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FACTORIAL STUDIES ON ENHANCEMENT OF DISSOLUTION RATE OF TELMISARTAN TABLETS BY CD COMPLEXATION AND SOLID DISPERSION TECHNIQUES

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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. 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. The objective of the present study is to enhance the dissolution rate of telmisartan tablets by two techniques namely i) Complexation by β CD alone and in combination with Tween 80 and ii) Solid dispersion in Primojel alone and in combination with Tween 80. The individual and combined effects of β CD, Primojel and Tween 80 in each case were evaluated in 2^2 factorial experiments. A comparative evaluation of the two techniques was also made. Telmisartan (40 mg) tablets were formulated in each case i.e.CD complexation and Solid dispersion techniques as per 2^2 factorial design. The two factors in CD complexation are β CD and Tween 80 and the two factors in solid dispersion technique are Primojel and Tween 80. The two levels of Factor A (β CD or Primojel) are 0 and 1:3 ratio of drug: carrier and the two levels of the Factor B (Tween 80) are 0 and 4% of drug and carrier content. Four telmisrtan tablets (40 mg) were formulated in each technique using selected combinations of the levels of the two factors. The tablets were prepared by direct compression method and the prepared tablets were evaluated for hardness, friability, disintegration time, drug content and dissolution rate and efficiency.

The dissolution rate and dissolution efficiency of telmisartan tablets were markedly enhanced by CD complexation and Solid dispersion techniques. In both the techniques the individual and combined effects of the factors involved i.e. β CD and Tween 80 in CD complexation and Primojel and Tween 80 in the case of solid dispersion technique, are highly significant ($P < 0.01$). Solid dispersion technique gave higher enhancement in the dissolution rate of telmisartan tablets than CD complexation technique. In both the techniques combined carriers gave higher enhancement in the dissolution rate than the carriers individually. Formulations CDab and SDab gave respectively 7.14 and 9.10 fold increase in the dissolution rate of telmisartan tablets. The dissolution efficiency of the telmisartan tablets was also significantly enhanced by CD complexation and Solid dispersion techniques.

Key words: *Telmisartan tablets, Dissolution rate, Cyclodextrin complexation, Solid dispersion technique, β CD, Primojel, Tween 80, Factorial study*

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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. 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[2-5], use of surfactants [6-8], solubilizers and super disintegrants [9,10], solid dispersion in water soluble and water dispersible carriers [11,12], 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.

The objective of the present study is to enhance the dissolution rate of telmisartan tablets by two techniques namely i) Complexation by β CD alone and in combination with Tween 80 and ii) Solid dispersion in Primojel alone and in combination with Tween 80. The individual and combined effects of β CD, Primojel and Tween 80 in each case were evaluated in 2^2 factorial experiments. A comparative evaluation of the two techniques was also made.

EXPERIMENTAL

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, magnesium stearate and MCC PH 102 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:

Telmisartan (40mg) tablets were formulated in each technique as per 2^2 factorial design. In the case of CD complexation the two factors are β CD (Factor A) and the Tween 80 (Factor B). The two levels of β CD are 0 and 1:3 ratio of drug and β CD content. The two levels of Tween 80 are 0 and 4% of drug and β CD content. Four formulations of telmisartan tablets prepared using selected combinations of the two factors as per 2^2 factorial design.

In the case of solid dispersion technique the two factors are Primojel (Factor A) and the Tween 80 (Factor B). The two levels of Primojel are 0 and 1:3 ratio of drug and Primojel content. The two levels of Tween 80 are 0 and 4% of drug and Primojel content. Four formulations of telmisartan tablets prepared using selected combinations of the the two factors as per 2^2 factorial design.

In each case the tablets are prepared by direct compression method as per formulae given in Table 1.

Table 1: Fomulae of Telmisartan Tablets Prepared using CD Complexation and Solid Dispersion techniques as per 2^2 Factorial Design

Ingredient (mg/tab)	Formulation code							
	CD Complexation				Solid Dispersion			
	CD 1	CD a	CD b	CD ab	SD 1	SD a	SD b	SD ab
Telmisartan	40	40	40	40	40	40	40	40
β-cylodextrin	-	120	-	120	-	-	-	-
Primojel	-	-	-	-	-	120	-	120
Tween 80	-	-	1.6	6.4	-	-	1.6	6.4
Talc	2.0	4.0	2.0	4.3	2.0	4.0	2.0	4.3
Magnesium Stearate	2.0	4.0	2.0	4.3	2.0	4.0	2.0	4.3
MCC PH 102	56.0	-	54.4	-	56.0	-	54.4	-
Total Weight (mg)	100	168	100	175	100	168	100	175

Preparation of Telmisartan Tablets:

CD complexes of telmisartan were prepared using β CD and Tween 80 initially by Kneading method. The required quantities of β CD and Tween 80 as per formulae of CDa, CDb and CDab were mixed in a dry mortar. Solvent blend of dichloromethane and alcohol (1:1) was added (10 ml) and the mixture was continuously triturated until the mixture is dry (kneading) to form CD complexes.

Solid dispersions of telmisartan in Primojel and Tween 80 were initially prepared by kneading method as above using the required quantities of Primojel and Tween 80 as per the formulae of SDa, SDb and SDab. The CD complexes and Solid dispersions prepared were then prepared in to tablets as follows.

The required quantities of CD complexes or Solid dispersions and other excipients as per the formulae in each case were blended thoroughly in a closed polyethylene 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 6 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 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_{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 enhance the dissolution rate of telmisartan tablets by two techniques namely i) CD Complexation and ii) Solid dispersion. In CD Complexation technique β CD alone and in combination with Tween 80 was tried to enhance the dissolution rate of telmisartan tablets. The individual and combined effects of β CD and Tween 80 on the dissolution rate of telmisartan tablets were evaluated in 2^2 factorial experiments. The two factors involved are β CD (Factor A) and Tween 80 (Factor B). The two levels of β CD are 0 and 1:3 ratio of drug and β CD and the two levels of Tween 80 are 0 and 4% of drug and β CD. Four formulations of telmisartan tablets (40mg) were prepared using selected combinations of the the levels of the two factors as per 2^2 factorial experiments. The tablets were prepared by direct compression method as per the formulae given in Table 1. The tablets prepared were evaluated for hardness, friability, disintegration time, drug content and dissolution rate and efficiency. Dissolution rate of telmisartan tablets prepared was studied in phosphate buffer of pH 7.5.The physical parameters

of the telmisartan tablets prepared are given in Table 2. The dissolution parameters are given in Table 3. The dissolution profiles are shown in Fig.1.

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 0.85% in all the cases. Drug content of the tablets was in the range of 100±3 % of the label content. The disintegration time of the tablets was in the range of 92 to 130 seconds. Much variation was observed in the dissolution rate and dissolution efficiency of the tablets prepared. Dissolution of the tablets was depended on the composition of the tablets. Tablets containing β CD and Tween 80 alone and in combination gave rapid and higher dissolution rate and dissolution efficiency than the tablets of telmisartan alone. A 2.20, 3.16 and 7.14 fold increase in the dissolution rate (K_1) was observed with CD a, CD b and C ab formulation when compared to CD 1 formulation. A combination of β CD and Tween 80 resulted in a much higher enhancement in the dissolution rate and dissolution efficiency of telmisartan tablets than is possible with them individually. Analysis of Variance (ANOVA) indicated that the individual and combined effects of β CD and Tween 80 on the dissolution rate of the telmisartan tablets are highly significant ($P < 0.01$).

In the case of Solid dispersion technique the two factors involved are Primojel (Factor A) and Tween 80 (Factor B). The two levels of Primojel are 0 and 1:3 ratio of drug and Primojel and the two levels of Tween 80 are 0 and 4% of drug and Primojel. Four formulations of telmisartan tablets (40mg) were prepared using selected combinations of the levels of the two factors as per 2^2 factorial experiments. The tablets were prepared by direct compression method as per the formulae given in Table 1. The tablets prepared were evaluated for hardness, friability, disintegration time, drug content and dissolution rate and efficiency. Dissolution rate of telmisartan tablets prepared was studied in phosphate buffer of pH 7.5.The physical parameters of the telmisartan tablets prepared are given in Table 2. The dissolution parameters are given in Table 3. The dissolution profiles are shown in Fig.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 0.80% in all the cases. Drug content of the tablets was in the range of 100±3 % of the label content. The disintegration time of the tablets was in the range of 34 to 126 seconds. Much variations were observed in the dissolution rate and dissolution efficiency of the tablets prepared. Dissolution of the tablets was depended on the composition of the tablets. Tablets containing Primojel and Tween 80 alone and in combination gave rapid and higher dissolution rate and dissolution efficiency than the tablets of telmisartan alone.

A 4.74, 3.16 and 9.10 fold increase in the dissolution rate (K_1) was observed with SD a, SD b and SD ab formulation when compared to SD 1 formulation. A combination of Primojel and Tween 80 resulted in a much higher enhancement in the dissolution rate and dissolution efficiency of telmisartan tablets than is possible with them individually. Analysis of Variance (ANOVA) indicated that the individual and combined effects of Primojel and Tween 80 on the dissolution rate of the telmisartan tablets are highly significant ($P < 0.01$).

Table 2: Physical Properties of Telmisartan Tablets Prepared using CD Complexation and Solid dispersion techniques as per 2^2 Factorial Design

Formulation Code	Hardness (Kg/sq.cm)	Friability (% wt Loss)	Disintegration Time (Sec)	Drug Content (%)
CD $_1$	5.0	0.85	130	98.4
CD a	4.5	0.60	115	99.6
CD b	5.0	0.45	92	102.8
CD ab	5.5	0.50	110	101.4
SD $_1$	4.5	0.75	126	98.2
SD a	5.0	0.65	42	100.8
SD b	5.0	0.80	85	101.6
SD ab	5.5	0.65	34	100.8

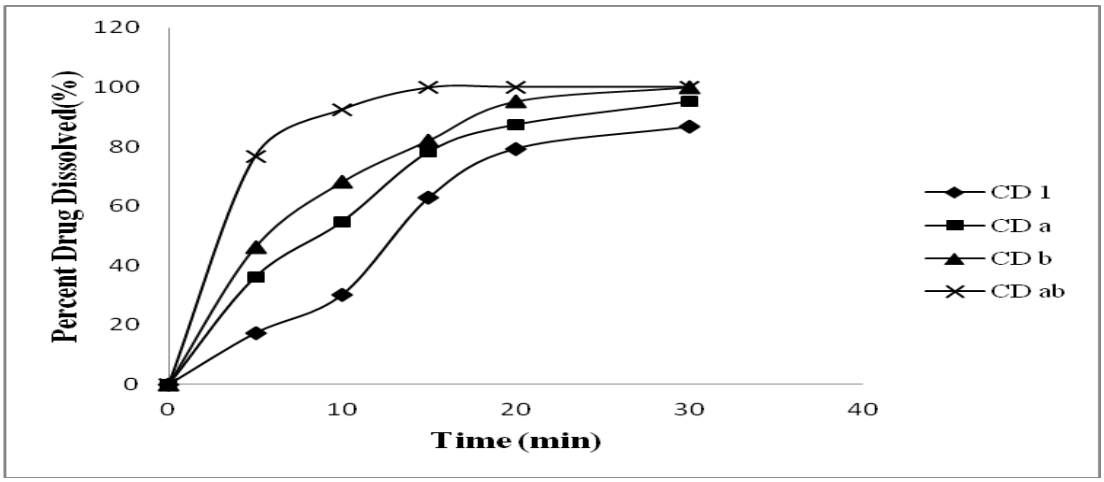

Fig.1: Dissolution Profiles of Telmisartan Tablets Prepared using CD Complexation technique as per 2^2 Factorial Design

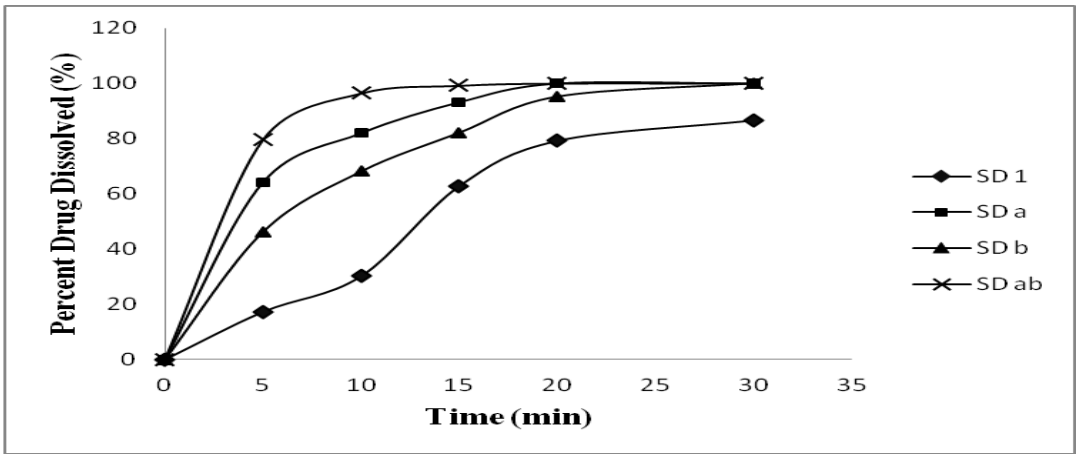

Fig.2: Dissolution Profiles of Telmisartan Tablets Prepared using Solid dispersion technique as per 2^2 Factorial Design

Table 3: Dissolution Parameters of Telmisartan Tablets Prepared using CD Complexation and Solid dispersion techniques as per 2^2 Factorial Design

Formulation Code	PD_{10} (%)	T_{50} (min)	DE_{30} (%)	Increase in DE_{30} (no. of folds)	$K_1 \times 10^3$ (min^{-1})	Increase in K_1 (no. of folds)
CD 1	30.2	19.19	52.61	-	36.1	-
CD a	54.8	8.72	65.93	1.25	79.45	2.20
CD b	68.1	6.05	73.2	1.39	114.4	3.16
CD ab	92.4	2.68	86.5	1.64	257.9	7.14
SD 1	30.2	19.17	52.61	-	36.15	-
SD a	82	4.03	81.56	1.55	171.57	4.74
SD b	68.1	6.05	73.2	1.39	114.4	3.16
SD ab	96.4	2.08	87.53	1.66	332.5	9.10

Comparison of CD Complexation and Solid Dispersion Techniques:

Both the techniques gave enhancement in the dissolution rate and dissolution efficiency of telmisartan tablets. Solid dispersion technique gave much higher enhancement in the dissolution rate than the CD complexation technique. Formulations CDa and SDa contain β CD and Primojel respectively at the same ratio of drug: carrier namely 1: 3. They respectively gave 2.2 and 4.74 fold increase in the dissolution rate of telmisartan tablets. In both the techniques combined carriers (β CD + Tween 80 and Primojel + Tween 80) gave higher enhancement in the dissolution rate when compared to individual carriers. Formulations CDab and SDab respectively gave 7.14 and 9.10 fold increase in the dissolution rate of telmisartan. In both the techniques the individual and combined effects of the factors involved are highly significant ($P < 0.01$). Hence solid dispersion technique is considered as a better technique than the CD complexation technique for enhancing the dissolution rate of telmisartan tablets.

CONCLUSIONS:

1.The dissolution rate and dissolution efficiency of telmisartan tablets were markedly enhanced by CD complexation and Solid dispersion techniques.

2.In both the techniques the individual and combined effects of the factors involved i.e. β CD and Tween 80 in CD complexation and Primojel and Tween 80 in the case of solid dispersion technique, are highly significant ($P < 0.01$).

3.Solid dispersion technique gave higher enhancement in the dissolution rate of telmisartan tablets than CD complexation technique.

4.In both the techniques combined carriers gave higher enhancement in the dissolution rate than the carriers individually.

5.Formulations CDab and SDab gave respectively 7.14 and 9.10 fold increase in the dissolution rate of telmisartan tablets.

6.The dissolution efficiency of the telmisartan tablets was also significantly enhanced by CD complexation and Solid dispersion techniques.

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