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COMMUNICATION

Analytical Study of Photodegradation of Inclusion Complexes of Nimodipine with α-, γ-Cyclodextrin, Methyl-β-Cyclodextrin, and Hydroxypropyl-β-Cyclodextrin

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ABSTRACT

The inclusion behavior of α-cyclodextrin (α-CD), γ-cyclodextrin (γ-CD), hydroxypropyl-β-cyclodextrin (HP-βCD), and methyl-β-cyclodextrin (M-βCD) with nimodipine (NM) in solution and in the solid state was investigated.

Inclusion complexes of nimodipine with cyclodextrins (at a molar ratio of 1:1) in the solid state were obtained by the kneading method. Photochemical stability of NM in the solid inclusion complexes was assessed by IR spectrometry. The modified derivatives of β-CD and α-CD were found to slow the photodegradation rate, whereas in the presence of γ-CD the photodegradation of NM was a bit faster than in the corresponding physical mixture.

Photochemical degradation of NM in liquid inclusion complexes was monitored by UV spectroscopy. According to the slowing effect on photodegradation of NM in the inclusion complexes, the studied cyclodextrins can be ordered as γ-CD < α-CD < HP-βCD < M-βCD.

INTRODUCTION

Pharmacological effect of nimodipine (NM) is similar to that of other calcium-channel blocking agents. However, at usual dosages nimodipine, unlike other currently available calcium-channel blockers, appears to affect preferentially the central nervous system. Similarly to other dihydropyridine (DHP) derivatives, nimodipine exerts a vasodilating effect by means of its calcium antagonistic properties. Nimodipine differs from the other known calcium antagonists by its predilective effect on the cerebral vessels. NM seems to have a useful therapeutic effect not only in cerebro-vascular disease but also in osychotic episodes occurring in advanced age (1–4).

Like other DHP derivatives, NM shows certain undesired physical and chemical properties such as low

solubility in water and fast photochemical decomposition. The 1,4-dihydropiridine family suffers from processes of photodecomposition. These drugs undergo important chemical changes, accompanied by alternations in their activities or potencies and the loss of therapeutic activity (5–8).

One method of improving photostability of the compounds from this group involves complexation with oligosaccharide derivatives—cyclodextrins (CD) (9,10). Among natural CDs, β-cyclodextrin (β-CD) is the most suitable for drug complexation. However, the use of β-CD is restricted by its low aqueous solubility that limits its application in the pharmaceutical field.

To avoid this problem, considerable attention has recently been paid to chemically modified CD, the physicochemical properties of which are largely modified with respect to the parent CD. For example, the hydroxypropyl-β-cyclodextrin (HP-βCD) and methyl-β-cyclodextrin (M-βCD) are extremely soluble in water, less hygroscopic than the modified β-CD, and more surface active (11). Furthermore, modified β-CD, like natural β-CD, can form inclusion complexes which modify the solubility, dissolution rate, and bioavailability of the guest molecules (12–14).

The present paper describes formation of the inclusion complexes between NM and M-βCD, HP-βCD, and γ-cyclodextrin (γ-CD). In addition, the photostability of the inclusion complexes was tested.

MATERIALS AND METHODS

HP-βCD, MW 1317.7 g/mol MS = 0.45; M-βCD, MW 1236.8 g/mol MS = 1.8 (Wacker-Chemie GmbH); α-CD, MW 972.9 g/mol; and γ-CD, MW 1297.1 g/mol (Merck) were used without further purification; nimodipine (NM) was from Siegfrieds.

Inclusion Complexes in Solution

Phase diagrams of solubility and the apparent stability constants K of the inclusion complexes of NM with CD were determined using the phase solubility method of Higuchi and Connors in Britton-Robinson buffer (pH = 6.16). After the solutions reached equilibrium, they were filtered and analyzed for drug content at 360.2 nm using a Shimadzu UV-160A spectrophotometer.

The course of the phase diagram obtained for the inclusion complexes of NM with γ-CD was atypical and difficult to classify, whereas for the clathrates with α-CD, M-βCD, and HP-βCD, the A_L type of diagram was observed. The apparent stability constants determined from the phase diagrams of solubility of the formed complexes of NM with α-CD, M-βCD, and HP-βCD were 3.31, 3.73, and 4.27, respectively.

Preparation of Inclusion Complexes in the Solid State

The solid inclusion complexes were prepared by the kneading method. A mixture of NM and CD at a molar ratio 1:1 was wetted with ethanol and kneaded thoroughly for 60 min. During this process an appropriate quantity of the solvent was added (approx. 1.2 g of ethanol). The resultant paste was dried under reduced pressure at room temperature.

The identity of the obtained clathrates was confirmed by the IR absorption spectra, ^{13}C-NMR studies, and DSC measurements as described in a previous paper (15).

RESULTS AND DISCUSSION

DHP derivatives are characterized by high photosensitivity and easily undergo conversion, most frequently to nitro- and nitroso-derivatives of pyridine which do not show any therapeutic activity. The possibility of improving the drug stability by complexation with cyclodextrins has recently attracted much interest.

Formation of inclusion complexes NM with CDs was investigated both in the liquid and solid state.

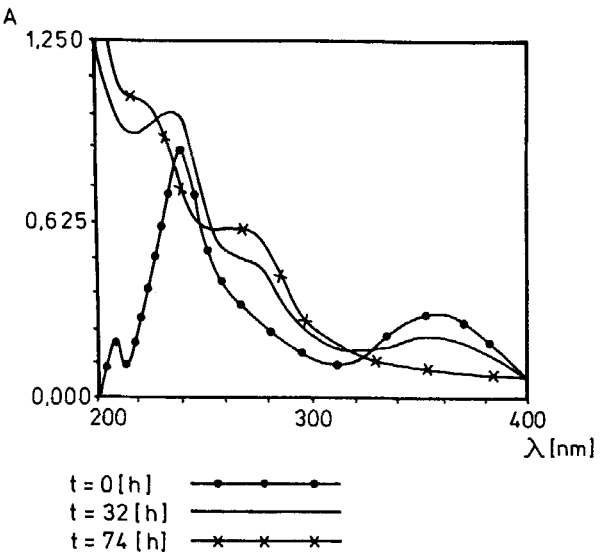

Figure 1. Photochemical decomposition of NM in the inclusion complex with M-βCD in UV light (λ = 254 nm) after 0, 32, and 74 hr.

In order to evaluate photochemical stability of NM in liquid inclusion complexes with the studied cyclodextrins, their solutions at the concentration of 1.3×10^{-4} mol/dm^3 were placed in quartz cuvettes and protected against solvent evaporation. The solutions were exposed to ultraviolet radiation for 80 hr (λ-254 nm, at distance 50 cm) and at proper time intervals the UV spectra were recorded in the range of 200–400 nm.

Changes in the spectra of clathrates with M-βCD after different time intervals of irradiation are illustrated in Fig. 1.

As follows from Fig. 1, as a consequence of irradiation, the absorption band with the maximum at λ = 360.2 nm, related to the presence of DHP ring, gradually decreased and a new maximum of absorption at 270 nm appeared. Similar changes were observed in UV spectra of irradiated liquid inclusion complexes of NM with other cyclodextrins.

The observed changes prove that photodegradation of the inclusion complexes of NM in the liquid state occurred in the way typical for this group of compounds, i.e., the products of NM decomposition showed the absorption maxima characteristic for nitrozo-derivatives of pyridine. Moreover, the photochemical decomposition of NM proved to be a relatively long process when compared, e.g., to photodecomposition of nisoldipine, which together with nifedipine belongs to photolabile ortho-nitrosubstitued DHP derivatives.

It was found that within the time intervals studied, the photodegradation of NM in solution obeyed the first-order kinetic equation and was a single-stage process.

The differences in the NM decomposition rate of different inclusion complexes were estimated from the photodegradation rate constant (k), half-degradation time ($t_{0.5}$) and the time of degradation of 10% of the compound ($t_{0.1}$). The first-order rate constants were calculated from the slope of linear plots of ln A versus time, where A is the concentration of the remaining intact NM (Fig. 2).

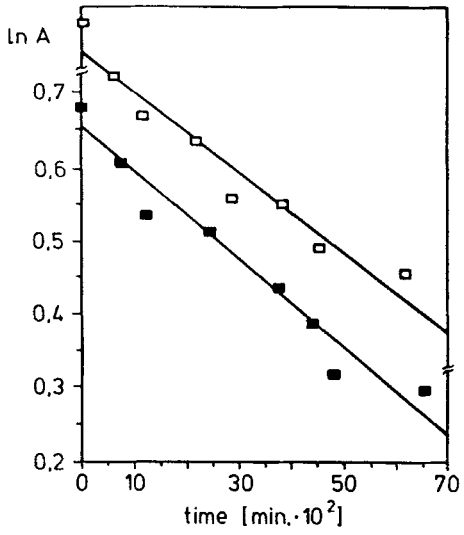

Figure 2. Curves of photodegradation of nimodipine in the inclusion complex with M-βCD; □: inclusion complex, ■: physical mixture.

The kinetic parameters of the process of NM photodegradation are given in Table 1.

As follows from the analysis of parameters given in Table 1, the complexation of NM with CDs in the liquid phase significantly delays its photodegradation. As a result of complexation with cyclodextrins, the half degradation time, which for the crystalline NM is about 1.48 hr, was observed to increase. Photochemical stability of NM in inclusion complexes with HP-βCD and M-β-CD was increased 30 and 70 times, respectively, in comparison its value for the uncomplexed compound.

Photochemical stability of the physical mixtures of NM and its clathrates with CD in the solid state was studied by IR spectrometry. The rate of NM decomposition upon irradiation was determined on the basis of

Table 1

Kinetic Parameters of Photochemical Decomposition of Nimodipine with Cyclodextrins in Solution (UV Light)

Inclusion Complexes and Crystalline NM	Rate Constant k (min^{-1})	$t_{0.5}$ (hr)	$t_{0.1}$ (hr)
NIMODIPINE	$7.82 \times 10^{-3} \pm 9.27 \times 10^{-5}$	1.48	0.23
α-CD	$2.97 \times 10^{-4} \pm 7.54 \times 10^{-5}$	38.89	5.91
γ-CD	$5.43 \times 10^{-3} \pm 8.27 \times 10^{-5}$	2.13	0.32
M-βCD	$1.09 \times 10^{-4} \pm 5.04 \times 10^{-6}$	105.62	16.06
HP-βCD	$2.44 \times 10^{-4} \pm 3.72 \times 10^{-5}$	47.15	7.17

Table 2

Kinetic Parameters of Photochemical Decomposition of Nimodipine with Cyclodextrins in the Solid State (UV light)

Inclusion Complexes and Crystalline NM	Rate Constants k (min^{-1})	$t_{0.5}$ (hr)	$t_{0.1}$ (hr)
NM	$7.02 \times 10^{-4} \pm 0.56 \times 10^{-5}$	16.45	2.50
MF-α-CD	$8.54 \times 10^{-5} \pm 1.08 \times 10^{-5}$	135.25	20.56
K-α-CD	$6.01 \times 10^{-5} \pm 3.17 \times 10^{-6}$	191.86	29.18
MF-γ-CD	$1.37 \times 10^{-4} \pm 3.86 \times 10^{-5}$	84.31	18.73
K-γ-CD	$9.14 \times 10^{-4} \pm 0.97 \times 10^{-5}$	12.64	1.92
MF-HP-βCD	$4.50 \times 10^{-5} \pm 7.28 \times 10^{-6}$	256.67	39.04
K-HP-βCD	$3.97 \times 10^{-5} \pm 5.91 \times 10^{-6}$	290.93	44.25
MF-M-βCD	$5.84 \times 10^{-5} \pm 4.40 \times 10^{-6}$	197.77	30.08
K-M-βCD	$4.11 \times 10^{-5} \pm 1.12 \times 10^{-6}$	281.02	42.74

changes in the absorption band 1700 cm^{-1} attributed to the vibrations of carbonyl group (= C = O). The band at this wave number disappeared proportionally to the time of the exposure to light.

The kinetic parameters of photochemical decomposition of NM in the solid phase were calculated similarly as for liquid complexes of NM. As follows from Table 2, the most pronounced inhibition of the process of photodegradation was observed for NM in inclusion complexes with HP-βCD. In this case the stability constant of NM was 17 times greater than for its crystalline phase.

Moreover, the stability of NM in complexes with HP-βCD and α-CD was also greater than in the corresponding physical mixtures. However, it should be emphasized that the presence of γ-CD in solid inclusion complexes increased the photochemical decomposition of NM.

CONCLUSION

Analysis of the determined parameters of photochemical decomposition of the studied complexes has proved that the studied cyclodextrins increase the photochemical stability of NM in solid and liquid inclusion complexes in the following order: γ-CD < α-CD < HP-βCD < M-βCD. The only exception is the solid inclusion complex of NM with γ-CD.

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