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FORMULATION DEVELOPMENT AND EVALUATION OF NIFEDIPINE SOLID DISPERSION

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ABSTRACT

Solid dispersion consists of a microcrystalline dispersion of a poorly soluble drug in a matrix consisting of physiologically inert, readily soluble carrier. In this study, an attempt was taken to enhance the solubility and dissolution characteristics of Nifedipine, poorly water soluble calcium channel blocking agent, by preparing solid dispersions with water soluble carriers. Polyethylene glycol (PEG)6000 and Urea by fusion method. The interaction between drug and carrier were characterized by IR spectroscopic studies. The IR results showed no interactions between the drug and carrier. The prepared solid dispersions were evaluated for various parameters such as percentage yield, drug content determination, solid dispersion efficiency and dissolution studies. Drug loading in solid dispersions was found Uniform and they produced satisfactory results on drug content analysis. *In vitro* dissolution study showed that all the formulations were found to be effective in improving the dissolution of nifedipine to several folds when compared with the pure drug. In conclusion PEG 6000 was found to be the most effective carrier to enhance the dissolution behavior of nifedipine.

KEY WORDS: Fusion method, Nifedipine, Polyethylene glycol, Solubility, Urea.

INTRODUCTION

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve increased dissolution rate, altered solid state properties, and enhanced release of drugs from ointment, suppository bases, improved solubility and stability. By increasing the dissolution rate in the gastro intestinal tract, the rate

of absorption can be increased. Many water soluble carriers such as mannitol, citric acid, Beta-cyclodextrin, succinic acid, polyvinyl pyrrolidine, urea and PEG have been used in the formulation of solid dispersion. [1, 2]

Nifedipine is a potent vasodilator used in the management of hypertensive emergencies particularly in patients with impaired renal efficiency during pregnancy and also used as a single drug in hypertensive patients with diabetes mellitus, as it does not affect the secretion of glucoregulatory hormones. [3] It acts as an efficient calcium channel blocker. Nifedipine is practically insoluble in water. Because of its poor aqueous solubility, conventional Nifedipine dosage forms shows absorption problem and its dissolution is considered to be rate determining step in its absorption from gastro- intestinal tract**.** The dispersion method allows the preparation of physically modified forms of the drug which are much more rapidly soluble in water than the pure compound. [4]

So to increase the solubility, dissolution rate and absorption it was aimed to formulate solid dispersion of Nifedipine by incorporating the drug with hydrophilic carriers such as Polyethylene glycol 6000 and Urea. In the present work, four formulations of Nifedipine solid dispersions(F_1-F_4) were prepared using two hydrophilic carriers such as Poly ethylene glycol 6000 and urea in the drug carrier ratio 1:1 and 1:2 by fusion method.

MATERIALS AND METHODS

Materials

Nifedipine was obtained from Quzer pharma, Gujarat, India. Polyethylene Glycol was procured from S.D Fine Chem Limited, Mumbai and Urea was procured from Chemspure, Chennai. India. All other reagents used were of analytical grade.

Methodology

Preparation of Nifedipine Solid dispersion[5]

Solid dispersion of Nifedipine with polyethylene glycol 6000 and urea in the ratio of 1:1 and 1:2 were prepared by fusion method. Accurately weighed amount of Polyethylene glycol 6000 was melted in a porcelain dish and to this calculated amount of Nifedipine was added with thorough mixing for 2-5minutes followed by quick cooling. The resulting products were dried in vacuum dessiccator for 24 hours. The dried preparations were passed through sieve No: 40.Final products were then stored in air tight containers for further studies. Similarly the above procedure was repeated with urea as carrier. The composition of different formulations of nifedipine solid dispersion is listed in Table 1.

Table 1- Composition of Nifedipine Solid dispersion Formulations

Formulation code	Drug: Carrier ratio	Quantity of		
		Drug	PEG6000	Urea
F_1	1:1	1g	1g	-
F_2	1:2	1g	2g	-
F_3	1:1	1g	-	1g
F_4	1:2	1g	-	2g

IR Spectral Analysis

IR spectra is used to study the interactions between the drug and carrier.[6] The drug and carrier must be compatible with one another to produce a stable, efficacious and safe product.IR spectral analysis of pure drug ,PEG 6000 ,Urea and combinations of drug carrier in highest proportions were carried out. The peaks and spectrum produced by the pure drug was compared with the peaks and spectrum produced by the combination of the drug and carrier. Drug and finely powdered sample is mixed with 100 parts of potassium bromide (KBr PRESS PELLET METHOD) and made in to a fine powder. [7] A small amount of finely powdered mixture is compressed under very high pressure in a press to form a small transparent pellet. The resulting pellet was introduced into IR radiation to get a spectrum.

Evaluation of Solid Dispersions of Nifedipine

Percentage Yield [8]

The percentage yield of various batches were calculated using the weight of final product after drying with respect to the initial total quantity of the drug and carrier used for preparation of solid dispersion. Percentage yield was calculated as per the formula mentioned below.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Estimation of Drug Content[9]

Nifedipine content in the solid dispersion was estimated by UV spectrophotometric method based on the measurement of absorbance at 235nm in Phosphate buffer solution pH7.4. 100mg of solid dispersion of Nifedipine was placed in 100ml volumetric flask, shaken and made up to the volume using methanol. From this, 10ml was pipetted out to 100ml volumetric flask and the volume was made up to the mark using phosphate buffer solution pH7.4.Again from this,10ml was pipetted out to 100ml volumetric flask and volume was made up to the mark using phosphate buffer solution pH7.4.The absorbance of the resulting solution was analyzed for Nifedipine content spectrophotometrically at 235nm.

Solid dispersion Efficiency[10]

Solid dispersion efficiency was calculated using the formula:

$$\text{Solid dispersion efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

***In Vitro* drug release studies** [11]

In vitro drug release of Nifedipine from solid dispersion was carried out by using USP Type – I dissolution test apparatus. 900ml of simulated intestinal fluid (Phosphate buffer, pH 7.4) was used as dissolution medium and the study was carried out for 60 min. A quantity of drug loaded solid dispersion equivalent to 20mg of Nifedipine was filled in empty capsule shell and placed in the basket and the basket was rotated at 50rpm. Bath temperature was maintained at 37±0.5˚C throughout the study. Aliquots of sample (10ml) were withdrawn at every 10 minutes. Samples withdrawn were replaced with equal volumes of the dissolution medium. The absorbance of samples was measured using UV Double beam spectrophotometer at 235nm after suitable dilution with the buffer. *In vitro* release studies of pure Nifedipine was carried out in similar manner and the results were compared.

RESULTS AND DISCUSSION

Formulation of solid dispersion of Nifedipine was aimed to increase the solubility of drug. Solid dispersion of Nifedipine with a carrier PEG 6000 and Urea could be prepared by fusion method in the drug, carrier ratio 1:1 and 1:2.

FT-IR studies were carried out to determine any interaction between drug and carrier. The IR spectral studies of pure nifedipine, urea, PEG 6000 and combinations containing highest proportion of nifedipine and urea, nifedipine and PEG 6000, were carried out to check the compatibility of the drug with carrier.

The IR spectra of nifedipine, urea, PEG 6000 and their combinations were shown in figure1 to 5. When characteristic peaks of nifedipine was compared with combination of nifedipine with urea and nifedipine with PEG6000, it was found that the same peaks were present in drug- carrier combination with negligible difference, indicating that there was no interaction between nifedipine with urea and PEG6000.

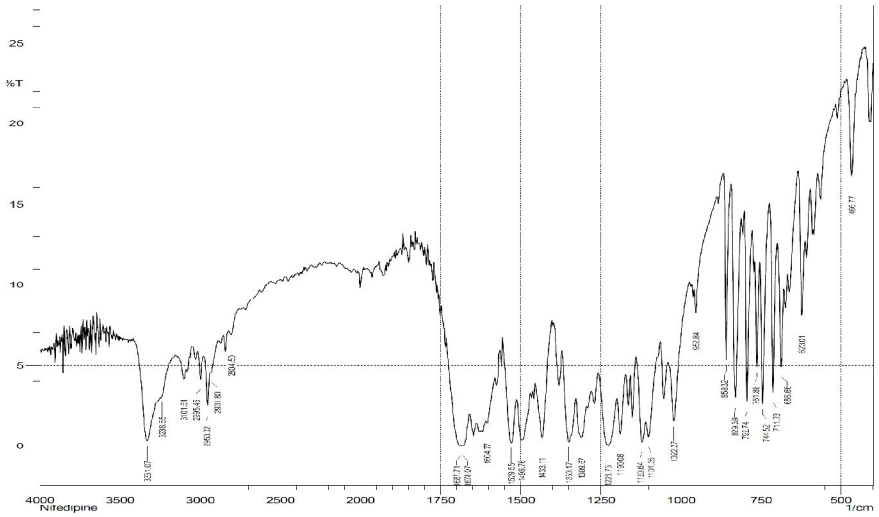

Fig 1- IR Spectrum of Pure Nifedipine

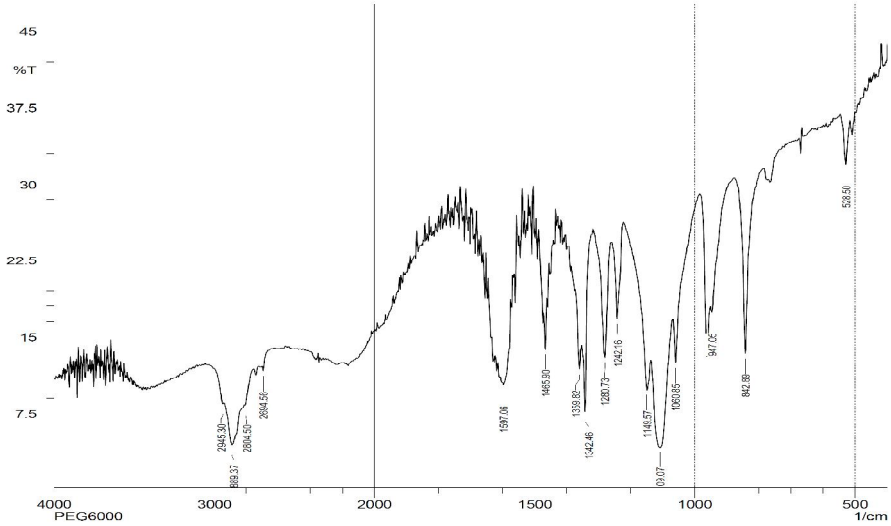

Fig 2- IR Spectrum of PEG 6000

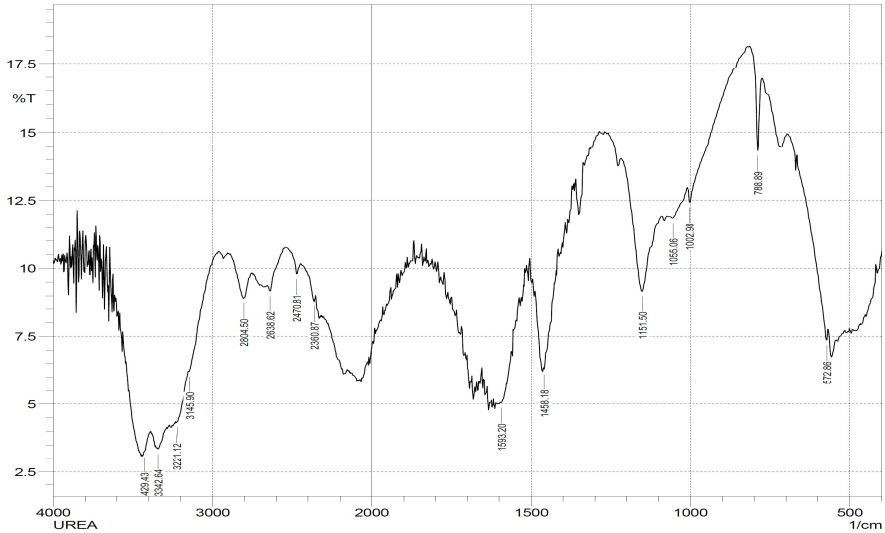

Fig 3- IR Spectrum of Urea

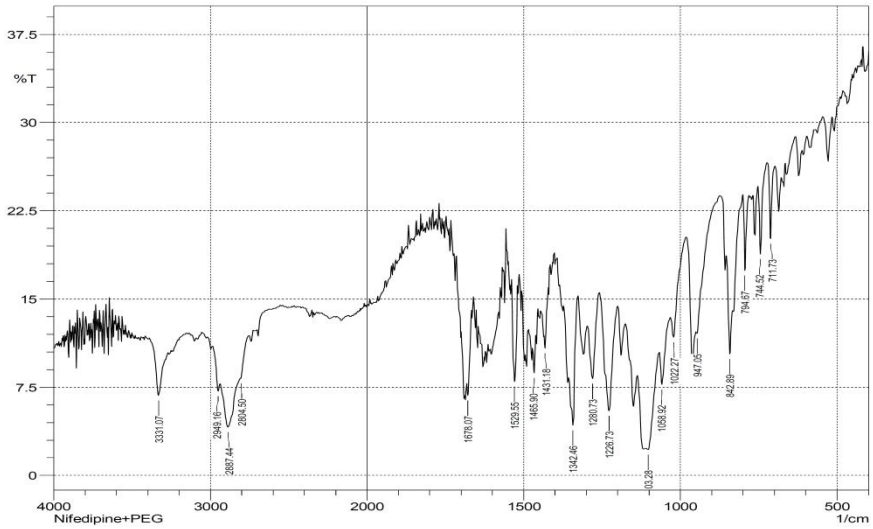

Fig 4- IR Spectrum of Nifedipine + PEG6000

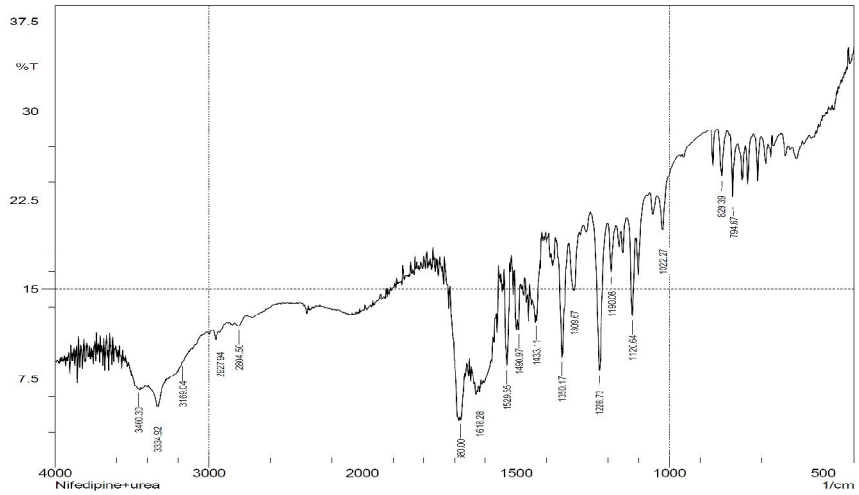

Fig 5- IR Spectrum of Nifedipine + Urea

Percentage yield of solid dispersions were found to be satisfactory. The formulation F_2 showed maximum yield. A decrease in percentage yield of solid dispersion in 1:1 ratio was observed. The reason may be sticking of substance to the wall of the china dish during solid dispersion formation. Drug content in different formulations were estimated by UV spectrophotometric method. Three samples were tested from each batch and the drug content was determined. The standard deviations among the three values are found to be small. This indicates that the drug was distributed almost uniformly throughout in the batch of solid dispersions. The solid dispersion efficiency was found in the range of to 60%±1.5 to 80%±1.1.The rank order of solid dispersion efficiency of various formulations was found to be as follows: F_1> F_2>F_3>F_4.The results of percentage yield, drug content and solid dispersion efficiency are given in Table.2.

Table 2-Evaluation of Nifedipine Solid dispersion formulations

Formulation Code	Percentage yield (%)	Drug content (mg)		Solid dispersion efficiency (%)
		Theoretical	Practical	
F_1	96.5	50.00	40±1.1	80±1.1
F_2	97	33.33	26±2.3	78.01±2.3
F_3	86.5	50.00	32±1.3	64±1.3
F_4	88	33.33	20±1.5	60±1.5

All the Values Are Expressed As Mean ± Standard Deviation; N=3

Nifedipine release from solid dispersion formulations were studied in phosphate buffer solution, pH 7.4 (Simulated intestinal fluid) for 60 min. The results revealed that Nifedipine solubility rate was increased in solid dispersion formulations. Drug release varied with varying proportion of carrier. Solid dispersion of Nifedipine in 1:2 ratio showed greater drug release than 1:1 ratio. This may be due to increased carrier content. A rapid drug release was observed in Solid dispersion formulations prepared using PEG6000 compared to Urea as carrier. After 1 hour of dissolution, pure drug powder released only 44.1% nifedipine, whereas 83.7%, 90.9%, 62.1% and 72.9% drug were released from formulations F_1, F_2, F_3, and F_4. This showed that the dissolution rate of Nifedipine has improved markedly by solid dispersion formulations. Hence the prepared Solid dispersions improved the dissolution characteristics of Nifedipine as evidenced from the drug release study. The *in vitro* release profile of Nifedipine formulations were shown in Fig.6.

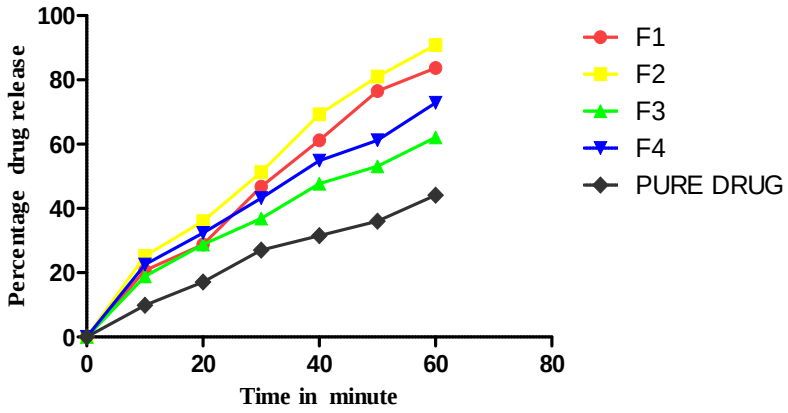

Fig 6- *In vitro* release profile of Nifedipine formulations

CONCLUSION

The solid dispersion formulations were easy to prepare, and found to be homogeneous. The IR spectral studies revealed that there was no interaction between drug and carrier. The dissolution study showed that maximum increase in dissolution rate was observed in solid

dispersion formulations compared to pure nifedipine. Solid dispersion of nifedipine prepared using PEG6000 as carrier showed rapid drug release compared to urea as carrier. From all the parameters studied, it can be concluded that, preparation of Nifedipine solid dispersions may be an effective strategy to increase the solubility and dissolution rate of Nifedipine thereby the absorption of drug can be improved which could maximize the bioavailability and therapeutic efficacy of drug.

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