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STUDIES ON SOLID DISPERSIONS OF NIFEDIPINE

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ABSTRACT

Nifedipine-Polyethylene glycol solid dispersions were prepared by melting or fusion method in order to improve nifedipine solubility in the aqueous body fluids. The dissolution rate of the drug was markedly increased in these solid dispersion systems. The increase in dissolution was a function of the ratio of drug to polyethylene glycol used and the molecular weight of polyethylene glycol. The dissolution rate was compared with a 10% w/w physical mixture of drug with polyethylene glycol.

The physical state of nifedipine after fusion was determined by X-ray crystallography on the pure drug and on the solidified melts. The X-ray diffraction studies indicated that nifedipine in the solid dispersion which was obtained by

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sudden cooling of the melt, was in the thermodynamically unstable metastable form. It was established that the slow cooling of the melt as well as powdering of solid dispersion resulted in the emergence of crystallinity.

The effect of aging on nifedipine-polyethylene glycol 6000 solid dispersions has been investigated. After storage at room temperature for six months, solid dispersions showed no change in the dissolution rate and the X-ray diffraction pattern showed slight enhancement in crystallinity.

INTRODUCTION

Solid dispersions of poorly soluble drugs with water soluble carriers increase drug dissolution and bioavailability[1]. Polyethylene glycols act as inert carriers inhibiting crystal growth and phase transformation along with improving dissolution rate of drug due to their rapidly water soluble nature.

Nifedipine, a calcium channel blocker, used in clinical practice as an antianginal, antihypertensive drug shows a very slight water solubility (11 mcg/ml at 37°C in distilled water[2]) and exhibits poor dissolution characteristics due to its poor wettability and dispersibility in the body fluids.

Because of limited aqueous solubility in the body fluids, the dissolution rate of the drug becomes the absorption rate limiting step. Therefore, an attempt has been made to modify the dissolution characteristics and thereby improve absorption rate. Solid dispersion technology methods, already employed by a number of authors[3] for improving the dissolution rate of many poorly water soluble drugs was utilized.

In this paper, the effects of cooling techniques and molecular weight of polyethylene glycol on drug dissolution

were investigated. The physical nature of drug in the solid dispersions was studied. The stability of nifedipine-polyethylene glycol 6000 solid dispersion systems was also studied.

EXPERIMENTAL

Materials

Nifedipine (Unichem Laboratories, India); Polyethylene glycol [PEG 4000, PEG 6000 (HICO Products, India)].

Methods

Preparation of Solid Dispersions

Solid dispersions consisting of nifedipine in various concentrations of PEG were prepared using the melting or fusion method clearly defined by Chio and Ringelman[4]. The samples corresponding to the weight fractions of 1, 5, 10, 15, 20 and 25 parts of PEG for one part of drug were prepared. Both the components were mixed in geometric proportion and roll mixed for ten minutes in a laboratory size mixer. The physical mixtures were heated directly on the hot plate at 70-80°C until completely melted. The fused mixtures were solidified by cooling with continuous stirring. Two types of cooling procedures were employed namely slow cooling at room temperature and quenching by immersion in a freezing mixture consisting of ice and sodium chloride. The solid dispersions were then stored for 24 hours in a dessicator containing fused calcium chloride. After hardening, the solidified melts were pulverized and sieved through a 100 mesh screen. Few solid dispersions were kept without powdering, in the slab form, and had dimensions of 2cm x 2cm x 2mm. The powders and slabs were immediately bottled in amber coloured glass containers and stored at room temperature until physical measurements could be made.

Physical mixture samples containing 10% w/w nifedipine with PEG were prepared by simple geometric mixing of these two pure components possessing the same particle size range (# 100).

Dissolution Rate Studies

Physical mixtures and solid dispersions of drug equivalent to 5mg nifedipine were filled in hard gelatin capsules No.4. The dissolution rate test on these capsules was carried in pH 6.2 phosphate buffer using USPXXI dissolution rate test equipment with the rotating basket assembly at 100 r.p.m. Aliquots of 10ml were withdrawn at 5, 10, 15, 20, 30 and 45 min and the drug content was analysed spectrophotometrically at 239 nm (Beckman DB model 25 spectrophotometer). $T_{50\%}$ and $T_{90\%}$ values were calculated.

Effect of PEG Molecular Weight on the Drug Release

Using PEG of two different molecular weights namely PEG 4000 and PEG 6000, solid dispersions and physical mixtures of nifedipine and PEG were prepared as described previously and evaluated by the dissolution rate test to study the effect of molecular weight of PEG on the dissolution rate of drug.

X-ray Diffraction Studies

An X-ray powder diffractometer (Philips X-ray generator PW1729 and automatic X-ray diffractometer model PW1710 unit) was used to determine the physical nature of nifedipine in the solid dispersions. Copper K_1 line from a sealed copper tube served as a source of radiation.

Powdered samples of nifedipine, PEG 6000 and physical mixture (10% w/w nifedipine in PEG 6000) were examined for comparison.

Thin Layer Chromatographic Studies

TLC studies were utilized for the detection of possible decomposition and chemical or physical changes that might have occured during the preparation of solid dispersions. The plates were developed by a solvent system of methanol : benzene (1:4) using iodine as detecting agent.

I.R. Analysis

Perkin-Elmer infrared spectrophotometer was used to obtain I.R. spectra of the pure drug and solid dispersions.

Stability Studies

Powdered samples were stored in glass bottles at room temperature for six months and the dissolution rates of the solid dispersions were determined. The X-ray diffraction patterns were also investigated during the tests.

RESULTS AND DISCUSSION

Dissolution parameters of pure drug nifedipine, PEG 6000 solid dispersions, PEG 4000 solid dispersions and physical mixtures are given in table-1 and figures 1 and 2.

The dissolution rate of the nonwetted, micronized nifedipine was very poor and during 45 min a maximum of about 50% drug was released ($T_{50\%}$ value = 47 min). The reason for poor dissolution of plain drug could be agglomeration of the particles and the poor wettability of drug leading to poor dispersion in the dissolution medium. Thus, unless steps are taken to assure appropriate dispersion and wetting, the administration of the micronized or fine particle of drugs may not produce the expected effect.

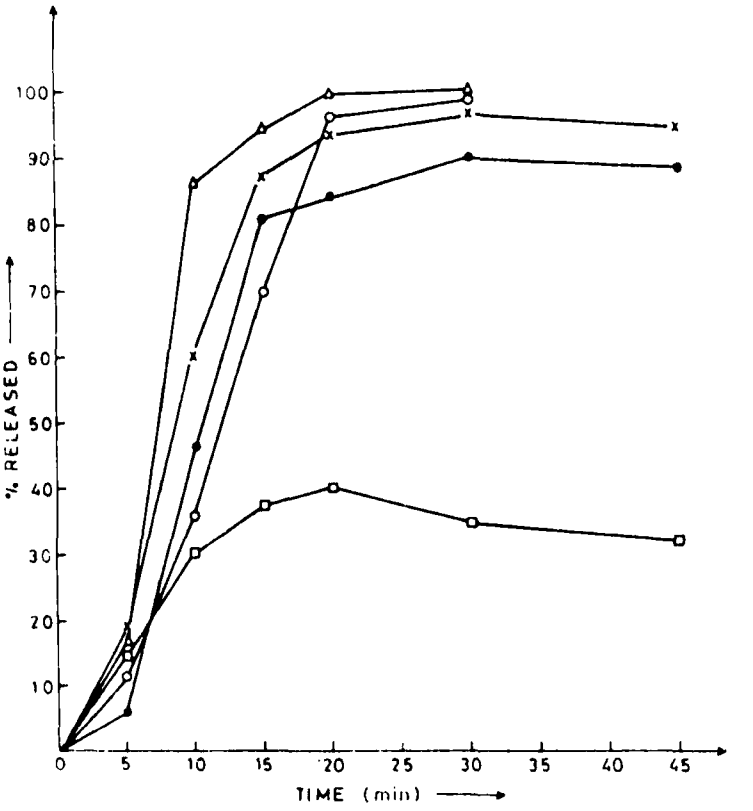

FIGURE 1

Dissolution profiles of pure drug, physical mixtures & solid dispersions.

—△— solid dispersion of nifedipine with PEG 6000 (1:10)
—○— solid dispersion of nifedipine with PEG 4000 (1:10)
—×— 10% physical mixture of nifedipine with PEG 6000.
—●— 10% physical mixture of nifedipine with PEG 4000.
—□— pure nifedipine.

Figure 1 compares the dissolution rate of pure drug, physical mixture of drug with the readily soluble carrier PEG 6000 and solid dispersion with PEG 6000. Physical mixture formation with the readily soluble carrier improved the dissolution rate and extent of solubilization of nifedipine. This could be attributed to a possible solubilization effect by the

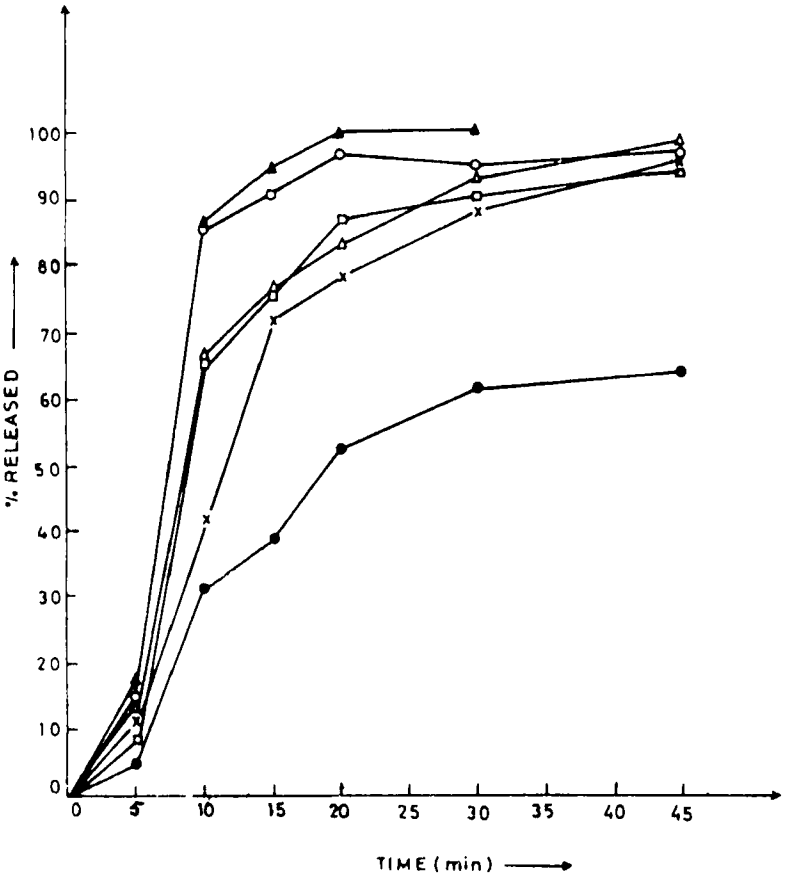

FIGURE 2

Dissolution profiles of the solid dispersions of nifedipine with PEG 6000 in different proportions.

Nifedipine : PEG 6000

- 1:10
- 1:20
- 1:25
- 1:15
- 1:5
- 1:1

carrier operating in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution[5], as the carrier completely dissolves in a short time. Solid dispersion formation further improved the dissolution rate of drug as can be observed from Table-1. Excellent wettabilityand dispersibility of drug from solid solution in the dissolution medium, micronization, absence of agglomeration and aggregation, solubilization effect by the carrier, and transformation from crystalline to other less stable forms may have contributed to the enhanced dissolution rate of nifedipine from the solid dispersion with PEG.

The effect of nifedipine-PEG ratio on the release rate of drug was next studied. Dissolution characteristics of nifedipine-PEG solid dispersion systems having different weight fractions of PEG such as 1, 5, 10, 15, 20 and 25 for 1 part of drug are shown in Figure 2 and Table-1. The best result was obtained with the (1:10) ratio. The $T_{50\%}$ values decreased as the proportion of PEG increased in the solid dispersion from 1 to 10 and further increase in the weight fraction of PEG didnot considerably affect the release rate although a slight delay in the dissolution was observed. It is probable that a critical mixture ratio exists for fastest dissolution of nifedipine from nifedipine-PEG solid dispersion systems and this weight fraction is approximately 10 parts of PEG. When the weight ratio of PEG decreased below 10 i.e. 1:1, the concentration of carrier being too small was probably insufficient to enhance dissolution to the maximum extent hence, as the proportion of PEG increased, the dissolution rate also increased. At 10 parts of PEG maximum increase in dissolution rate was observed. Increase in PEG weight fraction beyond 10 resulted in decrease in dissolution rate. It is probable that the drug in carrier system containing 10 parts of PEG existed in a metastable form at the saturation point, the point at which systems exhibit maximum enhancement in solubility[6] (later

TABLE-1

Comparative $T_{50\%}$, $T_{90\%}$, and 'r' values of pure nifedipine, physical mixtures and solid dispersions of drug with both PEG 6000 and PEG 4000.

Composition	$T_{50\%}$ (min.)	$T_{90\%}$ (min.)	'r'
Pure Nifedipine	47.00	98.92	0.9978
10% Physical Mixtures			
Nifedipine + PEG 4000	19.63	58.07	0.9735
Nifedipine + PEG 6000	6.99	20.99	0.9989
Solid Dispersions			
Nifedipine : PEG 6000			
1 : 1	24.39	92.92	0.9930
1 : 5	6.27	32.05	0.9875
1 : 10	6.23	12.08	0.9955
1 : 15	6.34	13.18	0.9890
1 : 20	7.88	18.50	0.9880
1 : 25	6.25	14.09	0.9939
Nifedipine : PEG 4000			
1 : 1	18.15	47.27	0.9985
1 : 5	14.33	40.71	0.9957
1 : 10	10.64	23.14	0.9880
1 : 15	9.71	57.73	0.9968
1 : 20	13.84	63.07	0.9967
1 : 25	9.84	80.23	0.9955

confirmed by X-ray diffraction studies). Above this saturation point, as the proportion of carrier increased, the longer time required for diffusion of the drug from the matrix probably resulted in a slightly decreased dissolution rate.

Effect of PEG Molecular Weight on Nifedipine Release

Table-1 also indicates the release rate of drug from nifedipine-PEG solid dispersions prepared by PEG having different molecular weights. PEG-6000 showed more rapid dissolution rates of nifedipine than PEG 4000. Similar results were obtained with physical mixtures of nifedipine and PEG. Hence solid dispersions of nifedipine with PEG 6000 were used in further studies and were retained for evaluation by X-ray diffraction to ascertain the nature of the drug in the solid dispersions.

X-ray Diffraction Studies

The X-ray diffraction patterns of nifedipine, PEG 6000, physical mixture and solid dispersions are illustrated in Figure 3.

The diffraction spectra of pure nifedipine showed that the drug was highly crystalline in nature as indicated by numerous distinctive peaks in the X-ray diffractogram. PEG 6000 exhibited some crystallinity as indicated by the two peaks of high intensity and some other peaks of lower intensity. In Figure 3(c) representing the physical mixture, the spectra possessed all the characteristic diffraction lines of PEG 6000 and in addition exhibited numerous distinct peaks characteristic of crystalline nifedipine. This reveals that, in spite of its small proportion in the mixture, crystalline nifedipine is detectable and nifedipine appears in crystalline state in the physical mixture.

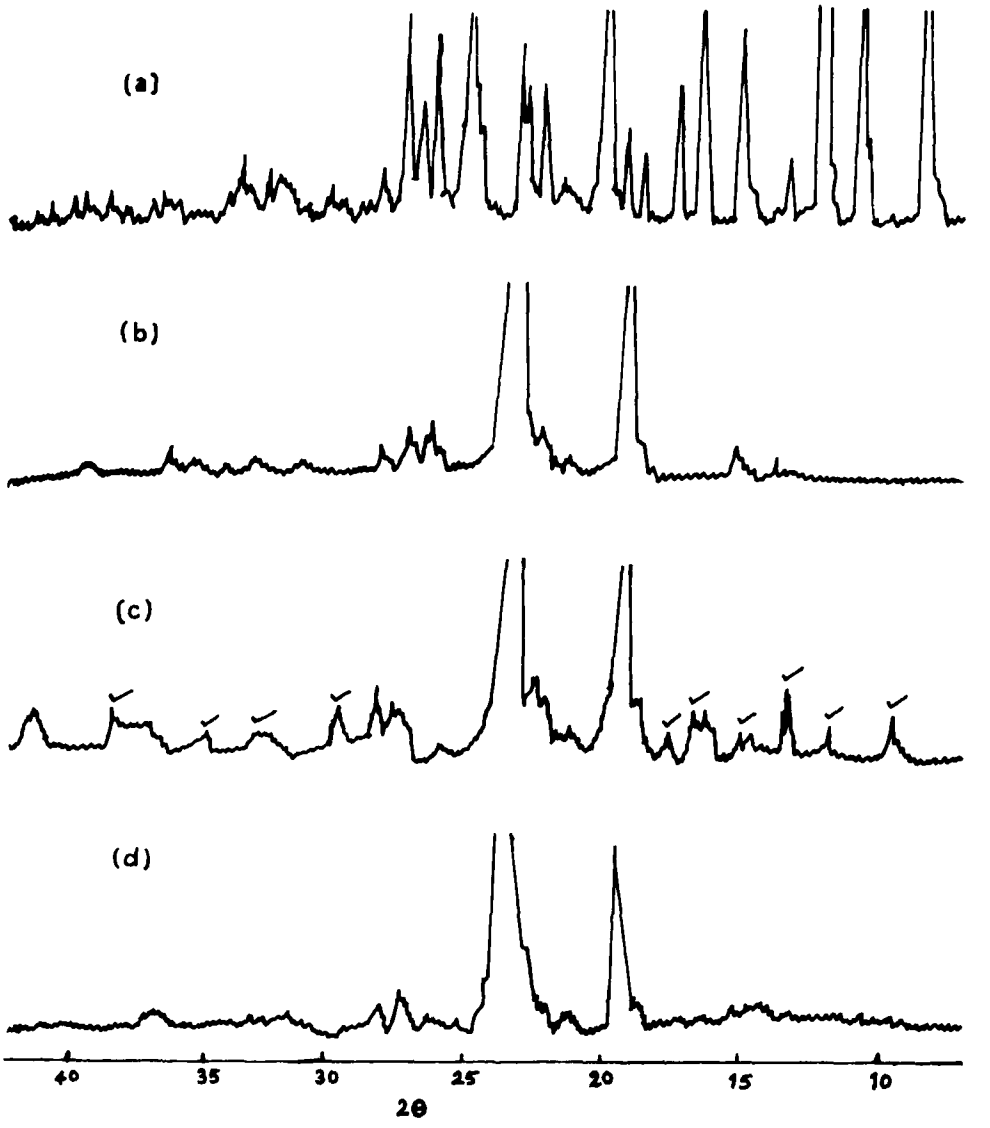

FIGURE 3

X-ray diffractograms of

a) pure nifedipine.
b) pure PEG 6000.
c) 10% physical mixture of nifedipine with PEG 6000.
d) 1:10 solid dispersion of nifedipine with PEG 6000 (slab form)

The X-ray diffraction spectra of freshly prepared solidified melt in the slab form showed the presence of peaks corresponding to PEG 6000. The lack of peaks characteristic of nifedipine in this diffractogram indicated that nifedipine had not crystallized out in these solid dispersions and thus indicated conversion to a metastable form or existance in ultra crystalline form. In this particular case, the lack of displacement of the PEG 6000 peaks leads to the conclusion that an interstitial solid solution has been formed during manufacturing[7]. The X-ray diffraction patterns run on the powdered solid dispersions (Figure 4(c)) showed the presence of peaks characteristic of nifedipine but of lower intensity indicating some amount of drug had crystallized out during powdering. The existence of slight crystallinity upon powdering indicates that the drug may be at the saturation point in the metastable form at this concentration, such that upon powdering, some drug crystallizes out. The faster dissolution rates from solid dispersions may be attributed to the formation of this high energy metastable state of the drug formed due to the inhibiting effect of PEG on drug crystallization[8].

Rapidly quenched solid dispersions exhibited better dissolution properties than a slowly cooled melt. Besides super-saturated systems and a much finer dispersion of crystallite can be obtained by quenching. As shown in Figure 4(a), quenching of melt helped to transform the drug from stable crystalline to metastable noncrystalline form as indicated by the absence of sharp diffraction peaks of crystalline nifedipine. The reappearance of these peaks in the non quenched melt (slow cooling at room temperature) indicated that an interstitial solid solution was not formed by this procedure. During quenching the abrupt changes in temperature might have enabled the transformation of drug from stable crystalline to metastable form. In addition, the rapid changes in the viscosity of PEG and the insufficient time for crystallization due to the rapidity

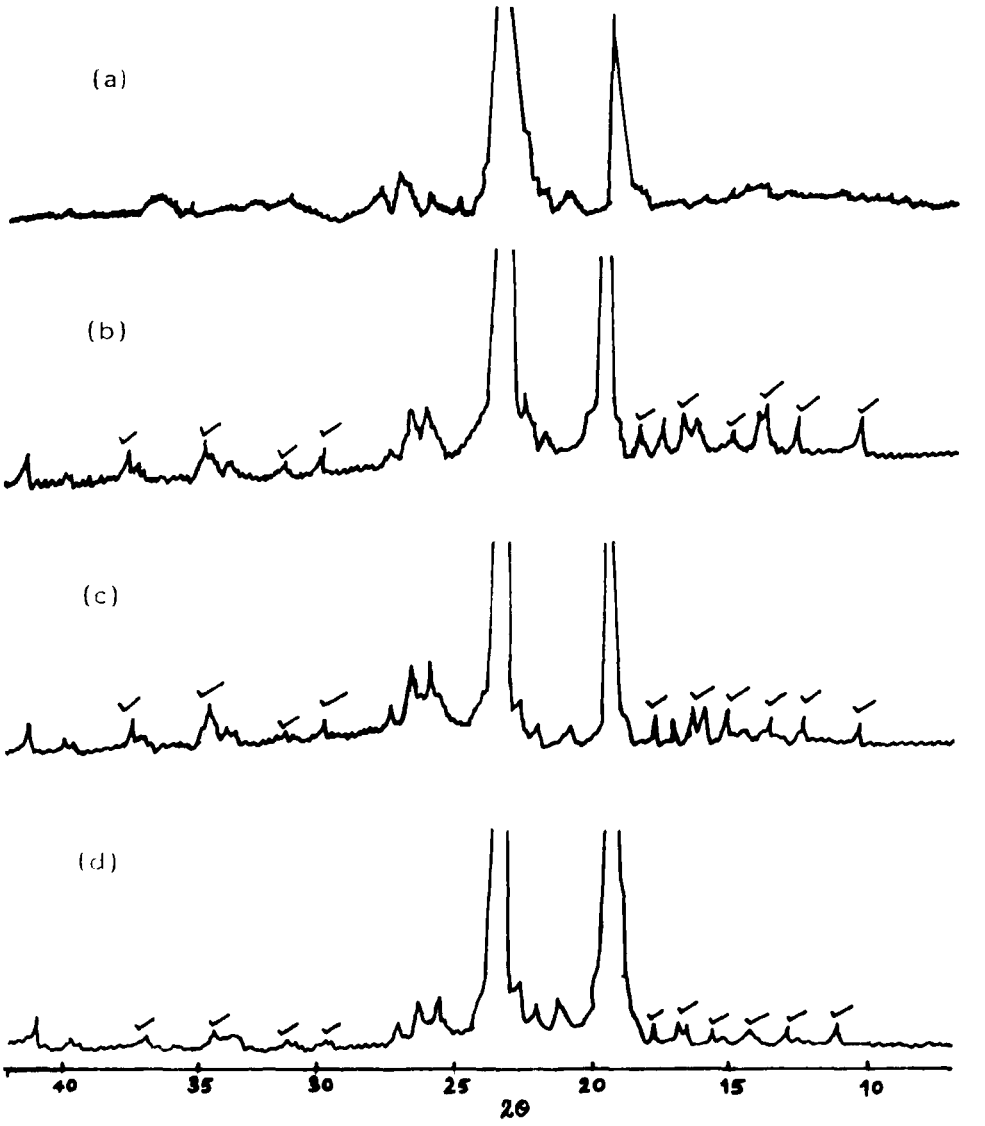

FIGURE 4

X-ray diffractograms of solid dispersions of nifedipine with PEG 6000 (1:10)

a) quenched solid dispersion (slab form)
b) slow cooled solid dispersion (slab form)
c) quenched & powdered solid dispersion
d) solid dispersion after 6 months at room temperature (slab form)

of the cooling process could have prevented the drug from crystallizing out.

Figure 5 shows the diffraction patterns of nifedipine-PEG 6000 solid dispersions composed of different drug to PEG ratios such as 1:1, 1:5, 1:10, 1:15 & 1:20. All the dispersions showed the presence of characteristic peaks of PEG 6000. The lack of peaks characteristic of crystalline nifedipine in dispersions containing 10 & more parts of PEG 6000 indicated the presence of metastable form of drug in these solid dispersions. All dispersions containing less than 10 parts of PEG 6000 for 1 part of nifedipine revealed the presence of nifedipine in the crystalline form. The peak sharpening denoted an increase in the crystallinity with an increase in nifedipine concentration in the solid dispersions.

Thin Layer Chromatographic Studies

No new spots were detected in the TLC study of solid dispersion of nifedipine with PEG 6000. This eliminated the possibility of chemical complexation of the drug molecules with the carrier molecules and also possible decomposition during the preparation of the solid dispersions by fusion.

I.R. Analysis

The I.R. spectrum of nifedipine showed sharp peaks at 1690, 1527, 1496 & 1310 cm^{-1} which were also present in the I.R. spectrum of nifedipine-PEG solid dispersion indicating absence of complex formation between nifedipine & PEG[9].

Stability Studies

Figure 4(d) shows the X-ray diffraction patterns of aged nifedipine-PEG 6000 solid dispersions. A slight increase in the nifedipine peak heights was observed which may be attributed

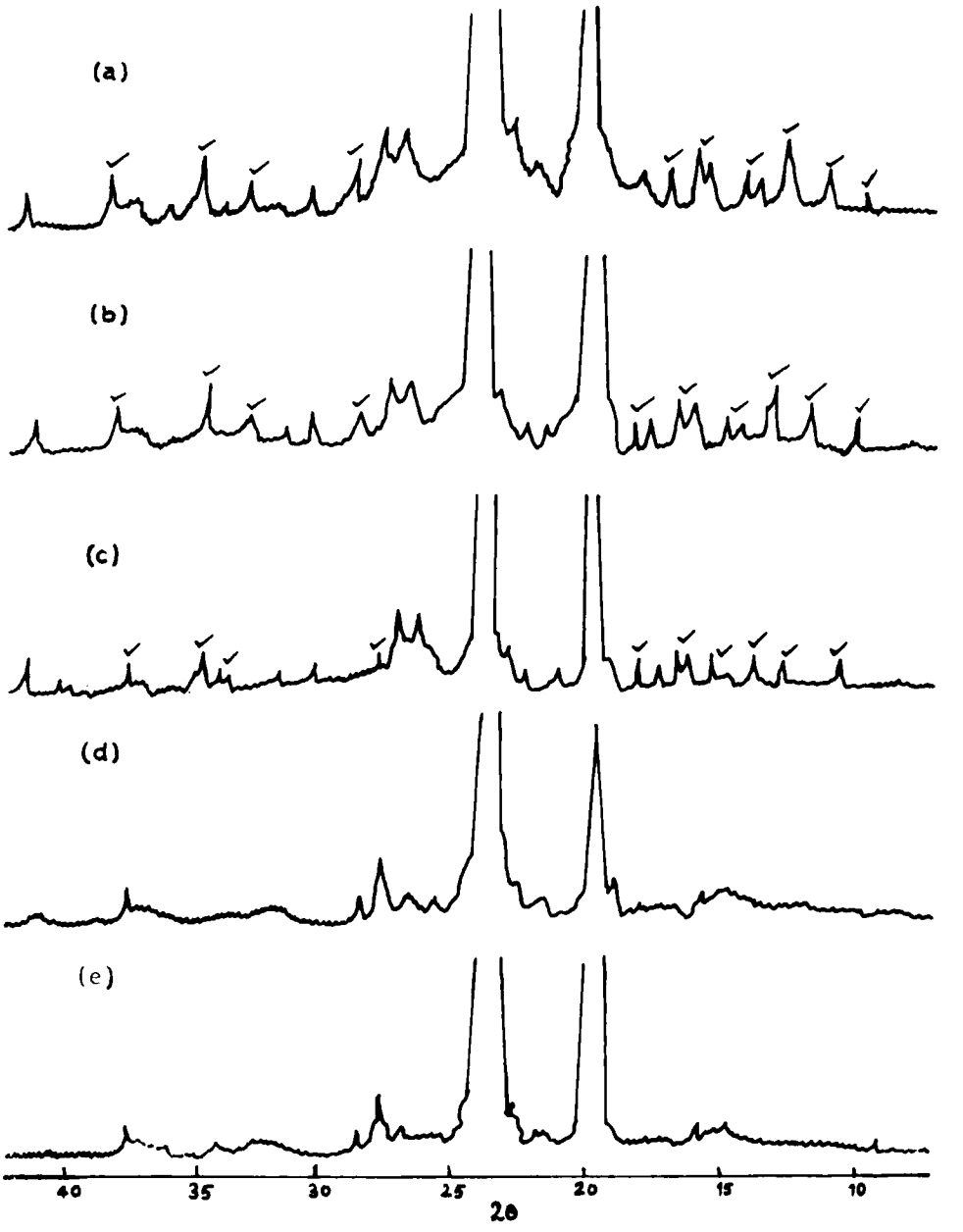

FIGURE 5

X-ray diffractograms of solid dispersions of nifedipine with PEG 6000 in different proportions.

a) 1:1
b) 1:5
c) 1:10
d) 1:15
e) 1:20

to an increase either in the degree of crystallinity or in the size of nifedipine particles[10]. No other changes or displacement of peaks in the diffractogram indicate the stability of solid dispersion at room temperature after six months. No significant changes in disssolution rate were however observed.

CONCLUSION

The modification of the dissolution behaviour of nifedipine PEG solid dispersion resulted in increased drug dissolution rate. PEG 6000 showed greater enhancement in the dissolution rate when compared with PEG 4000. Among the different compositions studied maximum enhancement in dissolution rate was observed at 1:10 (nifedipine : PEG 6000) when prepared by quenching. It is probable that in this composition a metastable solid solution of the drug existed at saturation point which crystallized out upon powdering. Quenching of the solid dispersion also gave better results.

The results of the stability study revealed that the enhanced dissolution rate was primarily due to the presence of the drug in the high energy metastable form in the solid dispersions. The increased wettability, dispersibility, and solubilization of drug by the carrier could have also been contributory factors.

It was also observed that after a storage period of six months at room temperature, no significant changes appeared in dissolution rate while the X-ray diffraction patterns revealed a slight rise in crystallinity.

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