Journal of Research in Medical and Dental Science
2022, Volume 10, Issue S1, Page No: 148-152

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Delivery of Drug across Blood Brain Barrier

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ABSTRACT

Various drug delivery approaches are currently being developed to reduce drug degradation and loss, avoid adverse side effects, and the fraction of the drug accumulated in the desired region like soluble polymers, micro particles consisting of insoluble or biodegradable polymers, natural and synthetic polymers, microcapsules, cells, liposomes, and micelles are examples of drug carriers. Blood Brain Barrier (BBB) aids in maintenance of a homeostatic state within the CNS. However, this is a serious barrier when attempting to administer medications through the systemic route. There are two forms of drug distribution namely invasive approach and non-invasive approaches. It is preferable to administer the medication using non-invasive methods to deliver drug to avoid risks. A number of nanoparticles have been created, to allow therapeutic drugs to cross the BBB. The recently developed delivery methods discussed in this study have potential to improve BBB permeability in a fewer invasive or even noninvasive way.

Keywords:

Ageing, focused ultrasound (FUS), invasive, nanoparticles, non-invasive

HOW TO CITE THIS ARTICLE: Sonal Setya, Saad Mohd Shakir, Jay Prakash, Bhupendra Chauhan, Sanjeev Mittal, Delivery of Drug across Blood Brain Barrier, J Res Med Dent Sci, 2022, 10(S1): 148-152. Delivery of Drug across Blood Brain Barrier, J Res Med Dent Sci, 2022, 10(S1): 148-152

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Received: 02/05/2022, Manuscript No. JRMDS-22-58451;
Editor assigned: 04/05/2022, PreQC No. JRMDS-22-58451(PQ);
Reviewed: 14/05/2022, QC No JRMDS-22-58451;
Revised: 18/05/2022, Manuscript No. JRMDS-22-58451(R);
Accepted: 24/05/2022,
Published: 15/06/2022

INTRODUCTION

The way a medication is handled will have a huge influence on its effectiveness. At or below the optimum dosage, benefit from medicine is greater. Doses above or below this range could have either hazardous or no medical value. In contrast, limited progress in the treatment of major diseases suggests that an interdisciplinary approach to therapeutic targeted delivery in tissues is increasingly necessary. The development of innovative ideas in controlling drug pharmacodyanimcs, pharmacokinetics, non specific toxicit y, bio recognition, immunogenicity,and efficacy led to a more complete understanding of pharmaceutical administration. To meet the varied needs of different healthcare providers, the current Drug Delivery Systems (DDS) which use multidisciplinary approaches including polymer science, pharmacology, molecular biology and bio-conjugate chemistry.

Current methods for delivering drugs and improving their bioavailability, including absorption enhancers, circulators, and targeting systems, are all designed to prevent degradation of drug and undesirable side effects while improving drug concentration and distribution in the target tissue. Once only a pipe dream or a potential, managed and unique medication delivery is now a reality. Over the past two decades and a half, drug researchers have performed several extensive and thorough investigations of drug industry.

The soluble polymers and the micro particles consisting biodegradable polymers or insoluble, natural and the microcapsules, synthetic polymers, cells, lipoproteins, cell spirits, liposomes, as well as micelles are examples of such drug carriers [1]. Several carrier (e.g., temperature or pH-sensitive) may be configured to slowly degraded, sensory cues, and directed. Targeting seems to be the term used to

describe directing drug-loaded gadget to the specific location of interest. There are two main frameworks for resolving the desired sites for addressing the desired sites for drug release, two main pathways can be distinguished:

- Passive targeting; and
- Aggressive targeting

A case in point of targeted delivery is the preferred accumulation of chemotherapeutic drugs in tumor cells, as a result of greater capillary permeability in tumor cells, as compared to normal tissue. One strategy that might improve active targeting is conductivity of drug delivery systems with ligands that are specifically recognized by receptor present on the surface of cells of concern. Selective targeting of the place of interest is achievable because ligand–receptor relationships may be more targeted [2].

System of Beaded Delivery:

Beaded delivery formulations, although not used with oxybutylin, are another approach used to obtain long-acting drug levels with the ease of once-a-day dosing. This device, known as Detrol LA, has been successfully connected to tolterodine tartrate (Pharmacia, Peapack, NJ). Essentially, the beaded device is made up of several tiny beads made of inert substances. Essentially, the beaded device is made up of several tiny beads made of inert substances (such as polystyrene). The active drug is encased in a delivery capsule that is overlaid on the beads. This system's drug distribution is acid sensitive, meaning that drug levels are dependent on gastric acidity for release. This protocol yields a pharmacokinetic pattern that is approximately equivalent to a zero-order pattern, with C max obtained 4 to 6 hours after ingestion and continuous values observed for 24 hours after initial dosing. Detrol LA outperforms immediate-release tolterodine in terms of potency (improved incontinence rates) and tolerability.In a randomized, double-blind, placebo-controlled trial of 1529 participants, the LA formulation results in 18% less incontinence events than the instant tolterodine, although both formulations were statistically superior to placebo in minimising urinary incidence and growing voided urinary amount. Tolterodine LA has a 23% lower average dry mouth risk than immediate-release tolterodine. Van Kerrebroeck came to the conclusion that the LA formulation of tolterodine outperformed the immediate-release formulation.

Liposomes are complexes made up of one or more concentric pheres of lipid bilayers isolated by water or aqueous buffer compartments. Phospholipids are the principal components of naturally occurring bilayers. Phosphatidylcholi is one of these phospholipids. The main characteristic that bilayer-forming compounds have in common is amphiphilicity, which means that they have distinct polar and non-polar areas. This is why the non-polar regions turn themselves towards the interior, away from the aqueous phase, while the Polar Regions are in contact with it. A.D. found liposomes around 40 years ago.

Drug Delivery to Brain:

Disorders and injuries affecting the central nervous system (CNS) are difficult to handle since most medicinal drugs are still unable to penetrate the blood–brain barrier (BBB) and blood–spinal cord barrier (BSC) (BSCB). Biological-based targeted therapies have increased in importance over the last decade. The majority of these compounds have a hydrophilic composition. As a result, it is vital to develop an appropriate distribution mechanism for such goods in order for them to cross a BBB and meet the target locations within the CNS.

BBB aids in the maintenance of a homeostatic state within the CNS. However, this is a serious barrier when attempting to administer medications through the systemic route. Since the medications are still unable to cross the BBB, they must be delivered directly through the help of invasive techniques. Ehrlich showed in the early twentieth century that when a dye is applied intravenously, all tissues but the brain become stained. Later, in the 1920s, it has been demonstrated that only compounds capable of penetrating cerebrospinal fluid (CSF) could impair CNS activity. In 1960, after calling this limited drug permeability "*barrierehematoencephaique*", Later, in the 1920s, it was demonstrated in 1960, after calling this localized drug permeability "*barrierehematoencephaique*", that only compounds with high lipid solubility may reach the CNS [3]. There are two forms of drug distribution to the CNS:

- Invasive methods
- Non-invasive approaches

Invasive drug delivery to CNS, like osmotic pump and prolifesprosan 20 depot formulations, causes a variety of complications, including neuronal injury, inflammatory reactions, and so on. As a result, it is preferable to deliver the drug to avoid risks, it is preferable to administer the medication using non-invasive methods. Trojan methods, prodrugs, nanodrug delivery, and other modifications can help to increase the therapeutic concentration of drugs.

BBB Disturbance: This is amongst one of the first strategies for increasing medication bioavailability in a CNS that was attempted. The idea of creating temporary pores in the BBB by infusing condensed substances was first suggested in the 1960s. Disrupting the BBB with hypertonic solutions like mannitol or drugs like a synthetic analogue of Bradykinin, RMP-7, a compound used in opioid distribution to the brain, may be accomplished. a material that plays a part in the modulation of the brain's endothelial cellular junction. The injection of hyperosmolar solutions into a central carotid artery, such as saline mannitol, arabinose, or urea, induces a transient disturbance of the BBB. This happens as a consequence of endothelial cell shrinkage, which allows pores to form in the endothelial junction. This method can be used to inject drugs into the CNS through

a transient hole in the BBB. Gentamicin was delivered into CSF through mannitol administration, which triggered a temporary disturbance of the BBB.

Nanotechnology: To allow therapeutic drugs to cross the BBB, a number of nanoparticles have been created. Since nanoparticles can be delivered intracerebrally and discharge their cargo in a prolonged fashion, they can overcome the BBB barrier. Nanoparticles can prevent loaded drugs from deterioration when given systemically. Tiny biochemical molecular agents can be integrated into nanoparticles using a range of chemical processes, such as adsorption, covalent linkage and encapsulation, while macromolecules can be added to surface of the nanoparticles to enhance targeting. Nanoparticles based biodegradable polymer and gold nanoparticles have recently been shown to be highly promising vectors for transporting drugs through the BBB to treat glioma.

Additionally, gold nanoparticles have been hypothesised to have greater abilities to infiltrate the BBB, which is done by means of an endocytic route. Using the ultrasonic atomic force microscope, scientists observed that 4 nm glucose-covered gold nanoparticles move at least three times larger than brain endothelium, which was not coated with glucose. RNA interference-mediated gold nanoparticle substrate termed as sphere nucleic have also been studied in the context of being capable of getting through the BBB and the blood-brain barrier in vivo and then being administered systemically.[4]. The above findings show that gold nanoparticles can be vehicles for therapeutic substances that can pass the blood-brain barrier.

While precise mechanisms through which nanoparticles cross BBB remain unknown, a number of nanoparticle groups, including polymeric, lipid nanoparticles and metallic, have been demonstrated to crose BBB and penetrate the brain via different types of endocytotic mechanisms. Metallic nanoparticles they are typically composed of inorganic materials that contain silver, iron oxides and gold particles, as well as some metallic nonmetal allotropes like carbon fullerenes. Metallic nanoparticles are usually smaller than that of lipid or polymeric nanoparticles, giving them an edge when it comes to crossing the BBB. Metallic nanoparticles can enter the brain by taking variety of routes, like CMT, passive diffusion and trans-synaptic transport.

Hyperthermia: A temporary and strongly localised, site-specific disturbance of the BBB is often caused by hyperthermia. Over the last 10 years, hyperthermia research has been centred around drug distribution which serves as a way of effective and appropriate process for treatment of the malignant glioma via multiple heat source instruments like radiofrequency, radiofrequency, microwaves ,magnetic energy and laser.

Techniques of hyperthermia: Hyperthermia is a surgical treatment that alters the functioning of structural components in body tissues by raising the temperature. Its activity depends on assumption with high temperatures (41°C–43°C, or even lower) will kill cancer cells in a manner which is selective and synergistic, since cancer cells are much more susceptible to a rapid temperature rise than normal cells. Hyperthermia's fundamental molecular mechanisms are not well known. The key mechanism is most likely permanent DNA damage [5], eventual denaturation and protein denaturation, which are all caused by temperature increases.

Focused Ultrasound (FUS): Focused ultrasound (FUS) focuses on acoustic energy to a single point, causing selective disturbance and increased permeability of blood-brain barrier (BBB). Since FUS is consistent with commercially approved treatments, it is expected to be a safe treatment that can be quickly replicated to meet chemo schedules. In past years, commonly produced contrast agents, such as the microbubbles (MBs), were been integrated into the FUS techniques to limit FUS impacts to blood vessel walls while causing limited destruction to nearby tissues of brain. Circulating MBs communicate closely to low-intensity FUS in MB-facilitated FUS, causing in temporary teardown of the tight junctions as well as the elevated permeability of BBB.

Electrohyperthermia: Electrohyperthermia is a condition under which the body's temperature rises due to the higher permittivity and conductivity of extracellular matrix in tumour tissue, Hyperthermia caused by microwave or radiofrequency electromagnetic waves has been shown to improve the BBB permeability in vivo.

Radiofrequency is also widely used during oncology to treat glioma, either individually or in conjunction with radiotherapy and/or chemotherapy. Researcher discovered that radiofrequency-induced hyperthermia increased adriamycin absorption in isotransplanted C6 glioma rats. Furthermore, other researchers have confirmed that by using local radiofrequency hyperthermia chemotherapy [6], a large levels of medication can be achieved.

Laser: Kiessling et al is the first researccher to propose that by applying focally a Nd:YAG laser pulse, it could also be used to cause a localised disturbance in the BBB. This has also been proven to have been a minimally invasive approach to treating glioma. Laser-induced membranous disruptions throughout capillary endothelium cause a temporary disturbance of the BBB, allowing molecules to enter the brain parenchym.

Magnetic hyperthermia: Magnetic hyperthermia can be defined as technique for attracting a medication towards the site of tumour by exposing the medicine filled or drug-free. MNPs to an external alternating magnetic field (AMF). MNPs are conducted locally. Locally administered MNPs communicate with external AMF and enhance MNP persistence at the tumour site. Externally applied AMF could allow for target-specific intravenous aggregation as well as encouraged MNP penetration through the BBB. Another distinct benefit of magnetic hyperthermia is the long-term durability of MNPs, which makes for several therapies without reinjection.

Magnetic hyperthermia has been tested in animal studies for its potential to allow MNP transmission through the BBB. Scientist showed, using fluorescent MNPs, that an additional AMF enhanced the effectiveness of MNP distribution through the standard BBB. Another distinct benefit of magnetic hyperthermia is the long-term durability of MNPs, which enables for several therapies without reinjection [7].

Magnetic hyperthermia has been studied in animal models for its potential to allow MNP transmission through the BBB. Kong et al. 76 showed, using fluorescent MNPs, that an additional AMF enhanced the effectiveness of MNP distribution through the standard BBB. The literature indicates that, throughout the lack of even an AMF, MNPs may be passively delivered to the glioma vasculature whilst allowing for continuous MNP delivery to a lesion, resulting in a fivefold rise in tumor susceptibility to MNPs.

An added AMF was able to retain the MNPs in the tumour for longer, enabling a five - fold improvement in tumor susceptibility to MNPs contrasted to mice given without the need for an AMF.

Receptor Mediated Transport

Utilizing endogenous influx transporters of BBB to deliver target agents from the bloodstream to the brain parenchyma is considered to be a successful technique for glioma care, particularly while using macromolecules or hydrophilic molecules that would otherwise have little potential to cross the BBB. This procedure requires transporting molecules across BBB through substrate–transporter interactions, with the two main mechanisms being:

Carrier-Mediated Transport (CMT) and Receptor-Mediated Transport (RMT): The specific substrate transporters positioned on BBB assist in passive flow of various nutrients, hormones, and tiny molecules through the BBB. That there will ever be a successful use of CMT again for treatment of glioma, with the exception of *catecholamines* and L-DOPA, which are water-soluble compounds that have been demonstrated to diffuse over the BBB. In CMT, tiny molecules are transferred from the blood flow to brain, whereas in RMT, these bigger endogenous compounds are managed on the BBB.

The low-density lipoprotein receptor-related protein receptor, neonatal Fc receptor, insulin receptor, lactoferrin receptor, and transferrin receptor interact to enable macromolecules to enter the brain across the BBB. The process by which a ligand attaches to its receptor and triggers an endocytic event remains unknown, however some scientists believe that the binding of a ligand to its receptor activates an endocytic process that ultimately leads to the creation of endocytic vesicles. To enable *transendothelial* administration of peptides, proteins, drug-loaded colloidal carriers such nanoparticles or gene materials, the following drug delivery receptors are now being functionalized into molecular Trojan horses.

Protein Transduction Domains (Ptds): A new approach to overcoming cell membrane impermeability and delivering a wide range of macromolecules and particles into cells, known as cell-penetrating pheromones, has recently appeared. Cell-penetrating peptides (CPPs), also called as protein transduction domains, are a type of peptide (PTDs). CPPs are cationic, water-soluble and/or amphipathic peptides that are typically short (up to 30 amino acids in length), making them attractive vehicles for therapeutic delivery, prompting a great deal of research into intracellular drug delivery. There are two kinds of CPPs that have been around for this purpose: cationic CPPs, which are made up of a short chain of amino acids (such as lysine or arginine).

The specified amino acids offer the peptide a cationic charge and cause it to associate with anionic motifs present on the plasma membrane through a receptor-independent mechanism. Amphipathic peptides, which have hydrophilic and lipophilic tails and are essential for peptide translocation through the plasma membrane (PM) directly. The most significant attribute of CPPs is their ability to translocate the PM in vivo and in vitro at lower micromolar concentrations without the use of receptors but without causing substantial membrane disruption. Another advantage of using CPPs for therapeutic delivery is their lack of toxicity as opposed to other cytoplasmic delivery devices, for instance polymers, liposomes and so on. The mechanism of CPP-facilitated cellular uptake is uncertain and is dependent on cargo and cellular form.

Furthermore, conventional absorption pathways such as transporters or protein-based receptors do not seem to be involved. Endocytosis, on the other hand, has been demonstrated as a widespread absorption process, although it is controversial. In a number of tests, CPP absorption was not prevented at 4°C or in the vicinity of endocytosis inhibitors; however, when soluble heparin sulphate was applied, CPPs were caught in endocytotic vesicles. Several other studies have shown that accumulation of the target cell glycosaminoglycan heparan sulphate (HS) is a concern. Many other experiments have shown that aggregation of cell surface glycosaminoglycan heparan sulphate (HS) is a crucial component of the uptake process. The task of the CPP approach must take into account the scale, non-specific, stability versus contextual interactions, and efficacy versus toxicity, all of which play a part in the development of delivery systems [8].

Drug delivery through cells:

Immune cells and stem cells as clinical vectors: Another promising choice for allowing therapeutic transmission through the BBB is to use cells' inherent versatility. To present, two large cell types are being studied as therapeutic carriers: stem cells and immune cells as well as stem cells, primarily NSCs (neural stem cells) and the MSCs (mesenchymal stem cells). It has been shown that stem cells and immune cells can cross the Blood Brain Barrier and move towards CNS through a

pathway which is inflammation-mediated. These cells are an appealing choice for supplying therapeutics to the CNS due to a variety of advantages. Cytokines, genes, nanoparticles and enzymes are only a few of the therapies that cells can deliver.

Furthermore, both stem cells as well as immune cells are spontaneously mobilized towards the sites where the tissue injury and inflammation had occurred, which is a general characteristic of CNS diseases such as brain cancer. Indeed, intravenously administration of such types of cell contributed to aggregation of brain tumours. As a result, cells may be used as targeted carriers to transmit medications towards the tissues which are inflamed around the Blood Brain Barrier. Immune cells move through the endothelial barriers, such as Blood Brain Barrier, through a mechanism called diapedesis, in which the cells are temporarily tethers to and it rolls around cells of endothelial before eventually transmigrating via associations between the *integrins* and *selectins*.

The mechanism through which the stem cells traverse the Blood Brain Barrier is debatable, although in the several reports of comparisons of immune cell diapedesis. Most, but then not all, of the similar receptors and the adhesion molecules are expressed by MSCs. MSCs, unlike in the case of immune cells, they does not travel laterally along with the endothelial wall, and they are also capable to cross the endothelial barriers far slowly, covering one to two hours to transmigrate (compared to minutes for immune cells) . Furthermore, while immune cells activate *diapadesis* through actin structures like *lamellipodia*, MSCs use membrane blebs.

The use of cell-mediated delivery in the therapy of brain tumours: Immune cells and the stem cell transportation have widely researched to a method for providing treatments to patients having cancers with central or the metastatic in brain lesions. Because of the resulting inflammation that these tumours induce, cell-based therapies were studied as the cure for metastases. Stem cells were shown to spread to metastases and inhibit development in a mouse metastatic brain cancer model. Cell-based therapies can also be efficacious in the management of the invasive glioblastoma (GBM) cells which have spread beyond tumour centre. NSCs, in specific, they are introduced to transporting tumour cells, where they provide protection.

NSCs, in general, were assigned to migrating tumour cells, allowing to the selective delivery of therapeutic agents to remote glioma cells after an intraparenchymal injection. NSCs thus appealing therapeutic choice too invading cancer cells, but signals which facilitate NSC movement to these cells are unclear.

Cell-mediated delivery's disadvantages: While the capacity of immune system and stem cells to traverse the Blood Brain Barrier makes these one of the most promising route to potentially distributing medications to CNS, cell-mediated drug delivery poses a range of challenges [9]. The possibly harmful impacts of payload on cell carrier itself are a major issue. The inherently toxic impacts of cargo on the cell carrier are a big concern. As a consequence, a therapeutic agent have to be either non-toxic to the carrier or protected from its cargo before cell reaches target.

DISCUSSION

The effect of ageing on brain drug distribution is a forgotten topic in the literature and science. This segment describes a few research findings. The BBB is made up of microvascular ECs in astrocytes, brain, basement membrane, pericytes and nerves. These BBB components can be affected by ageing. For example, studies revealed that genes associated with inflammation and scar forming were mutated. Genes associated with inflammation and formation of scar, for example, were shown to be upregulated in aged astrocytes. Aging affected astrocyte functions important for stroke rehabilitation in both male and female rats. Furthermore, astrocytes' secretion of trophic factors that inhibit neural degeneration decreases with age.

Since ageing affects the composition of the BBB, permeability to molecules changes with age. One research looked at NGF permeability in newborn rats with hypoxic-ischemic brain injury, as well as neonatal and adult stable rats. The findings found that NGF penetration through the BBB was substantially higher in newborn rats exposed to hypoxia than in adult rats and neonatal. The findings revealed that NGF penetration through the BBB was considerably higher in newborn rats during hypoxic conditions than in neonatal and adult rats; for the ageing effect. Furthermore, prevalent pressures in diseases can further change BBB function in elderly patients, despite the fact that BBB dysfunction happens early in the pathogenesis [10]. Researcher showed that lipopolysaccharide inhibited the BBB in old mice, mimicking the typical stress of sepsis.

CONCLUSION

This study also addressed recent drug delivery techniques to the brain in the last five years. A complete analysis of BBB disruption is needed to develop successful drug delivery mechanisms for brain diseases. Recent advances in science have shown not only the permeable BBB in brain damage, but also the pathways of BBB control. Given the lack of successful therapies to cure invading glioma cells that are protected by the BBB, there is little debate about the urgency of optimising drug distribution through the BBB. The prognosis for patients with glioma will stay grim until we discover the "golden finger" to ensure successful drug distribution. The recently developed delivery methods discussed in this analysis both have the potential to improve BBB permeability in a fewer invasive or even noninvasive way, as well as deliver therapeutics through the BBB to enter the brain parenchyma. Since no single technique is effective enough to provide a significant advance in glioma care, the potential use of collaborative efforts and therapeutic agents can result in a successful resolution.

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