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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF CARVEDILOL

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ABSTRACT

Carvedilol is a poorly water soluble oral antihypertensive agent, with problems of variable bioavailability and bioequivalence related to its poor water solubility. Carvedilol is a nonselective beta adrenergic blocking agent with alpha-1 blocking activity and is indicated for the treatment of hypertension and mild to moderate heart failure of ischematic or cardiomyopathic origin In the present work solubility was enhanced by using β- cyclodextrin as a complexing agent. Sweeteners and flavors were used to enhance the organoleptic properties of tablet. Solubility studies were performed to investigate the drug carrier interaction. I.R. and D.S.C studies carried out to investigate any interaction and stability of formulation. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. All the formulations were evaluated for the influence of disintegrates and their concentrations on the characteristics of fast dissolving tablets mainly in terms of disintegration time and dissolution studies. Optimized formulation of Ac-Di-Sol Superdisintegrant in the concentration of (6mg) i.e. F3 batch gives best results than all the formulation. Formulation F3 of Ac-Di-sol superdisintegrant required minimum disintegration time, wetting time Compared to Formulations of Crosspovidone, or Sodium-starch glycoate with same concentration. From this study it can be concluded that Carvedilol can be successfully complexed with Beta-cyclodextrin to prepare fast dissolving tablets in the ratio of 1: 4.

Keywords: Carvedilol, superdisintegrant, in-vitro disintegration time, β- cyclodextrin

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1.0 INTRODUCTION

Fast Dissolving Tablet is solid unit dosage form which disintegrates or dissolves rapidly in the mouth without chewing and water. To design fast dissolving oral tablet of Carvedilol in order to improve bioavailability, ease of administration and patient compliance. In the present study, fast dissolving tablet of Carvedilol was attempted with the aim to develop a dosage form that was easy to administer, provided fast release of drug and also enhanced bioavailability of the drug. Pregastric absorption through mouth, pharynx and oesophagus, could enhance the bioavailability by suitable formulation approaches and also provide local action, as the drug releases in saliva and passes down in to the stomach. The market survey revealed that the conventional tablets are available. Hence it was thought to formulate novel and convenient solid dosage form i.e. fast dissolving tablet. Carvedilol was selected as a drug candidate for the formulation of fast dissolving tablet for the following reasons, It is practically insoluble in water therefore taste related problems can be avoided.It is chemically stable.Having $t_{1/2}$ of – 7 to 10 hrs.In view of substantial first pas effect and its shorter plasma half life, therefore is an ideal drug candidate for fast dissolving tablet. Appropriate disintegrating agents and highly hydrophilic excipients are the main ingredients of fast dissolving tablets.

EXPERIMENTAL

Preparation of the Fast dissolving tablet of Carvedilol:

The tablet consisted of drug: β-CD complex, super disintegrant like Ac-di-sol/ Polyplasdone-XL /Primojel, Avicel pH102 (diluent), talk (lubricant), Magnesium stearate (lubricant), Lactose (filler), Dextrose (Binder/Diluent), sorbitol (Wetting agent), Xylitol (sweetener), Aerosil (glidant), Strawberry (flavor), . These ingredients were weighed and mixed stoichometrically to obtain the final formulation. The weight of the tablet in all formulations was kept constant to 130mg. All the batches were prepared by direct compression method using the 27-station rotary punch tablet compression machine using 7 mm biconvex plain on both side die-punches set. The variables maintained in the formulation were the different types of super-disintegrant and their concentration (in mg) in the formulation.

Firstly inclusion complex of Carvedilol and β-cyclodextrin in the ratio of 1:4 was prepared. The inclusion complex was prepared by kneading method. 1gm of Carvedilol was placed in the mortar and 4gm of β- cyclodextrin mixed to it, and then organic solvent methanol was added. Slowly grind the mixture of Carvedilol, β-cyclodextrin and organic solvent methanol still

paste is not prepared. Once paste was prepared paste was dried at 50^0C. Completely dried complex used for the preparation of fast dissolving tablet. Tablets were prepared from blends by direct compression method. All the ingredients including drug were passed through mesh no. 60 excepting lubricants. Lubricants were passed through mesh no.80. Lubricants were added at the time of compression. Blend is mixed uniformly by manually for 30 minutes. Tablets of convex faced weighing 130mg each with 3.3mm thickness and 7mm in diameter.

Table No. 1. Formulation of Fast dissolving tablet of Carvedilol

INGREDIENTS	F1	F2	F3	X4	X5	X6	Z7	Z8	Z9	C10	C11
Carvedilol (mg)	_	_	_	_	_	_	_	_	_	_	12.5
Drug: β-CD complex (mg)	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	_
Ac-Di-Sol (mg)	2	4	6	_	_	_	_	_	_	_	_
Polyplasdone-XL (mg)	_	_	_	2	4	6	_	_	_	_	_
Primojel (mg)	_	_	_	_	_	_	2	4	6	_	_
Dextrose(mg)	_	_	_	_	_	_	_	_	_	_	30
Lactose (mg)	14	12	10	14	12	10	14	12	10	20	36
Sorbitol (mg)	16	16	16	16	16	16	16	16	16	16	16
Xylitol (mg)	10	10	10	10	10	10	10	10	10	10	10
Avicel pH102 (mg)	17	17	17	17	17	17	17	17	17	17	17
Talk (mg)	2	2	2	2	2	2	2	2	2	2	2
Mg stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Flavour (Strawberry)	3	3	3	3	3	3	3	3	3	3	3
Aerosil	1	1	1	1	1	1	1	1	1	1	1
Total	130	130	130	130	130	130	130	130	130	130	130

- Equivalent to 12.5 mg of Carvedilol.

PREFORMULATIION STUDY

Solubility:

The solubility of Carvedilol and Carvedilol β - cyclodextrin complex was checked in various solvent at room temperature for 24 hours using rotary shaker / mechanical shaker.

Solubility of the drug was determined by saturation method. In 100 ml of solvent 100mg of drug was added so 1000µg/ml of solution prepared. Drug was saturated because of insolubility in the solvent. Out of that 25ml was taken in the 50 ml of volumetric flask. With the help of mechanical shaker shaking of 24hrs was completed. After 24hrs of shaking solution was filtered through Whatman filter paper and with suitable dilution absorbance recorded. Using slope of drug in the solvent concentration of drug in the solution was determined. From this concentration amount dissolved in the solvent i.e. solubility was determined.

Similar procedure was followed for the various complex of Carvedilol β – cyclodextrin.

Table No. 2. Solubility Analysis

Composition	Ratio concentration	Solubility in 0.1N HCl in mg/ml	Solubility in Phosphate Buffer 6.8 in mg/ml	Solubility in Phosphate buffer 7.4 in mg/ml
Carvedilol	Pure drug	1.062mg/ml	0.08528 mg/ml	0.0861 mg/ml
Dug & BCD.	1:1	1.366mg/ml	0.0945 mg/ml	0.0956 mg/ml
Dug & BCD.	1:2	1.558mg/ml	0.1133 mg/ml	0.1371 mg/ml
Dug & BCD.	1:3	1.801 mg/ml	0.1309 mg/ml	0.1509 mg/ml
Dug & BCD.	1:4	2.266 mg/ml	0.1436 mg/ml	0.1687 mg/ml
Dug & BCD.	1:5	2.372 mg/ml	0.1575 mg/ml	0.1826 mg/ml
Dug & BCD.	1:6	2.253 mg/ml	0.1763 mg/ml	0.2121 mg/ml
Dug & BCD.	1:7	2.772 mg/ml	0.1970 mg/ml	0.2247 mg/ml
Dug & BCD.	1:8	3.482 mg/ml	0.2220 mg/ml	0.2392 mg/ml
Dug & BCD..	1:10	3.166 mg/ml	0.2040 mg/ml	0.2260 mg/ml

Partition coefficient

A measurement of a drug's lipophilicity and an indication of its ability to cross cell membranes is the oil/water partition coefficient in systems such as octanol/water and chloroform/water. The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phase as equilibrium.

$$\text{Partition coefficient} = \frac{\text{concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

For series of compounds, the partition coefficient can provide an empiric handle in screening for some biologic properties. For drug delivery, the lipophilic/hydrophilic balance has been shown to be a contributing factor for the rate and extent of drug absorption. Although partition coefficient data alone does not provide understanding of in vivo absorption, it does provide a means of characterizing the lipophilic/hydrophilic nature of the drug.

Drugs having values of logP much greater than one are classified as lipophilic, whereas those with partition coefficients less than one are indicative of a hydrophilic drug.

Table No. 3. Process of Determination of Partition coefficient

S.No.	Drug (mg)	Octanol (ml)	Water (ml)
1.	10	50	50
2.	20	50	50
3.	30	50	50

Table No. 4. Observation and Calculation of Partition Coefficient

S.No	Conc. of drug in Octanol (µg\ml) x DF	Conc of drug in water (µg\ml) x DF	Po\w = conc. of octanol\conc. water	Average P o\w
1	0.8113	0.266	3.05	
2	0..80066	0.266	3.01	3.06
3	0.8299	0.266	3.12	

Preparation of blend:-

Accurately weighed all the ingredients. All the ingredients passed through sieve no.60 except lubricants; lubricants passed through sieve no.80. All ingredients mixed stoichometrically; lubricants added at the time of compression. This is the blend ready for compression.

Evaluation of Blend:-

Angle of Repose: - The angle of repose is the constant, three dimensional angle (relative to

horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.

Bulk Density: -

Bulk density often is the bulk density of the powder "as poured" or as passively filled into the measuring cylinder. Bulk density is determined by measuring the known mass of powder sample that has been passed through a screen in to a graduated cylinder or through a volume measuring apparatus into a cup.

Bulk Density= Mass/Volume= M/V_o

Tapped Density: -

The tapped density is a limiting density attained after "tapping down," usually in a device that lifts and drops a volumetric measuring cylinder containing the powder a fixed distance. Tapped density is achieved by mechanically taping a measuring cylinder containing a powder sample. After observing the volume, the cylinder is mechanically tapped, and volume reading taken until little further volume change is observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight a specified distance by either of two methods as described below. Devices that rotate the cylinder during tapping may be preferred to minimize any possible of the mass during tapping down.

Tapped Density= Mass/Tapped volume =M/V_f.

Compressibility Index and Hausner Ratio: - (Measure of powder compressibility)

The Compressibility Index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions, in a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

Compressibility Index – calculate by the formula

$100(V_o - V_f)$

Hausner Ratio calculates by the formula **V_o / V_f**

Determination of moisture content:-

Moisture content of the prepared blend was determined using Moisture Analyzer of A and D Co. Ltd of model no CE-N 92. 5gm of blend laced on moisture analyzer at 105^0C & it determines moisture content.

Phase Solubility Analysis of Carvedilol: - Phase solubility analysis is used to determine stoichiometric proportion of the drug and the complexing agent and to derive the stability constant of resulting complexes. For this, 0.02 M stock solution of ß–Cyclodextrin (ß–CD) was prepared. Stock solution was appropriately diluted with distilled water to give molar solutions in the range of 0.001 M to 0.02 M. Screwcapped bottles were filled with constant volume of these molar solutions and excess of drug quantities were added to these bottles. These solutions were equilibrated for 24 hours by constant shaking on rotary shaker. The supernatants were filtered and analyzed using UV-Visible spectrophotometer. A plot of molar concentrations of ß- CD vs. molar concentrations of drug was plotted.The stability constant was calculated according to equation,

Kc = Slope / Intercept (1 - slope)

Table No.5. Phase solubility Analysis

Moles of B-Cyclodextrin	Conc. of Carvedilol (µg / ml)	Moles of Carvedilol
0	32.72	0.0052
0.001	35.77	0.0057
0.002	42.46	0.0068
0.004	53.24	0.0085
0.006	70.14	0.011
0.008	80.23	0.013
0.010	95.10	0.015
0.012	106.27	0.017
0.014	114.06	0.019
0.016	134.03	0.021
0.018	136.68	0.021
0.020	140.86	0.022

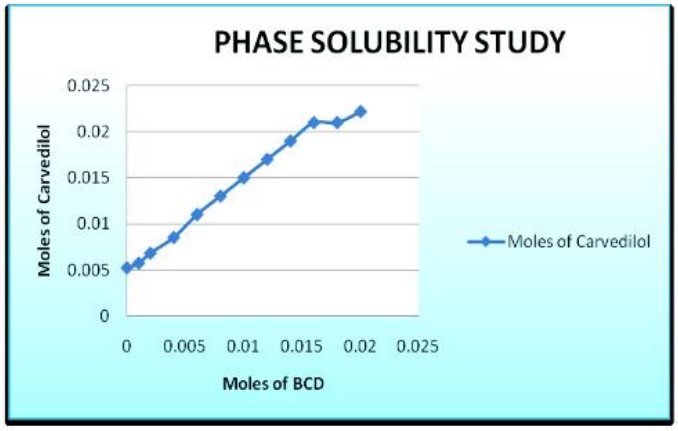


Figure 1: Phase Solubility Study of drug.

The phase solubility analysis diagram of Carvedilol with β-Cyclodextrin can be observed in above Figure. As can be seen, this diagram is an A_L type curve with a linear relationship between solubilized Carvedilol and β-Cyclodextrin with a negative curvature. The initial linear ascending part of solubility diagram in Figure is generally ascribed to the formation of a 1:4 complex. The apparent stability constant ($K_{1:4}$) calculated using formula.

$$\mathbf{K_{1:4}} = \boldsymbol{Slope} / \boldsymbol{S_0}\ \mathbf{(1 - } \boldsymbol{Slope}\mathbf{)}$$

Where S_0 is the intrinsic solubility of Carvedilol.

The apparent stability constant ($K_{1:4}$) for the Carvedilol: β-Cyclodextrin complex was calculated from the solubility data and found to be 2083 M^{-1s}.

Characterization of drug: β-CD complex.

Differential Scanning Calorimetry (DSC) Study:

The Differential Scanning Calorimetric study was carried out using Mettler Toledo Differential Scanning Calorimeter. Samples were placed in an aluminum crucible and the DSC thermograms were recorded at heating rate of 10^0 C/ min in the range 30 to 300^0C.

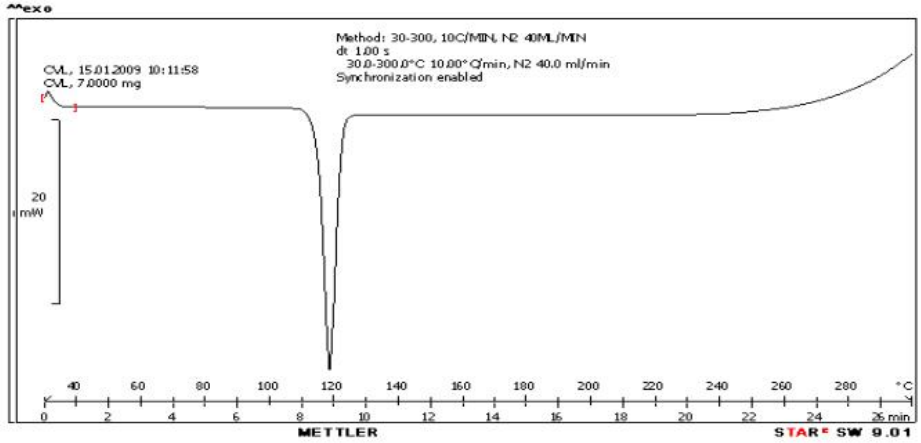


Figure No. 2. DSC curve of pure Carvedilol

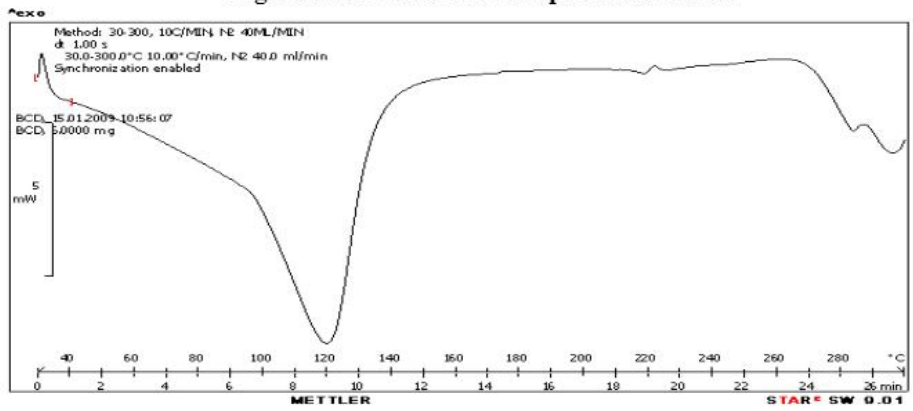


Figure No. 3. DSC curve of β-CD

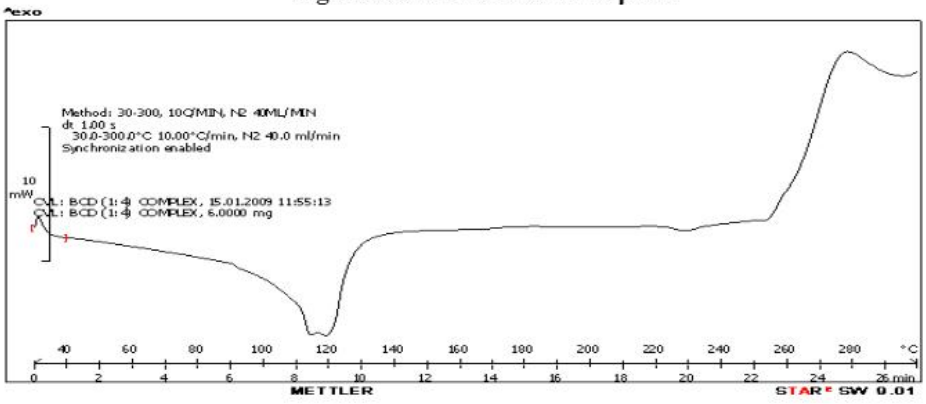


Figure No. 4. DSC curve of β-CD - Carvedilol complex.

Above Figure No, 23,24 and 25 shows the DSC thermograms of drug, β-CD and drug: β-CD (1:4). DSC studies revealed that endothermic peaks for pure Carvedilol and β-CD were obtained at 118.38°C and 122.46°C respectively. Thermogram of Drug: β-CD complex showed complete disappearance of sharp peak of Carvedilol and shift in endothermic peak of β-CD. This indicates successful complexation of Carvedilol with β-CD. Thus, DSC studies confirm interaction between drug and β-CD.

Physical properties of β- Cyclodextrin and complex:

1.Shape: - The shape of both β- Cyclodextrin and drug: β-CD complex was found to be irregular as determined by microscopic method.

2.Flow properties: The angle of repose was found to be 29.35^0 for drug: β-CD complex. The angle of repose of uniform spheres is 20° and angles larger than 45° exist for cohesive powders. So the Drug: β-Cyclodextrin complex can flow.

3. Bulk Density*:* The bulk density value was found to be 0.65 for drug: β-CD complex.

Table No. 6. Physical properties of drug: β-Cyclodextrin (1:4) complex

β – Cyclodextrin / Drug: β-CD complex	**Physical properties**		
	Shape	**Angle of repose**	**Bulk Density**
B – Cyclodextrin	Irregular	31.57^0	0.57
Drug: β-CD (1:4) complex	Irregular	29.35^0	0.65

RESULT AND DISCUSSION

PREPARATION OF BLEND:

Accurately weighed all the ingredients. All the ingredients passed through sieve no.60 except lubricants; lubricants passed through sieve no.80. All ingredients mixed stoichometrically; lubricants added at the time of compression. This is the blend ready for compression.

Evaluation of Blend:-

Table No. 7. Powder properties of Formulation Series

Formulation Series	Bulk Density	Tapped Density	Compressibility Index	Hausner Ratio	Angle of Repose
F1	0.510gm/ml	0.598gm/ml	15.81%	1.17	26.28
F2	0.512gm/ml	0.597gm/ml	15.38%	1.18	26.8554
F3	0.512gm/ml	0.60gm/ml	14.87%	1.17	27.14
X4	0.505gm/ml	0.591gm/ml	14.64%	1.17	27.758
X5	0.507gm/ml	0.595gm/ml	14.72%	1.1726	28.07
X6	0.5076gm/ml	0.597gm/ml	14.97%	1.176	28.07
Z7	0.512gm/ml	0.595gm/ml	13.846%	1.16	29.39
Z8	0.515gm/ml	0.598gm/ml	13.91%	1.161	29.74
Z9	0.515gm/ml	0.602gm/ml	14.43%	1.168	29.02
C10	0.510gm/ml	0.641gm/ml	20.40%	1.256	32.82
C11	0.534gm/ml	0.714gm/ml	25.13%	1.3357	34.59

Table No. 8. Evaluation of Formulation Series

Batch no.	Weight variation	Hardness kg/cm^2	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio	Drug Content (%)
F-1	Passes	3.1	3.3	0.41	42	63	75	99.78
F-2	Passes	3.2	3.3	o.37	31	55	88.72	99.62
F-3	Passes	3.1	3.3	0.37	25	49	96.29	101
X-4	Passes	2.9	3.3	0.38	48	69	67.40	100.2
X-5	Passes	3.1	3.3	0.4	35	59	85.82	100.4
X-6	Passes	3	3.3	0.41	29	50	94.77	100.3
Z-7	Passes	2.8	3.3	0.41	55	71	64.70	99.9
Z-8	Passes	2.9	3.3	0.41	41	65	82.82	99.7
Z-9	Passes	2.9	3.3	0.43	34	56	93.28	100.1
C-10	Passes	3.5	3.3	0.41	74	79	58.33	99.6
C-11	Passes	4.1	3.3	0.32	161	93	42.69	99.5
M-1	-	5.3	-	-	257	429	68.33	101.1
M-2	-	5.6	-	-	291	486	63.01	99.7

M1:- Marketed Tablet of Carvedilol (Cardivas)

M2:- Marketed Tablet of Carvedilol (Carca)

Determination of Drug content of the Drug: β-CD complex:

Drug: β-Cyclodextrin (1:4) complex was evaluated for the drug content. Drug: β-

Cyclodextrin complex equivalent to 12.5 mg of drug was stirred with 100ml of 0.1N HCl for 60 minutes, then thesolution was filtered and treated as stock solution containing 100 mg/ml drug. From this stock solution the concentration of 10 µg/ml was prepared and the drug content was determined using the calibration curve of pure drug in 0.1N HC1 spectrophotometrically at 242 nm using 0.1N HC1 as blank.

Procedure: - Dry drug: β-CD complex used for the drug release study. Complex equivalent to 12.5mg of the drug weighed accurately and subjected to release rate study using the above mentioned conditions. Carvedilol (12.5mg) was used as a control and subjected to release rate study. 10 ml of aliquots were withdrawn at different time intervals of 0, 1,2,3,4 up to 15 min and replacement was made each time with 10ml fresh dissolution medium. Each of 10ml sample was filtered through Whatman filter paper number 41. The absorbance was recorded for each sample by Schimadzu-1601 double beam spectrophotometer at 242 nm and drug concentration in the sample was determined from the standard curve of the drug in 0.1N HCl. The drug release studies were carried out in triplicate.

Table No. 9. Release of drug from Drug: β-CD (1:4) complex

Time(min)	Drug : β-CD (1:4)Complex*	Time(min)	Drug : β-CD (1:4)Complex*
1	85.62	9	98.56
2	92.87	10	98.02
3	95.01	11	97.46
4	100.60	12	97.92
5	100.21	13	96.82
6	99.10	14	96.73
7	98.09	15	96.11
8	97.56		

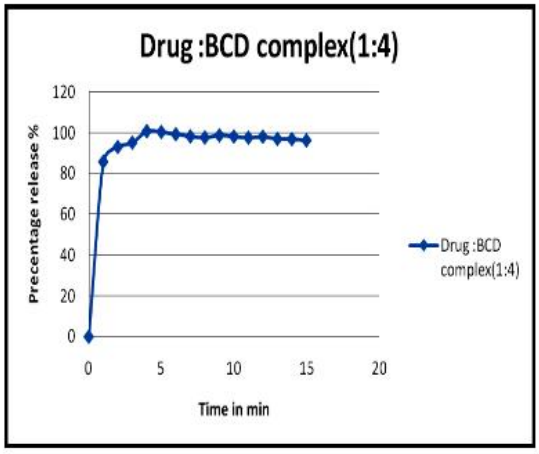


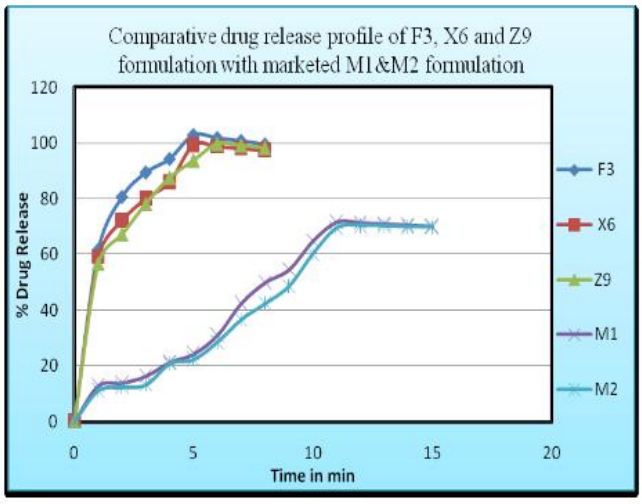
Figure No. 5. Release of Drug from Drug: β-CD (1:4) complex

Drug and Drug: β-CD (1:4) complex showed 100% dissolution within 4 min. As dose is very small, in the complex, drug may be dissolving rapidly.

Table No. 10. Drug release Profile Of various CVL-Betacyclodextrin complexes in 5 minutes:-

Time(min)	Drug : β-CD Complex*	% Drug Release
5	1:0.5	69.35
5	1:1	77.18
5	1:2	87.59
5	1:3	91.47
5	1:4	100.21
5	1:8	102.84
5	1:10	99.82

Figure No. 6. Comparative drug release profile of F3, X6 and Z9 formulations with marketed formulations (M1 and M2)



SUMMARY AND CONCLUSION

In the present study, fast dissolving tablet of Carvedilol was attempted with the aim to develop a dosage form that was easy to administer, provided fast release of drug and also enhanced bioavailability of the drug. In present work fast dissolving tablets of carvedilol prepared using Ac-di-sol, Crosspovidone and sodium starch glycollate are used as the superdisintegrant in the concentration of 2mg, 4mg and 6mg respectively. The prepared tablets were evaluated for various parameters such as weight variation, friability, hardness, disintegration time, wetting time, water absorption ratio, content uniformity, in vitro dissolution.Carvedilol is practically insoluble in water and it also possesses some unpleasant taste. So both these problems try to solve by using Betacyclodextrin.To determine required ratio of drug-BCD complex Solubility study, Phase solubility study carried out. From these studies it was found that required ratio is 1:4All the three superdisintegrant showed good compressibility, good compatibility, flowability and stability.Formulation F3 of Ac-Di-sol superdisintegrant required minimum disintegration time, wetting time Compared to Formulations of Crosspovidone, or Sodium-starch glycoate with same concentration.Formulation of Ac-Di-sol superdisintegrant (F3) had maximum Formulation of Ac-Di-sol superdisintegrant (F3) have maximum water absorption ratio, drug release than all other formulation in 5 min. Stability study conducted for a period of 45 days as per I.C.H. Guidelines for an optimized formulation of F3, X6 and Z9. All these three formulations did not show any significant difference in formulations physical or chemical parameter.From this study it can be concluded that Carvedilol can be successfully complexed with Beta-cyclodextrin to prepare fast dissolving tablets in the ratio of 1: 4.

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