OPTIMIZATION STUDIES OF LIPID NANOCARRIERS AS A TECHNOLOGICAL PLATFORM FOR THE OCULAR DELIVERY OF BIOACTIVE COMPOUNDS

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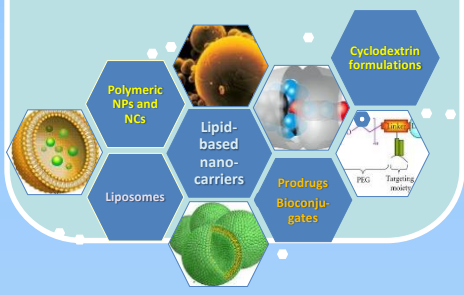
Because of the peculiar anatomical and physio-pathological features, administration of colloidal drug carriers to the anterior and posterior eye segments are challenging, and requires more than a mere adaptation of formulations designed for other routes of administration [1].

One of the ongoing activities at the NANO-*i* Research Center are pre-formulation studies on nanocarriers made of lipid materials for the delivery of bioactive compounds to the eye.

Various technological platforms oriented towards the ophthalmic application of drugs and gene material are pursued through the NANO-i Research Center.



In-lab-developed methods for the production of SLN and NLC

Quasi-emulsion solvent-diffusion (QESD) [2]

PROs: Use of ICH class 3 solvents; low amounts or no surfactant required; low working temperatures

Solvent injection (SI)

PROs: High reproducibility; large volume sampling; easy scale-up processes

Phase Invertion Temperature (PIT) [3]

PROs: an eco-friendly technique, due to the use of less energy in heating and avoidance of organic solvents.

Sterilization methods

* **Autoclave**
* **Gamma irradiation (10/25 kG)**
* **Sterile filtration (0.22 µm-filters made of different materials)**

have been tested for their influence on SLN properties and stability, and appear to be effective methods.

	Autoclave	Filtration
Size variation	no	20-30 nm smaller
PDI variation	no	limited changes
Zeta potential	no change	no change
Drug loading	unmodified	10% drug loss

Studies of LNs composition

Lipid matrix

Biocompatible, commercial lipid (glycerides, fatty acid esters, fatty alcohols, etc.) are used to produce safe LNs.

Lipid modifiers

Simple saturated alkanoic acids, like palmitic (PA) or stearic acid (SA), have been added to the main lipid to modulate the properties of the LNs (e.g.: fluidity, permeability, stability).

Surfactants and co-surfactants

A wide range of surfactants, commonly used for the production of SLN, have been tested both for their technological features in producing small SLN populations, and especially for their compatibility with the ocular tissues [4].

Cationic lipids (cSLN)

DDAB or DOTAP can be added at various weight ratios to modulate the surface charge (Zeta potential) and other properties of the LNs. Cationic SLN are of particular value to improve the adhesion to the negatively-charged surface of the cornea.

Lipid nanocarriers (LNs), including SLN and NLC, are among the most promising colloidal DDS, also for ocular application.

To some extent, they merge the large bio-compatibility of liposomal vesicles with the technological features and adaptability of polymeric nanocarriers.

Purification methods

* **Ultrafiltration (Vectaspin®): difficulty in SLN re-suspension**
* **Ultracentrifugation: may cause SLN aggregation**
* **Dialysis: seems to be the most suitable purification procedure.**

No significant physico-chemical changes in the LNs are usually observed.

Filtration

Both neutral SLN and cSLN can be filtered using GHP and TF 0.2-µm filters for purification and possible sterilization.

Liophylization

Both neutral and cationic SLN can be successfully liophylized by addition of cryoprotectant(s) (e.g., trehalose, mannitol, or cyclodextrins).

Among the mostly recent studied drugs with these ocular LN formulations are:

cSLN, containing SA as a lipid modifier, showed to be able to prolong the *in vitro* antioxidant activity of idebenone.

Melatonin-loaded SLN with various composition displayed in a rabbit model a lowering effect on the intraocular pressure (IOP) greater and longer than melatonin aqueous eye-drops.

SLN loaded with Erythromycin and, in particular, with Cyprofloxacin showed the ability of lowering the drug MIC values against many bacterial strains, and especially against *Lactobacilli spp.*

A siRNA silencing HuR protein has been associated to liposomes and SLN, achieving an efficient transfection efficiency *in vivo*.

GENERAL OUTCOMES

Lipid nanocarriers showed very interesting technological features and mid-term stability under different storage conditions.

SLN produced by various methods generally show high drug loading values, a mean diameter in the range of 100-250 nm and high size homogeneity (PDI < 0.3).

The produced systems can be easily sterilized and freeze-dried.

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