintegrants use and inclusion of β Cyclodextrin has significantly influence the dissolution rate of telmisartan tablets. The results of ANOVA of DE_{30} values indicates that the individual main effect of three factors such as Factor A (β Cyclodextrin), Factor B (Binder) and Factor C (Disintegrant) and combined effect of the three factors are significant ($P < 0.05$) thus the Binder, Disintegrant and β Cyclodextrin influence the dissolution efficiency of Telmisartan tablets.

Telmisartan tablets formulations F_{abc} formulated employing β Cyclodextrin (1:2) (Factor A) and Gelatin (2%) as a Binder (Factor B) and Primogel(5%) as Disintegrant (Factor C) gave highest dissolution rate of Telmisartan (97.5% in 60 min) shown in Fig. 1.

Table 4: Dissolution Profile of Telmisartan Tablets Prepared Employing as per 2^3 Factorial Design Formulations (F_1- F_{abc}) (n=4)

Time (min)	Mean Percent drug dissolved (%)							
	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}
0	0	0	0	0	0	0	0	0
10	8.695±1.56	11.05±1.4	20.56±1.1	17.75±1.9	20.98±2.9	22.41±1.2	24.15±0.8	17.53±3.3
20	11.94±1.5	14.23±2.2	24.52±2.4	19.51±2.8	34.19±2.2	35.08±.4.2	35.48±1.9	26.34±1.5
30	14.85±1.8	16.38±1.7	34.09±3.5	25.05±1.9	51.32±1.9	43.59±2.4	46.17±2.7	41.41±1.2
40	18.67±1.4	19.83±1.9	41.90±2.1	33.03±2.3	61.78±2.7	58.54±2.4	59.29±1.6	52.98±1.6
50	20.31±1.3	23.595±2.2	47.22±0.5	48.63±1.9	74.89±3.1	73.1±1.1.	70.58±1.4	70.60±4.1
60	24.70±0.4	29.197±1.0	55.82±3.6	62.94±2.7	90.17±1.3	86.11±2.4	94.11±0.5	97.5±4.4

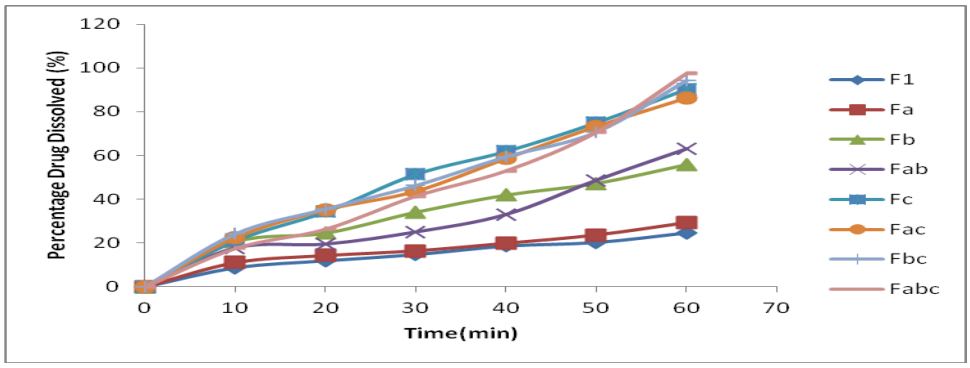

Fig.1: Dissolution Profiles of Telmisartan Tablets Prepared Employing as per 2^3 Factorial Designs (F_1- F_{abc}).

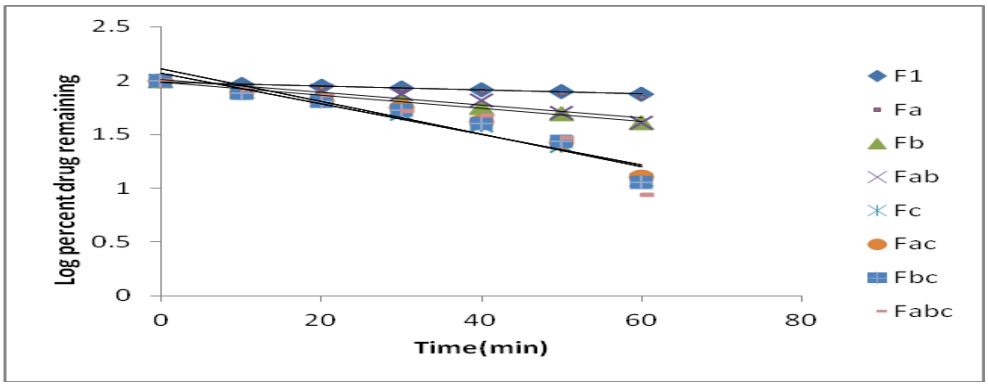

Fig.2: First order Dissolution Profile of Telmisartan Tablets Prepared Employing as per 2^3 Factorial Designs formulations (F_1- F_{abc}).

Table 5: Dissolution Parameters of Telmisartan Tablets

S.no	Formulation	PD_{30} (%)	$K_1 \times 10^3 (min^{-1})$	DE_{30} (%)
1	F_1	17.475	47.028±24.33	9.3425±1.27075
2	F_a	18.8	35.166±9.395	11.1685±1.5040
3	F_b	47.0	51.744±37.65	20.7125±7.4738
4	F_{ab}	34.17	18.367±19.622	17.59125±9.512
5	F_c	53.68	4.3439±2.2283	23.9425±2.4113
6	F_{ac}	45.67	1.81084±0.4244	24.541±5.7871
7	F_{bc}	54	3.370±2.555	26.57±4.0604
8	F_{abc}	44.5	2.1244±0.8880	27.49325±2.006

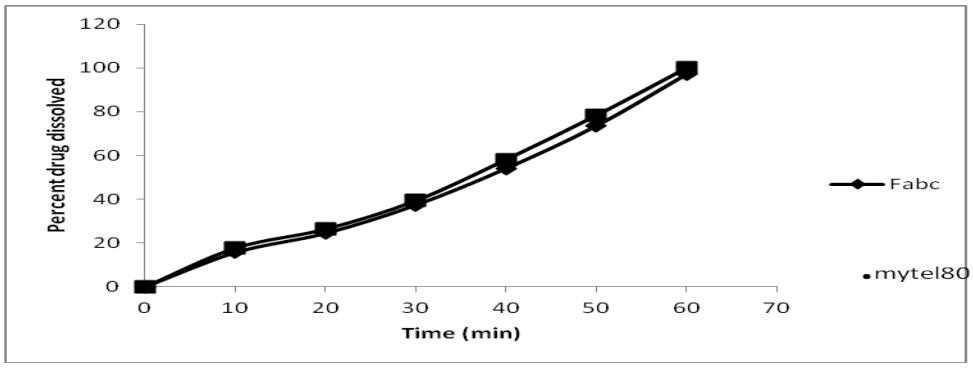

Fig.3: Dissolution Profile of Telmisartan Optimize Formulation (F_{abc}) and Marketed Product (mytel 80)

Table 6: Dissolution Profile of Optimized Formulation (Fabc) Before and After Storage for 6 Months during the Stability Testing

Time (min)	Percent Drug Dissolved ($\bar{x}$ ± s. d.)	
	Before Storage	After 6 Months Storage
0	0.00±0.00	0.00±0.00
5	24.44±1.11	33.25±1.25
10	35.93±1.98	42.80±1.64
15	56.18±2.21	66.65±1.40
20	68.8±1.22	79.20±0.95
30	70.66±1.65	82.50±0.80
40	81.94±1.85	93.25±1.25
50	94.0±2.21	98.52±1.10
60	95.96±1.85	99.25±0.80

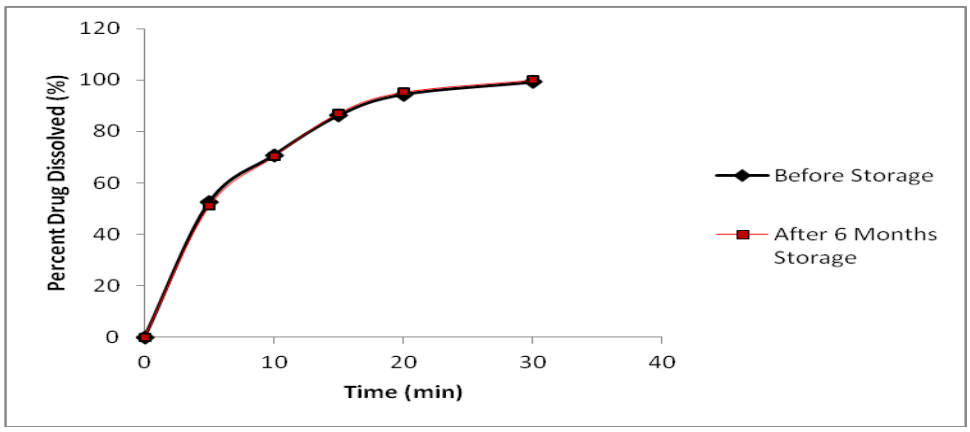

Fig.4: Dissolution Profile of Optimized Formulation (Fabc) Before and After Storage for 6 Months during the Stability Testing

The dissolution profile of optimize formula (F_{abc}) and Marketed product of telmisartan tablets (Valent80) in each case were compare by difference factor (f_1) and similarity factor (f_2). The values of f_1 and f_2 indicated similarity of the dissolution profile of optimize formula (F_{abc}) and Marketed product (mytel 80) of telmisartan tablets to meet comparable dissolution profile with commercial tablets (mytel 80) shown in Fig.3.

No visible changes were observed in the optimized tablets formulated employing after storage for 6 months at $40^0 \pm 2^0$ C and 75 ± 5 % RH. . The fast dissolution characteristics of the formulations tested remained unaltered during the storage period. The dissolution profiles of the products are similar before and after storage. The dissolution profile before and after storage in each case were compared by difference factor (f_1) and similarity factor (f_2). The values of f_1 and f_2 indicated similarity of the dissolution profiles before and after storage in all the cases. Thus, the dissolution profiles of the optimized tablets formulated quite stable during the short term accelerated stability testing shown in table.6 and Fig.4.

CONCLUSION:

1.All the prepared granules were studied for flow properties such as bulk density, true density, compressibility index to achieve excellent to good flow properties.

2.All the telmisartan tablets were prepared good quality with regard to drug content, hardness, friability and disintegration time to fulfill official (IP) specifications of uncoated tablets.

3.The ANOVA of dissolution rate (K_1) indicates the individual main effect and combined effect of β Cyclodextrin, Binders, disintegrants on the dissolution rate constant (K_1) are significant ($P < 0.05$).

4.The ANOVA of dissolution efficiency (DE_{30}) indicates that individual main effect and combined effect of β Cyclodextrin, Binders, disintegrants on the dissolution efficiency (DE_{30}) are significant ($P < 0.05$).

5. Telmisartan tablets formulations F_{abc} formulated employing 1:2 ratio of β Cyclodextrin (Factor A) and Gelatin (2%) as a Binder (Factor B) and Primogel(5%) as Disintegrant (Factor C) gave highest dissolution rate of Telmisartan 97.5% in 60 min.

6.The increasing order of dissolution rate observed with various formulations was $F_{abc} > F_{bc} > F_c > F_{ac} > F_{ab} > F_b > F_a > F_1$.

7. The optimize telmisartan tablets (Fabc) formulated employing1:2 ratio of β Cyclodextrin, Gelatin (2%) and Primogel(5%) are compare to the marketed product (mytel 80).

8. Differential factor (f_1) and similarity factor (f_2) indicate identical/similar dissolution profile comparable to marketed product (mytel 80)

9.No visible changes were observed in the optimized tablets formulated employing after storage for 6 months at $40^0 \pm 2^0$ C and 75 ± 5 % RH.

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