Preparation and characterization of organogels containing vitamin E for cosmetic application

Preparação e caracterização de organogéis contendo vitamina E para aplicação cosmética

Renata Miliani Martinez

Tese para obtenção do grau de DOUTOR

Orientador: Prof. Dr. André Rolim Baby

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PREPARATION AND CHARACTERIZATION OF ORGANOGEELS CONTAINING VITAMIN E FOR COSMETIC APPLICATION

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ABSTRACT

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Human skin is attacked daily by ultraviolet (UV) radiation and pollutants. Such aggressions can promote lipid peroxidation mediated by free radicals in cells, generating DNA damage and inflammatory processes, in addition to endogenous vitamin E depletion. The use of antioxidant cosmetic products has potential for treatment; however, the stability and permeation of these active ingredients may be a limiting factor in their use. Thus, the present work aimed at the development and characterization of organogels containing vitamin E and their dispersions in bigels, focusing on cosmetic application. The results derived from this investigation are ordered in three articles, being: (1) review on organogels in the cosmetic area; (2) application of organogels containing vitamin E in systems of bigels, their physicochemical characterization and evaluation of efficacy in vitro and ex vivo; and (3) characterization of organogels containing vitamin E regarding their microstructure and rheological profile. The results indicated that despite the potential for permeation of hydrophilic and hydrophobic actives through the skin, increased stability and sensory modification, organogels were still little explored in the cosmetic area. The bigels were characterized as weak viscoelastic oil-in-water gels, with adequate stability determined by thermal and centrifugal stress. The presence of vitamin E generated little influence on the rheological profile and efficacy in vitro and ex vivo of the bigels, emphasizing the need for further studies in the presence of stress in the biological sample. Organogels were characterized as weak pseudoplastic gels. The type of organogelling agent was relevantly influenced in the presence of vitamin E. 12-Hydroxysestearic acid had a reduction in gel strength, while candelilla wax showed increased strength. All phase transition temperatures were reduced in the presence of vitamin E. The results indicated the potential use of organogels and bigels in the delivery of vitamin E for topical application, enabling the development of formulations with stability and modulation of the rheological profile as needed.

Keywords: organogels, bigels, vitamin E, 12-hydroxystearic acid, candelilla wax.
A pele humana é agredida diariamente pela radiação ultravioleta (UV) e poluentes. Tais agressões podem promover a peroxidação lipídica mediada por radicais livres nas células, gerando danos ao DNA e processos inflamatórios, ademais da depleção da vitamina E endógena. O uso de produtos cosméticos antioxidantes apresenta potencial para o tratamento, porém, a estabilidade e permeação desses ingredientes ativos pode ser um limitante em sua utilização. Assim, o presente trabalho teve como objetivo o desenvolvimento e caracterização de organogéis contendo vitamina E e suas dispersões em bigéis, visando aplicação cosmética. Os resultados derivados dessa investigação estão ordenados em três artigos, sendo: (1) revisão sobre organogéis na área cosmética; (2) aplicação de organogéis contendo vitamina E em sistemas de bigéis, sua caracterização físico-química e avaliação de eficácia in vitro e ex vivo; e (3) caracterização de organogéis contendo vitamina E quanto à sua microestrutura e perfil reológico. Os resultados indicaram que apesar do potencial na permeação de ativos hidrofílicos e hidrofóbicos pela pele, aumento de estabilidade e modificação no sensorial, os organogéis ainda foram pouco explorados na área cosmética. Os bigéis foram caracterizados como géis viscoelásticos fracos tipo óleo-em-água, com estabilidade adequada determinada por estresse térmico e centrífugo. A presença de vitamina E gerou pouca influência no perfil reológico e eficácia in vitro e ex vivo dos bigéis, ressaltando a necessitando de estudos posteriores na presença de estresse na amostra biológica. Os organogéis foram caracterizados como géis pseudoplásticos fracos. O tipo de organogelificante sofreu influência relevante na presença da vitamina E, sendo que o ácido 12-hidroxiesteárico teve redução na força do gel, enquanto a cera de candelilila apresentou aumento de força. Todas as temperaturas de transição de fases foram reduzidas na presença de vitamina E. Os resultados indicaram o potencial uso de organogéis e bigéis na veiculação de vitamina E para aplicação tópica, possibilitando o desenvolvimento de formulações com estabilidade e modulação de perfil reológico conforme a necessidade.

Palavras-chave: organogéis, bigéis, vitamina E, ácido 12 hidroxiesteárico, cera de candelilila.
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1. INTRODUCTION

Oxidative stress promotes skin aging, represented by the formation of spots and wrinkles. The target cells in the skin are keratinocytes, fibroblasts and melanocytes (Nakamura et al., 2015; Qiao et al., 2017; Soeur et al., 2017). Extrinsic skin aging, caused by external agents, is closely related to oxidative stress, especially after exposure to ultraviolet (UV) radiation, increasing the expression of genes that translate matrix metalloproteinases enzymes (MMPs) into dermal fibroblasts, degrading collagen and elastin (Burke, 2018). Clinical studies corroborate the evidence of cutaneous aging in vitro (Hüls et al., 2016; Vierkötter et al., 2010). Despite the difficulties in isolating a single variable in a clinical study, skin aging has a strong correlation with exposure to solar radiation and pollutants (Krutmann et al., 2017). These "triggers" promote the formation of free radicals, usually in the form of reactive oxygen species, and lipid peroxidation products that follow the deleterious cascade, reducing the concentration of endogenous vitamin E to the cell nucleus, where they will activate transcriptional factors for the formation of enzymes capable of disrupting collagen and inflammatory factors, culminating in signs of premature skin aging and inflammation (Park, 2015). Chronic exposure to pollutants causes cumulative oxidative damage in the stratum corneum and a significant reduction in the reserves of endogenous antioxidants such as vitamin C and E. In the mitochondria, damage also occurs, reducing levels of adenosine triphosphate (ATP) and sirtuin-3 (protein involved in neutralizing oxidizing agents) (Mancebo & Wang, 2015). Thus, the replacement of vitamin E to the skin is essential for the maintenance of the protective antioxidant system of cells.

Vitamin E is a classic anti-aging agent used in the cosmetic and dermatological field. When applied topically, vitamin E can act against photoaging, reducing lipid peroxidation and photocarcinogenic markers, such as transcription factors of matrix metalloproteinases (MMP-1) and thymine dimers (Chen et al., 2012). It is a lipophilic compound formed by several molecules, and alpha-tocopherol is the most important to humans, as it is available in both the stratum corneum, epidermis and dermis. Unlike other antioxidant agents, vitamin E is not produced by the human body and should, therefore, be obtained through diet or topical application. Vitamin E is recognized for its antioxidant property, acting in the reduction of erythema caused by exposure to UVB radiation (Pegoraro et al., 2017) and attenuation of signs of skin aging (Rinnerthaler et al., 2015). In the presence of UV radiation, the alpha-tocopherol available in the stratum corneum decays at, approximately, 50% of its initial concentration. This process may be associated with a direct mechanism of absorption of UVB radiation and/or an indirect mechanism of interaction of the molecule with reactive oxygen.
species formed by UVA radiation photosensitive compounds. In this sense, vitamin E aids photoprotection when combined with oral or topical formulations, the latter being of great cosmetic interest. Topical formulations containing 0.1 to 1.0% (w/w) of alpha-tocopherol have effective potential to increase the antioxidant skin barrier protection (Thiele & Ekanayake-Mudiyanselage, 2007). However, its instability in the face of UV stress and heat lead to pharmacotechnical difficulties. Thus, the use of encapsulated or nanostructured vitamin E can be used (Pegoraro et al., 2017). In some cases, the high production cost and technical difficulties of preparing these systems may discourage formulators, and new ways of stabilizing vitamin systems are needed, such as organogels (Shi et al., 2014).

Organogels are thermoreversible organogelled matrices capable of functioning as asset delivery systems, convenient preparation and low cost. This technology comes from the food area, however, already has several pharmaceutical applications (Esposito et al., 2018). In the cosmetic field, organogels can be used per se, as used for the delivery of anticellulite agents (Morales-Rueda et al., 2009), or through the development of organogelled nanoparticles for dermocosmetics (Kirilov et al., 2014). There is also the possibility of incorporating organogels in emulsifiable systems, known as bigels (Lupi et al., 2016).

Among the various applications of organogels, its use as a delivery system differentiates this technology from other carrier systems for its convenience in preparation and low cost. Despite the possibilities described, there are still no reports in the literature for the development of organogelled cosmetic formulations containing vitamin E. Thus, the present study aimed at the development of stable dispersions of organogels and bigels containing vitamin E for cosmetic application.
2. OBJECTIVES

This research work aimed to produce and evaluate organogels and bigels loaded with vitamin E for skin cosmetic application.

2.1 SPECIFIC OBJECTIVES

- Review the literature regarding organogels in cosmetics.
- Produce and characterize organogels with candelilla wax or 12-hydroxystearic acid loaded with vitamin using rheology, polarized microscopy and small angle X-ray scattering (SAXS).
- Incorporate organogels into bigels and characterize them by rheology, microscopy, laser diffraction, antioxidant assay (DPPH) and in vitro and ex vivo efficacy tests.
3. PUBLICATIONS

The Thesis was organized in accordance with three published papers, derived from this investigation work, ordered by date of publication:

- Article 1 (Main features and applications of organogels in cosmetics): a review paper about the organogel’s state-of-art into the cosmetic field, published at *International Journal of Cosmetic Science*.

- Article 2 (Vitamin E-loaded bigels and emulsions: Physicochemical characterization and potential biological application): a full-length article about the application of vitamin E-loaded organogels into bigels, their characterization and biological effects, published at *Colloids and Surfaces B: Biointerfaces*.

- Article 3 (Influence of the Mixtures of Vegetable Oil and Vitamin E over the Microstructure and Rheology of Organogels): a full-length article about the characterization of vitamin E-loaded organogels, published at *Gels*. 
Main features and applications of organogels in cosmetics

INTERNATIONAL JOURNAL OF COSMETIC SCIENCE, v. 41, p. 109-117, 2019.

https://onlinelibrary.wiley.com/doi/full/10.1111/ics.12519
Vitamin E-loaded bigels and emulsions: Physicochemical characterization and potential biological application

Colloids and Surfaces B: Biointerfaces

MARTINEZ, RENATA MILIANI; MAGALHAES, WAGNER VIDAL; SUFI, BIANCA DA SILVA; PADOVANI, GIOVANA; SBRUGNERA NAZATO, LUCAS IDACIR; ROBLES VELASCO, MARIA VALERIA; DA SILVA LANNES, SUZANA CAETANO; BABY, ANDRE ROLIM. Vitamin E-loaded bigels and emulsions: Physicochemical characterization and potential biological application. **COLLOIDS AND SURFACES B-BIOINTERFACES**, v. 201, MAY 2021.

[https://www.sciencedirect.com/science/article/abs/pii/S0927776521000953](https://www.sciencedirect.com/science/article/abs/pii/S0927776521000953)
Influence of the Mixtures of Vegetable Oil and Vitamin E over the Microstructure and Rheology of Organogels

MARTINEZ, RENATA MILIANI; OSELIERO FILHO, PEDRO LEONIDAS; GERBELLi, BARBARA BIANCA; MAGALHAES, WAGNER VIDAL; VELASCO, MARIA VALERIA ROBLES; DA SILVA LANNES, SUZANA CAETANO; DE OLIVEIRA, CRISTIANO LUIS PINTO; ROSADO, CATARINA; BABY, ANDRÉ ROLIM. Influence of the Mixtures of Vegetable Oil and Vitamin E over the Microstructure and Rheology of Organogels. GELS, v. 8, n. 1, JAN 2022.

https://www.mdpi.com/2310-2861/8/1/36
4. CONCLUSIONS

Organogels show great potential in cosmetic field for its low-cost, rheological properties and enhanced delivery profiles. It can deliver hydrophilic and lipophilic molecules into the skin in tailor-made formulations. Despite the lack of information on safety and toxicological effects, previous knowledge from food and drug delivery applications may be used to reinforce its use in cosmetics. Regarding the bigels obtained in this research work, they were oil-in-water (O/W) dispersions with crystals located at the interface of phases with viscoelastic weak gel behavior and excellent thermal and centrifuge-stress stability. When 12-hydroxystearic acid was used, physical gel interactions strengthen when compared with candelilla wax. The type of organogelator in the organogel influenced the thixotropy, shear-thinning and consistency. Vitamin E showed little influence over rheological, biological and physical parameters, except for the increase in the size of oil globules. This was the first study comparing bigels and their emulsions and the 5/95 organogel/hydrogel ratio. Further investigation about topical delivery of vitamin E from these formulations in ex vivo model would present a strong argument for the use of the bigels over the emulsions used to compare in this investigation. We believe that the use of stress, such as irradiation or pollutants, could increase the potential of vitamin E bigels over ex vivo analysis. Further investigation of different organogel/hydrogel ratios could also contribute to highlight the role of each phase in rheology and microstructure.

Despite all organogels studied herein were characterized as weak gels with a shear-thinning behavior, the organogel’s composition plays an important role in its physical chemical and phase transition properties. Organogels containing 12-hydroxystearic acid showed highly packed network with thixotropy and a reduction in gel strength in the presence of vitamin E. On the other hand, candelilla wax showed sparse crystals and an increase in gel strength when vitamin E was added. All phase transition temperatures were reduced in a dose-dependent pattern, especially for 12-hydroxystearic acid organogels. Larger crystals that slightly increased upon heating were observed via SAXS for 12-hydroxystearic acid organogels when compared with candelilla wax. We brought two possible mechanisms for vitamin E and the oily phase interaction that required further investigation: (1) vegetable oil and vitamin E form a new oily phase with different properties or (2) vitamin E and organogelators compete for vegetable oil availability.

Our findings suggested that organogels and bigels showed great potential as vitamin E delivery systems for cosmetics. The concentration of vitamin E is an important factor for organogel production and must be addressed properly during the phase of formulation design. The versatility, stability and sensory modulation of organogels and bigels are the main advantages. However, further studies are required to evaluate biological effects under UV and/pollution exposition.
5. SCIENTIFIC PRODUCTION

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