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Formulation and Evaluation of Solid Dispersions of Carvedilol Using Different Polymers

Yash Paul*, Shashi Upasna

Lord Shiva College of Pharmacy, Sirsa (Haryana)

ABSTRACT

Carvedilol is a new antihypertensive drug. The major problem with this drug is its very low solubility in biological fluid which results in poor bioavailability after oral administration. Hence present study to enhance dissolution properties of Carvedilol. Solid dispersions of Carvedilol were prepared to enhance its water solubility. Physical mixtures and solid dispersions of Carvedilol were prepared by using Mannitol, Urea and PVP K30 as water soluble carrier(s) at various proportions (1:1, 1:2, 1:3, 1:5 and 1:6) by employing solvent evaporation method. The drug release profile was studies according to USP XXIII monograph in 0.1N HCl. Infrared (IR) spectroscopy, Differential Scanning Calorimetry (DSC) were identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. IR spectroscopy, DSC showed no change in crystal structure of Carvedilol. Improvement in dissolution of drug was observed in all physical mixtures and solid dispersions as compared to pure drug. Solid dispersion of Carvedilol: PVP K30 showed faster release than that of Mannitol and Urea. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of Carvedilol.

KEYWORDS: Carvedilol, Solid dispersion, Dissolution rate, Bioavailability

*** Corresponding Author**
Dr. Yash Paul Singla
Professor & Principal
Lord Shiva College of Pharmacy
Sirsa-125055 (Haryana), INDIA
E-mail: ypsingla@yahoo.co.in
Phone: +91-1666-329204(O); 232684(R); Fax 242695 (O)

INTRODUCTION

Carvedilol is a novel, multiple-action cardiovascular drug that is currently used treatment of hypertension. The reduction in blood pressure, produced by Carvedilol, results primarily from beta-adrenoreceptor blockage and vasodilatation, the latter resulting from alpha 1- adrenoreceptor blockage.[1-3]

Common oral dosage is 25 mg/day (dose/solubility ratio ≥250 ml; class II drug according to the BCS) with peak plasma concentrations occurring 1 to 2 h after the administration and elimination half-life of 6 to 10 h.[4] Being categorized as class II compound as per the BCS classification system, it posses very poor bioavailability and shows significant first pass metabolism[5-7]. Moreover, it is desirable to improve thesolubility as well as bioavailability of carvedilol. Wei et al.[8] reported the self emulsifying and self micro emulsifying drug delivery system to enhance the solubility of carvedilol. The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. The incorporation of drug into solid carriers has been reported to result in an increase in the dissolution of drug leading to improved bioavailability. The solid dispersion technique provides a means of reducing particle size to a molecular level. As the soluble carrier dissolves, the insoluble drug isexposed to the dissolution medium as very fine particles for quick dissolution and absorption. [9,10] Hydrophilic polymers have been widely investigated as carrier substances for solid dispersions. Mannitol, Urea and PVP K30 are amongst the most frequently investigated hydrophilic polymeric carriers.[11-13] The aim of the present study was to investigate the dissolution of carvedilol from solid dispersion and to characterize the solid dispersions using infrared spectroscopy. Solid dispersions were prepared by solvent evaporation method.

MATERIAL AND METHOD

Carvedilol was obtained from Ranbaxy Fine Chemical, Ltd., New Delhi. The other chemical were obtained from authenticated manufacturers i.e. Mannitol (Titan Biotech Ltd., Bhiwadi, Rajasthan), Hydrochloric acid, Methanol, PVP K30 and Urea (Nice Chemical Pvt, Ltd., Cochin, Kerala). All chemicals used were of analytical grades.

Phase Solubility Studies

Solubility measurements were performed according to method reported by Higuchi and Connors[14]. An excess amount of the drug was added to 10 ml volumetric flask containing 10%, 20%, 30%, 40% aqueous solution of carriers. The samples were allowed to shake for 24 h at 25 ± 1 °C. The solutions were filtered through whatman filter paper 42. After 24 h, the Carvedilol concentration was determined spectrophotometrically at 242 nm using UV spectrophotometer.

Preparation of Physical Mixtures

The physical mixture of drug (Carvedilol) and carriers (Mannitol, Urea and PVP K30) were prepared by homogeneously mixing of both the drug and carrier with the help of mortar and pestle and the mixtures thus obtained were passed through sieve no.100.

Preparation of Solid Dispersion

All the solid dispersions of Carvedilol were prepared using water-soluble carrier *viz.*, Mannitol and Urea and PVP K30 in various ratios (1:1, 1:2, 1:3, 1:5 and 1:6) employing using solvent evaporation method. In this method, the drug and the polymers were dissolved in a solvent, in which both drug and polymer have good solubility *i.e.* methanol, and initially the solvent was evaporated in tray drier and subsequent evaporation of solvent was carried in vacuum oven till constant weight. Finally, the dried dispersions were passed through sieve no. 100 and stored in a desiccator till further use.[15]

EVALUATION OF PHYSICAL MIXTURE AND SOLID DISPERSIONS OF CARVEDILOL

Drug Content

Solid dispersions and mixtures of Carvedilol were tested for drug content uniformity.Accurately weighed amount of sample was dissolved in 10 ml of methanol and stirred on magnetic stirrer for 10 min. The solution was filtered through whatman filter paper 42, diluted suitably and assayed for carvedilol content spectrophotometrically.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectra were obtained using FTIR spectrometer. Samples of Carvedilol, physical mixtures and solid dispersions were ground and mixed thoroughly with potassium bromide at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. The scanning range was 40 to 4000 cm–1 and the resolution was 4 cm–1.

In Vitro Dissolution Studies of Solid Dispersion

Dissolution studies were carried for all the formulation combinations in triplicate, employing USP XXIII paddle (Apparatus 2) using 900 mL 0.1N HCl as the dissolution medium at 50 rpm and 37±0.5^{0}C. An aliquot sample (5 mL) was periodically withdrawn at suitable time intervals and volume replaced with equivalent amount of plain dissolution medium. These samples

were filtered and diluted. Absorbance of the resulting solution at 241 nm using UV-visible spectrophotometer. The dissolution of pure drug (12.5 mg) was also conducted similarly.

RESULTS AND DISCUSSION

Solid dispersion of Carvedilol prepared by solvent evaporation method and they were found stable during preparation. No discoloration was found during heating or storage condition.

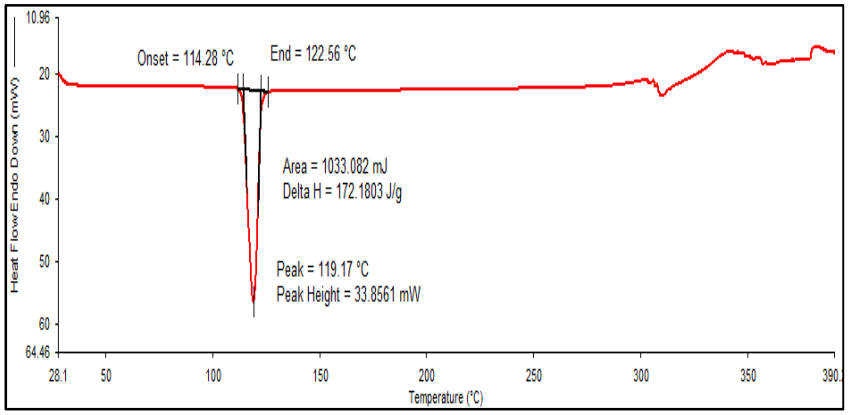

Fig.1: DSC thermogram of Carvedilol

The aqueous solubility of Carvedilol was found to be 1.035 mg/ml in 0.1N HCl and 1.814 in Methanol. Drug content of physical mixture and solid dispersions were was found to be between 91.45% - 99.98%.The DSC curve of carvedilol showed a sharp endothermic peak (T_{peak} = 119.17 °C) (Fig.1) corresponding to its melting point, indicating its crystalline nature.

Infrared spectroscopy was carried out tofurther elucidate the interaction of carvedilolwith PVP K30 in the solid dispersions orphysical mixtures. The FT-IR Spectra of physical mixture of CVD:PVP K30 (1:5 ratio) are shown Fig.2(a). It shows that characterstics absorption band at 3408.22cm^{-1} (N-H stretching and O-H stretching for CVD), 2957.88cm^{-1} (C-H alkane), 1633.71cm^{-1}(C=C alkene), 1446.61cm^{-1} (CH_3 bend) 1097cm^{-1} (C-O Carboxylic group). Where as, in FT-IR Spectra of solid dispersion of CVD:PVP K30 (1:5 ratio) are shown in Fig.2(b). It shows that absorption band at 3425.58 cm^{-1}(N-H stretching and O-H stretching for CVD), 2958.80 cm^{-1}(C-H alkane), 1649.14 cm^{-1}(amide group), 1429.80cm^{-1}(CH_3 bend), 1286.52 cm^{-1}(C-O Carboxylic group). The infrared spectra of physical mixture and solid dispersion are clearly showed the absorption band, illustrating the presence of Carvedilol and PVP K30.

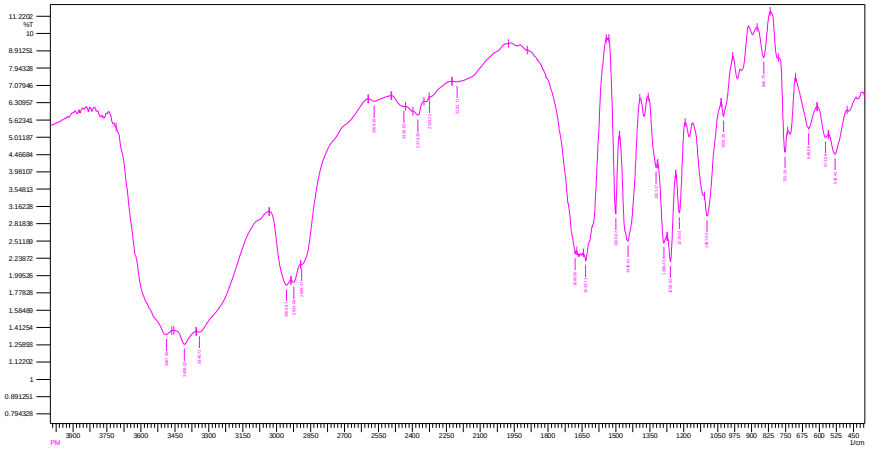

Fig.2(a): FT-IR spectral physical mixture of CVD with PVP K30

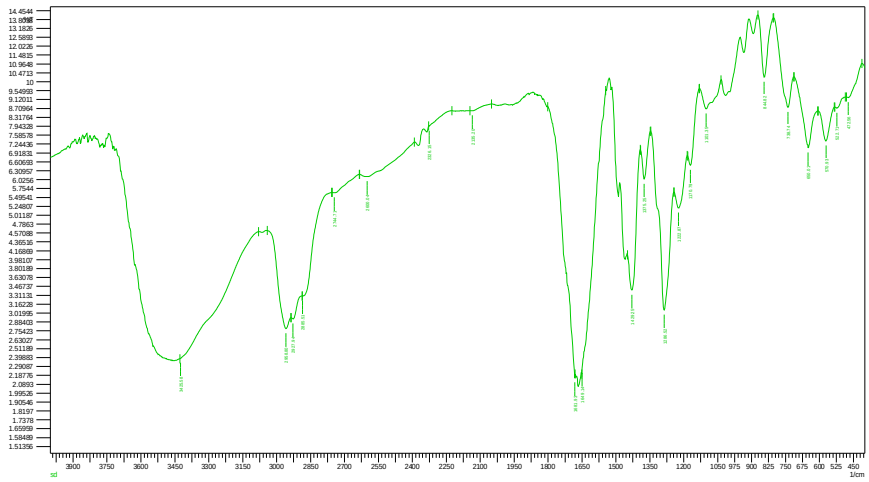

Fig.2(b): FT-IR spectral of solid dispersion of CVD with PVP K30

In Vitro Dissolution Studies

The dissolution performance of various physical mixtures and their corresponding solid dispersions prepared using CVD:Mannitol, CVD:Urea and CVD: PVP K30 in different ratios (1:1, 1:2, 1:3, 1:5 and 1:6) are depicted Fig.3,4. As indicative from the dissolution data of the physical mixtures, improvement in the drug dissolution rate could be attributed to the higher wettability and dispersibility. Mixing of the drug with hydrophilic carriers *viz.*Mannitol, Urea and PVP K30 result in greater wetting and increase surface availability for dissolution by reducing interfacial tension between the hydrophobic drug and dissolution medium.

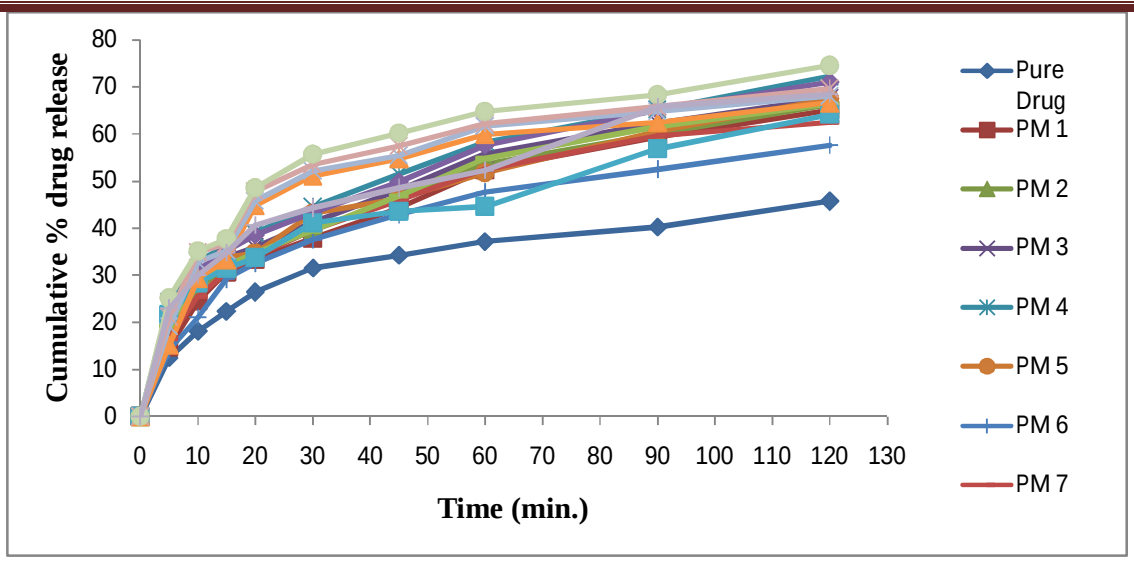

Fig.3: Plot between mean percent drug release and time for physical mixtures of CVD (PM1- PM15)

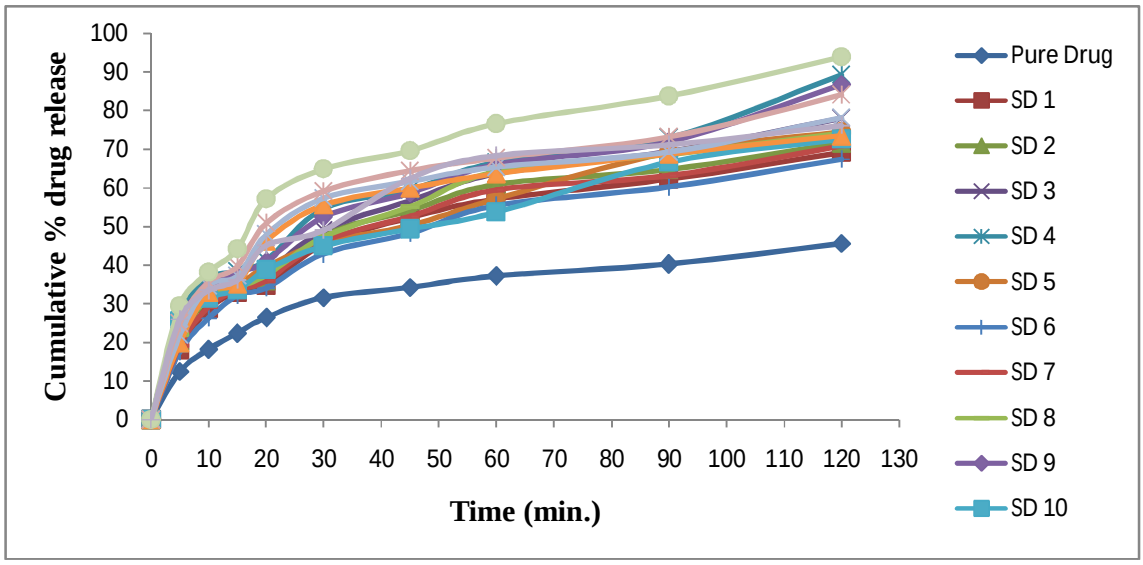

Fig.4: Plot between mean percent drug release and time for solid dispersions of CVD (SD1- SD15)

On the other hand, if the percentage of carrier (Mannitol, Urea and PVP K30) is too high the dissolution rate decreased. This could be attributed to changes in the type of CVD polymorph during the dissolution in the presence of high concentration of Mannitol, Urea and PVP K30 or might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. From Fig.4 it is evident that the CVD: PVP K30 dispersions up to a ratio of 1:5 showed distinct improvement in the release rate of drug. Maximum drug release (93.841±0.92%) was observed in case of SD 14 solid dispersions in 120 min. due to the formation of inter-molecular hydrogen bonding between the carbonyl group of PVP K30 and the hydrogen atom in the hydroxyl group of Carvedilol.Also, 2-3 fold increase in drug release rate was observed in case of CVD: PVP K30 solid dispersions vis-à-vis pure drug. On comparing Fig.3 with 4 it can be concluded that the release performance of solid dispersions was distinctly superior to that of their corresponding

physical mixtures developed using different carriers. In case of solid dispersion, increased wettability and dispersibility, particle size reduction, lack of crystallinity are consider to be important factor for the enhancement of dissolution rate.On mutually comparing the dissolution profiles of all the solid dispersion formulations (SD1- SD15), it has been observed that the maximum drug release rate was found in case of SD 14, i.e. CVD: PVP K30 (1:5) solid dispersions.

CONCLUSION

Dissolution rate and hence oral bioavailability of Carvedilol can be improved by formulating the drug into its solid dispersion form. The dissolution rate of carvedilol from solid dispersion was depended on the concentration of the carrier. Dissolution of drug increased with an increase in carrier content. A high proportion of PVP K30 in the solid dispersion significantly increased in the dissolution rate. FT-IR and DSC results confirmed the amorphous state of drug in solid dispersion.

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