



The 7th International Electronic Conference on Medicinal Chemistry (ECMC 2021)

01-30 NOVEMBER 2021 | ONLINE

Ionic liquids as an innovative solution to improve the delivery of phenolic compounds

**Ana Júlio^{1,2}, Rita Caparica^{1,2}, Filipe Fernandes³, Maria Eduarda M. Araújo⁴,
Tânia Santos de Almeida^{1,4,*}**

¹ CBIOS-Universidade Lusófona's Research Center for Biosciences & Health Technologies, Lisbon, Portugal

² Department of Biomedical Sciences, University of Alcalá, Ctra., Madrid, Spain

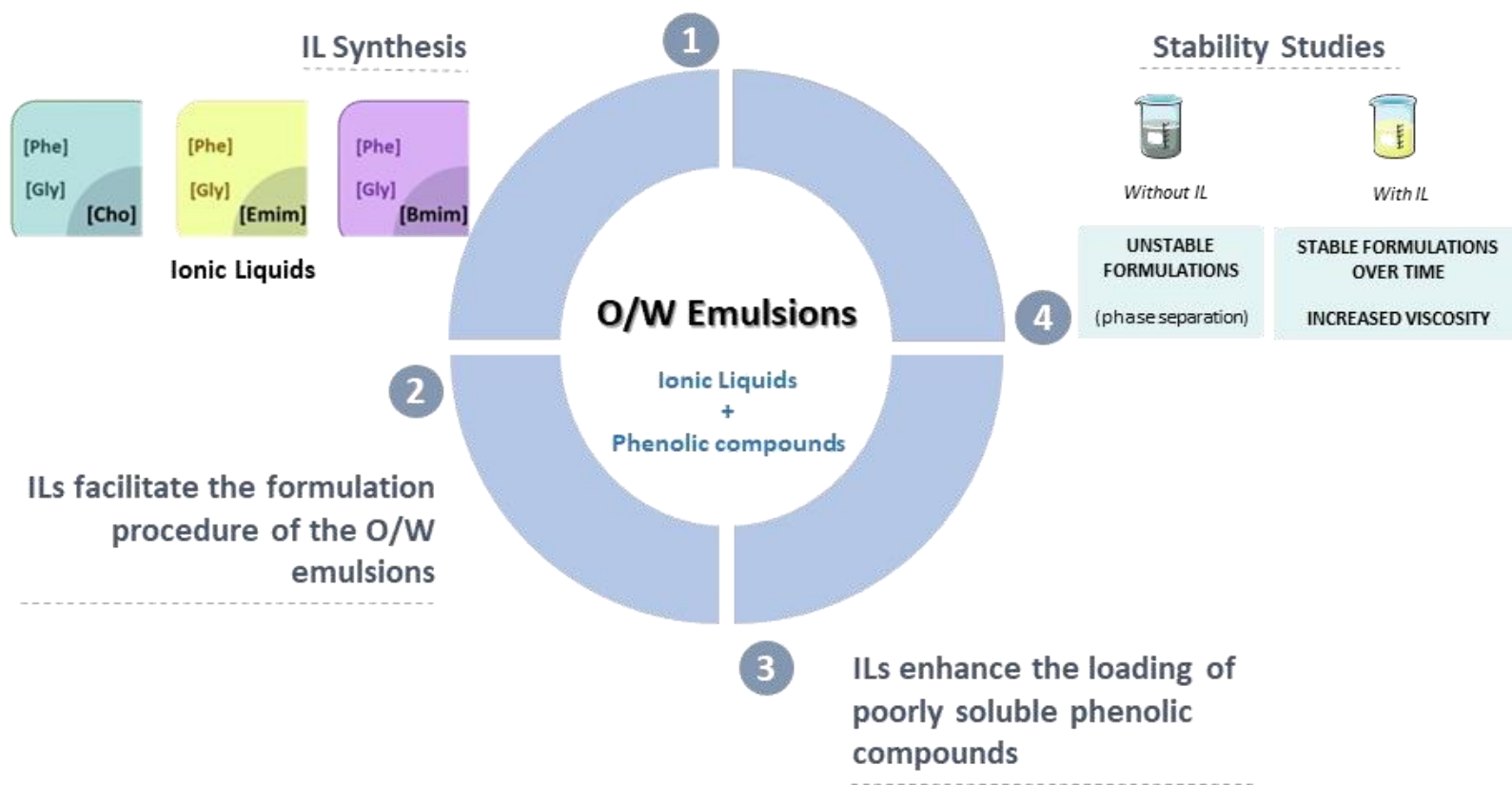
³ School of Sciences and Health Technologies, Lusófona University, Lisbon, Portugal

⁴ Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal

* Corresponding author: tania.almeida@ulusofona.pt



Ionic liquids as an innovative solution to improve the delivery of phenolic compounds



Abstract:

Phenolic compounds, such as ferulic, caffeic and *p*-coumaric acids and rutin, are commonly present in natural resources, for example plants (e.g. eggplant), cereals (e.g. rice), vegetables (e.g. beans) and fruits (e.g. oranges). Several studies have already demonstrated their potential on the pharmaceutical and cosmetic fields, as antioxidant, anti-inflammatory and anticancer. However, these compounds have a low aqueous solubility, restricting their applicability.

Ionic liquids (ILs) can act as multifunctional excipients, namely, to enhance drug solubility and incorporation into various delivery systems.

In this work six ILs containing natural amino acids, (2-hydroxyethyl)trimethylammonium phenylalaninate [Cho][Phe], (2-hydroxyethyl)trimethylammonium glycinate [Cho][Gly], 1-ethyl-3-methylimidazolium phenylalaninate [Emim][Phe], 1-ethyl-3-methylimidazolium glycinate [Emim][Gly], 1-butyl-3-methylimidazolium phenylalaninate [Bmim][Phe] and 1-butyl-3-methylimidazolium glycinate [Bmim][Gly], were prepared and their impact on the incorporation of the four phenolic compounds, in O/W emulsions, was evaluated.

The use of ILs allowed the incorporation of higher amounts of the studied drugs, since their solubility was enhanced. They also led to more viscous emulsions, improving the stability of the formulations.

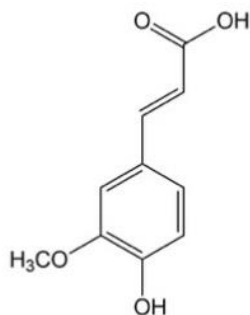
Keywords: ionic liquids; O/W emulsions; phenolic compounds; upgraded formulations.



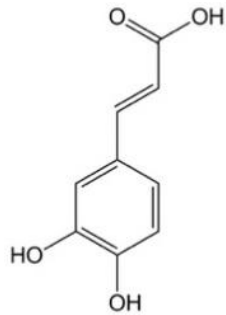
The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

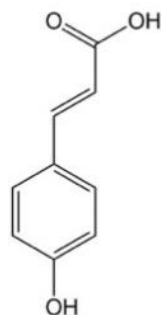
Phenolic compounds



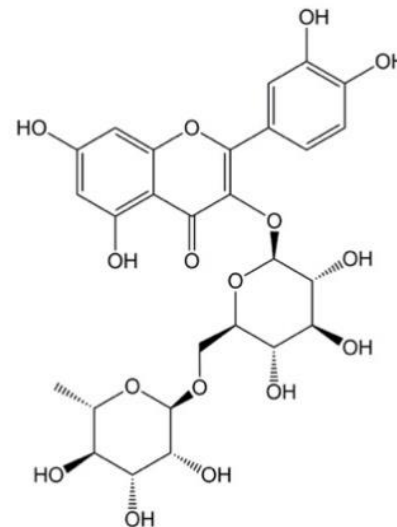
Ferulic acid



Caffeic acid



p-Coumaric acid



Rutin

**Present in natural
resources**

**Several applications in
the pharmaceutical and
cosmetic fields**



Ionic Liquids

Organic salts

Melting point below 100 °C

Anion (-) Ionic Liquid Cation (+)

High thermal and chemical stability

May be introduced in different solutions

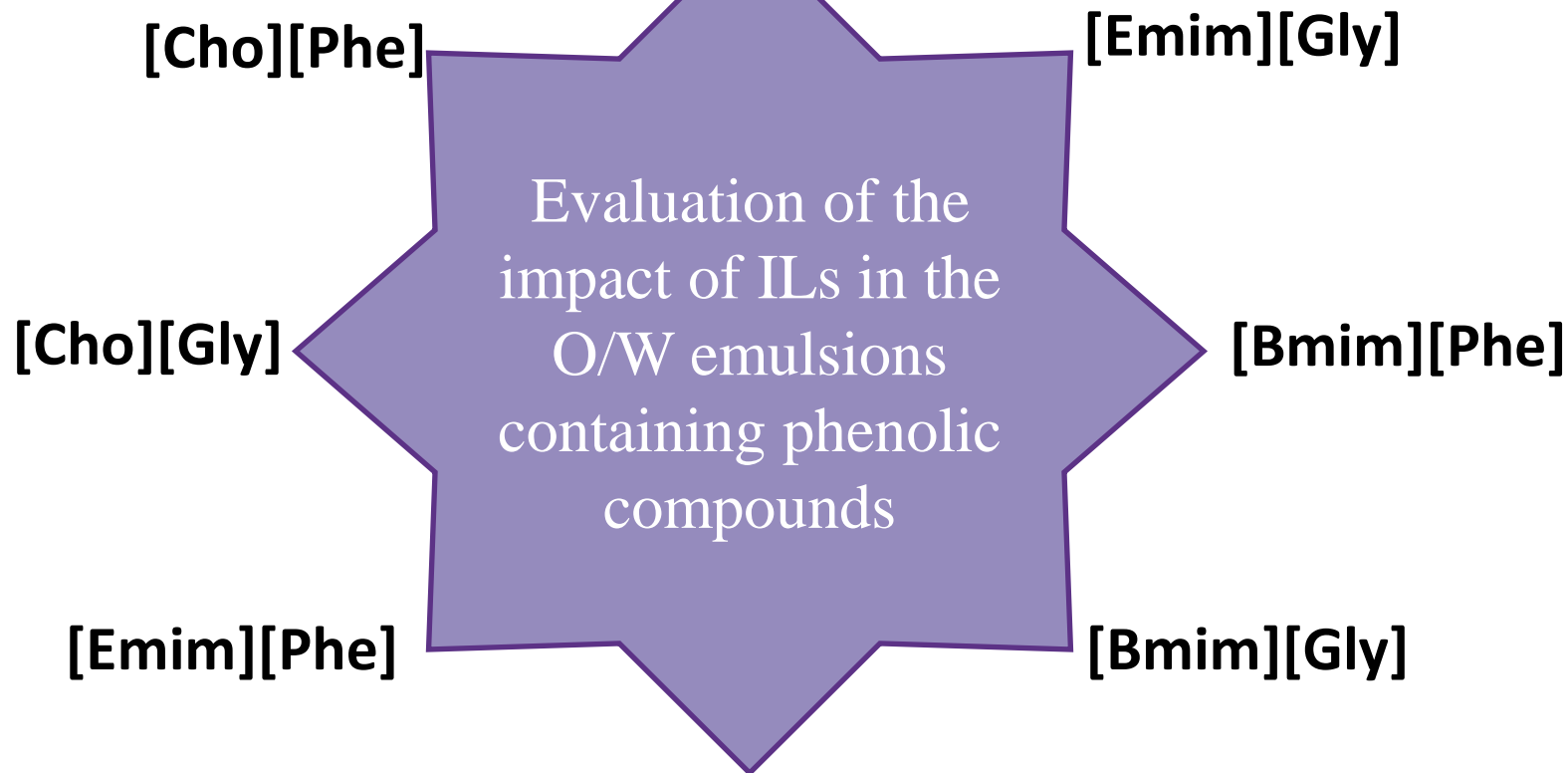
May be tailored to achieve the desired properties



The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

Aim



The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

Results and Discussion

Table 1: Results from the stability studies of the O/W emulsions prepared in the presence and absence of 0.2% (v/v) of each of the ILs (n = 3). Viscosity values were measured after formulation and following six temperature cycles (at -5 °C and 45 °C).

IL	% IL	After Formulation		Stability Studies		
		Visual Analysis	Viscosity (mPas)	After Centrifugation	After Gradual Heating	Viscosity (mPas) after 6 Temperature Cycles
Control	-	Stable	5170 ± 90	Unstable	Unstable	-
[Cho][Phe]	0.2	Stable	12,700 ± 102	Stable	Stable	15,400 ± 100
[Cho][Gly]	0.2	Stable	11,800 ± 52			13,100 ± 105
[Emim][Phe]	0.2	Stable	10,000 ± 132			12,400 ± 129
[Emim][Gly]	0.2	Stable	10,400 ± 188			13,100 ± 77
[Bmim][Phe]	0.2	Stable	9100 ± 80			11,000 ± 85
[Bmim][Gly]	0.2	Stable	9200 ± 120			11,400 ± 112

Caparica R., Júlio, A, *et al*, Int. J. Mol. Sci. 2021.



The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

Results and Discussion

Table 2: Results from the stability studies of the O/W emulsions prepared in the presence of each drug individually and in the presence or absence of the glycinate derived ILs (n = 3). Viscosity values were measured after formulation and following six temperature cycles (at -5 °C and 45 °C).

Drug	IL	% IL	After Formulation		Stability studies		
			Visual Analysis	Viscosity (mPas)	After Centrifuge	After Gradual Heating	Viscosity (mPas) after 6 Temperature Cycles
Ferulic Acid	Control 2a	-	Stable	8000 ± 80	Unstable	Unstable	-
	[Cho][Gly]	0.2	Stable	12,000 ± 75	Stable	Stable	12,500 ± 100
		0.5	Stable	13,700 ± 110			15,000 ± 90
	[Emim][Gly]	0.2	Stable	11,300 ± 100			12,000 ± 100
	[Bmim][Gly]	0.2	Stable	10,000 ± 130			12,600 ± 100
Control 2b	-	Stable	8500 ± 100	Unstable			Unstable
Caffeic Acid	[Cho][Gly]	0.2	Stable	11,000 ± 95	Stable	Stable	12,000 ± 90
		0.5	Stable	12,000 ± 100			15,500 ± 95
	[Emim][Gly]	0.2	Stable	11,200 ± 90			14,100 ± 80
	[Bmim][Gly]	0.2	Stable	11,000 ± 80			14,500 ± 90
	Control 2c	-	Stable	8200 ± 100			Unstable
<i>p</i> -Coumaric Acid	[Cho][Gly]	0.2	Stable	12,000 ± 100	Stable	Stable	15,500 ± 100
		0.5	Stable	13,500 ± 100			17,000 ± 90
	[Emim][Gly]	0.2	Stable	10,300 ± 90			14,600 ± 100
	[Bmim][Gly]	0.2	Stable	10,200 ± 100			14,000 ± 100
	Control 2d	-	Stable	7500 ± 150			Unstable
Rutin	[Cho][Gly]	0.2	Stable	12,800 ± 100	Stable	Stable	13,100 ± 105
		0.5	Stable	13,400 ± 90			16,000 ± 100
	[Emim][Gly]	0.2	Stable	10,400 ± 188			13,100 ± 77
	[Bmim][Gly]	0.2	Stable	9220 ± 50			11,140 ± 52

Caparica R., Júlio, A, *et al.*, Int. J. Mol. Sci. 2021.



The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

Results and Discussion

Table 3: Results from the accelerated and shelf-life stability studies of the O/W emulsions prepared in the presence of 0.2% (v/v) of each of the ILs and without the drug, in the presence of each drug individually with and without the glycinate derived ILs (n = 3). Viscosity values were measured after 90 days in an oven (40 ± 2 °C), in a refrigerator (5 ± 2 °C), or at room temperature.

Drug	IL	% IL	Viscosity after 90 days (mPas)		
			Accelerated Stability		Shelf Test
			Heating at Oven (40 ± 2 °C)	Cooling at Refrigerator (5 ± 2 °C)	Room temperature
Without Drug	[Cho][Phe]	0.2	15,500 ± 85	14950 ± 80	16,200 ± 65
	[Cho][Gly]	0.2	15,220 ± 50	15000 ± 80	16,050 ± 100
	[Emim][Phe]	0.2	12,200 ± 100	11950 ± 50	13,450 ± 70
	[Emim][Gly]	0.2	12,450 ± 100	12320 ± 100	14,120 ± 90
	[Bmim][Phe]	0.2	10,300 ± 50	10220 ± 100	11,000 ± 100
	[Bmim][Gly]	0.2	10,175 ± 50	10300 ± 70	11,110 ± 50
Ferulic Acid	[Cho][Gly]	0.2	15,500 ± 100	15,410 ± 50	16,250 ± 100
		0.5	16,300 ± 50	16,570 ± 110	17,120 ± 120
	[Emim][Gly]	0.2	12,320 ± 80	12,200 ± 50	14,200 ± 110
	[Bmim][Gly]	0.2	11,000 ± 50	10,900 ± 50	12,100 ± 100
Caffeic Acid	[Cho][Gly]	0.2	13,100 ± 50	13,310 ± 80	14,850 ± 50
		0.5	13,300 ± 60	13,140 ± 100	15,680 ± 50
	[Emim][Gly]	0.2	12,520 ± 100	12,600 ± 100	14,200 ± 150
	[Bmim][Gly]	0.2	12,100 ± 100	11,990 ± 100	14,620 ± 80
<i>p</i> -Coumaric Acid	[Cho][Gly]	0.2	13,250 ± 50	13,500 ± 100	16,000 ± 100
		0.5	13,900 ± 50	14,540 ± 100	17,120 ± 150
	[Emim][Gly]	0.2	11,950 ± 50	12,000 ± 100	14,850 ± 100
	[Bmim][Gly]	0.2	11,400 ± 50	11,355 ± 100	14,700 ± 100
Rutin	[Cho][Gly]	0.2	15,800 ± 50	16,000 ± 100	16,550 ± 120
		0.5	16,750 ± 60	17,010 ± 100	18,225 ± 115
	[Emim][Gly]	0.2	12,450 ± 50	12,800 ± 100	14,780 ± 100
	[Bmim][Gly]	0.2	11,500 ± 50	11,650 ± 100	12,380 ± 100

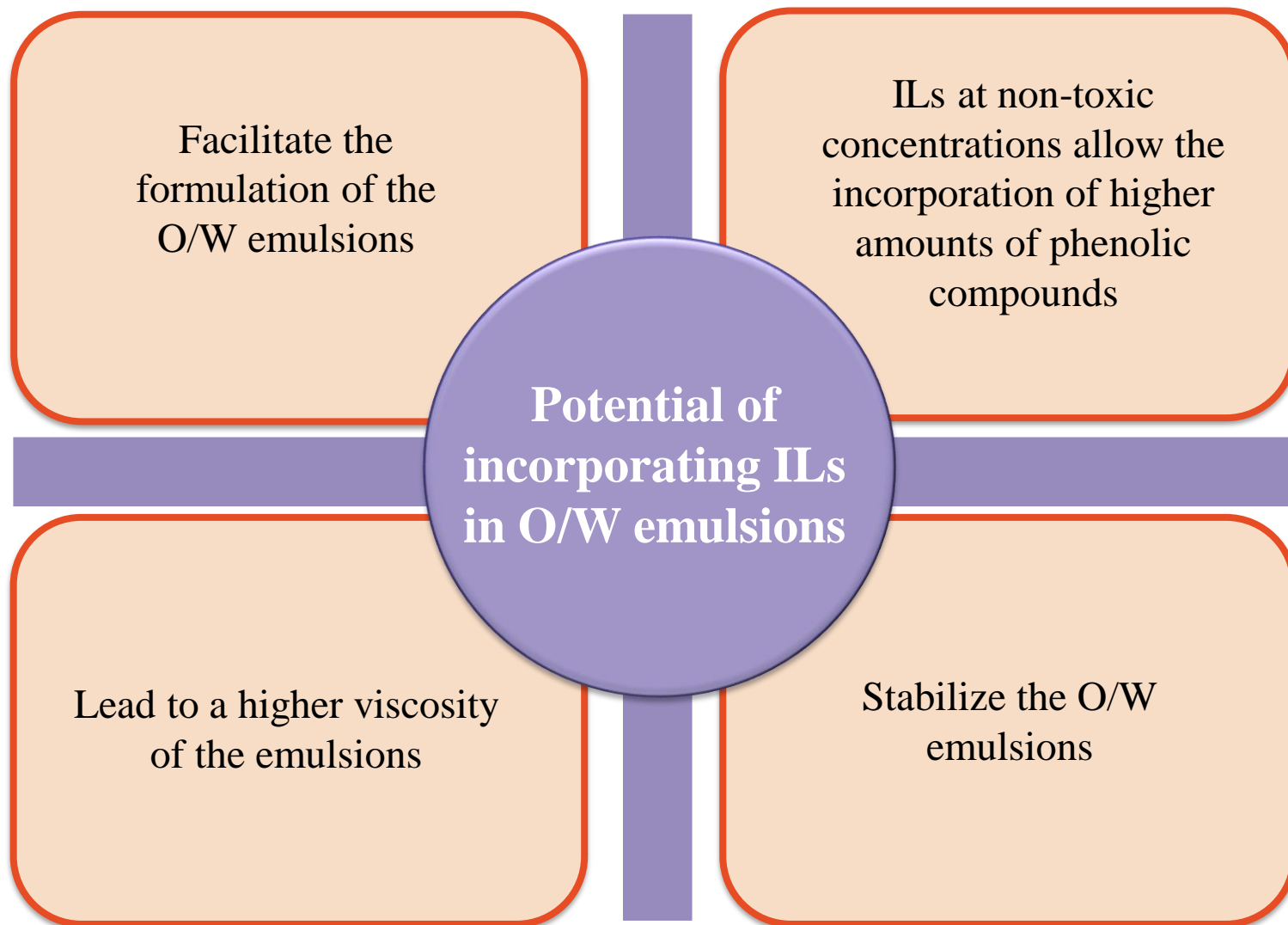
Caparica R., Júlio, A, *et al*, Int. J. Mol. Sci. 2021.



The 7th International Electronic Conference on Medicinal Chemistry

01-30 NOVEMBER 2021 | ONLINE

Conclusions



Funding



UID/DTP/04567/2019 and UIDB/0456/2020
(both general funding to CBIOS)



UNIVERSIDADE
LUSÓFONA

Grant Programme FIPID 2019/2020



THANK YOU



The 7th International Electronic Conference on Medicinal Chemistry
01-30 NOVEMBER 2021 | ONLINE