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# A Review: Recent Strategies Involved in Brain Targeting Through Ocular Route - Patents and Application

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## Abstract

The eye is a highly sensitive organ. Its physiology and anatomy leads to considering it as a highly protected organ. Effective therapy depends on designing of delivery system. Brain targeting through the ocular delivering system, is a formidable task. But now a day's ocular delivery plays a promising approach towards brain targeting. The Scientist has been found, some alternative models for brain targeting. These delivering systems have the ability to overcome limitations of current therapy. Treating brain tumors are kind of difficult task due to their uncontrollable growth & poor prognosis. Chemotherapy, aggressive surgical & radiotherapy is resulting in harmful side-effects to the human body. Toxicity and adverse effects can be minimized via the brain targeted delivery system. This will tend to enhance the accumulation of drug in tumor region. The ocular delivering system becomes a new strategy for brain therapy. This review deals with recent strategies, approaches, its vision, future aspects, patents & challenges in brain targeting. It also gives further insight for improved therapies in treating brain disorders via ocular route.

**Keywords: Chemotherapy; Brain targeting; Prognosis; Therapy; Ocular delivery**

## Introduction

It has been studied that 1.5 billion of population was suffering from brain disorders. Upsetting part of the CNS delivering drug was blood brain barrier (BBB). Blood brain barrier act as big obstacle in distribution of CNS drugs. Hydrophilic drugs like neuropeptides creates problem while passing through the BBB. Innovative approaches have been utilized in CNS drug formulations. The approach mainly concerns about delivering drug to its pertinent sites [1]. The most challenging aspect is treating brain disorders. It considered as so because of many obstacles occurs during delivery of drug. Localizing the drug at its site is the main concern of treatment. Brain targeting facilitates localization of the drug to its target site (Table 1). So, toxicity and other side effects would be minimized. It will also lead to efficient treatment. New strategies include certain approaches through which targeting will be easy. The most effective approach is targeting via ocular route than conventional ones. Now days, it becomes a rational approach to treat brain disorders. To achieve successful targeting, a brief intracellular characterization of blood brain barrier should be concerned [2]. Various harmful effects come out after chemotherapy. Accumulation of drug in peripheral tissues can be minimized through ocular route in brain targeting. In recent decades, active drug targeting extensively employed for treating brain tumors. As tumors have idiosyncratic features from peripherally present tumors. That's why, before targeting tumors, various factors should be kept in mind before targeting. Factors includes such as the microenvironment of tumors, the number of tumor cells (Table 2), extent of tumor cells, size, type of barriers present etc. [3]. Target specificity can be achieved through ocular route. This may reduces peripheral toxicity and direct targeting of drug towards site Brain targeted drug delivery deals with rate limiting step i.e. blood brain barrier. It is an major obstacle in delivery of drug for brain targeting [4]. This barrier has greater ability: To separate and restrict brain from circulatory network; allow molecules transportation which provides functional activity of brain; Prevents lipid and water soluble substance transportation to CNS; Improvement in BBB cell biology; restrain infiltration of the molecules [5]. For prevention of brain disorders, CNS related diseases; an effective amount of dose is needed for effective treatment. Optimum pharmaceutical composition, quantity of subject useful in ocular route of delivering drug system [2]. Ocular route preferred as an alternative route to deliver the drug to its target site. The effect of parameter such as physiochemical properties should be studied. Physiochemical properties include H-band capacity, shape, lipophilicity, size of molecules. Drug delivery vectors are also being utilized in crossing BBB. For example, mannitol modifies the BBB's structure and osmotic balance. By doing so, it tends to facilitate penetration of drug across the BBB. However, possibility

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**Table 1:** The Various barriers affect CNS drug delivery.

| S.NO. | Barriers | Features | Functions |
|---|---|---|---|
| 1. | Blood brain barrier | • Characterized by the presence of capillary endothelial cells.<br>• Tight junctions have been found in between cells.<br>• Fenestrations are absent.<br>• Pinocytic activity is less observed. [9] | Compound movements limited in the extracellular region of the brain via the blood. |
| 2. | Blood brain barrier | • Found in choroid plexus.<br>• Represented as BCSFB (blood-cerebro-spinal fluid barrier).<br>• BCSFB tend to separate cerebro-spinal fluid from the blood. | Provides \molecules movement through fenestrations and intracellular gaps. [10]. |
| 3. | Blood Tumor barrier | • Due to the presence of microvasculature which is heterogeneously distributed all over in interstitial tumor region. Hence, the delivering of drug is quite difficult in neoplastic cells present in tumors. | Affects the permeability of drugs in the cerebral microvasculature present in tumors than in normal region [11]. |

**Table 2:** Examples of Active Transporters.

| S.NO | Transporters | Features | Examples |
|---|---|---|---|
| 1 | Amino acid transporters | • These can be incorporated with large amino acid, LA transporters, action transporters, anion transporters or neutral amino acids [15]. | • A neurotransmitter known as dopamine precursor i.e L-dopa transported via LA transporters.<br>• It also employs transportation of drugs such as baleen, L-melphalan, gaboapentin through the blood into BBB [16]. |
| 2 | Glucose transporters | • Found in endothelial cells which are associated with brain capillaries.<br>• Due to having high transport efficiency (10-50 times more than) GLUT1 considered more important over another carrier transporters.<br>• It can be represented as most attractive target for delivering various drugs into the CNS. | • Properties like enhanced analgesic effect have been reported with drugs which are glycosylated analog pad compounds [17]. |
| 3 | Monocarboxylic acid transporter | • This transporter mainly transports organic acids. | • Cholesterol lowering drugs for example 3-hydroxy-3 methylglutaryl, reeducates inhibitors [18]. |
| 4 | Nucleoside Transporters | • Facilitative and sodium dependent nucleoside transporter are two types of nucleoside transporters. | • Antiviral drugs eg. 2', 3'-dideoxycytidine and anticancerous drugs [19,20] |
| 5 | Peptide transporters | • These transporters located in capillaries of the brain attached to endothelial cells forms the barrier i.e blood brain barrier. | • Growth factors, peptide hormones, Glutathione are transported via peptide transport system [21-23]. |

**Table 3:** Challenges of CNS concern during drug development in brain targeting.

| S.NO. | Challenges faced | Examples |
|---|---|---|
| 1 | Those CNS diseases which are treatable with small drug molecule therapy. | Such diseases are- Depression, Chronic pain, Schizophrenia, Epilepsy. |
| 2. | Those with brain disorders which are refractory to small drug molecule therapy. | **A)** Inflammatory disorders: Brain/spinal cord strokes.<br>b) CVS disorders.<br>c) Neurodegenerative disorders for e.g. Parkinson's disease, Alzheimer disease [24]. |

Routes of ocular delivery system

of complication may arise, such as ocular toxicity, seizures, etc. [6]. BBB considered as most challenging target site to exert therapeutic effects. For this it becomes important to maximize brain exposure towards drug instead of systemic exposure. Systemic exposure May leads to prevail systemic toxicity which would be undesirable. Due to incapability of providing sustained effect of the drug towards its specific site. Many formulations are rendered useless in the treatment of cerebral disorders. Current approaches are being employed for enhancing, delivering techniques through which drug can deliver into the brain. Now days, clinical failure is often not due to a potency deficiency in drug, but rather to method shortcomings through which drug can be delivered. That's why researchers have found some strategies through which delivering pattern have improved; there will be no need of invasive techniques requires treating cerebral disease [7].

## Overview of the BBB

It acts as a dynamic interface which separates the brain from systemic circulation of the body. It can be morphologically characterized through tight junctions, complex in nature present in-between endothelial cells [8]. 98% of potential neural-pharmaceuticals have been rejected as they won't cross the blood brain barrier. It mainly performs neuronal functions by creating ionic homeostasis [9]. Some tasks such as providing nutrients to the CNS performed through BBB. But, through various transport systems, it protects CNS from toxic insults [10]. Many neuropharmaceuticals for example-protein drugs, biopharmacons, and nucleic acids do not reach towards its target i.e. in CNS [11]. Due to which CNS disorders treatment remains unsatisfactory. To get positive results, delivering system of drugs have been improved to achieve brain targeting [12].

## Factors Involved in Brain Targeting

### Physiological factor

**Passive diffusion:** Uncharged particles, (<500 g/ml) small molecular size, lipophilicity, less hydrogen bonding potential are the main factors affecting drug diffusion across the BBB through this transport mechanism. This can be improved by reducing the size of molecules and enhancing lipophilicity which is dependent on ionization as well as the polarity of drug [7].

**Transport through vesicular:** It employs two types of transport mechanism, which are given below: i) Adsorptive endocytosis; ii) Fluid phase endocytosis. Possibility of binding phenomenon at the initial phase and the plasma membrane of cell also gets interacts in this process. Adsorptive endocytosis characterized via its steerable tendency & ligand selectivity properties. Transportation of various macromolecules from blood to brain occurs through endocytosis i.e receptor mediated endocytosis. This involves insulin & transferrin

**Table 4:** Routes of ocular drug delivery.

| Route | Features | Example | Merits | Demerits | Ref. |
|---|---|---|---|---|---|
| Topical ocular route | This is generally accomplished through ocular/eye drops. | Gels, ointments, inserts, eye drops, golfing dosage form. | Macromolecules or more lipophilic drugs can be absorbed through this route. | Short contact time. Slow volume and equilibrating bio-distribution in ocular tissues. | [31] |
| i) Sub-conjunctival administration | Subconjuctival- Injections. | Oligonucleotides, antibodies. | Small lipophilic drugs having similar permeability can easily be administered.. | Less effective cell targeting. | [32,33] |
| ii) Intra-vitreal administration | It involves drug instillation directly into the vitreous. Advantage of more straightforward access to the Vitreous and retina. | Implants, liposomes, MICR-spheres. | The drug can be easily accessible to the retina and vitreous. Smaller molecules can easily administer. The mobility of large molecules, particularly positively Charged, is restricted. | Thermobility of positively charged larger molecules are restricted via this route. There may be chances of drug elimination through the anterior and posterior barrier. | [34] |

The strategies involved in brain targeting & its applications: There are some strategies involved in brain targeting-[35]

**Table 5:** Various strategies involved in brain targeting.

| S.NO | Category | Pathways/methods | Examples | Strategies to overcome |
|---|---|---|---|---|
| 1. | Strategies for molecules modification. | a) Liposome coupled with cationic albumin. | Rhodamine-d dipalmitoyl phosphat idylethanolamine. | On increasing positive charge i.e cationic charge, targeting facilitates via adaptive mediated transcytosis. |
| | | b) Analogues-Lipophilic analogues. | DP-VPA (phospholipid-linked valproic acid). | Enhancement of lipophilicity of molecule. |
| | | c) Glutathione transporter. | Doxorubicin. glutathione-PEG liposomes. | Transportation of drug molecules through BBB. |
| | | d) Transferrin receptor. | Immunoliposomes, fusion proteins. | Targeting can be done through receptors present in BBB. |
| 2. | Strategies for altering BBB functions. | a) Phospholipid, modified fatty acids. | Mannitol, gadolinium, amino butyric acid. | Altering permeability of BBB. |
| | | b) Cationic polymers. | Albumin, peroxides, nobility. | On enhancing permeability of BBB. |
| 3. | Strategy to modulate BBB Transporters. | a) P-glycoprotein transcriptional regulation -COX-2 inhibitions. | Anti-epileptic agents. | On altering BBB transporters. |
| | | b) Inhibition of P-glycoprotein by Verapamil. | Quiacrine. | BBB transporter modulation. |
| | | c) Tariquidar drug inhibits P-glycoprotein transcription. | MPPF antagonist of serotonin 5HT1A. | On modifying BBB transporters portals. |

Recent patents involved-[36]

**Table 6:** Recent patent applications.

| S.NO | Work done/Formulation | Patent no. | Reference |
|---|---|---|---|
| 1 | Compositions & methods for delivering nucleic acid molecules and treating cancer. | US9289505 | [37] |
| 2 | Copolymer conjugates. | US9295728 | [38] |
| 3 | Benzenesulfonamide derivatives of quinoxalines, pharmaceutical composition thereof, and their use of methods for treating cancer. | US 9295671 | [39] |
| 4. | Substituted nucleotide analogs. | US9278990 | [40] |
| 5. | Therapeutic methods and compositions involving allosterickinase inhibition. | US9260417 | [41] |
| 6. | Lysophsphatidic acid receptor antagonists and their use in treatment of fibrosis. | US9272990 | [42] |
| 7. | Substituted nucleosides, nucleotides and analogues. | US9294917 | [43] |
| 8. | Heterocyclic autotoxin inhibitors and uses. | US9260416 | [44] |
| 9. | Substituted quinoxalines as B-RAF kinase inhibitors. | US9249111 | [45] |
| 10. | Method for central nervous system targeting through the ocular route of drug delivery. | US20030181354A1 | [46] |

Application of brain targeting through different.

receptor mediated transport [13].

**Active mediated transport:** This transport mechanism is also termed as carrier mediated transport. Amino acids, nucleotides, glucose, LAT1, GLUT1 are some carrier mediated transporters. They have better and higher transport capability [14]. New strategies are being utilized in improving the passage of drugs across the blood brain barrier transcellularly. This strategy includes endogenous compounds linked with drugs that can be delivered across BBB [15-23].

**Other factors are:** Concentration gradient of drug, Molecular weight of drug, Sequestration by cells, Metabolism of other tissues, Lipophilicity of drug, Affinity for efflux protein, Clearance rate of drug, Cellular enzymatic stability (Table 3), Pathological status, Systemic enzymatic stability.

## Elements of Blood Brain Barrier

**Transport pathways:** It regulates supply of minerals, proteins, amino acids, vitamins, sugars, etc. It also allows metabolite regulation, provides protection against xenobiotics.

**Metabolic barrier:** It facilitates protection against the undesirable effects of bioactive molecules.

**Anatomical barrier:** In between CNS and blood free exchange of

**Table 7:** Applications -Brain targeting through various routes.

| S.NO. | Route | Indications | Example | Reference |
|---|---|---|---|---|
| 1 | Brain targeting through ocular route. | Cholinergic brain damaging, neurodegeneraton. | Nerve growth factor. | [47,48] |
| 2 | Intraparenchymal route for cell/drug administration. | CNS disorders such as Parkinson's disease. | Neurotrophic infusionfactor derivedfrom (intraputamenal) glialcells. | [49] |
| 3 | Intrathecal route. | Pain, anesthesia. | Depo-Dur morphine (extended release). | [50] |
| 4 | Convection enhanced, delivering system. | Epilepsy. | Neurotoxins, botulism. | [51] |
| | | Glioblastoma multiforme. | Transmit/Transferrin conjugate-e. g. Diphtheria toxin. (Transmit). | [52] |
| 5 | Intracerebroventricular route. | Disease-Niemann-Pick A. | Acid-enzyme-Sphingomyelinase. | [53] |
| | | CNS infections | Antimicrobial drugs. | [54] |
| 6 | Brain targeting through nasal route. | Neuro-degenerative. | Factors-e. g. Nerve growth factor. | [55,56] |

cells & solutes get restricted through this barrier [24].

**Challenges of CNS in development of drug:** Following table represents the two main challenges faced during drug development for brain targeting.

## Approaches Employed for Increasing Brain Penetration

Brain penetration can be enhanced by using three approaches: invasive approach, non-invasive, miscellaneous approach [25,26].

### Invasive approach

In this approach, a hole is made in the head through drilling afterwards infusion /IC (intracerebral) is given via ICV i.e. intra-cerebral-ventricular. Invasive approach is of following types: a) intracerebral implants. b) Intra-cerebro-ventricular infusion; c) Disruption of BBB; d) Convection-enhanced delivery.

### Merits of invasive approach

Wide range of preparations can be employed in this approach either IC /ICV route. This approach can be applicable for delivering small as well as large molecules either in combination or alone itself. But, Invasive approach includes some limitations also given as below:

### Demerits of invasive approach

High cost, hospitalization and anesthetic condition are required. Disruption of BBB results in spreading of cancerous cells. The entering of unwanted blood components may be possible. Neurons can be permanently damaged after employing this approach.

### Noninvasive approach

Drug distribution in brain capillaries can be achieved through non-invasive technique. Noninvasive approach generally comprises of either manipulating drug or altering drug characteristics by using prodrug, colloidal/chemical techniques, liposomes, nanoparticles. It has some limitation also: a) Half life is short; b) stability is less; c) solubility is also low; d) Production cost is high; e) Leaking of encapsulated drug may be possible.

### Miscellaneous approach

Transport mechanism; b) Intranasal drug delivery Intranasal/ ocular delivery: Drugs are delivered in cavity/mucosa of nasal/ ocular. Many drugs such as sedatives, CVS drugs, Corticoids, hormones, analgesic & vaccines. Mechanism of route: It includes both extracellular &intracellular mediated routes.

### Ocular route: Drug delivery system

Ocular drug delivery is prompted through various barriers present in the eye. There are some factors which may affect the pharmacokinetics and future challenges of ocular delivery in brain targeting.

## Pharmacokinetics of Ocular Route

### Barriers of eye

**Loss of drug through ocular surfaces:** The lachrymal fluid tries to remove installed drug rapidly within a minute from ocular surface after instillation [27]. The elimination due to lachrymal flow decreases concentration of the drug in the blood. Therefore, ocular bioavailability of the drug in tear fluid becomes only 10% [28].

**Lachrymal fluid barrier:** Drug absorption of lachrymal fluid in the eye gets prohibited due to presence of corneal epithelium [29]. Hydrophobic drugs have great affinity across this barrier than hydrophilic drugs [30]. This will serve as an absorption route for peptides and proteins or larger bio-organic substances.

**Blood ocular barriers:** This barrier provides protection from xenobiotics to the blood. Blood ocular barrier constitutes two types of barriers: blood-retina barrier; and blood aqueous barrier. After crossing this barrier, drug can be easily reached to the choroid and retina. For this specific targeting is necessary.

## Future Prospective in Brain Targeting

Various Integrated blood brain barrier centers have been recognized itself in present scenario. This will bring all the researchers, scientists & beginners together to develop new targeting strategies through which brain targeting can be achieved. These BBB centers lead generating technologies for both large as well as small molecules based pharmaceutical preparations. It mainly concerns those drugs which have less or no permeability across the blood brain barrier. These centers will be based on applied sciences, technology based (Table 4 and 5). This focuses on developing new technologies regarding delivering drug molecules. Utilization of such technologies leads to re-formulate the drugs which will provide its passage across the BBB. Advancement in certain areas will help to achieve specific brain targeting such as new BBB transporters would be identified for brain targeting; Validating targeting system through in-vivo models; optimizing pharmacokinetics of in-vivo models; developing such targeting processes through which recombinant proteins and neurotherapeutics can be delivered properly (Table 6 and 7). Acquiring various strategies and technologies will lead to achieving better brain targeting.

## Conclusion

Brain targeting is quite challenging as delivered drugs get

prohibited across the brain. It remains non-effective as it does not cross the BBB due to the presence of a variety of obstacles barriers. Barriers such as bio-chemical, physiological and metabolic barriers, including BCB, BTB, and BBB obstruct drug movements from blood to brain. Present scenario faces patients who were suffering from untreated CNS disorders and treatment failure. But advancement in delivering technologies looks forward to utilize certain strategies to overcome BBB. It may lead to facilitate brain targeting and effective CNS treatment. Effective mechanisms through which drugs can deliver to its site facilitates direct brain targeting devoid of toxicity. Based on improved approaches followed by some more pioneering transport platform will be required for treating a wide range of neurological disorders such as epilepsy, stroke, Parkinson diseases, etc. This paper aims to provide recent strategies involved in brain targeting through ocular route. It also discusses about various approaches, patents and application of brain targeted neuropharmaceuticals.

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