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FORMULATION OF TELMISARTAN TABLETS EMPLOYING βCD, CROSPOVIDONE, POLOXAMER - OPTIMIZATION BY 2^3 FACTORIAL DESIGN

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ABSTRACT

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. It needs enhancement in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. In the present study β-cyclodextrin (βCD), crospovidone and Poloxamer188 were tried to enhance the dissolution rate of telmisartan in its tablet formulation development. The objective of the study is to optimize telmisartan tablet formulation by 2^3 factorial design to achieve NLT 85% dissolution in 10 minutes. For optimization of Telmisartan tablets as per 2^3 factorial design the βCD, crospovidone and Poloxamer188 are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD, the two levels of the factor B (crospovidone) are 2% and 30% of drug content and the two levels of factor C (Poloxamer188) are 0% and 2% of drug content. Eight Telmisartan tablet formulations employing selected combinations of the three factors i.e. βCD, crospovidone and Poloxamer188 as per 2^3 factorial design were formulated. The tablets were prepared by direct compression method and were evaluated. Telmisartan tablet formulations F_b and F_{bc} disintegrated rapidly with in 1min and gave very rapid dissolution of telmisartan, above 99% in 10 min.Higher levels of βCD and lower levels of crospovidone gave low dissolution rates of telmisartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{bc} > F_b > F_{ab} > F\ a_{bc} > F_a > F_{ac} > F_1 > F_c$.The polynomial equation describing the relationship between the response i.e. percent drug

dissolved in 10min (Y) and the levels of βCD (X_1) , crospovidone (X_2) and Poloxamer188 (X_3) based on the observed results is **$Y = 59.52 + 4.05(X_1) + 34.9(X_2) – 9.22(X_1\ X_2) – 3.82(X_3) - 3.0(X_1\ X_3) + 2.45(X_2\ X_3) + 1.52\ (X_1\ X_2\ X_3)$.** Based on the above polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD, crospovidone at 26.22% of drug content and Poloxamer188 at 1% of drug content. The optimized telmisartan tablet formulation gave 86.15% dissolution in 10min fulfilling the target dissolution set. Hence optimization by 2^3 factorial design could be used to formulate telmisartan tablets with the desired dissolution i.e., NLT 85% in 10 min.

KEYWORDS: Optimization, Telmisartan tablets, Factorial design, β Cyclodextrin, Crospovidone, Poloxamer188.

INTRODUCTION

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 to derive its maximum therapeutic efficacy. Among various techniques cyclodextrin complexation,[1-4] use of superdisintegrants,[5-6] and surfactants.[7-9] are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from solid dosage forms. In the present study β-cyclodextrin (βCD), crospovidone and Poloxamer 188 were tried to enhance the dissolution rate of telmisartan in its tablet formulation development. The objective of the present study is to optimize telmisartan tablet formulation by 2^3 factorial design to achieve NLT 85% dissolution in 10 minutes.

Optimization,[10] 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. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulation ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to

be optimal. 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.

EXPERIMENTAL

Materials

Telmisartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Crospovidone, Poloxamer188 and β-cyclodextrin 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 0.75% and 1.10% 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, crospovidone (superdisintegrant) and Poloxamer188 (a non ionic surfactant) are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD, the two levels of the factor B (crospovidone) are 2% and 30% of drug content and the two levels of factor C (Poloxamer188) are 0% and 2% of drug content. Eight Telmisartan tablet formulations employing selected combinations of the three factors i.e. βCD, crospovidone and Poloxamer188 as per 2^3 factorial design were formulated and tablets were prepared by direct compression method.

Preparation of Telmisartan Tablets

Telmisartan (40 mg) tablets were prepared by direct compression method as per the formula given in Table1. The required quantities of Telmisartan, βCD, crospovidone and Poloxamer188 as per the formula were blended thoroughly in a closed polyethene bag. Talc and magnesium stearate were the 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 9 mm 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.

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 6.8 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8 and assayed for Telmisartan at 250 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 6.8 (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 250 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_{30}) values were estimated as suggested by Khan.[11] 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, crospovidone and Poloxamer188 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, crospovidone (superdisintegrant) and Poloxamer188 (a non ionic surfactant) are considered as the three factors. The two levels of the factor A (βCD) are 1:1 and 1:5 ratio of drug: βCD, the two levels of the factor B (crospovidone) are 2% and 30% of drug content and the two levels of factor C (Poloxamer188) are 0% and 2% of drug content. Eight Telmisartan tablet formulations employing selected combinations of the three factors i.e. βCD, crospovidone and Poloxamer188 as per 2^3 factorial design were formulated and 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 analyzed 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. The hardness of the tablets was in the range 4.5-5.0 kg/cm^2. Weight loss in the friability test was less than 0.90% 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 sec to 7 min 25 sec.

Telmisartan tablet formulations F_b , F_{bc}, F_{abc} disintegrated rapidly with in 1min. All other tablets disintegrated rather slowly in about 2-7min 25 sec. As βCD level was increased the disintegration time was increased, whereas as crospovidone concentration was increased the disintegration time was reduced. 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 pH 6.8. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3. Dissolution of Telmisartan from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.942. 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_{30} values of the tablets prepared due to formulation variables. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, βCD, crospovidone and Poloxamer188 except F_{bc} (Combined effect of Crospovidone and poloxamer188) and F_{abc} (Combined effect of Crospovidone, βCD and Poloxamer188) in influencing the dissolution rate of telmisartan tablets are highly significant ($P < 0.01$).

Telmisartan tablet formulations F_{bc} and F_b gave very rapid dissolution of Telmisartan than others. These tablets (F_{bc} and F_b) gave above 99% dissolution in 10min. Higher levels of βCD and lower levels of crospovidone gave low dissolution of telmisartan tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{bc} > F_b > F_{ab} > F\ a_{bc} > F_a > F_{ac} > F_1 > F_c$.

Optimization

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of βCD as (X_1) , level of crospovidone as (X_2) and level of Poloxamer188 as (X_3) The polynomial equation describing the relationship between the response, Y and the variables, X_1 X_2 and X_3 based on the observed data was found to be $\mathbf{Y = 59.52 + 4.05(X_1) + 34.9(X_2) – 9.22(X_1\ X_2) – 3.82(X_3) - 3.0(X_1\ X_3) + 2.45(X_2\ X_3) + 1.52\ (X_1\ X_2\ X_3)}$. Based on the above polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3ratio of drug: βCD, crospovidone at 26.22% of drug content and Poloxamer188 at 1% of drug content. To verify telmisartan tablets were formulated employing the optimized levels of βCD,crospovidone, and Poloxamer188. 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 4.5 kg/sq.cm. Friability (percent weight loss) was less than 0.80%.

Disintegration time of the tablets was 30 sec. The optimized telmisartan tablet formulation gave 86.15% dissolution in 10min fulfilling the target dissolution set.

Table 1: Formulae of Telmisartan Tablets Prepared Employing, βCD, Crospovidone and Poloxamer188 as per 2^3 Factorial Design.

Ingredient (mg/tab)	F_1	F_a	F_b	F_{ab}	F_c	F_{ac}	F_{bc}	F_{abc}	FOpt.
Telmisartan	40	40	40	40	40	40	40	40	40
BCD	40	200	40	200	40	200	40	200	120
Crospovidone	0.8	0.8	12	12	0.8	0.8	12	12	10.48
Poloxamer188	-	-	-	-	0.8	0.8	0.8	0.8	0.40
Talc	1.6	4.8	1.8	5.0	1.7	4.8	1.8	5.0	3.68
Magnesium stearate	1.6	4.8	1.8	5.0	1.7	4.8	1.8	5.0	3.68
Total weight (mg)	84	250.4	95.6	262	85	85.6	96.4	262.8	178.24

Table 2: Physical Parameters of Telmisartan Tablets Prepared Employing βCD, Crospovidone and Poloxamer188 as per 2^3 Factorial Design

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (%)
F_1	4.0	0.72	7-25	98.1
F_a	4.5	0.90	5-45	99.4
F_b	4.5	0.60	0-20	99.4
F_{ab}	5.0	0.85	3-05	98.2
F_c	4.0	0.80	7-05	98.4
F_{ac}	4.5	0.85	2-05	99.5
F_{bc}	4.5	0.66	0-40	99.1
F_{abc}	4.5	0.75	0-55	98.4
FOpt	4.5	0.80	0-30	98.9

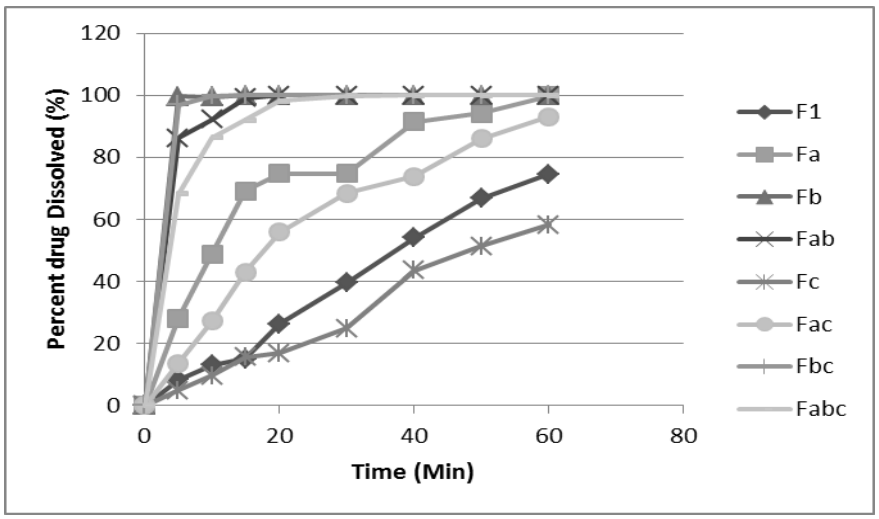

Fig.1: Dissolution Profiles of Telmisartan Tablets Prepared Employing βCD, Crospovidone and Poloxamer188 as per 2^3 Factorial Design

Table 3: Dissolution Parameters of Telmisartan Tablets Prepared Employing βCD, Crospovidone and Poloxamer188 as per 2^3 Factorial Design

Formulation	PD_{10} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K_1 x 10 (min^{-1}) ($\bar{x} \pm s\ d$)
F_1	13.08	37.5	85.0	13.75	0.2072±0.039
F_a	48.73	10.5	37.5	34.73	0.7446±0.579
Fb	99.50	1.5	5.0	74.52	0.3576±0.271
F_{ab}	92.10	2.0	7.5	71.22	0.2985±0.022
F_c	9.63	48.0	90.0	9.86	0.0138±0.000
F_{ac}	27.13	2.0	2.5	28.93	0.0414±0.201
F_{bc}	99.76	17.5	55.0	74.43	0.5365±0.079
F_{abc}	86.46	2.5	12.5	65.35	0.1880±0.007
F_{Opt}	86.15	2.5	12.0	66.86	0.1895±0.065

CONCLUSIONS

1. Telmisartan tablet formulations F_b and F_{bc} disintegrated rapidly with in 1min and gave very rapid dissolution of telmisartan, above 99% in 10 min.
2. Higher levels of βCD and lower levels of crospovidone gave low dissolution rates of telmisartan tablets.
3. The increasing order of dissolution rate (K_1) observed with various formulations was $F_{bc} > F_b > F_{ab} > F\ a_{bc} > F_a > F_{ac} > F_1 > F_c$.
4. The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of βCD (X_1) , crospovidone (X_2) and Poloxamer188 (X_3) based on the observed results is $\mathbf{Y = 59.52 + 4.05(X_1) + 34.9(X_2) – 9.22(X_1\ X_2) – 3.82(X_3) - 3.0(X_1\ X_3) + 2.45(X_2\ X_3) + 1.52\ (X_1\ X_2\ X_3).}$ Based on the above polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing βCD at 1:3 ratio of drug: βCD, crospovidone at 26.22% of drug content and Poloxamer188 at 1% of drug content.
5. The optimized telmisartan tablet formulation gave 86.15% dissolution in 10min fulfilling the target dissolution set.
6. Hence optimization by 2^3 factorial design could be used to formulate telmisartan tablets with the desired dissolution i.e., NLT 85% in 10 min.

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