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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF TELMISARTAN EMPLOYING β-CYCLODEXTRIN AND SOLUPLUS – A FACTORIAL STUDY

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Abstract:

Telmisartan, a widely prescribed anti hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The objective of the study is to enhance the solubility and dissolution rate of Telmisartan by cyclodextrin complexation along with Soluplus and to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD) and surfactant (Soluplus) on the solubility and dissolution rate of Telmisartan in a series of 2^2 factorial experiments. The effects of βCD and Soluplus alone on the solubility of Telmisartan were evaluated by phase solubility studies. The solubility of Telmisartan in four selected fluids containing βCD and Soluplus as per 2^2 factorial study was determined. Solid inclusion complexes of Telmisartan-βCD were prepared with and without Soluplus by kneading method as per 2^2- factorial design and were evaluated.

The aqueous solubility of Telmisartan was increased linearly as a function of the concentration of βCD as well as Soluplus. The phase solubility diagram of Telmisartan - βCD complexes is of type A_L. Increase in solubility of Telmisartan was due to the formation of a 1:1 M complex in solution with βCD with a stability constant (Kc) value of 326.0 M^{-1}. The individual and combined effects of βCD and Soluplus in enhancing the solubility and dissolution rate of Telmisartan were highly significant ($P<0.01$). βCD alone gave a 2.21 fold increase in the solubility of Telmisartan. Combination of βCD with Soluplus resulted in a much higher enhancement in the solubility of Telmisartan, 5.0 fold with βCD - Soluplus than with βCD alone. The dissolution of Telmisartan was rapid and higher in the case of Telmisartan - βCD complex systems when compared to Telmisartan pure drug. βCD alone gave a 1.96 fold increase in the dissolution rate (K1) of Telmisartan. When βCD is combined with Soluplus the dissolution rate (K1) was significantly enhanced to 4.37 fold with β CD - soluplus complexes. Hence complexation of Telmisartan with β CD - Soluplus is recommended to enhance the solubility and dissolution rate of Telmisartan, a BCS Class II drug.

Key words: *Telmisartan, β Cyclodextrin, Soluplus, Solubility, Dissolution rate, Factorial Study.*

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INTRODUCTION:

Telmisartan, a widely prescribed angiotensin II receptor antagonist belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically insoluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5]. Soluplus is a polymeric solubiliser with an amphiphilic chemical nature, which was particularly developed for solid solutions[6]. Soluplus is polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol graft co-polymer. Soluplus increased the solubility and enhanced the bioavailability of actives in solid solutions. Itraconazole and fenofibrate showed significant increase in the bioavailability with Soluplus[6]. The solubility and dissolution rate of valsartan was effectively enhanced by using Soluplus in the form of solid dispersions[7].

Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate. In the present investigation the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD), surfactant (Soluplus) on the solubility and dissolution rate of Telmisartan, a BCS class II drug were evaluated in a 2^2 factorial study.

EXPERIMENTAL:

Materials

Telmisartan was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. β-cyclodextrin and Soluplus were gift samples from M/s Natco Pharma Ltd., Hyderabad.

All other materials used were of pharmacopoeial grade

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 0 - 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.65% and 1.4% respectively. No interference by the excipients used in the study was observed.

Phase Solubility Study

The effects of βCD and Soluplus alone on the solubility of Telmisartan were evaluated by phase solubility studies as per Higuchi and Connors [8]. Excess drug (50 mg) was added to 15 ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature (28±1ºC) on Rotary Flask Shaker. After 24 h of shaking, 2 ml aliquots were withdrawn at 2 h interval and filtered immediately using a 0.45 µ disk filter. The filtered samples were diluted suitably and assayed for Telmisartan by measuring absorbance at 296 nm. Shaking was continued until two consecutive estimations are the same. The solubility experiments were replicated for three times each (n=3).

Preparation of Telmisartan - βCD Complexes

Solid inclusion complexes of Telmisartan - βCD - Soluplus were prepared as per 2^2 – factorial study by kneading method. Telmisartan, βCD and Soluplus were triturated in a mortar with a small volume of solvent consisting of a blend of dichloromethane: methanol (1:1). The thick slurry formed was kneaded for 45 min and then dried at 55ºC until dry. The dried mass was powdered and sieved to mesh No. 120.

Dissolution Rate Study

Dissolution rate of Telmisartan - βCD complexes prepared was studied in phosphate buffer of pH 7.5 (900 ml) employing eight station dissolution test apparatus (LABINDIA, DS 8000) using paddle at 50 rpm and at a temperature of 37°C ± 1°C. Telmisartan - βCD complex equivalent to 40 mg of Telmisartan 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:
Solubility and dissolution data were analyzed by analysis of variance (ANOVA) as per 2^2 factorial study.

RESULTS AND DISCUSSION:

The objective of the study is to enhance the solubility and dissolution rate of Telmisartan by cyclodextrin complexation along with Soluplus and to evaluate the individual main effects and combined (or interaction) effects of β cyclodextrin (βCD) and surfactant (Soluplus) on the solubility and dissolution rate of Telmisartan in a series of 2^2 factorial experiments.

The effects of βCD and Soluplus on the solubility of Telmisartan were initially evaluated by phase solubility studies . The individual and combined effects of βCD and Soluplus on the solubility and dissolution rate of Telmisartan were evaluated in a 2^2 experiment. The phase solubility diagrams showing the effects of βCD and Soluplus and their concentrations on the solubility of Telmisartan are shown in Figs. 1-2. The aqueous solubility of Telmisartan was increased linearly as a function of the concentration of βCD and Soluplus. The phase solubility diagram of Telmisartan - βCD complexes (Fig.1) can be classified as type A_L according to Higuchi and Connors [8]. Because the straight line had a slope <1, the increase in solubility was due to the formation of a 1:1 M complex in solution with βCD. The apparent stability constant (Kc) was calculated from the slope of the corresponding linear plot of the phase solubility diagram according to the equation, Kc = Slope/So (1-Slope), where So is the solubility of the drug in the absence of βCD. The estimated Kc value of Telmisartan - βCD complex was 326.0 M^{-1} indicating that the complexes formed between Telmisartan and βCD are quite stable.

The individual main effects and combined (interaction) effects of βCD (Factor A), Soluplus (Factor B) on the aqueous solubility of Telmisartan were evaluated in a series of 2^2-factorial experiments. For this purpose, two levels of βCD (0, 5 mM) and two levels of Soluplus (0, 1%) were selected in each case and the corresponding four treatments involved in the 2^2-factorial study were purified water (1); water containing 5 mM βCD (a); water containing 1% Soluplus (b); water containing 5 mM βCD and 1% Soluplus (ab).

Table 1: Solubility of Telmisartan in Various Fluids containing βCD and Soluplus as per 2^2 – Factorial Study

Fluids (Code as per 2^2 – Factorial Experiment)	Solubility (mg/100ml) (n=3) ($\bar{x}$ ± s. d.)	Increase in Solubility (Number of Folds)
Distilled water (1)	1.9±0.007	-
Water containing 5 mM βCD (a)	4.2±0.004	2.21
Water containing 1% Soluplus (b)	5.0±0.002	2.63
Water containing 5mM βCD and 1% Soluplus (ab)	9.5±0.003	5.00

Table 2: Dissolution Parameters of Telmisartan - βCD - Soluplus Solid Inclusion Complexes Prepared as per 2^2 Factorial Study

T-CD Complex	Composition	PD_{10} (%)	K_1x10^2 min^{-1}	Increase in K_1 (No. of folds)	DE_{30} (%)	Increase in DE_{30} (No. of folds)
TF1	T	47.4	6.45	---	41.09	---
TFa	T-βCD (1:2)	66.25	12.63	1.96	62.62	1.52
TFb	T-Soluplus (1%)	68.40	16.16	2.51	65.45	1.59
TFab	T-βCD (1:2) - Soluplus (1%)	92.68	28.16	4.37	82.65	2.01

T- Telmisartan; βCD - β cyclodextrin

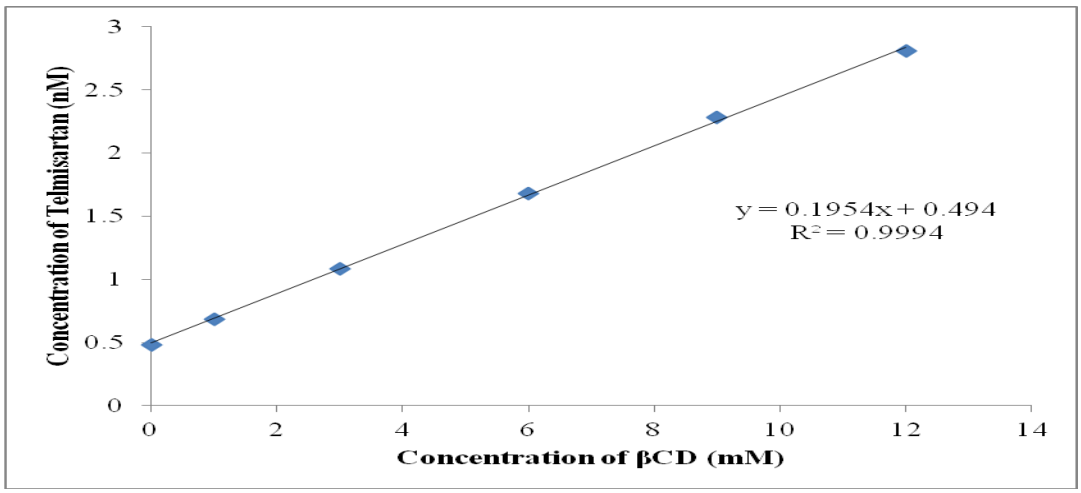

Fig. 1: Phase Solubility Studies - Effect of βCD Concentration on the Solubility of Telmisartan

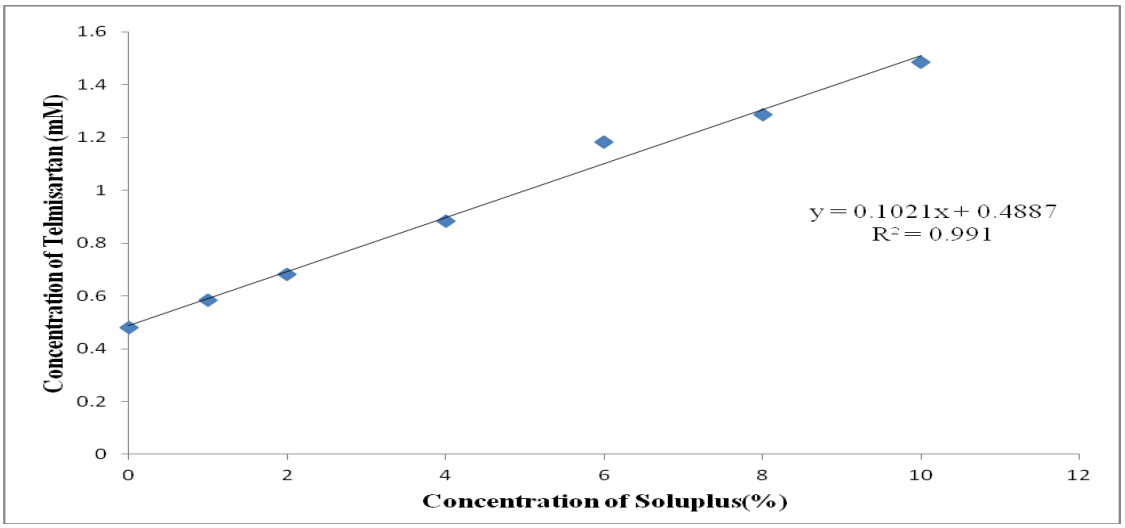

Fig. 2: Effect of Soluplus Concentration on the Solubility of Telmisartan

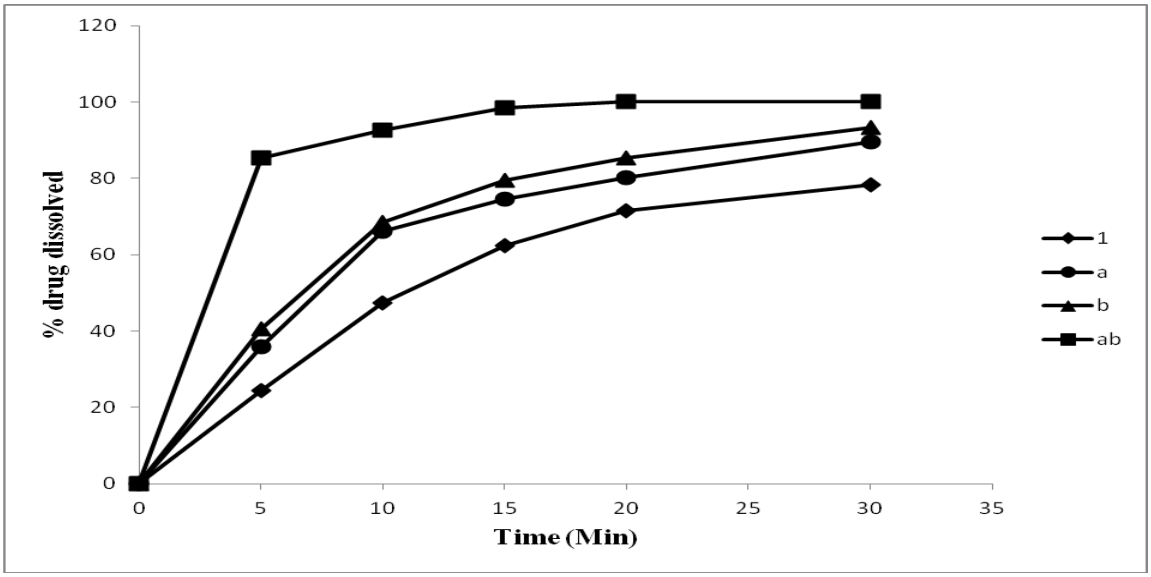

Fig.3: Dissolution Profiles of Telmisartan - βCD - Soluplus Solid Inclusion Complexes Prepared as per 2^2 Factorial Study

The solubility of Telmisartan in the above mentioned fluids was determined (n=3) and the results are given in Table-1.The solubility data were subjected to Analysis of variance (ANOVA) to find out the significance of main and combined effects of βCD and Soluplus. The results of ANOVA indicated that the individual and combined effects of βCD and Soluplus in enhancing the solubility of Telmisartan were highly significant ($P<0.01$)

βCD alone gave a 2.21 fold increase in the solubility of Telmisartan. Combination of βCD with Soluplus resulted in a much higher enhancement in the solubility of Telmisartan, 5.0 fold with βCD - Soluplus than with βCD alone. Soluplus also gave an enhancement of 2.63 folds in the solubility of Telmisartan.

To evaluate the individual and combined effects of βCD and Soluplus on the dissolution rate of Telmisartan, solid inclusion complexes of Telmisartan - βCD were prepared with and without Soluplus as per 2^2-factorial design. For this purpose two levels of βCD (0 and 1:2 ratio of drug : βCD) and two levels of Soluplus (0 and 1%) were selected and the corresponding four treatments involved in the 2^2-factorial study were Telmisartan pure drug (1); Telmisartan - βCD (1:2) inclusion binary complex (a); Telmisartan - Soluplus (1%) binary complex (b); Telmisartan - βCD (1:2) - Soluplus (1%) ternary complex (ab)

The CD complexes were prepared by kneading method. All the solid inclusion complexes of Telmisartan- βCD - Soluplus prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v.) values (< 1.2 %) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared. The dissolution rate of Telmisartan alone and from βCD complexes was studied in Phosphate buffer pH 7.5. The dissolution of Telmisartan followed first order kinetics with R^2 (coefficient of determination) values above 0.925. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[9]. The dissolution parameters are given in Table 2. The dissolution of Telmisartan was rapid and higher in the case of Telmisartan - βCD complex systems prepared when compared to Telmisartan pure drug as such. The dissolution profiles are given in Fig. 3.

The dissolution rate (K_1) values were subjected to ANOVA to find out the significance of the main and combined effects of βCD and Soluplus on the dissolution rate of Telmisartan. ANOVA indicated that the individual main effects of βCD and Soluplus and their combined effects in enhancing the dissolution rate (K_1)and dissolution efficiency (DE_{30}) were highly significant ($P < 0.01$). βCD alone gave a 1.96 fold increase in the dissolution rate of (K_1) of Telmisartan. When βCD is combined with Soluplus the dissolution rate (K_1) was significantly enhanced. A 4.37 fold increase in the dissolution rate (K_1) was observed with Telmisartan - βCD - Soluplus inclusion complex. DE_{30} values were also much higher in the case of βCD solid complexes when compared to Telmisartan pure drug.

Thus the ternary complex i.e., Telmisartan - βCD - soluplus gave higher enhancement in the dissolution rate of Telmisartan than βCD alone and Telmisartan - βCD complexes. Hence complexation of Telmisartan with βCD - Soluplus is recommended to enhance the solubility and dissolution rate of Telmisartan, a BCS Class II drug.

CONCLUSIONS:

1. The aqueous solubility of Telmisartan was increased linearly as a function of the concentration of βCD and Soluplus.
2. The phase solubility diagram of Telmisartan - βCD complexes is of type A_L. Increase in solubility of Telmisartan was due to the formation of a 1:1 M complex in solution with βCD with a stability constant (Kc) value of 326.0 M^{-1}.
3. The individual and combined effects of βCD and Soluplus in enhancing the solubility and dissolution rate of Telmisartan were highly significant ($P < 0.01$).
4. βCD alone gave a 2.21 fold increase in the solubility of Telmisartan. Combination of βCD with Soluplus resulted in a much higher enhancement in the solubility of Telmisartan, 5.0 fold with βCD - Soluplus than with βCD alone.
5. The dissolution of Telmisartan was rapid and higher in the case of Telmisartan - βCD complex systems when compared to Telmisartan pure drug. βCD alone gave a 1.96 fold increase in the dissolution rate of (K_1) of Telmisartan. When βCD is combined with Soluplus the dissolution rate (K_1) was significantly enhanced to 4.37 fold with β CD - Soluplus complex.
6. Hence complexation of Telmisartan with βCD - Soluplus is recommended to enhance the solubility and dissolution rate of Telmisartan, a BCS Class II drug.

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