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ENHANCEMENT OF DISSOLUTION RATE OF VALSARTAN BY COMPLEXATION WITH β-CYCLODEXTRINS

TASMEEN SK*, DIVYA S*, RAMYA SREE R*, VENKATA RAMANA M AND RAMARAO N

Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur-522034

***Corresponding Authors: Tasmeen Shaikh, Diyva S, Ramya Sree R: E Mail:** shaiktasmeen@gmail.com; divyasanagavarapu@gmail.com; raminenisree@gmail.com

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ABSTRACT

The objective of the study was to increase the solubility and dissolution rate of valsartan (VAL), a poorly water-soluble drug which is an angiotensin II blocker which forms an inclusion complexation with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD). The phase solubility studies indicated that the solubility of valsartan was significantly increased in the presence of β-CD and also in the presence of HP-β-CD and A_L type curve was obtained. Apparent stability constant (Ks) was found to be 165.4±M^{-1} for β-CD and 296±3 $M^{-1}$for HP-β-CD. The inclusion complexes were by kneading method, solvent evaporation method and spray drying method. The prepared complexes were characterized using FTIR, DSC. The inclusion complexes dissolution profile was compared with physical mixture and pure drug. All the complexes showed improved dissolution rate. The inclusion complexes compared with HP-β-CD by spray drying method exhibit greatest enhancement in solubility and dissolution rate i.e., 94.3% VAL release in 60min.

Keywords: 2-Hydroxypropyl-β-cyclodextrin, β-cyclodextrin, kneading method, solvent evaporation method, spray drying method

INTRODUCTION

In chemistry, the term "complex" refers to a molecule or ensemble of molecules generated by the interaction of ligands and metalions. A complexis defined as a reversible association of molecules, atoms, or ions held together by weak chemical bonds. Metal complexes are generated almost irreversibly, and the donor acceptor process is responsible for the formation of many complexes. The lone pair of electrons can be donated by a neutral molecule or ion of an on metallic material. The acceptor is usually a metallic ion, but it can also be a neutral atom **[1]**. Different type of complexes are given in **Table 1**.

Table 1: Types of complexes

Metal ion complexes	**Organic complexes**	**Inclusion complexes**
Inorganic complexes	**Quinhydrone complexes**	**Channel lattice complexes**
Chelates	**Picric acid complexes**	**Layer type complexes**
Olefin complexes	**Drug-polymer complexes**	**Clath rates**
Aromatic complexes		**Mono macromolecular complexes**

Mechanism of complexation:

There are four favorable interactions between cyclodextrin and the active medication that cause the equilibrium to move toward the formation of complexes. The polar water molecule is displaced from the polarcyclodextrin cavity. As the displaced water returns to the larger pool, a greater number of hydrogen bonds are produced. As the active medication inserts itself into the polar cyclodextrin cavity, the hydrophobic interaction increases.

The initial equilibrium for complex formation is fairly quick, but the final equilibrium can take a long time to achieve. The active drug adjusts its structure once inside the cyclodextrin cavity to take full advantage of the weak vanderwaal force **[2]**.

DRUG DESCRPTION

Valsartan was first approved for the treatment of hypertension in adults in Europe in 1996. This medicine was approved in the United States shortly after, in 1997. Valsartan is an angiotensin-receptor blocker inhibitor (ACE inhibitor) that is used to treat hypertensional one or in combination with other antihypertensive drugs, as well as to treat heart failure in individuals who are intolerant to ACE inhibitors. Valsartan is typically well tolerated, having a lower risk of adverse effects than other antihypertensive medications. Valsartan is an angiotensin II receptor blocker (ARB) that binds to angiotensin receptor 1 (AT1) and prevents angiotensin II from binding and exerting its hypertensive effects. Vasoconstriction,

aldosterone and ADH stimulation and production, cardiac stimulation, and sodium reabsorption by the kidneys are just a few of them. The physiologic effects of valsartan include lower blood pressure, lower aldosterone levels, reduced cardiac activity, and enhanced salt excretion **[3]**.

CYCLODEXTRINS:

In recent years, various methods of complexation with cyclodextrins have acquired widespread adoption in industry for improving the solubility and dissolution rate of poorly soluble medicines. Cyclodextrins are torus-shaped molecules having a hydrophilic outer surface and a lipophilic core chamber that may hold a wide range of lipophilic drugs. Many physicochemical qualities, including as solubility, dissolution rate, stability, and bioavailability, can be improved as a result of the inclusion process. Because of their clearance by various regulatory agencies, cyclodextrins have become more widely used in pharmaceutical formulations in recent years. Enzymatic conversion is used to create cyclodextrins from starch. CDs are cyclic oligosaccharides with six (α-CD), seven (β-CD), or eight (γ-CD) 1,4-linked glucopyranose units on the outside and a hydrophobic cavity in the center. There are only a handful energetically favorable interactions that can assist change the equilibrium in the direction of complex formation.

- The polar water molecule is displaced from the polar cyclodextrin cavity.
- As the displaced water returns to the larger pool, a greater number of hydrogen bonds are produced. The hydrophobic guest's repulsive contact with the watery environment is reduced.
- As the visitor inserts itself into the polar cyclodextrin cavity, the hydrophobic interaction increases **[4]**.

MODIFIE DCYCLO DEXTRIN:

It is known as 2-hydroxypropyl beta cyclodextrin (HP- β-CD). Because of the relatively strong intramolecular hydrogen bonding in the crystal lattice, CDs have reduced water solubility. Among all naturally occurring cyclodextrins, -cyclodextrin has the lowest water solubility. The solubility and inclusion capacity of parent CDs are improved by hydroxylation or methylation of the hydroxyl groups of-cyclodextrin. Chemical modification considerably increases the usefulness of cyclodextrins due to the availability of many reactive hydroxyl groups **[5]**.

MATERIALS AND METHODS

CHEMICALS:

The materials that were the analytical grade available are valsartan was supplied by

Hetero pharmaceuticals, polymers were purchased from Himedia and ethanol was purchased from Jiangsu Huaxi International trade Co.Ltd.

Phase solubility studies:

The method described by Higuchi and Connors was used to conduct phase solubility studies. Each containing different amounts of β-CD and Hydroxy propyl-β-CD such as 0, 2, 4, 6,8, and 10millimoles/liter, an excess of valsartan VAL (5mg) was added to a 10 ml quantity of distilled water. All of the above solutions were agitated in a rotary shaker for 72 hours with varying amounts of β-CD and HP-β-CD. After shaking, the sample was filtered and the dissolution and stability constants were computed using the phase solubility diagram and the equation below **[6-10]**.

Ke=slope/S0(1-slope)

Construction of calibration curve:

Weighed required quantity of valsartan and dissolved in suitable buffer. From the solution solar (1:1) ratio quantity of valsartan, β-cyclodextrin, hydroxylpropyl-β-cyclodextrin were weighed and mixed separately in a mortar by vigorous trituration for 1 hour. The mixtures were then passed throughsieveno.80 and stored in an air tight container.

Kneading method:

Valsartan with β-CD in 1:1 molar ratio was taken. First cyclodextrin is added to the mortar a small quantity of 50% ethanol is added triturating to get slurry like consistency. Then slowly drug is added while triturating to get slurry like consistency for one-hour. Slurry is then dried at 25ºC for 24hours, and then pulverized and passed through sieve no.80

Solvent evaporation method:

Inclusion complex (1:1) was prepared by dissolving equimolar amount of valsartan. Dissolve required amount of valsartan in 99.9% ethanol and β-CD, HP-β-CD were dissolved in water. The solutions were mixed together and stirred for one hour till a clear solution was observed. Ethanol was evaporated by heating at 50ºC under constant stirring, water was removed under reduced pressure using rotary evaporator. The mixture was placed overnight for 24 hours in an oven at 50ºC to remove residual solvent **[11, 12]**.

Spray drying:

Valsartan and β-cyclodextrin and hydroxypropyl propyl-β-cyclodextrin were spray dried which involves the spraying of liquid filled formulation into a hot drying medium (air, nitrogen). The droplets formed by the atomization process and dried through

solvent evaporation of orm particles which are collected as a dry powder the drying of the spray continues until the desired moisture content in the dried particles is achieved. And the product is recovered from the air **[13]**.

Drug content estimation:

100mg of drug β-CD complexes was accurately weighed and transferred to 100ml conical flask and volume was made upto the mark with methanol. From this 1ml was taken in10ml volumetric flask and volume is adjusted up to mark with same solvent. The absorbance of the solution was measured at 248 nm using appropriate blank. The drug content of valsartan was calculated using calibration curve.

Fourier transforms infrared (FT-IR) Spectroscopy:

Fourier transform IR spectra were recorded on Bruker. The spectra were recorded for valsartan β-CD physical mixture, kneaded and co-evaporated and precipitated method. Samples were prepared in KBr disc (2mg sample in 200mg KBr). The scanning range was 400-4000cm, resolution was 4 cm.

Differential scanning calorimeter (DSC):

The samples were analyzed by DSC. By placing 5mg of sample into pierced aluminum containers. The studies were performed under nitrogen gas in the temperature range of 20 to 300^{o}C at a heat range of 10^{o}c/min. The peak temperatures were determined after calibration with standard.

In vitro dissolution studies for Valsartan-CD complexes: In vitro dissolution of valsartan inclusion complex was studied in USP XXIV dissolution apparatus (Lab1) employing a paddle stirrer, 900ml of phosphate buffer of PH 6.8 was used as dissolution medium at 50 rpm. The temperature of 37±0.5^{o}C. Was maintained throughout the experiment. Complex equivalent to 5mg of VAL was used in each 5ml of sample of dissolution medium were withdrawn by means of syringe fitted at known intervals of time absorbance and analyzed for drug release by measuring the absorbance at 250nm after suitable dilution with phosphate buffer. The volume withdrawn at each time intervals was replaced with fresh quantity of dissolution medium. The amount of valsartan released was calculated and plotted against time and compared with pure drug. The percent drug release profile of inclusion complex.

Table 2: Formulation table

S. No.	Formulation	Abbrevation
1	F_1	VAL
2	F_2	VAL+β-CD(KM)
3	F_3	VAL+HP-β-CD(KM)
4	F_4	VAL+β-CD(SE)
5	F_5	VAL+HP-β-CD(SE)
6	F_6	VAL+β-CD(SD)
7	F_7	VAL+HP-β-CD(SD)

RESULTS

PHASESOLUBITLITYSTUDIES:

Phase solubility of drug with (2-hydroxypropyl) β-cyclodextrin:

Table 3: Phase solubility studies of drug with (2-hydroxypropyl) β-cyclodextrin:

S. No.	Concentration	Solubility
1	0	0.0234
2	0.1	0.12
3	0.2	0.21
4	0.3	0.30
5	0.4	0.38

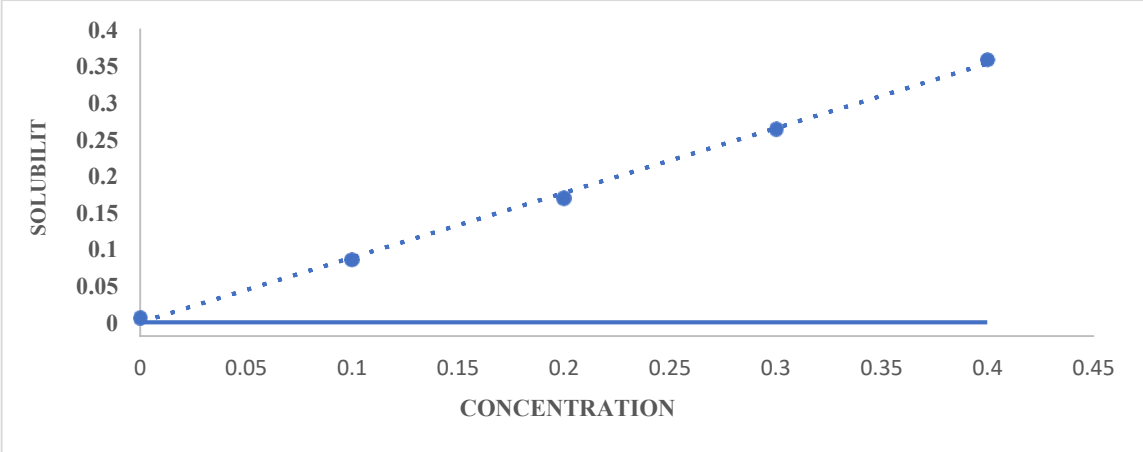

Figure 1: Phase solubility of drug with (2-hydroxypropyl)β-cyclodextrin

PHASE SOLUBILITY OF DRUG WITH β-CYCLODEXTRIN:

Table 4: Phase solubility studies of drug with β-cyclodextrin:

S. No.	Concentration	Solubility
1	0	0.234
2	0.1	0.1
3	0.2	0.18
4	0.3	0.27
5	0.4	0.36

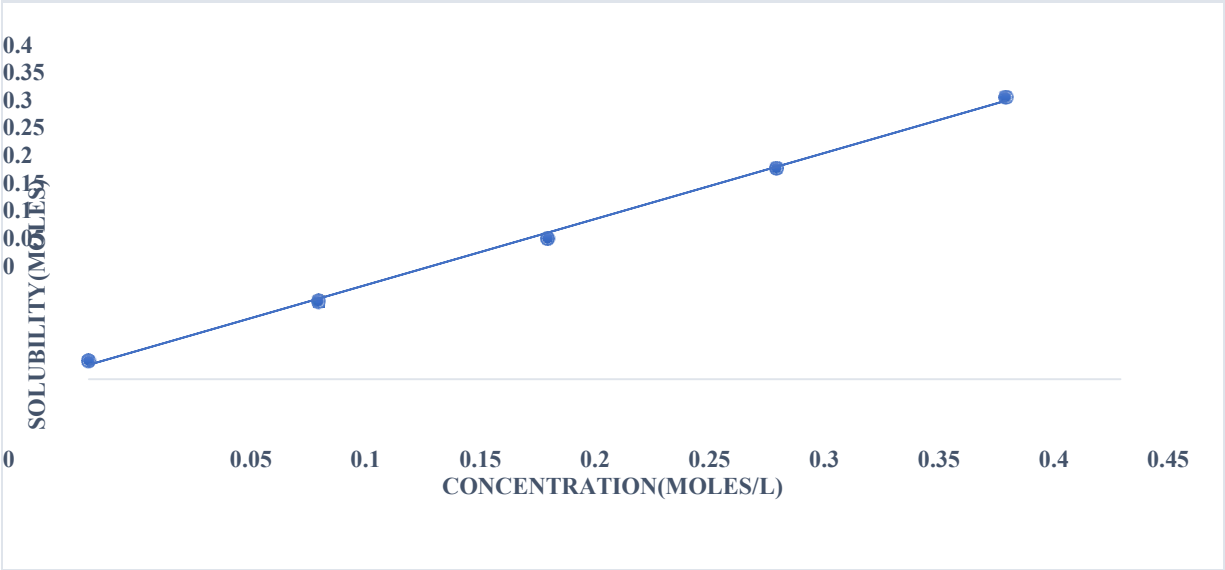

Figure 2: Phase solubility of drug with cyclodextrin

The solubility of valsartan in water was found to be 0.0234mg/ml. the phase solubility diagrams of VAL: β-CD and HP-β-CD was obtained by plotting the changes in guest solubility as a function of β-CD, HP- β-CD concentration. The solubility curves were classified as the AL according to Higuchi and Connors shown that the apparent solubility of VAL increases linearly as a function of β-CD and HP—CD over the entire concentration range and was the characteristic of AL type of curve, which suggests that water-soluble complex, was formed in solution. The phase solubility profile indicated that the solubility of valsartan was significantly increased in the presence of β-CD, HP-β-CD. The stability constant (K_S) was found to be 165.4±2M^{-1} for β-CD and 263±$M^{-1}$for HP-β-CD.

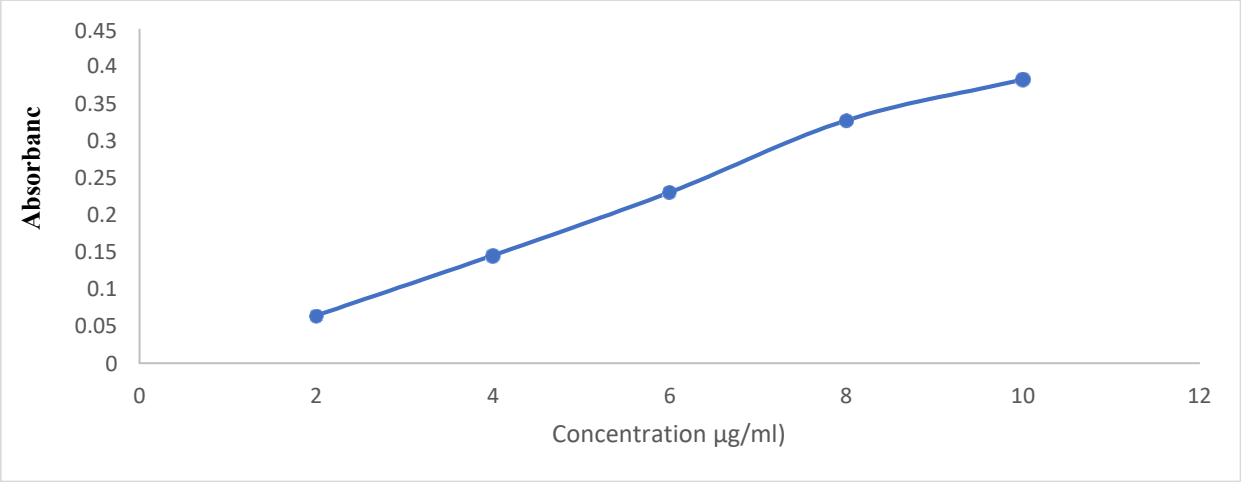

Figure 3: Standard Calibration Curve of Valsartan Drug Content Estimation

Table 5: Standard Calibration Curve of Valsartan at 250nm

S. No.	Concentration (µg/ML)	Absorbance at 250nm		
		Trail-I	Trail-II	Trail-III
1	2	0.066	0.063	0.064
2	4	0.144	0.147	0.145
3	6	0.245	0.215	0.230
4	8	0.292	0.363	0.327
5	10	0.375	0.390	0.382

UV spectroscopy was used to determine the drug content of the binary system of the β-CD,HP- β-CD: drug molar ratio (1:1). The β-CD, HP- β-CD drug ratio would therefore remain 1:1 in the in the final solution to calculate the drug content. The drug content in all the system was found to be 95 to 101%.

DIFFERENTIAL SCANNING CALORI-METRY:

DSC is a thermo analytical technique. In which the difference in the amount of heat required to increase the temperature of the sample and reference is measured as a function of temperature. Thermal transition temperature i.e melting point of valsartan with β-CD and HP-β-CD which are prepared by different methods were determined.

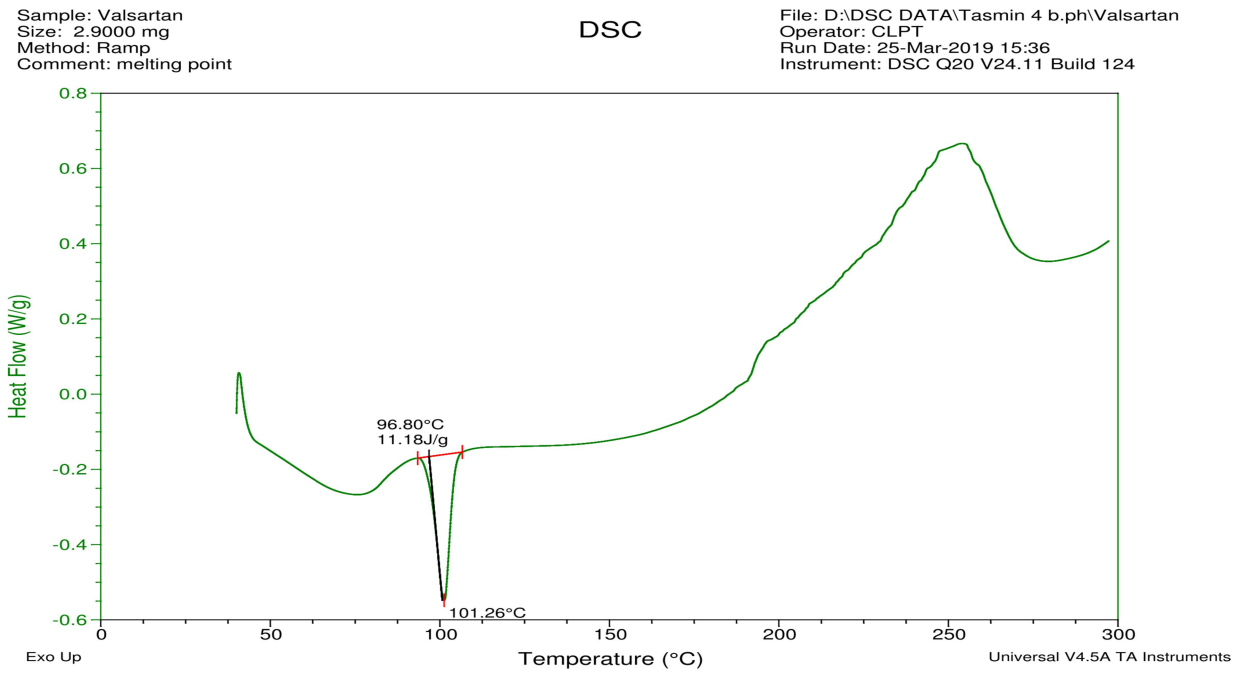

Figure 4: DSC curve of valsartan

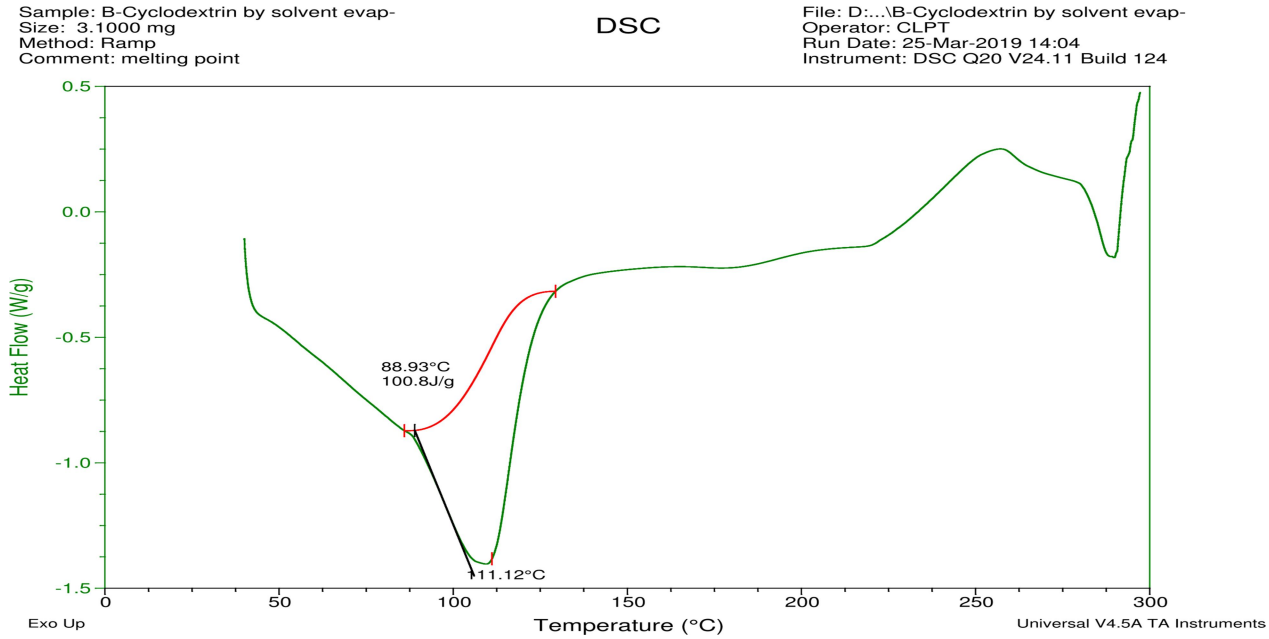

Figure 5: DSC curve of valsartan and β-cyclodextrin by solvent evaporation method

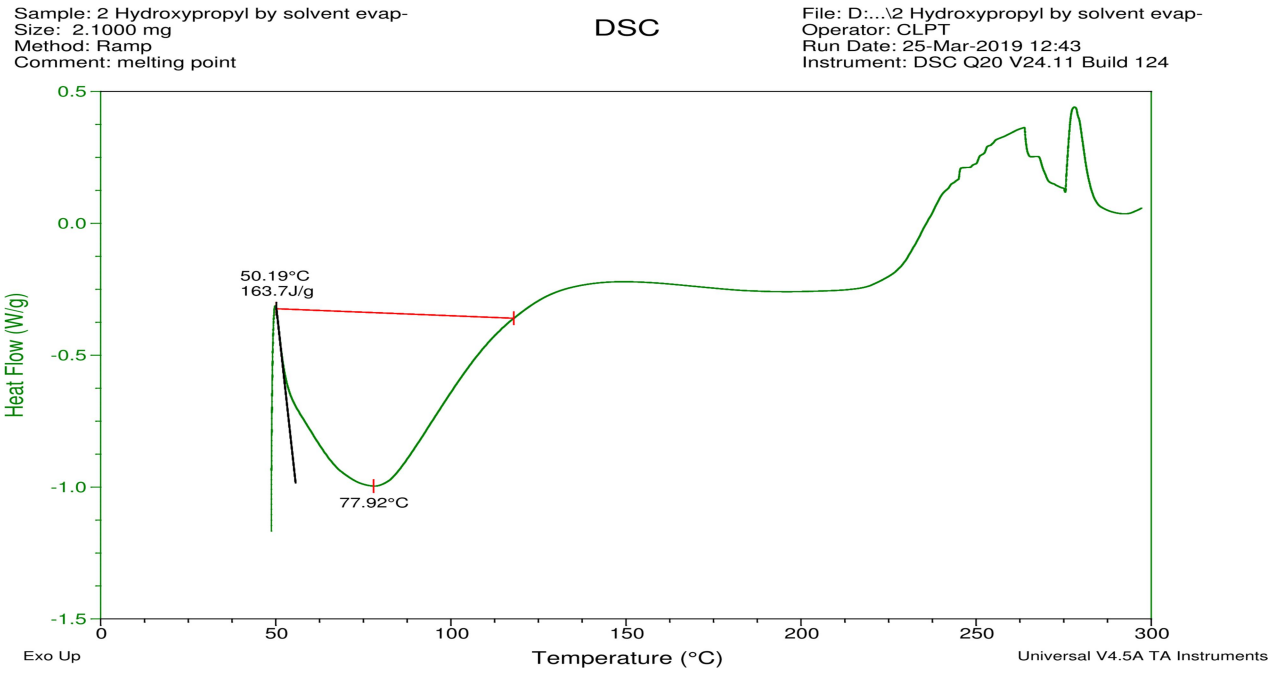

Figure 6: DSC curve of valsartan and (2-hydroxypropyl) β-cyclodextrin by solvent evaporation method

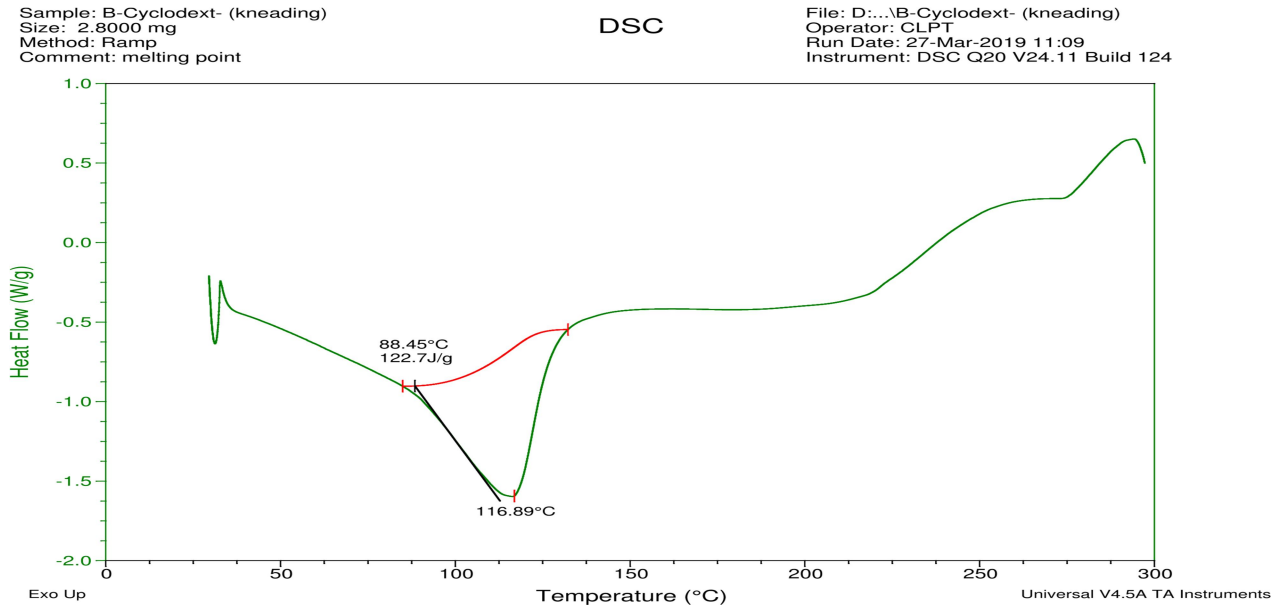

Figure 7: DSC curve of valsartan and β-cyclodextrin by kneading method

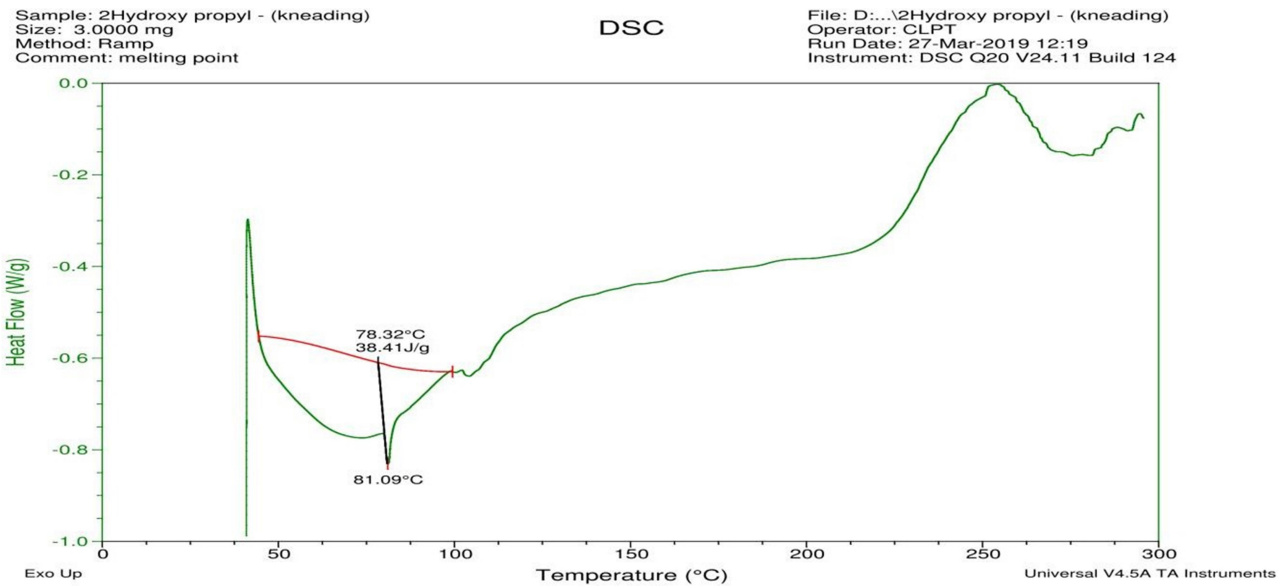

Figure 8: DSC curve of valsartan and (2-hydroxypropyl) β- cyclodextrin by Kneading method

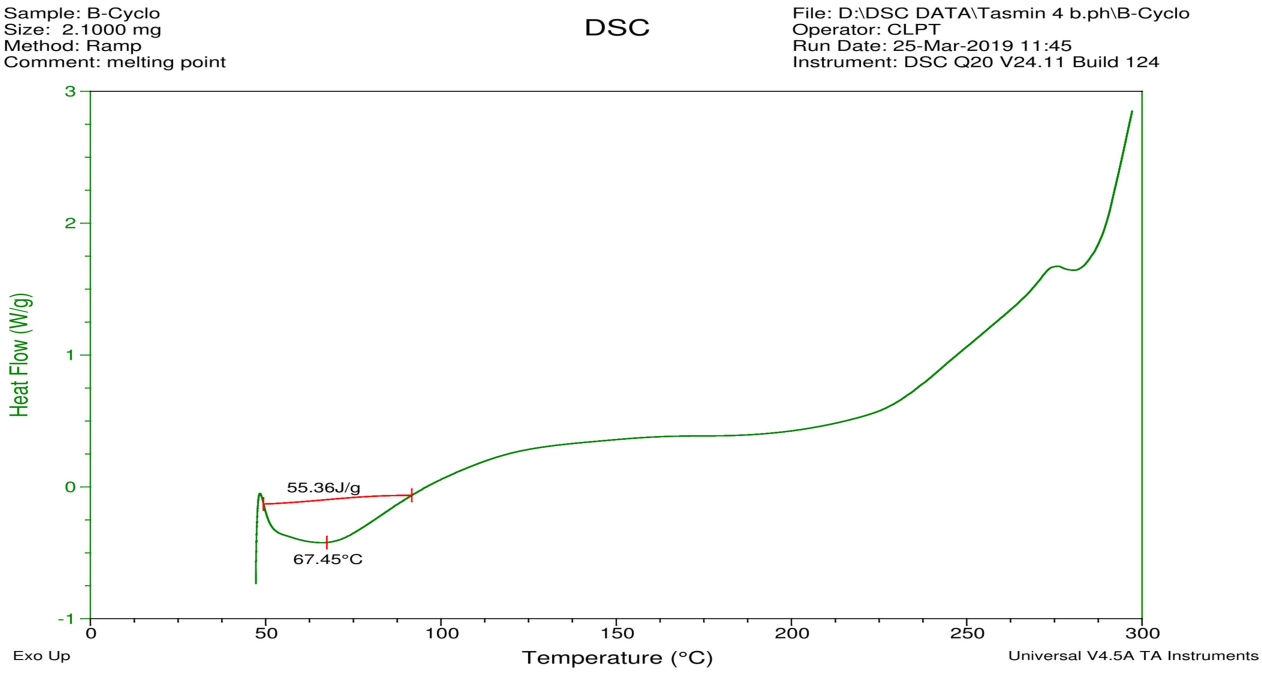

Figure 9: DSC curve of valsartan and β- cyclodextrin by spray drying method

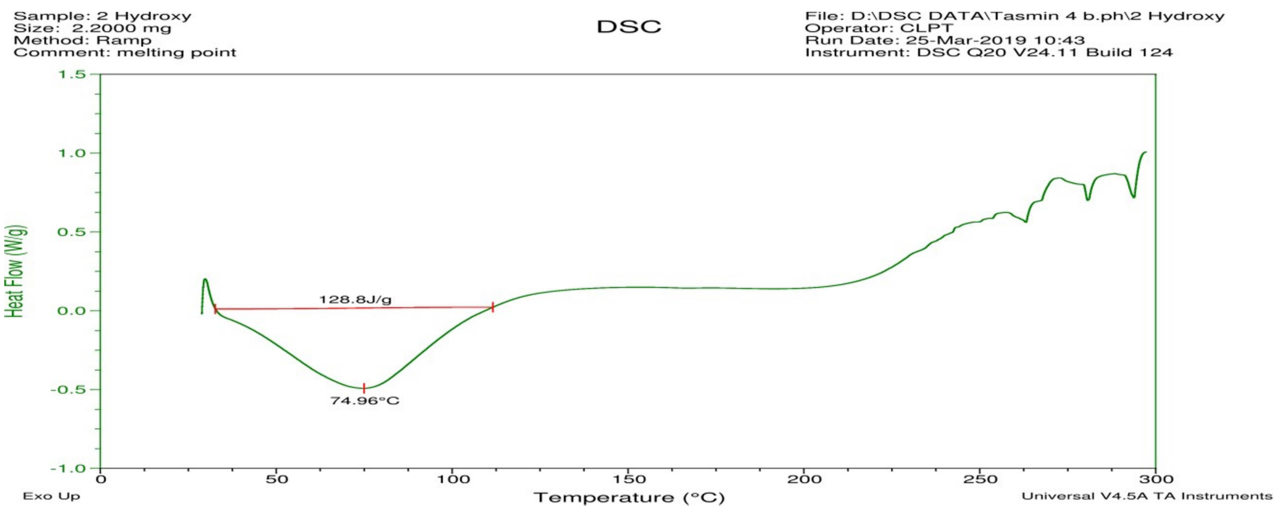

Figure 10: DSC curve of valsartan and (2-hydroxypropyl)β- cyclodextrin by spray drying method

IRSPECTROSCOPY:

Compatibility with carriers was confirmed by FTIR studies. The pure drug and carriers were subjected to FTIR studies. In this study, the potassium bromide disc (pellet) method was employed. IR spectra of pure drug and inclusion complexes of valsartan with β-CD, HP-β-CD prepared by different methods are given in **Figure 11**.

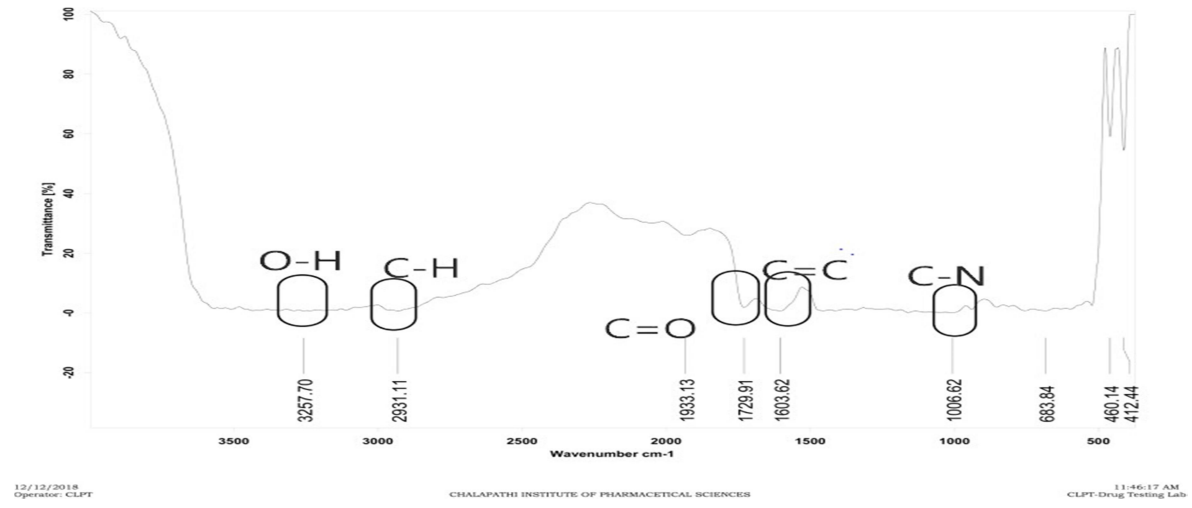

Figure 11: FTIR spectrum of valsartan

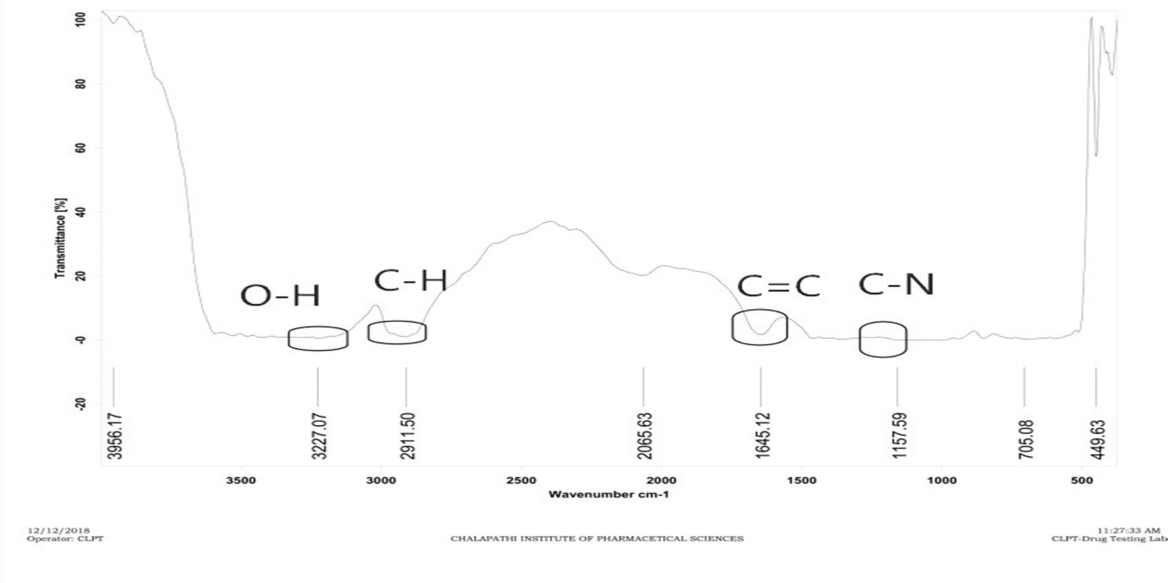

Figure 12: FTIR spectrum of inclusion complexes of valsartan and β-cyclodextrin by kneading method

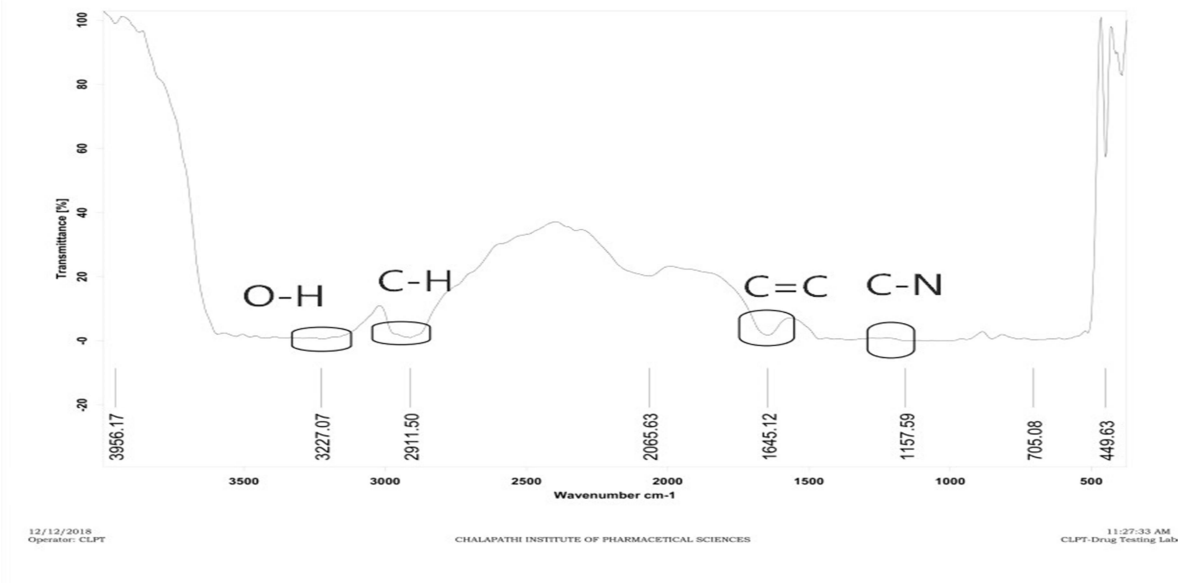

Figure 13: FTIR spectrum of inclusion complexes of valsartan and (2-hydroxypropyl) β-cyclodextrin by kneading method

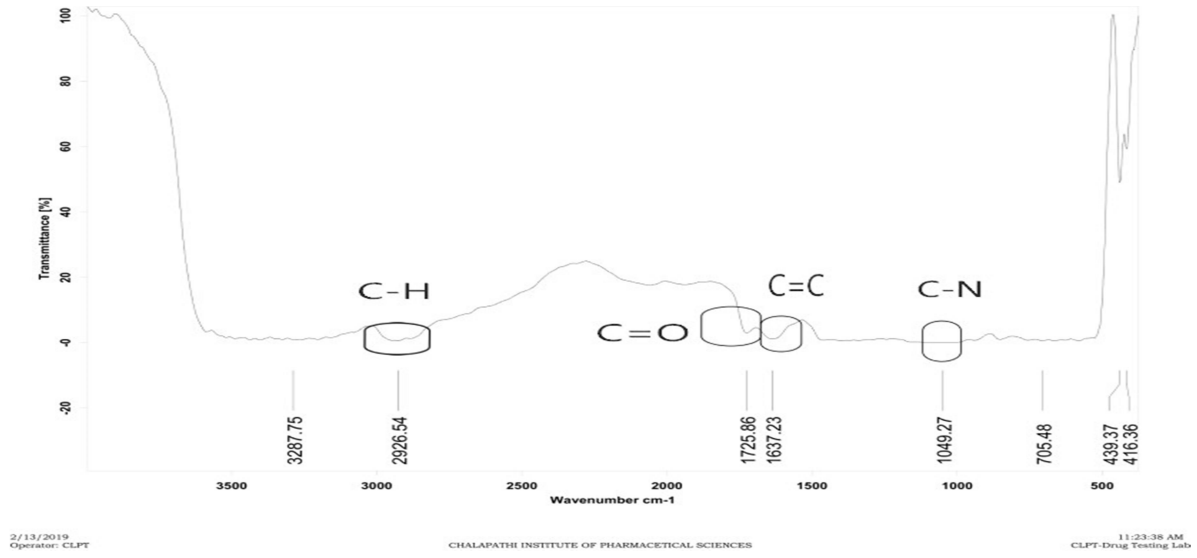

Figure 14: FTIR spectrum of inclusion complexes of valsartan and β-cyclodextrin by solvent evaporation method

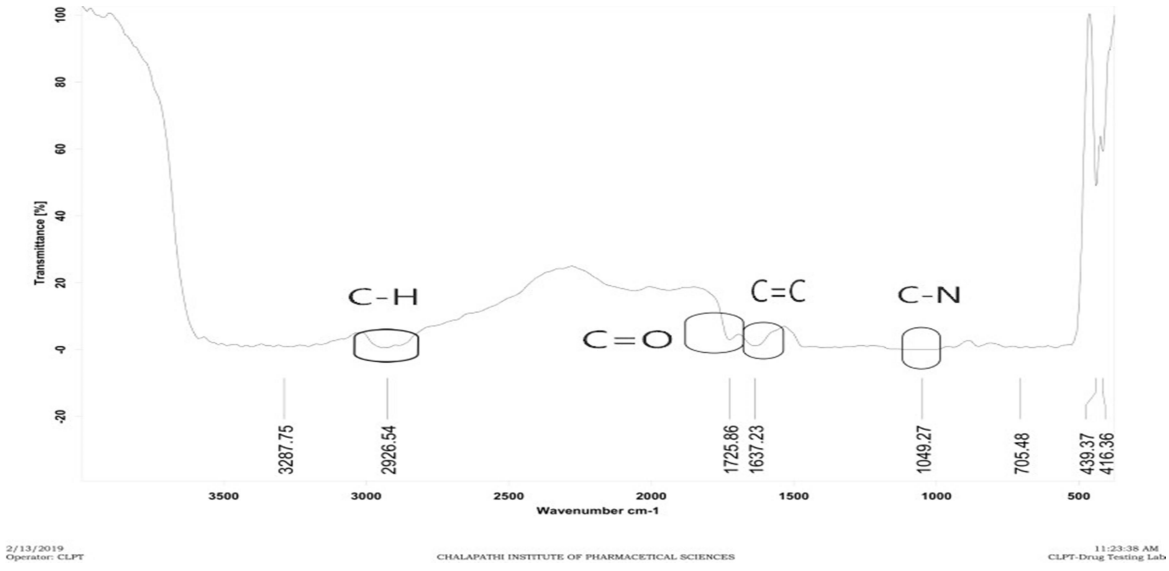

Figure 15: FTIR spectrum of inclusion complexes of valsartan and (2-hydroxypropyl) β-cyclodextrin by solvent evaporation method

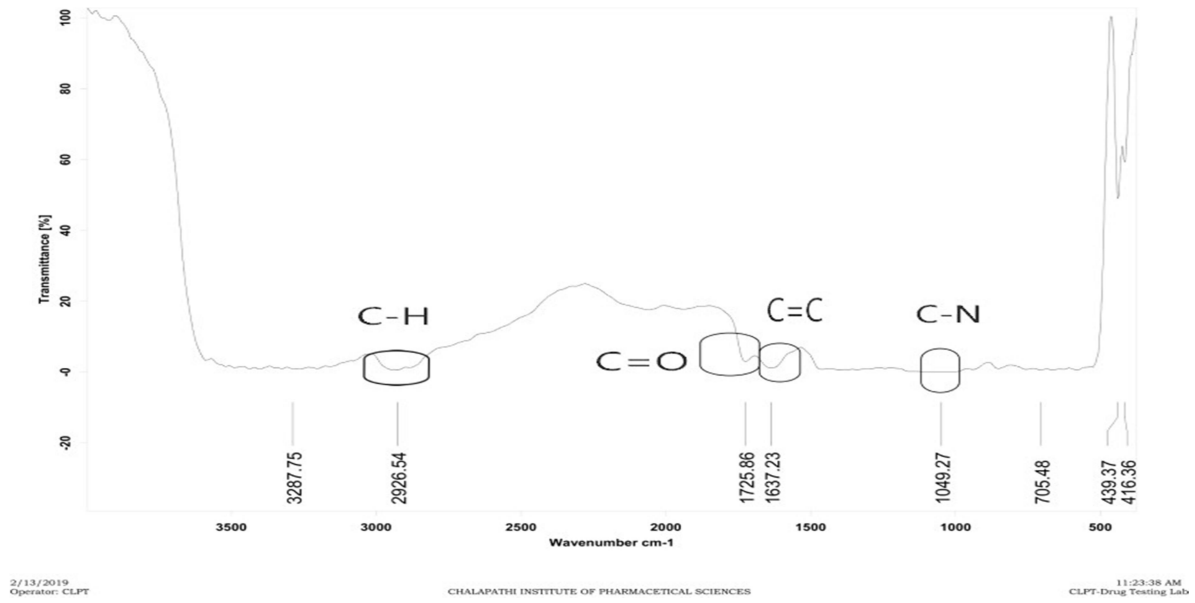

Figure 16: FTIR spectrum of inclusion complexes of valsartan and β-cyclodextrin by spray drying method

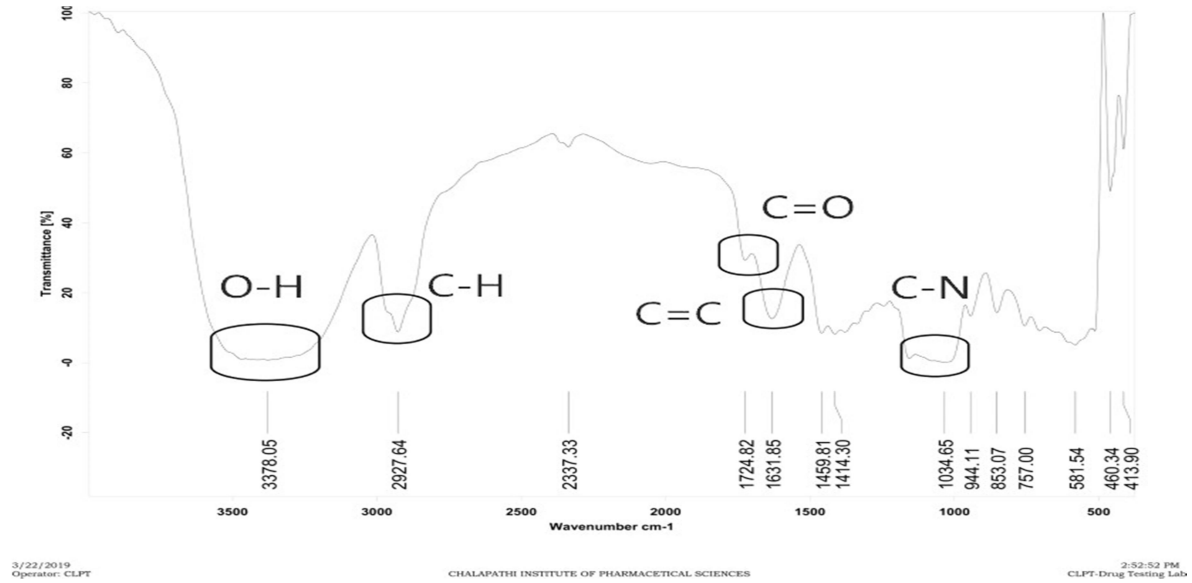

Figure 17: FTIR spectrum of inclusion complexes of valsartan and (2-hydroxypropyl) β-cyclodextrin by spray drying method

IN VITRO DISSOLUTION STUDIES:

Table 6: *In vitro* dissolution study of formulation F1, F2, F3, F4

Time (min)	% Drug Dissolved			
	F1	F2	F3	F4
5	2.5±0.892	8.2±0.298	12.1±0.356	15.3±0.775
10	5.4±0.695	24.2±0.892	25.4±0.653	29.3±0.987
20	11.3±0.461	30.3±0.982	40.2±0.417	41.3±0.772
30	21.2±0.581	40.5±0.829	55.4±0.983	70.4±0.876
45	27.5±0.815	44.3±0.678	62.3±0.473	76.2±0.678
60	33.4±0.158	50.3±0.689	72.2±0.503	79.5±0.549

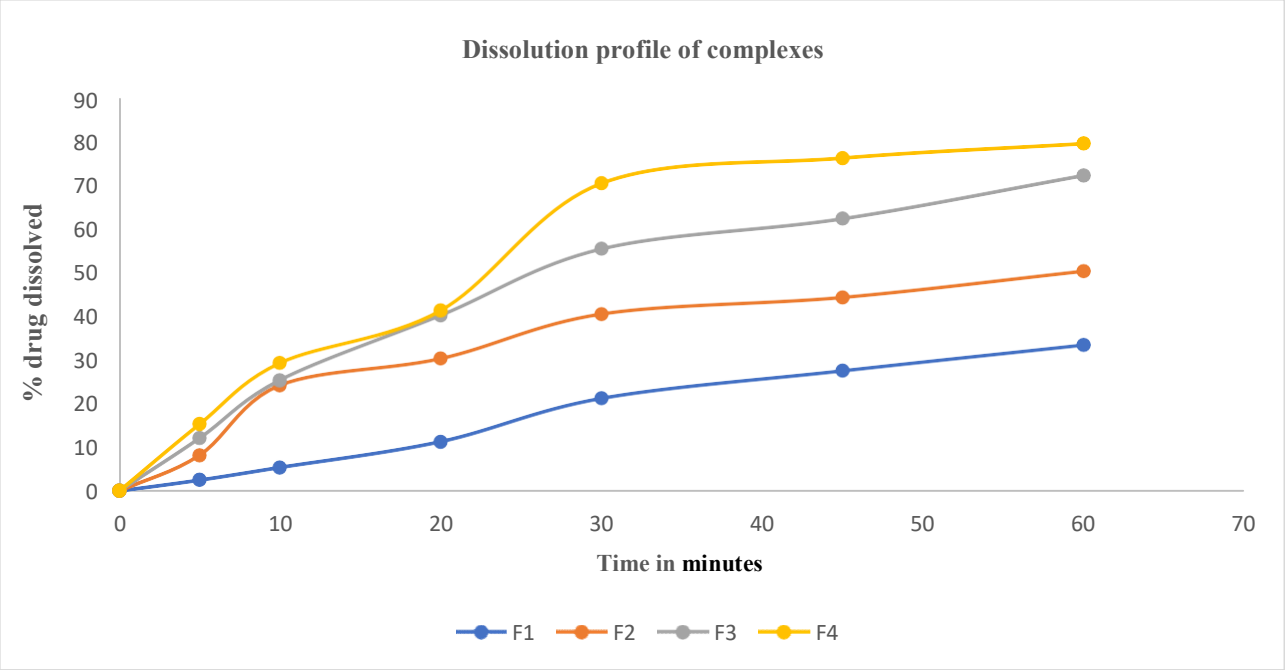

Figure 18: Dissolution profile of formulation F1, F2,F3, F4

Table 7: In vitro dissolution study of formulation F5, F6, F7

Time (min)	% DRUG DISSOLVED		
	F5	F6	F7
5	11.2±0.112	26.3±0.453	35.3±0.768
10	25.6±0.397	39.5±0.543	48.5±0.432
20	39.7±0.0604	42.5±0.765	56.2±0.675
30	60.4±0.685	61.12±0.235	76.5±0.843
45	65.3±0.542	70.23±0.876	84.5±0.245
60	83.5±0.442	89.45±0.675	94.3±0.564

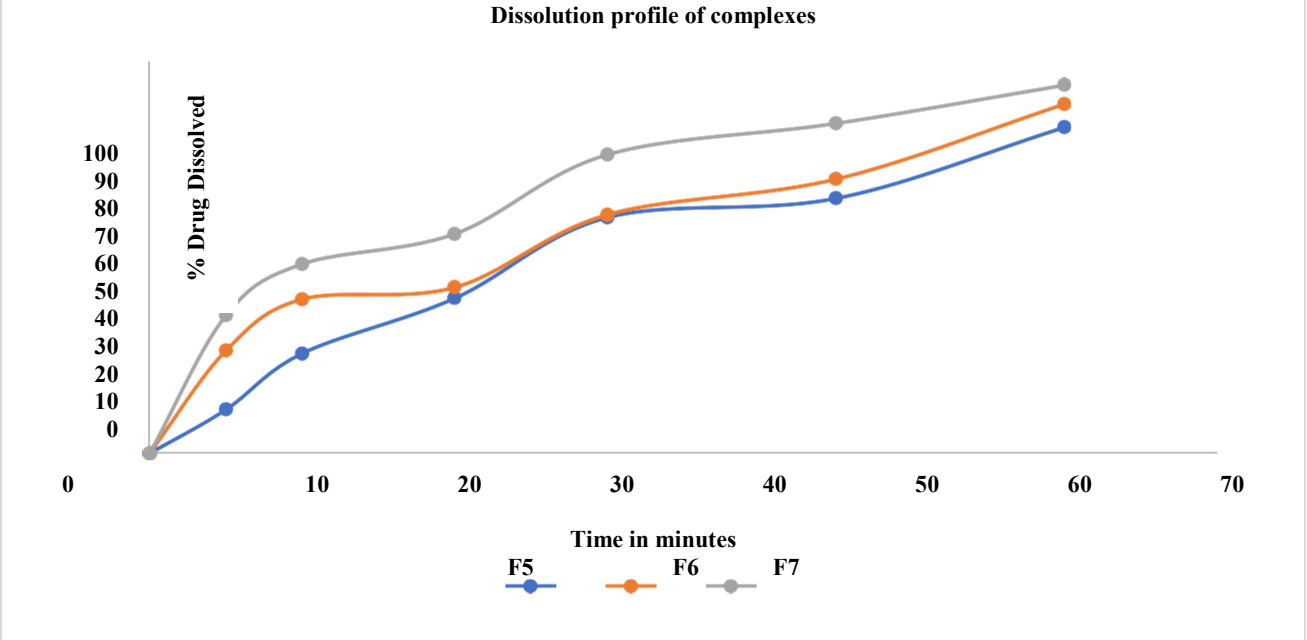

Figure 19: Dissolution profile of formulation F5, F6, F7

SUMMARY

Valsartan is a BCS class II drug which is poorly water soluble and highly permeable. The used dose of valsartan is 10mg orally once in a day for the treatment of anti–hypertension (angiotensin blocker). This research work is done to enhance the dissolution rate of valsartan with β –CD, HP-β-CD by complexation. The absolute bioavailability was found to be 25 %. The water solubility of valsartan was found to be 0.0234 mg/L the phase solubility studies AL type of curve. The variousinclusion complexes were prepared by using different methods like kneading, solvent evaporation, spray dryer method in 1:1 ratio by using carriers like β-CD, HP-β-CD. The prepared complexes were characterized by FRIR, DSC.

1. Formulation F2 which is drug and β-CD complexes was prepared by kneading method shows improved dissolution rate by 1.5folds compared to the pure drug. The FTIR shows no incompatibility between the drug and the

carrier. DSC shows melting point of 116.89ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates transition from crystalline to amorphous form.

2. Formulation F3 which is drug and 2HP-β-CD complexes was prepared by kneading method shows improved dissolution rate by 2.1 folds. The FTIR shows no incompatibility between the drug and the carrier. DSC shows melting point of 81.09ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates transition from crystalline to amorphous form.

3. Formulation F4 which is drug and β-CD complexes was prepared by solvent evaporation method shows improved dissolution rate by 2.3 folds. The FTIR shows no incompatibility between the drug and carrier. DSC shows melting point of 111.12ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates the transition from crystalline to amorphous form.

4. Formulation F5 which is drug and 2 HP-β-CD complexes was prepared by solvent evaporation method shows improved dissolution rate by 2.5 folds. The FTIR shows no incompatibility between the drug and carrier. DSC shows melting point of 77.92ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates the transition from crystalline to amorphous form.

5. Formulation F6 which is drug and β-CD complexes was prepared by spray drying method shows improved dissolution rate by 2.6 folds. The FTIR shows no incompatibility between the drug and carrier. DSC shows melting point of 67.45ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates the transition from crystalline to amorphous form.

6. Formulation F7 which is drug and 2 HP-β-CD complexes was prepared by spray drying methodshows improved dissolution rate by 2.8 folds. The FTIR shows no incompatibility between the drug and carrier. DSC shows melting point of 74.96ºC. The change in melting point indicates the formation of inclusion complex. The broad endothermic peak indicates the transition from crystalline to amorphous form.

CONCLUSION

Valsartan is a BCS class II drug which is poorly water soluble and highly permeable the absolute bioavailability was found to be 23%. It is used in the treatment of anti-

hypertension. In this research work mainly to enhance the dissolution rate of valsartan with β-CD and HP-β-CD by complexation. The phase solubility study gives AL type of curve. The various inclusion complexes were prepared by using different methods like kneading method, solvent evaporation method and spray drying methods in 1:1 molar ratio by using carriers like β-CD and HP-β-CD. To this complex we performed compatibility studies like FTIR and DSC. The prepared complexes showed improved dissolution rate compared to pure drug, hence the complexes will improve the bioavailability of drug. The inclusion complexes prepared by spray drying technique with 2.6 folds for β-CD and 2.8 folds for HP-β-CD increases the dissolution rate of the drug than the other methods.

ACKNOWLEDGEMENT

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