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Enhancement of carvedilol solubility by solid dispersion technique using cyclodextrins, water soluble polymers and hydroxyl acid

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ABSTRACT

Aim of the present work is to enhance aqueous solubility of carvedilol (CV) by solid dispersion technique using wide variety of carriers such as: β-cyclodextrin (βCD), hydroxypropyl-β-cyclodextrin (HPβCD), tartaric acid (TA), polyvinyl pyrrolidone K-30 (PVP K-30) and poloxamer-407 (PLX-407). Various products of 'CV-solid dispersion' had been studied extensively in various pH conditions to check enhancement of solubility and dissolution characteristics of carvedilol. Any physical change upon interaction between CV and carriers was confirmed by instrumental analysis: XRD, DSC, FTIR and SEM. Negative change of Gibb's free energy and complexation constants (K_c, 75–240 M^{-1}, for cyclodextrins and 1111–20,365 M^{-1}, for PVP K-30 and PLX-407) were the evidence of stable nature of the binding between CV and carriers. 'Solubility enhancement factor' of ionized-CV was found high enough (340 times) with HPβCD in presence of TA. TA increases the binding efficiency of cyclodextrin and changing the pH of microenvironment in dissolution medium. In addition, ionization process was used to increase the apparent intrinsic solubility of drug. *In vitro*, dissolution time of CV was remarkably reduced in the solid dispersion system compared to that of pure drug. This may be attributed to increased wettability, dispersing ability and transformation of crystalline state of drug to amorphous one.

1. Introduction

The development of many active pharmaceutical ingredients (APIs) has been discontinued because of their low aqueous solubility, which leads to poor bioavailability [1]. Some of these drugs belong to Biopharmaceutical Classification System (BCS) Class II compounds, which are characterized by low aqueous solubility and high permeability. The urgency to 'enhanced solubility' of BCS Class II APIs has generated special interest to the pharmaceutical scientists to achieve better oral bioavailability [2].

Out of numerous formulation strategies [3] exercised earlier, solid dispersion techniques have been used effectively to enhance the solubility of poorly water soluble drug, because it is economically viable and simple [4]. Some recently used methods to prepare amorphous solid dispersions are fusion, hot melt extrusion, spray drying, freeze drying, kneading, and solvent evaporation [5]. It is advantageous as no lattice structure has to be broken down for dissolution to take place because crystalline drug is transformed to amorphous state [6].

Carvedilol (CV), a cardiovascular drug is suitably chosen as a model drug to study enhancement of solubility by 'solid dispersion technique'. CV is chemically known as [(2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl]-amino)-2propanol, M.W.406.5] and it is basic in nature (pKa 7.8) [7]. It has emerged as one of the important and promising drug moieties for cardiovascular disease [8] owing to noticeable improvement of survival rates in patients with chronic cardiac insufficiency. It has 25–30% of bioavailability and six hours of biological half-life and ~75% of drug is lost owing to excretion through urine and metabolism reaction in liver. It reaches highest plasma level within 1.47 h after oral administration [9]. It is extremely low solubility in the alkaline pH may prevent the availability of drug for its absorption in small intestine and colon; this makes it a poor candidate for an extended release dosage form. In view of above limitations, it is a potential candidate for the design of solid dosage form. Several attempts have been proposed earlier to overcome its drawbacks. Various water-soluble inert materials such as cyclodextrin, gelucire, citric acid, porous silica, PVP K-30, surfactants and montmorillonite [10–19] have caused improvement of the dissolution rate and bioavailability of many other sparingly soluble drugs.

Polyvinyl pyrrolidone (PVP) is excellent as it is available in a wide range of molecular weight [20]. Poloxamer is grouped as block copolymers and non ionic surfactant used to solubilize many hydrophobic compounds owing to its ability to form micelles

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[21]. Cyclodextrins (CDs) are naturally available as water soluble cyclic oligosaccharides, composed of α-1,4-linked d-glucopyranose units. One of the most prominent groups of modified CDs is hydroxypropyl-β-cyclodextrin (HPβCD) which has greater solubility in water than that of parent CD (βCD) [22]. Owing to their high molecular weight, relatively low water solubility and possible parenteral toxicity, a possible tool to reduce their workable amount in pharmaceutical formulations is the addition of suitable auxiliary substances, (organic solvents, hydroxy-acids, water soluble polymers) which would augment the solubilizing capacity of cyclodextrin [23].

Few investigators reported addition of organic acid (citric acid) as an auxiliary agent, which causes a synergistic effect on solubility enhancement of CV [12].

The present work highlights on search of effective carrier and organic acid to prepare a solid dispersion of CV. The objective of the present study is to develop a CV-solid dispersion with improved solubility using various carriers such as β-cyclodextrin (βCD), hydroxypropyl-β-cyclodextrin (HPβCD), polyvinyl pyrrolidone K-30(PVP K-30), poloxamer-407 (PLX 407) and tartaric acid (TA). The study includes phase solubility study, characterization of solid dispersion, instrumental analyses of the product to check interaction between drug and additives.

2. Materials and methods

2.1. Materials

Carvedilol (CV, M.W:-406.5) (Sun Pharmaceutical Ltd., India), Beta cyclodextrin (βCD, M.W:-1135), Hydroxypropyl-β-cyclodextrin (HPβCD, M.W:-1380) (Roquette Pharmaceutical Ltd., India) were provided as a gift samples. Polyvinyl pyrrolidone (PVP, M.W:-45,000) (SD fine chem. India), Poloxamer 407 (PLX, M.W:-12,600) (Sigma Chemicals) and Tartaric acid, (TA, M.W:-150) were procured. All other reagents and solvents used were of analytical grade.

2.2. Determination of some physicochemical parameters of carvedilol

2.2.1. Determination of saturation solubility

To determine saturation solubility, an excess amount of drug was added to 10 mL of double distilled water contained in stopper volumetric flasks. These are placed into a water bath at a constant temperature of 37 ± 0.5 °C and shaken at 30 min interval until equilibrium was attained. Next, the contents of the vessel were centrifuged. The supernatant solutions were subsequently filtered through a Whatman filter paper (pore size 11 μm) and suitably diluted. Absorbance was recorded at 241 nm by UV-spectrophotometer. The same procedure was followed with the media of pH 1.2, 6.8 and 7.4.

2.2.2. Determination of a partition coefficient

The measurement of the partition coefficient is an important task because, passive diffusion is a common mechanism of drug absorption and it is very much dependent upon the partition coefficient of drug. The partition coefficient of drug was determined following standard method [24] and the experiment was performed in triplicates at 25 ± 1 °C. Partition coefficient ($K_{o/w}$) of CV was calculated by the ratio of concentration of the analyte distributed in two immiscible solvents (n-octanol and water).

2.2.3. Determination of pKa of carvedilol by potentiometric titration

Weak acid/base ionizes in solution to varying extent depending on pH. The pKa of an ionizable compound is an indicator of the charge state of the molecule at a particular pH. For insoluble drugs, the dependence of solubility on pH can be utilized to determine pKa values. 0.01 M of CV solution was prepared with solvent (0.15 M KCl solution) containing 2% tween 80 [25]. This solution was titrated against 0.01 M HCl with an increment of 0.1 mL of titrant and pH was observed after each addition. pH of drug solution was plotted against concentration of HCl solution and pKa was determined.

2.2.4. Phase solubility studies

The phase-solubility diagram was constructed according to Higuchi and Connor's method [26]. Aqueous solutions of various carrier systems such as βCD, HPβCD, HPβCD–TA (0.75:0.25), HPβCD–TA–PVP K-30 (0.74:0.25:0.01), PVP-K30 & PLX-407 were prepared at concentrations of 1, 2, 4, 6, 8, and 10%. Experiment was conducted with different aqueous media such as DD water, pH 1.2, pH 6.8. Excess amount of CV was added to each test tube containing 10 mL of prepared solution. The test tubes were sealed and shaken for 48 h in a mechanical shaker maintaining a constant temperature at 25, 37, 40 and 45 ± 0.5 °C and then the content of each test tube was centrifuged. The supernatant solutions were filtered through a Whatman filter paper (pore size 11 μm) and diluted with suitable media. Concentration of drug was determined by UV spectrophotometer (λ_{max} 241 nm) method. The experiment was repeated thrice for each.

Phase solubility curve was constructed by plotting solubility of CV (mol/L) against concentration of the carrier (mol/L). Slope and intercept as obtained from each profile were used to calculate apparent complexation constant (K_c) of the complex system from Eq. (1). Intercept is intrinsic solubility of drug in the absence of carrier at each temperature. Also, the change in enthalpy (ΔH) upon complexation between drug and carrier was determined using Van't Hoff equation Eq. (2)

$$K_{1:1} = \frac{\text{Slope}}{\text{Intercept}(1 - \text{Slope})} \quad (1)$$

$$\ln\left(\frac{K_{c_2}}{K_{c_1}}\right) = \Delta H \frac{T_2 - T_1}{RT_2T_1} \quad (2)$$

where K_{c_2} and K_{c_1} are the stability constants at 37 °C and 25 °C respectively. T_2 and T_1 are the corresponding absolute temperatures in Kelvin. The change in Gibbs-free energy ΔG ($\Delta G = -RT \ln k$) and entropy ΔS [$\Delta S = (\Delta H - \Delta G)/\Delta T$] was also determined. R is the universal gas constant (R = 8.314 J/mol/K).

2.3. Preparation of solid dispersion

Solid dispersions (SD) were prepared at various ratios (1:1 to 1:5) of drug and primary carrier (βCD, HPβCD, PVP K-30 and PLX-407); tartaric acid was added with 1/4th of the primary carrier (CV:HPβCD:TA, 1:1:0.25 to 1:5:1.25) and water soluble polymer was added with 1/100th of primary carrier(CV:HPβCD:TA:PVPK-30, 1:1:0.25:0.01 to1:5:1.25:0.05). In each preparation 200 mg of drug was used.

2.3.1. Solvent evaporation technique for PVP K-30, PLX-407

In solvent evaporation technique, first CV (200 mg) was dissolved in a mixture of dichloromethane and ethanol (50:50, v/v) [27,28] to produce a clear solution. Carrier substance was dispersed in the above clear solution, by stirring at 37 ± 0.5 °C in a magnetic stirrer. Next, clear solution was poured into the aluminum foil and solvent was allowed to evaporate at 40 ± 0.5 °C in a hot air oven. Finally, the resultant mass was dried at 37 °C for 24 h. This dried material was pulverized and passed through a sieve with a mesh number of 120.