

# Development, characterization and solubility study of solid dispersion of terbinafine hydrochloride by solvent evaporation method

Narendra Kumar, Akhilesh K Jain, Chhater Singh<sup>1</sup>, Rajesh Kumar<sup>1</sup>

Institute of Pharmacy, Bundelkhand University, Jhansi, UP, <sup>1</sup>SD College of Pharmacy and Vocational Studies, Bhopa Road, Mujzaffarnagar, India

**T**erbinafine HCl (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of Terbinafine HCl by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 using solvent evaporation methods. FT- IR spectra revealed no chemical incompatibility between drug and polyvinyl pyrrolidone K30. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC), Powder X-Ray Diffraction (PXRD).

**Key words:** polyvinyl pyrrolidone K30, solid dispersion, solvent evaporation methods, terbinafine HCl

## INTRODUCTION

Terbinafine HCl<sup>[1,2]</sup> is a synthetic allylamine derivative that has a broad spectrum of antifungal activity when used orally or topically. Terbinafine is fungicidal<sup>[3]</sup> against dermatophytes and some yeast but only fungistatic against *Candida albicans*. Terbinafine HCl is a poorly water soluble drug, it is necessary to improve the solubility and bioavailability of Terbinafine HCl. 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. 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),<sup>[4]</sup> solvent or the melting-solvent method. Chiou and Riegelmen outlined 6 types of drug carrier<sup>[5]</sup> interactions in solid state dispersions: simple eutectic mixtures, solid solutions,<sup>[6]</sup> glass solutions of suspension,<sup>[7,8]</sup> compound or complex formations between the drug and the carrier,<sup>[8]</sup> amorphous precipitations of a drug in a crystalline carrier.<sup>[9]</sup> Polyvinyl pyrrolidone K30 is most commonly used as a carrier in the solid dispersion system.

## MATERIALS AND METHODS

Terbinafine HCl sample from FDC Limited; Verna Industrial Estate Verna Goa, Polyvinyl pyrrolidone K30

was purchase in the market; all the chemicals were A.R. Grade.

### Preparation of physical mixture and solid dispersions

Physical mixtures were prepared by mixing the appropriate amount of Terbinafine HCl and Polyvinyl pyrrolidone K30 in pestle and mortar and passed through sieve # 60. Solid dispersions were prepared by solvent evaporation method. The carrier and adding amounts of Terbinafine HCl corresponding to ratio 1:1, 2:1, 3: 1 and 5:1 was accurately weighed and mixed properly. This physical mixture was solubilized in a common solvent that is in methanol (25 ml). The solvent was allowed to evaporate in hot air oven at 45°C ± 10°C. The process of evaporation was opted until the constant weight was obtained. This formulation was kept in dessicator for 24 h under vacuum. Then, solid dispersion formulation was pulverized using a porcelain mortar and pestle. The pulverized powder was classified using the sieves (size 60 # and 120 # mesh) and the particle size fraction of 100-250 mm was used for the study [Table 1].

### Estimation of terbinafine HCl

Terbinafine hydrochloride<sup>[10]</sup> was estimated at 283.2 nm using UV spectrophotometer (Shimadzu-1700). Standard curve for the estimation was prepared in 20% v/v methanolic citrate buffer pH 3.0 in concentration of 5-40 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R<sup>2</sup>) – 0.9999. The graph obeyed the Beer-Lambert's law in the selected concentration range.

#### Address for correspondence:

Dr. Narendra Kumar, Institute of Pharmacy, Bundelkhand University, Jhansi, UP, India.

### Phase solubility study

Solubility studies were performed according to the Higuchi<sup>[11]</sup> and Connors method. An excess amount of Terbinafine hydrochloride was placed in to 50 ml flask containing different concentration of polyvinyl pyrrolidone K30 in 25 ml distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent lose. The flasks were kept in the incubator shaker for 72 h. After 72 h the content of each flask was then filtered through Whatman filter paper; the filtrate was diluted and assayed spectrophotometrically (Shimadzu 1700 UV spectrophotometer) for Terbinafine HCl content at 283.2 nm. All solubility measurements were performed in triplicate [Figure 1].

### Drug loading

The dispersion system equivalent to 25 mg of Terbinafine hydrochloride was taken in 25 ml volumetric flask and dissolved in citrate buffer (pH = 3.0). The volume was made up to the mark with citrate buffer (pH = 3.0) and filtered. One ml of filtrate was further diluted to 10 ml with citrate buffer (pH = 3.0) and absorbance was recorded at 283.2 nm. The amount of drug in each dispersion system was determined spectrophotometrically [Table 1].

### *In vitro* drug release

*In vitro* release rate of Terbinafine hydrochloride solid dispersion of different samples was determined using single station USP dissolution test apparatus. The dissolution medium consisted of citrate buffer with pH 3.0 was used.

Samples of drug, solid dispersion equivalent with 100 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium at 37°C. Aliquots of 2 ml were withdrawn at regular intervals of time i.e. (5,10,15,20, up to 120 min) and the same is replaced with fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper no. 1. The filtrate was diluted up to 6 ml with citrate buffer (pH = 3.0). Then the absorbance was measured at 283.2 nm.

### Fourier transform infrared spectroscopy

FT-IR spectra (500-4000 cm<sup>-1</sup>) were obtained on a Nicolet Avatar 37- DTGS FT-IR spectrophotometer (Nicolet) with a resolution of 4 cm<sup>-1</sup>. KBr pellets were prepared by gently mixing 1 mg sample with 200 mg potassium bromide.

### Differential scanning calorimetry

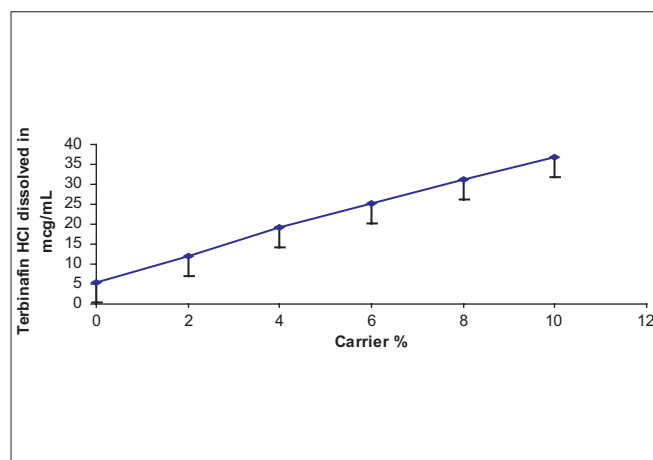
Differential scanning calorimeter measurements were carried out using a thermal analysis instrument USA-2910-MDS DSC equipped with a liquid nitrogen sub ambient accessory. Samples (2-6 mg) were accurately weighed in aluminum pans, hermetically sealed and subsequently scanned at 1°C/min under nitrogen gas purge [Figure 2].

### X-ray diffraction

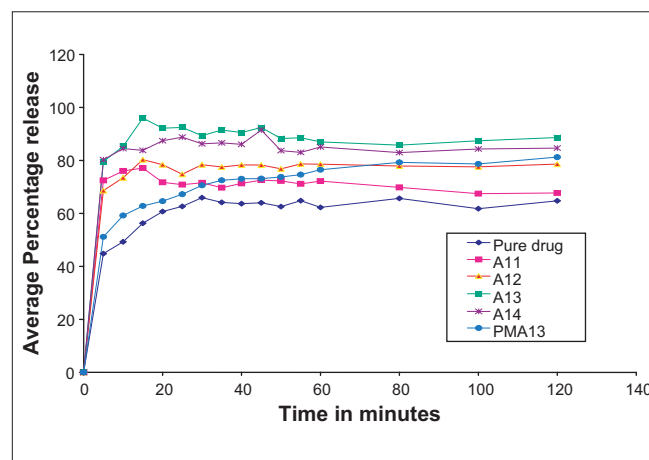
Diffraction patterns were obtained at room temperature on a Philips PW 1710 Diffractometer (Philips, Holland). Samples were exposed to Cu Ka radiation, wavelength 1.54060 Å through 1 × slits from 5.025 to 59.685 2θ with a step size

**Table 1: Coating composition, preparation method, and drug content of solid dispersion.**

Carrier	Product name	Drug (mg)	Carrier (mg)	Ratio of drug to carrier	Drug content (%)	Preparation and method
Polyvinyl pyrrolidone K30	A11	1500	1500	1:1	98 ± 4.32	Solvent evaporation
Polyvinyl pyrrolidone K30	A12	1000	2000	1:2	91 ± 1.06	Solvent evaporation
Polyvinyl pyrrolidone K30	A13	750	2250	1:3	86 ± 3.12	Solvent evaporation
Polyvinyl pyrrolidone K30	A15	500	2500	1:5	83 ± 1.59	Solvent evaporation
Polyvinyl pyrrolidone K30	PMA13	500	1500	1:3	96.2 ± 2.09	Physical mixture



**Figure 1:** Solubility diagram of terbinafine HCl in water at 27°C in presence of carrier (polyvinyl pyrrolidone K30)



**Figure 2:** Release profile of terbinafine HCl from different terbinafine HCl - polyvinyl pyrrolidone K30 solid dispersions in distilled water at 37°C

of  $0.60^\circ 2\theta$  and a count time of 1 sec. per step; the generator was set to 40 kV and 30 mA.

## RESULTS AND DISCUSSIONS

### Solubility studies

The Solubility of terbinafine HCl in distilled water at  $27^\circ\text{C}$  was found to be  $5.32\ \mu\text{g/mL}$ . The influence of polyvinyl pyrrolidone K30 upon the solubility of Terbinafine HCl is presented in [Figure 1] and shows the solubility of terbinafine hydrochloride first increases and thereafter a decrease was observed [Figure 1].

### *In vitro* dissolution studies

Terbinafine HCl release from the solid dispersion and alone was studied in citrate buffer (pH 3.0) up to 2 hours. The average percentage release of the pure terbinafine HCl was found to be 64% in 2 hours. In the solid dispersion formulation using Polyvinyl pyrrolidone K30 as carrier the dissolution rate increased with increased amount of Polyvinyl pyrrolidone K30. The best results among solid dispersions with Polyvinyl pyrrolidone K30 were obtained from the formulation A13 [Figure 2]. The increased dissolution rate may be due to the higher solubility of PVP in dissolution medium and better wettability of Terbinafine hydrochloride in the formulation.

**Table 2: FT-IR peaks of pure terbinafine HCl, polyethylene glycol 6000, solid dispersion of terbinafine HCl and polyethylene glycol 6000.**

Description	Characteristic peaks ( $\text{cm}^{-1}$ )
Terbinafine HCl	3040.94, 2968.26, 2863.67, 2444.93, 2223.76, 1262.32, 958.83 and 777.13
Polyvinyl pyrrolidone K30	2955.39, 1662.12 and 3433.66 (broad band)
Terbinafine HCl and polyvinyl pyrrolidone K30	3040.94, 2968.26, 2863.67, 2444.93, 2223.76, 1262.32, 958.83 and 777.13 2955.39, 1662.12 and 3433.66

On further increasing the amount of Polyvinyl pyrrolidone K30 (A15), the dissolution rate slightly decreased that may be due to the higher amounts of carrier itself takes time to dissolve [Figure 2].

### Fourier transform infrared spectroscopy

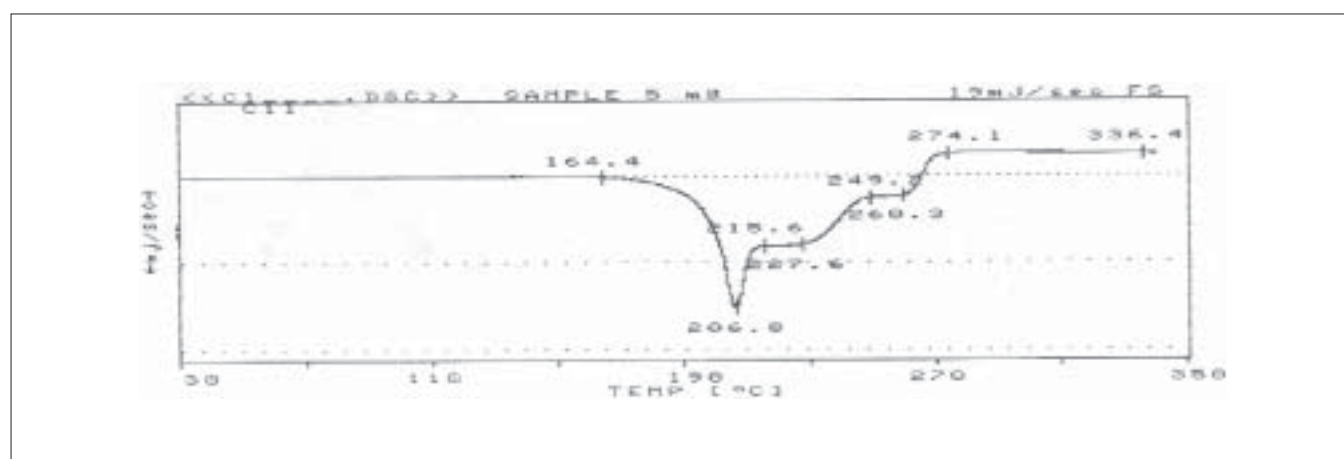
FT-IR studies were done to detect the possible interactions between the Terbinafine hydrochloride and Polyvinyl pyrrolidone K30 in the solid dispersion leading to crystalline state with Polyvinyl pyrrolidone K30. The characteristic peaks of Terbinafine hydrochloride, Polyvinyl pyrrolidone K30, physical mixtures and their formulations are given in table 1. Comparing the spectra of physical mixtures with those of solid dispersions prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state between Polyvinyl pyrrolidone K30 with Terbinafine HCl under investigation [Table 2]. The absence of any significant change in the IR spectral pattern of drug-polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

### Differential scanning calorimetry

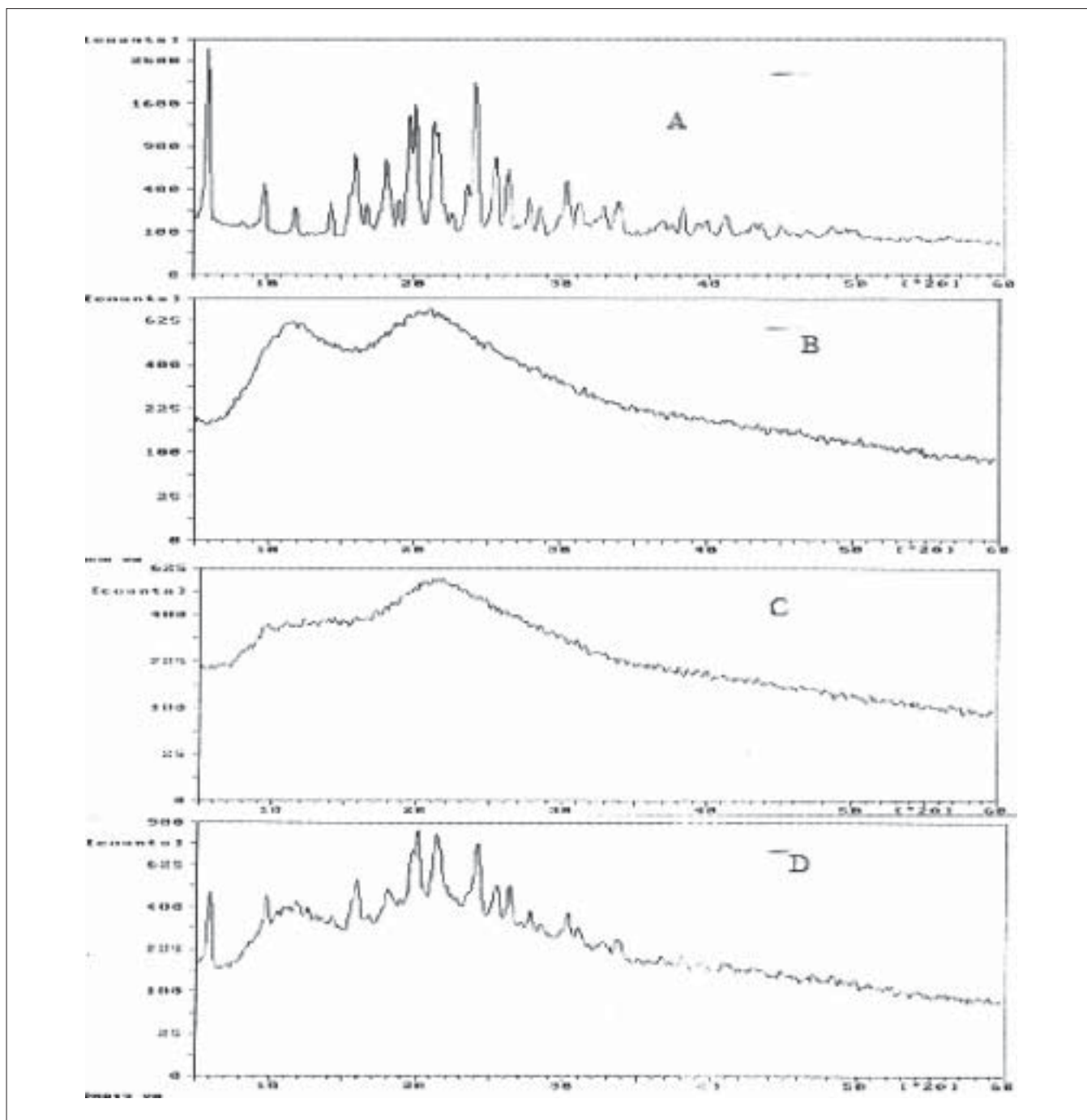
Differential scanning calorimetry shows sharp endothermic fusion peak at  $206.8^\circ\text{C}$ , which is corresponding to the melting point of Terbinafine HCl [Figure 3].

### Powder X-ray diffraction study

The diffraction spectra of Terbinafine HCl and Polyvinyl pyrrolidone K30 show numerous distinct peaks indicating that both are present in a highly crystalline state [Figure 4A, B]. The spectras of polyvinyl pyrrolidone K30 and terbinafine HCl formulation treated by fusion method are identical. The PXRD pattern of solid dispersion of sample A13 [Figure 4C] exhibits all the characteristic diffraction peaks of Polyvinyl pyrrolidone K30 and crystalline Terbinafine HCl, but of lower intensity. This study reveals that some Terbinafine HCl still exists in the crystalline state in the solid dispersion



**Figure 3:** Differential scanning calorimetry of terbinafine HCl



**Figure 4:** XRD of (A) Pure terbinafine HCl, (B) Polyvinyl pyrrolidone K30, (C) Solid dispersion of terbinafine HCl and polyvinyl pyrrolidone K30 and (D) Physical mixture of terbinafine HCl and polyvinyl pyrrolidone K30)

and that, at this concentration (25%), the proportion of the drug may equal or exceed its solid solubility. Comparison of the ratios of the intensities of the lines of solid dispersion formulation with the corresponding to physical mixtures reveals that the crystallinity of Terbinafine HCl is reduced in Polyvinyl pyrrolidone K30 and Terbinafine HCl formulation [Figure 4]. The reduction in crystallinity appears in solid dispersions independent of the solid dispersion preparation method used.

## CONCLUSION

The study clearly shows that addition of Polyvinyl pyrrolidone K30 to Terbinafine HCl improved its dissolution rate. Mechanisms involved are solubilization and improved wetting of the drug in the Polyvinyl pyrrolidone K30 rich micro-environment formed at the surface of drug crystals after dissolution rate compared with physical mixtures. No solid solution formation and no hydrogen bonding interaction

between Polyvinyl pyrrolidone K30 with Terbinafine HCl could be detected. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. Polyvinyl pyrrolidone K30.

## REFERENCES

1. Sweetman CS. Martindale the complete drug reference, 33<sup>rd</sup> ed. Pharmaceutical Press; 2002. p. 394.
2. USP DI, III, Chemistry and Compendial requirements. 449-50.
3. Drug Information Antifungal antibiotics, AHFS; 2001. p. 126-8.
4. Kushida I, Ichikawa M, Asakawa N. Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by preparing solid dispersion. *J Pharm Sci* 2002;91:258-66.
5. Chiou WL, Riegelman S. Pharmaceutical applications of Solid dispersion systems. *J Pharm Sci* 1971;60:1281-302.
6. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures: II, Experimental evaluation of a eutectic mixture: Urea-acetaminophen system. *J Pharm Sci* 1966;55:482-7.
7. Stupak EI, Bates TR. Enhanced absorption of digitoxin from orally administered digitoxin-polyvinylpyrrolidone coprecipitates. *J Pharm Sci* 1978;62:1806-9.
8. Geneidi AS, Ali AA, Salama RB. Solid dispersions of nitrofurantoin, ethotoin, and coumarin with polyethylene glycol 6000 and their coprecipitates with povidone 25000. *J Pharm Sci* 1978;67:114-6.
9. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, *et al.* Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm* 2003;267:79-91.
10. El-Sahraty HN, Metwally FH. Simultaneous determination of Terbinafine HCl and Triamcinolone acetonide by UV derivative spectrophotometry and spectrodensitometry. *J Pharm Biomed Anal* 2002;28:569-80.
11. Higuchi T, Connors KA. Phase-solubility techniques. *ADV Anal Chem Instrum* 1965;4:117-210.

**Source of Support:** Nil, **Conflict of Interest:** None declared.