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Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state

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Abstract

Nifedipine is a highly photosensitive drug that requires restricted protection from light during manufacturing, storage and handling of its dosage forms. Inclusion complexation of nifedipine with cyclodextrins (CDs) could be advantageous in protecting the drug against the effect of light. In this study, solid inclusion complexes of nifedipine with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and dimethyl-β-cyclodextrin (DM-β-CD) were prepared using the coprecipitation method. The obtained solid inclusion complexes have been confirmed by differential scanning calorimetry (DSC), X-ray diffraction and infrared spectroscopy (IR). The IR spectra indicated partial inclusion of nifedipine molecules into CD cavities through the dihydropyridine ring. Inclusion complexation was also associated with a dramatic enhancement of drug dissolution with magnitudes depended on the type of CD. The effect of exposure to fluorescent lamp and sunlight on the photodegradation of uncomplexed and complexed nifedipine was tested. Photodegradation of nifedipine was monitored using a high performance liquid chromatographic (HPLC) assay method. Inclusion complexation of nifedipine showed to retard drug photodegradation as indicated by degradation rate constant lowering with values depended on light source and type of complexing agent. This effect was the least with β-CD compared with that of modified β-CD. It was also interesting to notice that inclusion complexation of nifedipine offered much higher protection against the effect of fluorescent lamp than that of sunlight. The obtained results suggests that the design of solid dosage forms of nifedipine such as a fast dissolving nifedipine tablets is possible with the advantages of low required light protection.

Keywords: Nifedipine; Cyclodextrins; Inclusion complexes; Fluorescent lamp irradiation; Sunlight irradiation; Photostability

1. Introduction

Cyclodextrins (CDs) are known for their ability to molecular encapsulate a wide variety of drugs into their hydrophobic cavity (Stella and Rajewski, 1997). The interaction of CDs with labile compounds can retard drug degradation, accelerate degradation, or have no effect on drug

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molecules reactivity (Backensfeld et al., 1991; Loftsson, 1995). The protective effects of CDs against photodecomposition of some photosensitive compounds have been reported (Scalia et al., 1998; Mielcarek and Daczkowska, 1999; Sortino et al., 1999). Mielcarek (1995) studied the effect of inclusion complexation with β-cyclodextrin (β-CD) on the photostability of some 1,4 dihydropyridine derivatives. He concluded that the photostabilities of nimodipine, nitrendipine and nicardipine were improved by five to ten times while, photostability of the most photosensitive compound, nisoldipine, was increased 100 times upon inclusion.

Nifedipine is a dihydropyridine calcium channel antagonist that is practically insoluble in water and highly photosensitive. The main photodegradation products of nifedipine are nitroso-and nitro derivatives (Fig. 1) while, the others are just minors (Matsuda et al., 1989; Hayase et al., 1994). The kinetics of nifedipine photodegradation is strongly dependent on light intensity and spectral distribution of the used light source (Matsuda et al., 1989; Thoma and Klimek, 1991). Thus, nifedipine undergoes faster degradation in normal sunlight than under exposure to a light bulb (Thoma and Klimek, 1991). Although photodegradation of nifedipine proceeds more markedly in solution than in a solid form, various solid-state preparations of nifedipine decomposed completely in about 5 days under exposure to normal room light (Hayase et al., 1994). Ohkubo et al. (1992) also reported that the photodegradation of nifedipine in pulverized tablets, when used as a hospital prescription, was very marked when exposed to normal room light with a decrease of 20% in nifedipine content after 18 h.

The work in this study was performed to evaluate the effects of inclusion complexation with β-CD, hydroxypropyl-β-cyclodextrin (HP-β-CD) and dimethyl-β-cyclodextrin (DM-β-CD) against photodegradation of the extremely photosensitive nifedipine in solid state. The photodegradation of pure nifedipine and its inclusion complexes with CDs were monitored upon exposure to fluorescent lamp and sunlight.

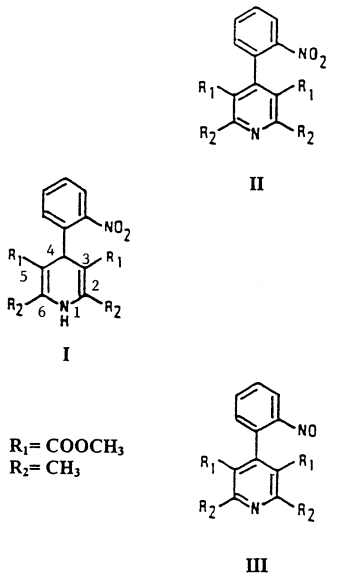

Fig. 1. Chemical structures of nifedipine (I) and its nitroso-derivative, 4-(2-nitrosophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl pyridine (II) and nitro-derivative, 4-(2-nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl pyridine (III).

2. Materials and methods

All experiments were carried out under restricted light-protection conditions and sodium lamp was used when necessary as a light source to prevent undesirable photodegradation of nifedipine.

2.1. Materials

Nifedipine (Batch no. N9708-54) was kindly provided by Dar Al Dawa (Na'ur, Jordan). The sample was shown to be free from any photodegradation products as indicated by HPLC assay. The drug was stored in an amber glass container wrapped with aluminium foil and kept in a refrigerator at 5–7 °C. The complexing agents β-CD, HP-β-CD with 0.8 average degree of substitution and DM-β-CD were purchased from Sigma chemical company (St. Louis, MO, USA). Nitro-derivative of nifedipine was obtained from Bayer (Wuppertal, Germany). Antipyrine was used as internal standard for nifedipine assay

and was purchased from Riedel-De Haenag (Seelze-Hannover, Germany). Acetonitrile and methanol used for chromatographic assay of nifedipine were of HPLC grade (BDH Chemicals Ltd, Poole, England). All other chemical and solvents were of analytical reagent grade.

2.2. Preparation of inclusion complexes

The inclusion complexes of nifedipine with different types of CDs were prepared at a stoichiometric ratio of 1:1 using the coprecipitation method. Nifedipine was dissolved in the least volume of ethanol at 40 °C and then the required amount of each type of CDs in distilled water was added gradually to the ethanolic solution with continuous sonication. The obtained solution in each case was then maintained under stirring for 24 h at room temperature. The solvent was then evaporated under vacuum at 40 °C using a rotary evaporator (Rotavapor RE120, Model B-465, Buchi, Switzerland) until a constant weight was obtained. All samples, after pulverization and sieving through a 63 μm opening size sieve (British standard), were protected from light and kept in a vacuum desiccator till further use.

2.3. Preparation of nifedipine-CDs physical mixtures

Physical mixtures of nifedipine with different types of CDs in 1:1 molar ratios were prepared by a dry mixing of exactly weighed amounts of nifedipine (1.4 gm) with each of β-CD (5.17 g), HP-β-CD (6.21 g) or DM-β-CD (5.67 g) for 15 min using a turbula mixer (Erweka-Appartebau, type S2Y220, Hensentamm, Germany) at 50 rpm in a dark glass vessel which was filled to about 25% of its capacity. All used powders were passed through a laboratory sieve of 63 μm opening size before mixing.

2.4. Differential scanning calorimetry (DSC)

The DSC analysis was carried out for pure nifedipine, pure CDs, physical mixtures of nifedipine and CDs at 1:1 molar ratio and corresponding solid coprecipitates. The DSC patterns were recorded on a Perkin-Elmer DSC-4 (Norwalk, USA) equipped with a thermal analysis data station. Each sample (2–4 mg) was heated in crimped aluminum pans at a scanning rate of 10 °C/min in an atmosphere of nitrogen using the range of 150–350 °C. The heat of fusion was calibrated with indium (purity: 99.99%, melting point: 157.07 °C, $\Delta H = 20.37$ J/g, heating rate: 10 °C/min) and was determined from an average of three measurements, which was within 3% of each other.

2.5. X-ray diffractometry

X-ray powder diffraction patterns were obtained with a Siemens D-5000 X-ray diffractometer (Germany) using a Ni filtered CuK(α) radiation at scanning rate of 2°/min under a voltage of 40 kV and at a current of 35 mA for the generator. The diffractograms were recorded from 5 to 35° (2θ) at a time constant = 1.0 s and step size = 0.040°.

2.6. Infrared spectroscopy (IR)

Infrared spectra of nifedipine-CDs solid complexes were obtained using a Perkin–Elmer Infrared Spectrophotometer (Mod. 580 B, USA) according to the potassium bromide disk method. The IR spectra of pure nifedipine and CDs as well as their physical mixtures of 1:1 molar ratio were also obtained by the same procedure for comparison.

2.7. Dissolution studies

Solid samples (after sieving through a 63 μm sieve) including nifedipine powder, physical mixtures of drug and CDs in equimolar ratio as well as corresponding solid complexes were subjected to dissolution studies. The dissolution studies were carried out at 37 ± 0.5 °C with 50 rpm paddle rotation speed in a USP XXIII dissolution test apparatus II (paddle method), using an automated monitoring system (Caleva Ltd., Model 85 T). The monitoring system consisted of an IBM computer PK 8620 series and PU 9605/60 dissolution system software, Philips UV/Vis/NIR single

beam spectrophotometer PU 8605/50 eight cell program, Epson LX 850 printer and Watson-Marlow peristaltic pump. Briefly, 10 mg of nifedipine or an equivalent amount of the complexes or the physical mixtures were added to 750-ml dissolution medium of simulated gastric fluid without pepsin. Drug dissolution was monitored spectrophotometrically at 236 nm for up to 3 h. Sink condition was maintained throughout the dissolution time since the amount of dissolved nifedipine in the medium was much lower than its solubility. Each experiment was carried out in triplicate and the mean of the three dissolution tests was recorded.

2.8. Preparation of samples for irradiation

All samples were passed through a 63-μm sieve to obtain fine powders with uniform particle sizes before irradiation tests.

2.9. Photoirradiation test

2.9.1. Irradiation by fluorescent lamp

The irradiation test was employed utilizing a fluorescent lamp (FL-15 Watt, vacuum tube length 42 cm, Chiyoda, Indonesia). Each sample of pure nifedipine powder, nifedipine-CDs physical mixtures at 1:1 molar ratio and corresponding nifedipine-CDs coprecipitated solid complexes was placed and spread uniformly as a thin film on a glass plate (75 × 52 mm). The fine powders on the glass plates were discrete enough to allow for uniform irradiation. Irradiation was conducted inside a light cabinet (Infos AG, CH-4015 Basel, Karl Kolb Scientific Technical Supplies, Buchschlag, Frankfurt, Germany) to protect samples from extraneous light. All sides of glass plates were allowed to expose to radiation. The distance between the lamp and samples was 30 cm. The accelerated irradiation test using this lamp was carried out at ambient temperature. Samples were assayed for their content of nifedipine prior to exposure and at 6, 12, 18, 24, 30, 36, 42, 54, 66, 78, 96, 120, 144 and 192 h of continuous exposure ($n = 3$ replicate samples/time interval) using a HPLC assay method.

2.9.2. Irradiation by sunlight

The photostability study using natural sunlight as a light source was performed on selected sunny and clear sky days (easy to get in our region). Each powder sample was spread on a glass plate as previously described in case of irradiation by fluorescent lamp. Samples were exposed to sunlight only during sunny hours. Total sample exposure time was calculated by adding times of exposure to sunny hours. Samples were tested for nifedipine content prior to exposure and at 2, 4, 6, 8, 12, 16, 24, 36 and 48 h of exposure to sunlight at ambient temperature ($n = 3$ replicates). All samples were exposed to light at same conditions to facilitate the comparative study for the effect of sunlight on complexed and uncomplexed nifedipine. The drug content of each sample was determined using a HPLC assay method.

2.10. Assay of nifedipine

Nifedipine have been assayed using a modified HPLC method to that described by Matsuda et al. (Matsuda et al., 1989). The HPLC system (Waters Associates, Milford, MA, USA) was equipped with model 6000 A reciprocating pump and a model U6K universal injector. A model 486 variable wavelength detector was used to monitor the drug and the output was recorded using model 730 data module (Waters Associates). Chromatographic separation was performed using a Nova-Pak C-18 Cartridge column (100 mm length × 5 mm i.d., 4 μm particles). The mobile phase consisted of a solvent system of methanol:acetonitrile:water (35:15:50% v/v). The mobile phase was pumped at a flow rate of 2.8 ml/min. The column effluent was monitored at 236 nm and attenuation at 0.007 a.u.f.s. Nifedipine working standard solution in methanol (100 μg/ml) was prepared and kept in an amber glass bottle, and stored tightly closed at 4 °C. Nifedipine solution was found to maintain its original concentration at these conditions for a period of at least 4 months. Antipyrine (internal standard, IS) stock solution in methanol (100 μg/ml) was also prepared. A calibration curve of nifedipine was constructed

by diluting different volumes of the nifedipine working standard solution into 1000 μl with methanol containing 25 μl of antipyrine stock solution to give 1, 2, 4, 6, 8 and 10 μg/ml of nifedipine. An aliquot of 25 μl of each sample was injected into the loop of the injector of the HPLC system and the ratios of drug to I.S. peak area were calculated. The obtained results were submitted to linear regression analysis. The standard curve was repeated six times and the mean values were reported and used for the determination of nifedipine in unknown samples. An aliquot of 2 ml of a methanol/chloroform (50:50 v/v) was added to a suitable weight (10 mg nifedipine or its equivalent) of each irradiated powder sample in a clean dry screw-capped glass centrifuge tube (10 ml). The mixture was shaken using a vortex mixer (Vortex-2 Genie, Scientific Industries Inc., Bohemia, NY, USA) for 1 minute and then centrifuged for 5 min using MSE Mistral 1000 centrifuge (Loughborough, Manchester, UK). An aliquot of 50 μl of supernatant solution was diluted to a final volume of 2 ml with 50% methanol/chloroform solution and vortexed for 30 s. An 80-μl volume of the diluted solution was then transferred to another glass centrifuge tube containing 25 μl of antipyrine stock solution. The sample was then evaporated to dryness in a rotary evaporator and reconstituted with 1000 μl of methanol and the solution was then shaken with a vortex mixer for 15 s and centrifuged for 2 min in a microcentrifuge (Model 1-13, Sigma Co., Osterode am Harz, Germany). An aliquot of 25 μl of each sample was then injected directly into the loop of the injector of the HPLC system and subjected to analysis to determine the concentration of unchanged nifedipine. Sample preparation and analysis were conducted at room temperature under sodium lamp.

3. Results and discussions

In order to study the photostability of complexed nifedipine, it was necessary to confirm and characterize the produced drug-CD inclusion complex.

3.1. Characterization of nifedipine-CD solid inclusion complexes

Characterization of the solid binary systems of nifedipine with different CDs was carried out using DSC, X-ray diffractometry and IR spectroscopy. The DSC curves of pure nifedipine, different CDs, respective drug-carrier equimolar physical mixtures and corresponding coprecipitates are depicted in Fig. 2. Nifedipine showed a characteristic sharp endothermic peak at 175.15 °C, indicating the melting point of the drug with thermal heat of fusion equal to 78.85 ± 2.17 J/g. The obtained DSC curves for all tested pure CDs did not show any endothermic peaks in the melting region of nifedipine (Fig. 2). All physical mixtures of nifedipine with CDs were nearly superpositioned with the recorded CD curves and drug melting endotherm with some broadening and reduction in intensity of nifedipine peak. On the other hand, marked broadening and distinct reduction in peak intensity with shifting of drug endotherm was displayed for nifedipine coprecipitate with each tested CD. Coprecipitation was also accompanied with a reduction in melting peaks of β-CD and DM-β-CD at about 320 and 340 °C, respectively. The modification in DSC curves could be assumed to indicate interaction between nifedipine and CDs in solid state. Furthermore, heats of fusion of coprecipitated nifedipine with CD were much smaller than those of corresponding physical mixtures. The enthalpy values were 13.43 ± 0.39, 12.58 ± 0.28 and 10.75 ± 0.22 J/g for nifedipine coprecipitated with β-CD, HP-β-CD and DM-β-CD, respectively, compared with 25.11 ± 0.58, 17.52 ± 0.47 and 16.07 ± 0.40 J/g, respectively, for the corresponding physical mixtures. The reduction in enthalpy values could be considered as an evidence for nifedipine-CDs interactions (Ahmed et al., 1998).

A further supporting evidence for the formation of inclusion complex was obtained from the X-ray diffraction patterns for powders of pure components, equimolar physical mixtures and corresponding coprecipitates of nifedipine and the tested CDs (Fig. 3). The diffraction patterns of the investigated physical mixtures of nifedipine and CDs at 1:1 molar ratios were apparently

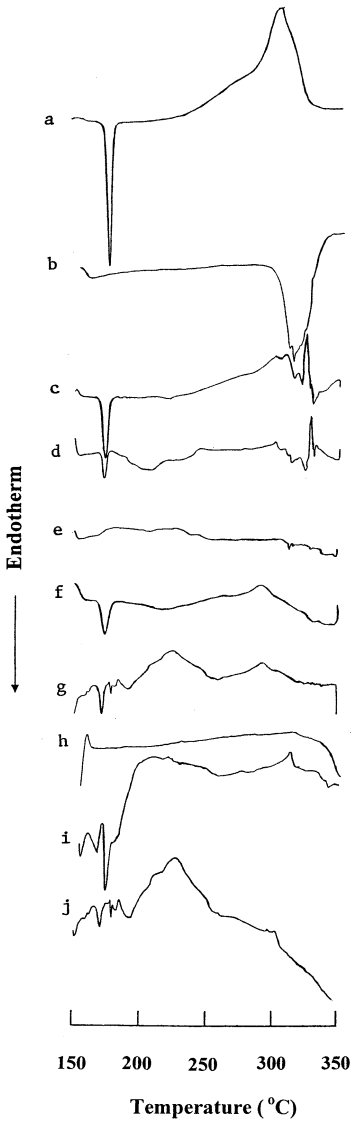

Fig. 2. DSC curves of nifedipine-CD systems. (a) Pure nifedipine; (b) pure β-CD; (c) nifedipine-β-CD physical mixture (d) nifedipine-β-CD coprecipitated complex; (e) pure HP-β-CD; (f) nifedipine-HP-β-CD physical mixture; (g) nifedipine-HP-β-CD coprecipitated complex; (h) pure DM-β-CD; (i) nifedipine-DM-β-CD physical mixture; (j) nifedipine-DM-β-CD coprecipitated complex.

superposition of diffraction pattern of the components in each mixture, indicating that drug maintained its crystallinity in the respective physical mixtures. On the other hand, the X-ray diffraction patterns of coprecipitated systems were apparently different from those of physical mixtures. The diffraction patterns of coprecipitated samples showed less degree of crystallinity for the drug as evidenced by fewer peaks of lower intensity. The

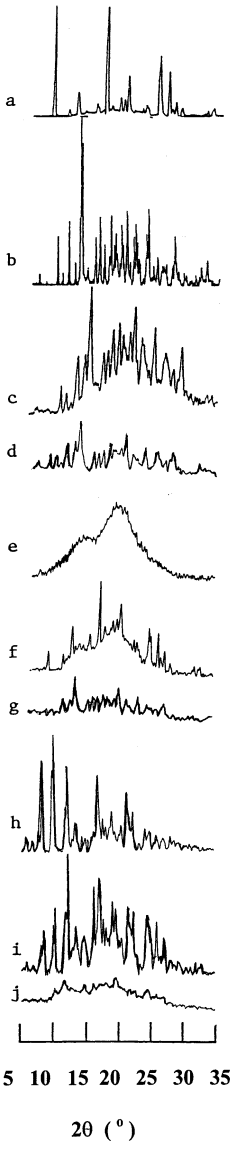

Fig. 3. X-ray powder diffraction patterns of nifedipine-CD systems. (a) Pure nifedipine; (b) pure β-CD; (c) nifedipine-β-CD physical mixture (d) nifedipine-β-CD coprecipitated complex; (e) pure HP-β-CD; (f) nifedipine-HP-β-CD physical mixture; (g) nifedipine-HP-β-CD coprecipitated complex; (h) pure DM-β-CD; (i) nifedipine-DM-β-CD physical mixture; (j) nifedipine-DM-β-CD coprecipitated complex.

characteristic diffractional peaks relevant to crystalline nifedipine at $2\theta = 8$ and 16° were with remarkable low intensity for nifedipine-β-CD coprecipitate. On the other hand, the characteristic nifedipine peaks were nearly disappeared with HP-β-CD and DM-β-CD coprecipitates. The modified and hollow patterns of the solid complexes could suggest the formation of different crystal structure or amorphous inclusion compounds (Zerrouk et al., 1998).

Fig. 4 show the IR spectra of different nifedipine-CDs systems compared with pure nifedipine. Pure nifedipine showed IR absorption bands at 1690 per cm for the ester carbonyl stretching band, 1120 and 1225 per cm for ether absorption bands of C3 and C5, respectively (Fig. 1). The absorption bands at 1496 and 1527 per cm were denoted for stretching vibration of C=C in the aromatic ring while, 1310 per cm was denoted for NO_2 group and 3331 per cm for N–H group. The spectra of pure CDs showed the vibration of free –OHs between 3300 and 3500 per cm and those of the bound –OHs at 2910 per cm (El-Mahrouk et al., 1994). The spectra of all nifedipine-CD systems did not show new peaks, indicating no chemical bonds were created in the formed compounds. It was clear that some of IR absorption peaks in coprecipitated products were different from that of the corresponding physical mixtures that showed superposition of the spectra of pure components. It was noticed that ester carbonyl stretching band of nifedipine has shifted from the value of 1690 per cm to lower frequencies of 1675, 1669 and 1665 per cm for β-CD, HP-β-CD and DM-β-CD coprecipitates respectively. These could indicate intermolecular hydrogen bonding between nifedipine and all tested CDs that led to restrictions within the CD cavity (Lin and Kao, 1989; Ozdemir and Ordu, 1998). Although no appreciable changes were observed at the bands of ether groups (1120 and 1225 per cm), the band at 1120 has nearly disappeared when inclusion complex was formed between nifedipine and DM-β-CD. These results served to confirm the existence of a strong interaction between nifedipine and DM-β-CD. On the other hand, the nitro band at 1310 as well as the C=C bands at 1496 and 1527 per cm of aromatic ring were not shifted and this could suggest that the aromatic ring was not included into the cavity of CDs. Moreover, the absorption band at 3331 per cm ascribed to stretching vibrations of the N–H bond in the dihydropyridine ring was broaden, slightly shifted

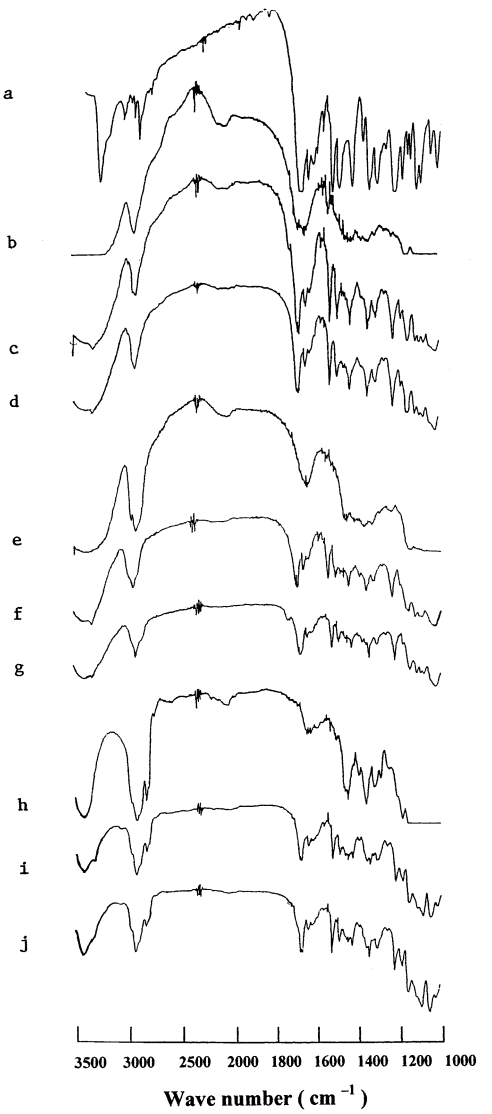

Fig. 4. IR spectra of nifedipine-CD systems. (a) Pure nifedipine; (b) pure β-CD; (c) nifedipine-β-CD physical mixture (d) nifedipine-β-CD coprecipitated complex; (e) pure HP-β-CD; (f) nifedipine-HP-β-CD physical mixture; (g) nifedipine-HP-β-CD coprecipitated complex; (h) pure DM-β-CD; (i) nifedipine-DM-β-CD physical mixture; (j) nifedipine-DM-β-CD coprecipitated complex.

or nearly disappeared in the coprecipitated samples spectra. Thus, the IR spectra may indicate that nifedipine molecule is partially included into CD cavities through the dihydropyridine ring. The above results of DSC, X-ray diffraction and IR spectroscopy clearly confirm that nifedipine-CDs coprecipitated solids exist in the form of inclusion complexes.

In addition, inclusion complexation of nifedipine with CDs showed to improve the dissolution properties of the drug (Fig. 5). The dissolution of nifedipine was significantly enhanced by inclusion complexation compared with pure drug and physical mixtures. The enhancement in nifedipine dissolution was explained to be mainly due to the increase in both wettability and solubility and/or the decrease in the crystallinity of the drug by inclusion complexation. The prepared solid inclusion complexes using HP-β-CD and DM-β-CD, exhibited superior enhancement in nifedipine dissolution compared with that prepared with the parent β-CD.

3.2. Photostability study of nifedipine

Good linearity was obtained for nifedipine calibration curve using concentrations in the range of 1–10 μg/ml. The least square linear regression analysis of the standard calibration curve data ($n = 6$) gave the equation: $y = 0.468\ x + 0.0424$, $r = 0.999$. The standard curves were constructed on six different days over three weeks. The coefficient of variation (CV%) for the slope of individual calibration curves was 2.14% indicating a high stability and precision for the assay and invariable good reproducibility of the data. The linear regression equation of the calibration curve was used to calculate nifedipine concentration in sample after irradiation. The limit for detection of nifedipine was found to be 0.2 μg/ml using this

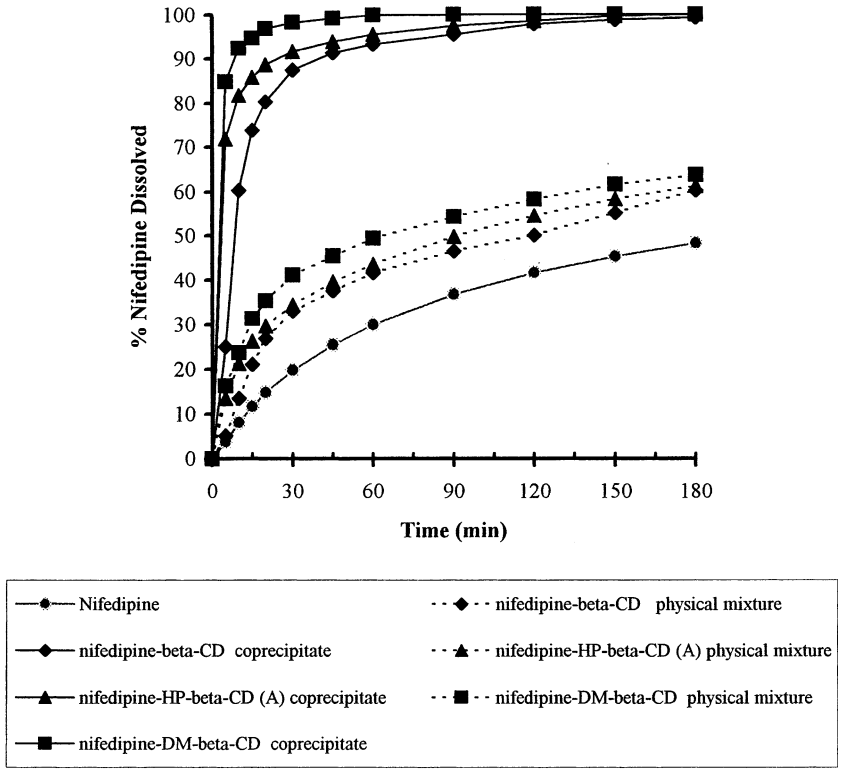

Fig. 5. Dissolution profiles of nifedipine from different nifedipine-CD systems in simulated gastric fluid without pepsin at 37 ± 0.5 °C.

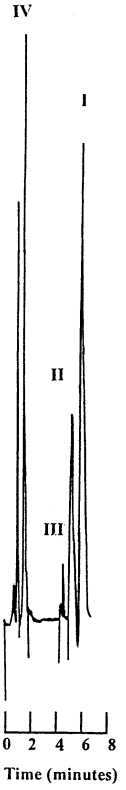

Fig. 6. Typical HPLC chromatogram of nifedipine and its photodegradation products after nifedipine irradiation by fluorescent lamp for 120 h. I. nifedipine (6.31 min); II. nitroso-derivative (5.50 min); III. nitro-derivative (4.65 min); IV. antipyrine (1.61 min)

system. The within-day precision was evaluated using six replicates of three concentrations (2.5, 4.5 and 7.5 μg/ml) and the CV% ranged between 1.55 and 1.85%. While, the between-day precision was assessed over three weeks using the above concentrations and the CV% ranged between 1.68 and 2.63%.

Fig. 6 shows a typical HPLC chromatogram of nifedipine after irradiation by a fluorescent lamp for 120 h. The two main photodegradation products, namely: nitroso- derivative [4-(2-nitrosophenyl)-2,6-dimethyl-3,5-dimethoxy carbonyl- pyridine] and nitro-derivative [4-(2-nitrophenyl) - 2,6 - dimethyl - 3,5 - dimethoxy-carbonyl-pyridine] were distinct. No interfering peaks were observed under the experimental conditions. It was observed that the peak corresponding to nitroso- and nitro-derivatives were eluted at 5.50 and 4.65 min, respectively, compared with 6.31 min for nifedipine and 1.61 min for antipyrine (I.S.). Some other known and unknown photodegradation products, which are produced in minor amounts, were previously reported (Matsuda et al., 1989; Hayase et al., 1994) and not detected in the present assay method. Similar results with different peaks intensity were obtained for samples irradiated with sunlight. In the solid state, the nitroso-derivative was formed in early stage of irradiation while nitro-derivative was slowly formed. Although temperature change was possible during irradiation of nifedipine, this change in temperature was shown to have no significant effect on degradation rate of nifedipine suggesting that, the activation energy for the degradation is negligibly small. The energy available in a photochemical reaction is much greater than that for a thermal reaction. Therefore, photochemical reaction depends very rarely on temperature in activating molecules. This also suggested that nifedipine will be easily decomposed by light even at very low temperature (Matsuda et al., 1989).

The decomposition of uncomplexed nifedipine was found to be very marked upon exposure to either fluorescent lamp or sunlight (the main source of light during manufacturing, storage and handling). The photodegradation of solid nifedipine followed apparent first-order kinetics and this was in agreement with previous reports (Matsuda et al., 1989; Teraoka et al., 1999). Table 1 shows that times for 50% drug degradation ($T_{0.5}$) were 174.72 ± 4.24 and 33.20 ± 0.88 h for irradiation by fluorescent lamp and sunlight, respectively while, times for 10% drug degradation ($T_{0.9}$) were reached after about 26.47 ± 0.64 and 5.02 ± 0.13 h of irradiation by both light sources, respectively. The calculated degradation rate constants for uncomplexed nifedipine (k_n) were $3.97 \pm 0.10\ 10^{-3}$ and $20.87 \pm 0.54\ 10^{-3}$ per h under irradiation by fluorescent lamp and sunlight, respectively, indicating that nifedipine powder undergoes more than 5-fold faster degradation on exposure to sunlight than that of fluorescent lamp.

Photodegradation of nifedipine exposed to fluorescent lamp occurred at wavelengths below 500 nm. Fluorescence light of 314, 366 and 402 nm irradiation contributed in the production of nitroso- and nitro-derivatives. However, nitroso-derivative can showed high levels even in the visible region. These facts suggest that the drug must be thoroughly protected from not only UV but also from visible light (Matsuda et al., 1989). Although the wavelengths of light incident on nifedipine samples from sunlight could not be accurately defined in this study, it was important to monitor the effect of sunlight on nifedipine photodegradation where this source of light is highly used in sunny regions.

The effect of inclusion complexation of nifedipine with CDs on the photostability of the drug was explored by studying the decomposition kinetics of the drug. Nifedipine was highly protected against photodegradation by inclusion complexation. The determined values of degradation rate constants of nifedipine present in physical mixtures with CDs or as inclusion complexes (k), $T_{0.5}$, as well as $T_{0.9}$ upon irradiation by both light sources are also shown in Table 1. It is clear that CDs in physical mixtures with nifedipine did not sufficiently protect the drug from photodegradation. The degradation rate constants lowering of nifedipine were only small and ranging between 1.03 and 1.07 folds. This small protective effect could be due to some screening effect of CDs particles for the passage of light to reach nifedipine molecules. On the other hand, inclusion complexation of nifedipine with CDs showed dramatic decreases in degradation rate constants and increases in the values of $T_{0.5}$, $T_{0.9}$ and degradation rate constants lowering (Table 1). However, the lowering in degradation rate constants of complexed nifedipine was the least with β-CD compared with that of modified β-CDs. It was interesting to notice that inclusion complexation of nifedipine with CDs offered much higher protection from the effect of fluorescent lamp than sunlight irradiation. The degree of degradation rate constants lowering were 8.53, 13.84, and 32.99 folds for nifedipine complexed with β-CD, HP-β-CD, and DM-β-CD, respectively, upon exposure to fluorescent lamp compared with 4.40,

Table 1
Stability of nifedipine and its solid inclusion complexes after exposure to fluorescent lamp or sunlight

Light source	Nifedipine status	K[b] ± S.D. ($\times 10^3$ per h)	$T_{0.5}$[c] ± S.D. (h)	$T_{0.9}$[d] ± S.D. (h)	K_n/k[e]
Fluorescent lamp					
	Uncomplexed	3.97 ± 0.10	174.72 ± 4.24	26.47 ± 0.64	1.00
	β-CD PM[a]	3.86 ± 0.24	179.72 ± 10.89	27.23 ± 1.65	1.03
	β-CD complex	0.47 ± 0.06	1491.19 ± 213.69	225.95 ± 32.38	8.53
	HP-β-CD PM	3.74 ± 0.17	185.38 ± 8.43	28.09 ± 1.28	1.06
	HP-β-CD complex	0.29 ± 0.04	2418.93 ± 336.24	366.52 ± 50.95	13.84
	DM-β-CD PM	3.70 ± 0.20	187.33 ± 0.39	28.38 ± 1.57	1.07
	DM-β-CD complex	0.12 ± 0.01	5764.14 ± 771.97	873.38 ± 117	32.99
Sunlight					
	Uncomplexed	20.87 ± 0.54	33.20 ± 0.88	5.03 ± 0.13	1.00
	β-CD PM	19.92 ± 1.16	34.78 ± 2.04	5.27 ± 0.31	1.05
	β-CD complex	4.74 ± 0.51	146.20 ± 16.11	22.15 ± 2.44	4.40
	HP-β-CD PM	19.67 ± 0.79	35.23 ± 1.43	5.38 ± 0.22	1.06
	HP-β-CD complex	2.66 ± 0.27	260.39 ± 26.77	39.45 ± 4.06	7.84
	DM-β-CD PM	19.53 ± 1.02	35.49 ± 1.84	5.38 ± 0.28	1.07
	DM-β-CD complex	1.70 ± 0.21	406.70 ± 47.92	61.62 ± 7.26	12.25

[a] Physical mixture.
[b] Degradation rate constants of nifedipine.
[c] Time to decompose 50% drug.
[d] Time to decompose 10% drug.
[e] Degradation rate constant lowering (x-fold).

7.84, and 12.25, respectively, for sunlight irradiation. Accordingly, fluorescent lamp is more suitable as a light source during product manufacturing rather than sunlight. Protection of complexed nifedipine against photodegradation could be due to inclusion of dihydropyridine ring into CD cavity where, dihydropyridine ring is involved in the first step of drug photodegradation (Hayase et al., 1994).

The results of this study indicated that it is possible to successfully prepare nifedipine-CD inclusion complex in solid state by coprecipitation. The formed inclusion complexes can efficiently retard the photodegradation of nifedipine upon exposure to fluorescent and sunlight. The degree of drug protection against the effect of light is dependent on source of light and type of complexing CD. Thus, the design of solid dosage form of nifedipine such as fast dissolving tablets is possible with the advantages of low required light protection during manufacturing, storage and handling.

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