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NANOTECHNOLOGY AS TARGET DRUG DELIVERY SYSTEM AS B.B.B. - A REVIEW

Dr. Abhishek Soni, Prof. Dr. Rajender Guleria, Shoaib*, Sanchit Thakur, Sahil and Nikhil Thakur

Abhilashi College of Pharmacay, Nerchowk, Mandi, H.P.

***Corresponding Author: Shoaib**
Abhilashi College of Pharmacay, Nerchowk, Mandi, H.P.

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ABSTRACT
Nanoparticles such as polymeric micelles or liposomes have been developed with progress in nanotechnology and have been applied to a wide range of fields such as drug/gene delivery. This chapter focuses on applications of these nanoparticles for targeted drug and gene delivery. More recently, nanoparticles have been used to improve immunity, adsorption of active oxygen, adjuvant material, virus neutralization, The blood-brain barrier (BBB) is one of the most essential protection mechanisms in the central nervous system (CNS). It selectively allows individual molecules such as small lipid-soluble molecules to pass through the capillary endothelial membrane while limiting the passage of pathogens or toxins. However, this protection mechanism is also a major obstacle during disease state since it dramatically hinders the drug delivery. In recent years, various tactics have been applied to assist drugs to cross the BBB including osmotic disruption of the BBB and chemical modification of prodrugs. Additionally, nanoparticles (NPs)-mediated drug delivery is emerging as an effective and non-invasive system to treat cerebral diseases. In this review, we will summarize and analyze the advances in the drug delivery across the BBB using various NPs in the last decade.

KEYWORDS: BBB, Nanoparticles, polymers, Nanotechnology, drug delivery.

1. INTRODUCTION

Nanoparticles are the fundamental components of Nano technology. Nano particles size ranges from 1 to 100nm which are made up of metal, metal oxides, organic matter, carbon. Nanoparticles differ from various dimensions, to shapes and sizes apart from their material. Surface can be irregular with surface variations or a uniform. Among nanoparticles some are crystalline or amorphous with single or multi-crystal solids either agglomerated or loose. In the process of synthesizing new drugs, most drug candidates are insoluble or poorly soluble in water which causes a huge downfall for the pharmaceutical industry. One of the main reasons for a drug‟s insolubility is its complex and large molecular structure. It has been reported that over 65% of new active pharmaceutical ingredients (APIs) are either poorly soluble in water or insoluble. Due to their low aqueous solubility properties and high permeability, they are categorized as class II of the Biopharmaceutics Classification System (BCS), where the dissolution step is the rate limiting factor in drug absorption. The pharmaceutical industries are now facing a challenge to improve the dissolution characteristic of poorly watersoluble drugs which is the key factor in enhancing drug bioavailability. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties. This review predominately focused on synthesis of different types of nanoparticles using chemical, physical and biological methods. However, chemical and physical methods are expensive and harmful but biological method is simple, non-toxic, rapid and eco- friendly. It also explains about the characteristics of nanoparticles and concluded with various applications.[1]

1.1 Classification of Nanoparticles

The nanoparticles are generally classified into the organic, inorganic and carbon based.

1. Organic nanoparticles: micelles, Dendrimers, ferritin and liposomes etc. are commonly known polymers or organic nanoparticles. These nanoparticles are non-toxic, biodegradable, and some particles such as liposomes and micelles have a hollow core also known as nano capsules and are sensitive to thermal and electromagnetic radiation such as heat and light.[2] The organic nanoparticles are most widely used in the biomedical field for example drug delivery system as they are efficient and also can be injected on specific parts of the body which is also known as targeted drug delivery. Examples of organic nanoparticles are liposomes, dendrimers and micelles.

2. Inorganic nanoparticles: Inorganic nanoparticles are particles which are not made up of carbon. Metal and metal oxide-based nanoparticles are generally categorized as inorganic nanoparticles.

a. Metal NPs: Almost all the metals can be synthesised into their nanoparticles. The commonly used metals for nanoparticle[3] synthesis are aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag) and zinc (Zn). These nanoparticles can be synthesized by chemical, electrochemical, or photochemical methods. In chemical methods, the metal nanoparticles are obtained by reducing the metal-ion precursors in solution by chemical reducing agents. These have the ability to adsorb small molecules and have high surface energy. These nanoparticles have applications in research areas, detection and imaging of biomolecules and in environmental and bioanalytical applications. For example, gold nanoparticles are used to coat the sample before analyzing in SEM. This was usually done to enhance the electronic stream, which helps us to get high quality SEM images. Due to their advanced optical properties, metal NPs find applications in many research areas.

b. Ceramic NPs: Ceramic nanoparticles are inorganic solids made up of carbides, carbonates, oxides, carbides, carbonates and phosphates synthesized via heat and successive cooling. They can be found in polycrystalline, dense, amorphous, polycrystalline, dense, porous or hollow forms. Therefore, these NPs are getting great attention of researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes. By controlling some physical properties, these nanoparticles can be formulated in drug delivery system especially in targeting tumors, glaucoma, and some bacterial infections.

c. Semiconductor NPs: Semiconductor nanoparticles have properties like those of metals and non-metals. They are found in the periodic table in groups II-VI, IIIV or IV-VI. These particles have wide bandgaps, which on tuning shows different properties. They are used in photocatalysis, electronics devices, photo-optics and water splitting applications. Semiconductor materials possess properties between metals and nonmetals and therefore they found various applications in the literature due to this property. Some examples of semiconductor nanoparticles are GaN, GaP, InP, InAs from group III-V; ZnO, ZnS, CdS, CdSe, CdTe are II-VI semiconductors and silicon and germanium are from group IV.[4]

d. Polymeric NPs: These are normally organic based NPs and in literature a special term polymer nanoparticle (PNP) is collectively used for it. Depending up on the preparation these are nanospheres or nano-capsular shaped. The former are matrix particles whose overall mass is generally solid and the other molecules are adsorbed at the outer boundary of the spherical surface. In the latter case the solid mass is encapsulated within the particle completely. The PNPs are readily functionalized and thus find bundles of applications in the literature. Some of the merits of polymeric nanoparticles are controlled release, protection of drug molecules, ability to combine therapy and imaging, specific targeting and many more. They have applications in drug delivery and diagnostics. The drug deliveries with polymeric nanoparticles are highly biodegradable and biocompatible.

e. Lipid-based NPs: Lipid nanoparticles are generally spherical in shape with a diameter ranging from 10 to 100 nm. It consists of a solid core made of lipid and a matrix containing soluble lipophilic molecules. The external core of these nanoparticles is stabilized by surfactants and emulsifiers. These nanoparticles have application in the biomedical field as a drug carrier and delivery and RNA release in cancer therapy.

3. Carbon-based NPs: Carbon-based nanoparticles include two main materials, namely, carbon nanotubes (CNTs) and fullerenes. CNTs are nothing but graphene sheets rolled into a tube. These materials are mainly used for the structural reinforcement as they are 100 times stronger than steel. CNTs can be classified into singlewalled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). CNTs are unique in a way as they are thermally conductive along the length and non-conductive across the tube. Fullerenes are the allotropes of carbon having a structure of hollow cage of sixty or more carbon atoms. The structure of C-60 is called Buckminsterfullerene, and looks like a hollow football. The carbon units in these structures have a pentagonal and hexagonal arrangement.[5]

These have commercial applications due to their electrical conductivity, structure, high strength, and electron affinity. The rolled sheets can be single, double or many walls and therefore they are named as single-walled (SWNTs), double-walled (DWNTs) or multi-walled carbon nanotubes (MWNTs), respectively. They are widely synthesized by deposition of carbon precursors especially the atomic carbons, vaporized from graphite by laser or by electric arc on to metal particles. Lately, they have been synthesized via chemical vapor deposition (CVD) technique. Due to their unique physical, chemical and mechanical characteristics, these materials are not only used in pristine form but also in nano-composites for many commercial applications such as fillers, efficient gas adsorbents for environmental remediation and as support medium for different inorganic and organic catalysts.[6]

1.2 Synthesis of Nanoparticles

The nanoparticles are synthesized by various methods that are categorized into bottom-up or top-down method. A simplified representation of the process is presented in synthesis process.

1. Bottom-up method: Bottom-up or constructive method is the build-up of material from atom to clusters to nanoparticles. Sol-gel, spinning, chemical vapour deposition (CVD), pyrolysis and biosynthesis are the most commonly used bottom-up methods for nanoparticle production.

Sol-gel: The sol – a colloidal solution of solids suspended in a liquid phase. The gel – a solid macromolecule submerged in a solvent. Sol-gel is the most preferred bottom-up method due to its simplicity and as most of the nanoparticles can be synthesized from this method. It is a wet-chemical process containing a chemical solution acting as a precursor for an integrated system of discrete particles. Metal oxides and chlorides are the typically used precursors in sol-gel process.[7] The precursor is then dispersed in a host liquid either by shaking, stirring or sonication and the resultant system contains a liquid and a solid phase. A phase separation is carried out to recover the nanoparticles by various methods such as sedimentation, filtration and centrifugation and the moisture is further removed by drying. ¬

Spinning: The synthesis of nanoparticles by spinning is carried out by a spinning disc reactor (SDR). It contains a rotating disc inside a chamber/reactor where the physical parameters such as temperature can be controlled. The reactor is generally filled with nitrogen or other inert gases to remove oxygen inside and avoid chemical reactions. The disc is rotated at different speeds where the liquid i.e., precursor and water are pumped in. The spinning causes the atoms or molecules to fuse together and is precipitated, collected and dried.[8] The various operating parameters such as the liquid flow rate, disc rotation speed, liquid/precursor ratio, location of feed, disc surface, etc. determines the characteristics nanoparticles synthesized from SDR.

Chemical Vapor Deposition (CVD): Chemical vapour deposition is the deposition of a thin film of gaseous reactants onto a substrate. The deposition is carried out in a reaction chamber at ambient temperature by combining gas molecules. A chemical reaction occurs when a heated substrate comes in contact with the combined gas.[9] This reaction produces a thin film of product on the substrate surface that is recovered and used. Substrate temperature is the influencing factor in CVD. The advantages of CVD are highly pure, uniform, hard and strong nanoparticles. The disadvantages of CVD are the requirement of special equipment and the gaseous by-products are highly toxic. ¬

Pyrolysis: Pyrolysis is the most commonly used process in industries for large-scale production of nanoparticle. It involves burning a precursor with flame.[10] The precursor is either liquid or vapour that is fed into the furnace at high pressure through a small hole where it burns.[11] The combustion or by-product gases are then air classified to recover the nanoparticles. Some of the furnaces use laser instead of flame to produce high temperature for easy evaporation. The advantages of pyrolysis are simple, efficient, cost effective and continuous process with high yield.

1.3 Biological synthesis of Nanoparticles ¬ The synthesis of nanoparticles by biological synthesis carried by the following methods Synthesis by plant extract: The synthesis by plant extract is free from toxicity and the plants tender the superior option for the synthesis of nanoparticles. The gold and silver nanoparticles can be produced from the plant extracts like Geranium, aloe vera, sun dried cinnamon camphora, azadiracta indica etc.[12]

Synthesis by bacteria: The synthesis of NPs in previous years has enlarged comprehensively due to its immense applications. Bacillus species are widely used in the production of metal nanoparticles, since this bacterium has ability to fabricate extracellularly. The size ranges from 10 to 20 nm. Gold nanoparticles can also be produced.[13]

Synthesis by fungi: The nanoparticles can be produced by using various species of fungi like aspergillus niger, aspergillus orizae, fusarium solani. Phoma globerta has been traced to produce silver nanoparticles and its efficacy against Ecoli, S.aureus, P.aeruginosa has been assessed.[14]

Synthesis by yeast: This uses candida glabarta and schizosaccharomyce pombe for the synthesis of cadmium nanoparticles. The silver and gold nanoparticles are also investigated using extremophilic yeast strain isolated from the acid drainage. The marine yeast rodosporidium diobovatum has been explored for the synthesis of stable lead sulphide nanoparticles.[15]

Synthesis by biological particles: The biological particles like proteins, peptides, virus, enzymes are used as biological particles in the synthesis of nanoparticles.[16] Tobacco mosaic virus helps in the mineralization of sulphides. Cowpea chlorotic mottle virus, cowpea mosaic virus have also been employed and these can be demonstrated on the surface of M13 bacteriophage.

2. Top-down methods Top-down or destructive method is the reduction of a bulk material to nanometric scale particles. Mechanical milling, nanolithography, laser ablation, sputtering and thermal decomposition are some of the most widely used nanoparticle synthesis methods.

Mechanical milling: Among the various top-down methods, mechanical milling is the most extensively used to produce various nanoparticles. The mechanical milling is used for milling and post annealing of nanoparticles during synthesis where different elements are milled in an inert atmosphere.[17] The influencing

factors in mechanical milling is plastic deformation that leads to particle shape; fracture leads to decrease in particle size and cold-welding leads to increase in particle size.

Nanolithography: Nanolithography is the study of fabricating nanometric scale structures with a minimum of one dimension in the size range of 1 to 100 nm. There are various nanolithographic processes for instance optical, electron-beam, multiphoton, nanoimprint and scanning probe lithography.[18] Generally, lithography is the process of printing a required shape or structure on a light sensitive material that selectively removes a portion of material to create the desired shape and structure. The main advantage of nanolithography is to produce from a single nanoparticle to a cluster with desired shape and size. The disadvantages are the requirement of complex equipment and the cost associated.[19]

Laser ablation: Laser Ablation Synthesis in Solution (LASiS) is a common method for nanoparticle production from various solvents. The irradiation of a metal submerged in a liquid solution by a laser beam condenses a plasma plume that produces nanoparticles. It is a reliable top-down method that provides an alternative solution to conventional chemical reduction of metals to synthesis metal-based nanoparticles.[20] As LASiS provides a stable synthesis of nanoparticles in organic solvents and water that does not require any stabilizing agent or chemicals, it is a „green" process.

Sputtering: Sputtering is the deposition of nanoparticles on a surface by ejecting particles from it by colliding with ions. Sputtering is usually a deposition of thin layer of nanoparticles followed by annealing. The thickness of the layer, temperature and duration of annealing, substrate type, etc. determines the shape and size of the nanoparticles.[21]

Thermal decomposition: Thermal decomposition is an endothermic chemical decomposition produced by heat that breaks the chemical bonds in the compound. The specific temperature at which an element chemically decomposes is the decomposition temperature. The nanoparticles are produced by decomposing the metal at specific temperatures undergoing a chemical reaction producing secondary products.[22]

1.4 Applications of Nanoparticles

1.4.1 General applications of organic nanoparticles

Micelles

- In treatment of malignant tumours
- Reduces enzymatic degradation and inactivation of drugs
- Improves stability of the drugs
- Reduces critical micellar concentration

Liposomes: Liposomes have also been used to fortify dairy products with vitamins to increase their nutritional value as well as to aid in digestion of constituents inherent to dairy products.Usually phospholipids are used to form the bilayer, and frequently used phospholipids are phosphatidyl choline (neutral charge), and the negatively charged phosphatidic acid, phosphatidyl glycerol, phosphatidyl serine, and phosphatidyl ethanolamine. Archaeosomes are liposomes made from one or more of the polar ether lipids extracted from the Archaeobacteria. As compared with liposomes (which is made from ester phospholipid), archaeosomes are relatively more thermostable and more resistant to oxidation, chemicals and enzymatic hydrolysis. They are also more resistant to low pH and bile salts that would be encountered in the gastrointestinal tract.

Dendrimers: Dendrimers can also be used in various fields like gene delivery, conjugate systems, boron neutron capture therapy, molecular recognition, and for drug delivery. It includes use as contrast agents, such as for magnetic resonance imaging (MRI), but more significantly, as a carrier for drug delivery in cancer treatment. Enzymatic degradation and inactivation is hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used. Enzymatic degradation and inactivation hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used. Enzymatic degradation and inactivation is hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used.[23]

1.4.2 General Applications of Inorganic Nanoparticles

Therapeutic applications of metallic nanoparticles

As anti-Infective Agents

Metallic nanoparticles have been described as a HIV preventative therapeutic. In a couple of studies, it has been shown that as virucidal agent silver acts directly on the virus by binding to the glycoprotein gp120. This binding in turn prevents the CD4 dependent virion binding which effectively decreases HIV1"s infectivity. and it has also been reported that metallic nanoparticles have been effective antiviral agents against herpes simplex virus, influenza, respiratory syncytial viruses.

As anti-Angiogenic: Angiogenesis is the development of new blood vessels and occurs during normal development and in some disease states. It plays a main role in number of diseases such as cancer, rheumatoid arthritis. In normal conditions, angiogenesis is tightly regulated between various pro-angiogenic growth factors (VEGF, PDGF, and TGF-B) and anti-angiogenic factors (platelet factor 4, TSP-1). Under diseased conditions, angiogenic is turned on. Some reviews have reported that these agents have serious toxicities such as fatal haemorrhage, thrombosis, and hypertension. It may be overcome if these nanoparticles alone can be efficacious as an anti-angiogenic agent.

In Tumour Therapy: It has been studied that naked gold nanoparticles inhibited the activity of heparinbinding proteins such as VEGF165 and bFGF in vitro and VEGF

induced angiogenesis in vivo. Further work in this area has been reported that onto the surface of AuNPs heparin binding proteins are absorbed and were subsequently denatured. The researchers also showed that surface size plays a main role in the therapeutic effect of AuNPs. Mukherjee and colleagues also experimented the effect of gold nanoparticles on VEGF mediated angiogenesis using a mouse ear model injected with an adrenoviral vector of VEGF. A week later, the AdVEGF administration, mice treated with AuNPs developed lesser edema than the same treated mice. Eom and Colleagues revealed the anti-tumour effects of 50 nm AgNps In vitro and In vivo.

In Multiple Myeloma: Researchers have designed a nanoparticle based therapy that is effective in treating mice with multiple myeloma. Multiple myeloma is a cancer that affects plasma cells.

Nanotechnology as target Drug Delivery System as B.B.B.

In Leukaemia: B-chronic Lymphocytic Leukaemia (CLL) is an incurable disease predominantly characterized by apoptosis resistance, by co-culture with an anti-VEGF antibody, found induction of more apoptosis in CCL B cells. In CLL therapy, gold nanoparticles were used to increase the efficacy of these agents. Gold nanoparticles were chosen based on their biocompatibility, very high surface area, surface functionalization and ease of characterization. To the gold nanoparticles, VEGF antibodies were attached and determined their ability to kill CLL B cells.

In Rheumatoid Arthritis: Scientists from the University of Wollongong (Australia) have built a new class of anti-arthritic drug which could be used by gold nanoparticles and it has fewer side effects. Rheumatoid arthritis is an autoimmune disease that occurs when the immune system does not function properly and attacks a patient‟s joints. New research has shown that gold particles can invade macrophages, and stop them from producing inflammation without killing them. In the Journal of inorganic biochemistry it has been published that by reducing the size of gold into smaller nanoparticles (50 nm), it was able to cause more gold to immune cells with lesser toxicity.

I**n Photo Thermal Therapy: Gold** nanoparticles absorb light strongly as they convert photon energy into heat quickly and efficiently. Photo-thermal therapy (PTT) is an invasive therapy in which photon energy is converted into heat to kill cancer. In Radiotherapy Tumours are loaded with gold, this absorbs more X-rays as gold is an excellent absorber of X-rays. Thus, deposition of more beam energy and resulting in a local dose which increases specifically to tumour cells. Gold nanoparticles have been more useful to treat cancer.[24]

1.4.3 Therapeutic applications of ceramic nanoparticles

Ceramic nanoparticles like titania have also been added into polymer matrices to adjust composite surface chemistry, topography, and wettability (surface energetics) of the polymer matrix, aiming at the promotion of osteogenic responses on the material surfaces.

- Functionalized magnesium oxide, zirconia, sulfate, and calcium carbonate are added to polymethylmethacrylate (PMMA) bone cement to reduce the exothermic effect of PMMA while increasing its cytocompatibility, X-ray radiopacity, as well as antibacterial potential
- Antibacterial effects of BaSO4 nanoparticles against Staphylococcus aureus and Pseudomonas aeruginosa have been discovered, suggesting their potential applications as anti-infective additives to bone cement, implant coating, and medical tubing.
- Therefore, these NPs are used by researchers across the globe in wide applications, such as catalysis, photocatalysis, photo degradation of dyes, and imaging applications. Medical technologies use nanoceramics for bone repair.
- Ceramic NPs are also used in energy supply and storage, communication, transportation systems, construction, and medical technology.
- One of the main uses of nanoceramics has been in biomedicine and medical technology, particularly in bone repair. Bioactive ceramics closely match the properties of bone and can act as a nanoscaffold to help support bone regrowth.
- It has also been suggested that nanoceramics might find uses in energy supply and storage, communications, transportation systems, aerospace and construction. They have also found use in electronics as insulators, semiconductors, conductors and magnets.
- Nanoceramics might also find a use in armor to replace the stiff, tough layers of woven fiber which absorbs impact. A hard body armor is under development that includes ceramic inserts and steel or titanium panels that could offer greater protection against blunt trauma and high velocity ammunition. The inserts could absorb kinetic energy of the projectile and dissipate it in a localized shattering of the ceramic insert.[25]

1.4.4 Therapeutic applications of Polymeric nanoparticles

- They develop innovative drug delivery system in the treatment of neurodegenerative and brain associated diseases.
- Polymeric NPs provide protection to the drugs via encapsulating, entrapping them inside the core, conjugating, or adsorbing them on to the particle surface
- Polymeric NPs deliver cargo-loaded molecules across the BBB by following endocytosis and transcytosis pathways
- This polymeric coating is thought to reduce immunogenicity, and limit the phagocytosis of nanoparticles by the reticulo-endothelial system,

resulting in increased blood levels of drug in organs such as the brain, intestines, and kidneys

- These have been applied in gene therapy to breast cancer cells, resulting in anti-proliferative effects.[26]

1.4.5 Therapeutic applications of lipid based nanoparticles

- These are mainly used to various types of cancer like GIT cancer, lung cancer, breast cancer, pancreatic cancer, prostate cancer.
- It significantly enhances transdermal penetration of phytomedicines inside skin.
- SLNs increase the therapeutic potential of eugenol and efficiently inhibited the growth of Candida infection during oral candidiasis
- It has enhanced antimicrobial activity.

1.4.6 Therapeutic applications of semiconductor nanoparticles: It has significant attention in research and applications in emerging technologies such as nanoelectronics, nanophotonics, energy conversion, nonlinear optics, miniaturized sensors and imaging devices, solar cells, catalysis, detectors, photography biomedicine etc.[27]

2 The Blood–Brain Barrier

The BBB is a structural, functional, and physiological barrier that intricately regulates the movement of ions, nutrients, and cell between the blood and the brain. Anatomically, the BBB consists of cerebral endothelial cells, pericytes, astrocytes, and basement membrane. The BBB acting together with neurons and glial cells forms the complete neurovascular unit (NVU) which is crucial for the function of the brain. The cerebral endothelial cells are non-fenestrated, contain a large number of mitochondria, and form tight junctions that highly regulate the molecule transport across the endothelium. The inter-endothelial space is characterized by the presence of transmembrane protein complexes composed of occludin, claudin, and junction adhesion molecules. These specialized tight junction proteins undertake homophilic interactions to form an intricate tight barrier that is exclusive to the cerebral endothelial cells.[28]

2.1 BBB Formation

Since chordate BBB growth is evolutionarily conserved, animal models may provide a gateway into human development, in mammals, the origination and identification of BBB are starting at the early embryonic interval. Although it is working soon after it is originated, mature cells like myelinated neurons and astrocytes do not show until shortly after birth.

The developmental studies evidence suggested that the BBB characteristics are shaped through the early development of CNS, where there is a coordinated interaction between the vascular and nervous systems for the convenient formation of BBB.

During embryogenesis, the brain, like every other organ, is vascularized by the vascular plexus surrounding it. The BBB is derived from the perineural vascular plexus (PNVP) that surrounds the neural tube Its foundation develops in a multistep mechanism driven by cellular interactions within the growing NVU and intricately linked to the developing CNS. That means that the BBB's growth is a complex process involving several cells and its secreted developmental factors. All cells in the NVU participate in the formation and development of the BBB.[2]

Table 2: Advantages and limitations of the various BBB models.

In vitro BBB models		Advantages	Drawbacks
2D	Petri dishes	• Very low-cost fabrication • Large quantities • Simple fabrication • Control over microenvironment optically	• No shear stress • Limited to monolayers • Cell dedifferentiate quite rapidly
	Transwells	• Very low-cost fabrication • Allows co-culture • Simple fabrication • Moderate scalability • Highly convenient for high-throughput screens	• No shear stress • Limited cell differentiation • Permeability to polar molecules is not stringent • Ideal for linear kinetic studies
3D	Dynamic	• Low-cost fabrication • High TEER • Allows co-culture • Complex fabrication • Enables the effect of sheer stress • Allows for hemodynamic studies	• Setup require high cell numbers • Time consuming • Technically challenging • Not ideal for high throughput screening and linear kinetic studies • Not permissive for visual microscopy
	Microfluidics	• Low-cost fabrication • Flexibility in the design • Requires less cell number • Realistic microenvironment • Control over microenvironment • Resembles more closely the actual in vivo brain anatomy • Consider the effect of sheer stress • Immediate permeability measurements • Improvement in paracellular barrier functions • Allows for cell inspection via visual microscopy	• Moderate TEER • Limited scalability • Complex fabrication • Lack of standardized quantification of parameters • Not ideal linear kinetic studies
	Microfluidics (fabricated via 3D printing)	• Low cost fabrication • Moderate fabrication • Flexibility in the design • Requires less cell number • Realistic microenvironment • Visualization of cells is possible • Precise control over microenvironment • Resembles more closely the actual in vivo brain anatomy • Consider the effect of sheer stress • Immediate permeability measurements • Improvement in paracellular barrier functions	• Lack of high-throughput • Complex process technically • Not ideal linear kinetic studies

BBB: blood–brain barrier.

2.2 BBB Structure

BBB may be present in all vertebrates and some of the extremely intelligent invertebrates with a well-developed CNS such as insects, squid, and octopus. The BBB's growth is critical to the complex brain's successful evolution. It is mainly made up of capillary endothelial cells, astrocytes, and pericytes, as well as some other elements, such as neurons, basement membrane, and microglia (Figure 1), that contribute to immunological function. These components, which are frequently referred to as a neurovascular unit (NVU), preserve a healthy BBB to guarantee appropriate central nervous system activity.[30]

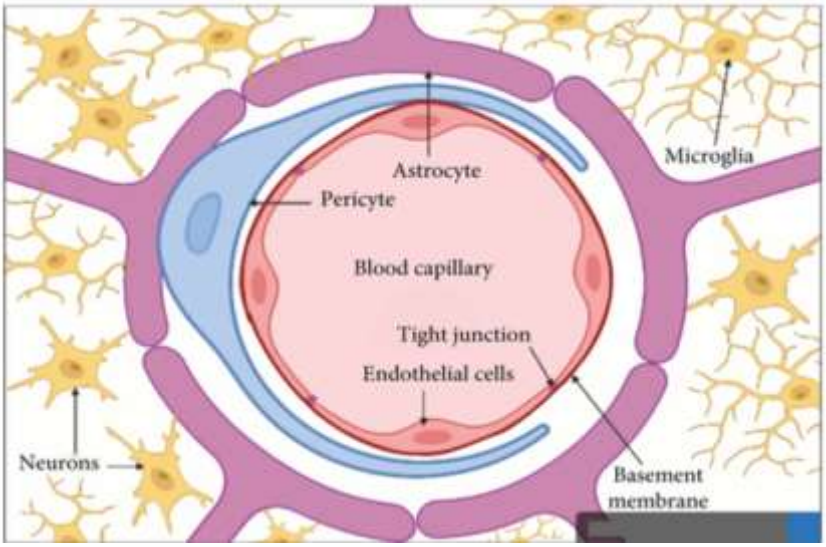

Figure 1: A Schematic Diagram of transverse section in blood brain barrier illustrating BBB,s cellular structure.

2.3 BBB Function

BBB is a physiological process responsible for modifying the permeability of cerebral capillaries, to preventing some materials, such as some drugs, from entering brain tissue, while allowing other materials free access. The major role of the BBB is to keep the brain from alterations in the concentrations of blood ions, amino acids, peptides, and other elements.

The brain's volume must be maintained since it is enclosed in a hard bony skull. The BBB has an important role in this mechanism, by restricting the unrestricted flow of water and salts from the bloodstream into the cerebral extracellular fluid. In contrast, the extracellular fluid in other bodily tissues is produced by leakage from the capillary, but the BBB secretes brain extracellular fluid at a regulated rate, which is important for maintaining appropriate brain volume. When the BBB is becoming leaky due to an injury or infection, water and salts enter the brain tissue, causing swelling and thus high pressure inside the skull; this can be fatal. Thus, the BBB is an essential element for the normal working of the brain and protects it from troubles in fluid formation in the rest of the body.[31]

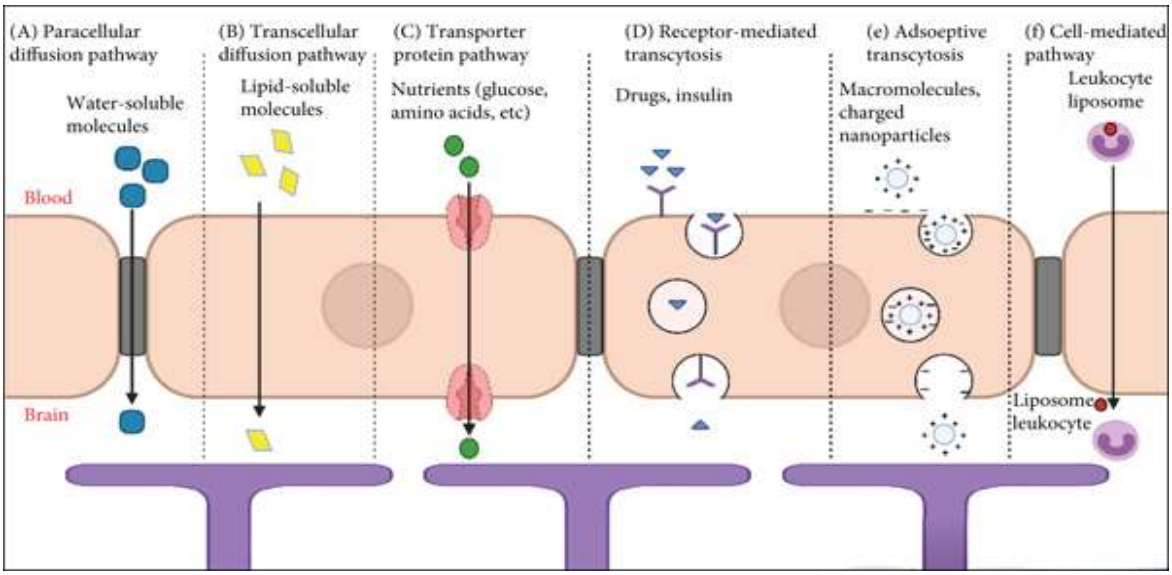

Figure 2.

A schematic diagram of the endothelial cells that form the BBB and their associations with the perivascular end feet of astrocytes showing pathways across the BBB. (a) Generally, tight junctions prevent water-soluble chemicals from penetrating. (b) On the other hand, the enormous surface area of the endothelium's lipid membranes provides an excellent diffusive pathway for lipid-soluble substances. (c) Transporter proteins for glucose, amino acids, purine bases, nucleosides, choline, and other chemicals are found in the endothelium. (d) Specific receptor-mediated endocytosis and transcytosis pick up drugs and particular proteins, such as insulin and transferrin. (e) Adsorptive-mediated transcytosis for transport macromolecules and charged agents to brain. (f) Cell mediated transcytosis pathway depends on leukocytes to pass the BBB.

3 Poloxamer 188

Poloxamers are non-ionic triblock amphiphilic copolymers consisting of poly(ethylene oxide)-poly(propylene oxide)- poly(ethylene oxide).The first two digits (e.g., 18 in poloxamer 188) indicate the approximate molecular mass of the polypropylene core (1800 g mol−1) and the last digit (e.g., 8 in poloxamer 188) multiplied by 10 gives the percentage of polyoxyethylene content (80%).In particular, Poloxamer 188 has been used in the field of drug delivery and is approved by the FDA under the trade name of Pluronic F68.Similar to PS80, Poloxamer 188 coated nanoparticles promote the adsorption of apolipoprotein on the surface of nanoparticles in plasma leading to LDL receptor-mediated transcytosis. Several polymeric nanoparticle systems have been successfully delivered to the brain using a poloxamer 188 coating, including PBCA and PLGA. In most studies, the BBB crossing efficiency for poloxamer 188 coating is similar to PS80, although the nanoparticle system seems to also have a minor influence.

4 Chitosan

Chitosan is a partially deacetylated polymer of Nacetyl glucosamine that can be obtained through alkaline deacetylation of chitin. It consists of a β- (1,4)-linked-D-glucosamine residue with the amine groups randomly acetylated. The amine and –OH groups endow chitosan with many special properties, making it applicable in many areas and easily available for chemical reactions. Chitosan is safe, non-toxic and can interact with polyanions to form complexes and gels. In this work, the preparation of chitosan nanostructures and their application as bioactive ingredient encapsulators or immobilizers are reviewed.

5 Current Research Challenges and Future Perspectives

The nanomedicine landscape is evolving rapidly, and new nanoparticle formulations are continuously being investigated in pre-clinical and in clinical trials. Some nanomedicine candidates have been successfully transitioned into the clinical practices, and polymeric nanoparticles have made a notable development with over ten formulations currently under clinical trial testing.

In relation to the treatment of neurological disorders, no nanoparticle formulations have received approval thus far. However, a cationic liposome (SGT-53) for gene therapy is being investigated for recurrent glioblastoma and CNS malignancies in clinical trials.

Current nanoparticle formulations have yet to show success for CNS drug delivery in the clinic, and this is attributed to the complexities of drug delivery to the CNS and in particular to cross the BBB. A drug delivery system needs to be specifically designed to overcome the BBB and reach the brain tissues.

Polymeric nanoparticles are especially well-suited to carry out this task due to the unique control over particle properties including engineering particle size, grafting BBB targeting agents, and controlling drug release profiles.

Recently, a number of new promising BBB targeting moieties have been discovered, including plasma proteins, antibodies, peptides, aptamers, and small molecules. A direct comparison of their performance is difficult due to the presence of several variables, such as the surface density of the ligand, nanoparticle size, the testing model (in vitro or in vivo), and characterization methods chosen. Nevertheless, intermediate affinity antibodies and LDL receptor family targeting peptides, such as angiopep-2 and ApoE, have shown better outcomes.

For example, paclitaxel conjugated angiopep-2 has been tested in phase II clinical trials for brain metastases, and iduronate-2-sulfatase conjugated to an anti-transferrin-receptor is currently under human clinical trials to treat Hunter syndrome.Nevertheless from a safety perspective, it is important to consider the acute and chronic effects of targeting brain receptors, for example, determining if nutrient transport and uptake is affected by targeting the transferrin or insulin receptor.

Furthermore, penetrating the BBB is only half of the story as additional targeting to the diseased site often is required, for example, in glioblastoma. Therefore, to use multiple types of ligands (i.e., dual-targeting strategy) or ligands that target receptors, which are highly expressed on both the BBB and targeted cells such as angiopep-2 and transferrin for brain cancers could be the game changer.

The size of nanoparticles plays a less important role in BBB transfer compared to surface functionality. However, particles that are smaller than 100 nm tend to penetrate deeper into the brain parenchyma.

Nevertheless, the nanoparticle size is instrumental to evade renal clearance as well as limit uptake by the MPS, which indirectly influences the chance on BBB transcytosis. A less studied aspect is the nanoparticle shape, and more investigations are needed to fully harness the potential benefits.

Other methods to enhance the CNS delivery of polymeric nanoparticles also show promise in preclinical studies. For example, focused ultrasound is an emerging treatment method that leverages acoustic energy to oscillate administered microbubbles resulting in a temporarily disruption of the BBB.[305] This disruption can be regionally targeted using MRI guidance.

Moreover, focused cranial radiation therapy is able to modulate the tumor BBB and has been shown to improve the uptake of PEGb-P(CL-co-LA) nanoparticles in glioblastoma, and convectionenhanced delivery even bypasses the BBB and can enhance nanoparticle distribution by utilizing hydraulic pressure to deliver an infusate directly into a target region. Nevertheless, additional studies are needed to further explore these methods in a clinical setting.

Despite the species-to-species differences, in vivo models are still commonly used to test the efficacy of nanoparticle to cross the BBB. Advanced imaging techniques have been exploited to accurately trace the in vivo fate of polymeric nanoparticles. Although fluorescence labeling is often used due to the ease of conjugation protocols and the availability of different wavelengths, the fluorescence has a limited penetration depth, which prevents quantification and real-time non-invasive assessment in large animals and human.

In contrast, radioisotopes have an unlimited penetration depth and their concentration can be quantitatively assessed in vivo via PET imaging or ex vivo using a gamma counter. Results should be assessed carefully, nevertheless, as nanoparticle delivery does not equate the delivery and release of the loaded pharmaceutical, and PD studies are essential, either by means of histology or in vivo imaging using PET or MRI.

It is also very important to consider carefully which disease model is the most suitable. For example, although subcutaneous brain cancer models are easy to set up, they do not recapitulate a BBB and are therefore not clinically relevant. Moreover, the physiology of the BB(T)B in orthotopic brain tumors depends on the chosen brain cancer cell and tumor size. Where some cancer cell lines result in a very dysfunctional and "leaky" BB(T)B that enables any nanoparticle to pass, others have an intact BBB, which more closely resembles lower grade diffuse gliomas and the periphery of clinical glioblastoma.[32]

Research Till Date

S.no.	Research	Diseases
1.	Development of Polymeric Nanoparticles for Blood–Brain Barrier Transfer—Strategies and Challenges[33]	Alzheimer's disease
2.	Nanoparticles for drug delivery to the brain[34]	Parkinson Disease
3.	Blood Brain Delivery Methods Using Nanotechnology[35]	Brain Disease
4.	Nanoparticle-based targeted drug delivery[36]	Cancer
5.	Formulation of Poloxamers for Drug Delivery[37]	Brain Disease
6.	Transport of drugs across the blood brain barrier by nanoparticles[38]	Brain tumor
7.	Crossing the blood brain barrier: Advance in nanoparticle technology for drug delivery Neuro-oncology[39]	CNS Disorder
8.	Crossing the blood brain barrier with nanoparticle[40]	Brain microvascular system
9.	Key for crossing the BBB with nanoparticles the rational design[41]	CNS disese
10.	Nanotechnology: A promising Approach for delivery of Neuroprotective drugs[42]	Neurological Disorder
11.	Role of Nanoparticles in Drug Delivery System[43]	Cancer

CONCLUSION

The foregoing discussion shows that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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