Photostability study of finasteride, diclofenac and naproxen through exposure to simulated sunlight and evaluation of packaging photoprotection of these drugs

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1-Introduction

The aim of this study was to investigate if an inappropriate drug package could cause any significant photodegradation of the active ingredient. As indicated in the European Pharmacopoeia [1], a drug should be opportunely protected from light exposure because it can lead to a reduction of concentration of the active ingredient with consequent lost of pharmaceutical efficiency. Furthermore, photodegradation products can be the reason of side effects not only on humans, but also on flora and fauna present in the environment in which drugs are dispersed, either directly or indirectly. It could also be possible that photodegradation products could be more toxic than starting reagents.
The implementation of ICH guidelines during photostability drug tests could be useful to obtain a scale of stability/recalcitrance of several active ingredients also for solving ecopharmacology problems [2]. So, the study was oriented to the comparison of photodegradation of three active ingredients among the most consumed in the Italian market during 2005 [3]: Naproxen [4], Diclofenac [5] and Finasteride [6] (two anti-inflammatory and a 5-alpha-reductase, commonly used for treatment of prostatic hypertrophy and androgenetic alopecia respectively).

2-Materials & Methods

2.1-Chemicals

All pure chemicals were purchased from Sigma-Aldrich. Pharmaceutical solid forms of active ingredients were purchased from pharmacies: *Prostide* containing 5 mg Finasteride (fig. 1), *Voltaren 50* containing 50 mg of Diclofenac sodium (fig. 2), *Momendol 220* containing 220 mg of Naproxen sodium (fig. 3). All of the marketing packs of three drugs consisted in opaque cardboard boxes.

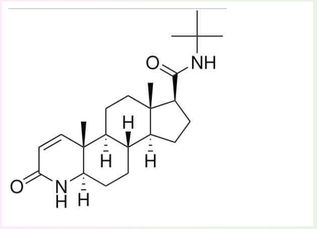


Fig. 1: Structure of finasteride
[CAS n. 98319-26-7]

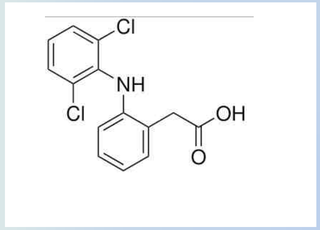


Fig. 2: Structure of diclofenac
[CAS 15307-79-6]

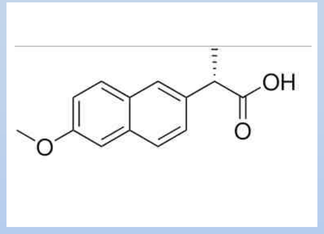


Fig. 3: Structure of naproxen
[CAS n. 26159-34-2]

2.2-Measure of solar irradiation

In order to simulate the natural sunlight, the values of irradiance (W/m^2) and the value of illuminance (lux) of a typical Italian summer day were studied. For this aim were used a radiometer/luxmeter (Gossen, model Mavolux Digital) and a polycrystalline photovoltaic panel. Because the radiometer hasn't any interface with data collectors we could only read values from the display. So coupling the radiometer with the photovoltaic panel and a data logger (Lascar, model EL-USB 3) we studied the correlation between sun irradiance and tension. We obtained straight line with a good correlation (R^2 = 0.9959) (fig. 4).
The solar energy reached the photovoltaic panel over 24 hours of an average sunny day is approximately equal to 2.76*10^7 J/m^2 (very similar to the value of 2.71*10^7 J/m^2 that was obtained from the web site of Directorate General of the European Commission - Joint Research Centre). From our calculations, the photovoltaic panel is irradiated with a value bigger or equal to 600 W/m^2 for about 50% of total exposure time to the sunlight (fig. 5).

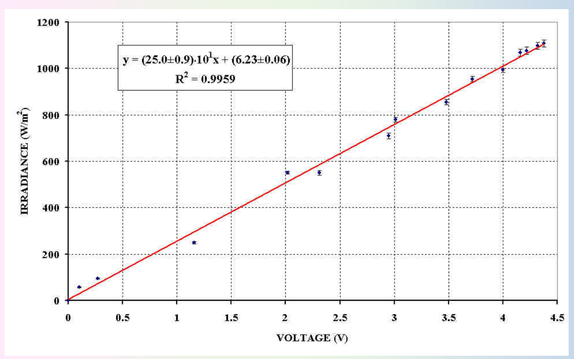


Fig. 4: Correlation between values of tension generated by photovoltaic panel and those ones of radiance measured with radiometer/luxmeter

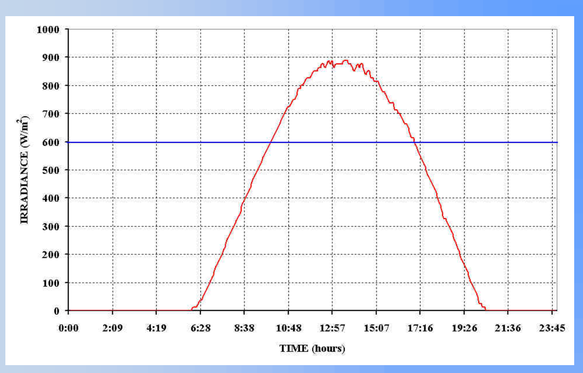
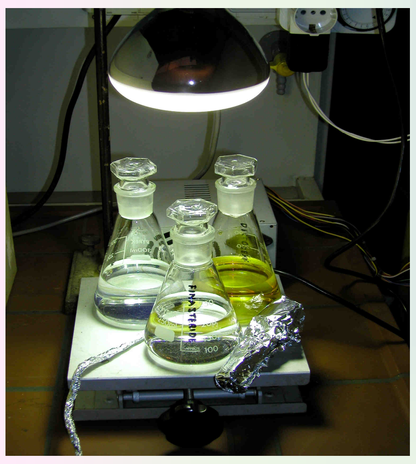


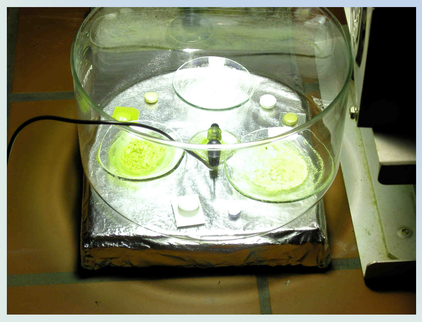
Fig. 5: Trend of data collected by datalogger during a period of 24 hours

2.3-Experimental apparatus

In order to carry out photodegradation tests, an Osram Ultra-Vitalux Sun Lamp was used. The lamp has a double source of electromagnetic radiation: the emission is generated by a tungsten filament lamp and by a discharge mercury one, and the bulb is made of a special glass that allows only the passage of some types of radiation which are able to simulate natural sunlight (fig. 6a and 6b). The distance of the source from the exposure plane of samples was selected in order to provide a value of 600 W/m^2 and a system of air cooling was used to minimise a possible heat degradation of samples. The tests were initially carried out on solutions of pure individual active ingredients and subsequently on their solid pharmaceutical forms. These latter were simultaneously exposed inside and outside of immediate pack and inside of marketing pack in order to carry out any photodegradation tests under the same conditions. Solutions were irradiated inside conical flasks of Pyrex England glass, equipped with emery cap, for a total time of 90 hours.



6a



6b

Fig. 6a and 6b: The experimental apparatus is made up of:
• A Osram Ultra-Vitalux lamp with emission spectrum, intensity and focusing near the summer sun in the Mediterranean places;
• Placed 60 cm below the lamp there are the degrading solution or a watchglass containing solid pharmaceutical forms;
• Below the reactor, an aluminium sheet was put to reflect to the beaker more light;
• The and lamp is connected to normal AC to 220V.

2.4-HPLC analysis

Chromatographic analysis was carried out using a HPLC system consisting in a Kontron pump mod. 422, a Kontron UV/VIS detector mod. 430 connected to a PC. Chromatographic separation was carried out with an Alltech reversed phase column (Alltima C8 250x4.6 mm I.D., 5µm). The chromatograms (fig. 7-9-11) were analysed with PeakFit v4.12. Temperature was maintained at 25±1℃ using a thermostatic bath in which the colum n was immersed.

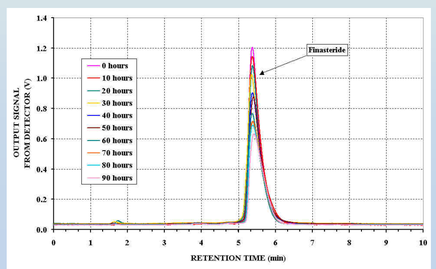


Fig. 7: Chromatograms of Finasteride solution during 90 hours of exposure to simulated sunlight

Finasteride solutions were analysed using parameters as below indicated:
•Injection: 20 µl
•Mobile phase: Acetonitrile/Water Plus - 95:5
•Flow: 1.000 ml/min
•Column: Alltech Alltima C8 5 µ m 250mm x 4mm Ø
•Detection ? : 205nm
•Temperature: 25±2℃

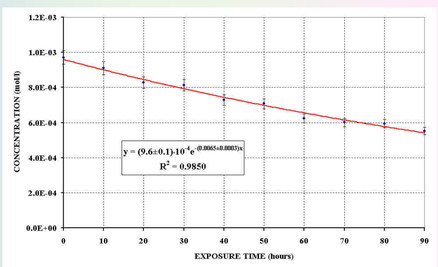


Fig. 8: Kinetic of photodegradation of Finasteride solution

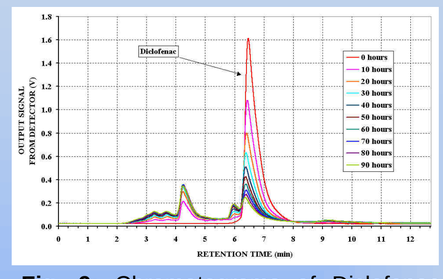


Fig. 9: Chromatograms of Diclofenac solution during 90 hours of exposure to simulated sunlight

Diclofenac sodium salt and Naproxen sodium salt solutions were analysed in both cases with parameters as below indicated:

•Injection: 20 µl
•Mobile phase: Acetonitrile/Methyl alcohol/Phosphate buffer at pH 3.3 - 35:35:30
•Flow: 1.250ml/min for Diclofenac sodium salt and 1.000ml/min for Naproxen sodium salt
•Column: Alltech Alltima C8 5 µ m 250mm x 4mm Ø
•Detection ?: 275nm for Diclofenac sodium salt and 262nm for Naproxen sodium salt
•Temperature: 25±2℃

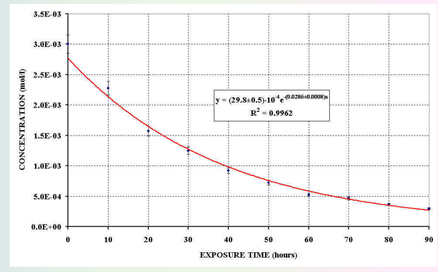


Fig. 10: Kinetic of photodegradation of Diclofenac solution

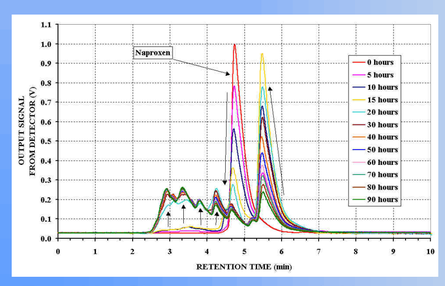


Fig. 11: Chromatograms of Naproxen solution during 90 hours of exposure to simulated sunlight

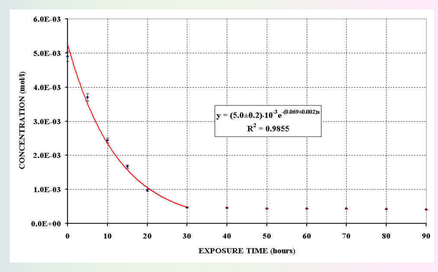


Fig. 12: Kinetic of photodegradation of Naproxen solution (until the 30th hour)

3-Results & Discussion

The analysis of samples showed the following experimental results. Naproxen is the pure active ingredient that has the fastest rate of photodegradation in all tested situations and the same order is maintained for active ingredients inside drugs. Finasteride and Diclofenac molecules show a concentration that decreases over time, with good correlation (R^2 = 0.9850 for Finasteride and R^2 = 0.9962 for Diclofenac), following an equation of first decay order (fig. 8-10). Photodegradation of Naproxen occurred for the first 30 hours of irradiation and then, also byproducts began their degradation. These secondary reactions interfered with the initial one of Naproxen modifying its kinetic. Until the 30th hour an equation of first decay order was obtained and the correlation coefficient is good (R2=0.9855). From the 30th to the 90th hour, the concentration of Naproxen decreases very slowly with a kinetic of a different order that was not determined (fig. 12).

		Prostide	Voltaren 50	Momendol 220
Tablets exposed for 90 hours inside the marketing pack	Area of the peak before photodegradation ± s (RSD %)	13.69 ± 0.04 (0.31 %)	54.0 ± 0.1 (0.2 %)	86.85 ± 0.09 (0.11 %)
	Area of the peak after photodegradation ± s (RSD %)	13.61 ± 0.05 (0.33 %)	53.2 ± 0.1 (0.2 %)	85.40 ± 0.09 (0.11 %)
	% of photodegradation ± s	0.66 % ± 0.04 %	1.52 % ± 0.03 %	1.70 % ± 0.05 %
Tablets exposed for 90 hours inside the primary pack	Area of the peak before photodegradation ± s (RSD %)	13.69 ± 0.04 (0.31 %)	54.0 ± 0.1 (0.2 %)	86.85 ± 0.09 (0.11 %)
	Area of the peak after photodegradation ± s (RSD %)	13.12 ± 0.05 (0.37 %)	51.3 ± 0.1 (0.2 %)	63.89 ± 0.09 (0.14 %)
	% of photodegradation ± s	4.13 % ± 0.05 %	5.06 % ± 0.03 %	26.4 % ± 0.4 %
Tablets exposed for 90 hours outside the primary pack	Area of the peak before photodegradation ± s (RSD %)	13.69 ± 0.04 (0.31 %)	54.0 ± 0.1 (0.2 %)	86.85 ± 0.09 (0.11 %)
	Area of the peak after photodegradation ± s (RSD %)	12.80 ± 0.06 (0.45 %)	45.9 ± 0.1 (0.3 %)	59.0 ± 0.1 (0.2 %)
	% of photodegradation ± s	6.52 % ± 0.07 %	15.1 % ± 0.3 %	32.1 % ± 0.5 %

Tab. 1: Summary of collected data from the analysis of solutions obtained from dissolution of tablets before and after 90 hours of exposure (5 tablets were tested for each drug , 3 replies were performed for each tablet)

		Solution of Finasteride	Solution of Diclofenac	Solution of Naproxen
HPLC analysis	Area of the peak before photodegradation ± s (RSD %)	25.7 ± 0.3 (1.3 %)	52.4 ± 0.1 (0.2 %)	38.57 ± 0.04 (0.11 %)
	Area of the peak after photodegradation ± s (RSD %)	14.7 ± 0.1 (0.7 %)	6.1 ± 0.1 (2.1 %)	3.3 ± 0.1 (3.0%)
	% of photodegradation ± s	42.9 % ± 0.8 %	88.4 % ± 0.3 %	91 % ± 4 %
Toxicity analysis	$I_{t\ photodegradated}$ ± s (RSD %)	0.39 ± 0.01 (2.56 %)	0.472 ± 0.005 (1.06 %)	0.137 ± 0.002 (1.46 %)
	$I_{t\ not\ photodegradated}$ ± s (RSD %)	0.507 ± 0.005 (0.99 %)	0.77 ± 0.01 (1.30 %)	0.77 ± 0.01 (1.30 %)
	% of reduction of the integral toxicity index ± s	23 % ± 3 %	39 % ± 2 %	82 % ± 8 %

Tab. 2: Summary of collected data from the analysis of solutions of active principle ingredients before and after 90 hours of exposure (3 replies were performed for each solution)

4-Conclusions

From tables 1 and 2 it could be seen that the tests performed on drugs contained in the marketing pack, lead to a reduction of the active ingredient less than 5%, as required by European Community laws. So the package has performed its function of protection against UV-visible radiation. Moreover, simulated solar radiation showed a good ability to degrade three tested drugs, especially against their pure active ingredients. Solar degradation could be used for improving wastewater treatment plants, in order to reduce the concentration and the toxicity of active ingredients, especially for molecules that show long environmental persistence like Finasteride. For more safety, plastic blister should be equipped with UV-blocker filters in order to assure additional protection from radiation. In addition, it could be useful the presence of a "stability indicator" that can show eventual deterioration due to temperature, photolysis, irradiation and recognise counterfeit or expired drugs that are so detrimental to public health and for the image of pharmaceutical companies.

5-References

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