Review Article

Novel frontiers in intranasal drug delivery of nanocarriers for Parkinson's treatment: A recent update

Manoj Kumar Katual[1]*, Gurfateh Singh[2], S. L. Harikumar[3]

[1]Deaprtment of Pharmacy, Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab, India, [2]Deaprtment of Pharmacy, University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, India, [3]Deaprtment of Pharmacy, Central University of Jharkhand, Ranchi, Jharkhand

Correspondence:
Manoj Kumar Katual, Deaprtment of Pharmacy, Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab, India.
E-mail: manojkumar.katual@gmail.com

How to cite this article: Katual MK, Singh G, Harikumar SL. Novel frontiers in intranasal drug delivery of nanocarriers for Parkinson's treatment: A recent update. Pharmaspire 2019; 11(1):1-9.

Source of Support: Nil,
Conflicts of Interest: None declared.

ABSTRACT

The role of nanotechnology has emerged as novel and effective tool for the treatment of various neurobehavioral dysfunctions which were sought to be incurable in an earlier time. The overprotective nature of BBB of the human central nervous system (CNS) has made the API agents unreachable to the actual site of action in its periphery. Parkinson's disease (PD) is 2nd most neurodegenerative disorder of the CNS, affecting 7–10 million people of worldwide as the report of WHO 2014. It occurs due to the death of dopamine-generating cells in the *Substantia-nigra*, a region of the midbrain. It is characterized by tremor, rigidity, bradykinesia, dementia, depression, and falls or emerges with the progression of the disease. Ropinirole HCl is a low molecular weight, highly water-soluble drug. It is rapidly absorbed from the G.I.T and mean peak plasma concentrations have been achieved within 1.5 h after oral doses. The oral bioavailability of ropinirole HCl is 50% due to extensive first-pass metabolism by the liver. Its mean plasma half-life is 5–6 h. The present study tries to enlighten the prior art related to Parkinson's treatment and to prepare Ropinirole HCl loaded nanostructured lipid carriers (NLC) that may overcome the problem of bioavailability and bypass the blood-brain barrier by preparing the intranasal drug delivery targeted to the brain thereby decreasing the dosing frequency and increasing patient compliance. The promising results of NLC of Ropinirole formulation suggested in this review work provides a futuristic approach for achieving better therapeutic efficacy by being able to target CNS.

Keywords: Bioavailability, nanostructured lipid carriers, nano-technology, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a common neurobehavioral dysfunction of the central nervous system (CNS) of a human being. It is named after James Parkinson, the U.K. physician. Its symptoms resulting the death of dopamine generating cells of the midbrain.[1] Shaking, rigidity, slowness of movement, and difficulty in walking are equivalent in patients suffering from PD. Symptoms also include sensory, sleep, and emotional problems.[2] It occurs in 0.3% of the population and it is common in elderly people of 60 years of age or over by 1%. It is idiopathic and the cause is not known. Levodopa (L-dopa) and dopamine agonists are the main treatments used to control the signs and symptoms of PD. Using these drugs for a long period may cause marked motor complications such as motor fluctuations and dyskinesia. It has been shown that after 4–6 years of levodopa therapy that nearly 40% of PD patients may suffer from these adverse effects, and this percentage increases over time.[3] Using of non-ergoline dopamine receptor agonists may reduce motor fluctuations in patients with advanced PD such as ropinirole and pramipexole. Restless legs syndrome (RLS) is a neurological disorder characterized by an irresistible urge to move the body to stop uncomfortable sensations. Legs, arms, and torso are affected and the movement modulates the sensation providing relief temporarily. These symptoms are alleviated by movement and are more common at rest, especially in the evening and at night. The sensations are similar to itching and tickling that do

Access this article online	
Website: www.isfcppharmaspire.com	**P-ISSN:** 2321-4732 **E-ISSN:** XXXX-XXXX

not stop. Limb jerking during sleep is an objective physical marker and disrupts restful sleep. This disease impairs neurological functions.[4] In the human population, approximately 5–10% suffer from RLS; however, only a small proportion seek medical treatment. The efficacy of L-dopa with a peripheral decarboxylase inhibitor has been established from the range of dopaminergic agents available. There is a high incidence of long-term side effects, which increase the severity of the symptoms. An effective and well-tolerated treatment has been found using of ropinirole for the treatment of RLS with improved sleep and cognitive functioning.[5]

Symptoms: The major symptoms are classified into motor and non-motor types.

Motor symptoms

PD is associated with resting tremor (initially unilateral), bradykinesia (slow movements), rigidity, shuffling gait, and postural instability. The onset is insidious where individuals may attribute the symptoms to aging processes. PD symptoms are progressive, but rates of motor progression are highly variable. Furthermore, subtypes of PD occur wherein tremor, rigidity, or postural instability dominate. In addition to the "classic" motor symptoms previously described, other motor manifestations are observed. These include masked facial expression (hypomimia), decreased eye blink rate, blurred vision, impaired upward gaze, dystonia, stooped posture, difficulty turning in bed, kyphosis, scoliosis, shuffling gait, "freezing" (inability to move), and speech impairment such as hypophonia (increasingly soft voice) or palilalia (repetition of word or phrase).[6]

Non-motor symptoms

Non-motor symptoms of PD include cognitive changes, behavioral/neuropsychiatric changes autonomic nervous system failure, sensory, and sleep disturbances. Notably, a number of non-motor features can precede the motor symptoms of PD by years, even decades. However, it is known that almost 90% of PD patients experience non-motor symptoms during the course of the disease.[7] In addition to the development of non-motor symptoms of PD as a component of the disease, therapy used in PD can exacerbate or cause the symptoms. For example, psychosis, orthostatic hypotension, and sleep attacks may relate to L-dopa dosing or side effects. Cognitive dysfunction and dementia are common in PD but develop over time. The dementia of PD is subcortical with an altered personality, psychomotor retardation, and memory problems. Problems with decision-making, multi-tasking, memory retrieval, and visuospatial perception are present. Dementia of PD occurs later in the disease. Early-onset dementia is associated with Parkinsonian syndrome and dementia with Lewy bodies (DLB). Psychosis and hallucinations can occur in PD patients. Visual hallucinations are the most common psychotic symptom. Mood disorders such as depression, anxiety, and apathy occur in PD patients. Mood disorders have been ranked among the most troublesome non-motor symptoms in both early and late PD patients.[8] Anxiety is the most frequent psychiatric mood disorder in PD and occurs in about 1/3 of patients. Apathy (loss of motivation) and abulia (loss of ability to think or act) can also occur. Both apathy and constant anxiety seriously erode the quality of life in PD patients. Sleep disturbance is another major non-motor symptom of PD, affecting up to almost 98% of PD patients. Most commonly, early morning awakening and frequent waking during the night are reported. Autonomic disturbance or aberration is manifested in multiple body systems in such conditions as orthostasis, constipation, dysphagia, urinary difficulties, sexual dysfunction, fecal incontinence, and sialorrhea (excessive salivation). The risk of dysfunction increases with higher age, greater disease severity, and higher doses of dopaminergic medication. Notably, the urinary difficulties that can occur in PD include such issues as urgency, frequency, nocturia, and urge incontinence.[9]

The skin may be affected by PD pathomechanisms but also by drug therapy. For example, amantadine, a drug used to treat dyskinesias, is associated with a rash called livedo reticularis. Looking like a purple network, the rash usually resolves with drug cessation. In addition, transdermal patches (e.g., rotigotine) can be associated with skin reactions. In some instances, local reactions are so severe that the drug patch must be discontinued. Most are mild to moderate in nature.[10]

Two other non-motor symptoms are frequently reported: Olfactory dysfunction and sensory symptoms of pain. Olfactory dysfunction (hyposmia) is detected in more than 90% of PD patients. Most affected PD patients are usually unaware of the deficit. Olfactory testing helps with differential diagnosis of idiopathic PD versus other Parkinsonian syndromes. Painful sensory symptoms can be localized or general and have been described as burning, tingling, or lancinating. Estimated to affect about 2/3 of PD patients, the pain is likely due to dystonia and disease-related joint and skeletal deformities that are common in PD. Some hypothesize that there is abnormal processing of nociceptive inputs in PD patients. Health-related quality of life can be enormously affected by chronic pain.[11]

RISK FACTORS/DIAGNOSIS

Age is the most potent risk for PD with an average age of onset of approximately 50–60 years. Two other risk factors have shown to be important: Family history (a genetic link) and pesticide exposure. Additional risk factors have been identified through how they may differentially affect men versus women is still unclear. Many other risk factors have been suggested though epidemiologic evidence is not as robust. These include use of well water, milk consumption, excess body weight, exposure to hydrocarbon solvents, living in rural areas, farming or agricultural work, living in urban areas, or industrialized areas with exposure to copper, manganese and lead, high dietary intake of iron, history of anemia, and higher levels of education.[12]

PD diagnosis is a clinical diagnostic decision that is based upon the presence of manifestations of rest tremor, rigidity, postural instability (gait disturbance), and bradykinesia. If a patient history reveals gradual symptom progression and then he/she responds well to drug therapy with levodopa, PD is likely the correct diagnosis.

Differential diagnosis is challenging, given the fact that the classic PD symptoms (e.g., rest tremor, rigidity, etc.) can be present in other neurodegenerative disorders. Careful history taking and astute physical

assessment coupled with initial medical therapy (e.g., the individual's response to pharmacotherapy) are necessary to distinguish idiopathic PD from essential tremor, DLB, corticobasal degeneration, multiple system atrophy (MSA), progressive supranuclear palsy, or secondary Parkinsonism due to drugs, toxins and head trauma.[13]

Despite decades of research, the diagnosis and management of PD are hampered by suboptimal methods for detection and prognosis. In other words, validated biomarkers (tests or screening mechanisms) with high sensitivity and specificity for the disease are critically needed but are currently lacking. This deficit constitutes a major research roadblock since clinical trial design demands a target or biomarker to test neuroprotective therapies. In addition, no single marker is presently able to predict PD progression with good reliability and validity.

Features that increase the likelihood of PD diagnosis include those associated with bradykinesia, such as micrographia, a shuffling walk, and difficulties performing motor tasks such as turning in bed, rising from a chair, and manipulating objects. Conversely, other symptoms decrease the likelihood of PD, including falls early in the disease, symmetric tremor at the beginning, rapid disease progression, little response to dopamine therapy, etc. Neurologic imaging plays a small role in PD diagnosis and is not used routinely. Studies such as magnetic resonance imaging, ultrasonography, and positron emission tomography scan, lack evidence in diagnosing PD. At best, they may help distinguish PD from MSA or essential tremor but not idiopathic PD itself. Despite the best of contemporary medical and surgical therapies, PD steadily worsens over time in both motor and non-motors aspects. Mortality rates are higher in PD patients versus matched controls. The mean age at death is about the same (mid-70s) regardless of the age of onset and quality disease management.[14]

PATHOPHYSIOLOGY

The pathological definition of PD is loss or degeneration of the dopaminergic (dopamine-producing) neurons in the *Substantia nigra* and development of Lewy bodies (a pathologic hallmark) in dopaminergic neurons. Pathologic changes may precede obvious symptoms by two decades or more.[15] This preferential loss of dopamine-producing neurons results in marked impairment of motor control. Lewy bodies, or abnormal intracellular aggregates, contain various proteins, including alpha-synuclein and ubiquitin, that impair optimal neuron functioning.

Recent publications suggest that environmental stress and aging itself may promote neuropathology. Specifically, exposure to environmental toxins (e.g., pesticides), drugs of abuse, or the stress of the aging process promotes chronic low-level inflammation in the brain ("Inflammaging"). This inflammatory process over time generates cellular senescence in brain neurons. From a pathologic perspective, the brain's *S. nigra* pars compacta and the pontine locus ceruleus are affected by typical abnormalities of PD patients, including depigmentation, neuronal loss, and gliosis. By the time PD symptoms occur, about 60–70% of the neurons in the *S. nigra* pars compacta are gone.[16]

Genetic mutations that code proteins of the CNS play a role in neuronal death. Specifically, alpha-synuclein becomes abnormal and self-aggregates. This aggregated, insoluble alpha-synuclein is a major constituent of Lewy bodies, cellular inclusions that are the hallmark of PD. In addition, systems designed to break down abnormal proteins like the ubiquitin-proteasome system also become impaired. Other impaired processes that may play a role in PD are mitochondrial dysfunction or abnormal oxidative stress through reactive oxygen species causing neuronal degeneration.[17]

PD patients often have prodromal olfactory deficits. Or the swallowing of nasal secretions introduces the pathogen to the gut and it enters the vagus nerve and the CNS. Pathologic supports for this hypothesis derives from the identification of Lewy bodies in the intestinal structures, vagus nerve, and brain structures.[18]

Nanostructured lipid carriers (NLC)

In the present era, not too many new chemical entities are coming in the market primarily due to the fact that either they have poor solubility or incomplete absorption. Various methodologies have been explored to overcome this issue, but none of them possess all the prerequisites. Hence, these NLCs are being explored present a relatively new type of colloidal drug delivery system that consists of solid lipid and liquid lipid and offers the advantage of improved drug loading capacity and release properties. NLCs are systems that have been successfully used for topical, dermal, and transdermal administration. These systems consist of aqueous dispersions of solid nanoparticles, composed of a mixture of solid and liquid lipids, and stabilized by one or two surfactants. NLCs are efficient systems to improve skin hydration due to their physiological lipid composition and occlusive effect properties. Typically, NLC dispersions present a low viscosity, which is not advantageous for topical application, because it decreases the time of permeance at the application site. To avoid this, NLCs can be incorporated into traditional semisolid systems (e.g., hydrogels), increasing the consistency of final formulations and also the long-term stability of the incorporated nanoparticles. NLCs have the usual particle diameter ranging 10–1000 nm. NLCs drug delivery system has many advantages such as high biocompatibility, controlled drug release, high bioavailability, and the possibility of large industrial scale production. Drug delivery system based on NLCs also has no problems with different routes of administration, such as oral, intravenous, pulmonary, and transdermal administration.[19] However, the various kinds of lipid NLC components result in the imperfections type structures, amorphous state type, or multiple type to adjust more drug and decrease the drug leakage during storage. Poorly water-soluble drugs loaded by lipid formulations have been studied for oral route and have reported to enhance the oral bioavailability by numerous research teams,[20] but there are very less reports for oral administration on NLC system) solid lipid nanoparticles (SLN) combining the advantages of colloidal carriers, had attracted increased attention as a drug delivery system when it was introduced in 1991. To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as SLNs and NLC, which are attracting wide attention of formulators worldwide.

METHODS EMPLOYED IN FABRICATION OF NLC'S

There are several methods for the preparation of lipid nanoparticulate DDS. In this type of DDS, the drug especially depends on solubility and stability, the lipid matrix, route of administration, etc.

High-pressure homogenization

High-pressure homogenization technique has been used as a reliable and powerful technique for the large-scale production of NLCs, lipid drug conjugate, SLNs, and parenteral emulsions. In high-pressure homogenization technique, lipids are pushed with high pressure (100–200 bars) through a narrow gap of few micron ranges. Hence, shear stress and cavitation are the forces which cause the disruption of the particle to the submicron range. Normally the lipid contents are in the range of 5–10%. In contrast to other preparation techniques, high-pressure homogenization does not show a scaling-up problem. Basically, there are two approaches for production by high-pressure homogenization, hot and cold homogenization techniques.[21] For both the techniques, the drug is dissolved in the lipid being melted at approximately 510°C above the melting point.

Hot high-pressure homogenization

In this process, the lipid and drug are melted (100°C above the melting point of the lipid) which are combined with an aqueous surfactant solution at the same temperature. A hot pre-emulsion is formed using a high shear device (e.g., Ultra-Turrax), then hot pre-emulsion is processed in a temperature-controlled high-pressure homogenization at 500 bar using piston gap homogenizer. The obtained nanoemulsion recrystallizes upon cooling down at room temperature leads to the formation of NLC's.[22]

Cold high-pressure homogenization

This method is suitable for heat-labile drugs or hydrophilic drugs. The lipid and drug are melted together and rapidly cooled under liquid nitrogen forming solid lipid microparticles, a pre-suspension is then further homogenized in a high-pressure homogenization at or below room temperature at predetermined homogenization condition to produce NLC. In this, both high-pressure homogenization techniques are suitable for processing lipid concentrations of up to 40%, and generally, they yield very narrow particle size distributions. Cold homogenization minimizes the thermal exposure of the sample.[23]

Microemulsion technique

The lipids (fatty acids or glycosides) are liquefied and drug is incorporated in liquefied lipid. A mixture of water, co-surfactant(s), and also the surface-active agent is heated to a similar temperature because the lipids are added beneath gentle stirring to the lipid soften. A clear thermodynamically stable system is created once the compounds are mixed within the correct ratios for microemulsion formation. Therefore, the microemulsion is the basis for the formation of nanoparticles of requisite size. This microemulsion is then spread in a very cold liquid medium beneath gentle mechanical mixing of hot microemulsion with water during a quantitative relation in the range 1:25–1:50. This dispersion in cold liquid medium ends up in the fast recrystallization of the oil droplets.[24]

Solvent emulsification-evaporation technique

In the solvent emulsification-evaporation technique, the hydrophobic drug and lipophilic material were dissolved in a water-immiscible organic solvent (e.g., cyclohexane, dichloromethane, toluene, and chloroform) and then that is emulsified in an aqueous phase using a high-speed homogenizer. To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the microfluidizer. Thereafter, the organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure leaving lipid precipitates of SLN's. Here, the mean particle size depends on the concentration of lipids in the organic phase. Very small particle size could be obtained with a low lipid load (5%) related to organic solvent. The big advantage of this method is the avoidance of any thermal stress, which makes it appropriate for the incorporation of highly thermolabile drugs. A clear disadvantage is the use of an organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent.[25]

Solvent emulsification-diffusion technique

In solvent emulsification-diffusion technique, the solvent used (e.g., benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, and methyl acetate) must be partially miscible with water and this technique can be carried out either in the aqueous phase or in oil. Initially, both the solvent and water were mutually saturated to ensure the initial thermodynamic equilibrium of both liquids. When heating is required to solubilize the lipid, the saturation step was performed at that temperature. Then, the lipid and drug were dissolved in a water-saturated solvent and this organic phase (internal phase) was emulsified with a solvent saturated aqueous solution containing stabilizer (dispersed phase) using a mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, was added to the system to allow solvent diffusion into the continuous phase, thus forming an aggregation of the lipid in the nanoparticles. Here, both the phases were maintain at the same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved. Throughout the process, constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization.[26]

Phase inversion temperature (PIT) method

Phase inversion of o/w to w/o emulsions and vice versa induced by temperature change is a long-known method to produce microemulsions stabilized with nonionic surfactants. The technique is based on the change in the properties of polyoxyethylated surfactants at different temperatures. The hydrophilic-lipophilic balance (HLB) value of surfactants defined by Griffin is valid at 25°C. At this temperature, the hydrophilic parts of the SAC molecules are hydrated to a certain extent. An increase in the temperature causes dehydration of the ethoxy groups. As a result, the lipophilicity of the molecules

of the SAC rises with a corresponding decrease in HLB value. At a certain point, the affinity of the SAC to the aqueous and lipid phase is equal – this temperature is defined as the phase inversion temperature. This particulate state is characterized by very low surface tension and presence of complex structures in the system. If the temperature is further increased, the SAC's affinity to the lipid phase becomes higher enough to stabilize emulsions of w/o type.[27]

Melting dispersion method

In the melting method, drug and solid lipids are melted in an organic solvent regarded as oil phase, and simultaneously water phase is also heated to the same temperature as the oil phase. Subsequently, the oil phase is added to a small volume of water phase and the resulting emulsion is stirred at high speed for a few hours. Finally, it is cooled down to room temperature to yield nanoparticles.[28]

Solvent injection (or solvent displacement) technique

The technique in which a solvent that distributes very rapidly in water (dimethyl sulfoxide, ethanol) is used.[29] First, the lipid is dissolved in the solvent and then it is quickly injected into an aqueous solution of surfactants through an injection needle. The solvent migrates rapidly in the water and lipid particles precipitate in the aqueous solution. Particle size depends on the velocity of distribution processes. Higher velocity results in smaller particles. The more lipophilic solvents give larger particles which may become an issue. The method offers advantages such as low temperatures, low shear stress, easy handling, and fast production process without technically sophisticated equipment (e.g., high-pressure homogenizer). However, the main disadvantage is the use of organic solvents.

Hot Homogenization method

Hot homogenization is carried out at temperatures above the melting point of the lipid and can, therefore, be regarded as the homogenization of an emulsion. A pre-emulsion of the drug-loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by a high-shear mixing device (such as Ultra-Turrax). Pre-emulsion is then passed through a high-pressure homogenization cycle at temperatures above the melting point of the lipid. Lipid nanoparticles are formed by the following cooling of the sample to room temperature or to temperatures below.[30]

APPLICATIONS OF NLC'S

Oral drug delivery

Interest in NLCs for oral administration of drugs has been increasing in recent years. Increased bioavailability and prolonged plasma levels are described for the peroral administration of NLCs. The lipid nanocarriers can protect the drugs from the harsh environment of the gastrointestinal (GI) tract. The lipophilic drugs can be entrapped by NLCs to resolve insolubility concerns. Repaglinide, an anti-diabetic agent with poor water solubility, has low oral bioavailability and a short half-life. It is suitable to load into NLCs for improving oral delivery. Date et al. prepare repaglinide NLCs with Gelucire 50/13 as an amphiphilic lipid excipient. Gelucire 50/13 (stearoyl macrogolglycerides) has been previously used for the preparation of solid dispersions for improving the aqueous solubility of lipophilic drugs.[31,32]

Drug delivery to brain

Brain targeting not only increases the cerebrospinal fluid concentration of the drug but also reduces the frequency of dosing and side effects. The major advantages of this administration route are avoidance of first-pass metabolism and rapid onset of action as compared to oral administration. LNC (e.g., NLC) of this generation is considered to be one of the major strategies for drug delivery without any modification to the drug molecule due to their rapid uptake by the brain, bioacceptability, and biodegradability. Further, the feasibility in scale-up and absence of burst effect makes them more promising carriers for drug delivery. In addition, NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of the major depressive disorder. NLCs of asenapine maleate to improve the bioavailability and enhance the uptake of ASN to the brain.[33] In bromocriptine loaded NLCs, the *in-vivo* results showed that bromocriptine NLCs have a rapid onset of action and longer duration and higher brain levels as compared to that of the solution, entrapment efficiency was also increased.

Pulmonary drug delivery

Inhalation drug delivery represents a potential delivery route for the treatment of several pulmonary disorders. NLCs have greater stability against the shear forces generated during nebulization compared to polymeric nanoparticles, liposomes, and emulsions. NLCs are comprised of an inner oil core surrounded by a solid outer shell and hence allow the high payload of a lipophilic drug. NLCs in pulmonary disorders seem to be promising strategy since lung epithelium can be directly reached, resulting in a faster onset of action, desired dose and dosing frequency can be reduced as compared to other administered routes like oral and undesirable side effects of drugs can be avoided**.** Bioadhesive properties of NLCs are due to their small particle size as well as lipophilic character leads to longer residence time in lungs.[34]

Intranasal drug delivery

The use of nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. These represent the key factors in the optimal processing and presentation of the antigen. Nasal administration is the promising alternative non-invasive route of drug administration due to fast absorption and rapid onset of action, avoiding degradation of labile drugs (peptides and proteins) in the GI tract (GIT) and insufficient transport across epithelial cell layers. The development of a stable NLC system as a carrier for curcumin (CRM) biodistribution studies showed higher drug concentration in the brain after the intranasal administration of NLCs than PDS. The results of the study also suggest that CRM-NLC is a promising drug delivery system for brain cancer therapy. In addition, NLC further enhanced the intranasal drug delivery of duloxetine in the brain for the treatment of major depressive disorder. NLCs of asenapine maleate to improve the bioavailability and enhance the uptake of ASN to the brain.[35]

Cosmetic applications of NLC

Lipid nanoparticles SLN and NLC can be used to formulate active compounds in cosmetics, for example, prolonged release of perfumes. The incorporation of cosmetic compounds and modulation of release is even more flexible when using NLC. In addition, the release of insect repellents has been described. A feature of general interest is the stabilization of chemically labile compounds. The solid matrix of the lipid nanoparticle protects them against chemical degradation, for example, retina and coenzyme Q10. A recently discovered feature is the sunscreen blocking effect of lipid nanoparticles. Similar to particles such as titanium dioxide, the crystalline lipid particles scatter ultraviolet (UV) light, thus protecting against UV irradiation. In addition, it was found that incorporation of sunscreens leads to a synergistic UV blocking effect of the particulate blocker lipid nanoparticle and the molecular blocker. *In vitro*, crystalline lipid nanoparticles with the same sunscreen concentration exhibited twice the UV protection effect compared with an O/W emulsion loaded with the sunscreen.[36]

Historical background of nasal drug delivery

Since last century intranasal delivery has been used for various purposes such as for relieving nasal decongestion, rhinitis, and migraine, crushed leaves of *Ranunculus acris* have been used through nasal inhalation by the Red Indian of North America to relieve headache. In China, extracts of aloe wood and sandalwood were used for treating emesis by inhalation through the nasal route. The nasal route has also been used to administer tobacco by nasal snuffing. American Indians used it as early as the 1400s. Indian tribes in Brazil used a V-shape instrument known as "*Tipi*" to blow powdered tobacco to one another for enjoyment and relaxation, and refresh their memory. The American Indian used an instrument known as "*tobaca*" or "*Tobago*," which is a hollow Y-shape pipe to inhale powdered tobacco. For snuffing, they placed two ends of the Y-shape pipe into each nostril and the lower end near the powdered tobacco. The nose is still the favored route for drug abuse, for instance, when using opium drugs.[37]

Rationale of nasal route

The oral route is the most convenient and popular route for drug delivery. Despite the popularity of the oral route, alternative routes such as transmucosal delivery have been extensively investigated for drugs lacking effective systemic absorption through the GIT, therapeutic agents having chemical instability in the GIT fluids, drugs that undergo first-pass hepatic deactivation and therapeutic molecules which cause GIT adverse effects. Alternative routes have been investigated such as intranasal and parenteral to achieve faster and higher drug absorption and hence offering improved drug bioavailability, enhanced therapeutic effect, and promoted patient compliance. Significant enhancement in the drug absorption following nasal administration compared to oral delivery has been demonstrated. However, for improvement of intranasal drug absorption with molecules larger than 1000 Daltons, permeation enhancers are needed in the formulation.[38] Nasal delivery is appropriate for the administration of drugs to treat local nasal diseases such as sinusitis and allergic rhinitis since low doses are sufficient to provide therapeutic effects with low systemic side effects. In addition, nasal delivery might be suitable for drugs which are effective in low doses and have low oral bioavailability.

Anatomy of the nose

The nasal passage is 12–14 cm deep and runs from the nasal vestibule to the nasopharynx. It has three main regions; vestibular, respiratory, and olfactory regions. The nose has a volume of 16–19 cm^3 and a surface area of approximately 180 cm^2 with two cavities (i.e., nostrils) separated by the nasal septum [Figure 1].

The vestibular region is located at the front opening of the nasal passages which filters out particles from the inhaled air. However, drug delivery and absorption in this region are least important. This area is covered with hairs which filter the air to prevent airborne particles entering the respiratory system. The respiratory area is large, with a high degree of vascularity and a surface area of about 130 cm^2. In this region, the majority of drug absorption occurs. It is lined with pseudostratified columnar epithelium and covered with a dense layer of mucus which moves toward the posterior apertures of the nasal cavity because of the ciliary rhythmatic movements.[39] The olfactory region is important for transporting the drug to brain and cerebrospinal fluid and has a surface area of about 15 cm^2. It is made of thick connective tissue and lamina propria, into which the olfactory epithelium rests. The thickness of nasal mucosa ranges between 2 and 4 mm. The epithelium cells line the nasal passage and are covered by a mucus layer 5 μm in thickness which traps unwanted particles. The mucous secretion consists of water (95%), mucin (2%), salts (1%), proteins (1%) such as albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids (1%). IgA, IgE, and IgG are also present in the mucous secretion. The pH of the nasal secretion is ranged from 5 to 6.5. Ciliary action is responsible for clearing the mucus layer from the nasal cavity and mucus is renewed 4–6 times/h. The mucus moves through the nose at a rate of 5–6 mm/min.

Applications of nasal delivery

Local effects

The nose is exploited to treat regional disorders at relatively low effective doses with less systemic effects. Low molecular weight water-soluble or hydrophobic drugs are used to treat local pathological conditions in the nose. For example, azelastine is a rapid-acting antihistamine, mainly acts as an antagonist on H1-receptors, and as a mast cell stabilizer available as a nasal spray. Beclometasone is an anti-inflammatory corticosteroid used to reduce inflammation

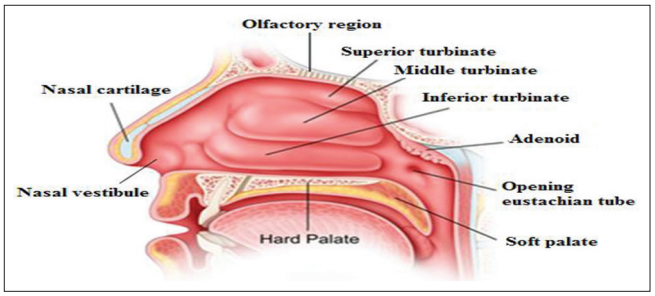

Figure 1: Anatomy of the human nasal cavity

and local allergy. It is a well-established drug for the treatment of allergic rhinitis. Nasal decongestants such as oxymetazoline are also administered through the nose for treating common colds.[40]

Systemic effects

Nasal delivery is convenient for acid-labile drugs, proteins, and peptides when rapid action is required such as in migraine relief. Nasal delivery offers rapid action and efficient drug absorption compared to oral and intravenous delivery. Most protein and peptide drugs have low bioavailability (1–2%) due to their high molecular weight and polarity, causing poor absorption through the nasal mucosal membranes. In contrast, the bioavailability of progesterone and propranolol through nasal epithelium is comparable to parenteral administration. Lower bioavailability can be improved using absorption enhancers in the formulations, thus prolonging the contact time of the drug with the mucous membranes using bioadhesive agents. A significant change in the relative bioavailability of isosorbide dinitrate was observed using 0.1% N-succinyl chitosan as an absorption enhancer (69.85%) compared to the 0.5% chitosan (55.36%) and control groups (43.32%) in rats. Goldman and Tanner have reported that the bioavailability of recombinant human growth hormone was increased significantly after nasal delivery in combination with N-trimethyl chitosan chloride as an absorption enhancer used in pheroid technology.[41]

Vaccines delivery

Vaccines and their applications through the nose to treat respiratory infections have been investigated. The localization of immune system components in the mucosal membrane means that the respiratory epithelium is the first defense line in the body against infections. The nasal mucosa is further enriched by lymphoid tissue. It enhances the systemic levels of specific immunoglobulin G and nasal secretory immunoglobulin A and the local immune responses which provide additional protection against invading microbes. Nasal mucosa is advantageous for immunization due to its permeability, low enzymatic activity, and accommodation of the nose-associated lymphoid tissue (NALT). The delivery of vaccine through the nose represents a convenient needle-free procedure for vaccination. Furthermore, NALT is an effective immune system. Nasal vaccines that have been investigated include influenza A and B, proteasome-influenza, adenovirus-vectored influenza, attenuated respiratory syncytial virus, and parainfluenza 3 virus. Commercially, available nasal vaccines include nasal spray of Human influenza vaccine (FluMist®) and nasal drop of equine influenza vaccine (Flu Avert®) manufactured by Medimmune Inc. and Heska, respectively.[42]

CNS delivery

The intranasal route is promising for the delivery of drugs to the brain through the exploitation of the olfactory neuroepithelium in the nose. This strategy has been considered for the treatment of Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disorders. Delivery of nerve growth factor to the brain in rodents has been reported and in humans, studies insulin and proteins have been directly transferred through olfactory path to the CNS through nasal cavity. Successfully transnasal delivery 0.5 mg/kg of siRNA to the CNS with highly brain concentration compared to the other tissue has been reported to treat neurological disorders using peptide-tagged PEGylated chitosan nanoparticles formulations to deliver siRNA through nose [Table 1].[43]

Table 1: Recent studies carried out to deliver drug molecules to the brain through nasal route[44,45]

Drug molecule	Purpose
siRNA	Treatment of neurological disorder
Levodopa	Treatment of Parkinson's disease
Clonazepam	Prevent and control seizures
Folic acid	Treatment or prevention of Alzheimer disease
Duloxetine	Treatment of depression

Advantages and limitations of nasal route

Advantages[44-46]

- Suitable for drugs that are acid labile in the stomach
- Applicable for drugs that undergo the extensive hepatic first-pass effect
- Rapid drug absorption and onset of action
- Offers higher drug bioavailability, thus lower doses of drug are needed
- Offers large surface area for drug absorption (approximately about 150 cm^2)
- No particular skills or expertise are required for nasal drug administration
- Direct transportation of drug to the systemic circulation or CNS is possible
- Offers lower risk of overdosing
- Needle-free and patient-friendly
- Offers induction of immune response when used for vaccine delivery.

LIMITATIONS[47]

- Volume that can be delivered into the nasal cavity is restricted to 25–200 µl
- High molecular weight compounds cannot be delivered through this route (mass cut off ≈1 kDa)
- Adversely affected by pathological conditions of the nose
- Large interspecies and patient to patient variabilities are observed when using this route
- Normal defense mechanisms like mucociliary clearance can affect the absorption of drug
- Local enzymes in the nasal cavity might degrade some drugs
- Local side effects like irritation might be happen
- Small surface area compared to the GIT.
- Nasal congestion from colds and flues may interfere with efficient drug delivery through this route
- Frequent delivery of drugs may cause mucosal damage; hence, the patient becomes liable to microbial invasion through the nasal epithelium.

SUMMARY AND CONCLUSION

Based on our review studies, the following conclusions can be drawn regarding Ropinirole HCl NLC's for the persistent treatment of PD

through nasal route. The review study confirmed that the NLCs can be prepared using the drug and the excipients such as IPM, Glyceryl monostearate, and Pluronic F-68 in very economical and industrially feasible methods. Further, it is advised that, after the dosage formulations prepared, it should be confirmed for its therapeutic efficacy with the animal/human clinical trials by *ex-vivo*/*in-vivo* study. If the *in-vivo* study will be successful, it will be definitely a great boon for mankind.

ACKNOWLEDGMENT

The authors are highly thankful to all faculty members and staffs of Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab and University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, for their valuable suggestions and efforts. The authors acknowledge the gratitude to all concerned contributors directly or indirectly for preparing this article and hereby declare "No conflicts of Interest."

REFERENCES

1. Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: Comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2013;74:1215-20.
2. Willis AW, Evanoff B, Lian M, Criswell A, Racette B. Geographic and ethnic variation in Parkinson disease: A population-based study of US medicare beneficiaries. Neuroepidemiology 2010;34:143-151.
3. Esposito E. Solid lipid nanoparticles as delivery systems for bromocriptine. Pharm Res 2018;25:1521-30.
4. Bhosale V, Nilesh R. Formulation and evaluation of transdermal patches of ropinirole HCL. Res J Pharm Biol Chem Sci 2017;2:138-48.
5. Misra A, Ganesh S, Shahiwala A. Drug delivery to the central nervous system: A review. J Pharm Pharm Sci 2013;6:252-73.
6. Ferrari C. Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta Endocrinol 2012;126:489-494.
7. Forno LS, Sternberger LA, Sternberger NH. Reaction of lewy bodies with antibodies to phosphorylated and nonphosphorylated neurofilaments. Neurosci Lett 2016;64:253-8.
8. Pardeshi CV, Belgamwar VS, Tekade AR, Surana SJ. Novel surface modified polymer lipid hybrid nanoparticles as intranasal carriers for Ropinirole hydrochloride: *In-vitro ex-vivo* and *in-vivo* pharmaco-dynamic evaluation. J Mater Sci 2013;24:2101-15.
9. De la Fuente-Fernandez R, Calne DB. Evidence for environmental causation of Parkinson's disease. Parkinsonism Relat Disord 2016;8:235-41.
10. Filloux F, Townsend J. Pre-and post-synaptic neurotoxic effects of dopamine demonstrated by intrastriatal injection. Exp Neurol 2013;119:79-88.
11. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J Am Geriatr Soc 2010;48:938-42.
12. Dawson VL. Neurobiology of flies and mice. Science 2015;4:631-2.
13. Fornstedt B, Pileblad E, Carlsson A. *In vivo* autoxidation of dopamine in guinea pig striatum increases with age. J Neurochem 2010;55:655-9.
14. Fritsch T, Smyth K, Wallendal M, Hyde T, Leo G, Geldmacher D. Parkinson disease: Research update and clinical management. South Med Assoc 2012;105:650-6.
15. Garbayo E, Ansorena E, Blanco-Prieto MJ. Drug development in Parkinson's disease: From emerging molecules to innovative drug delivery systems. Maturitas 2013;76:272-8.
16. Gavrieli Y, Sherman Y, Ben-Sasson SA. Identification of programmed cell death *in situ* via specific labeling of nuclear DNA fragmentation. J Cell Biol 2012;119:493-501.
17. Giasson BI, Uryu K, Trojanowski JQ. Mutant and wild type human alpha-synucleins assemble into elongated filaments with distinct morphologies *in vitro*. J Biol Chem 2012;274:7619-22.
18. Bhatt D, Ajmeri N, Mandal S, Rajesh KS. Nanoparticle: Design, characterization and evaluation for oral delivery of ropinirole hydrochloride. Elixir Pharm 2017;8:4687-4689.
19. Gibb WR. Accuracy in the clinical diagnosis of Parkinsonian syndromes. Postgrad Med J 2018;64:345-51.
20. Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR, Surana SJ. Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: Application of factorial design approach. Drug Deliv 2013;20:47-56.
21. Gjerstad MD, Wentzel-Larsen T, Aarsland D. Insomnia in Parkinson's disease frequency and progression over time. J Neurol Neurosurg Psychiatry 2017;78:476-9.
22. Golbe LI, Langston JW. The etiology of Parkinson's disease: New directions for research. In: Parkinson's Disease and Movement Disorders. Baltimore, Maryland: Williams and Wilkins; 2013. p. 93-101.
23. Nasare L, Shrikant D, Shagufta A. Nasal drug delivery system: An emerging approach for brain targeting. World J Pharm Pharm Sci 2018;3:539-53.
24. Pardridge WM. Drug transport in brain via the cerebrospinal fluid. Fluids Barriers CNS 2017;8:1-7.
25. Parvas M, Parada C, Bueno D. A blood-CSF barrier function controls embryonic CSF protein composition and homeostasis during early CNS development. Dev Biol 2008;321:51-63.
26. Barbeau A. L-Dopa therapy in Parkinson's disease. Can Med Assoc 1969;101:59-68.
27. Belluzi JD, Domino EF, May JM. A selective dopamineD2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease. Mov Disord 2014;9:147-54.
28. Gorell JM. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 1998;50:1346-50.
29. Shah H, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, *et al*. Formulation and comparative evaluation of transdermal patch and proniosomal gel of ropinirole. Int J Pharm Sci Nanotechnol 2016;9:3091-101.
30. Post B, Merkus MP, Haan RJ. Prognostic factors for the progression of Parkinson's disease: A systematic review. Mov Disord 2017;22:1839-51.
31. Pursiainen V, Haapaniemi TH, Korpelainen JT. Sweating in Parkinsonian patients with wearing-off. Mov Disord 2017;828-32.
32. Hartley A, Stone JM, Heron C. Complex I inhibitors induce dose dependent apoptosis in PC12 cells relevance to Parkinson's disease. J Neurochem 1994;63:1987-90.
33. Illum L. Nasal drug delivery: Possibilities, problems and solutions. J Control Release 2003;87:187-98.
34. Tetrud JW, Zigmond MJ. A novel formulation of selegiline for the treatment of Parkinson'sdisease. J Am Acad Neurol 2004;63:2-6.
35. Beitz JM. Parkinson's disease: A review. Front Biosci 2014;S6:65-74.
36. Jorga KM, Ben-Sasson SA. The effect of tolcapone on the pharmacokinetics of benserazide. Eur J Neurol 2016;6:211-9.
37. Leroy E, Boyer R, Auburger G. The ubiquitin pathway in Parkinson's disease. Nature 2018;395:451-2.
38. Katual MK, Harikumar SL. Drug delivery to CNS; various approaches for Parkinson's disease management: An update. Int J Recent Sci Res 2016;7:9148-55.
39. Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci 1999;22:123-44.
40. Appasaheb PS. A review on intranasal drug delivery system. Int J Pharm 2013;3:333-44.

41. Goldman SM, Tanner CM. Etiology of Parkinson's disease. Int J Pharm Sci Nanotechnol 2018;12:125-35.
42. Goldman JE, Yen SH, Chiu FC. Lewy bodies of Parkinson's disease contain neurofilament antigens. Science 2013;221:1082-4.
43. Blasi P, Giovagnolia A, Schoubbena A, Pugliab C, Boninab F, Rossia C, *et al*. Lipidnanoparticles for brain targeting I. Formulation optimization. Int J Pharm 2011;419:287-95.
44. Khan RA, Mustafa G, Chuttani K, Baboota A, Sahni JK, Ali J. Bromocriptine loaded chitosan nanoparticles intended for direct nose to brain delivery: Pharmacodynamic, pharmacokinetic and scintigraphy study in mice model. Eur J Pharm Sci 2012;32:158-72.
45. Pu T, Li X, Sun Y, Ding X, Pan Y, Wang Q. Development of a prolonged-release pramipexole transdermal patch: *In vitro* and *in vivo* evaluation. Am Assoc Pharm Sci 2016;11:3254-361.
46. Huang Z, Zhai Y, Zhai G. Etiology of Parkinson's disease. Can J Neurol Sci 2003;30:10-8.
47. Giladi N, McMahon D, Przedborski S. Motor blocks in Parkinson's disease. Neurology 2012;42:333-9.