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

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ABSTRACT

1,4-dihydropyridine antihypertensives (DHPs) are almost all dispensed in solid pharmaceutical formulations for their 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 when in solutions. 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 multivariate curve resolution (MCR) methodology to the spectral data recorded along the irradiation test. This technique was able to determine the kinetic parameters and resolve 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 by the use of polyethylene terephthalate (PET) containers. The best result was achieved for the felodipine solution in blue PET transparent bottle of 0.6 mm thickness, reaching an almost complete stabilization up to six hours under stressing irradiation. In contrast, the glass containers, whether or not coloured, did not provide a satisfactory photoprotection of the drugs, showing in any case $t_{0.1}$ values under 24 min. These results can be a good opportunity to design new photoprotective pharmaceutical packaging for DHPs in liquid dosage form.

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 (Ioele et al., 2016, 2014, 2010; Kawabe et al., 2008; Ragno et al., 2006).

DHP are used mainly as antihypertensive and act preferentially as calcium channel blockers in vascular smooth muscle.For this study, four DHPs commonly used in therapy were selected: felodipine (FEL), lercanidipine (LER), nimodipine (NIM) and the lead Nifedipine (NIF). FEL and LER are usually used against hypertension and certain forms of angina (Navadiya and Tiwari, 2015). NIF is used for some types of angina (Canova et al., 2012). NIM nowadays gives good results in preventing vasospasm associated with subarachnoid haemorrhage (Bele et al., 2015).

Photolability of DHPs is well known, as well as the oxidation of the dihydropyridine ring to pyridine derivative as the main degradation mechanism (Maafi and Maafi, 2013; Marinkovic et al., 2003; Vetuschi et al., 2002; Ragno et al., 1995). Some DHPs undergo a more complex degradation with the formation of secondary photoproducts (De Filippis et al., 2002; Kawabe et al., 2008; Mielcarek et al., 2000). The pyridine by-products have been shown to be devoid of any therapeutic effect (Marinkovic et al., 2003; Ragno et al., 2003; Zanocco et al., 1992). Production of singlet oxygen and superoxide species has been observed during the photodegradation process, inducing peroxidation of fatty acids and leading dermatitis (Onoue et al., 2008). Furthermore, the same degradation mechanism has been observed in the liver metabolism of these drugs through oxidation catalysed by the analogue of cytochrome P-450 (Niwa et al., 1995).

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.

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The potential toxicity of these drugs after photodegradation has initiated in recent years the interest for the synthesis of structural analogues more stable to light. A 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 (Ioele et al., 2009). At the same time, new approaches to protect the drugs from photodegradation remain a topical subject, including physical systems shielding the passage of light or pharmaceutical photoprotective matrices (Ioele et al., 2014).

Photodegradation of the DHPs are particularly fast in solution (De Filippis et al., 2002), and this is the main reason why most of the pharmaceutical specialties containing these drugs are marketed in solid formulations, usually tablets. Currently, only NIM and NIF are available in water-alcohol solutions, packaged in bottles of dark glass. The bottle containing NIF is covered by a thin layer of black plastic to maximize the protection of the solution from photo degradation.

The method most commonly used by the pharmaceutical industry to protect photosensitive drugs is through utilization of protective containers of coloured glass. Yellow-green glass offers good protection in the UV range while amber glass provides good protection from UV light, but little protection from infrared light. One of the problems associated in the adoption of these containers is the difficult visual inspection of the contents.

This work aims to test the photoprotective potential of polymer bottles to be candidates to contain DHP solutions, in order to increase 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 coloured glass because they offer greater transparency and shock 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 on DHP solutions in glass bottles. The choice of solvent was driven by the low solubility of DHPs in water and in analogy with the excipients used in the commercial specialties containing DHPS. The photodegradation tests were conducted in accordance with the ICH Guideline for drug photostability testing (International Conference on Harmonization, 2003). 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 (International Conference on Harmonization, 2003).

The photoprotective power of the containers tested was compared by adopting the parameter $t_{0.1}$, defined as the time required to degrade 10% of the drug.

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 structures. In this work, the experiments were monitored by UV–vis 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 (De Luca et al., 2010, 2012, 2013, 2014).

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), violet PET, amber PET, blue PET, polypropylene (PP). Table 1 lists all the containers tested and relative thickness. 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 was used to monitor irradiation and temperature conditions. Irradiation wavelength range was set to 300–800 nm, by means of a glass filter, according to the D65 standard of ICH rules. D65 is the internationally recognized standard for outdoor daylight. An appropriate filter was fitted to eliminate radiation below 290 nm. 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 a flow-through cuvette placed in the UV spectrophotometer. UV–vis ChemStation software supplied with the Spectrophotometer (Agilent Technologies, CA, USA) was used for control, data acquisition and initial data pre-processing.

All chemometric procedures were performed under Matlab® computer environment (Mathwork Inc., version 7). MCR routine computer methods were implemented as MATLAB functions. Source files containing these algorithms are available by visiting the web site "www.mcrals.info" (De Luca et al., 2010).

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 inside the light cabinet were set in agreement with the conditions for photostability testing described in ICH Q1B: radiant power 350 W/m^2, UV-filter glass >290 nm, temperature inside the chamber was maintained at 25 °C to

Table 1
Glass and polymeric container tested in the forced photodegradation tests.

Glass containers	Thickness (mm)	Polymeric containers	Thickness (mm)
Quartz	1.00	PET transparent	0.90
Pyrex	1.00	PET violet	0.60
Amber	1.00	PET amber	0.80
Amber covered	1.20	PET blue	0.15
		PET blue	0.30
		PET blue	0.45
		PET blue	0.60
		PET blue	0.75
		PET blue	0.90
		PP	1.50