International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 3 May - June 2021, pp: 257-267 www.ijprajournal.com ISSN: 2249-7781

A review onbarriers, transport mechanism and various nanocarrierbased approaches for CNSdrug delivery systems

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Date Of Submission: 05-05-2021 Date Of Acceptance: 20-05-2021

ABSTRACT: In recent era, Nanotechnology is a promising technique for the targeted delivery of drug at specific site of action. Nanomedicines have proven to be effective for the prognosis, diagnosis and treatment of various diseases related to CNS. The treatment of the brain related disorders are at the upfront of the challenge in the therapeutic sector and medical science, still no promising regimen is effective to circumvent the BBB. This review is directed towards the advancement and transformationof novel approaches, inclusive of nanoparticles, lipidic/protein conjugates, liposomes, colloidal carriers, dendrimers, micelles etc. for efficient brain targeting. Herein we have summarized the barriers, transport mechanism, novel theranostic strategies, targeting, applications of the nanotechnology in dealing the therapeutic limitations.

Key words: Nanotechnology, CNS, BBB, theranostic, targeting, liposomes.

I. INTRODUCTION

Amongst the vital organs, one which is most complex i.e. brain comprises just about 2% of the total body weight but controls the bodily functions, being the control centre of the nervous system. The voluntary bodily movements, hormonal levels, glandular secretions, maintenance of the basal metabolic rate, breathing and other involuntary activities are controlled by brain and nervous system(1). Complex emotions, feelings, deep thoughts, past memories and future plans are all also well-co-ordinated by brain. Anatomically, the brain is shielded by various physiological barriers including the BBB (Blood Brain Barrier) and the BCSFB (Blood cerebrospinal fluid barrier)(2). These barriers act as a checkpoint for the regulation of the entry of foreign particles to the brain, harmful stimuli, protection from the toxins, and maintenance of brain homeostasis. The neurological disorders are a result of variations of the functions and structural damage to brain due to changes in the ambience factors, presence of toxins, mutations, aging, infections, physical changes etc(1,3).

The treatment of the brain related disorders are at the upfront of the challenge in the therapeutic sector and medical science, still no promising regimen is effective to circumvent the BBB(4). So, the research sector has been directed to the developmental side for the novel approaches, such as nanoparticles, lipidic/protein conjugates, liposomes, colloidal carriers, dendrimers, micelles etc. for efficient brain targeting. Effective carrier system should possess specific chemical nature, including amphiphilic behaviour, small size, ability to load higher doses, controlled drug release, improvement patient compliance, protection of the drug from the surroundings(5). Some technological limitations includes inability to control the drug amount in the carrier, uncontrolled release, posing higher toxicity, poor loading, biological or chemical interaction with or due to some components of the carrier, the surface charge or the nature of the nano carrier, pose serious and unpredictable challenge to its therapeutic employability as reported by some researchers(6). On the other hand, there have been serious problems in terms of translational perspective, like the aberrant clinical and preclinical profiling, altered physiological response (could be due to difference in physiological and anatomical differences), lack in uniformity of developmental strategies are some of the reasons for limited commercial approval of the Nano carrier formulations(2). Herein we are summarizing the barriers(7), transport mechanism(3), novel theranostic strategies, targeting, applications of the nanotechnology in dealing the therapeutic limitations(8).

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II. BARRIERS FOR PROTECTION OF BRAIN:

To protect the brain from external stimuli, infectious pathogens, foreign materials, toxins etc. and to maintain the integrity of separation from the peripheral system by employing specific physiological barriers(9). Apart from protective role these barriers do maintain the brain homeostasis, and regulate the entry of vital supplies including nutrients, proteins, ions, and metabolites both sides of the physiological demarcation.The barriers mainly include Blood Brain Barrier(BBB) and Blood cerebrospinal fluid barrier (BCSFB)(1).

i) Blood Brain Barrier

Paul Ehrlichdiscovered that the barrier exists between brain and blood which plays protective role by protecting the brain from noxious stimuli, infections, toxins etc., and maintain the homeostasis. Anatomically, the structure consists of Capillary endothelial cells of brain (BCECs), pericytes, microglial cells, astrocytes and neurons(1,2). The primary component of BBB is BCEC, which imparts selective permeability to lipophilic molecules of small size. The BCEC are cemented to each other by the help of tight junctions, which further prevents the paracellular transport of the drugs. These tight junctions are the major cause of higher trans-endothelial resistance (TEER) amongst blood and brain, further restricting the passive diffusion of the external moieties(5). Other cellular components including pericytes and astrocytes play structural role to support BCECs and maintaining the functions of BBB. Being highly selective for small, low molecular weight (<400Da), non-polar compounds, the BBB is also decorated with several special transporter proteins, specific receptors, efflux transport mechanisms, ion-mediated channels etc(3,10). These appendages provide facilitated passage of vital components to the brain.The development of promising and efficient targeting carriers for the brain delivery, requires adequate understanding of physiology of BBB, function and nature of transport mechanism(11).

ii) Blood cerebrospinal fluid barrier

This barrier is located between the cerebrospinal fluid (CSF)and blood. This barrier checks for the entry of toxins, microbes, foreign particles including drugs to the CSF(1,12). This barrier consists of choroidal epithelial cells, arachnoidal epithelial cells, separating ventricular CSF to subarachnoidal CSF from peripheral circulation respectively(13). The choroid plexus is the primary component of choroidal part, which acts a physical, enzymatic, immunological demarcation to assist transport of drug, signalling factors, metabolites etc. These epithelial cells are joined by gap junctions, limiting the permeability of barrier. Being less stiff, the BCSFB are more permeable for external substances including drugs as shown in fig. 1(14).

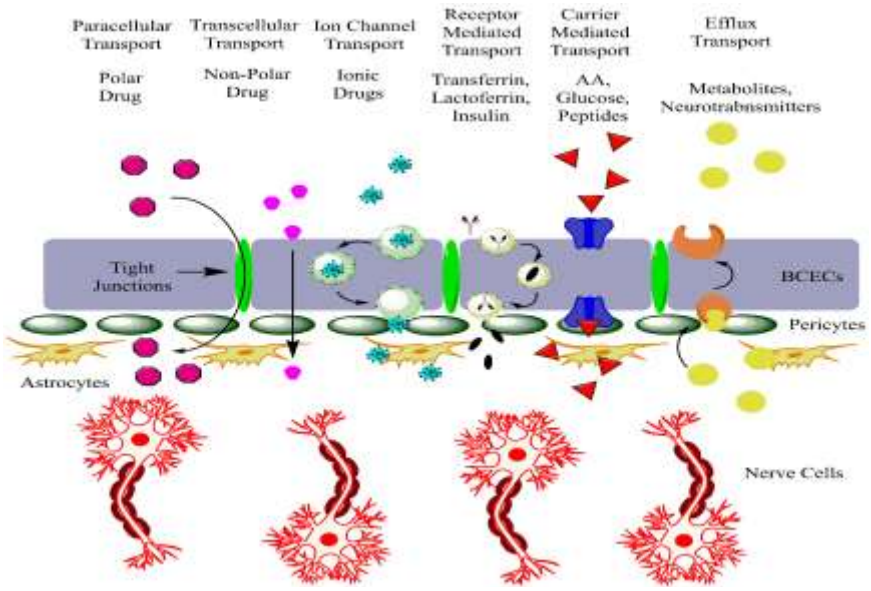

Fig. 1. Blood cerebrospinal fluid barrier mechanism.

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Volume 6, Issue 3 May - June 2021, pp: 257-267 www.ijprajournal.com ISSN: 2249-7781

III. BBB TRANSPORT MECHANISM

The transport across BBB is restricted to most foreign molecules, drugs, and toxins being highly selective. There are still mechanisms involved for assisting the essentials to be transported across brain. Hydrophilic moieties, polar compounds cross BBB through paracellular pathway/normal diffusion process(15). While a transcellular path is preferred by lipophilic moieties including steroids, and alcohol etc. The moieties transported actively are via carrier mediated flux, transcytosis(13), receptor mediated transport(16), & efflux transporters(17). Different mechanisms are as follows:

a) Passive Diffusion

Most of the essential nutrients, neurotransmitters, amino acids, hormones, and small lipophilic molecules/drugs enter brain via this ubiquitous mechanism of transport. The transfer through passive diffusion is gradient dependent(5,7). Also, it depends on the size, physicochemical nature of the molecules. The drug first disperses in lipid bilayer of the endothelial lining in micro-capillaries & is then released in the brain. This mechanism is specific to small size, low molecular weight neutral compounds(18).

b) Receptor mediated endocytosis

Also termed as clathrin mediated transcytosis and is highly specific involving the internalization of ligand-receptor complex in vesicles. It's a type of active transport involving the dissipation of energy(5,9). Ligand specificity towards a receptor is the key for transportation. Through a receptor mediated endocytosis the ligand complex enters cytoplasm of endothelium, followed by exocytosis of ligand complex at albuminal end. The ligand, artificial or natural, antibody/peptidal with an affinity to receptors at BBB.The most abundant receptors at the capillary endothelium surface are Low density lipoprotein receptors (LRP 1 and 2), assist the transfer of specific ligand or complex with a carrier/drug(1,19).

c) Adsorption Transcytosis

A type of active transport whereby the polycationic ligands especially proteins and peptides bind electrostatically to micro-anionic molecules to the luminal side of brain endothelium. Electrostatic interaction between negatively charged ligands (glycoproteins) and positively charged including albumin at the endothelium level is the major principal of adsorptive transcytosis(13,20). The transporters involved in adsorptive transcytosis include Glucose Transporter 1, Monocarboxylate Transporter 1, Excitatory amino acid transporters, cationic amino acids, various organic cationsetc(7).

d) Facilitated/Carrier mediated transcytosis

Endogenous substances including amino acids, glucose, vitamins and some neuropeptides to brain are mediated by carrier at BBB therefore termed as carrier mediated mode of transcytosis. This mechanism can be used as a targeting opportunity for several drugs to brain. Chemical modifications maybe done to achieve structural similarity with endogenous substances to ease up crossing of cellular barriers the enhance the uptake to brain(21). An example to fit into it is anti-parkinsonian drug, whereby exogenous dopamine as levodopa (neutral charge), is carried up by neutral amino acid transporters which enters brain easily(22).

e) Cellular Transport

During events of inflammation or any physiological dysfunction, cellular defence system which includes monocytes, macrophages, neutrophils etc. is activated. Accumulation of these cells at injury site result in protection and killing of infectious microbes. This physiological response can also be used to deliver drugs to particular sites of brain. These maybe related as Trojan horses which further assist the drug transport across BBB. Specifically, monocytes offer better carriage services for bioactives(1). Studies have demonstrated an improvement in the uptake of nanoparticles of superparamagnetic iron oxide to inflamed sites in brain. Also, improvement in permeation adds up to the permeation enhancement. Other reports also indicate a similar approach of using monocytes as preferred carriers to brain. Just not success reports but prominent failures as a result of poor drug loading, inadequate transport, an early release etc. pose certain limitations to the strategy(23,24).

f) Efflux Transporters

Again a type of active, energy dependent mechanism of transport, is responsible for an outward movement of toxins, metabolites, neurotransmitters, some drugs (antibiotics)(17). Presence of efflux mechanism confines the drug exposure to brain tissue, it doesn't matter whether small lipophilic moieties are involved too. The

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efflux mechanism comprises of several surface proteins at cellular surfaces or at BBB. A superfamily includes ABC (ATP-Binding Cassettes) which is present in almost all live beings(25). A key element of the superfamily includes, P-Glycoprotein or P-gp, which is responsible for actively regulating the efflux of several lipophilic drugs across BBB.P-gp is membrane bound protein expressed greatly over the luminal side of BCECs, and expressed in a lesser extent to brain parenchyma, glial cells, and nerve cells. P-gp is considered as the most important of ABC transporters in brain(26). The efflux mechanism alters the pharmacokinetics of several drugs, including anticancer molecules, other CNS targeting agents. To overcome the same, efflux inhibitors are a preferred resort to improve the therapeutic efficacy of drugs, & modifying the brain distribution. Therefore, a proper understanding of physiology of efflux mechanism is required for enhanced drug delivery to brain(20).

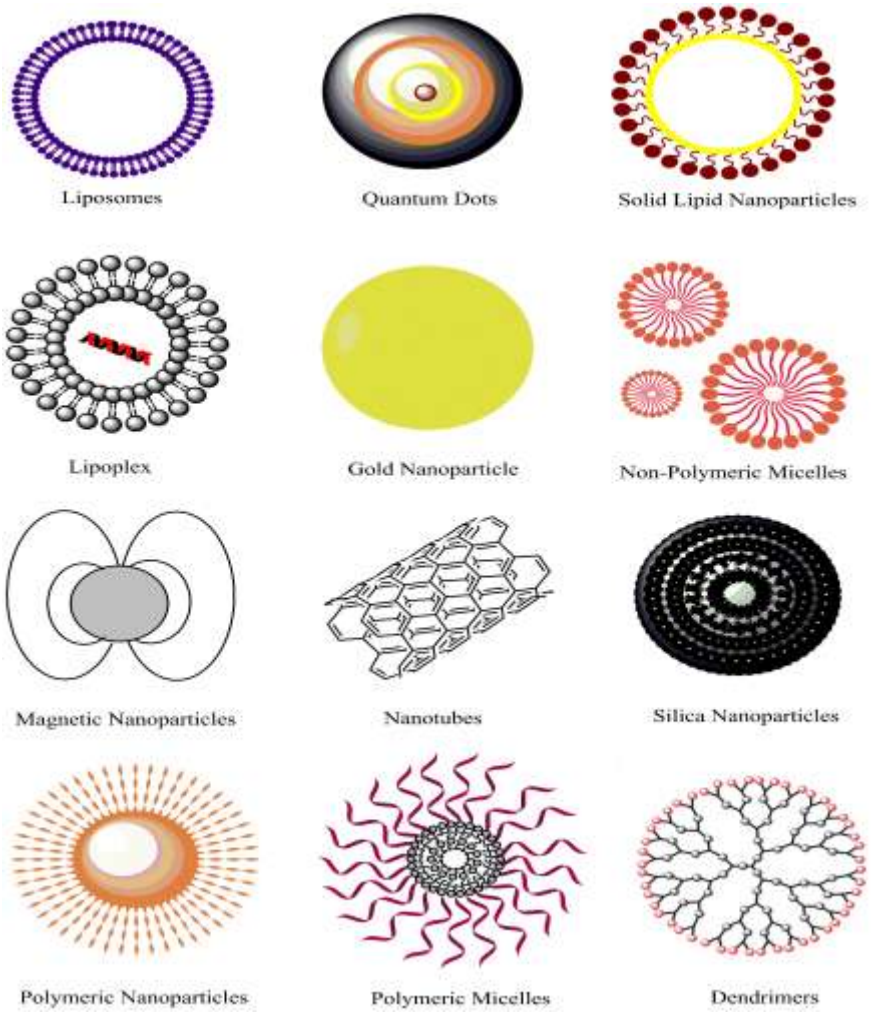

Fig 2. Novel nanocarriers for targeted drug delivery in brain.

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Volume 6, Issue 3 May - June 2021, pp: 257-267 www.ijprajournal.com ISSN: 2249-7781

The approach of nanotechnology aims at retaining the drug activity during the stage of preparation, ensuring the stability and the physicochemical properties under the control, and optimization of the drug release(18). The Nano carriers, basically are stable in a biological system whereby these represent a system of controlled release, also act as biological protectives when these are in contact with the biological fluids(27).

Nanotechnology is a promising technique for the targeted delivery of drug at specific site of action. Nanomedicines has proven to be effective for the prognosis, diagnosis and treatment of various diseases related to CNS. In recent era, Nanomedicines has also been used for biomedical applications. Nano formulations for target specific delivery across BBB can be engineered to carry out therapeutic action(11). The pharmacologically active constituent of drug is engineered with nanocarriers to protect drug from enzymatic degradation, cross BBB, release drug at specific pH which leads to delivery of drug at target site of brain with minimal loss. Nanocariers encapsulate the drug and helps to achieve the desired theranosticactivity(21).

IV. IDEAL PROPERTIES OF NANO FORMULATION FOR DRUG DELIVERY TO BRAIN:

Ideal characteristics of any drug molecule to cross BBB should have high lipophilicity and small size so that it can passively diffuse across the BBB. Because, lipophilicity of any drug molecule is correlated with permeability and solubility of a compound. Lipophilicity property is a two-edged sword and sometimes drug parameters are affected by lipophilicity. High lipophilicity may lead to the formation of compounds with rapid metabolism, low solubility, and poor absorption. So, nanotechnology can be used for drug delivery. NPs and nanostructures must have certain properties to be used for drug delivery to the CNS. Fig. 3 will depict summary of the ideal characteristics of NPs for the delivery of drugs to the brain(21).

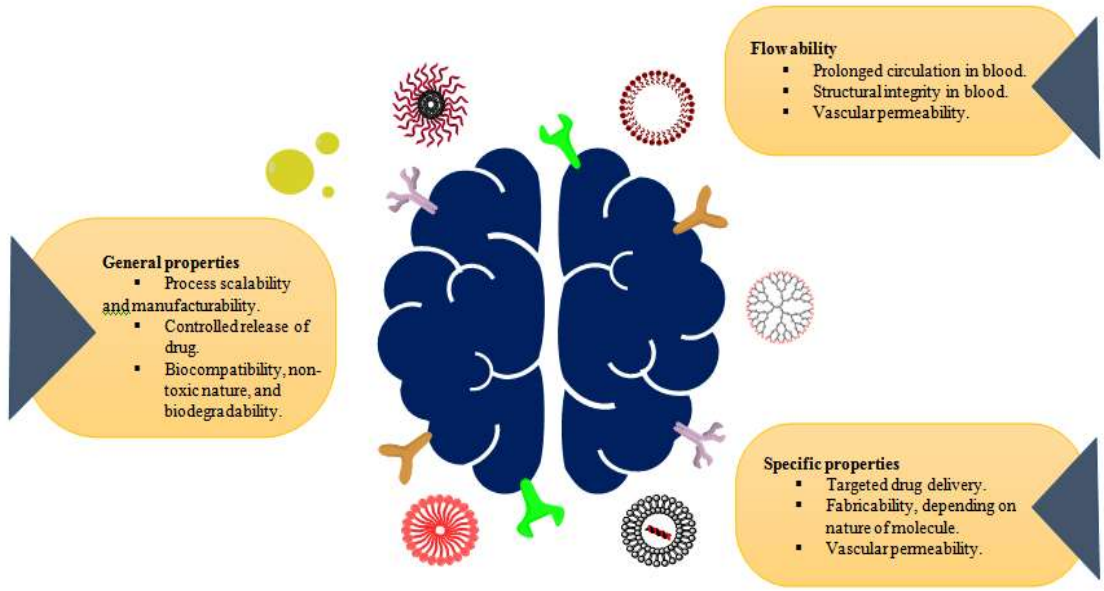

Fig 3: Ideal properties of Drug molecule to cross BBB

V. NANOFORMULATIONS FOR DRUG DELIVERY:

i) Liposomes as nanoformulation:

Liposomes are composed of natural and synthetic phospholipids and cholesterol. It consists of bilayervesicles in which hydrophilic core is encapsulated with lipophillic bilayer. Liposomes were invented by Bangham and co-workers during 1960s(28). Phospholipids are amphiphatic molecule having hydrophobic tail and hydrophilic head. Cholesterol acts as fluidity buffer. Liposome in blood stream has been taken by reticuloendothelial system and engulfed by macrophages by the process of endocytosis(29). Various methods has been developed till now for the preparation of liposomes like handshaking

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methods, freeze drying method, micro-emulsification, ultra-sonication , freeze thawing and solvent dispersion methods like double emulsion method and reverse phase evaporation etc(30). On the basis of structural parameters. We can classify liposomes assmallunilamellar having range from 10-50nm, Large unilamellar lies within 50-1000nm range and multilamellar having size range from 20-100 nm. Conventional liposomes have drawback of circulation for short time as it was easily recognized by the cells of RES. To enhance circulating time, Liposomes are being coated with PEG(10). Various ligands like monoclonal antibodies, transferring receptors, lactoferrin and glutathione are used for targeted delivery of liposomes in brain.Examples of liposomes for targeted delivery of drug in brain are depicted in table 1

Table 1. Liposomes for targeted delivery of drug

S.No.	Formulation	Outcome	Reference
1.	H102 peptide-loaded liposome	Increased uptake in hippocampal region after intranasal administration.	Zheng et al. (2015)
2.	Donepezil loaded liposomes	Higher encapsulation, sustained release behavior, improvement in bioavailability on intranasal administration.	Asmariet al. 2016
3.	Ascorbic acid thiamine disulfide modified liposome	Improvement in uptake on encapsulation.	Xiao et al. (2019)
4.	Liposome and polymeric nanoparticles for combined delivery of atorvastatin and curcumin to treat atherosclerosis	Improved cellular targeting, reduced side effects.	Li et al. (2019)
5.	(TAT) conjugated doxorubicin encapsulated liposomes.	Higher tumor distribution, high availability across BBB and specific cell targeting to the brain glioma.	Zonget al. (2014).
6.	Transferrin-conjugated liposomes with 5-fluorouracil to the brain facilitated by receptor-mediated endocytosis	Significant increased brain uptake.	Soniet al. 2008
7.	Conjugation Of prednisolone-loaded liposomes with mAbs	Better targeting, improved distribution.	Schmidt et al. (2003).
8.	a-tocopherol (Toc) and omega3 fatty acid were loaded into liposomes with anti-Alzheimer drug tacrine for the treatment of AD with intranasal route	Increased efficacy, increased cellular uptake.	Coraceet al. (2014)

ii) Polymeric nanoparticles

Polymeric nanoparticles are solid nanoparticles within range that varies from 10 nm to 1000nm(2). It is a special form of drug delivery system in which pharmacologically active drug is delivered to target site. In polymeric nanoparticles consists of biodegradable matrix of natural or synthetic origin. polylactide, polylactide–polyglycolide copolymers,κ-polycaprolactones, and polyacrylates(31)are examples of polymers of synthetic origin used for targeting brain(20). Polymers of natural origin like Alginate, albumin, or chitosan are most widely used polymers till now(32). Solvent evaporation, spontaneous emulsification, solvent diffusion, or polymerization are commonly used methods for the preparation of

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polymeric nanoparticles. Coating of polymers are used to encapsulate drug. Structural modifications such as size and shape of nanoparticles impact the transport mechanism in brain for example, polysorbate nanoparticles can easily penetrate into brain due to smaller size and also provide site specific therapeutic action as shown in table 2(33, 34).

Table 2.Polymeric nanoparticles for targeted delivery of drug.

S.No.	Formulation	Outcome	References
1.	Coating of poly (n-butylcyanoacrilate)(PBCA) NPs with 1% polysorbate 80 (PS80).	Amplification in theconcentration of rivastigmine or tacrine drug inside the brainas compared with free drug and selectively targeted to the CNSfor AD reducing the hepatic or gastrointestinal side-effectscoupled with conventional treatment approach.	Wilson et al. (2008).
2.	Dalargin containing PS80-coated PACA nanoparticles.	Improvement in crossing the BBB andproduce its antinociceptive effect, after oral administration.	Das and Lin(2005).
3.	PS80-coated PACA nanoparticles.	Act on ApoEandB from the bloodstream upon intravenous injection followedbytranscytosis across BBB using the low-density lipoproteinreceptors.	Kreuter (2013)
4.	PEG-PLGA nanoparticle.	Improvement inbraintargeting of shikonin to treat glioma.	Li et al. (2018)
5.	AAconjugated chitosan nanoparticle.	Effective targeting of adipeptidyl peptidase-4 enzyme inhibitor, saxagliptin.	Fernandeset al. (2018)
6.	Chitosan nanoparticle.	Improvement in the therapeuticefficiency of selegiline thereby actingas a potent anti-Parkinson's agent.	Rukmangathe net al. (2018)
7.	Folic acid and wheat germ agglutinin conjugated methoxy PEG-PCLnanoparticle.	Targeted carmustine, etoposide and doxorubicin to the glioblastoma cells of the human brain.	Kuoet al. (2019)

iii) Nanoemulsions asnanoformulation:

Nanoemulsions are dispersion of two immiscible liquids stabilised by surfactant molecules. It is thermodynamically stable dispersion of oil phase and water phase with a surfactant layer. Nanoemulsions are classified in three types oil in water, water in oil and bi-continuous(35). They are kinetically stable and having clear and translucent appearance having size within range of 100-500 nm(35). It has been used for targeted delivery to brain as it overcomes drawbacks of conventional drug delivery system. It can easily bioavailable, can easily penetrate BBB, provide targeted delivery and enhance site specific therapeutic actions which cannot be possible by conventional drug delivery systems. Surface modifiers used in preparation of nanoemulsions increase their versatility. Vegetable oils, peanut oil, flex seed oil and many other oils used in preparation of nanoemulsionincrease their biocompatibility. Nanoemulsions provide sustained drug release(35,36). Various nanoemulsions with

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Volume 6, Issue 3 May - June 2021, pp: 257-267 www.ijprajournal.com ISSN: 2249-7781

their outcome for targeted drug delivery have been given in table 3.

Table 3.Nanoemulsions for targeted delivery of drug.

S.No.	Formulation	Outcome	Reference
1.	Pretomanid loaded nanoemulsion for intranasal administration to enhance the brain permeation of thedrug.	Enhanced brain permeation	Shoboet al. (2018)
2.	Encapsulated the zolmitriptan, to the mucoadhesivenanoemulsion and deliveredit via intranasal route.	Improved bioavailability and permeation.	Abdouet al. (2017)
3.	Developed risperidoneloadedlecithinenanoemulsion for drug deliveryto the brain via parenteral route.	Improved delivery to brain.	Dordevicet al. (2015),
4.	Parenteralnanoemulsion for brain targeting of carbamazepineto treat seizure and evaluated its pharmacokinetic efficiency.	Improvement in bioavailability.	Tan et al. (2015)

iv) Solid lipid nanoparticles:

Solid lipid nanoparticles are emerging nowadays as effective nanoformulation for site specific therapeutic action. Solid lipid nanoparticles have introduced to overcome drawbacks associated with polymeric nanoparticles(37). These are novel nano carriers made of lipid with in size range of 10-1000nm. SLNs are made up of solid lipids, emulsifier and water. Lipids in SLNs consists of triglycerides, partial glycerides and fatty acids, sterids and waxes. Composition and particle size of SLNs directly affect drug release. SLNs are advantageous over other nanocarriers as it can easily be manufactured, has good shelf life, shows controlled release and also are biocompatible. SLNs when modified with PEG increases the circulation time and hence the sustained drug release(37,38).

Permeation through BBB which leads to enhancementof drug delivery to the CNS for example SLNs loaded with antitumor drugs like camptothecin and doxorubicin(39,40). Some examples of solid lipid nanoparticles for targeted drug delivery have been explained in table 4.

Table 4.Solid lipid nanoparticles for targeted delivery of drug

S. No.	Nanoparticles formulation	Outcome	Reference
1.	Sterylamine-based SLNs containing clozapine, an antipsychoticdrug for delivery in brain	Improved bioavailability.	Manjunath and Venkateswarlu, (2005).
2.	Quercetin loaded SLNsto treat AD	Improved targeting and better efficacy.	Dhawanet al.,(2011).
3.	Atazanavir loaded SLNsfor treatment of HIV-encephalitis	Enhanced uptake and better distribution.	Chattopadhyayet al.,(2008).
4.	Riluzole-loaded SLNs amyotrophic lateral sclerosis	Higher drug loading, better efficacy, and lower indiscriminate distribution.	Bondìet al.,(2010).

v) Dendrimers:

Dendrimers are artificial macromolecules composed of 3 dimensional highly branched structure. Dendrimers are one of the novel strategies used for target delivery of drugs in brain. There are various methods used for synthesis of dendrimers such as divergent, convergent, hypercore and branched monomer method, double exponential and mixed growth technique(1,13). Polyamidoamines commonly known as

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starbustdendrimers are the first synthesized dendrimers. Encapsulation, electrostatic interaction and covalent conjugation are the mechanisms of drug delivery. Dendrimers are widely applicable for targeted and controlled release drug delivery, formulation of nanodrugs, as coating agents, contrast agents,theranostic purpose, delivery of anti-cancerous drugs and gene transfection(41). Some examples of dendrimers formulations have given in table 5.

Table 5.Dendrimers for targeted delivery of drug

S. No.	Formulation	Outcome	Reference
1.	AnovelPEGylated quantum dot nanoprobe conjugated with aptamer32 for fluorescent imaging of brain tumor	Better permeation, and diagnostic improvements.	Tang et al. (2017)
2.	Cd-Se-ZnS quantum dots,incorporated into pH-triggered polymeric micelle and usedas fluorescent imaging nanoprobe.	Able to distinguish cerebralischemia affected region in the brain.	Yang et al. (2017)
3.	iRNA was complexed with a biodegradable PAMAM dendrimer as a gene vector.	fluorescent-labeledsiRNA appeared in the cytoplasm and processes of neurons and of glial cells in many brain regions, incorporating the amygdala, cerebralcortex, and striatum at 1 h after nasal administration.	Kim. et al. (2012)

VI. CONCLUSION

Since past few decades' scientists and researchers working in field of neurology are facing challenge for the targeted delivery of drugs to the brain by crossing BBB with high therapeutic efficacy and toxicity.Different novel drug carriers for targeted delivery in CNS like liposome,nanoparticles, dendrimers, nanoemulsions, nanogels,quantum dots, etc. have been found useful in brain targeting.These novel modes of delivery help to address the challenges of drug permeation, lipophillicity, expulsion from BBB. Also, the direct nose-to-brain drug delivery appears as apotential and alternative approach for effective brain drugdelivery. As literature revelead that nano particulate drug delivery system is very well suited for the diagnosis and treatment of brain disorders due to their physical, chemical and biological properties. Many of nano formulations are nowadays focused on improved administration of drug to CNS disorder patients by investigation of various new technology like biomedical sciences, biomaterials.

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