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Application of the quality-by-design (QbD) approach to improve the nose-to-brain delivery of diazepam-loaded nanostructured lipid carriers (NLC)

Cláudia Pina Costa[1,*], Sara Cunha[1], Andreia Peixoto[2], João Nuno Moreira[3,4], José Manuel Sousa Lobo[1] and Ana Catarina Silva[1,5]

[1] UCIBIO/REQUIMTE, MEDTECH, Laboratory of Pharmaceutical Technology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto;
[2] LAQV/REQUIMTE, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto;
[3] CNC - Center for Neuroscience and Cell Biology, Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Faculty of Medicine (Pólo I), Coimbra, Portugal;
[4] UC - University of Coimbra, CIBB, Faculty of Pharmacy, Pólo das Ciências da Saúde, Coimbra, Portugal.
[5] FP-ENAS (UFP Energy, Environment and Health Research Unit), CEBIMED (Biomedical Research Centre), Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal.

* Corresponding author: claudiaspinacosta@gmail.com

U.PORTO
FACULDADE DE FARMÁCIA
UNIVERSIDADE DO PORTO

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Abstract: The intranasal administration of nanostructured lipid carriers (NLC) has been suggested as a promising strategy to improve the fast treatment of epilepsy. This route allows drug passage directly from the nose to the brain, avoiding the need of bypassing the blood brain barrier. In addition, the quality-by-design (QbD) approach is a useful tool for the optimization of manufacturing variables, resulting in effective and safe pharmaceutical formulations. The aim of this work was to use the QbD approach to optimize a NLC formulation for the nose-to-brain delivery of diazepam. The studies began with the screening of excipients and the assessment of lipid-drug compatibility. The central composite design was used to evaluate the effects of critical material attributes (CMAs) (ratio of solid and liquid lipids and amount of emulsifiers) on the CQAs of the NLC formulation (particle size, polydispersity index (PDI), zeta potential (ZP) and encapsulation efficiency (EE)). The results showed that the most adequate ratios of lipids and emulsifiers were 6.65:2.85 and 4.2:0.3 (%, w/w), with values of 84.92 nm, 0.18, -18.20 mV and 95.48% for particle size, PDI, ZP and EE, respectively. This formulation was selected for further studies related to the optimization of critical process parameters (CPPs).

Keywords: Epilepsy; nose-to-brain delivery; intranasal delivery; nanostructured lipid carriers, quality-by-design.

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Methods

❖ Diazepam-loaded NLC formulation

Based on the screening of excipients (solid and liquid lipids and emulsifiers), compatibility between solid and liquid lipids and drug-lipid solubility.

Precirol® 5 ATO and **Cetiol® V** were selected as the solid lipid (SL) and liquid lipid (LL), respectively.

Tween 80® (E1) and **sodium deoxycholate** (E2) were selected as emulsifiers.

A **0.50% of drug concentration** was selected to prepare the final NLC formulation.

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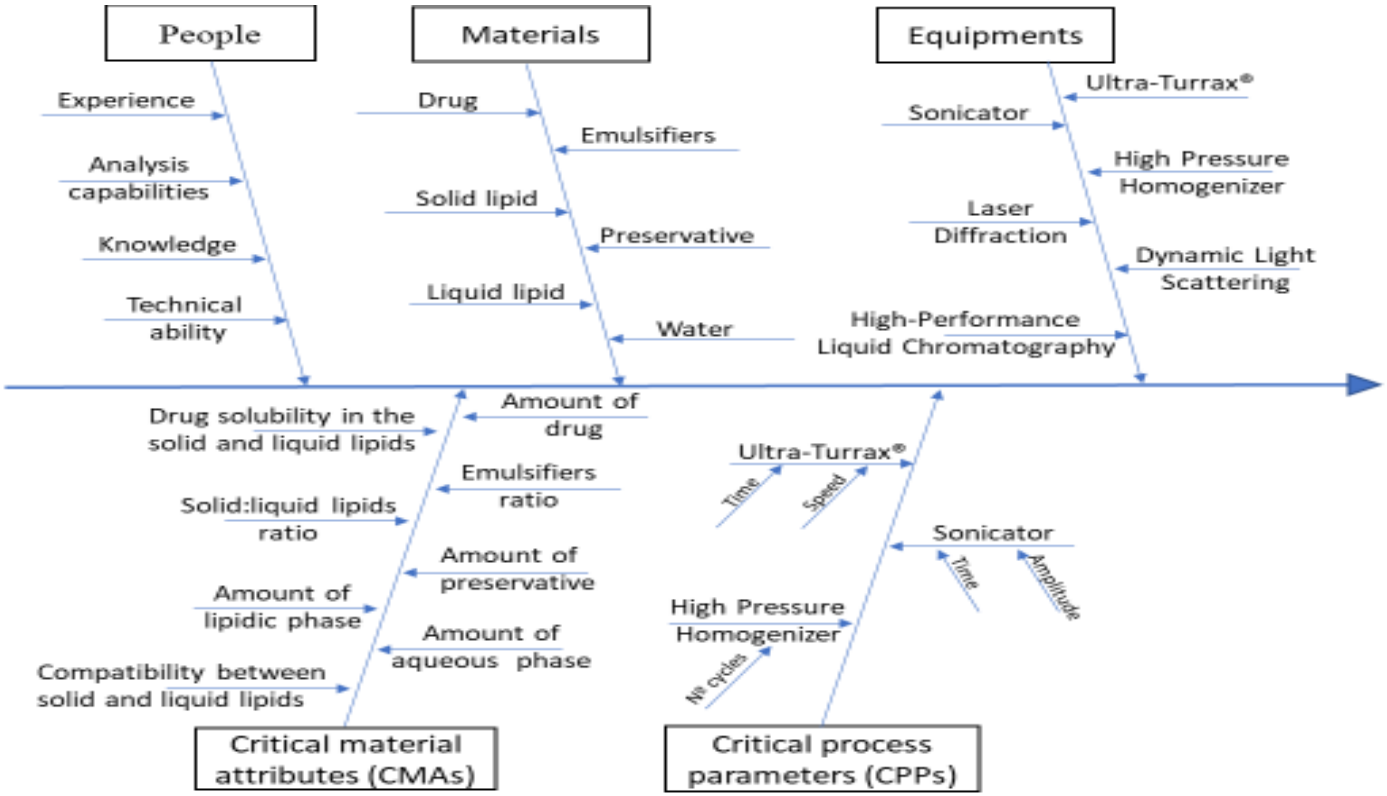
Methods

❖ Quality-by-design approach

✓ Effect of the CMAs and CPPs on the CQAs



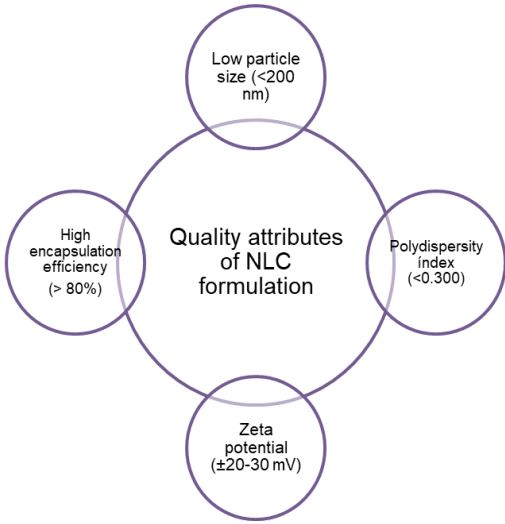


Figure 1. Ishikawa diagram showing the effects of critical material attributes (CMAs) and critical process parameters (CPPs) on critical quality attributes (CQAs), for the optimization of a NLC formulation.

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Results

❖ Diazepam-loaded NLC formulation

Table 1. Composition of diazepam-loaded nanostructured lipid carriers (NLC) formulation.

Composition	(w/w)%
Precirol® 5 ATO	6.65
Cetiol® V	2.85
Diazepam	0.50
Tween 80®	4.20
Sodium deoxycholate	0.30
Benzalkonium chloride	0.02
Ultrapure water	q.s. 100.00

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Results

❖ Quality-by-design approach

✓ Central composite design (CCD)

Table 2. Effect of the critical material attributes (CMAs) on the critical quality attributes (CQAs) of the diazepam-loaded NLC.

CMAs	D(50) nm	D(90) nm	Z-Ave (nm)	PDI	ZP (mV)	EE (%)
A1	57.100±0.001	167.000±0.003	129.300±46.960	0.179±0.000	-16.100±7.240	93.960±0.001
A2	60.600±0.000	146.000±0.004	107.000±44.690	0.188±0.000	-20.200±7.710	94.770±0.001
A3	53.700±0.002	141.000±0.002	140.300±48.400	0.205±0.000	-18.000±6.440	92.720±0.003
A4	55.300±0.000	145.000±0.003	93.980±47.430	0.180±0.000	-19.200±9.440	94,470±0.001
A5	77.200±0.000	126.000±0.007	109.600±40.260	0.157±0.000	-20.600±8.500	94,600±0.002
A6	68.700±0.001	192.000±0.005	113.900±47.660	0.185±0.000	-16.200±8.660	94.430±0.000
A7	55.700±0.003	155.000±0.009	158.400±45.660	0.164±0.000	-14.100±9.500	92.000±0.003
A8	53.300±0.000	137.000±0.003	84.920±45.750	0.178±0.000	-18.200±7.220	95.480±0.001
A9	75.500±0.005	134.000±0.007	110.900±40.080	0.153±0.000	-18.400±8.340	94.750±0.002
A10	75.200±0.001	133.000±0.008	110.500±42.760	0.151±0.000	-18.100±8.890	94.790±0.002

CMAs: critical material attributes; D(50): 50% of particles with size equal or lower to the given value; D(90): 90% of particles with size equal or lower to the given value; EE: encapsulation efficiency; PDI: polydispersity index; ZP: zeta potential; Z-Ave: mean particle size.

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Results

❖ Quality-by-design approach

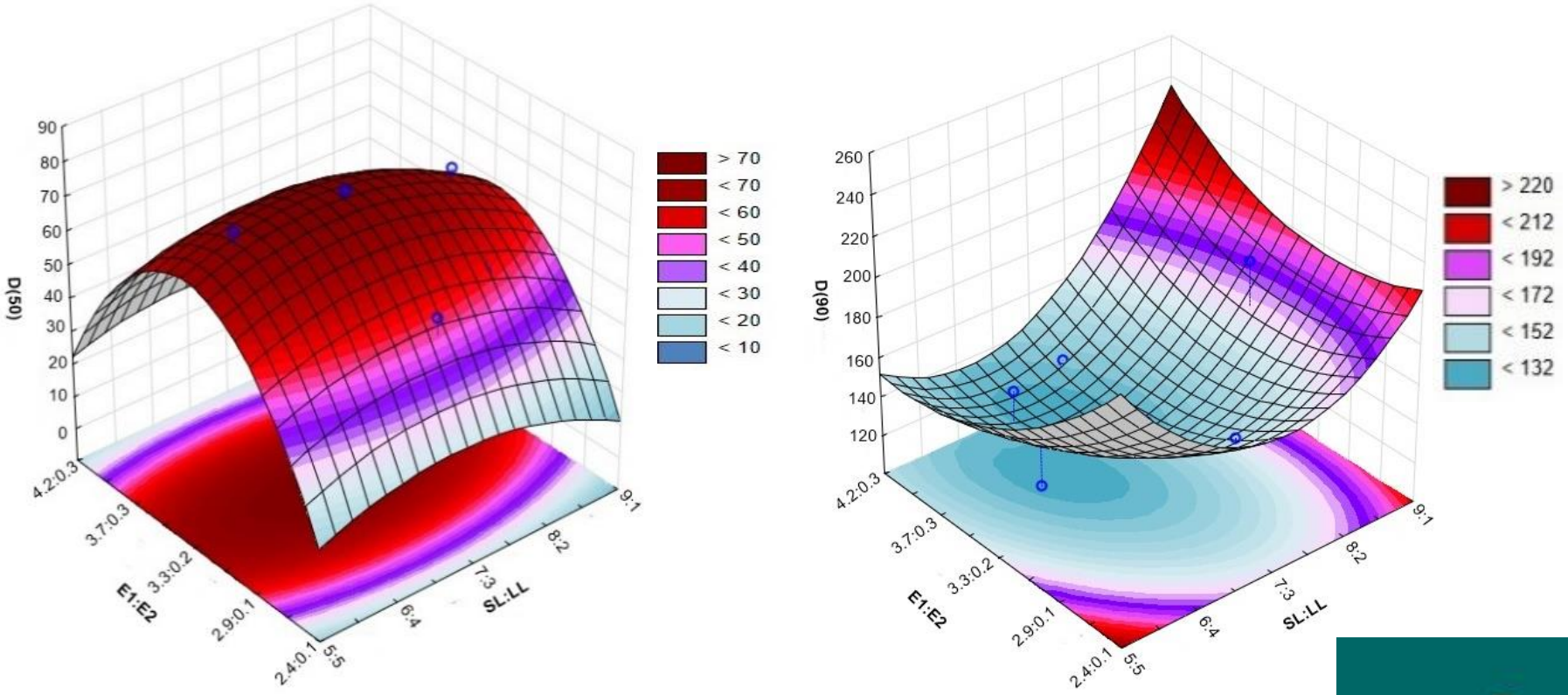

Figure 2. The 3-D surface plots portraying the effect of the ratio between the solid and liquid lipids (SL: LL) and the two emulsifiers (E1: E2) on the size (D(50): 50% of particles with size equal or lower to the given value, D(90): 90% of particles with size equal or lower to the given value).

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Results

❖ Quality-by-design approach

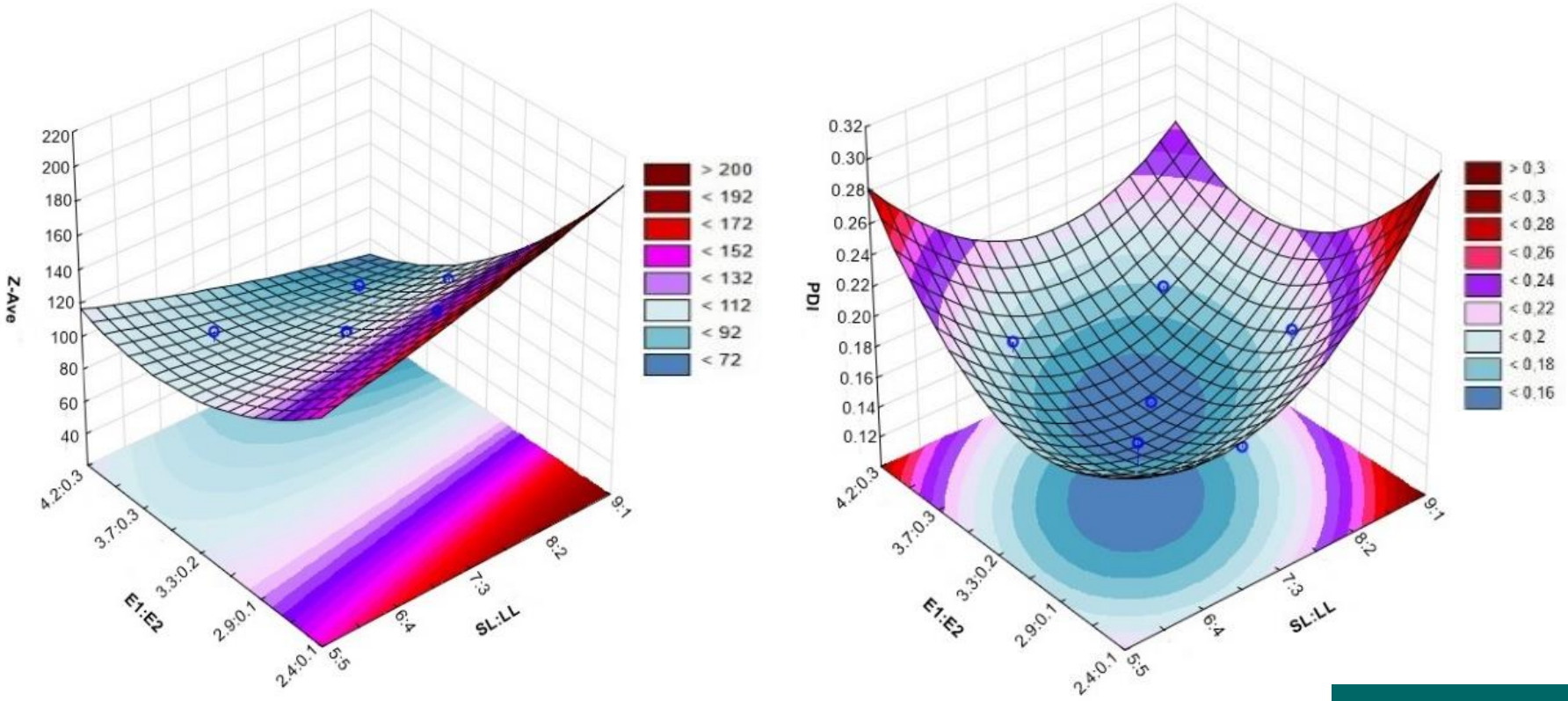

Figure 3. The 3-D surface plots portraying the effect of the ratio between the solid and liquid lipids (SL: LL) and the two emulsifiers (E1:E2) on the mean particle size (Z-Ave) and polydispersity index (PDI).

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Results

❖ Quality-by-design approach

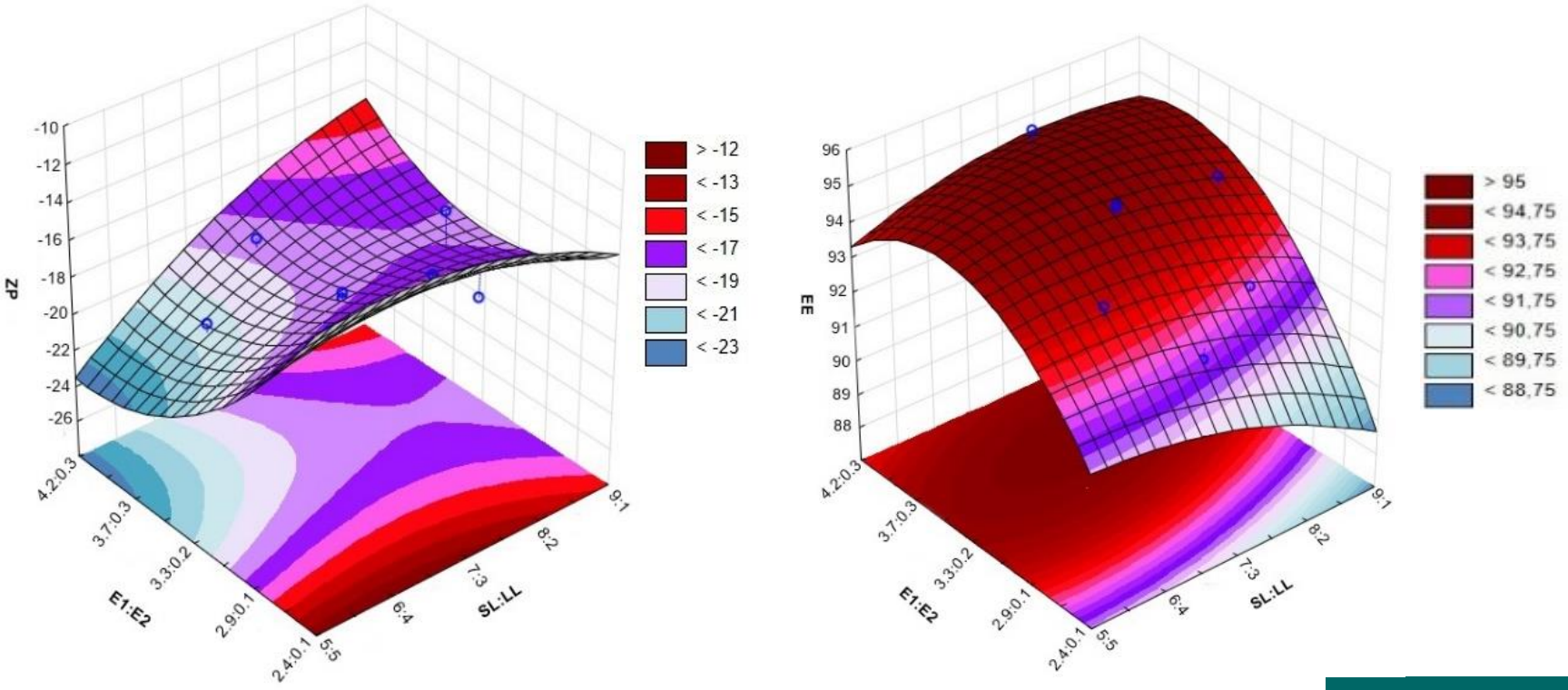

Figure 4. The 3-D surface plots portraying the effect of the ratio between the solid and liquid lipids (SL: LL) and the two emulsifiers (E1:E2) on the zeta potential (ZP) and encapsulation efficiency (EE).

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Discussion

- ✓ The most adequate ratios of lipids and emulsifiers were 6.65:2.85 and 4.2:0.3 (%, w/w), presenting values of 84.92 nm, 0.178, -18.20 mV and 95.48% for particle size, PDI, ZP and EE, respectively.

- ✓ The values are in accordance with the requisites of intranasal delivery of NLC, presenting a particle size less than 200 nm, a polydispersity index less than 0.3, a zeta potential close to -20 mV and an encapsulation efficiency higher than 80%.

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Conclusions

- ✓ Optimizing NLC formulations is critical to achieve a reproducible quality of pharmaceutical products, in terms of efficacy and safety.

- ✓ QbD approach is a useful tool for the development of lipid nanoparticles, such NLC.

- ✓ The formulation with the best CQAs was selected for further optimization related to the selection of the best CPPs using the same design of experiment, which will be tested *in vitro* and *in vivo* in the future.

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