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APPROACH TO ENHANCE THE SOLUBILITY OF CARVEDILOL USING β-CD COMPLEXATION

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ABSATRACT

The poor dissolution of relatively insoluble drugs has a major pharmacokinetic problem in the oral dosage form. This limits aspects such as absorption and bioavailability. Therefore, several approaches have been followed in improving the solubility of drugs, on being complexation. Carvedilol in HPMC in water and Tween 80 in water formulates as wet and direct compression method (F1-F4) and prepared by kneading method and physical mixture evaluated and characterized by IR, XRD and DSC studies 1:3 complex exhibit higher dissolution rate in direct compression method Cyclodextrin complexation (β-CD) enhanced the absorption rate of carvedilol.

KEYWORDS: Carvedilol, HPMC, Tween 80, Cyclodextrin complexation (β-CD).

INTRODUCTION

Hypertension represents the most common cardiovascular risk factor. Its prevalence is continuously rising, affecting more than 25% of the adult population in developed societies On the other hand, several previous studies have clearly shown longitudinal associations between hypertension and coronary artery disease, myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease and lowering blood pressure (BP) significantly reduces the cardiovascular morbidity and mortality However, control rates of hypertension is currently inappropriate and the majority of the hypertensive patients will require two or more antihypertensive agents to reach target BP goals.

Antihypertensive agents

- **Calcium channel blockers**
  - Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
- **β + α Adrenergic blockers:** Labetalol, Carvedilol
- **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
- **Central sympatholytics:** Clonidine, Methyldopa
- **Vasodilators**
  - Arteriolar: Hydralazine, Minoxidil, Diazoxide
  - Arteriolar + venous: Sodium nitroprusside
- **Others:** Adrenergic neurone blockers (Reserpine, Guanethidine, etc.), Ganglion blockers (Pentolinium, etc.)

Pharmacological properties

The plasma half-live of the various β-blockers range from just 9 minutes for esmolol to 24 hours for nadolol and penbutolol (median half-live of the class about 6 hours), but the effective half-life is longer mainly because of the active metabolites. Longer-acting compounds such as nadolol and extended-release formulations such as slow-release propranolol or extended-release metoprolol increase the probability of medication adherence and should be preferred for treatment of hypertension.

Carvedilol is rapidly absorbed after an oral dose, reaching peak plasma drug concentrations within 1 to 2 hours. Absorption is delayed an additional 1 to 2 hours when the drug is administered with food. The plasma half-life of carvedilol ranges from 7 to 10 hours in most subjects; thus, the drug requires twice-daily dosing. In plasma, 98% of the drug is bound to plasma proteins, predominantly to albumin. Carvedilol is almost exclusively metabolized by the liver and its metabolism is affected by genetic polymorphism of cytochrome P-450 2D6 activity.

Effects of carvedilol on lipid metabolism

Several studies have shown that β-blockers increase triglyceride levels and decrease high-density lipoprotein (HDL) levels. Cardioselective β-blockers with ISA have a lesser effect on triglycerides and HDL levels than non-cardioselective β-blockers without ISA. In a review of 474 studies, Kasiske et al showed also that long-term treatment with β-blockers reduces the effect on HDL levels.

In contrast to older β-blockers, carvedilol seems to have a neutral or beneficial effect on lipoprotein lipase activity and levels of triglycerides and HDL. In 45 patients with non-insulin-dependent diabetes and hypertension who were treated for 24 weeks, patients receiving carvedilol had a more favourable effect compared with atenolol in lowering triglyceride levels, increasing HDL levels, and decreasing lipid peroxidation. These beneficial effects of carvedilol on lipid levels is another important advantage of this agent in comparison to the conventional compounds.

Controlled release of carvedilol

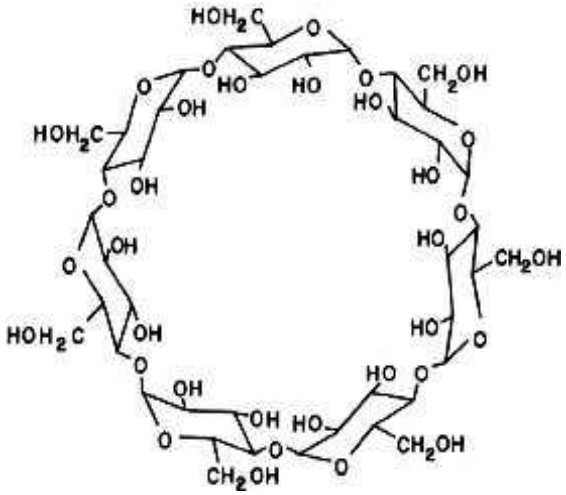
Recently, a controlled-release formulation of carvedilol (carvedilol CR) has been developed, allowing once-daily dosing and, thus, better adherence to medication Carvedilol CR is also indicated in patients with hypertension starting at a dose of 20 mg. A recently published study showed that carvedilol CR once daily were equivalent to carvedilol twice daily in bioavailability parameters (maximum plasma concentrations and trough drug concentration) in all doses likely to be used in hypertension (20, 40, and 80 mg).

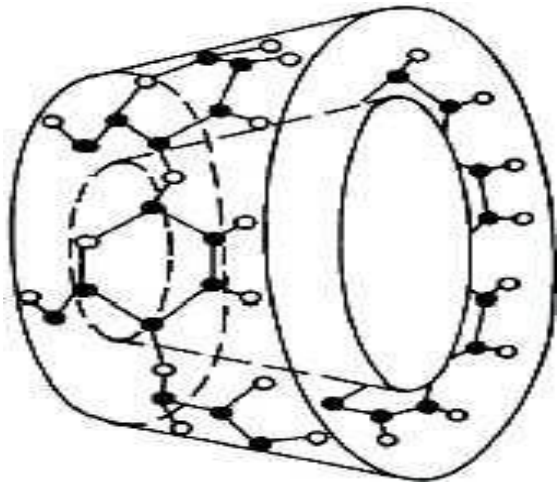
The maximum concentration of carvedilol with the controlled-release formulation is reached approximately 3.5 hours later than what is seen with the immediate-release preparation reducing the possibility of concentration-dependent side effects.

Enhance of solubility of carvedilol using β-cyclodextrin

Cyclodextrins (CD) are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in general they do not permeate lipophilic membranes. Cyclodextrins are widely used as "molecular cages" in the pharmaceutical, agrochemical, food and cosmetic industries.[3] In the pharmaceutical industry they are used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability.[4] In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactionsetc.

Cyclodextrin consists of (α-1, 4)-linked α-D-glucopyranose unit with a lipophilic central cavity and the structures are as shown in fig.1. Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge.





Complex Formation and Drug solubility of cyclodextrin

In aqueous solutions, cyclodextrins are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during complex formation, and the drug molecules in complex are in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity, hydrogen bonding, Vander Waals interaction, charge transfer interaction etc. The physicochemical properties of free cyclodextrin molecule differ from those in complex. The stoichiometry of the complexes formed and the numerical value of their stability constants can be determined by observing the changes in physicochemical properties like solubility, chemical reactivity, UV/VIS absorbance, drug retention, chemical stability, effects on drug permeability through artificial membranes etc. The formation of the inclusion complex between omeprazole (OME) and methyl-β-cyclodextrin (MβCD) has been studied and the stoichiometry of the complexes was found to be 1:1 mol: mol OME: cyclodextrin and the value of Ks were higher for OME: MβCD than for OME: βCD inclusion complexes.

Higuchi and Connors have classified complexes based on their effect on substrate solubility and it is indicated by the phase-solubility profiles as shown in Fig. A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e. drug) increases with increasing ligand (cyclodextrin) concentration. When the complex is first order with respect to ligand and first or higher order with respect to substrate then AL-type phase- solubility profile is obtained. If the complex is first order with respect to the substrate, but second or higher order with respect to the ligand then AP-type phase solubility profile is obtained. It is difficult to interpret the AN-type phase-solubility profile. The negative deviation from linearity maybe

associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self- association of cyclodextrin molecules. B-type phase-solubility. profiles indicate formation of complexes with limited solubility in the aqueous complexation medium.

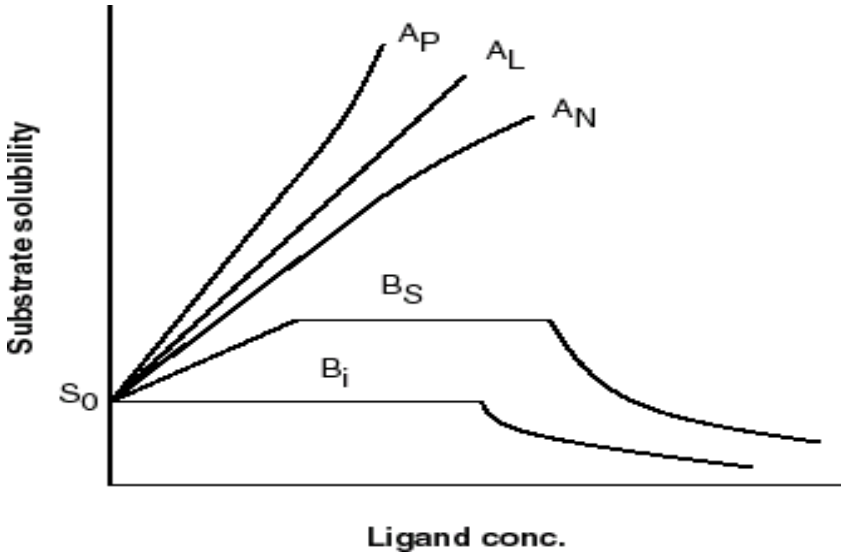


Fig. 2: Phase-solubility profiles.

In general, the water-soluble cyclodextrin derivatives form A-type phase solubility profiles, whereas the less soluble natural cyclodextrin forms B-type profiles. Most of the drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and the complex aggregates are capable of dissolving drugs through micelle-like structures.[13] The phase- solubility profiles only describe how the increasing cyclodextrin concentration influences the drug solubility. The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin (D/CD) complex where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD) and is given in eq.1.

Eq.1. $D + CD \xleftrightarrow{K_{1:1}} D/CD$

The value of $K_{1:1}$ is most often between 50 and 2000 M-1 with a mean value of 129, 490 and 355 M-1 for α-, β- and γ-cyclodextrin respectively.[14,15] Under such conditions, for an AL-type phase-solubility diagram with slope less than unity, the stability constant (K1:1) of the complex can be calculated from the slope and the intrinsic solubility (so) of the drug in aqueous complexation media (i.e., drug solubility when no CD is present) and is given in eq. 2.

Slope

Eq.2. $K1{:}1 = \frac{\text{Slope}}{So\,(1 - \text{Slope})}$

For 1:1 drug/CD complexes the complexation efficiency (CE) can be calculated from the slope of the phase-solubility diagram (eq. 3) by

Eq. 3.	D/CD = So.K1:1	Slope
	CD	So (1−Slope)

The most common stoichiometry of higher order D/CD complexes is the 1:2 D/CD complex resulting in Ap-type phase solubility diagram. Consecutive complexation is assumed where 1:2 complexes (eq. 4) is formed when one additional cyclodextrin molecule forms a complex with an existing 1:1 complex. The value of k1:2 frequently lies between 10–500 µ-1 and is lower than that of k1;1(50–2000µ-1).

Eq.4. $D/CD + CD \leftarrow\!\!- \overset{K1-:2}{} \rightarrow D/CD_2$

Various methods that are used to prepare D/CD complexes include solution method, co-precipitation method, neutralization method, slurry method, kneading method, grinding method etc.and water is essential for the successful complex formation. In solution, the cyclodextrin complexes are prepared by addition of excess amount of drug to an aqueous cyclodextrin solution.

Preformulationstudy

Solubility study of Carvedilol in Distilled water, blend of glycerin in water, HPMC in water and Tween 80 in water (0.5%, 1%, 2%, 4% and5%)

Phase solubility of carvedilol

Phase solubility studies for Carvedilol complexes were performed to determine how the complexes of β-cyclodextrin affect the solubility of the carvedilol. These studies also determine the stoichiometry of drug: β- cyclodextrin complexes and numerical values of their stability constant.

Procedure: For phase solubility studies of carvedilol complexes, an excess of drug (200 mg) was added to 20 ml portions of distilled water, each containing variable amount of β-cyclodextrin (β-CD) such as 0, 1, 3, 6, 9, 12 and $15x10^{-3}$ moles/liter. All the above solutions with variable amount of β-CD were shaken for 72 hours. After shaking, the solutions were

filtered and their absorbances were noted at 242 nm. The solubility of the Carvedilol in everyβ-CD solutions was calculated and phase solubility diagram were drawn between the solubility of carvedilol and different concentrations of β-CD.

The stability constant of carvedilol- β-CD complex was calculated using Higuchi and Connor's equation.

Slope S_0(1- slope)

S_0 = intrinsic solubility of CR in aqueous complexation media (distilled water). "Slope" was calculated from phase solubility diagram.

Sr No	β-CD (Mm)	Drug Dissolved (Mm)
1	0	0
2	1	0.03
3	3	0.08
4	6	0.14
5	9	0.23
6	12	0.32
7	15	0.41

Preparation of carvedilol complexes with β -cyclodextrin

Complexes of carvedilol with β-cyclodextrin (β-CD) were prepared by different methods using different molar concentrations of β-CD. The molar concentration used and methods adopted are summarized in table.

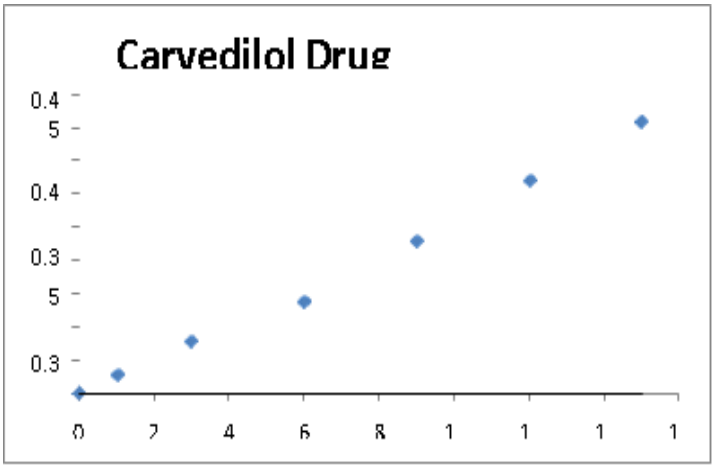
Method	Drug to Carrier	Drug to Carrierratio	Code
Physical Mixture	Carvedilol: β -CD	1:0.5	PC 1
	Carvedilol: β -CD	1:1	PC 2
	Carvedilol: β -CD	1:1.5	PC 3
	Carvedilol: β -CD	1:2	PC 4
	Carvedilol: β -CD	1:3	PC 5
Kneading Method	Carvedilol: β -CD	1:0.5	KC 1
	Carvedilol: β -CD	1:1	KC 2
	Carvedilol: β -CD	1:1.5	KC 3
	Carvedilol: β -CD	1:2	KC 4
	Carvedilol: β -CD	1:3	KC 5

Methods used in present work

Physical mixture: Carvedilol with β-CD in different molar ratios and were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccator over fusedcalcium chloride.

Kneading method: Carvedilol with β-CD in different molar ratios were taken. First cyclodextrin is added to the mortar, small quantity of 50 % ethanol is added while triturating

to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 45°C for 2 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fusedcalciumchloride.



Drug evaluation studies

Drug content estimation

Estimation of carvedilol in the inclusion complex procedure

50 mg of complex was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 242 nm using appropriate blank. The drug content of Carvedilol was calculated using calibration curve.

Dissolution characteristic

***In vitro* dissolution studies for carvedilol β -CD complexes**

Procedure: *In-vitro* dissolution of Carvedilol β -CD inclusion complexes were studied in USP XXIV dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer of pH 7.4 was used as dissolution medium. The stirrer was adjusted rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37° 0.5°C and was maintained throughout the experiment. Complex equivalent to 25 mg of carvedilol was used in each test. 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 242 nm after suitable dilution with phosphate buffer. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

Percentage amount of carvedilol released was calculated and plotted against time. The results are given in Table and shown in figure. For comparison, the dissolution of pure drug was studied.

Solubility (mg/ml) of carvedilol in various fluids.

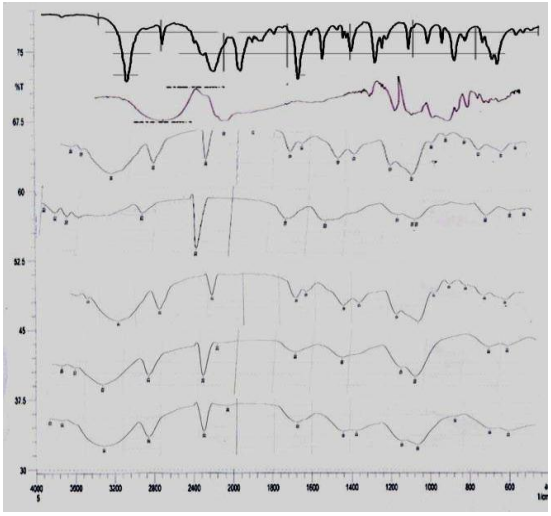
Fluid	Solubility(mg/ml)						
	Conc.(%) of added solvent/surfactant						
	0	0.5% (SD)	1.0% (SD)	2.0% (SD)	3.0% (SD)	4.0% (SD)	5.0% (SD)
Water	-	-	-	-	-	-	-
Water+ Glycerine	0.061± 0.005	0.110± 0.003	0.168± 0.005	0.294± 0.003	0.487± 0.004	0.620± 0.006	0.897± 0.003
Water+ Twee n 80	-	0.146± 0.006	0.188± 0.005	0.342± 0.004	0.391± 0.005	0.426± 0.061	0.479± 0.005
Water+ HPM C	-	0.164± 0.003	0.417± 0.005	0.769± 0.013	0.922± 0.010	1.271± 0.005	1.453± 0.011

Calibration curve of Carvedilol in phosphate buffer pH 7.4.

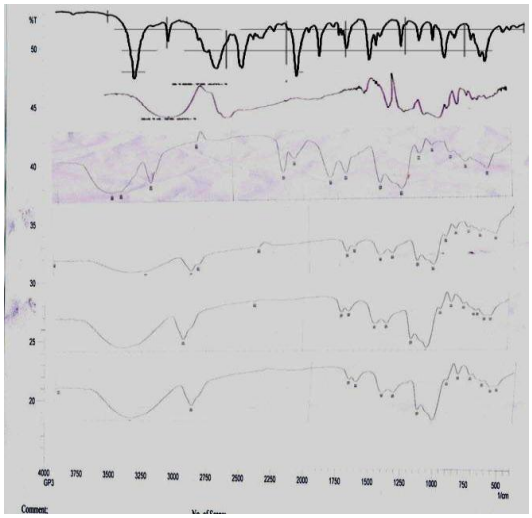
S. No	Concentration (mcg/ml)	Absorbance
1	0	0
2	06	0.190
3	09	0.248
4	12	0.340
5	15	0.436
6	18	0.549

Phase Sol ubility Study Data of Carvedilol with β-CD.

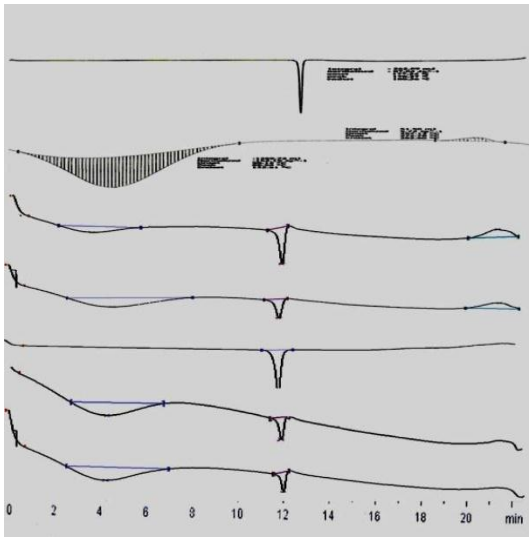
S. No	β-CD (Mm)	Drug Dissolved (Mm)
1	0	0
2	1	0.03
3	3	0.08
4	6	0.14
5	9	0.23
6	12	0.32
7	15	0.41



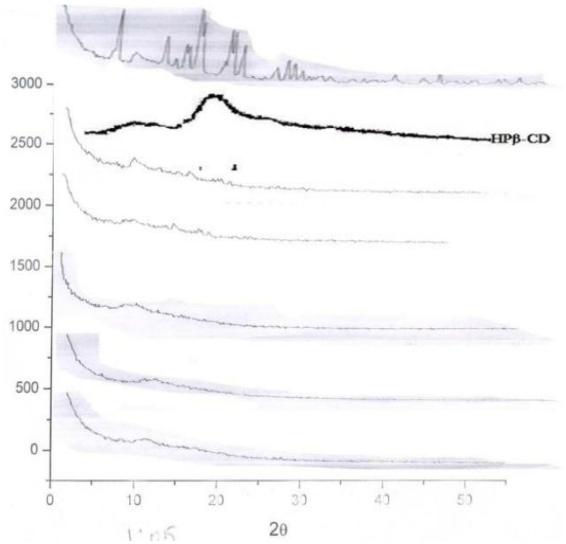
IR Profile of carvedilol and its β-CD inclusion complexes.



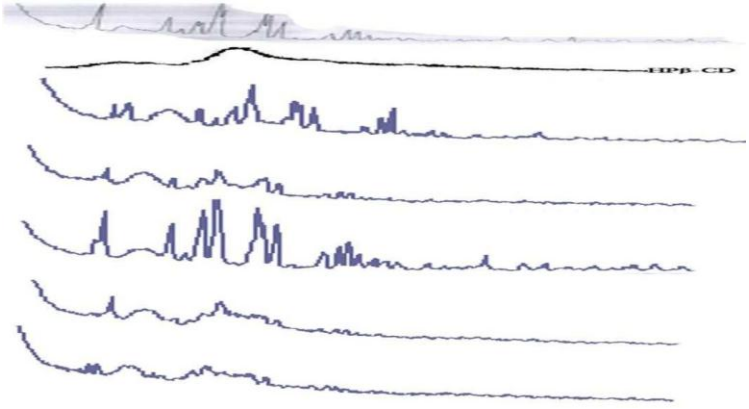
IR spectra of Carvedilol and its β-CD Physical Mixture.



DSC Profile of Carvedilol and its β-CD Inclusion complexes.



DSC Profile of Carvedilol and its β-CD Physical Mixture.



XRD Profile of Carvedilol and its β-CD Physical mixtures.

Drug content profile of Carvedilol and its β-CD inclusion complexes

Sample.	KC1	KC2	KC3	KC4	KC5
1	95.13	95.18	96.41	97.38	97.07
2	94.86	93.78	95.79	96.81	98.15
3	96.04	96.26	96.19	97.03	98.43
AVG mg	95.34	95.07	96.13	97.07	97.88
std dev+-	0.62	1.24	0.31	0.29	0.72
c.v. (%)	0.006	0.013	0.0032	0.0029	0.00733

Drug content profile of Carvedilol and its β-CD physical mixture.

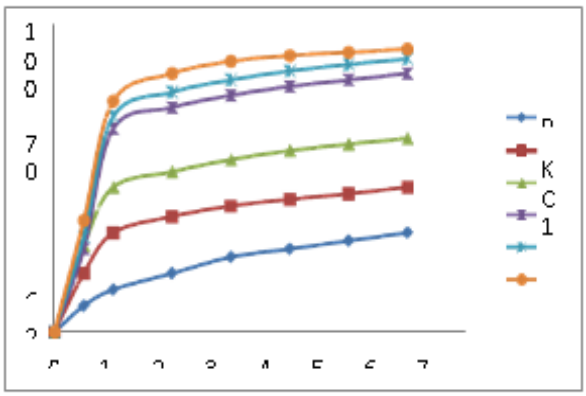
Sample.	PC1	PC2	PC3	PC4	PC5
1	95.13	95.18	96.41	97.38	97.07
2	94.86	93.78	95.79	96.81	98.15
3	96.04	96.26	96.19	97.03	98.43
AVG mg	95.34	95.07	96.13	97.07	97.88
S td dev+-	0.62	1.24	0.31	0.29	0.72
c.v. (%)	0.006	0.013	0.0032	0.0029	0.00733

Percentage of drug release data of Carvedilol and its β-CD inclusion Complexes (Kneading method).

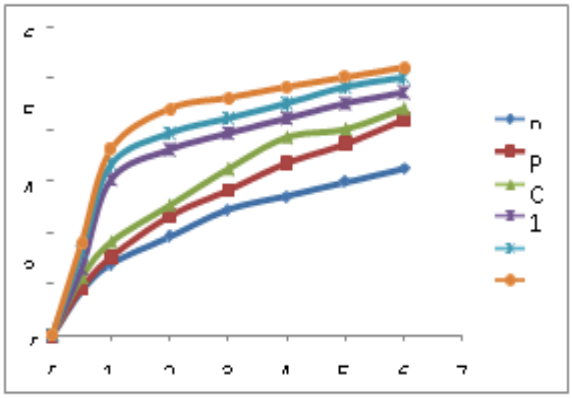
Time (min)	PC	KC1	KC2	KC3	KC4	KC5
0	0	0	0	0	0	0
5	8.529	19.118	28.118	27.059	31.029	36.324
10	13.824	32.353	47.176	66.235	70.206	75.235
20	19.118	37.647	52.206	73.118	78.147	84.235
30	24.412	41.088	56.176	77.088	82.118	88.206
40	27.059	43.206	59.088	80.000	85.029	90.059
50	29.706	45.059	61.206	82.118	87.147	91.118
60	32.353	47.176	63.059	84.235	89.000	92.176

Percentage of drug release data of Carvedilol and its β-CD complex (Physical mixture).

T Time (min)	PC	PC1	PC2	PC3	PC4	PC5
0	0	0	0	0	0	0
5	8.529	9.059	11.176	13.029	16.206	18.059
10	13.824	15.147	18.059	30.235	33.147	36.059
20	19.118	23.088	25.206	36.059	39.235	44.000
30	24.412	28.118	32.282	39.235	42.147	46.118
40	27.059	33.412	38.426	42.147	45.059	48.235
50	29.706	37.118	40.029	45.059	48.235	50.088
60	32.353	41.882	44.011	47.176	50.088	52.026



Data Profile graph of Carvedilol (Kneading Method).



Data Profile graph of Carvedilol (physical Method).

Correlation Coefficients (R^2) Values in the analysis of Carvedilol and its β-CD Dissolution data as per Zero order and First order of inclusion complexes and physical Mixtures.

Correlation coeffecient		
Formulation s	Zero order Equation	First order Equation
	Regression coefficient (R^2)	Regression coefficient (R^2)
CR	0.8965	0.9126
KC1	0.6815	0.8347
KC2	0.6661	0.376

KC3	0.6305	0.8466
KC4	0.5846	0.6178
KC5	0.59	0.8756
PC1	0.7336	0.7234
PC2	0.7477	0.844
PC3	0.7302	0.8169
PC4	0.6595	0.7486
PC5	0.6488	0.7603

Dissolution parameter data of Carvedilol and its β-CD Inclusion Complexes and Physical mixtures.

Formulation s	T 50%	T 80%	T 90%	DE (30%)	K_1 (min^{-1})	Increase in K_1 (Folds)
CR	-	-	-	08.62	0.005	
KC1	--	-	-	45.60	0.030	4.98
KC2	19.24	-	-	54.10	0.023	5.6
KC3	8.48	40	-	60.16	0.039	8.2
KC4	8.24	25	--	66.98	0.042	8.9
KC5	7.11	17.24	39.48	70.30	0.048	9.7
PC1	-	-	-	22.03	0.012	2.4
PC2	-	-	-	29.90	0.014	2.8
PC3	--	-	-	32.52	0.014	2.8
PC4	58.14	-	-	39.58	0.012	2.4
PC5	49.51	-	-	42.09	0.014	2.8

Drug content data of Carvedilol and its β-CD Tablets.

Sample	Tab1 W	1 Tab2 D	Tab3 W	3 Tab4 D
1	99.57	99.41	99.88	99.86
2	99.78	99.85	99.67	99.21
3	99.69	99.73	98.91	99.79
AVG mg	99.68	99.73	99.48	99.62
	0.105	0.227	0.510	0.356
Std Dev±				
c.v. (%)	0.001	0.002	0.005	0.003

TAB 1 W = Carvedilol Tablet (without β-CD) by Wet Granulation method

TAB 2 D = Carvedilol Tablet (without β-CD) by Direct compression method

TAB 3 W = Carvedilol-β-CD Tablet by Wet Granulation method

TAB 4 D = Carvedilol-β-CD Tablet by Direct compression method.

Hardness Data of Carvedilol and its β-CD Tablets post compression study.

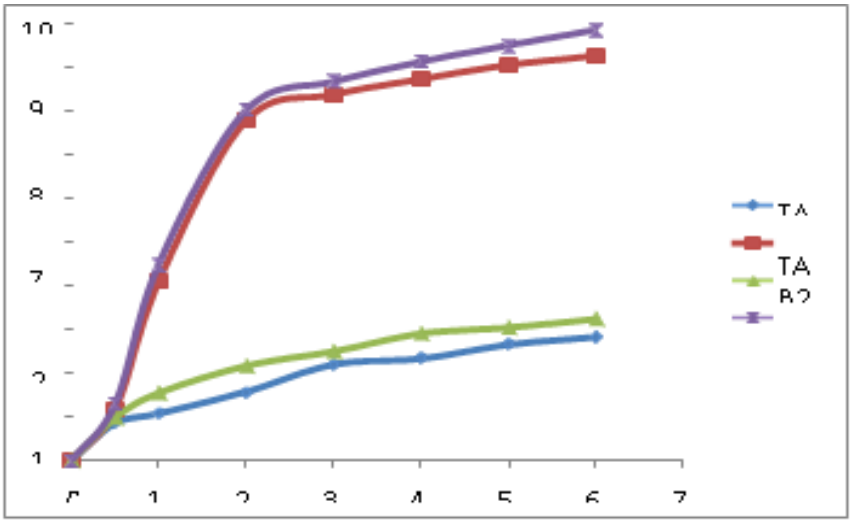
Formulation	Hardness	Hardness	Hardness	Avg. Hardness	Std. Dev.
Tab1 W	5.05(±0.132)	5.61(±0.132)	5.19(±0.132)	5.28(±0.132)	0.291
Tab2 D	4.78(±0.132)	4.79(±0.132)	4.93(±0.132)	4.83(±0.132)	0.083
Tab3 W	4.86(±0.132)	4.99(±0.132)	4.98(±0.132)	4.94(±0.132)	0.072
Tab4 D	4.74(±0.132)	4.97(±0.132)	5.02(±0.132)	4.91(±0.132)	0.149

Disintegration time data of Carvedilol and Its β-CD Tablets after stability study.

Formulation	Time (minutes)	Time (minutes)	Time (minutes)	Average Time (minutes)	(±)Std dev
Tab1	3.39	3.23	3.34	3.32	0.08
Tab2	3.07	3.02	3.17	3.08	0.07
Tab3	3.12	3.04	3.12	3.09	0.04
Tab4	2.45	2.39	2.48	2.44	0.04

Percentage of drug release Data of Carvedilol and Its β-CD Tablets.

Time (min)	Tab1 W	Tab2 D	Tab3 W	Tab4 D
0	0	0	0	0
5	8.47	9.71	11.53	12.85
10	10.69	15.4	40.95	44.92
20	15.71	21.58	77.72	80.04
30	21.85	24.89	83.61	86.58
40	23.24	28.97	87.15	91.14
50	26.42	30.34	90.35	94.83
60	28.21	32.32	92.54	98.36



SUMMARY AND CONCLUSION

Low RSD values ensured reproducibility of the method. No interference from excipients used was observed. Thus method was found suitable for the estimation of Carvedilol content in dissolution fluids.

The solubility of carvedilol is increasing as the concentration of solvent/surfactant increases. Solubility is more in a blend of water + HPMC than the Tween 80 and glycerin with water.

XRD patterns of carvedilol and complexes with β-CD. The diffraction peaks were much reduced in the case of carvedilol-β-CD complexes. The disappearance of carvedilol

crystalline peaks confirmed the stronger drug amorphization and entrapment in β-CD.

Solid inclusion complexes of carvedilol-β-CD in 1:0.5, 1:1, 1:1.5, 1:2 and 1:3 ratios were prepared by kneading method and physical mixture. The dissolution rate of carvedilol from CDs complex and physical mixture system was studied using phosphate buffer solution of pH 7.4 as a dissolution fluid.

The carvedilol tablets prepared with β-CD by wet granulation and direct compression methods. The physical characteristics like size, shape, thickness and appearance of all series of tablets prepared were found good.

Dissolution efficiency (DE_{30}) values are calculated as per Khan. T_{50}, T_{80} and T_{90} values were recorded from the dissolution profiles. The increase in K_1 and K_1 no. of folds of all the tablets of carvedilol prepared with β-CD found when compared with tablets of carvedilol prepared without β- CD.

The present work has been undertaken with an overall objective of studying the complexation of carvedilol, BCS class II drugs with β- cyclodextrin to evaluate the feasibility of enhancing their solubility, dissolution rate, bioavailability and therapeutic efficacy. The feasibility of formulating the CD complexes into tablets with enhanced dissolution rate characteristics was also investigated.

Solid inclusion complexes of carvedilol-β-CD were prepared by kneading method and physical mixture employing different ratios of carvedilol-β-CD. The inclusion complexes prepared by kneading and physical methods were evaluated and characterized by IR, XRD and DSC studies.

Kinetics and mechanism of drug dissolution from the inclusion complexes were evaluated by studying dissolution of solid inclusion complexes. Selected carvedilol-β-CD complexes were formulated into tablets by wet Granulation and direct compression methods and the resulting tables were evaluated for dissolution rate and other physical properties of tablets

- ✓ The phase solubility diagram of carvedilol was of type $A_L$withβ-CD.
- ✓ The phase solubility studies indicated the formation of carvedilol-β-CD inclusion complexes at a 1:1 M ratio in solution. The complexes formed werequite stable.
- ✓ The aqueous solubility of carvedilol was increased linearly as a function of concentration ofthe β-CD.

- ✓ Inclusion complex prepared by kneading method exhibited higher solubilizing efficiency when compared with physical mixture of carvedilol-β-CD.
- ✓ DSC and XRD indicated better drug inclusion in β-CD, and good drug amorphization and entrapmentinβ-CD.
- ✓ IR spectral studies indicated no chemical interaction between the carvedilol-β-CD.

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