Brain and bone delivery of drugs: a review on various techniques of drug delivery

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Changes in lifestyle have led to increased prevalence of many central nervous system diseases and disorders. The delivery of drug to the brain as well as to bone marrow has been a major challenge owing to the selectivity of physiological barriers. Several efforts have been made with different techniques to overcome such barriers for effective delivery of drugs to these two targets. These include chemical modification of the drug, receptor-mediated entry, nanotechnology-based drug transport, osmotic disruption, etc. The commonly used approaches, for delivery of drugs to the bone, are drug depots and targeted systemically delivered carriers. However, delivery of drugs to the brain and bone is highly challenging. Although there are various techniques for the delivery of drugs to the brain and the bone, the success rate of such techniques need crucial monitoring. Moreover, the techniques should be assessed for their safety, risks, and benefits to the patients and associated consequences. It is of utmost important that any delivery systems should have no significant effect on the normal healthy functions of the brain and the bone. Depending on the physico-chemical characteristics of a drug, the best method of drug delivery should be selected. Such techniques are discussed in this article.

Keywords:
blood-brain barrier, bone, brain, drug delivery, receptor, tumor

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Introduction

Present changes in the lifestyle have led to an increased prevalence of many diseases such as Alzheimer, tumors, HIV encephalopathy, multiple sclerosis, and stroke. Central nervous system (CNS) drugs have been widely used in the treatment of several such diseases [1]. CNS disorders are the leading cause of disability despite advances in brain research. The delivery of drugs to the brain is a major challenge owing to the presence of blood–brain barrier (BBB) [2]. BBB is a membrane barrier that segregates the brain from the circulating blood. Most of the drugs have been abandoned as the concentration of drugs in CNS do not achieve via the systemic circulation [3]. BBB is a well-structured barrier. BBB inhibits the passage of many drugs from the systemic circulation [4]. These drugs are unsuccessful in treating CNS disorders, because they cannot maintain required drug concentration in the brain owing to variable permeability through BBB [5]. Various techniques have been used to enhance the drug delivery to the brain. These techniques include chemical modification of the drug, receptor-mediated entry, nanotechnology-based drug transport, osmotic disruption (increasing capillary endothelial permeability by opening the BBB), vector coupling, and manipulation of chemical properties of the drugs or increasing the driving force for transport by increasing the plasma concentration of a drug. An intranasal route has also been used for delivery of certain drugs to CNS [6,7]. Intranasal delivery does not require any modification of drugs [8].

Similarly, delivery of drugs to the bone is an important phenomenon that can augment bone regeneration. The commonly used approach is drug depots and targeted systemically delivered carriers that deliver drugs to cells [9]. Systematically administered drugs are absorbed into the blood circulation and distributed to various organs of the body. These drugs are rapidly cleared from the body, and they poorly penetrate into the bone, because bones are less vascularized than other tissues. Owing to this reason, high doses of drugs are administered, which leads to systemic toxicity. Therefore, effective technique for delivery of drugs to the bone is an important need leading to avoidance of systemic toxicity of drugs. The drug carrier can transport the drug to the bone, which either promotes bone growth or reduces bone resumptions. The treatment strategies to limit bone loss and prevent fractures are divided into two main

groups: antirestorative drugs (target osteoclasts and bone-forming accelerators) or anabolic drugs (planned for osteoblast stimulation) [10]. In the present review, various techniques used for delivery of drugs to the brain and the bone are discussed.

Techniques for delivery of drugs to the brain

Drug delivery to the brain is a challenging task because of the presence of well-organized protective mechanism [11]. The route by which drug is transported via BBB is divided into paracellular and transcellular. Various types of transport through the brain occur via P-glycoprotein (P-gp) transporters, adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis, and monocyte and macrophage trafficking across the BBB. The protective effect of the BBB is also supported by the efflux transporters such as P-gp (endothelial cell protein) in the luminal membrane of the cerebral capillary endothelium [12]. The mechanism of drug entry is presented in Table 1. Various techniques used for the delivery of drugs in the CNS are summarized in Fig. 1.

Noninvasive techniques

Chemical approach

Delivery by modification of the drug molecule (lipophilic analogs)

The delivery of drugs across the BBB can be achieved by passive diffusion. Passive diffusion depends upon the lipophilicity and molecular size. Passive diffusion can be enhanced by (a) increasing the lipophilicity of the drugs or (b) reducing their molecular size. The lipophilicity of the drugs can be enhanced by the formation of prodrugs, for example, heroin is a lipophilic derivative of morphine, and has 100-fold more penetration than morphine [13]. Passive diffusion of drugs through the BBB totally depends upon their lipid solubility. Conversion of drugs to a more lipophilic form by chemical modification is helpful for CNS delivery of drugs. The main disadvantage of the lipophilic analogs includes their poor tissue distribution [14]. Prodrugs are the compounds that, after metabolism, undergo chemical transformation to an active pharmacological agent. Prodrugs method is used to make a drug more lipophilic after chemical transformation [15].

Chemical delivery system

In this delivery system, two types of moieties are attached to active substances. These moieties are removed biologically *in vivo*. Chemical delivery leads to lipophilicity. The main disadvantage of chemical modification includes the uptake of enhanced lipophilic drugs by other nontarget tissues, leading to high risk of toxicity [16]. The chemical delivery systems cross the BBB by trafficking drugs across the lipophilic precursors. Chemical delivery systems undergo successive metabolic conversions, undoing the modifier functions and finally excrete, after fulfilling their organ-targeting role [17]. Chemical delivery system, different from the prodrugs approach, requires only a single activation step [18].

Molecular packaging

CNS penetration of peptides through the BBB can be enhanced by molecular packaging strategy. Molecular packaging enhances the BBB penetration by (a) increase in lipophilicity leading to increasing passive transport, (b) increase in enzymatic stability, and (c) increase in targeting [19]. Peptides can be transported via BBB by the process of molecular packaging. In this process, peptides are attached to other bulky molecule, and the specialized group present on these molecules diffuses through the BBB and without recognition of peptides by peptidases. The first delivery with a package was for Tyr-D-Ala-Gly-Phe-D-Leu, an analog of leucine encephalin that binds to opioid receptors [20].

Drug carrier approach

Inhibition of efflux transport proteins

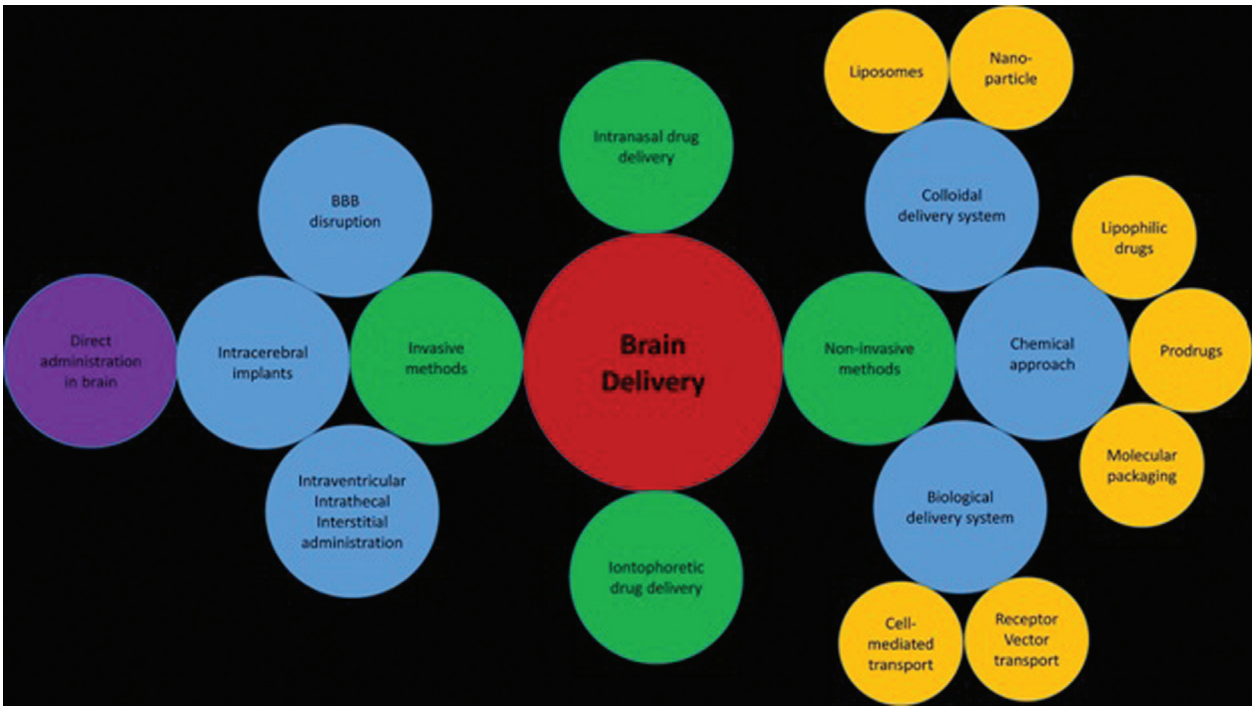
Efflux transporters (P-gp, multidrug resistant protein, and breast cancer-resistant protein) pump out drugs from the brain to the blood, leading to difficulty in

Table 1 Mechanisms of transport of various drugs

Mechanism	Molecules/drugs administered
Receptor-mediated transport (insulin, transferrin, and lectin receptor)	Insulin, transferrin, and lectin
Adsorptive-mediated transcytosis (peptide vectors)	Doxorubicin
Prodrugs (lipophilic analogs)	Codeine and heroin
Intracerebral/intraventricular drug delivery	Rituximab and vancomycin
Nasal drug delivery	Cephalosporin and meclizine
BBB disruption	Methotrexate, temozolomide, and cytarabine
Carrier-mediated approach	Valproic acid, melphalan, simvastatin, abacavir, and chlorothiazide

BBB, blood–brain barrier.

Figure 1



Different techniques for drug delivery to the brain.

Table 2 Efflux transporters present in the brain

Efflux transporter	Drug substrate
P-gp	Vinca alkaloids, epipodophyllotoxins, anthracyclines, cyclosporine A, digoxin, and various HIV protease inhibitors
BRCP	Doxrubicin
MRP1-6	Cisplatin, etoposide, and 6-mercaptopurine
Oatp1-3	Rosuvastatin
OATP-A	Bile acids
OAT3	Cepahalosporins

P-gp, P-glycoprotein.

achieving therapeutic concentrations. Therefore, the uptake of drugs, that are substrates for efflux transporters, can be enhanced by using efflux inhibitor [21]. Efflux pumps prevent many drugs from entering and accumulating in the brain. To circumvent this blockade, one strategy is to co-administer the drug with a pharmacological modulator, which inhibits efflux transport systems in brain capillary endothelial cells [22]. Examples of efflux transporters have been presented in Table 2.

Carrier-mediated transport

In this process, integral proteins present in BBB serve as passive transporters, leading to exchange of nutrients with similar structures. By using the carrier-mediated transport (CMT), delivery to the CNS can be enhanced. The main drawback of CMT is that, transport of drugs to other areas also takes place [23]. The large neutral amino acid (LNAA) carrier system has been used to deliver levodopa (endogenous dopamine precursor) to the brain. Levodopa has high affinity for the LNAA carrier system. In the cerebral endothelium, levodopa is decarboxylated to dopamine. The LNAA carrier has also been used to deliver melphalan to the brain [24].

Nanoparticulate drug delivery

Nanoparticulate drug delivery systems (e.g. micelles, dendrimers, and liposomes) have been widely used for enhanced delivery of drugs to the brain [25]. Nanoparticulate drugs should be (a) nontoxic, (b) biocompatible, (c) have particle diameter less than 100 nm, (d) nonimmunogenic, (e) have controlled release, (f) stable, (g) biodegradable, (h) without interaction with other biomolecules, (i) prolonged circulation time, and (j) inexpensive [26]. Liposomes were the first nanodelivery system with a hydrophilic head group and hydrophobic tail allowing easy permeability. Their biggest disadvantage includes the rapid uptake by the reticuloendothelial system, leading to a low circulation half-life [27]. However, the toxicity aspects associated with nanoparticulate delivery system should be critically considered [28].

Biological approach

Receptor-mediated transport

In this system, a nontransportable peptide is coupled to a transportable peptide. This coupling helps in passage

through the BBB via receptor-mediated transcytosis [29]. Endogenous receptor-mediated transcytosis helps for active targeting of BBB, in cases, when the target receptor is upgraded in disease conditions, such as diphtheria toxin receptor under inflammatory disease [30,31]. Receptor-mediated transport involves three steps for drug transport: (a) endocytosis after receptor binding, (b) movement through cytoplasm, and (c) exocytosis at the abluminal side [32]. Use of transport vectors activates natural transport routes. The endogenous CMT for nutrients and AMT for peptides can be gateways of entry to the brain for circulating drugs. This approach is generally less favored because it may interfere with the transport of nutrients and also for certain molecules (e.g. antibiotics) that do not have structures similar to endogenous ligands [33]. Following exocytosis at the abluminal plasma membrane and release into brain interstitial space, the active moiety of the chimeric peptide is released by enzymatic cleavage if a cleavable linkage between the vector and the drug is employed. The free peptide drug interacts with a specific target receptor. The covalent conjugate of cationized albumin and the opioid peptide D-Ala-β-endorphin has been used as a vector transport [34–36].

Adsorption mediated transport

AMT can also enhance the delivery of liposomes into the brain. Despite the huge success with some AMT-based drug delivery systems, one of the biggest shortcomings of AMT is its lack of selectivity, which potentially can cause adverse effects of drugs in nontargeted organs [31,37]. In this transport system, the efficiency of transport is determined based on the interaction between the cationic and anionic ligands [38,39].

Cell-mediated drug transport

Cell-mediated drug transport employs specific cells that take up drug-loaded nanocarriers or microcarriers and traffic them through the BBB and deliver the drugs to their target sites inside the brain [40].

Invasive techniques

Direct administration into the brain

For a drug to be effective, it must be enabled for brain entry and the drug should not be expelled out of the brain by transporters easily [41–43]. The delivery of drugs to the brain is important in diseases such as brain tumors and other brain disorder (neurodegenerative diseases). Direct delivery of drugs is 10 times more efficient for the accumulation of drugs in tumor tissues as compared with systemic circulation [44–46]. It has been suggested that other brain diseases could be treated in a similar manner [46]. Direct delivery of drugs to the brain (via injections, infusions, or implants) has been widely used for the treatment of many CNS disorders. By this technique, the penetration problem of drugs can be resolved and the higher bioavailability at the target site can be achieved leading to reduced systemic toxicity. Macromolecules, in addition to drugs, can also be administered by these techniques. However, the disadvantages include (a) limited brain parenchyma diffusion and (b) increase in the risk of trauma at the implant site [47].

Intracerebral implants

The intracerebral implant contains a biodegradable polymeric matrix, and it is a highly traumatic drug-delivery strategy. The disadvantages include cell injury and poor drug diffusion [48,49].

Intraventricular/intrathecal/interstitial delivery

Delivery of drugs directly to the intraventricular, intracavitary, or interstitial system is an important technique to avoid BBB. By using these techniques, the systemic toxicity of drugs can be reduced and desired concentration can be achieved at the target site in CNS [50]. Intraventricular route bypasses BBB by neurosurgical means. During intraventricular delivery, drugs are instilled directly into the cerebral ventricle. The advantages of this route include (a) lack of interconnection with brain interstitial fluid unlike intracerebral delivery and (b) the drug achieves a higher concentration in the brain. The major disadvantage is the chance of causing subependymal astrogliatic reaction [2,51,52]. With the help of intrathecal route, drugs can be injected directly into cerebrospinal fluid (CSF). Intrathecal administration bypasses the BBB, and many drugs enter in the brain, which are unable to cross the BBB via systemic route. The major advantages of this route include (a) requirement of a small dose, (b) minimal systemic toxicity, (c) low protein binding, and (d) poor metabolism, leading to less availability of the drug for longer periods. The disadvantages of this route include (a) weak CSF distribution, (b) hemorrhage, and (c) increased intracranial pressure [53]. Drug solutions are subcutaneously injected into the implanted reservoir and transported to the ventricles by manual compression of the reservoir through the scalp. The advantages include BBB bypass and high CSF drug concentration. The disadvantages include slow rate of drug distribution within the CSF and

increase in intracranial pressure, leading to high clinical incidence of hemorrhage, CSF leaks, and neurotoxicity [54,55].

Drug delivery by blood–brain barrier disruption

Modulated tight junction opening improves the passage of macromolecules across BBB. The osmotic disruption of the BBB is achieved with the help of a hyperosmotic solution. This solution causes shrinkage of cerebral endothelial cells and ultimately the expansion of blood volume leading to the transient opening of the tight junctions. The BBB returns to its normal position afterward [39,54]. The intracarotid arterial infusion of poorly diffusible solutes (e.g. mannitol) causes disruption of the BBB leading to osmotic shrinkage of the endothelial cells [56–59]. BBB disruption is of three types: (a) osmotic disruption, (b) biochemical disruption, and (c) ultrasound-guided disruption. The most frequently used technique for achieving BBB disruption is the intracranial infusion of a hyperosmolar solution of mannitol. The option of enhanced drug delivery to the CNS by inducing hyperthermia has been introduced in recent years. Ultrasound-induced mild hyperthermia may also offer promise [55,60–64].

Techniques for delivery of drugs by bypassing the blood–brain barrier

Intranasal delivery

In this process, the drugs reach the CSF by their entry through the olfactory epithelium and arachnoid membrane. Nasal delivery helps in bypassing of the drugs through the BBB [53,65–67]. Intranasal route is an attractive route for systemic and brain drug delivery. Although the intranasal route could avoid the first-pass metabolism of drugs in the liver and gastrointestinal tract, the metabolic conversions of drugs in systemic circulation and in brain should not be underrated. Metabolite formation after intranasal administration is not recognized as important owing to the following factors: (a) drug delivered via nasal route can avoid the first-pass metabolism, which affects collection of data of metabolite (s) and hence, information of metabolites after nasal delivery is scrimpy and (b) analytical methods might not be sensitive for identification of metabolites in the CNS. Hence, more effort should be put on the pharmacokinetic-pharmacodynamic correlations of active metabolites, which could facilitate the development of effective nasal drug delivery system [68,69]. Intranasal administration offers rapid onset of action, no first-pass effect, no gastrointestinal degradation or lung toxicity, and noninvasiveness application and improves bioavailability [2,51,70]. The disadvantages of intranasal drug delivery include (a) irritation of the nasal mucosa with some drugs, (b) nasal congestion may inhibit absorption of the drug, (c) decreased permeability of high-molecular-weight drugs, and (d) mucosal damage with frequent use. However, several efforts have been made for delivery of drugs via nasal route [71]. Various drugs administered by nasal route are presented in Table 3.

Table 3 Nasal delivery of drugs

Diseases	Drugs
Analgesia	Fentanyl citrate nasal spray
Migraine	Sumatriptan nasal spray/solution
Nasal congestion	Oxymetazoline nasal spray/ solution/drops
Perennial and seasonal allergic rhinitis	Budesonide nasal spray suspension

Techniques for delivery of drugs in bones

Despite several decades of drug delivery system development, bone drug delivery is still limited by the anatomical bone features. Direct delivery of drugs to the bone has been very helpful in diseases such as osteoporosis, osteoarthritis, osteomyelitis, infections, cancer, and fracture repair [72–74]. The targeted drug delivery system releases the drug at a preselected site. The bone targeting moieties and the carriers are most important elements in a drug delivery system targeting bone diseases. Targeted drug delivery minimizes the systemic toxicity and also improves the pharmacokinetic profile and therapeutic efficacy of chemical drugs [75]. Various techniques for drug delivery to bone are presented in Fig 2. Examples of drugs along with their moieties are summarized in Table 4.

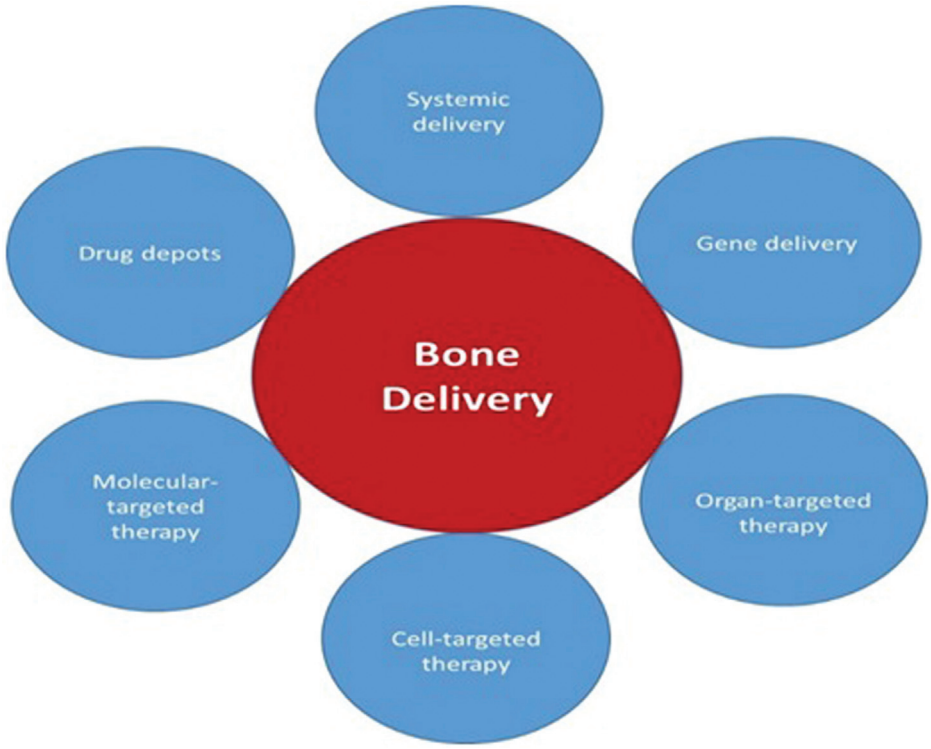
Drug depots

Basic diffusion dependent depots consist of a drug-loaded within a carrier. Direct depot often demonstrates an early uncontrolled burst drug release followed by first-order release [76–79].

Systemic delivery of drugs

Although drug depots provide site-specific drug delivery, similar to cell transplantation, they often require invasive procedures for placement. Drug carriers for systemic drug administration usually enable (a) prolonged circulation time in the blood, (b) distribution and accumulation in the targeted tissue, and (c) protection of the drug from degradation [80]. Nanoparticles and microparticles are taken up by a group of localized endothelial cells in the gastrointestinal tract leading to an increase in absorption [81]. Nanostructured particles have been

Figure 2



Different techniques for drug delivery to the bone.

Table 4 Bone drug delivery and target moieties

Drugs	Moieties
Acetazolamide	Tetracycline
Etidronate, clodronate, pamidronate, alendronate, and tiludronate	Bisphosphonate
Glutamic acid and aspartic acid oligopeptides	Oligopeptides
Estradiol analogs	Polymalonic acid
Osteoprotegerin	Alendronate
PGE1	d-aspartate 8-FITC

widely used for increasing treatment efficacy. Nanotechnology has been widely used for treating bone diseases such as bone regeneration. The advantages of using nanoparticle technique include (a) delivery of the drug at its destination by maximizing its effect and (b) protecting the drug from degradation by body fluids. The targeted delivery is primarily achieved by using drugs such as bisphosphonates used for treating bone diseases [74].

The local drug delivery provides some advantages over the systemic delivery: (a) the drug quantity is reduced; (b) unwanted adverse effects are minimized; (c) increased treatment time and efficacy, and (d) time-controlled delivery according to the needs [82].

Gene delivery to the bone

Gene therapy is the transfer of genetic material, a functional gene, or DNA/RNA fragment into specific cells to elicit a desired therapeutic phenotype to treat human disease. Gene delivery to the bone is a useful therapeutic strategy. There is a significant preclinical research demonstrating the successful transfer of genes to the bone. Recombinant vectors, as well as nonviral vectors, have been used for healing segmental defects in bones, cranium, and spinal fusion and in treating avascular necrosis.

Organ-targeted therapy

Drugs are concentrated in the bone by the affinity of hydroxyapatite in the bone. In addition to binding to hydroxyapatite, drugs can act directly on the bone to increase their concentration in bone tissues. This technique is widely used for the treatment of osteosarcoma [48,50].

Cell-targeted therapy

Chemical antibodies are short single-stranded DNA and RNA oligonucleotides or polypeptide fragments that are capable of connecting with targeted proteins. The cell-targeted therapy uses chemical antibodies combined with anti-tumor drugs to act on tumor cell surfaces [48,50]. Cell-based delivery is an ideal system for delivery of drugs. Cells are capable of

delivering drugs in response to an external stimulus, which maintains homeostasis in diseased patients [83–86].

Molecular-targeted therapy

This technique targets sites such as protein molecules or gene segments in tumor cells, thus leading specifically to the death of tumor cells, which is the key point of molecular-targeted therapy. This technique is also widely used for the treatment of osteosarcoma [48,87].

Bone-targeting moieties

For the targeted delivery of nanoparticles in bone, it is necessary to find moieties with a strong affinity to it. As bones are made of a mineralized matrix, hydroxyapatite, it could be a promising target for drug delivery. Moieties with high affinity to hydroxyapatite should be taken into consideration [75,88,89]. Some important bone-target moieties are summarized as follows.

Tetracycline and bisphosphonates

Tetracycline and bisphosphonates have been used as bone-targeting moieties because these have a strong affinity to the calcium present on hydroxyapatite [75].

Oligopeptides

Eight repeating sequences of aspartate bind to the bone-resorption surface, and Asp-Ser-Ser bind to the bone-forming surface. Both can be helpful for targeted delivery of drugs [75].

Conclusion

Brain and bone delivery of drugs is very challenging. Most of the techniques used for enhancing drug delivery to the brain are not only invasive and painful but also expose the patient to numerous other problems like susceptibility to infections. Although there are various techniques for the delivery of drugs to the brain and the bone, each technique should be assessed for their safety, risk, and benefit to the patients. It is of utmost importance that any delivery systems should have no significant effect on the functions of the brain and the bone. Depending on the physicochemical characteristics of a drug, it is possible to select the best method of drug delivery. There is a need for more research in looking for more specific and safe techniques.

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Conflicts of interest

There are no conflicts of interest.

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