IOCFB 2024 Conference

The 1st International Online Conference on Functional Biomaterials

10–12 July 2024 | Online

Rutin-loaded hybrid nanoparticles for controlled delivery: technological and in-vitro anti-inflammatory properties

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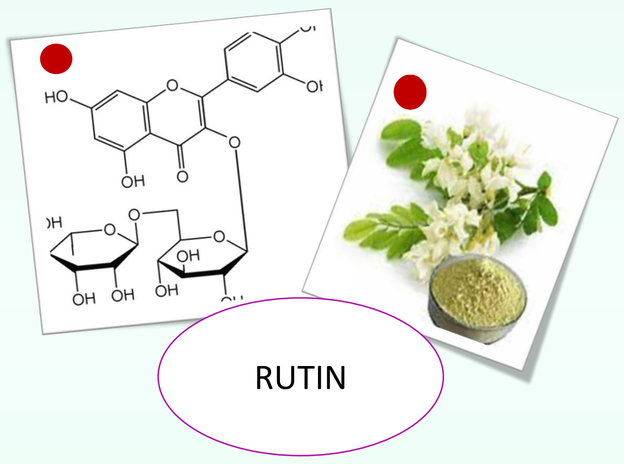
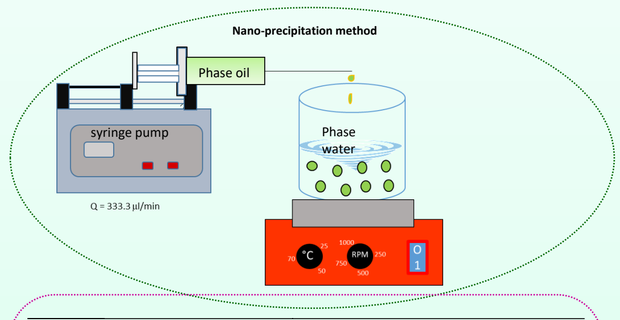
INTRODUCTION



The administration of anthracyclines, like doxorubicin and daunorubicin, epirubicin and idarubicin, plays a key role in treating many neoplastic diseases. Still, chronic administration of anthracyclines induces cardiomyopathy and brain damage caused by endothelial inflammation and oxidation-mediated cell damages. Rutin, a natural polyphenolic bioflavonoid derivative, benefits brain damages and improves doxorubicin-induced memory deficits in in vivo rat models. However, Rutin has low water solubility, poor oral bioavailability, and a short half-life, limiting its pharmacological use. The nasal route is an alternative administration route characterized by rapid and high absorption in the systemic circulation, avoiding the first-pass metabolism as well as the direct nose-to-brain transport. Here, polymer–lipid hybrid nanoparticles were developed as intranasal delivery systems for increasing rutin bioavailability and protecting the endothelial brain cells from epirubicin-induced brain damage. Nanoparticles were prepared using phosphatidylcholine (LP), cholesterol (Chol), poloxamers (P) without and with hyaluronic acid (HA) and palmitoylethanolamide (PEA), at different concentrations. PEA is an endogenous lipid mediator whose activity is mainly mediated by peroxisome proliferator-activated receptor (PPAR)-α with anti-inflammatory activity and metabolic and neuroprotective effects. HA has attracted significant attention because it can specifically bind CD44 and RHAMM receptors, which are overexpressed in many forms of inflammation4. Furthermore, HA is used in nasal formulations due to its mucoadhesive properties, which slow down the mucociliary clearance, and its penetration enhancer activity, which increases the mucosal absorption of drugs.

METHODS

- Nanoparticles were produced by nano-precipitation/solvent evaporation method
- Size analysis (PCS), zeta potential, stability studies in water (4 °C) and serum (37 °C)
- TEM analysis
- Thermal analyses were performed on phosphatidylcholine (LP), cholesterol (Chol), poloxamers (P) and hyaluronic acid (HA) and complexes by differential scanning calorimetry (DSC), 25-300°C at 5°C/min.
- In *vitro* permeation studies were carried out by PermeaPad® barriers[5] using phosphate buffer solutions as acceptor medium (spectrophotometric assay, λ = 364 nm)
- Lactate Dehydrogenase and Intracellular calcium expression studies
- NLRP-3 and MyD-88 expression studies



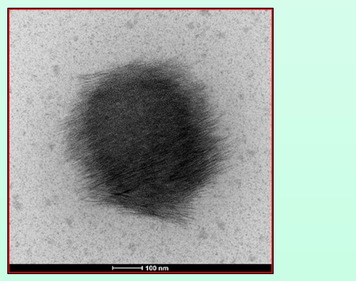
Acronym	PL (% w/v)	PEA (% w/v)	Chol (% w/v)	P (% w/v)	RUT (% w/v)	HA (% w/v)	P (% w/v)
LPH	4	2	3	3	-	0.6	0.05
LPHR	4	2	3	3	0.4	0.6	0.05
LPP	4	2	3	3	-	-	0.05
LPPR	4	2	3	3	0.4	-	0.05
LicpHA	5	-	3	3	-	0.6	0.05
LicpHAR	5	-	3	3	0.4	0.6	0.05

Composition and acronyms of the different formulations.

RESULTS

Formulation	Particle mean diameter (nm)	Polydispersity Index (PDI)	Zeta potential (mV)	Amount of Rutin (%)
LPH	255 ± 2.0	1.300 ± 0.01	-27.93 ± 0.01	
LPHR	247 ± 2.0	0.800 ± 0.01	-29.95 ± 1.00	80.53 ± 4.6
LPP	118 ± 1.0	0.300 ± 0.01	- 17.3 ± 1.10	
LPPR	256± 1.8	1.200 ±0.01	- 20,13 ± 0.49	80.53 ± 4.1
LicpHA	179± 3.8	1.0 ± 0.01	-35 ± 1.00	-
LicpHAR	209 ± 4.8	1.1 ± 0.01	-30 ± 1,00	69 ± 2

NPs Size, polydispersity index (PDI), zeta potential in time in bidistilled water at 4 °C. The drug content and standard deviations were calculated from the last three independent experiments.



Representative TEM image of H-NPs. In both cases spherical particles with a no regular surface were obtained.
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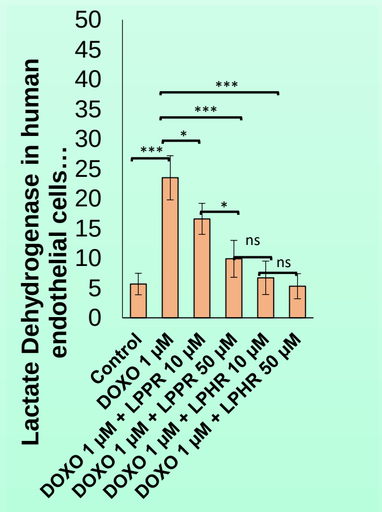
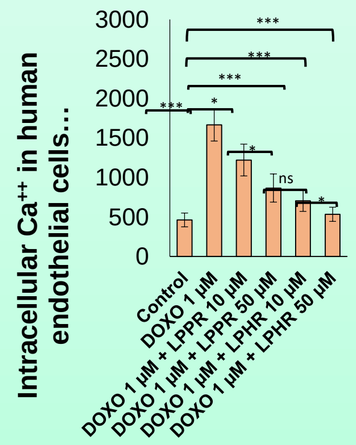
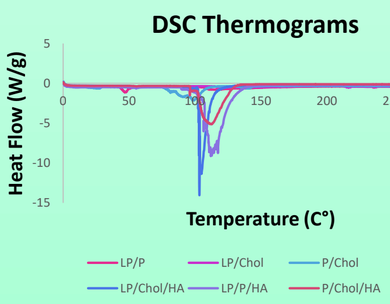
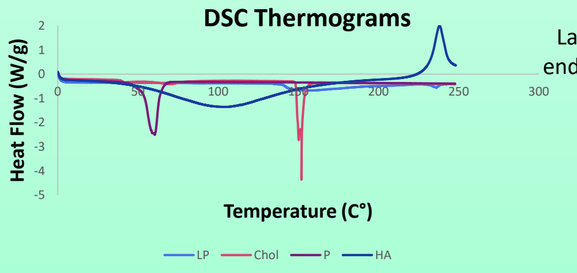


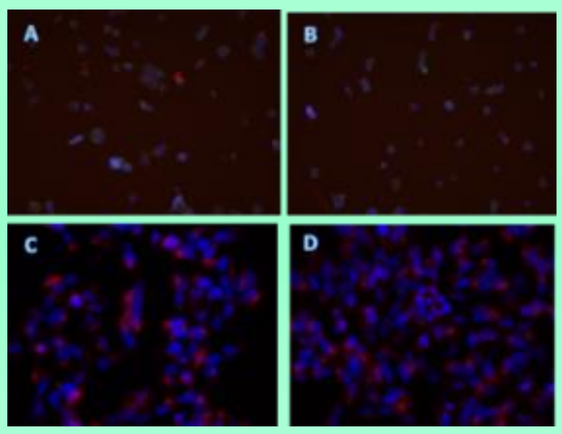




DSC thermograms of on phosphatidylcholine (LP), cholesterol (Chol), poloxamers (P) and hyaluronic acid (HA) and complexes used for nanoparticle preparation.

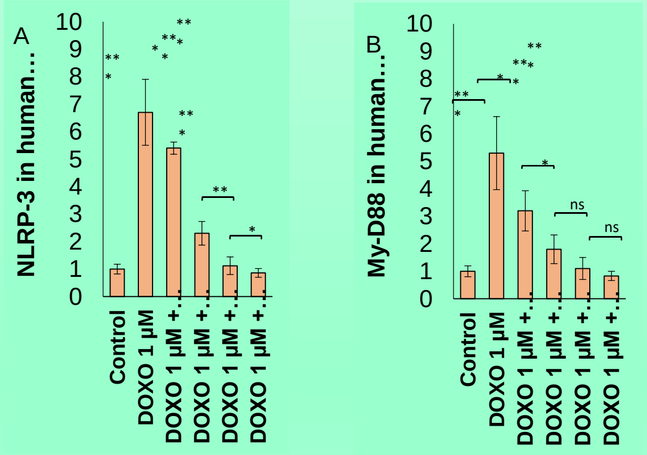


Lactate Dehydrogenase and Intracellular calcium (Ca2+),(ng/mL) in human endothelial cells incubated with Doxorubicin, unformulated Rutin at 1 and 10 µM, LPPR and LPHR loaded at 1 and 10 µM alone or combined with Doxorubicin.



Time course analysis of fluorescent (A) LPH, (B) LPP, (C) LPH and (D) LPH uptake in RPMI 2650 and SK-N-BE2 cells. LPP and LPH showed a rapid cell uptake at 3 h.

The permeation studies indicated that LPHR increased the amount of Rutin permeated more than LPPR and free-Rutin by the PermeaPad® system. P-values for the indicated compounds relative to Free-Rutin vs LPPR (*p<0.05), Free-Rutin vs LPHR (§p<0.05) and LPPR vs LPHR (#p<0.05).



(A) NLRP-3 and (B) MyD-88 expression (ng/mL) in human endothelial cells incubated with Doxorubicin, unformulated Rutin at 1 and 10 µM, LPPR and LPHR loaded at 1 and 10 µM alone or combined with Doxorubicin

CONCLUSIONS

The results indicate that LPH and LicpHA nanoparticles could be a promising candidate for Rutin encapsulation via intranasal delivery. Moreover, PEA nanoparticles loaded with Rutin exert more vasculoprotective properties in cellular models composed of HUVEC cells against doxorubicin-induced cell damage, significantly reducing IL-1, IL-6 and TNF-α levels concerning nanoparticles without PEA.

Acknowledgements

This work was supported by the Foundation of Sardinia (Bando Fondazione di Sardegna –2018-2020 e 2021–Progetti di ricerca di base dipartimentali), Grant numbers J89J21015120005