Comparative antioxidant activity of various ophthalmic product types for artificial tears under different experimental conditions

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Received August 11, 2021; Accepted October 9, 2022

DOI: 10.3892/etm.2022.11259

Abstract. Artificial tears or lubricants is a developing category in pharmaceutical research, due to the permanent increasing incidence of dry eye syndrome caused by the extensive use of personal computers and other gadget screens, associated with global warming and pollution. Considering the role of inflammation in dry eye syndrome, characterized by the production of free radicals, it is imperative to determine which elements are more significant in forming an artificial tear more effectively and more comfortably for the eye state and for the quality of life. Thus, the aim of the present study was to examine the evolution of the total antioxidant capacity of some frequently commercialized artificial tears via the photochemiluminescence method, using an antioxidant capacity of lipid soluble substances procedure, prior and subsequent to the exposure of these therapy agents to some physical agents. This is a preliminary research aiming to evaluate the impact of various environmental factors on these ophthalmic products, to be continued by evaluating whether the effectiveness of these products, in terms of objective examination and patient preference and adherence criteria, is impacted by the conditions of use and storage. Thus, the total antioxidant capacity of the evaluated artificial tear samples after UVC irradiation at 254 nm wavelength was studied, in order to investigate whether their status suffered any change in terms of antioxidant potential. In addition to the findings obtained in the study, some recommendations were also made.

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Key words: artificial tears, dry eye syndrome, total antioxidant activity, photochemiluminescence, UV irradiations

Introduction

Under the circumstances of the increasing incidence of dry eye disease, especially due to the extensive use of personal computers and other gadget screens, amplified during the Covid-19 pandemic, and associated with global warming and pollution, the use of artificial tears has become crucial for the comfort and maintenance of ocular health (1). The signs and symptoms of dry eye are of concern for ophthalmologists because of their diversity and persistence, sometimes despite adequate treatment (2-7). The requirement of a good adherence of the patients to treatment is a compulsory condition for success (8). The involvement of inflammatory mechanism in dry eye has led to new challenges and the need for new therapeutic agents (9-14). Considering the recognition of inflammation associated with free radical production, the present study focused on further investigating some widely used artificial tears. Previous studies dedicated to the evaluation of antioxidant activity of various artificial tears revealed significant differences among them (15-17).

Increasing exposure to pollution, global warming and expanding work on video terminals requires permanent use of artificial teardrops, so that the stability of their properties becomes an important effectiveness condition. In addition, artificial tears, as therapeutic agents in dry eye, may be more effective if they also neutralize successfully some higher amounts of free radicals. Thus, the aim of previous studies was to investigate the artificial tear samples after opening of the vial, a second time after one year of refrigeration and a third time after having exposed the samples to UV irradiation, having in mind the increase of natural environment UV irradiation caused by the thinning of the ozone protective layer of the atmosphere and its damaging potential for the eye (18,19). The present study is a preliminary research aiming to evaluate the impact of various environmental factors on these products, followed by evaluation of the effectiveness of these products, in terms of objective examination, patient preference and adherence criteria, and how it is impacted by the conditions of use and storage. The varying impact of the exposure to UV on the stability of the artificial tears, may offer recommendations regarding a more adequate medical behavior of dry eye subjects (3,4).

The term 'dry eye' includes a wide spectrum of ocular surface alterations with different etiology and pathophysiology, as multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage of the ocular surface, which is evident in the ophthalmological examination and quantified by special questionnaires (20-23). The dry eye is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (3,24).

The tested commercially available artificial tears lack both the antioxidant content and UV-absorbing characteristics of natural tears. Artificial tear formulations that help restore natural antioxidant and UV-absorbing properties to the tear film of the aging eye may help prevent or improve dry eye symptoms and promote ocular health (25). The literature data mention findings regarding the use of artificial tears with an adequate antioxidative effect, preserved or preservative-free, that may be beneficial in the treatment of dry eyes caused by environmental factors (26-30).

The aim of the present study was to evaluate the stability of the antioxidant activity of eight different artificial tears, including three different active principles (hydroxypropyl guar, hydroxypropyl methylcellulose, and carboxymethylcellulose), in order to identify any existing correlation between the chemical characteristics, the effectiveness of an artificial tear and the stability in time under various circumstances, by storage at +4˚C and to/by UV irradiation, hypothesizing that the effectiveness of an artificial tear may be influenced by exposure to the environment (31-33). Thus, the artificial tear samples were irradiated with UVC radiations at 254 nm wavelength.

Materials and methods

Types of artificial tears. For the experiment, artificial tear eye drops were used for ophthalmic administration. The tear eye drops were sterile, hypotone, soothing, moisturizing, lubricant solutions, frecquently recommended for eye dry syndrome (moderate to severe). A sample of each ophtalmic product was used. Tests were run on eight different pharmaceutical ophtalmic products, various types of artificial tears solutions, before and after exposure to UV starting from the opening moment of the bottles in the first year since their production, followed by preservation of the bottles at +4˚C, and retesting after one year and two years from the opening moment. The samples of artificial tears as eyedrops used in the experiments, frequently commercialized on the Romanian market, were required to have the following characteristics of active principles:

i) Hydroxypropyl guar artificial tears characterization. The artificial tears (samples 1, 2 and 3) based on hydroxypropyl guar characteristics, were: Derived from guar gum, a nonionic polymer made of naturally occurring guar or cluster bean, *Cyanopsis tetragonoloba* (L.), which presents specific properties such as developing a highly thickening effect, containing 30% ethanol, good compatibility with electrolytes, good stability in a large pH range of 5.0-7.0, and a yellow powder water-soluble form. Hydroxypropyl guar is an excipient used in the pharmaceutical industry as a thickening agent. It contains nutritional polysaccharides and has numerous benefits; it increases viscosity effectively, provides smooth skin feel and has characteristic high level of lubricity, has favorable film-forming properties, helps stabilize emulsions and has excellent salt and alcohol tolerance in aqueous solutions and can be used for gel products that can be pumped or sprayed (34). The effects of artificial tears based on hydroxypropyl guar recommendations are that it temporarily relieves the sensation of burning and irritation, due to dry eyes, power of action, intensive care; re-wetting of contact lenses made of silicone and soft hydrogel, is hydrophilic, in case of minor irritations, discomfort or blurred vision (35).

ii) Hydroxypropyl methylcellulose or hypromellose artificial tears characterization. The artificial tears (samples 4, 5 and 6) based on hydroxypropyl methylcellulose or hypromellose characteristics, were: A non-ionic cellulose ether made from natural cotton fiber under a series of chemical processing, which presents specific properties, including being an odorless, tasteless and non-toxic white powder, soluble in cold water to form a transparent viscous solution with the properties of thickening, binding, dispersing, emulsifying, film coating, suspending, absorbing, gelling, water retention and colloid protection (36). It is most commonly used in hydrophilic matrix fabrication and it allows for the controlled release of drug substances, thereby increasing the duration of therapeutic effects. The physical characteristics of this drug resemble natural tears, providing lubrication to the ocular surface and maintaining corneal hydration in dry eye syndromes (37). Known as an anti-caking agent, a polymer with moisturizing and vascoelastic properties that protect and lubricate the ocular surface, reducing the feeling of discomfort, it is the product with an epithelializing, a disinfecting and a moisturizing protective effect. At the surface of the cornea and conjunctiva, hydroxypropyl methylcellulose creates a temporary protective film, which moistens the outer surface of the eye and offers an alternative in case of insufficient tear secretion. Additionally, it induces rapid relaxation in the case of minor eye irritations of non-infectious origin and removes dry eye sensation. The presence of dexpanthenol, the alcoholic form of vitamin B_5, an active substance with a similar effect as pantothenic acid, helps the development and regeneration of mucous membranes and skin, and contributes to the rapid regeneration of cells on the surface of the cornea (epithelialization). The effects of artificial tears based on hydroxypropyl methylcellulose recommendations are that it offers calming and lubricating qualities and is used to relieve eye discomfort and irritation manifestations associated with dry eye syndrome and environmental factors such as wind, salt water, smoke or computer work (38).

iii) Sodium carboxymethylcellulose or cellulose gum artificial tears characterization. The artificial tears (samples 7 and 8) based on sodium carboxymethylcellulose or cellulose gum, a sodium salt of polycarboxymethyl cellulose characteristics (39), were: It is obtained from cellulose, the main polysaccharide and constituent of wood and all plant structures. It is obtained for commercial purposes from wood and is chemically modified. Sodium carboxymethylcellulose is

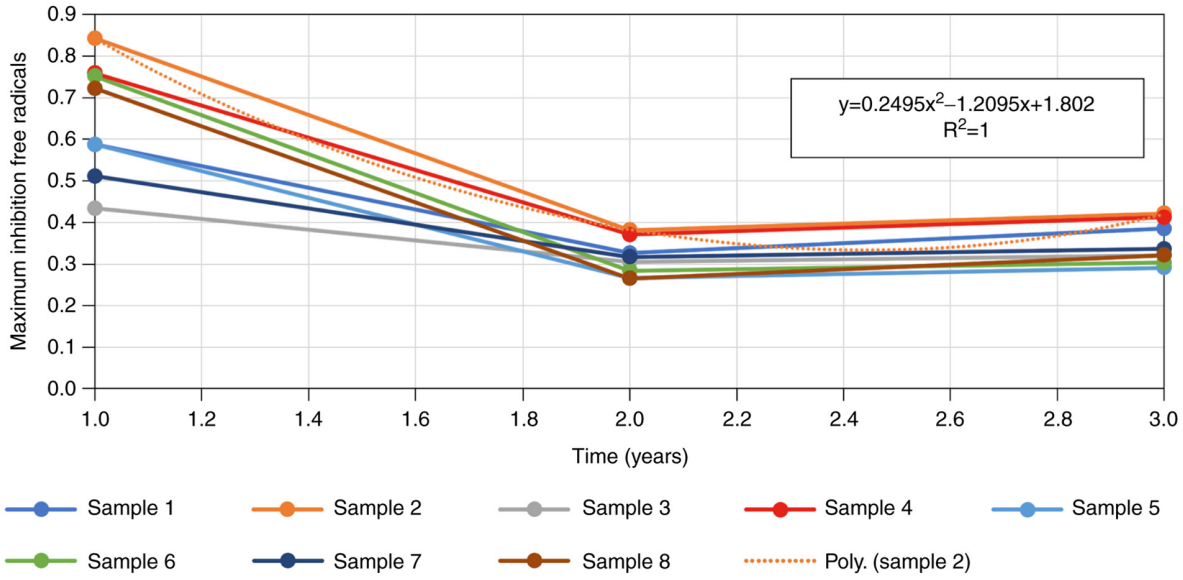

Figure 1. Maximum inhibition-free radicals for all the samples, during the 3-year study without exposure to UV-254 nm.

used as a thickening agent, but also as a filler, dietary fiber, anti-caking agent and emulsifier. It is similar to cellulose, but is very soluble in water (40,41). The effects of artificial tears based on sodium carboxymethylcellulose recommendations are that it lubricates the eye surface and moistens the cells on the eye surface by restoring the natural osmotic balance and it has a triple action: lubricating, humidifying, and osmoprotective (42-44).

Sample preparation. After opening, the ophthalmic pharmaceutical artificial tears solutions were stored at ambient temperature. Subsequently, 50 μl of each ophthalmic product sample were pipetted in the transparent well plate support and directly UVC-irradiated for 2 min, with 254 nm wavelength radiation. After irradiation, 5 μl working volume was taken from these samples and analyzed according to the Antioxidant Capacity of Lipid soluble substances (ACL) procedure (Analytik Jena AG).

UV irradiation. It is known from the literature that all bacteria and viruses tested, including various coronaviruses, respond to UVC disinfection. An Ultra-Lum Hand Held Portable Ultra Violet Lamp (Claremont) at 254 nm wavelength (UVC), specific for disinfection, was used to provide exposure of the samples to UV. Exposure to UV is commonly applied for disinfection as it generally affects the DNA structures of microorganisms, causing a photochemical effect on thymines, producing dimerization, which means that two adjacent information carriers are improperly linked. This molecular change means that DNA cannot be used for the essential process of transcription (metabolism) and replication (cell division) and as a result, the microorganism becomes harmless and dies. This study emphasized the impact of UVC radiation exposure on eight marketed artificial tears solutions, by irradiation of the samples. Despite the fact that in the natural environment there is no exposure to UVC radiation, because it is entirely absorbed by the ozone layer from the atmosphere, under the circumstances of Covid-19 pandemics we have witnessed new, increased disinfection needs followed by an enormous development of a very wide range of UVC disinfecting devices for both public, household and individual use. This reality led to higher risks of environmental accidental UVC irradiation of humans and objects, including medicine vials or disposals. Unintentional irradiation is favored by inadequate beam orientation, reflective surfaces or extended irradiation duration.

Total antioxidant capacity determination. According to the ACL-specific procedure, the total antioxidative capacity (TEAC) is provided by the superoxide anion-free radicals being produced by irradiation of a photosensitizer substance, these being partially eliminated from the sample by reaction with the antioxidants present in the sample. By optical excitation of a photosensitizing substance added in standardized volumes to the sample to be measured, superoxide anion radicals are being produced. Residual radicals cause the detector substance luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) to luminesce, which is then determined in a separate cell by means of a photomultiplier tube. In the measuring cell, the remaining radicals cause the detector substance, Luminol, to luminesce and thereby the antioxidant capacity of the sample is determined (45-47). The measuring signal produced by the luminescence is traced over 120 sec and the measuring curves show varied behavior. The calibration curve is constructed by measuring a series of 0.5, 1.0, 2.0 and 3.0 nmol Trolox (Hoffman-LaRoche's trade name for 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) standard solutions, an antioxidant used in biological applications to reduce oxidative stress or cell damage. Trolox equivalent antioxidant activity (TEAC) is a measure of a complex mixture of antioxidant strength, in units called Trolox equivalents (TE), nmol/sample, and used as a benchmark for the total antioxidant capacity of artificial tear mixture compounds considered (48,49). Apparatus used for TEAC was a photochemiluminometer PHOTOCHEM (Analytik Jena AG).

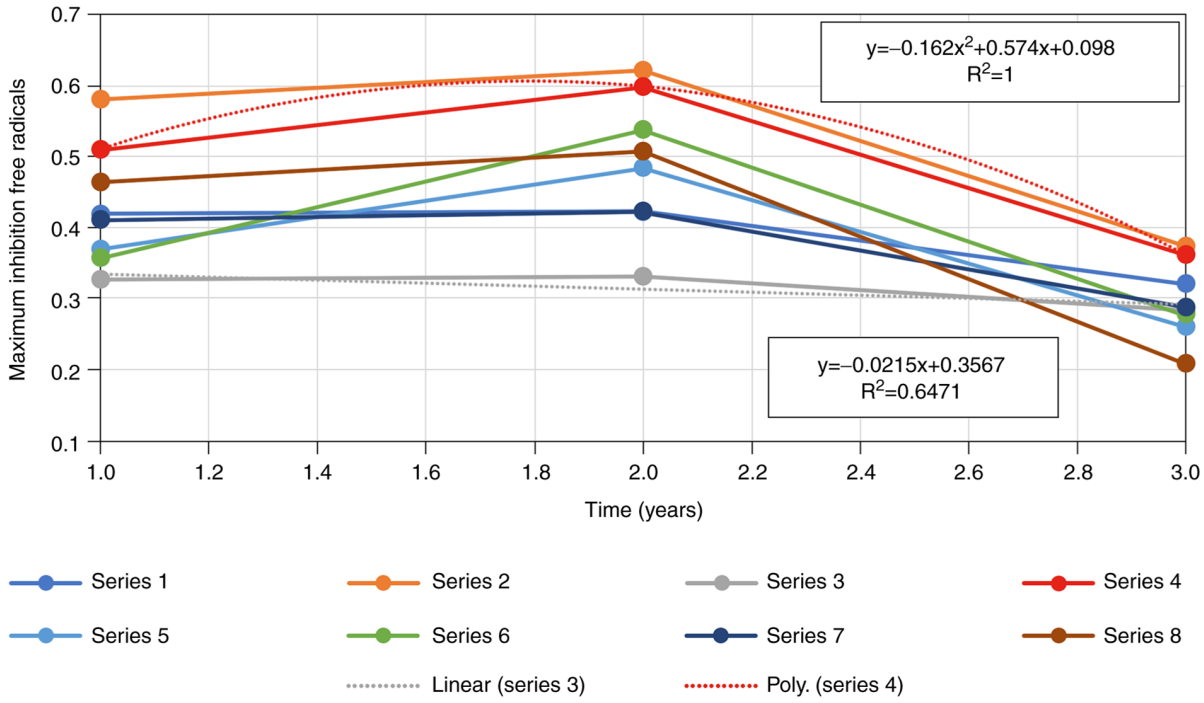

Figure 2. Maximum inhibition-free radicals for all the samples, during the 3-year study after exposure to UV-254 nm.

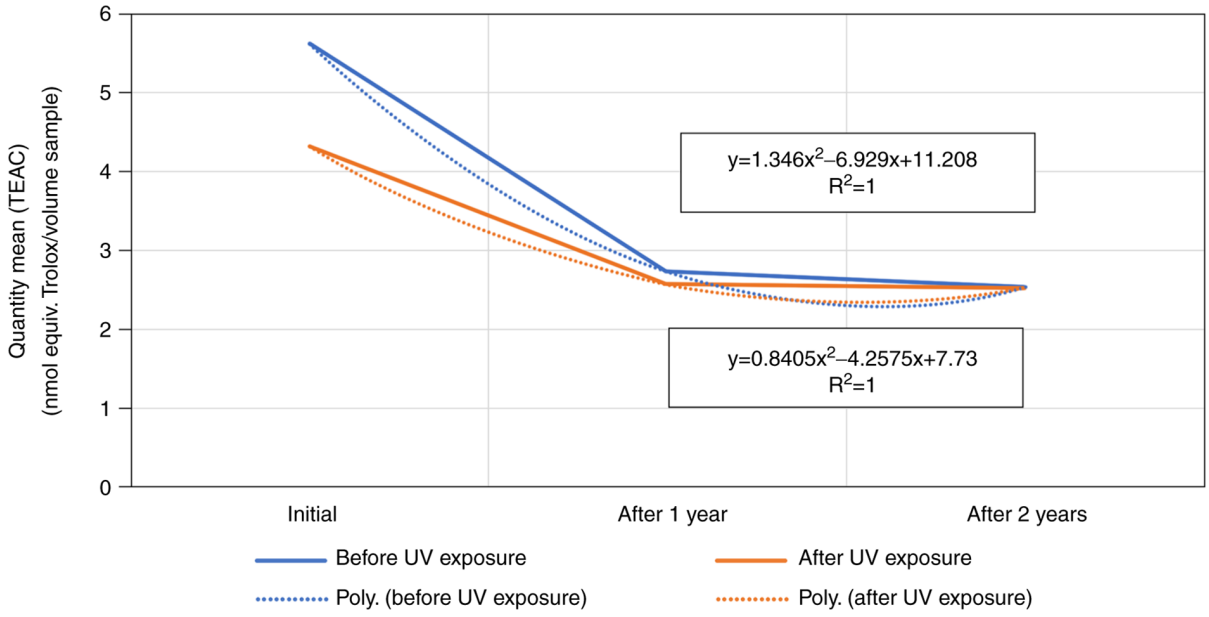

Figure 3. Quantity mean (TEAC) (nmol equiv. Trolox/volume sample) for sample 2.

Statistical analysis. The Student's t-test emphasized two-sample assuming unequal variances with P(T<=t) 0.05.

Results

Maximum inhibition-free radicals. The results obtained for the evolution in time, along two years (the study was performed on 2 years interval of time, if we consider the first measurement which was done at the end of the first year of the product fabrication time, while the product was still covered by the guarantee of the producer, still sealed, and respecting all the parameter that the manufacturer was written on its label) since the first exposure to UV, of total antioxidative capacity (TEAC) of artificial tear samples, before and after UVC irradiation (Figs. 1 and 2, respectively) for 2 min, at 254 nm wavelengths were assessed. For the observation period, the ophthalmic product samples were preserved tightly closed, at ambient temperature and by storage in the refrigerator (+4˚C).

All artificial tear samples showed a reduction in maximum inhibition-free radicals in the first year following opening of the vial. The drop was fitting to a polynomial equation of the

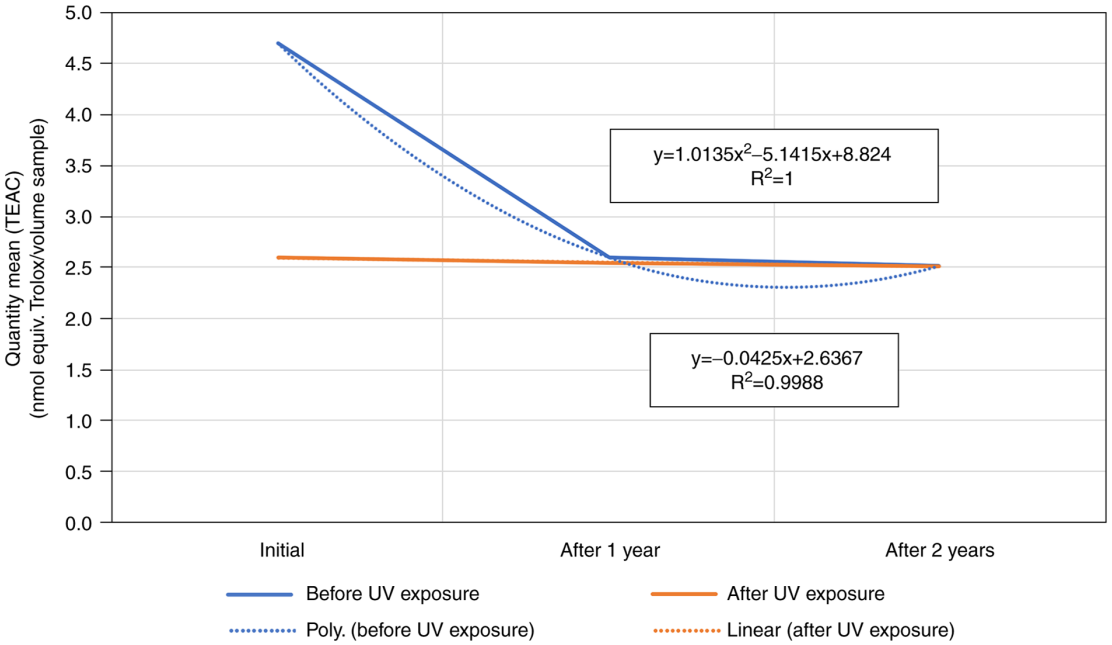

Figure 4. Quantity mean (TEAC) (nmol equiv. Trolox/volume sample) for sample 4.

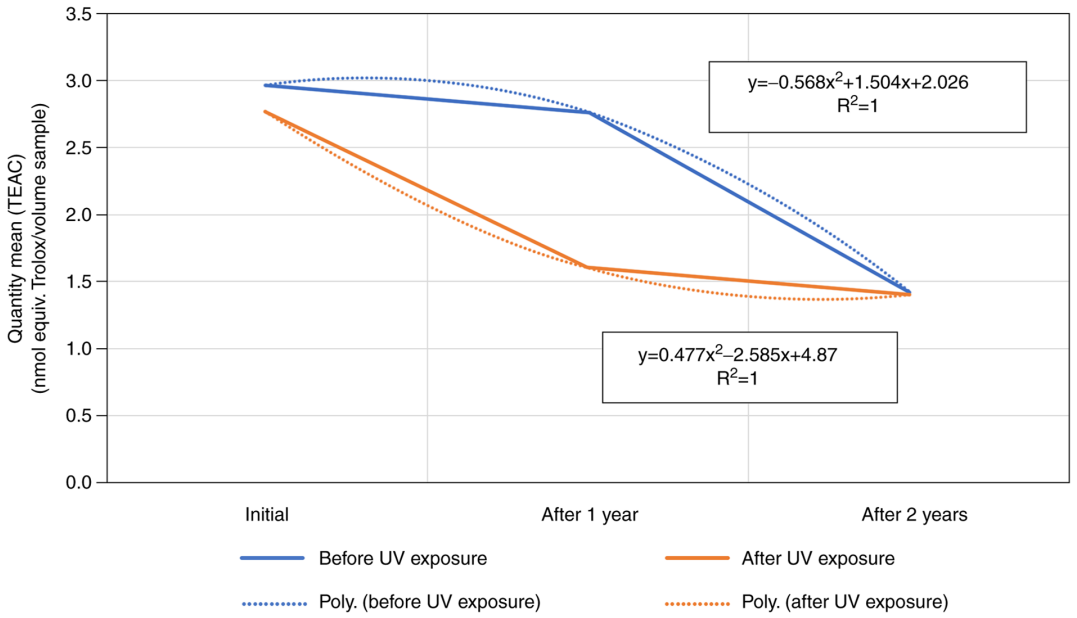

Figure 5. Quantity mean (TEAC) (nmol equiv. Trolox/volume sample) for sample 5.

2nd order. Samples 2, 4 and 6 show a more marked decrease compared to the remaining samples studied.

The data analysis emphasized there were no statistically significant differences between the properties of the sample-product before and after exposure to UV-254 nm, either from the opening of the vial to the final point of the experiment, 3 years later. Although the measured values showed improvement in the maximum inhibition-free radicals parameter in the first year of the study, in most cases this was followed by a decrease of this activity in the second year.

Total antioxidative capacity values. An important total antioxidative capacity (TEAC) value modification in time was observed at the working solution volume of 5 μl. A possible reason for this is that all the samples taken into consideration have lost the antioxidative capacity (quantified by TEAC values), even if they were subjected or not to UV exposure. The manner in which the characteristic was lost varied from sample to sample and there were differences between samples exposed to UV radiation and samples without exposure. Changes of this parameter for each sample in part are shown in Figs. 3-5.

A comparison between the mean quantity (TEAC) of the product based on hydroxypropyl guar, both before and after exposure of the samples as well as during the study period, a TEAC decrease in function (sample 2) correlated to a

polynomial function, whereas the other two product samples showed a linear decrease (Fig. 3).

Sample 4 mean quantity (TEAC) expressed as a nmol equivalent Trolox/volume sample, showed a linear behavior for the sample exposed to UV-254 nm over the 3-year study. By contrast, unexposed samples showed a sudden drop immediately after opening of the vial in the first year, and then remained almost constant, meaning the maximum decay after the first year was reached (Fig. 4).

The sample 5 product, based on hydroxypropylmethyl cellulose, had the most unusual behavior compared with the other two products. Without exposure to radiation, after opening the vial, the product favorably maintained the mean quantity (TEAC) initially, with the decrease manifesting in the second year. Following exposure to UV-254 nm sample 5 had a sudden polynomial drop in the first year of the (TEAC), albeit in the end, both exposed and unexposed samples to UV reached the same mean quantity (TEAC) at the end of the 3-year study (Fig. 5).

Discussion

The statistical t-test emphasize that two-sample assuming unequal variances, performed for all samples of the artificial tears before and after exposure to UVC-254 nm wavelength radiation along the 3-years study, did not show significant differences between the samples over the given period. However, a clear decrease of the maximum inhibition-free radicals value was evident, indicated by a linear drop starting from the beginning point, which is the opening of the vial, and ending after 3 years of conservation at +4˚C. There was one exception to this rule, that of sample 6. The sample drop in maximum inhibition-free radicals was of a polynomial type. This means a higher and more rapid rate of deterioration of the activity with and without exposure to UVC at a 254 nm wavelength (50-52).

The quantity mean of total antioxidant capacity (TEAC) (nmol equiv. Trolox/volume sample) had a rather linear drop, except for samples 2 and 5, where the decrease was of a polynomial type. Sample 5 tended to maintain an almost constant TEAC for the unexposed sample for almost one year, prior to its decrease. Furthermore, after exposure to UVC-254 nm wavelength the TEAC sample had a rapid decrease for the investigated samples (13,14,53).

Thus, ophthalmic product storage at +4˚C for a long period with UV irradiation of 254 nm wavelength, decreased TEAC for all the tested artificial tears.

The comparative determinations of the total antioxidant capacity activity emphasized the pharmaceutical product samples 2 and 4, which present at the bottle opening, before UVC-irradiation, the most increased values of TEAC.

Significant results after the first UVC irradiation with 254 nm wavelength radiations were registered, TEAC values were modified, decreasing for all considered dry eye products. Under these circumstances the highest scores of total antioxidative capacity suggested sample 2 artificial tears (based on hydroxypropyl guar), compounds with a favorable stability at first UVC irradiation.

The highest final TEAC values, for hydroxypropyl guar and hydroxypropylmethyl cellulose were registered, which emphasized a favorable stability over the 3-year study period.

The lowest final TEAC value, for lipidic artificial tears, followed by carboxymethylcellulose tears, was registered, which appeared to have an increased stability.

Evaluation of the clinical criteria regarding effectiveness and adherence of the patients, such as TBUT (tear breakup time, used to evaluate the stability of lacrimal film), DEQ (Dry eye questionnaire) and OSDI (Ocular surface disease index), used to evaluate the dryness symptoms, are in progress to determine whether there are relevant differences between effectiveness of irradiated and non-irradiated artificial tears.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the first author on reasonable request.

Authors' contributions

SJ, TNP, MH, MV and BSNP were involved in literature research and wrote the manuscript. MV supported the statistical analysis and reviewed the results. SJ, TNP, RC and BSNP conceived, planned and followed the execution of the experiments. All authors contributed to manuscript revision, read and approved the final version. SJ, TNP, MV and BSNP confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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