IJPSR (2020), Volume 11, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 December 2019; received in revised form, 31 January 2020; accepted, 11 March 2020; published 01 October 2020

LIPID-BASED NANOCARRIER DRUG DELIVERY SYSTEM FOR BRAIN TARGETING THROUGH NASAL ROUTE: A REVIEW

Krishnanand Anilkumar, Kavinkumar Sakthivel and Senthil Venkatachalam *

Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty - 643001, Tamil Nadu, India.

Keywords:

Nasal route, Blood-Brain Barrier, Permeability, Nanocarrier

Correspondence to Author:
Dr. Senthil Venkatachalam

Professor,
Department of Pharmaceutics,
JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty - 643001, Tamil Nadu, India.

E-mail: senthil.v@jssuni.edu.in

ABSTRACT: The majority of the drugs that are available in the market which are intended for activity in the central nervous system, are not capable of being transported across the Blood-brain barrier. The nasal route of drug administration is one of the most promising routes of drug administration that can permeate the drug through BBB. The permeability of drugs across the BBB is depending on the physicochemical properties of the drugs. Drugs with molecular weight lesser than 600Daltons and partition coefficient (Log P) within the range of 1.5-2.7 might pass through the BBB. Nanocarriers are capable of getting drugs with higher molecular weight transported across the BBB. Incorporating the drug into these carriers can facilitate the transfer of drugs across BBB. SLNs and NLCs are the most prominent carrier of drugs that can be employed for the transfer of drugs to the CNS. The drugs, when administered through nasal route, are carried across the BBB mainly through two major pathways, they are olfactory pathway and trigeminal pathway. The main disadvantage of nano carrier-based drug delivery is increased toxicity level; this is mainly because these carriers might not be removed from the brain, and this will get accumulated and thereby can cause toxicity. This review is focusing on the mechanism of drug transfer to the brain through the nasal route, the pathways involved, the nature of BBB, features of SLNs and NLCs, commonly employed excipients for the preparation of both and drugs that are administered using these carriers.

INTRODUCTION: The central nervous system required well-regulated conditions and homeostasis for the proper functioning. The optimum environment required for the CNS is different from the rest of the organs. These conditions required for the CNS is maintained with the help of blood-brain barrier [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(10).4774-83

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(10).4774-83

BBB protects CNS in normal physiological and pathological conditions. The BBB provides a separation between the nervous tissue of the brain and the spinal cord with the remaining part of the body. BBB isolates the brain from fluctuations in nutrients, hormones, metabolites, and other blood constituents present in the circulation. BBB is an important feature for the maintenance of the microclimate of the CNS and thereby to maintain secure neuronal transmissions [2, 3, 4, 5].

The most challenging part of drug targeting to the brain is permeating through the BBB. This is mainly due to the anatomical and physiological characteristics of the BBB.

More than 98% of the drugs intended for the CNS activity are impermeable to BBB. The permeability of drugs across the BBB is depending on the physicochemical properties of the drugs. Drugs with molecular weight lesser than 600 Daltons and partition coefficient (Log P) within the range of 1.5-2.7 might pass through the BBB [6, 7]. The permeation of drugs and other materials from blood circulation to the brain is limited by BBB along with it BBB contains some transporters, mainly P-glycoprotein (P-gp) efflux transporter limits the entry of drugs to the CNS [8]. This is creating difficulty to researchers in developing formulations for effective treatment of many CNS disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, etc. Researchers have developed many invasive and non-invasive methods to target the brain. Among the non-invasive techniques, nasal drug delivery has emerged as a promising approach for delivering the drug into the brain. The nasal administration of a drug into the brain can be done by exploiting the olfactory and trigeminal pathway. Many research has taken place to study the effect of brain delivery through the nasal route to overcome the limitations of brain delivery [6, 9-12]. The advantages of using the nasal drug delivery for brain targeting is that the method is useful in bypassing the hepatic first-pass metabolism, the method is a non-invasive, convenient method of administration, and reportedly safe mode of administration [13]. Only direct contact of the CNS with the peripheral environment is through the olfactory region. The drug that is administered through the nasal route comes in contact with mucosa it will get absorbed into the brain, thereby maintaining excellent bioavailability and reducing the dose and side effects.

In spite of having so many advantages, the nasal drug delivery system has many disadvantages, which include the low volume of the nasal cavity, mucociliary clearance, and nasal enzymatic barriers [14]. These limitations created a need for the development of advanced novel drug delivery methods. This lead to the evolution of nanotechnology-based drug delivery through nasal route [15]. Nanotechnology has great applications in the medical and allied fields of sciences. The problems associated with nanotechnology-based drug delivery is the toxicity related to them. Nanoparticles are capable of reaching the brain, but they may not get cleared from the brain. It will lead to the accumulation of nanoparticles in the brain and will cause toxicity [16, 17].

Blood-Brain Barrier: [18] Blood-brain barrier is the part of the CNS of all organisms that are having a well-developed nervous system. BBB is present in the brain and spinal cord of mammals. The anatomically BBB is the cerebral microvascular endothelium, which, along with astrocytes, pericytes, neurons, and the extracellular matrix, constitute a "neurovascular unit" that is essential for the health and functions of the CNS. The BBB provides about 12 - 18m^2 area for exchange in the brain for an average adult human. BBB consist of tight junctions formed by cerebral endothelial cells, the choroid plexus, epithelial cells, and the cells of the arachnoid epithelium.

Polar solutes reach the brain through paracellular diffusional pathways. The solutes diffuse through the endothelial cells from the blood plasma to the brain extracellular fluid. This mechanism is reduced due to the presence of tight junctions.

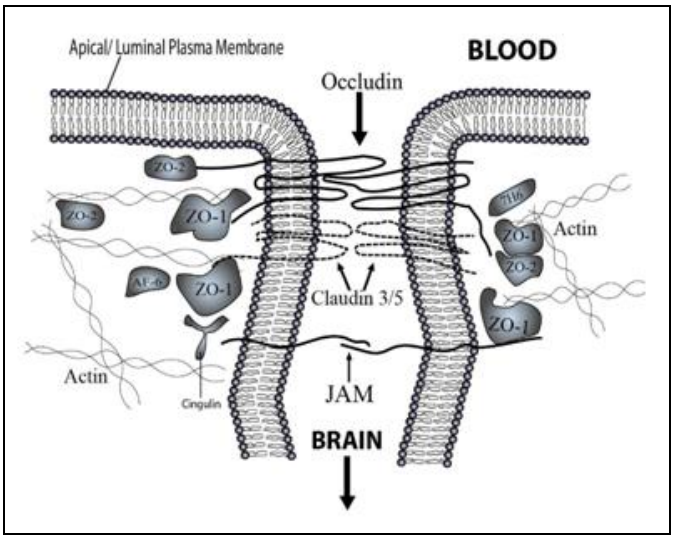

FIG. 1: BASIC MOLECULAR ORGANIZATION OF BLOOD-BRAIN BARRIER TIGHT JUNCTIONS

Most of the drugs available in the market are not capable of crossing the BBB. For a drug to cross BBB in pharmacologically significant amounts the drug molecule should have the following characters:

- The molecular mass of the drug should be under the 400-500Da threshold.
- High lipid solubility

Nasal Route: [19, 20] Since, the BBB is impermeable to most of the drugs, delivering the drugs in therapeutically sufficient concentration into the brain is a tedious task. Many methods are being employed for brain targeting of the drugs. One of the most convenient routes among them is the nasal route of drug administration. This method proves efficient in delivering the drugs without causing damage to the BBB. There is a unique connection between the brain and the nasal route through which the drug can be delivered, bypassing the BBB.

Drug administered through the nasal route reaches the brain mainly through two pathways [21, 22]. They are the olfactory pathway and trigeminal nerves. These pathways provide a safe and effective method for brain drug delivery.

Olfactory Pathway: Drug delivery through the olfactory pathway is accomplished by administering the drug deep into the nasal cavity. This will bring the drug in contact with the nasal mucosa, which will lead to the transfer of drugs directly into the brain through the olfactory pathway [23]. The mechanism of drug transport through the olfactory pathway is not clear. This pathway of the olfactory route is composed of the olfactory bulb, *Lamina propria* and epithelium [20]. The epithelium of the olfactory region consists of three different types of cells, they are supporting cells, progenitor cells, and neuronal cells, and these all are connected through tight junctions. The olfactory pathway has two methods for the transmission of the drug to the brain:

Olfactory Neurons: Drug is carried from the olfactory mucosa to the brain with the help of neurons. But this mechanism is slower in transmitting the drug to the brain.

Olfactory Epithelium: This mechanism is faster for the transmission of the drug. The drug is transmitted to the perineural space through the olfactory epithelium using the paracellular mechanism to get transferred into the brain directly.

Trigeminal Pathway: The trigeminal pathway is another mechanism for the transport of drug through the nasal route. In this pathway, the drug is absorbed from the nasal cavity, which is innervated by the cranial nerve V (trigeminal).

There are three branches for trigeminal nerve; they are ophthalmic nerve, maxillary nerve, and mandibular nerve and these branches are producing sensations in the nasal cavity. These nerves enter into the brainstem through the pons and it enters to forebrain through cribriform plate resulting in drug entering to caudal and rostral parts of the brain [24].

The olfactory pathway is delivering the drug only to the rostral area of the brain, but the trigeminal pathway delivers both to the rostral and caudal area of the brain [21, 22, 23], this makes it difficult to distinguish whether the drug reached the rostral area by olfactory or trigeminal pathway. Intranasally administered drug may get transported through the olfactory or trigeminal pathway

Mechanism of Nasal Transport: Drug administered through the nasal route has to overcome many hurdles like mucus layer and continuously beating cilia. The movements of cilia are controlled by the ciliated columnar cells present in the nasal epithelium [20]. Cilia in the olfactory region do not have a dynein arm, so they are immobile, but in the respiratory area, cilia are mobile. The drug which crosses this barrier is further carried across the nasal mucosa by either the transcellular mechanism or paracellular mechanism depicted in **Fig. 2**.

Transcellular Transport: Transcellular transport of molecules across BBB is a slow and time taking process. Endocytosis mediated by receptors is the pathway for the transport of molecules through BBB. Transcellular transport is receptor-mediated endocytosis by the mechanisms of clarithrin-dependant or independent transfer [25]. The trigeminal ganglions, olfactory epithelium, olfactory bulb contains nicotinic acetylcholine receptors, and these receptors are responsible for the receptor-mediated endocytosis.

Particle size plays an important role in the selection of a mechanism for endocytosis. Particle within the size range of 100-200nm is transported through caveolae-mediated endocytosis and particles less than the size of 200nm is transported through clathrin-dependent endocytosis [26]. The endocytosis pathway is affected by factors like cell type, surface charge, and concentration of the particles applied to the cells [27].

Paracellular Transport: Different junctions such as tight junction, zonula adherens, and macular adherens connects the cells in nasal epithelium with each other [28]. In normal conditions, these junctions are not permeable to large molecules, but on continuous turnover of neuronal and basal cells, it becomes permeable [29]. This process of increasing the permeation of these junctions will promote paracellular transport. The mechanism of drug transfer is depicted in **Fig. 2**.

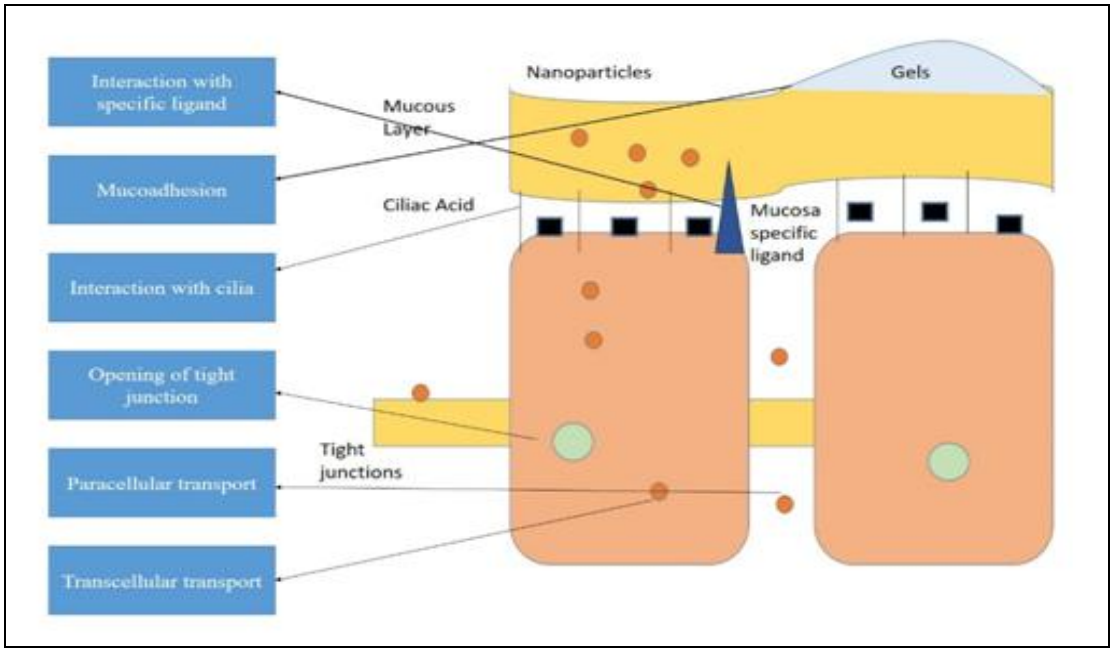

FIG. 2: POSSIBLE MECHANISMS FOR THE TRANSFER OF DRUG ACROSS THE BBB WHEN ADMINISTERED THROUGH NASAL ROUTE

Drugs for Nasal Administration: Different formulations can be prepared for the purpose of administration into the brain through the nasal route. The drug can be administered through the nasal route by mainly three mechanisms, drug delivery devices, and drug delivery systems like nano or micro-delivery system or with novel formulation strategies. The list of different formulation that can be administered through the nasal route is given in **Fig. 3**.

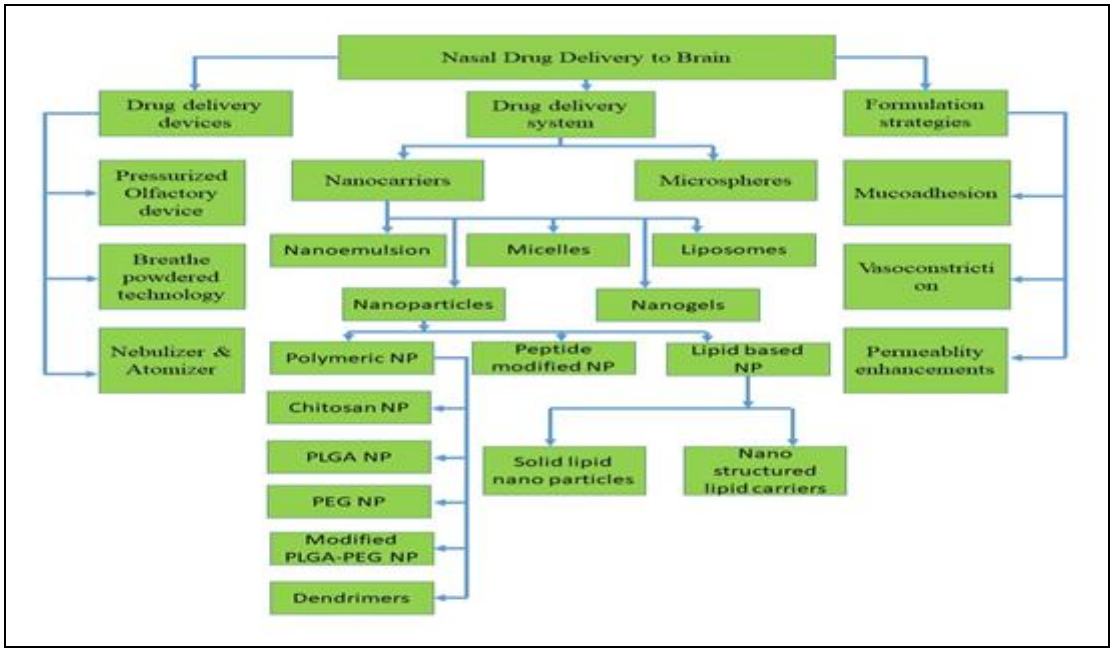

FIG. 3: DIFFERENT DRUG DELIVERY SYSTEMS THAT CAN BE EMPLOYED IN DELIVERING THE DRUG INTO THE BRAIN THROUGH NASAL ROUTE

Solid Lipid Nanoparticles: Solid lipid nanoparticles were developed during the first half of the 1990s, it was prepared by combining the advantages of solid particles, emulsions and liposomes combined [30]. The basic concept of SLNs is simple, the liquid lipid in emulsions is replaced by a solid lipid. SLNs are prepared mainly by the two methods; they are a high-pressure homogenization technique developed by Muller and Lucks [31] and a microemulsion technique invented by Gasco and Turin [32].

TABLE 1: LIPIDS AND EMULSIFIERS USED FOR PREPARATION OF SLN [33]

Lipids	Emulsifiers/coemulsifiers
Triglycerides	Soybean lecithin
Tricaprin	(Lipoid® S 75, Lipoid® S 100)
Trilaurin	
Trimyristin	Egg lecithin (Lipoid® E 80)
Tripalmitin	Phosphatidylcholine
Tristearin	(Epikuron® 170, Epikuron
Hydrogenatedcoco-glycerides	200)
(Softisan®142)	Poloxamer 188
	Poloxamer 182
Hard fat types	Poloxamer 407
	Poloxamine 908
Witepsol® W 35	Tyloxapol
Witepsol® H 35	Polysorbate 20
Witepsol® H 42	Polysorbate 60
Witepsol® E 85	Polysorbate 80
Glyceryl monostearate	Sodium cholate
(Imwitor®900)	Sodium glycocholate
Glyceryl behenate	
(Compritol® 888 ATO)	Taurocholic acid sodium salt
Glyceryl palmitostearate	Taurodeoxycholic acid sodium
(Precirol® ATO 5)	salt
	Butanol
Cetyl palmitate	Butyric acid
	Dioctyl sodium sulfosuccinate
Stearic acid	Monooctylphosphoric acid
Palmitic acid	sodium
Decanoic acid	
Behenic acid	
Acidan N12	

Advantages of SLNs: [33]

- Possibility of controlled release and drug targeting
- Increase in the stability of the drug
- Incorporation of lipophilic and hydrophilic drug
- Organic solvents can be avoided
- Scale-up of technology is easy
- Sterilization of large quantities is easy.

Disadvantages of SLN: [31]

- Insufficient drug loading
- Expulsion of the drug from carriers due to polymorphic changes during storage
- Relatively high water content

TABLE 2: LIST OF DRUGS THAT CAN BE INCORPORATED IN SLNS

Drugs
Timolol
Deoxycorticosterone
Doxorubicin
Idarubicin
[d–Trp–6]LHRH
Pilocarpine
Thymopentin
Diazepam
Gadolinium (III) complexes
Progesterone
Hydrocortisone
Paclitaxel
Retinol
Coenzyme Q10
Vitamin E palmitate
Aciclovir
Prednisolone
Tetracaine
Etomidate
Cyclosporine
Sunscreens
Nimesulide
30-Azido-30deoxythymidinepalmitate
Azido thymidine palmitate
Oxazepam
Diazepam
Cortisone
Betamethasone valerate
Prednisolone
Retinol
Menadione
Ubidecarenone
Camptothecin
Piribedil

Nanostructured Lipid Carriers: These NLCs are second-generation nanoparticle carriers for drug delivery. NLCs act as a bioactive carrier system. The above-mentioned limitations of SLNs can be overcome with the development of NLCs. The problem of drug expulsion is reduced in NLCs by using lipid blends that do not form a highly ordered crystalline arrangement.

The matrix system of NLCs is mixture of different lipids, normally solid lipid and liquid lipid is present in the matrix system. This arrangement will

provide imperfections to the matrix whereby more drugs can be incorporated in the carrier than that of SLN [33]. NLCs remain solid at room temperature and body temperature even after the incorporation of liquid lipids. The formulation of NLCs is having low systemic side effects [33, 34].

Advantages of NLCs:

- Physical stability is better.
- Scale up to a large scale is easy.
- Dispersibility in an aqueous medium can be increased.
- Entrapment efficiency for hydrophilic and lipophilic drugs is high.
- Particle size is controlled.
- Skin occlusion can be increased.
- Extended-release of drugs possible.
- Drug penetration is high.

Disadvantages of NLCs:

- The nature of matrix and concentration can lead to cytotoxic effects.
- Surfactants used can create irritations and sensitizing action.

TABLE 3: COMPONENTS USED IN THE MANUFACTURE OF NLCS [35]

Components	Solid lipids	Liquid lipids	Hydrophilic emulsifier	Lipophilic emulsifiers	Amphiphilic emulsifiers
Materials	Tristearin Stearic acid Cetyl palmitate Cholesterol Precirol® ATO 5 Compritol® 888 ATO Dynasan®116 Dynasan® 118 Softisan® 154 Cutina® CP Imwitor® 900 P Geleol® Gelot® 64 Emulcire® 61	Medium-chain triglycerides paraffin oil 2-octyl dodecanol oleic acid squalene isopropyl myristate vitamin E Miglyol® 812 Transcutol® HP Labrafil Lipofile® WL 1349 Labrafac® PG Lauroglycol® FCC Capryol® 90	Pluronic® F68 (poloxamer 188) Pluronic® F127 (poloxamer 407) Tween 20 Tween 40 Tween80 polyvinyl alcohol Solutol® HS15 Trehalose sodium deoxycholate sodium glycocholate sodium oleate polyglycerol methyl glucose distearate	Myverol® 18-04K Span 20 Span 40 Span 60	Egg lecithin soya lecithin phosphatidylcholines phosphatidylethanolamines, Gelucire® 50/13

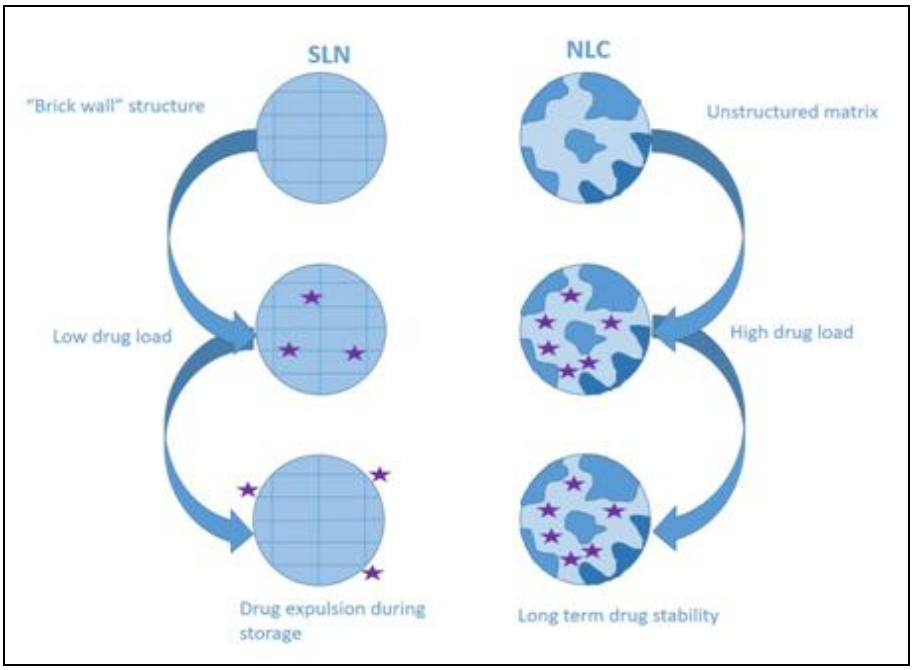

FIG. 4: SCHEMATIC DIAGRAM OF SLNS AND NLCS FOR HIGHLIGHTING THE ADVANTAGES OF NLCS

TABLE 4: LIST OF REPORTED FORMULATION OF NLCS ALONG WITH THE SAFETY DATA OF EACH INGREDIENTS AND TECHNIQUE USED FOR THE PREPARATION [36]

Drug	Solid Lipid		Liquid Lipid		Surfactant		Method
	Name	Toxicity data	Name	Toxicity data	Name	Toxicity data	
CoenzymeQ10	Hard Stearin	-	GTCC	-	Alkyl polyglycoside	-	HPH
Brimonidine base	Glyceryl monostearate (GMS)	LD_{50} (mouse, IP): 0.2 g/kg	Castor oil	Non irritant	Poloxamer188	LD_{50} (mouse, IV): 1 g/kg LD_{50} (mouse, oral): 15 g/kg LD_{50} (mouse, SC): 5.5 g/kg LD_{50} (rat, IV): 7.5 g/kg LD_{50} (rat, oral): 9.4 g/kg	HPH
Lornoxicame	Compritol-888ATO	LD_{50} (mouse, oral): 5 g/kg	Oleic Acid (OA)	LD_{50} (mouse, IV): 0.23 g/kg LD_{50} (rat, IV): 2.4 mg/kg LD_{50} (rat, oral): 74 g/kg	Pluronic F68	Same as poloxamer 188	HPH
Quercetin	Lanette O Imwitor 900 K	Non irritant LD_{50} (mouse, IP): 0.2 g/kg	Medium Chain Triglycerides (MCT)	LD_{50} (mouse, IV): 3.7 g/kg LD_{50} (mouse, oral): 29.6 g/kg LD_{50} (rat, oral): 33.3 g/kg	Span20 Tween80 Soybean lecithin	LD_{50} (rat, oral): 33.6 g/kg LD_{50} (mouse, IP): 7.6 g/kg LD_{50} (mouse, IV): 4.5 g/kg LD_{50} (mouse, oral): 25 g/kg LD_{50} (rat, IP): 6.8 g/kg LD_{50} (rat, IV): 1.8 g/kg 1.95% to 15.0% in rinse-off and leave-in products	HPH
Saquinavir mesylate	Precirol ATO5	LD_{50} (rat, oral): >6 g/kg	Miglyol812	Same as MCT	Tween80 Poloxamer188	Given above Given above	HPH
UvinulT 150	ACETEM	-	Hydrogenated palm oil	Non toxic	OlivemR8001 OlivemR1000	-	HPH
thymoquinone	Lipoid S100	1.95% to 15.0% in rinse-off and leave-in products	Olive oil	Non-toxic and non-irritant	Sorbitol Thimerosal Polysorbate80	LD_{50} (mouse, IV): 9.48 g/kg(20) LD_{50} (mouse, oral): 17.8 g/kg LD_{50} (rat, IV): 7.1 g/kg LD_{50} (rat, SC): 29.6 g/kg LD_{50} (mouse, oral): 91 mg/kg(40) LD_{50} (rat, oral): 75 mg/kg LD_{50} (rat, SC): 98 mg/kg Given above	HPH
Docetaxel	Stearic acid	LD_{50} (rat, inhalation): >2 mg/L(2) LD_{50} (rat, oral): >10 g/kg	MCT OA	LD_{50} (mouse, IV): 3.7 g/kg LD_{50} (mouse, oral): 29.6 g/kg LD_{50} (rat, oral): 33.3 g/kg LD_{50} (mouse, IV): 0.23 g/kg LD_{50} (rat, IV): 2.4 mg/kg LD_{50} (rat, oral): 74 g/kg	Cremophor EL Pluronic F68	LD_{50} Cat (oral) >10 g/kg LD_{50} Dog (IV) 0.64 g/kg LD_{50} Mouse (IV) 2.5 g/kg LD_{50} Rabbit (oral) >10 g/kg LD_{50} Rat (oral) >6.4 g/kg Given above	HPH
4-dedimethylamino sancycline	Glycerin monostearate	LD_{50} (mouse, IP): 0.2 g/kg			LutrolF68	Same as poloxamer 188	HPH
β-carotene	Hydrogenated palm kernel		Isopropyl palmitate	LD_{50} (mouse, IP): 0.1 g/kg	Sorbitan monopalmitate Polysorbate80	25 mg/kg body-weight Given above	HPH

Tocolsenzophenone-3	Glycerides	-	Isodecyl oleate	-	Poloxamer188	Given above	HPH
	Carnauba wax	upto 7 mg/kg body-weight			Polysorbate80	Given above	
β-Elemene	GMS	LD_{50} (mouse, IP): 0.2 g/kg	Maisine35-1	-	Polysorbate80	Given above	HPH
			Labrafil	-	soybean lecithin	Given above	
Fenofibrate	Compritol888, ATO	LD_{50} (mouse, oral): 5 g/kg	M1944CS	-	Soya lecithin	Given above	HPH
			Labrafil		Polysorbate80	Given above	
Lercanidipine HCl	GMS	LD_{50} (mouse, IP): 0.2 g/kg	Linseed oil	-	Polysorbate80	Given above	Ultra-sonication and emulsion evaporation
			Labrafil	-			
Minoxidil	Soya lecithin	1.95% to 15.0% in rinse-off and leave-in products	OA	LD_{50} (mouse, IV): 0.23 g/kg LD_{50} (rat, IV): 2.4 mg/kg LD_{50} (rat, oral): 74 g/kg	Polysorbate80	Given above	Ultra-sonication & emulsion evaporation
Dexamethasone	glycerol trilaurate		Tristearin	-	Phospholipids	Same as soy lecithin	Solvent diffusion
			Medium Chain Triglycerides Miglyol 812	LD_{50} (mouse, IV): 3.7 g/kg LD_{50} (mouse, oral): 29.6 g/kg LD_{50} (rat, oral): 33.3 g/kg			
Isoliquiritigenin	Soya lecithin, Cholesterol	Given above	Glycerol - trioleate	-	Polysorbate80	Given above	Solvent diffusion
					Poloxamer188	Given above	
Celastrol	Precirol ATO-5	LD_{50} (rat, oral): >6 g/kg	Labrasol	-	Lecithin, TPGS	Same as soy lecithin 0.15–2.0 mg/kg body-weight	Solvent diffusion
					Poloxamer188	Given above	
Gentiopicroside	Glycerin monostearate	LD_{50} (mouse, IP): 0.2 g/kg	OA	LD_{50} (mouse, IV): 0.23 g/kg	Polysorbate80	Given above	Solvent diffusion
Paclitaxel	Cholesterol	Exhibited experimental teratogenic and reproductive effects, and mutation data have been reported		LD_{50} (rat, IV): 2.4 mg/kg LD_{50} (rat, oral): 74 g/kg	Poloxamer188	Given above	Solvent diffusion
Curcumin	Cetyl Palmitate(CP)	LD_{50} (rat, oral): >16 g/kg	Miglyol 812	Same as MCT	Solutol HS15	Given above	Film-ultrasonic emulsion evaporation
Celecoxib	Kollicream CP	LD_{50} (rat, oral): >16 g/kg			Soya lecithin	Given above	low temperature solidification
Amoitone B	Polyethylene glycol stearate GMS	LD_{50} (mouse, IP): 0.2 g/kg	Caprylic/capric triglyceride	Same as MCT	Pluronic F68	Same as poloxamer 188	Emulsion evaporation, low temperature solidification
					Soya lecithin	Given above	
Paclitaxel DNA	GMS	LD_{50} (mouse, IP): 0.2 g/kg 1.95% to 15.0% in rinse-off and leave-in products	OA	Given above	Polysorbate80	Given above	Micro emulsion
	Soya lecithin						
Fenofibrate	Precirol ATO 5	LD_{50} (rat, oral): >6 g/kg	Captex100	Same as MCT	Polysorbate80		Melting-emulsification

Reported Combinations that gave Better Loading Efficiency: A combination of hard stearin and GTCC as lipids and alkyl polyglycoside as a surfactant was used for the preparation of Coenzyme Q10 NLCs using high-pressure homogenization is reported to have 99.58 ± 0.0061% entrapment efficiency [37]. Fenofibrate NLCs prepared using Compritol 888 ATO and M1944CS Labrafil with Soya lecithin and Polysorbate 80 as surfactant by HPH have reported 99% entrapment efficiency [38]. Another reported combination with good entrapment efficiency is using Compritol888 ATO and Lanette O as solid lipid, oleic acid as liquid lipid, and Pluronic F68 as a surfactant for the preparation of Lornoxicame by high-pressure homogenization. The entrapment efficiency reported is 97.89 ± 0.25% [39]. Isoliquiri-tigenin NLCs prepared using Soya lecithin and Cholesterol as solid lipids, and Glycerol trioleate as liquid lipid along with the surfactants Polysorbate80 and Poloxamer188 by Solvent diffusion method gave 96.74 ± 1.81% entrapment efficiency [40]. 96.7 ± 0.146% entrapment efficiency was reported for Curcumin NLCs prepared with Cetyl palmitate and Miglyol 812 as solid and liquid lipids and Solutol HS15 and Soya lecithin as surfactants by Film-ultrasonic emulsion evaporation technique [40].

CONCLUSION: Nano-carriers is one of the most promising techniques for the targeting of drugs to specific organs like the brain. The nano-carriers are capable of delivering less permeable drugs into the organs and are capable of sustained release of drugs. Nasal to brain route is one of the most promising routes of administration for delivering a drug into the brain, bypassing the first-pass metabolism. Also, this route can prevent the drug from reaching the circulation, thereby reducing the chance of toxicity to other organs. Both SLNs and NLCs are very good carriers of the drug. But NLCs are more advanced than SLNs and do not have many of the disadvantages that SLNs are having. Poloxamer 188, soy lecithin, compritol 888 ATO, medium-chain triglycerides, oleic acid, *etc*. are the most commonly used excipients in the preparation of NLCs and SLNs.

ACKNOWLEDGEMENT: The author thanks JSS Academy of Higher Education and Research, for providing the necessary facility to accomplish the work.

CONFLICTS OF INTEREST: The author(s) confirm that this article content has no conflict of interest.

REFERENCES:

1. Larsen Jm, Martin DR and Byrne ME: Recent advances in delivery through the blood-brain barrier. Current Topics in Medicinal Chemistry 2014; 14(9): 1148-60.
2. Abbott NJ, Rönnbäck L and Hansson E: Astrocyte–endothelial interactions at the blood–brain barrier. Nature Reviews Neuroscience 2006; 7(1): 41.
3. Braun LD, Cornford EM and Oldendorf WH: Newborn rabbit blood–brain barrier is selectively permeable and differs substantially from the adult. Journal of Neurochemistry 1980; 34(1): 147-52.
4. Zhao Z, Nelson AR, Betsholtz C and Zlokovic BV: Establishment and dysfunction of the blood-brain barrier. Cell 2015; 163(5): 1064-78.
5. Pardridge WM: Blood–brain barrier endogenous transporters as therapeutic targets: a new model for small molecule CNS drug discovery. Expert Opinion on Therapeutic Targets 2015; 19(8): 1059-72.
6. Pardridge WM: Drug transport across the blood–brain barrier. Journal of Cerebral Blood Flow & Metabolism 2012; 32(11): 1959-72.
7. Daneman R and Prat A: Cold spring harbor perspect. Biol 2015; 7: a020412.
8. Miller DS: Regulation of P-glycoprotein and other ABC drug transporters at the blood–brain barrier. Trends in Pharmacological Sciences 2010; 31(6): 246-54.
9. Fang C, Zhang C and Chang EC: An optimization model for aesthetic two-dimensional barcodes. In International Conference on Multimedia Modeling 2014 Jan 6 (278-290). Springer, Cham.
10. Chan KY, Jang MJ, Yoo BB, Greenbaum A, Ravi N, Wu WL, Sánchez-Guardado L, Lois C, Mazmanian SK, Deverman BE and Gradinaru V: Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems. Nature Neuroscience 2017; 20(8): 1172.
11. Mitragotri S, Anderson DG, Chen X, Chow EK, Ho D, Kabanov AV, Karp JM, Kataoka K, Mirkin CA, Petrosko SH and Shi J: Accelerating the translation of nanomaterials in biomedicine, ACS Nano 2015; 6644-54.
12. Yemisci M, Caban S, Gursoy-Ozdemir Y, Lule S, Novoa-Carballal R, Riguera R, Fernandez-Megia E, Andrieux K, Couvreur P, Capan Y and Dalkara T: Systemically administered brain-targeted nanoparticles transport peptides across the blood-brain barrier and provide neuroprotection. Journal of Cerebral Blood Flow & Metabolism 2015; 35(3): 469-75.
13. Zuchero YJ, Chen X, Bien-Ly N, Bumbaca D, Tong RK, Gao X, Zhang S, Hoyte K, Luk W, Huntley MA and Phu L: Discovery of novel blood-brain barrier targets to enhance brain uptake of therapeutic antibodies. Neuron 2016; 89(1): 70-82.
14. Mc Carthy DJ, Malhotra M, O'Mahony AM, Cryan JF and O'Driscoll CM: Nanoparticles and the blood-brain barrier: advancing from *in-vitro* models towards therapeutic significance. Pharmaceutical Res 2015; 32(4): 1161-85.

15. Ali J, Ali M, Baboota S, Kaur Sahni J, Ramassamy C and Dao L: Potential of nanoparticulate drug delivery systems by intranasal administration. Current Pharmaceutical Design 2010; 16(14): 1644-53.
16. Medina C, Santos- Martinez MJ, Radomski A, Corrigan OI and Radomski MW: Nanoparticles: pharmacological and toxicological significance. British Journal of Pharmacology 2007; 150(5): 552-8.
17. Sharma HS and Sharma A: Nanoparticles aggravate heat stress induced cognitive deficits, blood–brain barrier disruption, edema formation and brain pathology. Progress in Brain Research 2007; 162: 245-73.
18. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR and Begley DJ: Structure and function of the blood–brain barrier. Neurobiology of Disease 2010; 37(1): 13-25.
19. Vyas TK, Shahiwala A, Marathe S and Misra A: Intranasal drug delivery for brain targeting. Current Drug Delivery 2005; 2(2): 165-75.
20. Khan AR, Liu M, Khan MW and Zhai G: Progress in brain targeting drug delivery system by nasal route. Journal of Controlled Release 2017; 268: 364-89.
21. Erdő F, Bors LA, Farkas D, Bajza Á and Gizurarson S: Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Research Bulletin 2018; 143: 155-70.
22. Crowe TP, Greenlee MH, Kanthasamy AG and Hsu WH: Mechanism of intranasal drug delivery directly to the brain. Life Sciences 2018; 195: 44-52.
23. Leopold DA: The relationship between nasal anatomy and human olfaction. The Laryngoscope 1988; 98(11): 1232-8.
24. Samaridou E and Alonso MJ: Nose-to-brain peptide delivery–The potential of nanotechnology. Bioorganic & Medicinal Chemistry 2018; 26(10): 2888-05.
25. Pires PC and Santos AO: Nanosystems in nose-to-brain drug delivery: A review of non-clinical brain targeting studies. Journal of Controlled Release 2018; 270: 89-100.
26. Rejman J, Oberle V, Zuhorn IS and Hoekstra D: Size-dependent internalization of particles *via* the pathways of clathrin-and caveolae-mediated endocytosis. Biochemical Journal 2004; 377(1): 159-69.
27. Jones AT: Gateways and tools for drug delivery: endocytic pathways and the cellular dynamics of cell penetrating peptides. International Journal of Pharmaceutics 2008; 354(1-2): 34-8.
28. Van Itallie CM and Anderson JM: Claudins and epithelial paracellular transport. Annu Rev Physiol 2006; 68: 403-29.
29. Selvaraj K, Gowthamarajan K and Karri VV: Nose to brain transport pathways an overview: Potential of nanostructured lipid carriers in nose to brain targeting. Artificial Cells, Nanomedicine, and Biotechnology 2018; 46(8): 2088-95.
30. Chaudhri N, Soni GC and Prajapati SK: Nanotechnology: an advance tool for nano-cosmetics preparation. International Journal of Pharma Research & Review 2015; 4(4): 28-40.
31. Muller RH: Arzneistofftragerausfestenlipidteilchen (Feste Lipid nanospharen (SLN)). Eur. Patent EP 0605497 B1. 1996.
32. Abadier M, Jahromi NH, Cardoso Alves L, Boscacci R, Vestweber D, Barnum S, Deutsch U, Engelhardt B and Lyck R: Cell surface levels of endothelial ICAM- 1 influence the transcellular or paracellular T- cell diapedesis across the blood–brain barrier. European Journal of Immunology 2015; 45(4): 1043-58.
33. Balguri SP, Adelli GR and Majumdar S: Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. European Journal of Pharmaceutics and Biopharmaceutics 2016; 109: 224-35.
34. Kaur S, Nautyal U, Singh R, Singh S and Devi A: Nanostructure Lipid Carrier (NLC): the new generation of lipid nanoparticles. Asi Pac J Health Sci 2015; 2(2): 76-93.
35. Li Q, Cai T, Huang Y, Xia X, Cole SP and Cai Y: A review of the structure, preparation, and application of NLCs, PNPs, and PLNs. Nanomaterials 2017; 7(6): 122.
36. Poonia N, Kharb R, Lather V and Pandita D: Nanostructured lipid carriers: versatile oral delivery vehicle. Future science OA. 2016; 2(3): FSO135.
37. Tran TH, Ramasamy T, Truong DH, Choi HG, Yong CS and Kim JO: Preparation and characterization of fenofibrate-loaded nanostructured lipid carriers for oral bioavailability enhancement. AAPS Pharmscitech 2014; 15(6): 1509-15.
38. Yang X, Zhao L, Almasy L, Garamus VM, Zou A, Willumeit R and Fan S: Preparation and characterization of 4-dedimethylamino sancycline (CMT-3) loaded nanostructured lipid carrier (CMT-3/NLC) formulations. International Journal of Pharmaceutics 2013; 450(1-2): 225-34.
39. Zhang XY, Qiao H, Ni JM, Shi YB and Qiang Y: Preparation of isoliquiritigenin-loaded nanostructured lipid carrier and the *in-vivo* evaluation in tumor-bearing mice. European Journal of Pharmaceutical Sciences 2013; 49(3): 411-22.
40. Hong W, Chen DW, Zhao XL, Qiao MX and Hu HY: Preparation and study *in-vitro* of long-circulating nanoliposomes of curcumin. Zhongguo Zhong yao za zhi= Zhongguozhongyaozazhi= China journal of Chinese materiamedica 2008; 33(8): 889-92.

How to cite this article:
Anilkumar K, Sakthivel K and Venkatachalam S: Lipid-based nanocarrier drug delivery system for brain targeting through nasal route: a review. Int J Pharm Sci & Res 2020; 11(10): 4774-83. doi: 10.13040/IJPSR.0975-8232.11(10).4774-83.