Photostabilization studies of antihypertensive 1,4-dihydropyridines using polymeric containers

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ABSTRACT

The 1,4-dihydropyridine antihypertensives (DHPs) are nowadays almost all formulated in solid pharmaceutical formulations for easy lability when exposed to light. This paper reports a study on the photoprotective effect of containers in different glassy or polymeric matrices with regard to four known DHPs in solutions form. The samples were subjected to forced degradation by means of a xenon lamp, in accordance with the international rules on drug stability evaluation. The simultaneous determination of the drugs and their photoproducts was carried out by applying the chemometric algorithm MCR to the spectral data recorded along the irradiation test. This technique was able to determine the kinetics parameters and predict the spectra of the photoproducts. The time required to reduce by 10% the concentration of the drug ($t_{0.1}$) was adopted as a criterion to compare the protective ability of the containers.

A significant photoprotection for all drugs tested was obtained with the use of PET containers. The best result was achieved for the felodipine solution in blue PET bottles of 0.6 mm thickness, obtaining an almost complete stabilization up to six hours under stressing irradiation. In contrast, the glass containers, whether or not colored, did not proved a significant photoprotection of the drugs, showing in any case $t_{0.1}$ values under 24 min. These results may represent a good opportunity to prepare liquid formulations of DHPs drugs, using transparent and resistant containers and at the same time minimizing their light degradation.

Keywords

Photodegradation; Photostabilization; Dihydropyridines; PET containers; MCR analysis

1. Introduction

The focus of this study was to investigate the effect of light irradiation on a series of 1,4-dihydropyridine drugs (DHPs) and to test the photo-stabilizing features of polymeric containers with the aim to optimize storage and handling of these drugs in liquid dosage forms. The research work is justified by the intense lability to light shown by all the drugs of this class [X].

DHPs are widely used antihypertensives and act preferentially as blockers of the calcium channels in vascular smooth muscle. They inhibit voltage-gated ion channels, causing relaxation of arterial smooth muscles resulting in reduced blood pressure [X].

For the realization of this study, we selected four DHPs commonly used in therapy, felodipine (FEL), lercanidipine (LER), nimodipine (NIM) and the lead Nifedipine (NIF). NIF is used for the

treatment of short duration against some types of angina and particularly in vasospastic angina pectoris [X]. NIM has long been used as an antihypertensive but nowadays instead gives good results in preventing vasospasm that often is associated with subarachnoid hemorrhage [X]. FEL and LER are usually used against hypertension and certain forms of angina [X].

Photolability of DHPs is well known, as well as the oxidation of the dihydropyridine ring to pyridine derivative as the main degradation mechanism [X]. Some DHPs undergo a more complex degradation with the formation of secondary photoproducts [Xl]. The pyridine by-products have been shown to be devoid of any therapeutic effect [X]. Production of singlet oxygen and superoxide species has been observed during the photodegradation process, inducing peroxidation of fatty acids and then lead to dermatitis [X]. Furthermore, the same degradation mechanism has been relieved in the liver metabolism of these drugs through oxidation catalyzed by an analogue of cytochrome P-450 [X].

The potential toxicity of these drugs after photodegradation has increased in recent years the interest for the synthesis of structural analogues more stable to light. An interesting QSPR (quantitative structure-property relationships) model, correlating the stability of DHPs on a series of physico-chemical parameters of the chemical substituents, has been proposed [X]. At the same time, new approaches to protect the drugs from photodegradation remain a topical subject [X], including physical systems shielding the passage of light or pharmaceutical photoprotective matrices [X].

Photodegradation of the DHPs is particularly fast in solution, as already reported in several works [X], and this is the main reason why most of the pharmaceutical specialties containing these drugs are marketed in solid formulation, usually tablets. Currently, only NIM and NIF are available in water-alcohol solution, packaged in bottles of dark glass. The bottle containing NIF is in turn covered by a thin layer of black plastic to maximize the protection of the solution from the light.

The method most commonly used by the pharmaceutical industry to protect photosensitive drugs is still represented by the adoption of containers of colored glass. Yellow-green glass offers good protection in the UV range; amber glass provides good protection from UV light, but little protection from infrared light. One of the problems in the adoption of these containers is the difficult visual inspection of the content.

This work aims to test the photoprotective potential of polymer bottles to be candidates to contain DHPs solutions, increasing so the variety of dosage forms of these drugs. The main users of antihypertensive DHPs are elderly and the plastic containers are advantageous if compared to those of colored glass because they offers greater transparency and resistance. Furthermore, the possibility to use liquid formulations is very important for patients who have difficulty in taking solid dosage forms.

A series of photodegradation experiments were conducted on the hydro-alcoholic solutions of the above reported DHPs in polymer containers and the results were compared with those carried out by the use of glass bottles. The photodegradation tests were conducted in accordance with the ICH Guideline for drug photostability testing [X]. This Guide identifies the light test as part of the

overall assessment for the stability of a drug and the test is rated positively if light exposure does not involve significant changes. Detailed papers on ICH guideline and its application have been published [X].

Resolution of a photodegradation process is usually a complex problem because the mechanism of reaction is often unknown, as well as the number of the degradation products and their structure. In this work, the experiments were monitored by UV-visible spectrophotometry and the spectral data processed by the chemometric technique Multivariate Curve Resolution – alternative least squares (MCR-ALS). This algorithm was particularly useful to evaluate the kinetics of the photodegradation processes and to monitor the concentration profiles of drugs and photoproducts, drawing at the same time their spectra.

2. Materials and methods

2.1. Chemicals

DHP drugs were purchased from Sigma-Aldrich Co. (Italy). Ethanol for UV spectrophotometric analysis was purchased by Fluka (Italy). The following containers were selected for the photoprotection tests: quartz, pyrex glass, amber glass, transparent polyethylene terephthalate (PET) 0,90 mm, violet PET 0,60 mm, amber PET 0.80 mm, blue PET (0.15; 0.3; 0,45; 0.6; 0.75; 0.90 mm), polypropylene (PP) 1,5 mm. The company Vexel (Parma, Italy) on behalf of Flower Tales (Milan, Italy) kindly provided the PET containers.

2.2. Instruments and software

The absorption spectra were recorded by means of a spectrophotometer Agilent DAD UV/Vis 8453. The instrumental parameters were so fixed: quartz cell 10 mm, scanning speed 1 nm/s; response time 1 s; spectral band 1 nm. Spectra were recorded in the wavelength range 190-500 nm.

Photodegradation experiments were performed by using a light cabinet Suntest CPS+ (Heraeus, Milan, Italy), equipped with a Xenon lamp, able to closely simulate sunlight. An electronic device inside the camera provided to monitor irradiation and temperature. Irradiation wavelength range was set to 300 - 800 nm, by means of a glass filter, according to the ID65 standard of ICH rules.

The two above instruments were connected by means of a peristaltic pump (Pump FH15, Thermo-Scientific, Italy), creating a flow system. The peristaltic pump forced the advancement of the solution in the container placed inside the photodegradation chamber and then in the cuvette placed in the UV spectrophotometer. The entire sequence of the UV spectra was so recorded at prefixed times without interrupting the process of photodegradation.

All chemometric procedures were performed under Matlab® computer environment (Mathwork Inc., version 7). MCR routine computer methods were implemented as MATLAB functions.

2.3. Photodegradation tests

Standard solutions of all the analytes, at a concentration of about 20 μg/ml in 1:1 ethanol-water were prepared and used in the forced degradation experiments. The experimental conditions maintained inside the light cabinet were: temperature 25°C, radiant power 350 Watt/m^2, UV-filter glass >290 nm. The filter adopted mimicked the effect of the sunlight outside. The UV spectra were recorded at 2 min intervals up to a total time of 6 hours. The peristaltic flow system allowed to monitor the full process of degradation and record a very high number of spectra.

2.4. Data elaboration

All the experiments were performed in triplicate. The experimental data were processed by the advanced chemometric technique MCR-ALS. The MCR algorithm is a multivariate approach which decompose a matrix of experimental data from a chemical process in the contributions of the individual components. In the MCR algorithm, the matrix of the experimental data, D is decomposed into the product of two matrices of reduced size, C and ST:

$D = C + E\ ST$

D is the matrix of the spectral data recorded along the degradation process, C is the matrix of the concentration values of the species involved, ST is the matrix of the spectral data of the pure components, and E represents the explained variance of the data (50).

The model is similar to the law of Lambert-Beer and appears ideal to process a matrix of UV data. The MCR algorithm provides to a first estimation of the number of components and ST or C. After that, these preliminary results are optimized through an iterative process. MCR-ALS was able to resolve the kinetics of a degradation process, deducing both spectra and concentration of the different species throughout the full process.

3. Results and discussion

The 20 μg/ml solutions of the four studied drugs were subjected to forced photodegradation by setting the irradiation wavelength range over 290 nm, so as to obtain a simulation of outdoor light, and maintaining a temperature of 25°C into the light cabinet, to exclude any possible interference from thermal degradation. Spectral analysis was performed at time intervals of 120 sec up to a total time of 6 hours. During the tests using the colored PET containers (violet, amber and blue), the analysis was performed at intervals of 30, 60, 90, 120, 180, 240, 360 min.

In order to minimize any interference of extraneous light in the experiments, all laboratory procedures were executed in a dark room equipped with a red lamp of 60W at a distance of at least 2 m.

A fully automated flow system among light irradiation and spectrophotometric detection was designed to avoid any interruption during the photodegradation test. A peristaltic pump positioned between the sample into the light cabinet and a flow-through cell in the spectrophotometer assured the continuous flow of the drug solution.

Fig.1 shows the spectral sequences recorded along irradiation of the drug solutions in quartz volumetric flasks. These first experiments highlighted how the light affected the molecules in the

absence of any filtering action due to the container, being the quartz transparent to the irradiating wavelengths set in the experiments.

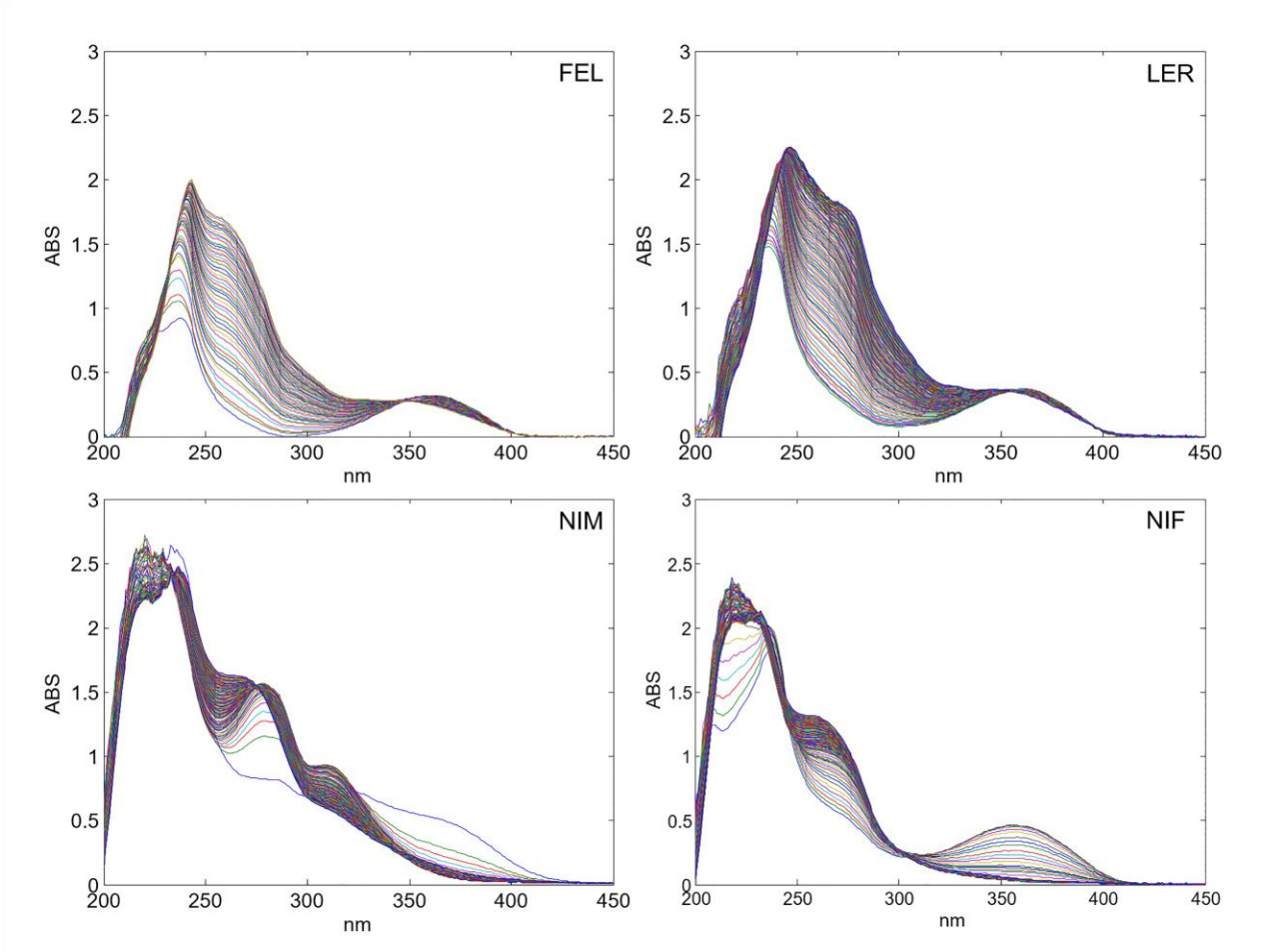

Fig.1. Sequence of the UV spectra for each drug solution (20.0 μg/ml) along the forced irradiation

Photolability of all analytes was clear, showing oxidation to the respective pyridine derivatives as main photoproducts. This reaction mechanism is demonstrated by the spectral sequence, characterized in all cases by a lowering of the peak in the area 350-370 nm, typical of the dihydropyridine group, and a simultaneous raising of a signal in the area 260-280 nm, characteristic of the pyridine group that is forming [X]. Table 1 summarizes the kinetic parameters calculated by MCR from all the tests using the different containers. This table also lists the parameter $t_{0.1}$, as the time causing a 10% reduction of the starting drug concentration. This parameter was very useful to compare the stability degree of the drugs.

Table 1.

Kinetics constants and $t_{0.1}$ (time need to reach 10% reduction of the drug concentration) calculated for DHPs in the different glass and polymer containers.

Container ***(mm thickness)***	**FEL**		**LER**			**NIM**			**NIF**		
	k_1*10^{-5}	$t_{0.1}$	k_1*10^{-5}	k_2*10^{-5}	$t_{0.1}$	k_1*10^{-5}	k_2*10^{-5}	$t_{0.1}$	k_1*10^{-5}	k_2*10^{-5}	$t_{0.1}$
quartz	16.86	10.2	77.18	17.21	2.5	77.16	2.50	2.1	100.98	16.39	2.2

glass	12.63	14.3	15.10	25.58	12.9	80.09	3.35	2.9	176.56	15.16	1.5
Amber glass	11.15	16.0	7.48	7.06	23.9	7.61	2.25	23.1	151.46	10.62	1.4
PP	10.48	17.1	6.75	9.32	16.1	12.54	3.47	4.5	43.91	10.19	3.6
PET	1.04	168.2	4.51	10.55	29.7	26.49	26.49	7.5	168.07	11.80	1.9
PET blue 0.6	0.21	828.2	2.37	12.25	74.8	15.96	8.25	11.7	58.53	9.36	3.3

$t_{0.1}$ is expressed as min

In some cases, deviation from the Lambert-Beer law occurred under 250 nm and the spectral signals provided bad information. Therefore, in the further modeling of the data matrices, these signals were not included. In applying MCR elaboration, the degradation of FEL described the pyridine by-product as single photoproduct while the formation of secondary photoproducts, successive to this first transformation, were revealed for the other drugs. Fig. 2 shows the concentration profiles of DHPs and respective photoproducts along the photodegradation processes. FEL showed to be the most stable drug with a $t_{0.1}$ value of 10.2 min. The other drugs showed a higher photolability with a 10% degradation below 3 min.

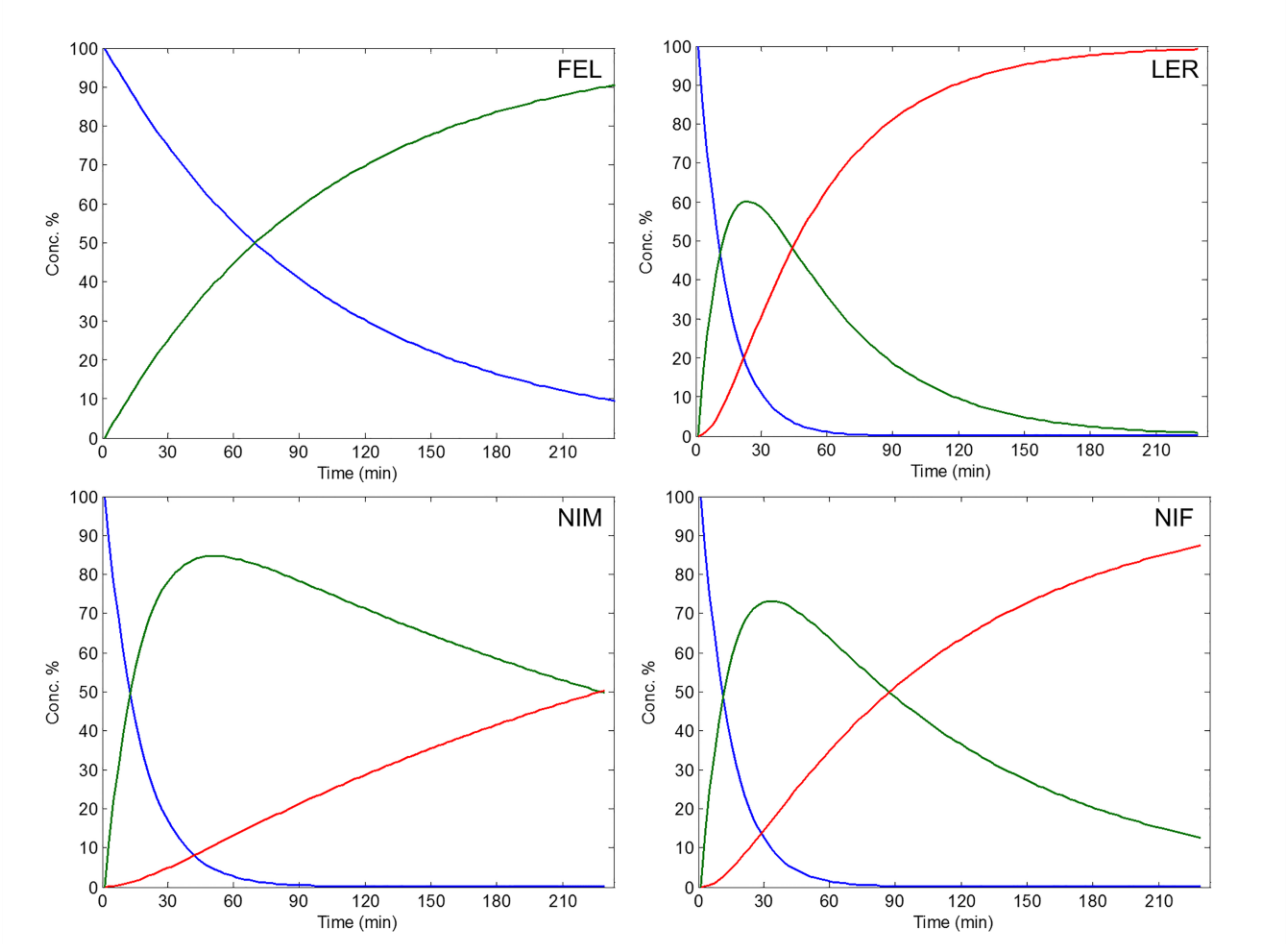

Fig.2. Concentration profiles of the drugs along the photodegradation test

3.1. Photodegradation in glass containers

The photodegradation experiments were performed on the drug solutions placed in transparent and amber glass containers, which, unlike quartz, absorb most of the UV radiation. The spectral sequences obtained from using the transparent glass volumetric flasks were similar to those obtained from using the quartz containers and degradation rate was only slightly lower. These results suggested that the radiation responsible for the degradation are in the visible spectral region.

Surprising results, however, were collected when the photodegradation test was executed on the drug solutions in amber glass. The use of colored glass provided a different degree of protection for the drugs tested. Degradation rate for FEL and NIF were not very different from the previous results obtained using containers in transparent glass. In contrast, a significant improvement was observed for LER and NIM, whose values of $t_{0.1}$ increased 2 and 8 times, respectively (see Table 1). The good level of protection provided for the NIM solution by the amber glass container justifies the fact that this drug has been for years the only one to be commercialized in liquid formulation.

Anyhow, the overall results obtained by the adoption of colored glass did not give the potential photoprotective effect expected. These results represent a serious obstacle for the liquid formulation of these drugs, because most of the glass containers used in the pharmaceutical industry are precisely in amber glass.

3.2. Photodegradation in polymeric containers

The above-described results led us to test polymeric containers to verify their potential photoprotective ability for the drugs studied. By adopting transparency and safety for health as selection criteria, polypropylene (PP) and polyethylene terephthalate (PET) were chosen to be tested.

Unfortunately, the tests on all drug solutions in PP containers did not give positive results and the degradation profiles were close to those obtained from the use of transparent glass. The tests conducted on PET containers instead showed contrasting results. The protection provided by PET was almost similar to that achieved by the use of amber glass for the LER and NIF solutions. On the contrary, the NIM solution showed a degradation much faster than that recorded in amber glass ($t_{0.1}$ = 7.5), although lower than that in transparent glass. The most interesting result was obtained from testing the FEL solution, which showed a dramatic reduction in the rate of degradation, with $t_{0.1}$ values equal to 168.2, almost 11 times higher than the results obtained in amber glass.

This result prompted us to focus the studies on the use of PET containers in the photostabilization of the FEL solution. The stressing tests were extended to a series of colored PET containers, precisely in blue, amber and violet, with the aim to verify a possible synergy between polymeric matrix and dyes in protecting the molecule.

The results from these experiments were very satisfactory, showing a very strong reduction in the degradation of FEL for the entire test time (6 hours). Fig. 3 shows the drug concentration profile recorded along the photodegradation tests on the FEL solution in the various PET containers

tested. The $t_{0.1}$ values were are all over 168 min. The best value of 828.2 min was extrapolated in the test using the blue PET container, in which the drug concentration remained almost unchanged up to 6 h.

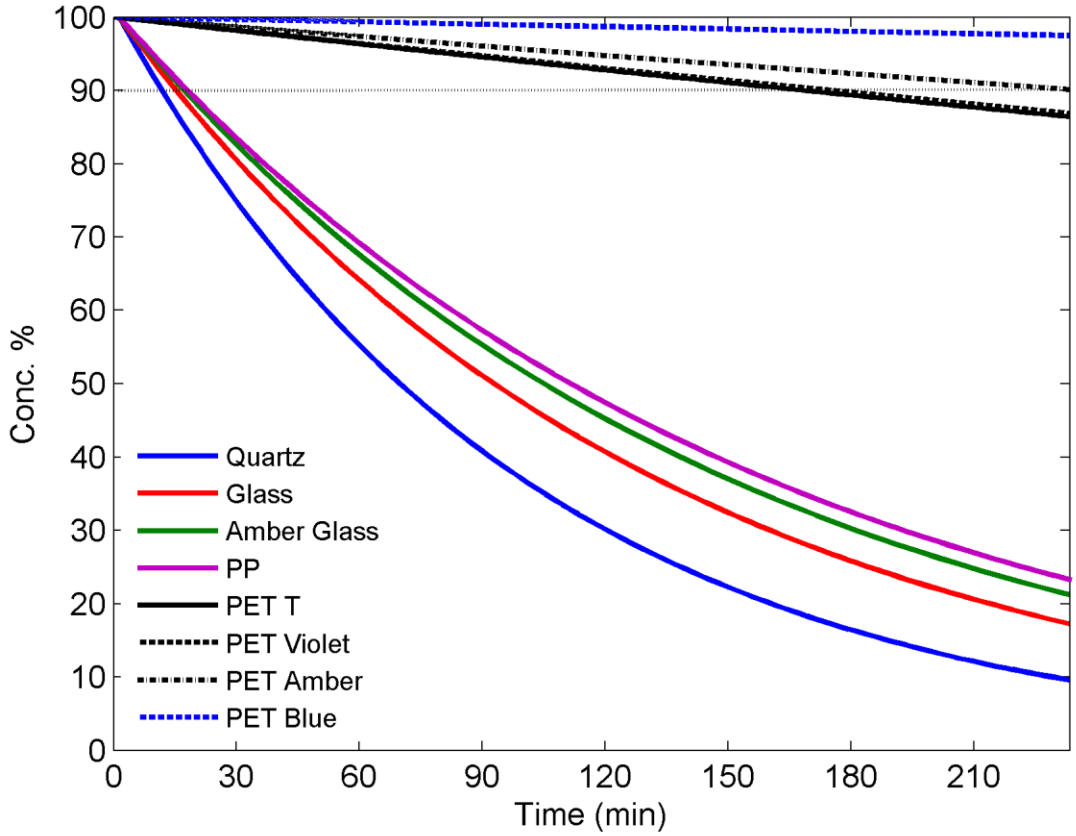

Fig.3 Kinetic curves resulted from degradation tests on FEL solution in different containers. The dashed line represents the degradation value equal to 10% ($t_{0.1}$).

3.3. Influence of the container parameters

The influence of the chemical-physical characteristics of the containers was investigated by evaluating their UV-visible spectra and wall thickness.

The spectra of the container walls are shown in Figure 4. All the matrices absorbed UV radiation below 300 nm except the quartz that is virtually transparent to all wavelengths. The transparent PET showed absorbance just under 330 nm but also a background absorption through the full visible region, probably due to a not perfect transparency. The amber glass had a background absorption and also an increasing absorption below 600 nm. The colored polymers showed additional typical absorption zones due to their dyes. The high photoprotective effect of the colored polymers relieved for some of the studied DHPs depended certainly by the overlap of the absorption bands of the dyes with the wavelengths responsible for the respective photodegradation.

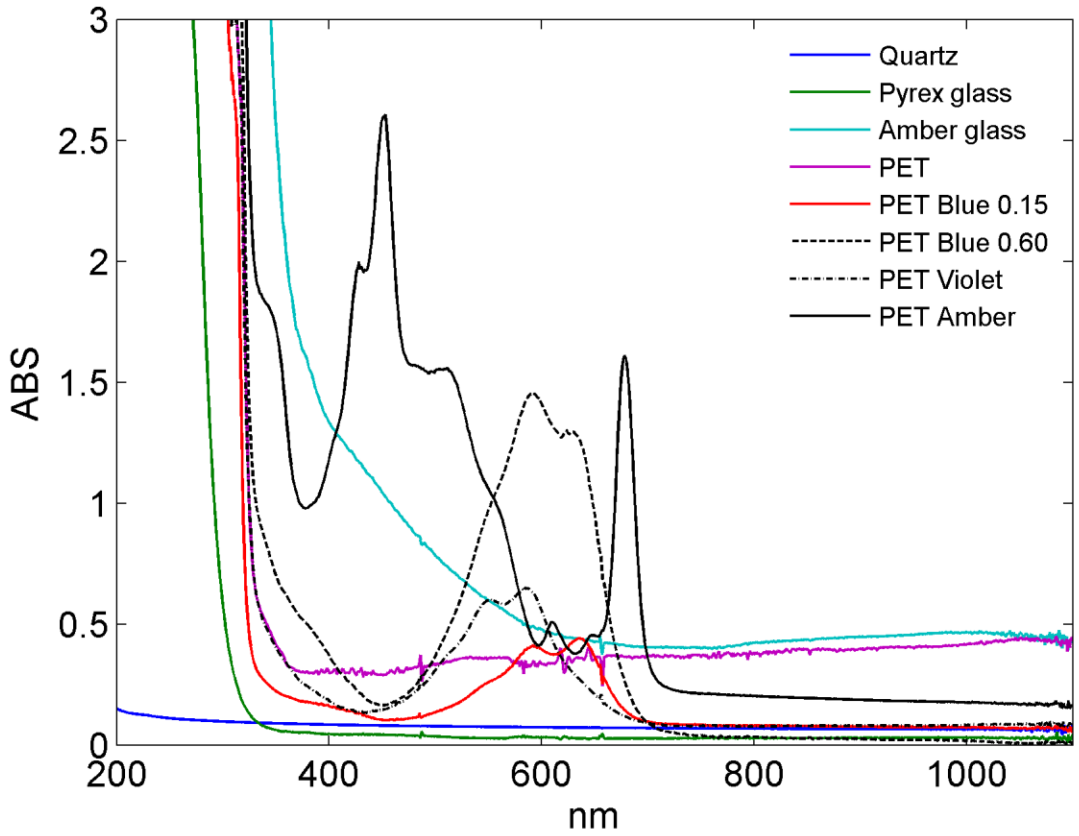

Fig. 4 Absorbance signal spectra of the glass and polymer containers

The influence of the container thickness in reducing degradation of the drugs was evaluated on a series of blue PET containers, which had shown the maximum photoprotective effect, of different thickness. The stressed degradation tests were executed on the FEL solution in blue PET containers of 0.15, 0.3, 0.45, 0.60, 0.75 and 0.90 mm thickness. Photoprotection power was shown to increase, as expected, with increasing thickness. However, the maximum shielding effectiveness was achieved already with a thickness 0.60 mm. The graphical relationship between the values of $t_{0.1}$ and the blue PET thickness is shown in Figure 5.

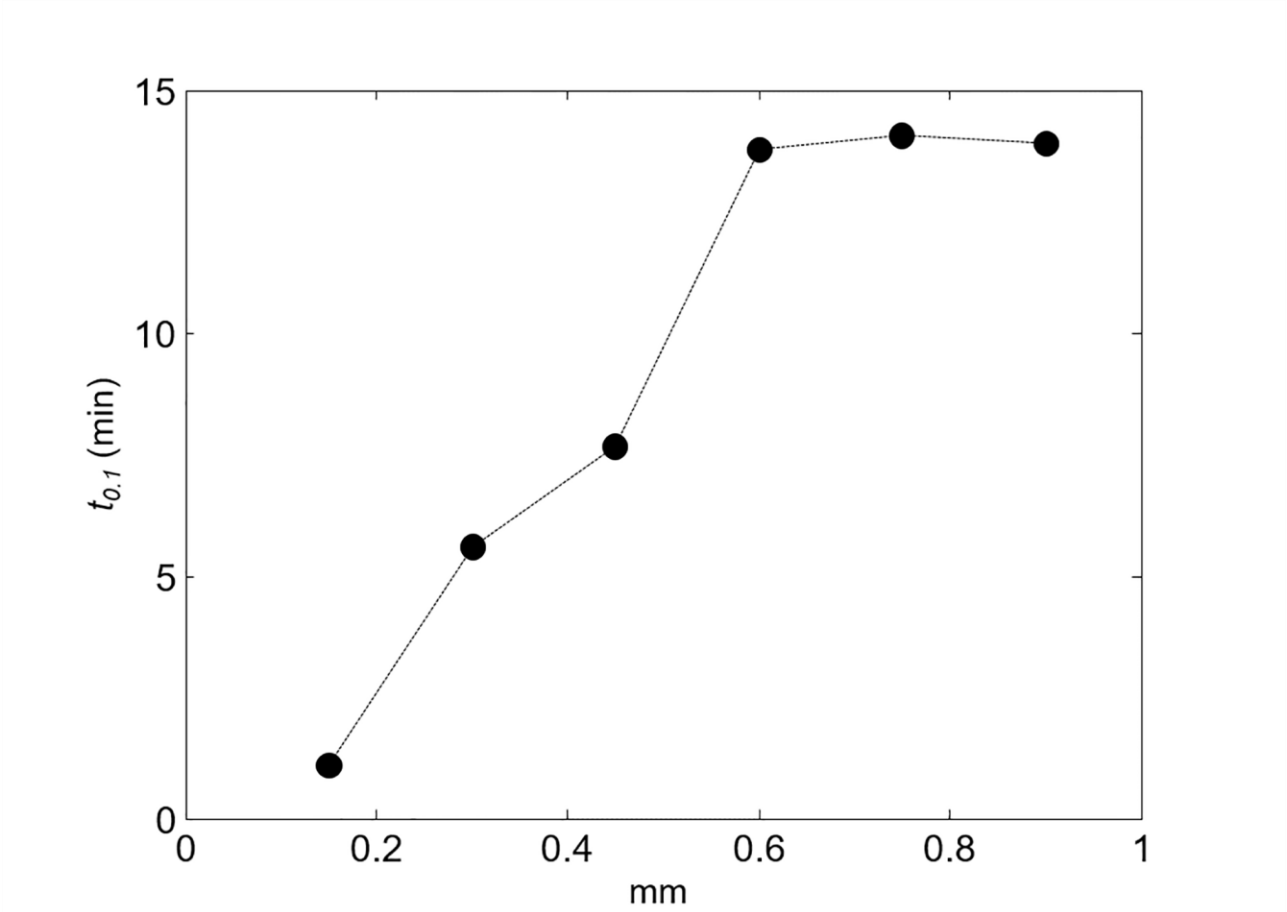

Fig. 5 Relationship between thickness and $t_{0.1}$ for the blue PET containers

4. Conclusions

This paper describes the results of stress tests on glass and polymeric containers aimed to assess their photoprotective ability for antihypertensive dihydropyridines in solution. This research had a dual purpose: the opportunity to prepare liquid formulations of these drugs, as an alternative to solid formulations, and the adoption of anti-shock and easy-to-handle containers in place of the conventional dark glass bottles. Both targets could be particularly appreciated by the elderly patients who are the main users of these drugs.

Four well-known dihydropyridine drugs, in hydroalcoholic solution, were subjected to forced photodegradation when placed in a series of glass or plastic containers. The degradation processes were monitored by spectrophotometry and the data matrices processed by the multivariate algorithm MCR, able to resolve the degradation kinetics of the drugs, carrying out at any time of the experiment the number of components and the relative concentrations.

Experiments have shown that the PET containers effectively protect some dihydropyridines from light. Excellent results were obtained in testing felodipine solution in transparent PET container. The time ($t_{0.1}$) required to degrade 10% of the drug was 168 min, much higher than that obtained in amber glass bottle, equal to 16 min. The photoprotective power was further optimized by testing

colored PET containers of different thickness. The best performance was shown by the container in blue PET of 0.6 mm thick. The drug concentration remained practically unaltered for the total experiment time of 6 hours, presenting an extrapolated value of $t_{0.1}$ equal to 828 min.

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Figure captions

Fig.1. Sequence of the UV spectra for each drug solution (20.0 μg/ml) along the forced irradiation

Fig.2. Concentration profiles of the drugs along the photodegradation test

Fig.3 Kinetic curves resulting from degradation tests on FEL solution in different containers. The dashed line represents the degradation value equal to 10% ($t_{0.1}$).

Fig. 4 Absorbance signal spectra of the glass and polymer containers

Fig. 5 Relationship between thickness and $t_{0.1}$ for the blue PET containers

Chemical compounds studied in the article

Felodipine (PubChem CID: 3333) Lercanidipine (PubChem CID: 65866) Nimodipine (PubChem CID: 4497) Nifedipine (PubChem CID: 4485)

Abbreviations

DHP, 1,4-dihydropyridine; ICH, International Conference on Harmonization; HS-MCR-ALS MCR, hard–soft multivariate curve resolution-alternating least squares; PET, polyethylene terephthalate; FEL, felodipine; LER, lercanidipine; NIM, nimodipine; NIF, Nifedipine; QSPR, quantitative structure-property relationships; PP, polypropylene.