Encapsulation of the antioxidants resveratrol, curcumin and piperine into nanostructured lipid carriers for skin application

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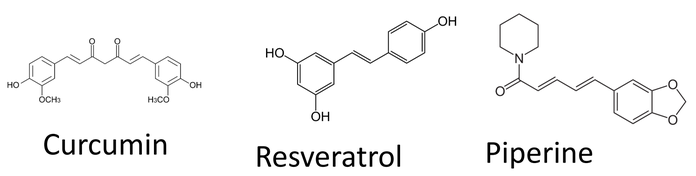
Introduction:

It is well known that premature aging, the development of carcinogenesis and depigmentation is enhanced by the excessive and recurrent production of reactive oxygen species in the skin (Ahmad,2017; Baumann, 2009; Chen, Li & Li, 2021; Narendhirakannan & Hannah, 2013). Natural products like curcumin, resveratrol and piperine are some phytochemicals with antioxidant properties which may be beneficial for the prevention or treatment of these skin conditions (Aziz, Afaq & Ahmad, 2005; Shabeeb, Musa, Abd & Najafi, 2020; Verma *et al.*, 2017). However, due to the fact that they are photosensitive compounds, chemically unstable and/or have low aqueous solubility, they have been formulated in different carriers, including nanostructured lipid carriers (NLC) (Alshehri, Haq & Shakell, 2018; Sandhir, Yadav, Sunkaria & Singhal, 2015). NLC are a type of lipid nanoparticles, made up of a mixture of liquid and solid lipids, which generates an imperfect matrix that allows a high encapsulation rate of active substances (Naseri, Valizadeth & Zakeri-Milani, 2015). The use of such nanocarriers has many advantages such as drug protection, controlled drug release, enhanced drug bioavailability, and improved skin penetration and deposition (Ghasemiyeh & Mohammadi-Samani, 2020).

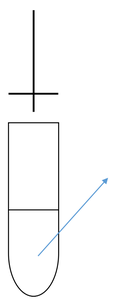
The combination of curcumin or resveratrol with piperine, known also for acting as a penetration enhancer (Lee, Kim, Back & Han, 2018), constitutes an interesting alternative to improve the appearance of depigmented skin. The above data prompted us to propose the preparation of NLC including mixtures of resveratrol-piperine and curcumin-piperine. This work aimed to: (i) prepare NLC loaded with resveratrol and curcumin, alone or combined with piperine, by the high-shear homogenization method; and (ii) characterize the obtained formulations by determining particle size (PS), polydispersity index (PDI), encapsulation efficiency (EE), loading capacity (LC) and thermal profile.

Methods:

Lipid selection



Drug solubility tests

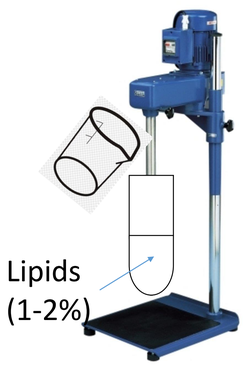


- Stearic acid
- Glyceryl monostearate
- Glyceryl distearate
- Glyceryl dibehenate
- Vitamin E
- Oleic acid
- PEG-8 caprylic/capric glycerides
- Glyceryl oleate
- Glyceryl monolinoleate

NLC preparation

Stabilizer selection (1-5%)

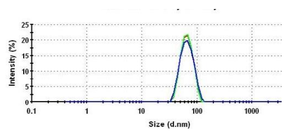
- Polysorbate 80
- Sorbitan monostearate
- Poloxamer 407
- Poloxamer 188
- Ceteth-20



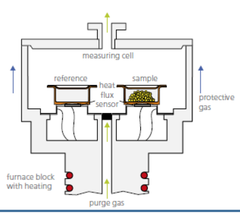
15000 rpm, 5 min, 70°C

NLC characterization

Particle size
Polydispersity index



Encapsulation Efficiency
Loading Capacity



Thermal profile

Results & Discussion:

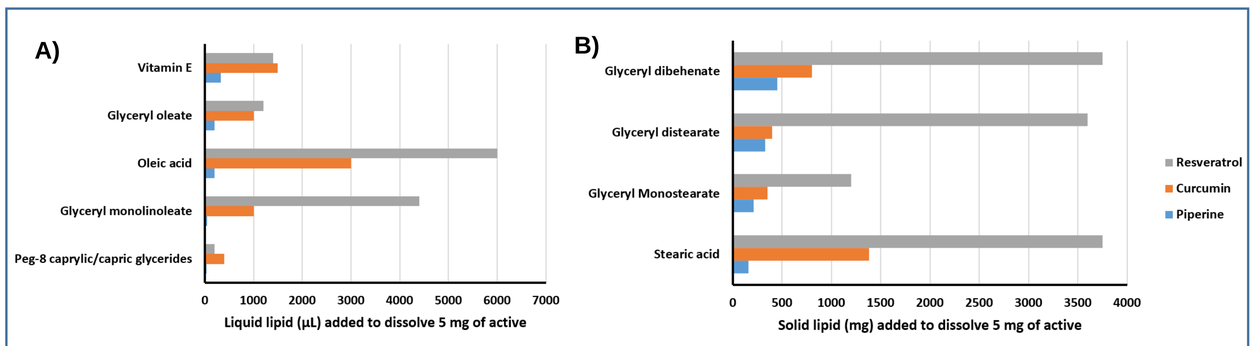


Figure 1. Solubility of resveratrol, curcumin and piperine in different liquid lipids (A) and solid lipids (B)

PEG-8 caprylic/capric glycerides and glyceryl monostearate were selected for the formulation of the NLC.

The most stable systems (2 weeks) were prepared with Ceteth-20 (3%), employing 2% of total lipid, in a ratio of 95:05 (solid lipid:liquid lipid).

Table 1. Characteristics of the prepared NLC loaded with resveratrol (R), curcumin (C) and piperine (P). Particle size (PS); polydispersity index (PI); entrapment efficiency (EE) and loading capacity (LC). Results are displayed as mean ± SD (*n*=3).

	PS (nm)	PDI	EE (%)	LC (µg/mL)
NLC	42 ± 1.52	0.184 ± 0.006	-	-
R-NLC	48 ± 1.15	0.200 ± 0.009	97.10 ± 1.07	4.72 ± 0.19
C-NLC	43 ± 0.57	0.180 ± 0.013	97.67 ± 0.74	5.11 ± 0.15
R-P-NLC	45 ± 2.0	0.186 ± 0.02	95.11 ± 3.74 (R) 92.18 ± 1.87 (P)	5.27 ± 0.19 (R) 4.35 ± 0.71 (P)
C-P NLC	40 ± 0.57	0.193 ± 0.011	95.07 ± 1.68 (C) 90.34 ± 1.53 (P)	5.07 ± 0.20 (C) 4.25 ± 0.41 (P)

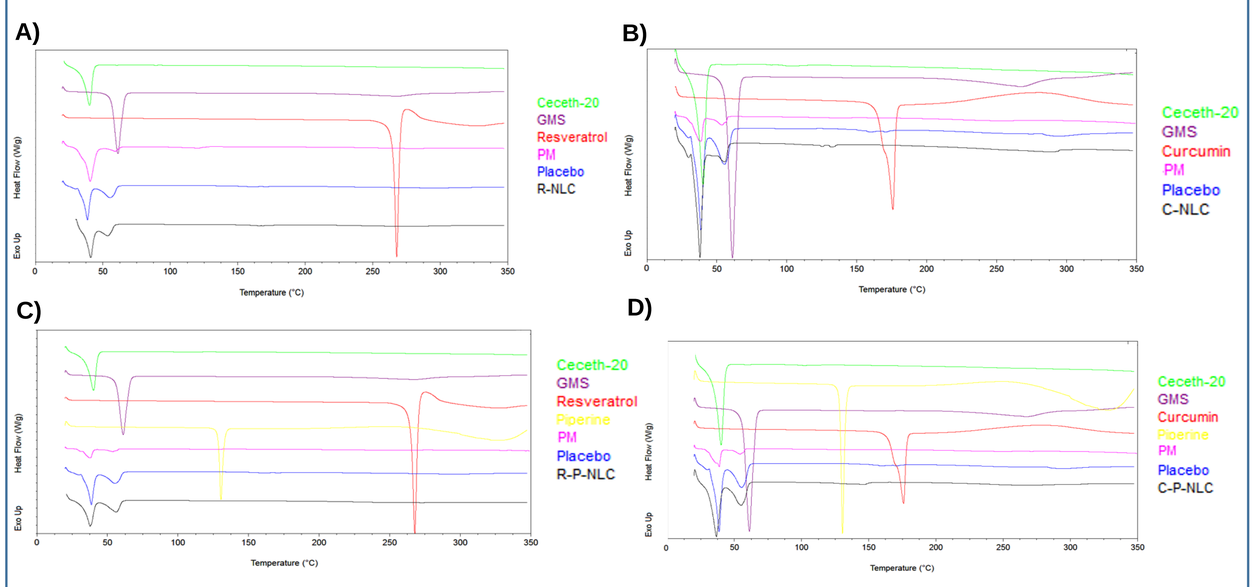


Figure 2. DSC thermograms of resveratrol-loaded NLC (R-NLC) (A), curcumin-loaded NLC (C-NLC) (B), resveratrol-piperine-loaded NLC (R-P-NLC) (C) and curcumin-piperine-loaded NLC (C-P-NLC) (D), its individual components (i.e., Ceteth-20, glyceryl monostearate (GMS) and the phytochemicals) and its corresponding physical mixture (PM).

Conclusions:

NLC containing resveratrol and curcumin, alone or combined with piperine were successfully prepared. The most stable NLC formulation was achieved with glyceryl monostearate and PEG-8 caprylic/capric glycerides (ratio of 95:05, respectively) at 2% of total lipids, and using Ceteth-20 (3%) as surfactant. NLC showed a unimodal particle size distribution, a PDI <0.3, and a PS < 50 nm that could facilitate its penetration into the skin. The formulations developed in this work showed good technological characteristics, to be tested as systems for the topical release of curcumin-piperine and resveratrol-piperine with potential antioxidant application

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References:

Ahmad, S. I. (2017). Ultraviolet Light in Human Health, Diseases and Environment. *Springer, 996*.
Alshehri, S., Haq, N., & Shakeel, F. (2018). Solubility, molecular interactions and mixing thermodynamic properties of piperine in various pure solvents at different temperatures. *Journal of Molecular Liquids, 250*, 63-70.
Aziz, M. H., Afaq, F., & Ahmad, N. (2005). Prevention of ultraviolet-B radiation damage by resveratrol in mouse skin is mediated via modulation in survivin. *Photochem Photobiol, 81*(1), 25-31. doi: 10.1562/2004-08-13-RA-274
Baumann, L. (2009). *Cosmetic dermatology, principles and practice* (2nd ed.): McGrawHill.
Chen, J., Li, S., & Li, C. (2021). Mechanisms of melanocyte death in vitiligo. *Med Res Rev, 41*(2), 1138-1166. doi: 10.1002/med.21754
Ghasemiyeh, P., & Mohammadi-Samani, S. (2020). Potential of Nanoparticles as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages. *Drug Des Devel Ther, 14*, 3271-3289. doi: 10.2147/DDDT.S264648
Lee, S. H., Kim, H. Y., Back, S. Y., & Han, H. K. (2018). Piperine-mediated drug interactions and formulation strategy for piperine: recent advances and future perspectives. *Expert Opin Drug Metab Toxicol, 14*(1), 43-57. doi: 10.1080/17425255.2018.1418854
Narendhirakannan, R. T., & Hannah, M. A. (2013). Oxidative stress and skin cancer: an overview. *Indian J Clin Biochem, 28*(2), 110-115. doi: 10.1007/s12291-012-0278-8
Naseri, N., Valizadeh, H., & Zakeri-Milani, P. (2015). Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. *Adv Pharm Bull, 5*(3), 305-313. doi: 10.15171/apb.2015.043
Sandhir, R., Yadav, A., Sunkaria, A., & Singhal, N. (2015). Nano-antioxidants: An emerging strategy for intervention against neurodegenerative conditions. *Neurochem Int, 89*, 209-226. doi: 10.1016/j.neuint.2015.08.011
Shabeeb, D., Musa, A. E., Abd Ali, H. S., & Najafi, M. (2020). Curcumin Protects Against Radiotherapy-Induced Oxidative Injury to the Skin. *Drug Des Devel Ther, 14*, 3159-3163. doi: 10.2147/DDDT.S265228
Verma, A., Kushwaha, H. N., Srivastava, A. K., Srivastava, S., Jamal, N., Srivastava, K., & Ray, R. S. (2017). Piperine attenuates UV-R induced cell damage in human keratinocytes via NF-kB, Bax/Bcl-2 pathway: An application for photoprotection. *J Photochem Photobiol B, 172*, 139-148. doi: 10.1016/j.jphotobiol.2017.05.018