ORIGINAL ARTICLE

Formulation and Evaluation of Cyclodextrin Inclusion Complex Tablets of Carvedilol

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Abstract

Objective: The aim of this series of experiments was to improve the solubility of a poorly soluble drug. **Materials and Methods:** Binary inclusion complexes of carvedilol and cyclodextrins derivatives were prepared by kneading method. Their solubility and dissolution behavior were compared with that of the pure drug and the marketed formulation of carvedilol. **Results:** Saturation solubility studies indicate that the solubility of the drug was increased and X-ray diffraction, differential scanning calorimetry, scanning electron microscopy showed that the crystalline nature of drug was lost or decreased significantly in the inclusion complex, indicating the drug was present in a solubilized form in the formulation. All inclusion complex tablets showed increase in dissolution rate than tablet prepared with pure drug. Formulation FT8 showed faster drug release in comparison to other formulations and data were fitted to various kinetic models. The mechanism of drug release from tablets was found to be Supercase 2 Transport. Stability studies suggested that there was no significant degradation or changes taking place in the tablets during the study period. **Conclusion:** It can be concluded that the inclusion complexation technique is an effective approach for the dissolution rate improvement of water insoluble drugs such as carvedilol.

Key words: Carvedilol, cyclodextrin, inclusion complexes, solubility enhancement

INTRODUCTION

Drug absorption, bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on the solubility of that compound in the aqueous medium. Solubility is the maximum amount of solute which can dissolve in a certain amount of solvent under standard conditions of temperature, pressure, and pH. It is an important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The poor bioavailability of a drug is mainly concerned with its poor water solubility. Low water solubility is the major problem encountered with the formulation development of new chemical entities. Therapeutic effectiveness of a drug depends upon the bioavailability.[1] Solubility is one of the very important parameters to achieve desired concentration of drug in blood for pharmacologic response to be shown. Poorly water-soluble drugs involve many difficulties in the development of pharmacological dosage forms for oral delivery systems because of their low bioavailability. The process of solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.[2]

Inclusion complex formation technique has been most frequently employed to improve the aqueous solubility, dissolution rate and bioavailability of poorly water-soluble drugs. Complexation of drugs with cyclodextrins (CDs) has been used to enhance aqueous solubility and drug stability. A strategy often used to improve complexation between drugs and CDs is the addition of small amounts of water-soluble polymers to the system, which causes an increase in solubilization efficiency. Ternary CD complexes, including hydrophilic polymers, were found to be more stable. The complexation efficiency and solubilizing effect of CDs in

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aqueous solution can be increased by addition of water-soluble polymers. When a water-soluble polymer, a CD and a drug are mixed together in a solution to obtain the so-called ternary complexes, it is possible to increase drug solubilization, when compared to the polymer and CD separately, which is a result of the synergistic effect between these components. The interaction of water-soluble polymers with drug molecules may occur by means of ion-ion, ion-dipole, and dipole-dipole electrostatic bonds, van der Waals force, or a 3-center, 2-electron bonds. Similarly, the interaction between polymers and CDs and drug: CD complexes begins to occur on the external surface of the CD molecule. CDs, polymers, and drug: CD complexes form aggregates capable of solubilizing drugs and other hydrophobic molecules. Obtaining complexes with CDs, drugs and water-soluble polymers have gained greater acceptance due to the relatively low cost of polymers. The amount of polymer must be such that the solubilizing effect is maximized, but not sufficient to cause a significant increase in viscosity. Among all the solubility enhancement techniques inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs.[3,4,30,31]

MATERIALS AND METHODS

Materials

The following materials were used (Grade-LR): Carvedilol - active pharmaceutical ingredients (API) (Shasun Pharma, Pondichery), hydroxypropyl β-CD, PVP K30, lactose (Yarrow Chem Pvt. Ltd, Mumbai), β-CD (Sance Laboratories Pvt. Ltd., Pala), Crospovidone, Talc, Magnesium Stearate (Chemdyes Corporation, Rajkot), Methanol (Nice Chemicals Pvt. Ltd, Cochin), marketed tablet - Carvepress - 12.5 mg.

Methods

Preformulation studies

Preformulation studies were performed on the drug (API), which included solubility, melting point determination and compatibility studies.[16-23]

Solubility

The solubility of carvedilol was observed in different solvents such as water, methanol, and chloroform. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 h under constant vibration. After this period, the solutions were filtered, diluted, and analyzed by ultraviolet (UV) - spectrophotometer.

Melting point determination

Melting point of pure carvedilol was determined using the open capillary method. The capillary tube was closed at one end by fusion and was filled with drug sample by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°C min rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded. This was performed thrice and the average value was calculated.

Fourier transform infra-red (FTIR) spectrum

FTIR spectral analysis of the obtained drug sample was carried out individually, using Shimadzu A213748 FTIR Spectrometer, observation was made. Potassium bromide was mixed with drug in 9:1 ratio and the spectra were taken. The absorption maxima in the spectra was compared with the reference spectrum.

Preparation of CD in inclusion complexes

Kneading method

Solid inclusion complexes of carvedilol-CD (βCD/HP βCD) - PVP K30 were prepared by kneading method. Polymers were triturated in a mortar with a small volume of a solvent consisting of a blend of water:methanol (1:1). The drug was slowly added to it. The thick slurry formed was kneaded for 45 min and then dried at 55°C until dry. The dried mass was powdered and sieved to mesh No. 120.[5-8]

Evaluation of CD inclusion complexes

CD inclusion complexes were evaluated and characterized by the following methods:

Percentage practical yield

The efficiency of the process is determined by the yield acquired from the process. Percentage practical yield was calculated to know the percent yield or efficiency of any method, and thus, it helps in selection of appropriate method of production. CD complexes were collected and weighed to determine practical yield from the following equation.[9-11]

$$\%\text{Practical yield} = \frac{\text{Practical mass inclusion complex}}{\text{Theoretical mass } (\text{drug} + \text{carrier})} \times 100$$

Percentage drug release

Dissolution studies were carried for all the formulations, employing USP dissolution apparatus Type 1, using 900 mL 0.1 N HCl as the dissolution medium at 50 rpm and 37 ± 0.5°C. The samples were periodically withdrawn at suitable time intervals 5, 10, 15, 20, 30, 45, and 60 min and volume replaced with the equivalent amount of plain dissolution medium. The samples were filtered and diluted. Absorbances of the resulting solutions were measured at 241 nm using UV-visible spectrophotometer.[9-11]

Drug content

An accurately weighed 100 mg of complex was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1 N HCl and assayed for drug content using the UV spectrophotometric method at 241 nm.[9-11]

Saturation solubility study

To evaluate increase in solubility of carvedilol after forming complexes with CDs saturation solubility measurements were carried out as follows: Known excess of CD formulations was added to 10 mL of distilled water. Samples were shaken for 24 h at room temperature in a rotary flask shaker. Samples were then filtered, suitably diluted, and analyzed spectrophotometrically at 241 nm. Saturation solubility of the pure drug was also determined.[9-11]

Scanning electronmicroscopy (SEM) analysis

The shape and surface morphology of the complexes was studied by SEM, JEOL JSM 6390, England. A small piece of double-sided adhesive tape was fixed onto an aluminum stub, and the powders were sprinkled and dispersed on the stub surface. Before examination, the samples were sputter coated with gold-palladium under argon atmosphere to render them electrically conductive.[12]

X-ray diffraction (XRD) study

X-ray powder diffraction patterns of carvedilol, carvedilol - HPβCD inclusion complex were conducted with a Phillips X'pert Pro P analytical diffractometer using a copper Kα target with a nickel filter at 45 kV voltage, 30 mA current and at scanning speed of 0.05 s over a 2θ range of 5-60°.[12]

Differential scanning calorimetry (DSC)

DSC thermogram of carvedilol and carvedilol inclusion complex was recorded on the DSC (PerkinElmer Pyris1 DSC). The samples were sealed in pans and scanned at a heating rate of 10°C min-1 over a temperature range of 50-300°C under nitrogen gas stream.[10]

Evaluation of precompression parameters of CD inclusion complexes

Flow properties, such as angle of repose, poured density, tapped density, and compressibility index of inclusion complexes, were evaluated to determine the suitability for tablet formulation.

- Angle of repose
  Angle of repose was determined using fixed funnel method. The powders were allowed to flow through the funnel fixed on a burette stand at definite height (h). The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the heap of granules formed.[13]

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

- Bulk density
  The bulk density of powder is dependent on particle packing and changes as powder consolidates. Apparent bulk density was determined by pouring a weighed quantity of powder into a graduated cylinder and measuring the volume of packing.[13]

Bulk density = Weight of the powder/volume of the packing

- Tapped density
  Tapped density is defined as the mass of a powder divided by the tapped volume. Tapped density was determined by tapping method. Weighed quantity of powder was placed in a graduated cylinder and tapped until no further change in volume of powder was noted, and the volume of tapped packing was noted.[13]

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

- Compressibility index
  The compressibility of the powder was calculated by determining the Carr's index (CI) and Hausner's ratio (HR).[13]

$$\text{Car's consolidation index } \% = \frac{\text{Tapped density-bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Preparation of tablets with carvedilol - CD inclusion complexes

Direct compression method

Solid inclusion complexes prepared by kneading method was formulated into tablets by direct compression method. In the case of direct compression, lactose, a directly compressible vehicle was used as filler. Crospovidone (5%), talc (2%), and magnesium stearate (5%) were incorporated, respectively, as disintegrant and lubricants. All the ingredients were blended thoroughly in a closed dry plastic container. The blend of powders was compressed into tablets on a single punch tablet machine having diameter 7 mm.[6,14,15]

Evaluation of tablets

Physico-chemical properties

Thickness

The tablet thickness was calculated using Vernier calipers. It is expressed as mm.[16-23]

Hardness

The hardness of the prepared tablets was estimated using Monsanto hardness tester. Three tablets from each formulation batch were selected and force is applied diametrically. It is expressed in kg/cm^2.[16-23]

Friability

Roche friabilator was used for testing the friability of prepared fast dissolving tablets. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for 4 min or 100 revolutions. Pre-weighed sample (Wi) of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted using a softmuslin cloth and reweighed (Wf). The friability (F) is given by the formula.[16-23]

$$F = \frac{Wi\text{-}Wf}{Wi} \times 100$$

Weight variation test

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with IP Limits, variation within the IP limits; it passes the weight variation test.[16-23]

Drug content

Five tablets were weighed and powdered using a glass mortar and pestle. An accurately weighed 100 mg of powder was taken into 50 ml volumetric flask, dissolved in methanol and the solution was filtered through what man filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 1.2. The drug content was determined at 241 nm by UV-spectrophotometer.[16-23]

Disintegration time

The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus. 900 ml distilled water was used as a disintegrating media at 37 ± 0.2°C. The time required to obtain complete disintegration of all the tablets were noted.[16-23]

Wetting time and water absorption ratio

Tablets were separately weighed (Wa) and carefully placed onto the surface of a piece of tissue paper twice folded in a 5 cm diameter Petri dish containing 6 ml of water. The time for complete wetting (water reaches the upper surface of the tablet) was noted and recorded as the wetting time. The wetted tablet was carefully removed and reweighed (Wb). Water absorption ratio (R) through the tablet was then determined according to equation below.[16-23]

$$R = 100 \times (Wb - Wa)/Wb$$

In vitro drug release study

The dissolution studies of inclusion complexes were performed using USP dissolution apparatus Type I. Dissolution study was performed in 900 mL 0.1 N HCl. The stirring speed was 50 rpm, and the temperature was maintained at 37 ± 0.5°C. The samples were withdrawn periodically and were replenished with fresh dissolution medium. The samples were filtered, diluted and analyzed by UV spectrophotometer at 241 nm.[16-23]

Kinetics of *in vitro* drug release

To study the release kinetics of *in vitro* drug release, data obtained from *in vitro* release study were plotted in various kinetic models: Zero order as % drug released versus time, First order as log % drug retained versus time, Higuchi as % drug released versus √time, Korsmeyer-Peppas as log % drug released versus log time.[24,25]

Comparison of optimized formulation with marketed formulation

The dissolution rate of the optimized formulation was compared with the marketed available tablet of carvedilol and compares the release profiles.

Stability studies

Stability is defined as the extent, to which a product retains within specified limits and throughout its period of strong and uses, i.e., shelf life. Stability studies were carried out an optimized formulation according to International Conference on Harmonization (ICH) guidelines.[26]

All the selected formulation FT8 was subjected to a stability testing for 6 weeks as per ICH norms at a temperature (40°C). All selected formulations were analyzed for the friability, hardness, % drug content, and *in vitro* drug release study by procedure stated earlier.

RESULTS AND DISCUSSION

Preformulation studies

The solubility of the drug in water, methanol, and chloroform was examined and found to be in conformity with pharmacopoeial specifications. Table 1 explains the results of solubility studies.

Table 1: Solubility profile of the drug

Solvent	Solubility
Water	Insoluble
Methanol	Freely soluble
Chloroform	Soluble

Melting point of the drug was found to be 115°C which is in conformity with the reported range. It indicates the purity of the drug sample.

IR spectrum of carvedilol was compared with the spectra of physical mixtures of carvedilol with the three different polymers used, (β-CD, HPβ-CD, and PVP K30). There was no disappearance of any characteristic peaks. This shows that there is no chemical interaction between drug and polymers used. The presence of characteristic peaks confirmed that the drug and polymers used were compatible [Figure 1].

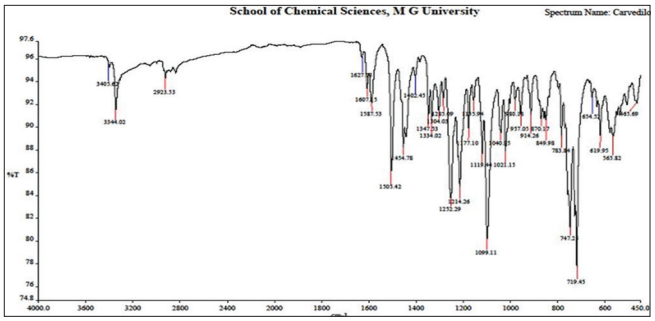

Figure 1: Infra-red spectrum of carvedilol+β-CD+HPβ-CD+PVP

Preparation of CD inclusion complexes

Kneading method

Solid inclusion complexes of carvedilol-CD (β-CD/HPβ-CD), carvedilol-CD (β-CD/HP β-CD) - PVP K30 were prepared by kneading method [Table 2].

Evaluation of CD inclusion complexes

The percentage yield of all formulations was found to be between 93.6% and 98.84%. As it can be seen, all the formulations give a yield of above 90%. The high % yield of all the formulations indicates the reproducibility of kneading technique for the preparation of inclusion complexes. The % drug content of inclusion complexes was found to be between 96.96% and 99.60%. All inclusion complex formulations showed the presence of high drug content. It indicates that the drug is uniformly dispersed in the powder formulation, and the kneading technique is highly efficient for the preparation of CD inclusion complexes [Figure 2 and Tables 3 and 4].

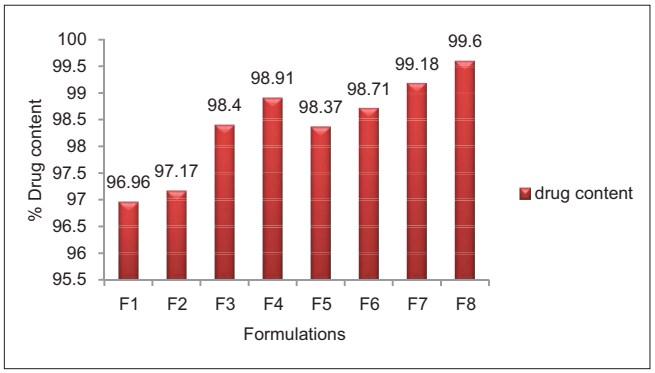

Figure 2: Percentage drug content of inclusion complexes

Table 2: Formulation code for inclusion complexes

Formulation code	Composition	
F1	Carvedilol:β-CD	1:1
F2	Carvedilol:β-CD	1:2
F3	Carvedilol:HPβ-CD	1:1
F4	Carvedilol:HPβ-CD	1:2
F5	Carvedilol:β-CD:PVP	1:1:0.04
F6	Carvedilol:β-CD:PVP	1:2:0.06
F7	Carvedilol:HPβ-CD:PVP	1:1:0.04
F8	Carvedilol:HPβ-CD:PVP	1:2:0.06

Percentage release of inclusion complexes at 1 h was found to be between 76.78% and 96.12%.

Saturation solubility study

The results of the saturation solubility study showed that β-CD and HPβ-CD were efficient carriers for solubility enhancement of poorly soluble drugs. Carvedilol showed 7-14 fold increase in the solubility. The addition of small amount of hydrophilic polymer PVP to the CD systems has enhanced the complexation and solubilizing efficiencies of β-CD and HPβ-CD. CD complex of carvedilol with HPβ-CD (1:2) with PVP (2%) showed the highest solubility. The enhancement in the solubility of complex is mainly attributed to the formation of stable inclusion complex of carvedilol with CDs [Figure 3 and Table 5].

Table 3: Percentage yield and percentage drug content of inclusion complexes

Formulation	Percentage yield	Percentage drug content
F1	94.40	96.96
F2	96.26	97.17
F3	93.60	98.40
F4	97.54	98.91
F5	95.80	98.37
F6	98.39	98.71
F7	97.24	99.18
F8	98.84	99.60

SEM is a qualitative method used to study the structural aspects of CDs and drugs, or the products obtained using different methods of preparation. Imaging of inclusion complexes by SEM is expected to provide information on the surface morphology. Morphological changes of these structures can be taken as a proof of the formation of an inclusion complex. The study shows change in crystal pattern

Table 4: Percentage drug release of inclusion complexes

Time (min)	Percentage drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	35.48	37.55	54.11	62.08	48.94	51.22	68.60	73.72
10	38.63	41.07	62.66	75.16	56.24	62.66	75.17	79.28
15	41.77	46.95	70.80	81.87	63.54	75.22	81.87	85.70
30	49.01	54.21	78.13	86.49	73.91	81.92	86.48	91.63
45	54.29	5.80	85.83	91.92	80.83	84.85	94.74	97.16
60	76.78	82.67	87.66	91.31	85.63	90.75	92.24	96.12

Table 5: Results of saturation solubility study of inclusion complexes

Formulation code	Solubility (mg/mL)	Solubility enhancement ratio
Pure drug	0.0124	-
F1	0.0895	07
F2	0.1110	08
F3	0.1341	10
F4	0.1571	12
F5	0.1182	9
F6	0.1398	11
F7	0.1686	13
F8	0.1829	14

of drug to amorphous form in complexes. This change in crystal pattern accounts for increased solubility. Drug and HPβ-CD inclusion complexes of drug showed a significant difference in the microscopic structure [Figure 4].

XRD study

The XRD pattern of pure drug carvedilol shows peaks which are intense and sharp shows the crystalline nature of the drug. The XRD pattern of inclusion complex prepared with HPβ-CD showed undefined, broad peaks with less intensity. The peak of diminished intensity shows the decrease in crystallinity of the drug and the nature of the drug converted to amorphous form and thus improved solubility of the drug [Figures 5 and 6].

DSC study

The DSC analysis provided additional evidence that inclusion complex was formed. When guest molecules were imbedded in CD cavities or crystal lattice, their melting, boiling, and sublimation points shifted to different temperatures or disappear. DSC thermogram of carvedilol pure drug shows an endothermic peak at 116.12°C, which is related to the melting point of the pure drug. It indicates that the drug carvedilol

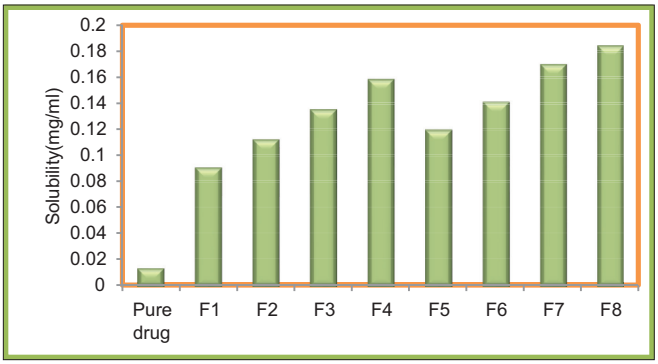

Figure 3: Saturation solubility study SEM analysis

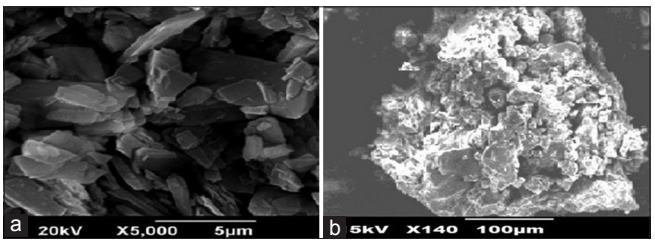

Figure 4: Scanning electronmicroscopy picture of (a) pure drug (carvedilol), (b) inclusion complex (carvedilol-HPβ-CD)

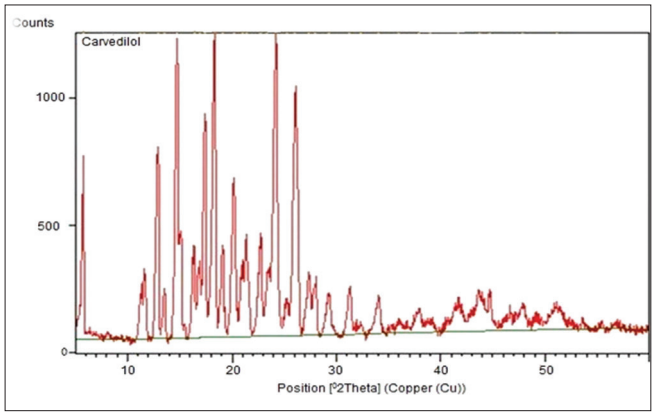

Figure 5: X-ray diffraction of carvedilol

used was in pure crystalline state. In DSC thermogram of carvedilol CD Complex sharp endothermic peak was absent, which is different from pure drug, suggesting that there is formation of the complex [Figures 7 and 8].

Precompression evaluation of CD inclusion complexes

The angle of repose of all formulations was found to be ranging from 28.36 to 30.46. As all values below 40, these possess sufficient flow properties. Bulk density was found to be 0.53-0.56 g/cc and Tapped density was in between 0.63 and 0.67 g/cc. CI values of all the formulations have the values below 20. Hence, the formulations possess acceptable flow properties. The HR value for all formulations was found to be in the range of 1.14-1.19. As the values were below 1.5, these possess acceptable flow properties. Precompression studies showed that all the inclusion complexes possess acceptable flowability and compressibility [Table 6].

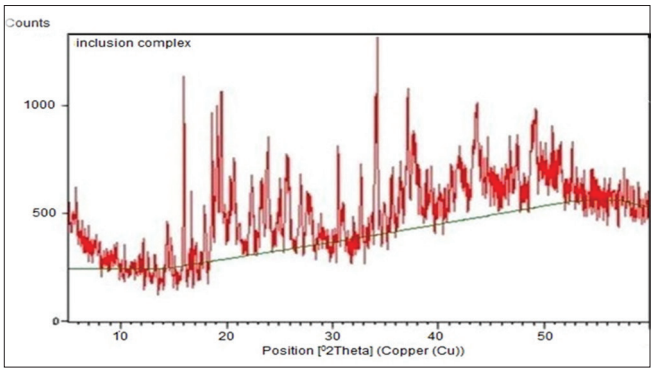

Figure 6: X-ray diffraction of inclusion complex

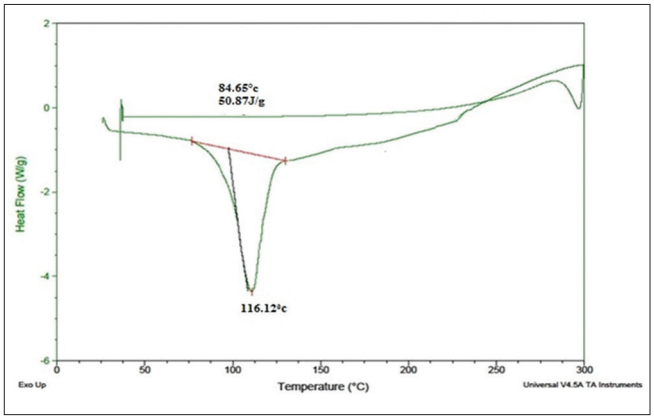

Figure 7: Differential scanning calorimetry thermogram of carvedilol

Preparation of tablets

Carvedilol - CD (β-CD/HPβ-CD)-PVP K30 solid inclusion complexes could be formulated into tablets by direct compression method [Table 7].

Evaluation of CD inclusion tablets

Physicochemical properties of tablets

The inclusion complex tablets were prepared by direct compression technique. The tablets were evaluated for thickness, hardness, friability, and weight variation and % drug content [Table 8].

The tablets of all the formulations disintegrate quickly. The *in vitro* disintegration time for the prepared fast dissolving tablets ranges between 20 ± 0.16 and 39 ± 0.33 s. The formulation containing carvedilol-HPβ-CD (1:2) - PVP inclusion complex, resulted in complete disintegration within 20 s. Wetting is closely related to inner structure of tablets and the hydrophilicity of the excipients. The wetting time was in range of 33 ± 0.2 and 48 ± 1 s. The prepared tablets have good capacity to absorb water. Water absorption ratio of the tablet formulations ranges from 48 ± 2.0 to 87 ± 0.5. All inclusion complex tablets showed increase in dissolution rate than tablet prepared with pure drug. Tablets formulated employing HPβ-CD with PVP K30 inclusion complexes gave higher dissolution values when compared to those formulated with β-CD inclusion complexes. The addition of PVP has markedly enhanced the complexation and solubilizing efficiencies of β-CD and HPβ-CD. *In vitro* release studies revealed that 87-98% drug release from formulations containing CD inclusion complexes. Formulation FT8 showed faster drug release in comparison to other formulations.

Table 6: Micrometric properties of the powder

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	CI	HR	Angle of repose (θ)
FT1	0.54	0.65	16.47	1.19	30.17±0.10
FT2	0.53	0.63	15.17	1.18	29.39±0.24
FT3	0.54	0.64	16.30	1.19	30.46±0.32
FT4	0.56	0.66	14.77	1.17	29.74±0.10
FT5	0.56	0.67	14.60	1.17	28.65±0.46
FT6	0.55	0.64	14.44	1.16	29.03±0.36
FT7	0.56	0.64	12.37	1.14	28.52±0.40
FT8	0.55	0.63	12.22	1.14	28.36±0.26
FT9	0.54	0.63	14.14	1.15	30.46±0.38

CI: Carr's index, HR: Hausner ratio

Postcompression evaluation indicates that the entire formulated tablets were within the acceptable limit [Figures 9-12].

Kinetics of *in vitro* drug release

Kinetic data of the best formulation is tabulated. R^2 values for plots of different kinetic models of formulation FT8 are given in table. Plot with the highest slope was that of first order. Thus, it can be concluded that the prepared tablets follow first order drug release kinetics. The slope of Korsmeyer-Peppas plot (*n* value) was found to be 1.296, which indicates that the release mechanism is Supercase 2 Transport.

Comparison with marketed formulation

The optimized formulation FT8 was compared with marketed tablet for different tests such as hardness, friability, thickness, uniformity of drug content, and *in vitro* dissolution study [Figure 13 and Table 9].

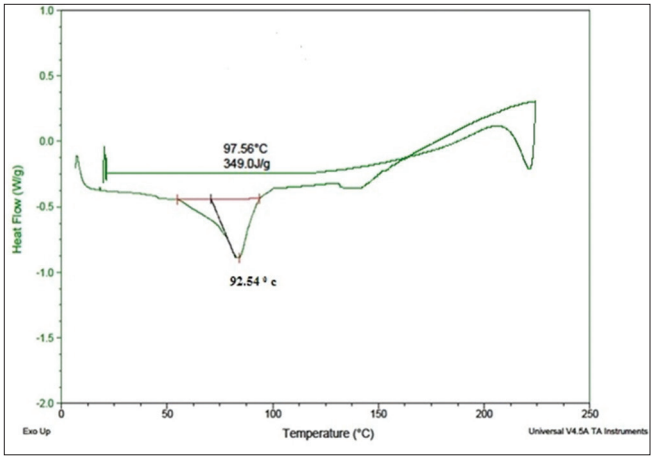

Figure 8: Differential scanning calorimetry thermogram of inclusion complex

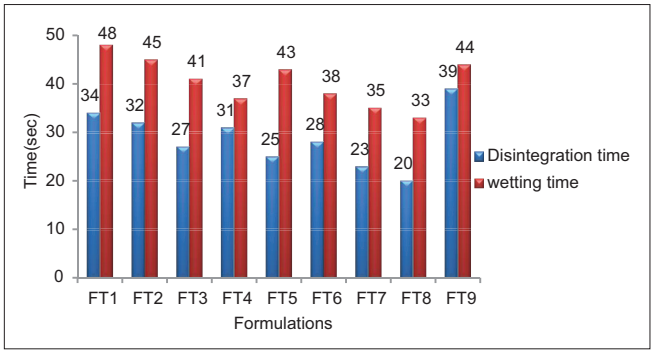

Figure 9: Comparison of disintegration time and wetting time of formulations FT1-FT9

Table 7: Formulation code of carvedilol inclusion complex tablets

Ingredients (mg)	Formulation code								
	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Carvedilol	-	-	-	-	-	-	-	-	12.5
Inclusion complex of carvedilol equivalent to 12.5 mg	25.78	38.61	25.40	37.92	25.93	38.77	25.72	38.40	-
Crosspovidone (5%)	10	10	10	10	10	10	10	10	10
Talc (2%)	4	4	4	4	4	4	4	4	4
Magnesium stearate (5%)	10	10	10	10	10	10	10	10	10
Lactose	150.2	137.3	150.6	138.0	150.0	137.2	150.2	137.6	163.5
Total weight	200	200	200	200	200	200	200	200	200

Table 8: Physicochemical properties of CD inclusion tablets

Formulation code	Thickness (mm)	Hardness (kg)	Weight variation	Friability (%)	Drug content (%)
FT1	4.3±0.17	5.0±0.23	Pass	0.870	97.22±0.62
FT2	4.4±0.15	4.4±0.14	Pass	0.716	97.59±0.45
FT3	4.2±0.12	4.2±0.26	Pass	0.718	98.40±0.62
FT4	4.3±0.13	4.8±0.13	Pass	0.632	98.46±0.1
FT5	4.4±0.17	5.0±0.20	Pass	0.810	98.07±0.36
FT6	4.5±0.13	4.6±0.13	Pass	0.621	98.28±0.48
FT7	4.5±0.11	4.4±0.17	Pass	0.763	98.93±0.62
FT8	4.3±0.18	4.8±0.20	Pass	0.585	99.78±0.16
FT9	4.2±0.11	4.4±0.33	Pass	0.528	97.32±0.45

SD: Standard deviation, *n*=3, CD: Cyclodextrins

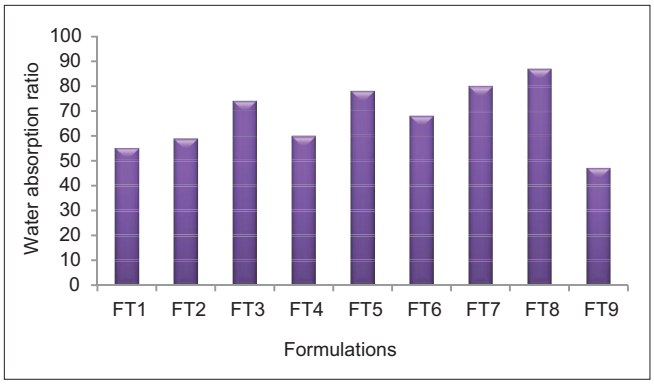

Figure 10: Water absorption ratio of formulations FT1-FT9

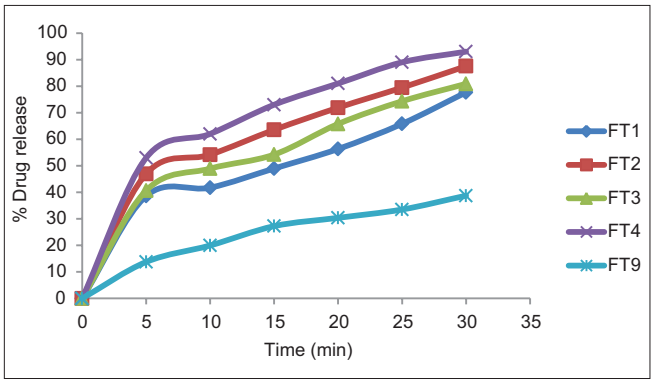

Figure 11: Comparative *in vitro* release profile of carvedilol inclusion tablets for formulation FT1, FT2, FT3 and FT4 with FT9

Stability study

The best formulation (FT8) was subjected to short-term stability study by storing the formulations at 40°C and 75% RH up to 6 weeks. After the time period, the tablets were analyzed for the hardness, % drug content, friability, and *in vitro* dissolution study.

No significant change was observed in the results of hardness, disintegration time, % drug content, and *in vitro* dissolution study of the selected formulation (FT8) [Table 10].

CONCLUSION

In this study, binary inclusion complexes of carvedilol and CD (β-CD/HPβ-CD) and carvedilol -CD (β-CD/HPβ-CD)-PVP K30 ternary solid inclusion complexes were prepared by kneading method. Saturation solubility studies indicate that the solubility of the drug was increased and XRD, DSC, SEM showed that the crystalline nature of drug was lost or decreased significantly in the inclusion complex, indicating the drug was present in a solubilized form in the formulation. All inclusion complex tablets showed increase in dissolution rate than tablet prepared with pure drug. Postcompression evaluation indicates that the entire formulated tablets were

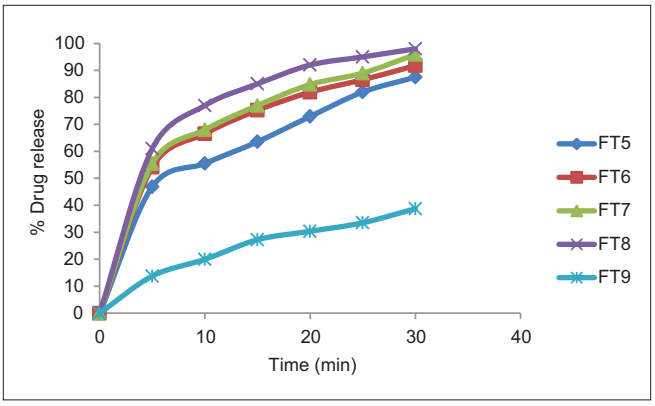

Figure 12: Comparative *in vitro* release profile of carvedilol inclusion tablets for formulation FT5-FT8 with FT9

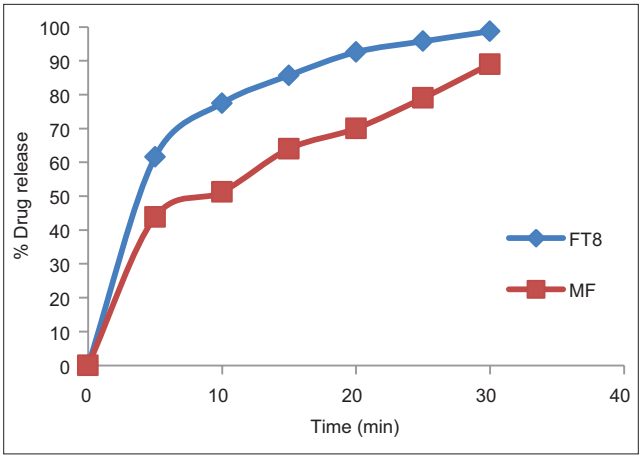

Figure 13: Comparison of *in vitro* drug release profile of FT8 with marketed product

Table 9: Details of marketed product

Evaluation parameter	Observations
Hardness(kg/cm^2)	5±0.17 kg/cm^2
Thickness (mm)	3.9±0.34 mm
Friability (%)	0.895%
Weight variation	Pass
% Drug content	98.78±0.11%

within the acceptable limit. *In vitro* release studies revealed that 87-98% drug release from formulations containing CD inclusion complexes. Formulation FT8 showed faster drug release in comparison to other formulations. The kinetic study suggested that the drug follows first order kinetics and the release is according to the concentration gradient and the *n* value indicates that the drug release follows supercase 2 transports. Formulation FT8 (inclusion complexation tablets formulated by direct compression method) showed faster drug release in comparison to the marketed formulations of carvedilol and was found to be stable and retained their original properties under accelerated storage conditions. It can be concluded that the inclusion complexation technique is an effective approach for the dissolution rate improvement

Table 10: Tablet properties after 45 days stability study

Formulation code	Hardness (kg/cm²)	Disintegrationtime(s)	% Drug content	Percentage drug release at 30th min
FT8	4.6±0.11	19±0.11	98.13±0.34	97.45±0.17

of water insoluble drugs such as carvedilol. Enhanced dissolution rates obtained in the present study is due to increased wetting and surface area available for dissolution.

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