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**Process optimization of nanoemulsion containing olive oil: high-pressure
homogenization and D-phase emulsification**

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**Processes optimization of nanoemulsion preparation containing olive oil:
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RESUMO

YUKUYAMA, M.N. Otimização de processos de obtenção de nanoemulsões contendo óleo de oliva: homogeneização a alta pressão e emulsificação empregando fase D. 2017. 215p. Dissertação (Mestrado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo.

O óleo de oliva apresenta elevado potencial de aplicação no desenvolvimento de produtos farmacêuticos e cosméticos. No campo farmacêutico, esse óleo tem sido utilizado para a preparação de nanossistemas de liberação de fármacos que apresentam baixa solubilidade em água. Tais nanossistemas, incluindo as nanoemulsões, podem ser obtidos empregando processos de alta (mecânico) e baixa energia (físico-químico). A proposta do presente estudo foi adquirir maior entendimento dos processos de preparação e da aplicação de nanoemulsão por homogeneização a alta pressão (HAP) e emulsificação empregando fase D (EFD), respectivamente métodos de alta e baixa energia. O conhecimento adquirido pela sistematização da pesquisa e das atividades executadas resultou em dois artigos de revisão e dois artigos de pesquisa. O primeiro artigo de revisão permitiu identificar tendo em vista o sucesso do desenvolvimento de nanoemulsão, a necessidade de conhecimento da interação entre o fármaco e os componentes da nanoemulsão; do impacto do processo de preparação nos componentes e na estabilidade da nanoemulsão; e da influência da formulação na liberação e na absorção do fármaco por diferentes rotas de administração. Além disso, apresentamos as diferentes nanoemulsões, considerando o tipo de tensoativo utilizado para sua preparação e seu respectivo uso. O segundo artigo de revisão evidenciou a adequada seleção de processo como o fator essencial para assegurar a obtenção de nanoemulsão com propriedades pré-determinadas, oferecendo aos pesquisadores alternativa realista para sua produção em escala industrial. Com referência aos artigos de pesquisa, o primeiro comprovou a possibilidade de obtenção de nanoemulsão contendo elevado teor de óleo vegetal (40% m/m) utilizando único tensoativo em

concentração de 2% m/m. Esse desempenho considerado como desafio nos processos convencionais de baixa energia, foi realizado com sucesso utilizando o processo EFD. O poliol foi confirmado como variável estatisticamente significativa para a redução do diâmetro hidrodinâmico médio (DHM) da nanoemulsão, influenciando de maneira sinérgica o comportamento do tensoativo durante a fase de transição nesse método. O estudo referente ao segundo artigo permitiu a identificação e o entendimento da relação entre as variáveis de composição e de processo e o DHM, no desenvolvimento de nanoemulsão contendo óleo de oliva, empregando os processos HAP e EFD. A abordagem estatística revelou os intervalos ótimos das variáveis de composição e de processo para a obtenção do DHM desejado, o atributo crítico de qualidade. Assim, foi adquirido maior entendimento dos respectivos processos. Adicionalmente, o conceito do espaço de design e a otimização por meio da função desejo permitiu a obtenção de nanoemulsão de 275 nm com sucesso, empregando a mesma composição para ambos os processos: HAP e EFD. Os conhecimentos adquiridos nesses estudos poderão direcionar o desenvolvimento de nanoemulsão inovadora, com êxito.

Palavras-chave: nanoemulsão, óleo vegetal, homogeneização a alta pressão, emulsificação empregando fase D, processo de alta energia, processo de baixa energia.

ABSTRACT

YUKUYAMA, M.N. Processes optimization of nanoemulsion preparation containing olive oil: high pressure homogenization and D-phase emulsification. 2017. 215p. Dissertação (Mestrado) – Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo.

Olive oil has an extensive applicability in the development of pharmaceuticals and cosmetics. In the pharmaceutical field, this oil has been used for the preparation of poorly water-soluble drug delivery nanosystems. Such nanosystems, including nanoemulsions, can be obtained by employing high (mechanical) and low energy (physicochemical) processes. The aim of the present study was to acquire the deep understanding of the processes of preparation and applicability of nanoemulsion by high-pressure homogenization (HPH) and D-phase emulsification (DPE), respectively high- and low-energy methods. The knowledge acquired through the careful systematization of the research and the activities performed resulted in two review articles and two research articles. The first review article allowed to identify, targeting development of a high efficacy nanoemulsion, the need to understand the interaction between the drug and nanoemulsion components; the impact of the preparation process on the components and the nanoemulsion stability; and the influence of the formulation on the release and uptake of the drug by different administration routes. In addition, we described the development of different nanoemulsions, according to the selected surfactant for their preparations, and their respective application. The second review article evidenced the appropriate process selection as the key factor to ensure obtaining nanoemulsions with desired properties, offering to researchers, a realistic industrial scale alternatives for the development of nanoemulsions. Regarding the research articles, the first one confirmed the possibility of obtaining nanoemulsions containing high vegetable oil content (40% w/w) using a single surfactant at a concentration of

2% w/w. This challenge, considered as a challenge in conventional low energy processes, was successfully accomplished using the DPE process. The polyol was confirmed to be a statistical significant variable for the reduction of the nanoemulsion mean particle size (MPD), by synergistically influencing the behavior of the surfactant during the transition phase in this method. The second research article allowed identifying and understanding the relationship between composition and process variables and MPS in the development of olive oil nanoemulsion, using HPH and DPE processes. The statistical approach allowed the identification of optimal ranges of composition and process variables for obtaining the desired MPS, which is the critical quality attribute. Therefore, a better understanding of the respective processes was acquired. In addition, the design space concept and the optimization by means of the desire function allowed obtaining a 275 nm nanoemulsion with success, using the same compositions for both HPH and the DPE processes. The knowledge acquired in these studies will successfully allow directions for the future development of innovative nanoemulsion.

Key words: nanoemulsion, vegetable oil, High Pressure Homogenization, D-Phase Emulsification, high-energy process, low-energy process.

Preface

This thesis is an original work by Megumi Nishitani Yukuyama completed under the supervision of Prof. Dr. Nádia Araci Bou-Chacra at the University of São Paulo. Most of this work was performed in the Dr. Bou-Chacra lab facilities. Some experiments were also carried out at different lab facilities at the University of São Paulo, as Dr. Kato lab at Department of Pharmacy and Dr. Oliveira and Dr. Fantini of Institute of Physics, both at University of São Paulo.

Chapter 1 of this thesis is the starting chapter focused on the current review of different nanoemulsion types and their applications, emphasizing their challenges and prospects. The drug interaction with the components of the formulation, as well as the drug mechanistic interaction with the biological environment of different routes of administration was also highlighted. It was published as Megumi Nishitani Yukuyama, Edna Tomiko Myiake Kato, Raimar Lobenberg and Nádia Araci Bou-Chacra, with the title of Challenges and Future Prospects of Nanoemulsion as a Drug Delivery System in **Current Pharmaceutical Design**, 2017, 23, 495-508.

Chapter 2 of this thesis highlighted the main high- and low-energy methods applicable in cosmetics and dermatological nanoemulsion development. It also mentioned their specificities, recent research of these methods in the cosmetics, and the consideration for the process selection optimization. It was published as Megumi Nishitani Yukuyama, Daniela Dal Molim Ghisleni, Terezinha de Jesus Andreoli Pinto and Nádia Araci Bou-Chacra, with the title Nanoemulsion: process selection and application in cosmetics – a review in **International Journal of Cosmetic Science**, 2016, 38, 13–24.

Chapter 3 of this thesis aimed attention at the D-phase emulsification (DPE) process, a less explored among the low energy methods, which can overcome the drawbacks of conventional phase inversion temperature and phase inversion composition methods for obtaining a nanoscaled emulsion. This process has an advantage by not requiring strict adjustment of hydrophilic-lipophilic balance for the preparation of fine particle emulsions, nor the presence

of initial water-in-oil (W/O) phase as in the conventional phase inversion methods. The behavior of the DPE process intermediate transition phase was investigated in this study, and a nanoemulsion with mean particle size of 20 – 30 nm was successfully obtained applying the DPE process and Box-Behnken design. This study will be published as Megumi Nishitani Yukuyama, PedroLeonidas Oseliero Filho, Gabriel Lima Barros de Araujo, Edna Tomiko Myiake Kato, Raimar Lobenberg, Cristiano Luis Pinto de Oliveira, and Nádia Araci Bou-Chacra, with the title D-phase emulsification as a unique low energy process: high internal vegetable oil nanoemulsion. It was submitted to the International Journal of Pharmaceutics.

Chapter 4 of this thesis highlighted the concept of Design Space and Quality by Design, using statistical approaches in obtaining nanoemulsions of olive oil, by high- and low-energy processes. In the high-energy process, also known as mechanical, high-pressure homogenization (HPH) was used. In the process of low-energy or physicochemical, the DPE process was employed. A deep understanding of input factors which influence the associated output responses of both methods was achieved. The optimization using the desired function provided a unique range of critical process parameters within the design space, where nanoemulsions with similar mean particle sizes of 275 nm could be achieved with equal composition, by both HPH and DPE processes. This work is under submission process for publication.

Appendix was a collaboration work for a book chapter. It summarized the principles of the formulation to develop nanoemulsions of an esthetic level and relates some specific applications, targeting cosmetic field. The chapter begins with a section on methods of obtaining nanoemulsion via high- and low-energy, pointing out their most relevant advantages, disadvantages and fundamental parameters. It also includes formulation parameters for controlling the stability and offering highly desirable sensory characteristics with functional performance. The end of the chapter provides a summary of the context and needs of the skin, hair care and scalp care, as well as the recent nanoemulsion researches on these fields. This work is under publication process.

JUSTIFICATION

Nanoemulsion is an oil-in-water or water-in-oil nanoscaled emulsion with the advantage over other nanostructured systems by allowing a high concentration of liquid lipid phase in its core, increasing the solubility of poorly water-soluble drugs. Virgin olive oil shows extensive applicability in several fields, providing anti-oxidant properties and acting as a drug carrier in the nanoemulsion system. One of the most used high-energy processes for obtaining nanoemulsion is the High-Pressure-Homogenization (HPH), and the Phase Inversion Temperature (PIT) in the low-energy process. Nevertheless, the conversion of vegetable oil into a nanoscaled emulsion by a conventional low-energy process, as PIT, is considered a challenge, due to the complex structure of vegetable oils compared to the most used hydrocarbon oils. Therefore, the D-Phase Emulsification method (DPE) has been explored as an alternative process to overcome this difficulty. Although the first studies of this process had been presented decades ago (most in the Japanese language), the advances in understanding mechanisms of DPE were modest. Therefore, a deeper study of this process is required to elucidate this unique low-energy process. Additionally, the design space, within the quality by design environment, targets the better understanding of the product and process aiming to improve the quality and safety of the final product. Thus, the appropriate statistical approach, as the experimental design applied in this study, rationally conducted the study of process and composition variables for HPH and DPE process, as well as their preparation optimization. Therefore, the present study offers significant benefits to the formulator and to the consumer. The acquired knowledge will allow the development of innovative products, expanding the perspectives of the application of nanoemulsions in the pharmaceutical and cosmetic fields, thus justifying the present work.

FINAL CONCLUSION

The proposal of this present study was to achieve a deep understanding of the preparation process and the applicability of nanoemulsion by high and low energy methods. These goals were successfully accomplished through the survey and systematization of the performed activities, within the scope of new search to be undertaken in the nanostructure systems. This careful systematization of knowledge provided two review articles and two research articles, which highlight the nanoemulsion as a potential alternative drug carrier. In the first review article, we found that the challenges for the development of a high efficacy nanoemulsion refer to the elucidation of the interactions between the drug and nanoemulsion's components; the investigation of the impact of the manufacturing process on the formulation composition and drug stability. Also, a better understanding of the influence of nanoemulsion formulation on drug release and drug uptake by different routes of administration is needed. The second review article clearly evidenced that the key factor for nanoemulsion preparation is the selection of the most suitable process, which ensure the desired properties of the final obtained nanodroplets. This review offers to the formulator a realistic commercial scale alternative for this emerging field of nanotechnology. Further studies need to carry out aiming in-depth understanding in how the oil–surfactant–water phases interact during the processing time and storage, according to the composition and the process selected.

The experimental study resulted in two research articles. The first one we concluded that it is possible to obtain a nanoemulsion with high vegetable oil content with low surfactant concentration. These features emphasized the unique property of the DPE method, enabled by presence of polyol, which provided the synergistic benefit when used in combination with single surfactant. The polyol was confirmed to be the statistically significant variable for MPS reduction of the nanoemulsion, influencing the behavior of phase transition structure in this method. The synergistic interaction between the polyol and the hydrophilic surfactant modified its apparent HLB, provided in this low energy process a

distinctive phenomenon. In the second research article, a systematic design of experiments approach was successfully applied to identify and understand the relationship between input factors and their associated output response in the development of olive oil nanoemulsion, by HPH and DPE processes. This approach allowed identify the optimized ranges of the input parameter and improved the process understanding, bringing the output response into the specification range (CQA). Implementation applying RSM optimization provided a unique range of CPP within the design space, where nanoemulsions with similar mean particle sizes of 275 nm could be achieved with equal composition, for both HPH and DPE processes.

These knowledges provided directions that might elucidate the performance of a particular nanoemulsion system as drug delivery. It also indicated the significant challenges and the multiple benefits of nanoemulsion, which has the potential to shape the future of pharmaceutical and cosmetic products.

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