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NANO STRUCTURED LIPID CARRIERS (NLCs): A NOVEL APPROACH FOR NOSE TO BRAIN DRUG DELIVERY

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ABSTRACT

Drugs administered through the oral route greatly deteriorate in the Gastrointestinal Tract (GIT) or Liver; for those drugs, nasal administration is a substitute route. The Nose to Brain delivery approach can replace invasive drug transportation methods to the brain with enhanced drug absorption and low systemic adverse effects. To improve nasal absorption, several strategies are available; one such is lipid nanocarriers (e.g., NLCs). Nanostructured lipid carriers (NLCs) are regarded as a good drug transport approach without any drug molecule alternatives. NLCs are composed of lipids, surfactants, and solvents. This review showcases the different types of NLCs, composition and mechanism, the rationale for developing nose-to-brain targeting, NLCs preparation methods and evaluation, guidelines for the design of lipid-based formulations, marketed products, future scopes, and toxicity studies of nose-to-brain drug delivery systems were also focused in this review.

Keywords: Non-invasive, lipids, nanostructured lipid carriers, nose to brain delivery, toxicity

INTRODUCTION

Drugs delivered through the brain are highly challenging because of their anatomy and physiology barriers, like blood-brain barriers (BBB). BBB restricts the entry of drug molecules into the brain when given by peroral route. Intranasal administration is proposed as a non-invasive method to transport the

medicinal molecules to the brain compared to oral administration. This path overcomes the problems faced by oral route of administration, like overcoming the Blood Brain Barrier (BBB), rapid onset of action, and avoiding the first-pass metabolism. Additionally, the intranasal administration provides effortless, does not require any sterile equipment and efficient administration methods. BBB acts as a major barrier to active molecules entry into the CNS **[1]**. Lipophilic drugs have a partition coefficient within the range of 1.5- 2.7. A compound having molecular weight lesser than 600 Dalton (Da) is likely to be pervious to the BBB **[2]**. The nasal route can substitute the drugs oral approach, which greatly deteriorates in the GIT or liver. Most of the drugs delivered intranasally for systemic outcomes comprise antiviral drugs, cardiovascular drugs, analgesics, anti-inflammatory agents, and hormones. Several actions are tested to improve nasal absorption; among all the advanced approaches is a lipidic system **[1]**.

Solid lipid nanoparticles (SLNs) are colloidal carriers, having a diameter between 50 to 1000 nm, having disadvantages like gelation tendency that is not predictable, particle growth, and unanticipated dynamics of polymeric shifts. Nanostructured lipid carriers (NLCs) arising from the second generation of lipid nanoparticles prevail over first-generation imperfections (SLNs) **[3, 4]**. Solid, liquid lipids and emulsifiers are utilized to formulate NLCs **[5]**. Using liquid lipids (oil) can cause solid lipids structural defect, leading to a lack of well defined crystalline nature that prevents drug leaching and leads to a high drug load. Previously, researchers have acquired attention towards NLCs as a substitute to SLNs, liposomes, emulsions, polymeric nanoparticles, micro particles, and so forth. These are now being utilized in chemotherapy, brain targeting, gene therapy, delivery of nutraceuticals, cosmeceuticals, and the food industry **[1]**.

The second-generation SLNs are a nanostructured lipid carrier (NLCs) is composed of physiological, biocompatible, ecological, non-sensitizing, and non-irritating lipids. NLCs are regarded to be a good approach to drug deliverance with no alternatives to the drug fragments. Nanocarriers having a small particle size make it flexible to be carried transcellular through the brains neuronal passage. After intranasal administration, the lipid nanocarriers are examined to be absorbed more effectively because of the brains rapid assimilation, biodegradability, and bio-acceptability. The drug is incorporated into NLCs and secured from degradation. It returns into the nasal

cavity, magnifying in the brain and available in the blood. The practicability in expansion and the nonexistence of a rupturing effect enables them favourable transporters for the delivery of drug molecules **[6]**.

The new and modified type of NLCs having a diligent nanostructure. These structures help to improve drug loading stability without leaking the drug as reported by SLNs and their by enhances the bioavailability **[7]**. An enormous nasal mucosal exterior area is suitable as it escapes the first-pass metabolism, and the gastrointestinal tract increases patient convenience and complies with the nasal drug delivery system **[8]**. NLCs also reduce the different problems related to the SLN for many drugs, like low payload, drug expulsion throughout storage, and SLNs dispersions due to the high-water content in it **[7]**. The main drawbacks of NLCs are sensitizing, irritation effects with surfactants, the absorption enhancers used may have histological toxicity **[8]** because the composition of the lipid matrix and concentration may give rise to cytotoxic action, maintaining the stability of lipids **[6]**.

TYPES OF NLCs

The site of integrated drug moieties in NLC helps to identify three types of morphological representations as shown in **Figure 1 [6]**.

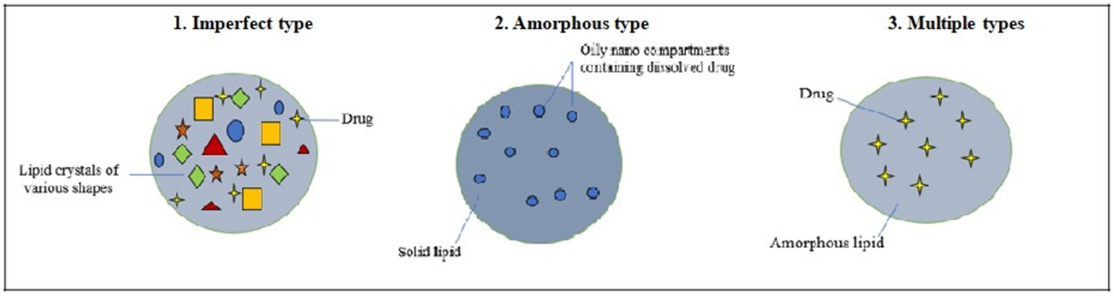

Figure 1: Types of NLCs

NOSE- TO- BRAIN DELIVERY MECHANISM

The nasal epithelium is categorized into two regions based on the drug delivery. The olfactory area is separated by the nasal cavity and near to the nares. The respiratory area is located closer to the nostrils. The nasal epithelium is competently vascularised, and olfactory neurons are exhibited within the olfactory area, helping to transport drug compounds right into the brain through the olfactory neurons **[9]**.

It has been recognized that the absorption of molecules happens at the respiratory as well as the olfactory epithelia. The molecules come into into the olfactory bulb from the olfactory area present near the nares via transcellular mechanism through

the sustentacular cells or the sensory neurons of the olfactory area which is exposed. The molecules are transported from the nasal respiratory epithelial tissue through the trigeminal nerves into the brain. After the molecules enter the brain, they are transported to the other regions of the brain (midbrain, brain stem) is by bulk flow via extracellular transport mechanism or through perivascular routes. Though the paracellular mechanism is not a significant pathway, it has been observed that the nanoparticles, when introduced intranasally, were found inside the olfactory bulb within a period of 5 minutes. Drugs which are introduced intranasally also come into into the regular blood passage through the nasal blood vessels, though this method of transport is observed only by low molecular weight compounds as the nasal blood vessels contain tight junction proteins, and fenestrations are absent.

Human nasal cavity volume, studied with magnetic resonance imaging is about 16, 449.81±4288.42 mm^3, with the region of the nostril opening with an area of 357.83±180.09 mm^2. A nostril opening corresponds with the volume of the nasal cavity.

In human clinical studies, intranasal insulin was found in the cerebrospinal fluid (CSF) of human beings under study. The study showed an improvement in the intellectual and memory power of Alzheimer's patients. Studies also showed no enhancement in blood insulin levels with intranasal insulin, designating that preferential brain deliverance of peptides within humans is feasible through this route. Studies indicate that if peripheral drug action needs to be eliminated, the nose-to-brain route of drug delivery within humans may be used **[9]**. Drug transport pathways via intranasal administration is shown in **Figure 2 [10]**.

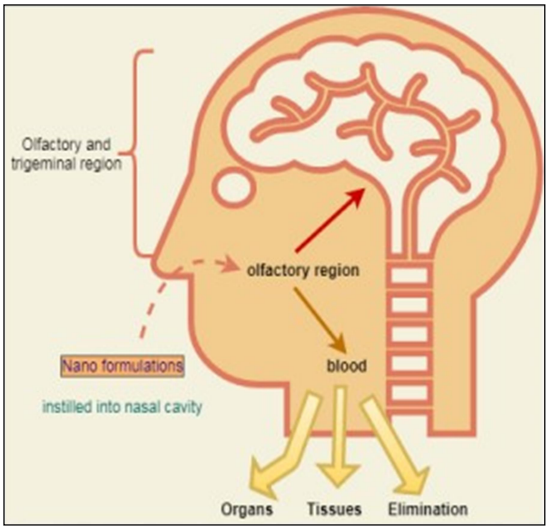

Figure 2: Drug transport pathway's via intranasal administration

COMPOSITIONS OF NLCs

In general, NLCs are made up of several ingredients like: lipids as a solid (solid lipids), lipids as liquids (liquid lipids), surfactants, organic solvents, surface modifying agents and counter-ions as shown in tabulated form **(Table 1) [2, 6, 11]**.

Table 1: Components utilized for the formulation of NLCs

COMPONENTS	EXAMPLES
Solid lipids	Cetyl palmitate, Tristearin, Cholesterol, Stearic acid, Palmitic acid, Emulcire® 61, Geleol®, Dynasan®116, Imwitor®900 P, Cutina®CP, Gelot®64, Dynasan®118, Compritol®888 ATO, Softisan®154.
Liquid lipids	Paraffin oil, Squalene, Labrafil, Medium-chain triglycerides, Labrafac®PG, Isopropyl myristate, Capryol®90, Miglyol®812, Lipofile®WL1349, Lauroglycol®FCC, Vitamin E.
Hydrophilic emulsifiers	Sodium deoxycholate, Sodium oleate, Sodium glycocholate, Polyvinyl alcohol, Trehalose, Polyglycerol, Tween 80, Tween 40, Tween20, Solutol®HS15, Methyl glucose distearate, Pluronic®F127(poloxamer407), Pluronic®F68(poloxamer 188)
Lipophilic emulsifiers	Span 20, Span 40, Span 60, Myverol® 18-04K.
Amphiphilic emulsifiers	Phosphatidylethanolamines, Phasphotidylcholines, Soya lecithin egg lecithin, Glucire® 50/13

THE RATIONALE FOR EXPANSION AND PROGRESS OF NOSE TO BRAIN TARGETING DRUG DELIVERY SYSTEM

The perspective of drug delivery of any pharmaceutical compound is the direct passage of pharmaceutical compound to the site of action. Therefore, nose-to-brain drug delivery approach is relevant for treating numerous CNS disorders like Brain tumors, Parkinsons, Schizophrenia, and other neurodegenerative conditions. This approach of drug delivery is more applicable to the rapture of large molecular weight compounds as in case of peptides and proteins. In this approach, the pharmaceutical molecules enter into the systemic circulation directly and thereby prevent presystolic metabolism. Hence, the nose to brain targeting drug delivery system is a non-invasive and suitable therapy for managing pharmaceutical molecules in treating neurological disorders **[12]**.

NLCS METHODS OF PREPARATION

Commonly used NLCs methods of preparations are **[13]**:

High-Pressure Homogenization (HPH): High pressure homogenization can be employed both as hot as well as cold technique.

(a) Hot HPH: Both the lipid and drug were mixed after melting by using a high shear piece of equipment, the aqueous phase containing surfactant was added, resulting in the formation of a hot pre-emulsion. The formed pre-emulsion was subsequently processed by HPH. The process of recrystallization was carried out cooling the formed nanoemulsion to room temperature, thereby preparing NLCs **[14, 15, 16].**

(b) Cold HPH: The selected lipid and drug were mixed rapidly under liquid nitrogen, which results in the formation of

microparticles. A chilled solution of the surfactant was homogenized with the particles to form a pre-suspension which was subsequently subjected to HPH.

The HPH method is advantageous in requiring less manufacturing time**,** reduced use of organic solvent, suitable for large-scale production**;** cold HPH can be useful for heat-sensitive drugs. Method does not eliminate the drug exposure to high temperatures completely **[17, 8, 18, 19, 20]**.

Solvent Diffusion: The organic solvents were dispersed through an aqueous phase to generate an initial thermodynamic stability. The temporarily formed oil-in-water emulsion was mixed with water while constantly stirring, ultimately leading to the formation of internal phase which was solidified because of the transmission of the organic solvent; thus, lipid nanoparticles were formed.

In this above mentioned method, lipids are commonly dissolved by the use of water-immiscible solvents. The drawback that this method offers is that a deposit of the organic solvent was retained in the mixture which required lyophilisation or ultra filtration **[21, 22]**.

Solvent emulsification-evaporation: The lipid is melted and then liquified in the water-insoluble organic solvents under continuous stirring and it was later blended in an aqueous surfactant. During the process of emulsification, the organic solvent is evaporated, leading to lipid precipitation.

This method is suitable for heat-sensitive drugs. However, extremely diluted nanoparticles were formed, and the organic solvent was retained in the preparation; evaporation or ultra filtration was essential **[23, 24]**.

Emulsification Sonication: The preparation of the nanoemulsion was like HPH, subsequently, which was ultrasonicated with a probe sonicator. The advantage of this method involves high shear mixing. The drawback of this method is metallic contamination during the process of sonication **[25]**.

Micro emulsion: In this method the lipid is melted above its melting point, and the hot surfactant solution was added simultaneously to form a hot microemulsion which was transferred into cold water, forming nanoemulsions, consequently recrys-tallizing to prepare NLCs.

This method is apt for production of industrial-scale microemulsions. Dis-advantage of the method lies in the fact that a rich concentration of surfactant is used, which is undesirable and resulted in highly diluted suspensions as large quantities of water were utilized to prepare NLCs **[17, 26-29]**.

Phase inversion: The lipid and drug were melted along with the addition of the surfactant in the aqueous phase with the use

of a magnetic stirrer. Three cycles of heating and cooling were applied, which was subsequently made dilute using the cold-water phase, thereby the emulsion resulted in the process of phase inversion, ultimately breaking and thus forming NLCs.

The Phase inversion method is very much suitable for the drugs that are heat-sensitive, and the use of organic solvents were avoided. The drawback of this method is that the technique involved is very tedious **[30]**.

Solvent displacement/ solvent injection: This procedure involved is very similar to the solvent diffusion method. A water immiscible solvent was used to dissolve the lipid and the surfactants were rapidly injected into the aqueous phase of the lipid using an injection needle.

The process is simple and can be rapidly manufactured without using complicated apparatus. The drawback is the usage of organic solvents **[31]**.

Membrane contractor: Small lipid droplets are formed when lipids are forced under pressure through a porous membrane. At the same time, the aqueous phase of the lipid is swirled within the membrane unit, removing the lipid droplets away from the aperture. Lipid nanoparticles were prepared after cooling at room temperature. This is an uncomplicated process and involves basic equipment **[32]**.

EVALUATION AND CHARACTE-RIZATION OF NLCs

Determination of zeta potential, particle size, and polydispersity index (PDI): The zeta potential, particle size, and polydispersity index (PDI) of the NLCs were measured using a particle size analyzer. PDI helps to calculate the particle size distribution and is used to establish the type and nature of nanoparticles as monodisperse or polydisperse **[15, 8, 33]**.

Determination of entrapment efficiency and drug loading: The percentage of drug encapsulated into NLC and the loading ability is evaluated ultimately by the centrifugation/filtration method. Aliquot of 1.5 mL of the prepared NLC diffusion was positioned in the higher compartment of a membrane concentrator and was centrifuged for about 8 min at rpm of 4000. The amount of the drug unentrapped was collected from the remains of the lesser compartment and then determined the concentration of the drug (assay) by UV spectroscopy.

The Entrapment efficiency (% EE) and Loading Capacity (% LC) were calculated by the formula as given below.

$$EE\% = \frac{W_{initial\ drug} - W_{free\ drug}}{W_{initial\ drug}} \times 100 \quad \text{-----1}$$

$$LC\% = \frac{W_{initial\ drug} - W_{free\ drug}}{W_{lipid}} \times 100 \quad \text{-----2}$$

Where "$W_{initial\ drug}$" is the initial amount of the drug required for formulation of NLC, "$W_{free\ drug}$" is the

amount of free drug noticed in the filtrate, and "W_{lipid}" is the total amount of lipid utilized [15, 34, 17].

Surface characterization

Transmission electron microscopy (TEM): The size and morphological analysis of NLCs is measured by utilizing a TEM. Single drop of the suitably diluted formulation was scattered on a gold-glazed copper grid with 400 mesh size followed by air-drying of the sample at room temperature using vacuum (24 h) prior to the examination **[8, 33]**.

Solid-state characterization

Fourier Transform Infrared Spectroscopy (FT-IR): To characterize the physical interactions between the drug and selected excipients, FTIR is employed. The formulated sample was ground finely in a glass mortar with potassium bromide (KBr); and finally placed the mixture (pellets) in the sample holder and scanned in the wave number region of 4000 – 400 cm^{-1} **[8]**.

Differential scanning calorimetry (DSC): To assess alterations in the drug in physical mixture (drug with excipients) and in formulation for glass transition temperature, melting enthalpy, and excipients interactions DSC is employed. Sample will be placed in standard aluminium pans, scanned in the temperature range starting at 5 °C to a value above the drugs melting point with the rate of increase of temperature at 10 °C/min. Nitrogen gas was used as sewage gas (with flow rate of 50 ml/ min) to maintain an inert atmosphere **[33]**.

X-ray diffraction (XRD): XRD helps to measure the physical characteristics of the drug in both; the pure form and lipid matrix. X-ray powder spreading capacities were performed to ensure the drug's crystallinity in untainted and lyophilized drugs. The sample is scanned in the range of 2θ values between 10° and 40° using a step size range of 0.01° at every step **[15, 8, 33]**.

***In-vitro* drug release:** The dialysis bag technique is used to evaluate the drug and NLCs formulations. A pre-treated dialysis bag was filled with an equivalent amount of the prepared formulation of NLC to mg of the pure drug and dipped into a volume of 100 ml phosphate buffer (pH 7.4) and stirred at rpm of 100 using a magnetic stirrer at a temperature of 37°C. During the period of 24 h, aliquots of 1.0 mL of the release dissolution medium were withdrawn at a preset interval of time while substituting with new phosphate buffer solution every time. The withdrawn solution is filtered, appropriately diluted and the concentration of the drug released was assessed using HPLC. Suitable software was used to study the *in-vitro* drug release and to understand the mechanism of release of the drug from the NLCs, a suitable release model such as zero order,

first order, Hixson-Crowell, Higuchi, and Korsmeyer Peppas is determined **[15, 8]**.

Stability study: Stability studies are determined by studying the stability of the formulation 30 ± 2 °C, 65 ± 5% RH for a period of three months by placing the conserved vials of formulation in the stability chamber. The formulation is later analyzed by determining the parameters such as zeta potential, particle size of NLCs, entrapment efficiency of NLCs and *in-vitro* release profile of the drug and comparing the results to the original formulation at regular intervals **[8]**.

***Ex-Vivo* permeability studies:** Sheep nasal mucosa/pig mucous was used to study the *Ex-Vivo* permeation studies for pure drug and drug-loaded lipid carriers using Franz diffusion cell. Finally, the samples were collected from the diffusion cell, and the concentrations of the drug diffused across the tissues were analyzed using UV Spectroscopy **[15, 34]**.

***In-Vivo* evaluation studies**

Animal experimentation: Healthy Albino Wistar rats are used for *In-vivo* animal studies of the pure drug under consideration, optimized formulation as well as the blank formulations. The bioavailability and bio-distribution of the drug in the brain is assessed by the determination of the concentrations of the drug using a suitable HPLC method **[34]**.

GUIDELINES FOR DESIGN OF LIPID-BASED FORMULATIONS

Designing Lipid-based preparations can be a challenge, and in the future, it will continue to be a vital tool to formulate poorly soluble drugs.

Guidelines for the proposal of lipid-based formulations are as listed below;

- It is essential that the drug under study remains in a soluble state in the formation and after dispersion until it reaches the targeted site.
- After absorption, the properties of the drug while in the dispersed state are more important than the properties of the drug in the formulated state.
- Lipid quantity (more than 60%), surfactant volume (less than 30%), and cosolvent volume (less than 10%) helps in stable drug solubilization even after dilution.
- Effective drug solubility and stable formulations are obtained using medium-chain triglycerides and long-chain triglycerides, which enabled lipid colloidal groups to form, resulting in greater bioavailability.
- The properties of the surfactant used play a key role for the formation of smaller-sized droplets.

- Two surfactants rather than one surfactant were beneficial in type IV formulations (cosolvent/ surfactant).
- Type IV formulations are designed to have better drug solubility if the drug does not form a precipitate after the process of dispersion.

When formulating oral lipid-based systems for low soluble drugs, these guidelines are significant to keep in mind. Experience-based design results in the successful formulation of lipid drugs **[35]**.

MARKETED PRODUCTS FOR INTRANASAL ADMINISTRATION

In the past eras, intranasal delivery has been mostly accomplished for systemic deliverance for drugs possessing low molecular weight to ensure the faster commencement of action. Some of the examples that include various marketed nasal products are drugs usually intended used in the therapy of migraine, e.g., Butorphanol tartrate (Stadol NS), Sumatriptan (Imigran®), and Zomatriptan (Zomig®), management of severe pain, e.g., Fentanyl (Instanyl®; PcFent®) for therapy of menopausal symptoms (Aerodiol®) and termination of smoking (Nicorette®). Nasal absorption enhancers were not used in the above-mentioned formulations as the drug molecules were lipophilic to ensure that the suitable therapeutic levels entered into the systemic circulation.

Though some drugs, such as a variety of nasal peptide products, reached the therapeutic levels at less systemic concentrations despite their low bioavailability. The marketed drugs include desmopressin (Ferring, Desmospray®), Oxytocin (Syntocinon®, Unites pharmacies the UK), calcitonin (Miacalcin®, Novartis; Unigene, Fortical®), Nafarelin (Synarel®, Pharmacia), buserelin (Suprecur®, Sanofi-Aventis).

No formulations containing lipid nanoparticles for intranasal delivery are currently available on the market as it is a novel approach to drug delivery **[36]**.

A RECENT REVIEW OF RESEARCH ON NLCs

A recent review of research on NLCs as shown in tabulated form **(Table 2)**.

Table 2: A Recent Review of Research on NLCs

S. No.	DRUG	INFERENCE	REFERENCE
1	Ziprasidone	Authors formulated Ziprasidone hydrochloride (ZRS) loaded NLCs for intranasal delivery. Authors reported that pharmacokinetic studies in rats had showed that when the drug was given intranasally the concentration of drug in blood brain ration was found to be increased to 10 times when compared with the intravenous administration of the drug. Similarly the drug concentration in the brain also showed an increase by 4 times at all points.	[15]
2	Zotepine (Nanosuspension)	Authors formulated intranasal zotepine (ZTP) nanosuspension. Authors reported that when the drug was administered intranasally through nanosuspension formulation showed an increased concentrations of 8.6 times by sonoprecipitation method and by 10.79 times by AUC0 during a period of 24h when compared with concentration of the drug when administered intravenously but the histopathology studies indicated that no changes in drug concentrations were observed.	[33]

3	**Hydrochlorothiazide**	**Authors asseseesd the formulations prepared by the use of synthetic and natural liquid lipids. For the study, two different methodologies were used, i.e., homogenization-ultrasonication (HU) and microemulsion (ME). It was reported that the drug loaded NLC formulations reported better stability than the SLNs under study.**	**[17]**
4	**Quercetin**	**Authors formulated NLCs loaded with quercetin. The authors reported that the drug loaded NLCs indicated that the drug release was sustained. Major targeting to the brain was attained when compared to Quercetin.**	**[34]**
5	**Asenapine**	**Authors formulated asenapine maleate nanostructured lipid carriers (ANLCs) using high shear homogenization and sonication methods. Authors reported that outcomes of behavior research of ANLC exhibited a major reduction in extrapyramidal adverse effects with the rising antipsychotic result after a period of 1 or 2 weeks of treatment.**	**[8]**

FUTURE SCOPE FOR NOSE-TO BRAIN DRUG DELIVERY SYSTEM

The future prospects of this study is based on the intention to comprehend the basic mechanism of intranasal drug transport to the CNS and utilization of gained knowledge to expand formulation strategies and transportation strategies to enhance the treatment and management of various neurological diseases **[36, 37]**.

The NLC formulations under study can propose further success to the lipid carrier approach for the reason of various advanced attributes compared to the previously used delivery systems.

The evaluation of toxicity and health risk analogous with nanostructures is of concern as further investigation in preclinical and clinical research will favour the formulations using nano-lipid structures. The preparation of cost-effective formulation with a good therapeutic effect is a problem. Therefore, detailed investigations are required to utilize this route tremendously and successfully **[6, 13]**.

TOXICITY ASPECTS OF NLCs

Lipid-based colloidal carriers usually adapt easily in the biological systems due to the presence of physiological compounds that lead to various metabolic pathways, thereby lowering the perils of acute and chronic toxicity. The toxicity of the use of the emulsifiers must be contemplated. Studies showed no cytotoxic effects were observed *in-vitro* when the lipids carriers were formulated with concentrations of 2.5% lipids and various concentrations of emulsifying agents. Further, though the lipid phase concentration was more than 10 %, about 80% of the human granulocytes in culture were viable. Though the toxicity of NLCs has not been reported, it has to be studied **[13]**.

CONCLUSION

The Nose-to-Brain delivery approach can replace invasive drug transportation methods to the brain in enhanced drug absorption and low systemic adverse effects. Considering the NLCs through intranasal route is recommended in various CNS disorders to help multiple products

reach the market. Extensive drug delivery studies from the nose to the brain by the utilization of NLCs may result in the decreased traditional therapy dosing and adverse effects. NLCs enhance the nasal drug absorption by improving nasal retention, drug permeation time and circumvent enzymatic degeneration to achieve giant therapeutic efficiency. Lipid nanocarriers may be appealing to the industrial sector due to the certified and endorsed scale-up of technology.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of this article.

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