Abstract
The blood-brain barrier (BBB) is performing as a shielding barrier which is designed to protect the environment in the brain. It prevents the entry of dangerous substances into the brain but hinder the administration of some drugs to treat brain and central nervous system. Recently nanoparticles are playing a major role in targeted drug delivery. For the nanoparticles to act as effective carriers in targeting brain their surface must be decorated with specific ligands. Lately peptides have been recognized as potential ligands for encapsulating nanoparticles. It is proposed to synthesize the active part of Thioredoxin, a small redox protein in all organisms, on a PS-HDODA support. The selected sequence with a disulfide bridge and functional groups such as –SH and –NH2, is expected to stabilize the nanoparticles in drug delivery applications.

Keywords: BBB; Nanoparticles; Drug delivery; Peptides; Solid phase synthesis

Abbreviations: BBB: Blood Brain Barrier; NH2: Amidogen; CNS: Central Nervous System; pep-NPs: Peptide-Based Nanoparticles; PS: Polystyrene; HDODA: Hexanediol Diacrylate

Blood Brain Barrier (BBB)
BBB is acting as a highly selective membrane that separates the circulating blood from brain fluid [1]. This barrier is formed by endothelial cells which are connected to each other at “tight” junctions that create a complete seal between them. Consequently, only lipophilic molecules are able to cross the barrier. Hydrophilic substances, in contrast, are unable to cross the lipid walls unless associated with a specific transporter. Because of this, BBB prevents the treatment in a number of brain diseases by blocking the delivery of drugs [2] (Figure 1).

Nanoparticles in Drug Delivery
Nanoparticles have a size range of 1-100nm. These particles can be used to transport drug molecules across the BBB [3-5]. They can penetrate the barrier and deliver pharmaceuticals to brain for treatments against disorders like Parkinson’s disease, Alzheimer’s disease and brain tumors. It is very difficult to treat these disorders because there is not an efficient method available to transfer drugs across BBB. Many of the CNS active drugs could not pass through the BBB. Thus nanoparticles which can penetrate the BBB could be effectively used in drug delivery (Figure 2).

But nanoparticles tend to agglomerate to minimize their energy. Thus they try to react with their surroundings to attain some minimum energy for stabilization. In order to overcome this, Nanoparticles can be functionalized with various ligands for tissue and cell targeting. Lately peptides have been described as potential ligands for achieving endothelial cells and more specifically BBB targeting of nanocarriers.

Peptide Encapsulated Nanoparticles
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Varkey JT (2016) Peptide Encapsulated Nanoparticles for Brain Drug Delivery. J Anal Pharm Res 3(5): 00069. DOI:

Selection of Peptide Sequence

It is proposed to synthesize the following sequence which includes the active part of Thioredoxin [11].

\[ \text{H-} \text{Ala-Glu-Trp-Cys-Gly-Pro-Cys-Lys-Met-OH (T29-37)} \]

Thioredoxin is a naturally occurring sulfur reducing protein containing 108 amino acids [12]. It is first identified in Escherichia coli. Since the activity of this enzyme is essential for cell growth and survival, it is a good target for anti-tumor therapy [13]. This enzyme is up-regulated in several types of cancer, including malignant mesothelioma [14]. Motexafin gadolinium is an inhibitor of thioredoxin reductase and ribonucleotide reductase. It has been proposed as a possible chemotherapeutic agent in the treatment of brain metastases.

Decorating Gold Nanoparticles with the Peptides

Gold particle bioconjugates are important constructs for cellular imaging [15]. Because of the large scattering cross section of metal particles, individual nanoparticles can be imaged under white-light illumination. This involves the covalent coupling of cysteine in the selected sequence to a particle surface via sulfur-gold bond [16]. This direct coupling affords a simple one-step procedure that produces particles with high surface coverage of peptide. One important aspect of thiol-gold chemistry is that the reaction proceeds at room temperature in aqueous solution.

Conclusion

Nanotechnology has opened a new path in drug delivery to brain and nanoparticles are developed as potential drug carriers. Nanocarriers are an emerging class of drug delivery systems that can easily deliver drugs to various compartments of the body. They possess unique features due to their size and they allow transport of a range of drugs. But because of their surface functionalization nanoparticle based drug delivery is complicated. Peptide conjugated nanoparticles are designed to explore their potential for brain targeting. The selected peptide sequences could be synthesized effectively on novel PS-HDODA support using solid phase methodology. Peptide-based nanoparticles (pep-NPs) are emerging as promising imaging and therapeutic agents against cancer due to their biocompatibility and tunability.

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Citation: Varkey JT (2016) Peptide Encapsulated Nanoparticles for Brain Drug Delivery. J Anal Pharm Res 3(5): 00069. DOI: 10.15406/japfr.2016.03.00069
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