

NLC and SLN Nasal Administration

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The nasal route has been used for many years for the local treatment of nasal diseases. More recently, this route has been gaining momentum, due to the possibility of targeting the central nervous system (CNS) from the nasal cavity, avoiding the blood–brain barrier (BBB). In this area, the use of lipid nanoparticles, such as nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN), in nasal formulations has shown promising outcomes on a wide array of indications such as brain diseases, including epilepsy, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease and gliomas.

nasal administration

nanostructured lipid carriers

solid lipid nanoparticles

in vitro cell cultures

3D nasal casts

1. Nasal Route

1.1. Anatomical and Physiological Considerations

The anatomical and physiological characteristics of the different regions of the nasal cavity are summarized in **Table 1** and the location of each region is shown in **Figure 1** ^{[1][2][3]}.

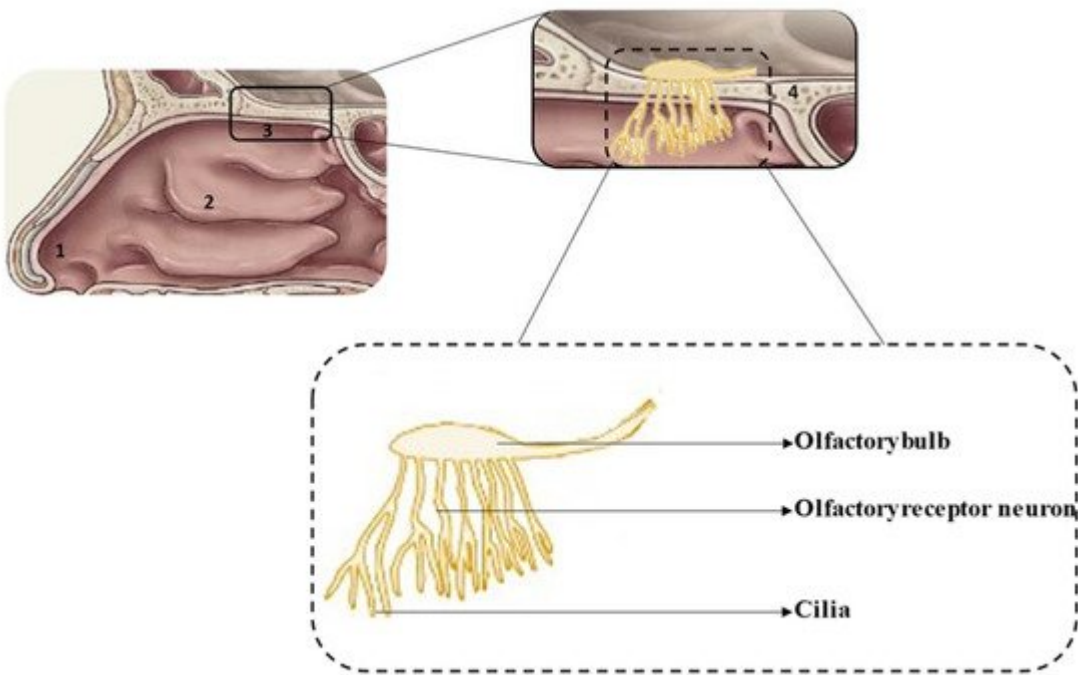


Figure 1. Schematic representation of the nasal cavity (**top**) and olfactory region (**bottom**): 1—vestibule, 2—respiratory region, 3—olfactory region, 4—cribriform plate.

Table 1. Characteristics of the different regions of the nasal cavity (data from [4][5][2][6][7][8]).

Region	Surface Area	Location	Characteristics	Vascularization	Epithelium
Vestibule	0.6 cm ²	Anterior part	<ul style="list-style-type: none">• Poor permeability and small surface area that limits drug absorption.• Presence of mucus and hairs or vibrissae, which constitute an important defense mechanism, preventing the entrance of toxic particles, pathogens and allergens from the external environment into the body.	Low	Squamous epithelium
Respiratory region	130 cm ²	Middle part and lateral walls	<ul style="list-style-type: none">• High permeability and large surface area, being the region where the greatest absorption of drugs occurs.• Divided into three turbinates: inferior, middle and superior.• Provides drug absorption to the systemic circulation.• Direct pathway of drug transport to the brain via the trigeminal nerve.• Presents cilia, microvilli and mucus.	High	Respiratory epithelium: ciliated pseudostratified and columnar epithelium

Region	Surface Area	Location	Characteristics	Vascularization	Epithelium
			<ul style="list-style-type: none">• Occurrence of mucociliary clearance mechanism.		
			<ul style="list-style-type: none">• Located above the respiratory region and below the cribriform plate.• Includes superior turbinate, and a small upper portion of the middle turbinate.		
Olfactory region	10 cm ²	Upper part	<ul style="list-style-type: none">• Enables drug access from the nose to the brain via the olfactory bulb, bypassing the blood–brain barrier (BBB).• Responsible for detecting odors.	High	Olfactory epithelium

1.2. Nose-to-Brain Delivery

After nasal administration, different pathways of drug transport from the nose to the brain can occur, which have been divided into direct transport, indirect transport and a combination of both. Besides, some drug can be eliminated by the mucociliary clearance mechanism before reaching the olfactory or/and respiratory regions. To our knowledge, there is no confirmation of the exact transport mechanism followed by intranasal drugs, which seems to be influenced by the drug’s molecular characteristics, formulation consistency (liquid or semi-solid) and type of application device. Thus, it is impossible to assess the exact amount of drug reaching the brain after intranasal administration via a specific transport mechanism, although good approaches have been reported in in vivo studies that compared the results of the amount of drug reaching the brain after intranasal and intravenous administrations. In addition, toxicological concerns were raised related to the possibility of an accumulation of excipients in the brain and the risk of impairment of the mucociliary clearance mechanism. **Figure 2** summarizes the different drug pathways after nasal administration [\[9\]](#)[\[4\]](#)[\[10\]](#)[\[11\]](#).

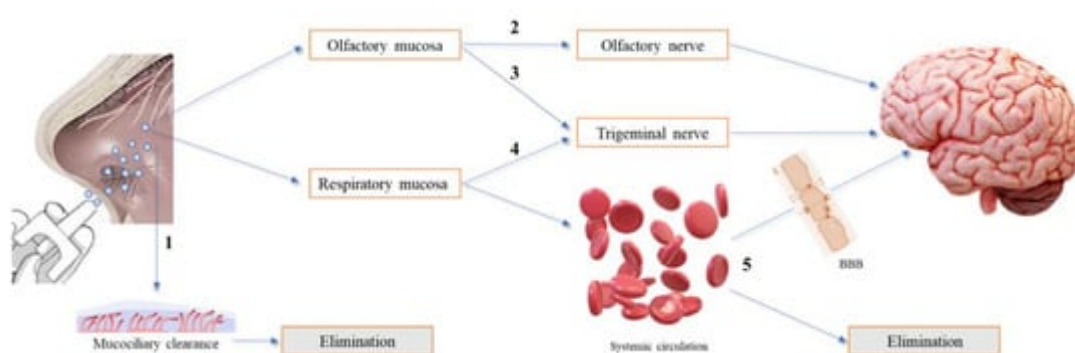


Figure 2. Overview of the different drug pathways after nasal administration. (1) The drug is eliminated by the mucociliary clearance mechanism. (2) The drug reaches the olfactory mucosa, passes through the olfactory nerve, via intraneuronal and/or extraneuronal transport, and reaches the brain. (3) The drug reaches the olfactory mucosa, passes through the trigeminal nerve and reaches the brain via the cribriform plate. (4) The drug reaches the respiratory mucosa, passes through the trigeminal nerve and reaches the brainstem. (5) The drug reaches the respiratory mucosa, is absorbed into the systemic circulation, and diverges between passage to the brain, upon crossing the blood–brain barrier (BBB), and elimination, before reaching the brain.

1.3. Requisites of Nasal Formulations

Some factors of the nasal formulations can interfere with drug absorption and should be considered. For instance, these formulations should be isotonic (i.e., osmolality between 280 mOsm/Kg and 310 mOsm/Kg) and have a pH close to that of the nasal cavity (5.0–6.8), to avoid discomfort, mucosal irritation and/or damage to the cilia, after administration [2][12]. In addition, the drug excipients used should be compatible with the nasal mucosa to avoid irritation and toxicity [13][14].

One of the main disadvantages of intranasal administration is the rapid elimination of the drug through mucociliary clearance (a physiological defense mechanism that eliminates foreign substances every 15–30 min). To avoid this, substances that interact with the mucus can be added to the formulations. The mucus is composed of water, mucin and other proteins, electrolytes, enzymes and lipids [6]. Mucin is a negatively charged glycoprotein and, therefore, positively charged formulations can easily bind it through electrostatic interactions, which facilitates mucoadhesion. In contrast, negatively charged formulations can penetrate mucin chains and hydrogen bonds can be formed, which improves mucoadhesion [2][15].

New strategies to overcome the drawbacks of the nasal formulations have been investigated. For example, the use of nanocarriers, such as lipid nanoparticles, to achieve prolonged release, protection against enzymatic degradation and improve targeting to the brain [16]. The use of permeation enhancers, including mucoadhesive polymers and in situ hydrogels to improve drug retention time in the nasal mucosa and, consequently, drug absorption is also a commonly used strategy [16]. There are already marketed nasal formulations (e.g., Nasonex and Rhinocort) that increase viscosity after administration, improving the retention time of the drug in the nasal cavity [2].

2. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for Nasal Delivery

The inclusion of lipid nanoparticles, such as SLN and NLC, in nasal formulations can improve the effectiveness of drugs. Regarding their advantages over other colloidal carriers, lipid nanoparticles have been described as superior carriers for nasal drug delivery. For instance, they enable the direct transport of drugs from the nose to the brain, via olfactory and trigeminal nerves, and adhere to the olfactory epithelium, increasing contact time with the nasal mucosa. In addition, they provide prolonged drug release, drug protection from nasal enzymatic degradation and have low or no toxicity due to the use of generally recognized as safe (GRAS) excipients [\[17\]\[9\]\[4\]\[18\]\[19\]](#).

To understand the specific features of lipid nanoparticles for nasal delivery, it is important to first clarify their specific characteristics. Briefly, SLN were first created and consist of aqueous dispersions of nanoparticles made by one solid lipid and stabilized by one or two emulsifiers. Their solid matrix enables prolonged release, while protecting the encapsulated molecules. Although SLN appear to be effective drug carriers, some drawbacks have been observed, in particular, poor storage stability related to the occurrence of lipid polymorphic transitions that originate molecule release and nanoparticle aggregation. To circumvent these problems, NLCs were developed, which also consist of aqueous dispersions of nanoparticles with a solid lipid matrix composed of one solid lipid and one liquid lipid and stabilized by one or two emulsifiers. The presence of oil within the lipid matrix causes a more disordered internal structure that leads to fewer lipid polymorphic transitions during storage, producing higher stability.

Thereby, the use of SLN and NLC has been extensively investigated to improve drug delivery through different administration routes, as they show advantages over other nanosystems, including the use of GRAS excipients, easy industrial manufacture, high encapsulation efficiency, protection and prolonged release of lipophilic molecules, and good storage stability. In this field, very complete review articles are available [\[20\]\[21\]\[22\]\[23\]\[24\]\[25\]\[26\]\[27\]\[28\]\[29\]\[30\]\[31\]\[32\]\[33\]\[34\]](#).

2.1. In Vitro Studies with Nasal Formulations of NLC and SLN

The use of aqueous dispersions of SLN and NLC show limitations in some administration routes, including cutaneous, ocular and nasal. For instance, the low viscosity of these dispersions decreases the contact time with the locale of application, reducing the therapeutic effectiveness of the drug. To avoid this, different strategies have been used, including the incorporation of SLN and NLC in conventional semisolid formulations, such as hydrogels, creams and ointments, or the addition of viscosifying agents, mucoadhesive polymers or in situ gelling polymers, directly to the aqueous phase of the SLN and NLC dispersions [\[24\]\[35\]\[36\]\[37\]\[38\]](#). Examples of viscosifying agents used in nasal formulations containing lipid nanoparticles include gellan gum, poloxamers, and carbomers [\[1\]\[39\]\[40\]](#), while commonly used mucoadhesive polymers are hypromellose, carbomers, alginate, hyaluronic acid, chitosan, polyethylene glycol, cyclodextrins, polyacrylic acid and cellulose derivatives, such as carboxymethylcellulose, hydroxypropyl methylcellulose and methylcellulose. Examples of in situ gelling polymers include poloxamers, such as poloxamer 407 and 188, gellan gum, pectin, sodium alginate, carrageenan and xyloglucan [\[1\]\[2\]\[11\]\[13\]\[40\]\[41\]](#).

Regarding nasal administration, the use of liquid and semisolid formulations has been investigated and it seems that both formulations promote the efficacy of drugs for different therapeutic applications. In the following sections, examples of the most relevant studies are reported. The main outcomes of these studies are summarized in **Table 2**. Over the past two years, about ten studies have been published investigating the use of SLN or NLC for intranasal delivery, mainly for the treatment of neurological disorders.

Table 2. Relevant outcomes from in vitro studies with nasal formulations of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
SLN-liquid	Curcumin	CNS disorders	Mouse fetal fibroblasts	<ul style="list-style-type: none">• High cell viability (80%) for curcumin-loaded NLC and curcumin-loaded SLN, in a concentration range of 1–10 µg/mL.• No significant difference in cell viability was observed between the drug-loaded lipid nanoparticles, blank nanoparticles and free curcumin.• At a concentration of 20 µg/mL, a slight reduction in cell viability was observed.	[42]
SLN-liquid	Dopamine and grape seed extract	Parkinson's disease	SH-SY5Y neuroblastoma and Olfactory ensheathing	<ul style="list-style-type: none">• None of the three formulations (grape seed-derived extract dopamine-loaded SLN, dopamine-loaded SLN and grape seed-derived extract-loaded SLN) presented cytotoxicity to	[43]

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
				olfactory ensheathing cells and SH-SY5Y neuroblastoma cells, in a concentration range of 18–75 µM and 4–34.5 µM for dopamine and grape seed-derived extract, respectively.	
NLC-liquid	Ketoconazole	Meningoencephalitis	Fungal cells	<ul style="list-style-type: none">In the yeast-extract peptone dextrose medium, the fungal growth inhibition effect of ketoconazole-loaded NLC was significant at concentrations above 0.5 µg/mL, having shown a growth inhibition of 92%, compared to a 50% inhibition shown by the ketoconazole solution.In the RPMI 1640 medium, the cell inhibition rate was 4-fold higher for the ketoconazole-loaded NLC formulation than for the ketoconazole solution.	[44]
SLN-liquid	Nalbuphine	Pain management	Human embryonic kidney (HEK-293)	<ul style="list-style-type: none">A concentration up to 750 µM was shown to be nontoxic to HEK-293 cells.	[45]

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
				<ul style="list-style-type: none">Percent cell survival was 100% for nalbuphine concentrations of 100, 250 and 500 μM, 80% for a concentration of 750 μM and almost 75% for a concentration of 1000 μM.	
SLN-semisolid	Paeonol	CNS disorders	RPMI 2650	<ul style="list-style-type: none">Cell viability of the in situ gel containing paeonol-loaded SLN, paeonol-loaded SLN, blank SLN, and blank in situ gel over a concentration range of 0.001–10 $\mu\text{g/mL}$ was greater than 90%, indicating good biocompatibility.The fluorescence intensity of dead cells was similar for the four formulations tested, indicating good cell viability.	[46]
NLC-liquid	Pioglitazone	Alzheimer's disease	SH-SY5Y	<ul style="list-style-type: none">The LC_{50} was 16.626 $\mu\text{g/mL}$ for pure pioglitazone and 17.387 $\mu\text{g/mL}$ for NLC loaded with pioglitazone.Cell viability was similar for both formulations, being 69.15% for NLC	[47]

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
				loaded with pioglitazone and 66.89% for pure pioglitazone at a concentration of 10 µg/mL.	
SLN-liquid	<i>Pueraria flavone</i>	CNS disorders	Caco-2	<ul style="list-style-type: none">Greater cellular uptake was observed for <i>Pueraria flavone</i>-loaded SLN modified with borneol and stearic acid, followed by <i>Pueraria flavone</i>-loaded SLN modified with borneol, <i>Pueraria flavone</i>-loaded SLN and <i>Pueraria flavone</i> free, at 37 °C and 4 °C, at concentrations 100, 200 and 400 mg/mL of <i>Pueraria flavone</i>.Cellular uptake of all formulations was achieved at the highest temperatures and concentrations.	[48]
NLC-liquid	Tacrine	Alzheimer's disease	SH-SY5Y	<ul style="list-style-type: none">Blank NLC and tacrine-loaded NLC, at the same concentration, showed similar cell viability.The cell viability of tacrine-loaded NLC conjugated to an	[49]

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
				amphipathic peptide drastically decreased compared to tacrine-loaded NLC at the same concentration. <ul style="list-style-type: none">The use of a concentration up to 10 µM of tacrine was considered safe.	
NLC-liquid	Tenofovir disoproxil fumarate	Acquired Immune Deficiency Syndrome (AIDS)	bEnd.3 cerebral cortex	<ul style="list-style-type: none">The two different tenofovir disoproxil fumarate-loaded NLC showed cell viability similar to blank NLC at a concentration of 5, 10 and 50 µg/mL.Cell viability decreased in a concentration of 100 µg/mL of tenofovir disoproxil fumarate after 72 h in both formulations.The use of emulsifiers did not cause any cytotoxicity below 100 µg/mL of tenofovir disoproxil fumarate-loaded NLC.	[50]
NLC-semisolid	Teriflunomide	Glioma	Human U-87	<ul style="list-style-type: none">Based on the percentage of viable cells, pure teriflunomide and the in situ gel containing teriflunomide-loaded NLC	[51]

exhibited greater inhibition rates even at low concentrations, indicating a higher cell uptake.

Jojo et al. [47] evaluated the nasal cytotoxicity of optimized pioglitazone-loaded NLC formulation for the treatment and management of Alzheimer's disease. This antidiabetic drug has been extensively investigated because the

Type of Lipid Nanoparticle Formulation	Drug	Targeted Disease	Cell Line	Relevant Results	Reference
[43]		[49]		<p>showed greater cytotoxicity compared to teriflunomide-loaded NLC.</p> <ul style="list-style-type: none">• After 48 h, cell viability was 4% for pure teriflunomide, 6% for in situ gel, and 48.2% for NLC, for a concentration of 100 µg/mL.• The IC50 concentration was 78.5 µg/mL for NLC, followed by the in situ gel at 7 µg/mL and by teriflunomide at 4.8 µg/mL.	

the SH-SY5Y neuroblastoma cells, in a concentration range of 18–75 µM and 4–34.5 µM of dopamine and grape seed-derived extract, respectively. Therefore, the authors concluded that the tested formulations can be used to improve Parkinson’s disease therapy.

Wang et al. [48] studied the in vitro efficacy of intranasal *Pueraria* flavone solution, *Pueraria* flavone-loaded SLN, *Pueraria* flavone-loaded SLN modified with borneol and *Pueraria* flavone-loaded SLN modified with borneol and stearic acid. *Pueraria* flavone is extracted from the *Pueraria thoom sonii* and *Pueraria lobata* and is used for the management of CNS diseases, such as Parkinson’s disease and Alzheimer’s disease. In this study, the cellular uptake of the different formulations was tested in Caco-2 cells. The results showed a higher cellular uptake for *Pueraria* flavone-loaded SLN modified with borneol and stearic acid and *Pueraria* flavone-loaded SLN modified with borneol, when compared to *Pueraria* flavone-loaded SLN and pure *Pueraria* flavone at a concentration of 100 mg/mL, 200 mg/mL and 400 mg/mL of *Pueraria* flavone. In addition, a higher cellular uptake was observed for higher temperatures and higher concentrations. From the results of their study, the authors concluded that the modified SLN containing *Pueraria* flavone could be used to improve the management of neurodegenerative diseases.

Malvajerd et al. [42] developed curcumin-loaded SLN and curcumin-loaded NLC to study their potential for brain delivery in the treatment of CNS disorders. Before performing in vivo experiments, the researchers evaluated the in vitro cytotoxicity of the formulations in mouse fetal fibroblast cells using the MTT assay. The results showed a high cell viability (abound 80%) for curcumin-loaded SLN and for curcumin-loaded NLC at concentrations of 1–10 µg/mL, while a slight decrease in cell viability was observed at higher concentrations (20 µg/mL). Thus, the authors

concluded that no remarkable cytotoxicity was observed in any of the tested formulations of lipid nanoparticles containing curcumin.

Khanna et al. [45] evaluated the safety of exposing nalbuphine-loaded SLN to human embryonic kidney cells (HEK-293). In this study, the in vitro cytotoxicity of nalbuphine-loaded SLN was tested in a drug concentration range of 100–1000 μM . The results showed a cell viability of 100% for concentrations of 100, 250 and 500 μM , a viability of 80% for a concentration of 750 μM and a viability of almost 75% for a concentration of 1000 μM . These results suggested that nalbuphine-loaded SLN containing drug concentrations up to 750 μM is safe for use in the management of pain.

Sarma et al. [50] investigated the in vitro cytotoxicity of two different tenofovir disoproxil fumarate-loaded NLC, one with Tween 80 and the other with Tween 80 and Pluronic F68, in bEnd.3 cells of the cerebral cortex, after 24 h and 72 h of exposure. Similar cell viability was observed for both formulations, and at both times, at concentrations of 5, 10 and 50 $\mu\text{g/mL}$. After 72 h, cell viability decreased at concentrations of 100 $\mu\text{g/mL}$ for both formulations. From these results, the authors concluded that the use of emulsifiers did not cause differences in cytotoxicity. In addition, at concentrations up to 100 $\mu\text{g/mL}$, tenofovir disoproxil fumarate-loaded NLCs are safe for intranasal administration. Based on these findings, the use of the tenofovir disoproxil fumarate-loaded NLCs for the treatment of Acquired Immune Deficiency Syndrome (AIDS) was proposed.

2.1.2. Semisolid Formulations

Gadhav et al. [51] developed a carbopol-gellan gum in situ gel containing teriflunomide-loaded NLC for the treatment of gliomas. Gellan gum is a natural anionic polysaccharide capable of forming a hydrogel in the presence of cations in the nasal cavity. In this sense, the objective of using gellan gum, as a gelling agent, and carbopol 974P, as a mucoadhesive polymer, was to increase the contact time of the formulation in the nasal cavity, promoting drug absorption. The antitumor activity of the in situ gel containing teriflunomide-loaded NLC, teriflunomide-loaded NLC and pure teriflunomide was evaluated in human U-87 glioma cells. The results showed that pure teriflunomide and the in situ gel containing teriflunomide-loaded NLC had higher cytotoxicity compared to teriflunomide-loaded NLC. After 48 h, cell viability was 4% for pure teriflunomide, 6% for in situ gel containing teriflunomide-loaded NLC and 48.2% for teriflunomide-loaded NLC, at a concentration of 100 $\mu\text{g/mL}$. The IC_{50} was 78.5 $\mu\text{g/mL}$ for the teriflunomide-loaded NLC, followed by 7 $\mu\text{g/mL}$ for the in situ gel teriflunomide-loaded NLC and 4.8 $\mu\text{g/mL}$ for the pure teriflunomide. Therefore, it was concluded that the in situ gel containing teriflunomide-loaded NLC and pure teriflunomide were more cytotoxic than teriflunomide-loaded NLC.

Sun et al. [46] evaluated the in vitro cytotoxicity in RPMI 2650 cells of an in situ gel containing paeonol-loaded SLN, paeonol-loaded SLN, blank SLN and a blank in situ gel, using the MTT method. The cell viability of all tested formulations, in the concentration range of 0.001–10 $\mu\text{g/mL}$, was higher than 90%, indicating biocompatibility. Additionally, the cell viability of blank SLN and paeonol-loaded SLN, without removing the free emulsifiers used to prepare these formulations, decreased with increasing concentration, with strong cytotoxicity being observed at 1000 $\mu\text{g/mL}$, presenting cell viability of 24.20% and 25.90%, respectively. Furthermore, the live/dead double

staining method showed similar dead cell fluorescence intensity in all tested formulations, which was in agreement with the MTT results and indicated good cell viability.

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