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OPTIMIZATION OF TELMISARTAN TABLET FORMULATION BY 2^3 FACTORIAL DESIGN EMPLOYING βCD, PRIMOJEL AND TWEEN 80

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ABSTRACT: The objective of the present study is optimization of telmisartan tablet formulation employing βCD, Primojel, and Tween 80 by 2^3 factorial design to achieve NLT 85% dissolution in 10 min. Eight telmisartan tablet formulations were prepared using selected combinations of the three factors as per 2^3 factorial design. Telmisartan tablets were prepared by direct compression method and were evaluated. Telmisartan tablet formulations F_b and F_{bc} disintegrated rapidly in 20 and 40 seconds and gave very rapid dissolution of telmisartan, 96.1% and 95.8% in 10 min respectively. The increasing order of dissolution rate (K_1) observed with various formulations was $F_c < F_1 < F_{ac} < F_a < F_{abc} < F_{ab} < F_{bc} < F_b$. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of βCD (X_1) , Primojel (X_2) and Tween 80 (X_3) based on the observed results is $Y = 55.327 + 3.613(X_1) + 35.072(X_2) - 9.182(X_1 X_2) - 3.757(X_3) - 3.317(X_1 X_3) + 2.06(X_2 X_3) + 1.765(X_1 X_2 X_3)$. Based on the above equation, the formulation of optimized telmisartan tablets with NLT 75% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Primojel at 27.84% of drug content, and Tween 80 at 1% of drug content. The optimized telmisartan tablet formulation gave 85.85% dissolution in 10min fulfilling the target dissolution requirement.

INTRODUCTION: About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs pose challenging problems in their pharmaceutical product development process.

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Telmisartan, a widely prescribed anti hypertensive drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development.

Several techniques [1] such as micronisation, cyclodextrin-complexation, use of surfactants, solubilizers and super disintegrants, solid dispersion in water soluble and water dispersible carriers, microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and

bioavailability of poorly soluble BCS class II drugs. Among the various approaches cyclodextrin complexation and use of superdisintegrants such as crosspovidone and sodium starch glycolate (Primojel) are simple industrially useful approaches for enhancing the dissolution rate of poorly soluble drugs in their formulation development.

Surfactants such as SLS, Tween 80 are also used for enhancing the solubility of poorly soluble drugs in formulation development. β-cyclodextrin (βCD), Primojel and Tween 80 were tried alone and in combination as per 2^3 factorial study for enhancing the dissolution rate of telmisartan in its formulation development. Formulation of telmisartan tablets with NLT 85% dissolution in 10 min employing Primojel, βCD and Tween 80 was optimized by 2^3 factorial design.

Optimization [2] of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of pharmacy. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality. In a few studies [3-9] optimization by factorial designs was employed in the formulation development of BCS Class II drugs.

The objective of the present study is optimization of telmisartan tablet formulation employing βCD, Primojel, and Tween 80 by 2^3 factorial design.

Materials: Telmisartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. β-cyclodextrin, Primojel and Tween 80 were gift samples from M/s Natco Pharma Ltd., Hyderabad. Talc and magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods:

Estimation of Telmisartan: An UV Spectrophotometric method based on the measurement of absorbance at 296 nm in phosphate buffer of pH 7.5 was used for the estimation of Telmisartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.3% respectively. No interference by the excipients used in the study was observed.

Formulation of Telmisartan Tablets: For optimization of telmisartan tablets as per 2^3 factorial design the βCD, Primojel and Tween 80 are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:6 ratio of drug: βCD, the two levels of the factor B (Primojel) are 2% and 30% of drug content and the two levels of factor C (Tween 80) are 0 and 2% of drug content. Eight telmisartan tablet formulations employing selected combinations of the three factors *i.e.* βCD, Primojel and Tween 80 as per 2^3 factorial design were formulated and prepared by direct compression method.

Preparation of Telmisartan Tablets: Telmisartan (40mg) tablets were prepared by direct compression method as per the formula given in **Table 1**.

The required quantities of telmisartan, βCD, Primojel and Tween 80 as per the formula in each case were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were then added by passing through mesh no.80 and blended. The blend of ingredients was then compressed directly into tablets using an 8- station RIMEK tablet punching machine employing 9mm or 12 mm round and flat punches.

Evaluation of Tablets: All the telmisartan tablets prepared were evaluated for drug content, hardness, friability, disintegration time and dissolution rate as follows.

TABLE 1: FOMULAE OF TELMISARTAN TABLETS PREPARED EMPLOYING β-CD, PRIMOJEL AND TWEEN 80 AS PER 2^3 FACTORIAL DESIGN

Ingredient (mg/ tablet)	Formulation Code								
	F1	F a	F b	F ab	F c	F ac	F bc	F abc	F opt1
Telmisartan	40	40	40	40	40	40	40	40	40
β-cylodextrin	40	240	40	240	40	240	40	240	140
Primojel	1.6	5.6	24	84	1.6	5.6	24	84	50.2
Tween 80	-	-	-	-	1.6	5.6	1.6	5.6	1.8
Talc	1.6	5.7	2	7.2	1.6	5.8	2.1	7.3	4.6
Magnesium stearate	1.6	5.7	2	7.2	1.6	5.8	2.1	7.3	4.6
Total Weight (mg)	84.8	297	108	378.4	86.4	302.8	109.8	384.2	241.2

F opt 1: Optimised Formulation to achieve NLT 85% Dissolution in 10 Minutes

Hardness: The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability: The friability of the tablets was measured in a Roche friabilator using the formula:

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Drug Content: Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 20 mg of telmisartan was taken into 100 ml volumetric flask, dissolved in phosphate buffer of pH 7.5 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 7.5 and assayed for telmisartan at 296 nm.

Disintegration time: Disintegration time of the tablets was determined using single unit disintegration test apparatus (Make: Paramount) employing water as test fluid.

Dissolution Rate Study: Dissolution rate of telmisartan tablets prepared was studied in phosphate buffer of pH 7.5 (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37 °C ± 1 °C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for telmisartan at 296 nm.

The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times.

Each dissolution experiment was run in triplicate (n=3).

Analysis of Data: The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{20}) values were estimated as suggested by Khan [10]. Dissolution rate (K_1) values were analyzed as per ANOVA of 2^3 factorial experiments.

RESULTS AND DISCUSSION: The objective of the present study is to optimize the telmisartan tablet formulation employing βCD, Primojel and Tween 80 by 2^3 factorial design to achieve NLT 85% dissolution in 10 min. For optimization of telmisartan tablets as per 2^3 factorial design the βCD, Primojel and Tween 80 are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:6 ratio of drug: βCD, the two levels of the factor B (Primojel) are 2% and 30% of drug content and the two levels of factor C (Tween 80) are 0 and 2% of drug content. Eight telmisartan tablet formulations employing selected combinations of the three factors *i.e.* βCD, Primojel, and Tween 80 as per 2^3 factorial design were prepared. The tablets were prepared by direct compression method as per the formulae given in **Table 1** and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics.

The dissolution rate (K_1) values were analysed as per ANOVA of 2^3 factorial design to find out the significance of the individual and combined effects of the three factors involved on the dissolution rate of telmisartan tablets formulated.

The physical parameters of the telmisartan tablets prepared are given in **Table 2**.

TABLE 2: PHYSICAL PROPERTIES OF TELMISARTAN TABLETS PREPARED EMPLOYING βCD, PRIMOJEL AND TWEEN 80 AS PER 2^3 FACTORIAL DESIGN

Formulation Code	Hardness (Kg/sq.cm)	Friability (% wt Loss)	Disintegration Time (Sec)	Drug Content (%)
F 1	4.5	0.78	385	98.2
F a	4.0	0.92	345	99.6
F b	5.0	0.70	20	100.2
F ab	4.5	0.80	185	99.6
F c	5.0	0.85	390	98.4
F ac	4.5	0.75	190	99.2
F bc	4.5	0.80	40	98.9
F abc	5.0	0.90	55	98.8
F opt1	5.0	0.85	25	99.2

The hardness of the tablets was in the range 4.0 - 5.0 kg/cm^2. Weight loss in the friability test was less than 0.92% in all the cases. Telmisartan content of the tablets prepared was within 100 ± 3 %. Much variations were observed in the disintegration and dissolution characteristics of the telmisartan tablets prepared. The disintegration times were in the range 20 to 390 sec. Telmisartan tablet formulations F_b and Fbc disintegrated rapidly with in 20 and 40 sec respectively. However, all the telmisartan tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.

Dissolution rate of telmisartan tablets prepared was studied in phosphate buffer of pH 7.5. The dissolution profiles of the tablets are shown in **Fig. 1** and the dissolution parameters are given in **Table 3**.

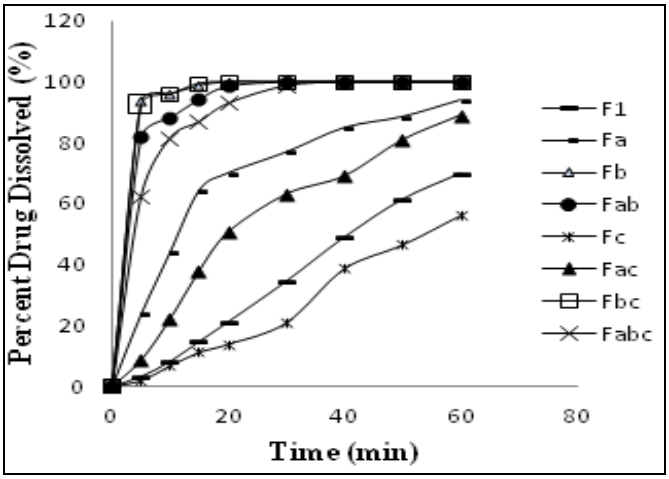

FIG. 1: DISSOLUTION PROFILES OF TELMISARTAN TABLETS PREPARED USING βCD, PRIMOJEL AND TWEEN 80 AS PER 2^3 FACTORIAL DESIGN

TABLE 3: DISSOLUTION PARAMETERS OF TELMISARTAN TABLETS PREPARED EMPLOYING βCD, PRIMOJEL AND TWEEN 80 AS PER 2^3 FACTORIAL DESIGN

Formulation Code	PD_{10} (%) ($\bar{x}$ ± S.D)	T_{50} (min)	DE_{20} (%)	$K_1 \times 10^3$ (min^{-1}) ($\bar{x}$ ± S.D)
F 1	8.18 ± 1.06	104.0	9.18	6.66 ± 1.78
F a	43.95 ± 1.23	11.9	41.65	57.9 ± 2.19
F b	96.1 ± 0.24	2.1	84.64	324.6 ± 6.28
F ab	88.08 ± 0.18	3.2	78.34	212.7 ± 1.55
F c	6.71 ± 0.27	101.9	6.90	6.96 ± 0.30
F ac	22.15 ± 1.33	27.7	23.58	25 ± 1.68
F bc	95.81 ± 0.46	2.1	84.46	318.03± 11.33
F abc	81.58 ± 0.74	4.0	69.40	169.26 ± 4.0
F opt1	85.85 ±1.25	2.8	75.65	204.5± 1.65

Dissolution of telmisartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.962. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) and DE_{20} values of the tablets prepared due to formulation variables. ANOVA (**Table 4)** of K_1 values indicated that the individual and combined effects of the three factors, βCD, Primojel and Tween 80 execept the combined effects of bc (Primojel-Tween 80) and abc (βcd-Primojel-Tween 80) in influencing the dissolution rate of telmisartan tablets are highly significant ($P < 0.01$).

TABLE 4: ANOVA OF DISSOLUTION RATE ($K_1 \times 10^3$, min^{-1}) OF TELMISARTAN TABLETS PREPARED EMPLOYING βCD, PRIMOJEL AND TWEEN 80 AS PER 2^3 FACTORIAL DESIGN

Source of Variation	DF	SS	MSS	F-ratio	Result
Total	23	853966.97	37128.99	-	-
Treatments	7	851248.48	121606.92	715.73	P<0.01
Error	16	2718.49	169.906	-	-
a	1	13723.3	13723.3	80.76	P<0.01
B	1	323013.6	323013.6	1901.13	P<0.01
ab	1	40812.7	40812.7	240.20	P<0.01
c	1	2564.7	2564.7	15.09	P<0.01
ac	1	1846.2	1846.2	10.86	P<0.01
bc	1	113.9	113.9	0.6703	P>0.05
abc	1	5.13	5.13	0.0301	P>0.05

$F_{0.01}(7, 16) = 4.03$; $F_{0.01}(1, 16) = 8.53$; $F_{0.05}(1, 16) = 4.49$

Telmisartan tablet formulations F_b and F_{bc} gave very rapid dissolution of telmisartan than others. These tablets (F_b and Fbc) gave 96.1% and 95.8% in 10min respectively. Higher levels of βCD and lower levels of Primojel gave low dissolution of telmisartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_c < F_1 < F_{ac} < F_a < F_{abc} < F_{ab} < F_{bc} < F_b$.

The polynomial equation describing the relationship between the response, percent drug dissolved in 10 min (Y) and the levels of βCD (X_1) , Primojel (X_2) and Tween 80 (X_3) based on the observed results was found to be $Y = 55.327 + 3.613(X_1) + 35.072(X_2) - 9.182(X_1 X_2) - 3.757(X_3) - 3.317(X_1 X_3) + 2.06(X_2 X_3) + 1.765(X_1 X_2 X_3)$. Based on the above equation, the formulation of optimized telmisartan tablets with NLT 75% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Primojel at 27.84% of drug content, and Tween 80 at 1% of drug content.

To verify telmisartan tablets were formulated employing the optimized levels of βCD, Primojel and Tween 80. The formula of the optimized telmisartan tablets is given in **Table 1**. The optimized telmisartan tablet formulation was prepared by direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in **Table 2** and dissolution parameters are given in **Table 3**. The hardness of the optimized telmisartan tablets was 5.0 kg/sq.cm. Friability (percent weight loss) was less than 0.85%. Disintegration time of the tablets was 25 sec. The optimized telmisartan tablet formulation gave 85.85% dissolution in 10 min fulfilling the target dissolution requirement.

The dissolution results also indicated validity of the optimization technique employed. Hence formulation of telmisartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

CONCLUSIONS:

1. The individual and combined effects of the three factors, βCD, Primojel and Tween 80 execept the combined effects of bc (Primojel-Tween 80) and abc (βcd-Primojel-Tween 80) in influencing the dissolution rate of telmisartan tablets are highly significant ($P < 0.01$).

2. Telmisartan tablet formulations F_b and F_{bc} disintegrated rapidly in 20 and 40 seconds and gave very rapid dissolution of telmisartan, 96.1% and 95.8% in 10 min respectively.

3. The increasing order of dissolution rate (K_1) observed with various formulations was $F_c < F_1 < F_{ac} < F_a < F_{abc} < F_{ab} < F_{bc} < F_b$.

4. The polynomial equation describing the relationship between the response, percent drug dissolved in 10min (Y) and the levels of βCD (X_1), Primojel (X_2) and Tween 80 (X_3) based on the observed results was found to be $Y = 55.327 + 3.613(X_1) + 35.072(X_2) - 9.182(X_1 X_2) - 3.757(X_3) - 3.317(X_1 X_3) + 2.06(X_2 X_3) + 1.765(X_1 X_2 X_3)$.

5. Based on the above equation, the formulation of optimized telmisartan tablets with NLT 75% dissolution in 10 min require βCD at 1:3.5 ratio of drug: βCD, Primojel at 27.84% of drug content, and Tween 80 at 1% of drug content.

6. The optimized telmisartan tablet formulation gave 85.85% dissolution in 10 min fulfilling the target dissolution requirement.

7. Formulation of telmisartan tablets with NLT 85% dissolution in 10 min could be optimized by 2^3 factorial design.

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