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NANO LIPID BASED DRUG DELIVERY SYSTEMS FOR TREATING VARIOUS NEURO-DEGENERATIVE DISORDERS

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ABSTRACT:

Drugs intended for treating various neuro-degenerative disorders possess significant challenge in crossing the Blood Brain Barrier (BBB) & reaching the site of action. As conventional drug delivery has not been successful in meeting the demands, the focus has been shifted to a novel delivery approach. Out of various delivery approaches, lipid based delivery systems proved to enhance the efficacy of drugs by crossing BBB and reaching target site by enhancing solubility, permeability and bioavailability. Hence in the present chapter the authors focused on various lipid-based drug delivery strategies like nanoemulsions, solid lipid nanoparticles and liposomes on Parkinsonism, Huntington's disease, Epilepsy and Alzheimers neuro-degenerative disorders. The chapter also highlighted few examples related to design of experiments & artificial neural networks.

Key words: Nano lipid-based drug delivery systems, Neuro-degenerative disorders, Design of experiments, Artificial neural networks

1. INTRODUCTION:

PARKINSONISM DISORDER (PD):

Parkinsonism is characterized by the progressive degradation and loss of dopaminergic neurons in the substantia nigra pars compacta, which are crucial for motor coordination. Aggregation of protein, a lack of oxygen delivery, dysfunctionality of mitochondria, neuronal inflammatory diseases, and BBB disruption are the most common factors that contribute to the disease's pathophysiology.

Quality by Design (QbD) approach was used in order to formulate selegiline, a Parkinsonian drug belonging to the monoamine oxidase B inhibitor group, loaded

nanoemulsion which was aimed at increasing the bioavailability of selegiline via nasal route. The resultant formulation had a droplet size of 61.43 nm and exhibited a 3.7 folds increase in drug permeation as compared to the oral suspension. The formulation was also tested for its behavioural efficacy in Wistar rats having Parkinson's by haloperidol induction.[1] The nanoemulsion approach was applied to overcome the problem of low bioavailability of Coenzyme Q10 and harness its antioxidant property in the management of Parkinsonism. In comparison to the suspension, optimized nanoemulsion formulation, with mean droplet diameter of 60.00 nm, showed 1.81 folds increase in bioavailability. Data obtained by biochemical estimation exhibited a subsequent increase and decrease in glutathione and thiobarbituric acid respectively.[2] The aqueous titration with homogenization induced by high shear was used in order to formulate Ropinirole nanoemulsion coated with chitosan. The resultant nanoemulsion globules reported a size of 58.61 nm and there was a significant increase in the Cmax as compared to intravenous. The study was successful in establishing the role of mucoadhesive nanocarriers for drug delivery to the brain via the intranasal route.[3]

A liposomal formulation was developed containing a combination of Ceftriaxone, FK506, and nilotinib with the intention to target the complexities of Parkinsonism. Penetration through the Blood-brain barrier and ability to adjoin with apoptotic neurons was brought about by Glutathione and Cardiolipin respectively. The resultant optimized formulation fulfilled the intended standards when compared to the native drug on the basis of drug release rate, toxicity profile, and efficiency. The study also concluded that particle size, zeta potential entrapment efficiency were modulated by the percentage of cardiolipin and dihexadecyl phosphate.[4] A study was carried out that demonstrated the extraction of phospholipids, pertaining to peanut seed, which was further employed in the preparation of liposomes having pH and thermosensitive characteristics. The drugs included were Folic acid, Levodopa, and Camptothecin. Thin-film hydration method was used to obtain optimized liposomes of size 1-2 micron. External stimuli conditions for optimum release of all the varieties of liposomes were reported to be pH 10, 2, 6 and temperature was found to be 57 degree, 37 degree, 47 degree for Folic acid, Levodopa, and Camptothecin respectively. The lowest toxicity was exhibited by Levodopa liposomes and highest anti-cancer activity was exhibited by Camptothecin liposomes with IC50 of 17.99 micro gram/ml.[5] A diacylglycerol moiety was linked to a peptide of amyloid precursor protein, well recognised by the BBB, and was incorporated into a liposome to increase the targeting efficiency of Dopamine when administered via intraperitoneal route. *In vivo study* was carried out in amphetamine treated mice which demonstrated that liposomal Dopamine with dose of 800 microgram/kg increased the dopamine level in striatum by 6.9 times in 5 minutes, which was almost constant for a period of 3 hours. Thus, the study concluded that liposomal dopamine via IP route needed much less amount of dosage as compared to levodopa and also a sustained release can be achieved by using the same.[6]

The problems associated with oral bioavailability and dosage interval of Ropinirole was overcome by formulating Solid lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC) of Ropinirole for oral delivery, and hydrogel form, by addition of Carbopol 934, of the same for topical delivery. The pharmacokinetic (PK) and pharmacodynamic studies were carried out in male Wistar rats. The PK data reported a increase of 2.1 and 2.7 times for oral delivery and 3.0 and 3.3 time for the topical delivery of the hydrogel, as compared to standard formulations respectively. Further, hydrogel form of the Ropinirole SLN and NLC exhibited 1.4 and 1.2 times increased bioavailability as compared to their counterparts for oral delivery.[7] A study was focused on targeting the mitochondrial abnormality as well as dopamine depletion by the help of solid lipid nanoparticles adsorbed with grape seed derived proanthocyanidins. The grape seed derivative had an antioxidant

effect which in turn decreased the oxidative stress related to PD. All studies concluded that the formulated particles were successful in satisfying the goals of the study. The oxidation of the Dopamine in particles was prevented by the Grape seed extract. SH-SY5Y cell viability, on administration of the formulation along with 6-hydroxydopamine (neurotoxin for inducing oxidative stress) served as the marker of antioxidant efficiency of the formulation. Furthermore, the particles showed a negative cytotoxic profile along with a mucoadhesive character which can be harnessed in various ways.[8] A solid lipid nanoparticle approach was devised to deliver Piribedil via nose to brain route, thus overcoming the limitations like high dosing frequency, low oral bioavailability, and gastrointestinal problems associated with the drug. The optimized formulation reported a size of 358 nm with nearly 15% drug loading. The resultant SLNs were formulated into in situ gel with the help of methylcellulose, thus increasing the residence. A 4 times increase in the AUC and 2.3 times reduction in C_{max}, confirmed the victory of the study.[9] A study was carried out with the intension of delivering Dopamine to the brain for the patients suffering from PD. The study utilised Solid lipid nanoparticles containing dopamine along with glycol chitosan. The presence of glycol chitosan and dopamine together (147 +/- 24), in the nanoparticles resulted in decreased particle size when compared to nanoparticles of Dopamine (171 nm) and glycol chitosan (265 nm) alone. Nearly 81% of dopamine was incorporated in the combinational nanoparticle. Still the studies are under progress.[10] An approach as tried to combine the anti-inflammatory and reversing mitochondrial abnormality property of Geraniol and ursodeoxycholic acid respectively. But the combination had a backlog of solubility, which was overcomed by entrapping them into nanoparticles (<200 nm), both solid lipid and polymeric. The solid lipid nanoparticulate formulation showed better results, as compared to polymeric nanoparticles, in terms of dissolution rate. The study was declared successful when the resultant formulation of GER-UDCA-SLN achieved a concentration range of 1.1 – 4.65 microgram/ml over a period of 30 to 150 min, in the CSF but not in the blood stream, which confirmed its brain targeting. Furthermore, no damage to the integrity of the nasal mucosa was observed on histopathological analysis, and this confirmed the safety prospect of the formulation.

HUNTINGTON DISEASE (HD):

Huntington's disease, commonly known as Huntington chorea, is another terrible neuropsychiatric player. This is a rare hereditary condition characterized by memory and cognitive impairment as well as chorea. Involuntary motions are most common in the hands, feet, face, and trunk. A significant predictor of disease progression is atrophy of the caudate and putamen regions of the basal ganglia. The cause is polyglutamine expansion in exon 1 of the Huntingtin gene.

The solid lipid nanoparticulate approach was utilized to improve the targeting profile of rosamirinic acid, via intra nasal route, to the brain. The hot homogenization method was used to achieve solid lipid nanoparticles with mean size of 149.2 nm. The optimized formulation was successful in combating the effects induced by 3-NP (Nitropropionic acid) in rats, thus increased pharmacokinetic values in the brain.[11] A study was directed with the intention of reducing the mitochondrial abnormality responsible for HD. SLNs encapsulating curcumin with size range of 72-148 nm were formulated, whose efficacy was checked in 3-NP treated rats. To the authors relief, the formulated SLNs reported marked increase in the functionality of mitochondrial complexes and other indicators of HD progression.[12] A targeted different pathway was developed which deals with synthesis of cholesterol in brain. Cholesterol in the form of liposomes labelled with deuterium were given intranasally and it's concentration in various desired locations is evaluated by Liquid chromatography mass spectroscopy (LCMS). A steady state concentration as well as, at the same time, a higher

concentration in brain than body was confirmed by kinetic studies. The repeated dosing of cholesterol liposomes intranasally reported cholesterol concentration to be 1.5 ng/mg throughout brain after 24 hours, thus indicating the efficacy of brain targeting.[13] The chorea reducing property of Tetrabenazine was utilized for management of Huntington disease. The target of study was to formulate nanoemulsion loaded with tetrabenazine with can be given by intranasal route with the intention of overcoming low oral bioavailability. QbD was applied to get optimised formulation with droplet size of 106.80+/- 1.96. The various pharmacokinetic and histopathological studies were carried out. As compared to the suspension form, the nanoemulsion of tetrabenazine showed 1.68 fold increase in permeation.[14]

EPILEPSY:

According to official data recorded by WHO, epilepsy has a toll of 50 million patients throughout the globe. It is a neurological disorder mainly accounted to abnormal electrical discharge by the neurons, affecting all age categories without any discrimination. Epilepsy is a sensory or psychiatric phenomena characterized by paroxysmal cerebral dysrhythmia which is manifested in the form of disturbance or loss of consciousness, that may or may not be accompanied by characteristic body movements (convulsions). Anti-epileptic drugs act by any of the three mechanisms – a) Prolongation of Na+ channel b) Facilitation of GABA mediated Cl- channel c) Inhibition of T type Ca2+ current

A letrozole-loaded nanoemulsion (LET-NE) was designed and developed to decrease the peripheral effects of LET through nose-to-brain delivery. The formulated LET-NE was compared against free LET in status epilepticus (SE) induced by kainic acid (KA) in mice. Aqueous microtitration method was used for the preparation of LET-NE, where Triacetin as oil phase, Tween 80 as a surfactant, and PEG-400 as co-surfactant. Size of the droplet, surface morphology, polydispersity index, zeta potential, % transmittance, and drug content are the evaluation parameters that have been studied for the prepared batches. The decreased levels of 17-β estradiol, increased levels of 5α- Dihydrotestosterone (5α-DHT) and 3α-androstanediol (3α-Diol) in hippocampus were disclosed by biochemical estimations. In comparison with LET, cresyl violet staining LET-NE revealed greater protection of the hippocampus from neurotoxicity. The overall study revealed that the LET-NE showed significant action as an anticonvulsant and neuroprotective agent.[15] A topiramate (TPM) loaded nanoemulsions was developed as intranasal delivery. TPM comes under BCS class II which has less bioavailability due to poor aqueous solubility. They have used the phase titration method for the preparation of TPM-loaded nanoemulsions which consists of Capmul MCM C8 (2% w/w), 2:1 Tween 20:Carbitol (32% w/w), and water (66% w/w). Globule size, polydispersity index, zeta potential, viscosity, pH, transmittance, conductivity values, and TEM are the evaluation parameters to be studied. With the help of Wistar albino rats, Pharmacodynamic, pharmacokinetic, and brain drug uptake studies were performed by administering through post intranasal and oral routes. The results of obtained formulation demonstrated that the globule size is about nanometric, stable for 6 months. When compared to the oral route, the post intranasal administration of formulation showed greater brain uptake of the drug. This discovery will aid in lowering the TPM dosage, hence minimizing dose-related side effects.[16] Response surface methodology was used to optimize the nanoemulsion loaded valproic acid delivered through the parenteral route. Medium-chain triglyceride (MCT) along with sunflower seed oil (SSO) and lecithin (natural surfactant) and tween 80 (non-ionic surfactant) (1:2) were used in the preparation. Five-level, three-factor central composite design (CCD) was used for the optimization of the high-energy ultrasonication method. The effect of ultrasonic intensity of pre-sonication (A), sonication

time (B), and the temperature (C) on the responses like droplet size and polydispersity index were studied. According to the results, the more significantly affected factors on droplet size of nanoemulsions were found to be the interaction between the time and intensity of ultrasonication. From optimization studies, it was found that short sonication time will favor the droplet size of nanoemulsion with suitable PDI. With a power intensity of about 60% for 15 mins at 60ºc, the droplet size of nanoemulsion was found to be 43.21 ± 0.11 nm, PDI about 0.211. The drug content was enhanced by 1.5 folds with good stability. Overall, the ultrasonication process was suggested as a helpful process for the preparation of valproic acid-loaded nanoemulsions.[17]

The chitosan-coated liposomes were prepared by encapsulating carbamazepine (CBZ) and coenzyme (CoQ10) using response surface methodology (RSM). The dependent factors were chosen as the encapsulation efficiency of CBZ as well as CoQ10, which were found that 76.13%±2.34% and 82.36%±3.15% respectively. Thus, CBZ and CoQ10 containing chitosan-coated liposomes cab be advised as a useful approach regarding the release, particle size, high encapsulation efficiency, and stability in the treatment of epilepsy.[18] A lamotrigine-loaded nanoliposomes (LTG-NLs) were developed for the treatment of seizures by using thin-film hydration and rehydration method, which consists of phospholipid 90G, tween 80, and cholesterol as main components. The prepared LTG-NLs were optimized by Placket Burman and response surface methodology (RSM). Increased permeation of drug across goat nasal mucosa was confirmed by the confocal laser microscopy study and *ex vivo* permeation study. They concluded that there is a significant effect of independent variables on dependent variables and considered a lipid carrier system for intranasal delivery.[19] A research study was carried to evaluate the acute effects of curcumin-loaded liposomes on increasing current electroshock seizures (ICES) test, status epilepticus, and pentylenetetrazole (PTZ)-induced seizures in mice. 25 mg/kg and 50 mg/kg curcumin-liposomes manifested enhance in seizure threshold current in ICES test and latency to myoclonic and generalized seizures in PTZ-induced seizures. In mice with status epilepticus, liposomal-entrapped curcumin enhanced the delay to start of seizures and lowered the duration of episodes. The conclusion of the study denoted curcumin entrapped liposomes possess anticonvulsant activity against status epilepticus in mice.[20] A liposome nanotechnology was useddto increase the prolonged delivery to the brain. They hypothesized that Glucocorticoids (GCs) can decrease inflammation of the brain and can alter epileptogenesis in a rat model. It has been described that GCs have been shown to successfully suppress seizures in pediatric epilepsy syndromes, presumably via inhibiting inflammation. Rats have been treated with glutathione pegylated liposomal methylprednisolone (GSH-PEG liposomal MP), Starting 4 h after onset of SE based on the treatment protocol. The status epilepticus (SE) duration of action and onset of action were not affected by the treatment with GSH-PEG liposomal MP, which was disclosed by the recordings of Continuous electroencephalogram (EEG). They concluded that the development of epilepsy was also unaffected by GSH-PEG liposomal MP.[21] Ruiqi Huang et al. utilised the solid lipid nanoparticle approach on curcumin to harness the antioxidant activity and to overcome the bioavailability related problems, thus optimising the neuroprotective activity of curcumin. *In vitro* studies reported a better protection against neuronal apoptosis as compared to curcumin alone. *In vivo* studies concluded that the formulation crossed the BBB and had a positive effect on behaviour of epileptic mice. Cell proportionality of NeuN and TUNEL moved towards the healthy side in the hippocampus.[22]

Alzheimers

Alzheimers also known as “Senile dementia”, AD is a member of the neurological disorder that affects older individuals. It can be defined as progressive neurodegeneration resulting in atrophy of the cortical and subcortical areas of the brain. AD can be associated with the deposition of beta amyloid protein and the formation of neurofibrillary tangles which synergistically result in decreased blood flow. It is the most common cause of dementia.

A study as carried to harness the neuro protective ability of Osthole (Coumarin). The problems related to solubility, bioavailability, and BBB permeability were the major hurdles to be dealt with in delivery of Ostholefor management of Alzheimers. The researchers’ utilised the liposome approach in order to overcome the ordeal. In addition to this, the study also used CXCR4 to modify the surface of Osthole liposomes (CXCR4-Ost-Lips). In-vitro studies were carried out which demonstrated that, the formulated liposomes had enhanced intracellular uptake by APP-SH-SY5Y cells. Apart from having cytoprotective effect the formulation was also successful in reducing pathologies related to alzheimers by increasing the concentration of Osthole in brain.[23] One more study was carried out by which focused on fabricating triple targeted liposomes. Liposomes with size range of 120-200 nm and PDI less than 0.25 were formulated out of Phosphatidylcholine and were used to carry epigallocatechin, quercetin, curcumin. Glutathione was used for crosslinking and were surface activated by apolipoprotein. The study was considered complete when an increased permeation of the drugs across BBB was observed, another parameters like decrease in tau protein, interleukin-6 and caspase-3 were evident of the efficiency of the targeting and activity of the formulated liposomes.[24] The nanoemulsion approach was used to overcome the low BBB permeability of naringenin (bioflavonoid). Naringenin nanoemulsions, with droplet size of 113.83+/- 3.35 nm as measured by photon correlation spectroscopy, were produced and effectiveness of the optimized formulation was determined by carrying out assessment of the protective ability against toxic effects of beta amyloid on cells lines of neuroblastoma (SH-SY5Y). Apart from this, determination of reactive oxygen species induced by amyloid beta, phosphorylated tau, total tau, beta-secretase were also carried out. All the information obtained from the study, concluded that use of nanoemulsion approach for delivery of naringenin is reliable and can be harnessed and refined as per requirements.[25] The intranasal approach was developed in order to deliver oil-in-water nanoemulsion of Donepezil for management of Alzheimer’s. Labrasol, glycerol, and cetyl pyridinium chloride were used to formulate the nanoemulsion containing drug in concentration of 1mg/ml. Particle size exhibited by the nanoemulsion was about 65.3 nm. Antioxidant activity, cytotoxicity, and uptake of drug in brain were the parameters focused corresponding to In vivo studies and were carried out in Sprague Dawley rats. Scintigrams were used to analyze the drug uptake data. *In vitro* release studies in phosphate-buffered saline, artificial cerebrospinal fluid, simulated nasal fluid were found to be satisfactory. All the findings finally concluded that intranasal approach can be utilised in the delivery of donepezil nanoemulsion.[26]

DESIGN OF EXPERIMENT & ARTIFICIAL NEURAL NETWORK TECHNOLOGY:

Some of the works focused on Design of experiment & Artificial Neural network technology were identified with respect to lipid based drug delivery systems for treating neuro-degenerative disorders were reported. The dependent & independent variables along with type of design highlighted (table 1), whereas inputs, outputs & network type along with statistical parameters (table 2) were highlighted in Artificial neural network technology.

Table 1: Representing Design of experiment technique used for formulating lipid based delivery systems for treating neuro-degenerative disorders

Lipid based drug Delivery system	Independent variables	Dependent variables	Design of experiment
Solid lipid nanoparticle	Lipid amount, Stabilizer Conc. (% w/v), Homogenization speed (rpm), Homogenization time, Ultrasonication amplitude, Ultrasonication time	Particle size, Polydispersity index, Zeta potential, Entrapment efficiency, Loading efficiency	Central Composite design
Nanoemulsion	Lipid concentration S_{mix} Concentration	Globule size, Polydispersity index (PDI), Percentage transmission	Central composite rotatable design
Liposome	Phosholipids (µmol), Cholesterol (µmol), Tween 80 %, Drug: Lipid %, Amount of organic solvent, Speed of rotary evaporator, Temperature, Aqueous volume (ml), Agitation time, Sonication time, Annelation time	Particle size, Entrapment efficiency, *In-vitro* release	Plackett-Burman design

Table 2: Representing Artificial neural network technique used for formulating lipid based delivery systems for treating neuro-degenerative disorders

Input	Output	Hidden layer	Network type	Statistical parameters
Drug-to-lipid ratio, %Tween 80, %Lecithin	Particle Size, Entrapment efficiency, Cumulative % permeated in 24 hour	1 Leave-one-out cross validation	Resilient back-propagation	Multiple regression analysis, Quadratic modelling, Bootstrap
Virgin coconut oil, Tween 80, Pluronic F68, Xanthan gum, Water	Particle Size	1 With nodes ranging from 1 to 15, Sigmoidal transfer function was used	Incremental backpropagation, Batch backpropagation, Quick propagation, Genetic algorithm, Levenberg-Marquardt backpropagation	Mean squared error, Root mean squared error
Lipid content, Sonication power, Sonication time	Encapsulation efficiency, Absolute loading	1 With 6 nodes	Levenberg-Marquardt algorithm, Quick prob, Back propagation, Batch back propagation	Coefficient of correlation, Absolute average deviation, Root mean square error

Amount of Cholesterol, Amount of edge activator, Phase in which TM is added, Addition of stearylamine, Type of edge activator	Vesicle size distribution, Surface charge, Polydispersity index, Percentage of timolol entrapped.	1 With 5-14 neurons	Feed-forward backpropagation	Multiple regression analysis

2. CONCLUSION:

The short comings of various neuro-degenerative disorders treatment can be overcome by utilizing and formulating them into various lipid-based drug delivery systems. Hence the in this context the chapter highlighted lipid based drug delivery strategies for treating various neuro-degenerative disorders. Apart from this these systems should be developed to reach target site with enhanced efficacy. Further the techniques like molecular modelling should be implemented in formulating lipid based systems for identifying the binding capacities of the drug with components. The screening of the formulation components and optimization of lipid based systems needs to be carried out by molecular dynamics, molecular simulation, Quality by Design and Artificial neural networks techniques there by cost of the systems would be reduced.

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4. DISCLOSURE STATEMENT

None

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