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FORMULATION OF TELMISARTAN TABLETS EMPLOYING SOLID DISPERSIONS IN MCC PH 102 AND POLOXAMER 188 AS PER 2^2 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 solid dispersion in micro crystalline cellulose (MCC) and Poloxamer 188 were tried alone and in combination 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 2^2 factorial design using solid dispersions in MCC PH102 (a water dispersible excipient) and Poloxamer 188 (surfactant) to achieve NLT 85% dissolution in 10 minutes. For optimization of Telmisartan tablets as per 2^2 factorial design using solid dispersions, the MCC PH102 and Poloxamer188 are considered as the two factors. The two levels of the factor A (MCC) are 1:1 and 1:5 ratio of drug: MCC PH102 and the two levels of the factor B (Poloxamer188) are 1% and 5% of drug content. Four Telmisartan tablet formulations employing selected combinations of the two factors i.e. MCC PH 102 and Poloxamer188 as per 2^2 factorial design were formulated. Solid dispersions of Telmisartan in combined carriers were initially prepared and were used to prepare the tablets. The tablets were prepared by direct compression method and were evaluated. Telmisartan tablet formulations F_a disintegrated rapidly with in 20 sec and gave very rapid dissolution of telmisartan, 100% in 10 min. The increasing order of dissolution rate (K_1) observed with various formulations was $F_a > F_{ab} > F_b > F_{1.}$ The polynomial equation

describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be **$Y = 57.35 + 40.42(X_1) + 2.8(X_2) – 5.03(X_1 X_2)$**. Based on the above polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing MCC at 1: 4.36 ratio of drug: MCC PH102, and Poloxamer 188 at 3% of drug content. The optimized telmisartan tablet formulation gave 85.95% dissolution in 10min fulfilling the target dissolution set. Hence optimization by 2^2 factorial design employing solid dispersions in MCC PH102 and Poloxamer188 could be used to formulate telmisartan tablets with the desired dissolution i.e., NLT 85% in 10 min.

KEYWORDS: Optimization, Telmisartan tablets, Factorial design, Solid dispersion, MCC PH102, Poloxamer 188.

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], solid dispersion and solvent deposition techniques[5,6], use of superdisintegrants[7,8] and surfactants[9-11] are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from solid dosage forms. In solid dispersions the poorly soluble drug is dispersed in an inert water-soluble carrier such as urea, polyethylene glycol, poly vinyl pyrrolidone and surfactants at solid state. In the case of solvent deposited dispersions the drug is deposited in minuscular form on an inert water insoluble excipient such as MCC, silica gel, starch and modified starches at solid state.

In the present study solid dispersion in micro crystalline cellulose (MCC) and Poloxamer 188 were tried alone and in combination 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 2^2 factorial design using solid dispersions in MCC (a water dispersible excipient) and Poloxamer 188 (surfactant) to achieve NLT 85% dissolution in 10 minutes.

Optimization[12] 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. Micro crystalline cellulose (MCC PH102) and Poloxamer 188 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 2^2 factorial design using solid dispersions the MCC PH102 and Poloxamer188 are considered as the two factors. The two levels of the factor A (MCC) are 1:1 and 1:5 ratio of drug: MCC and the two levels of the factor B (Poloxamer188) are 1% and 5% of drug content. Four Telmisartan tablet formulations employing selected combinations of the two factors i.e. MCC and Poloxamer 188 as per 2^2 factorial design were formulated. Solid dispersions of Telmisartan in combined carriers were initially prepared and were used to prepare the tablets by direct compression method.

Preparation of Solid Dispersions in Combined Carriers

Solid dispersions of Telmisartan in MCC and Poloxamer 188 as per 2^2 factorial design were prepared by kneading method. The required quantities of drug and Poloxamer 188 were dissolved in the solvent methanol to get a clear solution in a dry mortar. MCC was added to the drug- surfactant solution in the motor and mixed. The mixture was kneaded for 30 min by continuous trituration. Small volume of the solvent was added to maintain the mixture as thick slurry during kneading process. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50^0C for 1 hour in a hot air oven. The dried product was powdered and passed through mesh no. 100 in each case and was used for the preparation of telmisartan tablets.

Preparation of Telmisartan Tablets

Telmisartan (40 mg) tablets were prepared by direct compression method as per the formula given in Table1. Solid dispersions employing the required quantities of Telmisartan, MCC and Poloxamer 188 as per the formula were initially prepared as described above and were taken 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 9 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 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 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 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_{30}) values were estimated as suggested by Khan.[13] Dissolution rate (K_1) values were analyzed as per ANOVA of 2^2 factorial experiments.

RESULTS AND DISCUSSION

The objective of the present study is to optimize the Telmisartan tablet formulation employing solid dispersions in MCC PH102 and Poloxamer188 by 2^2 factorial design to achieve NLT 85% dissolution in 10 min. For optimization of Telmisartan tablets as per 2^2 factorial design using solid dispersions, the MCC PH102 and Poloxamer188 are considered as the two factors. The two levels of the factor A (MCC) are 1:1 and 1:5 ratio of drug: MCC and the two levels of the factor B (Poloxamer188) are 1% and 5% of drug content. Four Telmisartan tablet formulations employing selected combinations of the two factors i.e. MCC and Poloxamer188 as per 2^2 factorial design were formulated. Solid dispersions of Telmisartan in combined carriers were initially prepared and were used to prepare the tablets by direct compression method.

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 2^2 factorial design to find out the significance of the individual and combined effects of the two 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 4.5-5.5 kg/cm^2. Weight loss in the friability test was less than 0.91% 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 25 sec to 6 min 20 sec. Telmisartan tablet formulations F_a disintegrated rapidly with in 25 sec. All other tablets disintegrated rather slowly in about 3 min to 6 min 20 sec. 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 0.962. 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_{30} values of the tablets prepared due to formulation variables. ANOVA of K_1 values (Table 4) indicated that the individual and combined effects of the two factors, MCC PH102 and Poloxamer188 in influencing the dissolution rate of telmisartan tablets are highly significant ($P < 0.01$).

Telmisartan tablet formulations F_a and F_{ab} gave very rapid dissolution of Telmisartan than others. These tablets gave above 95% dissolution in 10min. The increasing order of dissolution rate (K_1) observed with various formulations was $F_a > F_{ab} > F_b > F_1$.

Optimization

For optimization, percent drug dissolved in 10 min was taken as response (Y) and level of MCC PH102 as (X_1) and level of Poloxamer188 (X_2). The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be $\mathbf{Y = 57.35 + 40.42(X_1) + 2.8(X_2) – 5.03(X_1\ X_2)}$. Based on the above

polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing MCC at 1: 4.36 ratio of drug: MCC PH102, and Poloxamer188 at 3% of drug content. To verify telmisartan tablets were formulated employing the optimized levels of MCC PH102 and Poloxamer 188. 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 0.86%. Disintegration time of the tablets was 20 sec. The optimized telmisartan tablet formulation gave 85.95% dissolution in 10min fulfilling the target dissolution set.

Table 1: Formulae of Telmisartan Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2^2 Factorial Design.

Ingredient (mg/tab)	SDF_1	SDF_a	SDF_b	SDF_{ab}	F_{opt}
Telmisartan	40	40	40	40	40
MCC PH102	40	200	40	200	174.4
Poloxamer188	0.4	0.4	2.0	2.0	1.2
Talc	1.6	4.8	1.6	4.8	4.4
Magnesium stearate	1.6	4.8	1.6	4.8	4.4
Total weight (mg)	83.6	250	85.2	251.6	224.4

Table 2: Physical Parameters of Telmisartan Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2^2 Factorial Design.

Formulation	Hardness (Kg/cm^2)	Friability (% Wt loss)	Disintegration Time (min-sec)	Drug Content (mg/tablet)
SDF_1	5.5	0.83	6-20	98.2
SDF_a	4.5	0.89	0-25	99.9
SDF_b	5.0	0.88	5-20	98.3
SDF_{ab}	4.5	0.91	3-25	98.9
F_{opt}	5.0	0.86	0-20	98.3

Table 3: Dissolution Parameters of Telmisartan Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2^2 Factorial Design.

Formulation	PD_{10} (%)	T_{50} (min)	T_{90} (min)	DE_{30} (%) ($\bar{x} \pm s\ d$)	K_1 X 10 (min^{-1}) ($\bar{x} \pm s\ d$)
SDF_1	9.09	60	>60	12.99±0.04	0.089±0.57
SDF_a	100	0.5	2.5	91.66±0	7.82±0
SDF_b	24.75	17.5	47.5	42.74±0.01	0.272±1.35
SDF_{ab}	95.54	1	7	88.48±0.25	2.586±0.09
F_{opt}	85.95	2.5	11.5	85.29±0.56	1.552±0.36

Table 4: ANOVA of Dissolution Rates (K_1) of Telmisartan Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2^2 Factorial Design.

Source of Variation	DF	SS	MSS	F-ratio
Total	11	11682.04	1062	_
Treatment	3	11681.84	3893.9	152598.5
Error	8	0.204	0.025	_
F_a	1	7567.6	7567.6	296564.2
F_b	1	1913.47	1913.43	74986.35
F_{ab}	1	2200.76	2200.76	86245.02

$F_{0.01(3, 8)} = 7.59$; $F_{0.01(1, 8)} = 11.3$.

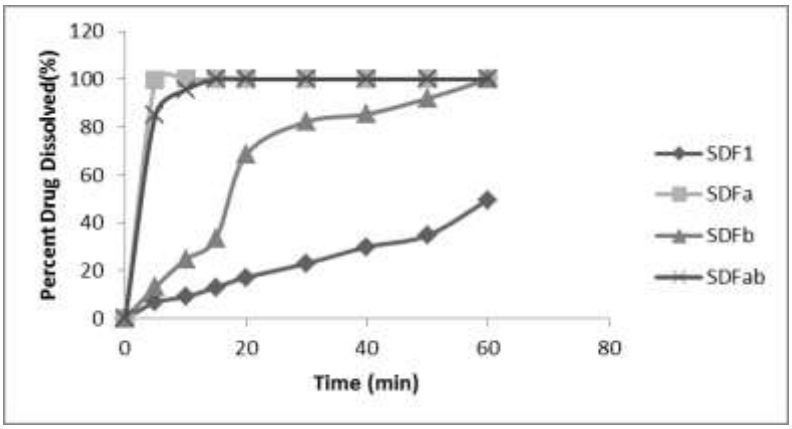

Fig.1: Dissolution Profiles of Telmisartan Tablets Prepared Employing Solid Dispersions in MCC and Poloxamer188 as per 2^2 Factorial Design.

CONCLUSIONS

1. Telmisartan tablet formulations F_a disintegrated rapidly with in 20 sec and gave very rapid dissolution of telmisartan, 100% in 10 min.
2. The increasing order of dissolution rate (K_1) observed with various formulations was $F_a > F_{ab} > F_b > F_{1.}$
3. The polynomial equation describing the relationship between the response, Y and the variables, X_1 and X_2 based on the observed data was found to be **$Y = 57.35 + 40.42(X_1) + 2.8(X_2) - 5.03(X_1 X_2)$**. Based on the above polynomial equation, the optimized telmisartan tablet formulation with NLT 85% dissolution in 10 min could be formulated employing MCC at 1: 4.36 ratio of drug: MCC PH102, and Poloxamer188 at 3% of drug content.
4. The optimized telmisartan tablet formulation gave 85.95% dissolution in 10min fulfilling the target dissolution set.

5. Hence optimization by 2^2 factorial design employing solid dispersions in MCC PH102 and Poloxamer 188 could be used to formulate telmisartan tablets with the desired dissolution i.e., NLT 85% in 10 min.

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