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POTENTIAL OF NANOPARTICLES FOR THE DELIVERY OF ANTIDEPRESSANTS

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INTRODUCTION

History: The development of the 20th century was the creation of categories to classify various mental illnesses. If you were having trouble with depression, you should go lay on the stereotypical psychologist's couch and engage in talk therapy. The Freudians were more interested in treating the psychological causes of mental illness, while the psychobiological camp argued that they could treat the symptoms with drugs. Also debated were the new categories of mental illness that were created to assist clinicians in making clear diagnoses purposes. Drug companies pushed for the new categories of drug under FDA regulations. The rate of depression in the U.S. has increased dramatically over the last century. In 1905, just 1% of Americans reported a major depressive episode by age 75. In 1955, 6% experienced a major depressive episode by age 24.[1]

Types of depression

- Major Depression
- Persistent Depressive Disorder
- Bipolar Disorder
- Seasonal Affective Disorder (SAD)
- Psychotic Depression
- Peripartum (Postpartum) Depression
- Premenstrual Dysphoric Disorder (PMDD)
- Atypical Depression

Major Depression

It is a condition were the patients feel depressed state or one who loses interest in pleasurable activities and show symptoms like.

- Weight gain or loss
- Lack of decision making
- Feeling restlessness
- Feeling guilt
- Trouble in concentrating
- Loss of physical activities
- Thoughts of suicide
- Loss of speech

In major depression, more than five symptoms are diagnosed and these symptoms last days for 2-3 weeks longer. For some patients with severe depression, the antidepressant medications are less effective. So electroconvulsive therapy (ECT) in this electric pulses used and repetitive transcranial magnetic stimulation (rTMS) is a special magnet used to stimulate certain areas in brain.

Persistent Depressive Disorder

The state of depression will lasts for 2-3 years or longer, so it is termed as persistent depressive. The term used to describe two conditions known dysthymia (low persistent depression) and chronic depression. The symptoms includes.

- Retardation of energy
- Feel hopelessness
- Loss of appetite
- Fatigue
- Low self-admiration

The patients are treated with antidepressant medications, psychotherapy or combination of both.

Bipolar Disorder

It is also known as manic depression, which is characterized by serious and fluctuation in mood swings. It affects more than 1-2% of world population. Bipolar disorder are of two types bipolar disorder I which is characterized low manic episodes in persons and bipolar

disorder II in the person has no manic episodes but significant single period of hypomanic depression. The symptoms are –

- Extreme energy
- High thoughts
- False hallucinations
- False delusions
- More distractions easily.[2,3]

Seasonal Affective Disorder (SAD)

It is a recurrent of individual struggle of a seasonal pattern of depression. People with seasonal disorder has alterations in serotonin neurotransmitter. Serotonin reuptake transporter (SERT) which transports serotonin from synaptic cleft region to presynaptic region where it leads in alteration of SERT levels (i.e higher the SERT activity, lower is the serotonin reuptake. The prevalence study on Seasonal Affective Disorder has revealed that it affects women than men and the ratio is 4:1 of the age 18 – 30 years.[4]

Premenstrual Dysphoric Disorder (PMDD)

Premenstrual Dysphoric Disorder is seriously characterized by cognitive and physical symptoms in women. The prevalence was found approximately 5 – 8% by epidemiology studies in women which are affected with dysfunction in premenopausal. The women who suffer from Premenstrual Dysphoric Disorder (PMDD) has most common alterations in mood and behavioral symptoms such as mood dominate, tension and irritability. About 15% of women suffering from symptomatic disorder leads to suicide attempts. The high risk factors in PMDD is traumatic episodes, evolutionary complications, sexual aggregation during pre-ovulation period. Also there is alteration in estrogen and progesterone levels. There is increased level of stress response in PMDD during luteal – phase reactivity (i.e late luteal – phase response). The symptoms (somatic) includes.

- Migraine
- Premenstrual headache
- Painful mense
- Dysmenorrhea
- Epilepsy
- Changes in comorbid.[5,6]

Atypical Depression

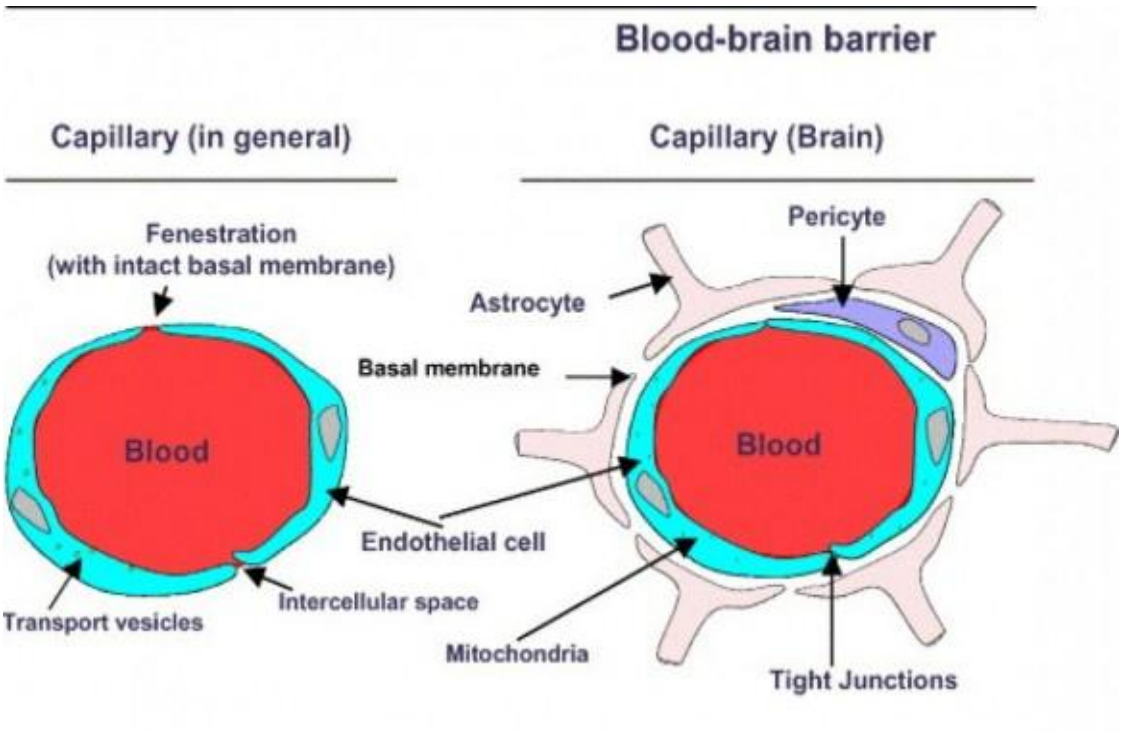
The study was carried by Diagnostic and Statistical Manual of Mental Disorder (DSM) on atypical depression and the symptoms are.

- Brighter mood to positive events
- High appetite
- A significant two or more features are present as symptoms
- Leaden paralysis (heavy feelings in legs and arms)
- Increased sleep
- Psychomotor activity
- Impairment of mood disturbance

Atypical depression is seen in outpatients of most common clinic psychiatry. The diagnosis of atypical depression consists of major depressive disorder. The patients with atypical depression has comorbid with severe anxiety (social phobia). Atypical depression is a multiple disorder (eating disorder, pain, insomnia, fatigue and poor body image) were manifested. The first atypical depression was observed in clinical trials of depressed patients by West and Dally in 1959.[7]

Blood-brain Barrier (BBB)

Blood-brain barrier is a barrier for brain structure and function. BBB is most important physical barrier which control the brain cells environment. It is formed by cerebral micro-vascular endothelial cells. The BBB has tight junction that controls the required nutrients transport to brain. Nearly 98% of all micro-molecular drugs cannot access through this tight junction. So to overcome this there are different techniques developed and that includes nose-brain transport, targeting transcytosis receptors, efflux transporters, osmotic BBB disruption and carrier-mediated transport. The risk of opening blood-brain barriers may lead to entry of neurotoxic endogenous molecules such as plasmin, proteins with iron and serum albumin through blood steam.[8,9]

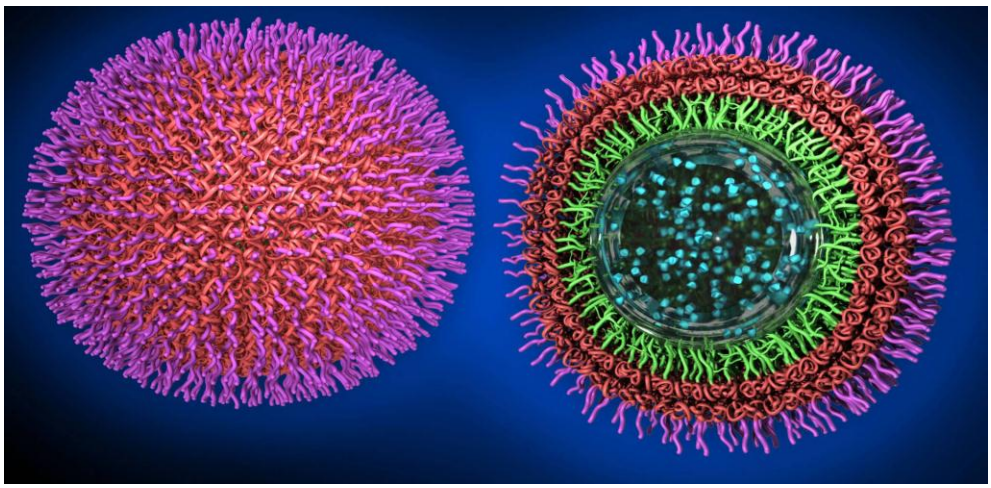


NANOPARTICLES

History

The specific construction of nanoparticles for drug delivery was accomplished by Paul Ehrlich. The attention of targeted drug delivery may be effective in therapy. The word ‘’Nano’’ derived from Greek that is Dwarf – ‘a tons’. In 19th century, the giant progress was seen in the field of pharmaceutics, biopharmaceutics and pharmacokinetics. Nanoparticles occurring naturally are organic nanoparticles (Proteins, viruses and others) and inorganic nanoparticles (Metals, iron oxyhydroxides and others).[10] Nanotechnology defined as a technique used for understanding and controlling the specific region of dimensions and size range from 1 – 1000nm, useful in novel applications. Golden era (1980s) for nanoparticles started. The book titled ‘’Engines of Creations: The coming era of Nanotechnology’’ by Taniguchi of Tokyo University in 1986. The 21st century began with marvelous interest in the field of nanotechnology. U.S President Bill Clinton has funded for research and development of nanoparticles in 2000. Further after 3 years, President G.W. Bush made a law for Nanotechnology Research and Development Act. Recent began of 21st century gained a framework in the interest by industrial applications and exponential growth. Nanotechnology has made a huge impact on human life with great potential in novel drug delivery. It led to emerge in additional scientific ethics and discipline in nanomedicine for beneficial of human health and environment. Nanomedicine includes biomaterials, bio-imaging, biosensors and

tissue engineering was studied to see benefits in development of novel drug delivery system.[11] Recently the researchers have higher information in nanoparticles which could be in psychiatric diseases like bipolar disorder, Major depressive disorder, Schizophrenia for brain drug delivery system. Nanoparticles applications in neurophysiology experiments for evaluations of certain physiology of normal brain function. Nanoparticles loaded medications in clinical research to know therapy strategies and behavioral physiology.[12]



Encapsulated nanoparticle

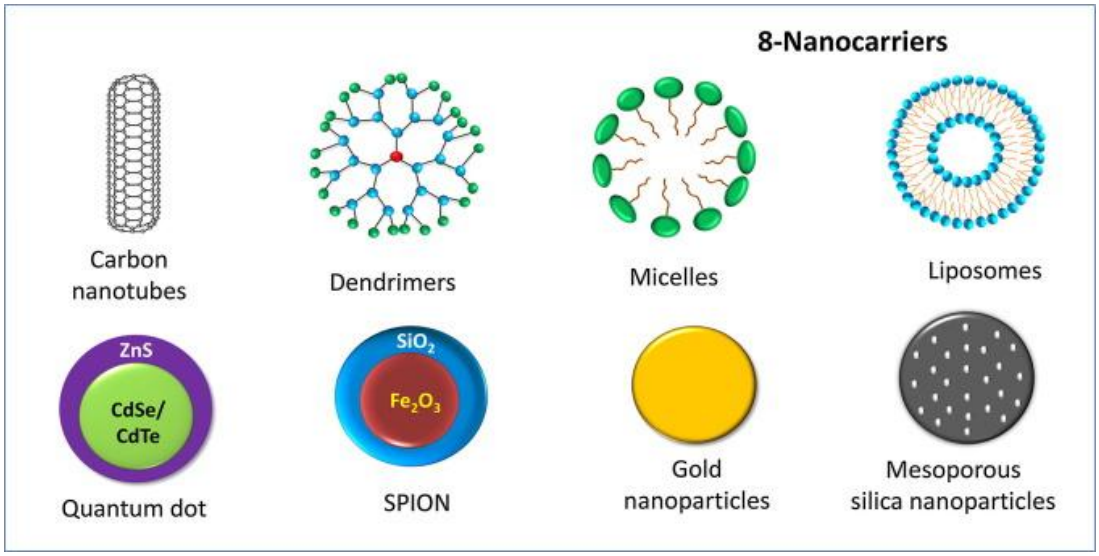
Nanoparticles for Blood Brain Barrier (BBB)

In neurology and psychiatry practice major challenges faced was inability of medications to pass through blood brain barrier. Research and development in pharmaceutical industry has lead role in new opportunities for researchers and medical foundation. Blood brain barrier delivers oxygen and essential nutrients to central nervous system with unique properties by tight junction help regulating the ion movements, cells and molecules between blood vessels and brain. A proper maintenance central nervous system homeostasis for a normal neural functioning and protection. Blood brain barrier contains two main cells that is mural cells and epithelial cells. Mural cells are made up of vascular smooth muscles with pericytes. And epithelial cells are made up of modified squamous epithelial cells that forms the walls of blood vessels.[13] Blood brain barrier is a unit of system like epithelial cells, astrocytes and pericytes. Recently in 2000, a study has targeted on antidepressant drugs with a main goal for effective and reduce toxicity. Major antidepressant drugs (duloxetine) was designed and formulated in solid lipid nanoparticles. Nanoparticles have physicochemical and biomimetic carriers of drugs which makes them more effective for medical applications. The different types of nanoparticles are liposomes, SLP, non-polymeric micelles, dendrimers, polymeric

nanoparticles, nanotubes, quantum dots and gold nanoparticles. The most common approach to pass BBB is to formulation of nanoparticles with neutral surface charges or coat the surface with hydrophilic surfactant (polysorbates). To expose stability with blood and long circulation time to be a successful targeting and crossing BBB. Nanoparticles should be non-toxic, non-inflammatory, biocompatible and non-immunogenic in nature. It is important for nanoparticles to enhance brain drug delivery and implement to cross BBB themselves. The role of nanoparticles is to increase drug concentration inside or establish a tropical high concentration gradient between blood and brain. Later the gradient itself should create a passive diffusion at tropical areas.[14] Nanoparticles strategies to target brain with specific receptors-mediated transcytosis. For example – Tween 80, LDL, OX26 – liposomes conjugated and anti-transferrin antibody receptors have been shown themselves a capable to transport drug into the brain. The chimeric gene (combination of portions of two or more coding sequences to form a new genes). Polymeric nanoparticles has been potent in both research and clinical therapeutic fields.[15]

Methods of Nanoparticles Preparations

- Solid Lipid Nanoparticles
- Polymeric Nanoparticles
- Dendrimers
- Liposomes
- Emulsification – Solvent Diffusion Method
- Salting out



Different types of nanocarriers

Solid lipid nanoparticles (SLNs)

These are lipid based nanoparticles (i.e. lipid drug conjugate type of eccentric carriers). There have been advantage of using body temperature for.

- Dermal
- Pulmonary
- Rectal and
- Parenteral delivery.

Solid lipid nanoparticles of highly purified triglycerides, use of waxes with different surfactants. Ideal characteristics of SLNs preparation which is protected by incorporated drugs, physical stability, controlled release of drugs. LDC are lipid modified particles to overcome from SLNs and they are developed for lipophilic drug carriers. SLNs are carriers which melts lipid in aqueous surfactant of high homogenization pressure and have solid colloidal with hydrophobic core. Several study reported that Solid lipid nanoparticles have enhanced mediated brain drug delivery.

Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles are prepared by coating material with nonionic surfactants, where drugs are embedded in polymer core. The size ranges from 50 – 150 nm. Drugs are incorporated by a process with polymerization. For example – Doxorubicin a antineoplastic agent with PEGylated or PLGA. Polymeric nanoparticles formulations may reduce immunogenic interaction and intermolecular interactions. The rate of drug release from polymeric nanoparticles is usually occurs by diffusion or desorption process. Some researchers have reported that poly (butyl cyanoacrylate) embedded polymeric nanoparticles delivery into neuronal cells has gained importance.[16]

Dendrimers

Dendrimers are highly branched, well – defined structure, branched with specific sites for ligands. Dendrimers has 3D – structural constituents and they are.

- Central core
- Branched sites
- Surface groups.

Dendrimers are water soluble and act as monomer molecules with core which forms a building complex of foaming layer and which partially reduce growth. Selection of core depends upon

- Monomers used
- Functional group.

The surface of dendrimers act as a active group which provides attaching ligand group. For example – Folic acids, antibodies, PEG etc.

PAMAM (poly amido amine) used as biomedical applications. PAMAM dendrimers are used with anticancer drugs. For example – 5-FU, Doxorubicin, Methotrexate. The size range influence cytotoxicity of PAMAM dendrimers. Positive dendrimers present in the systemic circulation and interact with blood components, resulting in non-stability/imbalance in the cell membrane and cell lysis.

Liposomes

Liposomes are nano vesicles r tiny lamellae drug delivery system with spherical shape consists of amphiphilic in nature. Liposomes are classified on basis of size and bilayer content, they are – SUV (Small unilamellae vesicles), LUV (Large unilamellae vesicles) and MLV (Multi lamellae vesicles). Small unilamellae vesicles are small size and have single lipid. i.e. 20 – 25nm. Large unilamellae vesicles have larger size >100 nm with single lipid layer. Multi lamellae vesicles consists of multiple lipid layers separated by aqueous layer. Liposomes are widely applied for brain drug delivery. For example – Cerebral ischemia and brain tumors. Liposomes reduce systemic toxicity and protect the incorporated drug from degradation. Liposomes are biocompatible used for improving or altering the ability of brain drug delivery by mitotic inhibition. For example – Paclitaxel. Liposomes are composed of cholesterol and phospholipids. Liposomes have been increase in drug stability, solubility and improve pharmacokinetic properties of rapid metabolic drugs, chemotherapeutics agents and reduce side effects. They also reported to increase in-vitro and in-vivo drug release of anticancer drugs. Drug release of incorporated drugs from liposomes is usually depends upon composition if lipids, pH, osmotic environment of liposomal formulation and surroundings.

Emulsification – Solvent Diffusion Method (ESD)

Emulsification – Solvent Diffusion Method is a basically consists of hydrophilic drugs are encapsulated by dissolving in partially water soluble. Polymer and drug products are

dissolved I organic solvents such as Chloroform, Ethyl acetate and aqueous emulsifier which will lead to solvent diffusion from internal phase to external phase until saturation occurs. The polymer water solution, leading to solvent evaporation to external phase and forming nanocapsules. The elimination of solvent through filtration or evaporation. ESD formulations have been prepared. For example – Doxorubicin loaded PLA nanoparticles and Plasmid – DNA loaded PLA nanoparticles.[17]

Salting Out

Salting out is a technique to formulate o/w type emulsion of two phases by mechanical mixing. This technique was to overcome from emulsion – solvent diffusion and nanoprecipitation methods. tcolloidal stable with high salting out agents. Solvent diffusion occurs due to influence in presence of salting out agents to form o/w type emulsion. At sufficient amount of salting out agents which enabling organic solvent to diffuse in water phase occurring interfacial interactions to form a PNPs. The solvent from PNPs suspensions is removed by distillation process. The repeated washing removes salting out agents. The common salting out agents used for PNPs formulation are ethanol, methanol and acetone. Addition of stabilizers enhances drug – entrapment efficiency and also viscosity.[18]

Advantages of nanoparticles

- Nanoparticles are used for large tissue study.
- The contrast agents not required provides high information of nanoparticles bio-distribution.[20]
- It make easy entry into tissues.
- They increase cellular uptake.
- The programmed nanoparticles used for recognizing tumor cells.
- They are small, rapid and highly sensitive tools for targeted drug delivery.
- They are used as long clearance period.
- They increase therapeutic effective.
- Increase bioavailability.
- They increase surface area of active agents.
- Helpful in development of new medicines.
- They enhance BBB permeation.

Disadvantages of nanoparticles

- Lack of therapeutic information on humans.
- Toxicity, environment of nanoparticles is primarily concern.
- They have limited targeting sites.[19]

Applications

- Nanoparticles are used to enhance transport across through endothelial cell layer.
- Nanoparticles leads fluidization of membranes.
- Nanoparticles (Poly alkyl cyanoacrylate) for anticancer drugs.
- Insulin loaded nanoparticles (Poly isobutyl cyanoacrylate) for peptide delivery.
- Nanoparticles for lymphatic delivery
  Ex – Poly (lactic-co-glycolide)
- Nanoparticles are used as therapeutic agents to cross through BBB.
- Pilocarpine loaded nanoparticles (polybutylcyanoacrylate) to reduce intraocular pressure.[20]
- Nano-suspensions used in controlled delivery of poorly soluble drugs.
- Polymeric nanoparticles are applicable for targeted drug delivery
  Ex – Biodegradable polymers.
- Dextran with Meghe mite used for diagnostic of medicines.
- Semi-conductors are used in the delivery of DNA.
- Dielectric core is applied for tumor targeting.
- Aerogel are controlled release carriers of drugs.
- Polypeptides for systemic drug delivery.
- Chitosan nanoparticles of immune long lasting used for nasal vaccine delivery
  Ex – Tetanus toxoid.
- Encoded protein antigens significantly reduce respiratory syncytial virus (RSV).
- Major psychotics medications used as drug nano-systems

Ex – PLA/PLGA with Haloperidol

Chitosan nanoparticles of Venlafaxine.[21]

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