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Accelerated stability study of sustained-release nifedipine tablets prepared with Gelucire®

Carmen Remuñán [1], María J. Bretal [1], Alberto Núñez [2] and José Luis Vila Jato [1]

[1] *Laboratorio de Farmacia Galénica and* [2] *Departamento de Edafología, Facultad de Farmacia, Universidad de Santiago de Compostela, Santiago de Compostela (Spain)*

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Summary

This paper describes an investigation of the chemical and physical stability of nifedipine sustained release dosage forms prepared with Gelucire® 53/10. Three formulations differing only in the applied tabletting force were stored for 6 months under four different controlled conditions of relative humidity (RH) and temperature (20°C/0% RH, 20°C/80% RH, 40°C/0% RH, 40°C/80%). It was found that nifedipine in the sustained release formulations was chemically stable against the effects of temperature and humidity. However, the variables, tabletting force, RH and storage time, exerted a significant influence on the dissolution behavior of nifedipine. The changes in dissolution behavior after storage under conditions of high humidity and temperature might be related to the formation of nifedipine microcrystals and to structural changes in the wax vehicle during storage. It is predicted that acceptable shelf-lives should result when moisture-resistant packaging is used for pharmaceutical formulations of this type.

Introduction

Nifedipine is a poorly water-soluble drug (11 mg/l, 37°C) (Sugimoto et al., 1980) of low bioavailability when administered orally in crystalline form (Raemsch and Sommer, 1983). On the other hand, the elimination half-life of nifedipine after administration of conventional formulations is very short. Thus, in the management of hypertension, very frequent administration of such dosage forms is required. Hence, the development of a nifedipine dosage form with good bioavailability and maintaining prolonged plasma levels presents an interesting challenge from the viewpoint of therapeutic use and patient compliance.

Various approaches have been undertaken in the attempt to improve the solubility of nifedipine (Sugimoto et al., 1980; Nozawa et al., 1986, 1989; Sumnu et al., 1986a; Pezoa et al., 1988;

Correspondence: J.L. Vila Jato, Laboratorio de Farmacia Galénica, Facultad de Farmacia, Avda Las Ciencias S/N, Universidad de Santiago de Compostela, Santiago de Compostela, Spain.

Sangalli et al., 1989) and to prolong the plasma levels of the drug (Hasegawa et al., 1985; Kohri et al., 1986, 1987; Leucuta, 1988; Bourke et al., 1989; Leucuta et al., 1989).

Starting from a 1:3 nifedipine/polyvinylpyrrolidone (PVP) coprecipitate and the wax excipient Gelucire® 53/10, we have developed several sustained release nifedipine dosage forms that differ only in the applied tabletting force. These formulations have proved to possess adequate in vitro and in vivo sustained release characteristics as compared with the reference Adalat® retard (Vila Jato et al., 1990; Remuñán et al., 1991).

This report describes an accelerated stability study of such dosage forms, as carried out using a procedure which has been found to be particularly suitable for formulations of this type on the basis of the following reasons:

(1) They include a coprecipitate system that is often susceptible to changes with aging. Although the use of solid dispersions has proved to constitute an appropriate means for enhancing the dissolution of several drugs, very few preparations have thus far been marketed owing to problems being encountered in the present technology and in the stability of the preparations: solid dispersions can exist as metastable systems, which undergo transformation into more stable forms during storage. Such drawbacks could therefore alter the biopharmaceutical profiles (Chiou and Riegelman, 1971; Duchêne, 1985; Frömming and Hosemann, 1985; Bloch and Speiser, 1987), and hinder the industrial development of these systems. Moreover, the hygroscopicity of PVP can be particularly disruptive (Umprayn and Mendes, 1987).

(2) Gelucire® is a wax excipient and, as such, is susceptible to undergoing polymorphic transitions with time (Vial-Bernasconi et al., 1988). On the other hand, at present, one of the major obstacles to the industrial use of Gelucire® is that due to the lack of information on the behavior of such excipients on aging.

(3) Finally, the formulations assessed here are sustained release dosage forms. It is well known that changes in this type of formulation are of greater significance compared to those in conventional forms, since they contain larger doses.

Materials and Methods

Active principle and excipients

All formulations were prepared by using nifedipine (Bayer S.A., lot no. 77F-0731), PVP 40000 (Ega-Chemie, lot no. CD N.06298) and Gelucire® 53/10 (Gattefossé, lot no. 742).

Formulations

Three nifedipine dosage forms were prepared according to our previously reported methodology (Vila Jato et al., 1990), in which granulation is performed on a mixture of a 1:3 nifedipine/PVP coprecipitate (90%) and molten Gelucire® (10%). The applied tabletting forces were 0 (granulate: formulation A), 6000 N (formulation B) and 12000 N (formulation C), with the nifedipine dose being 20 mg.

Storage conditions

Formulations were stored for 6 months under four different conditions of relative humidity (RH) and temperature (20°C/0% RH, 20°C/80% RH, 40°C/0% RH, 40°C/80%). The desired RH was achieved by putting samples into air-tight glass containers with silica gel (0% RH) or a water/H_2SO_4 mixture (80% RH) prepared beforehand. The containers were placed inside ovens in order to control the temperature.

Samples were protected from exposure to light and experiments were conducted in a dark-room owing to nifedipine being highly sensitive to natural light.

In order to correct for changes in weight caused by the absorption of moisture during storage, samples that had been stored were dried in a desiccator under reduced pressure at room temperature and over P_2O_5 prior to every experiment, as described by Sugimoto et al. (1981). Under these conditions for drying, sample weights attained a constant value.

Chemical stability

The nifedipine content of stored samples (four replicates) was assayed by performing direct spectrophotometric determinations at 238 nm on methanolic solutions of nifedipine. The presence

of carriers did not result in interference over this range.

Physical measurements

Both before and after storage, samples were examined by X-ray diffractometry and differential scanning calorimetry (DSC). Powdered samples were mounted on a sample holder and the X-ray diffraction patterns were recorded using a Siemens D-500 X-ray diffractometer. DSC thermograms were obtained by employing a Perkin-Elmer DSC-4 instrument. A scanning speed of 10°C/min was used encompassing the range 40–240°C.

Dissolution study

Evaluation of dissolution was carried out on four replicates of each formulation. The dissolution media used were artificial gastric fluid containing pepsin (according to USP XXII) and artificial intestinal juice without enzymes. The apparatus was of the flow-through type without an accumulation reservoir (LLabrés et al., 1977). A pH gradient was set up by placing 250 ml of simulated reservoir fluid in the dissolution chamber and the pumping of artificial intestinal fluid at a rate of 10 ml/min.

The concentration of nifedipine in the samples was determined spectrophotometrically at 238 nm, with the percentage of dissolved nifedipine subsequently being calculated (LLabrés et al., 1977).

The parameters employed for characterization of the dissolution of nifedipine were as follows: D_1, the percentage of nifedipine dissolved during a period of 1 h; D_4, the percentage of nifedipine dissolved during a period of 4 h; and E_{D8}, the efficiency of dissolution over a period of 8 h.

Experimental design and statistical analysis

The set-up for the stability study constituted a $3 \times 2 \times 2 \times 3$ factorial design for determination of the individual and joint influence of the independent variables, compression force (F: 0, 6000 and 12000 N), RH (0 and 80%), temperature (T: 20 and 40°C) and storage time (t: 0, 3 and 6 months) on the parameters employed to characterize the dissolution curves.

In view of the destructive nature of the assays, statistical analysis of the data was performed by using ANOVAS (Dixon, 1988) of the differences between the parameters evaluated at different time points and the initial mean values.

In order to ascertain which of the values among those found to be significant were the most important in determining the degree of stability, multiple sequential linear regression (Dixon, 1988) was performed and the corresponding response surfaces plotted graphically.

The data for each formulation were also separately subjected to evaluation by ANOVA and multiple sequential linear regression, based on $2 \times 2 \times 3$ factorial designs, with the aim of facilitating the explanation of the results.

Results and Discussion

Fig. 1 shows the initial dissolution profiles of formulations A–C, and Figs 2–4 depict the mean values and standard deviations corresponding to the parameters D_1, D_4 and E_{D8} used in characterizing the dissolution of the formulations under test.

Storage of these formulations under conditions of high RH, especially at 40°C, displays a significant influence on the dissolution behavior, particularly in the case of the granulate, which possessed the largest surface area exposed to the given storage conditions (Figs 2–4).

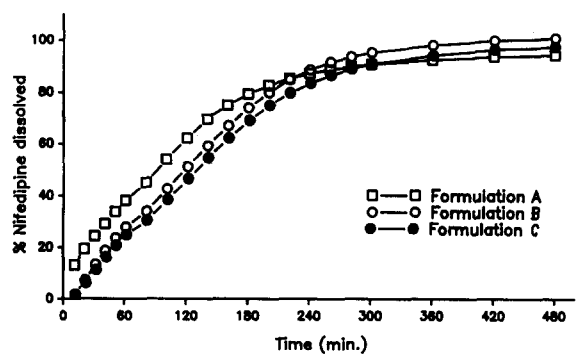

Fig. 1. Initial dissolution profiles of freshly prepared Formulations A (0 N), B (6000 N) and C (12000 N).

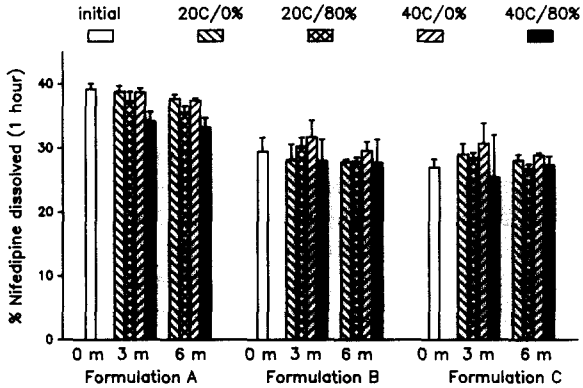

Fig. 2. Mean values and standard deviations (indicated by vertical bars above main bar) of D_1 (percentage of nifedipine dissolved in 1 h).

The ANOVAS evaluated for the above parameters demonstrate the considerable effect of both the assay variables and the interactions on all dissolution parameters (Table 1).

The regression equations determined for the parameters, i.e.

$$D_1 = 0.186 + 0.302 \times 10^{-3} \cdot F^2 - 0.355 \cdot t + 0.891 \times 10^{-3} \cdot TH$$

$$(R = 0.680;\ F = 5.79)$$

$$D_4 = -0.031 + 0.296 \cdot T + 0.145 \times 10^{-4} \cdot F^2T - 0.089 \cdot tT - 0.306 \times 10^{-2} \cdot TH$$

$$(R = 0.876;\ F = 8.77)$$

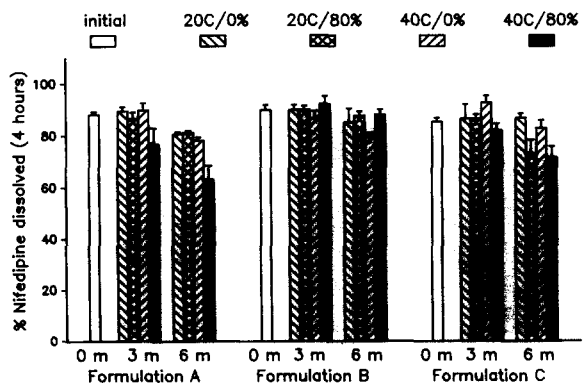

Fig. 3. Mean values and SD of D_4 (percentage of nifedipine dissolved in 4 h).

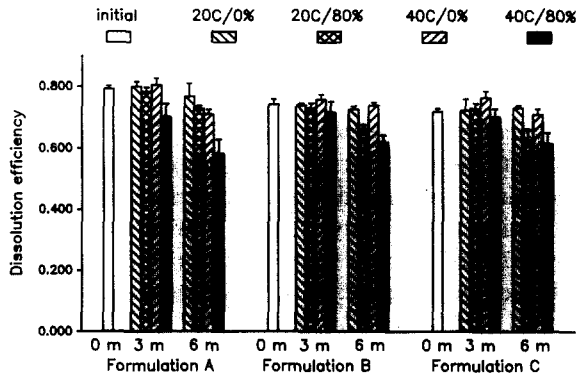

Fig. 4. Mean values and SD of E_{D8} (efficiency of dissolution in 8 h).

$$E_{D8} = 0.0317 + 0.135 \times 10^{-6} \cdot FT - 0.461 \times 10^{-3} \cdot tT - 0.174 \times 10^{3} \cdot tH$$

$$(R = 0.853;\ F = 31.64)$$

confirm that all the investigated variables are somehow responsible for the modifications induced in the dissolution of stored samples.

Thus, in order to simplify the treatment of the results, the data for each dosage form were fitted to a $2 \times 2 \times 3$ design. The corresponding regres-

TABLE 1

Probability levels (design 3 × 2 × 2 × 3)

Variable	Dissolution parameter		
	D_1	D_4	E_{D8}
F	0.001	0.001	0.001
F^2			
t	0.05	0.001	0.001
T		0.001	0.001
H	0.001	0.001	0.001
Ft			0.05
F^2t			0.05
FT		0.001	0.001
F^2T			0.05
tT		0.05	0.05
FH			
F^2H			
tH		0.05	0.001
TH	0.05	0.001	0.001
FtT			
FtH		0.05	0.05
FTH		0.05	0.05

sion equations have a high degree of predictive ability as shown by the following:
(Formulation A)

$$D_1 = 0.916 - 0.414 \cdot t - 0.133 \times 10^{-2} \cdot TH$$

$$(R = 0.889;\ F = 12.00)$$

$$D_4 = 2.076 + 0.433 \cdot T + 0.146 \cdot H - 0.108 \cdot t - 0.00801 \cdot TH$$

$$(R = 0.941;\ F = 11.06)$$

$$E_{D8} = -0.0208 + 0.376 \times 10^{-2} \cdot T + 0.120 \times 10^{-2} \cdot H - 0.916 \times 10^{-3} \cdot tT - 0.658 \times 10^{-4} \cdot TH$$

$$(R = 0.946;\ F = 11.87)$$

(Formulation B):

$$D_4 = 4.977 - 1.180 \cdot t - 0.0242 \cdot tH$$

$$(R = 0.857;\ F = 7.23)$$

$$E_{D8} = -0.00236 + 0.135 \times 10^{-2} \cdot H - 0.343 \times 10^{-3} \cdot tH - -0.177 \times 10^{-4} \cdot TH$$

$$(R = 0.915;\ F = 8.06)$$

(Formulation C):

$$D_4 = 9.946 - 1.782 \cdot t - 0.0255 \cdot tH$$

$$(R = 0.859;\ F = 12.86)$$

$$E_{D8} = 0.0699 - 0.0122 \cdot t - 0.189 \times 10^{-3} \cdot tH$$

$$(R = 0.860;\ F = 11.54)$$

The response surfaces demonstrate the influence of storage time and RH on the dissolution parameters of the granulate (i.e., the greater the RH and storage time, the greater is the variation in the dissolution parameters) (Figs 5–7). This effect is very sensitive to temperature. In the case

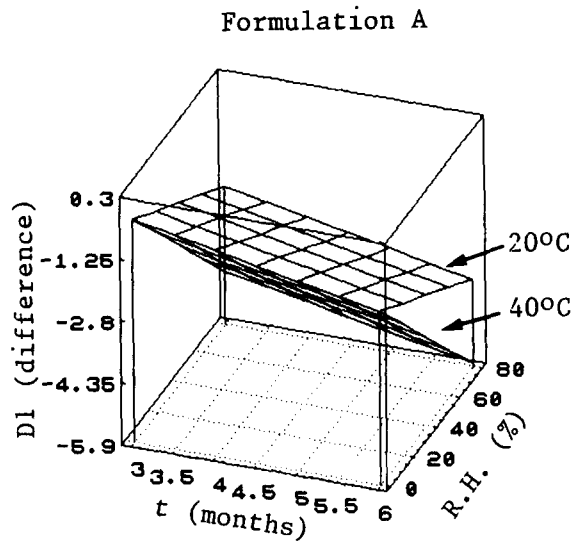

Fig. 5. Response surface of D_1 (formulation A).

of tablets, this variable exerts only a minor influence on the dissolution efficiency of formulation B. Therefore, the initial conclusion that may be drawn from the present study is that the thermal stability becomes greater with increasing compression force.

Three possible causes giving rise to the changes in dissolution were examined: (1) physical instability of the solid dispersion included in the dosage forms; (2) chemical instability of the active principle; and (3) structural modifications with regard to the excipient Gelucire®.

Humidity plays an important role in the decomposition of pure drugs in the solid state and of solid dosage forms. Even under routinely used storage conditions, adsorbed water is present on the surfaces of the active principles and dosage forms. Moreover, PVP is not only relatively stable thermally, but also very polar and hygroscopic (Umprayn and Mendes, 1987).

In the absence of moisture, the tablets under test (formulations B and C) were stable at the highest temperatures studied. This observation is consistent with the findings of other authors concerning the stability of a number of PVP coprecipitates and their dosage forms (El-Gamal et al., 1981; Jachowicz, 1987; Doherty and York, 1989).

In contrast, solid dispersions of PVP usually crystallize after storage under conditions of high RH (Frömming and Hosemann, 1985).

In freshly prepared formulations, nifedipine is present in the amorphous form and the diffraction patterns display no peaks that can be attributed to nifedipine crystals either before or after storage (Fig. 8), suggesting that crystallization does not occur in this case.

The lack of crystallinity of nifedipine is confirmed by the DSC data. Hence, changes in the dissolution behavior, in principle, cannot be explained in terms of the differences in crystallinity of nifedipine in the samples. Other factors could presumably contribute to the variation in dissolution, for example, chemical instability of the active principle.

Nevertheless, marked differences in nifedipine content were not observed during aging of the formulations (Fig. 9) and the chemical stability of nifedipine in nifedipine/PVP systems has been confirmed to occur by a number of workers (Sugimoto et al., 1980, 1981; Sumnu, 1986b).

Another possibility is that a structural change in Gelucire® takes place during storage (Boymond and Hans, 1978; Doelker et al., 1986;

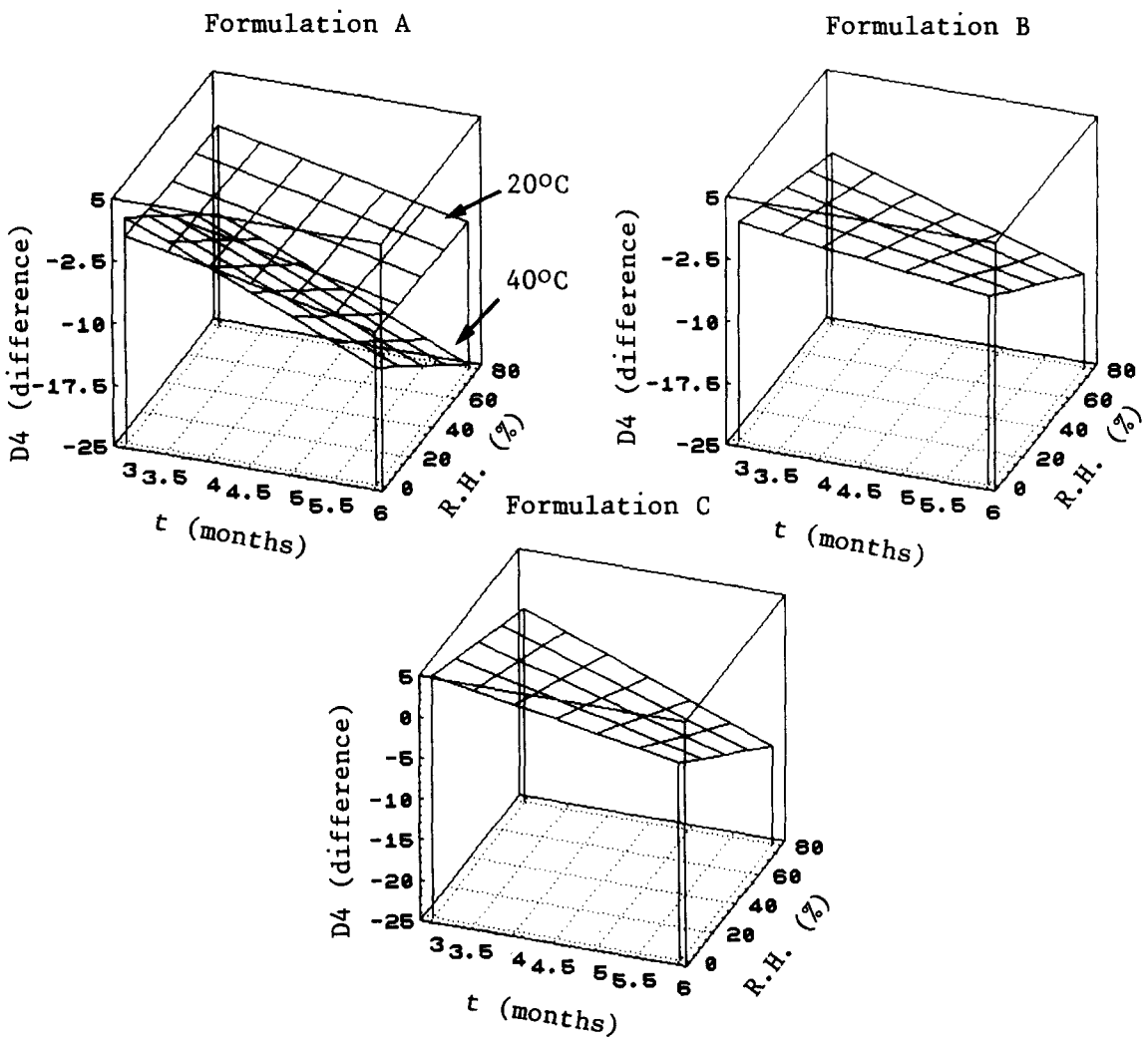

Fig. 6. Response surfaces of D_4 (formulations A–C).

Laine et al., 1988). Wax-containing materials are capable of spontaneously reacting with oxygen, i.e., undergoing oxidation (Naudet, 1963). Such auto-oxidation increases in extent with increasing unsaturation of the wax compound and rising temperature.

The lipid excipients composed of triglycerides can undergo polymorphic transitions, precipitation or crystallization with time, accompanied by corresponding changes in their properties and in the rate of release of the formulated active principles (Laine et al., 1988). Gelucire® has been claimed to be more stable as compared to other lipid excipients, it has a composition entirely made up of saturated, and thus more stable, compounds (Waginaire and Glass, 1981). However, to date, only a single study has appeared concerning examination of the effect of humidity on formulations containing Gelucire® (Delgado et al., 1990). The afore-mentioned work dealt with the stability of amoxicillin granulates with several varieties of Gelucire®. The results obtained by Delgado et al. demonstrated that, during aging, even under ambient environmental conditions, significant changes in the dissolution profiles were produced. The modifications were explained on the

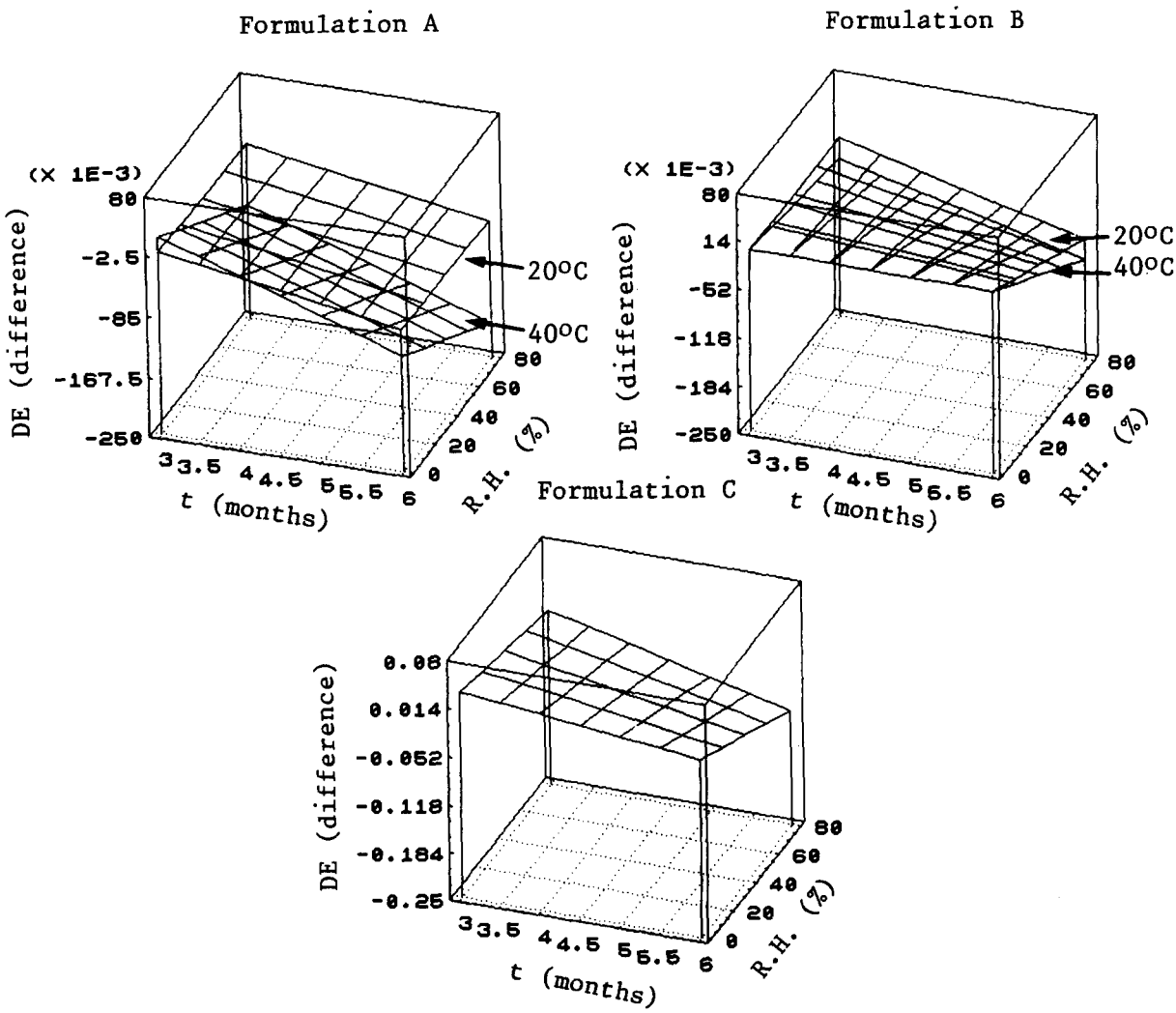

Fig. 7. Response surfaces of E_{D8} (formulations A–C).

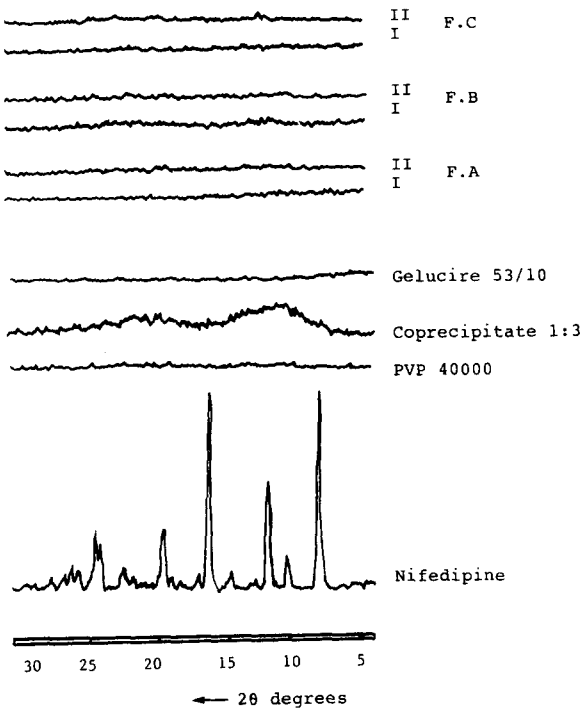

Fig. 8. X-ray diffraction patterns for nifedipine, PVP 40000, coprecipitate 1:3, Gelucire® 53/10 and nifedipine formulations A–C, initially (I) and after storage at 40°C/80% R.H. for 6 months (II).

basis of the crystallization of Gelucire® or amoxicillin.

From these results, we ascribe the changes in dissolution behavior of stored formulations both to the formation of microcrystals – which were undetectable with the experimental techniques employed – and to structural modifications in Gelucire®.

Therefore, in order to ensure the physicochemical stability of the dosage forms under test, protection against moisture is essential, particularly at elevated temperatures. For this purpose, moisture-resistant 'blister' packaging is indispensable, which is also desirable in view of the rapid degradation of nifedipine on exposure to natural light.

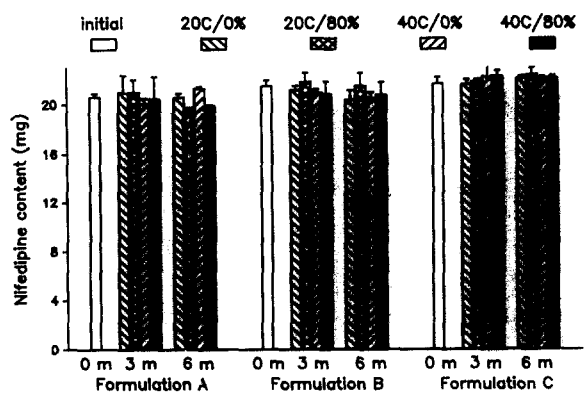

Fig. 9. Mean values and SD of nifedipine content (mg).

Conclusions

The present data have demonstrated that the stability of the formulations developed in this investigation can be maintained by protection from conditions of high humidity. In addition, the changes in dissolution behavior of stored formulations are related to the formation of microcrystals of nifedipine and to structural modifications in Gelucire®.

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