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Review

Lipid-based nanodelivery approaches for dopamine-replacement therapies in Parkinson's disease: From preclinical to translational studies

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ABSTRACT

The incidence of Parkinson's disease (PD), the second most common neurodegenerative disorder, has increased exponentially as the global population continues to age. Although the etiological factors contributing to PD remain uncertain, its average incidence rate is reported to be 1% of the global population older than 60 years. PD is primarily characterized by the progressive loss of dopaminergic (DAergic) neurons and/or associated neuronal networks and the subsequent depletion of dopamine (DA) levels in the brain. Thus, DA or levodopa (L-dopa), a precursor of DA, represent cardinal targets for both idiopathic and symptomatic PD therapeutics. While several therapeutic strategies have been investigated over the past decade for their abilities to curb the progression of PD, an effective cure for PD is currently unavailable. Even DA replacement therapy, an effective PD therapeutic strategy that provides an exogenous supply of DA or L-dopa, has been hindered by severe challenges, such as a poor capacity to bypass the blood–brain barrier and inadequate bioavailability. Nevertheless, with recent advances in nanotechnology, several drug delivery systems have been developed to bypass the barriers associated with central nervous system therapeutics. In here, we sought to describe the adapted lipid-based nanodrug delivery systems used in the field of PD therapeutics and their recent advances, with a particular focus placed on DA replacement therapies. This work initially explores the background of PD; offers descriptions of the most recent molecular targets; currently available clinical medications/limitations; an overview of several lipid-based PD nanotherapeutics, functionalized nanoparticles, and technical aspects in brain delivery; and, finally, presents future perspectives to enhance the use of nanotherapeutics in PD treatment.

1. Introduction

Parkinson's disease (PD) is the second most commonly reported neurodegenerative disorder and is predominantly characterized by the onset of motor deficits and progressive cognitive impairments in individuals older than 60 years [1,2]. The increasing lifespan of the global population has provoked an alarming rate of growth in the incidence of this idiopathic age-related disease, generating a greater impact on global socioeconomic status. Approximately 10 million people worldwide are estimated to have PD, with a male predominance [3,4]. More specifically, nearly one million [2.83% (≥90 years)] inhabitants in the United States and roughly 500,000 individuals in the United Kingdom were reported to be diagnosed with PD. In Western and Eastern countries, including those that are highly populated, such as China, India, and other Asian countries, the prevalence and incidence rates of PD are predicted to double by 2060 [5–8]. Subsequently, the global economic burden imposed by PD—that is, relating to medical expenses, caregiver wages, patient health care training and traveling—is also estimated to increase substantially over the next few years [9]. For decades, several therapeutic strategies have been in the clinical pipeline to curb PD progression; however, there is no successful cure clinically available at this time. The currently available clinical therapies for PD management

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only treat symptoms and provide momentary partial relief, whereas their side effects are exacerbated as the disease progresses [10,11]. Dopamine (DA) replacement therapy (DRT), or the process of restoring DA levels and potentially enhancing the dopaminergic (DAergic) neurotransmission in the brain, is one of the most commonly used therapeutic strategies for PD management at this time. Nevertheless, the conventional peripheral administration of DA to the brain is encumbered by several biological barriers: it is unable to pass the blood–brain barrier (BBB) due to its hydrophilic nature and displays poor bioavailability with a short plasma half-life [12,13]. In contrast, levodopa (L-dopa), a precursor of DA, easily bypasses the BBB via L-amino acid transportation and is decarboxylated to DA in DAergic neurons, thereby exerting sustainable therapeutic effects [13]. Although L-dopa supplementation is currently available as a gold-standard clinical treatment method for PD management, accumulating evidence suggests that the poor pharmacokinetic profile of L-dopa, as well as its short half-life in biological systems, low bioavailability (i.e., only approximately 1% of the administered dose reaches the brain milieu), and associated peripheral availability outside the BBB cause severe dyskinesia, motor fluctuations, and other minor detrimental side effects [14,15]. Recently, researchers have attempted to develop methods to curb dyskinesia induced by L-dopa [14]. Similarly, other therapeutic options to reinstate DA levels/DAergic synapses in the brain, such as DA agonists, monoamine oxidase B inhibitors and catechol-O-methyltransferase inhibitors have also been investigated [15,16]. However, most of these therapies share a weak pharmacokinetic profile, an inability to diffuse across the BBB, and limited bioavailability due to their physicochemical nature [17,18]. These findings have ultimately resulted in a significantly alarming scenario for current PD medications, as patients diagnosed with PD are clinically treated with long-term or relatively high-dose mono- and/or multiple-combination therapies to re-establish the synaptic plasticity at DAergic striatal neurons based on the individual's clinical conditions. Unfortunately, the use of these approaches alone results in long- or short-term synaptic signaling anomalies [19,20]. Thus, the identification of an active therapeutic strategy with an appropriately safe and effective delivery system is essential to overcome these limitations. With the recent advances made in nanotechnology, several nanoparticles have been successfully developed to facilitate effective drug delivery in biological systems [21,22]. More precisely, lipid-based nanodrug delivery systems exhibit positive biocompatibility and can be further functionalized to achieve safe, effectual, and tissue-targeted delivery, particularly to the brain [21,23]. This review discusses the current clinical perspective of PD progression and highlights recent updates regarding molecular targets, advances in PD therapeutics, and clinical limitations. Several recent review articles have provided descriptions of the applications of nanotechnology and the accessibility of different nanodrug delivery systems in PD therapeutics [21,24,25]. However, this review mainly focuses on lipid-based nanodrug delivery systems for DRT in PD (the most rarely discussed theme) and offers descriptions of potential challenges and future perspectives to develop successful lipid-based nano-PD therapeutics.

2. Background of PD

PD is a progressive neurodegenerative disorder that is characterized by motor-related dysfunction and which predominantly occurs in the aged population. The main features of PD include a significant loss of DAergic neurons in *substantia nigra pars compacta* (SNpc) and subsequent defects in synaptic plasticity in the striatal networks and basal ganglia [26]. Clinically, PD is characterized by motor deficits, such as bradykinesia, ataxia, stiffness, dystonia, resting tremors, and postural instability [27,28]. The early onset of PD motor symptoms is clinically diagnosed with the observation of unilateral asymmetrical tremors. The further progression of disease pathology is manifested as bilateral tremor sessions and evident postural instability [29]. During the intermediate stages, a substantial loss of balance and slowness of motor activities can be observed. In the later debilitating stages, patients typically exhibit severe postural instability, freezing/festination of gait, walking and functional disabilities and are typically bedridden and require around-the-clock nursing care [30,31]. Resting tremors involve the shaking of body parts (e.g., arms, legs, head) at some rhythmic frequency (3–6 Hz), while bradykinesia denotes unintentional motor activities and reductions in the intensity or movement. Moreover, muscular rigidity is characterized by increases in the stiffness of the muscles. These are the most common signs and reasons attributed to the motor functional instability observed in PD patients [30,31]. Cognitive decline and psychiatric mood fluctuations were also observed in PD progression, which reduces the activity associated with thought processing and increases the frequency of memory lapses—thus, patients with PD require extensive care [32,33]. Additionally, as the disease progresses to impact the olfactory sensory and visual neurons, a gradual loss of sensory abilities and distorted vision can be observed in patients with PD. Clinically, the loss of the sense of smell is one of the preliminary factors used to screen for the early stage of PD [33,34]. Furthermore, the dysfunction of the autonomic system in patients with PD leads to several secondary complications, including constipation, excessive sweating, scalp formation, blood pressure, headaches, and pain, which worsens the patients' quality of life [35,36]. Therapeutic strategies designed to curb, halt or reverse the progression of PD in the clinical management of patients with PD are urgently needed. Due to these multifaceted complications of PD, clinicians have encountered difficulties and complications in the administration of therapeutic agents, while researchers/scientists have been prompted to further investigate the potential underlying mechanisms and selective characteristic biomarkers of PD pathogenesis to develop an optimal therapeutic strategy.

3. Pathways and molecular mechanisms of DA-centered PD progression

The etiology of PD is believed to be influenced by aging, genetics, and environmental factors [37]. The appropriate mapping of these factors will potentially provide insights into disease progression. Briefly, the aging process and environmental toxins are well-documented to weaken the functional mitochondrial energy synthesis system. Mitochondrial dysfunction further decreases the energy supply and increases oxidative stress, potential Lewy body formation, and DAergic cell death. Indeed, a delay in the aging process was recently shown to curb PD progression in a *Caenorhabditis elegans* model [37,38]. On the contrary, mutations in certain gene sequences, such as *LRRK2, PINK1,* and *DJ-1*, have been reported to cause mitochondrial dysfunction-mediated DAergic cell death and further facilitate PD progression [39]. *SNCA* is the most important gene associated with PD incidence because it induces α-synuclein (α-syn) formation and aggregation, as well as Lewy body formation-mediated mitochondrial oxidative stress, neuroinflammation, excitotoxicity, and DAergic cell death/degeneration [40,41]. Additionally, mutations in *parkin* and *UCHL1* were reported to facilitate protein degradation mediated by the autophagy lysosomal pathway and Lewy body formation [40,41]. Therefore, the incidence and/or progression of PD involve several prominent molecular events, i.e., α-syn formation/aggregation, protein degradation, mitochondrial dysfunction, oxidative stress, neuroinflammation, excitotoxicity, Lewy body formation, and DAergic cell death. Here, we intend to correlate these crosslinked etiological molecular events with the corresponding biological pathways to provide a vivid picture of PD pathogenesis.

3.1. Dysregulation of the nigrostriatal pathway

Dopaminergic neurons are located at three major sites in the midbrain, including the *substantia nigra pars compacta* (SNpc), ventral

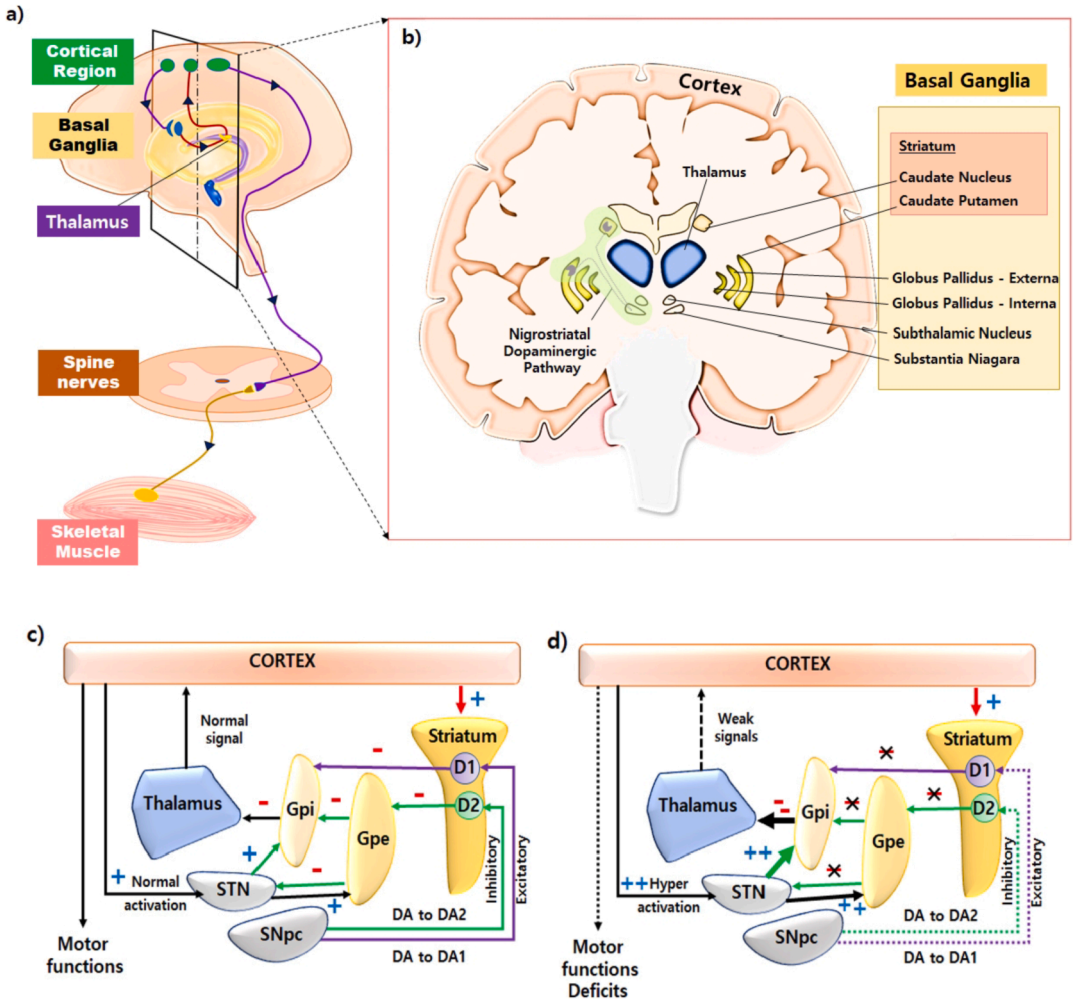

Fig. 1. a) Schematic mapping of the somatic peripheral nervous system, where the interloop processing of signals at the thalamocortical region in the brain and subsequent flow to the skeletal muscle via spine nerves is shown. b) Graphical illustration of the coronal section of the brain exhibiting the anatomy of the basal ganglia components; the green highlighted part denotes the nigrostriatal DAergic pathway. The firing intensities in the basal ganglia–thalamus–cortical loop circuit in c) a normal and d) a PD brain were represented, where the green and purple lines indicate the indirect and direct pathways, respectively. The black line indicates the thalamo–cortico–basal loop. The number of positive and negative symbols represent the intensity of the signals, while also the intensity of firing potentials is relatively represented by the thickness of the arrow. DA: dopamine; DA1/D1: dopamine receptor 1; DA2/D2: dopamine receptor 2; Gpe: globus pallidus externa; Gpi: globus pallidus interna; STN: subthalamic nucleus; SNpc: substantia nigra pars compacta.

tegmentum, and retrorubal field [42]. In the basal ganglia, DAergic neurons projecting from the SNpc to the striatum comprise the nigrostriatal pathway, which regulates the voluntary movements of the body and is principally damaged during PD pathogenesis (Fig. 1a and b) [43,44]. DAergic neurons in the SNpc secrete DA, which in turn functions as an inhibitory neurotransmitter to control and regulate the excitability of corticostriatal and spiny neurons via DA DA1 or DA2 receptors, thereby modulating the activation or suppression of the motor functions, respectively [45].

Overall, the signal for voluntary movement transmitted from cortical regions will be processed in the basal ganglia via direct/indirect pathways (based on DA1/DA2 receptors) and transmitted back to the cortical region via the thalamus. In turn, this processed signal is transmitted from the cortical region to the site of the action, i.e., the skeletal muscles, via spiny neurons to perform the desired motor functions [46,47]. This differential function of the DA receptors (DA1 and DA2) in mediating DA activities reveals the pivotal role of the DAergic system in PD progression [45,48]. Briefly, during PD progression, the nigrostriatal pathway exhibits a severe depletion of DAergic neurons in the SNpc and subsequent loss of DA neurotransmitters. This DA inadequacy results in a level of striatal neuron instability and induces excessive firing, leading to substantial motor deficits, such as tremor or rigidity (Fig. 1c and d) [48,49]. In addition to its effects on motor functions, the DAergic system of the SNpc is also reported to play roles in habitual control and goal-directed learning activities. Notably, the DAergic neurons of the ventral tegmentum area and retrorubral field play distinct roles in memory and psychological functions [50,51]. Although the DAergic systems of the midbrain have significant roles in psychological and motor activities via their inhibitory or excitatory functions, the exact interloop switching mechanisms among these DAergic systems are still being investigated. However, mechanisms employing other neurotransmitter receptors, i.e., glutamatergic (GLUTergic), gamma-aminobutyric acidergic (GABAergic), serotonin, and acetylcholine (ACh) neurotransmission, are associated with the progression of PD pathogenesis [52,53].

3.2. *Cascade of impediments in neurotransmitter systems*

GLUT, the most common excitatory neurotransmitter in the brain, is reportedly involved in approximately 70% of all synaptic transmission events [54,55]. GLUT primarily functions as an excitatory transmitter, while GABA functions as a presynaptic inhibitory transmitter in the mature brain. Ironically, GLUT is a precursor for GABA synthesis in the brain [55,56]. Generally, the neurons of the globus pallidus interna,

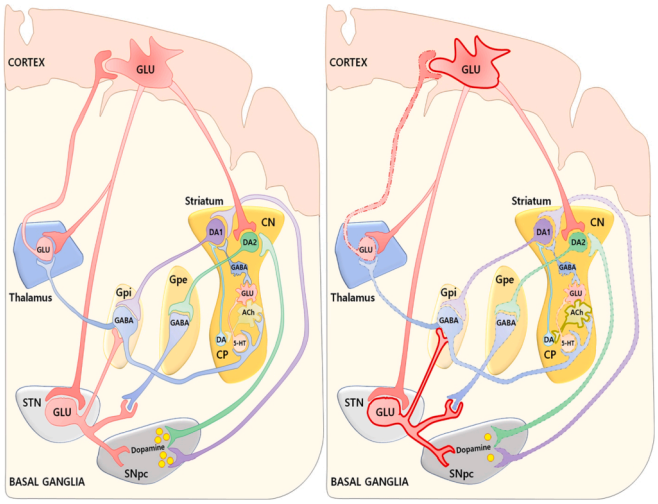

Fig. 2. Schematic representation of potential neurotransmitter circuit involved in the basal ganglia–thalamus–cortical loop. The figure in the left represent normal conditions and the right represent PD conditions. For clear understanding, only the presumed prominent neurotransmitter system involved in PD pathogenesis is represented. The red and blue color projections denote GLUTergic and GABAergic systems, respectively; the purple and dark green projections represent D1 receptor and D2 receptor associated DAergic systems, respectively; and the light green and orange projections represent acetylcholine and serotonin systems, respectively. The projections with a thick outline and dotted line represent the intense and weak transmissions, respectively. Glu: glutaminergic; GABA: GABAergic; ACh: acetylcholine; 5-HT: serotonin; DA: dopamine; DA1: dopamine receptor 1; DA2: dopamine receptor 2; Gpe: globus pallidus externa; Gpi: globus pallidus interna; STN: subthalamic nucleus; SNpc: substantia nigra pars compacta.

globus pallidus externa, and SNpc are GABAergic, whereas neurons in the thalamus and subthalamic regions are GLUTergic [57,58]. The signals from voluntary actions initiating in cortical regions are transmitted as an excitatory signal from cortico-striatal inputs to the caudate nucleus and putamen via GLUTergic projections that send inhibitory signals to globus pallidus interna and subsequently, the thalamus via a GABAergic circuit (direct pathway). Conversely, GABAergic projections from the caudate/putamen inhibit the subthalamus and excite the globus pallidus externa via GLUT, which in turn transmits inhibitory signals to the thalamus via a GABAergic circuit (indirect pathway) (Fig. 2) [59,60]. Ultimately, both pathways transmit the excitatory signal from the thalamus to the cortical regions via GLUT and thereafter, provoke the functional synaptic signal to the spinal nerves and skeletal muscles to induce motor functions [59,61]. The switching of both pathways is determined by DA and its receptors. DAergic neurons emerging from the SNpc facilitate the direct excitatory pathway at the level of the caudate/putamen when the released DA binds to the DA1 receptor, and, alternatively, facilitates the indirect pathway when DA binds to the DA2 receptor. In PD pathogenesis, despite the impaired function of nigrostriatal DAergic neurons and the loss of DA transmitters, an imbalance in GLUT and GABAergic transmitters has also been documented [48,62]. More precisely, in the putamen, GLUT/N-methyl-D-aspartate (NMDA) presynaptically inhibits DA2 on DAergic neurons, thereby substantially increasing DA deficits (Fig. 2) [63,64].

However, NMDA antagonists substantially reverse the dyskinetic effects, while the metabotropic GLUT receptor m5GluR has also been documented to exert a strong inhibitory effect on DAergic neurons in the putamen [65,66]. Nonetheless, the GABA receptors that regulate calcium influx in neurons, astrocytes, and glial cells are also reported to actively participate in PD pathogenesis, as their activity is altered by mitochondrial dysfunction [67]. Calcium-induced excitotoxicity caused by mitochondrial damage in patients with PD results in substantial DAergic neuronal loss in the SNpc. This decrease in GABA/calcium ion regulation has been reported to exert a cascade of effects, i.e., weakening of the BBB, accumulation of Lewy bodies (LB), and the formation of abundant calcium-binding protein deposits [67,68]. A postmortem analysis of the brains of patients with PD has shown a reduction in the number of GABAergic neurons in the basal ganglia circuit that precisely targets several regions of the thalamus. In patients with PD, the electrophysiological data obtained from the subthalamic region revealed hyperactivity due to the reduced inhibition of GABAergic activity from the globus pallidus extrena (Fig. 2) [69,70]. Ultimately, these anomalies in the GLUT and GABAergic systems have negative impacts on the outbound signals from the thalamus and motor deficits in PD pathogenesis.

The neurotransmitter ACh, which plays a role in cognitive functions, is prominently dysregulated in several neurodegenerative disorders, including PD. Histological studies of the brains of subjects with PD detected a substantial loss of neurons expressing choline acetyltransferase (ChAT) [71,72]. Although both DA and Ach are reported to be involved in learning, DAergic and cholinergic interneurons exhibit antagonistic interactions that are mediated by presynaptic GABAergic and GLUT–NMDA neurons [73,74]. Generally, ACh is rhythmically released by cholinergic interneurons into the striatum with a pause between release events and is autoinhibited by M4 muscarinic receptors. The pause response of ACh generally increases the release of DA to facilitate striatal synaptic plasticity [75]. Currently, researchers have hypothesized that ACh release is regulated by DA2 receptors on cholinergic neurons. Furthermore, nicotinic cholinergic neurons (nACh) were also reported to be involved in the activation of DA neurons in the caudate putamen via the β2 subunit of nicotinic ACh receptors [75,76]. The depletion of DAergic neurons and impairments in the DA-mediated nigrostriatal pathway in patients with PD leads to an imbalance in the D2 receptor and ACh levels, altering the DA2-mediated indirect pathway, extensively inhibiting the thalamocortical pathways and producing locomotor deficits in patients (Fig. 2) [77].

Serotonin (5-HT/SER) is another major neurotransmitter with multifaceted roles in neuronal synaptic signaling that is primarily found in the raphe nuclei of the midbrain and that is known to contribute to severe motor and nonmotor deficits, such as resting tremor and psychosis, in patients with PD [78]. Functional neuroimaging studies of the brains of patients with PD reported an approximately 30% reduction in serotonergic transporters (SER-T), which represents the denervation of the SER system and contributes to the intensity of tremors and other motor deficits in patients with PD [79]. Interestingly, PD tremors induced by the loss of the SERergic system in the raphe nucleus are relatively more intense and expected to precede tremors induced by DAergic neuron loss in the nigrostriatal pathway [80,81]. SER also facilitates L-dopa–induced dyskinesias (LIDs), potentially by altering the DA dynamics in SERergic systems due to the unmanageable conversion of L-dopa to DA and/or by inducing the development of SERergic terminals [82]. The DAergic–SERergic interaction at the caudate putamen was mediated by 5-HT_{2A} receptor binding; however, active 5-HT_{1A}/5-HT_{1B} receptor binding inhibits the striatal serotonergic afferents and blocks SERergic transmission (Fig. 2) [83,84]. This provides researchers with the opportunity to apply 5-HT_{2A} antagonists as potential therapeutics to reverse the effects of LIDs.

3.3. Protein misfolding/aggregate formations/proteolytic dysfunction

Protein misfolding is a common pathological event seen in several neurodegenerative disorders, including Alzheimer's disease [beta-amyloid (Aβ) and phosphorylated-tau (p-tau) proteins], PD (α-synuclein) and Huntington's disease (huntingtin protein) [85]. In PD, the cardinal misfolding of α-synuclein (α-syn) proteins results in the formation of aggregates and LBs, which damage the neuronal cell membrane; impair its stability; and subsequently, induce mitochondrial damage, oxidative stress, excitotoxicity, and neuroinflammation-mediated cell death [86,87]. In general, protein misfolding is a commonly occurring event

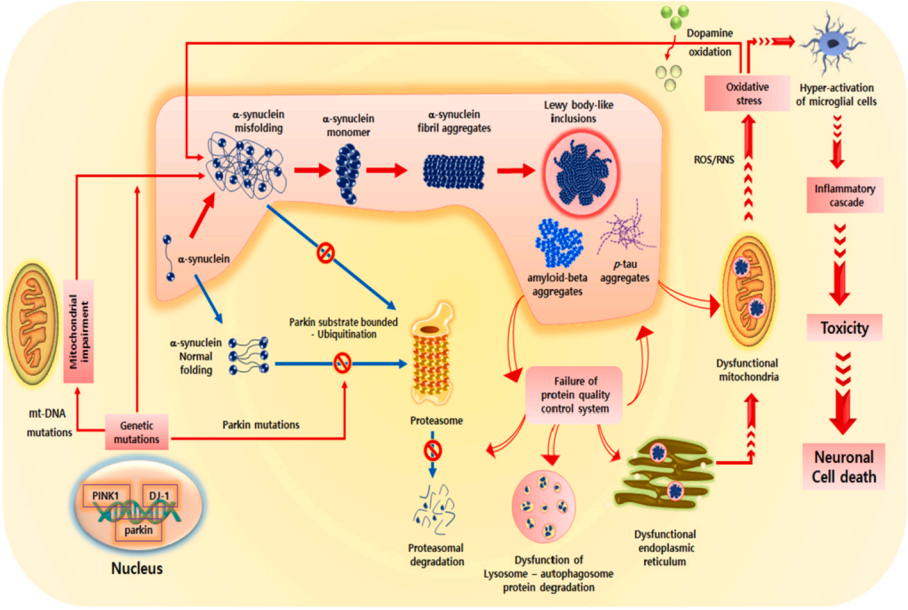

Fig. 3. Schematic representation of protein misfolding/aggregate formations/proteolytic dysfunction and other associated plausible events, potentially involved in the active neuronal cell-death mediated progression of PD pathogenesis. The genetic mutations of PINK1, DJ-1, and parkin potentially attribute to the inhibition of normal physiological proteolysis of undesirable α-synuclein, leading to α-synuclein misfolding and aggregation. On the other hand, mutations in mitochondrial DNA and DA oxidation were also presumably involved in the misfolding and aggregation of α-synuclein. The aggregates of misfolded α-synuclein (LBs) and other amyloid beta/p-tau proteins subsequently aggravate the disease conditions by inflicting mitochondrial dysfunction and ROS conditions, dysregulation of lysosomal-autophagosomal clearance of impaired proteins and endoplasmic reticulum, neuroinflammation and neuronal cell death. mt-DNA: mitochondrial DNA; ROS/RNS: reactive oxygen species/reactive nitrogen species.

in most eukaryotic cells, as the stability of the native form of the protein is low and its constant exposure to external environmental factors, such as increased temperature, oxidation, nitrosylation or other post-translational modifications, can lead to protein misfolding [88]. Biologically, our cells possess complex quality control (QC) surveillance systems, such as the ubiquitin–proteasome system, molecular chaperones (e.g., heat shock proteins), and the autophagy clearance system, which act to sense and either repair misfolded proteins or destroy those that are not capable of being repaired [88,89]. In patients with PD, the malfunctioning of these QC surveillance systems leads to the excess accumulation of misfolded α-syn proteins/aggregates and LB formation (Fig. 3) [90]. For instance, several *in vitro* and *in vivo* studies reported on the accumulation and overexpression of α-syn aggregates, particularly in the mitochondria, which impaired the bioenergetics and functional stability of the mitochondria [91,92]. Interestingly, according to recent histological evidence obtained from the brains of patients with PD complicated with dementia, α-syn protein aggregates were observed in addition to Aβ and p-tau (related to Alzheimer's disease pathogenesis) protein aggregates [93,94]. Further, patients with PD presenting frontotemporal dementia displayed the accumulation of p-tau aggregates in the cortical and SNpc regions that colocalized with LBs, suggesting a potential role of these signs in the denervation of the DAergic system [95]. These reports indicate the importance of protein clearance/proteolytic system in preventing the aggregation of misfolded proteins. This aberrant protein homeostasis in patients with PD is partially attributed to the commonly reported inheritable mutations in specific genes, i.e., *α-syn, parkin, PINK1, DJ-1,* and *LRRK2* [41]. For example, *parkin* (which regulates DA release in the SNpc), an E3 enzyme associated with the ubiquitin-proteasome system (UBS) required for the proteasomal degradation of misfolded proteins, differentially regulates poly- and monoubiquitination processes [96,97]. Specific mutations in *parkin* increase the accumulation and aggregation of misfolded proteins in the SNpc, promote LB formation, and facilitate several other molecular cascades involved in PD pathogenesis [96]. Similarly, other specific genes—for example, *DJ-1*, a dimer with antioxidant, transcriptional regulation, chaperone and proteasome activities; *PINK1*, a kinase that preserves mitochondrial functions in neuronal cells; and *LRRK2,* a kinase encoded by the *PARK8* gene that facilitates cytoskeletal maintenance, neurite outgrowth, and autophagic protein degradation with neuroprotective functions are mutated in patients with PD and facilitate disease progression by directly or indirectly hindering the proteolytic functions of the QC surveillance system (Fig. 3) [98–100]. Additionally, mutations in several other glucocerebrosidase (GBA), familial/autophagy-related genes, such as *PARK9, PARK 10, PARK11, PARK 3, VPS35, GRIN2a, SREBF,* and *GAK*, were also reported to be involved in PD pathogenesis [101–103]-.

3.4. Mitochondrial impairments, oxidative stress, and neuroinflammation

As the 'powerhouse' of the cell, the mitochondria are susceptible to several disease-mediated pathogenic cascades or stress conditions mediated by exogenous factors. In PD, the nonproteolyzed misfolded protein aggregates likely accumulate in the mitochondria and inhibit the mitochondrial respiratory complex (MRC)-mediated ATP production and bioenergetics of the cell, inducing oxidative stress and later, neuronal cell death [104]. Interestingly, the accumulation of α-synuclein aggregates was also reported to impair other key cellular functions, such as the functions of the endoplasmic reticulum in vesicular trafficking and autophagy–lysosomal degradation [105–107]. Post-mortem studies of the brains of patients with PD revealed prominent deficits in MRC-I precisely in the cortical and SNpc regions. Subsequently, a significant loss of MRC-III was also observed in the platelets and lymphocytes from patients with PD [108,109]. Indeed, the inhibition of MRC I and III was reported to exacerbate negative signaling cascades, leading to oxidative stress-mediated DAergic neuronal cell death. As oxidative phosphorylation plays a vital role in the bioenergetics required for mitochondrial ATP production, mitochondrial impairments exert a substantial impact on the oxidative metabolic pathway in cells [110,111]. Under normal physiological conditions, the oxygen utilized for MRC is converted to reactive oxygen species (ROS), which are later processed and eliminated by the endogenous antioxidant enzyme system. However, impairments in MRC systems can disrupt the homeostasis of the ROS/reactive nitrogen species–antioxidant system, as well as increase oxidative stress, mitochondrial dysfunction, and neuronal cell death cascades [112]. Notably, DA and SERT possess substantial antioxidant functions, while the relative breakdown of these monoamines by monoamine oxidase-B (MAO-B) also plays a critical role in free radical generation in the DAergic system [113]. Conversely, certain specific mutations in mitochondrial DNA and/or other associated familial mutations in α-syn, parkin, DJ-1, or PINK also potentially contribute to the imbalance in mitochondrial bioenergetics observed in PD pathogenesis (Fig. 3) [114]. Recently, researchers developed a special set of hybrid cells termed "cybrids," where the insertion of mitochondrial DNA from patients with PD into

neuroblastoma cells was performed to study the pathogenesis of PD [115]. Interestingly, these cybrids exhibit substantial MRC impairments and formed LBs in neuronal cells, analogous to the DAergic loss observed in patients with PD, thus supporting a role for mitochondrial dysfunction in PD progression [116,117]. However, damage induced by oxidative stress and mitochondrial dysfunction triggers inflammation and further exacerbates the disease condition [117,118]. Persistent inflammation is clearly established by activated microglial cells, the excess accumulation of cytokines (e.g., the pro-inflammatory cytokines tumor necrosis factor alpha, interleukin-1β, and interleukin-6) and other neuroinflammatory mediators in the cerebrospinal fluid and brain tissues of patients with PD that were collected in live and postmortem studies. Microglial activation in the nigrostriatal regions parallels the loss of DAergic cells in patients with early-stage PD [119–121]. An animal model of PD, which is established by chronically administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), revealed elevated levels of inflammatory cytokines along with a significant loss of DAergic neurons in the SNpc, thereby confirming the important contributions of inflammation to DAergic system impairments and successive PD progression [107,121].

4. Contemporary DA-centered PD therapeutics and their limitations

Therapeutic interventions that potentially ameliorate all facets of disease progression and cure PD are currently unavailable. However, a few symptomatic therapies are currently on the market to modestly delay disease progression and to provide temporary relief to patients with PD. An early diagnosis of PD and provision of appropriate care with symptomatic treatment can improve the life expectancy of patients with PD by up to several years. The clinical management of patients with PD is currently achieved using DA-based drug therapies (e.g., L-dopa, DA agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors) (Fig. 4), surgical procedures, such as deep brain stimulation and lesion-inducing operations, gene therapies [e.g., viral vectors encoding growth factors and clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 gene editing], stem cell transplantation procedures, like striatal and bone marrow transplants), as well as complementary and rehabilitation therapies, including diet and exercise modifications [122–125]. However, in this review, we mainly focused on DA-centered drug therapeutics. Although several therapeutic strategies have been investigated as PD treatments over the past few decades, currently, DRTs are widely used in clinical management [126].

Clinically, the primary and most effective treatment currently used to manage the symptoms of PD is L-dopa therapy, which acts to reverse DA depletion, either alone or in conjunction with other decarboxylase inhibitors [127,128]. L-dopa is a precursor of DA that is effectually metabolized into active DA and which potentially increases DA levels throughout the brain, including the extracellular regions of the dorsal striatum, thereby effectively restoring the striatal synaptic plasticity and ameliorating motor deficits observed during PD progression [129]. However, the acute administration of L-dopa shows relatively minimal therapeutic efficacy compared with long-term chronic administration, which is likely due to the substantial time required for L-dopa to restore considerable DA levels and synaptic plasticity. Thus, L-dopa therapies require a chronic dosing regimen to potentially alleviate long-term depression and long-term potentiation in patients with PD. In doing so, these therapies improve the patient's quality of life by ameliorating the characteristic motor symptoms [130,131]. Nevertheless, its ability to extend the patient's life expectancy is still debatable due to its chronic administration. As the gold standard PD therapy, L-dopa treatment can be initiated at any stage of PD progression. Nonetheless, its clinical bioavailability is approximately 1% and the peripheral availability of L-dopa outside BBB has been observed, which substantially alters synaptic plasticity in the striatal spiny neurons and results in time-dependent alterations in the DAergic and GLUTergic systems. These changes eventually result in LIDs, a hyperkinetic condition [132–134]. Researchers have been investigating the possible underlying mechanisms for LIDs and have identified several proposed pathways to date. For example, L-dopa–mediated sprouting of the axon terminals of SERTergic neurons facilitates hypersynaptic functions, which induces more DA release and results in LIDs [135,136]. However, from our perspective, although researchers have investigated other drugs to alleviate the side effects of the main drug (i.e., L-dopa), a focus on the core causes of its side effects, such as chronic dosage or a low “wearing-

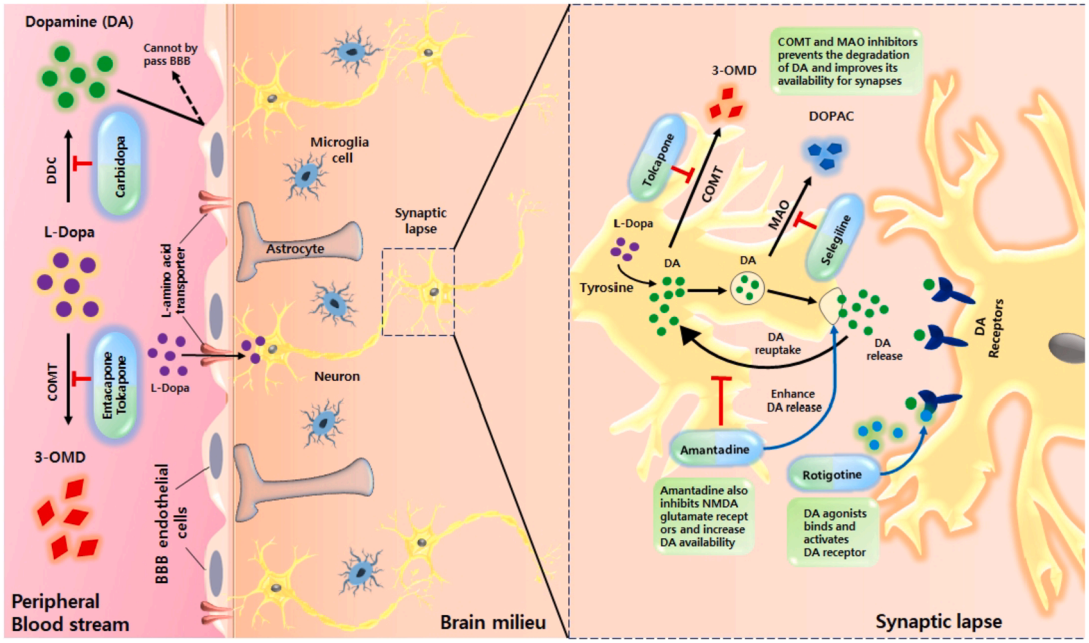

Fig. 4. Graphic representation of the potential mechanism of actions of various classes of drugs, i.e., L-dopa, DA agonists, COMT inhibitors, and MAOB inhibitors, showing some promising therapeutic effects in the clinical management of symptomatic PD. DA: dopamine; L-dopa: levodopa; DDC: dopamine decarboxylase; COMT: catechol-O-methyltransferase; 3-OMD: 3-O-methyldopa; MAO: monoamine oxidase B; DOPAC: 3,4-dihydroxyphenylacetic acid.

off" period, and addressing them appropriately, would be an ideally suitable solution to rectify this issue. Notably, researchers are currently working to increase the plasma half-life of L-dopa by developing sustained-release formulations to overcome the requirements for large doses and the wearing off issue [137,138]. Alternatively, the sustained delivery of DA across the BBB to the striatal regions represents another potential strategy to delay disease progression.

In addition to L-dopa, DA agonists are the second most commonly used therapeutics for the clinical management of PD. As the structures of DA agonists contain a DA-like moiety, they specifically bind to DA receptors and thereafter, reinstate endogenous DA levels with a reduced risk of dyskinesia. DA agonists have been recommended as a monotherapy for patients with early-stage PD (*de novo*) and paired with L-dopa as a combination therapy for patients with intermediate- or advanced-stage PD [139,140]. Currently, two classes of DA agonists have been administered in the clinic, i.e., ergot and nonergot derivatives [141]. Ergot derivatives (e.g., bromocriptine, pergolide) were recently reported to increase the incidence of valvular cardiac conditions, including the fibrosis of cardiac valves [142,143]. In a study comparing the effects of ergot and nonergot derivatives, 20% of patients treated with ergoline derivatives (i.e., pergolide and cabergoline) exhibited cardiac valvular complications; however, researchers have not yet obtained clear evidence that the ergot derivatives themselves directly induce cardiac complications [144]. Currently, nonergoline derivatives, such as ropinirole, pramipexole (oral), and apomorphine (AM) (injections) are the most commonly utilized treatments for PD management in the clinic. In addition to their effects on specific DA receptors, these compounds exhibit a longer half-life in plasma, thereby facilitating the sustained release of DA and preventing irregular fluctuations in DA-mediated dyskinesias in patients with PD [145–147]. However, pramipexole, a nonergoline derivative, was reported to induce unpredicted sleep manifestations or somnolence and is found at relatively higher percentages than ergolines [147,148]. Furthermore, the use of nonergoline DA agonists often induces several nonmotor psychological side effects, such as hallucinations, paranoia, delusions, depression, and autonomic events, including orthostatic hypotension and sleep anomalies [147,149]. Thus, patients with PD who are treated with DA agonists—specifically, nonergoline derivatives—should be cautioned about or monitored closely for these psychological effects and advised not to perform any critical activities, such as driving, until such effects have subsided [147]. On the other hand, AM, also exhibits a similar level of efficacy to that of L-dopa and is reported to result in a lower incidence of psychological effects; however, in contrast, it provokes relatively higher levels of other prominent adverse effects, such as an emetic response, nausea, and cutaneous abnormalities [150,151]. Recent advances in transdermal therapy have provided researchers with opportunities to establish specific formulations for the slow/sustained release of drugs, e.g., ropinirole or rotigotine administered via transdermal patches [152,153]. Interestingly, the use of low-dose rotigotine transdermal patches ensured favorable tolerance to sleep disturbances in patients with advanced PD, along with mild to moderate adverse events. Unfortunately, their previously reported side effects (i.e., psychological and sleep anomalies) were still observed in a considerable number of patients (38%) following long-term treatment. Thus, extensive safety investigations are still required to obtain a clear picture of the pervasiveness of adverse events [153,154].

Amantadine, an aliphatic primary amine, is a clinically well-known extended-release drug approved by the United States Food and Drug Administration (FDA) for the treatment of Parkinsonian symptoms. Amantadine substantially reduces tremors and rigidity and ameliorates dyskinesia in patients with PD [155,156]. Further, AM is potentially involved in blocking DA reuptake and facilitating DAergic transmission at synapses by actively blocking the GLUTergic NMDA receptors. Since AM is the only predominant GLUT receptor antagonist that exhibits strong antidyskinetic properties, the extended-release modality of AM has been approved by the FDA as the first medication available to treat LIDs and to alleviate the motor symptoms of PD [155,157]. However, regarding clinical administration, although the extended release of AM reduced the daily dosage and wearing off period when compared to AM hydrochloric acid, the common side effects, which include hallucinations, nausea, constipation, impulse control disorder, and livedo reticularis, have persisted. Notably, according to recent case reports, AM induces corneal edema in pediatric patients and induces delirium upon withdrawal [158–160].

Monoamine oxidase B (MAO_B) is an enzyme located in presynaptic terminals and glial cells that actively participates in the breakdown of DA, predominantly in the nigrostriatal pathway, and greatly exacerbates PD pathogenesis [161]. Presently, MAO_B inhibitors, such as selegiline and rasagiline, are some of the most commonly used treatments in the clinical management of PD. These drugs effectively inhibit DA metabolism and provide a considerable amount of extracellular DA for synaptic signaling; thus, they are typically administered as a monotherapy to patients with early-stage PD [162,163]. However, these compounds may also be administered as part of a combination treatment with L-dopa to overcome the wearing-off period. In terms of tolerability, MAO_B inhibitors induce less dyskinesis than L-dopa. Further, in combination with L-dopa, MAO_B inhibitors increase the risk of hallucinations [164,165]. Ultimately, although both MAO_B inhibitors showed substantial neuroprotective effects, their impacts on alleviating motor deficits are still being investigated, with selegiline producing fewer antidyskinetic effects [165].

Another enzyme, catechol-O-methyltransferase (COMT), is directly [COMT → DA → 3-methoxytyramine (3-MT) → homovanillic acid (HVA)] or indirectly (DA → MAO → COMT → HVA) involved in the metabolic cascades required for DA biosynthesis and suppresses endogenous DA levels [166]. Moreover, COMT and aromatic L-amino decarboxylase (AAD) also facilitate the degradation of extracellular L-dopa in the peripheral milieu of the BBB to 3-O-methyldopa (3-OMD) and peripheral DA, respectively [167]. As COMT plays a pivotal role in DA metabolism, the inhibition of COMT by COMT inhibitors (e.g., tolcapone, entacapone) effectually restores endogenous DA levels [166,167]. Thereafter, the administration of COMT inhibitors in combination with the AAD inhibitor carbidopa (which also prevents peripheral L-dopa breakdown) effectively suppresses motor deficits in patients with advanced-stage PD, similar to a cotherapy approach with L-dopa. Despite its potential clinical application as a combination therapy with L-dopa, COMT inhibitors still create dyskinesias and hallucinations as side effects [167].

Numerous DA-centered therapeutic candidates are currently being investigated as DA replacement therapies due to their substantial activities on ameliorating PD progression (Table 1). Based on the discussion presented above, the inability of DA to cross BBB and the low half-life, quick-release formulations of L-dopa that mediated chronic and prolonged administration have been considered as major hurdles in the elucidation of suitable DRTs. Currently, existing therapies have several limitations; thus, further work should take advantage of the advances in nanotechnology to overcome these barriers.

5. Nanotechnology in central nervous system (CNS) drug delivery systems

Nanotechnology is an advanced stream of biotechnology that encompasses the engineering of materials at the atomic/nanoscales and interactions with the biological entities at the molecular level. Recently, nanotechnology was reported to constitute a substantial revolution in the field of clinical therapeutics by facilitating effectual interactions, stimulation, disease-targeted drug delivery, and theragnostic functions to manage several clinical conditions, including neurodegenerative disorders [168,169]. Nanotechnology can be directly or indirectly involved in altering the physicochemical properties of drug candidates via masking or loading them into specific delivery systems and increasing their biocompatibility and bioavailability to reach the site of

Table 1
Investigational drugs representing possible DA replacement therapeutics in PD currently in the clinical pipeline.

No	Candidate	Background	Clinical trial no.	Clinical trial phase/status	Outcomes	Sponsor/pharmaceutical company
1	L-dopa	Effects of continuous duodenal L-dopa infusion on blood pressure and sweating in PD patients	NCT00914134	Phase IV/completed	Duodenal L-dopa infusion improves both motor and nonmotor symptoms in patients with advanced PD	Helsinki University/Solvay Pharmaceuticals [300]
2	L-dopa	Effect of L-dopa on postural motor learning in people with PD	NCT02239978	Cohort cross-section observational study/ completed	Short-term perturbation training, with optimal L-dopa medications improves the postural responses of PD patients	VA Office of Research and Development/Oregon Health and Science University [301,302]
3	L-dopa–carbidopa	Tolerability of healthy subjects to oral Sinemet® (L-dopa/ carbidopa)	NCT02486432	Phase I/completed	Not yet posted	NeuroDerm Ltd./Quotient Clinical [303]
4	L-dopa–carbidopa	The safety, efficacy, and PK/PD profiles of L-dopa/ carbidopa combinations, in terms of motor complications, onset of action, and response duration in PD patients	NCT00558337	Phase IIa/completed	Not yet posted	Osmotica Pharmaceutical US LLC [304]
5	L-dopa–carbidopa	Safety and efficacy of L-dopa–carbidopa intestinal gel (LCIG) for the treatment of nonmotor symptoms in advanced PD patients	NCT00335153	Phase III/completed	Intraduodenal LCIG improves motor performance, quality of life and daily "off" time and "on" time without troublesome dyskinesia	AbbVie [305]
6	L-dopa–carbidopa	Comparing the efficacy of LCIG/carbidopa-L-dopa enteral suspension on dyskinesia in advanced PD patients	NCT02799381	Phase III/recruiting	Not available	AbbVie [306]
7	Pramipexole (DA agonist)	The impact of pramipexole in the pharmacodynamics of L-dopa–treated PD patients	NCT00666653	Phase I/completed	Pramipexole augmented motor response by additive effects to L-dopa, but worsened the LID; appropriate balance of dosage regimen in combinational therapies should be considered	Oregon Health and Science University/Boehringer Ingelheim [307]
8	INP103 (DA agonist)	The safety, tolerability, and PK/PD profiles of intranasal L-dopa following administration of INP103 in PD patients during an "off" episode	NCT03541356	Phase IIa/recruiting	Not yet posted	Impel NeuroPharma Inc. [308]
9	Piribedil (DA agonist)	Efficacy and safety of long-term therapy with piribedil in PD patients under consideration of quality of life parameters and cognitive function	NCT01519856	Noninterventional study	Not yet posted; piribedil was considered as "efficacious" and "clinically useful" for the symptomatic treatment of PD, either as monotherapy or in conjunction with L-dopa by the last Movement Disorder Society Evidence-based Medicine guidelines, yet confirmatory trials are needed	Desitin Arzneimittel GmbH [309,310]
10	Ropinirole (DA agonist)	Study on absorption, distribution, metabolism and excretion of ropinirole in PD patients	NCT00460148	Phase II/completed	Not yet posted	GlaxoSmithKline [311]
11	Ropinirole (DA agonist)	Effect of ropinirole prolonged release once-daily versus twice-daily	NCT00986245	Phase IV/completed	Ropinirole 24-h prolonged release was effective and well-tolerated in early PD patients and multiple doses/day was preferred in many patients	Seoul National University Hospital [312]
12	Ropinirole (DA agonist)	Study on the efficacy of 18–24 mg/day ropinirole controlled release (CR) tablets in early and advanced PD patients	NCT01929317	Phase III/terminated	No additional clinical benefits were observed from the dose increase in the high-dose ropinirole CR group; though a few patients demanded ropinirole CR higher than 16 mg/day, the sample size of this study did not provide sufficient statistical power to conclude the same	GlaxoSmithKline [313]
13	Rotigotine (DA agonist)	Effect of rotigotine on motor symptoms in patients with advanced PD with motor deficits	NCT01536015	Phase III/Terminated (due to low enrolment)	Not yet published	UCB Pharma [314]
14	Rotigotine (DA agonist)	Efficacy of rotigotine in patients with advanced stage of idiopathic PD condition	NCT00244387	Phase III/completed	Rotigitine transdermal patch reduced the "off" time and increased the "on" time without troublesome dyskinesia; it also showed proximal efficacy similar to oral pramipexole in PD patients	UCB Biosciences GmbH [315]
15	Rotigotine (DA agonist)		NCT01711866	Phase IV/completed		

(*continued on next page*)

Table 1 (*continued*)

No	Candidate	Background	Clinical trial no.	Clinical trial phase/status	Outcomes	Sponsor/pharmaceutical company
		Study to assess the efficacy on motor and nonmotor symptoms of switching from pramipexole or ropinirole to rotigotine transdermal patch in advanced idiopathic PD patients			Switch from pramipexole or ropinirole to rotigotine (up to 14 mg/24 h) was shown to exhibit some beneficial effects in PD patients	UCB Biosciences GmbH/Otsuka Pharmaceutical Co., Ltd. [316]
16	Selegiline (MAOB inhibitor)	Efficacy of orally disintegrating selegiline in PD patients undergoing DA agonist adverse effects	NCT00443872	Phase IV/completed	The adjunct therapy of selegiline with increasing doses of DA agonists reduced its adverse effects without compromising efficacy in PD patients	Parkinson's Disease and Movement Disorder Center of Boca Raton/ Valeant Pharmaceuticals International, Inc. [317]
17	Safinamide (MAOB inhibitor)	The efficacy of safinamide as an add-on therapy in early idiopathic PD patients treated with a stable dose of a single DA agonist	NCT00642889	Phase III/completed	The exploratory analysis results of the study primary endpoint exhibited that the add-on therapy of safinamide to a stable dose of DA agonist reduced its side effects, i.e., impulse control disorders in early PD patients, warranting further investigation	Newron Pharmaceuticals SPA [318]
18	Rasagiline (MAOB inhibitor)	Study on the efficacy of rasagiline (1 mg) as a first add-on theraphy to DA agonist–treated early PD patients	NCT01049984	Phase IV/completed	Rasagiline was found to be well-tolerated and, at 1 mg, significantly improvements in DA agonist–treated PD patients	Teva Neuroscience, Inc./H. Lundbeck A/S [319]
19	L-dopa–carbidopa- + entacapone (COMT inhibitor)	Safety and efficacy of L-dopa–carbidopa + entacapone (LCE) in PD patients requiring initiation of L-dopa therapy	NCT00099268	Phase III/completed	L-dopa therapy with LCE failed to delay the time of onset or reduce the frequency of dyskinesia; results indicate that the employed dosage regimen of L-dopa equivalent in LCE did not provide continuous bioavailability	Novartis Pharmaceuticals/Orion Corporation, Orion Pharma [320]
20	L-dopa–carbidopa- + entacapone (COMT inhibitor)	Effects of L-dopa–carbidopa + entacapone (LCE) on motor function and quality of life in PD patients	NCT00219284	Phase IV/completed	Not yet published	Novartis Pharmaceuticals [321]
22	Stalevo® [L-dopa–carbidopa + entacapone] (COMT inhibitor)	Efficacy of switching to Stalevo® therapy in L-dopa–treated PD patients suffering from early "wearing-off"	NCT00462007	Phase IV/completed	Immediate switching of PD patients with end-of-dose wearing off to Stalevo improved the motor functions at Week 4 and quality of life by Week 8 in treated PD patients	Orion Corporation, Orion Pharma [322,323]
23	Entacapone and tolcapone (COMT inhibitors)	Effects of oral intake of COMT inhibitors in the plasma L-dopa levels achieved by intestinal L-dopa–carbidopa infusion in advanced PD patients	NCT00906828	Phase IV/completed	Not yet posted; previous multicenter randomized trial of switching entacapone to tolcapone enhanced the efficacy of L-dopa in patients with fluctuating PD despite optimized entacapone therapy	Uppsala University/Swedish Parkinson's Disease Foundation/ Swedish Society for Medical Research [324]
24	Amantadine	Evaluation of the long-term effects of amantadine in PD patients suffering from dyskinesia induced by L-dopa	NCT00632762	Phase IV/completed	Not yet posted; still, the data of the study conducted by Austrian Parkinson's Disease Study Group strongly reported that amantadine maintains its efficacy in the treatment of L-dopa–induced dyskinesias	University Hospital, Toulouse [325]
25	Extended release + amantadine hydrochloric acid (ADS-5102)	Evaluation of the safety, efficacy, and PK/PD profile in PD patients suffering from dyskinesia induced by L-dopa	NCT02136914 NCT01397422	Phase II/III/completed	ADS-5102 was well-tolerated and a 274 mg dose at bedtime is effective for treating dyskinesia and the "wearing-off" induced by L-dopa	Adamas Pharmaceuticals, Inc. [158,326]

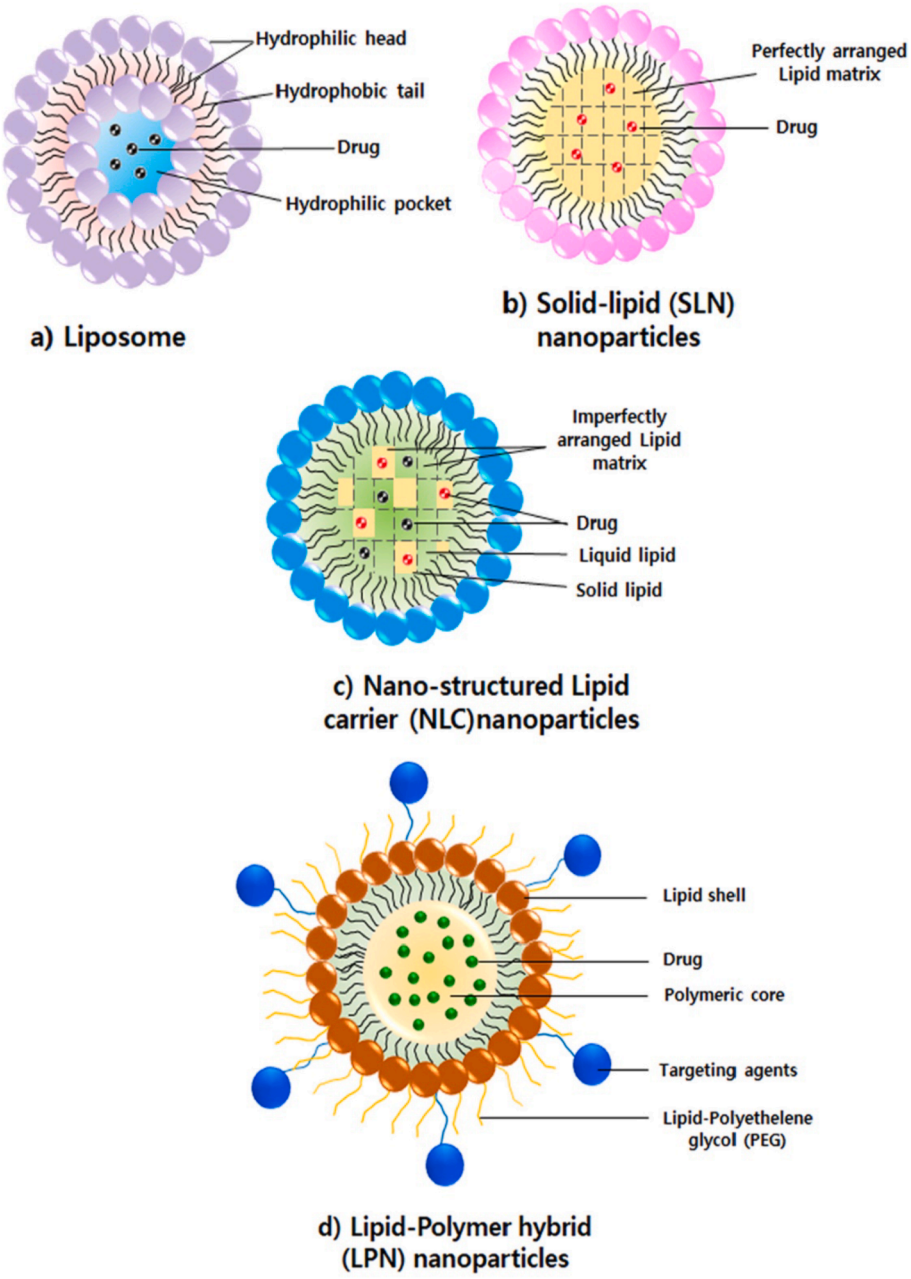

Fig. 5. Illustrations of potential lipid-based nanocarriers including a) liposomes, b) SLNs, c) NLCs, and d) LPNs, which are predominantly developed and investigated for active shuttling of potential drug candidates across the BBB. Such enhances the bioavailability and therapeutic efficacy of the bioactive candidates precisely in treating several neurodegenerative complications including PD.

action. Unlike subjects with other clinical conditions, patients with neurodegenerative disorders, such as Alzheimer's disease and PD, were reported to possess protective biological barriers in the CNS, which represents a critical challenge for therapeutics to attain maximum therapeutic efficacy [168,169]. The BBB, which acts as a defensive barrier in the brain, affords unidirectional, concentration-based, selective permeability of specific candidates into the brain parenchyma [170]. Thus, small, lipophilic candidates can easily traverse the BBB through transcytosis; conversely, larger molecules and hydrophilic candidates must use specific receptor-ligand, ion-gated channels for transport. This mechanism potentially prevents several drug candidates from passing through the BBB, which accounts for the failure of the primary PD therapeutic strategy, i.e., an exogenous supply of DA to the brain [171,172]. However, as discussed above, conventional neurotherapeutics fail to or reach the site of action only at low levels and exhibit lower or minimal efficacy at a relatively higher dose or following prolonged administration. This situation is further complicated when the drug candidates are bound to targets in the periphery and produce undesirable side effects [173]. Fortunately, with advances in nanodrug delivery systems, the nanoparticulate (NP) active candidates circumvented the CNS barriers, i.e., the BBB, and are transported to the targeted site with enhanced bioavailability. Moreover, the interaction of the nanoparticles (NPs) with biological systems potentially induces a prolonged and sustained release of the active drug candidates with enhanced efficacy [174,175]. The protracted circulation of NPs in the brain results in their absorption into the brain, based on the gradient concentration fluxes. However, the most widely accepted hypothesis is that NPs are transported into the brain parenchyma by endocytosis mediated by endothelial cells. Thereafter, the drug is released to the brain cells or is shuttled by transcytosis across the BBB to the brain cells

[176]. Additionally, the functionalization of nanocarriers with specific peptide sequences or ligands induces receptor-mediated BBB transport and the site-specific delivery of active drug candidates [174,175]. This finding was further supported by other research showing the existence of enhanced cellular uptake and a relative reduction in the dosage regimens of therapeutic candidates when compared to the administration of its free form [177]. Generally, nanocarriers are constructed from several organic (e.g., lipids, polymer) or inorganic (e.g., carbon nanotubes, mesoporous silica, metals) matrices that are further fabricated to achieve their functions in the targeted biological system [178]. Among the several reported delivery systems, lipid- or polymer-based matrices are the most commonly employed nanodrug delivery systems due to potential nondegradable traits of inorganic materials, such as carbon, metal, and silica in biological systems [178,179]. Lipids constitute the structural basis for most of the cells and tissues in our bodies; thus, the engineering of these lipid-based NPs provides enhanced biocompatibility and biodegradability and is widely implied in the development of nanocarrier systems [180]. The vesicle-like structures of lipid-based nanocarriers actively protect the loaded drug or candidate molecule from enzymatic degradation or physiological hindrances in the biological system. Notably, these lipid-based vesicular liposomes have already been approved by the FDA and are even used for several commercial purposes in the clinical and pharmaceutical industries [181,182]. Nevertheless, polymers have been adapted as substrates or as insulation materials for neural interfaces and implants for a substantial period of time without any harmful biological interferences as a result of their biocompatibility with the surrounding tissue. Several clinical devices that are composed of polymers, such as gels, microspheres, and biofilms have also been widely used in clinical applications [183,184]. This evidence supports the biocompatibility of lipid-/polymer-based nanocarriers compared with other inorganic materials in biological systems. However, recently, some synthetic polymer-coated NPs have been reported to cross-link with certain carcinogenic monomers and form toxic substrates, and these substances must be removed from the biological milieu [185,186]. Thus, as lipid-based nanocarriers have been broadly studied and widely applied in the field of nanomedicines more so than other materials to allow neurotherapeutics to pass through the BBB, extensive reviews of several drug delivery systems to the brain have also been recently reported [21,24,187–189]. As such, to the best of our knowledge, none have exclusively described the significance and updates to the lipid-based nanocarrier systems that are principally focused on DA-centered PD therapeutics. Here, we introduce this missing information and cover recent updates in lipid-based, DA-centered PD therapeutics.

6. Lipid-based nanodrugs and their applications in DA-centered PD therapeutics

Over the past few decades, several lipid-based NPs have been successfully developed as drug delivery systems to treat a wide range of clinical conditions [190,191]. Lipid-based NPs are classified into four major categories: liposomes, solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), and lipid–polymer hybrids (LPNs) (Fig. 5). Generally, these lipid-based nanocarriers share a common structure of cell membrane-like lipid bilayers involving both hydrophilic and hydrophobic moieties, which promotes the versatility of loading active molecules in conjunction with various characteristics in the pharmaceutical industry [180,190].

6.1. Liposomes

Liposomes are considered to be a first-class drug carrier and have been developed and characterized over the past few decades as a potential carrier system with favorable biocompatibility, lower toxicity, reduced immunoreactivity, and targeted delivery traits [191]. Liposomes are constructed from several types of lipids and phospholipids, such as phosphatidylcholine, phosphatidylserine, and cholesterol, which are the most frequently employed lipids due to their versatile traits [192,193]. Conventionally, the liposome formulation is prepared by the spontaneous interaction of the thin layer of the lipid film with the aqueous phase. In brief, lipids are initially dissolved in an organic solvent and condensed; this organic solvent–lipid mixture is then dispersed in aqueous media. Thereafter, the resultant liposomes are purified and characterized. Eventually, the drug candidates can be loaded in liposomes by either passive (during liposome formulation) or active (after liposomal formations) methods [194]. Most of the hydrophobic drugs can be passively loaded in the lipid compartments of liposomes during vesicle formation; however, the fate of loading hydrophilic drugs depends upon the solubility of the drug in aqueous vesicles entrapped in the lipid compartments. In contrast, hydrophilic drugs with protonizable amine function groups can be actively loaded into liposomes by altering the pH gradients of the suspension medium [194,195]. Interestingly, the physicochemical parameters of liposomes can also be altered based on clinical demands by providing external force/pressure using a homogenizer, microfluidizer, or another instrument [196,197]. As discussed above, small therapeutic molecules are easily transported across the BBB to treat CNS conditions. With the aid of these post-liposomal alterations, the NPs appear smaller and exhibit a homogeneous distribution. The liposomal construct contains a hydrophilic core that potentially facilitates the loading of hydrophilic drugs and further encapsulation by the lipid bilayer, which potentially entraps the lipophilic candidates to form the vesicular structure [194,198]. As discussed above, the inability of the hydrophilic molecule DA to pass through the BBB represents a significant hurdle for the use of DRTs in PD management.

A research team successfully loaded DA into the hydrophilic core of the liposomes (phosphatidylcholine:cholesterol in a 1:3 M ratio) and stereotactically implanted it in the striatum of rats with unilateral lesions in the SNpc. The liposome-administered rats exhibited partial recovery of behavioral deficits and a partial amelioration of PD-like symptoms [199]. However, the conventional sonication and extrusion liposome methods applied did not provide sufficient space for DA loading, likely due to the smaller inner volume of unilamellar vesicles, while the formation also exhibited substantial leakage and poor stability. Another research team developed DA liposomes (egg phosphatidylcholine:cholesterol:stearylamine in a 6:3:1 M ratio with a size of 200 nm and 40% entrapment efficiency) with an ammonium sulfate gradient to overcome these limitations. Results revealed that the ionic gradient of ammonium sulfate improved the entrapment and stability of DA liposomes for three weeks [200]. Additionally, alterations in the DA–lipid ratio were crucial in enhancing the efficacy of DA to suppress PD symptoms in a mouse model [200]. As shown in the study by Jain et al., DA hydrochloride–loaded multilamellar liposomes effectively deliver DA to the brain and are superior to L-dopa in PD management [201]. Interestingly, as the endothelial cells of BBB are enriched with amino-acid transporters, the authors developed glutamate stearylamine-conjugated DA liposomes (phosphatidylcholine:cholesterol:glutamate stearylamine in a 7:3:2 M ratio with a size of 290 ± 0.014 nm, charge of +16 mV, PDI of 0.92, and entrapment efficiency of 38.89% ± 1.94%) in their follow-up studies and reported enhanced therapeutic effectiveness towards chlorpromazine-induced catatonia, a PD-like symptom, in a rat model compared with using nonconjugated DA liposomes. This effect was potentially attributed to the enhanced BBB shuttling and sustained-release property of the glutamate-conjugated liposomes [202]. Eventually, several other strategies were developed to improvise the effectual shuttling of DA-loaded liposomes across the BBB. Polyethylene glycol (PEG), a polyether candidate that is generally inert under physiological conditions, was fabricated over the surface of liposomes (i.e., so-called "*stealthy liposomes*") and prolonged the circulating half-life of the liposomes (4–10 mol% of PEGylated lipids; size: 70–200 nm) in biological systems. Additionally, PEG was also reported to facilitate the conjugation of certain ligands,

such as proteins, vitamins, and antigens, to the surface of liposomes, which facilitated the development of targeted PEG/ligand-coated liposomal therapies [203,204]. Consistent with these findings, Kang et al. recently developed PEGlyated DA liposomes [distearoylphosphatidylcholine (5.2 mM); cholesterol (4.5 mM); DSPE (0.3 mM); and a linker lipid, DSPE-PEG_{2000} maleimide) (0.015 mM) with a size of 42–50 nm, zeta potential of 6 ± 1 mV, and entrapment efficiency of 35% ± 1%] fabricated with OX26 Mab, a monoclonal antibody, termed "PEGlyated immunoliposomes" (PILs). These PILs effectively increased DA uptake in the brains of PD rat models at an eightfold higher level than pure DA administration and a threefold higher level than conventional PEGlyated DA liposomes [205]. Lopalco et al. developed DA-loaded, ligand-functionalized liposomal nanocarriers (phosphatidylcholine:cholesterol in a 7:3 M ratio with 2.5 mol% of DSPE-PEG_{2000}-COOH, with a size of 181.7 ± 7.8 nm, zeta potential of 7.5 ± 1.2 mV, and entrapment efficiency of 35.4% ± 1.8%) targeting the CNS using transferrin (β-1 glycopeptide), which binds to the corresponding transferrin receptor in BBB endothelial cells and effectually shuttles the DA-loaded liposomes across the endothelial cells in an *in vitro* model of the BBB [206].

In contrast, the precursor of DA, L-dopa, easily traverses the BBB when administered to patients with PD in the clinic; however, only 1% of the administered L-dopa reaches the brain in this context and the circulating L-dopa in the periphery is converted to DA by decarboxylase enzymes and causes potential side effects, such as nausea, drowsiness, and dyskinesia [207,208]. Several researchers have recently developed liposomes loaded with L-dopa (L-3,4-dihydroxyphenylalanine), DA prodrug [2-amino-N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide], and DA derivatives [N-3,4-bis(pivaloyloxy)DA-3-(dimethylamino) propenamide] and reported on their potential therapeutic efficacy in *in vitro* and *in vivo* PD models. Stefano et al. synthesized maleic and fumaric diamide preparations of L-dopa prodrug (O,O-diacetyl)-L-dopa-methylester [(+)-4, (+)-5]–loaded liposomal (dipalmitoylphosphatidylcholine:cholesterol in a 10:1 M ratio with a size of 112.7 ± 2.7 μm, PDI of 0.21, charge of 0.31 ± 0.04 mV, and entrapment efficiency of 15.30% ± 0.04%) formulations. The study results revealed that these prodrug liposomes exhibited a slow release of L-dopa in human plasma and a relatively sustained delivery of DA in the striatal dialysate of intraperitoneally injected rats compared with simple L-dopa administration [209]. Xiang et al. directly loaded L-dopa into stealth liposomes (hydrosoy phosphatidylcholine:cholesterol:DSPE-PEG in a 20:10:2 M ratio or 0.3% DSPE-PEG:ClTx molar ratio with a size of 106.8 ± 3.01 nm, PDI of 0.196 ± 0.05, and charge of 0.385 ± 0.09 mV) fabricated with chlorotoxin, which exhibited enhanced BBB permeability in an *in vitro* model of brain-microvascular endothelial cells. Moreover, the intraperitoneal administration of these L-dopa liposomes in a mouse model of MPTP-induced PD alleviated behavioral deficits, restored the DA levels, and effectively reversed the loss of tyrosine hydroxylase (TH)-positive DAergic neurons in the SNpc and striatum [210]. In another study, 2-amino-N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide, a potential DA prodrug, was encapsulated in unilamellar liposomes [dimyristoyl-sn-glycero-phosphatidylcoline (7.5 mM), cholesterol (2.6 mM), and 2-amino-N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide (60 mM) with a size of 170.8 ± 7.6 nm, PDI of 0.22, charge of −75.50 ± 0.24 mV, and entrapment efficiency of 79.1% ± 0.8%]. This monodisperse liposome formulation exhibited substantial stability in plasma *in vitro* and may have prevented the photodegradation of the prodrug [211]. Subsequently, Li et al. successfully synthesized N-3,4-bis(pivaloyloxy)DA-3-(dimethylamino) propenamide (PDDP), a derivative of DA, loaded into liposomes (Lipoid S100:cholesterol:mPEG_{2000}-DSPE in a 3:1:1 M ratio with a size of 114.8 ± 5.06 nm, PDI of 0.195 ± 0.024, charge of −17.0 ± 0.57 mV, and entrapment efficiency of 55.30% ± 2.3%) and further engineered its surface with an N,N-dimethyl amino group. This efficiently aids in the transport of liposomes across the BBB via cationic transporters. The intravenous administration of the PDDP-loaded liposomes led to an increased concentration of PDDP in the brain tissue that was approximately 270-fold higher than L-dopa and effectively alleviated the 6-hydroxydopamine (6-OHDA)-induced lesions in the rat striatum [212]. Furthermore, more recently, another research team developed a stealth liposome encapsulating a different DA derivative, N-3,4-bis(pivaloyloxy)-DA (BPD), and functionalized it using RVG29 peptide as a targeting ligand (lipoid S100:cholesterol:mPEG_{2000}-DSPE:RVG29 peptide coupled with maleimide-PEG_{2000}-DSPE in a 300:100:33:66 M ratio with a size of 134.7 ± 2.66 nm, PDI of 0.250 ± 0.004, charge of −13.5 ± 0.37 mV, and entrapment efficiency of 52.52% ± 1.6%), which displayed affinity for ACh receptors, the BBB, and DAergic cells. Following intravenous administration, BPD-RVG29-liposomes were effectively shuttled across the BBB, as substantial concentrations reached the striatum and substantia nigra, and the treatment potentially alleviated PD-like molecular deficits observed in a unilateral 6-OHDA-lesioned mouse model [213].

The glial cell-derived neurotrophic factor (GDNF) gene is involved in promoting neurogenesis by facilitating the survival, differentiation, and synaptic efficacy of DAergic neurons. However, previous trials examining a direct infusion of GDNF in the caudate putamen of patients with PD did not yield desirable effects, which may have been attributed to the dosage and mode of delivery used [214]. Advances in gene delivery systems have achieved progress in certain promising liposome-gene complex therapies. Xia et al. successfully developed a TH promotor (for TH targeting)-engineered GDNF plasmid DNA and loaded it into the Trojan horse liposome [phosphatidylcholine (18.6 μmol), didodecyldimethylammonium bromide (0.6 μmol), DSPE-PEG2000 (0.6 μmol), and DSPE-PEG_{2000}–MAL (0.2 μmol) with a size of 117 ± 2 nm and entrapment efficiency of 21% ± 2%] PIL fabricated with monoclonal antibody targeting transferrin receptors. The intravenous administration of this PIL specifically delivered GDNF to the tissues expressing TH (i.e., the SNpc) and exerted sustained therapeutic effects on intra-cerebral 6-OHDA-induced lesions in a rat model of experimental PD [215]. Thereafter, Lin et al. developed a functionalized gene-liposome [DPPC:cholesterol:DSPE-PEG_{2000}-amine:α-tocopherol in a 3:1:1:0.004 M ratio with a size of 105 nm and entrapment efficiency of 72.8%] composed of a luciferase pLuc-N3 plasmid and GDNF gene. The intravenous administration of this liposomal–plasmid gene, assisted with a focused ultrasound, enhanced its BBB transmittance. Moreover, the formulation reached both neurons and astrocytes alike, thereby increasing the overall GDNF production in mouse brain tissues [216].

A liposomal delivery system was also extended to provide a sustained delivery system for several natural antioxidant candidates, such as resveratrol, quercetin, and curcumin, which exhibit poor bioavailability profiles. These antioxidant-loaded liposomes displayed increased bioavailability in the brain milieu, potentially ameliorated ROS-induced oxidative stress, and restored the antioxidant activities in the DAergic nigrostriatal pathways when compared with following the administration of its free form [217,218]. Glutathione is an enzyme that provides strong antioxidant defenses by scavenging the ROS generated by DA metabolism and other aerobic metabolic pathways in the brain. Glutathione-loaded liposomes exhibited a substantial therapeutic potential in PD models *in vitro* that was approximately 100-fold greater than that seen with its free form [219].

6.2. SLNs

SLNs are usually constructed from lipid matrices that typically remain in a solid state at physiological and room temperatures. The main advantage of SLNs is that they provide the collective benefits of both liposomes and polymeric NPs, as well as substantial space for loading both lipophilic and hydrophilic candidates [220,221]. One or more solid lipids, such as glyceryl monostearate, stearic acid, palmitic acid, trimyristin, tristearate, and cholesterol, are commonly employed to prepare SLNs. The interesting aspect is that most of these lipid

candidates are highly biocompatible and have been approved by the FDA for applications in the food sector due to their safety [222,223]. Furthermore, SLNs have efficiently been coated with various surfactants (polysorbates), polymers (PEG), lecithin, fatty acid esters, and sucrose derivatives, which were also approved for parental route dosage regimens in clinical and nutritional fields to improve the stability of the SLNs, bypass the liver reticuloendothelial system (RES) for SLN removal, and prevent plasma protein–bound SLN opsonization [224]. Thus, SLNs appear to be more biocompatible, as they involve the minimal usage of organic solvents for production and exhibit greater stability and sustained release potential than other nanodelivery systems [223,224]. Hot and cold homogenization, double emulsion, high-shear homogenization, microfluidization, and super-critical fluid techniques are the most commonly employed methods in SLN synthesis. In brief, the lipid phase is prepared by heating the solid lipid matrix at a high temperature beyond its melting point of 80 °C, together with the addition of surfactants/hydrophobic drugs under continuous stirring, whereas the aqueous phase is prepared by dissolving copolymers in distilled water and increasing the concoction's temperature close to that of the lipid phase. Initially, the hydrophilic drug is dissolved in distilled water, gently added to the hot lipid phase and then homogenized to form a primary water-in-oil emulsion. Thereafter, the hot aqueous phase with polymer is added dropwise to the hot drug-liquid phase emulsion subjected to homogenization under stirring. Finally, the nanosuspension is obtained by cooling down the nanoemulsion [225–227]. Typically, the size of SLNs range from 1 to 1000 nm, depending on the production methods and coating stabilizers/functionalizing materials used. However, with the aid of advances in homogenization, microfludization techniques, and coating strategies, the physicochemical properties of SLNs have become more compatible and desirable according to the therapeutic demands [228,229].

As discussed above, L-dopa and DA agonists directly or indirectly alter the DA status of the nigrostriatal pathway. However, the wearing-off and dyskinetic effects due to peripheral conversion of L-dopa outside the BBB and relative inability of DA agonists to pass through the BBB has necessitated a suitable delivery system. Thus, Demirel et al. performed a study to formulate SLN and micro-delivery systems for piribedil, a potential DA2 receptor agonist, which exhibits a short half-life, rapid elimination, and poor water solubility. The authors used commercial lipid excipients and emulsifiers, employing both hot and cold homogenization techniques to develop the solid lipid particles [compritol (2.5%), labrasol (1.2%) with a hot homogenization size of 40.4 μm and cold homogenization size of 2 μm and an entrapment efficiency of the hot homogenization of 88:1% ± 5:3% and cold homogenization of 67:3% ± 3:7%]. In animal models, both solid lipid suspensions exhibited sustained release and enhanced bioavailability when compared with the free form [230]. Eventually, Esposito et al. conducted another study to formulate an SLN delivery system for bromocriptine, the very first marketed DA agonist with a prolonged plasma half-life but that boasts a relatively slow onset of action. The authors developed a stable SLN delivery system [tristearin:tricaprin in a 2:1 ratio with aqueous poloxamer 188 (2.5%), with a size of 196 nm, PDI of 0.24 and entrapment efficiency of 84%] for bromocriptine using homogenization and ultrasonication methods. The bromocriptine-loaded SLNs exhibited a relatively rapid onset of action and sustained-release potential compared with the free form in the 6-OHDA hemilesioned rat model [231]. AM, another DA agonist that exhibits poor oral bioavailability of less than 2% and first-pass elimination effects, was successfully loaded in SLNs [tripalmitin (200 mg), hydrosoy phosphatidylcholine (50 mg), and aqueous pluronic F-68 (30 mg) with a size of 63.20 ± 0.98 nm, PDI pf 0.31 ± 0.02, charge of 7.23 ± 0.25 mV and an entrapment efficiency of 91.03% ± 0.14%] using hot homogenization and ultrasonication methods. The AM-SLNs showed a 12- to 13-fold greater bioavailability, a substantial AM distribution in the striatum, and enhanced therapeutic efficacy compared with the free form following administration to 6-OHDA-lesioned PD rats. Interestingly, this study also reported the control of the physicochemical traits, such as size, charge, and distribution, of the SLN particles by altering the percentage of emulsifiers added during the formulation process [232]. Ropinirole, a nonergoline agonist, selectively binds to DA2 receptors in the striatum and SNpc and increases the firing rates of striatal neurons, similar to DA. However, due to its hydrophilic nature, it exhibits a weak transmission across the BBB and, due to its extensive first-pass hepatic metabolism, exhibits poor bioavailability upon oral administration [233]. Pardeshi et al. developed a surface-modified SLN for the delivery of ropinirole hydrochloride using an emulsification–solvent diffusion technique. The research team employed a factorial design approach and optimized the concomitant ratio of solid lipids to prepare the SLN formulation [dynasan 114, stearylamine (varying molar ratio with total of 100 mg), and aqueous pluronic F-68 (1% w/v) with a size of 66.22 ± 6.22 to 271.61 ± 4.26 nm, PDI of 0.016 ± 0.06 to 0.460 ± 0.16, charge of −16.16 ± 2.17 to 47.13 ± 1.19 mV, and entrapment efficiency of 55.23% ± 0.45%–64.73% ± 0.34%], which exhibited the smallest particle size, lowest polydispersity index, and substantial entrapment efficiency. The formulations were stable and exhibited nonirritant traits toward the sheep nasal mucosa, later demonstrating sustained release and enhanced therapeutic efficacy via a nasal route compared with conventional oral medications [234]. Based on this evidence, although SLNs are suitable and effective delivery systems for both hydrophilic and lipophilic candidates, the compact structural organization of solid lipids was reported to decrease the loading efficacy of the drugs in SLNs. Therefore, the SLN system was further progressed to a next-level lipid delivery system, i.e., NLCs, to overcome this limitation.

6.3. NLCs

NLCs are considered to be an upgraded version of SLNs, where the compact arrangement of the uniformly structured solid lipids has been replaced with an unstructured lipid matrix established by blending both solid and liquid lipids, which eventually provide more space for loading drug candidates [235]. Generally, the solid lipids are used at a higher gradient than the liquid lipids (i.e., 70:30) and with less than 5% of the surfactant being present in the aqueous phase. The methods adopted for the construction of NLC delivery systems are similar to those used for SLNs, including homogenization, microfluidization, and double emulsion. However, high-shear homogenization is the most commonly employed method for preparing NLCs due to the lack of a requirement for organic solvents in the process [235,236]. In brief, the lipid phase is prepared by mixing solid lipids (e.g., stearic acid, cetyl palmitate) and liquid lipids (e.g., soybean oil, corn oil) in an optimized ratio and heating the concoction to a molten condition, with the addition of hydrophobic drugs/surfactants. In parallel, the aqueous phase is prepared by dissolving surfactants/copolymers/hydrophilic drugs in distilled water and increasing the temperature of such so as to be close to the lipid phase. Then, the aqueous phase is added gently in a dropwise fashion to the homogenizing hot molten lipid phase, with the resultant mixture sonicated and cooled down to obtain the NLC particles [237–239]. This high-pressure homogenization process was easily escalated for industrial-scale production in the pharmaceutical industry [236,240]. The processed NLCs exhibited enhanced stability compared with SLNs, potentially due to their lipid composition. Briefly, the relatively higher payload of drugs, lower level of drug leakage during storage, and substantial stability in biological systems make the use of NLCs a smarter option than SLNs [241,242].

AM (a DA agonist) was successfully intercalated in an NLC delivery system composed of cetyl palmitate and squalene as the lipid matrix, as well as a few other emulsifiers as interfacial additives, respectively [243]. This research team also comparatively evaluated the AM-loaded NLCs with SLN and lipid emulsion formulations [NLC-cetyl palmitate and squalene (10% w/v), 0.3% myverol, and aqueous pluronic F-68 (2.7% w/v); for SLNs, all are the same except only solid cetyl palmitate

lipid (10% w/v) was adapted; the size, NLCs: 372.7 ± 14.7 to 431.2 ± 17.5 nm and SLNs: 333.1 ± 13.8 nm; the PDI, NLCs: 0.24 ± 0.09 to 0.32 ± 0.10 and SLNs: 0.33 ± 0.02; the charge, NLCs: 42.1 ± 0.3 to 50.7 ± 1.7 mV and SLNs: 36.5 ± 0.5 mV; and the entrapment efficiency, NLCs: 58.7% ± 0.8%–69.9% ± 3.1% and SLNs: 50.3% ± 1.7%, were reported]. Interestingly, although the size of the NLC formulations was greater than that of the SLNs, the rate of drug release from the NLCs was slow and sustained, potentially because sizeable particles possess a reduced surface area for drug diffusion. The interactions among the core solid crystals and liquid lipids were confirmed using nuclear magnetic resonance spectroscopy. As anticipated, NLCs exhibited an enhanced entrapment efficiency (> 60%), prolonged half-life, and substantial biodistribution in the midbrains of treated rats [243]. Subsequently, the same research team developed NLCs to load the diester prodrugs of AM, di-acetyl AM, and di-isobutyryl AM [NLC-cetyl palmitate (4% w/v), sesame oil (4% w/v) 0.3% myverol, and aqueous pluronic F-68 (2.7% w/v) with a size of 250.1 ± 3.3 nm, PDI of 0.23 ± 0.03, and charge of 48.4 ± 0.6 mV] [244]. The addition of emulsifiers substantially increased the size of NLCs. Based on hydrolysis studies, both prodrugs underwent bioconversion in the plasma and brain. The NLCs exhibited sustained-release profiles for the loaded prodrugs, where di-isobutyryl AM exhibited a slower release and bioconversion rates. According to the results from bioimaging, the NLCs to which emulsifiers had been added exhibited a substantial and prolonged distribution in the rat brain. The sustained-release property of NLCs and the stability of prodrugs synergistically enhanced the therapeutic potential [244]. Interestingly, NLCs are effective delivery systems for brain-targeting therapeutics. Gabal et al. focused on investigating the impact of the surface charge of NLCs in brain delivery systems. The authors developed anionic NLC (a-NLC) and cationic NLC (c-NLC) systems for ropinirole hydrochloride (DA agonist) using the hot, high-shear homogenization method [a-NLC-compritol 888: Labrafac™ Lipophile WL1349 (Gattefossé, Lyon, France) in a 7:3 M ratio and PC:P188:Tween 80:SDC in a 1:2:2:1 M ratio; for c-NLCs, all are the same except only stearylamine (3% w/w) was added to the lipid phase; the size, a-NLCs: 103 ± 1 to 273 ± 7.6 nm and c-NLCs: 82 ± 1.7 to 314 ± 19 nm; the PDI, a-NLCs: 0.26 ± 0.01 to 0.46 ± 0.04 and c-NLCs: 0.26 ± 0.04 to 0.47 ± 0.06; the charge, a-NLCs: −23 ± 1.2 to −39 ± 2 mV and c-NLCs: −5.4 ± 0.3 to 37.4 ± 1.7 mV; and, the entrapment efficiency, a-NLCs: 35.5% ± 3.8%–73.7% ± 0.4% and c-NLCs: 32% ± 1.9%–79% ± 4.2%, were reported]. Both a- and c-NLCs exhibited size and surface-charge–based brain delivery, whereas the a-NLCs showed higher drug targeting efficacy in the brain and relatively mild and reversible inflammation in the nasal epithelium of rats in comparison with c-NLCs [245]. Cortesi et al. developed NLCs for loading several prodrugs of L-dopa, including 3,4-diacetyloxy-L-dopa-caffeic acid codrug, lipoic acid-DA codrug, lipoic acid-3,4-diacetoxy-DA codrug, and dimeric L-dopa codrug containing an alkyl linker, with homogenization or ultrasonication methods (tristearin:tricaprylin in a 2:1 M ratio w/w with aqueous poloxamer 188, with a size of 186.6 ± 1.1 to 196.6 ± 1.6 nm, PDI of 0.11–0.25, and entrapment efficiency of 72.91%–81.87%). The NLC formulations exhibited adequate sizes (< 200 nm), positive stability for up to two months, and sustained-release profiles *in vitro* [246]. Moreover, previous studies by these authors on the subject of NLC formulations of the L-dopa prodrug methyl O-acetyl-3-(acetyloxy)-N-[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]-L-tyrosinate) exhibited sustained effects (for 24 h) in ameliorating the behavioral deficits in a 6-OHDA, hemi-lesioned PD-like mouse model [247]. Recently, several researchers successfully developed GDNF-loaded NLCs coated with chitosan and further functionalized them with molecular peptides, i.e., transactivator of transcription peptide, for CNS targeting. The intranasal delivery of these functionalized GDNF-loaded NLCs [Precirol®AT05 (2.5% w/v), Miglyol® (0.25% w/v), and aqueous poloxamer 188 (2% w/v), with a size of 136.70 ± 14.14 nm, PDI of 0.26 ± 0.04, charge of 32 ± 2.51 mV, and entrapment efficiency of 98.1% ± 0.37%] significantly alleviated behavioral deficits and restored the number of tyrosine hydroxylase-positive fibers in STN and SNpc in PD-like animal models to a greater extent than the free form [248,249].

6.4. LPNs

In general, polymeric NPs are constructed with natural or synthetic polymers, with the use of NPs comprised of natural polymers, such as chitosan, remaining limited to monotherapies due to a possible lack of effectual cross-linking and requirements for additional cross-linkers that can denature the loaded therapeutic candidate [250,251]. This limitation led to a switch to synthetic polymers, i.e., polyglycolide (PGA), polylactide (PLA) copolymers, which provide enhanced cross-link sites and effective drug loading. Although polymeric NPs exhibit positive, sustained release of loaded candidates, as previously discussed, they also show substantial systemic toxicity that is potentially due to the residual organic solvent used during synthesis, detection by the immune system and internalization by the RES system [185,186]. This limitation was further reduced by encapsulating the polymeric NPs with lipid coatings, thereby increasing the bioavailability by effectively protecting the polymeric NPs from gastric enzymes and promoting intestinal wall permeability [252,253]. The idea of amalgamating the traits of both the lipid NPs and polymeric NPs to compensate for their inadequacies led to the emergence of LPNs. Despite the amphiphilic potential of loaded candidates, LPNs are more suitable for hydrophilic candidates, which are clinically employed in their salt forms [254,255]. The formulation of drug–polymer complexes using ionic polymers plays a crucial role in the enhanced drug loading capacity of LPNs and is also reported to effectively load multiple drug candidates that are relatively suitable for multidrug or combination therapies [256]. Polymeric NPs can be synthesized via various techniques, such as emulsification, nanoprecipitation, and homogenization. During the general emulsification procedure, the polymers are dissolved in a volatile organic solvent and then emulsified in the aqueous phase; the resultant mixture is processed with homogenization/ultrasonication and dried to yield the polymeric NPs [257]. However, LPNs can be prepared by two different strategies: in the first case, the performed polymeric NPs are simply mixed with the pre-prepared lipid vesicles and surface-assimilated by external electrostatic forces, while, in the second case, the performed polymeric NPs are added to the thin film of lipids during the hydration process and then subjected to homogenization or ultrasonication to obtain LPNs. Further, the resultant LPNs can be purified from free lipids by differential centrifugation [257,258]. Paradeshi et al., who previously developed SLNs for ropinirole hydrochloric acid, engineered the very first LPNs for CNS delivery through the nasal route [259]. These LPNs were produced using the emulsification–solvent diffusion technique [aqueous phase: hydroxypropylmethylcellulose (HPMC) K15 M (100 mg), Pluronic F-68 (1%), soy lecithin (1% w/v); organic phase: dsynasan 114 (10 mg), stearlyamine (0.05%); size of 98.43 ± 3.38 to 287.26 ± 5.72 nm, PDI of 0.011 ± 0.27 to 0.38 ± 0.21, charge of −20.81 ± 1.37 to 45.08 ± 1.24 mV, and entrapment efficiency of 65.90% ± 0.13%–75.84% ± 0.367%]. Briefly, the melted cationic lipids and adjuvant were dissolved in organic solvent and injected into the aqueous phase with surfactant. The resulting emulsion was nanoprecipitated using cold water and subjected to homogenization to obtain the LPNs. A Box–Behnken factorial experimental design was adapted to optimize the independent variables, i.e., Pluronic F-68 and stearyl amine, by measuring the particle size, zeta potential, and entrapment efficiency. Among the various sets, formulation P5, made of 1% Pluronic F-68 and 0.05% stearyl amine, was complied with the optimal criteria. The LPNs did not exhibit any significant toxicity to the nasal mucosa and showed an acceptable mucoadhesive potential. Interestingly, the therapeutic efficacy of LPNs was comparable with a marketed formulation [256,259]. Similarly, Zhao et al. developed nanostructured LPNs for loading a basic fibroblast growth factor (bFGF) and targeting it to the brain via nasal administration. Researchers have

Table 2
Lipid-based nanodrug delivery systems targeting DA replacement strategies in PD therapeutics.

Active drug/drug nature	Lipid type and composition	Adapted method for nanoparticle synthesis	Physicochemical parameters of NPs	Purpose of the study	Investigated experimental model	Pharmacological investigations
Dopamine prodrug DOPH {2-amino-N-[2-(3,4-dihydroxy-phenyl)-ethyl]-3-phenyl-propionamide} [*Hydrophobic*]	Unilamellar liposomes {Dimyristoyl-sn-glycero-phosphatidylcoline (DMPC): cholesterol in 7.5:2.5 M ratio}	"Thin-film" hydration	**Size:** 170.8 ± 7.6 nm to 295.6 ± 8.1 nm; **PDI:** 0.22 to 0.23; **charge:** −49.65 ± 1.09 to −75.5 ± 0.24 mV; **encapsulation:** 79.1% ± 0.8%–87.7% ± 0.6%	Enhance the bioavailability of DOPH in brain milieu	NA	NA [212]
Dopamine [*Hydrophilic*]	Liposomes {Soy phosphatidylcoline: cholesterol (7:3) and 1,2-stearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(poly (ethylene glycol)-2000)] – 2.5 mol%}	Modified dehydration − rehydration technique	**Size:** 181.7 ± 7.8 nm; **PDI:** 0.20; **charge:** 7.5 ± 1.2 mV; **encapsulation:** 35.4% ± 1.8%	Functionalization of DA liposomes with transferrin, ease its pass-through BBB via receptor-mediated transcytosis	Invitro BBB model (human cerebral microvascular endothelial cell line hCMEC/D3)	Invitro BBB transport analysis [206]
L-dopa precursor {methyl O-acetyl-3-(acetyloxy)-N-[(2E)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]-L-tyrosinate}	Solid lipid nanoparticle {tristearin (90.8g)/lecithin (0.005g), Labrasol® (0.2g) and poloxamer 188 (2.5%)}	Hot homogenization	**Size:** 149.9 ± 3.2 to 161.9 ± 0.8 nm; **PDI:** 0.26 ± 0.01 to 0.3 ± 0.02; **encapsulation:** 43.36% ± 6.63%–83.01% ± 9.38%	Transference of L-dopa precursor across BBB and provide adequate DA levels in the brain	6-OHDA hemi-lesioned PD like mice model	Bar and drag behavioral tests [327]
L-dopa (*partially hydrophilic*)	Solid lipid nanoparticle	Microemulsion technology	**Size:** 108 nm	Formulation and physicochemical characterization of L-dopa loaded SLNs	NA	NA [328]
L-dopa codrugs {PDA (3,4-diacetyloxy-L-dopa-caffeic acid), PDB (lipoic acid-DA), PDC (lipoic acid-3,4-diacetoxy-DA), PDD (dimeric L-dopa containing an alkyl linker)} *(hydrophilic)*	Nanostructured lipid carriers {solid lipid- tristearin:tricaprylin in a 2:1 ratio w/w; aqueous poloxamer (2.5%w/w)}	Homogenization and/or ultrasonication	**Size:** 180.1 ± 1.0 to 197.0 ± 2.1 nm; **PDI:** 0.20 to 0.36; **Encapsulation:** 24.57%–81.87%	To prolong the pharmacological potential of L-dopa by enhanced absorption and protection from biological metabolism	NA	NA [246]
L-dopa (*partially hydrophilic*)	Lipid-polymer hybrid nanoparticle {Eudragit®:sodium carboxymethylcellulose in a 0.5:1 ratio and/or chitosan; lecithin}	Mechanical agitation	**Size:** 152 nm–321 nm; **PDI:** 0.19 to 0.61; **Charge:** 15.8–43.3 mV; **Encapsulation:** 85%	To improve the absorption of L-dopa across BBB	NA	NA [329]
AM *(hydrophilic)*	Solid lipid nanoparticle {tripalmitin (200 mg), soy phosphatidylcholine (50 mg) and aqueous PF68 (30 mg)}	Hot homogenization	**Size:** 63.20 ± 0.98 to 154.9 ± 2.83 nm; **PDI:** 0.31 to 0.33; **Charge:** 7.23 ± 0.25 to 23.27 ± 0.70 mV; **encapsulation:** 90.38% ± 0.04%–91.03% ± 0.14%	To improve the oral bioavailability and enhance brain biodistribution of AM using solid lipid nanocarrier systems	AM loaded nanoparticles were orally administered to rats 6-OHDA lesioned PD like mice model	In vivo pharmacokinetics and biodistribution studies: the concentration of AM in rat plasma and the distribution of AM in cerebellum, brainstem, and striatum of rat's brain was investigated; rotational behavior test was performed [232]
AM diester prodrugs {diacetyl AM (DAA) and di-isobutyryl AM (DIA)} *(hydrophilic)*	Nanostructured lipid carriers {cetyl palmitate (4% w/v), sesame oil (4%) or PLGA and aqueous Pluronic F68 (2.7%)}	High-shear homogenization	**Size:** 250.1 ± 3.33 nm; **PDI:** 0.23 ± 0.03; **charge:** 48.4 ± 0.6 mV	To improve the solubility of AM prodrugs, and retain a sustained release profile without oral/parenteral administration of AM	Erythrocyte and neutrophils from blood samples; nude mice model for imaging studies	The toxicity of nanoparticles was investigated by invitro neutrophil lactate dehydrogenase (LDH) release and hemolysis tests The biodistribution of the nanoparticles and its duration were studied using *in vivo* and ex vivo bioimaging study. [244]

(*continued on next page*)

Table 2 (*continued*)

Active drug/drug nature	Lipid type and composition	Adapted method for nanoparticle synthesis	Physicochemical parameters of NPs	Purpose of the study	Investigated experimental model	Pharmacological investigations
Ropinirole hydrochloride *(hydrophilic)*	Lipid-polymer hybrid nanoparticle {hydroxypropylmethylcellulose (HPMC) K15 M (100 mg); soy lecithin (1% w/v); Dynasan 114 (10 mg) and stearylamine (0.05%)}	Emulsification-solvent diffusion technique	**Size:** 98.43 ± 3.38 nm; **PDI:** 0.031 ± 0.06; **entrapment:** 70.82% ± 0.18%	To develop a robust lipid-polymer hybrid nanocarrier for intranasal delivery of ropinirole hydrochloride to brain	Sheep nasal mucosa; chlorpromazine (CPZ) induced PD like symptoms in mice; reserpine induced PD like symptoms in mice	Ex vivo drug permeation studies; tremor scores; grooming episodes [259]
Ropinirole hydrochloride *(hydrophilic)*	Solid lipid nanoparticle {dynasan 114 and stearylamine}	Emulsification-solvent diffusion technique	**Size:** 66.22 ± 6.22 nm; **PDI:** 0.023 ± 0.21; **Entrapment:** 61.90 ± 0.18%	To deliver ropinirole hydrochloride to the brain via intranasal delivery by loading in lipid nanocarrier and avoid the hepatic first-pass metabolism	Sheep nasal mucosa; chlorpromazine (CPZ) induced PD like symptoms in mice	Histological examination of nanoparticles treated sheep nasal mucosa for damage and also for permeation studies; tremor scores [234]
Bromocriptine *(hydrophobic)*	Solid lipid nanoparticle {glyceryl monooleate (4/5% w/w) and poloxamer 407 (0.5% w/w)} Nanostructured lipid carriers {tristearin:miglyol in a 2:1 ratio w/w and aqueous poloxamer 188 solution (2.5% w/w)}	Homogenization and ultrasonication	**Size:** 204.8 ± 1.2 nm; **PDI:** 0.19 ± 0.01; **entrapment:** 70% ± 0.75%; **Size:** 195.1 ± 3.3 nm; **PDI:** 0.19 ± 0.03; **entrapment:** 84% ± 0.58%	To compare the physicochemical traits and efficacies of SLN and NLC nanocarrier systems in delivering the antiparkinsonian drug bromocriptine	6-OHDA lesion PD-like mice model	Bar test [330]
Bromocriptine *(hydrophobic)*	Nanostructured lipid carriers {tristearin: tricaprin in a 2:1 ratio and aqueous poloxamer 188 solution (2.5% w/w)}	Homogenization and ultrasonication	**Size:** 196 nm; **PDI:** 0.24; **entrapment:** 84% ± 0.58%	Develop effectual lipid nanocarriers to enhance bioavailability and efficacy of bromocriptine	6-OHDA lesion PD-like mice model	Bar test [231]
Bromocriptine and Resveratrol *(hydrophobic)*	Solid lipid nanoparticle {Compritol®}	High-speed homogenization and ultrasonication	**Size:** 100–220 nm; **entrapment:** 81.00% ± 0.92%–92.52% ± 0.10%	The nanoformulation of combination therapy was chosen to establish synergism, less side effects and enhance the bioavailability of bromocriptine	NA	NA [331]
Piribedil *(lipophilic)*	Solid lipid nanoparticle {Compritol® (2.5% w/w) and Labrasol® (1.2% w/w) }	Cold and hot homogenization methods	**Size:** 5.6 μm; **entrapment:** 54.1% ± 0.7%	To eliminate the low aqueous solubility and short half-life of piribedil and enhance its bioavailability	Oxotremorine inflicted tremor in mice; oral administration to rabbits	Tremor test; bioavailability and pharmacokinetic profile of piribedil in plasma [230]
basic fibroblast growth factor (bFGF) *(hydrophilic)*	Nanostructured lipid carriers {homogeneous gelatin solution (2.0% w/v); hydrogenated soy phosphatidylcholine and cholesterol}	Water-in-water emulsion and freeze-drying	**Size:** 172 ± 1.31 nm; **PDI:** 0.105 ± 0.01; **charge:** −27.6 ± 1.1 **entrapment:** 86.7% ± 1.1%;	The bFGF stimulates DAergic function and neuroprotection; delivery of exogeneous bFGF through NLCs can show substantial PD therapeutic effects	6-OHDA lesioned hemi-parkinsonian rats	Rotational behavior test was performed; mnoamine neurotransmitter levels; immunohistochemical analysis of tyrosine hydroxylase expression [260]

engineered LPNs by adapting water-in-water emulsion and freeze-drying methods, where the initial emulsion obtained by stirring the bFGF dispersed the gelatin polymer in the aqueous phase with nonionic copolymer, with the resulting emulsion subjected to freeze-drying. Thereafter, the freeze-dried drug–polymer complexes were dispersed and sonicated in a hydrogenated soy-phosphatidylcholine lipid phase; this secondary emulsion was further freeze-dried to obtain the bFGF-loaded LPNs [gelatin solution (2.0% w/v), poloxamer 188 (20% w/v), D,L-glyceraldehyde (0.1% w/v), and bFGF gelatin (2 mg/mL), with a size of 172 ± 1.31 nm, charge of −27.6 ± 1.1 mV, and entrapment efficiency of 86.7% ± 1.1%] [260]. These LPNs maintained the integrity of the nasal mucosa with no adverse effects, effectively transporting bFGF to the olfactory bulb and striatum, and thus, exhibited enhanced therapeutic efficacy in a 6-OHDA-induced hemi-parkinsonism rat model compared to the free form of unstable macromolecular bFGF [260]. Recently, several variations of lipid-based DA-targeted PD therapeutics were developed, as listed in Table 2, and most of the therapeutic strategies were focused on loading DA agonists and L-dopa to some extent.

7. Advantages and disadvantages of lipidic nanocarriers over other nanodelivery systems in DA-centered PD therapeutics

In general, the lipids (i.e., triglycerides, fatty acids, lecithin) employed for lipid-based nanoformulations are comparable to those available in the biological systems. First, phospholipid bilayer vesicles forming the liposomal vesicles of lipid NPs are found to be similar to that of the physiological cellular membrane [194]. Second, the cholesteric component of lipid vesicles retains the homeostasis of the lipid NPs in biological fluids, such as blood and synovial fluid, by reducing the water permeability into the nanoparticulate, thereby providing sustained and enhanced drug delivery [194,261]; Third, this lipidic encapsulation of drug candidates also prevents its early systemic metabolization by gastric enzyme degradation and also bypasses other physiological barriers, i.e., P-glycoprotein efflux systems and permeability issues in the BBB [262,263]. Fourth, though lipid NPs lack complementary processing proteins, which minimize the immune activation response, further coating them with biodegradable polymers, such as PEG, can enhance the immune-camouflage trait of lipid NPs [263,264]. Finally, lipid NPs in biological systems undergo comparable xenobiotic metabolism of food-based lipids and are degraded to non-toxic residues [263]. Moreover, due to the sustained-release properties of lipids, the drug dosage levels were sufficiently lowered, especially in NLCs and thereby exhibited enhanced therapeutic efficacy with limited adverse effects and favorable cost-effectiveness [265]. Conversely, the chemical and physical methods adapted to synthesize inorganic NPs, such as metallic nanoparticles made of materials like gold, silver, silica, and quantum dots, are relatively expensive and time-consuming to conduct compared with lipid NPs [266–268]. Additionally, certain metallic NPs, such as ZnO, CuO, and Co_3O_4, are reported to be highly toxic to humans and the environment [269]. It is noteworthy that, in recent years, metallic NPs derived from natural resources (biogenic/green synthesis) like bacteria, fungi, and actinomycetes are attracting interest due to their potential low toxicity [270,271]. NPs synthesized from naturally derived polymers, i.e., starch, chitosan, and cellulose, are biocompatible and biodegradable, whereas certain synthetic polymers like poly(ethylene oxide), poly(ortho ester), and poly(acrylic acid) were reported to undergo toxic degradation, toxic monomer aggregation, and long-term residual accumulation in biological systems [272]. Nonetheless, due to the enhanced therapeutic-based clinical applications of these inorganic NPs, researchers have engaged in several surface-functionalization efforts or alterations of physicochemical traits to attain the maximum level of efficacy with minimal toxicity [273,274]. Conversely, lipid NPs are surface-functionalized to avoid immune response activation [264] and site-specific targeted delivery, i.e., peptide-sequence functionalized liposomes are targeted to the tumor site and brain glioblastoma regions [275,276]. In terms of drug loading, due to the amphiphilic nature of lipid NPs, though both hydrophilic and hydrophobic drugs can be loaded, drug-loading efficacy relies on the choice of lipid selection, lipid–drug ratio, and the adapted method of formulations [277–279]. For instance, for loading hydrophilic drugs in liposomes, as compared with using the thin-film hydration method and reverse-phase evaporation methods (which achieves maximum encapsulation up to 65%), the pH gradient–mediated loading method can provide nearly 100% encapsulation efficacy [280]. Regardless of the nature of the drugs, the first-generation SLNs exhibit low drug loading efficacy due to their perfect crystalline structure. This has been efficiently contrasted by the imperfect crystalline matrix of NLCs provided by liquid lipids and having relatively more room for hydrophilic/hydrophobic drugs [265]. On the other hand, unlike lipid NPs, inorganic metallic NPs made from gold and silver have surface plasmon resonance traits, which provides more opportunity for surface functionalization and targeted drug delivery. Also, mesoporous silica nanoparticles have been appreciated for their enhanced loading capacity and plethora of potential surface modifications [281,282]. However, despite the improved performance of inorganic NPs in preclinical studies, unlike lipid NPs, their failure rate in clinical studies remains fairly high [282,283]. Thus, it is clear that a deeper understanding of the mechanism of action of nanocarriers in biological systems is highly crucial. It is also noteworthy that, besides the nature/type of the nanocarrier, optimizing the particle size, shape, targeted organs, mode of delivery, bioavailability, and surface properties of the nanoparticles are also important factors determining the fate of the drug delivery process and therapeutic effect.

Direct formulations of DA-loaded lipid nanoparticles, one of the DA replacement strategies available with the greatest potential (Fig. 6), have rarely been applied to date. If the nanodelivery systems for DA were ignored, possibly due to the hydrophilic traits of DA, the amphiphilic loading capacity of the advanced lipid systems, including SLNs, NLCs, and LPNs, should be considered. Notably, a few recent studies of DA-loaded lipid-/polymer-based NPs are attracting attention due to the anticipated therapeutic potential in the management of PD [205,284,285]. Therefore, the construction of novel and effective delivery systems for L-dopa and DA, either alone or in combination, will potentially provide new and direct approaches to overcome existing physicochemical barriers and promote the sustained release of DA-centered PD therapeutics.

8. Conclusion and future perspectives

As a multifactorial disorder, PD requires multiple combination therapies to ameliorate symptoms and disease progression in patients. Currently, clinicians treat patients with PD based on their age/symptoms and clinical stage. For example, patients with early-stage PD aged younger than 60 years are initially treated with DA agonists, anticholinergic agents, or β-blockers, while patients aged greater than 60 years are typically treated with L-dopa [286,287]. However, the progression of the disease requires an escalated chronic dosage regimen and combination therapies, which further burden patients' lifestyle and inflict psychological distress [288]. L-dopa, the gold-standard therapy for advanced PD, has a short half-life, requiring frequent dose escalations and eventually inducing dyskinesia and delayed "wearing-off" periods [289]. The subsequent approach of administering DA receptor agonists as a monotherapy to patients with early-stage PD and as a combination therapy with L-dopa in patients with advanced PD effectively alleviates the motor deficits observed in patients [290]. Nevertheless, the oral regimen of these concomitantly administered DA medications causes pulsatile and unstable DAergic activity in the striatum; thus, as an alternative strategy, continual DA stimulation was preferred via a sustained supply of DA agonists [291,292]. Recently, transdermal patches of DA agonists, such as ropinirole, showed effective sustained release of the drug in plasma; however, patients experienced prominent side effects of the drug, such as sleep disorders and

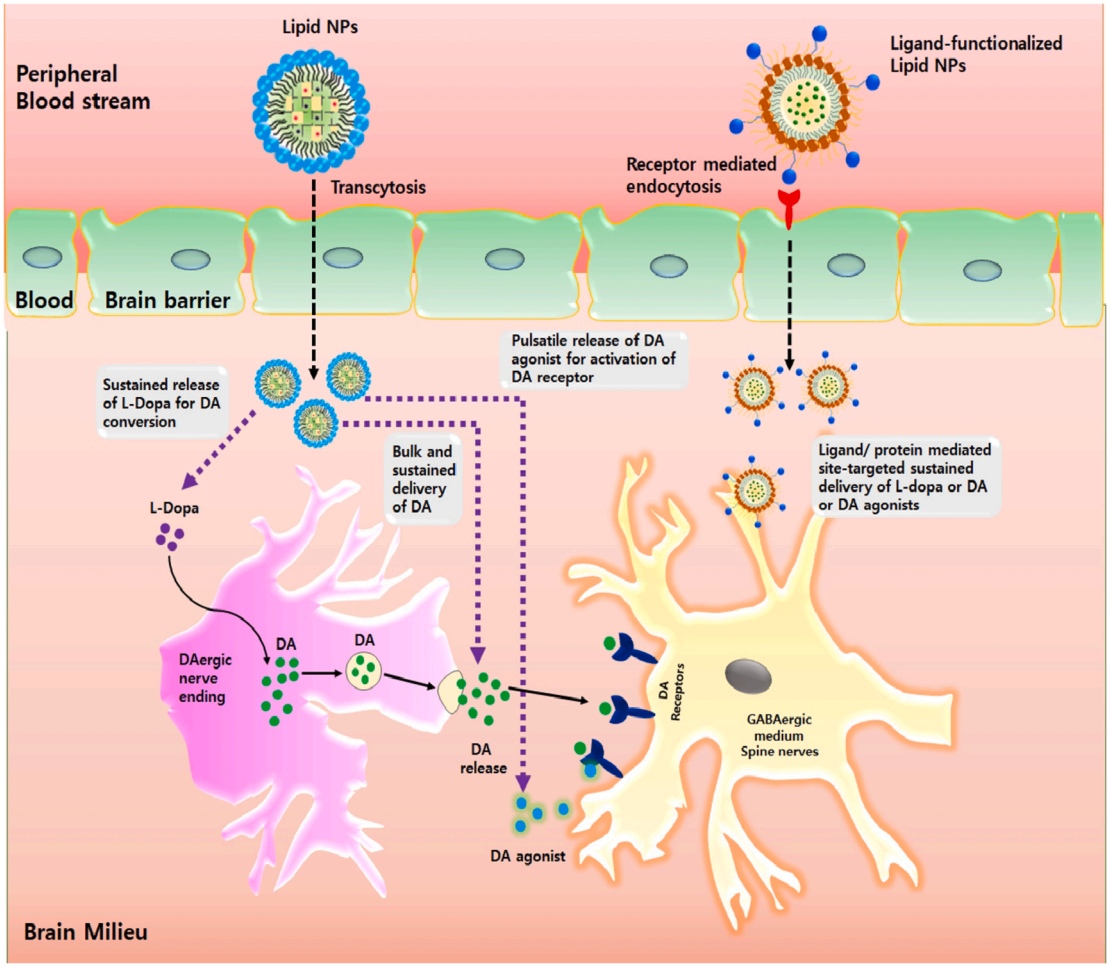

Fig. 6. Schematic representation of the potential mechanism of action of active PD therapeutic-loaded lipid nanocarriers likely involved in transportation across the BBB and which exhibit sustained and pulsatile release of the drugs. Also, the presumable potential of functionalized nanocarriers delivering drugs to the targeted site of action, i.e., nigrostriatal DAergic neurons, is represented. DA: dopamine; DAergic: dopaminergic; L-dopa: levodopa; NP: nanoparticles.

hallucinations [293]. Thus, among the various reasons, the reduced half-life and low bioavailability of the effective drug candidates following transport through the CNS barriers is one of the significant challenges for PD therapeutics. Hence, the development of appropriate biocompatible delivery systems for the sustained release of DA or other DA agonists to the targeted site of action, i.e., nigrostriatal region, will likely provide some promising disease-modifying PD therapeutics.

For the past several decades, advances in nanotechnology have been predominantly attributed to the biomedical and pharmaceutical sectors in terms of drug delivery applications. In particular, lipid-based nanodrug delivery systems exhibit the lowest toxicity among evaluated biological systems (biocompatible lipids) with enhanced loading/therapeutic efficacy, sustained-release, and safe drug-trafficking properties across the BBB as CNS therapeutics [193,240]. Moreover, advances in the functionalization of lipid carriers with appropriate genes/peptides/ligands have facilitated the active infiltration of nanodrugs across the BBB and the potential targeting of these therapeutics to the site of action [206,213]. Although nanodrug delivery approaches exhibit several benefits, they also show multiple substantial limitations, including the potential interaction of the biological serum/plasma substrates with the functionalized peptides on the surface of nanocarriers or adsorption of serum/plasma proteins onto the surface of the nanoparticles, which can alter the transport of NPs by forming an undesired complex biomolecular layer known as the "protein corona" [294,295]. The possible accumulation of lipid NPs at the RES sites, i.e., the liver, subsequently restricts or lowers the dose of NPs that reaches the systemic circulation and the targeted brain milieu. The synthetic components of the lipid NPs are potentially detected by the immune system, resulting in the formation of specific antibodies and rapid clearance, also known as accelerated blood clearance [21,296]. These limitations have been effectively overcome by altering the physicochemical properties of NPs and by making surface modifications. For example, PEGylation of NPs helps control the extent of "protein corona" formation by sterically inhibiting the hydrophobic and electrostatic interactions with serum/plasma proteins. PEGylated steric stabilization and alterations in the size of NPs hinder RES accumulation and improve the circulation of NPs [297]. The PEGylation of NPs (stealth NPs) is also generally believed to potentially exhibit immunocamouflage properties and evade immune checkpoints; however, the same mechanism has been reported to be involved in anti-PEG antibody formation and acceleration in blood clearance [297,298]. Thus, further comprehensive immunological investigations are required to confirm and establish an alternative for this issue.

Conversely, despite the development of several novel and functional nanodelivery systems, many lipid-based nanodrugs have failed to reach the global pharmaceutical market and are less active in the clinical trial pipeline [22,299]. According to the author, the lack of "extensive" therapeutic investigations of NPs in disease models are potentially responsible for the failure of several nanodelivery systems in clinical trials. For instance, a few chemists have developed novel nanodelivery systems and extensively studied the physicochemical properties of NPs; however, investigations of the therapeutic effects have only been based

on a few biological parameters, i.e., cytotoxicity, *in vitro/in vivo* release, and a few preliminary *in vivo* biomarkers. In contrast, some biologists have emphasized the search for novel biomolecular insights and therapeutic targets for the disease. Furthermore, they have extensively evaluated the efficacy of therapeutic candidates and determined the molecular mechanism of action, though few researchers have investigated the chemistry of the molecular targets of these drugs. Researchers focusing on these effects have also largely failed to focus on the ultimate outcomes of the therapeutic applications of these drugs in the clinic. The authors suggest that an interdisciplinary understanding and collaborative approaches between researchers in these two fields will facilitate extensive therapeutic investigations of the developed NPs, which will potentially succeed in clinical trials and become successful therapeutic candidates in the pharmaceutical market. Accordingly, in this review, we have extensively discussed the advances and findings from the clinic regarding therapeutics and lipid-based nanodelivery applications, focusing on DA-centered PD therapeutics, to provide critical information to a wide range of researchers/readers. This review will potentially enlighten researchers and support opportunities for the development of promising lipid-based nanotherapeutics for the clinical management of PD.

Declaration of competing interest

The authors declare no conflicts of interest exist.

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References

[1] J. Kulisevsky, M.R. Luquin, J.M. Arbelo, J.A. Burguera, F. Carrillo, A. Castro, J. Chacón, P.J. García-Ruiz, E. Lezcano, P. Mir, J.C. Martinez-Castrillo, I. Martínez-Torres, V. Puente, A. Sesar, F. Valldeoriola-Serra, R. Yañez, Advanced Parkinson's disease: clinical characteristics and treatment (part 1) [English version], Neurologia 28 (2013) 503–521, https://doi.org/10.1016/j.nrl.2013.05.001.

[2] Y. Yang, B. Tang, J. Guo, Parkinson's disease and cognitive impairment, Parkinsons. Dis. 2016 (2016) 1–8, https://doi.org/10.1155/2016/6734678.

[3] S. Konitsiotis, S. Bostantjopoulou, M. Chondrogiorgi, Z. Katsarou, G. Tagaris, I. Mavromatis, E.E. Ntzani, G. Mentenopoulos, Members of the Greek Parkinson Study Group, Clinical characteristics of Parkinson's disease patients in Greece: a multicenter, nation-wide, cross-sectional study, J. Neurol. Sci. 343 (2014) 36–40, https://doi.org/10.1016/j.jns.2014.05.003.

[4] I.S. Al-Busaidi, T.J. Anderson, Y. Alamri, Qualitative analysis of Parkinson's disease information on social media: the case of YouTube™, EPMA J. 8 (2017) 273–277, https://doi.org/10.1007/s13167-017-0113-7.

[5] J.-P. Bach, U. Ziegler, G. Deuschl, R. Dodel, G. Doblhammer-Reiter, Projected numbers of people with movement disorders in the years 2030 and 2050, Mov. Disord. 26 (2011) 2286–2290, https://doi.org/10.1002/mds.23878.

[6] A. Rossi, K. Berger, H. Chen, D. Leslie, R.B. Mailman, X. Huang, Projection of the prevalence of Parkinson's disease in the coming decades: Revisited, Mov. Disord. 33 (2018) 156–159, https://doi.org/10.1002/mds.27063.

[7] E.R. Dorsey, R. Constantinescu, J.P. Thompson, K.M. Biglan, R.G. Holloway, K. Kieburtz, F.J. Marshall, B.M. Ravina, G. Schifitto, A. Siderowf, C.M. Tanner, Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030, Neurology 68 (2007) 384–386, https://doi.org/10.1212/01.wnl.0000247740.47667.03.

[8] R. Savica, B.R. Grossardt, W.A. Rocca, J.H. Bower, Parkinson disease with and without Dementia: a prevalence study and future projections, Mov. Disord. 33 (2018) 537–543, https://doi.org/10.1002/mds.27277.

[9] T.M. Bovolenta, S.M.C. de Azevedo Silva, R. Arb Saba, V. Borges, H.B. Ferraz, A.C. Felicio, Systematic review and critical analysis of cost studies associated with Parkinson's disease, Parkinsons. Dis. 2017 (2017) 1–11, https://doi.org/10.1155/2017/3410946.

[10] Parkinson's: drug treatment, https://www.ncbi.nlm.nih.gov/books/NBK293715/?report=reader, (2015) , Accessed date: 21 December 2018.

[11] W. Oertel, J.B. Schulz, Current and experimental treatments of Parkinson disease: a guide for neuroscientists, J. Neurochem. 139 (2016) 325–337, https://doi.org/10.1111/jnc.13750.

[12] V. Bhatt-Mehta, M.C. Nahata, Dopamine and dobutamine in pediatric therapy, Pharmacotherapy 9 (1989) 303–314 http://www.ncbi.nlm.nih.gov/pubmed/2682552 , Accessed date: 21 December 2018.

[13] J. Rautio, H. Kumpulainen, T. Heimbach, R. Oliyai, D. Oh, T. Järvinen, J. Savolainen, Prodrugs: design and clinical applications, Nat. Rev. Drug Discov. 7 (2008) 255–270, https://doi.org/10.1038/nrd2468.

[14] A. Borgkvist, E.M. Avegno, M.Y. Wong, M.A. Kheirbek, M.S. Sonders, R. Hen, D. Sulzer, Loss of striatonigral GABAergic presynaptic inhibition enables motor sensitization in parkinsonian mice, Neuron 87 (2015) 976–988, https://doi.org/10.1016/j.neuron.2015.08.022.

[15] E. Manning, Review of Parkinson's disease treatment and future therapies, Annu. Rev. Chang. Healthc. 1 (2018), http://journals.findlay.edu/index.php/ARxCH/article/view/90 , Accessed date: 21 December 2018.

[16] H.J. Kim, B.S. Jeon, P. Jenner, Hallmarks of treatment aspects: Parkinson's disease throughout centuries including l-dopa, Int. Rev. Neurobiol. 132 (2017) 295–343, https://doi.org/10.1016/BS.IRN.2017.01.006.

[17] D. Deleu, M.G. Northway, Y. Hanssens, Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson??s disease, Clin. Pharmacokinet. 41 (2002) 261–309, https://doi.org/10.2165/00003088-200241040-00003.

[18] B.R. De Miranda, J.A. Miller, R.J. Hansen, P.J. Lunghofer, S. Safe, D.L. Gustafson, D. Colagiovanni, R.B. Tjalkens, Neuroprotective efficacy and pharmacokinetic behavior of novel anti-inflammatory para-phenyl substituted diindolylmethanes in a mouse model of Parkinson's disease, J. Pharmacol. Exp. Ther. 345 (2013) 125–138, https://doi.org/10.1124/jpet.112.201558.

[19] T. Müller, Drug therapy in patients with Parkinson's disease, Transl. Neurodegener. 1 (2012) 10, https://doi.org/10.1186/2047-9158-1-10.

[20] A.O. Pires, F.G. Teixeira, B. Mendes-Pinheiro, S.C. Serra, N. Sousa, A.J. Salgado, Old and new challenges in Parkinson's disease therapeutics, Prog. Neurobiol. 156 (2017) 69–89, https://doi.org/10.1016/j.pneurobio.2017.04.006.

[21] C. Saraiva, C. Praça, R. Ferreira, T. Santos, L. Ferreira, L. Bernardino, Nanoparticle-mediated brain drug delivery: overcoming blood–brain barrier to treat neurodegenerative diseases, J. Control. Release 235 (2016) 34–47, https://doi.org/10.1016/J.JCONREL.2016.05.044.

[22] G. Karthivashan, P. Ganesan, S.Y. Park, J.S. Kim, D.K. Choi, Therapeutic strategies and nanodrug delivery applications in management of ageing Alzheimer's disease, Drug Deliv. 25 (2018) 307–320, https://doi.org/10.1080/10717544.2018.1428243.

[23] A.M. Cardoso, J.R. Guedes, A.L. Cardoso, C. Morais, P. Cunha, A.T. Viegas, R. Costa, A. Jurado, M.C. Pedroso de Lima, Recent trends in nanotechnology toward CNS diseases, Int. Rev. Neurobiol. (2016) 1–40, https://doi.org/10.1016/bs.irn.2016.05.002.

[24] G. Leyva-Gómez, H. Cortés, J.J. Magaña, N. Leyva-García, D. Quintanar-Guerrero, B. Florán, Nanoparticle technology for treatment of Parkinson's disease: the role of surface phenomena in reaching the brain, Drug Discov. Today 20 (2015) 824–837, https://doi.org/10.1016/j.drudis.2015.02.009.

[25] G. Soursou, A. Alexiou, G.M. Ashraf, A.A. Siyal, G. Mushtaq, M.A. Kamal, Applications of nanotechnology in diagnostics and therapeutics of Alzheimer's and Parkinson's disease, Curr. Drug Metabol. 16 (2015) 705–712 http://www.ncbi.nlm.nih.gov/pubmed/26560322 , Accessed date: 21 December 2018.

[26] G.E. Alexander, Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder, Dialogues Clin. Neurosci. 6 (2004) 259–280 http://www.ncbi.nlm.nih.gov/pubmed/22033559 , Accessed date: 21 December 2018.

[27] K. Berganzo, B. Tijero, A. González-Eizaguirre, J. Somme, E. Lezcano, I. Gabilondo, M. Fernandez, J.J. Zarranz, J.C. Gómez-Esteban, Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups, Neurol. (English Ed. 31 (2016) 585–591, https://doi.org/10.1016/J.NRLENG.2014.10.016.

[28] E. Gökçal, V.E. Gür, R. Selvitop, G. Babacan Yildiz, T. Asil, Motor and non-motor symptoms in Parkinson's disease: effects on quality of life, Noro Psikiyatr. Ars. 54 (2017) 143–148, https://doi.org/10.5152/npa.2016.12758.

[29] E. Heinrichs-Graham, P.M. Santamaria, H.E. Gendelman, T.W. Wilson, The cortical signature of symptom laterality in Parkinson's disease, NeuroImage Clin 14 (2017) 433–440, https://doi.org/10.1016/J.NICL.2017.02.010.

[30] J. Massano, K.P. Bhatia, Clinical approach to Parkinson's disease: features, diagnosis, and principles of management, Cold Spring Harb. Perspect. Med. 2 (2012) a008870, , https://doi.org/10.1101/cshperspect.a008870.

[31] P. Mazzoni, B. Shabbott, J.C. Cortés, Motor control abnormalities in Parkinson's disease, Cold Spring Harb. Perspect. Med. 2 (2012) a009282, https://doi.org/10.1101/cshperspect.a009282.

[32] J.-G.G. Hou, E.C. Lai, Non-motor symptoms of Parkinson's disease, Int. J. Gerontol. 1 (2007) 53–64, https://doi.org/10.1016/S1873-9598(08)70024-3.

[33] G.S. Watson, J.B. Leverenz, Profile of cognitive impairment in Parkinson's disease, Brain Pathol. 20 (2010) 640–645, https://doi.org/10.1111/j.1750-3639.2010.00373.x.

[34] S.J. Frucht, S. Jain, Parkinson disease: an update, The Neurologist 10 (2004) 185–194 http://www.ncbi.nlm.nih.gov/pubmed/15245584 , Accessed date: 21 December 2018.

[35] C. Magerkurth, R. Schnitzer, S. Braune, Symptoms of autonomic failure in Parkinson?s disease: prevalence and impact on daily life, Clin. Auton. Res. 15 (2005) 76–82, https://doi.org/10.1007/s10286-005-0253-z.

[36] M.M. Goldenberg, P T, Medical management of Parkinson's disease, http://www.ncbi.nlm.nih.gov/pubmed/19750042, (2008) , Accessed date: 21 December 201833, 590–606.

[37] J.V. Hindle, Ageing, neurodegeneration and Parkinson's disease, Age Ageing 39 (2010) 156–161, https://doi.org/10.1093/ageing/afp223.

[38] J.F. Cooper, D.J. Dues, K.K. Spielbauer, E. Machiela, M.M. Senchuk, J.M. Van

Raamsdonk, Delaying aging is neuroprotective in Parkinson's disease: a genetic analysis in C. elegans models, Npj Park. Dis. 1 (2015) 15022, https://doi.org/10.1038/npjparkd.2015.22.
[39] M.R. Cookson, Parkinsonism due to mutations in PINK1, parkin, and DJ-1 and oxidative stress and mitochondrial pathways, Cold Spring Harb. Perspect. Med. 2 (2012) a009415, https://doi.org/10.1101/cshperspect.a009415.
[40] D.N. Hauser, T.G. Hastings, Mitochondrial dysfunction and oxidative stress in Parkinson's disease and monogenic parkinsonism, Neurobiol. Dis. 51 (2013) 35–42, https://doi.org/10.1016/j.nbd.2012.10.011.
[41] K. Nuytemans, J. Theuns, M. Cruts, C. Van Broeckhoven, Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update, Hum. Mutat. 31 (2010) 763–780, https://doi.org/10.1002/humu.21277.
[42] E.J. Huang, Ventral midbrain dopaminergic neurons: from neurogenesis to neurodegeneration, FEBS Lett. 589 (2015) 3691–3692, https://doi.org/10.1016/j.febslet.2015.11.008.
[43] J.M. Fearnley, A.J. Lees, Ageing and Parkinson's disease: substantia nigra regional selectivity, Brain 114 (Pt 5) (1991) 2283–2301 http://www.ncbi.nlm.nih.gov/pubmed/1933245 , Accessed date: 21 December 2018.
[44] H. Bernheimer, W. Birkmayer, O. Hornykiewicz, K. Jellinger, F. Seitelberger, Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations, J. Neurol. Sci. 20 (1973) 415–455 http://www.ncbi.nlm.nih.gov/pubmed/4272516 , Accessed date: 21 December 2018.
[45] C.L. Robertson, K. Ishibashi, M.A. Mandelkern, A.K. Brown, D.G. Ghahremani, F. Sabb, R. Bilder, T. Cannon, J. Borg, E.D. London, Striatal D1- and D2-type dopamine receptors are linked to motor response inhibition in human subjects, J. Neurosci. 35 (2015) 5990–5997, https://doi.org/10.1523/JNEUROSCI.4850-14.2015.
[46] M.R. DeLong, Primate models of movement disorders of basal ganglia origin, Trends Neurosci. 13 (1990) 281–285 http://www.ncbi.nlm.nih.gov/pubmed/1695404 , Accessed date: 21 December 2018.
[47] R.L. Albin, A.B. Young, J.B. Penney, The functional anatomy of basal ganglia disorders, Trends Neurosci. 12 (1989) 366–375 http://www.ncbi.nlm.nih.gov/pubmed/2479133 , Accessed date: 21 December 2018.
[48] C.R. Gerfen, D.J. Surmeier, Modulation of striatal projection systems by dopamine, Annu. Rev. Neurosci. 34 (2011) 441–466, https://doi.org/10.1146/annurev-neuro-061010-113641.
[49] J.A. Obeso, M.C. Rodríguez-Oroz, M. Rodríguez, J.L. Lanciego, J. Artieda, N. Gonzalo, C.W. Olanow, Pathophysiology of the basal ganglia in Parkinson's disease, Trends Neurosci. 23 (2000) S8–S19 http://www.ncbi.nlm.nih.gov/pubmed/11052215 , Accessed date: 21 December 2018.
[50] L. Yetnikoff, H.N. Lavezzi, R.A. Reichard, D.S. Zahm, An update on the connections of the ventral mesencephalic dopaminergic complex, Neuroscience 282 (2014) 23–48, https://doi.org/10.1016/j.neuroscience.2014.04.010.
[51] F. Morello, J. Partanen, Diversity and development of local inhibitory and excitatory neurons associated with dopaminergic nuclei, FEBS Lett. 589 (2015) 3693–3701, https://doi.org/10.1016/J.FEBSLET.2015.10.001.
[52] P. Barone, Neurotransmission in Parkinson's disease: beyond dopamine, Eur. J. Neurol. 17 (2010) 364–376, https://doi.org/10.1111/j.1468-1331.2009.02900.x.
[53] S.A. Factor, W.M. McDonald, F.C. Goldstein, The role of neurotransmitters in the development of Parkinson's disease-related psychosis, Eur. J. Neurol. 24 (2017) 1244–1254, https://doi.org/10.1111/ene.13376.
[54] Y. Zhou, N.C. Danbolt, Glutamate as a neurotransmitter in the healthy brain, J. Neural Transm. 121 (2014) 799–817, https://doi.org/10.1007/s00702-014-1180-8.
[55] J.T. Gass, M.F. Olive, Glutamatergic substrates of drug addiction and alcoholism, Biochem. Pharmacol. 75 (2008) 218–265, https://doi.org/10.1016/j.bcp.2007.06.039.
[56] R.W. Olsen, W. Sieghart, GABA A receptors: subtypes provide diversity of function and pharmacology, Neuropharmacology 56 (2009) 141–148, https://doi.org/10.1016/j.neuropharm.2008.07.045.
[57] S.F. Traynelis, L.P. Wollmuth, C.J. McBain, F.S. Menniti, K.M. Vance, K.K. Ogden, K.B. Hansen, H. Yuan, S.J. Myers, R. Dingledine, Glutamate receptor ion channels: structure, regulation, and function, Pharmacol. Rev. 62 (2010) 405–496, https://doi.org/10.1124/pr.109.002451.
[58] M.D. Bevan, C.M. Francis, J.P. Bolam, The glutamate-enriched cortical and thalamic input to neurons in the subthalamic nucleus of the rat: convergence with GABA-positive terminals, J. Comp. Neurol. 361 (1995) 491–511, https://doi.org/10.1002/cne.903610312.
[59] B.S. Freeze, A.V. Kravitz, N. Hammack, J.D. Berke, A.C. Kreitzer, Control of basal ganglia output by direct and indirect pathway projection neurons, J. Neurosci. 33 (2013) 18531–18539, https://doi.org/10.1523/JNEUROSCI.1278-13.2013.
[60] P. Calabresi, B. Picconi, A. Tozzi, V. Ghiglieri, M. Di Filippo, Direct and indirect pathways of basal ganglia: a critical reappraisal, Nat. Neurosci. 17 (2014) 1022–1030, https://doi.org/10.1038/nn.3743.
[61] I. Huerta-Ocampo, J. Mena-Segovia, J.P. Bolam, Convergence of cortical and thalamic input to direct and indirect pathway medium spiny neurons in the striatum, Brain Struct. Funct. 219 (2014) 1787–1800, https://doi.org/10.1007/s00429-013-0601-z.
[62] M. Cazorla, U.J. Kang, C. Kellendonk, Balancing the basal ganglia circuitry: a possible new role for dopamine D2 receptors in health and disease, Mov. Disord. 30 (2015) 895–903, https://doi.org/10.1002/mds.26282.
[63] J. Kornhuber, M.E. Kornhuber, Presynaptic dopaminergic modulation of cortical input to the striatum, Life Sci. 39 (1986) 699–74 http://www.ncbi.nlm.nih.gov/pubmed/2874471 , Accessed date: 21 December 2018.
[64] C. Cepeda, V.M. André, E.L. Jocoy, M.S. Levine, NMDA and Dopamine: Diverse Mechanisms Applied to Interacting Receptor Systems, CRC Press/Taylor & Francis, 2009, http://www.ncbi.nlm.nih.gov/pubmed/21204414 , Accessed date: 21 December 2018.
[65] I. Ahmed, S.K. Bose, N. Pavese, A. Ramlackhansingh, F. Turkheimer, G. Hotton, A. Hammers, D.J. Brooks, Glutamate NMDA receptor dysregulation in Parkinson's disease with dyskinesias, Brain 134 (2011) 979–986, https://doi.org/10.1093/brain/awr028.
[66] J.W. Dickerson, P.J. Conn, Therapeutic potential of targeting metabotropic glutamate receptors for Parkinson's disease, Neurodegener. Dis. Manag. 2 (2012) 221–232, https://doi.org/10.2217/nmt.12.6.
[67] J.W. Błaszczyk, Parkinson's disease and neurodegeneration: GABA-collapse hypothesis, Front. Neurosci. 10 (2016) 269, https://doi.org/10.3389/fnins.2016.00269.
[68] M.J. Hurley, B. Brandon, S.M. Gentleman, D.T. Dexter, Parkinson's disease is associated with altered expression of CaV1 channels and calcium-binding proteins, Brain 136 (2013) 2077–2097, https://doi.org/10.1093/brain/awt134.
[69] M. Gerlach, W. Gsell, J. Kornhuber, K. Jellinger, V. Krieger, F. Pantucek, R. Vock, P. Riederer, A post mortem study on neurochemical markers of dopaminergic, GABA-ergic and glutamatergic neurons in basal ganglia-thalamocortical circuits in Parkinson syndrome, Brain Res. 741 (1996) 142–152, https://doi.org/10.1016/S0006-8993(96)00915-8.
[70] J.E. Rubin, C.C. McIntyre, R.S. Turner, T. Wichmann, Basal ganglia activity patterns in parkinsonism and computational modeling of their downstream effects, Eur. J. Neurosci. 36 (2012) 2213–2228, https://doi.org/10.1111/j.1460-9568.2012.08108.x.
[71] M. Ruberg, F. Rieger, A. Villageois, A.M. Bonnet, Y. Agid, Acetylcholinesterase and butyrylcholinesterase in frontal cortex and cerebrospinal fluid of demented and non-demented patients with Parkinson's disease, Brain Res. 362 (1986) 83–91 http://www.ncbi.nlm.nih.gov/pubmed/3942870 , Accessed date: 21 December 2018.
[72] N.I. Bohnen, R.L. Albin, The cholinergic system and Parkinson disease, Behav. Brain Res. 221 (2011) 564–573, https://doi.org/10.1016/j.bbr.2009.12.048.
[73] J.L.W. Bosboom, D. Stoffers, E.C. Wolters, The role of acetylcholine and dopamine in dementia and psychosis in Parkinson's disease, J. Neural Transm. Suppl (2003) 185–95 http://www.ncbi.nlm.nih.gov/pubmed/12946056 , Accessed date: 21 December 2018.
[74] T. Aosaki, M. Miura, T. Suzuki, K. Nishimura, M. Masuda, Acetylcholine-dopamine balance hypothesis in the striatum: an update, Geriatr. Gerontol. Int. 10 (2010), https://doi.org/10.1111/j.1447-0594.2010.00588.x S148–S157.
[75] G. Morris, D. Arkadir, A. Nevet, E. Vaadia, H. Bergman, Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons, Neuron 43 (2004) 133–143, https://doi.org/10.1016/j.neuron.2004.06.012.
[76] I.W. Jones, J.P. Bolam, S. Wonnacott, Presynaptic localisation of the nicotinic acetylcholine receptor beta2 subunit immunoreactivity in rat nigrostriatal dopaminergic neurones, J. Comp. Neurol. 439 (2001) 235–247 http://www.ncbi.nlm.nih.gov/pubmed/11596051 , Accessed date: 21 December 2018.
[77] G. Rizzi, K.R. Tan, Dopamine and acetylcholine, a circuit point of view in Parkinson's disease, Front. Neural Circuits 11 (2017) 110, https://doi.org/10.3389/fncir.2017.00110.
[78] Z. Qamhawi, D. Towey, B. Shah, G. Pagano, J. Seibyl, K. Marek, P. Borghammer, D.J. Brooks, N. Pavese, Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease, Brain 138 (2015) 2964–2973, https://doi.org/10.1093/brain/awv215.
[79] M. Politis, C. Loane, Serotonergic dysfunction in Parkinson's disease and its relevance to disability, ScientificWorldJournal 11 (2011) 1726–1734, https://doi.org/10.1100/2011/172893.
[80] F. Magrinelli, A. Picelli, P. Tocco, A. Federico, L. Roncari, N. Smania, G. Zanette, S. Tamburin, Pathophysiology of motor dysfunction in Parkinson's disease as the rationale for drug treatment and rehabilitation, Parkinsons. Dis. 2016 (2016) 1–18, https://doi.org/10.1155/2016/9832839.
[81] M. Hallett, Parkinson's disease tremor: pathophysiology, Park. Relat. Disord. 18 (2012), https://doi.org/10.1016/S1353-8020(11)70027-X S85–S86.
[82] M. Politis, K. Wu, C. Loane, D.J. Brooks, L. Kiferle, F.E. Turkheimer, P. Bain, S. Molloy, P. Piccini, Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients, J. Clin. Investig. 124 (2014) 1340–1349, https://doi.org/10.1172/JCI71640.
[83] I. Raote, A. Bhattacharya, M.M. Panicker, Serotonin 2A (5-HT2A) Receptor Function: Ligand-dependent Mechanisms and Pathways, CRC Press/Taylor & Francis, 2007, http://www.ncbi.nlm.nih.gov/pubmed/21204452 , Accessed date: 21 December 2018.
[84] Y. Ohno, S. Shimizu, K. Tokudome, Pathophysiological roles of serotonergic system in regulating extrapyramidal motor functions, Biol. Pharm. Bull. 36 (2013) 1396–1400 http://www.ncbi.nlm.nih.gov/pubmed/23995648 , Accessed date: 21 December 2018.
[85] P. Brundin, R. Melki, R. Kopito, Prion-like transmission of protein aggregates in neurodegenerative diseases, Nat. Rev. Mol. Cell Biol. 11 (2010) 301–307, https://doi.org/10.1038/nrm2873.
[86] D.J. Moore, A.B. West, V.L. Dawson, T.M. Dawson, Molecular pathophysiology of Parkinson's disease, Annu. Rev. Neurosci. 28 (2005) 57–87, https://doi.org/10.1146/annurev.neuro.28.061604.135718.
[87] L. Xu, J. Pu, Alpha-synuclein in Parkinson's disease: from pathogenetic dysfunction to potential clinical application, Parkinsons. Dis. 2016 (2016) 1–10, https://doi.org/10.1155/2016/1720621.
[88] A.L. Santos, A.B. Lindner, Protein posttranslational modifications: roles in aging and age-related disease, Oxid. Med. Cell. Longev. 2017 (2017) 5716409, https://doi.org/10.1155/2017/5716409.

[89] R.K. Leak, Heat shock proteins in neurodegenerative disorders and aging, J. Cell Commun. Signal. 8 (2014) 293–310, https://doi.org/10.1007/s12079-014-0243-9.

[90] C. Cook, C. Stetler, L. Petrucelli, Disruption of protein quality control in Parkinson's disease, Cold Spring Harb. Perspect. Med. 2 (2012) a009423, https://doi.org/10.1101/cshperspect.a009423.

[91] A. Bender, P. Desplats, B. Spencer, E. Rockenstein, A. Adame, M. Elstner, C. Laub, S. Mueller, A.O. Koob, M. Mante, E. Pham, T. Klopstock, E. Masliah, TOM40 mediates mitochondrial dysfunction induced by α-synuclein accumulation in Parkinson's disease, PLoS One 8 (2013) e62277, , https://doi.org/10.1371/journal.pone.0062277.

[92] M. Zaltieri, F. Longhena, M. Pizzi, C. Missale, P. Spano, A. Bellucci, Mitochondrial dysfunction and α-synuclein synaptic pathology in Parkinson's disease: who's on first? Parkinsons. Dis. 2015 (2015) 108029, https://doi.org/10.1155/2015/108029.

[93] L. Parnetti, P. Tiraboschi, A. Lanari, M. Peducci, C. Padiglioni, C. D'Amore, L. Pierguidi, N. Tambasco, A. Rossi, P. Calabresi, Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies, Biol. Psychiatry 64 (2008) 850–855, https://doi.org/10.1016/j.biopsych.2008.02.016.

[94] R.S. Weil, T.L. Lashley, J. Bras, A.E. Schrag, J.M. Schott, Current concepts and controversies in the pathogenesis of Parkinson's disease dementia and Dementia with Lewy Bodies, F1000Research. 6 (2017) 1604, https://doi.org/10.12688/f1000research.11725.1.

[95] K. Obi, H. Akiyama, H. Kondo, Y. Shimomura, M. Hasegawa, T. Iwatsubo, Y. Mizuno, H. Mochizuki, Relationship of phosphorylated α-synuclein and tau accumulation to Aβ deposition in the cerebral cortex of dementia with Lewy bodies, Exp. Neurol. 210 (2008) 409–420, https://doi.org/10.1016/j.expneurol.2007.11.019.

[96] T.M. Dawson, V.L. Dawson, The role of parkin in familial and sporadic Parkinson's disease, Mov. Disord. 25 (Suppl 1) (2010) S32–S39, https://doi.org/10.1002/mds.22798.

[97] F.P. Manfredsson, C. Burger, L.F. Sullivan, N. Muzyczka, A.S. Lewin, R.J. Mandel, rAAV-mediated nigral human parkin over-expression partially ameliorates motor deficits via enhanced dopamine neurotransmission in a rat model of Parkinson's disease, Exp. Neurol. 207 (2007) 289–301, https://doi.org/10.1016/j.expneurol.2007.06.019.

[98] H. Ariga, K. Takahashi-Niki, I. Kato, H. Maita, T. Niki, S.M.M. Iguchi-Ariga, Neuroprotective function of DJ-1 in Parkinson's disease, Oxid. Med. Cell. Longev. 2013 (2013) 683920, https://doi.org/10.1155/2013/683920.

[99] J.-Q. Li, L. Tan, J.-T. Yu, The role of the LRRK2 gene in Parkinsonism, Mol. Neurodegener. 9 (2014) 47, https://doi.org/10.1186/1750-1326-9-47.

[100] R. Marongiu, B. Spencer, L. Crews, A. Adame, C. Patrick, M. Trejo, B. Dallapiccola, E.M. Valente, E. Masliah, Mutant Pink1 induces mitochondrial dysfunction in a neuronal cell model of Parkinson's disease by disturbing calcium flux, J. Neurochem. 108 (2009) 1561–1574, https://doi.org/10.1111/j.1471-4159.2009.05932.x.

[101] C. Klein, A. Westenberger, Genetics of Parkinson's disease, Cold Spring Harb. Perspect. Med. 2 (2012) a008888, https://doi.org/10.1101/cshperspect.a008888.

[102] E.-K. Tan, L.M. Skipper, Pathogenic mutations in Parkinson disease, Hum. Mutat. 28 (2007) 641–653, https://doi.org/10.1002/humu.20507.

[103] Y. Tsuboi, Environmental-genetic interactions in the pathogenesis of Parkinson's disease, Exp. Neurobiol. 21 (2012) 123–128, https://doi.org/10.5607/en.2012.21.3.123.

[104] G. Ganguly, S. Chakrabarti, U. Chatterjee, L. Saso, Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease, Drug Des. Dev. Ther. 11 (2017) 797–810, https://doi.org/10.2147/DDDT.S130514.

[105] A.A. Cooper, A.D. Gitler, A. Cashikar, C.M. Haynes, K.J. Hill, B. Bhullar, K. Liu, K. Xu, K.E. Strathearn, F. Liu, S. Cao, K.A. Caldwell, G.A. Caldwell, G. Marsischky, R.D. Kolodner, J. Labaer, J.-C. Rochet, N.M. Bonini, S. Lindquist-, Synuclein blocks ER-golgi traffic and Rab1 rescues neuron loss in Parkinson's models, Science 313 (2006) 324–328, https://doi.org/10.1126/science.1129462 80-..

[106] W.W. Smith, H. Jiang, Z. Pei, Y. Tanaka, H. Morita, A. Sawa, V.L. Dawson, T.M. Dawson, C.A. Ross, Endoplasmic reticulum stress and mitochondrial cell death pathways mediate A53T mutant alpha-synuclein-induced toxicity, Hum. Mol. Genet. 14 (2005) 3801–3811, https://doi.org/10.1093/hmg/ddi396.

[107] E. Lindersson, R. Beedholm, P. Højrup, T. Moos, W. Gai, K.B. Hendil, P.H. Jensen, Proteasomal inhibition by α-synuclein filaments and oligomers, J. Biol. Chem. 279 (2004) 12924–12934, https://doi.org/10.1074/jbc.M306390200.

[108] P.M. Keeney, J. Xie, R.A. Capaldi, J.P. Bennett, Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled, J. Neurosci. 26 (2006) 5256–5264, https://doi.org/10.1523/JNEUROSCI.0984-06.2006.

[109] S. Shinde, K. Pasupathy, Respiratory-chain enzyme activities in isolated mitochondria of lymphocytes from patients with Parkinson's disease: preliminary study, Neurol. India 54 (2006) 390–3 http://www.ncbi.nlm.nih.gov/pubmed/17114849 , Accessed date: 21 December 2018.

[110] W.-S. Choi, R.D. Palmiter, Z. Xia, Loss of mitochondrial complex I activity potentiates dopamine neuron death induced by microtubule dysfunction in a Parkinson's disease model, J. Cell Biol. 192 (2011) 873–882, https://doi.org/10.1083/jcb.201009132.

[111] D.A. Drechsel, M. Patel, Differential contribution of the mitochondrial respiratory chain complexes to reactive oxygen species production by redox cycling agents implicated in parkinsonism, Toxicol. Sci. 112 (2009) 427–434, https://doi.org/10.1093/toxsci/kfp223.

[112] A.H. Schapira, V.M. Mann, J.M. Cooper, D. Dexter, S.E. Daniel, P. Jenner, J.B. Clark, C.D. Marsden, Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease, J. Neurochem. 55 (1990) 2142–2145 http://www.ncbi.nlm.nih.gov/pubmed/2121905 , Accessed date: 21 December 2018.

[113] J. Liu, A. Mori, Monoamine metabolism provides an antioxidant defense in the brain against oxidant- and free radical-induced damage, Arch. Biochem. Biophys. 302 (1993) 118–127, https://doi.org/10.1006/abbi.1993.1189.

[114] A. Bose, M.F. Beal, Mitochondrial dysfunction in Parkinson's disease, J. Neurochem. 139 (2016) 216–231, https://doi.org/10.1111/jnc.13731.

[115] E.N. Cronin-Furman, M.K. Borland, K.E. Bergquist, J.P. Bennett, P.A. Trimmer, Mitochondrial quality, dynamics and functional capacity in Parkinson's disease cybrid cell lines selected for Lewy body expression, Mol. Neurodegener. 8 (2013) 6, https://doi.org/10.1186/1750-1326-8-6.

[116] D.M. Arduíno, A.R. Esteves, R.H. Swerdlow, S.M. Cardoso, A cybrid cell model for the assessment of the link between mitochondrial deficits and sporadic Parkinson's disease, Methods Mol. Biol. 1265 (2015) 415–424, https://doi.org/10.1007/978-1-4939-2288-8_31.

[117] E. Naik, V.M. Dixit, Mitochondrial reactive oxygen species drive proinflammatory cytokine production, J. Exp. Med. 208 (2011) 417–420, https://doi.org/10.1084/jem.20110367.

[118] A.D. Cherry, C.A. Piantadosi, Regulation of mitochondrial biogenesis and its intersection with inflammatory responses, Antioxidants Redox Signal. 22 (2015) 965–976, https://doi.org/10.1089/ars.2014.6200.

[119] G. Boka, P. Anglade, D. Wallach, F. Javoy-Agid, Y. Agid, E.C. Hirsch, Immunocytochemical analysis of tumor necrosis factor and its receptors in Parkinson's disease, Neurosci. Lett. 172 (1994) 151–154 http://www.ncbi.nlm.nih.gov/pubmed/8084523 , Accessed date: 21 December 2018.

[120] M. Mogi, M. Harada, T. Kondo, P. Riederer, H. Inagaki, M. Minami, T. Nagatsu, Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients, Neurosci. Lett. 180 (1994) 147–150 http://www.ncbi.nlm.nih.gov/pubmed/7700568 , Accessed date: 21 December 2018.

[121] Y. Ouchi, E. Yoshikawa, Y. Sekine, M. Futatsubashi, T. Kanno, T. Ogusu, T. Torizuka, Microglial activation and dopamine terminal loss in early Parkinson's disease, Ann. Neurol. 57 (2005) 168–175, https://doi.org/10.1002/ana.20338.

[122] B.S. Connolly, A.E. Lang, Pharmacological treatment of Parkinson disease, J. Am. Med. Assoc. 311 (2014) 1670, https://doi.org/10.1001/jama.2014.3654.

[123] J. Zhang, L.C.-S. Tan, Revisiting the medical management of Parkinson's disease: levodopa versus dopamine agonist, Curr. Neuropharmacol. 14 (2016) 356–363, https://doi.org/10.2174/1570159X14666151208114634.

[124] L. Dezsi, L. Vecsei, Monoamine oxidase B inhibitors in Parkinson's disease, CNS Neurol. Disord. - Drug Targets 16 (2017) 425–439, https://doi.org/10.2174/1871527316666170124165222.

[125] T.M. Axelsen, D.P.D. Woldbye, Gene therapy for Parkinson's disease, an update, J. Parkinson's Dis. 8 (2018) 195–215, https://doi.org/10.3233/JPD-181331.

[126] L. V Kalia, A.E. Lang, Parkinson's disease, Lancet 386 (2015) 896–912, https://doi.org/10.1016/S0140-6736(14)61393-3.

[127] A.K. Admani, S. Verma, G.J. Cordingley, R.I. Harris, Patient benefits of l-dopa and a decarboxylase inhibitor in the treatment of Parkinson's disease in elderly patients, Pharmatherapeutica 4 (1985) 132–140 http://www.ncbi.nlm.nih.gov/pubmed/4059292 , Accessed date: 21 December 2018.

[128] R. Fackrell, C.B. Carroll, D.G. Grosset, B. Mohamed, P. Reddy, M. Parry, K.R. Chaudhuri, T. Foltynie, Noninvasive options for 'wearing-off' in Parkinson's disease: a clinical consensus from a panel of UK Parkinson's disease specialists, Neurodegener. Dis. Manag. 8 (2018) 349–360, https://doi.org/10.2217/nmt-2018-0020.

[129] I.A. Prescott, J.O. Dostrovsky, E. Moro, M. Hodaie, A.M. Lozano, W.D. Hutchison, Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients, Brain 132 (2009) 309–318, https://doi.org/10.1093/brain/awn322.

[130] B. Picconi, V. Paillé, V. Ghiglieri, V. Bagetta, I. Barone, H.S. Lindgren, G. Bernardi, M. Angela Cenci, P. Calabresi, l-DOPA dosage is critically involved in dyskinesia via loss of synaptic depotentiation, Neurobiol. Dis. 29 (2008) 327–335, https://doi.org/10.1016/j.nbd.2007.10.001.

[131] A.Y. Deutch, R.J. Colbran, D.J. Winder, Striatal plasticity and medium spiny neuron dendritic remodeling in parkinsonism, Park. Relat. Disord. 13 (2007), https://doi.org/10.1016/S1353-8020(08)70012-9 S251–S258.

[132] C. DiCaudo, M. Riverol, I.-C. Mundiñano, C. Ordoñez, M. Hernández, I. Marcilla, M.-R. Luquin, Chronic levodopa administration followed by a washout period increased number and induced phenotypic changes in striatal dopaminergic cells in MPTP-monkeys, PLoS One 7 (2012) e50842, , https://doi.org/10.1371/journal.pone.0050842.

[133] Y. Zhang, G.E. Meredith, N. Mendoza-Elias, D.J. Rademacher, K.Y. Tseng, K. Steece-Collier, Aberrant restoration of spines and their synapses in L-DOPA-induced dyskinesia: involvement of corticostriatal but not thalamostriatal synapses, J. Neurosci. 33 (2013) 11655–11667, https://doi.org/10.1523/JNEUROSCI.0288-13.2013.

[134] H. Nishijima, S. Suzuki, T. Kon, Y. Funamizu, T. Ueno, R. Haga, C. Suzuki, A. Arai, T. Kimura, C. Suzuki, R. Meguro, Y. Miki, J. Yamada, K. Migita, N. Ichinohe, S. Ueno, M. Baba, M. Tomiyama, Morphologic changes of dendritic spines of striatal neurons in the levodopa-induced dyskinesia model, Mov. Disord. 29 (2014) 336–343, https://doi.org/10.1002/mds.25826.

[135] D. Rylander, M. Parent, S.S. O'Sullivan, S. Dovero, A.J. Lees, E. Bezard, L. Descarries, M.A. Cenci, Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia, Ann. Neurol. 68 (2010) 619–628, https://doi.org/10.1002/ana.22097.

[136] B.J. Stansley, B.K. Yamamoto, L-dopa and brain serotonin system dysfunction, Toxics 3 (2015) 75–88, https://doi.org/10.3390/toxics3010075.

[137] F. Stocchi, Optimising levodopa therapy for the management of Parkinson's disease, J. Neurol. 252 (2005), https://doi.org/10.1007/s00415-005-4009-4 iv43–iv48.

[138] S.-M. Aquilonius, D. Nyholm, Development of new levodopa treatment strategies in Parkinson's disease—from bedside to bench to bedside, Upsala J. Med. Sci. 122 (2017) 71–77, https://doi.org/10.1080/03009734.2017.1285374.

[139] U. Bonuccelli, N. Pavese, Dopamine agonists in the treatment of Parkinson's disease, Expert Rev. Neurother. 6 (2006) 81–89, https://doi.org/10.1586/14737175.6.1.81.

[140] O.K. Sujith, C. Lane, Therapeutic options for continuous dopaminergic stimulation in Parkinson's disease, Ther. Adv. Neurol. Disord. 2 (2009) 105–113, https://doi.org/10.1177/1756285608101378.

[141] D.J. Brooks, Dopamine agonists: their role in the treatment of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 68 (2000) 685–689, https://doi.org/10.1136/JNNP.68.6.685.

[142] V.G. Rasmussen, S.H. Poulsen, E. Dupont, K. Østergaard, G. Safikhany, H. Egeblad, Heart valve disease associated with treatment with ergot-derived dopamine agonists: a clinical and echocardiographic study of patients with Parkinson's disease, J. Intern. Med. 0 (2007) 07112716544900 3-???, , https://doi.org/10.1111/j.1365-2796.2007.01874.x.

[143] G. Van Camp, A. Flamez, B. Cosyns, C. Weytjens, L. Muyldermans, M. Van Zandijcke, J. De Sutter, P. Santens, P. Decoodt, C. Moerman, D. Schoors, Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease, Lancet 363 (2004) 1179–1183, https://doi.org/10.1016/S0140-6736(04)15945-X.

[144] S. Junghanns, J.T. Fuhrmann, G. Simonis, C. Oelwein, R. Koch, R.H. Strasser, H. Reichmann, A. Storch, Valvular heart disease in Parkinson's disease patients treated with dopamine agonists: a reader-blinded monocenter echocardiography study, Mov. Disord. 22 (2007) 234–237, https://doi.org/10.1002/mds.21225.

[145] F. Stocchi, B.P. Hersh, B.L. Scott, P.A. Nausieda, L. Giorgi, Ease-PD Monotherapy Study Investigators, Ropinirole 24-hour prolonged release and ropinirole immediate release in early Parkinson's disease: a randomized, double-blind, non-inferiority crossover study, Curr. Med. Res. Opin. 24 (2008) 2883–2895, https://doi.org/10.1185/03007990802387130.

[146] W. Poewe, G.K. Wenning, Apomorphine: an underutilized therapy for Parkinson's disease, Mov. Disord. 15 (2000) 789–794 http://www.ncbi.nlm.nih.gov/pubmed/11009181 , Accessed date: 21 December 2018.

[147] R. Constantinescu, M. Romer, M.P. McDermott, C. Kamp, K. Kieburtz, CALM-PD Investigators of the Parkinson Study Group, Impact of pramipexole on the onset of levodopa-related dyskinesias, Mov. Disord. 22 (2007) 1317–1319, https://doi.org/10.1002/mds.21292.

[148] R.A. Hauser, L. Gauger, W.M. Anderson, T.A. Zesiewicz, Pramipexole-induced somnolence and episodes of daytime sleep, Mov. Disord. 15 (2000) 658–663 http://www.ncbi.nlm.nih.gov/pubmed/10928575 , Accessed date: 21 December 2018.

[149] J.A. Borovac, Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology, Yale J. Biol. Med. 89 (2016) 37–47 http://www.ncbi.nlm.nih.gov/pubmed/27505015 , Accessed date: 21 December 2018.

[150] K. Wenzel, C.N. Homann, G. Fabbrini, C. Colosimo, The role of subcutaneous infusion of apomorphine in Parkinson's disease, Expert Rev. Neurother. 14 (2014) 833–843, https://doi.org/10.1586/14737175.2014.928202.

[151] P.A. LeWitt, W.G. Ondo, B. Van Lunen, P.B. Bottini, Open-label study assessment of safety and adverse effects of subcutaneous apomorphine injections in treating "off" episodes in advanced Parkinson disease., Clin. Neuropharmacol.. 32 (n.d.) 89–93. doi:10.1097/WNF.0B013E31816D91F9.

[152] B. Nilesh, H. Sharwaree, B. Ashok, Formulation and evaluation of transdermal patches of ropinirole HCl, n.d. https://www.rjpbcs.com/pdf/2011_2(1)/18.pdf , Accessed date: 21 December 2018.

[153] M. Braun, W. Cawello, J.-O. Andreas, D. Math, H. Boekens, R. Horstmann, Lack of pharmacokinetic interactions between transdermal rotigotine and oral levodopa/carbidopa, J. Clin. Pharmacol. 49 (2009) 1047–1055, https://doi.org/10.1177/0091270009338481.

[154] M. Rosa-Grilo, M.A. Qamar, R.N. Taddei, J. Pagonabarraga, J. Kulisevsky, A. Sauerbier, K.R. Chaudhuri, Rotigotine transdermal patch and sleep in Parkinson's disease: where are we now? Npj Park. Dis. 3 (2017) 28, https://doi.org/10.1038/s41531-017-0030-4.

[155] R.A. Hauser, R. Pahwa, W.A. Wargin, C.J. Souza-Prien, N. McClure, R. Johnson, J.T. Nguyen, R. Patni, G.T. Went, Pharmacokinetics of ADS-5102 (amantadine) extended release capsules administered once daily at bedtime for the treatment of dyskinesia, Clin. Pharmacokinet. (2018), https://doi.org/10.1007/s40262-018-0663-4.

[156] G. Hubsher, M. Haider, M.S. Okun, Amantadine: the journey from fighting flu to treating Parkinson disease, Neurology 78 (2012) 1096–1099, https://doi.org/10.1212/WNL.0b013e31824e8f0d.

[157] K. Mizoguchi, H. Yokoo, M. Yoshida, T. Tanaka, M. Tanaka, Amantadine increases the extracellular dopamine levels in the striatum by re-uptake inhibition and by N-methyl-D-aspartate antagonism, Brain Res. 662 (1994) 255–258 http://www.ncbi.nlm.nih.gov/pubmed/7859080 , Accessed date: 21 December 2018.

[158] R. Pahwa, C.M. Tanner, R.A. Hauser, K. Sethi, S. Isaacson, D. Truong, L. Struck, A.E. Ruby, N.L. McClure, G.T. Went, M.J. Stempien, Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study), Mov. Disord. 30 (2015) 788–795, https://doi.org/10.1002/mds.26159.

[159] M. Bera, B. Okyere, J. Vova, Amantadine induced corneal edema in a pediatric patient, Arch. Phys. Med. Rehabil. 98 (2017), https://doi.org/10.1016/J.APMR.2017.08.098 e31–e32.

[160] F. Marxreiter, J. Winkler, M. Uhl, D. Madžar, A case report of severe delirium after amantadine withdrawal, Case Rep. Neurol. 9 (2017) 44–48, https://doi.org/10.1159/000460814.

[161] T. Nagatsu, M. Sawada, Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson's disease: possible implications of glial cells, J. Neural Transm. Suppl (2006) 53–65 http://www.ncbi.nlm.nih.gov/pubmed/17447416 , Accessed date: 21 December 2018.

[162] E. Cereda, R. Cilia, M. Canesi, S. Tesei, C.B. Mariani, A.L. Zecchinelli, G. Pezzoli, Efficacy of rasagiline and selegiline in Parkinson's disease: a head-to-head 3-year retrospective case-control study, J. Neurol. 264 (2017) 1254–1263, https://doi.org/10.1007/s00415-017-8523-y.

[163] C. Peretz, H. Segev, V. Rozani, T. Gurevich, B. El-Ad, J. Tsamir, N. Giladi, Comparison of selegiline and rasagiline therapies in Parkinson disease: a real-life study, Clin. Neuropharmacol. 39 (2016) 227–231, https://doi.org/10.1097/WNF.0000000000000167.

[164] I. Shoulson, D. Oakes, S. Fahn, A. Lang, J.W. Langston, P. LeWitt, C.W. Olanow, J.B. Penney, C. Tanner, K. Kieburtz, A. RudolphParkinson Study Group, Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial, Ann. Neurol. 51 (2002) 604–612, https://doi.org/10.1002/ana.10191.

[165] S.H. Fox, R. Katzenschlager, S.-Y. Lim, B. Barton, R.M.A. de Bie, K. Seppi, M. Coelho, C. Sampaio, Movement Disorder Society Evidence-Based Medicine Committee, International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease, Mov. Disord. 33 (2018) 1248–1266, https://doi.org/10.1002/mds.27372.

[166] K. Kanellakopoulou, E.J. Giamarellos-Bourboulis, Carrier systems for the local delivery of antibiotics in bone infections, Drugs 59 (2000) 1223–1232, https://doi.org/10.2165/00003495-200059060-00003.

[167] M.J. Bonifácio, P.N. Palma, L. Almeida, P. Soares-da-Silva, Catechol-O-methyltransferase and its inhibitors in Parkinson's disease, CNS Drug Rev. 13 (2007) 352–379, https://doi.org/10.1111/j.1527-3458.2007.00020.x.

[168] A. Kumar, A. Tan, J. Wong, J.C. Spagnoli, J. Lam, B.D. Blevins, N.G.L. Thorne, K. Ashkan, J. Xie, H. Liu, Nanotechnology for neuroscience: promising approaches for diagnostics, therapeutics and brain activity mapping, Adv. Funct. Mater. 27 (2017) 1700489, https://doi.org/10.1002/adfm.201700489.

[169] A. Chowdhury, S. Kunjiappan, T. Panneerselvam, B. Somasundaram, C. Bhattacharjee, Nanotechnology and nanocarrier-based approaches on treatment of degenerative diseases, Int. Nano Lett. 7 (2017) 91–122, https://doi.org/10.1007/s40089-017-0208-0.

[170] W.M. Pardridge, The blood-brain barrier: bottleneck in brain drug development, NeuroRx 2 (2005) 3–14, https://doi.org/10.1602/neurorx.2.1.3.

[171] R.K. Upadhyay, Transendothelial transport and its role in therapeutics, Int. Sch. Res. Not. 2014 (2014) 309404, https://doi.org/10.1155/2014/309404.

[172] J. Rautio, K. Laine, M. Gynther, J. Savolainen, Prodrug approaches for CNS delivery, AAPS J. 10 (2008) 92–102, https://doi.org/10.1208/s12248-008-9009-8.

[173] M.S. Alavijeh, M. Chishty, M.Z. Qaiser, A.M. Palmer, Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery, NeuroRx 2 (2005) 554–571, https://doi.org/10.1602/neurorx.2.4.554.

[174] M. Yemisci, S. Caban, Y. Gursoy-Ozdemir, S. Lule, R. Novoa-Carballal, R. Riguera, E. Fernandez-Megia, K. Andrieux, P. Couvreur, Y. Capan, T. Dalkara, Systemically administered brain-targeted nanoparticles transport peptides across the blood—brain barrier and provide neuroprotection, J. Cereb. Blood Flow Metab. 35 (2015) 469–475, https://doi.org/10.1038/jcbfm.2014.220.

[175] A. Zensi, D. Begley, C. Pontikis, C. Legros, L. Mihoreanu, S. Wagner, C. Büchel, H. von Briesen, J. Kreuter, Albumin nanoparticles targeted with Apo E enter the CNS by transcytosis and are delivered to neurones, J. Control. Release 137 (2009) 78–86, https://doi.org/10.1016/j.jconrel.2009.03.002.

[176] P.R. Lockman, R.J. Mumper, M.A. Khan, D.D. Allen, Nanoparticle technology for drug delivery across the blood-brain barrier, Drug Dev. Ind. Pharm. 28 (2002) 1–13, https://doi.org/10.1081/DDC-120001481.

[177] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (2015) 941–951, https://doi.org/10.1038/nbt.3330.

[178] J.M. de la Fuente, V. Grazu, Nanobiotechnology Inorganic Nanoparticles vs Organic Nanoparticles, (2012) https://www.researchgate.net/profile/Africa_Gonzalez-Fernandez/publication/258554478_Nanotoxicology/links/0fcfd50b8ffdb822b1000000/Nanotoxicology.pdf , Accessed date: 21 December 2018.

[179] C. Medina, M.J. Santos-Martinez, A. Radomski, O.I. Corrigan, M.W. Radomski, Nanoparticles: pharmacological and toxicological significance, Br. J. Pharmacol. 150 (2007) 552–558, https://doi.org/10.1038/sj.bjp.0707130.

[180] M. Alavi, N. Karimi, M. Safaei, Application of various types of liposomes in drug delivery systems, Adv. Pharmaceut. Bull. 7 (2017) 3–9, https://doi.org/10.15171/apb.2017.002.

[181] A.S. Abu Lila, T. Ishida, Liposomal delivery systems: design optimization and current applications, Biol. Pharm. Bull. 40 (2017) 1–10, https://doi.org/10.1248/bpb.b16-00624.

[182] A. Puri, K. Loomis, B. Smith, J.-H. Lee, A. Yavlovich, E. Heldman, R. Blumenthal, Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic, Crit. Rev. Ther. Drug Carrier Syst. 26 (2009) 523–580 http://www.ncbi.nlm.nih.gov/pubmed/20402623 , Accessed date: 21 December 2018.

[183] M. Ramasamy, J. Lee, Recent nanotechnology approaches for prevention and treatment of biofilm-associated infections on medical devices, BioMed Res. Int.

2016 (2016) 1851242, https://doi.org/10.1155/2016/1851242.
[184] C. Hassler, T. Boretius, T. Stieglitz, Polymers for neural implants, J. Polym. Sci., Part B: Polym. Phys. 49 (2011) 18–33, https://doi.org/10.1002/polb.22169.
[185] C.-H. Lee, D. Kasala, Y. Na, M.S. Lee, S.W. Kim, J.H. Jeong, C.-O. Yun, Enhanced therapeutic efficacy of an adenovirus-PEI-bile-acid complex in tumors with low coxsackie and adenovirus receptor expression, Biomaterials 35 (2014) 5505–5516, https://doi.org/10.1016/j.biomaterials.2014.03.060.
[186] D. Zhong, Y. Jiao, Y. Zhang, W. Zhang, N. Li, Q. Zuo, Q. Wang, W. Xue, Z. Liu, Effects of the gene carrier polyethyleneimines on structure and function of blood components, Biomaterials 34 (2013) 294–305, https://doi.org/10.1016/j.biomaterials.2012.09.060.
[187] M.S. Gunay, A.Y. Ozer, S. Chalon, Drug delivery systems for imaging and therapy of Parkinson's disease, Curr. Neuropharmacol. 14 (2016) 376–391, https://doi.org/10.2174/1570159X14666151230124904.
[188] G.H. Hawthorne, M.P. Bernuci, M. Bortolanza, V. Tumas, A.C. Issy, E. Del-Bel, Nanomedicine to overcome current Parkinson's treatment liabilities: a systematic review, Neurotox. Res. 30 (2016) 715–729, https://doi.org/10.1007/s12640-016-9663-z.
[189] I. Posadas, S. Monteagudo, V. Ceña, Nanoparticles for brain-specific drug and genetic material delivery, imaging and diagnosis, Nanomedicine 11 (2016) 833–849, https://doi.org/10.2217/nnm.16.15.
[190] C.J.H. Porter, N.L. Trevaskis, W.N. Charman, Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs, Nat. Rev. Drug Discov. 6 (2007) 231–248, https://doi.org/10.1038/nrd2197.
[191] R. Singh, H.S. Nalwa, Medical applications of nanoparticles in biological imaging, cell labeling, antimicrobial agents, and anticancer nanodrugs, J. Biomed. Nanotechnol. 7 (2011) 489–503 http://www.ncbi.nlm.nih.gov/pubmed/21870454 , Accessed date: 21 December 2018.
[192] L. Sercombe, T. Veerati, F. Moheimani, S.Y. Wu, A.K. Sood, S. Hua, Advances and challenges of liposome assisted drug delivery, Front. Pharmacol. 6 (2015) 286, https://doi.org/10.3389/fphar.2015.00286.
[193] J. Li, X. Wang, T. Zhang, C. Wang, Z. Huang, X. Luo, Y. Deng, A review on phospholipids and their main applications in drug delivery systems, Asian J. Pharm. Sci. 10 (2015) 81–98, https://doi.org/10.1016/J.AJPS.2014.09.004.
[194] A. Akbarzadeh, R. Rezaei-Sadabady, S. Davaran, S.W. Joo, N. Zarghami, Y. Hanifehpour, M. Samiei, M. Kouhi, K. Nejati-Koshki, Liposome: classification, preparation, and applications, Nanoscale Res. Lett. 8 (2013) 102, https://doi.org/10.1186/1556-276X-8-102.
[195] P.R. Cullis, L.D. Mayer, M.B. Bally, T.D. Madden, M.J. Hope, Generating and loading of liposomal systems for drug-delivery applications, Adv. Drug Deliv. Rev. 3 (1989) 267–282, https://doi.org/10.1016/0169-409X(89)90024-0.
[196] V.P. Torchilin, V. Weissig, Liposomes : a Practical Approach, Oxford University Press, 2003, https://global.oup.com/academic/product/liposomes-a-practical-approach-9780199636549?cc=kr&lang=en& , Accessed date: 21 December 2018.
[197] U. Bulbake, S. Doppalapudi, N. Kommineni, W. Khan, Liposomal formulations in clinical use: an updated review, Pharmaceutics 9 (2017) 12, https://doi.org/10.3390/pharmaceutics9020012.
[198] A. Schnyder, J. Huwyler, Drug transport to brain with targeted liposomes, NeuroRx 2 (2005) 99–107, https://doi.org/10.1602/neurorx.2.1.99.
[199] M.J. During, A. Freese, A.Y. Deutch, P.G. Kibat, B.A. Sabel, R. Langer, R.H. Roth, Biochemical and behavioral recovery in a rodent model of Parkinson's disease following stereotactic implantation of dopamine-containing liposomes, Exp. Neurol. 115 (1992) 193–199, https://doi.org/10.1016/0014-4886(92)90053-S.
[200] I.V. Zhigaltsev, A.P. Kaplun, V.G. Kucheryanu, G.N. Kryzhanovsky, S.N. Kolomeichuk, V.I. Shvets, V.V. Yurasov, Liposomes containing dopamine entrapped in response to transmembrane ammonium sulfate gradient as carrier system for dopamine delivery into the brain of parkinsonian mice, J. Liposome Res. 11 (2001) 55–71, https://doi.org/10.1081/LPR-100103170.
[201] N.K. Jain, A.C. Rana, S.K. Jain, Brain drug delivery system bearing dopamine hydrochloride for effective management of parkinsonism, Drug Dev. Ind. Pharm. 24 (1998) 671–675, https://doi.org/10.3109/03639049809082370.
[202] P. Khare, A. Jain, N.K. Jain, V. Soni, S.K. Jain, Glutamate-conjugated liposomes of dopamine hydrochloride for effective management of parkinsonism's., PDA J. Pharm. Sci. Technol. 63 (n.d.) 372-9. http://www.ncbi.nlm.nih.gov/pubmed/20158043 (accessed December 21, 2018).
[203] D.D. Lasic, D. Needham, The "stealth" liposome: a prototypical biomaterial, Chem. Rev. 95 (1995) 2601–2628, https://doi.org/10.1021/cr00040a001.
[204] M.L. Immordino, F. Dosio, L. Cattel, Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential, Int. J. Nanomed. 1 (2006) 297–315 http://www.ncbi.nlm.nih.gov/pubmed/17717971 , Accessed date: 21 December 2018.
[205] Y.-S. Kang, H.-J. Jung, J.-S. Oh, D.-Y. Song, Use of PEGylated immunoliposomes to deliver dopamine across the blood-brain barrier in a rat model of Parkinson's disease, CNS Neurosci. Ther. 22 (2016) 817–823, https://doi.org/10.1111/cns.12580.
[206] A. Lopalco, A. Cutrignelli, N. Denora, A. Lopedota, M. Franco, V. Laquintana, Transferrin functionalized liposomes loading dopamine HCl: development and permeability studies across an in vitro model of human blood–brain barrier, Nanomaterials 8 (2018) 178, https://doi.org/10.3390/nano8030178.
[207] K.J. Black, J.L. Carl, J.M. Hartlein, S.L. Warren, T. Hershey, J.S. Perlmutter, Rapid intravenous loading of levodopa for human research: clinical results, J. Neurosci. Methods 127 (2003) 19–29 http://www.ncbi.nlm.nih.gov/pubmed/12865145 , Accessed date: 21 December 2018.
[208] D.G. Waller, A.P. Sampson, D.G. Waller, A.P. Sampson, Extrapyramidal movement disorders and spasticity, Med. Pharmacol. Ther. (2018) 325–336, https://doi.org/10.1016/B978-0-7020-7167-6.00024-5.
[209] A. Di Stefano, P. Sozio, A. Iannitelli, C. Marianecci, E. Santucci, M. Carafa, Maleic- and fumaric-diamides of (O,O-diacetyl)-L-dopa-methylester as anti-Parkinson prodrugs in liposomal formulation, J. Drug Target. 14 (2006) 652–661, https://doi.org/10.1080/10611860600916636.
[210] Y. Xiang, Q. Wu, L. Liang, X. Wang, J. Wang, X. Zhang, X. Pu, Q. Zhang, Chlorotoxin-modified stealth liposomes encapsulating levodopa for the targeting delivery against the Parkinson's disease in the MPTP-induced mice model, J. Drug Target. 20 (2012) 67–75, https://doi.org/10.3109/1061186X.2011.595490.
[211] Y. Li, Y. Zhou, B. Qi, T. Gong, X. Sun, Y. Fu, Z. Zhang, Brain-specific delivery of dopamine mediated by *N* , *N* -dimethyl amino group for the treatment of Parkinson's disease, Mol. Pharm. 11 (2014) 3174–3185, https://doi.org/10.1021/mp500352p.
[212] M. Carafa, C. Marianecci, L. Di Marzio, V. De Caro, G. Giandalia, L.I. Giannola, E. Santucci, Potential dopamine prodrug-loaded liposomes: preparation, characterization, and *in vitro* stability studies, J. Liposome Res. 20 (2010) 250–257, https://doi.org/10.3109/08982100903384129.
[213] M. Qu, Q. Lin, S. He, L. Wang, Y. Fu, Z. Zhang, L. Zhang, A brain targeting functionalized liposomes of the dopamine derivative N -3,4-bis(pivaloyloxy)-dopamine for treatment of Parkinson's disease, J. Control. Release 277 (2018) 173–182, https://doi.org/10.1016/j.jconrel.2018.03.019.
[214] M.J. Bourque, L.E. Trudeau, GDNF enhances the synaptic efficacy of dopaminergic neurons in culture, Eur. J. Neurosci. 12 (2000) 3172–3180 http://www.ncbi.nlm.nih.gov/pubmed/10998101 , Accessed date: 21 December 2018.
[215] C.-F. Xia, R.J. Boado, Y. Zhang, C. Chu, W.M. Pardridge, Intravenous glial-derived neurotrophic factor gene therapy of experimental Parkinson's disease with Trojan horse liposomes and a tyrosine hydroxylase promoter, J. Gene Med. 10 (2008) 306–315, https://doi.org/10.1002/jgm.1152.
[216] C.-Y. Lin, H.-Y. Hsieh, W.G. Pitt, C.-Y. Huang, I.-C. Tseng, C.-K. Yeh, K.-C. Wei, H.-L. Liu, Focused ultrasound-induced blood-brain barrier opening for non-viral, non-invasive, and targeted gene delivery, J. Control. Release 212 (2015) 1–9, https://doi.org/10.1016/j.jconrel.2015.06.010.
[217] W. Fu, W. Zhuang, S. Zhou, X. Wang, Plant-derived neuroprotective agents in Parkinson's disease, Am. J. Transl. Res. 7 (2015) 1189–1202 http://www.ncbi.nlm.nih.gov/pubmed/26328004 , Accessed date: 21 December 2018.
[218] Z.E. Suntres, Liposomal antioxidants for protection against oxidant-induced damage, J. Toxicol. 2011 (2011) 152474, https://doi.org/10.1155/2011/152474.
[219] G.D. Zeevalk, L.P. Bernard, F.T. Guilford, Liposomal-glutathione provides maintenance of intracellular glutathione and neuroprotection in mesencephalic neuronal cells, Neurochem. Res. 35 (2010) 1575–1587, https://doi.org/10.1007/s11064-010-0217-0.
[220] D'Arrigo Joseph, LCM and nanoparticle subpopulations for drug delivery, Stud. Interface Sci. 25 (2011) 223–228, https://doi.org/10.1016/B978-0-444-53798-0.00018-3.
[221] C.D. Pizzol, F.B. Filippin-Monteiro, J.A.S. Restrepo, F. Pittella, A.H. Silva, P. Alves de Souza, A. Machado de Campos, T.B. Creczynski-Pasa, Influence of surfactant and lipid type on the physicochemical properties and biocompatibility of solid lipid nanoparticles, Int. J. Environ. Res. Public Health 11 (2014) 8581–8596, https://doi.org/10.3390/ijerph110808581.
[222] A. Zielińska, I. Nowak, Solid lipid nanoparticles and nanostructured lipid carriers as novel carriers for cosmetic ingredients, Nanobiomaterials Galen. Formul. Cosmet. (2016) 231–255, https://doi.org/10.1016/B978-0-323-42868-2.00010-3.
[223] I. Cacciatore, M. Ciulla, E. Fornasari, L. Marinelli, A. Di Stefano, Solid lipid nanoparticles as a drug delivery system for the treatment of neurodegenerative diseases, Expert Opin. Drug Deliv. 13 (2016) 1121–1131, https://doi.org/10.1080/17425247.2016.1178237.
[224] L. Becker Peres, L. Becker Peres, P.H.H. de Araújo, C. Sayer, Solid lipid nanoparticles for encapsulation of hydrophilic drugs by an organic solvent free double emulsion technique, Colloids Surfaces B Biointerfaces 140 (2016) 317–323, https://doi.org/10.1016/j.colsurfb.2015.12.033.
[225] J. Ezzati Nazhad Dolatabadi, H. Hamishehkar, H. Valizadeh, Development of dry powder inhaler formulation loaded with alendronate solid lipid nanoparticles: solid-state characterization and aerosol dispersion performance, Drug Dev. Ind. Pharm. 41 (2015) 1431–1437, https://doi.org/10.3109/03639045.2014.956111.
[226] Z. Bakhtiary, J. Barar, A. Aghanejad, A.A. Saei, E. Nemati, J. Ezzati Nazhad Dolatabadi, Y. Omidi, Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer, Drug Dev. Ind. Pharm. 43 (2017) 1244–1253, https://doi.org/10.1080/03639045.2017.1310223.
[227] E. Nemati, A. Mokhtarzadeh, V. Panahi-Azar, A. Mohammadi, H. Hamishehkar, M. Mesgari-Abbasi, J. Ezzati Nazhad Dolatabadi, M. de la Guardia, Ethambutol-loaded solid lipid nanoparticles as dry powder inhalable formulation for tuberculosis therapy, AAPS PharmSciTech 20 (2019), https://doi.org/10.1208/s12249-019-1334-y.
[228] L. Battaglia, M. Gallarate, P.P. Panciani, E. Ugazio, S. Sapino, E. Peira, D. Chirio, Techniques for the preparation of solid lipid nano and microparticles, Appl. Nanotechnol. Drug Deliv. InTech, 2014, , https://doi.org/10.5772/58405.
[229] G. Amoabediny, F. Haghiralsadat, S. Naderinezhad, M.N. Helder, E. Akhoundi Kharanaghi, J. Mohammadnejad Arough, B. Zandieh-Doulabi, Overview of preparation methods of polymeric and lipid-based (niosome, solid lipid, liposome) nanoparticles: a comprehensive review, Int. J. Polym. Mater. Polym. Biomater. 67 (2018) 383–400, https://doi.org/10.1080/00914037.2017.1332623.
[230] M.M. Demirel, Y. Yazan, R.H. Müller, Y. Yazan, R.H. Müller, F. Kiliç, B. Bozan, Formulation and in vitro and in vivo evaluation of piribedil solid lipid micro- and nanoparticles, J. Microencapsul. 18 (2001) 359–371, https://doi.org/10.1080/02652040010018119.
[231] E. Esposito, M. Fantin, M. Marti, M. Drechsler, L. Paccamiccio, P. Mariani,

E. Sivieri, F. Lain, E. Menegatti, M. Morari, R. Cortesi, Solid lipid nanoparticles as delivery systems for bromocriptine, Pharm. Res. 25 (2008) 1521–1530, https://doi.org/10.1007/s11095-007-9514-y.
[232] M.-J. Tsai, Y.-B. Huang, P.-C. Wu, Y.-S. Fu, Y.-R. Kao, J.-Y. Fang, Y.-H. Tsai, Oral apomorphine delivery from solid lipid nanoparticles with different monostearate emulsifiers: pharmacokinetic and behavioral evaluations, J. Pharm. Sci. 100 (2011) 547–557, https://doi.org/10.1002/jps.22285.
[233] W.H. Jost, D. Angersbach, Ropinirole, a non-ergoline dopamine agonist, CNS Drug Rev. 11 (2006) 253–272, https://doi.org/10.1111/j.1527-3458.2005.tb00046.x.
[234] C.V. Pardeshi, P.V. Rajput, V.S. Belgamwar, A.R. Tekade, S.J. Surana, Novel surface modified solid lipid nanoparticles as intranasal carriers for ropinirole hydrochloride: application of factorial design approach, Drug Deliv. 20 (2013) 47–56, https://doi.org/10.3109/10717544.2012.752421.
[235] R.H. Müller, U. Alexiev, P. Sinambela, C.M. Keck, Nanostructured lipid carriers (NLC): the second generation of solid lipid nanoparticles, Percutaneous Penetration Enhanc. Chem. Methods Penetration Enhanc. Springer Berlin Heidelberg, Berlin, Heidelberg, 2016, pp. 161–185, , https://doi.org/10.1007/978-3-662-47862-2_11.
[236] A. Beloqui, M.Á. Solinís, A. Rodríguez-Gascón, A.J. Almeida, V. Préat, Nanostructured lipid carriers: promising drug delivery systems for future clinics, Nanomed. Nanotechnol. Biol. Med. 12 (2016) 143–161, https://doi.org/10.1016/J.NANO.2015.09.004.
[237] J. Ezzati Nazhad Dolatabadi, A. Azami, A. Mohammadi, H. Hamishehkar, V. Panahi-Azar, Y. Rahbar Saadat, A.A. Saei, Formulation, characterization and cytotoxicity evaluation of ketotifen-loaded nanostructured lipid carriers, J. Drug Deliv. Sci. Technol. 46 (2018) 268–273, https://doi.org/10.1016/j.jddst.2018.05.017.
[238] I.D.L. de Souza, V. Saez, V.E.B. de Campos, C.R.E. Mansur, Size and vitamin E release of nanostructured lipid carriers with different liquid lipids, surfactants and preparation methods, Macromol. Symp. 383 (2019) 1800011, https://doi.org/10.1002/masy.201800011.
[239] A. Khosa, S. Reddi, R.N. Saha, Nanostructured lipid carriers for site-specific drug delivery, Biomed. Pharmacother. 103 (2018) 598–613, https://doi.org/10.1016/j.biopha.2018.04.055.
[240] R.H. Müller, R. Shegokar, C.M. Keck, 20 years of lipid nanoparticles (SLN and NLC): present state of development and industrial applications, Curr. Drug Discov. Technol. 8 (2011) 207–227 http://www.ncbi.nlm.nih.gov/pubmed/21291409 , Accessed date: 21 December 2018.
[241] N.P. Aditya, A.S. Macedo, S. Doktorovova, E.B. Souto, S. Kim, P.-S. Chang, S. Ko, Development and evaluation of lipid nanocarriers for quercetin delivery: a comparative study of solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid nanoemulsions (LNE), LWT - Food Sci. Technol. (Lebensmittel-Wissenschaft -Technol.) 59 (2014) 115–121, https://doi.org/10.1016/J.LWT.2014.04.058.
[242] N. Naseri, H. Valizadeh, P. Zakeri-Milani, Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application, Adv. Pharmaceut. Bull. 5 (2015) 305–313, https://doi.org/10.15171/apb.2015.043.
[243] S.-H. Hsu, C.-J. Wen, S.A. Al-Suwayeh, H.-W. Chang, T.-C. Yen, J.-Y. Fang, Physicochemical characterization and *in vivo* bioluminescence imaging of nanostructured lipid carriers for targeting the brain: apomorphine as a model drug, Nanotechnology 21 (2010) 405101, https://doi.org/10.1088/0957-4484/21/40/405101.
[244] K.-S. Liu, C.-J. Wen, T.-C. Yen, K.C. Sung, M.-C. Ku, J.-J. Wang, J.-Y. Fang, Combined strategies of apomorphine diester prodrugs and nanostructured lipid carriers for efficient brain targeting, Nanotechnology 23 (2012) 095103, , https://doi.org/10.1088/0957-4484/23/9/095103.
[245] Y.M. Gabal, A.O. Kamel, O.A. Sammour, A.H. Elshafeey, Effect of surface charge on the brain delivery of nanostructured lipid carriers in situ gels via the nasal route, Int. J. Pharm. 473 (2014) 442–457, https://doi.org/10.1016/j.ijpharm.2014.07.025.
[246] R. Cortesi, E. Esposito, M. Drechsler, G. Pavoni, I. Cacciatore, M. Sguizzato, A. Di Stefano, L-dopa co-drugs in nanostructured lipid carriers: a comparative study, Mater. Sci. Eng. C 72 (2017) 168–176, https://doi.org/10.1016/j.msec.2016.11.060.
[247] L. Ravani, M.G. Sarpietro, E. Esposito, A. Di Stefano, P. Sozio, M. Calcagno, M. Drechsler, C. Contado, F. Longo, M.C. Giuffrida, F. Castelli, M. Morari, R. Cortesi, Lipid nanocarriers containing a levodopa prodrug with potential anti-parkinsonian activity, Mater. Sci. Eng. C 48 (2015) 294–300, https://doi.org/10.1016/J.MSEC.2014.12.014.
[248] S. Hernando, E. Herran, J. Figueiro-Silva, J.L. Pedraz, M. Igartua, E. Carro, R.M. Hernandez, Intranasal administration of TAT-conjugated lipid nanocarriers loading GDNF for Parkinson's disease, Mol. Neurobiol. 55 (2018) 145–155, https://doi.org/10.1007/s12035-017-0728-7.
[249] O. Gartziandia, E. Herrán, J.A. Ruiz-Ortega, C. Miguelez, M. Igartua, J.V. Lafuente, J.L. Pedraz, L. Ugedo, R.M. Hernández, Intranasal administration of chitosan-coated nanostructured lipid carriers loaded with GDNF improves behavioral and histological recovery in a partial lesion model of Parkinson's disease, J. Biomed. Nanotechnol. 12 (2016) 2220–2280, https://doi.org/10.1166/jbn.2016.2313.
[250] M. Hans, A. Lowman, 23 Nanoparticles for Drug Delivery, (2006) http://homes.nano.aau.dk/fp/self-assembling/lecture notes/nanoparticles_for_drug_delivery_CRC.pdf , Accessed date: 21 December 2018.
[251] B. Bellich, I. D'Agostino, S. Semeraro, A. Gamini, A. Cesàro, The good, the bad and the ugly" of chitosans. Mar. Drugs 14 (2016), https://doi.org/10.3390/md14050099.
[252] M. Muthu, Nanoparticles based on PLGA and its co-polymer: an overview, Asian J. Pharm. Free Full Text Artic. from Asian J Pharm. 3 (2014), https://doi.org/10.22377/AJP.V3I4.276.
[253] C. Martins, F. Sousa, F. Araújo, B. Sarmento, Functionalizing PLGA and PLGA derivatives for drug delivery and tissue regeneration applications, Adv. Healthc. Mater. 7 (2018) 1701035, https://doi.org/10.1002/adhm.201701035.
[254] L. Zhang, J.M. Chan, F.X. Gu, J.-W. Rhee, A.Z. Wang, A.F. Radovic-Moreno, F. Alexis, R. Langer, O.C. Farokhzad, Self-assembled Lipid − Polymer hybrid nanoparticles: a robust drug delivery platform, ACS Nano 2 (2008) 1696–1702, https://doi.org/10.1021/nn800275r.
[255] H.L. Wong, A.M. Rauth, R. Bendayan, J.L. Manias, M. Ramaswamy, Z. Liu, S.Z. Erhan, X.Y. Wu, A new polymer–lipid hybrid nanoparticle system increases cytotoxicity of doxorubicin against multidrug-resistant human breast cancer cells, Pharm. Res. 23 (2006) 1574–1585, https://doi.org/10.1007/s11095-006-0282-x.
[256] B. Mandal, H. Bhattacharjee, N. Mittal, H. Sah, P. Balabathula, L.A. Thoma, G.C. Wood, Core–shell-type lipid–polymer hybrid nanoparticles as a drug delivery platform, Nanomed. Nanotechnol. Biol. Med. 9 (2013) 474–491, https://doi.org/10.1016/j.nano.2012.11.010.
[257] C.I.C. Crucho, M.T. Barros, Polymeric nanoparticles: a study on the preparation variables and characterization methods, Mater. Sci. Eng. C 80 (2017) 771–784, https://doi.org/10.1016/j.msec.2017.06.004.
[258] A. Mukherjee, A.K. Waters, P. Kalyan, A.S. Achrol, S. Kesari, V.M. Yenugonda, Lipid-polymer hybrid nanoparticles as a nextgeneration drug delivery platform: state of the art, emerging technologies, and perspectives, Int. J. Nanomed. 14 (2019) 1937–1952, https://doi.org/10.2147/IJN.S198353.
[259] C.V. Pardeshi, V.S. Belgamwar, A.R. Tekade, S.J. Surana, Novel surface modified polymer–lipid hybrid nanoparticles as intranasal carriers for ropinirole hydrochloride: in vitro, ex vivo and in vivo pharmacodynamic evaluation, J. Mater. Sci. Mater. Med. 24 (2013) 2101–2115, https://doi.org/10.1007/s10856-013-4965-7.
[260] Y.-Z. Zhao, X. Li, C.-T. Lu, M. Lin, L.-J. Chen, Q. Xiang, M. Zhang, R.-R. Jin, X. Jiang, X.-T. Shen, X.-K. Li, J. Cai, Gelatin nanostructured lipid carriers-mediated intranasal delivery of basic fibroblast growth factor enhances functional recovery in hemiparkinsonian rats, Nanomed. Nanotechnol. Biol. Med. 10 (2014) 755–764, https://doi.org/10.1016/j.nano.2013.10.009.
[261] S. Vemuri, C.T. Rhodes, Preparation and characterization of liposomes as therapeutic delivery systems: a review, Pharm. Acta Helv. 70 (1995) 95–111, https://doi.org/10.1016/0031-6865(95)00010-7.
[262] S. Mizrahy, I. Hazan-Halevy, D. Landesman-Milo, B.D. Ng, D. Peer, Advanced strategies in immune modulation of cancer using lipid-based nanoparticles, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.00069.
[263] G. Poovi, N. Damodharan, Lipid nanoparticles: a challenging approach for oral delivery of BCS Class-II drugs, Futur. J. Pharm. Sci. 4 (2018) 191–205, https://doi.org/10.1016/j.fjps.2018.04.001.
[264] B.S. Zolnik, Á. González-Fernández, N. Sadrieh, M.A. Dobrovolskaia, Minireview: nanoparticles and the immune system, Endocrinology 151 (2010) 458–465, https://doi.org/10.1210/en.2009-1082.
[265] M.A. Iqbal, S. Md, J.K. Sahni, S. Baboota, S. Dang, J. Ali, Nanostructured lipid carriers system: recent advances in drug delivery, J. Drug Target. 20 (2012) 813–830, https://doi.org/10.3109/1061186X.2012.716845.
[266] T. Hendel, M. Wuithschick, F. Kettemann, A. Birnbaum, K. Rademann, J. Polte, In situ determination of colloidal gold concentrations with UV–vis spectroscopy: limitations and perspectives, Anal. Chem. 86 (2014) 11115–11124, https://doi.org/10.1021/ac502053s.
[267] J. Conde, J.T. Dias, V. Grazú, M. Moros, P.V. Baptista, J.M. de la Fuente, Revisiting 30 years of biofunctionalization and surface chemistry of inorganic nanoparticles for nanomedicine, Front. Chem. 2 (2014), https://doi.org/10.3389/fchem.2014.00048.
[268] D. Mahl, J. Diendorf, W. Meyer-Zaika, M. Epple, Possibilities and limitations of different analytical methods for the size determination of a bimodal dispersion of metallic nanoparticles, Colloids Surfaces A Physicochem. Eng. Asp. 377 (2011) 386–392, https://doi.org/10.1016/j.colsurfa.2011.01.031.
[269] A.B. Seabra, N. Durán, Nanotoxicology of metal oxide nanoparticles, Metals 5 (2015) 934–975, https://doi.org/10.3390/met5020934.
[270] J. Valdez, I. Gómez, One-step green synthesis of metallic nanoparticles using sodium alginate, J. Nanomater. 2016 (2016), https://doi.org/10.1155/2016/9790345.
[271] S.K. Dorcheh, K. Vahabi, Biosynthesis of nanoparticles by fungi: large-scale production, Fungal Metab. Springer International Publishing, Cham, 2016, pp. 1–20, , https://doi.org/10.1007/978-3-319-19456-1_8-1.
[272] I.I. Muhamad, S. Selvakumaran, N. Asmak, M. Lazim, Designing Polymeric Nanoparticles for Targeted Drug Delivery System, (n.d).
[273] S. Kango, S. Kalia, A. Celli, J. Njuguna, Y. Habibi, R. Kumar, Surface modification of inorganic nanoparticles for development of organic-inorganic nanocomposites - a review, Prog. Polym. Sci. 38 (2013) 1232–1261, https://doi.org/10.1016/j.progpolymsci.2013.02.003.
[274] A. Sukhanova, S. Bozrova, P. Sokolov, M. Berestovoy, A. Karaulov, I. Nabiev, Dependence of nanoparticle toxicity on their physical and chemical properties, Nanoscale Res. Lett. 13 (2018), https://doi.org/10.1186/s11671-018-2457-x.
[275] X. Jia, Q. Han, Z. Wang, Y. Qian, Y. Jia, W. Wang, Z. Hu, Targeting peptide functionalized liposomes towards aminopeptidase N for precise tumor diagnosis and therapy, Biomater. Sci. 5 (2017) 417–421, https://doi.org/10.1039/c6bm00898d.
[276] Z. Belhadj, C. Zhan, M. Ying, X. Wei, C. Xie, Z. Yan, W. Lu, Multifunctional targeted liposomal drug delivery for efficient glioblastoma treatment, Oncotarget 8 (2017), https://doi.org/10.18632/oncotarget.17976.
[277] R. Nisini, N. Poerio, S. Mariotti, F. De Santis, M. Fraziano, The multirole of liposomes in therapy and prevention of infectious diseases, Front. Immunol. 9 (2018), https://doi.org/10.3389/fimmu.2018.00155.

[278] Y. Okamoto, K. Taguchi, K. Yamasaki, M. Sakuragi, ichi Kuroda, M. Otagiri, Albumin-Encapsulated Liposomes: A Novel Drug Delivery Carrier with Hydrophobic Drugs Encapsulated in the Inner Aqueous Core, (2018), https://doi.org/10.1016/j.xphs.2017.08.003.

[279] J.O. Eloy, M. Claro de Souza, R. Petrilli, J.P.A. Barcellos, R.J. Lee, J.M. Marchetti, Liposomes as carriers of hydrophilic small molecule drugs: strategies to enhance encapsulation and delivery, Colloids Surfaces B Biointerfaces 123 (2014) 345–363, https://doi.org/10.1016/j.colsurfb.2014.09.029.

[280] Q. Wang, Y. Chao, Multifunctional quantum dots and liposome complexes in drug delivery, J. Biomed. Res. 32 (2018) 91–106, https://doi.org/10.7555/JBR.31.20160146.

[281] J.K. Patra, G. Das, L.F. Fraceto, et al., Nano based drug delivery systems: recent developments and future prospects, J Nanobiotechnol 16 (2018) 71, https://doi.org/10.1186/s12951-018-0392-8.

[282] A. Watermann, J. Brieger, Mesoporous silica nanoparticles as drug delivery vehicles in cancer, Nanomaterials 7 (2017), https://doi.org/10.3390/nano7070189.

[283] S.-J. Choi, J.K. Lee, J. Jeong, J.-H. Choy, J.H. Choy, Toxicity evaluation of inorganic nanoparticles: considerations and challenges, Mol Cell Toxicol 9 (2013) 205–210, https://doi.org/10.1007/s13273-013-0026-z.

[284] Y. Lin, Q. Zhou, D. Tang, Dopamine-loaded liposomes for in-situ amplified photoelectrochemical immunoassay of AFB $_1$ to enhance photocurrent of Mn^{2+}-doped $Zn_3(OH)_2V_2O_7$ nanobelts, Anal. Chem. 89 (2017) 11803–11810, https://doi.org/10.1021/acs.analchem.7b03451.

[285] R. Pahuja, K. Seth, A. Shukla, R.K. Shukla, P. Bhatnagar, L.K.S. Chauhan, P.N. Saxena, J. Arun, B.P. Chaudhari, D.K. Patel, S.P. Singh, R. Shukla, V.K. Khanna, P. Kumar, R.K. Chaturvedi, K.C. Gupta, Trans-blood brain barrier delivery of dopamine-loaded nanoparticles reverses functional deficits in parkinsonian rats, ACS Nano 9 (2015) 4850–4871, https://doi.org/10.1021/nn506408v.

[286] D.E. Silver, S. Ruggieri, Initiating therapy for Parkinson's disease, Neurology 50 (1998) S18–S22 discussion S44-8 http://www.ncbi.nlm.nih.gov/pubmed/9633682 , Accessed date: 22 December 2018.

[287] G. DeMaagd, A. Philip, P T. Parkinson's Disease and its Management: Part 3: Nondopaminergic and Nonpharmacological Treatment Options vol. 40, (2015), pp. 668–679 http://www.ncbi.nlm.nih.gov/pubmed/26535023 , Accessed date: 22 December 2018.

[288] A.O. Pires, F.G. Teixeira, B. Mendes-Pinheiro, S.C. Serra, N. Sousa, A.J. Salgado, Old and new challenges in Parkinson's disease therapeutics, Prog. Neurobiol. 156 (2017) 69–89, https://doi.org/10.1016/J.PNEUROBIO.2017.04.006.

[289] E. V Mosharov, A. Borgkvist, D. Sulzer, Presynaptic effects of levodopa and their possible role in dyskinesia, Mov. Disord. 30 (2015) 45–53, https://doi.org/10.1002/mds.26103.

[290] Y. Smith, T. Wichmann, S.A. Factor, M.R. DeLong, Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa, Neuropsychopharmacology 37 (2012) 213–246, https://doi.org/10.1038/npp.2011.212.

[291] J.A. Obeso, C.W. Olanow, J.G. Nutt, Levodopa motor complications in Parkinson's disease, Trends Neurosci. 23 (2000), https://doi.org/10.1016/S1471-1931(00)00031-8 S2–S7.

[292] A.H. V Schapira, Present and future drug treatment for Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 76 (2005) 1472–1478, https://doi.org/10.1136/jnnp.2004.035980.

[293] S. Bunten, S. Happe, Rotigotine transdermal system: a short review, Neuropsychiatric Dis. Treat. 2 (2006) 421–426 http://www.ncbi.nlm.nih.gov/pubmed/19412491 , Accessed date: 22 December 2018.

[294] M. Mahmoudi, S.N. Saeedi-Eslami, M.A. Shokrgozar, K. Azadmanesh, M. Hassanlou, H.R. Kalhor, C. Burtea, B. Rothen-Rutishauser, S. Laurent, S. Sheibani, H. Vali, Cell "vision": complementary factor of protein corona in nanotoxicology, Nanoscale 4 (2012) 5461, https://doi.org/10.1039/c2nr31185b.

[295] P. Verderio, S. Avvakumova, G. Alessio, M. Bellini, M. Colombo, E. Galbiati, S. Mazzucchelli, J.P. Avila, B. Santini, D. Prosperi, Delivering colloidal nanoparticles to mammalian cells: a nano-bio interface perspective, Adv. Healthc. Mater. 3 (2014) 957–976, https://doi.org/10.1002/adhm.201300602.

[296] S. Barua, S. Mitragotri, Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects, Nano Today 9 (2014) 223, https://doi.org/10.1016/J.NANTOD.2014.04.008.

[297] S. Palchetti, V. Colapicchioni, L. Digiacomo, G. Caracciolo, D. Pozzi, A.L. Capriotti, G. La Barbera, A. Laganà, The protein corona of circulating PEGylated liposomes, Biochim. Biophys. Acta Biomembr. 1858 (2016) 189–196, https://doi.org/10.1016/J.BBAMEM.2015.11.012.

[298] Q. Yang, S.K. Lai, Anti-PEG immunity: emergence, characteristics, and unaddressed questions, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 7 (2015) 655–677, https://doi.org/10.1002/wnan.1339.

[299] J. Godyń, J. Jończyk, D. Panek, B. Malawska, Therapeutic strategies for Alzheimer's disease in clinical trials, Pharmacol. Rep. 68 (2016) 127–138, https://doi.org/10.1016/j.pharep.2015.07.006.

[300] V. Pursiainen, J. Lyytinen, E. Pekkonen, Effect of duodenal levodopa infusion on blood pressure and sweating, Acta Neurol. Scand. 126 (2012), https://doi.org/10.1111/j.1600-0404.2012.01648.x e20–e24.

[301] K. Van Ooteghem, J.S. Frank, F.B. Horak, Postural motor learning in Parkinson's disease: the effect of practice on continuous compensatory postural regulation, Gait Posture 57 (2017) 299–304, https://doi.org/10.1016/j.gaitpost.2017.06.021.

[302] D.S. Peterson, F.B. Horak, The effect of levodopa on improvements in protective stepping in people with Parkinson's disease, Neurorehabilitation Neural Repair 30 (2016) 931–940, https://doi.org/10.1177/1545968316648669.

[303] NeuroDerm Ltd., A single period investigation to assess the tolerability of healthy subjects to oral Sinemet® (Levodopa/Carbidopa) - full text view - ClinicalTrials.gov (n.d.), https://clinicaltrials.gov/ct2/show/NCT02486432 , Accessed date: 22 December 2018.

[304] U.S.L.L.C. Osmotica Pharmaceutical, Efficacy, safety, and pharmacokinetics/pharmacodynamic study of L-dopa/carbidopa to treat Parkinson's disease - full text view - ClinicalTrials.gov (n.d.), https://clinicaltrials.gov/ct2/show/NCT00558337 , Accessed date: 22 December 2018.

[305] F.C.F. Chang, V. Kwan, D. van der Poorten, N. Mahant, N. Wolfe, A.D. Ha, J.M. Griffith, D. Tsui, S.D. Kim, V.S.C. Fung, Intraduodenal levodopa-carbidopa intestinal gel infusion improves both motor performance and quality of life in advanced Parkinson's disease, J. Clin. Neurosci. 25 (2016) 41–45, https://doi.org/10.1016/J.JOCN.2015.05.059.

[306] A. AbbVie, Study comparing efficacy of levodopa-carbidopa intestinal gel/carbidopa-levodopa enteral suspension and optimized medical treatment on dyskinesia in subjects with advanced Parkinson's disease (DYSCOVER) - full text view - ClinicalTrials.gov (n.d.), https://clinicaltrials.gov/ct2/show/NCT02799381 , Accessed date: 22 December 2018.

[307] M.A. Brodsky, B.S. Park, J.G. Nutt, Effects of a dopamine agonist on the pharmacodynamics of levodopa in Parkinson disease, Arch. Neurol. 67 (2010) 27–32, https://doi.org/10.1001/archneurol.2009.287.

[308] Impel NeuroPharma Inc., Therapeutic potential for intranasal levodopa in Parkinson's disease -off reversal - full text view - ClinicalTrials.gov, n.d. https://clinicaltrials.gov/ct2/show/NCT03541356 , Accessed date: 22 December 2018.

[309] Desitin Arzneimittel GmbH, PIRLONG-PD safety and efficacy of piribedil in Parkinson's disease during long term therapy - full text view - ClinicalTrials.gov (n.d.), accessed, https://clinicaltrials.gov/ct2/show/NCT01519856 , Accessed date: 22 December 2018.

[310] S. Perez-Lloret, O. Rascol, Piribedil for the treatment of motor and non-motor symptoms of Parkinson disease, CNS Drugs 30 (2016) 703–717, https://doi.org/10.1007/s40263-016-0360-5.

[311] GlaxoSmithKline, Parkinson's disease patient study on absorption, distribution, metabolism and excretion of ropinirole - full text view - ClinicalTrials.gov (n.d.), accessed, https://clinicaltrials.gov/ct2/show/NCT00460148 , Accessed date: 22 December 2018.

[312] J.Y. Yun, H.-J. Kim, J.-Y. Lee, Y.E. Kim, J.S. Kim, J.-M. Kim, B.S. Jeon, Comparison of once-daily versus twice-daily combination of Ropinirole prolonged release in Parkinson's disease, BMC Neurol. 13 (2013) 113, https://doi.org/10.1186/1471-2377-13-113.

[313] N. Hattori, K. Hasegawa, K. Sato, E. Mitsuyama, Y. Numachi, Clinical evaluation of ropinirole controlled-release formulation at 18–24 mg/day in Japanese patients with Parkinson's disease, Park. Relat. Disord. 40 (2017) 33–39, https://doi.org/10.1016/j.parkreldis.2017.04.005.

[314] UCB Pharma, Effect of rotigotine on motor symptoms in patients with advanced Parkinson's disease (PD) with motor fluctuations and symptoms of gastrointestinal dysfunction - full text view - ClinicalTrials.gov (n.d.), accessed, https://clinicaltrials.gov/ct2/show/NCT01536015 , Accessed date: 22 December 2018.

[315] W.H. Poewe, O. Rascol, N. Quinn, E. Tolosa, W.H. Oertel, E. Martignoni, M. Rupp, B. Boroojerdi, S P, 515 Investigators, Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial, Lancet Neurol. 6 (2007) 513–520, https://doi.org/10.1016/S1474-4422(07)70108-4.

[316] S.J. Chung, J.-M. Kim, J.W. Kim, B.S. Jeon, P. Singh, S. Thierfelder, J. Ikeda, L. Bauer, Asia Pacific Rotigotine Switching Study Group, Switch from oral pramipexole or ropinirole to rotigotine transdermal system in advanced Parkinson's disease: an open-label study, Expert Opin. Pharmacother. 16 (2015) 961–970, https://doi.org/10.1517/14656566.2015.1030336.

[317] K.E. Lyons, J.H. Friedman, N. Hermanowicz, S.H. Isaacson, R.A. Hauser, B.P. Hersh, D.E. Silver, J.W. Tetrud, L.W. Elmer, S.A. Parashos, L.K. Struck, M.F. Lew, R. Pahwa, Orally disintegrating selegiline in Parkinson patients with dopamine agonist-related adverse effects, Clin. Neuropharmacol. 33 (2010) 5–10, https://doi.org/10.1097/WNF.0b013e3181b7926f.

[318] F. Stocchi, R. Borgohain, M. Onofrj, A.H.V. Schapira, M. Bhatt, V. Lucini, R. Giuliani, R. Anand, Study 015 Investigators, A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients, Mov. Disord. 27 (2012) 106–112, https://doi.org/10.1002/mds.23954.

[319] R.A. Hauser, D. Silver, A. Choudhry, E. Eyal, S. Isaacson, ANDANTE study investigators, Randomized, controlled trial of rasagiline as an add-on to dopamine agonists in Parkinson's disease, Mov. Disord. 29 (2014) 1028–1034, https://doi.org/10.1002/mds.25877.

[320] F. Stocchi, O. Rascol, K. Kieburtz, W. Poewe, J. Jankovic, E. Tolosa, P. Barone, A.E. Lang, C.W. Olanow, Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study, Ann. Neurol. 68 (2010) 18–27, https://doi.org/10.1002/ana.22060.

[321] Novartis Pharmaceuticals, Effects of carbidopa/levodopa/entacapone on motor function and quality of life in patients with Parkinson's disease - full text view - ClinicalTrials.gov, n.d. https://clinicaltrials.gov/ct2/show/NCT00219284 , Accessed date: 22 December 2018.

[322] P. Damier, Evidence for the use of levodopa–carbidopa–entacapone (STALEVO) to improve motor fluctuations in Parkinson's disease, Eur. Neurol. Rev. 3 (2008) 37, https://doi.org/10.17925/ENR.2008.03.02.37.

[323] M.F. Lew, M. Somogyi, K. McCague, M. Welsh, On behalf of the LCE QoL study grou, immediate versus delayed switch from levodopa/carbidopa to levodopa/carbidopa/entacapone: effects on motor function and quality of life in patients with Parkinson's disease with end-of-dose wearing off, Int. J. Neurosci. 121 (2011) 605–613, https://doi.org/10.3109/00207454.2011.598982.

[324] Entacapone to Tolcapone Switch Study Investigators, Entacapone to tolcapone switch: multicenter double-blind, randomized, active-controlled trial in advanced

Parkinson's disease, Mov. Disord. 22 (2007) 14–19, https://doi.org/10.1002/mds.21131.

[325] E. Wolf, K. Seppi, R. Katzenschlager, G. Hochschorner, G. Ransmayr, P. Schwingenschuh, E. Ott, I. Kloiber, D. Haubenberger, E. Auff, W. Poewe, Long-term antidyskinetic efficacy of amantadine in Parkinson's disease, Mov. Disord. 25 (2010) 1357–1363, https://doi.org/10.1002/mds.23034.

[326] R. Pahwa, C.M. Tanner, R.A. Hauser, S.H. Isaacson, P.A. Nausieda, D.D. Truong, P. Agarwal, K.L. Hull, K.E. Lyons, R. Johnson, M.J. Stempien, ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study), JAMA Neurol 74 (2017) 941, https://doi.org/10.1001/jamaneurol.2017.0943.

[327] L. Ravani, M.G. Sarpietro, E. Esposito, A. Di Stefano, P. Sozio, M. Calcagno, M. Drechsler, C. Contado, F. Longo, M.C. Giuffrida, F. Castelli, M. Morari, R. Cortesi, Lipid nanocarriers containing a levodopa prodrug with potential anti-parkinsonian activity, Mater. Sci. Eng. C 48 (2015) 294–300, https://doi.org/10.1016/j.msec.2014.12.014.

[328] Shui-ming Zhan, Hou Dong-zhi, Ping Qi-neng, Yan Xu, Preparation and entrapment efficiency determination of solid lipid nanoparticles loaded levodopa–《Chinese Journal of Hospital Pharmacy》2010年14期, Chin. J. Hosp. Pharm. 002 (2010), http://en.cnki.com.cn/Article_en/CJFDTOTAL-ZGYZ201014002.htm , Accessed date: 21 December 2018.

[329] Ngwuluka Ndidi, Pillay Viness, DuToit Choonara Yahya Essop, Lisa Claire, Polymeric Matrix of Polymer-Lipid Nanoparticles as a Pharmaceutical Dosage Form, (2011) https://patents.google.com/patent/WO2012070031A1/en , Accessed date: 21 December 2018.

[330] E. Esposito, P. Mariani, L. Ravani, C. Contado, M. Volta, S. Bido, M. Drechsler, S. Mazzoni, E. Menegatti, M. Morari, R. Cortesi, Nanoparticulate lipid dispersions for bromocriptine delivery: characterization and in vivo study, Eur. J. Pharm. Biopharm. 80 (2012) 306–314, https://doi.org/10.1016/j.ejpb.2011.10.015.

[331] K.M. Asha Spandana, Jawahar Natarajan, Mahendran Baskaran, Dual drug-loaded lipid nanoparticles for the treatment of Parkinson's disease, J. Neurol. Neurosci. 2018, https://doi.org/10.21767/2171-6625-C1-009 iMedPub.