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Research Article

IMPROVEMENT OF SOLUBILITY OF CINNARIZINE BY USING SOLID DISPERSION TECHNIQUE

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ABSTRACT
The aim of present work was to improve the solubility of a poor water soluble drug, cinnarizine, by using solid dispersion technique. Cinnarizine is a H1-receptor antagonist and widely used in the treatment of motion sickness, vomiting and vertigo. In the present work solid dispersion of cinnarizine were prepared with a polyethylene glycol 4000 and polyvinyl pyrrolidone K30 by using solvent evaporation and fusion method in the 1:1, 1:2 and 1:3 ratio of drug and carrier respectively. Solid dispersion of cinnarizine was evaluated for drug content, Infrared spectroscopy and *In vitro* dissolution study. The solid dispersion with PEG and PVP exhibited enhanced dissolution rate of cinnarizine. IR spectra revealed no chemical incompatibility between drug and carrier. The dissolution of the solid dispersion was carried out in 0.1N HCl. The *In vitro* dissolution study showed a significant increase in the release rate of cinnarizine in solid dispersion of cinnarizine with polyvinyl pyrrolidone K30 in the ratio 1:3 prepared by solvent evaporation method.

KEYWORDS: Solid Dispersion; cinnarizine; polyvinyl pyrrolidone K30; polyethylene glycol 4000; Solubility

INTRODUCTION
Cinnarizine is used in the treatment of motion sickness, vomiting and vertigo. It binds to the H1 receptor and to muscarinic acetylcholine receptors. It also inhibits contractions of vascular smooth muscle cells by blocking L type calcium channels. Cinnarizine is absorbed from the gastro-intestinal tract, peak plasma concentrations occurring 2 to 4 h after oral administration. Cinnarizine is practically insoluble in water (750 mg/L) [1-3]**.** There are many techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, which includes the surfactants, micronization, and the formation of solid dispersion[4].
The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or the melting-solvent method. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates, and consequently, the bioavailability of poorly water-soluble drugs[5-7].

MATERIALS AND METHODS
Cinnarizine was received as a gift sample from Erica Pharma, Mumbai. Polyethylene glycol 4000 and polyvinyl pyrrolidone K30 were gift sample from Signet Chemical Corporation, Mumbai. All other ingredients were of analytical grade.

Preparation of Solid Dispersions of Cinnarizine with carriers
Solid dispersions containing cinnarizine and carrier in the proportion of 1:1, 1:2 and 1:3 were prepared by fusion method and solvent evaporation method [8] (Table 1). Solid dispersions of drug with carrier (PEG 4000, PVP K30) were prepared by fusion method. In this method, cinnarizine was dissolved in acetone,

and the solution was incorporated into the melt of carrier (PEG 4000, PVP K30) at 165°, by pouring into it. It was kept in an ice bath for sudden cooling. The mass was kept in the desiccator for complete drying. The solidified mass was scrapped, crushed, pulverized, and passed through sieve no 80 mesh.

Solid dispersions of drug with PEG 4000 and PVP K30 were prepared by solvent evaporation method. In this method, accurately weighed quantities of carriers (PEG 4000, PVP K30) in the stated proportions were carefully transferred into boiling test tubes, and dissolved in acetone. To these solutions, accurately weighed quantities of cinnarizine were added, and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at room temperature, and the dispersions were dried at room temperature for 1 h, and then dried at 65° for 6 h in a hot air oven. The mass obtained in each case was crushed, pulverized, and sifted through sieve no 80 mesh.

Drug Content Analysis

An accurately weighed quantity of solid dispersion equivalent to 100 mg cinnarizine was taken into 100 ml volumetric flask and shaken with 100 ml of 0.1N HCl. One ml was pipette out and than dilute up to 100 ml. Resulting solution was filtered and assayed at 253.5 nm using double beem UV/Vis spectrometer.

Infrared Spectroscopy

Solid dispersion of cinnarizine was characterized by infrared (IR) spectroscopy. Infrared spectra were recorded on a Jasco FT/IR 5300 infrared spectrophotometer, by using KBr disc method. The scanning range was 400 to 4000 cm^{-1} (figure 1).

***In vitro* dissolution study**

The quantity of solid dispersions equivalent to 100 mg of cinnarizine, was filled in colorless hard gelatin capsule by the hand filling method.[9] The drug-release study was carried out using a USP XXIV type-1 apparatus (Electrolab, TDT-06T, India) at 50 rpm using 900 ml of 0.1 N HCl as a dissolution medium. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20 and 30 min and withdrawn volume was replaced with fresh dissolution media. The withdrawn samples filtered through a 0.45-micrometer membrane filter, diluted suitably, and analyzed spectrophotometrically. The concentration of cinnarizine in each sample was determined by using standard curve equation.

RESULTS AND DISCUSSION

Drug Content Estimation

The drug content of cinnarizine solid dispersion was found to be in range 97.24 to 102.01 and these values are within the acceptable range. Low values of standard deviation in respect of with respect to drug content, indicate uniform drug distribution in all the solid dispersions of cinnarizine.

Fourier Transform Infrared (FTIR) Spectroscopy

IR spectra of cinnarizine and its binary systems with PVP K30 and PEG 4000 are presented in Figure 1. Pure cinnarizine spectra showed sharp characteristic peaks at 3040.9, 2808.2, 2765.7, 2678.9, 2341.4 and 1926.6 cm^{-1}. All the above characteristic peaks appear in the spectra of all binary systems at same wavenumber indicating no modification or interaction between the drug and carrier.

***In vitro* dissolution studies**

Cinnarizine release from the solid dispersion and alone was studied in 0.1 N HCl media up to 30 min. The average percentage release of the pure cinnarizine was found to be 53% in 30 min. In the solid dispersion formulation using Polyethylene glycol 4000 and polyvinyl pyrrolidone K30 as carrier, the dissolution rate increased with increased amount of carrier. The best results among solid dispersions with Polyethylene glycol 4000 were obtained from the formulation PE6 (Table 2) and Polyvinyl pyrrolidone K30 were obtained from formulation PV6 (Table 3) which is prepared by solvent evaporation method. Among all these formulation, PV6 is best due to higher dissolution rate that is 96.82% at 30 min (figure 2). The increased dissolution rate may be due to the higher solubility of PVP in dissolution medium and better wettability of cinnarizine.

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Table 1: Composition and batch code of solid dispersion of cinnarizine with carrier

Batch code	Carrier	Ratio of drug and carrier	Method of preparation	Drug content (%)
PE1	PEG 4000	1:1	Fusion	99.85
PE2	PEG 4000	1:2	Fusion	99.16
PE3	PEG 4000	1:3	Fusion	97.24
PE4	PEG 4000	1:1	Solvent evaporation	101.40
PE5	PEG 4000	1:2	Solvent evaporation	97.68
PE6	PEG 4000	1:3	Solvent evaporation	99.90
PV1	PVP K30	1:1	Fusion	100.05
PV2	PVP K30	1:2	Fusion	102.01
PV3	PVP K30	1:3	Fusion	97.92
PV4	PVP K30	1:1	Solvent evaporation	101.87
PV5	PVP K30	1:2	Solvent evaporation	100.43
PV6	PVP K30	1:3	Solvent evaporation	98.29

Table 2: Percentage release of cinnarizine from PEG 4000 solid dispersion

Time (min)	Pure	PE1	PE2	PE3	PE4	PE5	PE6
5	16.57	16.88	19.10	20.09	21.47	22.29	21.68
10	25.61	37.19	32.36	34.39	35.67	32.26	36.57
15	31.81	48.21	52.80	51.62	61.02	50.75	63.54
20	43.56	70.51	75.61	76.98	67.06	71.71	78.28
30	53.63	82.19	85.60	86.92	72.53	84.65	87.63

Table 3: Percentage release of cinnarizine from PVP K30 solid dispersion

Time (min)	Pure	PV1	PV2	PV3	PV4	PV5	PV6
5	16.57	22.91	20.65	22.91	22.08	24.24	26.31
10	25.61	39.96	37.39	39.56	39.24	42.43	47.22
15	31.81	58.29	67.20	64.17	69.52	78.47	82.19
20	43.56	76.74	83.32	85.34	86.60	91.33	93.53
30	53.63	84.55	88.04	92.29	91.43	94.82	96.82

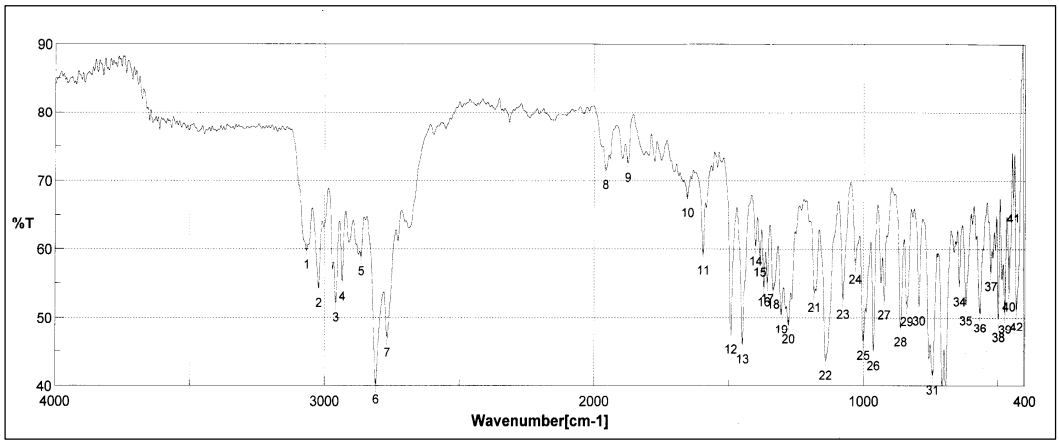

Figure 1(A): IR spectra of pure cinnarizine

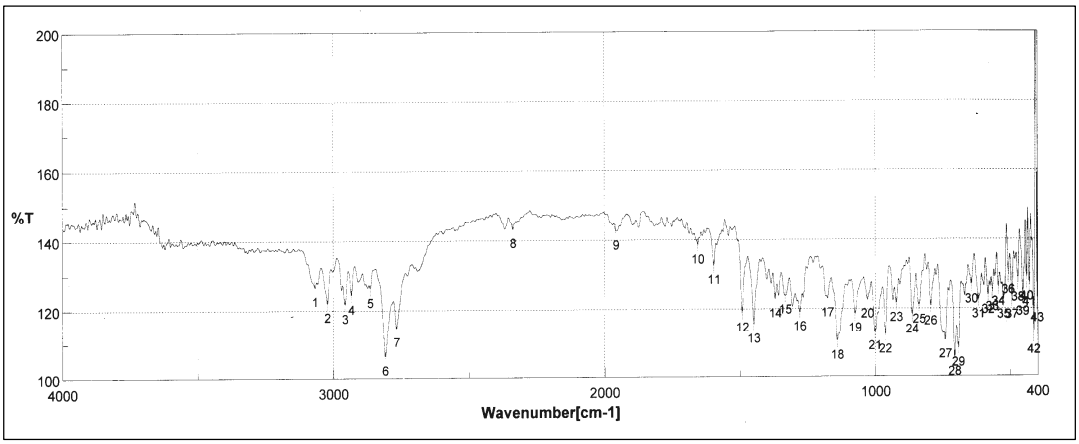

Figure 1(B): IR spectra of solid dispersion of cinnarizine and PEG 4000

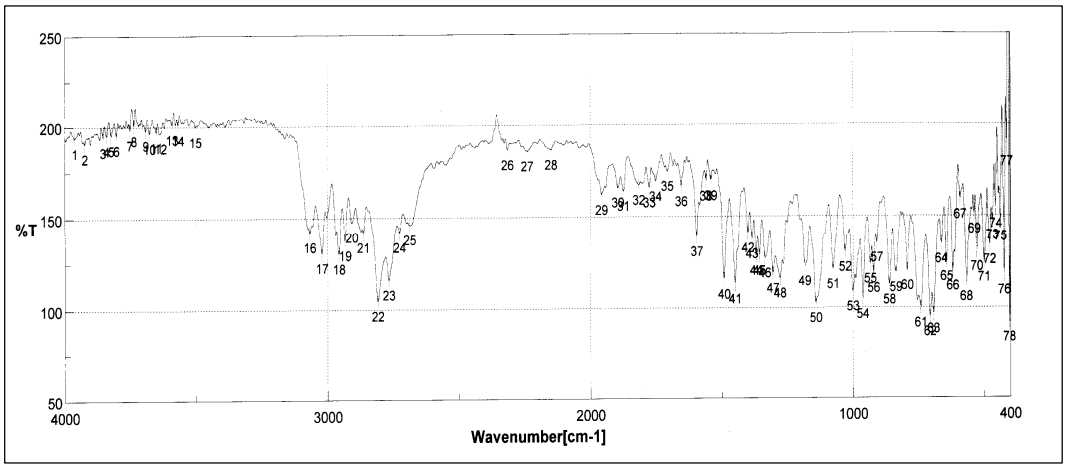

Figure 1(C): IR spectra of solid dispersion of cinnarizine and PVP K30

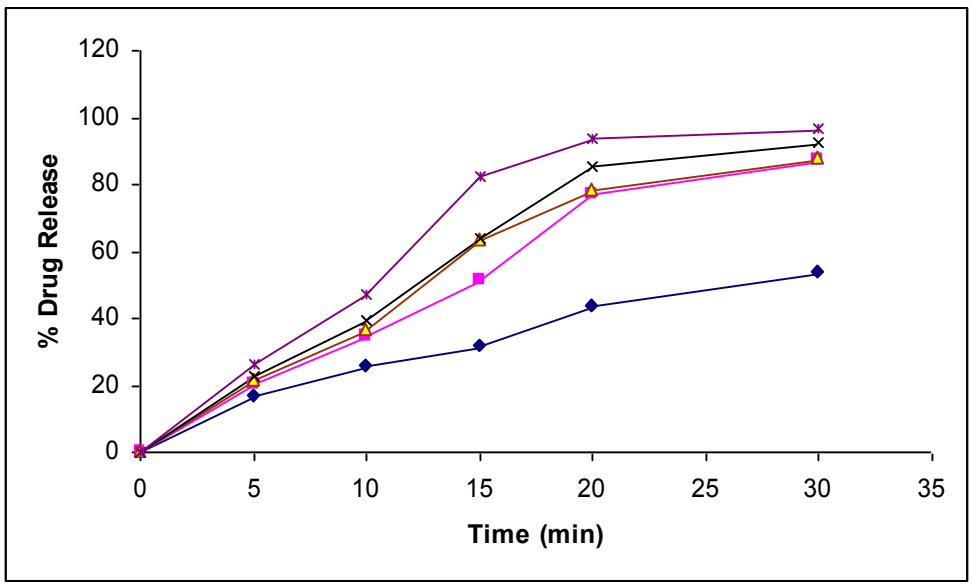

Figure 2: %Drug release profile of pure drug (—♦—), for PE3 (—■—), for PE6 (—▲—), for PV3 (—X—) and for PV6 (—☂—)

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