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Ionic liquids: game changers for the development of controlled delivery systems?

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

pharmaceuticals MDPI

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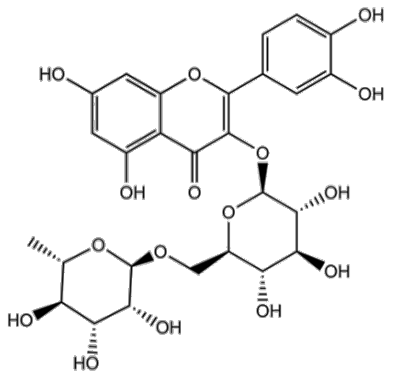
Ionic liquids: game changers for the development of controlled delivery systems?

Ionic Liquids

Controlled Delivery Systems



Lipidic Implants

- Easier to formulate
- Less material loss
- Facilitated drug incorporation
- Improved drug release
- Wrinkled surface

TransfersomILs

- Smaller size
- Higher drug loading
- Enhanced total drug release
- Improved storage stability

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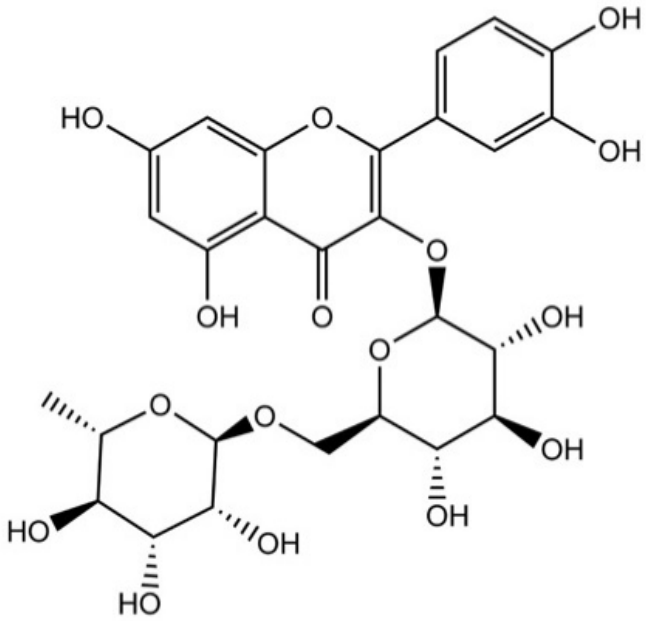
Abstract

Poor drug solubility or loading, inflexible drug release profiles, and poor storage stability are some of the most difficult issues to surpass in the production of efficient and safe controlled delivery systems. Due to their suitable properties, ionic liquids (ILs) may be used as new functional materials to overcome these drawbacks. ILs are organic salts, that may be introduced in different types of drug delivery systems. Herein, 5 ILs were synthesized and their applicability in drug delivery systems was evaluated. Firstly, their cytotoxicity in human keratinocytes was determined, and considering these results, controlled drug delivery systems with or without ILs were developed. Each IL was incorporated at their upper concentration allowing the maintenance of cell viability. Lipidic im-plants and transfersomes (TransfersomILs) were the chosen lipid-based controlled delivery systems to investigate the impact of adding ILs. In these studies, rutin was used as model drug with poor aqueous solubility. Our results showed that ILs promoted a significantly higher drug loading, with choline-based ILs displaying better results when compared with imidazole-based ILs. The incorporation of ILs seems to modulate the drug release profile from lipidic implants. TransfersomILs had a higher association efficiency, higher total amount of drug release and better colloidal and storage stability when compared with conventional transfersomes. In conclusion, the incorporation of ILs, at non-toxic concentrations, allowed the development of more efficient delivery systems, showing that ILs may be multifunctional and valuable materials to boost performance.

Keywords: Controlled delivery systems, Ionic liquids, Lipidic implants, Rutin, TransfersomILs.

Model compound: Rutin

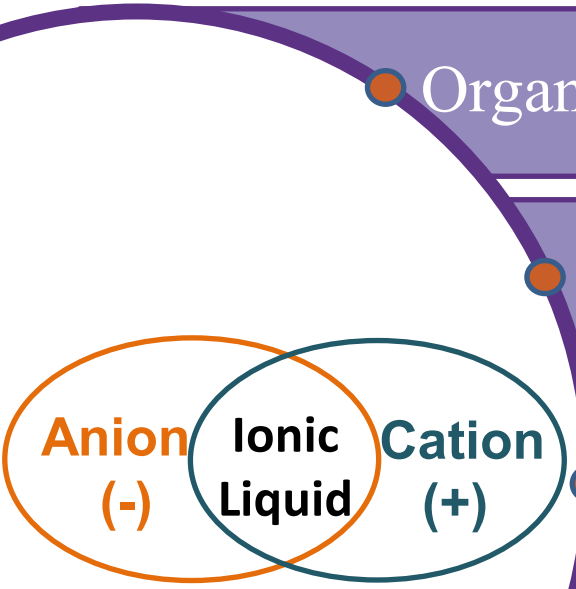


Flavonoid

Buckwheat

Poor aqueous solubility (0.2 mg/mL)

Ionic Liquids



- Organic salts
- Melting point below 100 °C
- High thermal and chemical stability
- May be introduced in different solutions
- May be tailored to achieve the desired properties

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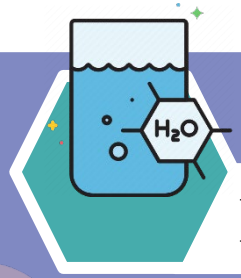
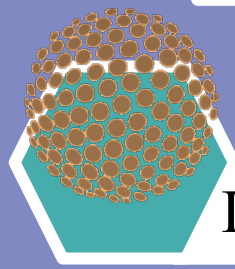


Enhance drug solubility

Drug Dev. Ind. Pharm, **2017**
Biomed Biopharm Res, **2018**

Ensure a higher drug loading

Pharmaceutics, **2018**
Biomolecules, **2020**



IL-polymer nanoparticles hybrid systems with higher performance

Nanomaterials, **2019**
J Drug Deliv Sci Tec, **2020**

Development of new controlled drug delivery systems and evaluation of the impact of ILs on their performance

Controlled drug delivery

Advantages

Maintenance of therapeutic dosage

Reduction of side effects

Targeted delivery

1) Lipidic implants

Sustained release and delivery

Targeted delivery

Low drug solubility and loading

Formulation difficulties

2) Transfersomes

Easy to produce

Drug protection

Low stability of the developed systems

Inadequate release profile

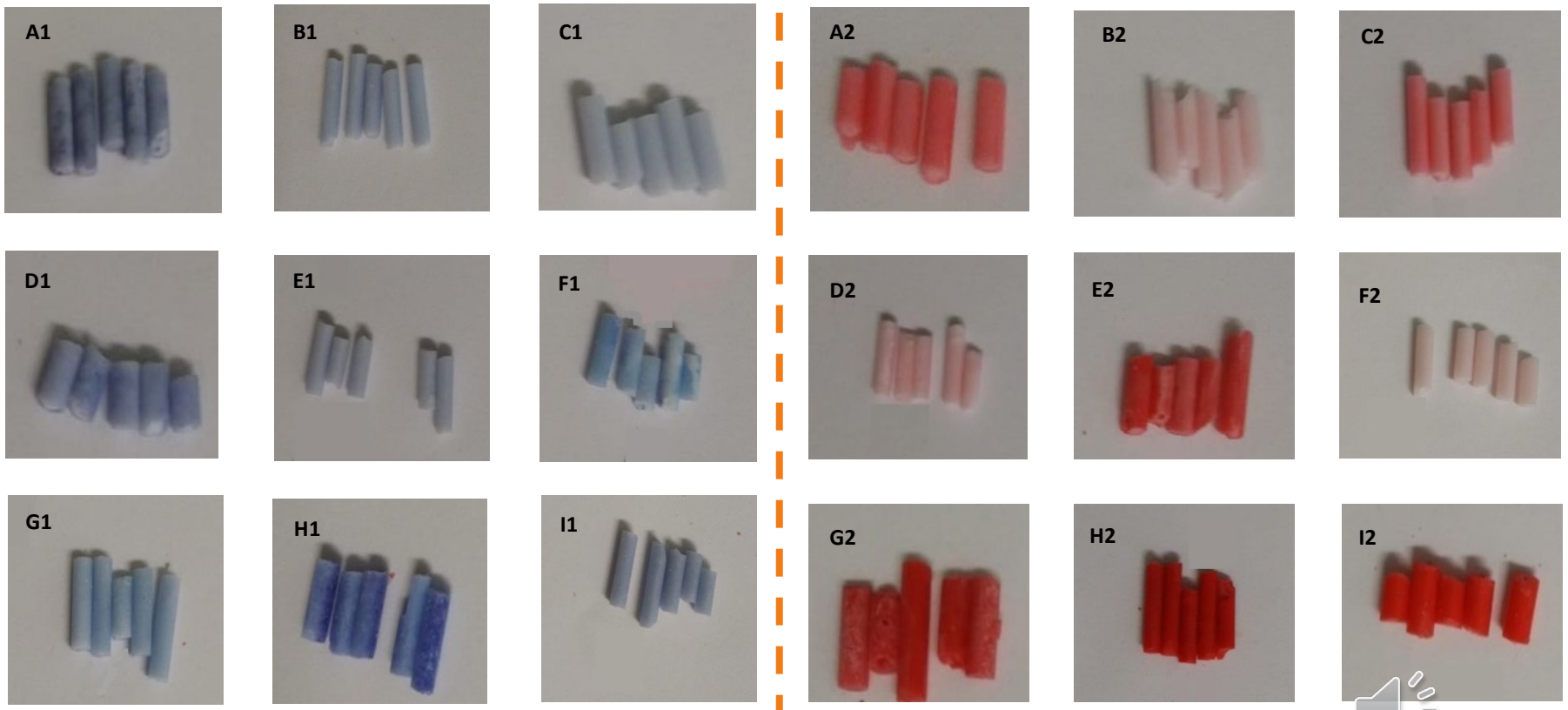
1) Lipidic Implants

Composition

Formulation	% w/w					
	Dynasan® 118	Gelucire® 50/02	Sucrose	[Cho][Phe]	[Cho][Glu]	Drug
A		-	-	-	-	
B		-	-	0.2	-	
C		10.0	-	-	-	
D		10.0	-	0.2	-	
E	q.b. 100.0	-	10.0	-	-	-
F		-	10.0	0.2	-	
G		-	-	-	0.2	
H		10.0	-	-	0.2	
I		-	10.0	-	0.2	
A_{Drug}		-	-	-	-	
B_{Drug}		-	-	0.2	-	
C_{Drug}		10.0	-	-	-	
D_{Drug}		10.0	-	0.2	-	
E_{Drug}	q.b. 100.0	-	10.0	-	-	10.0
F_{Drug}		-	10.0	0.2	-	
G_{Drug}		-	-	-	0.2	
H_{Drug}		10.0	-	-	0.2	
I_{Drug}		-	10.0	-	0.2	

1) Lipidic Implants

Content uniformity

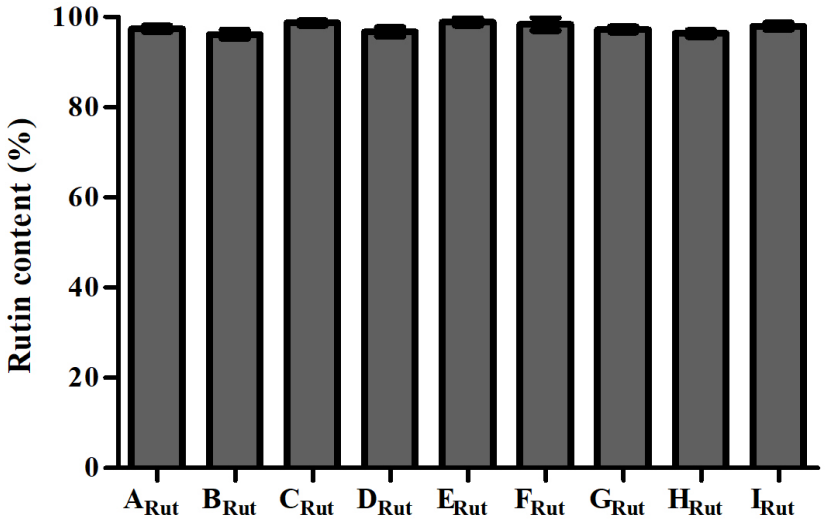


Hydrophilic Dye - **Methylene Blue**

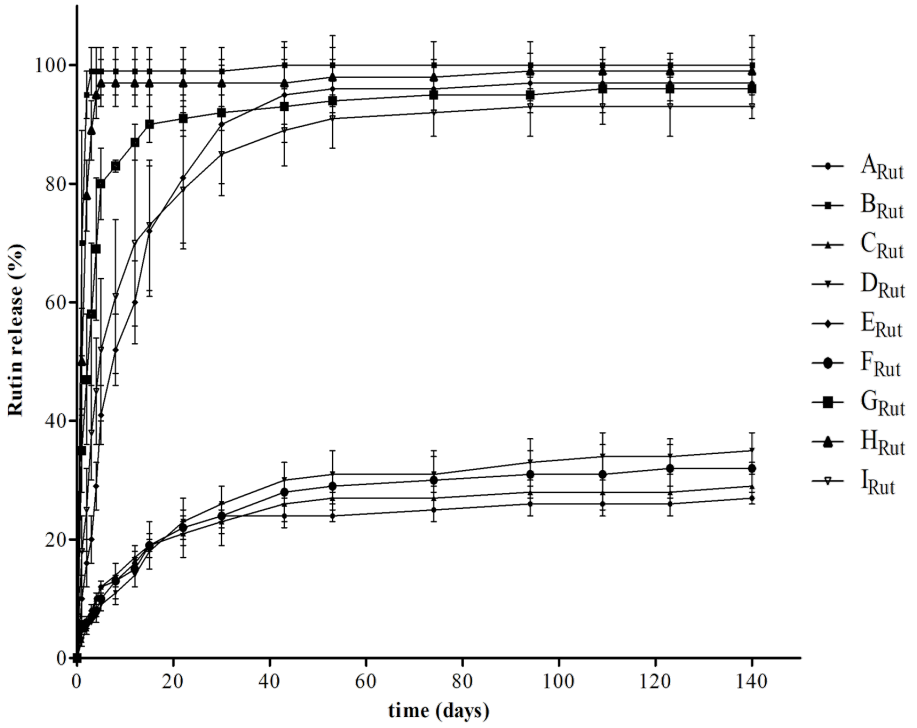
Lipophilic Dye - **Sudan III**

1) Lipidic Implants

Drug Content



Drug Release



1) Lipidic Implants

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Article

Biobased Ionic Liquids as Multitalented Materials in Lipidic Drug Implants

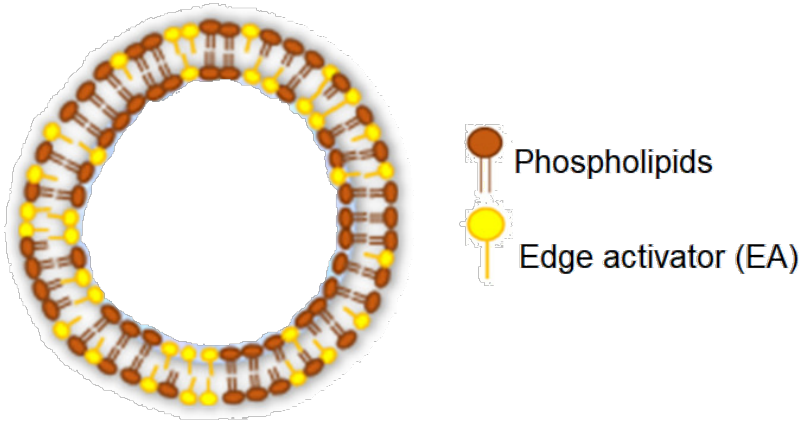
Ana Júlio [1,2], Anaisa Sultane [1], Ana Silveira Viana [3], Joana Portugal Mota [1] and Tânia Santos de Almeida [1,3,*]

The studied ILs :

- Facilitate the formulation
- Favour the drug incorporation
- Allow to attain drug uniformity
- Modify the drug release profile

2) Transfersomes

- ✓ Phospholipid: soy phosphatidylcholine
- ✓ EA: Tween® 80
- ✓ Produced by the thin-film hydration method followed by sonication



2) Transfersomes

↓ Better colloidal stability

Higher drug loading

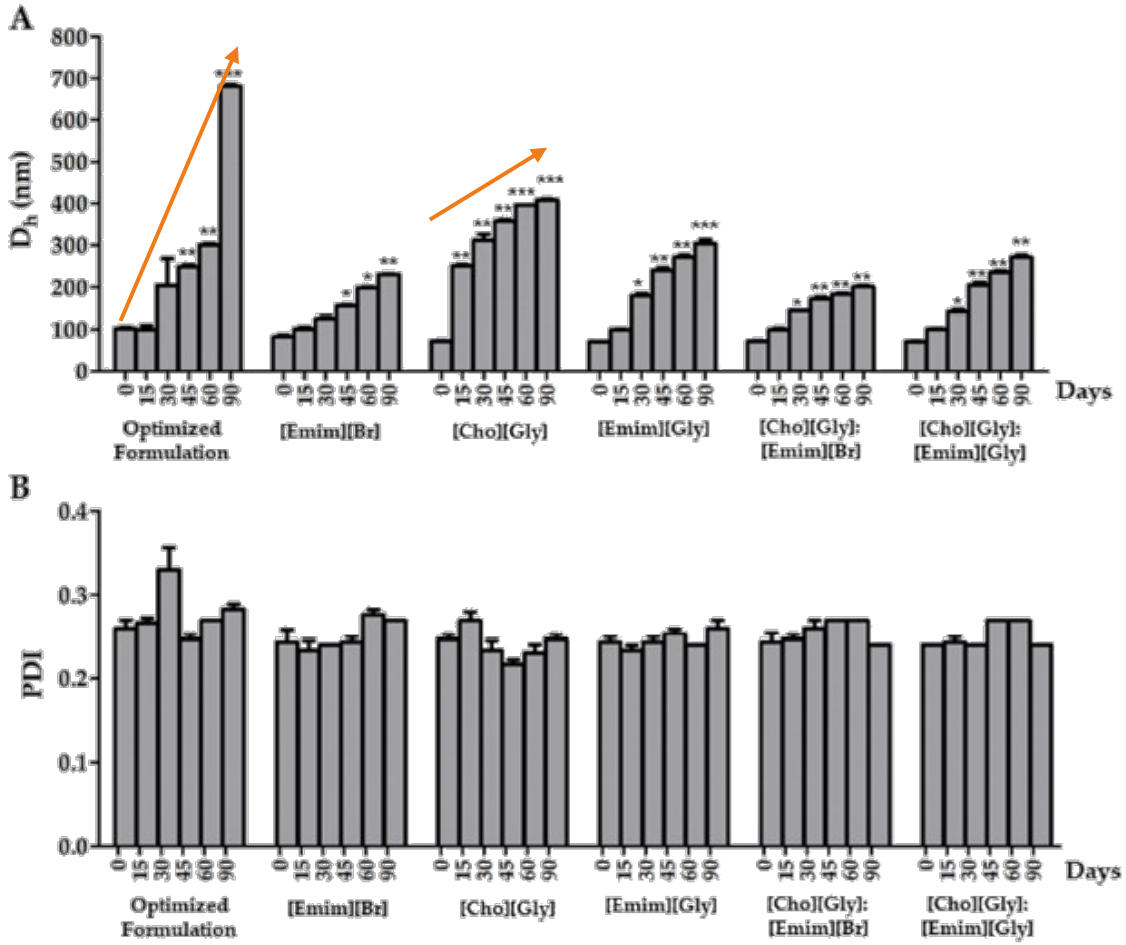
Characterization

Formulation	Rutin (mg/mL)	IL (%)	D_h (nm)	PDI	ZP (mV)	AE (%)	LC (%)
Water	0	0	111 ± 5	0.22 ± 0.01	-	-	-
	0.21	0	102 ± 3	0.26 ± 0.01	−31 ± 3	86.3 ± 2.1	0.43 ± 0.01
Water:[Emim][Br]	0.22	0.2	83 ± 4 *	0.24 ± 0.02	−36 ± 2	82.1 ± 5.2	0.43 ± 0.01
Water:[Cho][Gly]	1.50	0.2	73 ± 2 **	0.25 ± 0.01	−41 ± 4 *	98.1 ± 0.1 **	3.68 ± 0.01 ***
Water:[Emim][Gly]	1.60	0.2	71 ± 1 **	0.24 ± 0.01	−39 ± 5 *	98.7 ± 0.1 **	3.70 ± 0.02 ***
Water: [Cho][Gly]:[Emim][Br]	0.79	0.1:0.1	72 ± 1 **	0.24 ± 0.01	−38 ± 3 *	93.6 ± 0.2 *	2.20 ± 0.01 ***
Water: [Cho][Gly]:[Emim][Gly]	0.92	0.1:0.1	73 ± 1 **	0.24 ± 0.01	−36 ± 3	97.9 ± 0.1 **	1.76 ± 0.01 ***

IL, ionic liquid; D_h, hydrodynamic diameter; PDI, polydispersity index; ZP, zeta potential; AE, association efficiency; LC, loading capacity. $n = 3$, mean ± SD, * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

2) Transfersomes

Storage stability

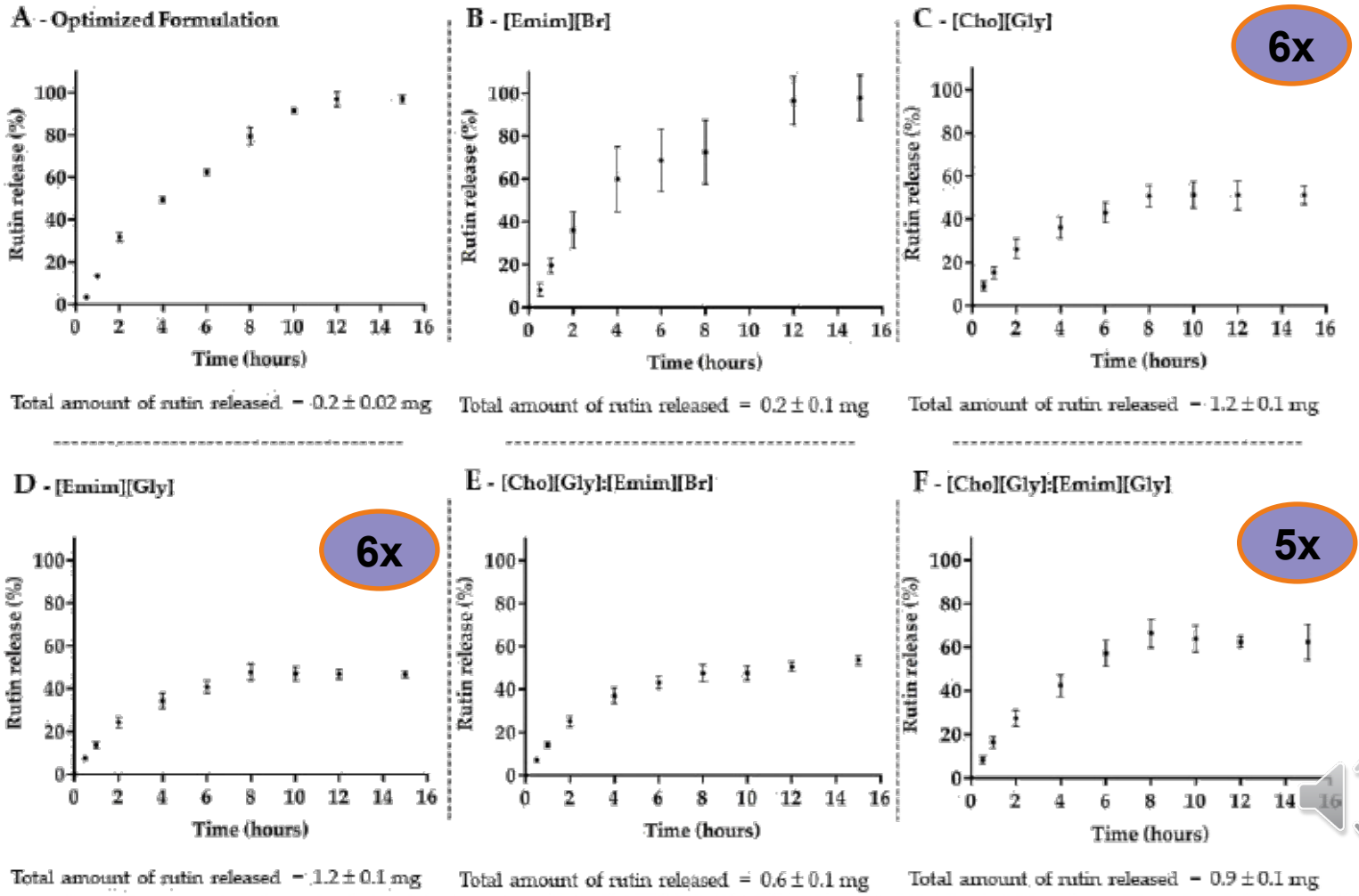


[Cho][Gly]: less pronounced increase

Júlio A *et al*. *Nanomaterials*. 2022

2) Transfersomes

In vitro release



2) Transfersomes

nanomaterials
MDPI

Article

TransfersomILs: From Ionic Liquids to a New Class of Nanovesicular Systems

Ana Júlio [1,2], João Guilherme Costa [1], Catarina Pereira-Leite [1,3,#] and Tânia Santos de Almeida [1,4,#,*]

The studied ILs :

- Facilitate the formulation
- High drug loading
- Promote storage stability
- Promissing physicochemical properties for skin delivery

Júlio A *et al. Nanomaterials*. 2022

General Conclusions

ILs at non-toxic concentrations facilitate the formulation procedures

The developed sustained delivery systems, containing ILs, are stable

Potential of combining ILs with controlled drug delivery systems

ILs modify the release profile of the lipidic implants and allow drug uniformity

ILs favor drug incorporation

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