International Journal of Basic Medical Sciences and Pharmacy (IJBMSP)
Vol. 5, No. 1, June 2015, ISSN: 2049-4963

www.ijbmsp.org

Brain targeting Drug Delivery System: A Review

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Abstract – The Overall prevalence rate for CNS pathology has demonstrated that approximately 1.5 billion people undergoing from disorders of central nervous system. The most distressing fact about delivery of drugs to the CNS is the presence of blood brain barrier that have a tendency to impair the drug distribution and denotes the major impediment for the development of CNS drugs. Neuropeptides and many drugs which are hydrophilic in nature, possibly will encompass the intricacy while passing the blood brain barrier. The net amount of delivered drug (medicinal agent) and its capability to gain access to the pertinent target sites are the main considering points for CNS drug development. In order to distribute the drugs into the CNS via passing the blood brain barrier, many new emerging approaches have been developed for example Magnetic drug targeting, chemical delivery Systems, Drug carrier systems (antibodies, liposomes or Nanoparticles). Among drug carrier system, Nanoparticles exhibit an impressive attention in the field of targeted drug delivery system because of possessing solid colloidal particles with a size range between 1- 1000nm. Gradual drug release reduced peripheral toxicity and potential to target specific brain sites by crossing the blood brain barrier are major benefits contributed by Nanoparticles. In this review we will discuss the methodologies for targeting the brain site.

Keywords – brain barrier, Drug delivery to brain, Nanotechnology, Colloidal drug carriers.

1. Introduction

In the central nervous system, targeted action can be achieved by direct administration of the drugs in to the CNS [1]. Blood brain barrier can considerably impair the effect of the large number of drugs (e.g. antibiotics, antineoplastic agents and Neuropeptides-CNS stimulant drug)because of its obstinate hindrance affect [2]. From some recent studies, it has been represented that the blood brain barrier is usually does not cross by almost 100% of large molecule drugs and 98% of small molecule drugs [3]. Presently, numerous approaches with enhanced pharmacodynamics effects, have been developed for the treatment of brain disorders [4]. Drug discovery and drug delivery technologies are the two main fields where advancement is required for drug delivery to the brain [5]. Nanoparticles drug delivery system (NDDS) is one of the advanced technology that can be utilized to deliver drug molecules directly into the brain and proved to be very effective against several CNS disorders [6]. Significant benefits of the Nanoparticles drug delivery system (NDDS) are given in table 1.

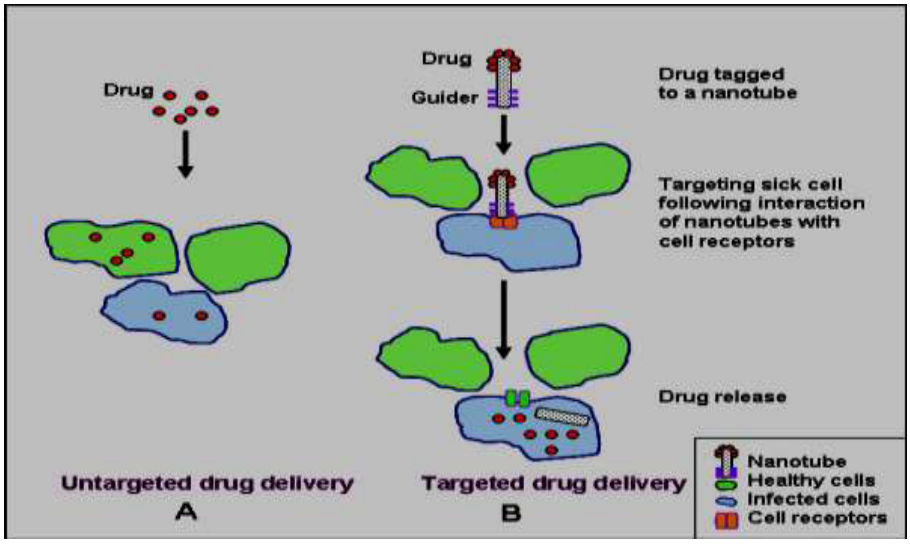

Figure 1. Drug targeting technology [7]

Table 1. Benefits of nano drug delivery system and example of drugs

Benefits	Example of the drugs that can be formulated in NDDS
1. The restraining attributes of the blood brain barrier can be masquerade by NDDS [8] 2. NDDS is an appealing system that offer decreased toxic effects, enhancement of therapeutic efficacy and gradual release of drugs [9] 3. This system have potential to target the desired tissues and attain sustained drug release for long time(days/weeks) [10]	• Polysorbate 80-coated nanoparticles • Polar hexapeptide dalargin[11] • Tubocurarine[12] • lipid-soluble P-glycoprotein substrates loperamide[2] • doxorubicin[13]

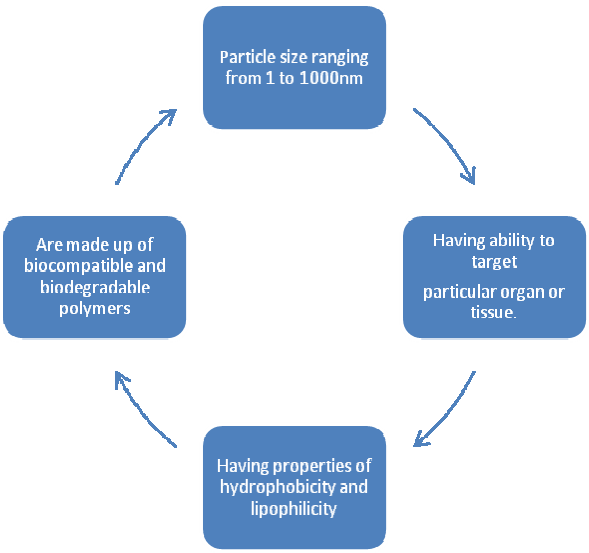

Figure 2. nanoparticles as a targeting drug delivery system [14]

1.1. Types of Nanoparticles [15]

Depending on the arrangement of drug and polymer matrix, Nanoparticles are of two types:

1.1.1. Nanospheres:.

Spherical particles having nanometric dimensions and acting as a drug carrier in which drug is enclosed inside the polymer matrix [16]

1.1.2. Nanocapsules

Inner liquid core containing drug, and outer surface of nano particles are sorrounded by the polymeric membrane [17].

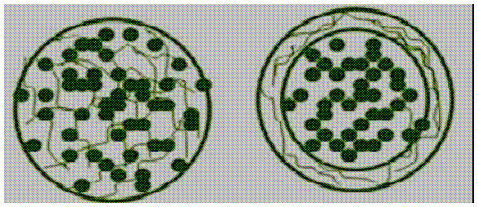

Figure 3. Schematic diagram of Nanosphere and Nanocapsule [18].

Table 2. Advantages and disadvantages of Nanoparticles

Advantages of Nanoparticles	Disadvantage of Nanoparticles
1.Drug carrying capacity is high[19]	1.Manufacturing cost is very high for this drug delivery system[20]
2.Nanoparticles releases the drug in sustained manner[21]	2.May possibly cause allergic reactions[22]
3.Drug Having extended time of circulation/show stability in bloodstream [23]	3.Nanoparticles may cause some toxic/unwanted reactions due to the over use of polyvinyl alcohol in their formulation[24]

1.2. Manufacturing methods of Nanoparticles [25]

- Emulsion polymerization[26].
- Interfacial polymerization[27].
- Desolvation evaporation[28].
- Solvent deposition[29].

1.3. Characterization of nanoparticles

To understand the potential of nanoparticles a deeper knowledge of their synthesis and application is needed. Characterization is done by using a variety of different techniques, mainly drawn from materials science

Table 3. In generally, nanoparticles are characterized by utilizing the following techniques.

Characterization techniques	**References**
Atomic force microscopy (AFM)	[30]
X-ray photoelectron spectroscopy (XPS)	[31]
Electron microscopy (TEM, SEM)	[32]
Dynamic light scattering (DLS)	[33]
Powder X-ray diffraction (XRD)	[34]
Dual polarization interferometry	[35]
Nuclear magnetic resonance (NMR)	[36]
Ultraviolet-visible spectroscopy	[37]
Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDITOF)	[38]
Fourier transform infrared spectroscopy (FTIR)	[39]

1.4. Brain Targetted Drug Delivery

1.4.1. Rate-limiting role of the BBB in brain drug development

i. Blood brain barrier is the major confront toward brain targeted drug delivery[40].
ii. BBB have efficient ability to restrict and separate the human brain from circulatory network, and only allow the transportation of molecules that play vital role in functional activity of brain[41].
iii. It also limits the transport of water and lipid soluble substances from blood circulation into CNS[42].
iv. Advancement in the perception of the cell biology of blood brain barrier has started the innovative path or opportunities for better drug delivery to the brain[43].
v. Various receptors, enzymes and transport systems have been recognized in the endothelium of BBB that restrain the molecules infiltration , for example protein and peptides are transported by Receptor-mediated transcytosis[44].

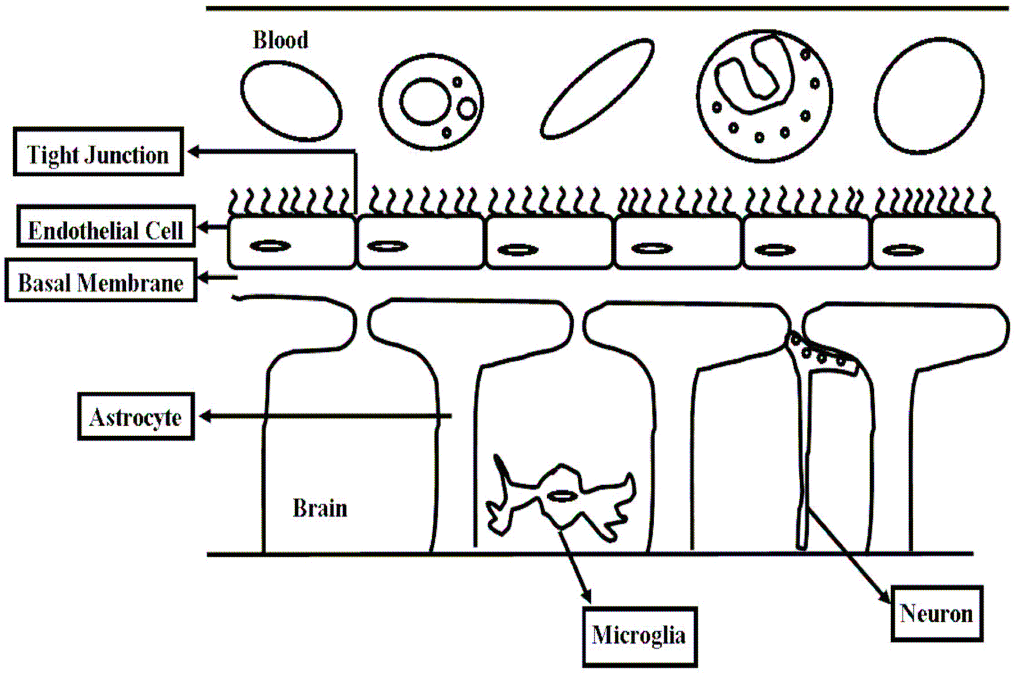

Figure 4. Schematic representation of BBB[45].

Table 4. Transport mechanism of drugs through blood brain barrier

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<table>
<tr><th>S. No.</th><th>Transport Mechanism</th><th colspan="3">Description</th></tr>
<tr><td rowspan="5">1.</td><td rowspan="5">Passive Transport</td><td colspan="3">The main factors that affect passive transfer are: drug ionization, lipophilicity, molecular weight, and protein binding.</td></tr>
<tr><td>Factor</td><td>Description</td><td>Effect on transport</td></tr>
<tr><td rowspan="2">Ionization of drug</td><td>Acidic compound's ionization</td><td>Decreased</td></tr>
<tr><td>Basic compound's ionization</td><td>No effect</td></tr>
<tr><td>Molecular weight (>600 Dalton is limiting factor)</td><td>Inversely related to passive transport</td><td>Increased or decreased accordingly</td></tr>
<tr><td>Lipophilicity</td><td>Directly related to passive transport</td><td>Increased or decreased accordingly but due to entrapment of compound inside the membrane, too high values may Decrease the transport rate. log P values (- 0.2 to 1.3) responsible for optimal cerebral transport due to dependence on blood flow and permeability coefficient and this permeability coefficient has good correlation with log P when molecular weight <800 daltons.</td></tr>
<tr><td>Protein binding</td><td>Protein-drug complex size and characteristics of BBB are responsible for transport</td><td>Free fraction of drug is transported.</td></tr>
<tr><td>2.</td><td>Active transport</td><td colspan="3">For higher rate transfer, active or facilitated transport can be responsible and requires energy. Efflux proteins may be Involved wherein the transfer rate is lower. Transfer rate of some drugs through BBB can be lower or higher than that Expected from physical and chemical properties.</td></tr>
<tr><td>3.</td><td>Adsorptive-mediated Transcytosis and endocytosis</td><td colspan="3">Adsorptive-mediated transcytosis induced by some macromolecules like cationic macromolecules e.g. histone, avidine and cationized albumin. Adsorptive-mediated endocytosis is hardly used for drug targeting to the brain, because this process also occurs to a large extent in other organs of the body (e.g. liver, kidneys), which decreases brain specificity. Furthermore, the cationic charge may lead to aggregate formation in the circulation. Brain targeting using adsorptive-mediated endocytosis has been accomplished though, by using cationized human serum albumin (cHSA) as a transport vector. This charged protein coupled to 3H-biotin is able to cross the BBB in significant amounts.</td></tr>
</table>

Table 5. Different strategies that can be utilized to manipulate the BBB to target the brain

Different strategies that can be utilized to manipulate the BBB to target the brain
• Osmotic and chemical opening of the blood-brain barrier[46] • By passing the BBB [47] • Direct invasive methods[48] • Various pharmacological agents to unblock the BBB[49].

1.4.2. Transfer mechanism across blood brain brrier

In BBB, several transport systems are present to control the transfer (either influx or efflux) of different essential solutes and drug molecules such as Diffusion (Passive and active diffusion), Facilitated diffusion, Active transport and Transcytosis [50].

1.5. Brain Targeting Technologies

a. Non invasive approach: Lapidate the drug molecules e.g transnasal route[51] .
b. Drug conjugates with liposomes and Nanoparticles [52].
c. Intrathecal and intra cerebroventricular delivery of drug molecules in to CNS by using different devices and needles[53].
d. Sustained and controlled release of drugs is considered along with systemic therapy in order to optimize the drug action in to the CNS[1].

1.5.1. Possible systems for drug delivery to brain

- Colloidal drug carriers systems for example vesicle, macular solutions, liquid crystal dispersions and liquid crystal dispersions(particle size range 10 to 400 nm)[54].
- Nanotechnology[55].

1.5.1.1. Nanotechnology

Improved drug delivery to the brain can be achieved by Nanotechnology, a more competent technology[56]. Materials used to prepare Nanoparticles are Polyacetates, poly(alkylcyanoacrylates), polysaccharides Copolymers, polysorbate-coated nanoparticles etc [57].

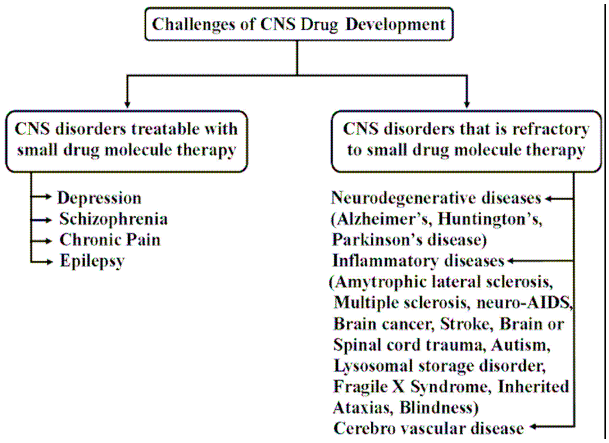


Figure 5. Schematic representation of challenges faced during CNS Drug development[58].

1.5.2. Mechanisms of Nanoparticle Transport across the blood brain barrier

There are six enhancing mechanisms for transport of nanopartilces across blood brain barrier.

1. Adhesion of nanoparticles to brain blood vessel walls[59]
2. Fluidization of BBB endothelium by surfactants[60]
3. Opening of tight junctions of endothelium[61]
4. Transcytosis across the brain endothelial cells[62]
5. Blockage of the glycoprotein in the brain endothelial cells[63]
6. Endocytosis by the brain vessel endothelial cells[64]

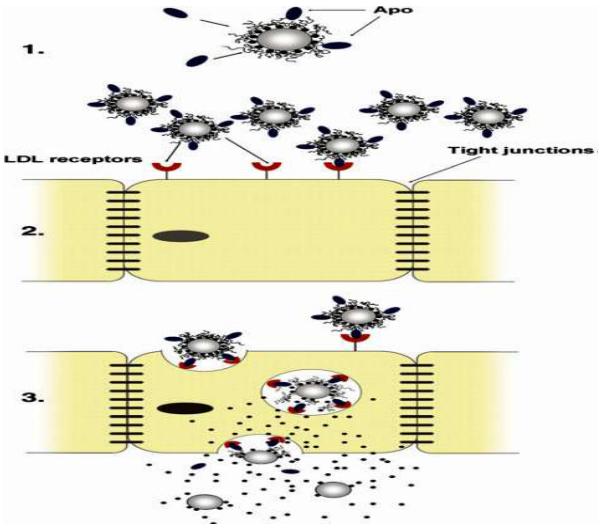


Figure 6. Mechanism of nanoparticles through endocytosis process[65]

1.5.3. Nanoparticulate systems for brain targeted delivery of drugs

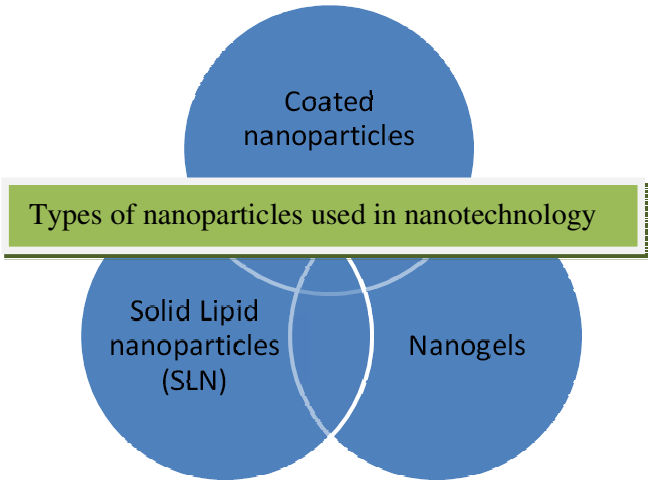
Size range of Nanoparticles is about 10 and 1000 nm and are usually made of various polymers(natural/artificial) [66]. Nanoparticles have ability to entrap and encapsulate the drug molecules [67].Example of the Nanoparticles drugs are vaccines and anticancer drugs to treat metastatic brain tumors [68]. At the same time the,employing of nanoparticles in the field of ophthalmic and oral delivery was also investigated [69].

1.5.3.1. Significance of nanoparticulate system

- Easily penetrate in to small capillaries and taken up by the target cells and as a result sustained release of drugs can be achieved over a period of days or even weeks[9].
- Biodistribution of active compounds can be mediated by this system[70].
- Enhance the drug loading, transport, release and interaction with biological barriers because carriers possess long circulating properties and suitable surface Characteristics[71]

Table 6. Drugs use in brain targeting

Drugs	References
Hexapeptide dalargin (Tyr-D-Ala- Gly- Phe-Leu-Arg),A Leu-enkephalin analogue with opioid activity.	[72]
PEGylated PHDCA (n-hexadecylcyanoacrylate) nanoparticles containg PEGyalated amphiphilic copolymer, easily penetrate in to the brain.	[1]
Valproic acid-loaded nanoparticles	[73]
dipeptide kytorphin,	[74]
loperamide	[75]
tubocurarine	[76]
the NMDA receptor antagonist MRZ 2/576	[77]
doxorubicin	[78]
Tacrine fwith polysorbate80-coated poly(n- butylcyanoacrylate) nanoparticles	[79]



1.5.3.2. Other novel Approaches

- Photodynamic therapy (PDT), Photofrin along with iron oxide nanoparticles which is used to target tumor cells. In this, iron oxide is used as contrast agent to get improved magnetic resonance imaging (MRI)[80].
- Trojan horses coated with sugar layer, is another modern approach containing magnetized, iron-containing nanoparticles[81]

1.5.4. Future aspects of brain targeting

Technological challenges need to be addressed are:

- ➢Attainment of controlled release profiles particularly for sensitive drugs[82].
- ➢Improvement/enhancement of nanoparticles release from implantable devices/ nanochips[83].
- ➢cytotoxicity of nanoparticles should be reduced to improve the biocompatibility[84].

- Multifunctional nanoparticles[85].
- Universal formulation schemes that can be used as I/V, I/M or per oral drugs.
- Nanoparticles for tissue engineering such as cytokines to restrain the cellular growth, discrimination and promote regeneration[86].
- Encapsulation of implants by nanoparticles containing biodegradable polymer for sustained release[87][88].

2. Conclusion

Now a day, many young researchers are attracted toward brain targeting due to its immense application in the treatment of various CNS diseases because mostly drugs are unable to cross the Blood brain barrier. This short review discuss the one of the novel technology " nanotechnology" that has been developed to target the brain and possess various clinical benefits such as reduced drug dose, less side effects, non invasive routes, and better patient compliance.

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