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# Solid Dispersion Preparation of Carvedilol and its Evaluation

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**Abstract**

The present research has two parts preparation and evaluation of the solid dispersion of the said drug carvedilol. The first pat and also the largest part give an account of strategies that can be employed to enhance the bioavailability of the drugs. The emphasis has been given on dispersion of insoluble drugs in soluble polymer matrix and their behavior in the gastrointestinal tract that leads to enhanced absorption of drugs. This part also deals with history, definition, classification, characterization of solid dispersion, advantages and disadvantages, unmet needs and challenges and applications of solid dispersion in dosage forms. Second part contain some evaluation parameter of the solid dispersion, such as drug content, solubility studies.

**Keywords:** Solid dispersion, Carvediol, Evaluation

## Introduction

Compound with poor water solubility is increasingly posing challenges in the development of new drugs. With the recent advent of high throughput screening of potential therapeutic agents, the member of poorly soluble drug candidates has risen sharply and formulation poorly soluble compounds for oral delivery, since a large number of drugs coming directly from synthesis or from high throughput screening have a very poor solubility[1].

The therapeutic efficacy of a drug product intended to be administered by the oral route depends first of all on its absorption by the gastrointestinal tract. However, for a drug substance to be adsorbed, it needs to be solubilized. Solubilization is the stage that precedes absorption. Together with permeability, the solubility of a drug is a key determinant of its oral bioavailability. It is well known that that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence comprising oral bioavailability.

## Theory of Solid Dispersion

The term “Solid dispersion” refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

The solid dispersion may also be called solid state dispersions. The term "coprecipitates” has also been frequently used to refer to those preparation obtained by methods such as. To achieve a faster release of a drug from the matrix, it is generally necessary that the active drug be a minor component in the dispersion system in terms of percent weight (not on molar basis).

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**Mechanism of Drug release from Solid dispersions in water soluble polymers**

There are number of factors in increasing the dissolution rate of solid dispersion. But some of them are very important that observed.

Particle size reduction and reduced agglomeration: Size reduction has been classically considered to be a result of eutectic or solid solution formation. In case of glass solution and amorphous dispersions, the same is happen. There are many carriers which are used for solid dispersions, may have some wetting properties and improved wetting may lead to reduce agglomeration and hence increased surface area. Increased solubility or dissolution rate of the drug: Many of the carriers used may increase the solubility of the drug. Carrier and drug may form a soluble complex, as it is prominent with cyclodextrins. Changes to the physical property of drug, like crystallinity and dissolution rate of the drug. Dobois and Ford (1985) shows that the dissolution rate of the drug is controlled by that of inert carrier. This again implies that it is the dissolution rate of the carrier and not the drug that may dominate the process[2,3].

**Advantages**

Dissolution rates of poorly water-soluble drugs are enhanced, so the absorption rate also increased.

- Bioavailability increased.
- Dose is reduced.
- Cost effective.
- This is very simple process.
- Recently, solid dispersion also prepared by insoluble carrier.
- This concept is applicable for formulating sustained release dosage form.

**Limitations**

These limitations are mentioned in the following[4].

**Method of Preparation:** There are some difficulties associated with melting method. The high temperature used in this process decomposed the drug and carrier. That may produce interactions. In case of solvent evaporation method, it is difficult to choose the common solvent or the ratio of mixture of solvent it used. To evaporate the total solvent is also a challenging factor

**Dosage Form Development:** In the process of development of the dosage form of capsule and tablets, some difficulties are shown like problem of pulverization, sifting of dispersion which is soft and tacky, poor flow and mixing properties of power or granule thus prepared poor compressibility, drug-carrier incompatibility and poor stability of dosage form.

**Reproducibility of Physicochemical Properties:** Melting temperature decomposed the drugs and carriers. This melting method greatly influenced the physicochemical properties of solid dispersion formed. In solvent evaporation method, some crystallinity of the drug may be observed where amorphous form is desirable.

**Scale Up of Manufacturing Process:** The physicochemical properties and stability of solid dispersion may also be affected by scale up because heating and cooling rates of solid dispersions under large scale manufacturing conditions may differ greatly from that in small scale. Solvent is tough to evaporate all the solvent from solid dispersion in large quantities. The cost of recovery may be very high.

**Stability:** In a solid dispersion prepared by the melt method, a certain fraction of drug may remain molecularly dispersed depend on its stability in the carrier used thus forming a solid solution. However, the excess drug that exists may greatly depend on the method of manufacture of the system; It may, as a whole or in part, from a super saturated solution, separate outs an amorphous phase, or crystallize out. The conversion of drug to crystalline state is also primary stability issue with solid dispersion prepared by solvent method.

## Material and Methods

**Drug and Polymer Profile**

**Drug Profile[5,6,7]**

Carvedilol

**Chemical Structure**

1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]-2 propanol Synonyms: BM-14190; DQ-2466.

**Proprietary names:** Carvipress; Dilatrend; Dimitone; Eucardic; Kredex; Querto.

**Molecular Formulae:** $C_{24}H_{26}N_2O$.

**Molecular Weight:** 406.5.

**Melting Point:** 114° to 115°

**pKa Value:** 7.6

**Partition Coefficient:** Log P(octanol/water), 4.19.

**Dose:** It is recommended that all receive orally 12.5 mg for the first 2 days and then increase if necessary up to 50 mg daily.

| **Materials** | |
|---|---|
| Methanol, LR Grade | |
| Sodium Orthophosphate, Purified | |
| Sodium Hydroxide (pellets), LR Grade | Merck, Mumbai CDH, New Delhi CDH, New Delhi LOBA Chemie, |
| Polyethylene Glycol 4000 | India LOBA Chemie, |
| Polyethylene Glycol 6000 | India Trizma Chemical Co. Orchid |
| Polyvinyl Pyrrolidone K-30 | Pharmaceuticals CDH, Mumbai |
| Polyvinyl Pyrrolidone K-90 | |
| Sodium Lauryl Sulphate, LR Grade | |

**Physical State:** A white to off-white powder.

**Solubility:** It is practically insoluble in water; freely soluble in dimethyl sulfoxide; soluble in methylene chloride and in methanol; sparingly soluble in ethanol and in isopropyl alcohol; slightly soluble in ethyl ether. It exhibits a predictable solubility behavior in neutral or alkaline media, i.e. above pH 9.0, the solubility is relatively low (<1 mcg/ml). The solubility increases with decreasing pH and eventually reaches a plateau with a broad peak (about 0.2 mg/ml) at a pH of 4-5.

**Mechanism of Action:** It works as a peripheral vasodilator via selective α-1 adrenergic receptor blocking with concomitant non selective β-adrenergic receptor antagonism property.

**Uses**: It prevents reflex tachycardia when used in the treatment of antihypertension. Also, carvedilol, as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation, is useful in organ protection, in particular, cardio protection. Additionally, carvedilol is useful in the treatment of congestive heart failure.

**Pharmacokinetics**

Disposition in the Body: Carvedilol is rapidly and well absorbed after oral administration, but is subject to considerable first-pass metabolism in the liver. The rate of absorption is impaired by the co-administration with food but the bioavailability is not affected. The drug is widely distributed and extensively metabolised, primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites undergo further metabolism by glucuronidation and sulfation. The metabolites are excreted mainly via bile into faeces. Approximately 16% of a dose is detected in urine with less than 2% as the unchanged drug. Some of the metabolites have beta-blocking and vasodilating activity; one metabolite has greater beta-blocking activity than carvedilol but all have weaker vasodilating effects than carvedilol.

**Bioavailiability:** Absolute bioavailability, 25 to 35%; S (−)-enantiomer, 15%; R (+)-enatiomer, 31%.

**Plasma Half Life:** 4 to 7 h Volume of Distribution: 1.5 to 2.0 L/kg.

**Plasma Clearance:** 0.52 L/h/kg. **Protein Binding**: In plasma, more than 98% with R (+)-enantiomer being more tightly bound.

**Instruments**

| | |
|---|---|
| FTIR Spectrophotometer (CE) FTIR-8400 | Shimadzu, Japan |
| UV Visible Spectrophotometer UV – VIS 117 | Systronics |
| UV-Visible Spectrophotometer | Schimadzu, Japan |

Water bath shaker
Remi Equipmen Pvt.Ltd, India
Host air oven
Indian Equipment Corporation
Sonicator
Indian Equipment Corporation
Dissolution test Apparatus
D-Compact, Electrolab.

## Methods

**Determination of Carvedilol**

Any work with formulation of drug requires knowledge of the analytical method of drug so that the formulation can evaluate at different stages. With this in mind, the first step in our study was the development of an analytical

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method. Though the analysis of carvedilol in dosage form has been reported in the literature.
Therefore, the method was established which is accurate, reproducible, efficient and economical. Moreover, it does not suffer from interference due to common excipients usually present in the formulation.

**Development and Validation of Spectrophotometric Method of Analysis for Carvedilol**

From the solubility study, cited in literature and those carried out, it was found that the drug is practically insoluble in water; freely soluble in dimethyl sulfoxide; soluble in methylene chloride and in methanol; sparingly soluble in ethanol and in isopropyl alcohol; slightly soluble in ethyl ether. Methanol was selected for drug content in the formulations and for phase solubility study. During the development of method, effect of different analytical media viz. water, methanol, phosphate buffer of pH 6.8 and phosphate buffer 6.8 with SLS 0.25, 0.50, 0.75 % (w/v) was explored. With the change of media there was insignificant change in absorption maxima.

**Determination of absorption maxima (λmax) in MeOH the absorption**

maxima were determined by scanning on UV-VIS spectrophotometer in the wave length 200-350 nm using a stock solution of 10 mcg/ml of carvedilol. The absorption maxima were found to be 242.8 nm.

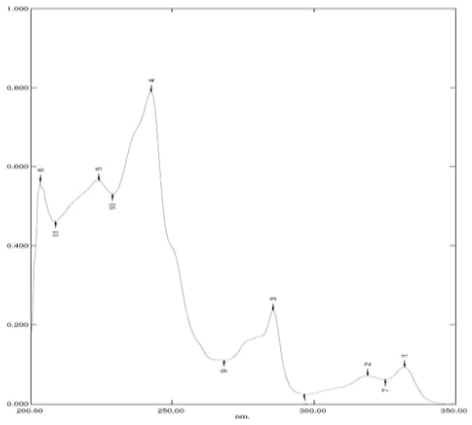

**Fig. 1: Carvedilol in MeOH**

**Preparation of Standard Curve of Carvedilol in MeOH**

Carvedilol (10 mg) was weighed accurately on digital balance (Mettler Toledo AB265-S) and dissolved in 100 mL of methanol to give a stock solution of 100 µg/mL. Aliquots were diluted suitably with methanol to get working standard solutions viz. 2, 4, 6, 8, 10, 12, 14 µg/mL. Next, the absorbance of each solution was measured at 242.8 nm spectrophotometrically in double beam UV-Visible spectrophotometer (Sysytronic-117). Three such determinations were made in each case. A plot of mean absorbance versus concentrations gave the standard curve. The proposed method obeys Beer's law (Fig. 5.3) in the concentration range of 2-25 µg/mL with r = 0.9998 ± 0.0002 (P<0.001), intercept
= 0.0006 ± 0.001and slope = 0.1148 ± 0.0008 [O.D. = 0.1148 x conc. + 0.0006]

**Contemplation of the Method in MeOH**

Verification of the method of analysis was done by using various concentration of stock as 1, 3, 5, 7, 9, 11, 13 mcg/ml. The absorbance of each stocks, treated exactly in the same manner as describe above, was measured
spectrophotometrically at absorbance maxima λmax of 242.8 nm. The per cent recovery was found in the range of 99.23 to 101.57 %.

**Table 1: Contemplation Study in MeOH**

| Sl. No. | Concentration (mcg/ml) | | % Found |
|---|---|---|---|
| | Actual | Calculated | |
| 1 | 1 | 1.02 | 101.57 |
| 2 | 3 | 3.01 | 100.35 |
| 3 | 5 | 4.96 | 99.23 |
| 4 | 7 | 7.04 | 100.55 |
| 5 | 9 | 9.06 | 100.62 |
| 6 | 11 | 11.12 | 101.09 |
| 7 | 13 | 13.10 | 100.75 |

**Optimization of Dissolution Media**

For determining the dissolution media, solubility of carvedilol in different media has been investigated viz. phosphate buffer of pH 6.8 (PB 6.8) and 0.25, 0.50, 0.75 per cent (w/v) SLS of PB 6.88. The study was carried out in triplicate, by taking excess amount of drug (25 mg) in 10 ml of of each solution. Mixtures were continuously shaken in water bath shaker at 37˚C for 24 hrs,

followed by filtration through whatman filter paper no.1. Filtrates were diluted suitably and analyzed spectrophotometrically at 242.8 nm. After getting the solubility in different media the λmax of drug in 0.25, 0.50, 0.75 per cent (w/v) SLS of PB 6.8. has been determined and then standard curve in each solution also prepared. The dissolution study of marketed carvedilol of 12.5 mg has been carried out in[8,9], different media at 37˚C.

**Phase Solubility Studies**

Phase solubility study of CVD was investigated in various water-soluble polymers viz., PEG 4000, PEG 6000, PEG 8000, PVP K-30 and PVP K-90. The
study was carried out in triplicate, by taking excess amount of drug (25 mg) in 10 ml of Phosphate Buffer 6.8 containing 2.5, 5, 7.5, 10, 12.5, 15 per cent (w/v) of each polymer. Mixtures were continuously shaken in water bath shaker at 25˚C and 37˚C for 24 hrs, followed by filtration through Whatman filter paper no.1. Filtrates were diluted suitably with MeOH and analyzed spectrophotometrically at 242.8

**Preparation of Solid Dispersion and Physical Mixture**

Soid dispersion of carvedilol were prepared by using solvent evaporation method with different water-soluble carriers viz. PEG 4000, PEG 6000, PEG 8000, PVP K-30 and PVP K-90 in three ratio i.e., 1:1, 1:3 and 1:5. Based on the preliminary trials, the combination of methanol and dichloromethane in 1:2 volume ratio was evolved as the suitable common solvent system. The drug and each of these carriers in different ratio, one by one, in sufficient amount were weighed and mixed. This admixture of the drug with each of the carrier was dissolved separately in a minimum amount of chosen solvent system with stirring to produce the clear solution (in each case). The solvent from the solution was evaporated with continuous stirring with gentle heating. The damp mass so obtained was dried under vacuum for 24 hrs. under 40˚C. Then the dried mass was pulverized using a mortar and pestle then passed through sieve no. 36 and finally stored in a desiccator until further evaluation[10,11].

Physical mixtures were prepared by triturating individual component (all passed through sieve no.36) in equal weight ratios, in glass mortar pestle[12].

**Drug Content**

Assay of each type of solid dispersions were carried out individually to determine the drug content. The powdered solid dispersion equivalent to 10 mg of carvedilol was dissolved in 100 mL of MeOH and filtered through Whatman filter paper (No. 1, 90 mm dia., Whatman Int. Ltd., England). Next, the filtered solution was suitably diluted and absorbance was measured spectrophotometrically at 242.8 nm. The carvedilol content was calculated from the slope and intercept obtained from standard curve[13].

## Results and Discussion

The present study was aimed preparation and evaluation of solid dispersion of carvedilol. Carriers play an important role in this technique, in which drug is dispersed in a carrier matrix. Such simpler and more robust systems assure a reliable release from the matrix. Solid Dispersion of carvedilol was prepared using different type and varying ratio of drug:polymer to get desired overall immediate drug release. Different grade of polyethylene glycol (PEG 4000, PEG 6000, PEG 8000) and polyvinyl pyrrolidone (PVP K-30, PVP K-90) were used as carrier. The results of the present studies are discussed in the following.

**Phase Solubility Studies**

Phase solubility study of carvedilol was investigated in various water soluble polymers viz., PEG 4000, PEG 6000, PEG 8000, PVP K-30 and PVP K-90. Equations used for determining thermodynamic parameters (Table 2)-

(i) Stability Constant (Ka) = slope Intercept (1-slope)

(ii) Van"t Hoff Equation, $\Delta G^\circ = -R.t.\ln Ka$ [R=8.314 J/mol.K ]

(iii) $\ln Ka2/Ka1 = [\Delta H^\circ/R].[(T2-T1)/ T1.T2]$ or $\Delta H^\circ = [R \times \ln (Ka2/Ka1)] / (T2-T1/T1.T2)$

[T1 and T2 are temperature at 25˚C and 37 ˚C accordingly]

(iv) Gibbs-Helmholtz Equation, $\Delta G^\circ = \Delta H^\circ - T.\Delta S^\circ$ Or $\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ) / T$

Solubility of the drug in PB 6.8 increases linearly with increase in the polymer concentration.

On the basis of Stability Constant (Ka) and Gibbs free energy ($\Delta G^o$) at 37˚C and PVP K-30 and PVP K-90 exhibits better solubility and stability of CVD.

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Different thermodynamic parameters were calculated from the per cent (w/v) polymer concentration vs. solubility (mg/ml) plot of different polymers using
Gibbs free energy and Van't Hoff equations.

Free energy changes were composed of enthalpy ($\Delta H^o$) and entropy ($\Delta S^o$) changes.
Contribution of $\Delta H^o$ and $\Delta S^o$ to the whole Free Gibbs energy ($\Delta G^o$) value confirms that this type of interaction is enthalpy rather than entropic driven.

**Table 2: Solubility of Carvedilol in PEG 4000**

| Conc. % (w/v) | Solubility (mg/ml) at 25°C | Solubility (mg/ml) at 37°C |
|---|---|---|
| 0 | 0.028 | 0.04 |
| 2.5 | 0.08 | 0.101 |
| 5 | 0.132 | 0.162 |
| 7.5 | 0.184 | 0.223 |
| 10 | 0.236 | 0.284 |
| 12.5 | 0.288 | 0.345 |
| 15 | 0.34 | 0.406 |

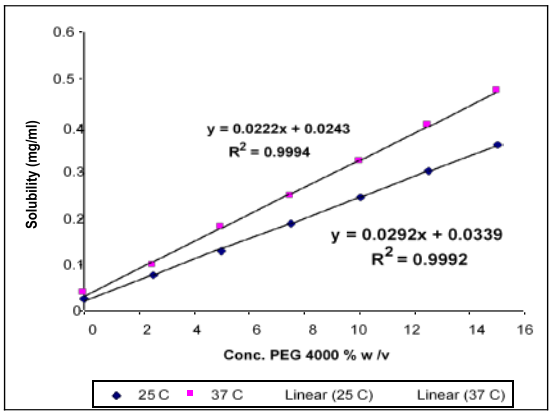


**Fig. 2: Solubility Profile of Carvedilol in PEG 4000**

**Preparation of Solid Dispersion**

Soid dispersion of carvedilol were prepared by using solvent evaporation method with different water-soluble carriers viz. PEG 4000, PEG 6000, PEG 8000, PVP K-30 and PVP K-90 in three ratios i.e., 1:1, 1:3 and 1:5 (Fig.3). Every carrier showing better dissolution characteristics with increasing their concentration in solid dispersion and physical mixture. Solid dispersion of PVP K-90 in 1:5 ratio was not prepared for its high stickiness and scraping problem for collecting the solid dispersion with the apparatus used for preparation.

**Drug Content Study**

Assay of each type of solid dispersions were carried out individually in MeOH to determine the drug content. The carvedilol content was calculated from the slope and intercept obtained from standard curve. Percentage recovery was found in all ratios of each carrier in the range of 100.20 to 101.54 (Table 3).

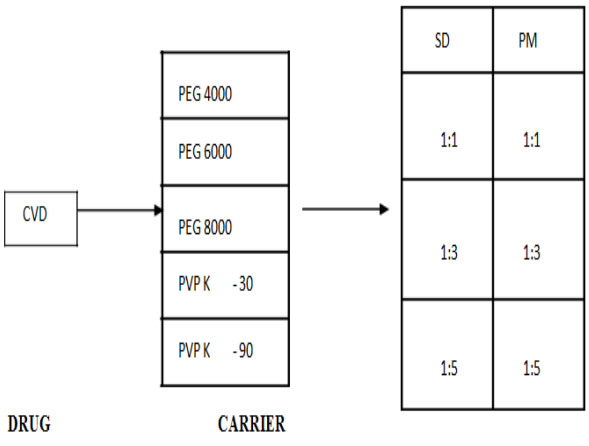


Fig. 3: Preparation Solid Dispersion and Physical Mixture with Different Carrier in Different Ratio

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**Table 3: Drug Content study**

| Carrier | Conc. Used (mcg/ml) | Drug: Carrier | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 :1 | | 1 : 3 | | 1 : 5 | |
| | | Conc. Found (mcg/ml) | % Reco - very | Conc. Found (mcg/ml) | % Reco-very | Conc. Found (mcg/ml) | % Reco -very |
| PEG 4000 | 10 | 10.077 ± 0.082 | 100.77 | 10.038 ± 0.041 | 100.38 | 10.071 ± 0.069 | 100.71 |
| PEG 6000 | | 10.028 ± 0.031 | 100.28 | 10.045 ± 0.049 | 100.45 | 10.003 ±0.009 | 100.03 |
| PEG 8000 | | 10.104 ± 0.031 | 101.54 | 10.020 ± 0.026 | 100.20 | 10.067 ± 0.061 | 100.67 |
| PVP K-30 | | 10.054 ± 0.062 | 100.54 | 10.084 ± 0.018 | 100.84 | 10.079 ± 0.071 | 100.79 |
| PVP K-90 | | 10.103 ± 0.062 | 101.03 | 10.073 ± 0.067 | 100.73 | 10.072 ± 0.065 | 100.72 |

## Conclusion

Compounds with poor aqueous solubility are extremely challenging to be developed as new drugs. It is well known that the drug dissolution rather than permeation through the epithelia of the gastrointestinal tract is responsible for low oral absorption. One of the pharmaceutical strategies to improve the oral bioavailability is the formulation of solid dispersions. In this project carvedilol were selected for the study, because it has a poor aqueous solubility and low dissolution rate, while high permeability. This drug was formulated as solid dispersions in order to improve the drug dissolution rate.

The solubilizing capacity of polymers for carvedilol was studied in comparison to the solubility of pure Carvedilol. Carvedilol were prepared into binary solid dispersion. Higher solubility was obtained in the presence of polymers viz. PEG 4000, PEG 6000, PEG 8000, PVP K-30 and PVP K-90 as their increasing concentration. The selected test products are better in their Physico-chemical and in-vitro dissolution characteristics. An immediate controlled release of drug is indicated by the fact that the per cent cumulative amount of drug

release versus time plot, thus supporting the test products‟ efficiency.

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