Recent advancements in ropinirole hydrochloride embedded nano-techniques in Parkinson's treatment

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

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

***Corresponding Author: Manoj Kumar Katual**
Email: manojkumar.katual@gmail.com

Abstract
Parkinson's Disease (PD) is effecting 7-10 million people of worldwide as the report of WHO 2014. It has proved to be 2nd most a neuro-degenerative disorder of the central nervous system (CNS). 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 Nano-structured lipid carriers (NLC) that may overcome the problem of bioavailability and bypass the blood brain barrier by preparing the intra-nasal drug delivery targeted to the brain thereby decreasing the dosing frequency and increasing patient compliance.

Keywords: Parkinson's Disease, Bioavailability, NLC, Nano-technology.

Introductory

Parkinson's disease

Parkinson's disease is a common neurodegenerative disorder of the central nervous system (Jankovic, 2008). It is named after James Parkinson the English Physician. Its symptoms resulting the death of dopamine generating cells of the midbrain (Olanow et al., 2001). Shaking, rigidity, slowness of movement and difficulty in walking are equivalent in patients suffering from Parkinson's disease. Symptoms also include sensory, sleep and emotional problems (Jankovic, 2008). It occurs in 0.3% of the population and it is common in elderly people of 60 years of age or over by 1% (Olanow et al., 2001; Samii et al., 2004). 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 Parkinson's disease.

a. Symptoms

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 (Fritsch T et al., 2012). Also, subtypes of PD occur wherein tremor, rigidity, or postural instability dominate (Chou K, 2013).

Non-motor symptoms: Non-motor symptoms of PD include cognitive changes, behavioral/neuropsychiatric changes autonomic nervous system failure, sensory and sleep disturbances (Jain S, 2011). 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 (Lohle M et al., 2009). 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.

b. Risk factors/diagnosis

Age is the most potent risk for PD (MacPhee G et al., 2011) with an average age of onset of approximately 50 to 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 though how they may differentially affect men vs. women is still unclear (Savica R et al.,2013). 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 (Jankovic J et al., 2013).

c. 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 (Gazewood J et al., 2013). 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.

Nanostructured lipid carriers

In the present era not too many new chemical entities are coming in 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 this Nanostructured lipid carriers (NLCs) is 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. Nanostructured lipid carriers (NLCs) are systems that have been successfully used for topical, dermal, 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 (Mk Sahu et al., 2012). 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 [HGs]), 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 have many advantages like high biocompatibility, controlled drug release, high bioavailability, and the possibility of large industrial scale production. Drug delivery system based on NLCs also have no problems with different routes of administration, such as oral, intravenous, pulmonary and transdermal administration (Cavalli et al., 2002).

a. 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 lipid are pushed with high pressure (100-200bars) through a narrow gap of few micron ranges. So shear stress and cavitation are the forces which cause the disruption of particle to submicron range. Normally the lipid contents are in the range of 5-10%.

Hot High pressure homogenization: In this process the lipid and drug are melted (100°C above the melting point of the lipid) are combined with an aqueous surfactant solution at the same temperature. A hot pre-emulsuion is formed using 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 formation of NLC's (MR Gasco, 1993).

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 upto 40% and generally they yield very narrow particle size distributions. Cold homogenisation minimises the thermal exposure of the sample (SP Moulik et al.,1998).

Microemulsion technique: The lipids (fatty acids or glycosides) are liquified and drug is incorporated in liquified 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 a 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 fast recrystallisation of the oil droplets. (Dianrui Zhang et al., 2003).

Solvent emulsification-evaporation technique: In solvent emulsification-evaporation technique, the hydrophobic drug and lipophilic material were dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then that is emulsified in an aqueous phase using 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. (M Trotta et al., 2005).

Solvent emulsification-diffusion technique: In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid. When heating is required to solubilize the lipid, the saturation step was performed at that temperature. Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. (Sarabjot kaur et al., 2015).

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 non-ionic surfactants. The technique is based on the change in the properties of polyoxyethylated surfactants at different temperatures. The hydrophilliclipophillic 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 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 (H Reithmeier et al., 2001).

Melting dispersion method: In melting method, drug and solid lipid are melted in an organic solvent regarded as oil phase, and simultaneously water phase is also heated to the same temperature as 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 few hours. Finally, it is cooled down to room temperature to yield nanoparticles (Eldem et al.,1991).

Solvent injection (or solvent displacement) technique: Technique in which a solvent that distributes very rapidly in water (DMSO, ethanol) is used (Date et al., 2007). 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 homogeniser). 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 high-shear mixing device (such as Ultra-Turrax). Pre- emulsion is then passed through 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 (Kamble et al., 2012).

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 peroral administration of NLCs. The lipid nanocarriers can protect the drugs from the harsh environment of the gastrointestinal 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 (Jain SK et al., 2006). 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 (Priya et al., 2010).

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 are considered to be one of the major strategies for drug delivery without any modification to the drug molecule because of their rapid uptake by the brain, bioacceptability and biodegradability. (Silva et al., 2011).

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 an outer solid shell and hence allow the high payload of a lipophilic drug. NLCs in pulmonary disorders seems to be promising strategy since lung epithelium can be directly reached resulting in 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**.** (J.M et al.,1997).

Intranasal drug delivery: The use of nanocarriers provides 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 and insufficient transport across epithelial cell layers. The development of a stable nanostructured lipid carrier (NLC) system as a carrier for curcumin (CRM) biodistribution studies showed higher drug concentration in brain after intranasal administration of NLCs than PDS.

Cosmetic applications of NLC: Lipid nanoparticles SLN and NLC can be used to formulate active compounds in cosmetics, e.g. prolonged release of perfumes. 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 stabilisation of chemically labile compounds. The solid matrix of the lipid nanoparticle protects them

against chemical degradation, e.g. Retin 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 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.(Jenning V, et al., 2001)

Nasal drug delivery

Historical background: 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 via 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 (Quraishi et al., 1997).

Why the nasal route?: The oral route is the most convenient and popular route for drug delivery. Despite the popularity of oral route alternative routes such as transmucosal delivery have been extensively investigated for drugs lacking effective systemic absorption via the gastrointestinal tract (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 intra-nasal and parenteral in order to achieve faster and higher drug absorption and hence offering improved drug bioavailability, enhanced therapeutic effect and promoted patient compliance (Mathias and Hussain, 2010). Significant enhancement in the drug absorption following nasal administration compared to oral delivery has been demonstrated (Dhakar et al., 2011). However, for improvement of intranasal drug absorption with molecules larger than 1000 Daltons, permeation enhancers are needed in the formulation (Ozsoy et al., 2009). Nasal delivery is appropriate for 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 (Dhakar et al., 2011).

Anatomy of the nose: The nasal passage is 12-14 cm deep and runs from the nasal vestibule to the nasopharnyx. 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. 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 is 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 towards the posterior apertures of the nasal cavity because of the ciliary rhythmatic movements (Chien et al., 1989).

Applications of nasal delivery

i) 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 (Horak, 2008) 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 (Ghimire et al., 2007) is an anti-inflammatory corticosteroid used to reduce inflammation and local allergy. It is a well-established drug for the treatment of allergic rhinitis. Nasal decongestants such as oxymetazoline are also administered via the nose for treating common colds (Pires et al., 2009; Sharma et al., 2006).

ii) Systemic effects: Nasal delivery is convenient for acid labile drugs, proteins and peptides when rapid action is required such as in migraine relief (Swamya and Abbasb, 2012). Nasal delivery offers a rapid action and efficient drug absorption compared to oral and intravenous delivery (Furubayashi et al., 2007). 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 via nasal epithelium is comparable to parenteral administration (Hagan and Illum, 1990). Lower bioavailability can be improved by using absorption enhancers in the formulations, thus prolonging the contact time of the drug with the mucous membranes using bioadhesive agents.

iii) Vaccines delivery: Vaccines and their applications via 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 defence line in the body against infections (Bitter et al., 2011). Nasal mucosa is further enriched by lymphoid tissue. It enhances the systemic levels of specific immunoglobulin G and nasal secretary immunoglobulin A and the local immune responses which provide additional protection against invading microbes (Mestecky et al., 1997). Nasal mucosa is advantageous for immunization due to its permeability, low enzymatic activity and accommodation of the nose-associated lymphoid tissue (NALT) (Bitter et al., 2011). The delivery of vaccine via the nose represents a convenient needle-free procedure for vaccination. Furthermore, the nose-associated lymphoid tissue (NALT) is an effective immune system (Brandtzaeg, 2011). Nasal vaccines that have been investigated include

influenza A and B (Huang et al. 2004), proteasome-influenza (Langley et al., 2006), adenovirus-vectored influenza (Van Kampen et al., 2005), attenuated respiratory syncytial virus and parainfluenza 3 virus (Belshe et al., 2004). Commercially available nasal vaccines include nasal spray of Human influenza vaccine (FluMist®) and nasal drop of Equine influenza vaccine (Flu Avert®) manufactured by Medlmmune Inc. and Heska respectively.

iv) CNS delivery: The intranasal route is promising for the delivery of drugs to the brain via the exploitation of the olfactory neuroepithelium in the nose. This strategy has been considered for the treatment of Alzheimer's disease, brain tumours, epilepsy, pain and sleep disorders (Pires et al., 2009). Delivery of nerve growth factor to the brain in rodents has been reported (Frey et al., 1997; Chen et al., 1998) and in humans studies insulin (Hinchcliffe and Illum, 1999) and proteins have been directly transferred through olfactory path to the CNS via nasal cavity. Successfully transnasal delivery 0.5mg/kg of siRNA to the CNS with highly brain concentration compared to the other tissue has been reported by Malhotra co-workers to treat neurological disorders using peptide-tagged PEGylated chitosan nanoparticles formulations to deliver siRNA via nose (Malhotra et al., 2013).

Table 1.2: Recent studies carried out to deliver drug molecules to the brain via nasal route.

Drug molecule	Purpose	Reference
siRNA	Treatment of neurological disorder	Malhotra et al., 2013
Levodopa	Treatment of Parkinson's disease	Sharma et al., 2013
Clonazepam	Prevent and control seizures	Abdel- Bar et al., 2013
Folic acid	Treatment or prevention of Alzheimer disease	Nagaraju et al., 2013
Duloxetine	Treatment of depression	Alam et al., 2013

Advantages and limitations of nasal route (Behl et al., 1998; Singh et al., 2012).

Advantages

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

Limitations

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

Objective of the Review

The main objective of the formulation design is listed below:

1. To study in details regarding the drug Ropinirole HCl as per the existing standards.
2. To study in details the NLC/Lipid nanoparticles of Ropinirole HCl by using simple and industrially feasible methods.

Literature Review

Parkinson's disease

Gorell *et al.,* (1998) described the risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. According to their research Farming as an occupation was significantly associated with PD (OR, 2.79; 95% CI, 1.03, 7.55), but there was no increased risk of the disease with rural or farm residence or well water use. The association of occupational exposure to herbicides or insecticides with PD remained after adjustment for farming. The association of farming with PD was maintained after adjustment for occupational herbicide exposure and was of borderline significance after adjustment for occupational insecticide exposure. These results suggest that PD is associated with occupational exposure to herbicides and insecticides and to farming and that the risk of farming cannot be accounted for by pesticide exposure alone.

Huang *et al.,* (2003) described the etiology of Parkinson's disease. According to him the growing recognition that Parkinson's disease (PD) is likely to arise

from the combined effects of genetic predisposition as well as largely unidentified environmental factors. The relative contribution of each varies from one individual to another. Even in situations where more than one family member is affected, the predominant influence may be environmental. Although responsible for only a small minority of cases of PD, recently identified genetic mutations have provided tremendous insights into the basis for neuro-degeneration and have led to growing recognition of the importance of abnormal protein handling in Parkinson's as well as other neurodegenerative disorders. Abnormal protein handling may increase susceptibility to oxidative stress; conversely, numerous other factors, including oxidative stress and impaired mitochondrial function can lead to impaired protein degradation. A limited number of environmental factors are known to be toxic to the substantia nigra; in contrast, some factors such as caffeine intake and cigarette smoking may protect against the development of PD, although the mechanisms are not established. We review the various genetic and environmental factors thought to be involved in PD, as well as the mechanisms that contribute to selective nigral cell death.

Karlsen *et al.,* (1993) described the fatigue in patients with Parkinson's Disease he compare the prevalence of fatigue in patients with Parkinson's disease (PD) with that in healthy elderly people and to explore the suggestion that fatigue is an independent symptom of PD.

Marsden, (1989) described slowness of movement in Parkinson's disease. According to him loss of the ability to move is the most characteristic and fundamental motor deficit in Parkinson's disease. Parkinsonian patients exhibit akinesia (inability to initiate movement), hypokinesia (reduced movement), and bradykinesia (slowness of the movement itself). (All these phenomena will be subsumed under the title akinesia.) Rigid muscles may contribute to akinesia, but they are not the cause. This is evident from the effects of both stereotactic surgery and treatment with levodopa. Stereotactic thalamotomy is an effective means of abolishing contralateral rigidity (and tremor), but does not relieve akinesia, which progresses to cause increasing disability. Levodopa therapy, on the other hand, dramatically relieves akinesia, even in those who have undergone previous stereotactic surgery. The akinesia of Parkinson's disease represents a major negative symptom and, as such, probably gives the best clue as to what goes wrong with basal ganglia function in that condition. However, analysis of the pathophysiology of akinesia has proved difficult. One is dealing with higher-order motor function in all its complexity.

Pappert *et al.,* (1998) described hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's Disease. In a series of consecutively randomized outpatients who had Parkinson's disease (PD), we examined the association of three behaviors: sleep fragmentation, altered dream phenomena, and hallucinations/illusions. Using a loglinear model methodology, we tested the independence of each behavior. Sixty-two percent of the subjects had sleep fragmentation, 48% had altered dream phenomena, and 26% had hallucinations/illusions. Eighty-two percent of the patients with hallucinations/illusions experienced some form of sleep disorder. The three phenomena were not independent. The interaction between sleep fragmentation and altered dream phenomena was strongly statistically significant. Likewise, a significant interaction existed between altered dream phenomena and hallucinations/illusions. No interaction occurred between sleep fragmentation and hallucinations/illusions. Sleep fragmentation, altered dream phenomena, and hallucinations/illusions in PD should be considered distinct but often overlapping behaviors. The close association between altered dream phenomena and hallucinations suggests that therapeutic interventions aimed at diminishing dream-related activities may have a specific positive impact on hallucinatory behavior.

Ropinirole HCl for Parkinson's disease

Priya *et al.,* (1998) the aim of their study was to formulate and evaluate the Solid Lipid Nanoparticles (SLNs) of Ropinirole Hydrochloride (ROP). ROP-loaded SLNs were prepared by a double emulsion method using glyceryl monostearate (GMS) as lipid and soya lecithin as a stabilizer. All formulated ROP-loaded SLNs were characterized for its particle size and size distribution, zeta potential, % Entrapment Efficiency (EE) and drug loading. The formulations were optimized in terms of GMS to soya lecithin ratio and sonication time of primary emulsion. Shape and surface morphology of the optimized formulation was studied using optical microscopy and scanning electron microscopy. In vitro and ex vivo Study of optimized formulation was also performed and compared with a pure drug solution.

Gupta *et al.,* (2006*)* prepared Microspheres of Ropinirole hydrochloride (RH) loaded with ethyl cellulose and carbopol 934P were prepared usingsolvent evaporation method. Formulations (RH1-RH5) with different ratios were evaluated for various parameters percent yield, shape, particle size, drug content, entrapment efficiency, swelling ratio, powder X-ray diffraction studied (PXRD) and in-vitro release studies. All the particles of prepared microspheres were in micrometric range (73.04-120.16 μm). Entrapment efficiency and percent drug content was found to be highest for formulation RH3. In vitro release studies revealed that all the formulations showed sustained release pattern with highest release in RH3 formulation (96.09%) and selected for further studies.

Raghubabu *et al.,* (1995) performed assay of Ropinirole Hydrochloride in pharmaceutical preperations by Visible Spectrophotometry. Two simple and sensitive direct visible spectrophotometric methods (M1 and M2) have been developed for the determination of Ropinirole hydrochloride in bulk and solid dosage forms. These methods are based on the reaction of drug with aromatic aldehydes such as Vanillin or Para dimethyl amino Benzaldehyde (PDAB) in the presence of sulphuric acid in non aqueous medium and formed colored condensation products with an absorption

maximum of 560nm for method M1 and 660nm for method M2.

Jayesh *et al.,* (1999) formulate buccal tablets of Ropinirole Hydrochloride. Ropinirole Hydrochloride after oral administration shows a lesser bioavailability up to 55% and biological half-life of 4 to 6 hours. So, present investigation deals with formulation and evaluation of buccal tablet of Ropinirole Hydrochloride. Ropinirole Hydrochloride buccal tablets were prepared by wet granulation method using Polycarbophil and HPMC K15M as mucoadhesive polymers.

Jafarieh *et al.,* (2014) prepared mucoadhesive nanoparticles of Ropinirole for intranasal drug delivery. The purpose of the present study was to investigate the possibility of targeting an anti-Parkinson's drug ropinirole (RH) to the brain using polymeric nanoparticles. Ropinirole hydrochloride (RH)-loaded chitosan nanoparticles (CSNPs) were prepared by an ionic gelation method. The RH-CSNPs were characterized for particle size, polydispersity index (PDI), zeta potential, loading capacity, entrapment efficiency in vitro release study, and in vivo distribution after intranasal administration.

Bhatt *et al.,* (2011) formulated nanosuspension of Ropinirole Hydrochloride for oral delivery**.** The aim of the present study was to develop Ropinirole hydrochloride nanoparticle and to study its release profile. Ropinirole hydrochloride alleviates this deficiency by stimulating striatal dopamine receptors. Ropinirole hydrochloride has got complete but variable oral absorption with less bioavailability approximately 50%. Hence, nanoparticles of Ropinirole hydrochloride was developed to improve drug diffusion profile and hence the oral bioavailability. Ropinirole hydrochloride nanosuspension stabilised by poloxamer F-68 was first prepared by milling technique and was lyophilized to obtain nanoparticle using mannitol (1:1 w/v) as cryoprotectant. Developed nanoparticle was characterized for its particle size and size distribution, drug content and % drug entrapment. In vitro dissolution study using dissolution bag (12000 D) and ex vivo study in rat ileum were carried out using 0.1N hydrochloric acid as dissolution medium.

Bhimani *et al.,* (2013) prepared sublingual tablets of Ropinirole HCL by direct compression procedure using different concentration of Crospovidone and Croscarmellose Sodium. The pre-compression parameters were in acceptable range of pharmacopoeia specification. The disintegration time of optimized formulation (F5) was up to 40 sec. The in vitro release of Ropinirole hydrochloride was up to 9 minutes. The percentage relative permeability of Ropinirole hydrochloride from optimized sublingual tablets was found to be 90.51% after 30 minutes. Sublingual tablets Ropinirole hydrochloride of were successfully prepared with improved bioavailability.

Nitin B *et al.,* (2012) formulate sustained release orodispersible tablets of Ropinirole Hydrochloride by spray drying method. The Parkinsonism patients taking Ropinirole HCl conventional tablet cannot swallow the dosage form due to reduced muscular activity, unavailability of water, dryness of mouth and dysphagia. The frequency of administration of this dosage form is minimum thrice a day due to lower dose (upto 8 mg) and shorter half-life (5 hrs), so the problem arises in the number of doses. To overcome both these problems the sustained release orodispersible tablet dosage form of Ropinirole HCl is developed which will deliver the drug over a longer period of time. Microspheres of Ropinirole HCl were prepared by spray drying technique. The microsphere of Ropinirole HCl showed an increasing trend of entrapment efficiency and in-vitro drug release. The in vitro drug release study suggests the sustained release of drug despite being highly water soluble. Scanning electron microscopy, differential scanning calorimetry and FT-IR study of the drug and formulation was carried out.

Pardeshi *et al.,* (2012) prepared Ropinirole hydrochloride loaded solid lipid nanoparticles (SLNs) for intranasal delivery by application of factorial design. Prime objectives of this experiment are avoidance of hepatic first pass metabolism and to improve therapeutic efficacy in the treatment of Parkinson's disease. SLNs were fabricated by emulsification-solvent diffusion technique. A 3^2-factorial design approach has been employed to assess the influence of two independent variables, namely Pluronic F-68 and stearylamine concentration on particle size, z-potential and entrapment efficiency of prepared SLNs. Prepared samples were further evaluated for in vitro drug diffusion, ex vivo drug permeation, histopathological and stability studies. Differential scanning calorimetry analysis revealed the encapsulation of amorphous form of drug into lipid matrix, while scanning electron microscopy studies indicated the spherical shape.

Sharma *et al.,* (2013) prepared thermo-reversible gel of Levodopa. Hence, levodopa is co-administered with carbidopa, a peripheral amino acid decarboxylase inhibitor. In an attempt to improve brain uptake and to avoid degradation of levodopa in peripheral circulation and the use of carbidopa in combination, nose to brain drug delivery of levodopa alone via the olfactory route and the trigeminal nerves has been investigated. Chitosan nanoparticles loaded with levodopa (CNL) were prepared and were incorporated in a thermo-reversible gel prepared using Pluronic PF127 (CNLPgel).

Priya *et al.,* (2015) formulated Solid Lipid Nanoparticles of Ropinirole Hydrochloride. From the results, they concluded that drug released from SLNs follows sustained release pattern and it will enhance the overall activity of the drug. ROP-loaded SLNs were prepared by a double emulsion method using glyceryl monostearate (GMS) as lipid and soya lecithin as a stabilizer. All formulated ROP-loaded SLNs were characterized for its particle size and size distribution, zeta potential, % Entrapment Efficiency (EE) and drug loading.

Goyal *et al.,* (2015) prepared in-situ gel of levodopa using chitosan-thioglycolic acid conjugate and musk ketone by efflux transport modulation for brain targrtting. Conventional levodopa therapy has problems like peripheral oxidation, poor penetration through blood brain barrier and

efflux through the P-gp efflux pump that limits the drug bioavailability. The rationale of project was aimed to formulate and evaluate pluronic thermosensitive nasal gel of levodopa for brain targeting using chitosan-thioglycolic acid conjugate as P-gp efflux transport inhibitor and nitromusk (musk ketone) as fragrance compound that stimulates the sensation and thus permeability in the nasal cavity.

Nilesh *et al.,* (2011) made transdermal patch of Ropinirole Hydrochloride. Ropinirole HCl is a drug used to treat Parkinson's disorder and it is suitable drug candidate for transdermal delivery due to its small molecular size, optimum log P and low oral bioavailability due to first pass metabolism. Hence the present study was aimed at development of transdermal patch of Ropinirole HCl to show its prolonged release. The combination of HPMC K15 and Eudragit RL100 was tried as a porous matrix to control the release of Ropinirole HCl up to 12 hrs. The transdermal patches were prepared by solvent casting method.

Mohan *et al.,* (2001) formulate Ropinirole HCL extended release matrix tablets. The objective of the study is to prepare and evaluate the controlled release matrix tablets of a water soluble drug (ropinirole hydrochloride) using direct compression and Wet granulation technology. Ropinirole Hydrochloride is a hydrophilic drug and has pH independent solubility. It is used in the treatment of idiopathic parkinsons disease. The controlled release matrix tablets of ropinirole hydrochloride were prepared using various polymers: guargum, sodium alginate and carbopol 940P.The matrix tablets were prepared & evaluated for the various quality control parameters and the drug release was evaluated in pH 1.2 and in pH 7.4 buffer. The optimized formulation containing drug and guar gum controlled the drug release up to 8 hours.

Drug delivery

Shah *et al.,* (2016) prepared transdermal patch and proniosomal gel of Ropinirole Hydrochloride. They concluded that proniosomal gel system have shown great potential for delivery of Anti-Parkinson drugs. The proniosomal gel also appears to be an effective alternative vehicle for delivering adrug through the topical and transdermal route. Ropinirole HCL is a drug used to treat Parkinson's disorder and is suitable drug candidate for transdermal delivery due to its small molecular size. The combination of different HPMC grades with PVP K-30 was used to formulate transdermal matrix by solvent evaporation method.

Bobade *et al.,* (2015) conducted research on design and in vitro charactrization of novel phase transition systems for nasal drug delivery. The purpose of this study was the design and in vitro characterization of phase transition systems for nasal drug delivery based on muco-adhesive polymers. Muco-adhesive drug delivery systems that utilized the property of bioadhesion of certain polymers, which becomes adhesive on hydration and hence can used for targeting a drug to a particular region of the body for extended periods of time.

Azeem *et al.,* (2011) made oil based nanocarrier system for transdermal delivery of ropinirole. Ropinirole, a recent introduction in the clinical treatment of Parkinson's disease, suffers with the problems of low oral bioavailability and frequent dosing. An effective transdermal nano-emulsion drug delivery system can however resolve these issues effectively with greater therapeutic benefits and clinical significance. Therefore, the present work focuses precisely on pharmacokinetic, biochemical and mechanistic assessment of transdermal nanoemulsion gel in rats induced with Parkinson lesioned brain by 6-OHDA. DSC and FT-IR studies showed that NEG affects the normal lipid packing of stratum corneum to enhance the drug permeation. Study of pharmacokinetic parameters (AUC, Cmax, and Tmax) revealed a greater and more extended release of ropinirole from nanoemulsion gel compared to that from a conventional gel (RPG) and oral marketed tablet (Ropitor®).

Shahdab *et al.,* (2012) the primary aim of this study was to investigate the potential use of chitosan nanoparticles as a delivery system to enhance the brain targeting efficiency of bromocriptine (BRC) following intranasal (i.n.) administration. The BRC loaded chitosan nanoparticles (CS NPs) were prepared by ionic gelation of CS with tri- 29 polyphosphate anions. These NPs had a mean size (161.3 ± 4.7 nm), zeta potential (+40.3 ± 2.7 mV), loading capacity (37.8% ± 1.8%) and entrapment efficiency (84.2% ± 3.5%). The oral administration of haloperidol (2 mg/kg) to mice produced typical Parkinson (PD) symptoms. Singh *et al.,* (1996) fabricated and evaluated novel surface modified polymer–lipid hybrid nanoparticles (PLN) as robust carriers for intranasal delivery of ropinirole hydrochloride. Sustained release, avoidance of hepatic first pass metabolism, and improved therapeutic efficacy are the major objective of this experiment. PLN were fabricated by emulsification-solvent diffusion technique and evaluated for physicochemical parameters, in vitro mucoadhesion, *in-vitro* diffusion, *ex-vivo* permeation, mucosal toxicity and stability studies. Blasi *et al.,* (2011) The aim of this study was to optimize the formulation of lipid nanoparticles (NPs), intended for brain targeting, with the aid of a computer generated experimental design. The high pressure homogenization technique, selected for this purpose, was suitable to formulate the 3 investigated lipids (i.e., Softisan® 142, SOFT; Compritol® 888 ATO, COMP; cetyl palmitate, CP) into nanometre-length particles, while the computer generated experimental design helped to individuate the best preparation conditions with a small number of experimental assay. Even though all the 3 optimized formulations were suitable for intravenous infusion, CP NPs showed the smallest particle size and the appropriate thermal behaviour to be used as carriers in brain targeting applications.

Azeem *et al.,* (2009) investigated the potential of nanoemulsions as nanodrug carrier systems for the percutaneous delivery of ropinirole. The purpose of the present study was to investigate the potential of nanoemulsions as nanodrug carrier systems for the

percutaneous delivery of ropinirole. Nanoemulsions comprised Capryol 90 as the oil phase, Tween 20 as the surfactant, Carbitol as the cosurfactant, and water as an external phase. The effects of composition of nanoemulsion, including the ratio of surfactant and cosurfactant (Smix) and their concentration on skin permeation, were evaluated. All the prepared nanoemulsions showed a significant increase in permeation parameters such as steady state flux (Jss) and permeability coefficient (Kp) when compared to the control ($p<0.01$).

Esposito *et al.,* (2008) described a formulative study for the development of innovative drug delivery systems for bromocriptine. They concluded that nanostructured lipid carriers encapsulation may represent aneffective strategy to prolong the half-life of bromocriptine. Solid lipid nanoparticles (SLN) based on different lipidic components have been produced and characterized. Morphology and dimensional distribution have been investigated by electron microscopy and Photon Correlation Spectroscopy. The antiparkinsonian activities of free bromocriptine and bromocriptine encapsulated in nanostructured lipid carriers were evaluated in 6-hydroxydopamine hemilesioned rats, a model of Parkinson's disease.

TingtingPu. *et al.,* (2016) developed a prolonged-release pramipexole (PPX) transdermal patch for the treatment of Parkinson's disease. The current study aimed to develop a prolonged-release pramipexole (PPX) transdermal patch for the treatment of Parkinson's disease. Permeation parameters of PPX were investigated using human cadaver skin. Pramipexole patches were prepared usingDURO-TAK® pressure-sensitive-adhesive (PSA) and evaluated for drug stability, drug loading, in vitro drug release, and in vitro permeation throughmouse skin. The results indicated that blends of DUROTAK ® 87-2852 and DURO-TAK® 87-2510 were suitable for creating a prolonged-release PPX patch due to their advantages in drug release, drug loading, and stability. The final formulation consisted of 87-2852/87-2510 (70:30), 10% PG, and 15%PPX and showed a cumulative permeation amount of 1497.19 ± 102.90 μg/cm2 with a continuous flux over 6.0 μg/(cm2·h) across human cadaver skin for 7 days. In vivo studies in rats indicated that PPX patch produced a significantly longer ($p< 0.001$) half-life (t1/2, 75.16 ± 17.37 h) and mean residence time (MRT, 135.89 ± 24.12 h) relative to oral tablets (Sifrol®) and had a relative bioavailability of 51.64 ± 21.32%. Therefore, this study demonstrated the feasibility of developing a prolonged-release PPX patch, which proposed the potential to serve as an alternate to conventional oral tablets and may therefore improve patient compliance.

Fang *et al.,* (2012) Nanostructured lipid carriers (NLCs) are drug-delivery systems composed of both solid and liquid lipids as a core matrix. It was shown that NLCs reveal some advantages for drug therapy over conventional carriers, including increased solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery. NLCs have attracted increasing attention in recent years.

Karamsetty *et al.,* (2015) the primary objective of writing this article is to put the emphasis on the importance of nano structured based drug delivery systems. Although drugs as such can be delivered in the body using different routes but most of the routes esp. have its own limitations like poor solubility, absorption, first pass metabolism and poor bioavailability, hence need for this nano structured based drug delivery systems was developed. This technique not only will help us in overcoming the above mentioned drawbacks but also this helps us in reducing the dose, systemic side effects and in addition to these, this also helps us in delivering the drugs to the site of action. These nano based systems can be used to deliver variety of drugs through different routes of administration including oral, topical, transdermal, ocular and parenteral. This review outlines the process involved in the preparation of NLC's, its characterization and evaluation and its pharmaceutical applications.

Eskandari *et al.,* (1998) the treatment of brain disorders is one of the greatest challenges in drug delivery because of a variety of main barriers in effective drug transport and maintaining therapeutic concentrations in the brain for a prolonged period. The objective of this study was delivery of valproic acid (VPA) to the brain by intranasal route. For this purpose, nanostructured lipid carriers (NLCs) were prepared by solvent diffusion method followed by ultrasonication and characterized for size, zeta potential, drug-loading percentage, and release. Six groups of rats each containing six animals received drug-loaded NLCs intraperitoneally (IP) or intranasally. Brain responses were then examined by using maximal electroshock (MES).

Kaur *et al.,* (2011) Nanotechnology having developed exponentially, the aim has been on therapeutic undertaking, particularly for targetted drug therapy. In 1980 K. Eric Drexler developed and popularized the concept of nanotechnology. The nanocarriers has became a revolutionary approach. Nanocarriers are at forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicines and research. Nanostructure lipid carriers have attracted expanding scientific and commercial vigilance in the last couple of years as alternate carriers for the pharmaceutical consignment.

Drug profile

Drug name: Ropinirole Hydrochloride.

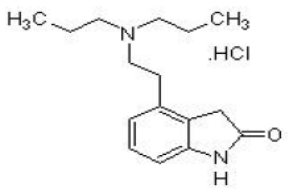
Synonyms: Ropinirole HCl

Description: Selective D_2 receptor agonist.

Biological description: Selective D_2 like receptor agonist. Displays high affinity for D_2 and D_3 but little for D_1 receptor.

Molecular Formula: $C_{16}H_{24}N_2O.HCL$

Chemical structure



Molecular weight: 296.84g/mol.
Chemical name: 4-[2-(Dipropylamino) ethyl]-1, 3-Dihydro-2H-indole-2-ol hydrochloride.
Appearance: white to yellow powder.
Half life: 6 hours.
Melting point: 243-250°C
Water solubility: 133mg/ml
Log P: 2.70
Volume of distribution: 7L/Kg
Protein binding: 10-40%
Pka: 9.5

Pharmacodynamics: Clinical experience with dopamine agonists, including ropinirole, suggests an association with impaired ability to regulate blood pressure with resulting orthostatic hypotension, especially during dose escalation. In some patients in clinical trials, blood pressure changes were associated with the emergence of orthostatic symptoms, bradycardia, and, in one case in a healthy volunteer, transient sinus arrest with syncope. The mechanism of orthostatic hypotension induced by ropinirole is presumed to be due to a D2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Nausea is a common concomitant symptom of orthostatic signs and symptoms. At oral doses as low as 0.2 mg, ropinirole suppressed serum prolactin concentrations in healthy male volunteers. Ropinirole had no dose-related effect on ECG wave form and rhythm in young, healthy, male volunteers in the range of 0.01 to 2.5 mg. Ropinirole had no dose-or exposure-related effect on mean QT intervals in healthy male and female volunteers titrated to doses up to 4 mg/day. The effect of ropinirole on QTc intervals at higher exposures achieved either due to drug interactions, hepatic impairment, or at higher doses has not been systematically evaluated.
Mechanism of action: Ropinirole is a non-ergoline dopamine agonist. The precise mechanism of action of ropinirole as a treatment for Parkinson's disease is unknown, although it is thought to be related to its ability to stimulate dopamine D2 receptors within the caudate-putamen in the brain. The precise mechanism of action of ropinirole as a treatment for Restless Legs Syndrome is unknown, although it is thought to be related to its ability to stimulate dopamine receptors.
Pharmacokinetics: Ropinirole displayed linear kinetics over the dosing range of 1 to 8 mg three times daily. Steady-state concentrations are expected to be achieved within 2 days of dosing. Accumulation upon multiple dosing is predictive from single dosing.

Absorption: Ropinirole is rapidly absorbed after oral administration, reaching peak concentration in approximately 1 to 2 hours. In clinical trials, more than 88% of a radio labeled dose was recovered in urine and the absolute bioavailability was 45% to 55%, indicating approximately 50% first-pass effect. Relative bioavailability from a tablet compared with an oral solution is 85%. Food does not affect the extent of absorption of ropinirole, although its Tmax is increased by 2.5 hours and its Cmax is decreased by approximately 25% when the drug is taken with a high-fat meal.
Distribution: Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg. It is up to 40% bound to plasma proteins and has a blood-to-plasma ratio of 1:1.
Metabolism: Ropinirole is extensively metabolized by the liver. The major metabolic pathways are N- despropylation and hydroxylation to form the inactive N-despropyl metabolite and hydroxyl metabolites. The N-despropyl metabolite is converted to carbamyl glucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated. *In-vitro* studies indicate that the major cytochrome P^{450} enzyme involved in the metabolism of ropinirole is CYP1A2, an enzyme known to be induced by smoking and omeprazole and inhibited by, for example, fluvoxamine, mexiletine, and the older fluoroquinolones such as ciprofloxacin and norfloxacin.
Elimination: The clearance of ropinirole after oral administration is 47 L/h and its elimination half-life is approximately 6 hours. Less than 10% of the administered dose is excreted as unchanged drug in urine. N-despropyl ropinirole is the predominant metabolite found in urine (40%), followed by the carboxylic acid metabolite (10%), and the glucuronide of the hydroxy metabolite (10%).

Drug Interactions
Digoxin: Coadministration of REQUIP (2 mg three times daily) with digoxin (0.125 to 0.25 mg once daily) did not alter the steady-state pharmacokinetics of digoxin in 10 patients.
Theophylline: Administration of theophylline (300 mg twice daily, a substrate of CYP1A2) did not alter the steady-state pharmacokinetics of ropinirole (2 mg three times daily) in 12 patients with Parkinson's disease. REQUIP (2 mg three times daily) did not alter the pharmacokinetics of theophylline (5 mg/kg IV) in 12 patients with Parkinson's disease.

Ciprofloxacin: Coadministration of ciprofloxacin (500 mg twice daily), an inhibitor of CYP1A2, with REQUIP (2 mg three times daily) increased ropinirole AUC by 84% on average and Cmax by 60% (n = 12 patients).
Estrogens: Population pharmacokinetic analysis revealed that estrogens (mainly ethinylestradiol: intake 0.6 to 3 mg over 4-month to 23-year period) reduced the oral clearance of ropinirole by 36% in 16 patients. L-dopa*:* Co administration of carbidopa + L-dopa (10/100 mg twice daily) with REQUIP (2 mg three times daily) had no effect

on the steady-state pharmacokinetics of ropinirole (n = 28 patients). Oral administration of REQUIP 2 mg three times daily increased mean steady-state Cmax of L-dopa by 20%, but its AUC was unaffected (n = 23 patients).
Uses: Parkinson's disease, Restless legs Syndrome.
Side effects: Nausea, vomitting, constipation, dizziness, weakness, unusual sweating, headache, dry mouth, hallucinations, depression.
Storage: Store below 25°C. Protect from sunlight and moisture.

Summary and Conclusion

Based on our review studies the following conclusions can be drawn regarding Ropinirole HCl NLC's for the persistent treatment of Parkinson's disease. The review study confirmed that the NLCs can be prepared by using the drug and the excipients such as IPM, Glyceryl mono stearate 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.

Acknowledgement

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 conflict of Interest".

Source of funding

None.

Conflict of interest

None.

References

1. 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* 2000;48:938–42.
2. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis* 2010;37:13–25.
3. Barbeau A. L-Dopa therapy in Parkinson's disease. *Can Med Assoc* 1969;59–68.
4. Belluzi JD, Domino EF, May JM. A selective dopamineD2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease. *Mov Disord* 1994;147-54.
5. Carlo Ferrari. Cabergoline in the long-term therapy of hyperprolactinemic disorders. *Acta Endocrinol* 1992;489-94.
6. Dawson VL. Neurobiology of flies and mice. *Sci* 2000;631-2.
7. De la Fuente-Fernandez R, Calne DB. Evidence for environmental causation of Parkinson's disease. Parkinsonism and Related Disorders, 2002;235-241.
8. Elisabetta Esposito, Martina Fantin, Matteo Marti, Markus Drechsler, Lydia Paccamiccio, Paolo Mariani et al. Solid Lipid Nanoparticles as Delivery Systems for Bromocriptine. *Pharm Res* 2008;25(7):1521-30.
9. Filloux F, Townsend J. Pre- and post-synaptic neurotoxic effects of dopamine demonstrated by intrastriatal injection. *Exp Neurol* 1993;119:79–88.
10. Forno LS, Sternberger LA, Sternberger NH. Reaction of Lewy bodies with antibodies to phosphorylated and nonphosphorylated neurofilaments. *Neurosci Lett* 1986;64:253–8.
11. Fritsch T, K Smyth, M Wallendal, T Hyde, G Leo, D Geldmacher: Parkinson Disease: Research update and clinical management. *South Med Assoc* 2012;105(12):650-6.
12. 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* 1999;274,7619–22.
13. Gibb WR. Accuracy in the clinical diagnosis of parkinsonian syndromes. *Postgrad Med J* 1998;64:345–51.
14. Goldman JE, Yen S-H, Chiu F-C, Lewy bodies of Parkinson's disease contain neurofilament antigens. *Sci* 1983;221:1082–4.
15. Gorell JM. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. U.S *Natl Lib Med* 1998;1346-50.
16. Harding AJ, Stimson E, Henderson JM. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. *J Neurol* 2002;125:2431–45.
17. Hartley A, Stone JM, Heron C. Complex I inhibitors induce dose dependent apoptosis in PC12 cells relevance to Parkinson's disease. *J Neurochem* 1994;1987–90.
18. Illum L. Nasal drug delivery: possibilities, problems and solutions. *J Cont Release* 2003;187-98.
19. James W Tetrud, Zigmond MJ. A novel formulation of selegiline for the treatment of Parkinson'sdisease. *J Am Acad Neurol* 2004;2-6.
20. Janice M Beitz. Parkinson's disease: a review, Frontiers in Bioscience, 2014;S6,65-74.
21. Karin M Jorga, Ben-Sasson SA. The effect of tolcapone on the pharmacokinetics of benserazide. European Journal of Neurology, 1996;6(2):211-9.
22. Kruger R., Kuhn W, Muller T. Ala30Pro mutation in the gene encoding alpha-synucleinin Parkinson's disease. *Nat Genet* 1998;18(2):106-8.
23. Latika Nasare, Shrikant D, Shagufta A. Nasal drug delivery system: an emerging approach for brain targeting. *World J Pharm Pharm Sci* 1998;3(4):539-53.
24. Leroy E, Boyer R, Auburger G. The ubiquitin pathway in Parkinson's disease. *Nat* 1998;395(6701):451-2.
25. Manoj Kumar Katual., Harikumar S.L., 2016. Drug delivery to CNS; various approaches for Parkinson's disease management. *Int J Recent Sci Res* 2016;7(3):9148-9155.
26. Muhammad U Ghori. Nasal Drug Delivery Systems: An Overview. American Journal of Pharmacological Sciences, 2015;3(5):110-9.
27. Nishan N Bobade, Ashish K Khrobragade, Jaymin M Patel, Shrikant D, Shagufta A Khan. Design and in vitro characterization of novel phase transition systems for nasal drug delivery. *World J Pharm Pharm Sci* 2015;4(11):1231:51.
28. Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. *Annu Rev Neurosci* 1999;123-144.
29. Pagar Swati Appasaheb. A Review on Intranasal Drug Delivery System. *Int J Pharm* 2013;3(4):333-44.
30. Popoulos MH, Lavedan C, Leroy E. Mutation in the alpha-synucleingene identified in families with Parkinson's disease. *Sci* 1997;2045-47.
31. Sherer TB, S Chowdhury, K Peabody. D Brooks: Overcoming obstacles in Parkinson's Disease. *Int J Pharm Pharm Sci* 2012;1606-11.
32. Sumit Sharma. Shikha Lohan, RSR Murthy. Formulation and character- ization of intranasal mucoadhesive nanoparticulates

and thermo-reversible gel of levodopa for brain delivery. Drug Development and Industrial Pharmacy, 2013;1–10.
33. Tsong-Long Hwang, Xiaohui Li, Yuming Sun, Xue Ding, Yaqing Pan, Qing Wang. Development and evaluation of perfluorocarbon nanobubbles for apomorphine delivery. *J Pharm Sci* 2009;98(10):3735-47.
34. Wright Willis A, B Evanoff, M Lian, S Criswell, B Racette. Geographic and ethnic variation in Parkinson Disease: A population-based study of US Medicare Beneficiaries. Neuroepidemiol 2010;143-51.
35. Zhigao Huang, Yingjie Zhai, Guangxi Zhai. Etiology of Parkinson's disease. *Canadian J Neurol Sci* 2003;30:10-8.