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DOCTORAL THESIS

RETINOIDS BIOIMPREGNATIONS ON VITREOUS MICROSPHERES FOR DERMATOLOGICAL APPLICATIONS

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SUMMARY

The research presented in this doctoral thesis was directed towards the identification of retinol-based formulations for the treatment of various skin disorders, such as acne, photoaging, and hyperpigmentation, designed to ensure high therapeutic efficiency while minimizing the risk of skin irritation. The thesis is structured into five chapters, the first being dedicated to a theoretical study on the current state of research regarding the preparation and conditioning of bioglass, the controlled release of active principles (such as retinol) through encapsulation, experimental strategies for dermal delivery of retinol, and conditioning of active agents to enhance the effectiveness of dermal treatments applied to volunteers.

The subsequent four chapters present the results of experimental investigations. The evaluation of the controlled release rate of retinol from bioglass particles was performed using comparative thermogravimetric (TG) analysis with an adsorbent biomaterial exhibiting microstructural characteristics markedly different from those of bioglass, namely biochar. The tests revealed higher mass losses for bioglass compared to biochar at low heating rates.

To assess the influence of the dermal delivery formulation on retinol stability, three types of dermato-cosmetic formulations were studied, combining bioglass and retinol synergistically: direct emulsion, reverse emulsion, and hydrogel. The characterization of these formulations was conducted using TG, DSC, FTIR, XRD, electrical conductivity measurements, pH determination, stability tests, and microbiological analyses.

Bioglass type 58S was synthesized via the sol–gel method and subsequently conditioned through thermal treatment in the presence of PEG 4000, with the aim of obtaining a completely non-crystalline structure. The resulting material was characterized using advanced analytical techniques such as TG/DTA, FTIR, and SEM, while the degree of crystallinity was determined by XRD. The results indicated that the thermal treatment in the presence of PEG 4000 favored the formation of vitreous bioglass (within the detection limits of XRD), without significant alterations of the other material properties.

Based on these findings, the hydrogel formulation was selected as the optimal system for dermal delivery of retinol. Tests conducted with the bioglass–retinol hydrogel confirmed its efficacy, the proposed composition demonstrating high performance in reducing wrinkles, UV-induced spots, pigmented lesions, and erythematous areas.

INTRODUCTION

In contemporary scientific research, the trend toward interdisciplinary approaches is becoming increasingly important for generating innovative solutions in areas of high complexity, such as regenerative medicine, tissue engineering and applied dermatology. A relevant direction in this regard is the use of bioactive vitreous materials – especially compositions of type 45S5 and 58S – for the development of modern systems for controlled release of biologically active agents. Originally used in surgery and bone implantology, these bioglasses have shown valuable properties, including the ability to promote tissue regeneration and biochemically integrate with bone and soft tissues, due to its biocompatibility and bioabsorbability.

On the other hand, the growing interest in safe and effective dermo-cosmetic products has led to more research on optimizing the transdermal penetration of active ingredients such as retinoids. Retinol, along with its derivatives, is well known for its beneficial effects in treating skin conditions such as acne, but also in reducing signs of aging, smoothing skin texture and accelerating cellular regeneration processes. However, the vulnerability of retinol to environmental factors (light, oxygen, temperature) and the risk of causing irritation from application to the skin, require the development of pharmaceutical formulations to ensure chemical stability and its controlled release into the dermis.

In this context, bioactive vitreous microspheres can be an effective vector for encapsulating and stabilizing retinoids, providing a gradual release kinetics that maintains therapeutic efficiency and minimizes adverse reactions. The structure and physico-chemical properties of these materials can be adapted by using modifiers such as polyethylene glycol (PEG), thus allowing for porous, stable and compatible systems with dermal application.

This paper aims to obtain, characterize and functional testing of bioactive vitreous microspheres impregnated with retinoids, for their use in the dermatological field. The research focuses on obtaining the 58S type glass composition, its treatment with PEG 4000 to improve porosity and stability, followed by retinol impregnation and controlled release assessment using specific analysis methods (thermogravimetry and spectroscopy).

Through this study, we aim to identify an innovative formula with dermato-cosmetic application, able to meet the current requirements of efficiency, safety and tolerability in topical administration of retinoids. This need comes from the fact that retinoids, although extremely potent in curing and treating a wide range of dermatological conditions, are still perceived negatively by consumers because they can generate a number of unpleasant side effects when applied to the skin: erythema, irritation, inflammation, dryness and skin desquamation, dermatitis, photosensitization, hyperpigmentation or hypopigmentation, temporary exacerbation of acne, etc. However, retinoids remain the gold standard in modern dermatology in terms of anti-wrinkle rituals, are extremely beneficial in reducing severe forms of acne and hyperpigmentation, and are the last resort in this type of therapy. Hence the need to continue and develop research on reducing the adverse effects of retinosa on the skin and by extension,

to improve the public's perception of them. This paper is placed at the intersection of materials chemistry, biotechnology, dermatology and pharmaceutical science, contributing to the development of modern solutions in personalized skin therapy.

The present paper is structured in two sections, each addressing essential aspects for the development of an advanced dermal delivery system of retinol, a valuable but unstable compound commonly used in dermocosmetics. The first section is dedicated to the critical study of literature data, including a chapter that thoroughly analyzes the properties of retinol and current solutions to improve its stability. The second section includes the author's original contributions and includes four experimental chapters: Thermogravimetric evaluation of retinol release from bioglass and biochar; Assessment of the influence of the dermal delivery system on the stability of retinol; Production of type 58S bioglass by conditioning with PEG 4000 and dispersion of retinol as hydrogel for skin delivery. The third section is reserved for general conclusions, and the last section brings together the bibliography used in the research.

The following are summarized the content and objectives of each chapter of the paper:

Chapter 1. ***Documentary study on the obtaining of bioglass and use in retinoid***-embedded cosmetics: Provides an in-depth analysis of the literature on retinol and its physico-chemical characteristics. It emphasizes its instability toward light, oxygen and temperature, as well as its irritating potential in topical applications. Modern formulation and encapsulation solutions are presented, as well as controlled delivery systems that can improve bioavailability and reduce adverse effects.

Chapter 2. ***Thermogravimetric evaluation of retinol release from bioglass and biochar:*** Investigates the influence of the microstructure and morphology of adsorbants with different porous characteristics and focuses on the thermogravimetric evaluation of retinol release from two adsorbent materials with different nature and properties: bioglass and biochar. Characterisation by specific techniques (BET, DLS, XRD and SEM) has enabled the link between microstructure, porosity and morphology, on the one hand, and retinol desorption behavior, on the other. The biochar, obtained from grape seeds, was distinguished by a mesoporous structure and a superior adsorption capacity, but with a slow and incomplete release of the active principle, influenced by stronger interactions between retinol and micropores. In contrast, the bioglass, with lower porosity and vitreous character, demonstrated a faster and more efficient release, especially at higher temperatures, due to differences in polarity and pore size. These observations underline the importance of selecting the support material according to the objectives, demonstrating that the structural nature of adsorbants decisively influences the kinetics of controlled release of bioactive compounds.

Chapter 3. ***Evaluation of the influence of dermal delivery system on retinol stability:*** explores in detail the influence of delivery system composition on retinol stability. Three delivery systems were formulated – direct emulsion, reverse emulsion and hydrogel – which were physiochemically characterized and tested for stability. Complex analyzes performed (TG, DSC, FTIR, XRD, Turbiscan, microbiological assessments) have shown that direct emulsion provides the best results in terms of colloidal stability, while hydrogel provides

a faster release. All formulations have proven to be microbiologically safe. Bioglass hydrogel was distinguished by an optimal balance between controlled release and stability.

Chapter 4. ***Obtaining type 58S bioglass by conditioning with PEG 4000: It is dedicated to obtaining and characterizing the*** type 58S bioglass functionalized with PEG 4000, obtained by the sol-gel method. Thermal treatments and XRD analysis have shown inhibition of crystallinity, and morphological analysis (SEM-EDX) and specific porosity (BET) have confirmed the appropriate structure for skin applications. The use of PEG in the calcination phase has resulted in a non-crystalline material, stable and optimal for– active adsorbents.

Chapter 5. ***Dispersion of retinol in the form of hydrogel for skin delivery***: Details the preparation of a dermato-cosmetic hydrogel with retinol and bioglass, emphasizing the complete characterization of the formulation by physico-chemical and microscopic methods. The results confirmed the non-crystalline structure of the system, good dispersion and colloidal stability, without the formation of crystalline structures. The study validates the effectiveness of hydrogel as a safe and effective platform for topical retinoid administration.

The paper concludes with a set of general conclusions, which synthesize the main scientific contributions and provide directions for further research in the field of advanced systems of delivery of active ingredients in dermatocosmetic products.

2-THERMOGRAVIMETRIC EVALUATION OF RETINOL RELEASE FROM BIOGLASS AND BIOCHAR

Controlled release of bioactive compounds is an essential aspect in the development of functional materials used in cosmetic and biomedical applications. In this context, thermogravimetric analysis (TG) provides an accurate and relevant method for investigating the thermal behavior of adsorbed compounds, as well as the kinetics of the release process.

This chapter aims to assess the thermal release of retinol from two types of adsorbants – bioglass and biochar – by analyzing the TG curves obtained at different heating speeds. This approach allows to determine the influence of the microstructural, dimensional and structural properties of the two materials on the efficiency and release profile of retinol.

By linking the porous and structural characteristics of adsorbers (determined by BET, DLS, SEM and XRD) with the mass losses recorded during controlled heating, relevant conclusions can be drawn on the thermal release mechanism and the adaptability of these materials for controlled delivery applications of active compounds.

2.2- Results and discussions on the thermo-gravimetric evaluation of retinol release

2.2.1. Porosity by BET method

The adsorption isotterma of liquid nitrogen on biochar practically overlaps with desorption, indicating that the process of conditioning the precursor, namely removal of volatiles and activation with steam, favored the complete formation of pores (Figure 2.1). Also,

the adsorption capacity of liquid nitrogen on biochar has high values even at low pressure values.

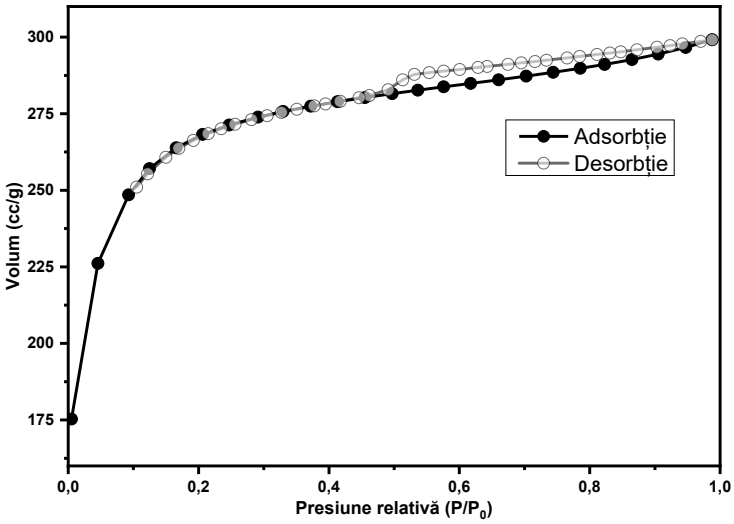


Figure 2.1. The adsorption-desorption isotherm of N2 in biochar

The analysis of the pore size distribution curve in biochar shows that the sample shows a relatively uniform distribution of pores with a high mesopor content. The mesoporous structure favors the acceleration of surface processes, respectively the adsorption and desorption of the active principles in the pores of the adsorbent (Figure 2.3).

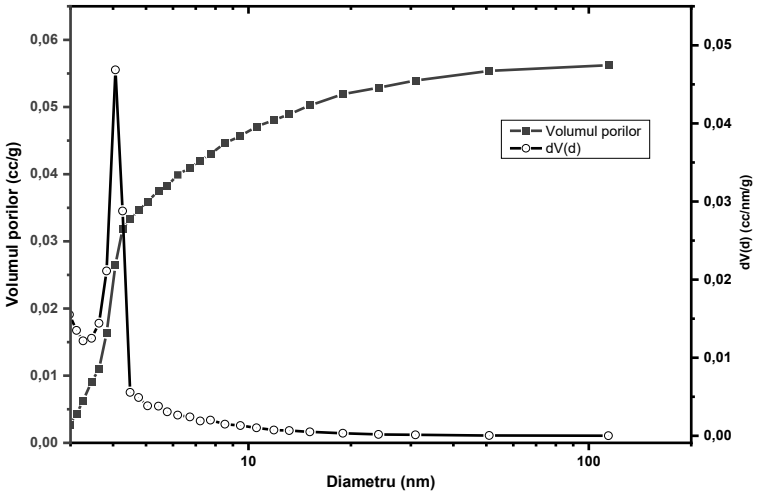


Figure 2.3. Distribution of biochar pore size

2.2.5- Thermal release of retinol from bioglass and biochar depending on the heating speed

The controlled release of retinol adsorbed on the two types of adsorption was evaluated by thermodesorption performed at different heating speeds. Thus, the sample warm-up speed ranged from 1 °C/min to 10 °C/min. The thermogravimetric curves (TG) of the two retinol-impregnated adsorbent samples are shown in Figure 2.11 and Figure 2.12.

According to the TG profile, there is a differentiated variation in the mass loss of the biochar sample depending on the heating speed. Thus, in the range of 50 – 300 °C, both the slope of the curve variation and the final value of the mass loss have different values. It is noted that at a low heating speed (1 °C/min.) The decrease in the mass of the sample with the temperature increase is much lower than in the case of a higher heating speed (4 °C/min, 7 °C/min and 10 °C/min respectively) due to a wide distribution of the pore size (Figure 2.11). At the same time, mass loss is mitigated at higher temperature values.

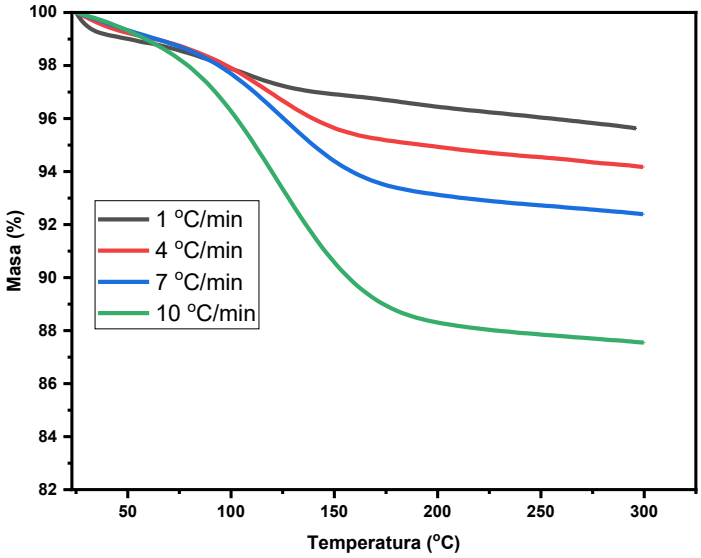


Figure 2.11. The TG profile of the biochar sample at different heating speeds

In the case of bioglass-type desiccant, although the average particle size was about 70% lower than that of biochar particles, a smaller difference in mass loss with heating speed is observed for the same temperature range. Thus, the slope of the curves, but also the final value of the mass loss, have much lower values than in the case of biochar. At the same time, the loss of mass of the sample shows close values at lower temperature values (below 200 °C) and is accentuated at higher temperature values (above 200 °C). Unlike biochar, mass losses increase at temperatures above 200 °C and show close values for the values of the heating speeds studied. These differences are due to the lower amount of retinol adsorbed in the pores of the bioglass due to the much lower total volume of pores in the bioglass than in the biochar (Figure 2.12).

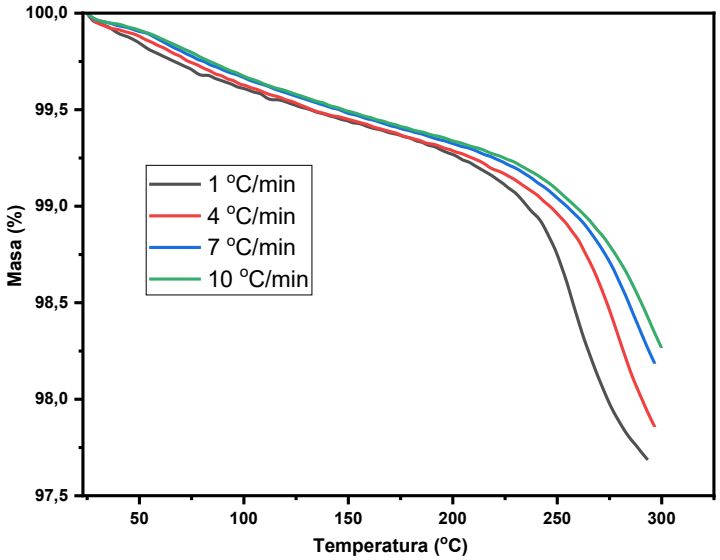


Figure 2.12. The TG profile of the bioglass sample at different heating speeds

3- EVALUATION OF THE INFLUENCE OF DERMAL DELIVERY SYSTEM ON RETINOL STABILITY

Retinol (vitamin A) is known for its outstanding dermatocosmetic properties, being widely used in anti-aging, depigmentating and anti-acne treatments. However, its chemical instability in the presence of light, air and high temperatures, as well as its high irritating potential, limit its direct use in topical formulations. Thus, the development of effective dermal delivery systems becomes essential for the protection and controlled release of retinol.

In this context, hydrogels and emulsions (both direct and reverse) formulations were investigated as functional media for the incorporation and delivery of retinol. These systems can significantly influence the physical-chemical stability of the active ingredient, thermal behavior, interaction with other excipients and, ultimately, the therapeutic efficacy of the final product. By integrating bioglass as a bioactive adsorber, it aims not only to improve the stability of retinol, but also to enhance the regenerating and antioxidant properties of formulations.

This chapter proposes a complex approach, combining thermal characterization methods (TG and DSC), spectroscopy (FTIR), X-ray diffraction (XRD), physical stability assessments (Turbiscan) and microbiological tests, to determine the influence of the composition of the delivery system on its stability under controlled conditions.

3.2- Experimental results on the stability of the delivery system

3.2.2.Inalize the differential baling calorimetry of dermal systems with retinol

The impact of the physico-chemical characteristics of cosmetic creams on thermal transitions is elucidated by the differential baling calorimetry (DSC) thermogram as described in Figure 3.3. Hydrogel thermograms (1) and the two types of emulsion have a comparable profile. In particular, the initial segment of all three curves reveals an endothermic peak,

characterized by an endothermic maximum occurring at temperatures above 120 °C, attributed to water evaporation.

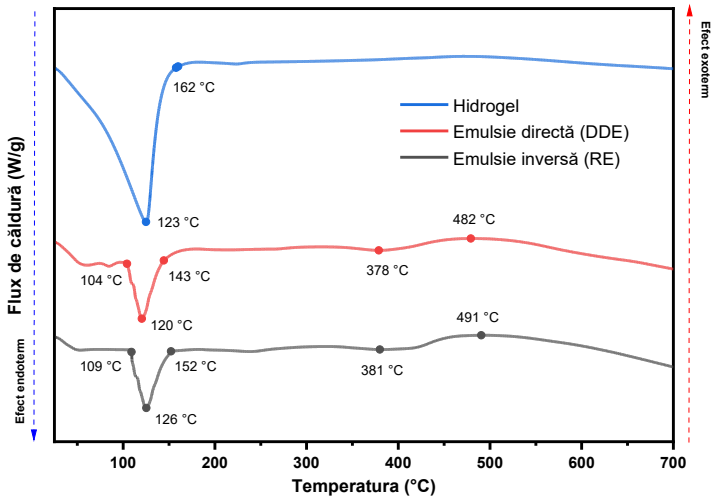


Figure 3.3. DSC thermogram of hydrogel (1) and two emulsions

The temperature at which this endothermic peak is observed is influenced by the nature of the interactions between water molecules and other constituents present in that formulation [1.2]. Thus, the thermal stability of emulsions is conditioned by both the type of emulsion and its composition [3]. More specifically, in the case of direct emulsion, the interactions between water molecules (acting as a continuous phase) and other components are diminished, resulting in a maximum temperature for water evaporation that is recorded at a point 3 °C lower than that of hydrogel (1) [4.5]. On the other hand, the hydrophilic polymer used in the formulation of hydrogel (1) facilitates the retention of water molecules through hydrogen bonds and electrostatic interactions. Conversely, reverse emulsions show potentially greater stability due to their hydrophobic characteristics. For these indirect emulsions, the interactions of water molecules (in the discontinuous phase) with other components are intensified, requiring higher energy input for the migration of water molecules from drops into the environment. As a result, the maximum temperature of the water evaporation peak is observed at a temperature 3 °C higher than that of the hydrogel (1).

In addition, the presence of minor endothermic peaks identified in both direct and reverse emulsions at high temperatures (approximately 380 °C) may indicate thermal degradation of organic constituents, such as surfactants or vegetable oils incorporated into emulsions. The observed discrepancy between DDE and RE can be attributed to variations in the composition of continuous and dispersed phases, thus influencing the thermal stability of the organic compounds present in each formulation.

4 - OBTAINING BIOGLASS OF TIP58S BY CONDITIONING WITH PEG 4000

This chapter examines the influence of PEG 4000 treatment on 58S type bioglass, with potential applications in the cosmetic industry. The main objective was to achieve a stable

non-crystalline structure and to assess the microstructural, morphological and thermal characteristics relevant to the use of bioglass as a vector for releasing active principles. The selection of the 58S composition is due to the particular interest shown for this type of bioglass in medical and cosmetic applications, due to the high biocompatibility and the increased SiO_2 content compared to 45S5, as well as the absence of Na_2O. The surface-gel method aimed at obtaining a superior homogeneity and vitreous structure bioglass, and the treatment with PEG 4000 was investigated in particular for its effects on thermal stability and dispersion in aqueous environments, aspects such as optimizing pore distribution and particle size will be detailed in future research.

4. 2 - Results obtained

4.4 - Conclusions on the characterization of bioglass and the influence of treatment with PEG 4000

The treatment of the bioglass with PEG 4000 before calcination allows a material with a completely non-crystalline structure to be obtained.

The SEM analysis shows that after the calcination of the bioglass in the presence of PEG 4000, there are numerous agglomerations of very small particles that are formed as a result of the acceleration of the condensation reactions that accompany the calcination process.

The EDX analysis of the BST sample highlights a uniform distribution of all identified elements in the sample mass. Porosity analysis showed that the nitrogen adsorption isothermies in the BSsample correspond to type V, indicating a mesoporous structure. In addition, treatment with PEG 4000 does not significantly alter the structure of the pores of the original bioscale.

After treatment with PEG 4000, the particle size distribution changes. Thus, the particle size distribution for the sample treated with PEG 4000 is wider.

Treatment of bioglass with PEG 4000 makes its use in the cosmetic industry safer by improving dispersion in aqueous environments without significant changes in the other characteristics.

Studies to date have shown that the type 58S bioglass has effective biocompatibility properties with human tissue, but there is no conclusive evidence of antibacterial, antioxidant and mechanical properties [6]. Due to the limited time available for the experiments, the bioglass synthesized in its own research could not be thoroughly tested, which makes these aspects remain insufficiently explored. As a result, future research will focus on assessing antibacterial and antioxidant properties and possibly correcting these characteristics, both by improving porosity and by additive with essential oils and/or compounds with antioxidant characteristics such as tocopherols. At the same time, the influence of the content of PEG 4000 on the distribution of pore size will be evaluated in order to optimize it. Based on the results obtained, the procedure for the approval of the 58S type bioglass with improved characteristics will be possible to initiate experimental skin testing studies of hydrogel formulations prepared with this optimized bioglass.

5 - RETINOL DISPERSION IN THE FORM OF HYDROGEL FOR SKIN DELIVERY

Based on the results obtained from the characterization of the three types of formulations (DDE, RE and hydrogel (1)), the hydrogel formulation was selected for further research because it ensures a lower concentration of particles and implicitly a slower release of retinol. The effectiveness of a new hydrogel dermocosmetic formulation, which combines retinol with other active principles, in the presence of bioglasses, shall be assessed in order to improve retinol performance in the treatment of certain skin conditions. This formula aims to harness the synergistic effects of retinol's cellular renovation properties, along with the regenerative capabilities of bioglass, providing a promising solution for those seeking effective and tolerable skin rejuvenation treatments. The new elements are given by the use of two competing mechanisms for delayed release of retinol on the surface of the epidermis, namely the reduction of diffusion in the fluid phase by increasing the viscosity of the product and the adsorption of retinol in the pores of a desiccant in the form of a powder. Thus, the increase in viscosity was achieved by transforming the retinol solution into a hyaluronic acid hydrogel and a Carbopol Aqua SF-1 OS copolymer. The adsorber used for controlled release is the powder-form bioglass, a vitreous solid, with various uses in the cosmetic and medical field.

5.2.1 - Experimental procedure for the study of accelerated stability

Test conditions: The study is carried out in a 35°C phase for a period of 30 consecutive days. After the preparation of the sample, the physico-chemical parameters are noted at the initial time, before the introduction into the test.

Set the etuva to 35°C and 100% ventilation until the temperature reaches 35°C, and then the ventilation is moved to 0% for 30 days. Once the set parameters have been reached, insert the sample into the tank and close tightly. At the end of the 30 days, the sample is removed from the chamber, kept at room temperature for 24 hours, and then the physico-chemical parameters of the product, namely the temperature inside the chamber, the organoleptic parameters (color, appearance, smell), the pH and the volume of the sample are noted.

The product is considered stable under the conditions performed, and implicitly for an equivalent period of approximately 6 months, if the changes occurred vary less than +/-5% from the results obtained before the initiation of the protocol.

5.3 - Experimental results on characterization of hydrogel with retinol

5.3.1 - Thermogravimetric analysis of hydrogel stability with retinol

Hydrogel (2) demonstrated a pronounced loss of mass in the area of the initial portion of the TG curve (Figure 5.3), in particular in the temperature range from 40 °C to 130 °C, with a maximum loss of mass observed on the differential thermogravimetric curve (DTG) around 125 °C. This significant loss of mass is primarily attributed to water evaporation.

In the subsequent heating phase, extending from 130 °C to 230 °C, the loss rate of mass has decreased, with the maximum loss recorded on the DTG curve at approximately 225 °C. This phenomenon is due to the evaporation of various volatile organic compounds, including triethanolamine (TEA). At temperatures above 230 °C, additional but lower mass loss was observed without additional maximum detection during this temperature range. These losses can be attributed both to the evaporation of organic compounds produced by inert gas and to the thermal degradation of non-volatile organic constituents such as hyaluronic acid, retinol and the Carbopol Aqua SF-1 polymer, as suggested by Altaleb [7-9].

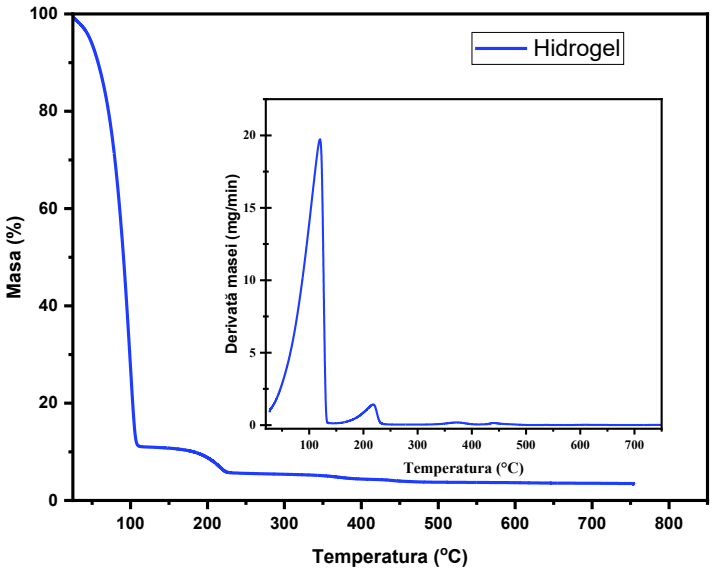


Figure 5.3. Thermogravimetric hydrogel analysis (2)

5.3.7 - Results of stability under accelerated conditions

Hydrogel sample parameter values (2) at the start of the test and after the test is complete:

1. The inside temperature was maintained at 35°C throughout the test;
2. Organoleptic parameters (color, appearance, smell): The suspension remained white and odorless after the test was completed;
3. The pH increased after the test was completed from the initial value of 12.4 to 12.5;
4. The initial volume was 100 mL and after the test was completed 99.8 mL.

In conclusion, the product complies with the admissibility limits (+/-5%) and is considered stable. This assessment was carried out in accordance with Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. The cosmetic product stability assessment is a mandatory component of the cosmetic product safety report (CPSR) and is included in the product dossier. The stability tests thus combine both accelerated and real-time conditions, analyzing parameters such as appearance, pH, viscosity, and microbiological quality of the finished product. Compliance with the variation limit of ± 5 % is considered a consolidated practice in the cosmetics industry, validating the stability of the product and its compliance with the regulatory requirements in force.

Thus, at the end of the 30-day study period all organoleptic and physico-chemical parameters meet the specifications and acceptability criteria.

The results obtained in this study confirm that the hydrogel cosmetic product (2) showed stable sensory and physico-chemical characteristics for a period of 30 days of storage under conditions of accelerated aging.

5.3.8 - Microscopic analysis of the size of hydrogel droplets

The qualitative assessment of hydrogel stability (2) was made by microscopic visualization at a 160x increase in particle content up to 0.5 µm at different time periods after preparation (Figure 5.8). Microscopic analyzes indicated that the particles in the hydrogel (2) were up to 1.5 µm in size. The most abundant drops were the lowest of 0.5 µm, which were distributed relatively evenly. The effectiveness of discontinuous phase dispersion in the prepared formulation was assessed by comparing the number of particles less than 0.5 µm with the total number of particles present in a 1 µl sample (Figure 5.8).

The stability of the formulation was monitored for a period of 6 hours after their preparation, with an intermediate measurement performed 3 hours thereafter. A slight increase in particle aggregation over time was observed, evidenced by a sharp decrease in particle content of less than 0.5 µm. The maximum error of determination was 2.3%.

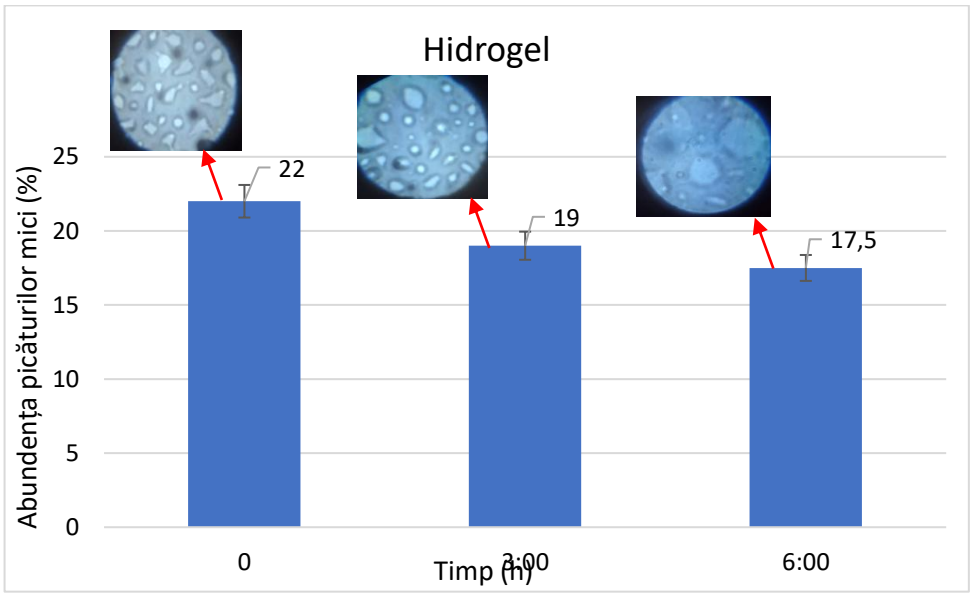


Figure 5.8. The evolution of the abundance of small droplets in the hydrogel formula (2) over a period of 6 hours, measured at 0, 3 and 6 hours after preparation and their microscopic appearance at 160x magnification.

5.4.2 - Skin analysis studies with the VISIA system

Figure 5.11 shows a 3D scan of skin evolution for one of the volunteers in two weeks. It is a comparative evolution at the level of UV spots, pigmentation spots, red and porphyrin areas between the start date and the end date of the tests.



Figure 5.11 . Skin evolution by 3D scanning

The 3D scan captured in the VISIA system shows a good score in improving red areas of the skin. This is a very good result and an appropriate tool to assess the skin response to hydrogel treatment (2) because the volunteer himself has sensitive skin. Thus, from the 3 D image of the skin (Figure 5.12) it is noted that red areas and inflammation were reduced after 2 weeks of topical application.

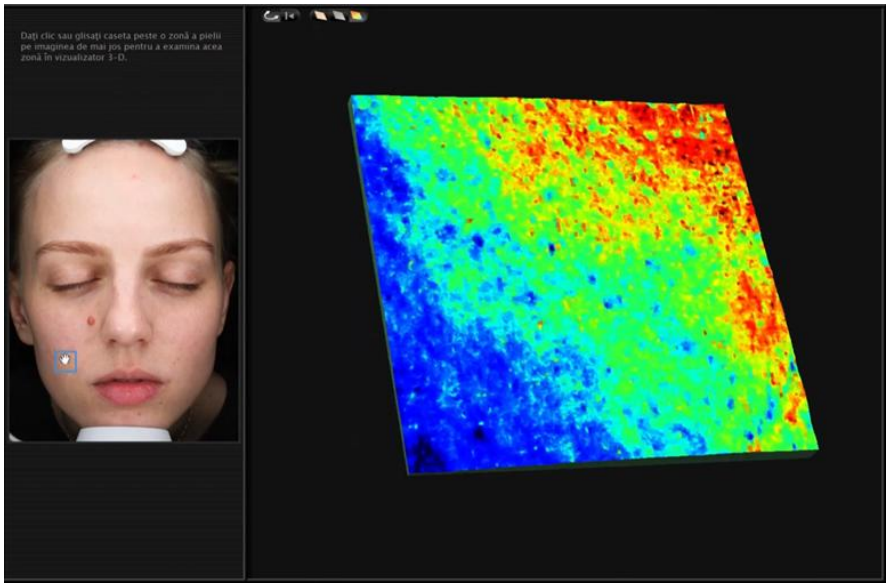


Figure 5.12 . 3D scanning captured in the VISIA system

The comparative evolution of pigmentation spots between the start and end date is shown in Figure 5.13.

It is noted that the VISIA system recorded a difference in the presence of pigmentation spots. Thus, after applying the hydrogel (2), the score for pigmentation spots was better.

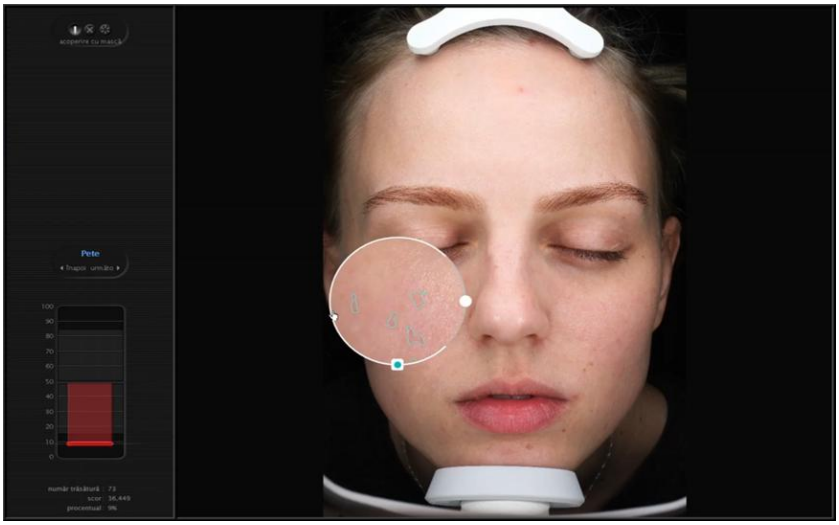


Figure 5.13 . Comparative evolution at the level of pigmentation spots between the start and end date

C- GENERAL CONCLUSIONS

The controlled release of active principles is the modern version that streamlines the delivery of these principles, with applications in various fields such as the medical field, the field of fertilizers, food packaging, but also the cosmetic industry. The doctoral paper entitled "retinoid bioimpregnations on vitreous microspheres for dermatological applications" explores the development of an innovative solution for controlled retinoid release using bioactive vitreous microspheres as a support system. The theme falls within the scope of applied research, being at the confluence of materials chemistry, applied dermatology and modern pharmaceutical technologies, and responds to a stringent market demand: Dermo-cosmetic formulations with high efficiency, high stability and optimal tolerability. The purpose of this thesis was to demonstrate the superiority of modern techniques of controlled retinoid delivery with applications in the cosmetic field. A defining element of the paper is the original proposed formula, consisting of loading retinoids (retinol) into bioglass microspheres. This system allows both the protection of the active ingredient and a gradual and controlled release over time, contributing to the effectiveness of the skin application.

1. The qualitative assessment of the efficiency of the controlled release of retinol impregnated on the bioglass was made by comparing the thermo-gravimetric curve of the retinol-impregnated bioglass with the thermo-gravimetric curve of a biochar showing microstructural characteristics different from that of the bioglass.
    a. The two adsorbers were characterized by the determination of microstructural characteristics, the determination of particle size distribution, the surface structure by electronic scopy of scavenging and the crystallization behavior by X-ray diffraction. The biochar showed a relatively uniform distribution of pores with a high mesopor content, and the adsorption isotherm of liquid nitrogen revealed that the formation of pores is complete. The porosity analysis of the bioglass used revealed a predominantly

macroporous structure, which partially diminishes the adsorption capacity of the active principles in the adsorbent pores, but favors a total release of them.

2. The influence of retinol dermal delivery formula on the stability of these formulations has been studied for three variants of innovative dermo-cosmetic formulations that synergistically combine bioglass with retinol: direct emulsion, reverse emulsion and hydrogel. The objective of this study was to reduce the irritating potential of retinoids and extend therapeutic efficacy over a longer period of time.

    a. The characterization of the three formulations prepared in this study was made by the following analyzes: Thermogravimetric analysis, Differential Scanning Calorimetry, infrared spectroscopy with Fourier transform, X-ray diffraction, electrical conductivity, pH, stability analyzes, microbiological analyzes. Thus, the electrical conductivity of the formulations is influenced by both the water content and the polarity of the continuous phase, the hydrogel having a significantly higher electrical conductivity compared to the two emulsions.

    b. TG and DSC analyzes suggested a significant change in temperature at which maximum water loss occurred, indicating stronger interactions between water molecules and organic compounds present, especially in emulsions, as opposed to hydrogel. The XRD analysis suggests a completely vitreous structure of the bioglass used, but also the absence of other crystalline organic superstructures that could prevent the controlled release of retinol.

3. Concerns about obtaining biosolglass by the surface-gel method were directed toward diminishing the degree of crystallinity. Thus, the presence of a crystalline phase in the final product is not desired, as it can have negative effects on the health of the people who use it as well as the speed of release. The condition variant of the 58S type bioglass, obtained by the surface-gel method, in order to eliminate crystalline microstructures is an original method and consists of applying a post-heat treatment in the presence of an oxygenated oligomer, such as PEG 4000. The moderate exothermic effect of the decomposition of this class of oxygenated oligomers correlated with the high polarity of these polymers, favors an efficient dissipation of the heat released during the calcination of the bioglass, thus avoiding the orderly placement of the bioglass clusters with the formation of a vitreous structure.

    a. The bioglass obtained has been characterized by techniques such as TG/DTA, FTIR and SEM, highlighting its potential for integration into new-generation dermocosmetic products. Thus, the assessment of the degree of crystallinity of the prepared materials was carried out by XRD analysis. This method also checks the effectiveness of the proposed technical solution to reduce the crystallization of the biofilm sample following heat treatment. The absence of crystalline phase in the treated bioglass in the presence of PEG 4000 leads to the idea that the presence of PEG in the gel structure inhibits the formation of crystals during calcination, up to the limit of detection of the XRD method.

b. The SEM analysis revealed the microstructure of the surface of the samples calcined with and without PEG 4000 and showed that the non-PEG-free calcined bioglass sample had uniform surfaces. Instead, the PEG 4000 calcined sample has numerous groups of different sizes formed due to accelerated condensation reactions during calcination. The EDX analysis of the calcined sample in the presence of PEG 4000 also showed a uniform distribution of all the chemical elements identified in the sample.

c. The variation in the mean diameter of the pores of the bioglass sample after treatment with PEG was recorded by bet analysis. It is noted that the average pore diameter of the bioglass sample remains at the lower mesopor limit, which means that the addition of PEG does not significantly change the initial porous structure of the bioglass. The larger diameter of the PEG 4000 macromolecules slightly changed the distribution of the pore size to higher values. Porosity analysis also showed that the nitrogen adsorption isotherm in the bioglass sample corresponds to type V, indicating a mesoporous structure. This mesoporosity is beneficial for the gradual release of adsorbed species in the pores of the bioglass.

4. Based on the results obtained, the hydrogel formulation variant was selected for the retinol dermal delivery study. This study evaluated the effectiveness of a new hydrogel-based dermocosmetic formulation that combines retinol and other active principles, infused in bioglass, to enhance skin benefits. This formula aims to capitalize on the synergistic effects of retinol's cellular renovation properties, along with the regenerative capabilities of other active principles and bioglas, providing a promising solution for those seeking effective skin rejuvenation treatments.

   a. The new elements are given by the use of two competing mechanisms for delayed release of retinol on the surface of the epidermis, namely the reduction of diffusion in the fluid phase by increasing the viscosity of the dermatological product and respectively the adsorption of retinol in the pores of an adsorber in the form of a hydrogel. Thus, the increase in viscosity was achieved by using retinol incorporated in a hydrogel based on an inflatable acrylate-type copolymer in an alkaline environment. The adsorber used for controlled release is the powder-form bioglass, a vitreous solid, with various uses in the cosmetic and medical field.

   b. The characterization of the hydrogel obtained in the study was made by the following analyzes: Thermogravimetric analysis, Differential Scanning Calorimetry, infrared spectroscopy with Fourier transform, X-ray diffraction, electrical conductivity, pH, stability analyzes and skin administration tests.

E - BIBLIOGRAFIE

1. Gadea, J.L.; Cesteros, L.C.; Katime, I. Chemical–physical behavior of hydrogels of poly(vinyl alcohol) and poly(ethylene glycol). *European Polymer Journal* **2013,** *49*, 3582-3589, doi:https://doi.org/10.1016/j.eurpolymj.2013.07.027.

2. Tananuwong, K., Reid, D.S. DSC and NMR relaxation studies of starch–water interactions during gelatinization. *Carbohydrate polymers* **2004,** *58*, 345-358, doi:https://doi.org/10.1016/j.carbpol.2004.08.003.
3. Akbari, S.; Nour, A.H. Emulsion types, stability mechanisms and rheology: A review. *International Journal of Innovative Research and Scientific Studies* **2018,** *1*, 11-17, doi:10.53894/ijirss.v1i1.4.
4. Bulgarelli, N.A.V.; Bizarre, L.; Monte Verde, W.; Pulido, A.F.C.; Castro, M.S.d. Rheological behavior of the stable water-in-oil emulsion associated to water droplets arrangement. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* **2025,** *707*, 135512, doi:https://doi.org/10.1016/j.colsurfa.2024.135512.
5. Luo, B.; Wen, J.; Wang, H.; Zheng, S.; Liao, R.; Chen, W.; Mahian, O., Li, X. A Biomass-Based Hydrogel Evaporator Modified Through Dynamic Regulation of Water Molecules: Highly Efficient and Cost-Effective. *ENERGY & ENVIRONMENTAL MATERIALS* **2023,** *6*, e12353, doi:https://doi.org/10.1002/eem2.12353.
6. Singh, I.; Shakya, K.; Gupta, P.; Rani, P.; Kong, I.; Verma, V.; Balani, K. Multifunctional 58S Bioactive Glass/Silver/Cerium Oxide-Based Biocomposites with Effective Antibacterial, Cytocompatibility, and Mechanical Properties. *ACS Applied Materials & Interfaces* **2024,** *16*, 18327-18343, doi:10.1021/acsami.3c17400.
7. Khaleghi, M., Ahmadi, E.; Khodabandeh Shahraki, M., Aliakbari, F., Morshedi, D. Temperature-dependent formulation of a hydrogel based on Hyaluronic acid-polydimethylsiloxane for biomedical applications. *Heliyon* **2020,** *6*, e03494, Doi:https://doi.org/10.1016/j.heliyon.2020.e03494.
8. Larrañeta, E. Henry, M.; Irwin, N.J.; Trotter, J.; Perminova, A.A.; Donnelly, R.F. Synthesis and characterization of hyaluronic acid hydrogels crosslinked using a solvent-free process for potential biomedical applications. *Carbohydrate polymers* **2018,** *181*, 1194-1205, doi:https://doi.org/10.1016/j.carbpol.2017.12.015.
9. Ndiaye, M.; Myler, P.; Kandola, B.K. Thermoplastic Composites: Modelling Melting, Decomposition and Combustion of Matrix Polymers. *Journal of Composites Science* **2022,** *6*, doi:10.3390/jcs6010027.