Poster n°8

SIMPOSIO AFI
RIMINI 11·12·13
GIUGNO 2025

Associazione Farmaceutici Industria
Società Scientifica

SOLID LIPID NANOPARTICLES AS NEW STRATEGY FOR ORAL DELIVERY OF NEBIVOLOL HYDROCHLORIDE

Alice Beni, Alessandro Mancini, Serena Orlandini, Natascia Mennini, Marzia Cirri, Ilaria Chiarugi, Camilla Vannucchi, Silvia Fiani, Francesca Maestrelli

University of Florence, Department of Chemistry "Ugo Schiff" (DICUS), via Ugo Schiff 6, Sesto Fiorentino, Italy

INTRODUCTION

Nebivolol Hydrochloride (Neb), a third-generation β-blocker, is commonly used in the treatment of hypertension, but suffers from low oral bioavailability due to its poor aqueous solubility. Solid lipid nanoparticles (SLNs) have emerged as a promising strategy to enhance drug solubility and control the release rate, offering several advantages over other nanocarriers, including increased drug loading of lipophilic drugs and safety.

Improvements to drug stability and pharmacokinetics

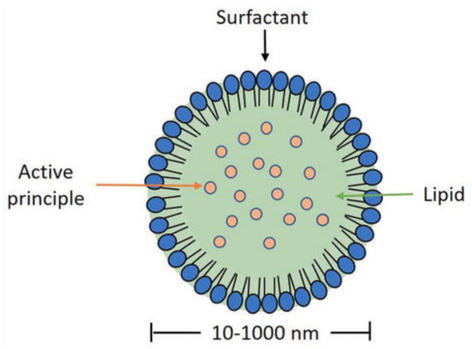
SLNs

Particle sizes range from 50 nm to 1000 nm

Colloidal particles made up of a lipid matrix maintained by surfactants

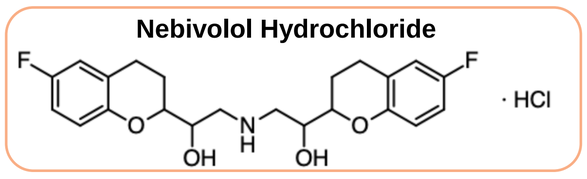
AIM OF THE WORK

SLNs + Neb

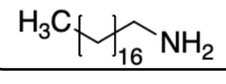


- Minimize drug degradation
- Controlled release system
- Biocompatible system
- Minimize drug expulsion

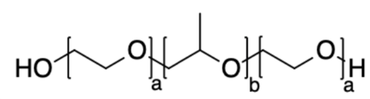
Nebivolol Hydrochloride



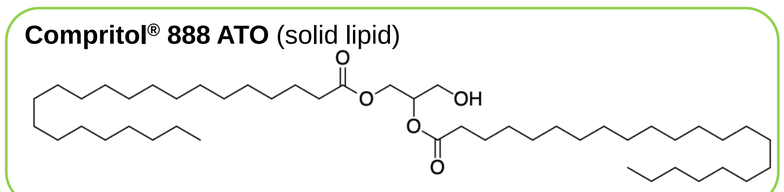
Octadecylamine (stabilizer)



Pluronic F68® (surfactant)



Compritol® 888 ATO (solid lipid)



OPERATING PROCEUDRE

1. Design of Experiments (DoE)

Matrix: asymmetric screening design

Software: Nemrow-W (LPRAI sarl, Marsiglia, Francia)

Optimization of the SLNs formulation was achieved screening eight different factors involved in the formulation process:

1. Weight of Pluronic® F68 (Plur),
2. Weight of Compritol® 888 ATO (Comp),
3. Weight of Octadecylamine (Oct),
4. Ultra-Turrax (UT) speed (rpm),
5. Homogenization time,
6. Amplitude (Amp) of the sonicator,
7. Sonicator pulse mode (Pul),
8. Sonication time.

Optimized formulation:

1	2	3	4	5	6	7	8	Neb
100 mg	120 mg	10 mg	20k rpm	5 min	80 %	6 s	5 min	5.48 mg

2. Neb quantification

→ HPLC

Instrument: Shimadzu SPD-6A apparatus equipped with an injector valve with a 20 mL sample loop.

Flow rate: 1.0 mL/min (LC-10AS Shimadzu pump).

λ: 280 nm.

Column: C18 Zorbax CN (5 µm 4.6x150 mm).

Retention time: 4 minutes.

3. SLNs Preparation

→ Hot High Shear Homogenization method (Ultra turrax - IKA® T25 digital)

Solvent-free and green technique

Lipid and aqueous phase

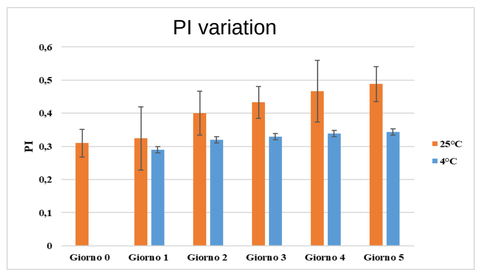
Homogenization

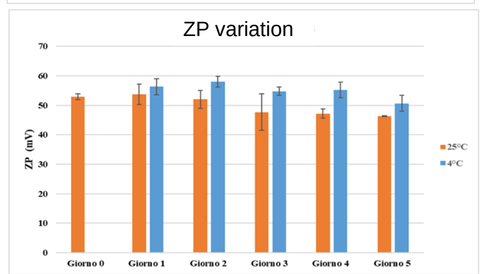
Ultrasonic processor

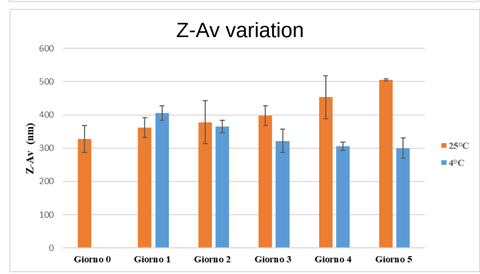
4. Stability studies

The optimized SLNs exhibited:

- particle size (Z-Av) of (292.8 ± 89.7) nm,
- a Polydispersity Index (PDI) of 0.266 ± 0.075,
- a Zeta Potential (ZP) of (61.7 ± 1.9) mV.







The formulations remained stable at both room temperature and 4°C for one week.

5. Entrapment Efficiency (EE%) Loading Capacity (LC%)

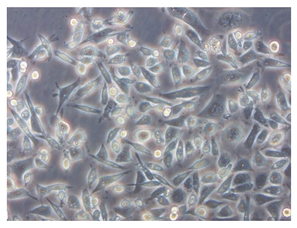
→ Indirect method

EE%: 70%

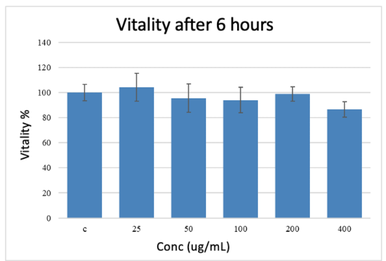
$$EE\% = \frac{\text{Total amount of Neb} - \text{Free Neb}}{\text{Total amount of Neb}} \times 100$$

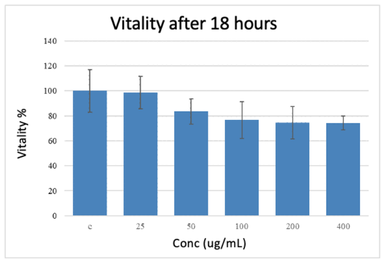
6. MTT Test

→ MTT test was used to determine the toxicity of the formulation on AGS cells



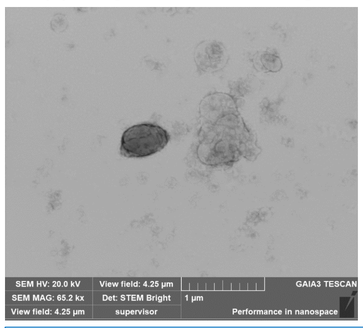
The formulation was incubated with AGS cells for 6 and 18 hours at different concentrations. In no case significant toxicity values were observed.





7. Scanning Electron Microscopy (SEM)

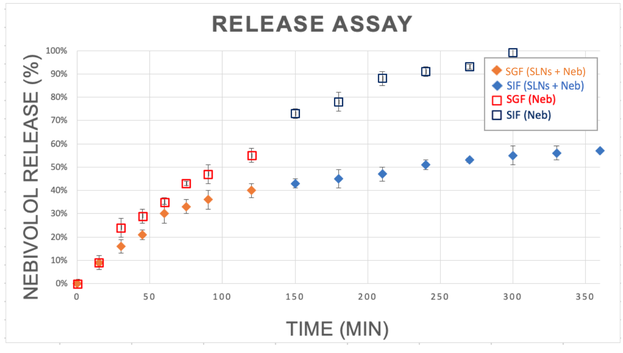
→ Samples were stained with 1% (w/v) phosphotungstic acid for 30 s and placed on copper grids for viewing



- smooth, spherical morphology
- well dispersed and separated
- average diameter: 300 nm

8. Drug Release Assay

→ Dialysis bag method at 37°C



Simulated gastric fluid (SGF) 2 hours

Simulated intestinal fluid (SIF) 4 hours

BIPHASIC RELEASE

In the first 2 hours drug release was fast: 40% of Neb after 2 hours.

In the subsequent 4 hours the quantity of drug release was lower: 57% of Neb after 6 hours.

From the comparison of the 2 curves in the graph above, it is possible to claim that the formulation allow a more controlled and prolonged drug release with respect to the drug powder.

CONCLUSION

- The application of DoE proved useful for optimizing the formulation.
- Sustained release of the drug from SLN was achieved.
- The stability over time changed significantly with temperature variations, suggesting that this is a critical parameter.
- Oral nanosuspensions of Neb are a promising way to increase the absorption rate and bioavailability of this drug.
- Toxicity studies are indicative of a good safety profile.

REFERENCES

[1] Monton S.S. et al., "Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects", *Front. Mol. Biosci.* **2020**, 7.

[2] Kathe N. et al., "Physicochemical characterization techniques for solid lipid nanoparticles: principles and limitations", *Drug. Dev. Ind. Pharm.* **2014**, 1-11.

[3] Seleme V.B et al., "Nebivolol for the Treatment of Essential Systemic Arterial. Hypertension: A Systematic Review and Meta-Analysis", *Am. J. Cardiovasc. Drugs* **2020**.

Reference author: Alessandro Mancini
E-mail: alessandro.mancini2@edu.unifi.it