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ENHANCEMENT OF DISSOLUTION RATE OF TELMISARTAN BY INCLUSION COMPLEXES WITH β-CYCLODEXTRINS

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ABSTRACT

The objective of the study is to increase the dissolution rate of telmisartan, a poorly water-soluble drug, an angiotensin-II receptor antagonist used in the treatment of hypertension. To improve the dissolution rate of telmisartan, prepared inclusion complexes with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD). The phase solubility studies indicated that the solubility of telmisartan was significantly increased in the presence of β-CD and the presence of HP-β-CD and A_L type curve was obtained. The apparent stability constant (Ks) was found to be 1230 M^{-1} for β-CD and 1300 M^{-1} for HP-β-CD. The inclusion complexes in the 1:1 molar ratio of telmisartan and carriers were prepared by the spray-drying method. The prepared complexes were characterized using differential scanning calorimetry (DSC), and Powder X-ray diffractometry. The DSC and X-RD showed conversion of telmisartan from crystalline to amorphous form in the prepared complexes. The prepared complexes are made into different dispersible tablet formulations F1 to F8 by varying the percentage of super disintegrants. All the prepared formulations showed an improved dissolution rate of telmisartan. The inclusion complex prepared with HP-β-CD formulation F8 shows the enhancement of dissolution rate by three folds. The accelerated stability studies for 1 month indicate there is no significant difference in quality control tests the results indicate that the prepared formulation is stable.

Keywords: Telmisartan, β-cyclodextrin, Hydroxypropyl-β-cyclodextrin, inclusion complex.

INTRODUCTION

Telmisartan is an angiotensin-II receptor antagonist used in the treatment of hypertension. It binds to the angiotensin-II type 1 (AT1) receptors with high affinity, inhibiting the action of angiotensin-IIon vascular smooth muscle, thus causing a reduction in arterial blood pressure.1 Telmisartan belongs to the Biopharmaceutics Classification system (BCS), a class 2 drug, having low solubility and high permeability the improvement of solubility increase the dissolution rate and bioavailability. Several techniques to improve the dissolution rate like solid dispersions, inclusion complexes[2]. The development of improving the solubility of poorly water drugs by using the hydrophilic carriers, The term complexation refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug[3]. in this study inclusion complexes of telmisartan with the β-cyclodextrins are prepared by solvent evaporation with the help of spray drying technique[4]. The central cavity of the cyclodextrin molecule is lined with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included.

No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity[5]. Inclusion complexation: These are formed by the insertion of the non-polar molecular or the nonpolar region of one molecule (known as a guest) into the cavity of another molecule or group of molecules (known as a host). The cavity of the host must be large enough to accommodate the guest and small enough to eliminate the water. The most commonly used host molecules are cyclodextrins. Lipophilic drug cyclodextrin complexes, commonly known as inclusion complexes can be formed simply by adding the drug and the excipient together, resulting in enhanced drug solubilization. Cyclodextrins are a group of structurally related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface.Derivatives of β- cyclodextrin (HP – β-CD) are most commonly used in pharmaceutical formulation. Cyclodextrin complexes have been shown to increase the stability, wettability, and dissolution of many lipophilic drugs. Cyclodextrins can also be used as membrane permeability enhancer and stabilizing agents[6].

MATERIALS AND METHODS

MATERIALS

Telmisartan drug is obtained as a gift sample from Hetero Pharma Pvt Ltd, Hyderabad. β-cyclodextrin and hydroxypropyl β-cyclodextrins are purchased from Himedia. All other ingredients are purchased from local suppliers all ingredients used are of laboratory grade.

METHODS

Standard calibration method

Accurately weighed 10 mg of telmisartan is transferred into a 10ml volumetric flask and made up to the mark with phosphate buffer pH 7.5. Different concentrations are prepared from the stock solution and the absorbance is measured at λ_{max} 296nm using a UV visible spectrophotometer[7].

Phase solubility studies

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Telmisartan was added to 10 mL portions of distilled water, each containing a variable amount of β-CD and HP- β-CD. All the above solutions with a variableamount of β-CD were shaken in a water bath shaker for 24 hours. After shaking, the solutions were filtered and their absorbance was noted at 296nm.The apparent stability constants (Ks) were calculated from the phase solubility diagrams, by using the following equation:

$$Ks = slope / So(1-slope)$$

WhereS_0=solubility of Telmisartanin water[8]

Preparation of Telmisartan cyclodextrin inclusion complexes by spray dryer

The inclusion complexes of telmisartan with β-cyclodextrins were prepared by spray-drying methods. Telmisartan and β-cyclodextrins with a 1:1 molar ratio were accurately weighed. The beta cyclodextrins are solubilized with the help of water the drug is solubilized in ethanol both the solutions were mixed and placed in a spray dryer at the peristaltic movement of 12ml/min with input temperature 90-110^{0}c and output temperature 70-80^{0}c in pressure of 10psi[9].

The drug content in complexes

The prepared solid complex equivalent to 10 mg was weighed accurately and solubilized using phosphate buffer pH 7.5 the solution was filtered using filter paper. The obtained solution is used to measure the drug content by UV visible spectrophotometry[10].

Preparation of dispersible tablets

The various formulations from F1 to F8 are made by using the ingredients for the table (table:1). All the ingredients were accurately weighed and mixed properly using motor and pestle and then compressed by tablet compression machine using 8mm flat punches **(Table:1 Formula used of Telmisartan tablets).**

Differential Scanning Calorimetry (DSC)

Pure Telmisartan, spray-dried complexes of Telmisartan with β-cyclodextrin, and hydroxypropyl-β-cyclodextrin were subjected to DSC studies using TA instruments Q20 model. Accurately weigh 2mg of sample, place in an aluminum pan, and seal. The empty aluminum sample pan was used as reference material. Samples were scanned at the rate of 10°C/ min fromroom temperature to 300°C wherein nitrogen gas was used as purge gas at a flow rate of 50mL/min[11].

Powder X-Ray Diffractometry (PXRD)

Pure Telmisartan, spray-dried complexes of Telmisartan with β-cyclodextrin, and hydroxypropyl-β-cyclodextrins were subjected to XRD studies. The scanning rate employed was 2°C/min, and samples were analyzed

between 2θ angles 10-80° at an operating voltage of 40kV and a current of 30mA[12].

Angle of repose

An angle is determined using a funnel. The accurately weighedpowder was taken in a funnel. The height of the funnel is adjusted in such a way the tip of the funnel just touches the apex of the head of the blend. The powder is allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured, and the angle of repose is calculated using the following equation.

$$\theta = \tan^{-1} h/r$$

Where θis the angle of repose, h is the height of the pile and **r** is the radius of the base pile[13].

Bulk Density

Apparent bulk density is determined by pouring a weighed quantity of blend into a graduated cylinder and measuring the volume and weight. Bulk density is calculated using thefollowing formula:[13]

Bulkdensity=Weightofpowder/bulkvolumeofpowder

Tapped Density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for an affixed number of times until there is no more change in the volume was attained. Using the formula, the tapped density was calculated.[14]

Tapped density = Weight of the powder/tapped volume of the powder

Carr's compressibility index

The Best way for finding out the free flow of the granules is the compressibility index; it is the indication for the ease of flow of the granules it is calculated by the given formula[14].

Carr's index = (Tapped density-Bulk density)/ Tapped density×100

Hausner ratio

It is the indirect index for the ease of powder flow. It is calculated by the following formula[15].

Hausner ratio=Tapped density / Bulk density

Hardness

The hardness of the tablets was tested by using a labindia automatic tablet hardness tester (model no.TH1050S).[15]

Thickness

The thickness of the tablets was tested by using a labindia automatic tablet thickness tester(model no.TH1050S).[16]

Weight variation test

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight[16].

Uniformity of Content

Ten tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of Telmisartan was dissolved in 100 mL of pH (7.5) phosphate buffer. From this 1ml was taken in a 10 ml volumetric flask and the volume is adjusted up to the mark with the same solvent. The absorbance of the solution was measured at 296 nm. The drug content of Telmisartan was calculated using calibration curve data[16].

Friability test

Six tablets from each batch were examined for friability using Roche Friabilator and the equipment was run for 4min at 25 rpm. The tablets were taken out, dedusted, and reweighted, and % friability was calculated[17].

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

***In-vitro* disintegration testing**

The disintegration test was performed using a USP disintegration apparatus, with distilled water at 37±0.5°C. The time reported to obtain complete disintegration of six tablets was recorded and the average was reported[17]**.**

***In vitro* dissolution rate testing**

A dissolution study was conducted for all the formulation using USP type-II apparatus (Labindia, Mumbai, India.). The dissolution test was performed using 900 ml of phosphate buffer (pH 7.5) was taken as the dissolution medium at 75 rpm and 37±0.5°C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 296nm[18].

RESULTS AND DISCUSSION

Standard calibration graph of Telmisartan
Accurately weighed 10 mg of telmisartan is transferred into a 10ml volumetric flask and made upto the mark with phosphate buffer pH 7.5. Different concentrations are prepared from the stock solution 2, 4, 6, 8, 10µg/ml and the absorbance is measured at λ_{max} 296nm using a UV visible spectrophotometer. The R2 value of this equation is calculated and this value is found 0.9992 which indicates linearity (Figure:1 Standard calibration graph of Telmisartan).

Phase solubility studies
The solubility of Telmisartan in water is found to be 0.0886mg/ml. The phase solubility diagrams of Telmisartan: β-CD and HP-β-CD were obtained by plotting the solubility of Telmisartan against the concentration of carriers. The solubility curves were classified as the A_L type, which indicates that the inclusion complex in the molar ratio of 1:1 between the guest and the host molecule improved the solubility. The phase solubility profile indicates that the solubility of Telmisartan was significantly increased in the presence of β-CD, HP-β-CD, and apparent stability constant (Ks) was found to be 1230M^{-1} for β-CD and 1300 M^{-1} for HP-β-CD (Figure 2: Phase solubility studies).
And the percentage yield was found to be 85%.

Drug Content of complexes
UV spectrophotometry was used to determine the drug content of all inclusion complexes. The results of drug content in all the prepared complexes ranged from 93.77%to 95.88%.

Differential Scanning Calorimetry (DSC) studies
The thermal behavior of Telmisartan -β-CD, HP-β-CD complexes was studied using DSC to confirm the formation of the complex. DSC thermogram of Telmisartan, β-CD, HP-β-CD and all inclusion complexes are shown in the below figures.The DSC thermogram of Telmisartan showed an exothermic peak at 269°C corresponding to its melting point. The DSC thermogram of Telmisartan-β-CD,HP-β-CD complex showed an endothermic peak at different temperature 113.24°C and 83.18° C by spray-dried preparation, which is different fromthe pure drug, which gives clear evidence that there is the formation of the complex. (Figure 3: DSC thermograms of Telmisartan, Telmisartan + β-cyclodextrin complex, Telmisartan + hp-β-cyclodextrin complex).

Powder X-Ray Diffractometry (PXRD) studies
The XRD patterns of pure telmisartan show sharp intensity peaks at a diffraction angle of 2θ at 10.21, 14.30, 24.20 indicate the crystalline nature of the drug. The XRD patterns of a complex of telmisartan with β-cyclodextrin shows intensity peaks at diffraction angles of 2θ at 12.32,18.66.14.09 this indicates that the complex was in amorphous form and the XRD patterns of complex of hydroxypropyl- β-cyclodextrin shows intensity peaks at diffraction angles of 2θ at 18.94, 18.22, 22.22 this indicates that the complex was in amorphous form. (Figure: 4 XRD of Telmisartan, Telmisartan + β-cyclodextrin complex, Telmisartan + hydroxypropyl-β-cyclodextrin complex).

Precompression parameters (Table:2)
All the powder characters are evaluated by the standard formulas and the results were obtained within the limits **(Table: 2 Precompression parameters for the powder).**

Tablet evaluation parameters (Table:3)
All the tablet formulations were evaluated and the obtained results are within the limits.

Table: 3 Tablet evaluation test results

Dissolution profiles
Cyclodextrins are highly water-soluble it was expected to instantly dissolve in the medium under the condition of the dissolution test. The release rate profile was drawn as the cumulative percent release on the y-axis and time on the x-axis which showed in (fig5,6). The prepared telmisartan tablets were performed dissolution rate testing and compare to all formulations F8 is given more dissolution rate **(Figure:5 Dissolution profile for Telmisartan with β-cyclodextrin complexes and Figure:6 Dissolution profile for Telmisartan with hydroxypropyl β-cyclodextrin complexes)**.

Stability studies
Accelerated studies were performed for the best formulation over 1 month. The tablets were placed in a glass container kept in a stability chamber, the temperature was maintained at 40^0±2^0C and the relative humidity was maintained over 75%±5%. After 30 days the tablets were tested for quality control tests like hardness, disintegration test, dissolution rate tests are performed and the results found to be 3.20 Kg/sq.cm^2,3 minutes and 93% drug release there is no significant difference in the tablets so that the prepared formulation is stable.

CONCLUSION

The present study is to increase the dissolution rate of telmisartan, a poorly water-solubledrug, an angiotensin-II receptor antagonist used in the treatment of hypertension. The improvement of the dissolution rate of telmisartan is observed by preparing inclusion complexes with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD). The formulated tablets were showed good enhancement of dissolution among all the formulations F8 higher dissolution rate. For the prepared tablet performed a quality control test and it was given a good result and there is no specific difference so that it indicates that formulation F8 was stable.

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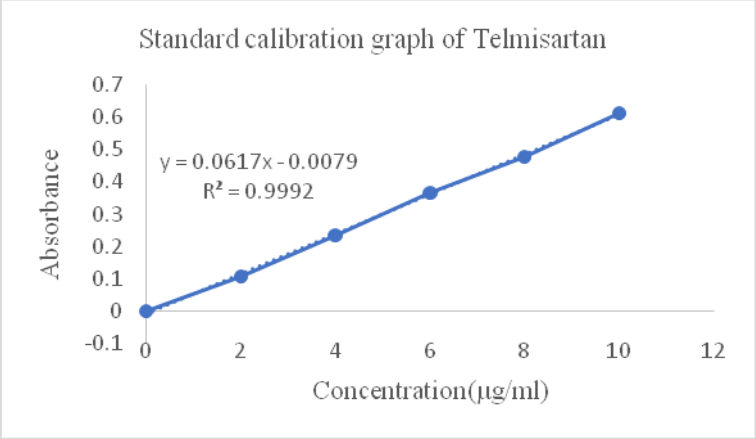

Fig. 1: Standard calibration graph of Telmisartan

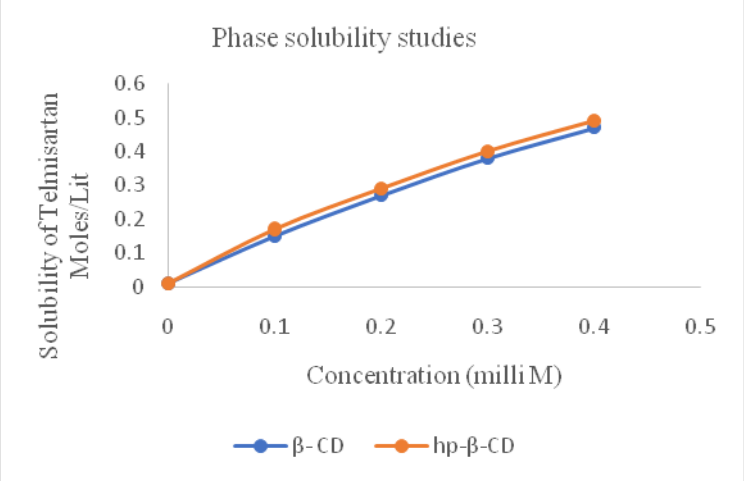

Fig. 2: Phase solubility studies

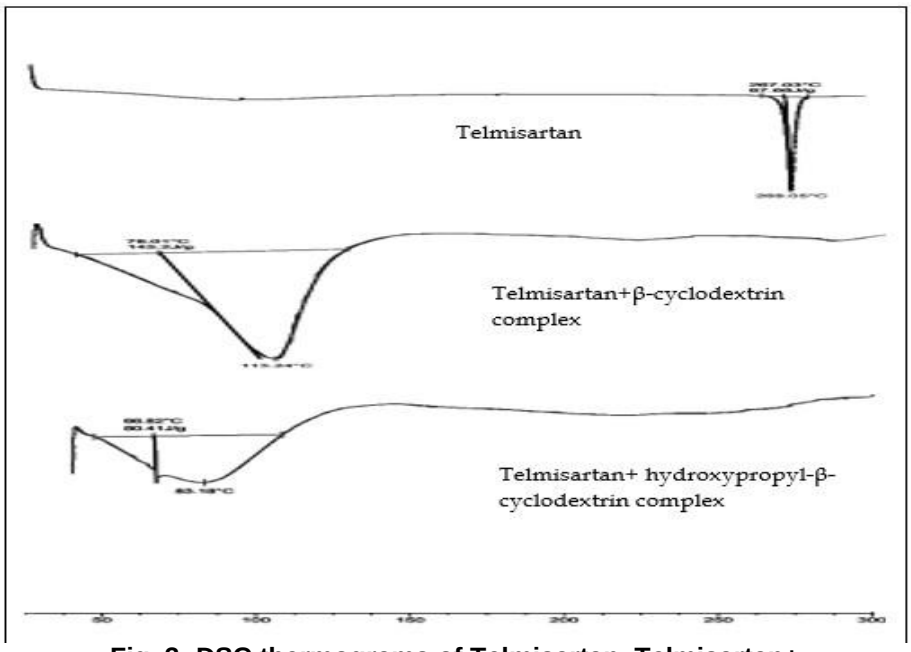

Fig. 3: DSC thermograms of Telmisartan, Telmisartan+ β-cyclodextrin complex, Telmisartan+ hp-β-cyclodextrin complex

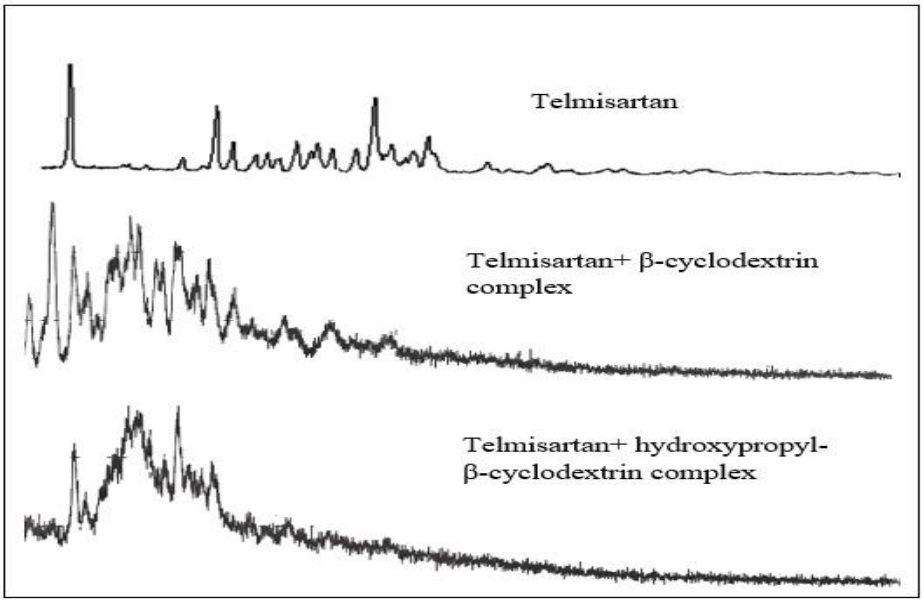

Fig. 4: XRD of Telmisartan, Telmisartan+ β-cyclodextrin complex, Telmisartan+ hydroxypropyl-β-cyclodextrin complex

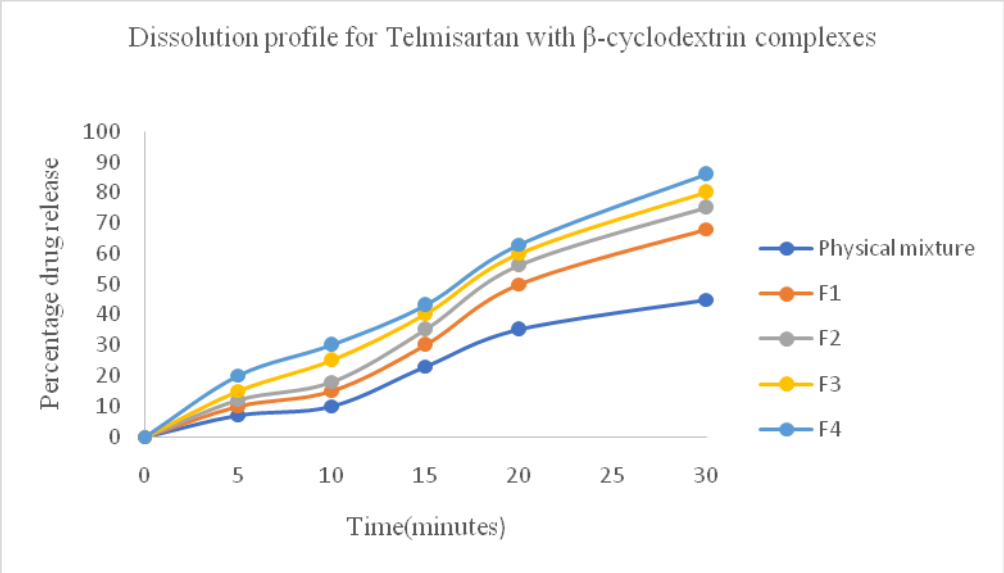

Fig. 5: Dissolution profile for Telmisartan with β-cyclodextrin complexes

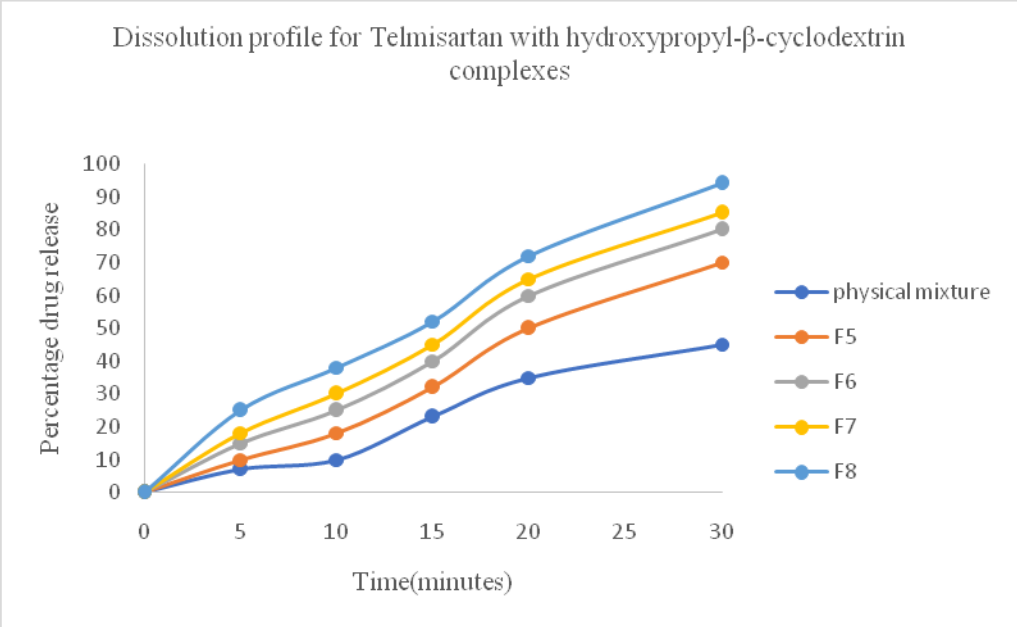

Fig. 6: Dissolution profile for Telmisartan with hydroxypropyl-β-cyclodextrin complexes

Table 1: Formula used of Telmisartan tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Telmisartan+β-cyclodextrin complex (equivalent to 40mg)	128	128	128	128	--	--	--	--
Telmisartan+ hydroxypropyl-β-cyclodextrin complex (equivalent to 40mg)	--	--	--	--	148	148	148	148
Sodium starch glycolate (%)	2	3	4	5	2	3	4	5
Magnesium stearate	10	8	6	4	12	8	6	4
Talc	10	8	6	4	12	8	6	4
Avicel PH 102 qs to	200	200	200	200	200	200	200	200

Table 2: Precompression parameters for the powder (the values are Mean ± SD, n=3)

Formulation code	Bulk density	Tapped density	Angle of repose	Carr's Compressibility index	Hausner's Ratio
F1	0.260±0.056	0.305±0.011	29.54 ± 1.92	14.55±0.18	1.17±0.01
F2	0.214±0.096	0.246±0.002	30.78 ± 1.65	12.77±0.12	1.14±0.02
F3	0.283±0.038	0.321±0.004	27.68 ± 1.78	11.81±0.16	1.13±0.06
F4	0.257±0.085	0.295±0.011	26.64 ± 1.52	12.87±0.12	1.14±0.04
F5	0.285±0.068	0.327±0.005	30.85 ± 0.92	12.67±0.11	1.14±0.05
F6	0.258±0.086	0.334±0.048	28.16 ± 1.55	14.42±0.17	1.16±0.03
F7	0.285±0.064	0.321±0.013	26.63 ± 2.31	11.21±0.15	1.12±0.07
F8	0.269±0.056	0.315±0.049	27.55 ± 0.77	14.43±0.14	1.16±0.07

Table 3: Tablet evaluation test results (the values are Mean±SD, n=3)

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/sq.cm^2)	Friability (% wt Loss)	Content uniformity (%)	Disintegration time(minutes)
F1	200±0.571	3.21±0.36	2.89±0.021	0.41±0.01	98±0.3	5±0.5
F2	203±0.573	3.05±0.74	3.51±0.03	0.52±0.05	98±0.2	6±0.6
F3	199±0.579	3.01±0.54	3.79±0.14	0.41±0.02	98±0.8	7±0.3
F4	204±0.576	3.03±0.24	3.08±0.04	0.38±0.10	98±0.1	4±0.8
F5	202±0.521	3.05±0.47	3.26±0.54	0.62±0.14	98±0.6	6±0.4
F6	197±0.587	3.01±0.63	3.61±0.23	0.48±0.06	98±0.7	5±0.5
F7	205±0.535	3.00±0.35	3.82±0.12	0.63±0.08	98±0.9	4±0.7
F8	201±0.531	3.02±0.45	3.18±0.18	0.51±0.10	98±0.1	3±0.5

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