Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Formulation and Dissolution Studies of Solid Dispersions of Nifedipine

*K. NAGARAJAN[1], M. GOPAL RAO[2], SATYAJIT DUTTA[1], R. PAVITHRA[3], G. SWETHA[3]

[1]Division of Bio-Medicinal Chemistry R&D Laboratory, Dept. of Pharmacy, IIMT College of Medical Sciences, 'O' Pocket, Ganga Nagar, Mawana Road, Meerut-250001, Uttar Pradesh.

[2] Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore- 641044, Tamilnadu.

[3]Division of Bio-Medicinal Chemistry R&D Laboratory, Periyar College of Pharmaceutical Sciences, Tiruchirapalli-620021, Tamilnadu.

ARTICLE DETAILS

Article history:
Received on 22 October 2009
Modified on 25 June 2010
Accepted on 12 July 2010

Keywords:
Nifedipine
Polyethyleneglycol
Antianginal
Tolbutamide

ABSTRACT

Nifedipine is a water insoluble antianginal drug and its dissolution rate from solid dispersion was affected largely by the carrier concentration. The common solvent evaporation method and melting fusion method were used for the preparation of solid dispersion in different ratios (9:1, 3:1, 1:1, 1:3, 1:9) using polyethyleneglycol (PEG 4000) to enhance the solubility of drugs. The interaction between drug and carrier were characterized by TLC and IR spectroscopic studies. The R_f value of prepared dispersions was similar to that of the pure drug (0.18) in UV_{254} nm light. No extra spots were detected which indicated that there was no interaction between the drug and carrier. In addition, the IR result of the prepared dispersions showed no interactions between the drug and carrier. Hence the prepared solid dispersions improved the dissolution characteristics of Nifedipine as evidenced from the reported results.

INTRODUCTION

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[1]. It acts as an efficient calcium channel blocker.

Nifedipine is practically insoluble in water. 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[2]. The influence of various excipients, such as poly vinyl pyrrolidine (PVP), poly ethylene glycol (PEG), Sorbiton mono laurate, 1, 2-propanedoil, ethanol and PEG-200 has been investigated already and found that, poly ethylene glycol (PEG) coprecipitates seemed to be stable under all conditions[3, 4]. It was also reported that the enhanced solubility of the tolbutamide[5, 6] was observed in solid dispersion of PEG 4000 and 6000.

Chiou and Riegelman[7], recommended polyethylene-glycol, a water soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs.

Author for Correspondence:
Email: nagarajan_mph@yahoo.co.in

They reported that the dissolution rate of griseofulvin, as well as its absorption and total availability in both dog and man significantly were higher when the solid was dispersed in PEG 4000, 6000 or 2000 as compared to the traditionally micronized forms of the drug [8, 9].

Most of the drugs studied proved to be stable at the temperature of the polymer-drug melt and therefore the fusion method was used. However, in case of cardiovascular drug digitoxin, a sign of thermal degradation was observed and accordingly the authors recommended for the use of solvent method. Similarly Nifedipine on exposure to light, high temperature and presence of oxidizing agents yield predominantly two degradation products[10]. Such flexibility demonstrated the advantages of solid dispersion techniques over the eutectic mixture method where fusion is utilized[11, 12].

Our objective is to investigate both the above mentioned methods of solid dispersion for drawing conclusion in improving the rate of dissolution, absorption and therapeutic efficiency of drugs.

MATERIALS AND METHODS

Solid dispersions of Nifedipine were prepared using the carrier PEG 4000 by melting fusion method and solvent evaporation method. After initial trials with different ratios of the carriers, the drug carrier ratios were selected in the following manner.

The physical mixture of Nifedipine and PEG 4000 in the ratios of 1:9, 1:3, 1:1, 3:1, 9:1 were obtained by mixing the drugs and carrier which was heated directly until it is

melted. The melted mixture was then cooled and solidified rapidly in an ice-bath with vigorous stirring. The final solid mass was crushed, pulverized and sieved.

In case of solvent evaporation method, chloroform was used as a solvent. The physical mixture of Nifedipine and PEG 4000 in the ratios 1:9, 1:3, 1:1, 3:1, 9:1 were obtained by mixing the drug and carrier which was dissolved in chloroform to get a clear solution. The solvent was then removed by evaporation at 40 °C under reduced pressure (8 mm Hg. Atm.). The mass obtained was crushed, pulverized and sifted through sieve no. 100.

Characterization:

The intactness of the drug in the formulation was evaluated by TLC, using chloroform: diethylamine : cyclohexane (60:15:75) as the solvent system and pure Nifedipine as the reference sample. The drug was detected by visualizing the TLC plates in UV Chamber at Shorter wavelength (254 nm) and longer wavelength (365 nm)[13]. The substance appears at R_f value of 0.18 as yellow spot in UV_{254} nm.

The infra red spectrum of pure Nifefidine was compared with the spectrum obtained with Nifedipine and PEG in different ratios with a Perkin-Elmer 1420 ratio recording infrared spectrophotometer from a KBr pellet[14]. The structural assignments were correlated for NH stretching vibrations (3331 cm^{-1}), CH-aromatic (3102 cm^{-1}), CH aliphatic (2931-2842 cm^{-1}), C=O ester (1689-1679 cm^{-1}), -C=C aromatic (1625-1574 cm^{-1}), NO_2 (1530 cm^{-1}), -C-CH_3 (1380 cm^{-1}) and -C-O ester (1121 cm^{-1}) respectively with band frequencies.

Dissolution Studies:

900 ml of 0.1 N HCl was used as dissolution medium. Dissolution studies of the pure drug (20 mg) and solid dispersion sample equivalent to 20 mg of Nifedipine was taken in a gelatin capsule and used in each test. The stirrer was adjusted to rotate at 50 rpm, at a temperature of 37.0 ± 1 °C and maintained constantly throughout the experiment. A 5 ml aliquot liquid of dissolution medium was drawn at various time intervals and the same was replaced with fresh quantity of dissolution medium. The samples withdrawn were suitably diluted and assayed for Nifedipine by measuring the absorbance at 238 nm using SL 151 PC based UV-visible Spectrophotometer.

RESULTS AND DISCUSSIONS

Solid dispersions were prepared by using the drug Nifedipine and the carrier PEG 4000 in different ratios (9:1, 3:1, 1:1, 1:3, 1:9) by melting fusion method and solvent evaporation method. In both the methods used, the rate of dissolution was increased as the carrier concentration increased. The efficiency of carrier in various ratios in improving the dissolution of Nifedipine is in the following order,

10:90 > 25:75 > 75:25 > 90:10

(Drug : carrier)

Further, the prepared dispersions were resolved into clear yellow spots with R_f value similar to that of pure drug (0.18) in UV_{254} nm light. No extra spots were detected which indicated that there was no interaction between the pure drug and carrier.

The IR band frequencies obtained from the drug and carrier matches with the spectra of pure drug alone and the studies clearly indicates that there is no interaction between the drug and carrier irrespective of different methods used for preparing dispersions. Hence, it can be concluded that the solid dispersions prepared by both solvent evaporation and melting fusion method improved the dissolution characteristics of Nifedipine. In specific, the solvent evaporation method shows better dissolution and enhanced bioavailability with the studies conducted as from Table 1 and 2.

Table 1: Dissolution of Nifedipine from Nifedipine-PEG 4000 Solid Dispersions of Different Drug Carrier Ratios (Melting Fusion Method)

Sl. No.	Time (Min)	Percentage of Nifedipine Dissolved Form					
		Physical Mixture	A 9 : 1	B 3 : 1	C 1 : 1	D 1 : 3	E 1 : 9
1	0	0	0	0	0	0	0
2	5	23.85	19.35	20.25	22.95	23.40	27.00
3	10	33.75	23.40	27.45	27.45	32.85	51.75
4	15	40.5	31.95	42.75	42.75	54.90	67.95
5	30	47.25	42.30	51.75	65.25	70.20	76.50
6	45	55.35	49.95	65.70	73.35	74.25	83.25
7	60	67.50	55.35	72.90	81.00	85.95	92.25

Table 2: Dissolution of Nifedipine from Nifedipine-PEG 4000 Solid Dispersion of Different Drug Carrier Ratios (Solvent Evaporation Method)

Sl. No.	Time (Min)	Percentage of Nifedipine Dissolved Form					
		Physical Mixture	A 9 : 1	B 3 : 1	C 1 : 1	D 1 : 3	E 1 : 9
1	0	0	0	0	0	0	0
2	5	23.85	20.25	20.70	22.50	23.40	27.00
3	10	33.75	27.00	29.25	31.50	36.45	51.75
4	15	40.5	42.30	47.25	51.75	51.75	68.40
5	30	47.25	49.50	56.25	69.75	69.75	76.95
6	45	55.35	54.90	67.95	78.75	78.5	86.40
7	60	67.50	63.45	78.75	83.25	87.75	94.95

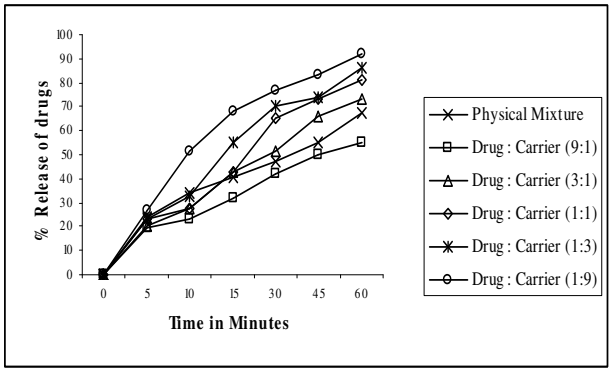

Figure 1: Dissolution of Nifedipine from Nifedipine-PEG 4000 Solid Dispersions of Different Drug Carrier Ratios (Melting Fusion Method)

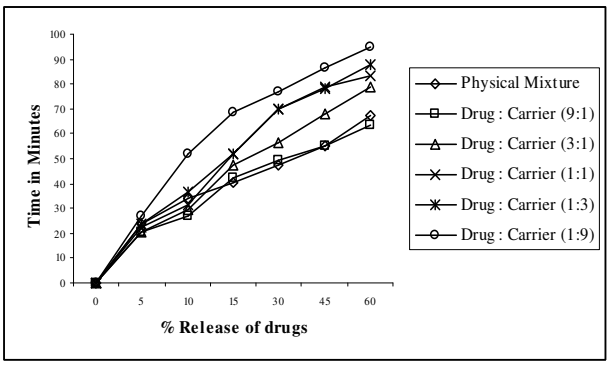

Figure 2: Dissolution of Nifedipine from Nifedipine-PEG 4000 Solid Dispersion of Different Drug Carrier Ratios (Solvent Evaporation Method)

ACKNOWLEDGEMENT

The authors are very much thankful to Dr. T. K. Ravi, Principal, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamilnadu for his constant encouragement & continuous support throughout the project work.

REFERENCES

[1] Satoskar RS, Bhandarkar SD, Ainapure SS. Pharmacology and pharmacotherapeutics. 19th ed. Mumbai: Popular Prakashan Ltd.; 2005. 379-383.

[2] Hamed MA. Bioavailability and bioequivalence. Pennsylvania: Mark Publishing Company; 1989. 272-276.

[3] Potter H, Hulm M. Assay of nifedipine and its by- and degradation products in the drug substance and dragees by liquid chromatography on formamide-saturated silica gel columns. Journal of Pharmaceutical and Biomedical Analysis. 1988; 6(1): 115-9.

[4] Grooff D, De Villiers MM, Liebenberg W. Thermal methods for evaluating polymorphic transitions in nifedipine. Thermochimica Acta. 2007 Feb; 454(1): 33-42.

[5] Miralles MJ, McGinty JW, Martin A. Combined water-soluble carriers for coprecipitates of tolbutamide. Journal of Pharmaceutical Sciences. 2006 Sep; 71(3): 302-4.

[6] Ali SL. Nifedpine, profiles of drug substances. *In* Florey K. ed. New York: Academic Press; 1989.

[7] Chiou WL, Riegalman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J. Pharm. Sci. 1969; 58 (12): 1505-10.

[8] Chiou WL, Riegalman S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 1971; 60 (9): 1281–302.

[9] Chiou WL, Riegalman S. Absorption characteristics of solid dispersed and micronized griseofulvin in man, J. Pharm. Sci. 1971; 60 (9): 1376-80.

[10] Yoshihisa M, Teraoka R, Sugimoto I. Comparative evaluation of photostability of solid-state nifedipine under ordinary and intensive light irradiation conditions. International Journal of Pharmaceutics. 1989 Sep; 54 (3): 211-21.

[11] Mehta AC, Hart-Davies S, Kay EA. In vitro dissolution studies on nifedipine capsules. J. Clin. Pharm. Ther. 1995; 20: 243-5.

[12] Pillay V, Fassihi R. A new method for dissolution studies of lipid-filled capsules employing nifedipine as a model drug. Pharmaceutical Research. 1999 Feb; 16(2): 333-7.

[13] Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. Int. J. Pharm. 1991; 67: 169–75.

[14] Florey K. Analytical profile of drug substances. New Delhi: Elsevier; 2005. 233-6.