Note

Characterization of nifedipine solid dispersions

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Abstract

The sublingual administration of nifedipine (NIF) is currently used in clinical practice. The sublingual administration of NIF solid dispersions (SD), by using a suitable dispenser, appears an interesting approach in the treatment of moderate and severe hypertensive emergencies. With this aim nine SD made of NIF and a low viscosity hydroxypropylmethylcellulose (HPMC) in different ratio were prepared by means of spray-drying technique and their structure was studied. Moreover, the drug dissolution properties from SD were verified. The characteristic peaks of crystalline NIF were not detectable by using the X-ray analysis when the NIF/HPMC ratios were lower than 50/50 w/w. In thermograms obtained from SD, the NIF melting endothermic peak disappeared when NIF/HPMC ratios were lower than 30/70 w/w; the experimental Tg values of SD were lower than the Tg values predicted by Gordon Taylor equation suggesting some type of non-ideality of mixing. In the SD FTIR spectra the NH stretching vibrations and the C=O stretch in esteric groups of NIF shift to free NH and C=O regions indicating the rupture of intermolecular hydrogen bond in the crystalline structure of NIF. The prepared SD improved the NIF dissolution rate in comparison with that of commercial NIF or NIF/HPMC physical mixtures. Moreover, the concentration of NIF in the dissolution medium increased decreasing the NIF content. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Nifedipine; Solid dispersion; Sublingual administration; HPMC

1. Introduction

The sublingual administration of nifedipine (NIF) is currently used in clinical practice in the treatment of moderate and severe hypertensive emergencies (Erbel et al., 1983; Abraham et al., 1986; Save et al., 1994). However, the actual mode of administration involves a number of disadvantages. Indeed, NIF is usually administered as solution using liquid oral drug preparation or by cutting a soft gelatine capsule and by squeezing out the fluid content beneath the tongue. This mode of administration can lead to dosage and absorption variability. The administration of NIF solid dispersions (SD), by using a suitable dispenser, appears an interesting approach in order to improve dosage accuracy, residence time beneath the tongue and patient compliance. A low viscosity hydroxypropylmethylcellulose (HPMC) was used as carrier be-

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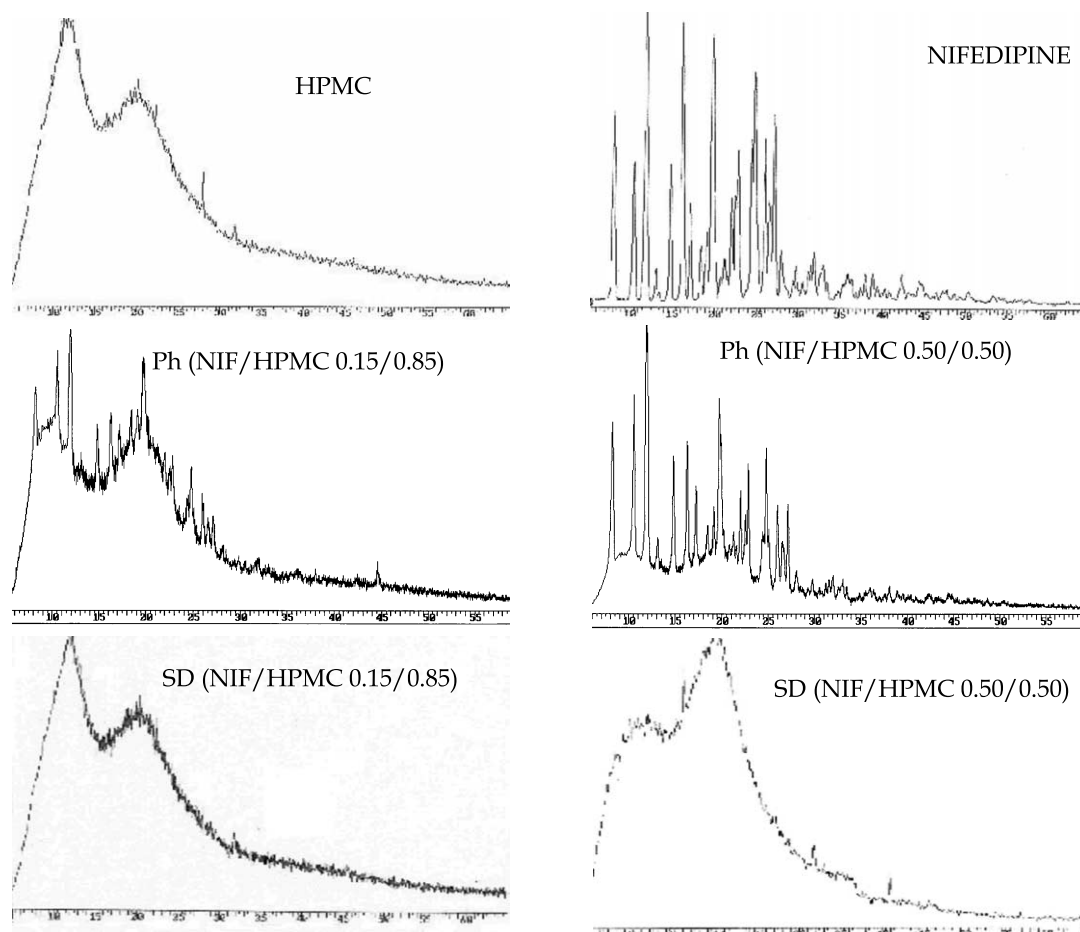*E-mail address:* francesco.cilurzo@unimi.it (F. Cilurzo).

Fig. 1. X-ray diffraction patterns of HPMC and NIF and two examples of physical mixture (Ph) and SD.

cause of its compatibility with NIF and inhibitory effect on NIF crystallization from supersatured solutions (Suzuki and Sunada, 1998). Nine SD containing from 5 to 75% w/w of NIF were prepared by means of spray-drying technique. The specific objective in this study was to elucidate the structure of these SD and detect possible drug–polymer interactions. The physical state of NIF was investigated by using differential scanning calorimetry, X-ray diffraction analysis and Fourier transform IR technique. Moreover, the microparticles were characterized in terms of morphology and in vitro dissolution profile.

The SD were prepared by using the spray-dryer Lab-Plant SD04 (Lab-Plant LTD, West Yorkshire, UK). Feed composition: solution of Methocel E50 (HPMC) (Colorcon, Italy) 2.5% w/w in methylene chloride:ethanol 90/10 v/v containing NIF (P.F.C., Italy) in the NIF/HPMC ratios 5/95, 10/90, 15/85, 30/70, 40/60, 50/50, 60/40 and 75/25 w/w; flux rate, 20 ml/min; air flux rate, 44 m^3/min; inlet temperature, 60 °C; outlet temperature, 40 °C.

The SD shape and surface were analyzed by using SEM (JSM-T 800-JEOL Italia, I).

The densities of NIF and HPMC were determined with a helium displacement pycnometer (Multivolume pycnometer 1305 Micromeritics, US).

Thermal analysis was performed on samples of NIF, spray dried HPMC and SD by using a DSC 2010 TA (TA Instruments, US). The deviation of

Table 1
NIF onset melting fusion, enthalpy and glass transition temperature of SD

NIF/HPMC ratio (w/w)	T_f onset (°C)	ΔH_{fus} (J/g)	T_g (°C)
0.00/1.00	–	–	162
0.05/0.95	–	–	134
0.10/0.90	–	–	124
0.15/0.85	–	–	113
0.20/0.80	–	–	95
0.30/0.70	172.02	1.41	71
0.40/0.60	172.38	10.61	61
0.50/0.50	172.17	35.88	58
0.60/0.40	172.11	42.90	57
0.75/0.25	171.28	66.05	57
1.00/0.00	172.96	103	50

where w_1 and w_2 are the weight fractions of each component, T_{g1} and T_{g2} are the corresponding T_g values of each component; the constant K can be estimated using free volume theory with a knowledge of the densities (ρ_1 and ρ_2) of both components:

$$K \approx \frac{\rho_1 T_{g1}}{\rho_1 T_{g1}}$$

FT-IR spectra were recorded with a Perkin–Elmer Spectrum 1.0 spectrometer (Perkin–Elmer, US). Samples were prepared in KBr discs.

Powder X-ray diffraction spectra of NIF and SD were obtained by using a Rigaku D III/max diffractometer for powder diffraction, CuKα radiation (Rigaku, J.).

Dissolution tests of commercial NIF, SD and corresponding physical mixtures were carried out by using the USP 24 paddle dissolution apparatus. Temperature, 37 ± 0.5 °C; paddle speed, 100 rpm; dissolution medium, 900 ml of water; time, 1 h; wavelength, 235 nm. Each sample was previously mixed with Avicel PH 101 1:2 w/w.
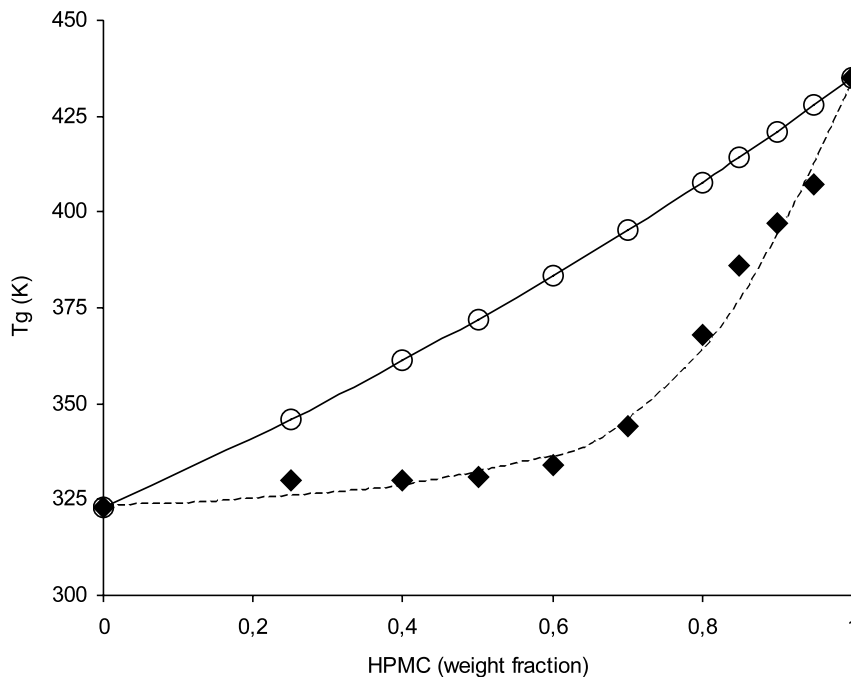
SD from ideal mixing was verified by comparison of the experimental T_g with those predicted by Gordon Taylor equation:

$$T_g = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2}$$

Fig. 2. T_g values of SD in function of composition. The solid line represents the prediction of the Gordon Taylor equation, the dotted line represents the pattern of the T_g experimental values.

NIFEDIPINE

SOLID DISPERSIONS

Commercial NIF

Spray dried NIF

Amorphous NIF

NIF/HPMC
0.75/0.25
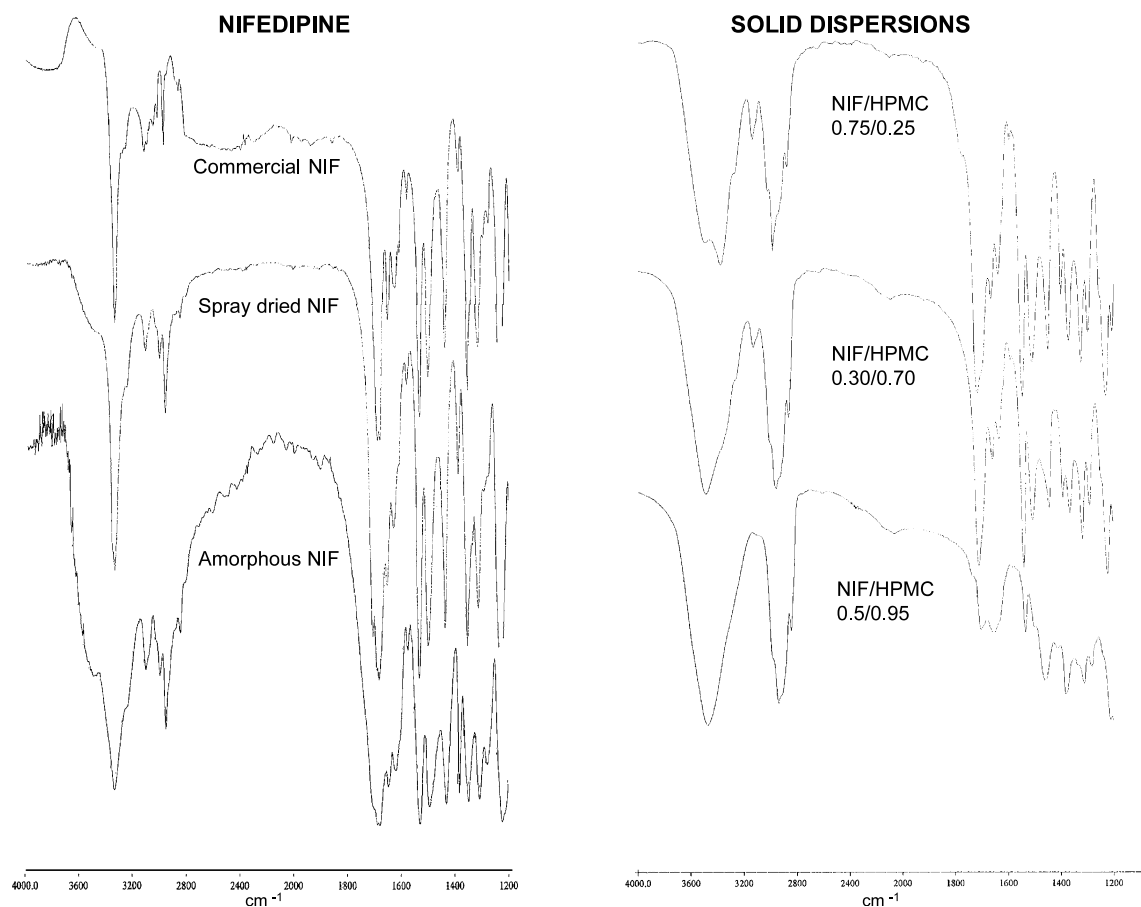
NIF/HPMC
0.30/0.70

NIF/HPMC
0.5/0.95

cm⁻¹

cm⁻¹

Fig. 3. FT IR spectra.

In all cases the prepared particles had a smooth surface and an irregular shape. The X-ray diffraction patterns of physical mixtures appeared as the sum of the spectra of the single components according to NIF/HPMC ratio (Fig. 1). In the SD X-ray diffraction patterns the characteristic peaks of crystalline NIF disappeared and the X-ray diffraction patterns of the SD were similar to the spectrum of HPMC, only when the NIF/HPMC ratios were higher than 50/50 w/w some peaks of crystalline NIF appear (Fig. 1).

DSC thermogram of HPMC exhibited a glass transition at about 162 °C. DSC thermogram of commercial NIF showed an onset melting temperature at 172 °C; DSC thermogram, conducted after melting and cooling of NIF, exhibited a glass transition of the drug at about 50 °C and produced an exothermic peak at 116 °C which could be attributed to crystallization of the amorphous drug; spray dried NIF showed an exothermic peak probably due to the presence of a small fraction of amorphous NIF and an endothermic peak at 172 °C. In thermograms obtained from SD, the endothermic peak at 172 °C disappeared when NIF/HPMC ratios were lower than 30/70 w/w; the exothermic peak was not noticeable in all cases, moreover only one T_g was observed indicating miscibility between NIF and HPMC (Table 1). The experimental T_g values of SD were lower than the T_g values predicted by Gordon Taylor equation suggesting some type of non-ideality of mixing at the considered concentrations (Fig. 2).
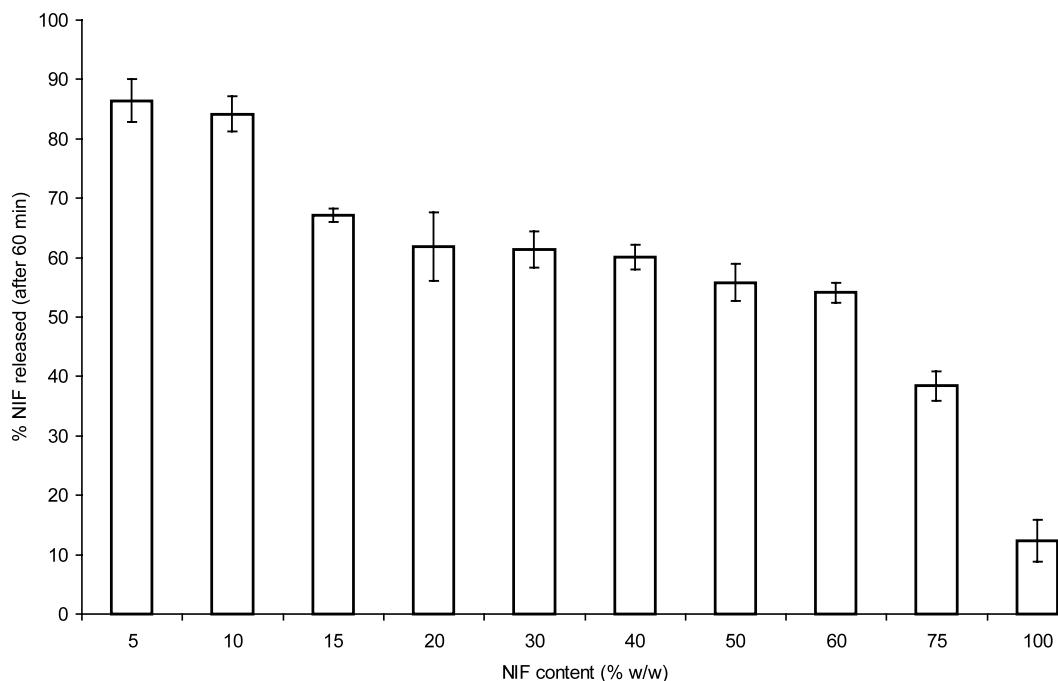
Fig. 4. Percentage of NIF released from SD after 60 min.

The most interesting bands of NIF FT-IR spectra are the NH stretching vibrations and the C=O stretch in esteric groups. In the crystalline NIF these bands are, respectively, at 3331 and at 1688 cm^{-1} while, in the case of amorphous NIF, these bands shifted to highest wavenumbers and appeared as strong broad bands (Fig. 3). The morphological changing and the shift of these bands to free NH and C=O regions could be attributed to the rupture of intermolecular hydrogen bond between the two functional groups evidenced in the crystalline structure of NIF (Triggle et al., 1980). In the SD, the NIF NH stretching vibration disappeared at the lowest NIF/HPMC ratios, while it became evident at the ratio NIF/HPMC 30/70 w/w and its intensity grew increasing the percentage of loaded NIF; the morphology of the two considered peaks appeared most similar to that of amorphous NIF rather than crystalline NIF (Fig. 3).

The prepared SD improved the NIF dissolution rate in comparison with the commercial NIF or NIF/HPMC physical mixtures. In the case of SD,

the maximum concentration of NIF in the dissolution medium increased decreasing the NIF content (Fig. 4).

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