THE EFFECT OF ACCELERATED LIGHT (STRESS) AND NATURAL SUNLIGHT EXPOSURES ON CETUXIMAB (ERBITUX®): EVALUATION OF AGGREGATE FORMATION AND FUNCTIONALITY

[1,3]A Torres-García, [1,3]A Torrente-López, [1,3]Jesús Hermosilla, [1]Alberto Aguilera-Ortega, [2,3]J Cabeza, [2,3]A Salmerón-García, [1,3]N Navas

[1] Department of Analytical Chemistry, Science Faculty, University of Granada, Granada, Spain
[2] Department of Clinical Pharmacy, San Cecilio University Hospital, Granada, Spain
[3] Biomedical Research Institute of Granada (ibs.Granada), Granada, Spain
*anabeltl@ugr.es

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Background and importance

Cetuximab (CTX) is a monoclonal antibody indicated for treatment of metastatic colorectal cancer and squamous cell cancer of head and neck. This kind of proteins are susceptible to degrade during long-term storage and/or during exposure to environmental conditions (high temperature, agitation, light exposure, etc) when handled in hospitals. Therefore, it is essential to detect critical degradation points before the administration to patients to ensure the efficacy and safety of the medicine.

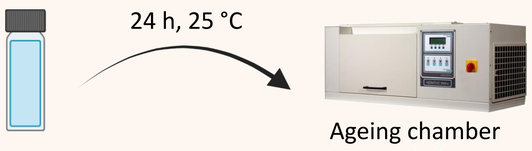
Aim and objectives

To assess the impact of accelerated light (stress) and natural sunlight exposures on CTX (Erbitux®, 5 mg/mL) safety and efficacy through the study of aggregate formation and functionality when mishandling in real hospital conditions.

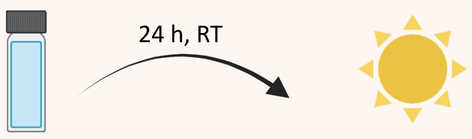
Materials and Methods

Cetuximab 5 mg/mL

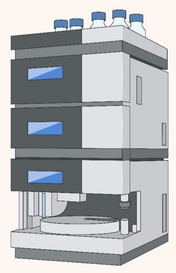
1. Light stress:



2. Natural sunlight:



Aggregate profile was determined by Size-Exclusion High-Performance Liquid Chromatography (SE/UHPLC-UV)

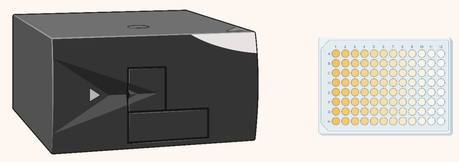


Dionex UltiMate 3000 chromatograph (Thermo Scientific, Waltham, MA, USA)

Chromatographic conditions

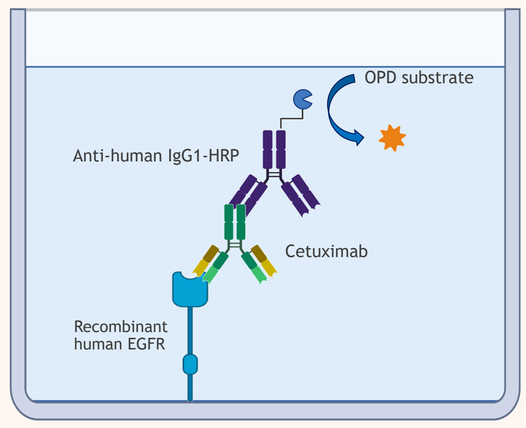
Column	SEC 300 A, 2.7 µm, 4.6 × 300 mm (AdvanceBioSec, Agilent technologies)
Mobile phases	150 mM phosphate buffer pH 7.0
Flow rate	0.3 mL/min
Injection	20 µg of Keytruda®
Column temperature	30 °C
Total analysis time	18 min
Detection wavelength	λ=214 nm, 220 nm, and 280 nm Reference 360 ± 10 nm
Bandwidth	5 nm
Elution mode	Isocratic

Functionality was evaluated by Enzyme-Linked Immunosorbent Assay (ELISA)



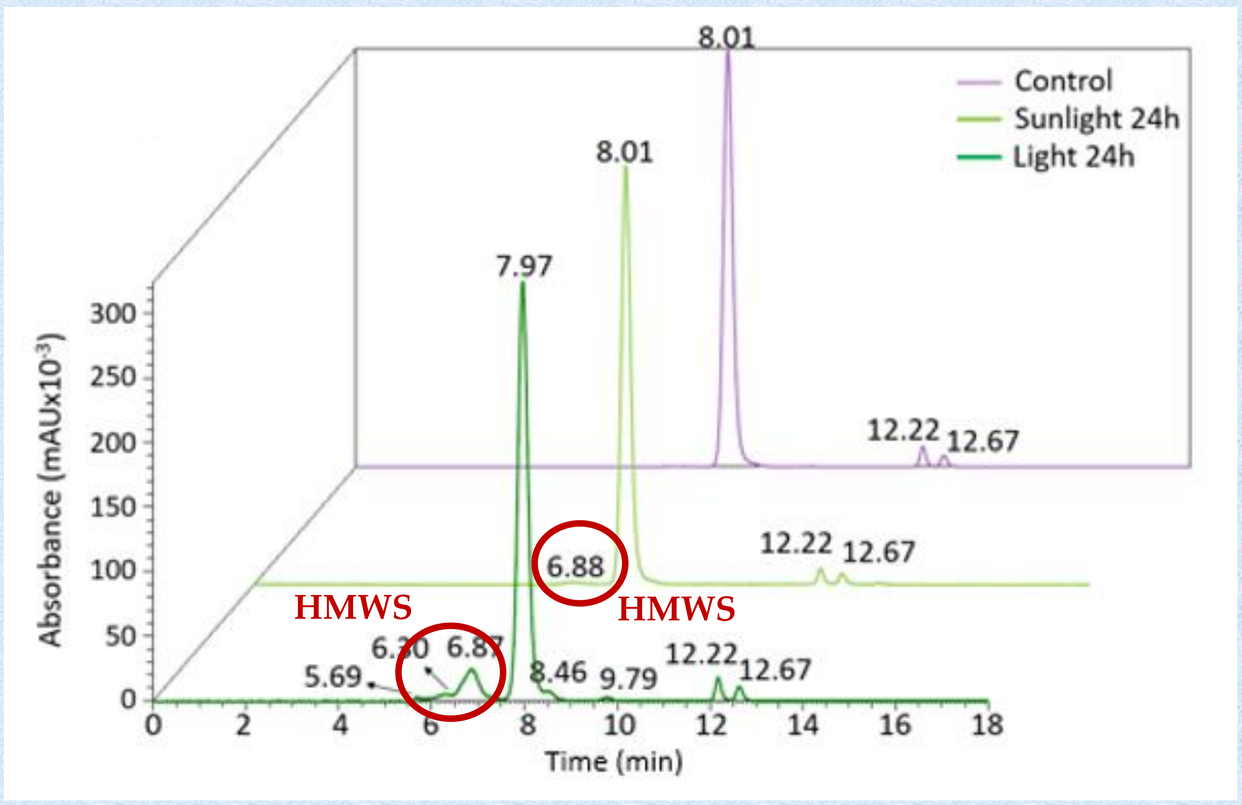
- NanoQuant Infiniti 200 Pro
- Nunc MaxiSorp™ 96-well plates

Non-competitive ELISA method

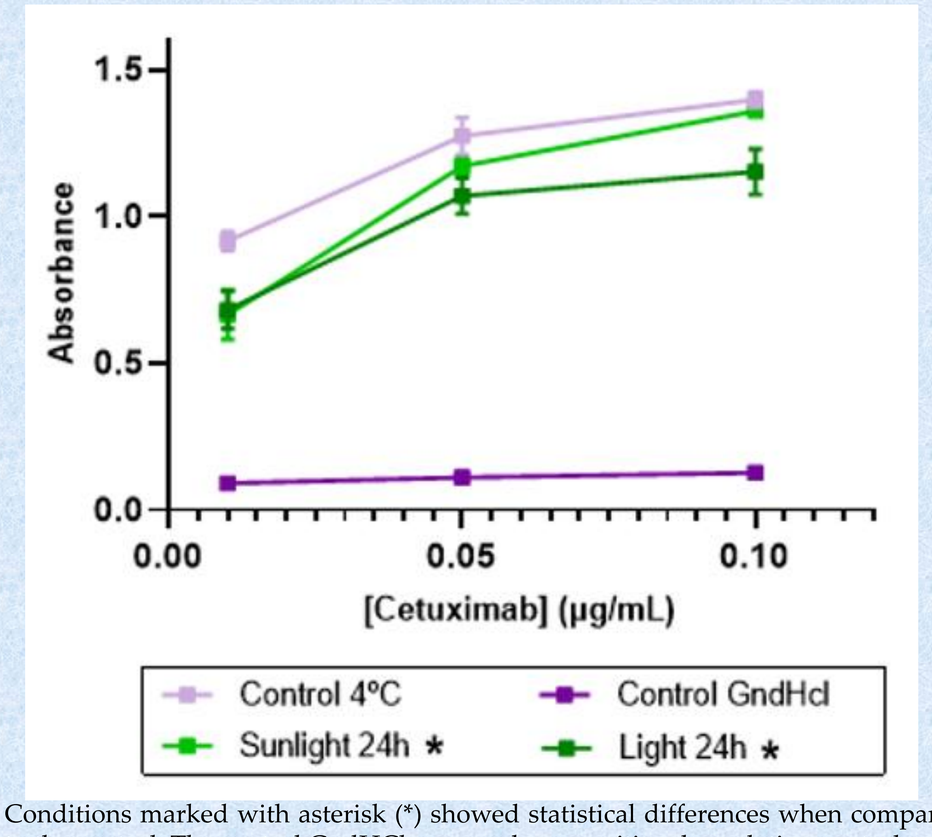


Results

SE/HPLC-DAD chromatograms



ELISA graphs



Conditions marked with asterisk (*) showed statistical differences when compared to the control. The control GndHCl was used as a positive degradation control.

SE/UHPLC-UV chromatograms of CTX control sample (5 mg/mL) showed a main chromatographic peak assigned to CTX monomers. The sample subjected to light stress revealed the appearance of three new chromatographic peaks assigned to high molecular weight species (HMWS). However, exposure to natural sunlight only revealed the appearance of one small new peak assigned to HMWS with a low relative abundance. ELISA showed a significant loss of functionality of CTX medicine in both stressful conditions: light stressed sample revealed a loss of biological activity (BA) of around 20%, while the sample exposed to natural sunlight showed a loss of BA of 10%.

Conclusion and relevance

Exposure to light promotes aggregate formation in CTX (Erbitux®), being this effect more noticeable in accelerated light exposure. Moreover, CTX functionality was also affected after the exposure to both stressful conditions, revealing a loss of biological activity. Thus, we recommend preventing CTX from light exposure when handled in hospitals.

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