Inclusion Complexation of Antihypertensive Drug for Solubility Enhancement to Increase Its Bioavailability

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Author’s contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Carvedilol is a β- adrenergic receptor blocker, and it has the ability to decrease the heart rate, myocardial contractility and myocardial oxygen demand. It competitively blocks β-1, β-2 and α-1 receptors. It also lacks sympathomimetic activity and has vasodilating properties that are extended primarily through α-1 blockade. The poor aqueous solubility of carvedilol leads to poor bioavailability and poor dissolution rate in the biological fluid. Therefore, it can be overcome by inclusion complexation using β- cyclodextrin. The inclusion complexes of carvedilol were made using different concentrations of β- cyclodextrin and behaviour of β-cyclodextrin was studied towards the carvedilol in order to develop a new oral dosage form having enhanced dissolution rate and bioavailability. On studying the phase diagram of carvedilol it showed AL type phase solubility. Inclusion complexes with β-cyclodextrin and its physical mixture with different ratios were studied for dissolution study and their characterisation was confirmed by DSC, FTIR and SEM analysis. Inclusion complexes of carvedilol were successfully formed and showed more drug release profile as compared to their physical mixtures. The significant improvement in the rate of release of β-CD complex formulation can help in appreciable reduction in the lag time of the drug absorption, characterised by high $t_{max}$ values (120 minutes), thereby can improve the rate of bioavailability and onset of its therapeutic effects.
Keywords: Inclusion complex; carvedilol; solubility enhancement; cyclodextrins (CDS).

1. INTRODUCTION

The term complexation is defined as the reversible association of “m” molecules of a substrate with ‘n’ molecules if ligand species to form a new species “SmLn” as per equation given below

\[ ms + nl \xrightarrow{K_{m:n}} SmLn \]

Where, \( K_{m:n} \) is the equilibrium constant and is described using equation given above.

\[ K_{m:n} = \frac{[SmLn]}{[S][m][L]} \]

Cyclodextrins represents a group of structurally related oligosaccharide [1]. They have cylindrical shaped cavities that have their capacity to form inclusion complexes with drugs by taking the whole drug molecule or part of it into the cavity. The cyclodextrins are the water soluble in nature due to the presence of large no hydroxyl groups in it. Their tendency to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity without forming covalent bond make them special in drug delivery. Inclusion complexes are the entities comprising of two or more molecules in which one of the molecule which is the host molecule and second one is guest molecule. The ability of cyclodextrins to form an inclusion complex with guest molecule is depends upon two key factors [2].

Stearic factor: It depends on the relative size of the cyclodextrins to the size of the guest molecule or the functional groups present within the guest molecule. If the size of guest is of the wrong size it will not fit into cyclodextrin cavity [3].

Thermodynamic interactions: It is the interactions between different components of the inclusion complex system i.e. cyclodextrin, guest and the solvent. For a complex to form there must be a favourable net energy driving force that helps to pull the guest into the cavity of cyclodextrin. Under physiological conditions the complexes of cyclodextrin undergo into dissociation due to no covalent binding between host and the guest molecule [4,5]. The various parameters that influences the dissolution rate are summarised in Table 1.

1.1 Advantages of Cyclodextrin as Drug Carriers

- They provide number of potential sites for chemical modification.
- They can entrap the drugs with different molecular size/dimension due to different cavity size
- The microenvironment in the cavity is relatively non polar and lipopholic
- Low toxicity and low pharmacologically active
- They have good aqueous solubility
- They are resistant to hydrolysis due to organic acids, alpha amylase and also resistant to yeast fermentation and beta amylase
- Not decomposed by hot alkali.
- High thermal stability.
- They protect the included/conjugated drugs from biodegradation

Table 1. Parameters influencing the dissolution rate

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Symbols</th>
<th>Effect on dissolution of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion coefficient of drug</td>
<td>D</td>
<td>Greater the value faster the dissolution rate</td>
</tr>
<tr>
<td>Surface area of solid drug</td>
<td>A</td>
<td>Greater the surface area of drug, faster the dissolution rate</td>
</tr>
<tr>
<td>Water/oil partition coefficient</td>
<td>K(W/O)</td>
<td>Higher the value, more is the hydrophobicity and faster is the dissolution rate</td>
</tr>
<tr>
<td>Thickness of unstirred water layer</td>
<td>H</td>
<td>More is the thickness, lesser is the diffusion and dissolution of drug</td>
</tr>
<tr>
<td>Concentration gradient</td>
<td>(C_S-C_B)</td>
<td>Greater is the concentration gradient, faster is the diffusion and drug dissolution</td>
</tr>
</tbody>
</table>
2. MATERIALS AND METHODS

Carvedilol was kindly supplied by M/s Shodhana Labs Ltd. Hyderabad, India as a gift sample. β-cyclodextrin was gifted by M/s Aarti Drugs Ltd. Mumbai, India.

2.1 Preliminary Studies

2.1.1 Characterisation of Drug

The procured sample of carvedilol was characterised in terms of its physical description, organoleptic properties, melting point and solubility in various solvents [6,7].

2.1.2 Melting Point Determination

A small quantity of carvedilol was filled in the capillary tube sealed at one end and kept in melting point apparatus. The melting point was recorded and compared with literature value of carvedilol [8].

2.1.3 Solubility Studies

The solubility of carvedilol was checked in distilled water and 0.1 N HCL using rotary shaker for 24 hrs at room temperature. The solubility of drug was determined by saturation method. In this 1mg/ml saturated solution of drug in the solvent was made. Out of this solution 25 ml. was taken in 50 ml of volumetric flaks and was shaked with the help of rotary shaker for 24 hours. The solution was filtered with the help of Whatman filter paper and suitable dilutions were made to note the absorbance. Concentration of drug in the solution was determined and from this concentration amount dissolved in the solvent i.e. solubility was determined [8].

2.2 Establishment of Calibration Plot

To conduct the in vitro drug dissolution studies, standard plot for pure drug was constructed. 100 mg of carvedilol was accurately weighed and transferred to a 100 mL volumetric flask and volume was made upto 100 mL with 0.1 N HCL. The contents of flask were shaken to dissolve the carvedilol [9].

The resulting solution was 1000 μg/mL and labeled “Stock solution.” 10 mL of this solution was transferred to another volumetric flask and was diluted up to 100 mL with 0.1 N HCL to obtain 100 μg/ml solution of carvedilol. 10 mL of this solution (100μg/mL) was transferred to another volumetric flask and was diluted up to 100 mL with 0.1 N HCL to obtain 10 μg/mL solution of carvedilol and it was labeled as “Standards solution.” Aliquots of 2 to 10 mL portion of this standard solution of carvedilol were transferred to series of previously labelled test tubes. The volume of each test tube was then adjusted up to 10 mL with 0.1 N HCL. The absorbance of solution from each test tube was measured at 241.2 nm using UV visible spectrophotometer against blank. Using the absorbance of carvedilol at varied concentrations, calibration curve was constructed by PCP disso V3 software. The calibration equation for straight line was observed which was further used for determination of concentration of unknown samples [10,11].

2.3 Studies on Interference of Carries(s) on Drug UV Spectrum

Carvedilol (12.5 mg) was dissolved in methanol and volume was made up to 100 ml. with 0.1 N HCL. After suitable dilutions, the U.V. spectrum of drug was obtained. In a similar way, U.V. spectra of carrier(s) viz. Mannitol, PVP K- 30, PEG-6000 and β-Cyclodextrin were obtained in the wavelength region 200 - 400 nm at their respective maximum amounts employed in the study [12,13,11].

2.4 Phase Solubility Studies

Excess of Carvedilol was added to 50 ml of volumetric flasks containing distilled water (25 ml). To these volumetric flasks β-cyclodextrin was added in successively increasing amount i.e. 0,2,4,6,8,10 and 10 Mm and then sealed. The flasks were brought to solubility equilibrium at room temperature after shaking for 72 hrs. The contents of flasks were filtered through milipore membrane (0.45) and then diluted appropriately. The amount of dissolved carvedilol was determined using spectrophotometer. The Apparent stability constant (Kc) was calculated from the phase solubility diagram as given in equation below [14,15].

\[ K_c = \frac{\text{slope}}{S_0(1-\text{slope})} \]

Where, \( S_0 \) is solubility of carvedilol in the absence of CDs.
2.5 Preparation of Physical Mixture and Inclusion Complexes with - β CD

The Physical mixtures of carvedilol with β-cyclodextrin were prepared by simple trituration method in ratios [CRL: β-CD (1:1, 1:2, 1:3 and 1:5 M)] for 1 hr using glass. Then the mixture was passed through the sieve no 100 and kept in dessiccator. Similarly for inclusion complexes stochiometric quantities of carvedilol and β-CD (1:1, 1:2, 1:3 and 1:5 M) were well tritured with small amount of ethanol (50%). The slurry with ethanol was kneaded for 1 hr and then dried at 25°C for 24 hrs. After drying it was pulvriosed and passed through sieve no. 100 and stored in desiccators [16,17].

2.6 Dissolution Studies

The dissolution study of inclusion complexes of carvedilol was studied using USP XXIII dissolution apparatus having paddle stirrer. The dissolution medium used during the study was 0.1N HCl (900 ml) was maintained at 37±0.5°C throughout the experiment. Inclusion complexes equivalent to 12.5 mg of carvedilol were used in each test and 5ml samples of dissolution medium were withdrawn by syringe pre-fitted with a filter. The absorbance of samples withdrawn was analysed for drug release at 241.2 µm [18,19,20].

2.7 Characterisation of Physical Mixture and Inclusion Complex Formulations of Carvedilol

2.7.1 X-Ray Diffractometry

X-ray Diffractometry is used for crystallography characterisation of various APIs (Active Pharmaceutical Ingredients) and excipients. It also used for study and identify the changes in APIs and excipients. The PXRD patterns were recorded using high power x-ray diffractometer with Cu as the target filter (40 KV/40 mA, 4 deg /min) using Philips PW 170 x-ray diffractometer (USA) [8,14,21].

2.7.2 Differential Scanning Calorimetry (DSC)

DSC analysis of the drug, carriers, one of the selected formulation and its physical mixture were carried out by heating the samples from 25° C to 250°C at a rate of 10°C per minute. Diffraction patterns were obtained on Philips PW 1050 diffractometer [22,13].

2.7.3 Fourier Transforms Infrared Spectroscopy (FTIR)

FTIR spectral study was performed on excipients and formulations. Samples were prepared with KBr pellets on KBr press using Perkin-Elmer 2000 FT-IR. The scanning range was 400-4000 cm⁻¹ and the resolution was 4cm [18,19,23].

2.7.4 Scanning Electron Microscopy (SEM)

The surface morphology of API, excipients and formulation was investigated by scanning electron microscopy (SEM). The samples were coated with thin gold-palladium layer using sputter coater unit and surface topography was analysed with (JCM-6100, Scanning Electron Microscope, Japan) [7,8].

3. RESULTS AND DISCUSSION

3.1 Preliminary Studies

3.1.1 Melting Point Determination

The melting point of carvedilol was observed to be 115.33°C (Table 2) which is in close agreement of reported values i.e. 114˚- 115°C.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Melting point (°C)</th>
<th>Mean value ± S.D.(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>119</td>
<td>115.33 ± 2.334</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

3.1.2 Studies on Interferences of Carrier(s) on Drug UV Spectrum

No interaction of the carrier(s) viz. Mannitol, PVP K-30, PEG-6000 and β-cyclodextrin is seen on the UV spectrum of carvedilol.

3.1.3 Solubility studies

Solubility studies were carried out as an attempt to find out whether the medium 0.1 N HCL was able to maintain sink condition during the dissolution studies or not. The solubility of pure drug in distilled water and 0.1 N HCL is depicted in Table 3. The result indicated that the solubility of carvedilol in 0.1 N HCL was 1.062 mg/ml. Since a total dose of 12.5 mg of drug was planned to be subjected for dissolution using 900 mL of medium, the equilibrium solubility was much higher than the maximum concentration of
the drug any time during the dissolution process. Therefore, 0.1 N HCL was chosen as the dissolution medium because sufficient amount of drug can dissolve in it, necessary to maintain sink conditions [19,22].

Table 3. Solubility (mg/mL) of Carvedilol in various solvents

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Solvents</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Distilled water</td>
<td>0.323 mg/mL</td>
</tr>
<tr>
<td>2</td>
<td>0.1 N HCL</td>
<td>1.062 mg/mL</td>
</tr>
</tbody>
</table>

3.2 Inclusion Complex of Carvedilol

3.2.1 Solubility Studies of Carvedilol and its Inclusion Complex

Table 4 enlists the results of solubility studies of carvedilol and its inclusion complexes with β-CD in 0.1 N HCL.

Table 4. Solubility studies of Carvedilol and its inclusion complex with β-CD in 0.1 N HCL

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Carvedilol : β-CD</th>
<th>Solubility in 0.1 N HCL in mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:0</td>
<td>1.062</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>1.366</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>1.558</td>
</tr>
<tr>
<td>4</td>
<td>1:3</td>
<td>1.801</td>
</tr>
<tr>
<td>5</td>
<td>1:5</td>
<td>2.372</td>
</tr>
</tbody>
</table>

3.2.2 Phase Solubility Studies

The phase solubility diagram for complex formation between carvedilol and β-cyclodextrin is given in Fig. 1. According to Higuchi and Connors classification, the phase solubility diagram shows the AL type curve. In the AL type phase solubility diagram the negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complexes solubility or self association of cyclodextrin.

Table 5. Phase solubility data

<table>
<thead>
<tr>
<th>Moles of β-CD</th>
<th>Conc. of Carvedilol (µg/mL)</th>
<th>Moles of Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32.71</td>
<td>0.0055</td>
</tr>
<tr>
<td>0.001</td>
<td>35.76</td>
<td>0.0058</td>
</tr>
<tr>
<td>0.002</td>
<td>42.44</td>
<td>0.0066</td>
</tr>
<tr>
<td>0.004</td>
<td>53.23</td>
<td>0.0089</td>
</tr>
<tr>
<td>0.006</td>
<td>70.12</td>
<td>0.010</td>
</tr>
<tr>
<td>0.008</td>
<td>80.22</td>
<td>0.014</td>
</tr>
<tr>
<td>0.010</td>
<td>95.15</td>
<td>0.015</td>
</tr>
<tr>
<td>0.012</td>
<td>107.22</td>
<td>0.016</td>
</tr>
<tr>
<td>0.014</td>
<td>114.34</td>
<td>0.020</td>
</tr>
<tr>
<td>0.016</td>
<td>133.9</td>
<td>0.022</td>
</tr>
<tr>
<td>0.018</td>
<td>135.88</td>
<td>0.021</td>
</tr>
<tr>
<td>0.020</td>
<td>140.88</td>
<td>0.022</td>
</tr>
</tbody>
</table>

From the phase solubility diagram it can be seen that apparent solubility of carvedilol increased linearly due to the formation of a solute inclusion complex between carvedilol and β-cyclodextrin [10,15]. The value of apparent stability constant for carvedilol: β-cyclodextrin was calculated from the solubility data was found to be 2083M$^{-1}$.

\[
y = 0.912x + 0.005 \\
R^2 = 0.984
\]

Fig. 1. Phase solubility diagram of Carvedilol with - β-CD
3.2.3 In-vitro Dissolution Studies

Table 6 enlists the dissolution performance of inclusion complex of carvedilol (K1 and K2) and their corresponding physical mixture (P1 and P2). Fig. 2 shows the percent drug released v/s time profile of carvedilol, P1, P2, K1 and K2. Table 6 clearly reveals that the β-CD complexes with carvedilol have a profound influence on the release profile of the carvedilol. The results, however, were almost identical at 1:1 and 1:2 drug: β-CD ratios. Fig. 2 vouches of the same. Physical mixtures of carvedilol with β-CD (P1 and P2) portray distinct superiority in the release profiles vis-a-vis that of pure drug. The results again were almost identical for P1 as well as for P2. When K1 and K2 were compared with P1 and P2 it was observed that K1 and K2 exhibited better release performance vis-a-vis P1 and P2, particularly in the initial phase of dissolution profile. However, at above 45 minutes almost identical release performance was observed in case of carvedilol - β-CD complexes as well as physical mixtures.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Pure drug</th>
<th>K1</th>
<th>K2</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>25.153±0.67</td>
<td>76.932±0.13</td>
<td>85.840±0.12</td>
<td>65.530±0.32</td>
<td>68.436±0.03</td>
</tr>
<tr>
<td>20</td>
<td>47.121±0.68</td>
<td>98.810±0.25</td>
<td>99.264±0.10</td>
<td>77.511±0.81</td>
<td>78.129±0.08</td>
</tr>
<tr>
<td>30</td>
<td>53.110±1.23</td>
<td>98.730±0.28</td>
<td>98.331±0.03</td>
<td>85.483±0.42</td>
<td>86.110±0.10</td>
</tr>
<tr>
<td>45</td>
<td>64.162±0.38</td>
<td>97.50±0.41</td>
<td>98.293±0.09</td>
<td>97.204±0.10</td>
<td>97.106±1.03</td>
</tr>
<tr>
<td>60</td>
<td>70.652±1.32</td>
<td>96.421±0.10</td>
<td>97.120±0.31</td>
<td>97.128±0.81</td>
<td>98.103±0.32</td>
</tr>
<tr>
<td>90</td>
<td>80.352±1.64</td>
<td>94.262±0.34</td>
<td>96.082±0.83</td>
<td>96.110±0.03</td>
<td>96.990±0.46</td>
</tr>
<tr>
<td>120</td>
<td>88.431±1.32</td>
<td>92.131±0.18</td>
<td>95.021±1.16</td>
<td>95.08±1.01</td>
<td>95.850±0.11</td>
</tr>
</tbody>
</table>

4. CHARACTERISATION OF INCLUSION COMPLEX

4.1 Differential Scanning Calorimetry

Table 7 depicts various DSC characteristics of the pure carvedilol; β-cyclodextrin, selected inclusion complex formulation prepared using β-cyclodextrin and its corresponding physical mixture. Their respective thermograms are shown in Figs. 3, 4, 5 and 6. The DSC curve for pure carvedilol shows a single fusion endotherm, representing the melting point at 116.77ºC and exhibits the normalised value of 127.4 Jg⁻¹. Pure β-cyclodextrin shows two endothermic peaks at 136.68ºC and 293.21ºC and the later represent the melting point of the sample. The end of thermogram of β-cyclodextrin corresponds to the breakup of β-cyclodextrin, probably due to its decomposition. The Thermogram of the physical mixture of carvedilol with β-CD possesses endothermic peak at 173.57ºC. A shift in melting point was observed, so an interaction might be inferred between carvedilol and β-cyclodextrin resulting the decrease in melting point [24,25].

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Normalised value (J/g⁻¹)</th>
<th>On set of endotherms (degrees)</th>
<th>Peak of endotherms (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Carvedilol</td>
<td>127.4</td>
<td>113.27</td>
<td>116.77</td>
</tr>
<tr>
<td>2 β-cyclodextrin Peak 1</td>
<td>427.5</td>
<td>125.34</td>
<td>136.68</td>
</tr>
<tr>
<td>2 β-cyclodextrin Peak 2</td>
<td>34.27</td>
<td>282.28</td>
<td>293.21</td>
</tr>
<tr>
<td>3 Physical mixture with β-CD</td>
<td>1150.3</td>
<td>163.66</td>
<td>173.57</td>
</tr>
<tr>
<td>4 Inclusion complex with β-CD Peak 1</td>
<td>186.8</td>
<td>51.75</td>
<td>58.23</td>
</tr>
<tr>
<td>5 Inclusion complex with β-CD Peak 2</td>
<td>207.9</td>
<td>377.34</td>
<td>404.5</td>
</tr>
</tbody>
</table>
4.2 X-Ray Diffraction Studies

The x-ray diffractogram for the pure drug carvedilol, β-cyclodextrin, selected inclusion complex with β-cyclodextrin and its corresponding physical mixture are shown in Figs. 7, 8 and 9. Whereas their characteristics peaks at 2θ (in degrees) are listed in Table 8. On comparing the x-ray diffractogram of the selected inclusion complex formulation with β-CD and its physical mixture, it can be deciphered that the crystallinity of carvedilol is reduced drastically in the inclusion complex vis-à-vis their corresponding physical mixture. Significant diminution in the number of peaks as well as in the corresponding amplitude of peaks is vividly discernable [13,17].
Fig. 4. DSC Thermogram of physical mixture of Carvedilol with $\beta$-CD

Fig. 5. DSC Thermogram of inclusion complex of Carvedilol with $\beta$-CD

DSC curve for pure carvedilol shows a single fusion endotherm, representing the melting point at 116.77°C and exhibits the normalised value of 127.4 Jg$^{-1}$.

Table 8. Characteristics peaks of pure Carvedilol, $\beta$-Cyclodextrin, inclusion complex and its corresponding physical mixture

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>Characteristic peak at 2(\theta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carvedilol</td>
<td>5.7, 8.1, 11.8, 12.9, 13.6, 14.7, 15.5, 16.9, 17.8, 19.1, 20.9, 21.6, 22.8, 23.5, 24.3, 25.3, 26.1, 27.5, 28.1, 29.3, 31.4, 32.4, 34.1, 36.6, 38.0, 41.8, 42.7, 43.5, 44.7, 46.6, 48.0</td>
</tr>
<tr>
<td>2</td>
<td>$\beta$-CD</td>
<td>6.2, 9.0, 9.7, 10.5, 11.7, 12.4, 13.5, 14.6, 16.7, 17.7, 18.8, 19.5, 20.7, 21.4, 22.8, 23.9, 24.2, 25.1, 26.5, 27.5, 28.7, 29.5, 30.2, 31.9, 33.8, 34.7, 35.1, 36.5, 37.7, 39.7, 40.6, 41.4, 42.7, 43.7, 44.9, 47.7, 48.9</td>
</tr>
<tr>
<td>3</td>
<td>Physical Mixture with $\beta$-CD</td>
<td>6.3, 9.8, 10.7, 11.8, 12.5, 13.6, 14.7, 15.3, 17.7, 18.9, 19.7, 20.7, 21.6, 22.8, 24.3, 25.7, 26.4, 27.6, 28.6, 29.5, 30.3, 31.2, 33.9, 34.7, 35.9, 36.6, 37.0, 38.3, 39.8, 40.9, 42.8, 44.1, 45.0</td>
</tr>
<tr>
<td>4</td>
<td>Inclusion Complex with $\beta$-CD</td>
<td>5.8, 6.2, 8.9, 9.5, 10.7, 11.6, 12.9, 14.8, 15.2, 16.5, 17.9, 18.4, 20.7, 21.4, 22.9, 24.3, 26.2, 27.0, 31.2, 34.2, 38.0, 39.1, 44.0, 45.0</td>
</tr>
</tbody>
</table>
Fig. 6. DSC thermogram of Carvedilol

Fig. 7. XRD pattern of β-CD

Fig. 8. XRD pattern of inclusion complex of Carvedilol with β-CD
4.3 FT –IR Studies

Figs. 10, 11, 12 and 13 shows the infrared spectra of pure drug, β-CD, kneaded complex and it corresponding physical mixture. Analysis of the IR spectra of physical mixture and inclusion complexes showed dramatic change in the absorption peaks. Differences were observed in the C-Hstr. region (2900 cm\(^{-1}\) - 3050 cm\(^{-1}\)) as well as \(\text{C} = \text{C}\), vibration region (1450 cm\(^{-1}\) -1650 cm\(^{-1}\)) of the aromatic ring. The low frequency region (400 cm\(^{-1}\) - 1000 cm\(^{-1}\)) also deployed change in the intensity and as well as shape of the peaks. Further the changes were prominent in case of inclusion complex as compared to that of physical mixture. This indicates that the vibration and bending of carvedilol the guest molecule was restricted due to formation of inclusion complexes with beta-cyclodextrin. Thus it indicates that the aromatic ring in carvedilol was inserted into the cavity of beta-cyclodextrin [20,25,26].
4.4 Scanning Electron Microscopy (SEM)

Analysis of SEM of carvedilol and β-CD reveals that the drug, as well as the carrier, exists in the crystalline form. The crystalline nature of carvedilol and β-CD has already been conformed through their corresponding DSC and XRD spectra. From the photomicrograph of selected inclusion complex of carvedilol with β-CD illustrates through amorphous inclusion complex of the drug in the cavity of β-CD. Further it also limpid that the drug crystallinity is very significantly diminished in the erstwhile crystalline lattices, characteristics of the
individual ingredients viz carvedilol, β-CD. This reduction in crystallinity has also been corroborated earlier using x-ray diffraction spectra. Finally, it can be connoted that the inclusion complex using β-CD leads to distinct improvement in the dissolution profile of the drug. Ostensibly, this can be attributed to the decreased crystallinity of the drug, as is vouched from characterisation using XRD, DSC and SEM.

![Fig. 13. I.R. Spectra of physical mixture of Carvedilol with β-CD](image)

![Fig. 14. Scanning electron microphotograph of Carvedilol](image)
5. CONCLUSION

- Carvedilol is an important antihypertensive drug. The drug belongs to BCS class-II and hence its bioavailability often limited by its dissolution rate.
- The enhancement of dissolution rate through solid dispersion as well as through inclusion complex techniques has been well documented.
- Inclusion complexes of carvedilol- β-cyclodextrin and their corresponding physical mixture in various ratios were formulated and studied for their dissolution performance.
- Inclusion complex of β-CD showed the desirable result with distinct superiority in a dissolution profiles vis-a-vis their corresponding physical mixture.
- Promising results were exhibited by inclusion complex of carvedilol: β-CD in the ratio of 1:2. Thereafter, the formulation was further evaluated in terms of DSC, XRD, FT-IR and SEM.
- The significant improvement in the rate of release of carvedilol- β-CD complex
formulation can help in appreciable reduction in the lag time of the drug absorption, characterized by high $t_{\text{max}}$ value (120 minutes), thereby can improve the rate of bioavailability and onset of its therapeutic effects.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES


