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Efficacy of Red Glass in Protecting 1,4-Dihydropyridine Antihypertensive Drugs in Liquid Formulations

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Abstract: A series of different-colored glasses were tested to evaluate their ability to protect dihydropyridine antihypertensives in solution from light. The work aims to define a primary packaging capable of guaranteeing photoprotection for this class of drugs in liquid formulations as an alternative to the current formulations, which are dispensed almost exclusively in solid form. The photostability tests were performed according to international rules by exposing 11 dihydropyridine drugs in ethanol and PEG-ethanol solution to stressing light, shielded by quartz, transparent, amber, or red glass. The transparent glass proved to be completely ineffective, recording a dramatic degradation of all compounds, some of which by 10% in less than 1 min, and with complete disappearance in just 1 h. The amber glass showed a valid photoprotection for almost all compounds, apart from nifedipine and nisoldipine, which degraded by 10% in less than 20 min. The adoption of red glass in filtering the light led to a satisfactory photoprotection for these two drugs, detecting concentrations above 90% for all drugs after 1 h under forced light. The results obtained can help to define safe dispensing systems of liquid formulations of dihydropyridine drugs, which are necessary for those patients who cannot take tablets.

Keywords: dihydropyridine drugs; photoprotection; stressing test; glass containers; multivariate curve resolution

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1. Introduction

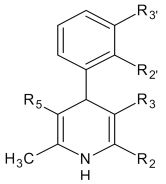
Drug-stability studies are a fundamental requirement for the registration of new molecules, but also represent a guarantee for patient safety. These studies focus mainly on the chemical–physical stability of drugs and medicinal specialties, and on the causes that compromise their quality over time under the influence of a series of factors. The transformation processes and the degradation kinetics must be defined, as well as the strategies able of stopping or reducing the reaction rate. Numerous reviews and articles on this topic have been published in recent years [1–4]. Most of the protocols adopted for the study of drug stability are established in the guidelines of the ICH (International Conference on Harmonization) [5]. These rules are used to define any variations suffered by the drug due to different environmental factors, and allow the establishment of optimal storage conditions. Stability tests are applied to both drugs and their pharmaceutical forms in the packaging used for storage and distribution. The ICH rules include photostability tests to evaluate the overall photosensitivity of the pharmaceutical products and to define the information necessary for handling, packaging, and labeling. The main effect of photodegradation of drugs in many cases is the loss of pharmacological activity, but some cases are known that describe the formation of toxic products [6,7]. Over the years, this last aspect has stimulated even more the study of the mechanisms and chemical kinetics of photodegradation of many drugs and their formulations. Parallel to the studies on drug degradation, great attention has been devoted to the systems to protect the pharmaceutical

products and minimize their degradation [1,2,8–10]. Most of these studies focus on defining new formulations that can protect drugs from light [11–13].

Dihydropyridine drugs (DHPs) are an important class of antihypertensives that interact on the L-type calcium channels of the smooth muscle of the arterioles, where they counteract the entry of calcium, prolonging the duration of the action potential and thus reducing vasoconstriction [14,15]. Unfortunately, DHPs are particularly sensitive to light, and many papers deal with this topic. The photodegradation process mainly involves the oxidation of the dihydropyridine ring to pyridine, and only for some DHPs have secondary photoproducts been detected [16,17]. The oxidation of the molecule causes the total loss of pharmacological activity with the simultaneous production of singlet oxygen and superoxide species, potential inducers of phototoxic reactions [7]. Due to the rapid photodegradation kinetics in solution, DHPs are formulated almost exclusively in solid form, especially tablets. Currently on the market, only nimodipine (NM) and nifedipine (NF) are also formulated as hydroalcoholic solutions in amber glass containers. The bottle containing NF is in turn covered by a black plastic film, which certainly increases the degree of protection, but unfortunately prevents viewing of the content. The use of liquid formulations may be necessary in cases of difficulty in swallowing tablets. Several approaches have been proposed to design liquid pharmaceutical formulations of DHPs: addition of excipients with large absorption regions, incorporation in supramolecular matrices as liposomes or cyclodextrins, and incorporation in microspheres or nanocapsules [18,19]. A different approach involves the synthesis of new DHP structures more stable to oxidation [20]. However, today the adoption of dark glass or plastic containers remains the most common method used by the pharmaceutical industry to protect photosensitive drugs.

In the present work, the stability in hydroalcoholic solution of 11 DHPs, all currently used in antihypertensive therapy, was tested under transparent, amber, and red glass. The stability test was also carried out using a quartz container as a reference, as this material is known to be transparent at all wavelengths. The following DHPs were involved in this study: amlodipine (AM), cilnidipine (CL), felodipine (FL), isradipine (IS), lacidipine (LC), manidipine (MN), nicardipine (NC), nifedipine (NF), nimodipine (NM), nisoldipine (NS), and nitrendipine (NT). The chemical groups characterizing the studied drugs are schematized in Table 1. Degradation experiments were also applied on the drugs dissolved in a mixture of ethanol and polyethylene glycol (PEG), which are excipients commonly used in pharmaceutical formulations. The sample solutions were prepared with drug concentrations close those used in the commercial specialties. In order to verify the behavior of the drugs when exposed to natural light, some solutions were exposed to daylight. Although showing significant degradation, the results were affected by the variability of climatic conditions. The photodegradation tests were so performed under stressful light conditions, according to the international rules of ICH. These tests have the undoubted advantage of guaranteeing the standardization of the experimental conditions as an alternative to the experiments under natural light that are influenced by geographical and meteorological conditions [21]. The photodegradation experiments were monitored by UV spectrophotometry, and the spectral data processed by the chemometric technique known as multivariate curve resolution (MCR), which is able to continuously monitor the concentration of all the species involved in the degradation process and, at the same time, resolve their spectra [22,23].

Table 1. DHP chemical structures.



Drug	R_2	R_3	R_5	$R_{2'}$	$R_{3'}$
AM	$CH_2OCH_2CH_2NH_2$	$COOC_2H_5$	$COOCH_3$	Cl	H
CL	CH_3	$COOCH_2(CH)_2Ph$	$COOCH(CH_3)_2$	H	NO_2
FL	CH_3	$COOC_2H_5$	$COOCH_3$	Cl	Cl
IS	CH_3	$COOCH_3$	$COOCH(CH_3)_2$		
LC	CH_3	$COOC_2H_5$	$COOCH_3$	H	$CH_2CH_2COOC(CH_3)_3$
MN	CH_3	$COOCH_2CH_2$-piperazin-$CH(Ph)_2$	$COOCH_3$	H	NO_2
NC	CH_3	$COO(CH_2)_2N(CH_3)CH_2Ph$	$COOCH_3$	H	NO_2
NF	CH_3	$COOCH_3$	$COOCH_3$	NO_2	H
NM	CH_3	$COOCH_2CH_2OCH_3$	$COOCH(CH_3)_2$	H	NO_2
NS	CH_3	$COOCH_2CH(CH_3)_2$	$COOCH_3$	NO_2	H
NT	CH_3	$COOC_2H_5$	$COOCH_3$	H	NO_2

2. Materials and Methods

2.1. Materials

The DHP drugs were purchased from Sigma-Aldrich Co. (Milan, Italy). The ethanol and polyethylene glycol (PEG) were purchased from Fluka Research Chemicals (Milan, Italy). The pharmaceutical specialties Nimotop 30 mg/0.75 mL (Bayer SpA, Milan, Italy) and Nifedicor 20 mg/mL (Meda Pharma SpA, Milan, Italy) were obtained commercially.

2.2. Instruments and Software

The absorption spectra were recorded in the wavelength range of 190–450 nm in a 10 mm quartz cell, using an Agilent 8453 spectrophotometer (Agilent Technologies, Santa Clara, CA, USA) under the following conditions: scanning speed 1 nm/s; response time 1 s; spectral band 1 nm. The UV-VIS ChemStation software provided with the spectrophotometer was used for data acquisition.

The photodegradation experiments were conducted using a Suntest CPS+ light cabinet (Heraeus, Milan, Italy), equipped with a Xenon arc lamp, in accordance with Option 1 established by the ICH standards for the photostability test, which allows the emission of a light spectrum with wavelength distribution very similar to sunlight. The instrument is equipped with a cooling unit, which neutralizes the increase in temperature caused by the lamp, and an electronic system monitoring irradiation and temperature conditions inside the cabinet. The solution flow was obtained through a peristaltic pump (Pump FH15, Thermo-Scientific, Rodano (MI), Italy).

The chemometric elaboration of data was performed in a MATLAB computer environment (MathWorks Inc., Natick, MA, USA). Routine methods of the MCR computer were implemented as MATLAB functions. The source files containing these algorithms are available by visiting the www.mcrals.info website, accessed on 20 July 2020.

2.3. Laboratory Solutions

The photodegradation experiments on DHPs were conducted on standard hydroalcoholic solutions and PEG–ethanol mixtures. The standard solutions were prepared by weighing exactly 10 mg of pure product powder and dissolving them in 50 mL of 50% hydroalcoholic solution. This solution was then diluted with the same solvent to a concentration of 20 µg/mL. The sample solutions, simulating common pharmaceutical formulations, were prepared by dissolving 50 mg of DHP in 10 mL of PEG:ethanol 95% (8:2). An aliquot

of these solutions was diluted with ethanol to a concentration of 20 μg/mL immediately before recording the spectra.

2.4. Photodegradation Tests

The DHP standard solutions were subjected to forced photodegradation shielded by the different types of glass. The experimental conditions inside the light cabinet were set in accordance with the conditions for the photostability tests described in ICH Q1B: UV-filter glass >290 nm, radiant power 350 W/m^2, corresponding to a dose energy of 21 kJ (min m^2)$^{-1}$. The temperature inside the cabinet was kept at 25 °C to minimize the increase of temperature due to the lamp. A fully automated flow system between the light cabinet and spectrophotometer was designed to avoid any interruption of the photodegradation test. For this aim, a peristaltic pump between the sample inside the irradiation cabinet and a flow-through cell placed in the spectrophotometer assured the continuous flow of the solution. The flow was fixed at 3 mL/min, and the UV spectra were recorded at 2 min intervals up to a total time of 140 min. To minimize any interference of extraneous light in the experiments, all laboratory procedures were performed in a room illuminated by a 60 W red lamp.

2.5. Multivariate Curve Resolution-Alternating Least Squares (MCR-ALS)

The multivariate processing of the analytical data recorded during a chemical degradation allows the consideration of all the species involved in the experiments. In this work, the chemometric multivariate curve resolution (MCR) method was adopted, based on an alternating least squares algorithm (MCR-ALS). The application of MCR to a degradation process allows the collection of information on all the species involved, such as their spectrum and concentration along the process. In this work, since the degradation was followed by spectrophotometry, a data matrix **D** (*n*,*m*) was arranged, in which the *n* samples (or individual spectra) represented the time evolution of the kinetic process, and *m* was the absorption values at the recorded wavelengths. MCR decomposes the matrix **D** in a bilinear model consisting of two smaller matrices, **C** and $\mathbf{S}^{\mathrm{T}}$, and can be considered an extension of the Lambert–Beer's law to multiwavelength and multisample analysis:

$$\mathbf{D} = \mathbf{C}\mathbf{S}^{\mathrm{T}} + \mathbf{E} \quad (1)$$

where **C** (*n*,*k*) describes the concentration evolution of the *k* components in the chemical system; $\mathbf{S}^{\mathrm{T}}$ (*k*,*m*) contains the pure spectra of *k* components; and **E** (*n*,*m*) is the variance unexplained in the modeling.

At every ALS iteration, non-negativity, unimodality, and concentration-closure constraints were considered to achieve the final solutions with a chemical meaning, and to reduce the possible intensity or rotation ambiguity. Kinetic constraint was also applied using a hard/soft-MCR routine (HS-MCR-ALS), which allowed in-depth analysis of photodegradation kinetics and evaluation of the reaction-rate constants. The figures of merit used to describe the achievement of the results and the quality of the model were the percentage of lack of fit (%LOF) and the explained variance (%R^2):

$$\%LOF = 100 \times \sqrt{\frac{\sum_{ij}\left(d_{ij} - d^{*}_{ij}\right)^2}{\sum_{ij} d^2_{ij}}} \quad (2)$$

$$\%R^2 = 100 \times \frac{\sum_{ij} d^{2*}_{ij}}{\sum_{ij} d^2_{ij}} \quad (3)$$

Detailed information on the mathematical principles underlying the MCR technique can be found in various articles [24–26].

3. Results and Discussion

3.1. Photodegradation in Quartz Containers

The DHP standard solutions were first tested in quartz containers to ascertain their sensitivity to light in the absence of any filter, given the known transparency of the quartz at the set wavelengths. UV spectra were recorded for 140 min at very close intervals because of the high degradation rate of some DHPs. The processing of the large amount of spectral data collected was performed by MCR. Figure 1 shows, as an example, the sequence of spectra recorded on the NF sample ($\mathbf{D_{NF}}$), lead of these drugs, the resolved spectra of the drug and its photoproducts ($\mathbf{S_{NF}}$), and the concentration profiles of all the species involved in the process ($\mathbf{C_{NF}}$).

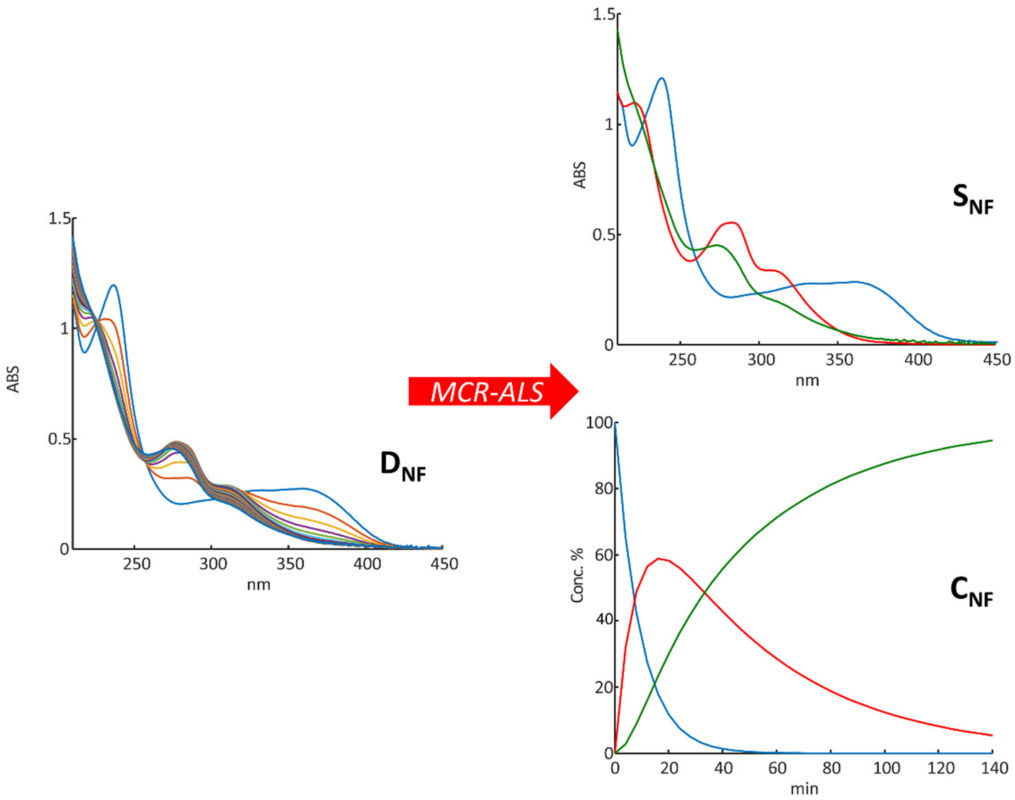


Figure 1. Sequence of the UV spectra of NF solution (20.0 μg/mL) along the forced irradiation ($\mathbf{D_{NF}}$); and spectra ($\mathbf{S_{NF}}$) of the species involved in the photodegradation process predicted by MCR processing and their concentration profiles ($\mathbf{C_{NF}}$).

The kinetic photodegradation rate for all the DHPs was calculated by applying the routine HS-MCR-ALS and the kinetic constraint to the spectral data. The decrease in DHP concentration is shown in Figure 2, in which the curves were made linear by the log transformation of the concentration values. Reaction pathways were resolved through single or consecutive first-order reactions. MCR modeling identified in most cases the formation of a single photoproduct, resulting from the oxidation of the dihydropyridine ring. This process was characterized by the lowering of the peak in the area of 350–370 nm, typical of the DHP structure, and by the simultaneous raising of a new signal in the area of 260–280 nm, characteristic of the pyridine group. For some DHPs, MCR resolved a second photoproduct, in accordance with the results reported in previous works [4].

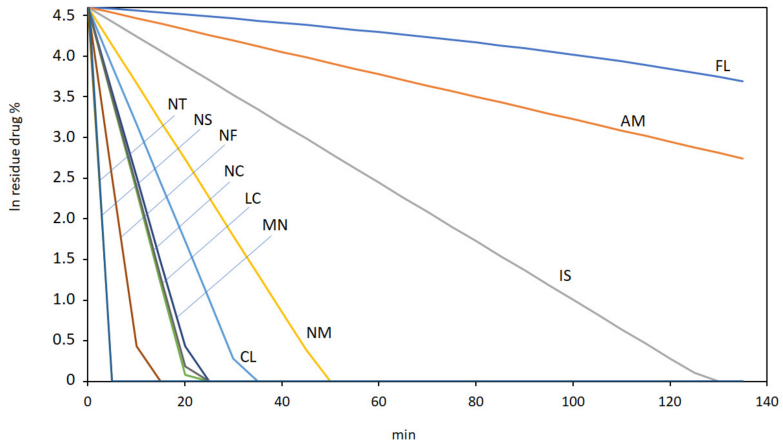


Figure 2. Kinetic curves resulting from the degradation test on hydroalcoholic DHP solutions in quartz containers: amlodipine (AM), cilnidipine (CL), felodipine (FL), isradipine (IS), lacidipine (LC), manidipine (MN), nicardipine (NC), nifedipine (NF), nimodipine (NM), nisoldipine (NS), and nitrendipine (NT).

Some DHPs showed an impressive degradation rate. Among these, NS and NT degraded completely in less than 5 min; and NM, CL, NC, MN, NF, and LC within 30 min. In contrast, IS, AM, and above all FL proved to be more stable, with a significant residual content of drug even after 120 min of forced irradiation.

The same solutions were kept completely in the dark to monitor any degradation processes not caused by light. The differences detected in the UV spectra recorded at zero time and after 10 days of storage showed, in any case, nonsignificant differences.

In order to quickly compare the light stability of the analytes, the parameter t_{10} was adopted as the irradiation time necessary to obtain a 10% degradation of the initial drug concentration. The use of this parameter was justified by the fact that the drug or a formulation containing it should no longer be used if its concentration reaches a value below 90% of the starting value. The results obtained demonstrated the high photosensitivity in solution of the tested drugs, of which 9 out of 11 showed a t_{10} value of less than 3 min (Figure 3).

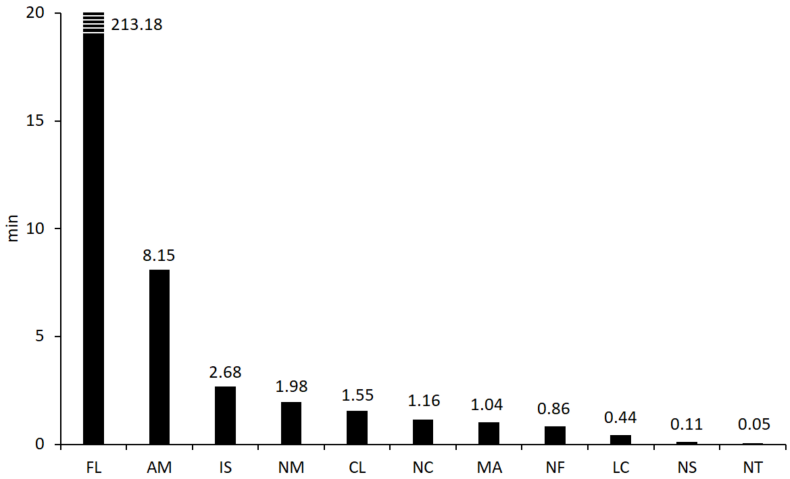


Figure 3. Irradiation time (min) causing a 10% degradation (t_{10}) of the hydroalcoholic DHP solutions in quartz containers, under a radiant power corresponding to a dose energy of 21 kJ $(\text{min m}^2)^{-1}$.

FL and AM, which showed the highest photostability values, have in common the lack of the nitro group on the benzene ring. Indeed, the drugs that have a nitro group in $R_{2'}$ or $R_{3'}$ showed lower stability. The influence of the nitro group on the stability of these

molecules had already been highlighted in previous works [17]. An exception is given by LC, which, although not having nitro groups, showed low photostability.

3.2. Photodegradation in Transparent Glass Containers

The photodegradation experiments, under the same instrumental conditions reported above, were performed on the DHP standard solutions in transparent glass containers (borosilicate glass flasks), which cut the wavelengths below 300–320 nm. MCR processing of the spectral data recorded in this second set of experiments showed, in most cases, only a slight reduction in t_{10} values, but the overall results were not significantly different from those recorded using the quartz containers. These results indicated that the main wavelengths responsible for the degradation process of DHPs were not included in the region cut by the transparent glass.

3.3. Photodegradation in Amber Glass Containers

A third series of photodegradation experiments was conducted on the DHP standard solutions in amber glass flasks. The experimental conditions were the same as those adopted in the previous experiments with quartz and transparent glass. The results obtained from the elaboration of the spectral data showed a marked improvement in the stabilization of the drugs. These results support the routine adoption of amber containers in the primary packaging of many specialties. However, the results calculated on the photodegradation tests of NF and NS solutions showed only a moderate increase in the values of t_{10} up to 5.87 and 6.25 min, respectively, still considered unsatisfactory. Figure 4 shows the kinetics calculated on the data from this series of experiments.

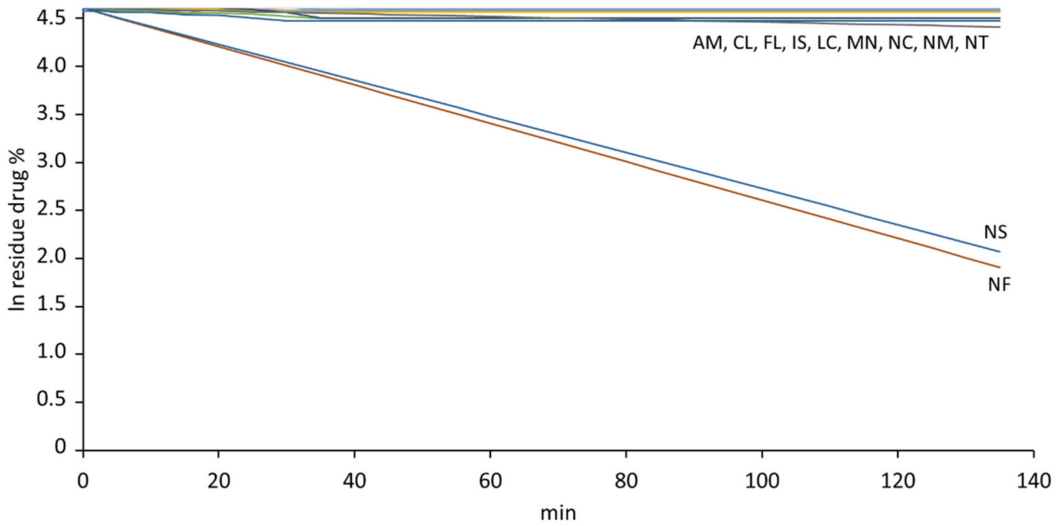


Figure 4. Kinetic curves resulting from degradation tests on hydroalcoholic DHP solutions in amber glass.

Amber glass can fully absorb wavelengths below 400 nm, but is much less effective for wavelengths up to 600 nm, beyond which it becomes completely transparent, as evident in Figure 5. The results collected so far suggested that, for most of the DHPs studied, the radiation responsible for degradation was mainly located in the visible region of the electromagnetic spectrum below 400 nm, suitably retained by the amber glass. On the contrary, the radiation responsible for the degradation of NF and NS must be located among those with the lowest energy above 400 nm. The good level of protection provided by the amber glass for NM justifies the fact that this drug is the only currently marketed in liquid formulation and packaged in an amber bottle. NF is also formulated in solution, but as the photoprotection of the amber glass is insufficient, as verified in this study, the bottle is coated with opaque black plastic. Unfortunately, this limits the view of the content, which remains an important feature of the liquid formulations.

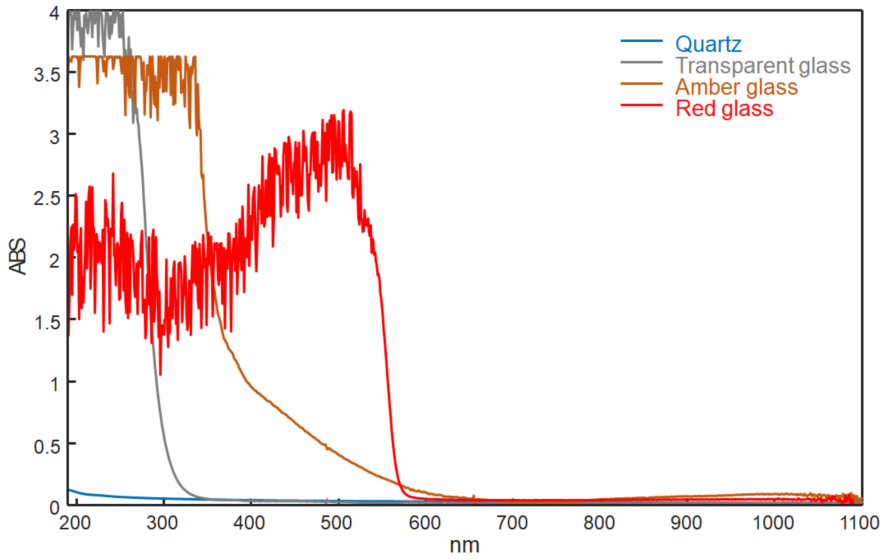


Figure 5. Absorbance spectra of quartz, transparent, amber, and red glass.

3.4. Photodegradation under Red Glass

To extend the shielding wavelength region by means of transparent glass, it was decided to test a red glass used in the photographic field. In BW photography, the red filter is used precisely to enhance the colors from orange to red by blocking the typical radiation of blue and green, included in the region 450–570 nm. To our knowledge, red glass containers are not available on the market for pharmaceutical use, but they are used in cosmetic and nutraceutical fields. The absorption spectra of the glasses involved in this work are shown in Figure 5, where their notable difference in filtering the light is evident. Quartz was indifferent to all wavelengths; transparent glass filters radiation below 300 nm; amber glass completely absorbs wavelengths below 380 nm and, less intensively, radiation up to 600 nm; and red glass is able of absorbing radiation up to 570 nm.

The photodegradation tests, under the same instrumental conditions applied in the previous experiments, were carried out on the standard solutions of NF and NS. The solutions were placed in an amber beaker covered with the red glass. With the lamp placed at the top of the cabinet, the light reached the solution through the filter and only in a minimal percentage through the wall of the beaker. MCR processing of the recorded spectra showed a remarkable reduction of the degradation rate of both products, with t_{10} values of 40.36 and 51.37 min for NF and NS, respectively. The photodegradation test using the red glass was applied to the other DHPs and an optimal degree of protection was confirmed for all drugs, with residual values of over 94% after 120 min of forced irradiation.

3.5. Photostability Test on DHP Formulations

The stressing test was performed on the NF and NM specialties currently on the market, containing the drugs at a concentrations of 20 and 40 mg/mL, respectively. The samples were exposed to light in the original bottles and analyzed immediately before the experiment (zero time) and after 120 min of irradiation. Before recording the spectra, an aliquot of the solution was diluted with ethanol to obtain a concentration of 20 µg/mL. At the end of the experiments, the residual concentrations of NF and NS formulations were 74.33 and 91.08%, respectively. The photoprotective capacity of the red glass was then tested on all the studied DHPs, formulated in solution with excipients commonly used in pharmaceutical technology. These formulations were prepared in 95% PEG:ethanol (8:2) at a drug concentration of 20 mg/mL, very similar to those used in commercial specialties, and exposed to light under the same instrumental conditions, using the red glass as a light shield. The use of these solvents in the formulation of DHPs can be advantageous, as it

has been reported that the formation of hydrogen bonds with alcohols could significantly increase photostability [27].

The samples were analyzed at time zero and after 120 min of irradiation. The samples were diluted with ethanol to 20 µg/mL before analysis. The residual concentration of the drugs after 120 min of stressing irradiation are listed in Table 2. The parameter t_{10} could not be calculated, as for most drugs the residual concentrations remained above 90% at the end of the experiments. The residual concentrations of NF and NS formulations were 84.33 and 93.15%, respectively, while the values for all the other DHPs were all above 95%.

Table 2. Residue percentage of drug in hydroalcoholic and PEG–ethanol solutions protected by different glasses after 120 min of forced irradiation.

	Standard Solutions				Sample Solutions
DHP	**Quartz**	**Transparent**	**Amber**	**Red**	**Red**
AM	19.09	31.6	97.41	98.32	97.68
CL	0.00	0.00	96.10	99.10	97.23
FL	46.72	62.56	94.37	94.84	96.21
IS	1.33	5.61	94.08	96.23	95.98
LC	0.00	0.00	94.33	99.28	97.56
MN	0.00	0.00	95.56	96.20	96.74
NC	0.00	0.00	95.23	95.47	95.30
NF	0.00	0.00	9.10	69.77	84.33
NM	0.00	0.00	97.52	98.51	96.32
NS	0.00	0.00	10.50	74.98	93.15
NT	0.00	0.00	95.24	97.89	95.49

The results showed a further increase in the stability of the NF and NS samples, even with respect to the values recorded on the pharmaceutical specialties. It was found that the photostability of the two products was also improved compared to the relative standard solutions, but this could be due to the higher concentration of the drugs. This dependence had already been reported in previous works [28]. However, the degradation test was repeated on hydroalcoholic solutions of the drugs at a concentration of 20 mg/mL, identical to the PEG/EtOH solutions, obtaining comparable results. This allowed us to exclude the influence of PEG on the photodegradation rate of the products.

The results obtained with the use of red glass can be considered very satisfactory in consideration of the stressful irradiation conditions and the exposure time in the tests adopted. At the same time, they allow us to estimate a potential high stabilization of DHP drugs under normal conditions of storage and use.

4. Conclusions

This paper describes a study on the shielding properties of different types of glass for the photoprotection of dihydropyridine antihypertensives. The study aims to propose a valid alternative to the current, almost total formulation of these drugs in tablets, given their high photosensitivity in solution. Eleven DHPs, all currently used in antihypertensive therapy, have been exposed in hydroalcoholic solution to stressing light, according to international rules. Quartz and clear glass showed poor protection for all the substances. Amber glass demonstrated a good photoprotective effect towards most of the compounds, except for nifedipine and nisoldipine. The photodegradation test on these two substances was repeated by filtering the light through a transparent red glass, capable of absorbing the wavelengths up to 570 nm. Both drugs showed a marked decrease in the degradation process, with residual concentrations of unchanged drug of 84.33% and 93.15% for NF and NS, respectively, after 120 min of forced irradiation. Values higher than 95% were recorded when the degradation test with the aid of red glass was carried out on all the other DHPs. These results demonstrated the effectiveness of red glass in protecting drugs from light,

being able to absorb wavelengths above the values normally absorbed by amber glass, which is the glassy material usually used in pharmaceutical field.

Author Contributions: Conceptualization, M.D.L. and G.R.; methodology, M.D.L. and G.R.; software, M.D.L.; validation, G.I. and F.G.; formal analysis, G.I. and F.G.; investigation, M.D.L., G.I., F.G., and G.R.; resources, G.R.; data curation, M.D.L.; writing—original draft preparation, M.D.L., G.I., F.G., and G.R.; writing—review and editing, M.D.L. and G.R.; visualization, G.R.; supervision, G.R.; project administration, M.D.L. and G.R.; funding acquisition, M.D.L. and G.R. All authors have read and agreed to the published version of the manuscript.

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