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ORIGINAL RESEARCH ARTICLE

In-Vivo Evaluation Of Carvedilol-B-Cyclodextrin Inclusion Complexes

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ABSTRACT

Carvedilol (BCS Class II drug) is a nonselective β-adrenergic blocking agent with α_1-blocking activity having poor oral bioavailability. The objective of this study is to enhance the oral bioavailability of carvedilol. To improve oral bioavailability of carvedilol, carvedilol *β*-Cyclodextrin complex were formulated by employing the kneading method with the drug: complexing agent1:2. The complexes and pure drug were subjected to pharmacokinetic studies in rabbits. The plasma samples were analyzed by LC-MS/MS method. Various pharmacokinetic parameters were calculated. Carvedilol *β*-Cyclodextrin complex showed higher Ka, AUC values compared with pure drug. Carvedilol *β*-Cyclodextrin complex showed 1.78 fold increases in extent of absorption.

Key Words: Carvedilol, *β*-Cyclodextrin, Bioavailability.

INTRODUCTION

Over recent years, Cyclodextrins and their derivatives have received considerable interest in the pharmaceutical field due to their potential to form complexes with a variety of drug molecules. The resulting complexes generally show some favorable changes of the characteristics of the guest molecules, such as increased solubility, enhanced bioavailability, improved stability, reduced side effects etc. Cyclodextrins are cyclic oligosaccharides produced by the enzymatic degradation of starch by the enzyme, cyclodextrin glycosyl transferees produced by Bacillus macerans. They consists of multiple (α, D1-4) linked glucopyranose units that display amphoteric properties of a lipophilic central cavity and hydrophilic outer surface. Cyclodextrins have been found to be very useful in enhancing the solubility of poorly water soluble drugs owing to the formation of inclusion complex of drug in its hydrophobic cavity. The most common natural cyclodextrins are *α*, *β* and *γ*-cyclodextrins which are formed by 6, 7 and 8 glucose units respectively. Among all the available cyclodextrins, *β*-cyclodextrins (*β*-CD) are the cheapest and non-toxic for oral use [1, 2].

Carvedilol (BCS Class II drug) is a nonselective β-adrenergic blocking agent with α_1-blocking activity and it is mainly used in the treatment of hypertension. Carvedilol (CRL),is chemically (±)-1-(Carbazol-4-yloxy)-3-[2-(o-methoxyphenoxy) ethyl] amino]-2-propanol. It is a white to off-white powder with a molecular weight of 406.5. It is freely soluble in dimethylsulfoxide, soluble in methylene chloride and methanol, sparingly soluble in 95% ethanol and isopropanol, slightly soluble in ethyl ether and practically insoluble in water [3]

The preliminary studies conducted with cyclodextrin complexes showed that the complex prepared with kneading method and having the drug: complexing agent 1:2 ratio showed better in vitro dissolution rate and hence the resulting complex bioavailability was compared with the pure drug and the results are reported here[4].

MATERIALS AND METHODS

Chemicals and Reagents : Carvedilol working standard (gift sample from Sun pharmaceutical industries Ltd, India). *B-Cyclodextrin* was purchased from HiMedia laboratories Pvt. Ltd, Mumbai, Ammonium formate, Acetonitrile and all the chemicals and reagents used were of analytical grade and obtained commercially.

Animals:

New Zealand male rabbits (1.8 -2.0 kg) maintained at 25+ 1 °C were used for the study. The animals were housed in stainless steel

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metabolic cages and provided standard diet and water *ad libitum*[5]. **Preparation of Carvedilol β-cyclodextrin inclusion complexes:**

One part of β-Cyclodextrin was placed in a mortar and wetted with a few drops of ethanol/water mixture (15/85, V/V) and then kneaded. Two parts of carvedilol was added slowly and kneaded with addition of few drops of ethanol/water mixture. Finally the wetted mass was dried at room temperature and sieved by using sieve no#100 [6].

***In-Vivo* Evaluation:**

To conduct this study, approval was obtained from Institutional animal's ethics committee

Pharmacokinetic Evaluation:

The pharmacokinetic performance of carvedilol pure drug and carvedilol β-cyclodextrin inclusion complexes following oral administration was studied in a randomized cross over design in rabbits.

Subject selection:

Six healthy New Zealand Albino rabbits with a mean age 10± 2 weeks and with a mean body weight of 2± 0.2 kg included in the above investigation.

Study design:

The study was of a non-blinded, open-label design. Subjects were fasted for at least 24 hrs prior to timing of dose and animals were fed 6 hours after oral dose (1mg/kg). The drug was administered in a single dose formulated as suspension containing sodium carboxy methyl cellulose. One month time interval was given for wash out period. After the wash out period Carvedilol βcd complex was administered to the animals.

Blood sampling:

About 1 ml of blood sample was collected using 22 gauge needle from the shaved marginal ear vein into heparinized eppendorf micro centrifuge tubes at time intervals of 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 16.(7) Xylene was applied to the marginal ear vein before withdrawal, which causes blood vessel to dilate. The blood samples were immediately centrifuged at 3000 rpm for 10 min and plasma samples were stored at -20°C until analysis by known LC-MS/MS method[8, 9]

Estimation of Carvedilol β-Cyclodextrin inclusion complexes in plasma :

The estimation of carvedilol in plasma was carried out by LC-MS/MS method. These samples were analyzed in Perkin Elmer HPLC system on a Vertisep-BDS, 5µ, 4.6X150mm, C18 column, using mobile phase containing 20 mm ammonium formate buffer and acetonitrile (30:70 v/v) at ambient temperature. The elution was carried out isocratically at flow rate of 1 mL/min. Mass spectrometer was equipped with API 2000.

Determination of Pharmacokinetic Parameters:

Various pharmacokinetic parameters such as peak plasma concentration (Cmax), time at which peak occurred (Tmax), area under the curve (AUC), absorption rate (Ka), and biological half-life (t1/2) were calculated using the noncompartmental pharmacokinetic data analysis software PK solutions 2.0 (Summit Research Services, montrose, CO, USA).

Statistical analysis of the pharmacokinetic parameters:

The pharmacokinetic parameters of carvedilol pure drug and carvedilol *β*-Cyclodextrin complexes were statistically analyzed using paired samples t-test for normal distributed results of Cmax, Ka, AUC values. All tests were performed at 0.001 level of significance.

RESULTS AND DISCUSSION:

Plasma concentrations of Carvedilol pure drug and β Cyclodextrin complexes were measured. Shown in (**Fig 1**). Pharmacokinetic parameters such as absorption rate constant, biological half life, AUC $_{0-\infty}$ were calculated from the plot of time versus plasma concentration and reported in (**Table 1)**. The results were compared. It indicated that the pharmacokinetic parameters of Carvedilol β Cyclodextrin complexes were differed from the Carvedilol pure drug except in biological half life and Tmax.

The highest mean Cmax value was observed for Carvedilol β Cyclodextrin 282±2.99 ng/ml compared to Carvedilol pure drug 194±1.99ng/ml and these values were statistically significant. The time taken to reach peak plasma concentration Tmax was 2 hrs in both pure drug and complexes. The mean Ka for pure drug and complex were found to be 0.7242±0.02226 $h^{-1}$and 0.8214±0.00722 h^{-1}, respectively.

The AUC_0-- ∞ values observed with drug βCD complex 2354±37.93 ng hr/ml in compared to pure drug values 1317±27.13 ng hr/ml. These results were also statistically significant the biological half life for 3.732±0.047 hrs for Carvedilol pure drug and 3.75±o.0521 hrs for Carvedilol β Cyclodextrin complex. However the difference in $t^{1/2}$ values recorded for pure drug and complexes was statistically insignificant. The pharmacokinetic parameters were treated statistically with paired sample's t-test. Significant differences in absorption related terms such as extent of absorption (AUC) and rate of absorption

(ka) were noticed. However no differences in elimination phase were observed

The present study concluded that the Cyclodextrin complexes of Carvedilol significantly increased the extent (1.78) and rate of absorption.

Table 1: Statistical treatment of pharmacokinetic parameters

	Cmax ng/ml	Tmax (Hrs)	Ka $^{h-1}$	AUC ng hr /ml	t½ hrs
Pure drug	194±1.99	2	0.7242±0.0222	1317±27.13	3.732±0.047
βCD complex	282.9±2.99	2	0.8214±0.0722	2354±37.93	3.755±0.052
Calculated t value	29.67	------	4.51	22.23	0.7482
Level of significance	<0.0001	------	0.0020	<0.0001	NS

Fig 1 : Plasma Concentration Of Carvedilol And Carvedilol Bcd Complex

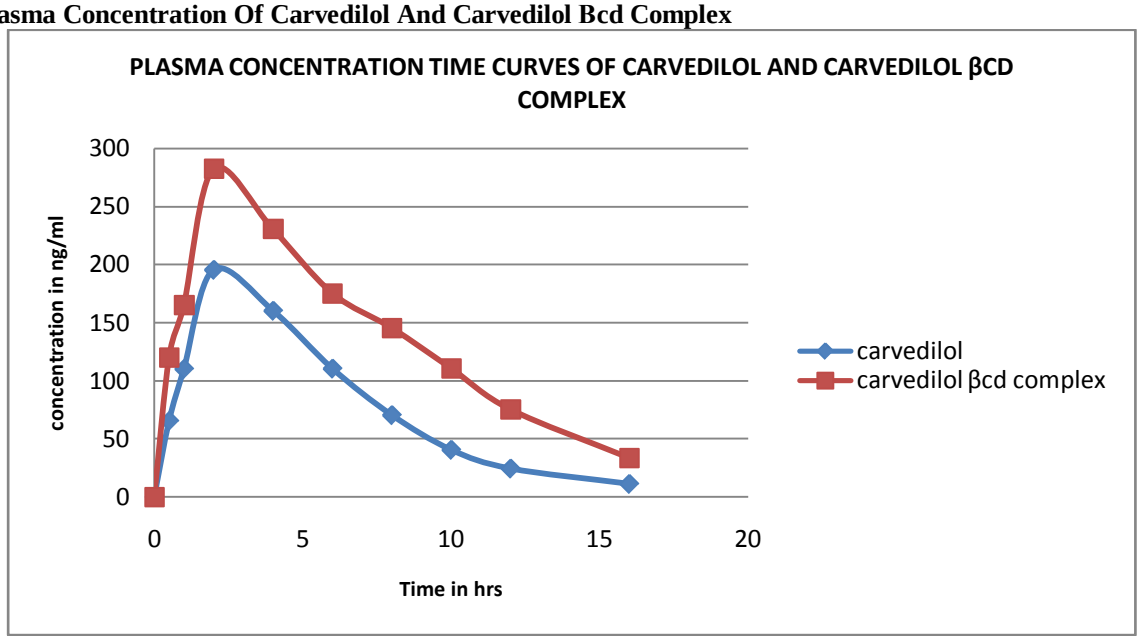


Fig 2 : Calibration Curve Of Carvedilol

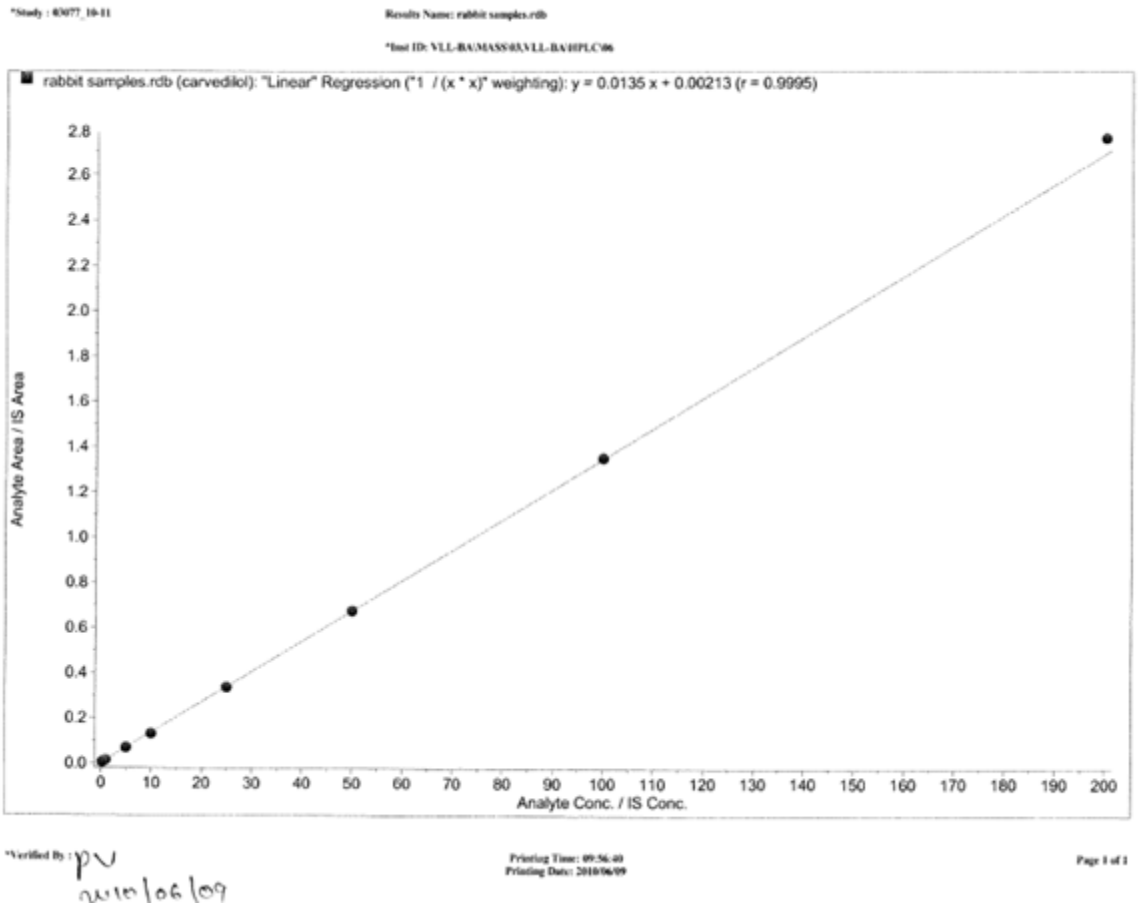
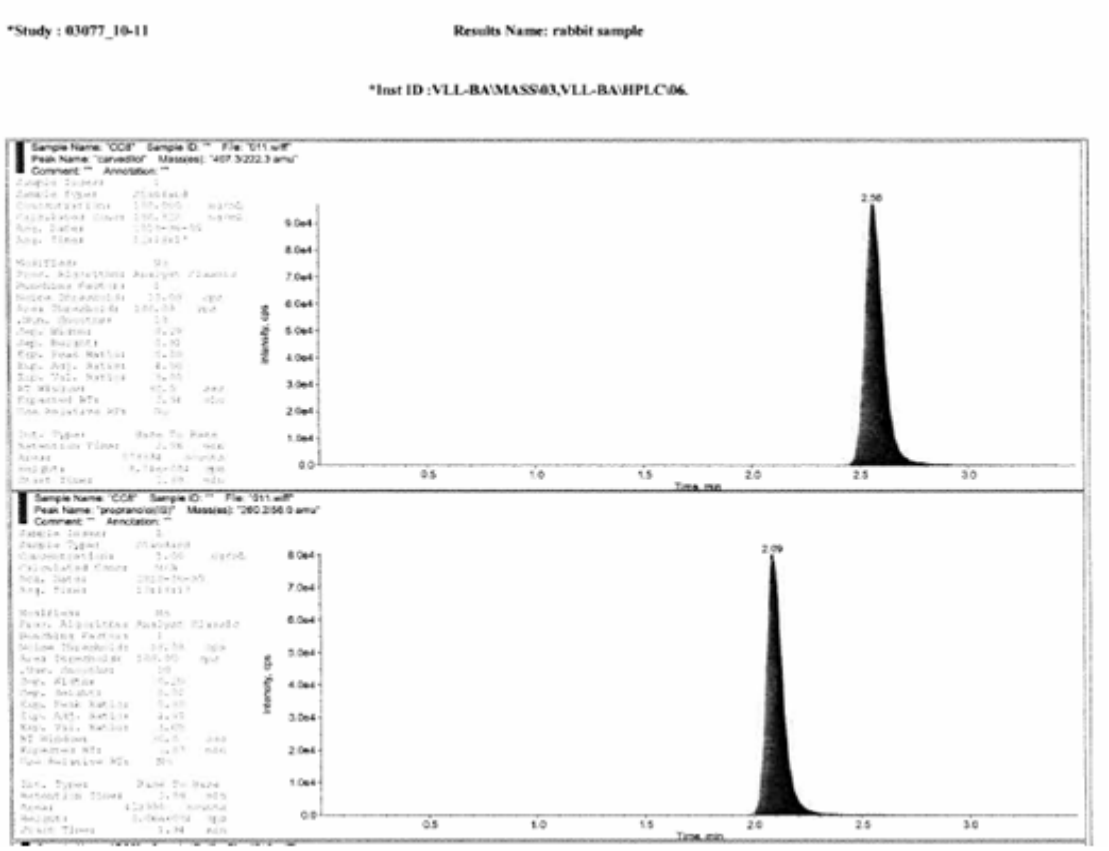


Fig 3 : Standard Chromatograms Of Carvedilol In Plasma



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