Research Article

Solubility and Dissolution Enhancement of Carvedilol by Solid Dispersion Technique Using Gelucire 50/13

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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. Inclusion behavior of gelucire 50/13 was studied towards carvedilol, an antihypertensive agent in order to develop mucoadhesive oral dosage form with enhanced dissolution rate and bioavailability, following gelucire carvedilol solid dispersion. The present work was investigated to examine the release of carvedilol from various molecular weight fractions of gelucire solid dispersions. Solid dispersions of carvedilol were prepared in different molar ratios of drug: carrier by using solvent evaporation and melting methods. The physical mixture and solid dispersion (s) were characterized for drug-carrier interaction, drug content, solubility and dissolution rate. The release rate of carvedilol from the resulting complexes was determined from dissolution studies by use of USP dissolution apparatus 2 (paddle method). The physical state and drug: gelucire interaction of solid dispersions and physical mixtures were characterized by X-ray diffraction (XRD), Infra Red Spectroscopy (IR) and Differential Scanning Calorimetry (DSC). The dissolution rate of carvedilol was increased significantly in all of the solid dispersion systems compared to that of the pure drug and physical mixtures. The solid dispersion prepared in the molar ratio of 1:2 by the solvent evaporation method was found to have the fastest dissolution profile.

Keywords: Carvedilol, Gelucire 50/13, Solvent Evaporation method, Melting method, Dissolution enhancement.

INTRODUCTION

Carvedilol is an antihypertensive agent used in the treatment of hypertension, congestive cardiac failure, angina pectoris, cardiac arrhythmias and myocardial infarction. It is a nonselective beta adrenoreceptor blocker with selective alpha adrenergic blocking. [1] However drug bioavailability is very limited (25-30%), since it is practically insoluble in water and its dissolution is the rate limiting step for its absorption through gastrointestinal tract.[2, 3] Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug.[4,5] Solid dispersion, which was introduced in the early 1970s, is essentially a multi-component system, having drug dispersed in hydrophilic carrier(s) by different methods. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers.[6-7]

The present study aims to enhance the aqueous solubility and dissolution rate of carvedilol through formation of solid dispersions of carvedilol and gelucire 50/13 in different molar proportions viz. 1:1 and 1:2 (drug:carrier) by using various techniques, physical mixing, melting method and solvent evaporation method thereby to improve its oral bioavailability.

MATERIALS AND METHODS

Materials

Carvedilol was provided by Cipla Ltd., Kurkumbh, India and gelucire 50/13 from Glenmark Pharmaceutical Ltd., Sinnar, India as a gift sample. All other chemicals and reagents were used of analytical grade.

Phase solubility studies[8]

Solubility measurements were performed according to method reported by Higuchi and Connors. An excess amount of the drug was added to 10 ml volumetric flask containing 10%, 20%, 30%, 40%, 50% aqueous solution of gelucire 50/13. The samples were shaken for 48 hours at room temperature 25±1°C on an orbital shaker incubator. After 48 hours of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn after 1 hour and filtered immediately using membrane filter (0.45 µ). The filtered samples were diluted suitably and assayed for carvedilol by measuring absorbance at 284 nm using UV/Visible spectrophotometer (Jasco-V630). Solubility studies of physical mixtures and solid dispersion were also performed in same manner. The apparent 1:1 stability constant, K_c1:1, were calculated from the linear portion of phase solubility diagrams using the equation:

$K_c(1:1)$= Slope/S_0 (1-Slope)

Where, S_0 is the drug solubility in the absence of gelucire 50/13 (intercept).

Preparation of Physical Mixtures and Solid Dispersions of` Carvedilol

The solid dispersions of carvedilol and gelucire 50/13 were prepared 1:1M and 1:2M by three methods, physical mixture, melting and solvent evaporation method.

Physical mixture

Carvedilol and gelucire 50/13 in molar ratio of 1:1 and 1:2 (PM1, PM2) were prepared by simple trituration for 1 hr in glass mortar with pestle and passed through a sieve no 100 and stored in a desiccator. [9, 10, 11]

Melting method

Carvedilol and gelucire 50/13 in molar ratio of 1:1 and 1:2 (M1, M2) were taken. Gelucire was heated at 50ºC in an oil bath, until it melted completely. The drug was added to the molten polymer and mixed thoroughly in mortar with pestle. The dispersion was cooled to ambient conditions, milled, and passed through a 40-mesh sieve and stored in a desiccator.[12]

Solvent evaporation method

Carvedilol and gelucire 50/13 were dissolved in minimum quantity of methanol. Different molar ratios of 1:1 and 1:2 (S1, S2) of carvedilol and gelucire 50/13 were taken. This solution was continuously stirred using magnetic stirrer and solvent was evaporated. Then it was stored over night in a desiccator. Solid dispersion thus obtained was grounded by using a mortar and pestle and sieved through a 40 mesh screen.[13, 14]

Characterization of Physical Mixtures and Solid Dispersions of Carvedilol

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectra were obtained using Shimadzu FTIR- 8400S spectrometer, Japan. Samples of carvedilol, gelucire 50/13, 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}. [15, 16, 17]

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) analysis of the samples was carried out on a Perkin-Elmer DSC. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10^0C/min over the temperature range of 50 to 300^0C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2. [18,19,20]

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 1-40°. Powder X- ray diffraction patterns were traced for carvedilol, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container. [21, 22]

***In vitro* Dissolution Studies** [17, 18, 23, 24]

The release rate of carvedilol from solid dispersions was studied using *USP XXIV* dissolution testing apparatus 2 (paddle method; Electrolab, Mumbai, India). The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer, at 37±0.5 ℃ and 50 rpm for 2 hours. Complex equivalent to 12.5 mg of carvedilol was used in each test. Samples (5 ml each) of dissolution medium were withdrawn at predetermined time interval and analyzed for drug release by measuring absorbance at 284 nm after suitable dilution with pH 6.8 phosphate buffer. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium.

RESULTS AND DISCUSSION

Phase solubility studies

Phase solubility diagram for complex formation between carvedilol and gelucire 50/13 in water is A_L type according to Higuchi and Connors, (Figure 1) which illustrate solubility enhancement capability of gelucire 50/13. The aqueous solubility of carvedilol increased linearly (r=0.977) as a function of gelucire concentration with K_C of 246.01 M^{-1}.

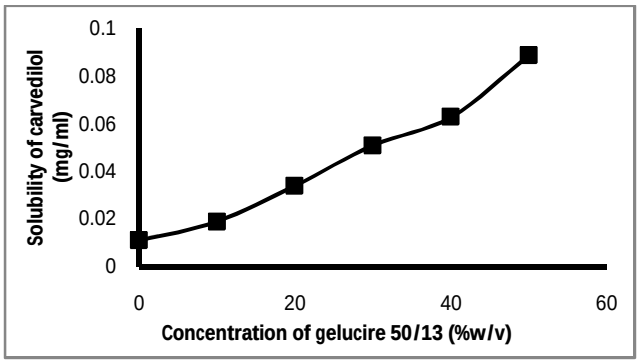

Figure 1: Phase solubility curve of carvedilol with gelucire 50/13.

FTIR Studies

FTIR spectra of carvedilol (Figure 2) 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 FT-IR spectra of physical mixtures PM1, PM2 retain all the characteristic peaks of pure drug. No significant shifts in the peaks corresponding to the drug were observed on storage. The binary systems M1, M2, S1 and S2 revealed disappearance of the characteristic

peaks suggesting possible entrapment of carvedilol moiety into the gelucire 50/13 cavity. As such, the FTIR spectra of carvedilol and gelucire 50/13 compositions did not show significant shifts suggestive of an interaction. Instead, the spectra show few to no changes in the absorption bands characteristic of carvedilol. The study indicates that carvedilol has strong physical interaction with gelucire 50/13 in solid state. FTIR spectroscopy revealed the possibility of inter-molecular hydrogen bonding in solid dispersions.

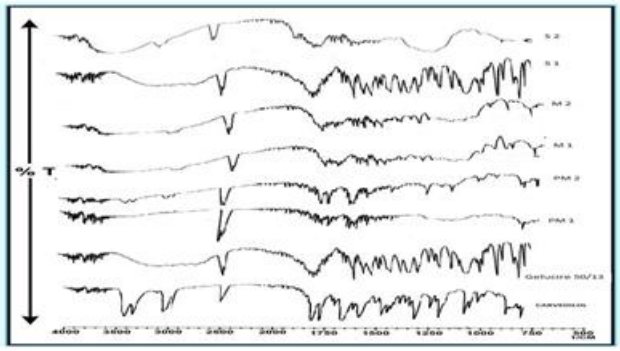

Figure 2: FTIR spectrums of pure carvedilol, gelucire 50/13 and formulations (PM1, PM2, M1, M2, S1 and S2)

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The thermal behavior was studied using differential scanning calorimetry in order to confirm the formation of solid dispersions. The thermograms for pure carvedilol and gelucire 50/13, physical mixture and solid dispersions are presented in Figure 3.

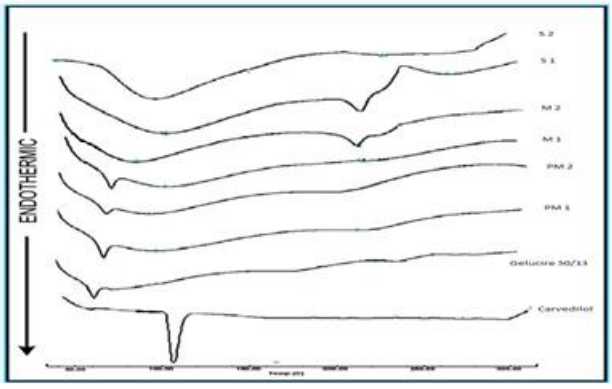

Figure 3: DSC thermograms of pure carvedilol, gelucire 50/13 and formulations (PM1, PM2, M1, M2, S1, S2)

The carvedilol showed a melting endotherm at 115 °C whereas gelucire 50/13 showed a melting endotherm at 45^{0}C. Thermograms of carvedilol and gelucire 50/13 physical mixture (PM1, PM2) and melting (M1) method showed endothermic peak at 90^{0}C. This is may be due to shift of characteristics peak of carvedilol, which was observed at 115 °C, indicates weak interaction of drug and gelucire 50/13. Thermal curve of carvedilol gelucire 50/13, prepared by melting (M2) method has shown broadened endothermic peak at 70°C. Complete disappearance of endothermic peak due to carvedilol with these systems indicated the formation of an amorphous solid dispersion of drug in case of complexes prepared by solvent evaporation method at 1:1M (S1) and 1:2M (S2).

Powder X- Ray Diffraction (PXRD)

Powder X-ray diffraction 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. PXRD could be used to study any changes in crystallinity of the drug which could be one of the mechanisms responsible for improved dissolution. 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. Gelucire 50/13 is crystalline in nature and gives two characteristic peaks: one at 19° and the other broader one between 22° and 27°. XRD-scanning of physical mixture (PM1, PM2) showed decreasing number of peaks with lower intensity indicating partial amorphous nature of the drug in its binary mixtures (Figure 4). In case of solid dispersion prepared by melting (M1, M2) method, there was a decrease in the intensity of carvedilol but the major peaks remained at the same positions. The PXRD of solid dispersion prepared by solvent evaporation (S1, S2) method exhibited the absence of characteristic peaks of carvedilol, suggesting that carvedilol is completely soluble in the liquid phase with gelucire 50/13 and confirming that carvedilol, is in amorphous form with SDs.

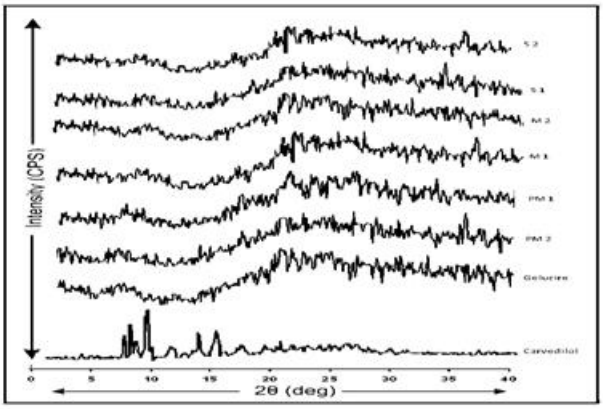

Figure 4: X ray diffractograms of pure carvedilol, gelucire 50/13 and formulations (PM1, PM2, M1, M2, S1, S2)

***In vitro* Dissolution Studies**

The *in vitro* dissolution profiles of the pure drug, various solid dispersions prepared by using gelucire 50/13, and their respective physical mixtures in pH 6.8 phosphate buffer for 2 hours shown in Figure 5. At the end of 2 hours, 53.16 %, 61.23 %, 64.46 %, 72.59 %, 84.63 % 92.65 % and 99.85 % carvedilol was released from pure drug sample, PM1, PM2, M1, M2, S1 and S2 respectively. All of the physical mixture and solid dispersion samples showed improved dissolution of carvedilol over pure drug. All of

the solid dispersions revealed more improved carvedilol dissolution than their respective physical mixtures. This observation indicated that the increased dissolution of carvedilol from solid dispersion due to presence of drug in amorphous state as compared the physical mixtures and pure drug, where drug is present in crystalline state. This can be attributed to the reduction of crystallinity of drug resulting in improved release (supported by X-ray diffraction); reduction of particle size to expand the surface area for dissolution.

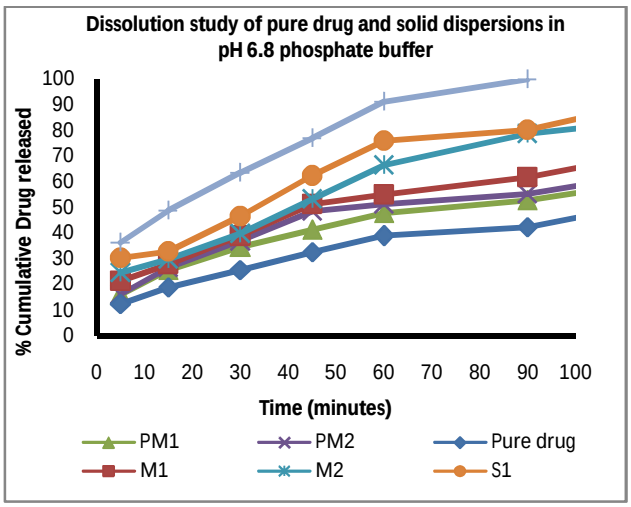

Figure 5: Dissolution profile of pure drug, physical mixtures and solid dispersions of carvedilol.

CONCLUSION

Gelucire 50/13 can be used to prepare carvedilol solid dispersions. Solubility of carvedilol in pH 6.8 phosphate buffer was improved greatly as a result of complex formation with gelucire 50/13 in comparison to pure drug carvedilol. A marked increase in the dissolution of solid dispersion was observed with gelucire 50/13 at 1:2M ratio prepared by solvent evaporation method. Carvedilol-gelucire 50/13 complexation results in an increase of solubity and dissolution rate for the drug suggesting a possible enhancement of its oral bioavailability.

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