RESEARCH ARTICLE

STUDIES ON DISSOLUTION ENHANCEMENT OF POORLY WATER SOLUBLE DRUG USING WATER SOLUBLE CARRIERS

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Abstract: The purpose of this study was to prepare and characterize solid dispersions of the poorly water soluble anti hypertensive lacidipine with water-soluble carriers such as Polyethylene glycol 4000, Polyethylene glycol 6000, hydroxy ethyl cellulose and dextrin with the intension of improving its dissolution properties. The solid dispersions were prepared by solvent evaporation method. Evaluation of the dispersions was performed using dissolution studies, Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy and X-ray powder diffraction. The results obtained showed that the rate of dissolution of Lacidipine was considerably improved when formulated in solid dispersions as compare to pure drug. The order of increasing dissolution rate observed with various carriers in different concentration was F4 > F16 > F8 > F12.

Keywords: Lacidipine, solid dispersions, carrier, rate of dissolution.

INTRODUCTION

Lacidipine (LAC) is one of the most vascular selective of the dihydro pyridines, act as calcium channel blocker [1]. It is chemically diethyl (E) – 4 – {2-[(*tert*- butoxyl carbonyl) vinyl] phenyl} -1, 4-dihydro-2, 6-dimethyl pyridine -3, 5-dicarboxylate. It is completely absorbed from the GIT. Peak plasma concentration occurs in 1 to 1.8hr and it is highly protein bound. It is white to pale yellow crystalline, water insoluble (84 µg/lit), freely soluble in acetone and sparingly soluble in absolute alcohol [2]. The solubility and dissolution rate might be increased using solid dispersion technology.

The incorporation of drugs into hydrophilic carriers has frequently been reported to increase the dissolution rate of poorly soluble dugs, often leading to improved drug bioavailability [3, 4]. Such dosage forms are referred to as solid dispersions. This system provides the possibility of reducing the particle size of drugs to nearly a molecular level, to transform the drug from the crystalline to the amorphous state and/ or locally increase the saturation solubility [5-7].

Several carriers have been employed in preparing solid dispersions; among those is the use of polyethylene glycol (PEG), hydroxy ethyl cellulose (HEC) and dextrin (DX). PEG polymers are widely used due to their low melting point, low toxicity, high viscosity, wide drug compatibility and hydrophilicity.

The aim of the study was to prepare and characterize different solid dispersions of Lacidipine with PEG 4000, PEG 6000, HEC and DX so as to improve its dissolution properties. In order to evaluate the effect of these carriers on Lacidipine, dissolution and solubility studies were performed. Physical analysis based on differential scanning calorimetry (DSC), FT-IR spectroscopy and powder X-ray diffraction was performed to elucidate the structure of dispersions and to detect possible drug-carrier interaction.

MATERIALS AND METHODS

Lacidipine was obtained as gift sample form Dr. Reddy's Laboratories, Hyderabad. PEG 4000, PEG 6000, HEC and DX were procured from SD Fine Chemicals Ltd., Mumbai. All other materials were of analytical grade.

Preparation of physical mixtures

Physical mixtures were prepared by mixing lacidipine with PEG 4000, PEG 6000, HEC and DX for three minutes in a mortar until a homogeneous mixture was obtained. The resulting mixture was sieved through sieve no. 100 and then stored in a desiccator at room temperature until use.

Preparation of solid dispersions

Solid dispersions (SDs) were prepared with Lacidipine: PEG 4000, PEG 6000, HEC and DX in 1:1, 1:2, 1:4 and 1:9 weight ratios by solvent evaporation method. To a solution of Lacidipine in dichloromethane the carrier was added. The solvent was removed by evaporation under reduced pressure (vacuum) at 40°C and dried in desiccator until they attained constant weight. The samples were pulverized in a mortar and passed through a sieve no. 100.

Estimation of lacidipine

Lacidipine content was estimated by UV-Visible spectrophotometric method by measuring absorbance at 284 nm. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 0-15 µg/ml.

Estimation of drug content of lacidipine SDs

10 mg of SD was dissolved in 10 ml of methanol in a 100 ml volumetric flask and the volume was made with 1% tween 20 solution. This solution was further diluted with 1% tween 20 if necessary and the absorbance was measured at 284 nm.

Differential scanning calorimety (DSC)

DSC studies of the dispersions were performed at a scanning rate of 10 °C/min. On Seiko, Japan DSC 220C model Differential Scanning Calorimeter. Samples (10 mg) were heated on sealed aluminium pans form 30 °C to 400 °C.

Dissolution rate studies

Dissolution rate of lacidipine as such and from various solid dispersions was studied using USP XXIII six-station dissolution rate test apparatus (DISSO 2000, Labindia) with paddle stirrer. The dissolution rate was studied by placing lacidipine 2 mg or SD equivalent to 2 mg on the surface of dissolution medium (900 ml of 1% tween 20 solution), maintained at 37 ± 0.5 °C with a speed of 50 rpm. A 5 ml aliquot was withdrawn at different time intervals, filtered (though 0.45µ) and replaced with 5 ml of fresh dissolution medium. The samples were estimated for dissolved lacidipine by measuring absorbance at 284 nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The solid dispersions of lacidipine with PEG 4000, PEG 6000, HEC and DX in 1:1, 1:2, 1:4 and 1:9 weight ratios were prepared by solvent evaporation method. In the present work total 16 formulations were prepared and their composition is shown in Table 1. All the dispersions prepared were found to be fine and free flowing. Their dissolution characteristics and drug carrier interactions (DSC and FTIR) were studied. DSC thermograms of Lacidipine, PEG 4000, PEG 6000, HEC, DX and solid dispersions (1:9) had shown no significant evidence of chemical interaction between the drug and carrier, which confirmed the stability of the drug with its SD.

The dissolution rate of lacidipine and from various SDs was studied in 1% tween 20 solutions. It was suitable as dissolution medium to maintain sink condition (i.e. large difference in the saturation concentration and dissolved drug concentration) during dissolution rate study. The dissolution of lacidipine from all the SDs was rapid and more than the lacidipine. The dissolution data was fitted into zero order, first order and Hixson-crowell's cube

Table 1. Formulation of lacidipine solid dispersions

Formulations	Composition	Ratio (Drug : Carrier)
F1	Lacidipine + PEG4000	1:1
F2	Lacidipine + PEG4000	1:2
F3	Lacidipine + PEG4000	1:4
F4	Lacidipine + PEG4000	1:9
F5	Lacidipine + PEG6000	1:1
F6	Lacidipine + PEG6000	1:2
F7	Lacidipine + PEG6000	1:4
F8	Lacidipine + PEG6000	1:9
F9	Lacidipine + HEC	1:1
F10	Lacidipine + HEC	1:2
F11	Lacidipine + HEC	1:4
F12	Lacidipine + HEC	1:9
F13	Lacidipine + DX	1:1
F14	Lacidipine + DX	1:2
F15	Lacidipine + DX	1:4
F16	Lacidipine + DX	1:9

root models to asses the kinetics and mechanism of dissolution. The model that gave higher 'r' value was considered as the best fit model. The 'r' values were found to be higher in the first order model than zero order. DE_{30} values were calculated in each case as per Khan et al. [7]. Only 41.3% of lacidipine dissolved in 60 min giving the slowest dissolution rate in the case of pure drug this may be due to hydrophobic property of the powder i.e. lacidipine to float on the surface of the dissolution medium which prevented its surface contacting the dissolution medium. The increase in dissolution rate from dispersions may be due to molecular level dispersions of drug in solid dispersion. The dissolution rate of lacidipine in solid dispersions was strongly depends upon the type of carrier and relative concentration of the drug to carrier ratio. The order of increase in dissolution rate was F4 > F16 > F8 > F12, the release data obtained for the solid dispersions was tabulated in Table 2. Figures 1, 2, 3 and 4 shows the plot of cumulative percent drug released as a function of time for different formulations.

Table 2. Dissolution parameters of lacidipine solid dispersions

Formulations	T_{50} (min)	1st order 'r' value	K_1 (min^{-1})	DE_{30} (%)
Lac	86.6	0.963	0.008	30±0.25
F1	57.75	0.915	0.012	49±1.09
F2	49.5	0.893	0.014	59±1.35
F3	34.65	0.908	0.029	72±1.03
F4	15.4	0.982	0.045	81±0.96
F5	49.5	0.920	0.014	52±0.75
F6	40.76	0.932	0.018	68±2.13
F7	34.65	0.894	0.021	67±1.32
F8	23.80	0.963	0.029	75±0.76
F9	53.3	0.925	0.013	51±0.29
F10	43.32	0.953	0.015	61±0.32
F11	34.65	0.957	0.020	62±1.91
F12	30.1	0.948	0.023	75±1.21
F13	43.3	0.921	0.016	59±0.32
F14	39.4	0.928	0.018	62±0.79
F15	34.7	0.953	0.023	65±1.21
F16	21.6	0.965	0.034	76±0.39

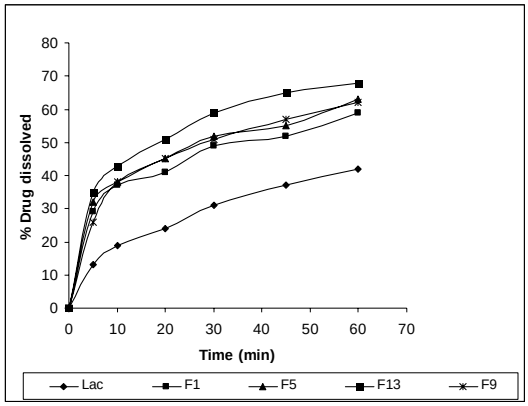

Figure 1. *In vitro* dissolution profile of solid dispersion of lacidipine in 1:1 ratio

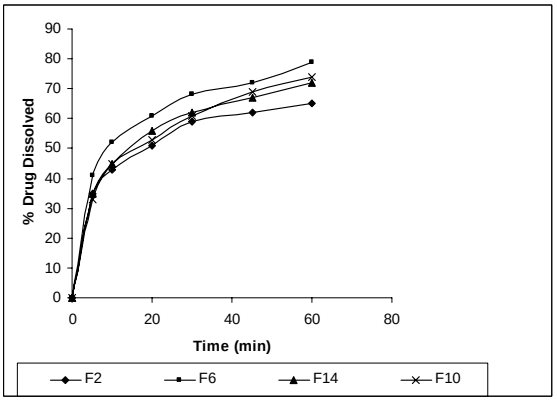

Figure 2. *In vitro* dissolution profile of solid dispersion of lacidipine in 1:2 ratio

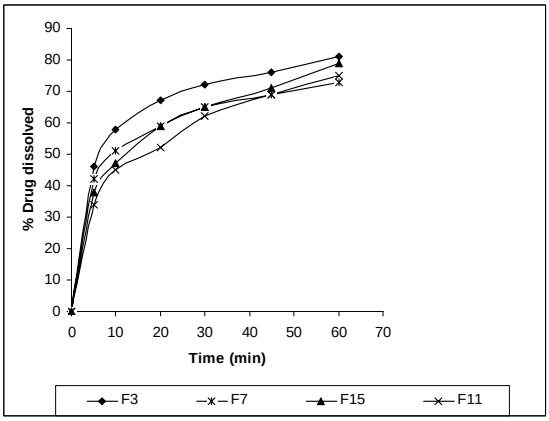

Figure 3. *In vitro* dissolution profile of solid dispersion of lacidipine in 1:4 ratio

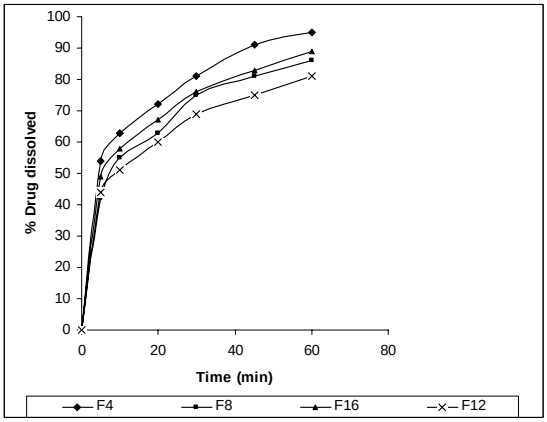

Figure 4. *In vitro* dissolution profile of solid dispersion of lacidipine in 1:9 ratio

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