

Preparation and characterization of solid dispersions of carvedilol with PVP K30

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Abstract

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs. The poor solubility of carvedilol leads to poor dissolution and hence variation in bioavailability. The purpose of the present investigation was to increase the solubility and dissolution rate of carvedilol for enhancement of oral bioavailability. In the present investigation solid dispersions with PVP K30 were prepared by solvent evaporation method. The physical mixture and solid dispersion(s) were characterized for drug-carrier interaction, drug content, solubility and dissolution rate. The solubility of drug increased with increasing polymer concentration. The dissolution rate was substantially improved for carvedilol from its solid dispersion compared with pure drug and physical mixture. As indicated from X-ray diffraction pattern and DSC thermograms carvedilol was in the amorphous form, which confirmed the better dissolution rate of solid dispersions. The solid dispersion was stable under accelerated storage conditions. The solid dispersion technique with PVP K30 as a carrier provides a promising way to enhance the solubility and dissolution rate of carvedilol.

Keywords: Carvedilol; PVP K30; Solid dispersions; Solubility; Dissolution rate

INTRODUCTION

Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The reduction in blood pressure, produced by carvedilol, results primarily from beta-adrenoceptor blockade and vasodilation, the latter resulting from alpha 1-adrenoceptor blockade (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 poses very poor bioavailability and shows significant first pass metabolism (5-7). Moreover, it is desirable to improve the solubility 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 nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed 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. Polyvinylpyrrolidone (PVP) is 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

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differential scanning calorimetry, infrared spectroscopy and power X-ray diffractometry. Solid dispersions were prepared by solvent evaporation method.

MATERIALS AND METHODS

Carvedilol was provided by Sun Pharmaceutical Ltd., Baroda, India as a gift sample and PVP K30 purchased from SD fine chem., Mumbai, India. All other chemicals and reagents used were of analytical grade.

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 48 h at 25 ± 1 °C. The solutions were filtered through membrane filter (0.45 μ). After 48 h, the carvedilol concentration was determined spectrophotometrically at 285 nm using Shimadzu UV 1800, Japan.

Preparation of physical mixture by trituration method

Carvedilol and PVP in the ratio of 1:1 were sifted through a 40-mesh (425 μ m) screen, mixed together (with trituration in a pestle-mortar), and stored in a desiccated environment.

Preparation of solid dispersions by solvent method

Carvedilol and PVP were taken in ratio of 1:1, 1:3 and 1:5 (SD1, SD2, SD3). The polymer was dissolved in an adequate amount of methanol. The solvent was then rapidly evaporated with the aid of mild heat (up to about 50 °C) and surface airflow with constant vigorous stirring to form a uniform solid mass. The co-precipitate was crushed and desiccated under vacuum for 24 h, pulverized (again, after formation of a more fragile mass), vacuum desiccated again for a day, sized into different sieve fractions and stored in a desiccators, until further use (15).

Characterization 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 membrane filter (0.45 μ m), diluted suitably and assayed for carvedilol content spectrophotometrically (16).

Fourier transform infrared spectroscopy

Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. 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} .

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded using Philips PW 1729 X-ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 mA. The scanning rate was 1°/min over a 2θ range of 1-50°. PXRD patterns were traced for carvedilol, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container.

Differential scanning calorimetric (DSC)

DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 5 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2 .

Dissolution studies

The release rate of carvedilol from solid dispersions was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method; Veeco Scientific, Mumbai, India). The dissolution test was performed using 900 ml of simulated

gastric fluid, at 37 ± 0.5 °C and 50 rpm for 2 h (17). Samples equivalent to 12.5 mg of carvedilol were taken for dissolution studies. The release of carvedilol was measured by withdrawing samples at regular intervals and filtered through a membrane filter (pore size 0.45 μ m). The samples withdrawn were replaced with fresh medium maintained at the same temperature. Absorbance of these solutions was measured spectrophotometrically at 285 nm. The dissolution efficiency (DE) of the samples was calculated by the method mentioned by Khan (18). The DE% of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t , expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.

$$\text{Dissolution efficiency} = \frac{\int_0^t y \, dt}{y_{100} (t_2 - t_1)} \times 100\%$$

Stability studies

The accelerated stability study of prepared solid dispersion was carried out at 40 °C/75% RH for a period of up to 3 months (19). An accurately weighed amount of sample was placed into glass vials with aluminum-lined caps and stored in microprocessor controlled humidity chamber; samples were characterized as a function of exposed time. The samples were removed and evaluated for solubility, drug content, dissolution, PXRD, FTIR and DSC studies.

RESULTS

The effect of carrier concentration on the aqueous solubility of carvedilol is shown in Fig. 1. The aqueous solubility of carvedilol was found to be 0.002 mg/ml. The solubility of drug was increased up to 35 fold in 5% w/v PVP K30 aqueous solution at 25 °C compared with pure drug. Drug content of physical mixture and solid dispersions were found to be between 94.52% and 104.83%.

The X-ray diffractograms of pure carvedilol, PVP, physical mixture and solid dispersions are shown in Fig. 2. Numerous diffraction peaks of carvedilol were observed at 2θ of 12.8°, 15.62°, 17.46°, 18.56°, 20.1°, 24.3° and 26.2° indicating the presence of crystalline nature of carvedilol. The powdered PVP K30 was amorphous where it showed only few peaks with weak intensities. The physical mixture also showed some crystallinity. On the other hand, 1:5 solid dispersion did not show any crystallinity of carvedilol.

The DSC curve of carvedilol showed a sharp endothermic peak ($T_{\text{peak}} = 115$ °C) corresponding to its melting point, indicating its crystalline nature. The thermal behavior of the PVP K30 is that expected for hygroscopic, amorphous substances, with a large endothermal effect in the 90-140 °C range due to polymer dehydration. Thermal behavior of carvedilol and corresponding drug carrier system are depicted in Fig. 3.

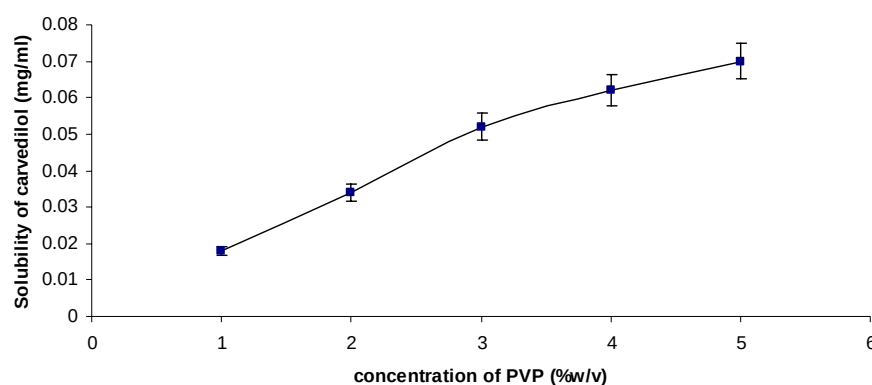


Fig. 1. Effect of carrier concentration on solubility of carvedilol.

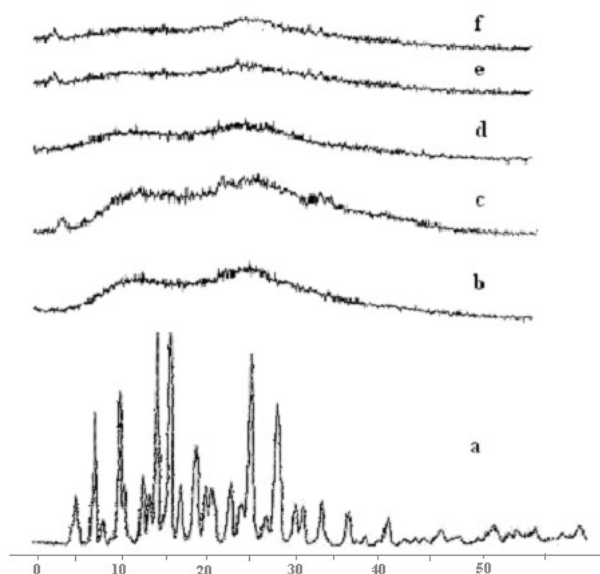


Fig. 2. PXRD a) Carvedilol b) PVP c) Physical mixture d) SD1 e) SD2 f) SD3

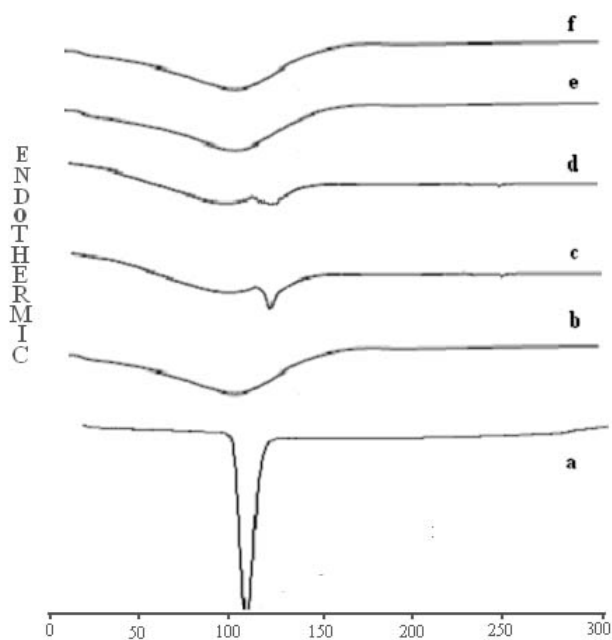


Fig. 3. DSC thermogram a) Carvedilol b) PVP c) Physical mixture d) SD 1 e) SD 2 f) SD 3

Infrared spectroscopy was carried out to further elucidate the interaction of carvedilol with PVP K30 in the solid dispersions or physical mixtures. The infrared spectra of the physical mixture and the solid dispersion are shown in Fig. 2 together with those for carvedilol alone and PVP K30 alone as

references. Carvedilol showed characteristic peaks at 3346.27 cm^{-1} (O-H and N-H stretching vibration peaks merged together), 2925.81 cm^{-1} (C-H stretching vibrations), 1598.88 cm^{-1} (N-H bending vibrations) and 1253.64 cm^{-1} (O-H bending and C-O stretching vibrations). The most distinct peak

in the IR spectrum of PVP K30 was the stretching vibration of the carbonyl group that would typically appear around 1689.53 cm^{-1} . FTIR spectrum of PVP displayed a broad peak at about $3000\text{--}3700\text{ cm}^{-1}$ due to O-H stretching vibrations of absorbed water. The

infrared spectra of the physical mixture clearly showed the absorption bands, illustrating the presence of carvedilol and PVP K30 (Fig. 4).

The dissolution profile of carvedilol, physical mixture and solid dispersions are shown in Fig. 5.

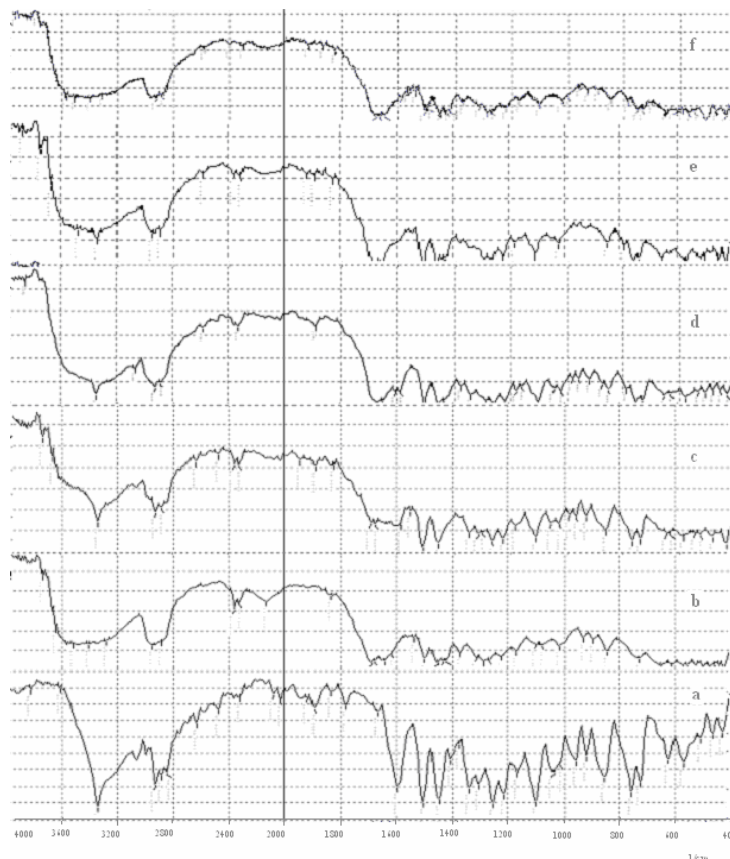


Fig. 4. FTIR Curves a) Carvedilol b) PVP c) Physical mixture d) SD 1 e) SD 2 f) SD 3

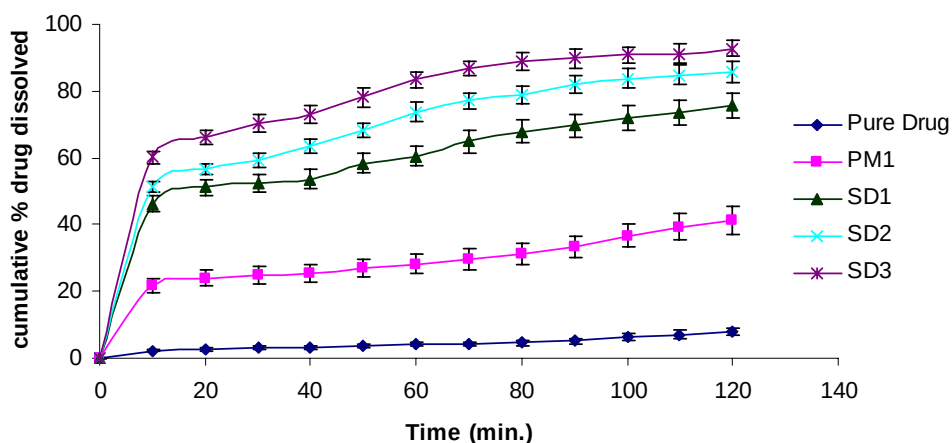


Fig. 5. Dissolution profile of carvedilol, physical mixture and solid dispersions.

Table 1. Dissolution efficiency values at 10 and 120 min and time to dissolve 50% of drug, physical mixture and solid dispersions.

S. No.	Formulation Code	DE ₁₀ % min	DE ₁₂₀ % min	t 50% (min.)
1	carvedilol	1.18	3.95	>120
2	PM	9.86	28.1	>120
3	SD 1	20.3	45.56	<120
4	SD 2	23.06	58.75	<100
5	SD 3	25.60	68.40	<10

In Table 1, dissolution efficiency (%DE) at 10 and 120 min are reported together with the time needed to dissolve 50% of drug (t 50%). It is evident that the dissolution rate of carvedilol has improved in solid dispersion.

Stability studies were carried out for the solid dispersions obtained by solvent evaporation method by exposing them to 40 °C/75% RH. The solubility, dissolution, drug content, PXRD, FTIR and DSC studies were carried out at the end of 3 months and compared to day zero. No significant changes observed in solubility, drug content and in dissolution rate after three months. Also the PXRD, FTIR and DSC patterns of the solid dispersion recorded gave identical patterns to the initial ones through out the study period.

DISCUSSION

In the presence of PVP K30 the aqueous solubility of carvedilol increased significantly with increasing concentration of PVP K30. This may be attributed to the improved wetting of carvedilol in the presence of PVP K30 probably due to the formation of intermolecular hydrogen bonding between the carbonyl group of PVP K30 and the hydrogen atom in the hydroxyl group of carvedilol. The solubility curves obtained highly resembled to the A_L type curve described by Higuchi and Connors (14). This finding is in accordance with Zidan et al. regarding the increased solubility of rofecoxib (20).

Low values of standard deviation in physical mixture and solid dispersions in respect of drug content indicated uniform drug distribution in all the formulations. Therefore, the method used in this study appeared to be

reproducible for the preparation of solid dispersions.

PXRD analysis can be used to judge any changes in crystallinity of the drug which precipitated in an amorphous form, when formulated into a solid dispersion. Changes in crystallinity of the drug could be one of the mechanisms responsible for improved dissolution. The diffraction spectrum of pure carvedilol showed that the drug was of crystalline in nature as demonstrated by numerous, distinct peaks. The X-ray diffraction patterns of carvedilol solid dispersion with PVP K30 showed amorphous pattern. On the other hand, diffraction pattern of 1:1 physical mixture showed partial amorphization of the carvedilol. According to these results, the amorphous property of carvedilol in its formulation with PVP K30 was considered to be mainly responsible for the dissolution enhancement (21).

In DSC studies, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in both physical mixtures as well as in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer (22).

No difference was shown in the position of the absorption bands spectra of physical mixture. The spectra can be simply regarded as the superposition of drug and carrier. In the spectra of solid dispersions, the broadening of peaks of O-H and N-H stretching vibration was due to intermolecular hydrogen bonding between the hydroxyl group of carvedilol and

the carbonyl group of PVP K30(23).

Both physical mixtures and solid dispersions showed enhanced dissolution rate as compared with pure drug. Physical mixture increased the solubility and maximizing the surface area of the drug that came in contact with the dissolution medium as the carrier dissolved. This might be due to the surface tension lowering effect of polymer to the medium, resulting in the wetting of hydrophobic drug of crystalline surface, which can be attributed to the reduction of crystallinity of drug, and therefore improved release profile (supported by X-ray diffraction), reduction of particle size to molecular level, and expansion of the surface area for dissolution. The initial high drug release was observed at the 10 min time point and reduced at subsequent time points. This may be because of initial rapid flux of the drug from the solid dispersion particles to the dissolution medium resulted in a high concentration, which reduced with time. Slow dissolution was observed subsequently till the equilibrium concentration was reached.

As can be seen, all dissolution parameters demonstrated that binary products had better dissolution properties than pure drug alone. The value of DE_{10} % for carvedilol (1.18%) was enhanced in physical mixture (9.86%) as well as in formulation SD3 having highest drug to carrier ratio (25.64%). The value of DE_{120} % for the pure drug was increased to 28.1% in physical mixture and up to 68.41% in formulation SD3. However, dissolution enhancement up to 17.5 fold in the dissolution rate with SD3 was observed in comparison to pure drug in overall study period.

Data from different analytical techniques together indicated that in solid dispersion, the drug did not show any physical change after storage at 40 °C/75% RH for 1 month. All the batches of solid dispersion and physical mixture were found to be stable through out the study period.

CONCLUSION

Solid dispersions prepared from hydrophilic polymers using the solvent evaporation technique were effective in improving drug dissolution. The above studies indicated that

PVP K30 inhibited the crystallization of drug, resulting in the amorphous state form of the drug in solid dispersion. 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. PXRD and DSC results confirmed the amorphous state of drug in solid dispersion. In the stability study, no significant changes were recorded with respect to drug content, solubility, dissolution rate, PXRD, DSC and FTIR over a period of 3 months.

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