Review Article

V-Smart Nanomedicine: a review on brain targeted drug delivery system

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Abstract

Brain specific drug delivery is a process of passing therapeutically active molecules across the Blood brain barrier (BBB) for treating the brain diseases. Most of the therapeutic agents do not reach the brain due to the tight junction presence in between the epithelial cells. Formulation of brain specific drug is a challenge for formulation scientist to treat several brain diseases such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, brain cancer, trauma and cerebrovascular disease etc. Above-mentioned problems may be overcome by using different techniques like intracranial pumps, viral gene therapy, intra nasal therapy, intra-arterial therapy etc. But such methods have facing various difficulties like brain surgery or required some modification of drug molecules. V-smart nanomedicine is a newer technique which may be used in near future to overcome the problem related to brain targeted drug delivery system. In this system therapeutic agents are successfully reached into the brain without disrupting BBB and also it has high encapsulating efficacy. The innovative v-smart drug delivery is universal, versatile, flexible and able to overcome difficulties or limitation associated with other brain targeted drug delivery system. Under the V smart nanomedicine different products are under trial phase, various preclinical test is done for procure the foremost effectiveness. The objective of this review article is to describe the different approaches for delivering drug in brain and also characterization of the effectiveness of V Smart nanomedicine with its significance.

Keywords: Blood brain barrier (BBB), Structure of BBB, Invasive and non-invasive techniques, V-Smart nanomedicine

Introduction

Now days, most scientists are enticed regarding brain targeting drug delivery system because of its tremendous application for different type of CNS diseases specially related to brain in where most of the drugs are incapable to reach due to the presence of Blood brain barrier (BBB) [1]. In current situation CNS diseases is a dangerous problem related to the brain disorders. It is worldwide health issue because approximately 1.5 billion people encountering through disorders of CNS [2]. Though, development of the new drug molecules for treatment of brain diseases is a very challenging work for research scientists because the rate of success is very low compared to other drug development for different areas. And also, it is a time-consuming process to develop a CNS targeted drug compared to non-CNS targeted drug development process. The CNS targeted drug development is problematic because the Clinical trials are very complicated process due to the structure of BBB [3].

The brain is a highly susceptible and flimsy neural organ which desires a frequent furnish of fuels, gases, and nourishment to sustain homeostasis also other crucial responsibilities [4]. BBB is a vascular of the CNS which works as a physical hindrance also enforce various difficulties to pass any molecules. So, BBB is an important barrier present in our body, which helps to protect our brain from any foreign particles. The endothelial cells of brain blood vessel from tight junction of each other and prevent the uncontrolled transport of any molecules between the vasculature and the parenchyma [5]. Due to the aforementioned nature of the BBB, most potential therapeutics for brain diseases cannot cross the BBB and does not enter the brain or central nervous system [4]. Several current surveys

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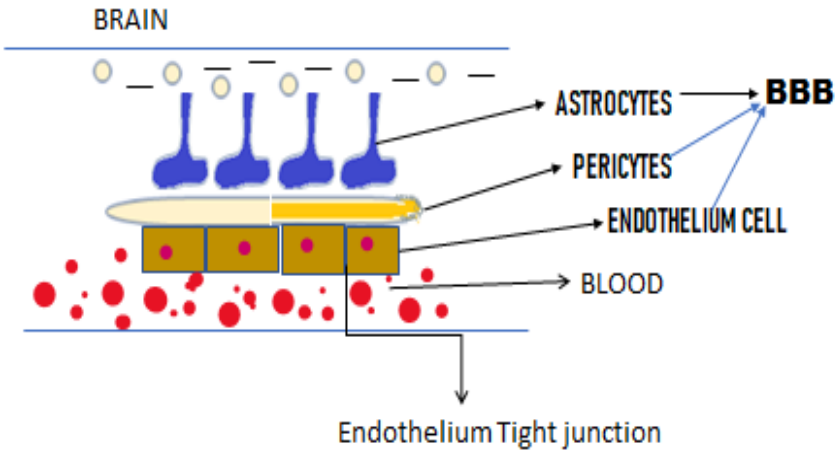

Figure 1: Blood brain barrier

indicate that approximately 100% of large therapeutic molecules and 98% of small therapeutic molecules are usually fails to enter the BBB [1]. Very small lipophilic drug molecules with molecular weight within 400 Da can able to pass the BBB [6]. A recognized factor is that the hydrophobic drugs molecules having more affinity against the BBB compared to hydrophilic drugs molecules [7]. For this reason, the maximum potential drug molecules facing a big obstacle for reaching the brain with acceptable concentration and its leads to a main drawback for developing of brain targeted drug [8].

It is possible to treat different CNS diseases like schizophrenia, depression, epilepsy, chronic pain, etc. by small drug molecular therapy. But some CNS disease like Alzheimer's disease, Parkinson's disease, Multiple sclerosis, Brain cancer, trauma, cerebro-vascular disease, Blindness is unmanageable or very difficult to treat by using small drug therapy [9]. In recent years different techniques are used to deliver the drug to the brain in appropriate concentrate like intracranial pumps, viral gene therapy, intra nasal therapy, intra-arterial therapy nano medicine etc. These techniques are help to permeate the therapeutics through BBB and reinforce the effectiveness of the treatment [10]. Those techniques are delivering the drug into the brain but this all suffer from a few or many difficulties and limitation like brain surgery or required some modification of drug molecules or required to disrupt BBB. A newer technique V-smart nanomedicine (under investigation) may be developed to treat the various CNS disease without disrupt the BBB. By using the V-smart techniques the therapeutic molecules are efficiently reach the brain and its having ability to overcome the problem which is related to traditional drug delivery system in to the brain. V-Smart Nanomedicines became proved to encapsulate potential medicinal component in to the brain, particularly hydrophilic molecules which cease penetrate the BBB on their own [11].

1. **Blood Brain Barrier**

The blood–brain barrier (BBB) is an unrivaled quality of the microvasculature of the CNS [12]. The influx and efflux of biologic substances is very necessary for metabolic activity of brain along with the neuronal functions and it is control by the BBB [13]. The blood-brain communicates by interceding transmission among CNS and periphery and its segregate the spreading from the brain [14]. On the basis of the existence of particularized tight endothelial junction the BBB not merely a physical barrier it also prevents unregulated leakage [15].

The BBB is an extremely discriminating impediment and approximately resistive structure of capillary endothelial which is protects the brain despite various organisms and undesired destructive molecules [16]. The BBB inhere of capillary endothelial cell that are associated along together by uninterrupted tight intercellular junction [17] additionally adherent's junctions (AJs) which impede paracellular transportation Figure 1 [18]. The integrity of BBB is maintained by pericytes which form a tight network junction throughout the blood-brain barrier and the astrocyte also help to protect the neuron and sustain the homeostasis balance of the brain [19, 20]. Specifically, CSF present in the choroid plexus of the lateral, 3rd and 4th ventricles. Other than BBB another one barrier is present in CNS which is known as blood ceribro spinal fluid barrier (BCSFB) that acts as a hindrance to potential molecules to ingress the CNS, but lipid soluble drug able to penetrate the BCSF barrier [21, 22].

Different factors like concentration gradient and molecular weight of the drug, lipophilicity of the potential component these are important consideration to crossing through the BBB, also blood movement in the brain and enzymatic solidity affect the penetration of the drug in BBB. Presences of various disorders also alter the penetration power of drug through the BBB [23, 24].

Several physiological condition like passive diffusion and various transporter like amino acid transporter, active transport, glucose transporters, mono carboxylic acid transporter, these are further consequence for permeate the drug molecules through the BBB Figure 2 [25].

2. **Strategy for deliver the drug into the brain (CNS)**

There are two pathways by which the drug molecules are arrived at the central nervous system, one is invasive and

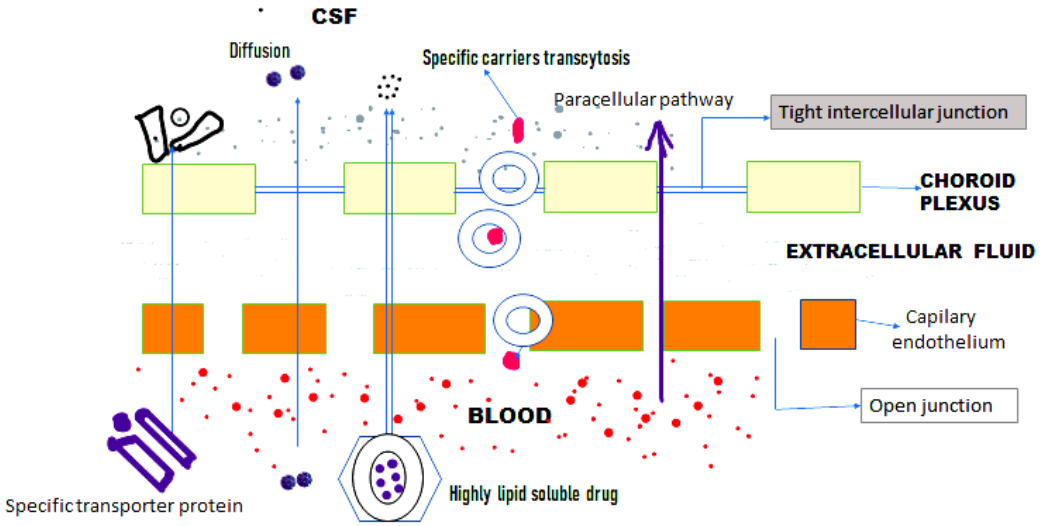

Figure 2: Different pathway across the BBB

another one is non-invasive system. The permeability of BBB is increased, and disruption of BBB is done by various method in case of invasive drug delivery system and also disruption is done, although the non-invasive system associate with the alteration of the characteristics of drug molecules by applying several techniques. Apart from above two systems now days some alternative systems are used for delivery the drug into the CNS [26].

2.1. Invasive drug delivery system

Any small or large surgery or cutting is required for delivery the drug by invasive methods. Wide variety of preparations can deliver to the brain through this system, it is possible to delivery small or large therapeutic molecules in single or combination form into brain by using invasive drug delivery systems. But this technique is expensive, complex and seeks anesthetic based surgery. Furthermore, interruption of BBB enhanced the risk of spreading cancerous cell within the brain [27]. Various approaches are used to deliver the drug to the brain by invasive system, these are:

- Intra cerebral implants or Intra cerebral injection
- Intra cerebro Ventricular infusion
- Convection enhanced delivery
- Microchip therapy or polymeric systems
- Disruption of BBB

2.1.1 Intra cerebral implants or Intra cerebral injection

Intracerebral injection is a method by which the drug is directly injected (several bolus injection) to the brain and the therapeutic molecules distributed throughout the brain without any severe toxicity [28 - 30]. In case of intra cerebral implants different types of biodegradable polymers are used to deliver the drug into the brain (parenchymal space or surrounding the spinal cord). The drug molecules are embedded within the polymer matrices which are implanted within the brain by a surgery. These techniques are utilized for treatment of Parkinson's disease and primary brain tumor [31-33].

2.1.2. Intra cerebral Ventricular infusion

Intra cerebral ventricular infusion is an approach in where the drag is direct injected to the cerebral lateral ventricles and the potential molecules circulated through the cerebrospinal fluid [34]. The drug molecules reach to the brain parenchyma, from the cerebrospinal fluid through the blood cerebrospinal fluid barrier but the drug concentration is low in brain parenchyma due to the presence of blood cerebrospinal fluid barrier. If the target site is near to the ventricles, then the intra cerebral-ventricular infusion is a very efficient technique for drug delivery [35, 36].

2.1.3. Convection enhanced delivery

In this method a smaller width catheter which is grafted with drug molecule introduced or inserted to the brain parenchyma by using any surgical procedure. The drug is released from the catheter by pumping and diffused through the brain parenchyma for respective days. [37-39]. Locating of catheter in the right place by surgery of the brain is a complex process [40]. But High molecular weight potential component can be delivered to the brain by using this method and the drug molecules are widely distributed throughout the brain [41, 42].

2.1.4. Microchip therapy or polymeric systems

The microchip is formulated by biodegradable polymer for delivered the drug to the brain. Different kind of synthetic and natural polymer like human serum albumin, chitosan, polylactic acid and poly lactic-co-glycolic acid, polycaprolactone, are used to deliver the drug into control release manner [43]. The combination form of drugs is embedded within the polymeric matrix and then it is incorporate with the microchip reservoirs [44]. The release of the drug molecules from the microchip is moderated by altering the composition of the polymer in various ratios. This technique used to deliver the drug to the

brain parenchyma either single or combination drug therapy [45, 46].

2.1.5. Disruption of BBB

Disruption of BBB is a common method to bypass the drug into the brain. The BBB can disrupt by using different methods like osmotic disruption, ultrasound disruption, and bradykinin-analogue mediated disruption [47].

2.1.5.1. Osmotic disruption

The BBB can open temporary by using some component which create high osmotic pressure like fructose, urea, mannitol, milk amide, glycerol etc [48, 49]. Mannitol-sugar solution injected to the neck arteries and brain capillaries having an elevated sugar concentration which generate to the shrinking and interruption of the tight junctions; for this reason, drug molecules enter to the brain. After disruption of the BBB also allow some foreign molecule which alter the normal function of the CNS [50-52].

2.1.5.2. Ultrasound disruption

MRI guided ultrasound technique also used to disrupt the BBB. This technique is based on the energy of preformed microbubbles which help to change the structure of vascular endothelium [53]. As a result of an ephemeral drug presence, it reversibly crosses through the BBB of potential molecules which reach the CNS and shows the therapeutic effects [54, 55]. But due to the disruption of BBB by the ultrasound create unwanted distribution of anti-cancer drug into the normal brain cell [56].

2.1.5.3. Application of bradykinin-analogue

The endothelium tight junction of BBB is also open by the help of bradykinin-analogue which activated the bradykinin B2 receptor by the calcium mediated mechanism [36].

2.2. Non-invasive drug delivery system

Under the non-invasive drug delivery systems different approaches like physiological approach, biological approach, chemical approach, and colloidal approach, are used to deliver the drugs to the brain [10].

2.2.1. Physiological approach

Under the physiological approach adsorption mediated drag transport mechanism like receptor mediated drugs transport, carrier mediated drug transport etc has been used to deliver the drug to the brain [57].

Different physiological approaches are:

- Receptor mediated delivery
- Transport mediated drug delivery
- Transferring receptor mediated drug delivery
- Insulin receptor mediated transcytosis
- Adsorptive mediated transcytosis

Different receptors like transparent receptors insulin receptor these are more relevant on the endothelial cells through the BBB. Different ligands like specific ligands, modified ligands, and different antibodies are targeted to those receptors which will transfer the drug into the brain [58]. Adsorptive-Mediated drug delivery is one more significant technique for delivery the drug into brain. A nonspecific mechanism of endocytosis, adsorptive endocytosis provides the proteins and peptides from the luminal plasma membrane of the cell [59].

2.2.2. Biological approach

Biological approaches for delivery the drug into the brain is a well-known mechanism which is based on the anatomical and physiological niceties structure of the BBB. Conjugation of drug with antibody, molecular trojan horses approach, use of genomics, autonomic nervous system are the different techniques which are used to deliver the drug into CNS [60-62].

2.2.3. Chemical approach

In case of chemical approach, the structure and physio chemical characteristics of drugs can be modified with the help of different technique. Cationic protein approach, chimeric peptides approach, pro drug approach, and p glycoprotein inhibition approach are used to deliver the drug to the BBB [10, 63]. The chemical structure of the drug compound can be modified by using the prodrug technique like morphine (not able to enter in CNS). It's become more lipophilic after chemical modification and then its cross the BBB without any difficulties. [64, 65].

2.2.4. Colloidal approach

Different nano carrier, nano particles, liposome, Niosomes, microemulsion, nano suspension, nano emulsion, are used to target the drug into the brain. Those techniques are capable to distribution of the drug into the brain through the BBB and increase the efficacy of the drug with minimal toxicity [66, 67].

3. V Smart nanomedicine (under pre-clinical stage)

It is a greatest innovation by Lauren Sciences, invented by Professors Sarina Grinberg, Charles Linder, and Eliahu Heldman. V-Smart platform exclusively resolve the problem related to the brain diseases because maximum therapeutic component unable to reach the brain.

The V-Smart nanomedicine is a non-invasive technique. Specifically hydrophilic component which incapable to cross the BBB this type of potential components is encapsulate with the V-Smart nanomedicine which deliver the drug in particular region of the brain by (micro target) V-Smart nanomedicine cross the BBB by (macro target) and release the drug safe and efficiently in systemic manner which is already proven in animal model Table 1 [11].

V-Smart can overcome various common problems which is related to the treatment of brain disease like V-Smart nanomedicine is an universal, adaptable, and flexible platform

Table 1. V-Smart nanomedicine (product) which is under preclinical animal study

V-Smart	Planned for Brain Disorder	Designed to Target	Customized with Non-BBB Permeating Therapeutic Agent
LAUR-101	PD	Dopaminergic Neurons	GDNF (Protein)
LAUR-201	Neuro HIV	All CNS	Tenofovir (Small Molecule)
LAUR-301	ALS (Orphan Disease)	Deteriorating Motor Neurons	GDNF (Protein)
LAUR-401	GBM (Orphan Disease)	Tumor Specific Antigen	Chemotherapeutic (Small Molecule)
LAUR-501	NPC (Orphan Disease)	All CNS	Cyclodextrin (Small molecules)
LAUR-601	AD	Deteriorating Brain Neurons in AD	Neurotrophin (Protein)

having various advantage like:

- Encapsulation Capacity is very high.
- Stable in storage & blood circulation.
- No need to modification of therapeutic agent.
- Efficient controlled release mechanism.
- Penetrates intact through biological barriers.
- Administration options are both oral & parenteral.
- Can be designed for selective release.
- Has wide range of therapeutic window.
- Can be designed for specific targeting within the brain and/or elsewhere (11].

Conclusion

Drug delivery to the brain is a complex process due to the presence of the BBB which is very selective in nature. Now days various innovative techniques are applied to overcome the problem related transportation of any potential component which is used to deliver the drug to the CNS through the BBB. Recently Invasive, non-invasive techniques are widely used to deliver the drug into the specific area of the brain. Different receptor mediated drug delivery and transport mediated drug delivery system also successfully used to deliver the drug through the BBB. V-Smart is another innovative technique which is able to deliver the drug to the brain without any disruption of BBB and also absence of any chemical modification of the drug molecules. V-Smart nanomedicine helps to reach the potential component to the brain safely and effectively which is established in animal model. The inventive V-smart drug delivery is universal, versatile, flexible and able to overcome difficulties or limitation associated with other brain targeted drug delivery system.

In this review article various current approach regarding brain targeted drug delivery system are discussed and also give an outline about the significance of the innovative V-Smart nanomedicine which is under the preclinical study.

Conflict of Interest

The authors declare no conflict of interest.

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