The 9th International Electronic Conference on Medicinal Chemistry (ECMC 2023)

01–30 November 2023 | Online

# Single or Mixed edge activators: a Shift in transfersomes properties?

Chaired by **Dr. Alfredo Berzal-Herranz** and **Prof. Dr. Maria Emília Sousa**

*pharmaceuticals* MDPI


**João Vieira [1,2]*, Jéssica Castelo[3] , Íris Guerreiro[1,2], Marta Martins[1,2], Marta Rodrigues[4], Ana Sofia Fernandes[1], Nuno Saraiva[1], Catarina Rosado[1], Catarina Pereira-Leite[1,5]**

[1] CBIOS, Universidade Lusófona´s Research Center for Biosciences & Health Technologies, Campo Grande 376, 1749-024, Lisbon, Portugal
[2] Department of Biomedical Sciences, University of Alcalá, Ctra. Madrid-Barcelona Km. 33.600, Alcalá de Henares, 28871, Madrid, Spain
[3] School of Health Sciences and Technologies, Universidade Lusófona– Centro Universitário de Lisboa, Campo Grande 376, 1749-024, Lisbon, Portugal
[4] School of Psychology and Life Sciences, Universidade Lusófona – Centro Universitário de Lisboa, Campo Grande 376, 1749-024, Lisbon, Portugal
[5] LAQV, REQUIMTE, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto , R. de Jorge Viterbo Ferreira 228, 4050-313, Porto, Portugal

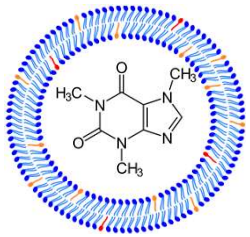
cbios INTEGRATED HEALTH STRATEGIES UNIVERSIDADE LUSÓFONA • LISBOA • PORTUGAL
UNIVERSIDADE LUSÓFONA
ects escola de ciências e tecnologias da saúde
Universidad de Alcalá
LAQV requimte
FCT Fundação para a Ciência e a Tecnolcgia MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

* Corresponding author: joao.manuel.vieira@ulusofona.pt

The 9th International Electronic Conference on Medicinal Chemistry
01–30 November 2023 | Online

# Single or Mixed edge activators: a shift in transfersomes properties?

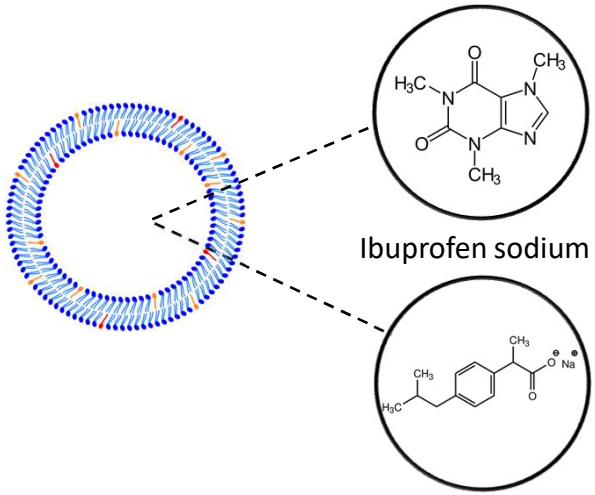
## A Preliminary Study



Tween® 80

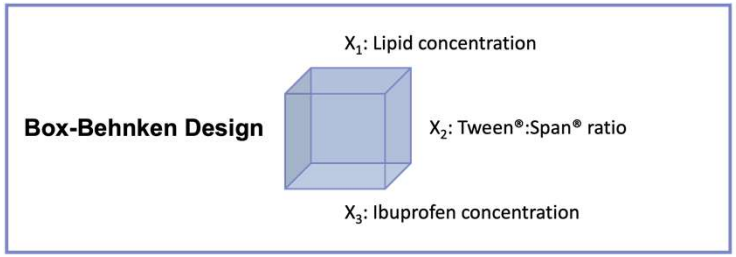
Span® 80

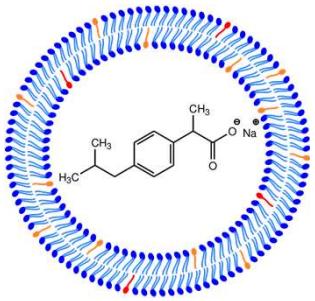
Caffeine



Ibuprofen sodium salt

## B Mixed Edge Activators – An innovative optimization



Optimized formulation

**Potential for skin delivery**

Proper vesicle size and PDI

Suitable storage stability

Biocompatible

## Abstract:

Transfersomes, a novel lipid-based vesicular system, have revolutionized drug delivery by improving the skin delivery of bioactive compounds. These deformable lipid vesicles are composed of phospholipids and edge activators (EA), which play a crucial role in conferring flexibility and deformability to the vesicles, thereby enabling efficient drug loading as well as an improved drug transport across biological barriers. Traditionally, transfersomes have a single EA; however, recent research suggests the benefits of mixing different edge activators to optimize their performance. Quality-by-design strategies, like Box-Behnken factorial design (BBD) offer a valuable manner to develop new formulations. This study aimed to assess the impact of single or mixed EA on transfersomes´ physicochemical properties and their cytotoxicity profile. Transfersomes were prepared with and without two model drugs, ibuprofen sodium salt (IBU) and caffeine. The effect of EA on transfersomes physicochemical properties was evaluated by measuring vesicle size (Vs), polydispersity index (PDI), encapsulation efficiency (EE), and loading capacity (LC) during 60 days of storage. Moreover, In vitro cytotoxicity studies were performed using HaCaT cells. All formulations whether composed of single or mixed EA, presented interesting results (Vs < 300 nm, and PDI < 0.3), considering the cutaneous delivery target. IBU exhibited good EE and LC, while caffeine encapsulation requires improvement. These results remained stable under refrigerated conditions for at least 30 days. Additionally, cell viability assays indicated transfersomes´ compatibility with human keratinocytes. Overall, by combining the distinct physicochemical properties of diverse edge activators it was possible to tailor transfersomes as skin delivery carriers, enhancing their characteristics and addressing challenges related to the colloidal stability.

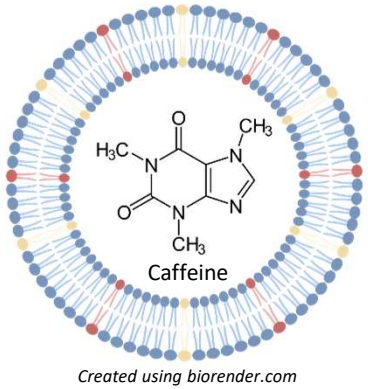
**Keywords:** transfersomes; nanovesicular systems; edge activators; physicochemical properties; cytotoxicity.

# Introduction

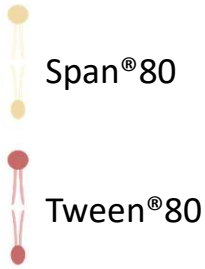
## *Preliminary study*

**Aim: Evaluate edge activators ratio impact on transfersomes**

**Starting point:** pre-optimized formulation




*Created using biorender.com*




EA:Lipid ratio (15:85)

**New defined ratios**

| Tween®80 : PC (w/w) | Span®80 : PC (w/w) |
|---|---|
| 15:85 | - |
| 7.5:85 | 7.5:85 |
| - | 15:85 |

**Analysis**

- Physicochemical characterization (Vs and PDI)
- Storage stability studies
- Cytotoxicity assay

Biomedical and Biopharmaceutical Research
Jornal de Investigação Biomédica e Biofarmacêutica
Biopharmaceutical Sciences | *Ciências Biofarmacêuticas* *Biomed Biopharm Res.*, 2021; 18(2):238-251
doi: 10.19277/bbr.18.2.267

**Single *versus* mixed edge activators in caffeine-loaded transfersomes: physicochemical and cytotoxicity assessment**

*Ativadores de superfície únicos* versus *mistos em transferossomas para veicular cafeína: avaliação físico-química e de citotoxicidade*

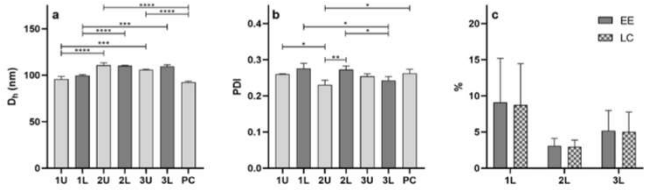
Íris Guerreiro [1,2#], Marta Rodrigues [3#], Ana Sofia Fernandes [1], Catarina Rosado [1], Catarina Pereira-Leite [1,4*]

# Results and discussion

## *Preliminary study*

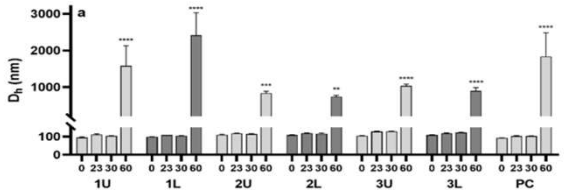
### ***Physicochemical Properties***

- Vs **varied** according to the **type of EA** used



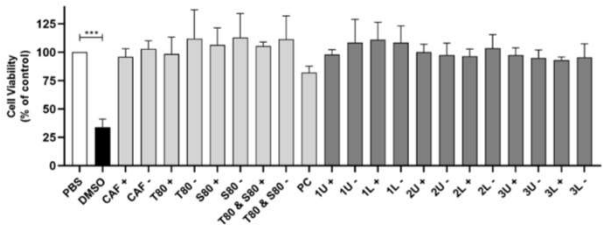

### ***Storage stability***

- Properties remained stable for **1 month**




### ***Cytotoxicity***

- All formulations were compatible with **HaCaT cells** upon 24 h treatment

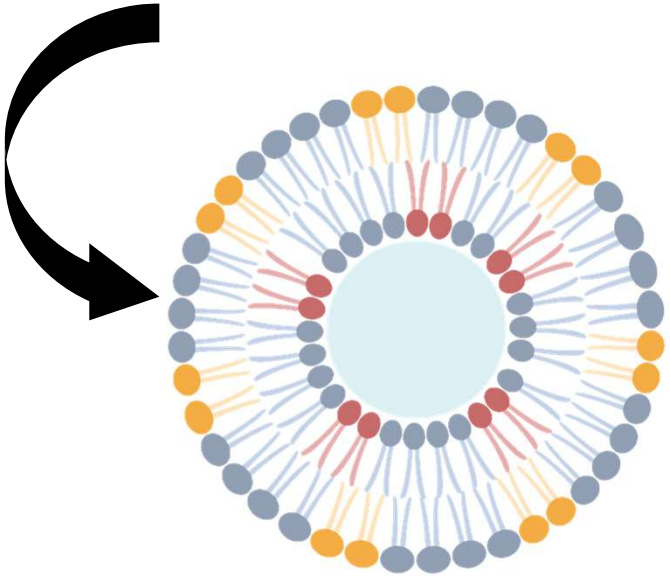



Doi:10.19277/bbr.18.2.267

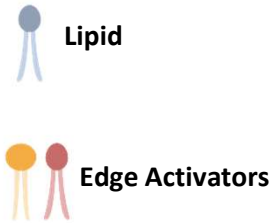
Vs: Vesicle Size

# Conclusions

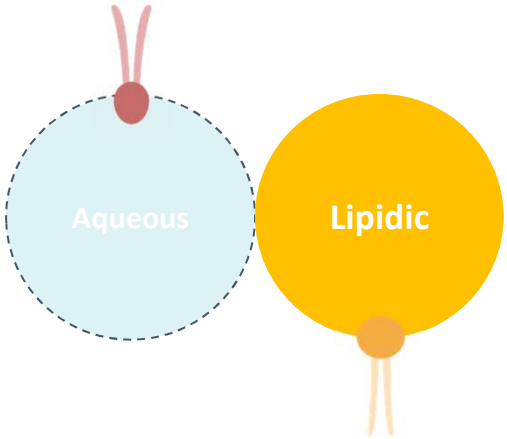
## Question: Single or Mixed edge activators?



*Created using biorender.com*



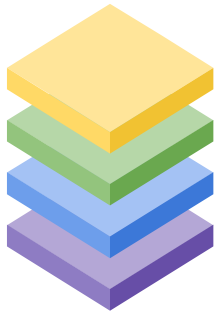

**Transfersomes = 2 compartments**




*Is there potential in combining both moieties?*

**Explore the possibility of mixing EA!**

# Introduction



## Aim: Mixed edge activators – An innovative optimization

- **Box-Behnken design** (BBD) strategy
- **Optimization** of a ibuprofen-loaded transfersomal formulation
- **Experimental validation** of BBD theoretical predicitions
- **Cytotoxicity** in a 3D HaCaT cultures
- **Storage** stability

| Optimized content | | |
|---|---|---|
| [Pc] % (w/v) | EA ratio | [Ibu] % (w/v) |
| 4 | 2.5:12.5 | 0.125 |

Doi:10.3390/pharmaceutics15041209

Pc: Soy Phosphatidylcholine | EA: Edge Activator | Ibu: Ibuprofen

# Results and discussion

***Model validation***

- Experimental results **validated** BBD model

***Cytotoxicity:***

- Transfersomes **did not impact** cell **death**

***Storage stability:***

- Stable for **2 months**

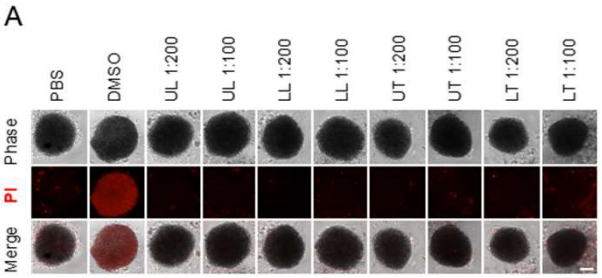
pharmaceutics
MDPI

Article

**Mixed Edge Activators in Ibuprofen-Loaded Transfersomes: An Innovative Optimization Strategy Using Box–Behnken Factorial Design**

João Vieira [1,2], Jéssica Castelo [3], Marta Martins [1,2], Nuno Saraiva [1], Catarina Rosado [1] and Catarina Pereira-Leite [1,4,*]

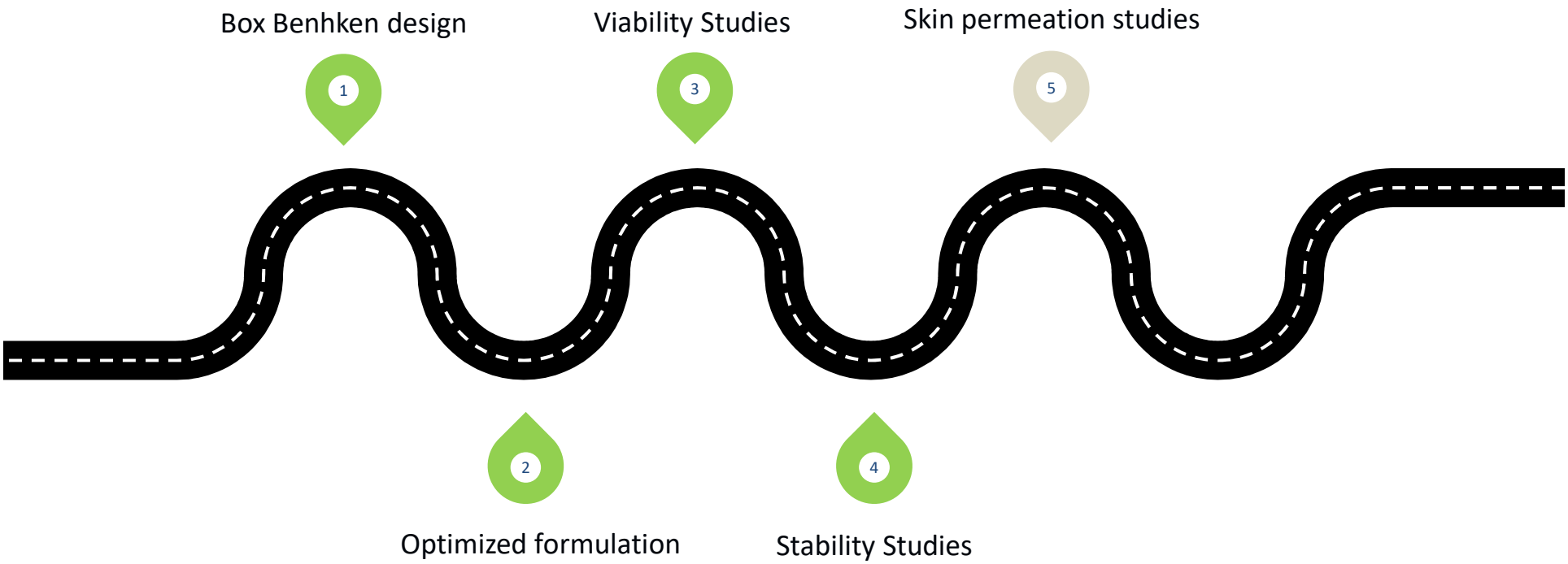
| BBD responses (Theoretical vs Experimental) | | | | |
|---|---|---|---|---|
| | Size | PDI | EE | LC |
| Theoretical | 153.1 | 0.19 | 34 | 1.1 |
| Experimental | 166 ± 20 | 0.23 ± 0.03 | 34 ± 9 | 1.1 ± 0.3 |




Doi:10.3390/pharmaceutics15041209

UL: Unloaded Lipossomes | LL: Loaded Lipossomes | UT: Unloaded Transfersomes | LT: Loaded Transfersomes

# Conclusions



## Acknowledgments

This research was funded by national funds through FCT – Foundation for Science and Technology, I.P., under the EXPL/BTM-MAT/0112/2021, UIDB/04567/2020, and UIDP/04567/2020 projects attributed to CBIOS and by the research grants attributed to J.V, M.M. (UI/BD/151424/2021) and I.G. (2020.07813.BD). The APC was funded by FCT – Foundation for Science and Technology, I.P., EXPL/BTM-MAT/0112/2021 project.

# THANKS!

**Any questions?**

You can find me at:
✗ joao.manuel.vieira@ulusofona.pt