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Original article

[Translated article] Physicochemical and microbiological stability study of two new preservative-free methylprednisolone eye drops

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ABSTRACT

Objective: To study the physicochemical and microbiological stability over 90 days of two preservative-free methylprednisolone sodium succinate (MTPSS) 1 and 10 mg/mL eye drops for use in ocular pathologies such as Sjögren's syndrome and dry eye syndrome.
Method: The two eye drops were prepared from injectable MTPSS (Solu-moderin® and Urbason®), water for injection and normal saline solution. In accordance with ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) guidelines, they were then stored in triplicate under refrigerated conditions (5 ± 3 °C), at room temperature (25 ± 2 °C), and at 40 °C (± 2 °C). In accordance with the USP (United States Pharmacopeia), physicochemical controls of the active ingredient content were carried out by HPLC-UV (High Performance Liquid Chromatography with Ultraviolet detection), together with controls of pH, osmolality, and visual examination. Microbiological sterility was also tested under refrigerated conditions up to 30 days in open containers and up to 90 days in closed ones.
Results: The eye drops stored at 5 °C were the most stable; in the 1 mg/mL eye drops, degradation of the drug fell below 90% from day 21, and in the 10 mg/mL eye drops, from day 42. pH change did not vary by ≥1 unit in formulations stored at 5 °C, unlike the other formulations. Changes in osmolality did not exceed 5% on day 90 in any storage conditions. Samples of non refrigerate eye drops at 10 mg/mL, presented a white precipitate from day 14 and 28, respectively. Non-refrigerated 1 mg/mL eye drops presented suspended particles on day 90. There were no color changes. Microbiological analysis showed that sterility was maintained for over 90 days in the closed containers, although microbial contamination was detected from day 21 in the open containers.
Conclusions: 1 mg/mL MTPSS eye drops show physicochemical and microbiological stability for 21 days under refrigeration, compared to 42 days for 10 mg/mL eye drops stored under the same conditions. However, since they do not include preservatives in their composition, they should not be used for more than 7 days after opening.

Estudio de estabilidad fisicoquímica y microbiológica de dos nuevos colirios de metilprednisolona sin conservantes

Palabras clave:
Estabilidad de Medicamentos
Soluciones Oftálmicas

RESUMEN

Objetivo: Estudiar la estabilidad fisicoquímica y microbiológica de dos colirios de metilprednisolona succinato sódico (MTPSS) a 1 mg/mL y 10 mg/mL sin conservantes durante 90 días para su uso en patologías oculares como el síndrome de Sjögren y el síndrome del ojo seco.

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Glucocorticoides
Síndrome de Sjogren
Síndromes del Ojo Seco

Método: los dos colirios se elaboraron partiendo de MTPSS inyectable (Solu-moderin® y Urbason®), agua para inyectables y suero salino fisiológico. Posteriormente se almacenaron, según normas ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) por triplicado en condiciones de refrigeración (5 ± 3 °C), temperatura ambiente (25 ± 2 °C) y a 40 °C (±2 °C). De acuerdo con la USP (United States Pharmacopeia), se realizaron controles fisicoquímicos de contenido en principio activo por HPLC-UV (High Performance Liquid Chromatography-Ultraviolet detector), control de pH, control de osmolalidad y controles visuales. Además, se realizó un estudio de esterilidad microbiológica en las condiciones de refrigeración, tanto en envases abiertos (hasta 30 días), como en envases cerrados (hasta 90 días).
Resultados: Los colirios almacenados a 5 °C fueron los más estables y el principio activo se degradó por debajo del 90% a partir del día 21 en el colirio a 1 mg/mL.y a partir del día 42 en el colirio a 10 mg/mL. La variación del pH no fue ≥1 unidad en las formulaciones almacenadas a 5 °C, al contrario que en el resto. La osmolalidad no presentó cambios superiores al 5% a día 90 en ninguna de las condiciones de almacenamiento. Las muestras de los colirios a 10 mg/mL no refrigerados presentaron un precipitado blanco a partir del día 14 y 28 respectivamente. Los colirios a 1 mg/mL no refrigerados presentaron partículas en suspensión el día 90. No hubo cambios de color. El análisis microbiológico demostró esterilidad durante los 90 días en los envases cerrados, pero en los abiertos se detectó contaminación microbiana a partir del día 21.
Conclusiones: Los colirios de MTPSS a 1 mg/mL presentan una estabilidad fisicoquímica y microbiológica de 21 días en refrigeración, frente a los 42 días que admiten los colirios a 10 mg/mL almacenados bajo las mismas condiciones. No obstante, al no incluir conservantes en su composición, no se deben utilizar durante más de 7 días desde su apertura.

Introduction

The design and compounding of medicines, aimed at fulfilling the needs not met by the therapies available on the market, is one of the key roles of hospital pharmacy departments. Specifically, the treatment of ophthalmologic disorders often requires formulating an active ingredient in a vehicle, for which a series of safety and efficacy conditions must be guaranteed. Such is the case of methylprednisolone, where the available dosage forms include tablets for oral administration and lyophilized vials for intravenous administration,[1] yet no formulation amenable to ophthalmic administration exists.

According to the literature, eye drops based on methylprednisolone sodium succinate (MTPSS) can be formulated at varying concentrations, ranging from 1 to 10 mg/mL. The results is an intermediate-potency corticosteroid with the advantage of not containing preservatives in its formulation. These eye drops are often used for indications different from those for which they were officially approved,[2] i.e. ocular surface diseases such as Sjögren's syndrome[3,4] or dry eye syndrome. In the latter case, they have been found beneficial at low concentrations (0.05%).[5]

When designing medicines for ophthalmic administration, it is essential to consider the peculiarities of the eye's anatomy and physiology. Such biological barriers as the non-porous corneal epithelium and reflex actions such as blinking and tear secretion—essential for the mechanical clearance of the ocular surface—only allow MTPSS concentrations below 5% to penetrate the cornea. The excess volume administered to the conjunctival sac is quickly drained through the lacrimal canaliculi thanks to the pumping mechanism that accompanies blinking. This increased drainage results in an increase in absorption, with 50–90% of the dose entering the systemic circulation. This fact should be taken into consideration given the risk of adverse events at systemic level, which may be of particular significance for the pediatric population.[6]

Both the tolerance of eye drops and the irritability they cause are mainly dictated by their osmolarity, pH, and limpidity. In fact, poorly tolerated eye drops are rapidly cleared from the body, which may compromise their efficacy. For that reason, the minimum requirements to be met by eye drop formulations include limpidity, neutrality, isotonicity and sterility.[6,7] Meeting these requirements will ensure minimization of the irritation caused by tear secretion, which could lead to premature clearance of the drug.

To prevent microbiological contamination and preserve sterility, eye drops are on occasion used without preservatives, even if preservative-free eye drops have demonstrated a poorer toxicity profile than eye drops containing preservatives.[8]

The goal of this study was to analyze the physicochemical and microbiological stability of two kinds of preservative-free MTPSS eye drops used in the context of ophthalmologic disorders.

Methods

Reagents

The formulations prepared consisted of methylprednisolone 40 mg (as sodium succinate, Urbason®, Sanofi-Aventis, France), methylprednisolone 500 mg (as sodium succinate, Solu-moderin®, Pfizer, USA), water for injection (Fresenius-Kabi, Germany), and sodium chloride 0.9% solution for injection (Fresenius-Kabi, Germany). A 10 mL sterile white light-proof polypropylene dropper bottle (Bexen Medical, Spain) was also used. The reagents employed (analytical-quality methylprednisolone, glacial acetic acid, and HPLC grade acetonitrile) were acquired from Sigma–Aldrich (Darmstadt, Germany). HPLC analyses were carried out with ultrapure water (type I).

General compounding procedure

MTPSS eye drops were compounded at concentrations of 1 and 10 mg/mL (Table 1) by personnel with experience in handling sterile products. The recommendations of the *Best-practice compounding guidelines for pharmacy departments*[7] were followed.

Storage conditions

The study was designed considering the conditions governing the use and storage of the different solutions in real-world settings. All MTPSS eye drops at 1 and 10 mg/mL concentrations were stored in white polypropylene sterile bottles and distributed into 3-unit batches in accordance with ICH guidelines[9] in the following temperature and relative humidity (RH) conditions:

a. Refrigeration (5 ± 3 °C).
b. Room temperature (25 ± 2 °C)/60 ± 5% RH.
c. Accelerated conditions (40 ± 2 °C)/75 ± 5% RH.

Table 1
Compounding of methylprednisolone sodium succinate (MTPSS) eye drops at 1 and 10 mg/mL concentrations.

MTPSS eye drops 1 mg/mL	MTPSS eye drops 10 mg/mL
Methylprednisolone (Urbason®)…….. 40 mg	Methylprednisolone (Solu-moderin®)… 500 mg
Water for injection……..…..10 mL	Water for injection……..……10 mL
Sodium chloride 0.9% csp……..…..…..…..40 mL	Sodium chloride 0.9% csp……..……..…..50 mL

1. Reconstituting MTPSS with 10 mL of API.
2. Dilution with sodium chloride 0.9% in a 50 mL syringe up to 40 mL (1 mg/mL formulation) and up to 50 mL (10 mg/mL formulation).
3. Storing 5 mL aliquots in a sterile white light-proof polypropylene dropper bottle through sterilizing filtration (0.22 μm syringe filter, 25 mm, PES PharmAssure®, Pall Medical, USA) in a laminar flow cabinet.
4. Closing the lid and labeling.

Physicochemical stability analyses

Analytical model validation (high performance liquid chromatography)

High-performance liquid chromatography (HPLC), as proposed by the European Pharmacopeia (Ph. Eur. 10.ª ed)[10] was the technique selected to demonstrate the chemical stability of MTPSS. The procedure was carried out using a 1260 *Infinity* chromatographer (Agilent®, Waldbronn, Germany) in combination with an ultraviolet diode array detector (UV-DAD). Chromatographic conditions were as follows: flow: 1.0 ml/min; mobile phase: 2% glacial acetic acid, 31% acetonitrile, and 67% ultrapure water; injection volume: 20 μl; column temperature: 25 °C; and detector wavelength: 254 nm. The column was a Cortecs® T3 C18 4.6×150 mm, 2.7 μm (Waters®). Sample extraction and analysis was performed on days 0, 7, 14, 21, 28, 42, 60, and 90.

The analytical method used to quantify MTPSS was validated in accordance with the ICH guidelines.[11] The linearity of the method was demonstrated by preparing 6 concentration levels on the basis of an MTPSS analytical standard. The results were used to prepare a calibration curve. An analysis of variance (ANOVA) for linear regression was performed, which yielded a statistical significance of 0.05 ($\alpha = 0.05$). Accuracy and precision were expressed as a percent recovery and as standard deviations for low-, intermediate-, and high concentrations within the linearity range on one single day (intra-day precision) and over 5 consecutive days (inter-day precision). The limit of detection (LOD) and the limit of quantification (LOQ) were calculated based on the standard deviation of the response and the slope of the calibration curve. A two-dimensional (2D) ultraviolet spectral analysis was performed to examine the specificity of the method used. A three-dimensional (3D) spectral analysis was conducted to determine the selectivity of the method.

Extreme degradation conditions

To demonstrate that the method was capable of indicating the stability of MTPSS and to investigate the conditions predisposing to greater degradation of the active ingredient,[12] each of the eye drop formulations was subjected to various extreme conditions for 48 h. Such conditions were as follows: oxidation (H_2O_2 15% *v*/*v*), base conditions (NaOH 1 N), acid conditions (HCl 1 N), and high temperature conditions (80 °C). This was done by extracting 5 ml aliquots from each eye drop formulation and mixing them with 5 ml aliquots from each of the degradation solutions to induce a degradation reaction in extreme conditions. The degradation of MTPSS was evaluated at 48 h with an HPLC system.

pH control

The pH of the 2 MTPSS formulations was determined on the same days the HPLC analysis was performed. The determination was made with a Crison GLP21 phmeter (Crison Instruments S.A., Spain). The pH stability range established by the US Pharmacopeia (USP-43) for MTPSS in sodium chloride solution 0.9% is 7.0–8.0.[13]

Osmolarity control

Both formulations were subjected to osmolarity measurements on days 0 and 90 using an OM6050 OsmoStation (AKRAY, Japan). The device was previously calibrated with 100 and 1000 mOsm/kg-H_2O solutions.

Visual inspection and control

The simples stored at each temperature were subject to visual control using an Apollo II liquid viewer (Adelphi, United Kingdom) in accordance with the specifications of the European Pharmacopeia (Ph. Eur. 10ª ed., chapter 2.9.20).[14]

Data analysis

The target stability for each formulation was set at 90–110% MTPSS recovery over the 90 days of the study. ChemStation v4.03b (Agilent Technologies®, Germany) software was used to obtain and process the data.

Microbiological stability study

The microbiological stability study was carried out in accordance with the procedures laid out in USP-43 and in the theoretically most stable physicochemical conditions, i.e., under refrigeration (5 ± 3 °C). This analysis was performed over a 90-day period in closed eye drop bottles (with determinations made on days 0, 7, 14, 21, 30, 42, 60, and 90) and over 42 days in open eye drop bottles. In the latter case, determinations were made on days 0, 7, 14, 21, 30, and 42, emula,ting the actual daily dose of the preparation.[15] Before this, a determination had to be made of the microbial growth potential of the formulation under analysis. This was done by selecting a series of control strains (*Pseudomonas aeruginosa* (Schroeter), Migula (ATCC® 9027™), *Bacillus subtilis* subsp. *spizizenii,* Nakamura et al. (ATCC® 6633™), *Candida albicans* (Robin), Berkhout (ATCC® 10231™), *Aspergillus brasiliensis,* Varga et al. (ATCC® 16404™), *Staphylococcus aureus* subsp. *aureus*, Rosenbach (ATCC® 6538™), and *Clostridium sporogenes* (Metchnikoff), Bergey et al. (ATCC® 19404™)) (LGC Standards, S.L.U., Barcelona, Spain). The strains were added to thioglycolate (TG) broth containing 1 mL of both MTPSS eye drop formulations, and incubated for 14 days at 35 °C. Each strain was subsequently inoculated in MTPSS-free TG broth and incubated in the same conditions as control. The results of the assay were considered correct when growth was observed in the control strains in both TG mediums. The eye drops were tested for microbiological stability on all test days. According to the USP-43 acceptance criteria, they were required to exbibit a total absence of any kind of microbial growth in order to be considered sterile.

Results

Physicochemical stability

High performance liquid chromatography analysis

The ANOVA for linear regression confirmed the linearity of the technique by rejection of the null linearity hypothesis. The coefficient of variation (CV) of the method was below 2%. The linear regression equation obtained corresponded with the expression y = 39.229x–6.6252 (n = 18; R^2>0.9999). Accuracy was 99.8–101.1% and the CV for intra- and inter-day precision was below 3%. Detection and quantification limits

were 0.01 and 0.06 mg/mL, respectively. 2D and 3D spectral UV analysis confirmed the technique's selectivity, peak purity, and specificity in the absence of secondary or interfering peaks. The chromatograms obtained for the MTPSS eye drops at 1 mg/mL concentration at days 0 and 90 are shown in Fig. 1; those for eye drops formulated at 10 mg/mL concentration are shown in Fig. 2. The evolution of the remaining concentrations of both eye drop formulations showed temperature-dependent degradation (Fig. 3), with the refrigerated condition (5 ± 3 °C) being the most stable for both formulations. Additionally, the eye drops formulated at 10 mg/mL concentration were found to be the most stable. These were seen to fall below the established stability limit (losses in excess of 10% of the nominal concentration) from day 42 onwards, as compared with 21 days for eye drops formulated at 1 mg/ml concentration.

Analysis under extreme degradation conditions

The analysis under extreme degradation conditions shows that the method is a good stability indicator, with acid and base conditions having been found to be the ones inducing greater degradation of MTPSS eye drops at the concentrations examined.

pH control

pH fell below the lower stability threshold for MTPSS (pH = 7.0) very rapidly in formulations stored at room temperature (25 ± 2 °C) and in accelerated conditions (40 ± 2 °C), regardless of their MTPSS concentration. However, eye drops stored in refrigerated conditions (5 ± 3 °C) exhibited a more gradual decrease, which was slightly faster in those at 1 mg/ml concentration than in those at 10 mg/mL concentration (Fig. 3).

Osmolality control

No significant changes in osmolality were observed in the course of the 90 days of the study (<5%) in any of the storage conditions for either eye drop formulation. Osmolality remained around 300 mOsm/kg-H_2O.

Visual control

In MTPSS eye drops at 1 mg/mL concentration stored in accelerated conditions (40 °C ± 2 °C), precipitates were observed from the 14th day into the study, whereas in eye drops formulated at 10 mg/mL concentration such precipitates appeared at day 90. At room temperature (25 ± 2 °C), however, eye drops formulated at 1 mg/mL concentration exhibited a certain degree of turbidity from day 28, while eye drops formulated at 10 mg/mL concentration exhibited turbidity from day 90.

Microbiological stability

The growth potential of the ATCC strains in both formulations was confirmed. In addition, refrigerated (5 ± 3 °C) MTPSS eye drops at 1 and 10 mg/mL concentrations remained sterile in their closed containers throughout the 90 days of the study. However, once the containers were opened, sterility was maintained for only 21 days, with microbial growth being observed from day 30.

Discussion

The present analysis examined the physicochemical and microbiological stability of two preservative-free MTPSS eye drops at 1 and 10 mg/mL concentrations in different storage conditions. The findings obtained revealed that the stability of both eye drop formulations was temperature-dependent (the higher the temperature, the faster the degradation) as well as concentration-dependent, with stability increasing with higher concentrations of MTPSS.

Other authors have looked into the stability and compatibility of different MTPSS formulations.[16–19] Pyter et al.,[20] for example, analyzed injectable MTPSS solutions at 10 mg/mL concentration in 5% physiological saline solution (PSS) and 5% glucose solution, stored at 25 °C for 24 h. The authors used nephemoletry to measure stability and concluded that the MTPSS formulations in the PSS solution remained stable for 24 h, whereas their stability in 5% glucose was more variable (8–24 h). Stability was also seen to be dependent on the formulation's MTPSS concentration. Gupta,[21] for his part, using benzyl alcohol as a preservative, studied the chemical stability of MTPSS at 10 mg/mL concentration in polypropylene syringes for several days, at temperatures of 5 and 25 °C, and found that they remained stable for 4 days at 25 °C and for 21 days at 5 °C, which is in line with the findings of this study.

In a recent study, Ratprasatporn et al.[22] examined the stability and sterility of various eye drop formulations containing different preservative-free active ingredients, including MTPSS eye drops a 10 mg/mL. The study was conducted in refrigerated conditions (5 °C) and at room temperature (25 °C), using UV spectrophotometry for determining the concentration of MTPSS. The authors came to the conclusion that MTPSS eye drops at 10 mg/mL concentration stored under refrigeration (5 °C) and at room temperature (25 °C) remained stable (losses below 10%) for the duration of the study (28 days). These results differ significantly from those obtained in the present study as, in room temperature conditions, our MTPSS eye drops at 10 mg/mL concentration degraded beyond the stability threshold (losses in excess of 10%) from the 7th day of the study. This difference is probably related to the technique employed to determine the concentration of MTPSS as Ratprasatporn et al. did not use a separation technique such as HPLC, with allows separation of each of the degradation byproducts obtained in the course of the study, as well as their individual quantification. This is probably one of the reasons why HPLC has been used as the technique of choice for determining de MTPSS in the various clinical monographs of some of the leading drug formularies at a global level.[10,13,23]

As regards microbiological stability, it has been determined in only a handful of studies. One of these is Ratprasatporn et al.,[22] who conducted a 28-day-long evaluation, but did not follow the recommendations set out in the world's leading pharmacopeias.

This study is not without limitations. Although the majority of controllable conditions were duly defined and registered according to the ICH guidelines and the relevant pharmacopeia standards, microbial exposure to the environment was likely to vary from one laboratory to another, giving rise to a different contamination profile from that reported in this article. Additionally, it would have been interesting to develop a longer-term study but, given the variable stability of the active ingredient even under refrigerated conditions, the results obtained are unlikely to have been satisfactory or even useful. As a result, a future line of research could consist in assessing the impact of refrigeration on the stability of the eye drops analyzed, and even examine their stability in single-dose bottles with a view to improving the efficiency of preparations, particularly in the context of heavy clinical workloads.

In sum, it is possible to assign MTPSS eye drops stored in refrigerated conditions (5 °C) a shelf life of 42 days when prepared at 10 mg/mL concentration and of 21 days when formulated at 1 mg/mL concentration. However, being preservative-free, once the bottle is open the shelf life (for both concentrations) will not exceed 7 days. These shelf lives are long enough for MTPSS eye drops to be amenable to dispensation as preservative-free ophthalmological preparations in routine clinical practice with all the required safety guarantees.

Contribution to the literature

The present study characterizes the physicochemical and microbiological stability of two preservative-free methylprednisolone eye drop formulations by means of the analytical techniques recommended by the most prestigious pharmacopeias. As a result, a more precise determination of the shelf life of both formulations has been obtained than that published in previous reports.

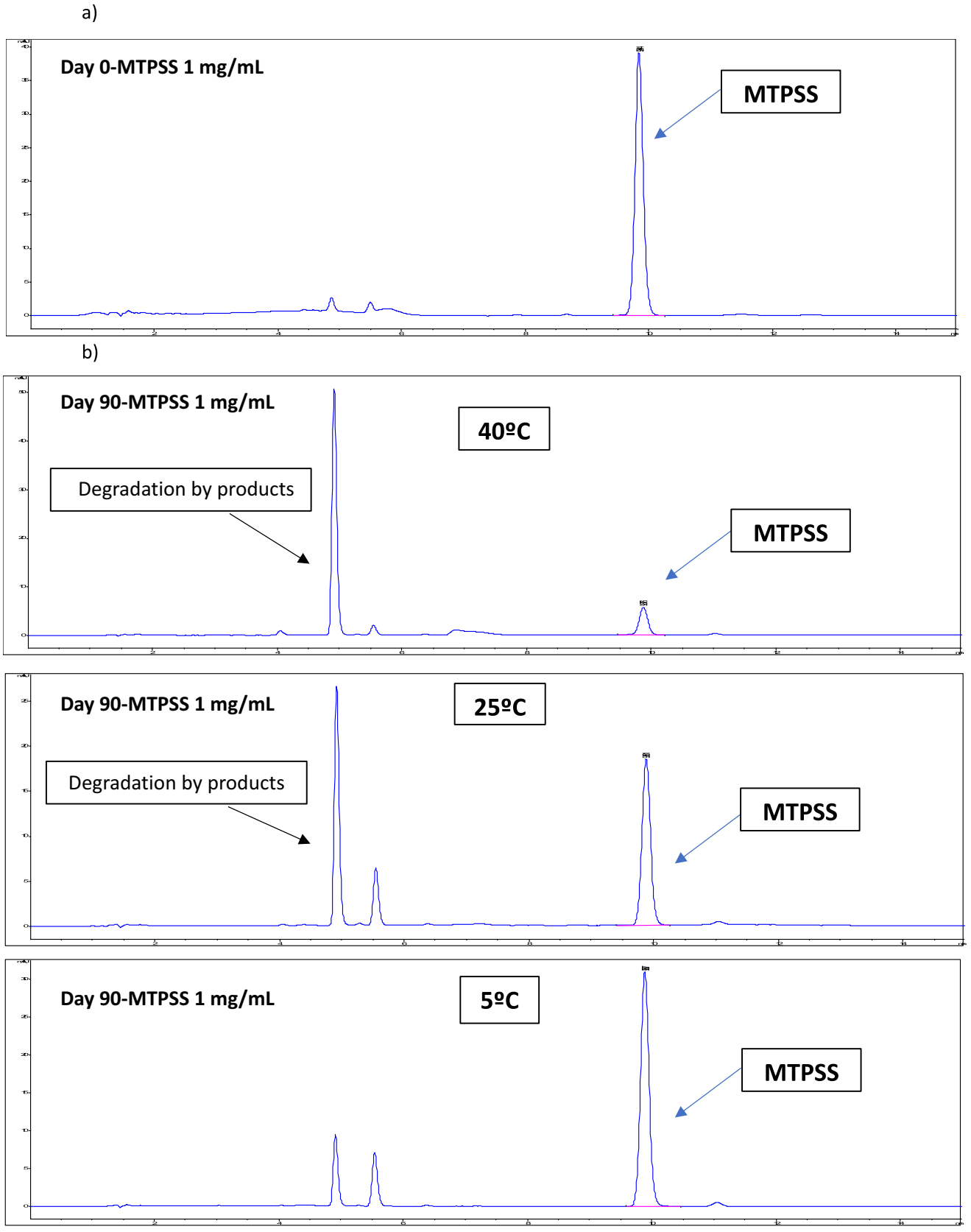


Fig. 1. Chromatograms for MTPSS eye drops at 1 mg/mL concentration in different conservation conditions, at: (a) day 0 and (b) day 90. X axis: signal intensity in absorbance units; Y axis: retention time (minutes).

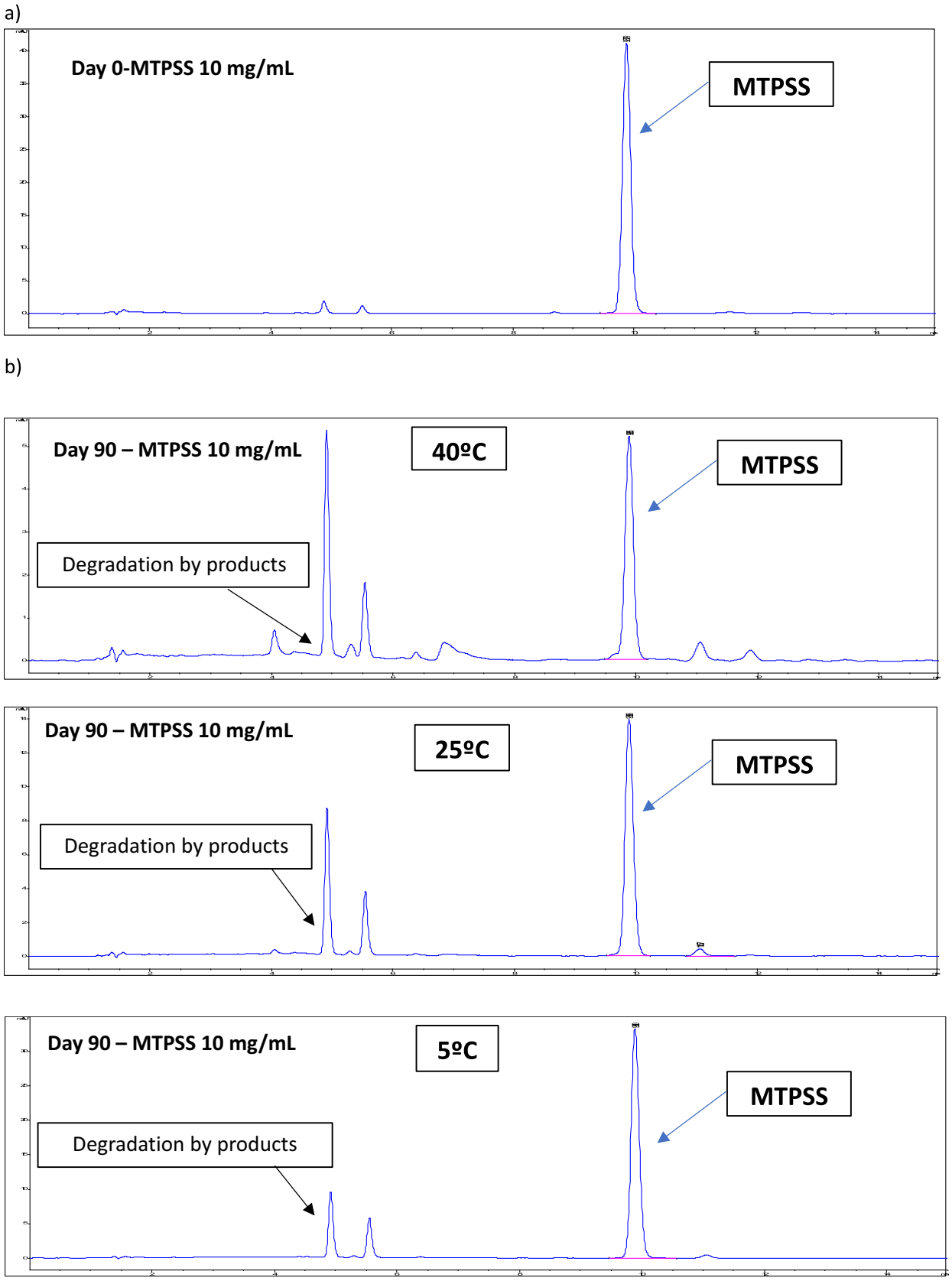
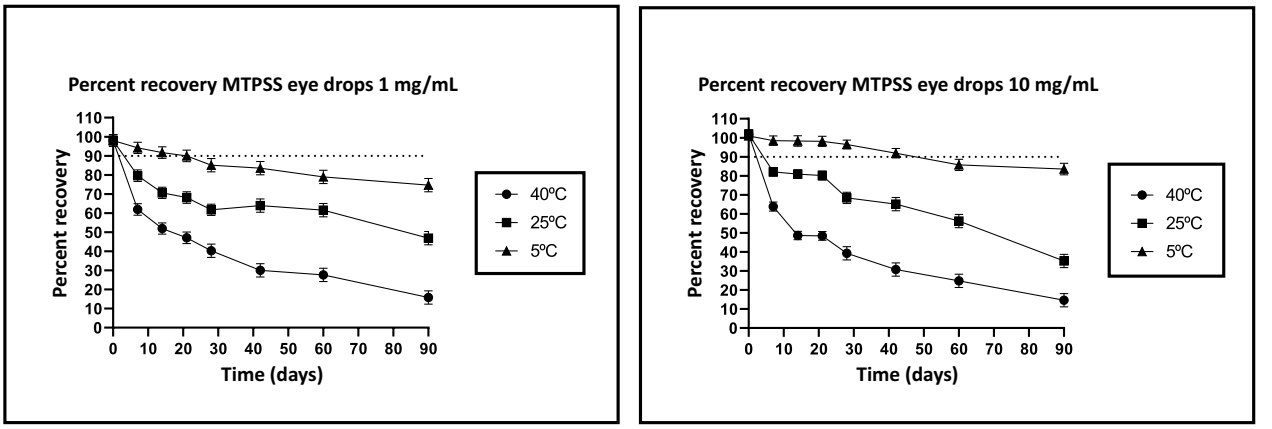


Fig. 2. Chromatograms for MTPSS eye drops at 10 mg/mL concentration in different conservation conditions, at: (a) day 0 and (b) day 90. X axis: signal intensity in absorbance units; Y axis: retention time (minutes).

a)



b)

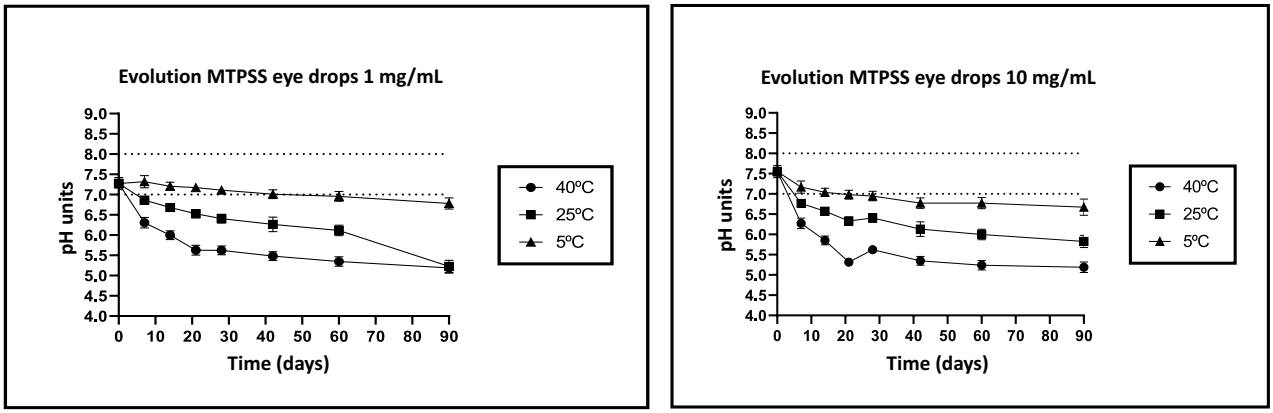


Fig. 3. Evolution over time of: (a) percent recovery of MTPSS eye drops at 1 and 10 mg/mL concentrations, (b) pH of MTPSS eye drops at 1 and 10 mg/mL concentrations.

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CRediT authorship contribution statement

Vicente Merino-Bohórquez: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Silvia Berisa-Prado:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization. **Mercedes Delgado-Valverde:** Investigation, Methodology, Supervision. **María José Tirado-Pérez:** Investigation, Methodology, Supervision. **Marta García-Palomo:** Methodology, Supervision, Validation. **José María Alonso-Herreros:** Methodology, Supervision, Validation, Visualization. **Carme Cañete-Ramírez:** Methodology, Validation, Visualization. **María del Dávila-Pousa**: Methodology, Supervision, Validation, Visualization.

Declaration of competing interest

None of the co-authors had any conflicts of interest to declare.

References

1. Agencia Española de Medicamentos y Productos Sanitarios. Centro de Información de Medicamentos. [Internet]. [citado 14 de septiembre de 2023]. Available from: https://cima.aemps.es/cima/publico/lista.html.
2. Ministerio de Sanidad y Política Social. Real Decreto 1015/2009, de 19 de junio, por el que se regula la disponibilidad de medicamentos en situaciones especiales [Internet]. Sec. 1, Real Decreto 1015/2009; Jul 20, 2009. p. 60904–13. Available from: https://www.boe.es/eli/es/rd/2009/06/19/1015.
3. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. Ophthalmology. 1999;106(4):811–6.
4. Hong S, Kim T, Chung SH, Kim EK, Seo KY. Recurrence after topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren's syndrome. J Ocul Pharmacol Ther Off J Assoc Ocul Pharmacol Ther. 2007;23(1):78–82.
5. Byun Yj, Kim T, Kwon SM, Seo KY, Kim SW, Kim EK, et al. Efficacy of combined 0.05% cyclosporine and 1% methylprednisolone treatment for chronic dry eye. Cornea. 2012;31(5):509–13.
6. McElhiney LF. Compounding Guide for Ophthalmic Preparations. American Pharmacists Association; 2013.
7. Guía de Buenas Prácticas de Preparación de Medicamentos en Servicios de Farmacia Hospitalaria. Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014.
8. Hedayatfar A, Hashemi H, Asgari S, Chee SP. Comparison of efficacy and ocular surface toxicity of topical preservative-free methylprednisolone and preserved prednisolone in the treatment of acute anterior uveitis. Cornea. abril de 2014;33(4):366–72.
9. Stability Testing of New Drug Substances and Products Q1A(R2). International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use [Internet]. [citado 26 de junio de 2022]. Available from: https://ich.org/page/quality-guidelines.
10. European Pharmacopoeia (Ph. Eur.). Methylprednisolone hydrogen succinate official monography 10th Edition. Strasbourg: Council of Europe; 2020.

11. Validation of Analytical Procedures: Text and Metodology Q2(R1). International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use [Internet]. [citado 26 de junio de 2022]. Available from: https://ich.org/page/quality-guidelines.
12. Sonawane JK, Chavan SM, Narkar IP, Jale SC, Tendulkar NV, ProfV Jadhav, et al. A review of stability indicating methods and forced degradation studies. Int J Res Publ Rev. 2023;4(5):4703–15.
13. The United States pharmacopeia (USP). Methylprednisolone sodium succinate for injection official monograph, 43nd rev., and the national formulary 38 th ed. Rockville (MD): United States Pharmacopeial Convention; 2020.
14. European Pharmacopoeia (Ph.Eur.). Chapter 2.9.20. Particulate contamination: visible particles, 2020, Strasbourg: Council of Europe; 2020.
15. The United States pharmacopeia (USP). Sterility tests. Chapter <71>. 43nd rev., and the national formulary 38 th ed. Rockville (MD): United States Pharmacopeial Convention; 2020.
16. Strom JG, Miller SW. Stability and compatibility of methylprednisolone sodium succinate and cimetidine hydrochloride in 5% dextrose injection. Am J Hosp Pharm. junio de 1991;48(6):1237–41.
17. Townsend RJ, Puchala AH, Nail SL. Stability of methylprednisolone sodium succinate in small volumes of 5% dextrose and 0.9% sodium chloride injections. Am J Hosp Pharm. septiembre de 1981;38(9):1319–22.
18. Stewart JT, Warren FW, King AD. Stability of ranitidine hydrochloride and seven medications. Am J Hosp Pharm. 15 de julio de 1994;51(14):1802–7.
19. Gellis C, Sautou-Miranda V, Arvouet A, Vasson MP, Chopineau J. Stability of methylprednisolone sodium succinate in pediatric parenteral nutrition mixtures. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 15 de junio de 2001;58(12):1139–42.
20. Pyter RA, Hsu LC, Buddenhagen JD. Stability of methylprednisolone sodium succinate in 5% dextrose and 0.9% sodium chloride injections. Am J Hosp Pharm. agosto de 1983;40(8):1329–33.
21. Gupta VD. Chemical stability of methylprednisolone sodium succinate after reconstitution in 0.9% sodium chloride injection and storage in polypropylene syringes. Int J Pharm Compd. 2001;5(2):148–50.
22. Ratprasatporn N, Wittayalertpanya S, Khemsri W, Chatsuwan T, Chongpison Y, Chamsai T, et al. Stability and sterility of extemporaneously prepared nonpreserved cefazolin, ceftazidime, vancomycin, amphotericin b, and methylprednisolone eye drops. Cornea. agosto de 2019;38(8):1017–22.
23. The Japanesse Pharmacopeia. Methylprednisolone succinate official monograph 18th ed. Tokio (JP): Pharmaceuticals and Medical Devices Agency (PMDA); 2021.